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Recent developments in chemical diversity

John A. Porco Jr

Editorial

Address:
Boston University, Department of Chemistry, 590 Commonwealth Avenue, Boston MA 02215, USA

Email:
John A. Porco Jr - porco@bu.edu

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This article is part of the Thematic Series "Recent developments in chemical diversity".

Guest Editor: J. A. Porco Jr.

Diversity-oriented synthesis (DOS) is an important field involving the synthesis of libraries of diverse small molecules for applications including biological screening. The last decade has witnessed major progress in the field, with continued emphasis on structural and functional diversity for DOS library construction. A number of recent reviews have updated the community on this topic, including recent successes of biologically active molecules obtained from DOS compound collections [1,2].

This Thematic Series of the *Beilstein Journal of Organic Chemistry* attempts to capture recent developments in the area of chemical diversity and highlights the development of chemical reaction methodologies, the construction of novel chemotypes, and the advances in technology that enable progress in these areas. In the original paradigm for DOS, compound and library design were substantially based on the incorporation of functional, skeletal, and stereochemical diversity elements. An emerging theme in the area, as evident from many of the participating contributions in the Thematic Series, involves the development of novel reaction methodologies as a means to access or discover new “chemotypes”. In this way, organic chemists are empowered by the paradigm of “chemical diversity as a function of novel chemical reactions”.

“*Recent developments in chemical diversity*” in the *Beilstein Journal of Organic Chemistry* represents contributions from leading organic chemists exploring a diverse repertoire of approaches to access novel chemical diversity. I would like to thank all the authors for their important contributions to this issue and this vibrant area of research.

John A. Porco Jr.

Boston, May 2012

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An intramolecular inverse electron demand Diels–Alder approach to annulated α-carbolines

Zhiyuan Ma, Feng Ni, Grace H. C. Woo, Sie-Mun Lo, Philip M. Roveto,
Scott E. Schaus and John K. Snyder*

Full Research Paper

Address:
Department of Chemistry and the Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215

Email:
John K. Snyder* - jsnyder@bu.edu

* Corresponding author

Keywords:
α-carboline; chemical diversity; inverse electron demand Diels–Alder; isatin; pyrido[2,3-*b*]indole; 1,2,4-triazine

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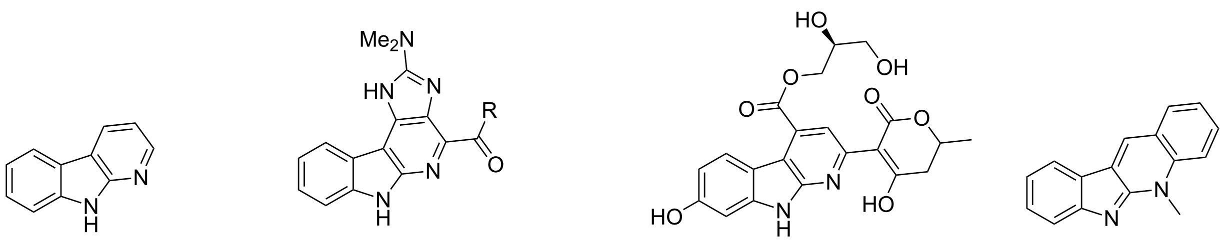
Abstract

Intramolecular inverse electron demand cycloadditions of isatin-derived 1,2,4-triazines with acetylenic dienophiles tethered by amidations or transesterifications proceed in excellent yields to produce lactam- or lactone-fused α-carbolines. Beginning with various isatins and alkynyl dienophiles, a pilot-scale library of eighty-eight α-carbolines was prepared by using this robust methodology for biological evaluation.

Introduction

In comparison with the well-known β-carbolines, α-carboline alkaloids are quite rare, and only a few natural products isolated to date contain this pyrido[2,3-*b*]indole (α-carboline, **1**, Figure 1) core. The most prominent examples are grossularine-1 (**2**) and grossularine-2 (**3**), which are marine cytotoxic agents that were isolated from the tunicate *Dendrodoa grossularia* (Stylidae) [1,2], and desmethylgrossularine-1 from tunicate *Polycarpa aurata* [3]. Other natural α-carbolines include mescengricin (**3**), an inhibitor of L-glutamate excitotoxicity in neutrons, isolated from *Streptomyces griseoflavus* [4], and cryptotackieine (**4**) [5], also known as neocryptolepine [6], isolated from roots of the West African plant *Cryptolepis sanguinolenta* [7]. Cryptotackieine, a member of the indolo[2,3-*b*]quinoline class of heterocycles [8], has been shown to be a strong inhibitor of *Plasmodium falciparum* growth [9]. 2-Amino-α-carbolines have also been identified as mutagens produced in the pyrolysis of proteins [10,11] as well as the pyrolysis of tryptophan [12]. Isoeudistomin U, isolated from the ascidian *Lissoclinum fragile*, was originally reported to have an α-carboline skeleton [13], but this assignment was later shown to be incorrect [14].

Given their isomeric relationship to β-carbolines, α-carbolines have, unsurprisingly, attracted attention from synthetic chemists for a long time [15], and more recently from medicinal chemists [16]. Synthetic members of this class were shown to have a



α-carboline (**1**)

grossularine-1 (**2**), R = 3-indolyl
grossularine-2 (**3**), R = 4-hydroxyphenyl

mescengricin (**4**)

cryptotackieine (**5**)

Figure 1: Natural products with α-carboline subunits.

wide range of activities, including topoisomerase II inhibition [17], and 4-amino-α-carbolines have also been shown to possess anxiolytic properties by stabilization of the open chloride channel [18,19]. Relatively few patents have been granted on the medicinal use of α-carbolines, particularly in comparison to β-carbolines, with recent applications including use as antiviral agents [20], inhibitors of ApoB-100-associated lipoprotein production for cholesterol lowering [21], and more recently, as inhibitors of CDK1 kinase as potential anticancer agents [22]. This later filing has triggered investigations into α-carbolines as potential multikinase inhibitors [23].

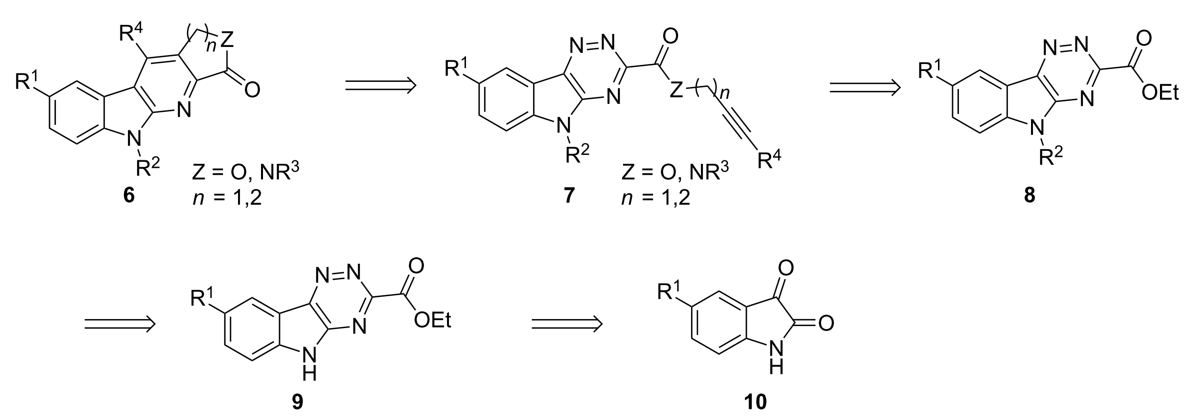
Existing synthetic approaches to α-carbolines are numerous and often independent of a specific target, but are instead methodology oriented. Exceptions include those efforts to target the grossularines [24-30] and the more popular cryptotackieine [31-35].

The first reported synthesis of an α-carboline by Robinson in 1924 [15,36] proceeded through the acid-catalyzed decomposition of 1-(2-pyridyl)benzotriazole, a modification of the Graebe–Ullmann carbazole synthesis, which closes the indole ring. This procedure was improved upon and exploited for decades [37-40]. Later, reversing the roles of the benzene and pyridine rings, with the former as the nucleophile and latter as electrophile through the diazonium salt, led to improved yields in the indole ring closure [41], as did microwave promotion of the original methodology [42]. Nitrene insertion chemistry of appropriately substituted 3-arylpyridines also found application [43,44], and likewise falls into the category of indole ring closure onto an existing substituted pyridine, though in this case with the formation of the C–N bond. More recently, the group of Cuny has reported two strategies that exploit cross-couplings to prepare anilinopyridines, with final indole ring closure occurring by either a second cross-coupling [45] or a photocyclization [46]. The former, sequential cross-coupling strategy closely follows the previous work by Queguiner [47]. A Fischer indole synthesis route through the 2-pyridylhydrazone of cyclohexanone, catalyzed by PPA, followed by dehydrogenation over Pd–C has also been reported for the preparation of the unsubstituted α-carboline [48], but no other successful applications of this strategy have appeared in the literature.

A more common strategy to α-carbolines closes the pyridine ring onto an existing indole framework. In general, applications of this construction sequence fall into two major camps, namely condensations routed through a 2-aminoindole synthon [49-56], and those targeting pyridine closures onto a 2-oxindole [57,58]. In addition, intramolecular Hartwig–Buchwald cross-coupling onto a 2-bromoindole, with formation of the pyridine was reported by Dodd [59], and C–N bond closures in presumed nitrogen-radical processes have also been reported by Narasaka [60,61]. Electrocyclic ring closures forming the pyridine ring from 2-aminoindole-derived intermediates are also known [62-64]. In addition, cycloadditions of 3-vinyl-7-azaindole have also been used to close the pyridine ring [65], as have intramolecular dipolar cycloadditions of 2-azidoindole derivatives [66], and intramolecular cycloadditions of carbodiimides [67,68].

We had envisioned that a library of annulated α-carboline structures **6** could be prepared by the intramolecular inverse electron demand Diels–Alder reaction (IEDDA) of isatin-derived 1,2,4-triazines **7** with tethered electron-rich dienophiles (Scheme 1) [69]. Inverse electron demand Diels–Alder cycloadditions employing electron-deficient heteroaromatic azadienes are well-established for the synthesis of heterocyclic compounds, and have been previously applied to the synthesis of α-carbolines. Intramolecular IEDDA chemistry to prepare α-carbolines employing 2-*N*-(*o*-alkynylanilino)pyrimidine systems have been successful in a limited number of examples [70,71]. Hoornaert and co-workers have also employed pyrazinones as dienes in IEDDA reactions to prepare α-carbolines [72].

Though the existing synthetic routes can readily produce various α-carbolines, the intramolecular IEDDA approach outlined in Scheme 1 has several advantages from the perspec-



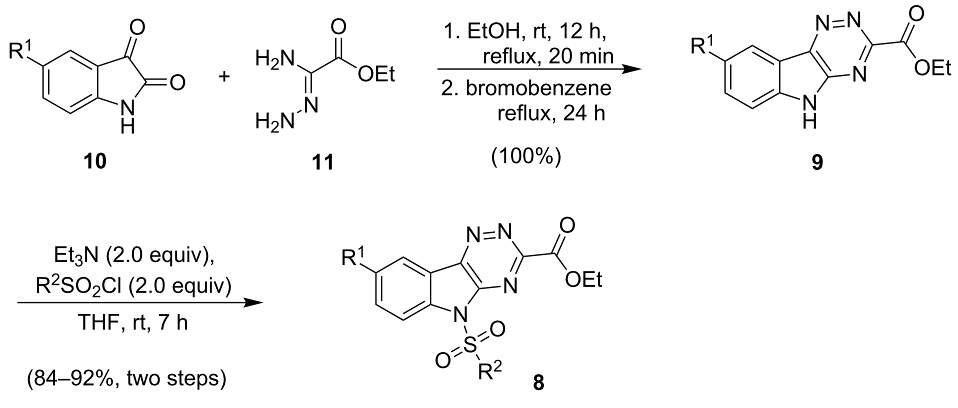
Scheme 1: Retrosynthetic inverse electron Diels–Alder approach to α-carbolines.

tive of library synthesis. First, easy access exists to a wide selection of commercially available or easily synthesized starting materials, i.e., isatins, propargylic and homopropargylic amines and alcohols. Second, three easily modifiable diversification sites, R^1, R^2 and R^4, can be built into the core α-carboline structure. Furthermore, construction of the annulated lactam or lactone as the fourth ring would be easily accomplished by the IEDDA reactions, thereby adding two more diversification points in the form of R^3 and the lactam/lactone ring size. A particular goal in this work was to establish the reaction chemistry and scope in order to build a library of α-carbolines for biological screening. The targeted α-carbolines **6** (X = O) are similar to those prepared by Dodd by a rather lengthy route, but with a transposed carbonyl group on the lactone ring [59].

One consideration in this design was the electron donation from the indole nitrogen into the isatin-derived triazine ring of **9**, which would result in an elevated LUMO of the triazinyl azadiene, and thereby inhibit the desired cycloaddition. Thus, it was anticipated that an electron-withdrawing group R^2, which could also serve as a diversification point, would be needed on the indole nitrogen.

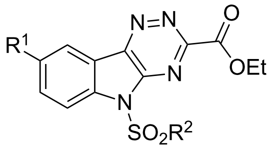
Results and Discussion

Feasibility studies began with isatin-derived 1,2,4-triazine **9a** (**9**, R^1 = H) [73,74], which was easily prepared by the condensation of isatin (**10**, R^1= H) with ethyl oxaloamidrazonate [75-77] (**11**) in quantitative yield (Scheme 2). The first step in the cyclocondensation was accomplished by stirring in ethanol at rt for 12 h and heating under reflux for 20 min, after which the solvent was removed and the cyclocondensation completed by heating under reflux in bromobenzene (bp 156 °C) for 24 h. The two-step condensation with different solvents was needed to optimize the triazine formation. Sulfonylation of the indole nitrogen also proceeded routinely to give triazine **8a** (R^1 = H, R^2 = *p*-Tol), and served two purposes. As noted, the reduction of electron donation from this nitrogen into the triazine ring was thought to be important for the subsequent cycloaddition to proceed, as was shown to be correct in later studies. Further-



Scheme 2: Condensation of isatins with ethyl oxaloamidrazonate to form triazines.

Table 1: Preparation of N-protected isatin-derived 1,2,4-triazines **8**.[a]



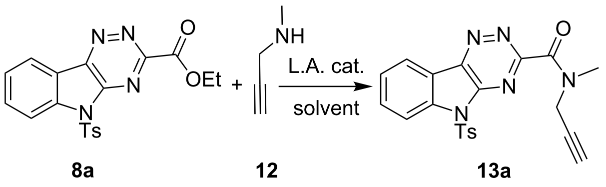
R^2	R^1 = H	R^1 = Me	R^1 = MeO	R^1 = F
p-MePh	**8a**, 88%	**8b**, 92%	**8c**, 89%	**8d**, 85%
p-MeOPh	**8e**, 90%	**8f**, 87%	**8g**, 84%	**8h**, 88%
Ph	**8i**, 90%	**8j**, 88%	**8k**, 87%	**8l**, 91%

[a] Isolated yield over two steps (Scheme 2).

more, sulfonylation greatly improved the solubility of the triazines **8** in organic solvents in comparison to **9**, which showed only limited solubility in dichloromethane, chloroform, THF, toluene, methanol and acetone. Starting with other 5-substituted isatin derivatives, analogous triazines were similarly prepared in good yields (84–92%, Table 1). 5-Nitro- and 5-carboxamidoisatins also readily participated in the cyclocondensation with the oxaloamidrazonate **11** to form the corresponding triazines (**9**, $R^1 = NO_2$, $CONH_2$), but due to the electron withdrawing nature of the isatin substituents, subsequent sulfonylations were not successful (not shown).

The intermolecular IEDDA reactions of **8a** with various electron-rich dienophiles, including ethyl ethynyl ether, the enamines (*E*)-1-*N*-propenylpyrrolidine, 1-pyrrolidino-1-cyclohexene, and 2-(dimethylamino)imidazole [78-80], all of which have been shown to react quite well with triazines or tetrazines in intermolecular IEDDA cycloaditions, were investigated. However, **8a** showed no reactivity with any of these dienophiles under any conditions, further confirming the importance of the proposed intramolecular strategy for preparing α-carbolines.

Lewis acid catalyzed amidation of **8a** with methyl propargyl amine (**12**) gave the cycloaddition precursor **13a** in excellent yield when $Al(Me)_3$ was used as catalyst (Scheme 3, Table 2) [81-84]. However, the most convenient procedure for library protocols employed 1.2 equiv of Zr(O*t*-Bu)$_4$ [85]. Weinreb amidation with $Al(Me)_3$ also gave excellent yields, but required the extra step of first mixing $Al(Me)_3$ and the amine, then cannulating this amine–$AlMe_3$ complex into the triazine solution in order to avoid ketonization of the ester [86]. Other Lewis acids, $MgCl_2$, $Mg(OTf)_2$, $Zn(OTf)_2$, $Yb(OTf)_3$ and $Sc(OTf)_3$, were not successful in catalyzing the amidation. Stoichiometric amounts of catalyst were required for the amidation, presumably due to the product itself sequestering the catalyst and preventing efficient turnover.



8a **12** **13a**

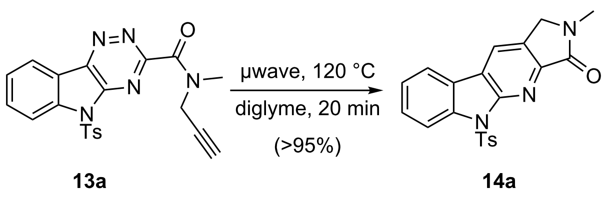
Scheme 3: Amidation of triazine ester **8a**.

Table 2: Lewis acid catalysis of amidation of triazine **8a**.[a]

Entry	Catalyst	Loading (equiv)	Solvent	Yield (%)
1[b]	$Al(Me)_3$	1.5	DCM	>95
2	Zr(O*t*-Bu)$_4$	0.5	toluene	60
3	Zr(O*t*-Bu)$_4$	1.2	toluene	90
4[c]	Zr(O*t*-Bu)$_4$	1.2	DCM	>95

[a] All reactions were carried out at rt for 20 h unless otherwise noted; isolated yield. [b] Mix catalyst and amine, then transfer the mixture of the amine–aluminum complex into a triazine solution by cannula. [c] Reaction time was 16 h.

The intramolecular cycloaddition of **13a**, the alkyne-tethered triazine, was studied under various conditions (Scheme 4, Table 3). Ultimately, it was found that the IEDDA reaction proceeded smoothly under microwave irradiation, in diglyme (120 °C, 20 min; Table 3, entry 3) to give the γ-lactam annulated α-carboline **14a** in quantitative yield. The microwave reaction conditions were preferred over the more traditional heating (Table 3, entry 1) due to the shorter reaction time. Attempts to lower the temperature and/or shorten the reaction time led to lower yields (Table 3, entries 2, 4 and 5). Little reaction occurred in toluene under microwave irradiation (Table 3, entry 6) unless silicon carbide chips were added as a microwave facilitator (Table 3, entry 7) [87].



Scheme 4: Microwave-promoted IEDDA reaction of isatin derived triazines.

Table 3: IEDDA reaction conditions of **13a** to give cycloadduct **14a**.[a]

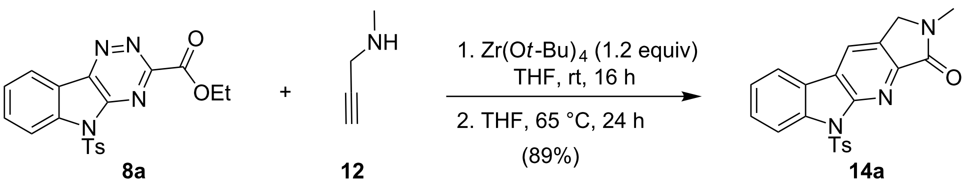
Entry	Solvent	Temperature (°C)	Time	Yield
1[b]	diglyme	164	7 h	>95%
2	diglyme	100	20 min	40%
3	diglyme	120	20 min	>95%
4	diglyme	120	10 min	70%
5	diglyme	160	10 min	85%
6	toluene	160	30 min	trace
7[c]	toluene/Si–C	160	30 min	60%

[a] IEDDA reactions were carried out under microwave irradiation unless otherwise noted. All yields were determined by UPLC unless otherwise noted. [b] Heating in oil bath. [c] Si–C chip was added to the reaction under microwave irradiation. Isolated yield.

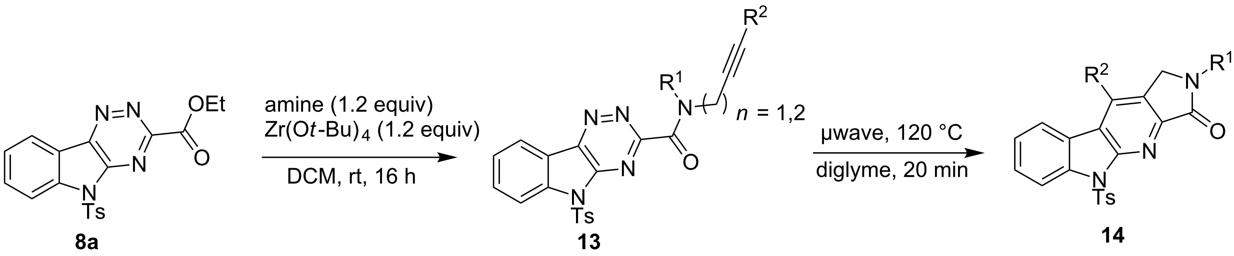
Upon further exploration of the reaction conditions, it was discovered that the amidation/cycloaddition sequence could be accomplished in one pot (Scheme 5). The Zr(IV)-catalyzed amidation was thus accomplished in tetrahydrofuran (16 h, rt), then the reaction mixture was heated under reflux at 65 °C for another 24 h to yield cycloadduct **14a**. This one-pot procedure gave a yield (89%) that was comparable to the overall yield (94%) of the corresponding two-step sequence, with isolation of the intermediate amide. Control experiments were carried out to determine the possible catalytic role of Zr(O*t*-Bu)$_4$ in the cycloaddition. In two side-by-side reactions, **13a**, with and without Zr(O*t*-Bu)$_4$ catalyst, was heated to 65 °C. The two reactions required the same amount of time (24 h) to achieve complete conversions, indicating that the presence of amidation catalyst Zr(O*t*-Bu)$_4$ in the one-pot two-step sequence had no effect on the cycloaddition of **13a**. For the library synthesis, the two-step sequence was adopted in order to isolate the triazine intermediates **13**, which can also serve as library members.

With the two-step sequence optimized for the preparation of **14a**, the scope of this chemistry was then probed with other alkynyl amines. The amidations all proceeded in high yields under the optimized conditions with Zr(O*t*-Bu)$_4$ as catalyst. The cycloaddition precursors were then subjected to the optimized microwave-promoted cycloadditions to give the final cycloadducts **14** (Scheme 6 and Table 4).

Tertiary propargyl amides **13a**, **13d**, and **13e** with terminal alkyne dienophiles all showed comparable reactivity (Table 4, entry 1, 4, and 5), under the optimized cycloaddition conditions (diglyme, microwave irradiation, 120 °C, 20 min), producing the desired α-carbolines in excellent yields (96–98%). However, propargyl amide **13f** with the internal alkyne (Table 4, entry 6)

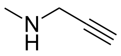
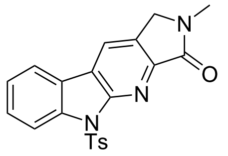
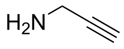
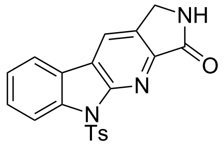
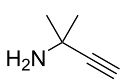
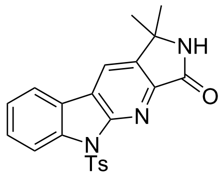
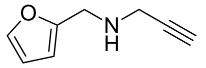
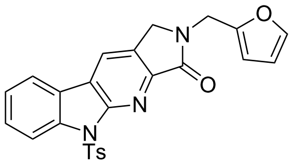
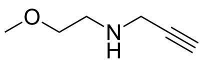
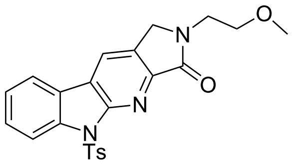
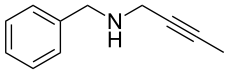
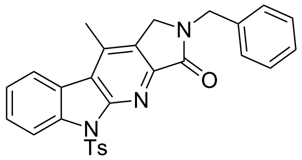
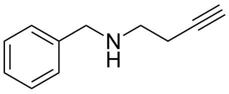
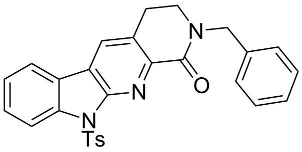
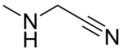


Scheme 5: One-pot amidation/cycloaddition of triazine ester **8a**.



Scheme 6: Amidation/cycloaddition forming α-carbolines **14**.

Table 4: Amidation-IEDDA sequence to α-carbolines **14** from triazine **8a**.[a]

Entry	Amine	Cycloaddition precursor **13** (yield)	Cycloadduct **14** (yield)[b]
1		**13a** (98%)	 **14a** (96%)
2[c]		**13b** (90%)	 **14b** (83%)
3[d]		**13c** (89%)	 **14c** (91%)
4		**13d** (96%)	 **14d** (98%)
5		**13e** (96%)	 **14e** (97%)
6[e]		**13f** (95%)	 **14f** (93%)
7[f]		**13g** (93%)	 **14g** (95%)
8		**13h** (95%)	no reaction

[a]Amidation reactions were carried out in DCM, with 1.2 equiv of amine and 1.2 equiv of Zr(O*t*-Bu)$_4$ at rt for 16 h, 0.25 M. IEDDA reactions were carried out in diglyme under microwave irradiation at 120 °C for 20 min, unless otherwise noted. All IEDDA reaction concentrations were 0.1 M. [b]Isolated yields. [c]IEDDA in DMF at 160 °C for 30 min. [d]IEDDA in diglyme at 160 °C for 30 min. [e]IEDDA in diglyme at 120 °C for 40 min, 0.1 M. [f]IEDDA in diglyme at 160 °C for 30 min.

required a longer reaction time (40 min) for the cycloaddition to be completed to good yield (93%). Increasing the tether length between the alkyne group and the amide linkage also decreased the reactivity (Table 4, entry 7). The cycloaddition of tertiary propargyl amide **13g** to produce the δ-lactam **14g** required higher temperatures (160 °C versus 120 °C) to proceed in high yield, still in 30 min.

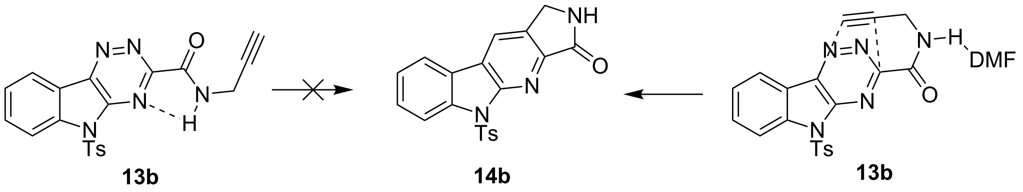
In contrast to the tertiary amides, the secondary amides **13b** and **13c** (Table 4, entry 2 and 3) showed no or very little reaction under the standard microwave conditions. The reason for this lack of reactivity was thought to be strong intramolecular hydrogen bonding, which inhibits the rotation of the alkyne group to the proper position for the cycloaddition to occur (Scheme 7).

The NMR spectra also supported this hypothesis: While all tertiary amides showed the presence of two rotamers in a 1:1 ratio in $CDCl_3$, the secondary amides **13b** and **13c** showed only a single rotamer in the NMR spectra. In the ^1H NMR spectrum for **13b**, a very slowly exchanging proton (48 h for complete exchange) at δ 8.254 supported the presence of a single conformation with strong intramolecular hydrogen bonding. When the cycloaddition of **13b** was run in DMF instead of diglyme (160 °C, 20 min), the cycloadditions proceeded in good yield to give the desired cycloadduct **14b** (83%; Table 4, entry 3). Presumably the significantly greater capabilities of DMF to accept hydrogen bonds in comparison to diglyme help to disrupt the intramolecular hydrogen bonding and enable the cycloaddition to proceed. When **13c**, with the gem dimethyl substituted propargylic carbon, was run in diglyme at a higher temperature (160 °C, 30 min), the cycloaddition proceeded in good yield to give the desired product **14c** (91%; Table 4, entry 3), presumably aided by the Thorpe–Ingold effect [88-90].

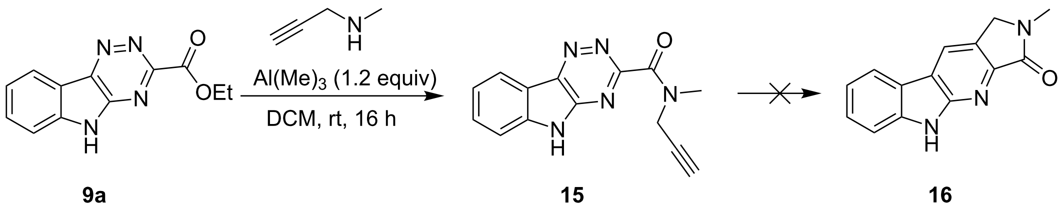
To confirm the importance of the electron-withdrawing group on the original indole nitrogen position, the reactivity of amide **9a** (R^1 = H) was also examined (Scheme 8). As expected, no cycloaddition was observed under any conditions, presumably due to the greater electron donation from the indole nitrogen, which elevates the LUMO of the triazine ring, thereby preventing the desired cycloaddition.

In addition to the amide linkage of the alkyne dienophiles, transesterification of **8a** with alkynyl alcohols led to tethered alkynyl esters as cycloaddition precursors **17a** and **17b** in good yields (Scheme 9). Various catalysts for the transesterification reaction were screened. Boronic acid [91] and indium(III) iodide [92] yielded no transesterification product with propargyl alcohol, while $Ti(OiPr)_4$ [93] gave only a trace of the desired product, with mostly detosylation resulting. Otera's catalyst [94] proved to be optimal, giving cycloaddition precursors **17a** and **17b** in excellent yields (84% and 87%, respectively).

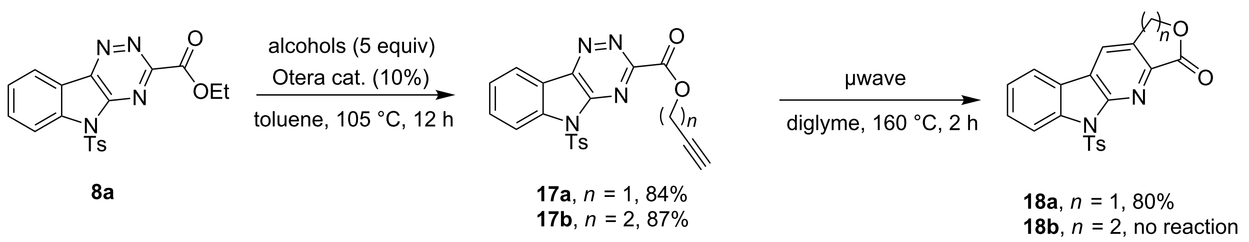
Cycloaddition precursors **17a** and **17b** showed a much lower reactivity in the cycloadditions in comparison to the amides **13**. For ester **17a**, after microwave irradiation at 160 °C for 2 h, the desired cycloadduct **17a** with the annulated γ-lactone was produced in good yield (80%). In contrast, **17b**, with the longer tether (*n* = 2) failed to produce the desired δ-lactone under any conditions. A sharp decrease in reactivity in intramolecular IEDDA reactions of alkynes tethered to 1,2,4-triazines upon progression from 5- to 6-membered ring annulations was previously noted by Taylor [95-98], and has been ascribed to the



Scheme 7: Intramolecular hydrogen bonding prevents IEDDA cycloaddition of **14b**.



Scheme 8: Preparation of unprotected triazine **15**, and its lack of reactivity in cycloadditions.



8a

17a, *n* = 1, 84%
17b, *n* = 2, 87%

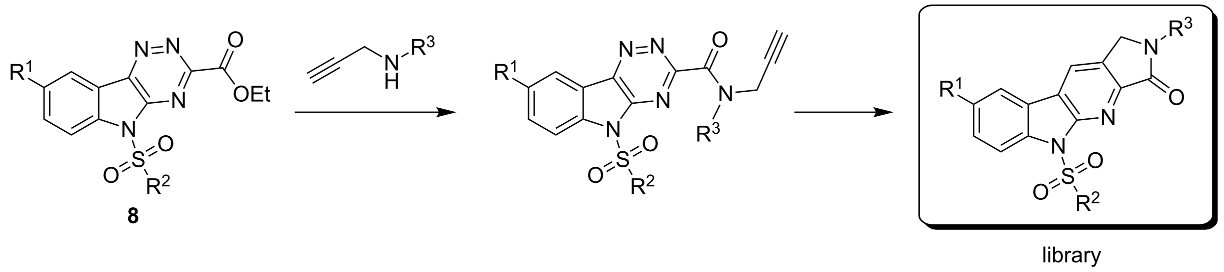
18a, *n* = 1, 80%
18b, *n* = 2, no reaction

Scheme 9: Transesterification and subsequent cycloaddition of **17a**.

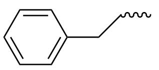
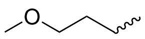
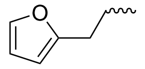
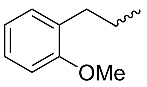
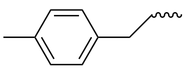
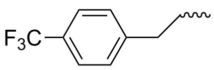
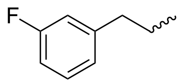
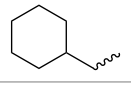
greater entropy loss for the larger rings [99]. Indeed, it has been estimated that the effective molarity for 5-membered ring closures can be as high as 1,000-fold greater in comparison to 6-membered ring cyclizations [100].

Using this optimized two-step amidation-IEDDA reaction-sequence methodology, an 88-membered pilot-scale library of α-carbolines was prepared by using triazine analogues **8** and alkynyl amines (Table 5). The crude library was analyzed by

Table 5: Library synthesis matrix.[a]



8

		R¹ = H			R¹ = Me			R¹ = OMe		R¹ = F		
R³ ↓	R² (*p*-) →	MeOPh	MePh	Ph	MePh	MeOPh	Ph	MeOPh	Ph	MeOPh	MePh	Ph
		100	100	100	50	100	50	90	72	100	100	85
		100	94[b]	100	100	100	66	100	100	99	100	100
		97	94[b]	100	77	98	90	100	100	100	98	100
		40	100	97	98	90	85	95	97	80	93	96
		100	100	100	100	100	95	100	100	100	100	100
		100	100	100	100	100	100	100	100	100	100	100
		65	100	95	100	100	92	100	100	100	100	100
		–[c]	100	100	100	–[c]	56	–[c]	–[c]	94	100	–[c]

[a]UPLC yields against starting materials. [b]Isolated yields. [c]Members were not prepared due to the limited amount of cyclohexyl propargylamine.

UPLC. The average yield of the library was 94%, with 90% of the library members produced in yields greater than 85%. Purification by LC–MS produced the final library.

Conclusion

Isatin-derived 1,2,4-triazines have proven to be excellent heteroaromatic azadienes for intramolecular inverse electron demand Diels–Alder reactions with tethered alkynyl dienophiles. These cycloadditions led to lactam-annulated α-carbolines in excellent yields under microwave assistance. The scope of the chemistry was probed by using various alkynyl amines and alkynyl alcohols, and by variation of the tether length between the aminoalkyne and the triazine. The triazines with ester linkages showed significantly less reactivity in cycloadditions compared to those with amide linkages. The longer tether length also led to a decrease in cycloaddition reactivity. This chemistry was subsequently applied to a library synthesis, producing a focused library of eighty-eight members. Diversity was introduced by using a combination of various substituted isatin-derived triazines, with various sulfonylations of the indole nitrogen, and propargyl amine derivatives as dienophiles.

Experimental

General procedure A, preparation of isatin-derived triazines 9: Freshly prepared ethyl oxalamidrazonate (**11**) [76] was dissolved in anhydrous EtOH (0.1 M) and the isatin (1.0 equiv) was added at rt under stirring. The reaction mixture was stirred at rt for 12 h, and then heated under reflux for 20 min. After removal of the EtOH in vacuo, the residue was dissolved in anhydrous bromobenzene (0.2 M) and refluxed for 24 h. After removal of the solvent in vacuo, the residue was dried by the addition and evaporation of toluene three times, and used directly in the next step without any further purification.

General procedure B, preparation of sulfonamides 8: The isatin-derived triazine **9** was suspended in THF (0.25 M) and triethylamine (2.0 equiv) was added to the solution at rt. The reaction mixture was stirred at rt for 30 min until dissolution was completed, then the sulfonyl chloride (2.0 equiv) was added at rt, and the reaction mixture was stirred at rt for 7 h. After removal of the solvent in vacuo, the residue was purified by flash chromatography to yield the desired sulfonylated triazine **8**.

Representative example: Ethyl 5-[(4-methylbenzene)sulfonyl]-5*H*-[1,2,4]triazino[5,6-*b*]indole-3-carboxylate (**8a**). According to general procedures A and B, beginning with isatin (350 mg, 2.38 mmol, 1.0 equiv) and *p*-toluenesulfonyl chloride (907 mg, 4.76 mmol, 2.0 equiv). Purification by flash chromatography, R_f 0.68 (hexanes/EtOAc, 1:1) gave **8a** (827 mg, 2.09 mmol, 88% yield) as a yellow solid: mp 145–146 °C; IR (neat): 2982, 1742, 1379, 1191, 1180, 671, 579 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (t, J = 7.0 Hz, 3H), 2.36 (s, 3H), 4.60 (q, J = 7.0 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.58 (ddd, J = 8.0, 7.4, 0.8 Hz, 1H), 7.83 (ddd, J = 8.6, 7.4, 1.0 Hz, 1H), 8.20 (d, J = 8.4 Hz, 2H), 8.49 (ddd, J = 8.0, 0.8, 0.8 Hz, 1H), 8.52 (ddd, J = 8.6, 1.0, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 21.9, 63.1, 115.1, 118.9, 123.4, 125.8, 128.8 (2C), 130.1 (2C), 133.7, 134.4, 140.5, 145.0, 146.8, 146.9, 152.6, 162.7; HRMS–ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{19}H_{16}N_4O_4SNa$, 419.0790; found, 419.0770 (100%).

General procedure C, amidation of 8 to amides 13: To a solution of triazine **8** (1.0 equiv) and propargyl amine (1.2 equiv) in CH_2Cl_2 (0.25 M) was added Zr(O*t*-Bu)$_4$ (1.2 equiv) at rt. The reaction mixture was stirred at rt for 16 h, then the mixture was diluted with CH_2Cl_2 (2 mL) and passed through an HM/HCl plug (hydro-matrix plug saturated with 0.1 M HCl aqueous solution) eluting with CH_2Cl_2. The filtrate was dried over sodium sulfate, and then the solvent was removed in vacuo. The residue was purified by flash chromatography to yield the desired amide **13**.

Representative example: *N*-Methyl-5-[(4-methylbenzene)sulfonyl]-*N*-(prop-2-yn-1-yl)-5*H*-[1,2,4]triazino[5,6-*b*]indole-3-carboxamide (**13a**). According to general procedure C, beginning with **8a** (80 mg, 0.20 mmol, 1.0 equiv) and *N*-methylpropargylamine (16.7 mg, 0.24 mmol, 1.2 equiv). Purification by flash chromatography, R_f 0.54 (DCM/EtOAc, 10:1, 83 mg, 0.19 mmol, 98% yield) gave **13a** as a brown-orange oil: IR (neat): 2933, 1655, 1370, 1192, 1178, 732, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (t, J = 2.4 Hz, 0.37H, minor rotamer), 2.34–2.36 (overlap, 3.63H), 3.12 (s, 1.89H, major rotamer), 3.31 (s, 1.11H, minor rotamer), 4.22 (d, J = 2.4 Hz, 0.74H, minor rotamer), 4.52 (d, J = 2.4 Hz, 1.26H, major rotamer), 7.29 (d, J = 8.6 Hz, 2H), 7.57 (dd, J = 8.0, 8.0 Hz, 1H), 7.81 (dd, J = 8.2, 8.0 Hz, 1H), 8.11 (d, J = 8.6 Hz, 1.24H, major rotamer), 8.12 (d, J = 8.6 Hz, 0.74H, minor rotamer), 8.44 (d, J = 8.0 Hz, 1H), 8.49 (d, J = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, (33.2, 36.0, 1C), (36.6, 40.9, 1C), (73.1, 73.9, 1C), (77.4, 77.9, 1C), 115.0, 119.1, 123.0, 125.8, 128.3 (2C), 130.3 (2C), 133.3, 134.4, 139.9, 144.3, 146.8, 147.0, (156.6, 156.8, 1C), 164.6; HRMS–ESI (*m*/*z*): $[M + Na]^+$ calculated for $C_{21}H_{17}N_5O_3SNa$, 442.0950; found, 442.0935 (100%).

General procedure D, cycloaddition of 13 to 14: A solution of the amide **13** in diglyme (0.1 M) was placed in a thick-walled microwave tube, and then the reaction mixture was subjected to microwave irradiation at 160 °C for 20 min under stirring, unless otherwise noted. After the irradiation, the solvent was removed in vacuo and the residue was purified by flash chromatography to yield the cycloadducts **14**.

Representative example: 13-Methyl-8-[(4-methylbenzene)sulfonyl]8,10,13-triazatetracyclo[7.7.0.0^{2,7}.0^{11,15}]hexadeca-1(16),2(7),3,5,9,11(15)-hexaen-12-one (**14a**). According to general procedure D, beginning with **13a** (30 mg, 0.071 mmol). Purification by flash chromatography, R_f 0.17 (DCM:EtOAc, 2:1, 27 mg, 0.069 mmol, 96% yield) gave product **14a** as a white yellow solid: mp 271–272 °C; IR (neat): 3057, 2987, 1739, 1692, 1375, 1175, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.26 (s, 3H), 4.40 (s, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.32 (dd, *J* = 8.0, 7.8 Hz, 1H), 7.51 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 8.13 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 2H), 8.42 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 30.4, 49.7, 115.0, 120.3, 121.1, 121.7, 122.8, 123.9, 128.6 (2C), 129.3, 129.6 (2C), 130.6, 135.5, 138.8, 145.4, 147.7, 151.3, 166.3; HRMS–ESI (*m/z*) [M + Na]$^+$ calcd for $C_{21}H_{17}N_3O_3SNa$, 414.0888; found, 414.0873 (100%).

Supporting Information

Supporting Information File 1

Experimental details and characterization data of new compounds, ^{1}H NMR and ^{13}C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-93-S1.pdf]

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Synthesis and characterization of Sant-75 derivatives as Hedgehog-pathway inhibitors

Chao Che[1,2], Song Li[1,2], Bo Yang[1], Shengchang Xin[1], Zhixiong Yu[1], Taofeng Shao[1], Chuanye Tao[1], Shuo Lin[*1,3] and Zhen Yang[*1,4]

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Address:
[1]Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China, [2]Shenzhen Shengjie Biotech Co., Ltd., Shenzhen 518055, China, [3]Department of Molecular, Cell and Developmental Biology, University of California, Los Angeles, USA and [4]Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), College of Chemistry, Peking University, Beijing 100871, China

Email:
Shuo Lin* - shuolin@ucla.edu; Zhen Yang* - zyang@pku.edu.cn

* Corresponding author

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Abstract

Sant-75 is a newly identified potent inhibitor of the hedgehog pathway. We designed a diversity-oriented synthesis program, and synthesized a series of Sant-75 analogues, which lays the foundation for further investigation of the structure–activity relationship of this important class of hedgehog-pathway inhibitors.

Introduction

The Hedgehog (Hh) signaling pathway plays an essential role in embryonic development and adult tissue homeostasis in metazoans. The Hh ligands activate pathway signaling by binding to a 12-transmembrane protein receptor Patched (Ptch). In the unbound state, the Ptch receptor inhibits the activity of the downstream seven-pass transmembrane receptor Smoothened (Smo). Binding of Hh ligands to Ptch leads to the alleviation of this inhibition and eventually triggers activation of the glioma (Gli) family of transcription factors and their translocation to the nucleus. This activation results in the expression of specific genes that promote cell proliferation and differentiation [1,2]. The role of the Hh signaling pathway in human cancers was first confirmed through a study of Gorlin syndrome predisposing to basal cell carcinoma, arising from autosomal dominant mutations in Ptch [3]. Indeed, aberrant Hh signaling has been reported in a variety of other malignancy diseases, such as small-cell lung cancer, pancreatic cancer, prostate cancer, breast cancer and multiple myeloma [4-9]. Taken together, the development of Hh pathway antagonists has thus represented an attractive strategy for anticancer therapy [10,11]. Because mutated Ptch or Smo proteins are mostly responsible for the abnormal activation of Hh related to human diseases, intense efforts have been invested to identify therapeutic inhibitors acting on the Smo protein. Cyclopamine (Figure 1), a natural alkaloid isolated from *Veratrum californicum* [12,13], was disclosed as the first small molecule inhibitor of the Hh pathway through direct interaction with Smo [14,15]. Cyclopamine can effectively induce a decrease in proliferation and an increase of apoptosis in several murine models [16,17]. However, the clinical development of cyclopamine as a therapeutic in cancer is hampered by its poor aqueous solubility (ca. 5 μg/mL) and acid lability. Subsequently, Infinity Pharmaceuticals developed cyclopamine-based Smo inhibitors IPI-926 through structural modification on the A and D rings. IPI-926 exhibited improved pharmaceutical properties as well as a favorable pharmacokinetic profile, and showed complete tumor regression in a Hh-dependent medulloblastoma allograft model [18,19]. IPI-926 is currently being evaluated in the phase II trial of a safety and efficacy study of patients with metastatic or locally advanced (unresectable) chondrosarcoma and myelofibrosis [19,20]. Vismodegib (GDC-0449) [21-24], developed by Genentech and Curis, is another Smo antagonist which is progressing into the phase II clinical trial for the treatment of various cancers, including advanced basal cell carcinoma, and metastatic colorectal and ovarian cancers [25-27]. Recently, vismodegib was approved by the U.S. FDA to treat adult patients with basal cell carcinoma. In addition, a number of man-made inhibitors with a Smo binding affinity have been identified and reported [2,28-34], and some of them have entered phase I development.

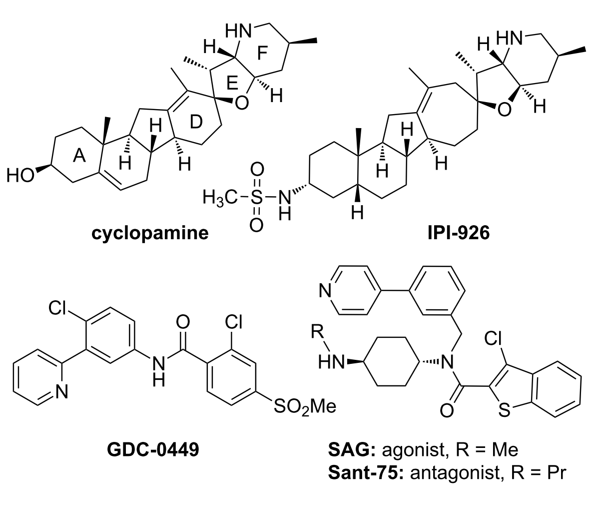


Figure 1: Structures of Smo antagonists and agonists.

SAG is a synthetic Hh pathway agonist that directly targets Smo in a manner that antagonizes cyclopamine action, and thus it may serve as an interesting scaffold for drug development [35,36]. Recently, we have identified a Smo antagonist Sant-75 through zebrafish-based screening of a SAG-derived chemical library [37]. Interestingly, this antagonist differs from agonist SAG only in the chain length of the secondary alkylamine due to the different conformational changes induced. This promising result prompted us to further investigate the structure–activity relationships (SAR) of Sant-75. Herein we describe our efforts in the development of synthetic methods for the construction of a library of Sant-75.

Results and Discussion

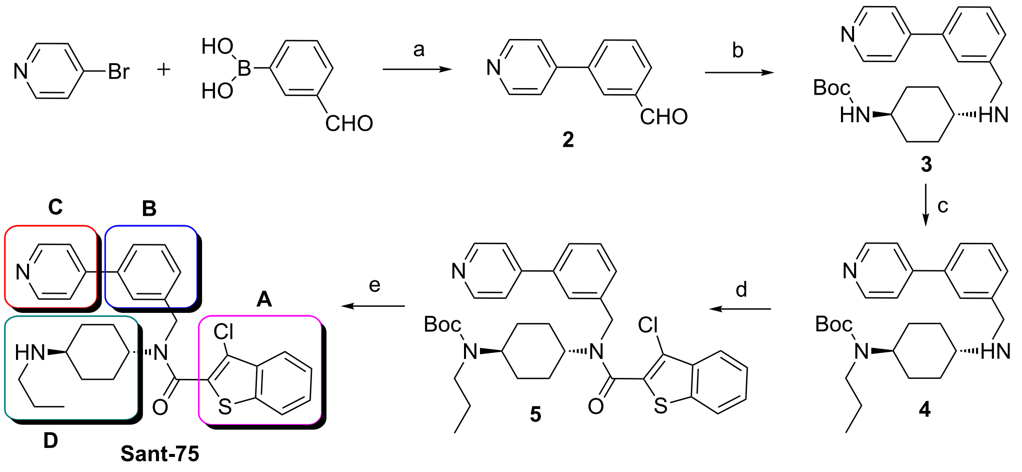
Chemistry

The scaffold of Sant-75 is divided into four distinct parts, namely 3-chlorobenzothiophene (motif A), a phenyl ring (motif B), 4-pyridine (motif C) and *N*-propyl-cyclohexane-1,4-diamine (motif D) (Scheme 1). In our earlier studies, the nature of the substituents on these regions was shown to have a profound effect on the activity. Examples of substituents that impart favorable activity include the alkyl group in region D.

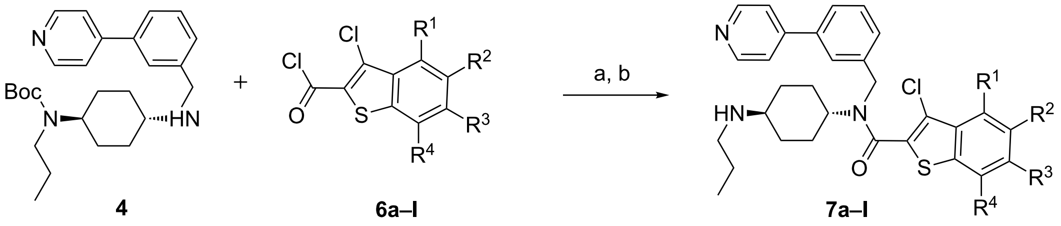
By modification of our first generation of synthetic methodology [38], the new general synthesis of the derivatives of Sant-75 is illustrated in Scheme 1. Accordingly, Suzuki coupling of 4-bromopyridine and 3-formylphenylboronic acid afforded biaryl aldehyde **2**, which was then subjected to a reductive amination by condensation of aldehyde **2** with *N*-Boc-cyclohexane-1,4-diamine, followed by reduction with $NaBH(OAc)_3$ to afford secondary amine **3**. Selective alkylation of the newly generated secondary amine was achieved by treatment of amine **3** with NaH, followed by reaction with an alkylating reagent to give amine **4** in high yield. To complete the synthesis, amine **4** was reacted with acyl chloride in the presence of Et_3N, and the formed amide was subjected to treatment with TFA to remove the Boc group.

Substituent-modifications on the motif A

The first series of derivatives is characterized by substituent modifications (Scheme 2, Scheme 3) and core modifications (Scheme 4) on the motif A. With respect to the substituent modifications, various groups, such as polar and hydrophobic groups, were introduced to the phenyl ring in motif A. Scheme 2 described the synthesis of derivatives **7a–l** through the reaction of compound **4** with a number of substituted acyl chlorides **6a–l**, which were prepared from the corresponding cinnamic acids by Higa cyclization [39,40]. It is noteworthy that some polar groups, including amino, hydroxy and sulfonamide, could not tolerate the conditions of Higa cyclization, and



Scheme 1: General synthetic route for Sant-75. Reagents and conditions: (a) Pd(PPh_3)$_4$, PhMe, Na_2CO_3, H_2O, 85 °C; (b) *N*-Boc-cyclohexane-1,4-diamine, THF, NaBH(OAc)$_3$; (c) DMF, NaH, PrI, 0 °C to rt.; (d) 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride, CH_2Cl_2, Et_3N; (e) CH_2Cl_2, TFA.



6a: R^1 = H, R^2 = H, R^3 = SO_2Me, R^4 = H
6b: R^1 = H, R^2 = H, R^3 = H, R^4 = SO_2Me
6c: R^1 = H, R^2 = H, R^3 = NO_2, R^4 = H
6d: R^1 = H, R^2 = H, R^3 = CO_2Me, R^4 = H
6e: R^1 = H, R^2 = OCH_2–, R^3 = OCH_2–, R^4 = H
6f: R^1 = H, R^2 = F, R^3 = H, R^4 = F
6g: R^1 = H, R^2 = H, R^3 = F, R^4 = F
6h: R^1 = Cl, R^2 = H, R^3 = H, R^4 = H
6i: R^1 = H, R^2 = H, R^3 = Cl, R^4 = H
6j: R^1 = F, R^2 = F, R^3 = F, R^4 = H
6k: R^1 = H, R^2 = H, R^3 = Cl, R^4 = Cl
6l: R^1 = H, R^2 = H, R^3 = Me, R^4 = H

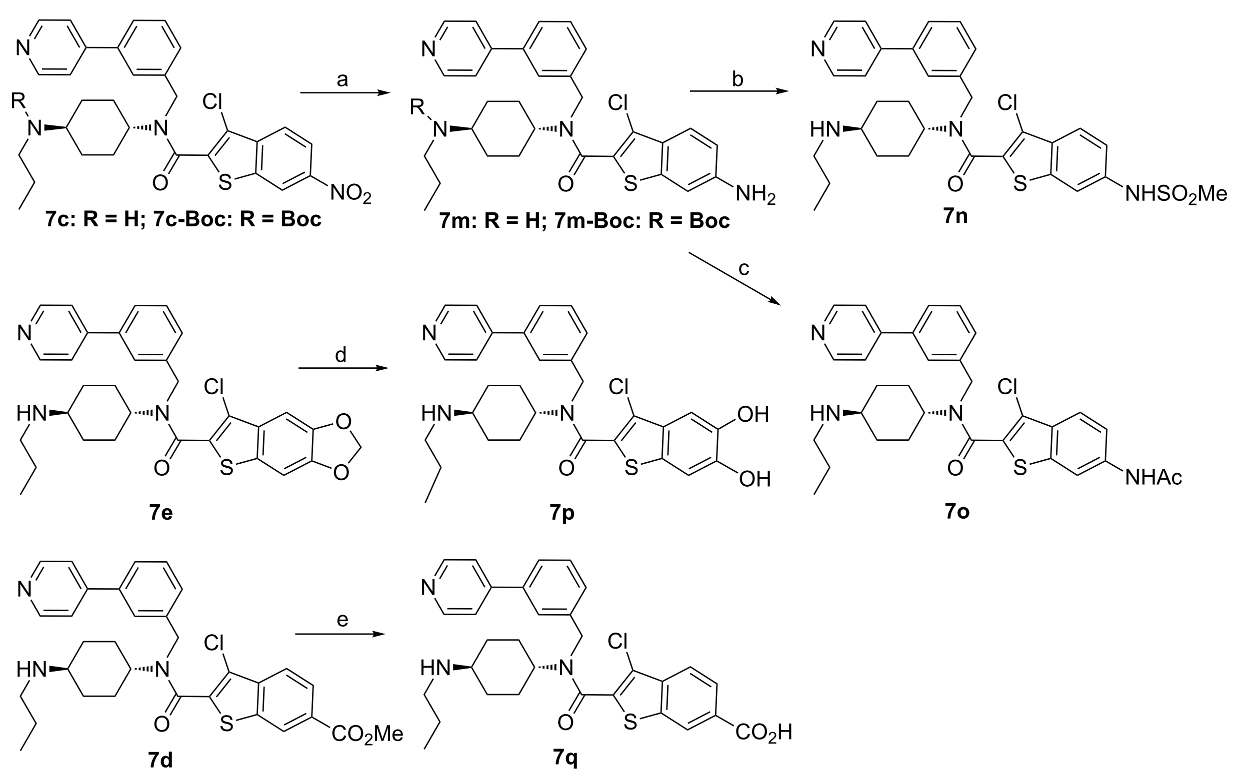
7a: R^1 = H, R^2 = H, R^3 = SO_2Me, R^4 = H
7b: R^1 = H, R^2 = H, R^3 = H, R^4 = SO_2Me
7c: R^1 = H, R^2 = H, R^3 = NO_2, R^4 = H
7d: R^1 = H, R^2 = H, R^3 = CO_2Me, R^4 = H
7e: R^1 = H, R^2 = OCH_2–, R^3 = OCH_2–, R^4 = H
7f: R^1 = H, R^2 = F, R^3 = H, R^4 = F
7g: R^1 = H, R^2 = H, R^3 = F, R^4 = F
7h: R^1 = Cl, R^2 = H, R^3 = H, R^4 = H
7i: R^1 = H, R^2 = H, R^3 = Cl, R^4 = H
7j: R^1 = F, R^2 = F, R^3 = F, R^4 = H
7k: R^1 = H, R^2 = H, R^3 = Cl, R^4 = Cl
7l: R^1 = H, R^2 = H, R^3 = Me, R^4 = H

Scheme 2: Substituent-modifications on the motif A. Reagents and conditions: (a) CH_2Cl_2, Et_3N; (b) CH_2Cl_2, TFA.

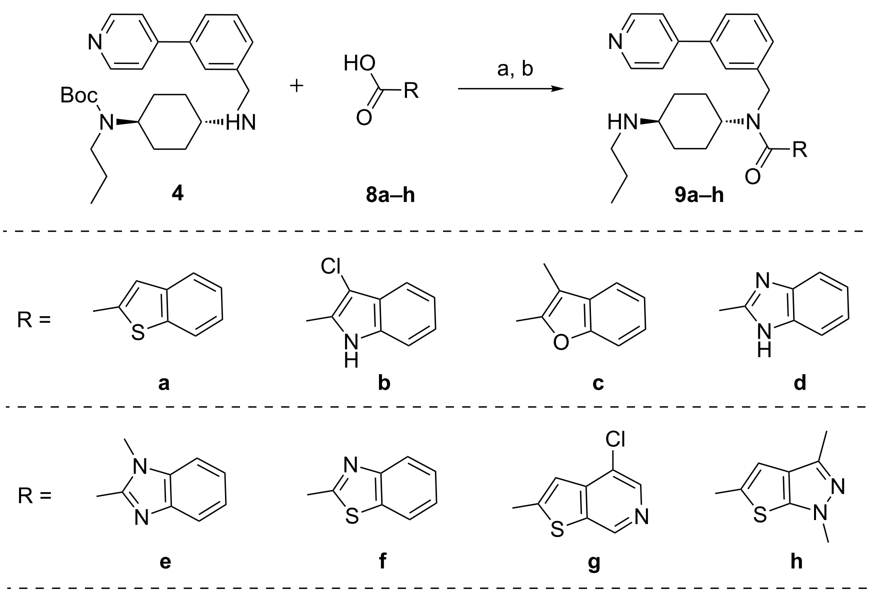
had to be introduced through transformation reactions after the N-acylation step.

As depicted in Scheme 3, NH_2-derivative **7m** was prepared from the NO_2-substituted precursor **7c** by the reduction of the nitro group to an amino group using an $FeCl_3$–Zn system [41]. Subsequently, capping the amino group with a sulfonyl or acetyl group led to **7n** and **7o**, respectively. In regard to hydroxy or acid modification, the demethylation or hydrolysis released the corresponding hydroxy group or carboxylic acid. Accordingly, **7e** was treated with BBr_3 in CH_2Cl_2 at −78 °C to afford the expected product **7p**. **7d** was directly subjected to basic hydrolysis in MeOH to yield carboxylic acid derivative **7q**.

To increase structural diversities, compound **4** was further reacted with various heteroaryl acids **8a**–**h** to yield **9a**–**h** (Scheme 4). The following considerations were taken for the selection of the heteroaryl acids: removal of the Cl atom (**8a**); replacement of the S atom with N or O atoms (**8b**, **8c**); two heteroatoms in a five-membered ring (**8d**–**f**); and a 5,5-fused ring heterocycle (**8h**), all of which will help us to more



Scheme 3: Substituent-modifications on the motif A. Reagents and conditions: (a) (i) $FeCl_3$, Zn, H_2O, DMF, 100 °C; (ii) TFA, CH_2Cl_2; (b) (i) $MeSO_2Cl$, CH_2Cl_2, Et_3N; (ii) TFA, CH_2Cl_2; (c) (i) AcCl, CH_2Cl_2, Et_3N; (ii) TFA, CH_2Cl_2; (d) BBr_3, CH_2Cl_2, −78 °C; (e) KOH, MeOH, H_2O.



Scheme 4: Core modification on the motif A. Reagents and conditions: (a) BOP, DIEA, DMF; (b) CH_2Cl_2, TFA.

distinctly study the SAR in motif A. Compounds **8a–h** were either synthesized using reported methods [42-46] or are commercially available.

Substituent-modifications on the motif B

In the second series of novel scaffolds, structural modification was focused on alternatives to the phenyl ring to improve aqueous solubility. As illustrated in Figure 2, we replaced the phenyl ring with a variety of structurally diverse heteroaryl groups, including pyridine, pyrimidine and imidazole rings. In order to investigate the effect of the N-position in the heteroaryl ring, different pyridine and pyrimidine substituents were also incorporated. Generally, the compounds **10a**–**g** were synthesized following the general route in Scheme 1, by using aldehydes **11a**–**g** as key intermediates. As described in Scheme 5, **11a**–**d** were prepared through Pd-catalyzed Suzuki coupling of 4-pyridylboronic acid with corresponding formyl-functionalized pyridylbromides **12a**–**d**, which were commercially available. However, application of the reaction conditions identical to those used in the synthesis of compound **2** (Scheme 1) resulted in very low yields. After systematic optimization of the reaction conditions, we found that the reaction proceeded well in 1,4-dioxane at 100 °C for 8 h with Na_2CO_3 as base in the presence of $Pd(OAc)_2$ as catalyst, and PPh_3 as ligand, providing the products in 73–85% yield.

Different from the synthetic strategy of **11a**–**d**, the pyrimidine nucleus in biaryl aldehydes **11e**–**f** had to be constructed through condensation of a protected β-ketoaldehyde with the corres-

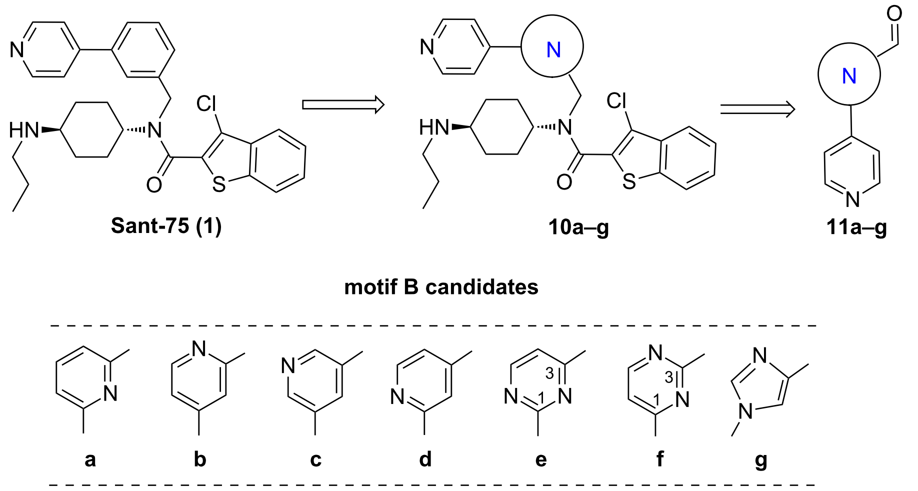
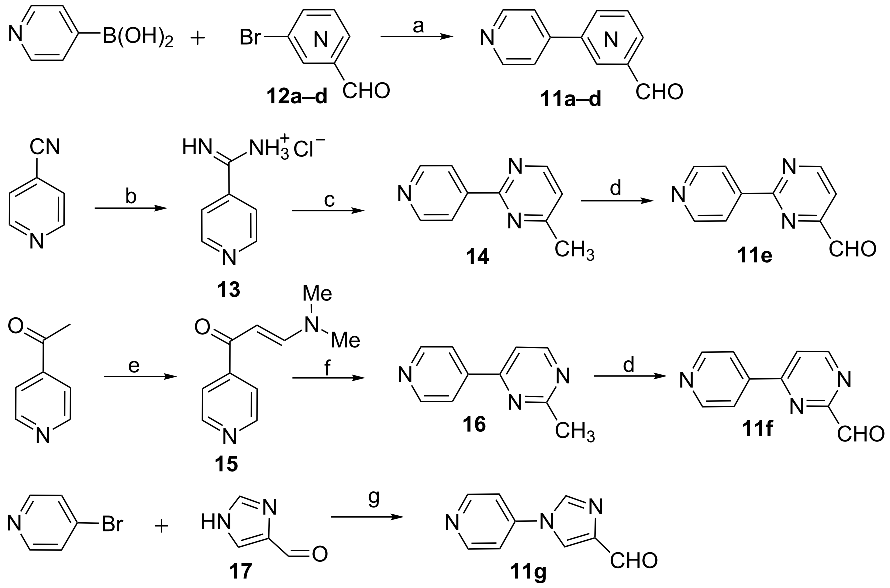


Figure 2: Core modification on the motif B.



Scheme 5: Synthesis of key intermediate biaryl aldehydes. Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, 1,4-dioxane, Na_2CO_3, 100 °C; (b) cat. NaOMe, MeOH; then NH_4Cl; (c) acetylacetaldehyde dimethyl acetal, 1,4-dioxane, reflux; (d) SeO_2, 1,4-dioxane, reflux; (e) DMF-DMA, PhMe, reflux; (f) acetamidine hydrochloride, Na, EtOH, reflux; (g) 1*H*-imidazole-4-carbaldehyde, DMF, CuI, Cs_2CO_3.

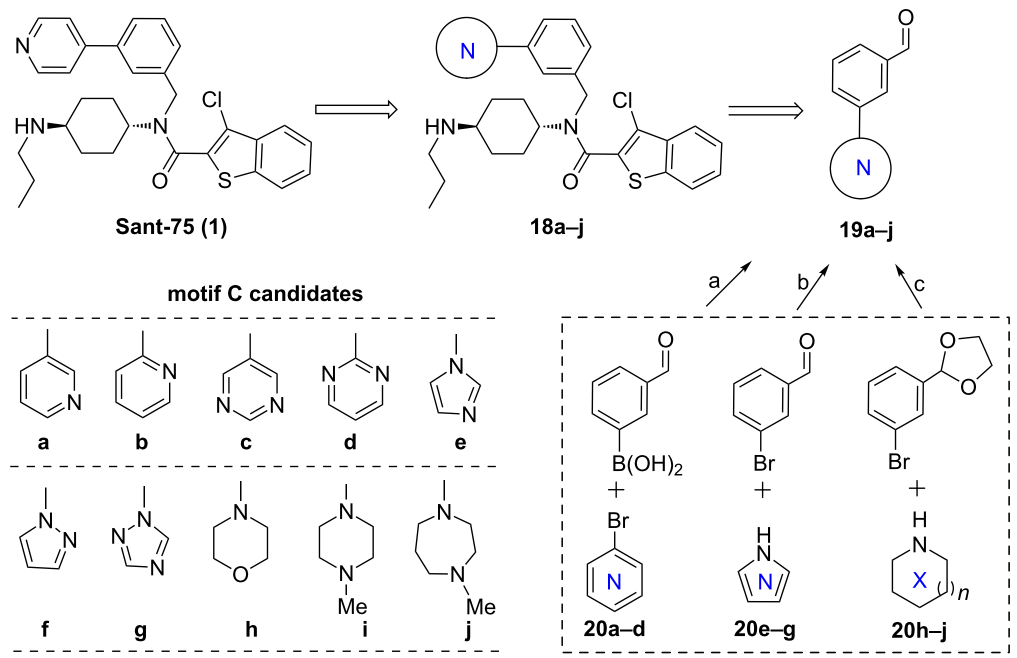
ponding amidine. Compound **11e** was synthesized from isonicotinonitrile through three steps described previously. Isonicotinonitrile was converted to isonicotinamidine hydrochloride **13** upon reaction in MeOH in the presence of catalytic NaOMe, followed by treatment with NH_4Cl. Then, condensation of **13** with acetylacetaldehyde dimethyl acetal in 1,4-dioxane afforded 6-methyl-2-(4-pyridinyl)pyrimidine **14** in 62% yield [47]. Consequent allylic oxidation of **14** with selenium dioxide gave **11e** in moderate yield. Likewise, compound **11f** was prepared though SeO_2-oxidation of **16**, which was prepared by the reported method using 4-acetylpyridine as the starting material [48]. 4-Acetylpyridine was converted to enaminone intermediates **15** upon treatment with DMF-DMA in toluene under reflux, followed by condensation cyclization with acetamidine to give **16**. Compound **11g** could be installed in single step by Ullmann coupling of **17** with 4-bromopyridine, in good yield.

Substituent-modifications on the motif C

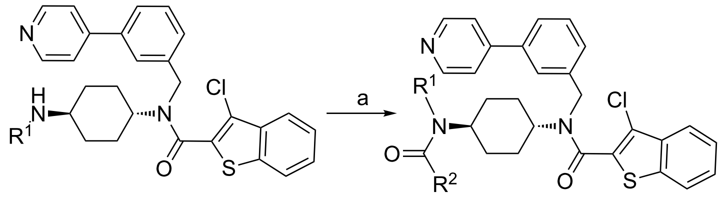
In the third round of structural modifications, chemical diversity was explored by varying the nature of the heterocycles (motif C) and the position of the nitrogen atom in pyridine. As shown in Scheme 6, *para*-substituted pyridine was first replaced with *meta*- and *ortho*-pyridine, and other heterocycles, including pyrimidines and five-membered heteroaryl rings, as well as nonaromatic heterocycles, such as morpholine, piperazine and homo-piperazine, were also investigated. Accordingly, a small series of Sant-75 analogues **18a**–**j** were synthesized in a parallel fashion from the corresponding intermediates **19a**–**j**. For intermediates **19a**–**j**, different coupling reactions were required to achieve their synthesis, depending on the type of structure. **19a**–**d** were prepared through Suzuki coupling as described above, and **19e**–**g** were obtained in 70–85% yield by Ullmann coupling of 3-bromobenzaldehyde with an excess of the appropriate amines **20e**–**g** [49]. The Buchwald coupling of protected 3-bromobenzaldehyde with amines **20h**–**j** proceeded smoothly in toluene with NaO*t*-Bu as base by using a $Pd_2(dba)_3$/*rac*-BINAP catalysis system [50].

Substituent-modifications on the motif D

It has previously been shown that the substitution pattern on the nitrogen atom of *trans*-1,4-diaminocyclohexane moiety plays a critical role in the activity of the compounds as Hedgehog-pathway inhibitors. Therefore, the emphasis of the fourth series of structural optimization was placed on the nitrogen atom through capping of the amino group with various acyl chlorides, delivering the corresponding amides **21a**–**j**. It should be noted that the capping of the amino group can increase the metabolic stability of the compounds. The R^2 group in modified compounds was extensively studied, including alkyl, cycloalkyl, phenyl and heteroaryl groups, and a selection of the generated compounds is listed in Scheme 7.

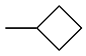
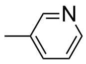
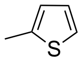
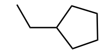
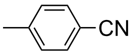
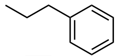
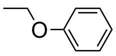
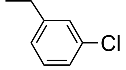
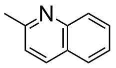
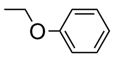


Scheme 6: Chemical modifications on the motif C. Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, 1,4-dioxane, Na_2CO_3, 100 °C; (b) CuI, DMF, Cs_2CO_3, 120 °C; (c) (i) $Pd_2(dba)_3$, *rac*-BINAP, NaO*t*-Bu, PhMe, 100 °C; (ii) aq. HCl, THF.



22: R^1 = H
Sant-75: R^1= *n*-Pr

21a-j

Comp.	R^1	R^2	Comp.	R^1	R^2
21a	*n*-Pr		**21f**	*n*-Pr	
21b	*n*-Pr		**21g**	H	
21c	*n*-Pr		**21h**	H	
21d	*n*-Pr		**21i**	H	
21e	*n*-Pr		**21j**	H	

Scheme 7: Chemical modifications on the motif D. Reagents and conditions: (a) R^2COCl, CH_2Cl_2.

Conclusion

By modification of our first generation of synthesis of **SAG** derivatives, a second generation of the synthetic program was established, which allows structurally diverse derivatives of Sant-75 to be synthesized in a systematic manner. The constructed library was fully characterized, which provides a foundation for the further investigation of their biological activities. The biological investigation of this library is currently underway in our laboratories, and the results will be reported in due course.

Supporting Information

Supporting Information File 1

Experimental details.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-94-S1.pdf]

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Two-directional synthesis as a tool for diversity-oriented synthesis: Synthesis of alkaloid scaffolds

Kieron M. G. O'Connell, Monica Díaz-Gavilán§, Warren R. J. D. Galloway
and David R. Spring*

Full Research Paper

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Address:
Department of Chemistry, University of Cambridge, Lensfield Rd,
Cambridge, CB2 1EW, UK

Email:
David R. Spring* - spring@ch.cam.ac.uk

* Corresponding author
§ Present address: Departemento de Química Farmacéutica y
Orgánica, Facultad de Farmacia, Campus de Cartuja, s.n. 18071
Granada, Spain

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Abstract

Two-directional synthesis represents an ideal strategy for the rapid elaboration of simple starting materials and their subsequent transformation into complex molecular architectures. As such, it is becoming recognised as an enabling technology for diversity-oriented synthesis. Herein, we provide a thorough account of our work combining two-directional synthesis with diversity-oriented synthesis, with particular reference to the synthesis of polycyclic alkaloid scaffolds.

Introduction

Diversity-oriented synthesis (DOS) aims to prepare structurally diverse compound collections in an efficient manner [1-3]. Of the possible "types of diversity" that can be incorporated into a compound collection, the most important, in terms of creating a functionally (biologically) diverse collection, is generally considered to be *scaffold* (or *skeletal*) *diversity*, i.e., the variation of molecular frameworks between compounds [4,5]. Therefore, one of the key challenges in DOS is the development of strategies that allow the efficient generation of a range of complex molecular scaffolds. A large number of approaches towards this goal have been reported, with some of the most effective being based around the "folding-up" of functionalised linear substrates into cyclic molecular architectures [6-8]. The design and synthesis of these linear substrates can, in itself, represent a significant challenge as it is desirable that these compounds are easily accessible in a small number of synthetic steps. Two-directional synthesis [9-12] offers a powerful method for the synthesis of such substrates, because each synthetic transformation has the potential to provide twice as much molecular complexity compared to standard approaches.

We have recently reported a strategy for DOS that combined two-directional synthesis with the use of these folding reaction pathways [13]. In this work, two-directional synthesis was used to rapidly generate a series of linear aminoalkenes, which were then folded into bicyclic and tricyclic scaffolds through Lewis acid mediated cascade processes. The compounds produced in this campaign were reminiscent of naturally occurring alkaloids, such as the *Coccinellidae* natural products, which are secreted by ladybirds to deter predators [14]. The total synthesis of one of their number, myrrhine, was also achieved by the elaboration of one of the compounds produced. In this article, the work is presented in more detail, alongside additional results from our work combining two-directional synthesis with DOS. Treated together, we believe these works provide useful insights into the potential utility of two-directional synthesis as an enabling technology for DOS.

The initial DOS campaign was largely inspired by the pioneering work of Robert Stockman on combining two-directional synthesis with tandem reactions to create complex molecular architectures [15-18]. The key folding step in the DOS was the Lewis acid mediated pairing reaction of a nucleophilic amino group with suitable electrophilic functionality, provided by Michael acceptor α,β-unsaturated ester groups. Two-directional synthesis was used to append these electrophilic groups at two positions around the linear substrates, allowing bicyclisation processes to be instigated. The scaffold diversity between the products then resulted from the different ring sizes that it was possible to form from these linear substrates. (Figure 1 shows an overview of the DOS strategy.)

Results and Discussion

Synthesis of linear precursors

Our initial studies explored the synthesis and reactivity of four *N*-Boc-aminoalkenes containing α,β-unsaturated ester groups (**1**–**4**, Scheme 1), as substrates for intramolecular pairing reactions. The *N*-Boc protecting group was chosen to give the potential for deprotection to be carried out in tandem with the Lewis acid catalysed cyclisation reactions by intramolecular conjugate addition. Three of these compounds (**1**–**3**) were obtained from the corresponding alcohols [19,20] in three steps: Mitsunobu reaction with NH-Boc-tosylate, followed by tosyl deprotection with magnesium, and finally two-directional cross metathesis with ethyl acrylate to install the desired α,β-unsaturated ester functionality. This sequence provided the desired *N*-Boc-aminoalkenes in respectable overall yields of 38–56%. Compound **4** was prepared in a four-step sequence from the requisite phenyldialkyl alcohol. Ritter reaction with chloroacetonitrile followed by cleavage of the resulting chloroacetamide with thiourea gave the free amine [21], which was then protected with Boc anhydride. Finally, cross metathesis with ethyl acrylate furnished the desired compound **4** in 24% overall yield.

Cyclisation reactions

The first attempts at the tandem Boc-deprotection/bicyclisation of these substrates were performed by using $AlCl_3$ as the Lewis acid (Scheme 2); compounds **1**–**4** were treated with 1.1 equiv of $AlCl_3$ in dichloromethane at room temperature. These conditions proved effective at promoting bicyclisation for compounds **1**, **2** and **4**, for which the desired bicyclic products were obtained in 67–85% yield, as a mixture of diastereomers. The cyclisation of **1** gave pyrrolizidine **5** as a mixture of 4,10-*trans*-7,10-*trans (**trans-5**)* (42%) and 4,10-*cis*-7,10-*trans (**cis-5**)* (28%) isomers, which proved to be separable by flash chromatography. The stereochemistry of ***cis*-5** was confirmed by analogy to known ^{1}H and ^{13}C NMR values [22] and by NOESY spectroscopy, which showed enhancements between H-7, H-4 and H-10. In this case, it proved possible to achieve an improved yield of both diastereomers by treating **1** with an excess (163 equiv) of trifluroacetic acid, which furnished ***trans*-5** and ***cis*-5** in 53% and 34% yield, respectively. The corresponding reaction of phenyl-substituted analogue **4** also gave a mixture of

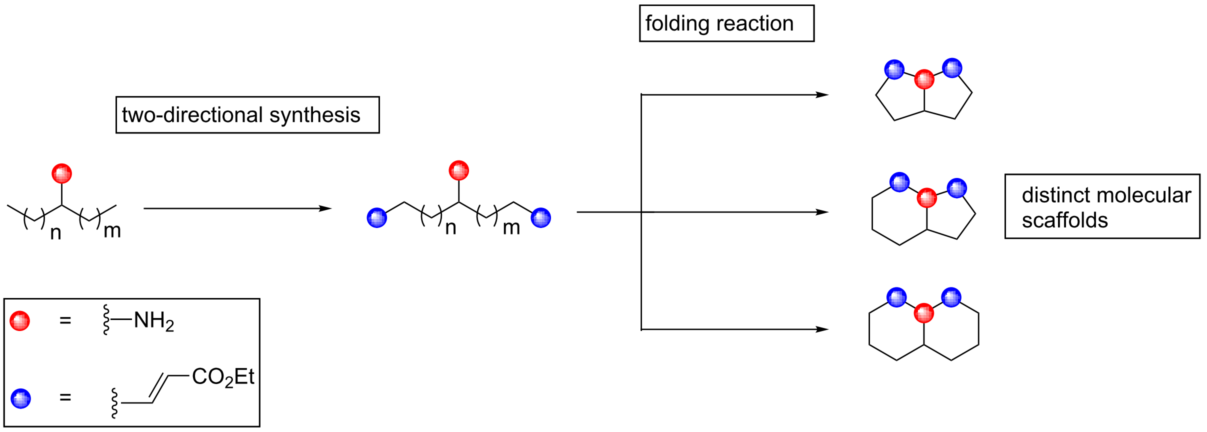
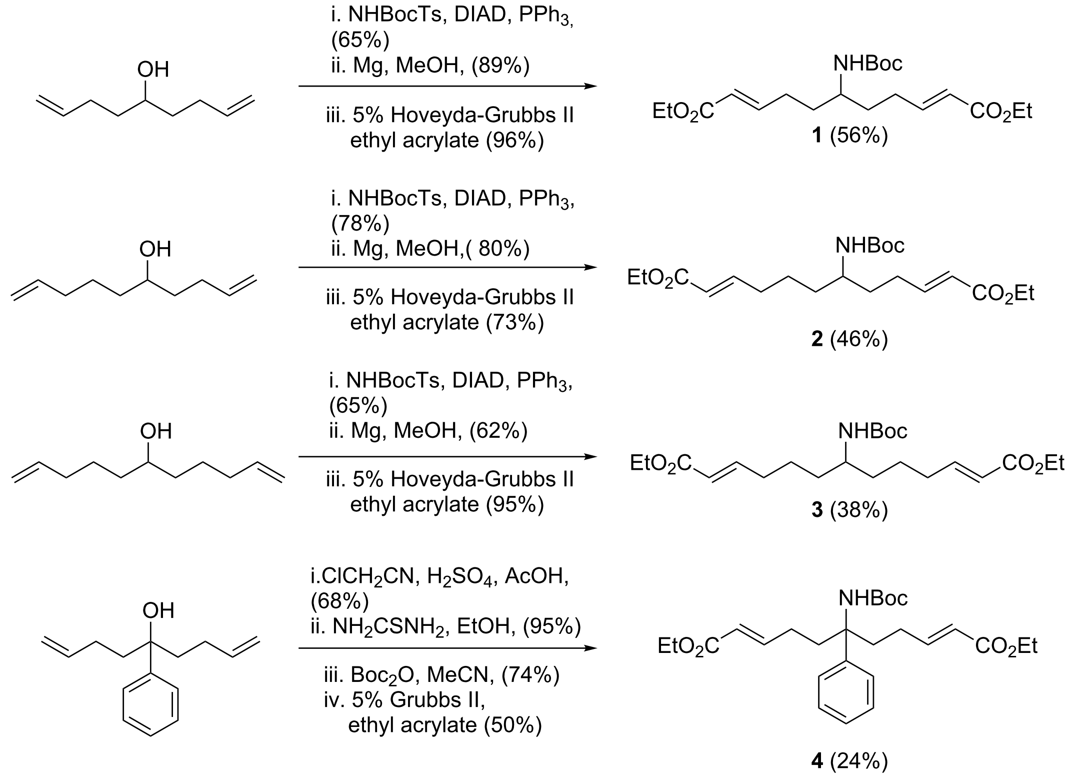


Figure 1: Overview of the DOS strategy.

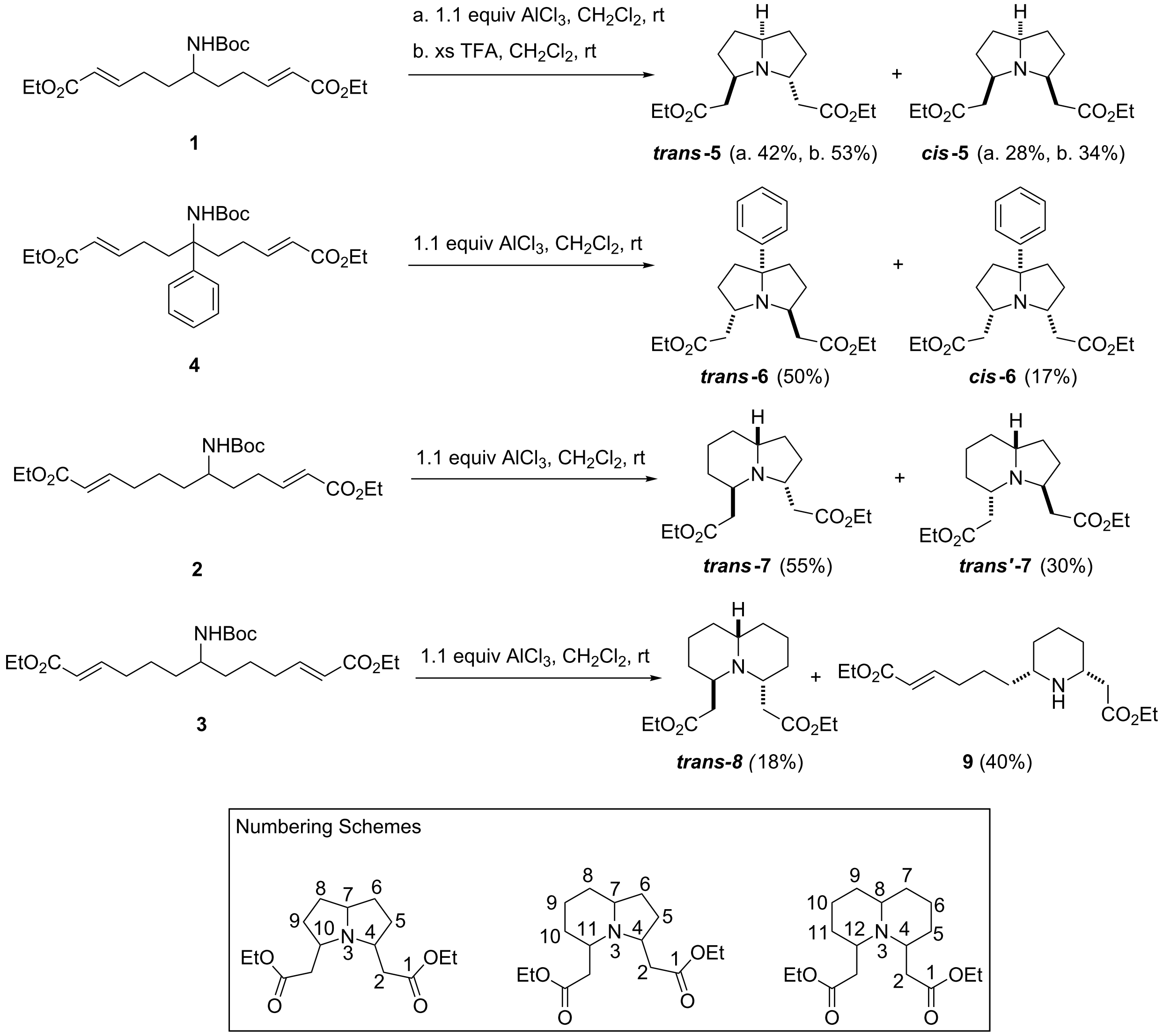


Scheme 1: Synthesis of linear cyclisation precursors **1–4**.

two diastereomers; the major diastereomer was 4,10-*trans*-7,10-*cis* isomer (***trans*-6**), which was formed in 50% yield, and a 17% yield of the 4,7,10-*cis*-isomer (**cis-6**) was also obtained.

Indolizidine **7** was produced in very good overall yield (85%). The unsymmetrical nature of this compound gave rise to the possibility of formation of additional diastereomers when compared to **5** and **6**; however, once again only two were formed in any appreciable amount. The compounds obtained were both found to have a *trans*-fused geometry at the ring junction, as indicated by IR (strong absorbance at 2850 cm^{-1}) and ^1H NMR (H-7 chemical shift around 2.4 ppm) spectroscopy [23,24]. The ester-bearing side chains were also found to be *trans* to each other in both cases, meaning that the two products obtained differ from each other only in which ring has the side chain *cis* to the ring junction hydrogen. The favoured product was the 4,11-*trans*-7,11-*cis* isomer (***trans*-7**) in which the side chain of the 6-membered ring is *cis* to the ring junction proton; this compound was isolated in 55% yield. The alternative 4,11-*trans*-4,7-*cis* isomer (***trans'*-7**) was obtained in 30% yield. Despite the good yields obtained for these three examples, the cyclisation of **3** under these conditions proved disappointing, with 4,12-trans-8,12-cis-quinolizidine (***trans*-8**) only obtained in 18% yield, along with 40% of monocyclic species **9**.

In light of the difficulties encountered in producing the desired bicyclic species, an optimisation study of the cyclisation of **3** was undertaken, which resulted in a number of interesting findings that are summarised in Table 1. The initial alterations made little difference to the process; increasing the reaction time up to seven days had essentially no effect on the product ratio, with ***trans*-8** and **9** obtained in 21% and 37% yield, respectively, and increasing the temperature to the point of reflux in dichloromethane also had little effect on the conversion. However, when the reaction solvent was changed to toluene and the reaction mixture heated to reflux, ***trans*-8** and **9** were still formed in similar proportions (24% and 21%), but in this case an additional product was also isolated in 30% yield. This compound was found to be tricyclic compound **10** (Scheme 3a), which was obtained as a single diastereomer with all of the ring junction protons on the same face. This all–*cis*-stereochemistry was surprising, as so far **8** had only been obtained with the side chains in *trans*- configuration; however the configuration of **10** was unambiguously confirmed by X-ray crystallography. In some ways the formation of a tricyclic species such as **10** was not altogether surprising, as a similar tricyclic species was generated in Stockman's synthesis of hippodamine [25]. In that work, bicycle ***trans*-8** was transformed into the corresponding tricyclic compound (possessing *cis–trans* ring junction stereochemistry) by a base-mediated Dieckmann cyclisation

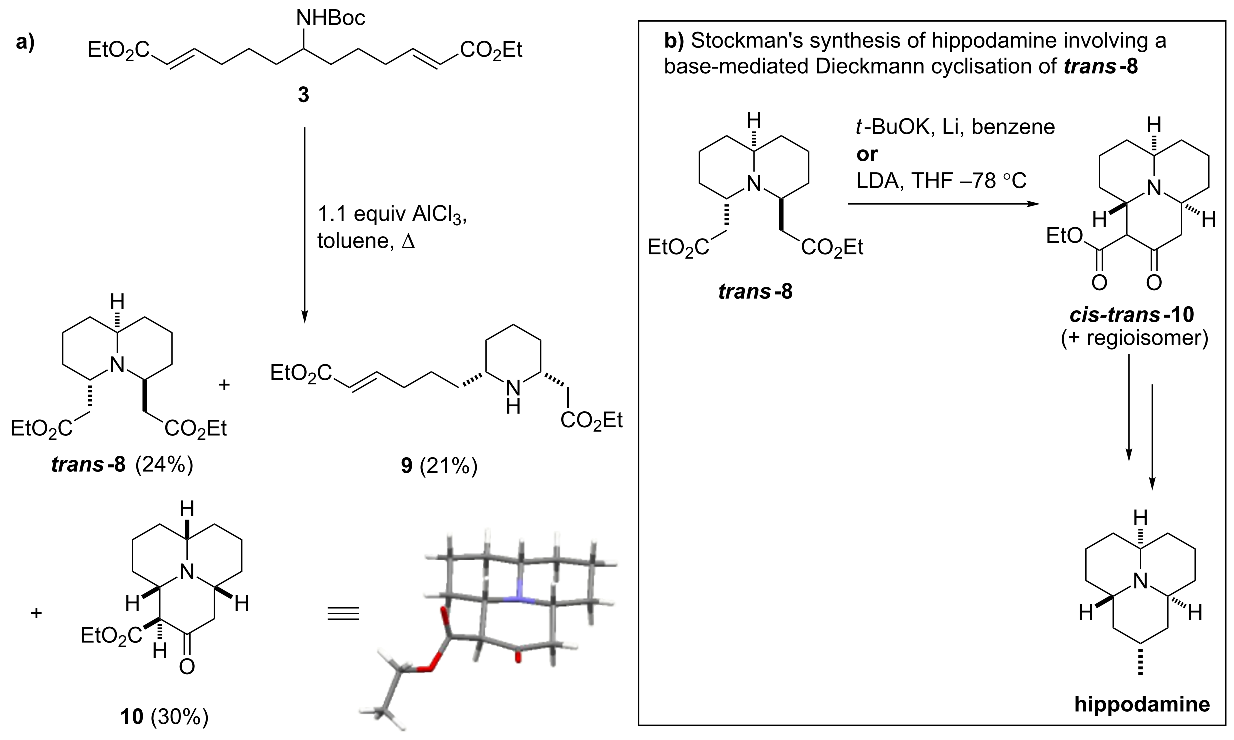


Scheme 2: $AlCl_3$ catalysed tandem Boc-removal/bicyclisation processes; the yields quoted refer to the isolated yields of single compounds.

Table 1: Overview of the Lewis acid mediated folding reactions of **3**.

solvent	Lewis acid (equiv)	temp.	% yield ***trans*-8**	***cis*-8**	**9**	**10**
DCM[a]	$AlCl_3$ (1.1)	rt	18	—	40	—
DCM[b]	$AlCl_3$ (1.1)	rt	21	—	37	—
toluene[a]	$AlCl_3$ (1.1)	reflux	24	—	21	30
toluene[a]	$AlCl_3$ (3)	reflux	43	—	13	—
toluene[a]	$Sc(OTf)_3$ (3)	reflux	50	—	21	—
toluene[a]	$Sn(OTf)_2$ (0.5)	reflux	—	9	—	72
toluene[a]	$Sn(OTf)_2$ (1.1)	reflux	30	13	—	23
toluene	$Sn(OTf)_2$ (3)	reflux	29	—	10	—

[a] Reaction stirred overnight; [b] reaction stirred for seven days.



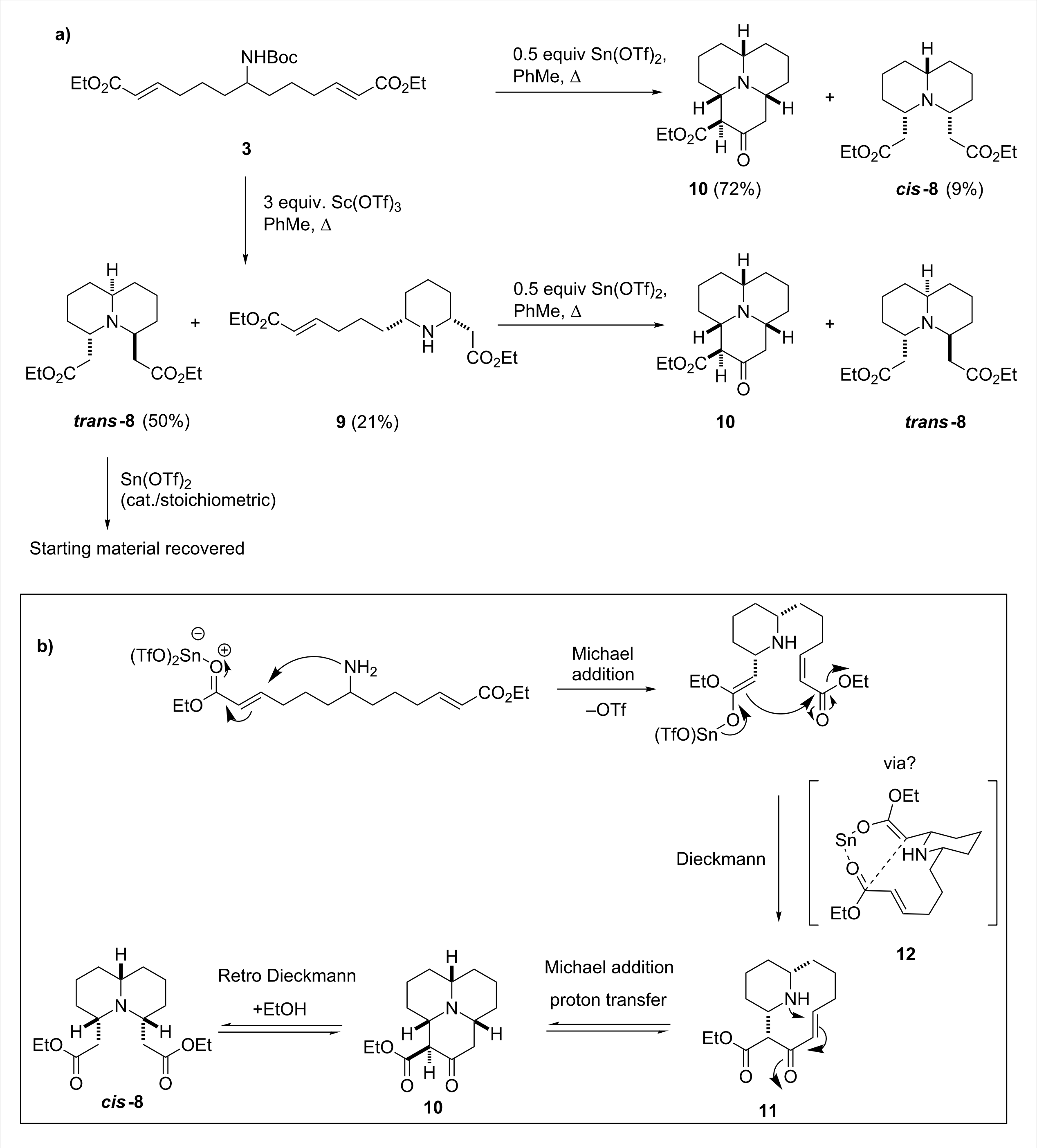
Scheme 3: (a) $AlCl_3$ catalysed formation of tricyclic alkaloid **10** along with an X-ray crystal structure of **10**; (b) base-mediated Dieckmann cyclisation of ***trans*-8** employed by Stockman and co-workers in the synthesis of hippodamine [25].

(Scheme 3b). It seems in our case that, under the correct conditions, a Dieckmann reaction can be made to occur in tandem with the Boc-deprotection and double-conjugate addition processes. This one-pot, four-step reaction process is extremely interesting for the amount of molecular complexity generated in a single transformation, and also because the all-*cis*-stereochemistry of **10**, which differs from the *cis–trans*-stereochemistry observed by Stockman for the Dieckman cyclisation of ***trans*-8**. For these reasons, further investigations into the process were carried out.

The amount of $AlCl_3$ was increased to 3 equiv; however, this led to the suppression of tricycle formation in favour of a slight increase in the yield of ***trans*-8** to 43% (a 13% yield of **9** was also obtained). Switching the Lewis acid to $Sc(OTf)_3$ and still using 3 equiv, gave a slight improvement in the yields of the ***trans*-8** to 50% and **9** to 21% but no formation of **10**. Switching the Lewis acid again to $Sn(OTf)_2$ resulted in a decrease in the yields of ***trans*-8** to 29% and **9** to 10% and again no formation of **10**. The amount of Lewis acid was then reduced to 0.5 equiv, which dramatically altered the course of the reaction. Performing the reaction under reflux in toluene with 0.5 equiv $Sn(OTf)_2$ produced tricycle **10** in 72% isolated yield. Thus both ***trans*-8** and **10** could be accessed in good yields from the same substrate simply by varying the amount and identity of the Lewis acid used.

Interestingly, the catalytic variant of the reaction also produced 9% of the bicyclic ***cis*-8**, which had not been isolated from any of the previous reactions. For completeness, one further reaction was performed by using 1.1 equiv of $Sn(OTf)_2$; careful purification of this reaction gave 23% of **10**, 30% of ***trans*-8** and 13% of ***cis*-8**. The presence of the previously undetected ***cis*-8** in these two final reactions was intriguing and led us to speculate as to whether a different mechanistic pathway could be in operation depending on the amount of Lewis acid used.

A number of factors led to this mechanistic speculation; principal among them was the fact that ***cis*-8** was never detected in reactions in which **10** was not formed. In all of the earlier experiments the only bicycle detected was ***trans*-8**, implying that the double-conjugate addition process heavily favours the formation of this compound. Therefore it was considered that ***cis*-8** could be forming from **10**; suggesting, somewhat counter intuitively, that the Dieckmann cyclisation to give 6,10-bridged bicycle **11** could in some cases be favoured over the expected double-conjugate addition. Transannular conjugate addition across the 10-membered ring of **11** would give **10**, and a retro-



Scheme 4: (a) Optimal conditions to obtain ***trans*-8** and **10** and the control experiments carried out to probe the mechanism of the process; (b) proposed mechanistic pathway for the tricyclisation of **3**.

Dieckmann process could then form ***cis*-8**. Several control experiments were run in an attempt to validate this hypothesis (Scheme 4a).

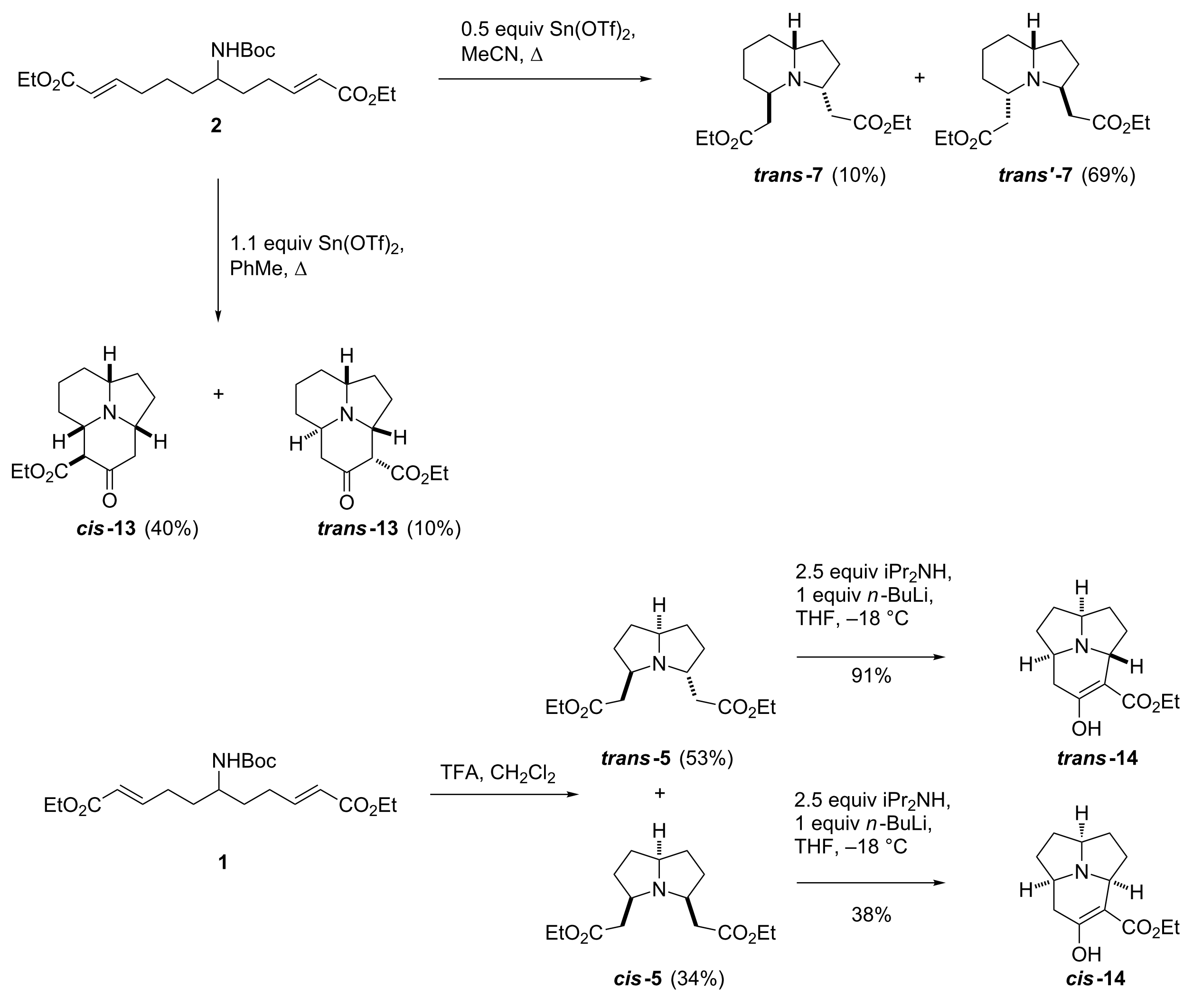
***Trans*-8** was treated with both stoichiometric and catalytic amounts of Sn(OTf)$_2$ and there was no evidence of tricycle formation in either case, with only starting material recovered from the reactions. The direct formation of **10** from ***trans*-8** was not thought to be possible due to their differing stereochemistry; however, an alternative diastereomer of **10** may be expected to form (as observed by Stockman for the corresponding base-mediated process) [25]. Monocycle **9** was treated with catalytic Sn(OTf)$_2$, which led to a mixture of ***trans*-8** and **10**. As the formation of **10** from ***trans*-8** had been proven not to occur, it seemed reasonable to assume from this that it is possible to form both species from **9**. It is also noteworthy that the best yields of **10** were obtained when the reaction was performed while fitted with a Dean–Stark apparatus containing pieces of sodium to trap the ethanol formed in the Dieckmann cyclisation, and thus inhibit the retro-Dieckmann reaction. Finally, **10** was treated with catalytic $Sn(OTf)_2$, which, as expected, gave ***cis*-8**, suggesting that the retro-Dieckmann reaction does occur.

Taking these results into account, we tentatively suggest that the mechanism for the tricyclisation of **3** does indeed proceed via a Dieckmann cyclisation to form the 10-membered ring followed by transannular conjugate addition (Scheme 4b). The fact that this appears to occur when lower amounts of Lewis acid are used (0.5 or 1.1 equiv) but not when three equiv are used indicates that the mechanistic path of the cascade is dependent on the amount of the Lewis acid present. When three equiv of Lewis acid are present (the "stoichiometric" process), it is feasible that during the course of the reaction both of the carbonyl groups are activated simultaneously, allowing the double-conjugate addition to proceed smoothly. However, when fewer equiv are used (the "catalytic" process) there is a relative deficiency of Lewis acid present, and thus, it is less probable that both carbonyl groups can be coordinated to separate Lewis acid molecules simultaneously. If the Dieckmann reaction occurs via a standard 6-membered transition state, it requires both carbonyls to be either coordinated to, or bonded to, a single metal centre, and so this could go some way towards explaining the apparent course of the reaction. Assuming that the Lewis acid remains bonded to the carbonyl of the enol form of the ester group after the first conjugate addition, there may be insufficient Lewis acid free in solution to activate the second ester group separately, leaving it effectively inert to conjugate addition (and Dieckmann cyclisation). However, if the second carbonyl group becomes coordinated to the metal centre that is bonded to the first, the Dieckmann reaction becomes the most favourable process and so occurs preferentially to the second conjugate addition. For these reasons, we cautiously postulate that the Dieckmann reaction may occur via a chelated transition state such as **12**, in which both carbonyls are coordinated to a single metal centre.

The data in Table 1 provides further support for the suggestion that different mechanisms can operate depending on the amount of Lewis acid used. This support is provided by the fact that the formation of **10** proceeds best under truly catalytic conditions: when 0.5 equiv $Sn(OTf)_2$ were used, a 72% yield of **10** was obtained compared to 23% when 1.1 equiv were used. In fact, it appears that when 1.1 equiv of Lewis acid are used both mechanisms can occur, as indicated by the formation of both ***trans*-8** and **10** in these reactions, but when 0.5 equiv are used the formation of ***trans*-8** is not observed suggesting that under these conditions the simple double-conjugate addition cannot occur. The identity of the Lewis acid used in the reaction seems not to overtly affect the course of the reaction in terms of the products obtained, as similar product distributions were observed for the reactions using three equiv of $AlCl_3$, $Sc(OTf)_3$ and $Sn(OTf)_2$. The formation of **10** was also not limited to the use of $Sn(OTf)_2$, as a 30% yield of **10** was obtained for the reaction using 1.1 equiv of $AlCl_3$.

Between them, the catalytic and stoichiometric variants of this reaction provide a useful illustration of the use of reagent-based diversification within a predominantly substrate-based strategy. Attempts were then made to apply this reagent-based diversification to the other linear substrates (Scheme 5). Compound **2** was treated with 0.5 equiv of $Sn(OTf)_2$ in acetonitrile, which surprisingly did not lead to the formation of the 6-6-5-tricyclic species, instead producing ***trans*'-7** in 69% yield along with 10% ***trans*-7**. While this reaction did not produce any tricyclic species, it was an interesting result, as the selectivity for ***trans*'-7** over ***trans*-7** was the opposite of that observed for the original $AlCl_3$ catalysed process. Performing the reaction in toluene with 1.1 equiv of $Sn(OTf)_2$ did produce the expected tricyclic species in 50% yield as a mixture of two diastereomers (***cis*-13** and ***trans*-13**) in a 4:1 ratio, proving that the folding of this linear substrate into tricyclic species in one-pot was also possible. Unfortunately, this did not prove to be the case for **1**; all attempts to transform **1** into a tricyclic species in one pot, using either stoichiometric or catalytic Lewis acid were unsuccessful. However, it did prove possible to perform the Dieckmann reaction on the bicyclic compounds ***cis*-5** and ***trans*-5** to access the tricyclic architectures. The bicyclic species were treated with LDA at −18 °C, which affected the desired cyclisation in both cases. Strangely, the process proved far more efficient for ***trans*-5,** giving ***trans*-14** in 91% yield, compared to 38% for the *cis*-isomer. In both cases the ^1H NMR suggested that these compounds exist as the usually disfavoured enol tautomer.

These reactions, along with the reactions of **1**, clearly illustrate the power of this two-directional approach to DOS. Using this methodology it was possible to access five bicyclic and tricyclic scaffolds covering a range of 3D shapes, including pyrrolizidines, indolizidines and quinolizidines, along with 6-6-6 and 5-6-6 azatricyclic species in a single transformation from a small collection of structurally simple linear starting materials. One further tricyclic scaffold (5-5-6) was also accessible in one further synthetic step. The effective introduction of reagent-based diversification into the strategy was extremely satisfying, as by altering the choice of Lewis acid and reaction temperature we were able to adjust the course and selectivity of the



Scheme 5: DOS of 5-5-6 and 5-6-6 tricyclic alkaloids **13** and **14**.

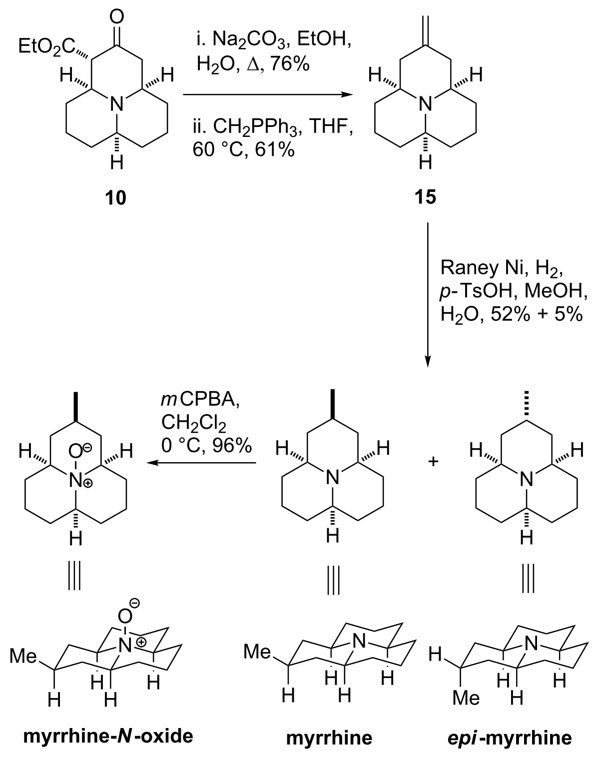
reactions to generate different scaffolds and stereochemistry. This combination of reagent and substrate-based approaches for the generation of molecular diversity can afford many interesting possibilities not achievable by either approach alone.

Total synthesis of myrrhine

Inspired by Stockman's syntheses of the related alkaloids hippodamine and *epi*-hippodamine [26], tricyclic species **10** was identified as a potential intermediate for the total synthesis of myrrhine, which was then achieved in three steps from **10** (Scheme 6). Compound **10** was treated with Na_2CO_3 in a mixture of EtOH and H_2O under reflux to achieve ester saponification, which was followed by decarboxylation, proceeding smoothly to give the corresponding ketone in 76% yield. The ketone was then transformed to the exocyclic alkene **15** in 61% yield by Wittig reaction with the appropriate phosphonium salt. The final step in the synthesis was a diastereoselective reduction of the double bond with hydrogen gas and Raney-nickel. This was achieved in a moderate 57% yield and with good (~10:1) diastereoselectivity by complexing the nitrogen lone pair with tosic acid, effectively blocking the undesirable face of the tricycle during the course of the reduction. This reduction also produced 5% of the unnatural (or as yet undiscovered) isomer *epi*-myrrhine. The *N*-oxide of myrrhine, which has also not been isolated from natural sources, was then synthesised in 96% yield by treating myrrhine with *m*CPBA. This synthesis of myrrhine compares favourably with previously reported syntheses [26-28], achieving the feat in eight steps and 7% overall yield.

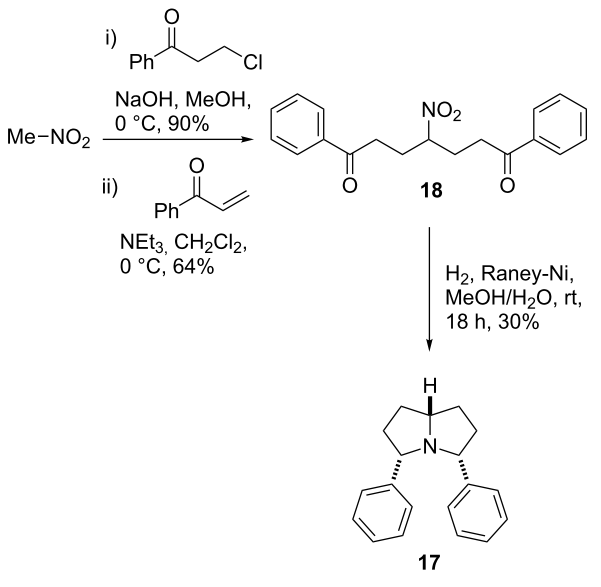
Alternative starting materials

The evident efficiency of two-directional synthesis in a DOS context, as exemplified by our synthesis of these alkaloid scaffolds, has led us to continue investigations in this area and to



Scheme 6: Total synthesis of myrrhine, *epi*-myrrhine and myrrhine-*N*-oxide.

phenylvinylketone. Subjecting diketone **18** to H_2 gas and Raney-nickel then reduced the nitro group and effected the desired double reductive amination to give **17** in 30% yield. It is likely that the scope of this sequence could be extended to include indolizidine and quinolizidine scaffolds, and so provide an alternative route to these frameworks, instead of the double Michael addition strategy.



Scheme 7: Use of nitromethane in DOS: Synthesis of *meso*-diphenylpyrrolidizine **17**.

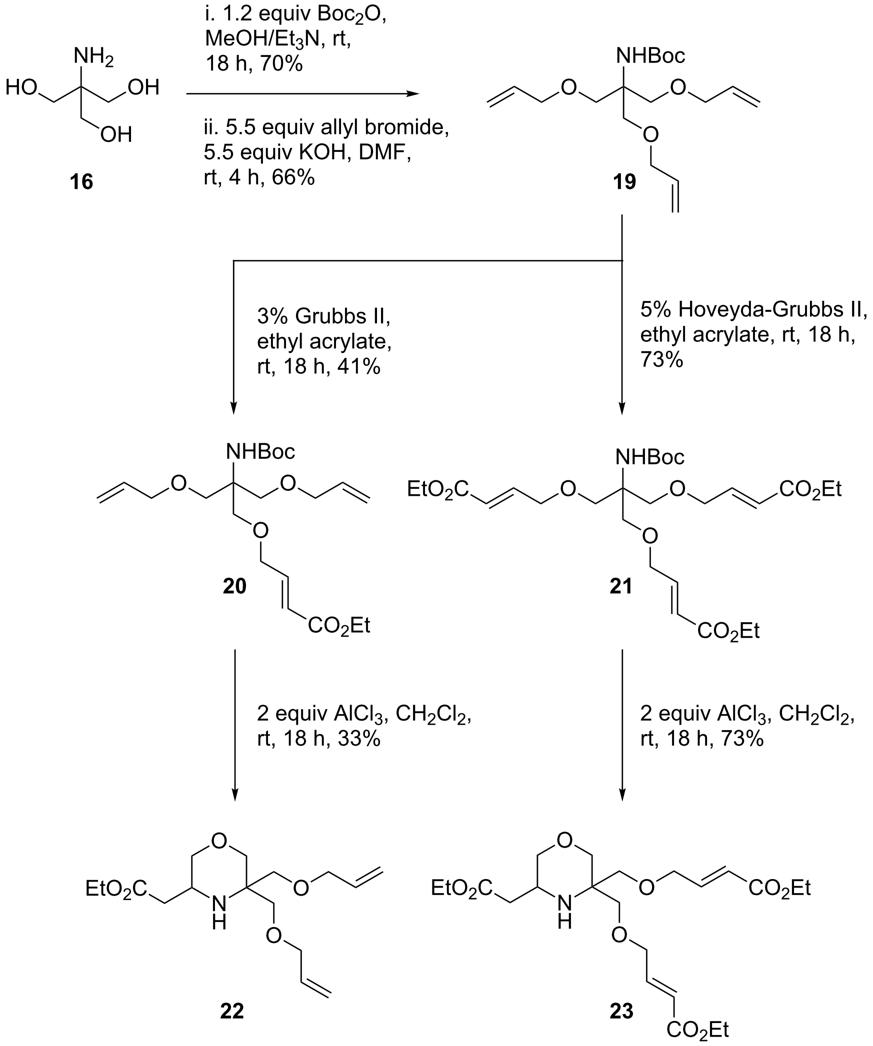
explore the potential utility of this approach for a range of different substrates. Among these substrates, two that stand out as particularly promising are nitromethane and tris(hydroxymethyl)aminomethane (Tris) **16**.

Nitromethane is of great interest to us as a potential DOS substrate, as we have a long-standing interest in developing divergent reaction pathways from small and simple starting materials [29,30]. As it represents a one-carbon unit, nitromethane is an ideal substrate for investigation. For Tris, the central quarternary carbon centre is the key point of interest, as we believe that, with the judicious selection of appendages, it should allow us to access a range of bicyclic structures, including examples of fused, bridged and spiro bicycles. Preliminary studies into the utility of these substrates in a DOS context have yielded some promising results.

Our work with nitromethane has so far led to the synthesis of *meso*-diphenylpyrrolizidine **17**, which was achieved in three steps (Scheme 7). Nitromethane was treated with NaOH, and the resulting anion was used to displace the chloride from 3-chloro-1-phenylpropan-1-one giving a 90% yield of the nitroketone. Two-directional synthesis of diketone **18** in this fashion did not prove to be feasible; however, it was achieved in good yield by Michael addition of the nitroketone anion to

The three hydroxy and single amino groups of Tris give the potential for many variations in substitution; however, our studies have so far focused on allylated derivatives, in particular the triallyl derivative **19** (Scheme 8). The synthesis of **19** was achieved in two steps from Tris: *N*-Boc protection proceeded in 70% yield, and was followed by alkylation with an excess of allyl bromide to provide the desired triallyl species in 66% yield. Cross metathesis of **19** with ethyl acrylate was then performed. Fortunately, it proved to be possible to achieve some selectivity for different products by varying the catalyst used. Treating **19** with 3% Grubbs II catalyst in neat ethyl acrylate at room temperature gave monoester **20** in 41% yield, whereas performing the reaction with 5% Hoveyda-Grubbs II catalyst gave a 73% yield of triester **21**.

These two metathesis products were then subjected to the tandem deprotection-cyclisation conditions, this time by using two equiv of $AlCl_3$ in dichloromethane at room temperature. For monoester **20**, only a single conjugate addition was possible, leaving the pendant terminal alkene groups as handles for further reactivity. This cyclisation proceeded to give the expected, functionalised morpholine scaffold **22** in a moderate



Scheme 8: Use of Tris as a substrate for DOS: Synthesis of decorated morpholines **22** and **23**.

33% yield. A similar product was also obtained for **21**, with a single conjugate addition process occurring to give **23** in 73% yield and no trace of the bicyclic product detected. A number of attempts were then made to force the reaction to occur, by varying the Lewis acid to $Sn(OTf)_2$ and $Sc(OTf)_3$ and by heating under reflux in toluene, all of which produced varying amounts of **23**, with no trace of the bicyclic product detected. This result was disappointing and also, to some degree, surprising given the relative ease of formation of the corresponding quinolizidine compounds. We speculate that the relative difficulty in the reaction is due to the reduced availability of the lone pair of the morpholine nitrogen compared to the piperidine nitrogen (pK_a 8.36 versus 11.22) [31], retarding the rate of nucleophilic attack. Another possibility is that the oxygens in the pendant chains can form a stable hydrogen-bonded species with the NH group that inhibits the reaction of the nitrogen with the Michael acceptor ester groups. Studies involving the use of Tris as a potential DOS substrate remain on-going within our laboratories.

Conclusion

The work presented in this article serves to illustrate the potential power of two-directional synthesis in DOS. The use of two-directional synthesis allowed us to access a range of bicyclic and tricyclic molecular scaffolds, rapidly and efficiently, by following a common reaction scheme. The nature of the two-directional synthesis lends itself to the formation of bicyclic compounds by the folding up of doubly substituted precursors, and it proved to be a very effective strategy for the synthesis of natural-product-like alkaloid scaffolds. Our work so far in this area has focused mainly on the synthesis of fused bicyclic compounds; however, we hope in the future to be able to apply a two-directional synthesis approach to the DOS of a wide range of molecular scaffolds and structural classes.

Supporting Information

Supporting Information File 1

Experimental procedures and spectral data for all previously unreported compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-95-S1.pdf]

Supporting Information File 2

NMR Spectra of novel compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-95-S2.pdf]

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Parallel and four-step synthesis of natural-product-inspired scaffolds through modular assembly and divergent cyclization

Hiroki Oguri[*1], Haruki Mizoguchi[1], Hideaki Oikawa[1], Aki Ishiyama[2], Masato Iwatsuki[2], Kazuhiko Otoguro[2] and Satoshi Ōmura[3]

Full Research Paper

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Address:
[1]Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo, Kita-ku, Hokkaido 060-0810, Japan, [2]Research Center for Tropical Diseases, Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan and [3]Graduate School of Infection Control Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

Email:
Hiroki Oguri[*] - oguri@sci.hokudai.ac.jp

[*] Corresponding author

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Abstract

By emulating the universal biosynthetic strategy, which employs modular assembly and divergent cyclizations, we have developed a four-step synthetic process to yield a collection of natural-product-inspired scaffolds. Modular assembly of building blocks onto a piperidine-based manifold **6**, having a carboxylic acid group, was achieved through Ugi condensation, *N*-acetoacetylation and diazotransfer, leading to cyclization precursors. The rhodium-catalyzed tandem cyclization and divergent cycloaddition gave rise to tetracyclic and hexacyclic scaffolds by the appropriate choice of dipolarophiles installed at modules 3 and 4. A different piperidine-based manifold **15** bearing an amino group was successfully applied to demonstrate the flexibility and scope of the unified four-step process for the generation of structural diversity in the fused scaffolds. Evaluation of in vitro antitrypanosomal activities of the collections and preliminary structure–activity relationship (SAR) studies were also undertaken.

Introduction

Biologically intriguing natural products often possess cyclic scaffolds bearing dense arrays of functional groups and hydrogen-bond donors or acceptors. The incorporation of multiple sp^3-centers on the scaffold creates a unique three-dimensional shape of the surface, which is responsible for specific molecular recognition with biomacromolecules in the cellular context [1-3]. To generate diverse collections of the elaborated cyclic scaffolds, nature has evolved biosynthetic machinery and often employs (1) modular assembly and (2) divergent cyclization [4]. As the simplest example of this structural diversification, the biosynthesis of aromatic polyketides is outlined in Figure 1a. Employing acetyl CoA as a starter unit, modular and iterative assembly of malonate extender units produces a linear tetraketide intermediate capable of being folded in at least two ways [5]. Intramolecular Claisen condensation and subsequent enolization produce phloracetophenone (path A), while aldol condensation followed by enolization and hydrolysis of the thioester yield orsellinic acid (path B). Inspired by this simple yet universal biosynthetic strategy, which generates structural variation among natural products, we envisioned the construction of chemical libraries featuring modular assembly for the rapid connection of simple building blocks, as well as divergent cyclization of a common precursor leading to distinct skeletons with complex molecular architectures.

Since the naturally occurring indole alkaloids share indole and piperidine as common substructures (Figure 1b) [6], we conceived the assembly of the substructures and subsequent intramolecular cyclization between these substructures to form the fused skeletons (Figure 1c). As a pioneering approach to shape the foundation of the "Build-Couple-Pair" (B/C/P) strategy [7-15] for diversity-oriented synthesis [16,17], a synthetic process to access indole-alkaloid-like scaffolds utilizing a piperidine-based manifold **1**, was developed in 2005 [18]. By exploiting lactam, carboxylic acid and β-ketocarbonyl func-

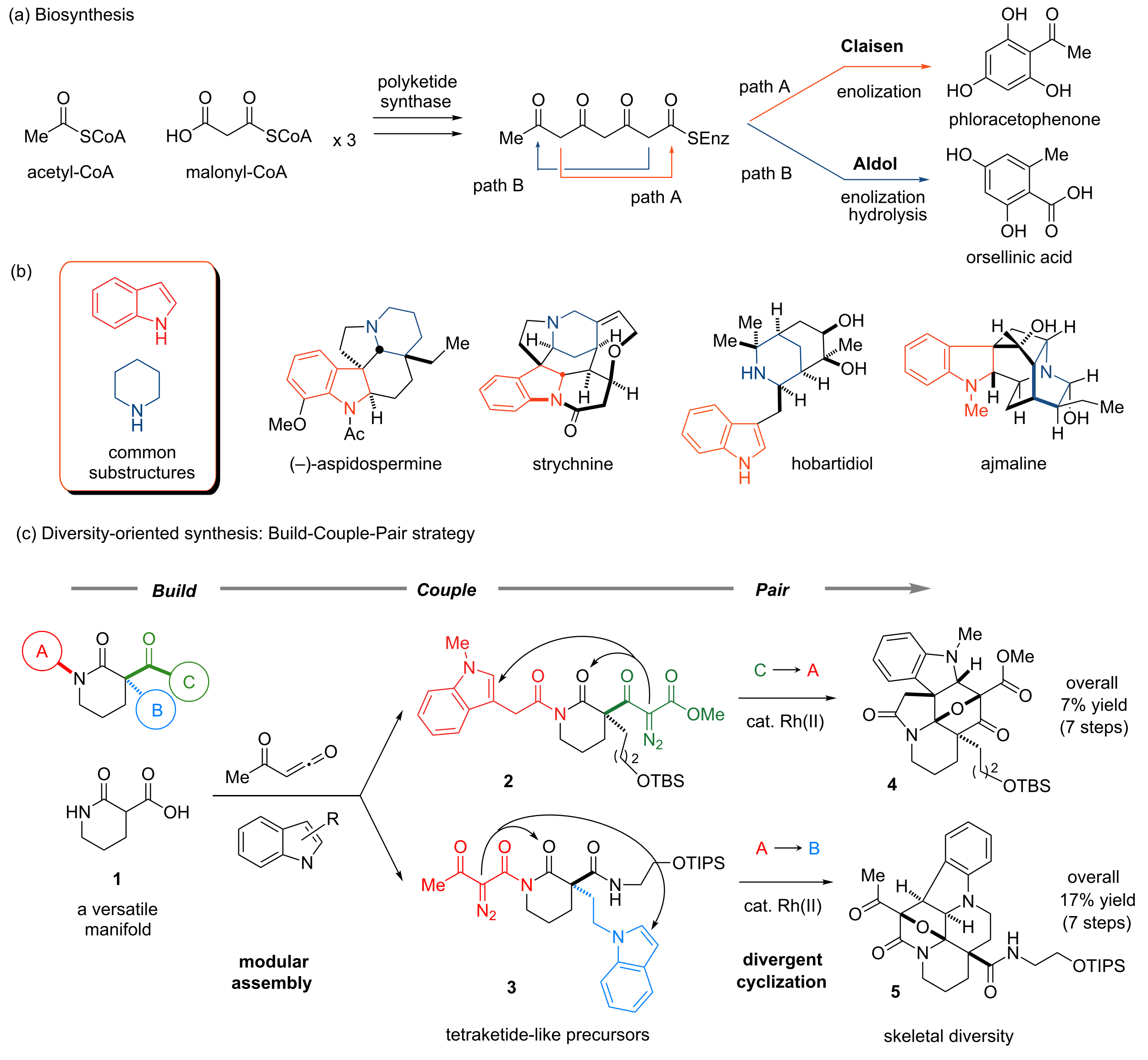

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Figure 1: (a) Biosynthetic outline of aromatic polyketides; (b) structure of indole alkaloids composed of indole (red) and piperidine (blue) groups; (c) divergent cyclizations to generate scaffold variations as an illustration of the "Build-Couple-Pair" strategy in diversity-oriented synthesis.

tional groups on **1**, α-diazoketocarbonyl and indole groups were installed to produce a set of tetraketide-like precursors, **2** and **3**. Rhodium(II)-catalyzed tandem cyclization–cycloaddition [19-21] of the tetraketide-like precursors produced distinct multicyclic scaffolds, **4** and **5**, differing in the relative orientations of the substructures. This approach illustrates a systematic way of diversifying skeletal arrays in a controlled manner.

With the intention to produce screening collections, we then devised a second-generation strategy applicable for a parallel synthetic protocol. This approach allows unified four-step access to a series of indole-alkaloid-like scaffolds. Some of these results were previously reported as a preliminary communication in 2009 [22]. As shown in Figure 2a, we conceived the modular assembly of three building blocks onto the piperidine-

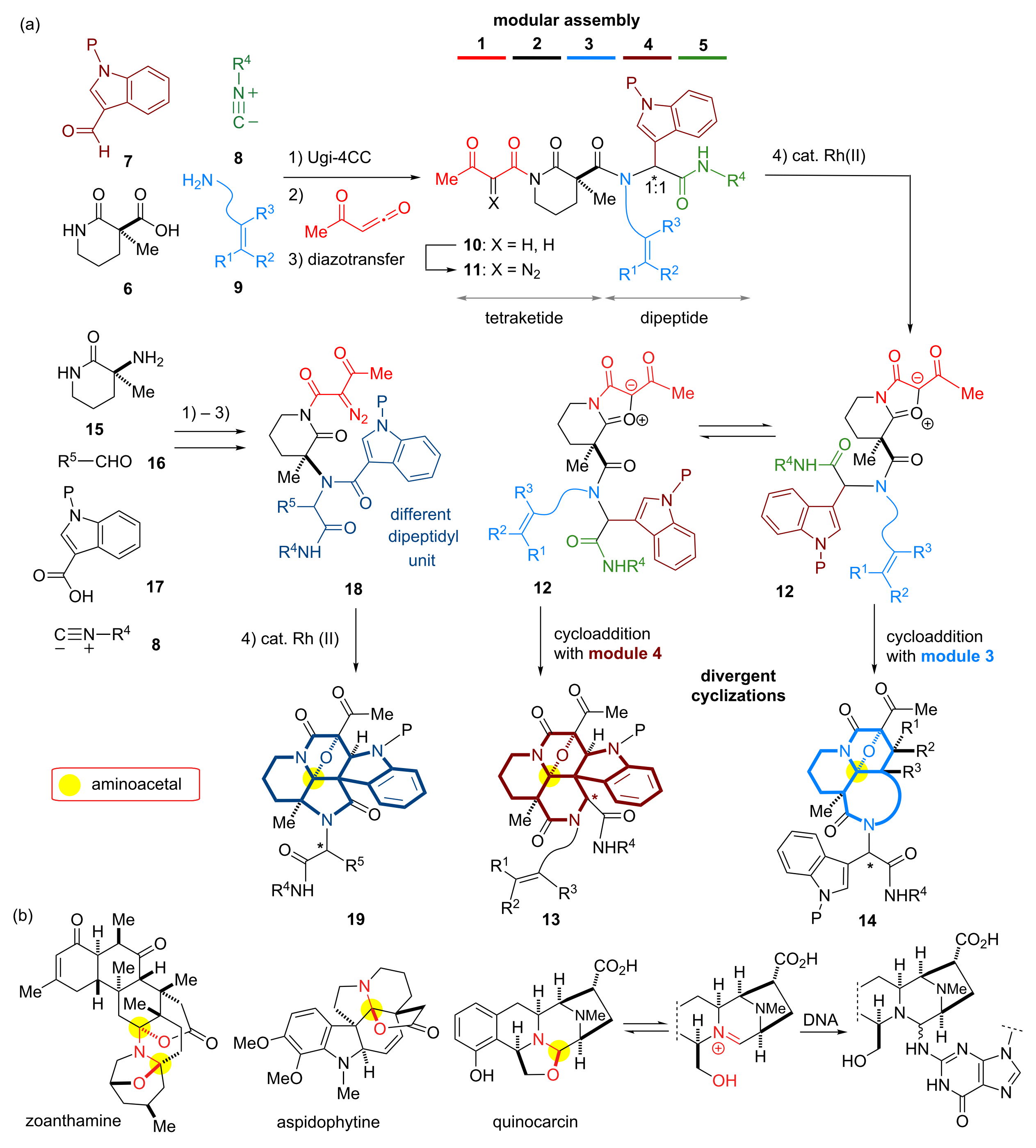


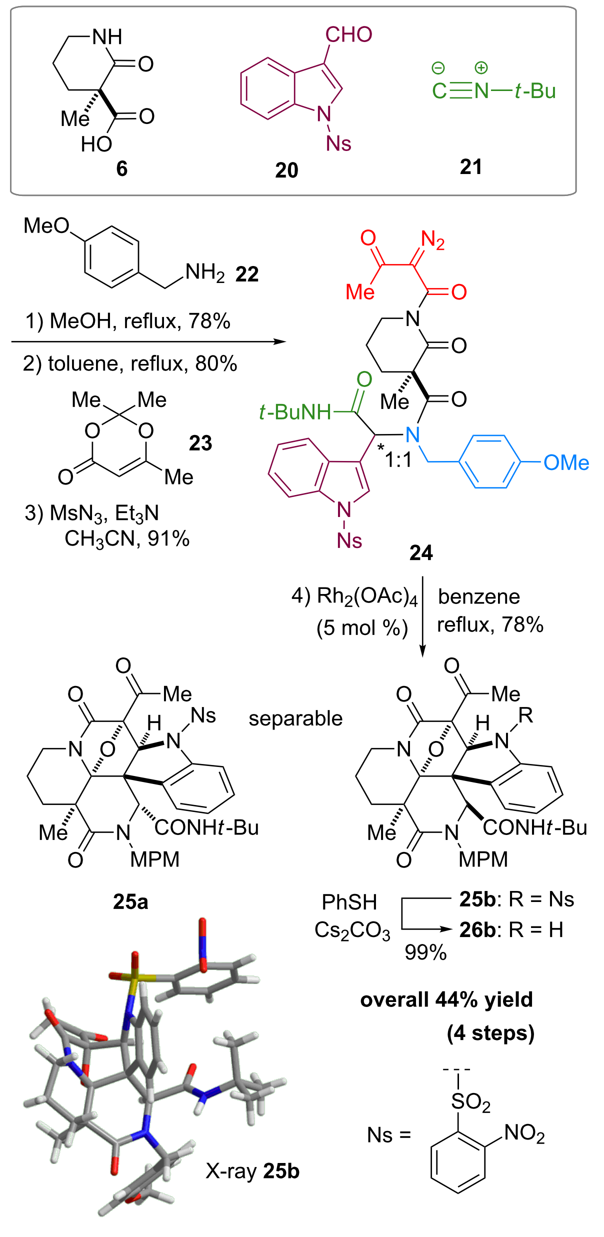
Figure 2: (a) Synthetic plans based on modular assembly and divergent cyclizations leading to fused skeletons; (b) structures of naturally occurring alkaloids bearing aminoacetal moieties and a proposed mode of action of quinocarcin.

based manifold **6** with a carboxylic acid group. Ugi condensation [23-25] of **6** with indole-3-carbaldehyde **7**, isonitrile and amine building blocks **8** and **9**, followed by reaction with an acetylketene [26] would produce a tetraketide-like precursor **10** composed of five modules. Since two methylene groups in module 2 in the tetraketide-like moiety **10** are masked as an imide group and a quaternary center, respectively, the remaining methylene in module 1 would be regiospecifically manipulated through diazotransfer to form diazoimide **11** [27]. Rhodium(II)-catalyzed cyclization of **11** between modules 1 and 2 could generate a carbonium ylide intermediate **12**. In this system, there is a dynamic conformational equilibrium of the tertiary amide, which is expected to allow divergent cycloadditions with the dipolarophiles installed at modules 3 and 4 leading to either tetracyclic **14** or hexacyclic **13**. In this full account, we also employ a piperidine-based manifold **15** bearing an amino group in order to expand the applicability of the various building blocks in the four-step parallel synthesis. The modular assembly of **15** with **16**, **17** and **8** based on Ugi condensation could produce a different dipeptidyl array of the precursor **18**, which is expected to produce the distinct scaffold **19** compared to those produced from manifold **6**. According to this strategy employing rhodium(II)-catalyzed tandem reactions, four sp^2-centers were efficiently converted into the corresponding sp^3-centers, including an aminoacetal core. In nature, there are a variety of alkaloids that possess an aminoacetal group (Figure 2b). The aminoacetal groups embedded in the skeleton are prone to undergo C–O bond cleavage to form electrophilic iminium species, which allow covalent bond formation with biomacromolecules (nucleic acids, proteins) in a cellular environment, and thereby play pivotal roles in defining their biological activities [28,29]. As a mechanistic rationale for the antitumor activities of quinocarcins, DNA alkylation exploiting the iminium moiety was proposed as shown in Figure 2b [30].

Inspired by these biosynthetic strategies, we report herein the development of parallel and four-step synthetic processes, employing manifolds **6** and **15**, leading to collections of fused molecules with installations of diverse functional groups comprising aminoacetal, β-ketoimide and indole groups [31-34]. Evaluation of in vitro antitrypanosomal activities of the synthetic collections and preliminary SAR studies are also described [35-41].

Results and Discussion

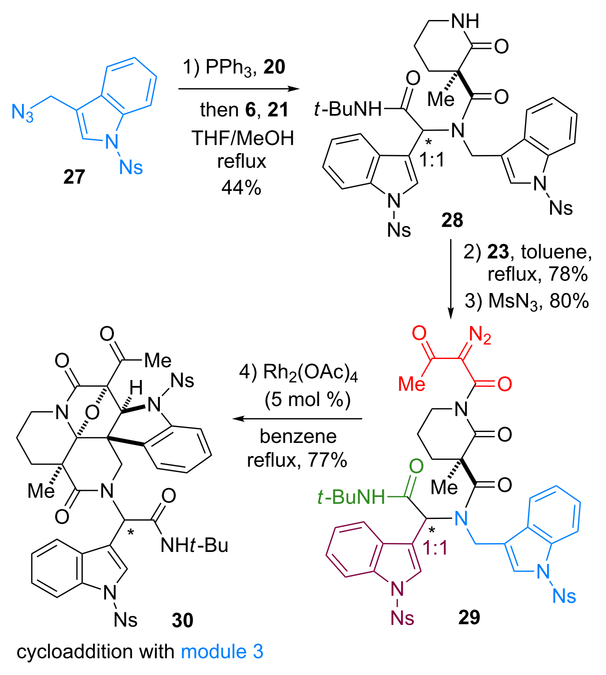
First, we assembled a linear precursor **24** with installation of a *p*-methoxybenzyl group and an indole ring at modules 3 and 4, respectively (Scheme 1), according to a procedure previously reported in our preliminary communication [22]. Racemic manifold **6**, indole-3-carbaldehyde derivative (**20**), *tert*-butylisonitrile (**21**) and *p*-methoxybenzylamine (**22**) were condensed in methanol under reflux to furnish a dipeptidyl product as a 1:1 diastereomeric mixture in 78% yield. *N*-Acetoacetylation of this intermediate was achieved by reaction with an acetylketene generated by heating of **23**. Subsequent diazotransfer reaction afforded the precursor **24** with a diazoimide group in 73% yield (two steps). Cyclization of **24** and subsequent cycloaddition between the resulting carbonium ylide and the indole C2–C3 double bond efficiently proceeded by the treatment with 5 mol % Rh$_2$(OAc)$_4$ catalyst in benzene under reflux to afford hexacyclic scaffold **25** in 78% yield. The cyclized products were obtained as a 1:1 diastereo-



Scheme 1: Four-step synthesis of hexacyclic skeleton **25**.

meric mixture of **25a** and **25b** and were easily separable by conventional silica-gel chromatography. X-ray analysis of crystalline **25b** unambiguously determined the relative stereochemical relationships of the multiple sp^3 centers embedded in the complex hexacyclic scaffold. In addition, removal of the *N*-nosyl protecting group by treatment with benzenethiol led to **26b** in quantitative yield [42].

To generate skeletal variations by altering the sites of the cycloadditions, we next synthesized a branched precursor **29** bearing a pair of identical indole units at modules 3 and 4 (Scheme 2), as reported previously [22]. Due to the instability of the corresponding amine building block bearing the indole unit, azide **27** was employed as a precursor. Staudinger/aza-Wittig reaction [43] of **27** and **20** and subsequent condensation with **6** and **21** afforded the peptidyl product **28**. Installation of a β-keto imide followed by diazotransfer reaction produced **29**. Upon the treatment of **29** with $Rh_2(OAc)_4$ catalyst (5 mol %), the cycloaddition occurred in a highly site-selective manner at module 3 to form **30** in 77% yield. Cycloaddition with the other site (module 4) is likely to be hindered by the sterically demanding amide moiety (module 5) in the vicinity of the reaction centers.

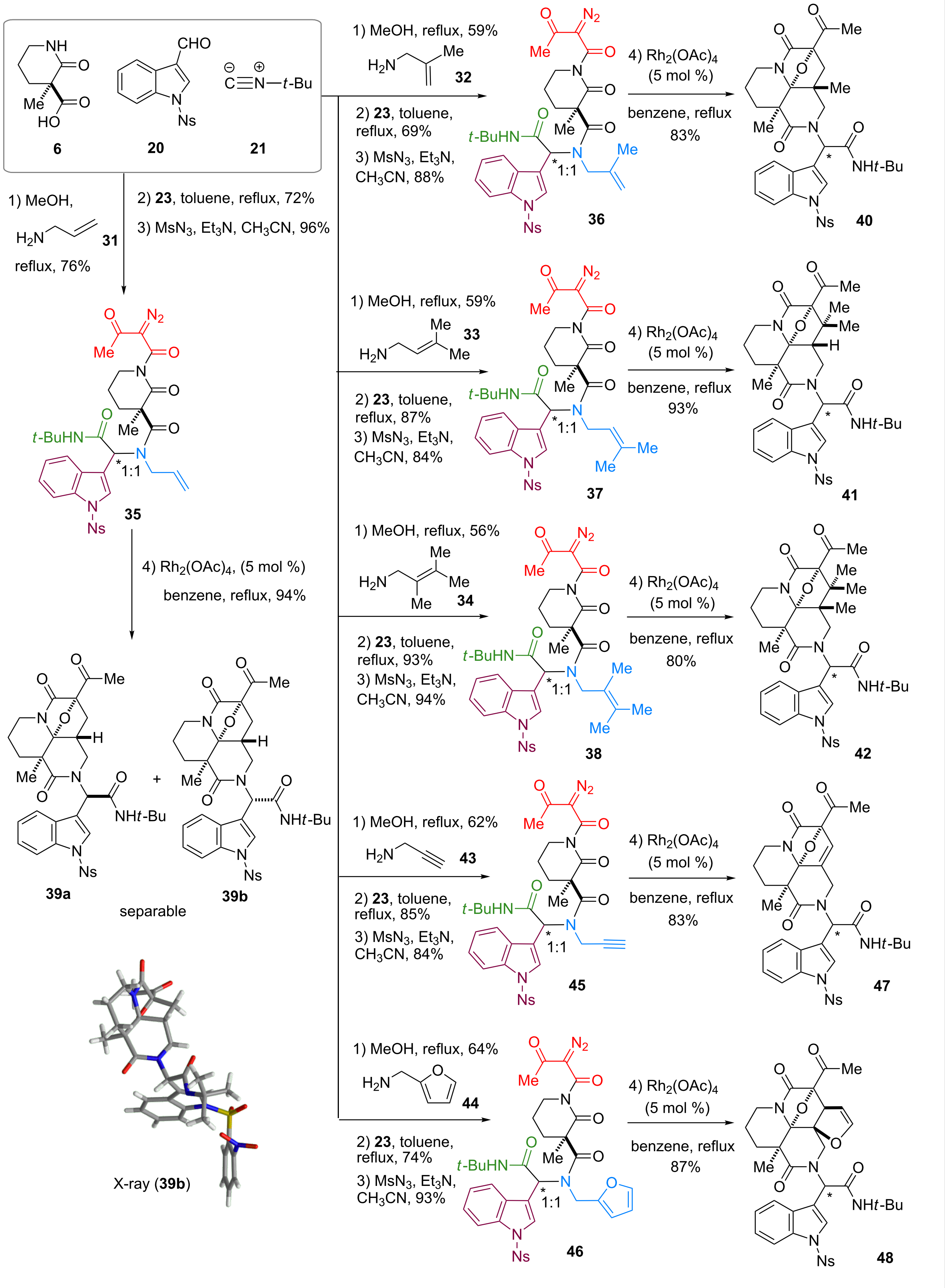


Scheme 2: Four-step synthesis of hexacyclic skeleton **30**.

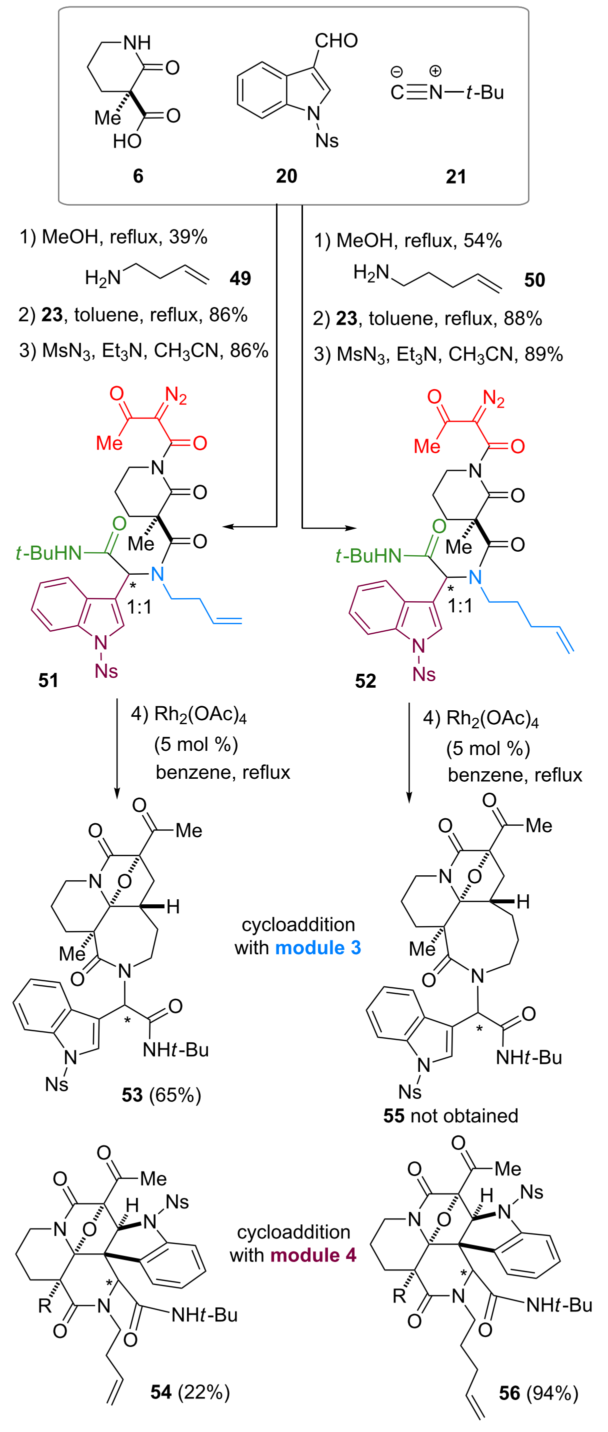
Taking into account the predominant involvement of the dipolarophile installed at module 3, we then designed a branched precursor **35** having a terminal olefin and an indole group at modules 3 and 4, respectively (Scheme 3). According to the previously reported protocol [22], Ugi reaction employing allylamine (**31**) and stepwise installation of a diazoimide group provided **35** in good yield. Upon treatment of **35** with $Rh_2(OAc)_4$ in benzene under reflux, 1,3-dipolar cycloaddition of the ylide intermediate with the terminal olefin at module 3 proceeded to give **39** as a separable 1:1 diastereomeric mixture in 94% yield. The relative stereochemistry of **39** was unambiguously determined by X-ray analysis of the crystalline **39b**.

In an effort not only to verify the reaction scope of the olefinic group installed at module 3 but also to shift the reaction site (module 3→4), we then prepared a series of cyclization precursors **36**–**38** in order of increasing steric hindrance of the olefinic groups as reported previously [22]. Allylamines **32**–**34** having a di-, tri- or tetra-substituted olefin were employed to synthesize precursors **36**–**38** based on the unified three-step protocol. The Rh(II)-catalyzed tandem cyclization–cycloaddition of the branched precursors **36**–**38** exclusively occurred at module 3. The cyclized products **40**–**42**, having the indole group at module 4 intact, were obtained in good yields. It is worth noting that the cycloadditions efficiently incorporated consecutive quaternary centers into the complex fused skeleton, overriding the considerable steric hindrance of the dipolarophiles composed of the tri- and even tetra-substituted olefin groups. To test the generality of the site-selective cycloaddition at module 3, we then synthesized precursors **45** and **46** with a terminal alkyne and a furan ring, respectively, by using amine building blocks **43** and **44** according to the reported procedure [22]. The Rh(II)-catalyzed tandem reactions of **45** and **46** again proceeded at module 3 to produce cyclized products **47** and **48** in good yields. Despite our concern for the potential instability of the aminoacetal moiety adjacent to the double bond, **47** is stable under the standard manipulations. Overall, the pair of diastereomers generated by the Ugi condensations were converted equally through the unified three-step transformations and easily separated after the cycloadditions.

Whilst the cycloadditions described above demonstrate the preference for the dipolarophile installed at module 3, we then attempted to alter the cyclization mode (module 3→4) by increasing the entropic barrier for medium-sized ring formation (Scheme 4) as reported previously [22]. For this purpose, we designed precursors **51** and **52**, synthesized through the three-step protocol employing amines **49** and **50**, respectively. Upon the treatment of **51** with $Rh_2(OAc)_4$, cycloaddition predominantly occurred at module 3 to produce tetracyclic **53** in 65% yield with formation of a seven-membered ring. Despite the minor pathway, cycloaddition at module 4 also competed to give **54** in 22% yield. On the other hand, cycloaddition of **52** exclusively occurred with the indole group at module 4, giving rise to **56** in 94% yield without eight-membered ring formation



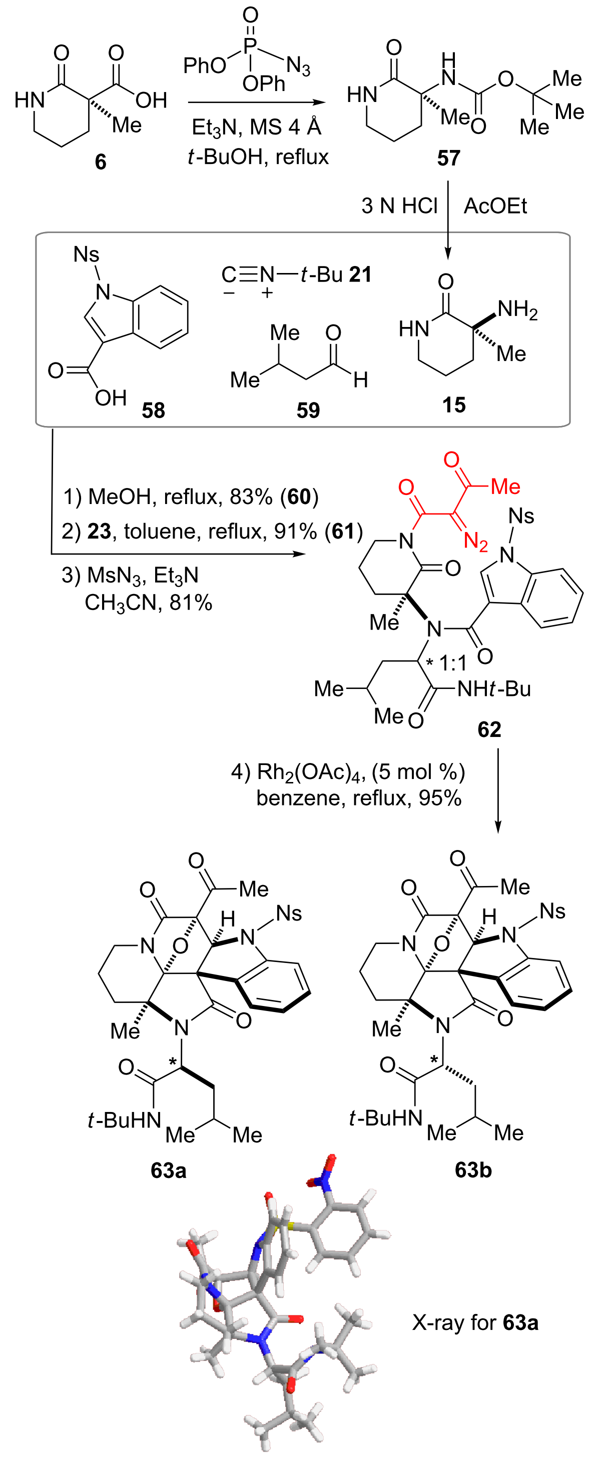
Scheme 3: Parallel and four-step synthesis of tetracyclic skeletons **39–42** and **47–48**.



Scheme 4: Synthesis of branched precursors, **51** and **52**, using amines **49** and **50**, with different methylene lengths and attempts to switch reaction sites.

leading to **55**. X-ray analysis of the crystalline **56b** confirmed the structure [22]. Accordingly, alteration of the cyclization mode was achieved by modulating the ring sizes formed via cycloaddition, which allowed divergent access to hexacyclic and tetracyclic skeletons.

In this study, we designed and synthesized a piperidine-based manifold **15** bearing an amino group in order to produce variations of branched precursors leading to distinct scaffolds (Scheme 5). The manifold **15** was readily prepared through



Scheme 5: Four-step synthesis of hexacyclic scaffold **63** employing manifold **15**. For details of the synthesis of **60** and **61** see Supporting Information File 1.

Curtius rearrangement of **6** and subsequent removal of the resulting carbamate group. Ugi four-component condensation of **15**, isonitrile **21**, indole-3-carboxylic acid derivative **58** and aldehyde **59** produced a 1:1 diastereomeric mixture of the dipeptidyl intermediate. Stepwise installation of the α-diazocarbonyl group produced **62** in good yield. The cyclization precursor **62** has a different arrangement of the branched dipeptidyl unit linked to the piperidine-based manifold compared with those derived from **6**. Rhodium-catalyzed tandem cyclization–cycloaddition proceeded smoothly to produce **63** in 95% yield. After separation of the diastereomers, X-ray analysis of crystalline **63a** allowed its structural determination. The flexibility and divergence of the synthetic process with high levels of stereoselectivity are promising for the development of small-molecule libraries with structural diversity and complexity.

With collections of the natural-product-inspired molecules in hand, in vitro anti-trypanosomal activities [35-41] were evaluated by employing a GUTat 3.1 strain of *T. brucei brucei* (Table 1) according to the previously reported protocols (Supporting Information File 1). We found several hit compounds in the series of the cycloadducts exploiting module 3 as

Table 1: In vitro anti-trypanosomal activities of natural product analogues and approved drugs against *T. brucei brucei* GUTat 3.1[a].

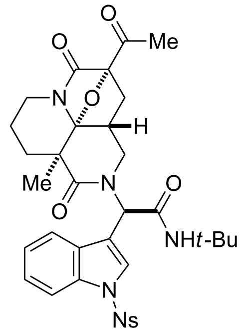
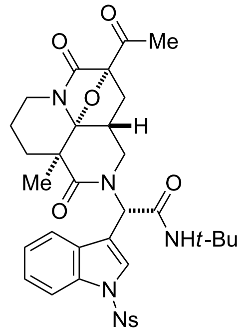
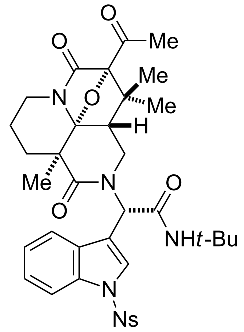
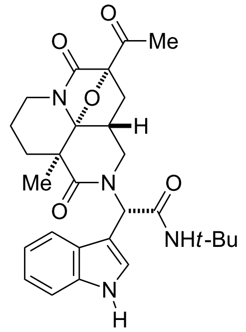
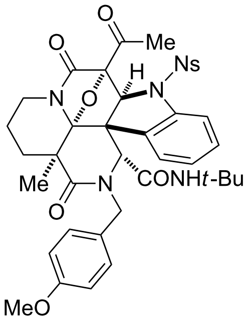
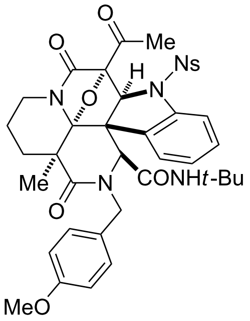
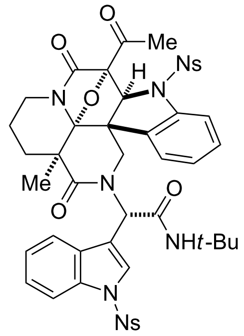
entry	compound	IC$_{50}$ (μg/mL)		Selectivity Index (SI)
		anti-trypanosomal activity	cytotoxicity	
1	 **39a**	>12.5	ND[b]	(–)
2	 **39b**	0.46	4.02	8.7
3	 **41b**	5.89	34.64	5.9

Table 1: In vitro anti-trypanosomal activities of natural product analogues and approved drugs against *T. brucei brucei* GUTat 3.1[a]. (continued)

4	 **39c**	>12.5	ND[b]	(–)
5	 **25a**	5.9	24.47	4.1
6	 **25b**	>12.5	ND[b]	(–)
7	 **30b**	>12.5	ND[b]	(–)
8	pentamidine[c]	0.00158	5.71	3600
9	suramin[c]	1.58	>100	>63
10	eflornithine[c]	2.27	>100	>44

[a]Culture of trypanosome (2.0–2.5 × 10^4 trypanosomes/mL for GUTat 3.1 strain) was used. The cytotoxicities were evaluated with MRC-5 cells, and the selectivity index (SI) for trypanosomiasis was calculated as (IC_{50} for MRC-5)/(IC_{50} for *T. brucei brucei*). [b]ND means "not determined". [c]Existing antitrypanosomal drugs.

dipolarophiles. While compound **39a** shows negligible activities, the diastereomer **39b** exhibits the most potent activity (IC_{50} = 0.46 μg/mL), indicating the critical importance of the stereochemistry on the peptidyl unit (Table 1, entries 1 and 2). The IC_{50} value of the antitrypanosomal activity is comparable to or greater than those of the approved drugs, suramine and eflornithine. Unfortunately, **39b** exhibits relatively potent cytotoxicity (IC_{50} = 4.02 μg/mL) against a human cell line (MRC-5 cells), and its selectivity index (SI) is calculated to be 8.7 as a means to assess the combined potencies of both antitrypanosomal and cytotoxic activities. Incorporation of dimethyl substituents on the scaffold resulted in diminished activity (**41b**: IC_{50} = 5.89 μg/mL) (Table 1, entry 3). Removal of the nosyl group (**39b**→**39c**) also caused substantial loss of the activities, suggesting the critical role of the aromatic sulfone amide moiety (Table 1, entry 4). Aside from **25a**, which shows moderate activity (IC_{50} = 5.9 μg/mL) (Table 1, entry 5), the antitrypanosomal activities of hexacyclic compounds, **25b** and **30b**, (Table 1, entries 6 and 7) are negligible. In addition, the hexacycles (**63a** and **63b**) generated from manifold **15** also showed insignificant activities (data not shown). Thus, this preliminary assessment supports the idea that the collections of natural-product-inspired scaffolds could have high hit rates against biological screenings, even without having structural information about the biological targets and small-molecule modulators related to the targeted cellular functions. Further screening investigations of the synthetic collections prepared in the four-step process are currently underway in our laboratories.

Conclusion

Inspired by biosynthetic strategies, we devised a modular assembly of five components employing manifold **6** and subsequent installation of a diazoimide group. This allowed three-step access to collections of cyclization precursors with a linkage of the piperidine and the indole units as key substructures shared with naturally occurring alkaloids. Rhodium-catalyzed cyclizations of diazoimides and subsequent divergent cycloadditions produced tetracyclic and hexacyclic scaffolds with exquisite regio- and stereocontrols. By the choice of dipolarophiles incorporated in modules 3 and 4, we have demonstrated site-selective cycloadditions leading to distinct scaffolds, which could be a rational approach to generate skeletal variations in synthetic collections. We further demonstrated the applicability of the manifold **15** bearing an amino group, which elicits further scaffold diversity. The parallel synthetic process based on the unified four-step sequences allows installation of dense arrays of various functional groups featuring aminoacetal, β-ketoimide and indole/olefin groups into multicyclic scaffolds reminiscent of natural products. Evaluation of antitrypanosomal activities of the collections allowed primary screenings of several hit compounds. The preliminary SAR study provided insights into the potential pharmacophore, based on the key features of scaffold, substructure and stereochemistry, which could be the proof of concept of our synthetic approach toward lead generation exploiting natural-product-inspired collections.

Supporting Information

Supporting Information File 1

Experimental procedures and NMR spectra of compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-105-S1.pdf]

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Expanding the chemical diversity of spirooxindoles via alkylative pyridine dearomatization

Chunhui Dai, Bo Liang and Corey R. J. Stephenson*

Letter

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Address:
Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, USA

Email:
Corey R. J. Stephenson* - crjsteph@bu.edu

* Corresponding author

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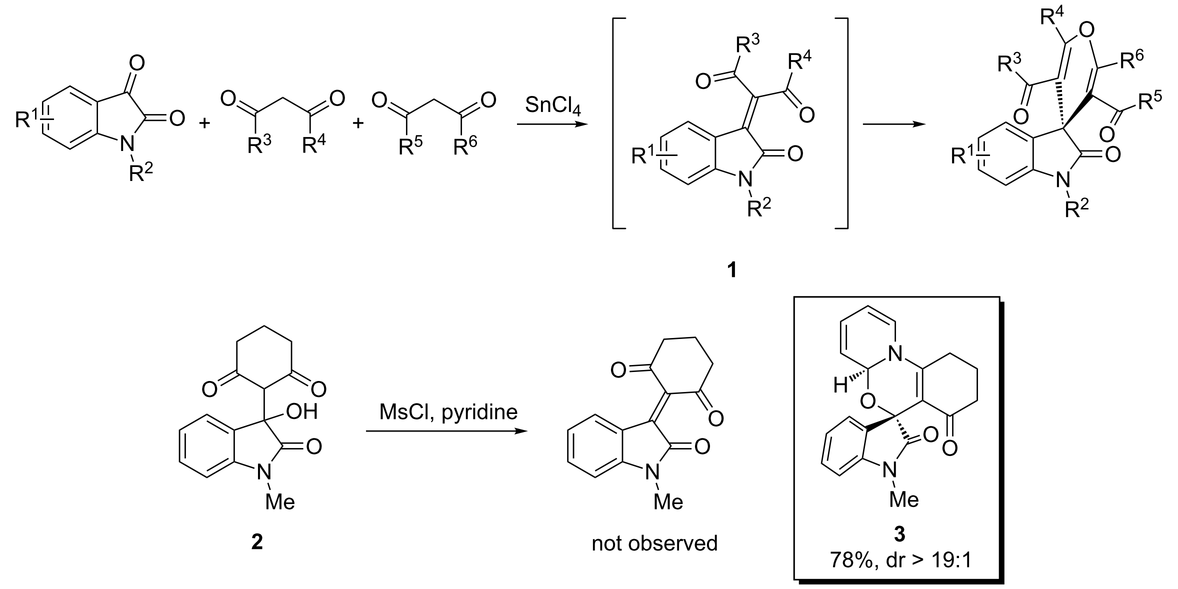
Abstract

A mild and practical synthesis of spirooxindole [1,3]oxazino derivatives from *N*-substituted isatins and 1,3-dicarbonyl compounds with pyridine derivatives is reported. The reactions provided good to excellent yields. Further exploration of the molecular diversity of these compounds is demonstrated through Diels–Alder reactions.

Introduction

The spirooxindole is a common structural motif found in a variety of complex alkaloids [1]. Many compounds that possess a spirooxindole moiety exhibit significant biological activity, thus exemplifying their role in drug development [2-8]. Moreover, the challenging molecular architecture of spirooxindoles is appealing to chemists because it evokes novel synthetic strategies that address configurational demands and provides platforms for further reaction development [9-11]. To our knowledge, most studies of these types of molecules focus on spirooxindoles bearing a pyrrolidine ring at the 3-position of the oxindole core, while few reports expand to formulate the syntheses of other spiro rings. As part of our ongoing reaction-screening objective [12,13], we previously reported a Lewis acid catalyzed, three-component synthesis of spirooxindole pyranochromenedione derivatives using isatin and two 1,3-dicarbonyl compounds (Scheme 1) [14]. Mechanistically, we believed this reaction to proceed through an intermediate isatylidene **1** [15-17]. As a means to support our mechanistic hypothesis, we attempted to prepare and isolate the isatylidene; however, our attempts were unsuccessful. Interestingly, treatment of **2** with methanesulfonyl chloride (MsCl) in pyridine provided the dearomatized alkylation product **3** in 78% yield. In the context of developing novel and practical methods for the preparation of diverse heterocyclic compounds, herein, we



Scheme 1: Unexpected alkylative pyridine dearomatization during our previous work on the synthesis of spirooxindole pyranochromenediones.

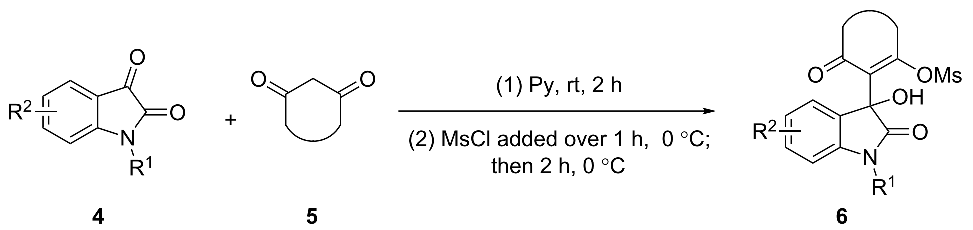
report our extended investigation on the efficient synthesis of spirooxindole [1,3]oxazino derivatives by means of alkylative pyridine dearomatization [18-21].

Results and Discussion

Reactions of *N*-substituted isatins and 1,3-dicarbonyl compounds in pyridine

Based on preliminary results, we commenced with the reaction of *N*-substituted isatins **4** and 1,3-dicarbonyl compounds **5** in pyridine. After addition of the reagents, the mixture was allowed to react at room temperature for 2 h to ensure initial coupling, whereupon methanesulfonyl chloride was added slowly over a 1 h period at 0 °C and another 2 h at the same temperature to trap the vinylogous acid as vinyl mesylates **6**. Various *N*-substituted isatins and 1,3-dicarbonyl compounds were then explored and the results are presented in Table 1. Beginning with isatin and 1,3-cyclohexanedione (**5a**) as coupling partners, we isolated a relatively poor yield of product **6a** (Table 1, entry 1). We speculated that the free indole nitrogen was inhibiting the reaction, thus we switched to

Table 1: Reaction of isatins **4** and 1,3-dicarbonyl compounds **5** in pyridine.



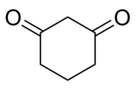
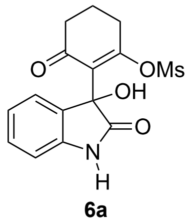
entry[a]	R^1	R^2	5	product	yield (%)[b]
1	H	H	 **5a**	 **6a**	31

Table 1: Reaction of isatins **4** and 1,3-dicarbonyl compounds **5** in pyridine. (continued)

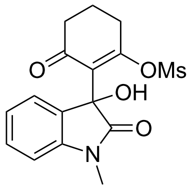
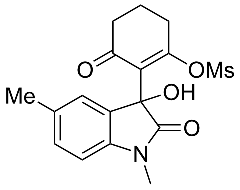
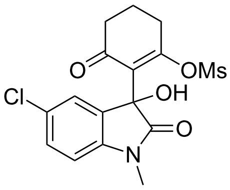
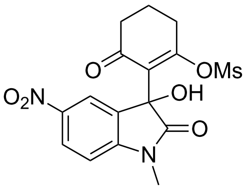
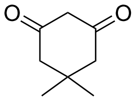
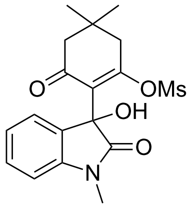
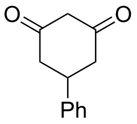
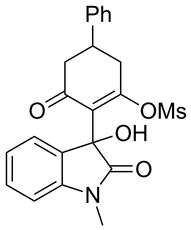
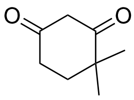
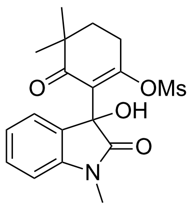
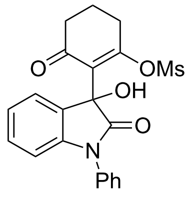
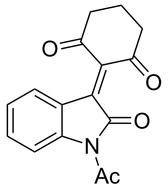
2	Me	H	**5a**	 **6b**	80
3	Me	5-Me	**5a**	 **6c**	57
4	Me	5-Cl	**5a**	 **6d**	84
5	Me	5-NO_2	**5a**	 **6e**	89
6	Me	H	 **5b**	 **6f**	87
7	Me	H	 **5c**	 **6g**	61
8	Me	H	 **5d**	 **6h**	71

Table 1: Reaction of isatins **4** and 1,3-dicarbonyl compounds **5** in pyridine. (continued)

9	Ph	H	**5a**	 **6i**	73
10[c]	Ac	H	**5a**	 **6j**	74

[a]Reactions were carried out on a 10 mmol scale in pyridine (8.0 mL) with 1.0 equiv of isatins **4** and 1,3-dicarbonyl compounds **5** at room temperature for 2 h, followed by the addition of 1.5 equiv of MsCl at 0 °C over 1 h and another 2 h stirring at the same temperature. [b]Isolated yield. [c]The adduct **6j** was isolated as the only product.

N-substituted isatins and found that the reaction improved to provide moderate to high yields (Table 1, entries 2–10). Subtle substitution effects were observed when the C(5)–H of isatin was replaced with various functionalities. Specifically, an electron-donating group at the 5-position, such as a methyl group, decreased the reactivity and only gave 57% yield (Table 1, entry 3). As a comparison, electron-withdrawing groups at the 5-position, such as chloro and nitro groups, increased the reactivity and provided products in higher yield (Table 1, entries 4–5). Other 1,3-dicarbonyl compounds were also investigated. 5,5-Dimethyl-1,3-cyclohexanedione (**5b**) worked well (Table 1, entry 6), in contrast to 5-phenyl-1,3-cyclohexanedione (**5c**), which gave a slightly lower yield (Table 1, entry 7). Interestingly, nonequivalent 1,3-dicarbonyl compound **5d** afforded single constitutional isomer (Table 1, entry 8), presumably due to the increased sterics and overall ring strain associated with substituents alpha to the vinylogous sulfonyl ester. *N*-Phenylisatin provided a similar yield to *N*-methylisatin (Table 1, entry 9). However, when *N*-acetylisatin was subjected to the reaction conditions, the reaction failed to provide the desired product and instead delivered compound **6j** exclusively in 74% yield (Table 1, entry 10). We predict that the formation of **6j** by dehydration is due to the electron deficiency of the oxindole ring and subsequent stability gained from the ene–trione moiety. The structure of compound **6b** was established by single-crystal X-ray analysis (Figure 1).

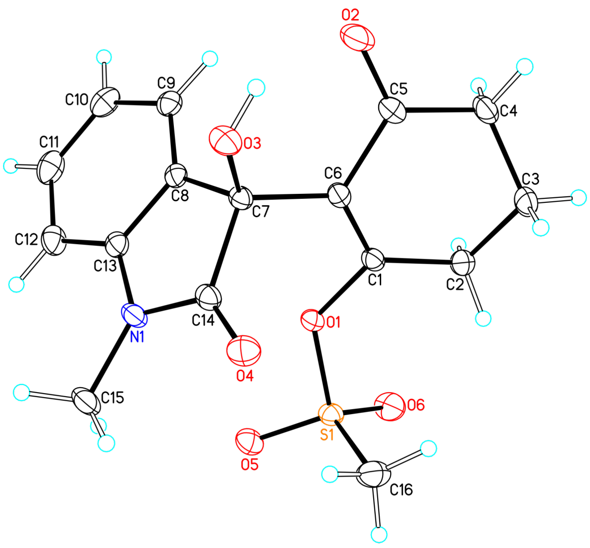
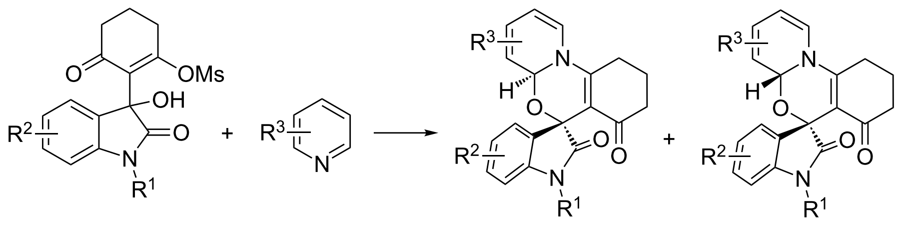


Figure 1: X-ray crystal structure of compound **6b**.

Having established a facile route to our desired vinylogous sulfonyl esters **6**, we next examined their reactivity towards alkylative pyridine dearomatization reactions (Table 2). During optimization studies, we discovered that the reaction performed best at 45 °C using pyridine as the solvent. The substituent groups on the isatin moiety did not have a great effect on the reactivity of compounds **6**. Generally, the reaction was complete in 12 h and provided inseparable diastereoisomers with good to excellent yields (Table 2, entries 1–5). 4-Picoline (**7b**) gave a lower yield after 12 h at 45 °C (Table 2, entry 6). 4-Methoxypyridine (**7c**) provided the desired product **3g** in 78% isolated yield in only 6 h at room temperature (Table 2, entry 7). Isoquinoline (**7d**) and 4-acetylpyridine (**7e**) also underwent the reaction to provide the desired products in moderate yields

Table 2: Reactions of vinylogous sulfonyl esters **6** with pyridine derivatives **7**.



6 **7** **major 3** **minor 3**

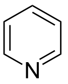
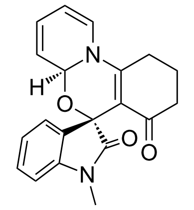
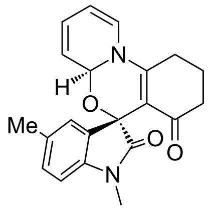
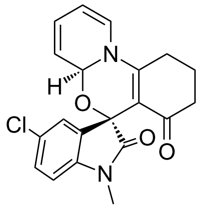
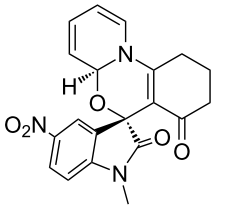
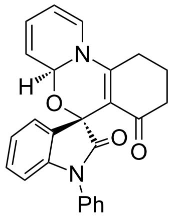
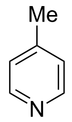
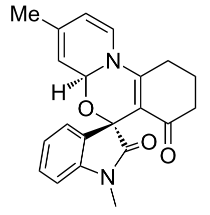
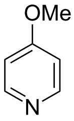
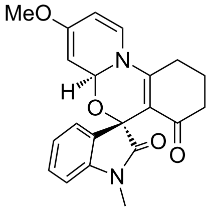
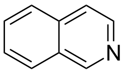
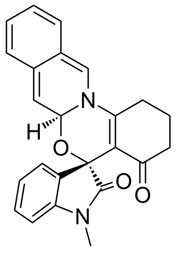
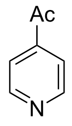
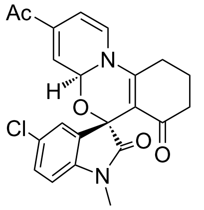
entry[a]	**6**	**7**	T (°C)	h	product **3**	dr[b]	yield (%)[c]
1	**6b**	 **7a**	45	12	 **3a**	5:1	90
2	**6c**	**7a**	45	12	 **3b**	9:1	83
3	**6d**	**7a**	45	12	 **3c**	7:1	90
4	**6e**	**7a**	45	12	 **3d**	5:1	91
5	**6i**	**7a**	45	12	 **3e**	5:1	74

Table 2: Reactions of vinylogous sulfonyl esters **6** with pyridine derivatives **7**. (continued)

6	**6b**	 **7b**	45	12	 **3f**	8:1	48
7	**6b**	 **7c**	23	6	 **3g**	3:1	78
8	**6b**	 **7d**	60	18	 **3h**	2:1	65
9	**6d**	 **7e**	60	18	 **3i**	8:1	67

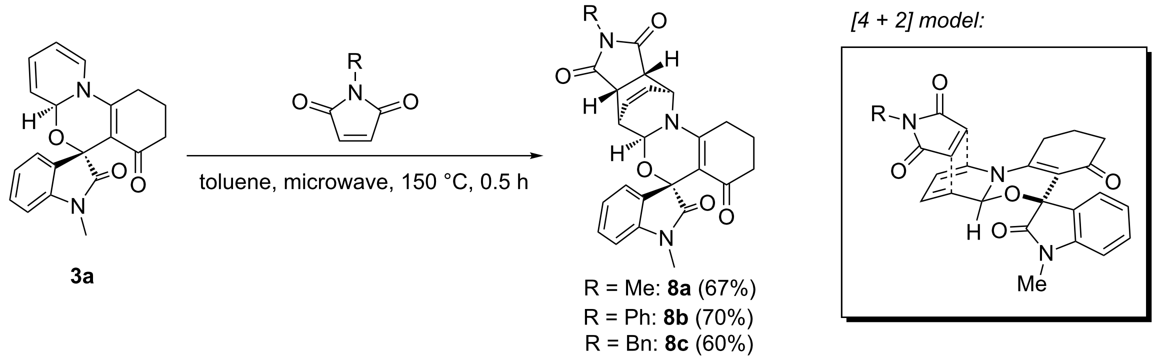
[a]Reactions were conducted with vinylogous sulfonyl esters **6** (1.0 mmol) and pyridine derivatives **7** (1.0 mL) at 23–60 °C. Reaction time varied from 6–18 h. [b]Determined by ^{1}H NMR integration. [c]Isolated yield.

(Table 2, entries 8–9), but required an elevated temperature (60 °C) and a longer reaction time (18 h). On the basis of the results in Table 2, we speculate that the unexpected formation of compound **3** in Scheme 1 was due to the evaporation of solvent after the reaction at elevated temperature (45 °C), providing an opportunity for the vinylogous sulfonate ester, generated during the reaction, to react with pyridine. Finally, the structure of compound **3d** was established by single-crystal X-ray analysis (Figure 2).

Further plans to expand the molecular diversity of these compounds utilizing available functionalities are currently underway. As an illustrative example, spiro [1,3]oxazino compounds having a diene moiety within their molecular framework are susceptible to Diels–Alder (D–A) reactions [22]. Scheme 2 highlights three examples in which compound **3a** was exposed to *N*-substituted maleimides in toluene at 150 °C under microwave irradiation for 0.5 h, and D–A products **8a–c** were isolated in moderate yields. Finally, the structure of compound **8a** was established by single-crystal X-ray analysis (Figure 3).

Conclusion

In summary, we developed a practical and efficient method to synthesize spirooxindole derivatives with a [1,3]oxazine fused-ring system. The reaction conditions are very mild and tolerant of functional groups, providing moderate to high yields. The application and versatility of these spirooxindole derivatives to quickly access complex molecules is further demonstrated in good yielding D–A reactions.



Scheme 2: Application of spiro [1,3]oxazino compound **3a** in D–A reactions.

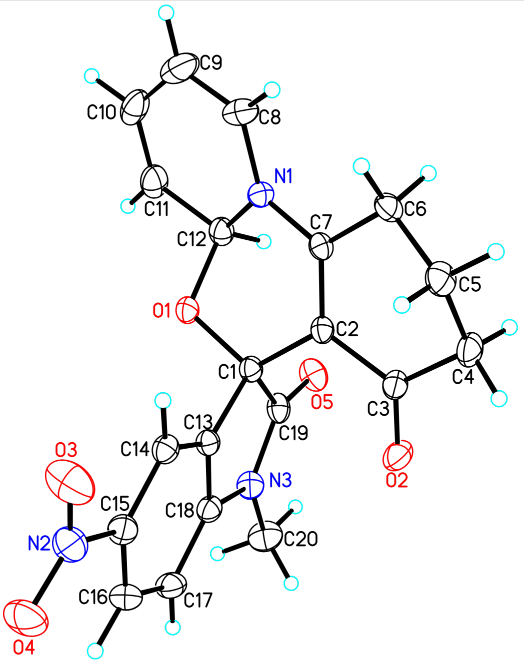


Figure 2: X-ray crystal structure of compound **3d**.

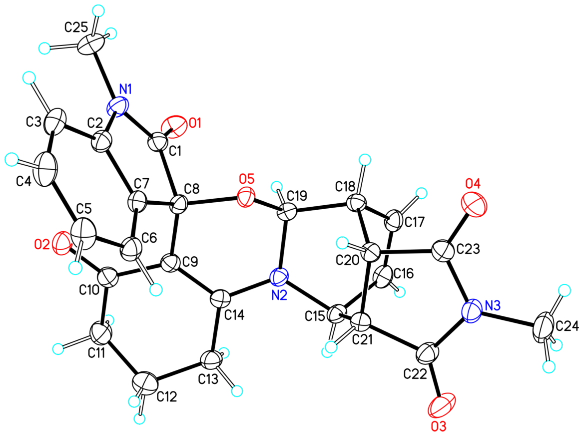


Figure 3: X-ray crystal structure of compound **8a**.

Supporting Information

Supporting Information File 1

Full experimental details and analytical data and crystallographic information.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-111-S1.pdf]

Acknowledgements

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Parallel solid-phase synthesis of diaryltriazoles

Matthias Wrobel[1], Jeffrey Aubé[2] and Burkhard König[*1]

Full Research Paper

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Address:
[1]Fakultät für Chemie und Pharmazie, Universität Regensburg, D-93040 Regensburg, Germany, Fax: +49 9419431717 and
[2]Department of Medicinal Chemistry and the Chemical Methodology and Library Development Center, University of Kansas, Delbert M. Shankel Structural Biology Center, 2121 Simons Drive, West Campus, Lawrence, KS 66047, USA

Email:
Burkhard König[*] - burkhard.koenig@chemie.uni-regensburg.de

* Corresponding author

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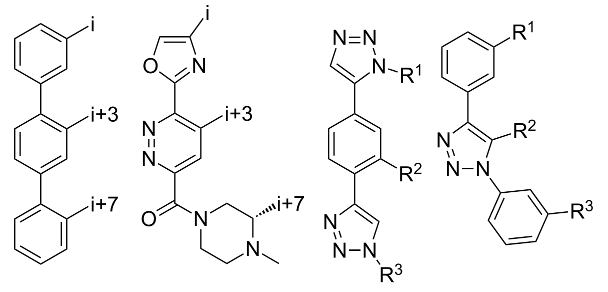
Abstract

A series of substituted diaryltriazoles was prepared by a solid-phase-synthesis protocol using a modified Wang resin. The copper(I)- or ruthenium(II)-catalyzed 1,3-cycloaddition on the polymer bead allowed a rapid synthesis of the target compounds in a parallel fashion with in many cases good to excellent yields. Substituted diaryltriazoles resemble a molecular structure similar to established terphenyl-alpha-helix peptide mimics and have therefore the potential to act as selective inhibitors for protein–protein interactions.

Introduction

The α-helix was the first-described secondary structure of peptides discovered by Linus Pauling in 1951 [1]. With about 30% of the amino acids in proteins being part of α-helices [2], it is the most common secondary structure found in proteins [3]. Protein–protein as well as protein–DNA and protein–RNA interactions often involve α-helices as recognition motifs on protein surfaces [4]. These helices are important targets for new drugs, but stabilization of the helix folding for small structures with less than 15 residues still remains a challenge [5,6]. Thus, new attempts have been made to design low-molecular-weight ligands that disrupt protein–protein interactions [7]. For example, fast proteolytic degradation observed with small peptide-based compounds [8], can be overcome by compounds stabilized by non-natural amino acids [9] or cross-linked between side chains and the backbone [10]. Replacement of the complete backbone by a nonpeptidic scaffold, which positions side chains in the typical i, i+3 and i+7 arrangement of an α-helix is another successful strategy [11]. Horwell pioneered this type of peptidomimetics and showed that 1,6-disubstituted indanes can imitate the helix residues i and i+1 [12,13]. Hamilton reported a 3,2′,2″-substituted terphenyl scaffold with a spatial orientation that mimics the i, i+3 and i+7 moieties on the surface of an α-helical peptide [14]. Inspired by the terphenyl-based α-helix mimetics **1**, several related compounds



1 **2** **3** **4**

Scheme 1: Terphenyl scaffold **1** [13,14]; oxazole-pyridazine-piperazine **2** [14,15] and aryl-triazoles **3** and **4** [15,16] as α-helix mimetics.

containing three or more adjacent aryl rings (Scheme 1), such as **2**, were reported [15]. However, the synthesis of substituted triaryl compounds can be tedious, and the predictability of their potency and selectivity as inhibitors is still limited. We have recently reported the synthesis of triazole-based α-helix mimetics **3** and **4** [16], which are efficiently available through azide–alkyne cycloadditions [17]. We now report the use of this chemistry to prepare libraries of potential inhibitors of protein–protein interactions.

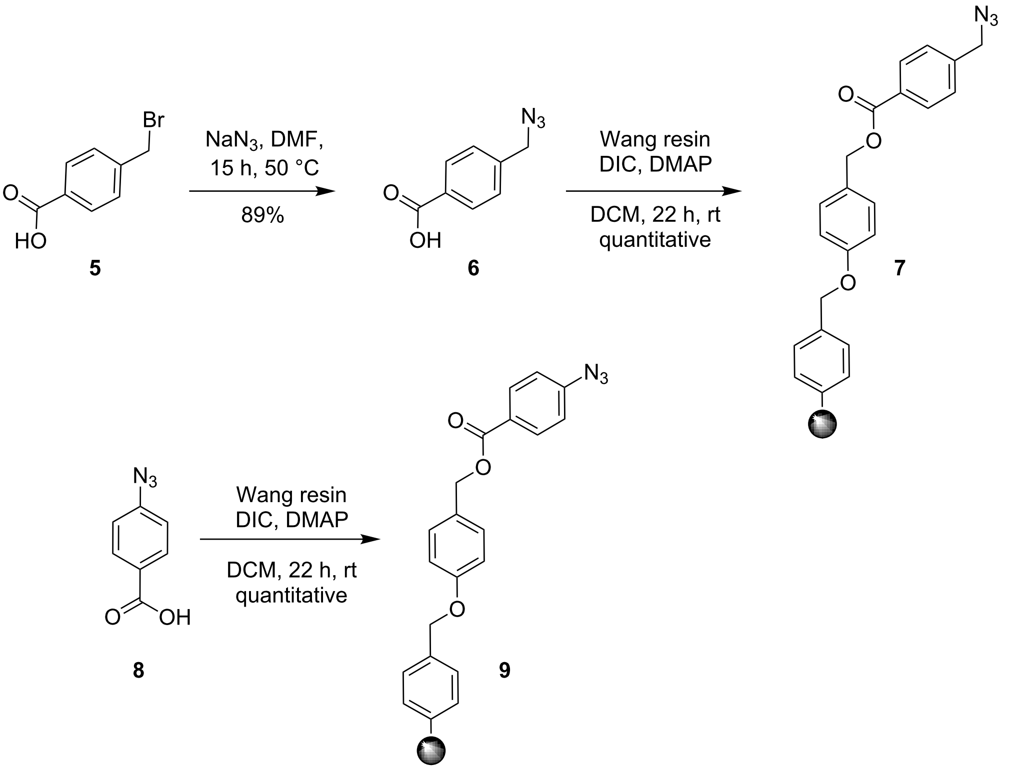
Results and Discussion

Synthesis of azide-functionalized Wang resins

Two azide-functionalized resins were prepared for the solid-phase synthesis of diaryl-triazoles. The commercially available 4-(bromomethyl)benzoic acid (**5**) was converted into azide **6** in anhydrous DMF with sodium azide under heating. Coupling to Wang resin in dichloromethane, by using DIC and DMAP as coupling reagents, gave resin **7** in quantitative yield (Scheme 2) [18]. Commercially available 4-azidobenzoic acid (**8**) gave resin **9** in an analogous esterification of a Wang resin.

Solid-phase synthesis of diaryltriazoles

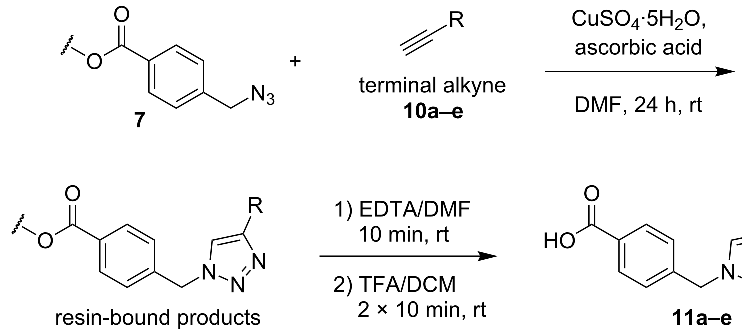
The conditions for the solid-phase synthesis of diaryltriazoles on functionalized Wang resin **7** were optimized by using five different alkynes **10a**–**e**, containing acyclic or cyclic aliphatic moieties, simple arenes and 1-(but-3-yn-2-yl)-3-(4-chlorophenyl)-1-methylurea (**10c**) as an example of a more complex alkyne. The azide–alkyne [3 + 2] cycloaddition was catalyzed with copper(II) sulfate pentahydrate and L-ascorbic acid in DMF overnight at room temperature. A solution of EDTA was added to remove the remaining copper cations from the resin. Resin cleavage under acidic conditions with TFA in DCM gave

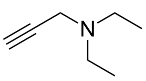
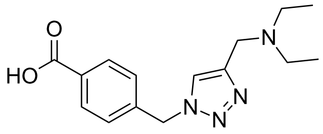
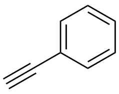
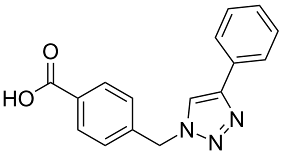
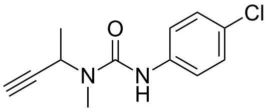
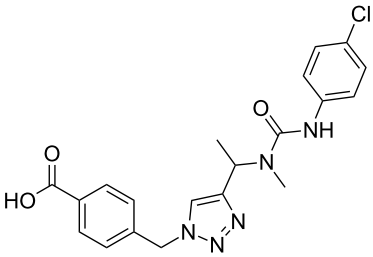
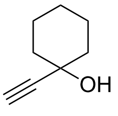
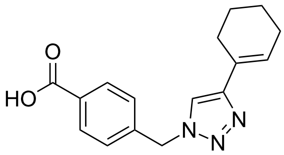
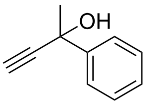
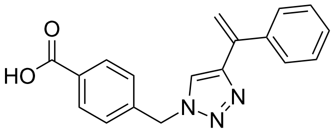


Scheme 2: Synthesis of azido-functionalized resins **7** and **9**.

compounds **11a**–**e** in moderate to excellent overall yields of 57 to 90% (Table 1). Due to the solid phase synthesis protocol the crude material purity was typically high, ranging from 70 to 90%. Alkyne **10d** and **10e** bearing hydroxy groups were converted quantitatively, but elimination of water occurred in the presence of TFA. The dehydrated products were obtained in 57 and 71%. The remaining material was the corresponding hydroxylated product.

Table 1: Copper-catalyzed [2 + 3] cycloadditions of resin-bound azide **7** with five terminal alkynes.



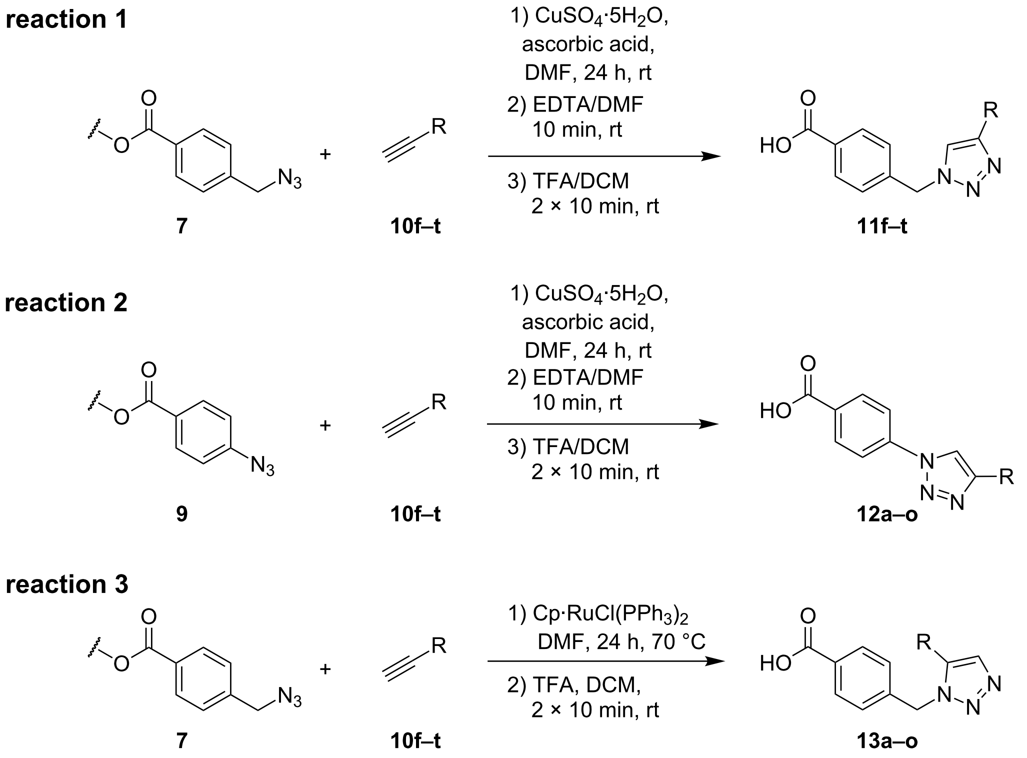
terminal alkyne **10**	product **11**	yield [%]
 **10a**	 **11a**	63
 **10b**	 **11b**	90
 **10c**	 **11c**	81
 **10d**	 **11d**	57
 **10e**	 **11e**	71

Parallel synthesis of a compound library

A larger compound library was prepared by using resins **7** and **9**, 15 different terminal alkynes **10f–t** and either copper or ruthenium-catalyzed [2 + 3] cycloadditions. The three reactions and the obtained products **11** (reaction 1), **12** (reaction 2) and **13** (reaction 3) are summarized in Table 2.

Reaction 1 follows the established protocol and, gave after removal of the copper salts with a solution of EDTA and TFA cleavage, the corresponding products in good to quantitative yields (88–99%). Resin **9** was used in reaction 2 under otherwise identical reaction conditions. The use of an aromatic azide leads to more rigid products containing three adjacent aromatic rings: The central triazole and the phenyl ring of the benzoic acid as constant structural elements and the third ring consisting either of substituted benzenes, heteroarenes or a polycyclic aromatic compound. Lower product yields were obtained in this series of compounds, ranging from 21 to 63%. The lower reactivity of the aromatic azide and the increased steric demand may explain the decrease in yield in comparison to that of the

Table 2: Copper-catalyzed [2 + 3] cycloadditions of resin bound azide **7** with five terminal alkynes. Compounds **13**, with the exception of **13f**, were only characterized during compound library synthesis, by HPLC–MS analysis.



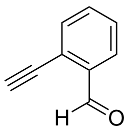
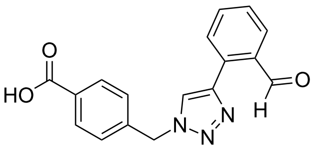
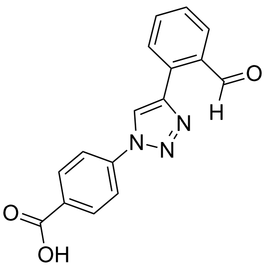
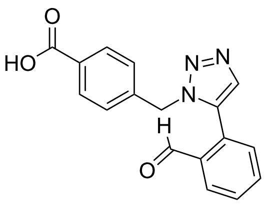
alkyne **10**	product after cleavage from resin (yield)		
	reaction 1 resin **7**, catalyst $CuSO_4$	**reaction 2** resin **9**, catalyst $CuSO_4$	**reaction 3** resin **7**, catalyst $Cp·RuCl(PPh_3)_2$
 **10f**	 **11f** (95%)	 **12a** (49%)	 **13a** not obtained

Table 2: Copper-catalyzed [2 + 3] cycloadditions of resin bound azide **7** with five terminal alkynes. Compounds **13**, with the exception of **13f**, were only characterized during compound library synthesis, by HPLC–MS analysis. (continued)

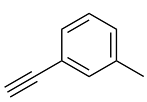
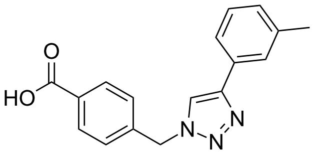
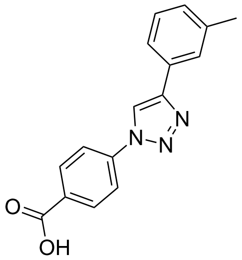
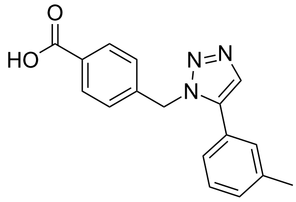
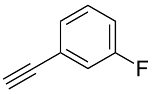
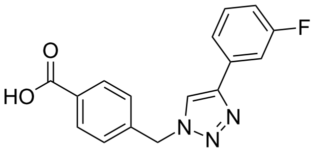
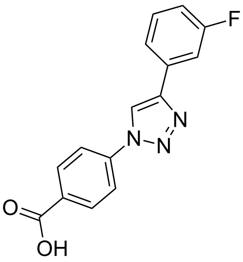
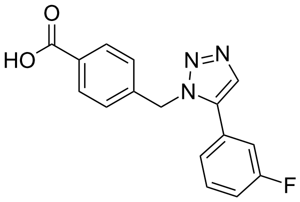
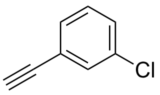
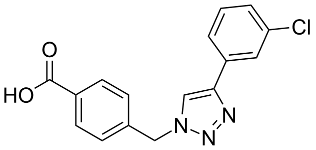
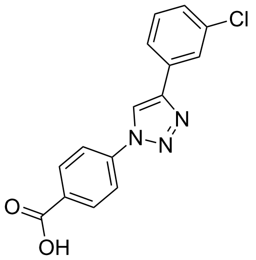
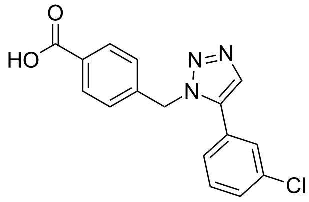
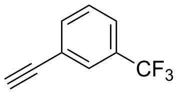
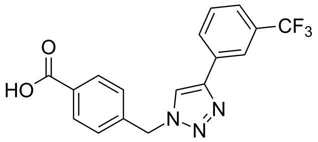
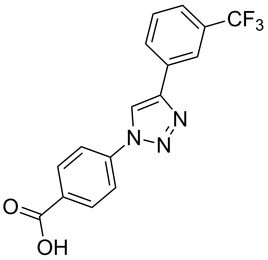
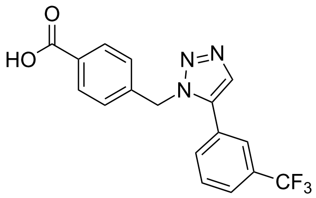
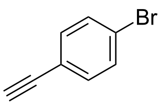
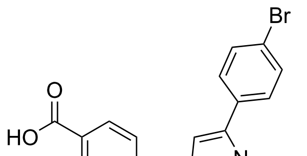
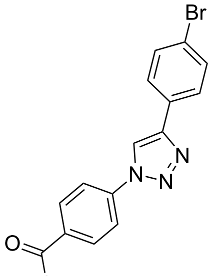
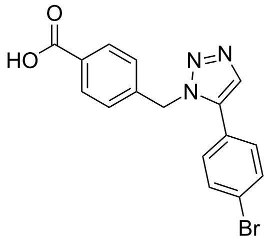
 **10g**	 **11g** (99%)	 **12b** (44%)	 **13b** (43%)
 **10h**	 **11h** (97%)	 **12c** (45%)	 **13c** (89%)
 **10i**	 **11i** (98%)	 **12d** (44%)	 **13d** (89%)
 **10j**	 **11j** (98%)	 **12e** (41%)	 **13e** (90%)
 **10k**	 **11k** (97%)	 **12f** (21%)	 **13f** (48%)

Table 2: Copper-catalyzed [2 + 3] cycloadditions of resin bound azide **7** with five terminal alkynes. Compounds **13**, with the exception of **13f**, were only characterized during compound library synthesis, by HPLC–MS analysis. (continued)

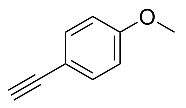
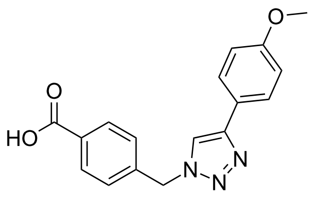
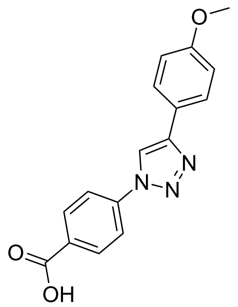
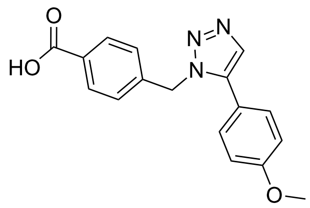
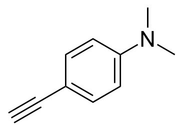
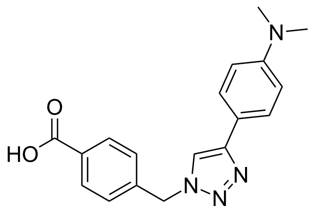
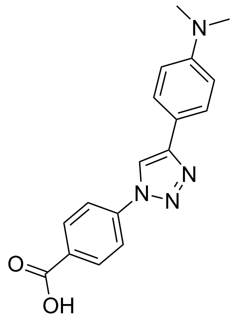
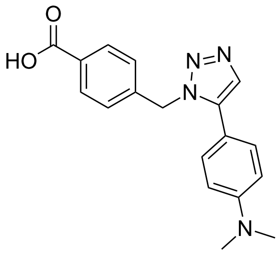
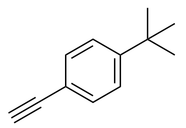
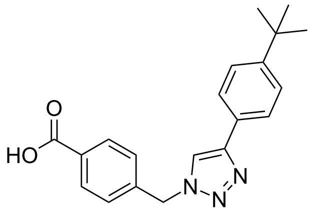
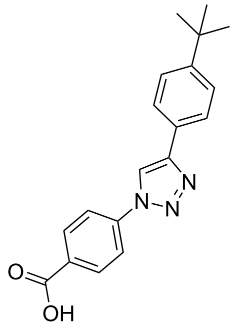
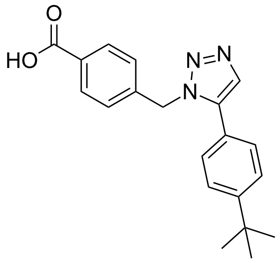
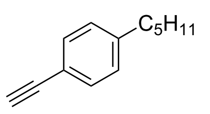
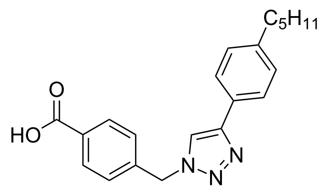
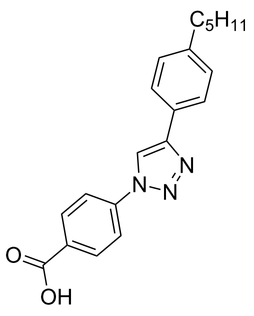
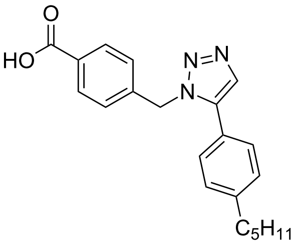
 **10l**	 **11l** (98%)	 **12g** (52%)	 **13g** (94%)
 **10m**	 **11m** (88%)	 **12h** (38%)	 **13h** (96%)
 **10n**	 **11n** (98%)	 **12i** (41%)	 **13i** (80%)
 **10o**	 **11o** (97%)	 **12j** (63%)	 **13j** (82%)

Table 2: Copper-catalyzed [2 + 3] cycloadditions of resin bound azide **7** with five terminal alkynes. Compounds **13**, with the exception of **13f**, were only characterized during compound library synthesis, by HPLC–MS analysis. (continued)

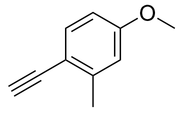
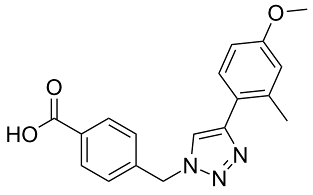
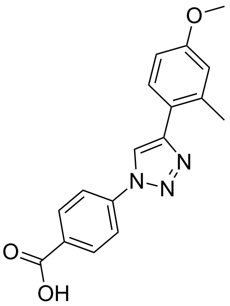
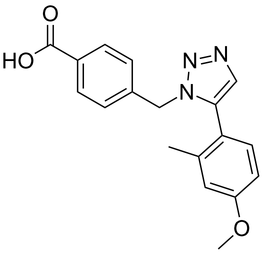
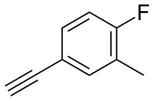
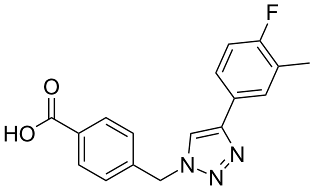
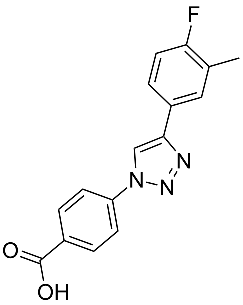
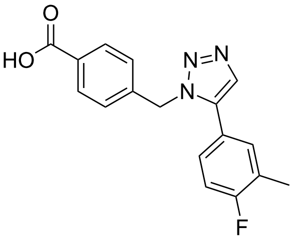
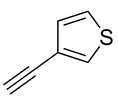
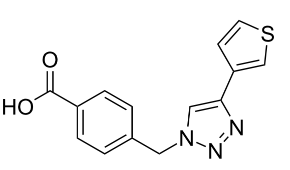
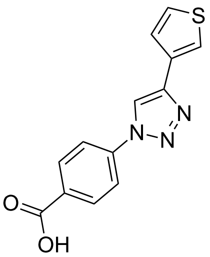
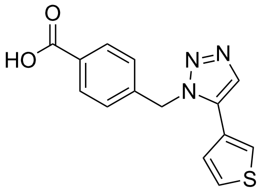
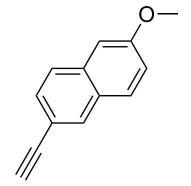
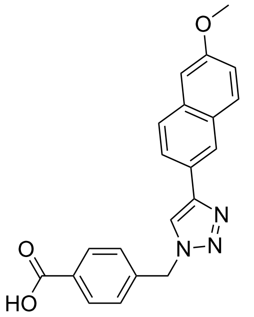
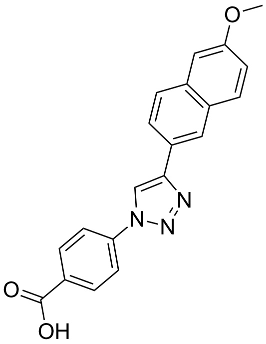
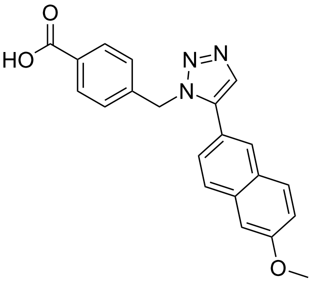
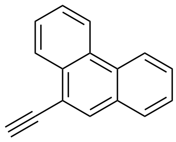
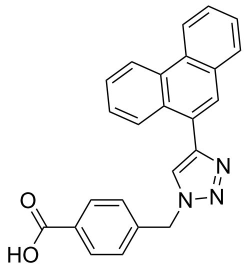
 **10p**	 **11p** (99%)	 **12k** (47%)	 **13k** (89%)
 **10q**	 **11q** (98%)	 **12l** (40%)	 **13l** (89%)
 **10r**	 **11r** (98%)	 **12m** (61%)	 **13m** (92%)
 **10s**	 **11s** (94%)	 **12n** (26%)	 **13n** (95%)

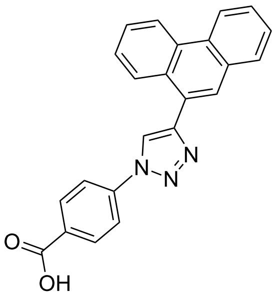
Table 2: Copper-catalyzed [2 + 3] cycloadditions of resin bound azide **7** with five terminal alkynes. Compounds **13**, with the exception of **13f**, were only characterized during compound library synthesis, by HPLC–MS analysis. (continued)



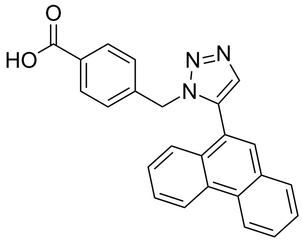
10t



11t (96%)



12o not obtained

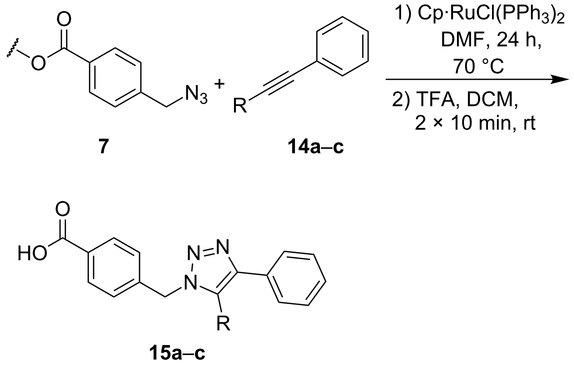


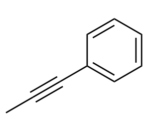
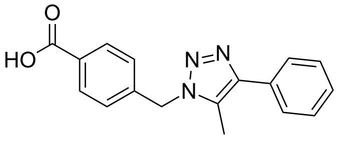
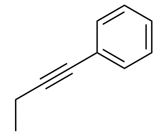
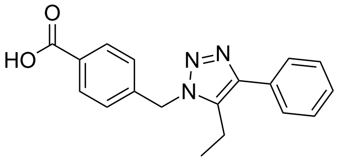
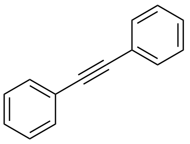
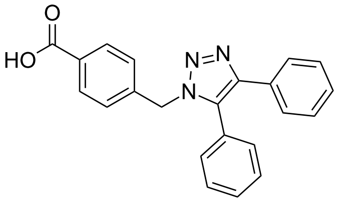
13o (74%)

former series of compounds. The formation of the compound **12o**, bearing a particularly bulky substituent, was not observed. Replacing the copper(I) catalyst by a ruthenium(II) complex allows the preparation of regioisomers in reaction 3. Instead of the 1,4-disubstituted triazoles obtained from copper(I) catalysis, the complex pentamethylcyclopentadienylbis(triphenylphosphine)ruthenium(II) chloride leads to 1,5-disubstituted triazole compounds [19]. 4-(Azidomethyl)benzoic acid functionalized Wang resin **7** and the alkynes **10f**–**t** were reacted in DMF at 70 °C overnight, and the products **13b**–**o** were obtained after TFA cleavage from the resin in moderate to good yields ranging from 43–96%. Only compound **13a** could not be obtained. The proton NMR analysis allows us to clearly distinguish between 1,4- and 1,5-disubstituted triazoles due to a characteristic shift of the triazole proton resonance. The triazole proton of the 1,4-disubstituted ring in compound **11k** shows a ^{1}H NMR resonance at δ = 8.71 (400 MHz, DMSO-d_6), while the resonance signal for the triazole proton of product **13f** is observed at δ = 8.00 (400 MHz, DMSO-d_6). Compounds **13**, with the exception of compound **13f**, were only characterized by mass spectrometry during the synthesis of the compound library.

The copper-mediated [2 + 3] cycloadditions are restricted to terminal alkynes. However, the ruthenium-catalysis allows the use of internal alkynes. In preliminary work, resin **7** was therefore reacted with internal alkynes **14a**–**c** and pentamethylcyclopentadienylbis(triphenylphosphine)ruthenium(II) chloride as catalyst in DMF at 70 °C overnight followed by TFA cleavage [20]. LC–MS analysis of the crude product revealed the formation of compounds **15a**–**c** in high yields of 78–98% (Table 3).

Table 3: Ruthenium-catalyzed [2 + 3] cycloadditions of resin-bound azide **7** with three disubstituted alkynes.



alkyne	product **15** (yield)^a
 **14a**	 **15a** (78%)
 **14b**	 **15b** (84%)
 **14c**	 **15c** (98%)

^{a}Yields based on LC–MS; compound **12b** was used as standard.

Conclusion

Diaryltriazoles were obtained in an efficient three-step solid-phase procedure. Immobilization of aromatic azides on commercial Wang resin followed by copper(I)- or ruthenium(II)-catalyzed 1,3-cycloaddition and subsequent cleavage of the product from the resin gave the target structures in good to excellent yields with the possibility to introduce a wide variety of different substituents. The alternative use of copper or ruthenium catalysis for the on-bead cycloaddition gives regioisomeric products, which extends the diversity of the compound collection. The method may find application in the combinatorial search for selective protein–protein inhibitors. To that end, most of the compounds prepared herein were submitted to the Molecular Libraries Small Molecular Repository for ongoing inclusion in high-throughput screening activities.

Experimental

General procedures

GP 1 – Coupling of benzoic acid derivatives 6 and 8 on Wang resin: Wang resin (1 equiv) was preswollen in dichloromethane (0.8 mL/100 mg resin) for 2 h at room temperature. Subsequently, both coupling reagents *N*,*N'*-diisopropylcarbodiimide (3.5 equiv) and dimethylaminopyridine (0.5 equiv) were added. After the addition of the benzoic acid derivative **6** or **8** (2.5 equiv) the reaction mixture was stirred for 20 h at room temperature. The resin was first washed with dimethylformamide, methanol and dichloromethane (each solvent 3 × 0.8 mL/100 mg resin), and then dried in high vacuum for 3 h.

GP 2 – Huisgen 1,3-dipolar cycloaddition of solid-phase-immobilized azides with terminal alkynes by copper(I) catalysis: An azide-functionalized Wang resin **7** or **9** (1 equiv) was preswollen in dimethylformamide (1.5 mL/100 mg resin) for 2 h at room temperature. The copper(I) catalyst was prepared in situ by using L-ascorbic acid (0.5 equiv) as reducing agent and copper(II) sulfate pentahydrate (10 mol %). After the terminal alkyne (4 equiv) was added, the reaction mixture was stirred for 22 h at room temperature. The resin was washed with dimethylformamide, methanol and dichloromethane (each solvent 2 mL/100 mg resin). The remaining copper cations were complexed and removed by using a solution of ethylenediaminetetraacetic acid disodium salt. For this purpose, a 1:1 mixture of dimethylformamide and disodium EDTA (aq., sat.) was added to the resin and stirred for 10 min at room temperature. Again washing steps with water, dimethylformamide, methanol and dichloromethane (each solvent 3 × 2 mL/100 mg resin) were carried out.

GP 3 – Huisgen 1,3-dipolar cycloaddition of solid-phase-immobilized azides with terminal or internal alkynes by ruthenium(II) catalysis: The azide functionalized Wang resin (1 equiv) was preswollen in dimethylformamide (2 mL/100 mg resin) for 2 h at room temperature. Subsequently, the catalyst complex pentamethylcyclopentadienylbis(triphenylphosphine)ruthenium(II) chloride, $Cp·RuCl(PPh_3)_2$, (5 mol %) and either a terminal or an internal alkyne (4 equiv) were added. After the reaction mixture was stirred for 22 h at 70 °C, the resin was washed with dimethylformamide, methanol and dichloromethane (each solvent 3 × 2 mL/100 mg resin).

GP 4 – Cleavage of solid-phase resin-bound molecules with TFA: The swollen resin was treated with a 1:4 mixture of trifluoroacetic acid and dichloromethane (1 mL/100 mg resin). After being stirred for 10 min at room temperature, the cleaved product was rinsed out of the resin using dichloromethane (1.5 mL/100 mg resin). The resin was treated once more with the 20% trifluoroacetic acid solution (1 mL/100 mg resin), stirred for 10 min at room temperature and washed with dichloromethane (3 × 1 mL/100 mg resin). The solvent was evaporated and the product was dried in high vacuum for 4 h.

4-(Azidomethyl)benzoic acid (6) [21]**:** The synthetic procedure leading to this literature-known compound was improved. 4-(Bromomethyl)benzoic acid (**5**, 1.2 g, 5.58 mmol, 1.0 equiv) and sodium azide (907 mg, 13.95 mmol, 2.5 equiv) were suspended in 25 mL of anhydrous dimethylformamide under a nitrogen atmosphere. After the reaction mixture was stirred for 15 h at 50 °C the solvent was evaporated. The colorless residue was dissolved in 90 mL of water and the solution was treated with 17 mL of hydrochloric acid (*c* 1 mol/L). The precipitate was separated with a Büchner funnel, dissolved in dichloromethane and dried over potassium sulfate. After filtration, and evaporation of the solvent, 4-(azidomethyl)benzoic acid (**6**, 880 mg, 4.97 mmol, 89%) was yielded as a colorless solid and dried in high vacuum overnight; mp 135.6–136.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (s, 2 H, H-6), 7.44 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-4), 8.14 (d, $^3J_{HH}$ = 8.3 Hz, 2H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.3 (−, 1C, C-6), 128.0 (+, 2C, C-4), 129.1 (C_q, 1C, C-2), 130.8 (+, 2C, C-3), 141.5 (C_q, 1 C, C-5), 171.4 (C_q, 1C, C-1); IR (cm^{-1}) $\tilde{\nu}$: 2933 (w), 2880 (w), 2817 (w), 2656 (w), 2110 (m), 2086 (m), 1950 (w), 1682 (s), 1293 (s), 1239 (s), 707 (s), 545 (s); EIMS *m/z*: 177.0 (40) $[M]^+$, 148.0 (80) $[M - N_2]^+$, 135.0 (100) $[M - N_3]^+$; Anal. calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.98; N, 23.72; found: C, 54.28; H, 4.25; N, 23.75.

Supporting Information

Supporting Information File 1

Experimental details and spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-115-S1.pdf]

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Synthesis and in silico screening of a library of β-carboline-containing compounds

Kay M. Brummond*[1], John R. Goodell[1], Matthew G. LaPorte*[1],
Lirong Wang[2] and Xiang-Qun Xie*[2]

Full Research Paper

Address:
[1]Department of Chemistry, Chemical Methodologies and Library Development, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA and [2]Department of Pharmaceutical Sciences and Computational Chemical Genomics Center, School of Pharmacy; Drug Discovery Institute; Department of Computational Biology; University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

Email:
Kay M. Brummond* - kbrummon@pitt.edu; Matthew G. LaPorte* - mgl12@pitt.edu; Xiang-Qun Xie* - xix15@pitt.edu

* Corresponding author

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Abstract

The synthesis of a library of tetrahydro-β-carboline-containing compounds in milligram quantities is described. Among the unique heterocyclic frameworks are twelve tetrahydroindolizinoindoles, six tetrahydrocyclobutanindoloquinolizinones and three tetrahydrocyclopentenoneindolizinoindolones. These compounds were selected from a virtual combinatorial library of 11,478 compounds. Physical chemical properties were calculated and most of them are in accordance with Lipinski's rules. Virtual docking and ligand-based target evaluations were performed for the β-carboline library compounds and selected synthetic intermediates to assess the therapeutic potential of these small organic molecules. These compounds have been deposited into the NIH Molecular Repository (MLSMR) and may target proteins such as histone deacetylase 4, endothelial nitric oxide synthase, 5-hydroxytryptamine receptor 6 and mitogen-activated protein kinase 1. These in silico screening results aim to add value to the β-carboline library of compounds for those interested in probes of these targets.

Introduction

Identification of a comprehensive set of small organic molecules capable of selectively modifying the function of biological targets tremendously impacts modern medical research and drug discovery efforts [1]. Currently, this set of small molecules is largely occupied by in-house libraries and commercially available compounds. The NIH Roadmap initiative was established to address a recognized limitation of current compound diversity resulting in the Molecular Libraries Probe

Centers Network (MLPCN) which has, since its inception, garnered a library of over 370,000 chemically diverse small molecules in a central molecule repository [2]. This supply of compounds has been made possible by researchers across the disciplines, but largely by synthetic chemists who are preparing compounds with an eye towards biologically relevant targets. Another goal of the NIH Roadmap is the development of enabling methods for the synthesis of these structurally diverse compound libraries; amongst these methods, skeletal diversification strategies have emerged as particularly efficient for maximizing structural diversity [3].

Previous work in the Brummond laboratory has demonstrated that an allene-containing β-carboline provided a good starting point for synthesizing six novel types of hetero-frameworks, all skeletally unique [4]. Moreover, scope and limitation studies contributed to an understanding of chemistries that would possess the robustness necessary for library preparation. Information gained from these experiments was then utilized in the construction of a virtual library of 11,748 compounds. A diversity analysis was performed using B (Burden) C (CAS) UT (Pearlman at the University of Texas) metrics and Tanimoto coefficients (Tc) and this virtual compound library was mapped onto the existing chemical space of the NIH Molecular Libraries Small Molecule Repository (MLSMR) [4]. When considering the physical properties most important to bimolecular interactions, atomic Gasteiger–Hückel charges, polarizabilities, and hydrogen-bond acceptors, these virtual compounds were found to occupy new chemical space when compared to the 327,000 compounds in the MLSMR. A small subset of these compounds was subsequently identified as ones representing a maximally diverse chemical space. The synthesis of a modified subset of this virtual compound library is described within, where modifications were mainly driven by studies of compound stability. Furthermore, a high throughput, in silico screening analysis of this library identified a number of potential biological targets for the compounds.

Results and Discussion

Scaffolds **1**, **2** and **3** (Figure 1) were chosen for library preparation based upon favorable Tanimoto coefficient (Tc) scores when compared to the MLSMR, conformational constraints imposed by the β-carboline moiety, and the number of building blocks available for the diversifying elements R^1 and R^2.

The syntheses of tetrahydro-β-carbolines **6{1–16}** were accomplished in a manner entirely analogous to that reported previously (Table 1, entries 1–16) [4]. For example, the allenic methyl ester of tryptophan **4** was reacted with a number of aldehydes **5{1–15}** under acidic conditions to produce the corresponding products in yields ranging from 54–89%. A range of aldehydes were accommodated in the Pictet–Spengler reaction, including formaldehyde (Table 1, entry 1), alkyl aldehydes (Table 1, entries 2 and 3), aryl aldehydes with electron-withdrawing and electron-donating groups (Table 1, entries 4–7, 14 and 15), heteroaromatic aldehydes (Table 1, entries 8–13) and glyoxalates (Table 1, entry 16). Moreover, useful quantities of β-carboline-containing products were obtained (43–100 mg). For entries 2–15, mixtures of two diastereomers were obtained. Since the mixtures could not be readily separated by column chromatography, diastereomeric ratios were determined by ^{1}H NMR and were advanced without further purification. Reaction of allene **6** under the silver-nitrate-mediated cyclization conditions afforded the desired fused pyrrolines **1**. However, in the initial phases of this cyclization process, a color change was noted during the purification process. Indeed, when NMR stability studies were performed on the syn- and anti-pyrrolines **1{5}**, decomposition of both diastereomers was evident. Although it was generally difficult to isolate the individual diastereomers, they could be separated by column chromatography. It was found that anti-**1{5}** decomposed more rapidly than syn-**1{5}** during the ^{1}H NMR stability studies, when compared to an internal standard. These results combined with previously reported skeletal reorganization processes of functionalized β-carbolines, led to concerns about the long-term storage of these compounds and their inclusion in the MLSMR [5].

To increase the stability of this class of compounds, a toluenesulfonyl group was added to the indole nitrogen of **1{1–7}** to give *N*-tosyl-tetrahydro-β-carbolinepyrroline derivatives **7{1–7}**. These tosylated derivatives exhibited improved stability as evidenced by ^{1}H NMR (Table 1, entries 1–7, and Supporting Information File 1, S76–S81). Incorporation of the tosyl group

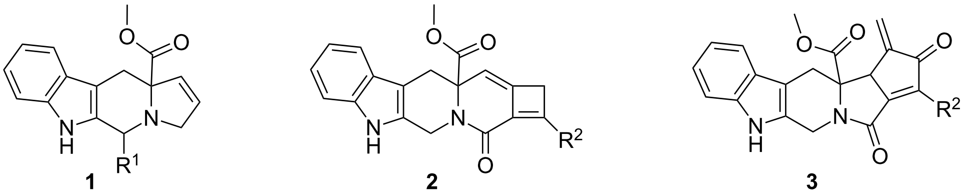
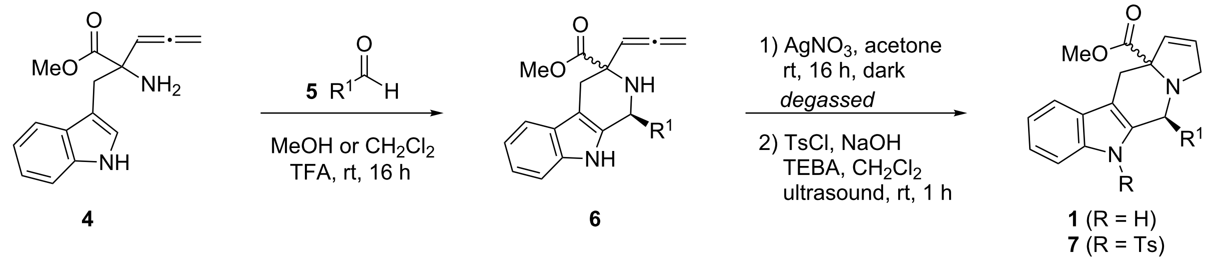


Figure 1: Tetrahydro-β-carboline containing scaffolds **1–3**.

Table 1: Library of *N*-tosyltetrahydro-β-carbolinepyrrolines **7{1–7}**.



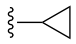
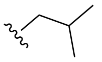
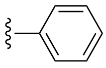
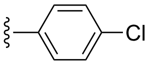
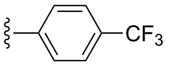
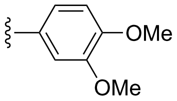
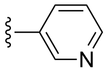
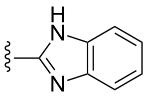
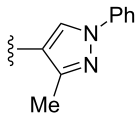
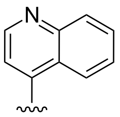
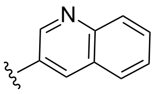
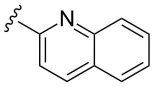
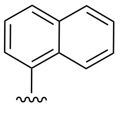
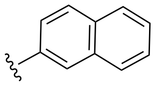
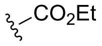
entry	R^1		yield of **6**^{a} (%)	anti:syn^b	yield of **7**^{a} (%)	purity^c
1	–H	**5{1}**	68 **6{1}**	NA	28 **7{1}**	98%
2		**5{2}**	74 **6{2}**	2.5:1	17 syn-**7{2}**	98%
3		**5{3}**	81 **6{3}**	2.1:1	23 syn-**7{3}**	98%
4		**5{4}**	73 **6{4}**	2.4:1	11 anti-**7{4}** 28 syn-**7{4}**	98% 98%
5	 Cl	**5{5}**	75 **6{5}**	2.4:1	34 anti-**7{5}** 17 syn-**7{5}**	98% 98%
6	 CF$_3$	**5{6}**	74 **6{6}**	1.3:1	35 anti-**7{6}** 10 syn-**7{6}**	98% 98%
7	 OMe OMe	**5{7}**	54 **6{7}**	2.7:1	12 anti-**7{7}** 17 syn-**7{7}**	98% 98%
8	 N	**5{8}**	89 **6{8}**	2.3:1	ND^d	
9	 H N N	**5{9}**	78 **6{9}**	1.2:1	ND^e	
10	 Ph N N Me	**5{10}**	80 **6{10}**	1:1.1	ND^d	
11	 N	**5{11}**	70 **6{11}**	1.3:1	ND^e	
12	 N	**5{12}**	80 **6{12}**	3.5:1	ND^e	
13	 N	**5{13}**	63 **6{13}**	1:1.4	ND^e	
14		**5{14}**	58 **6{14}**	2.3:1	ND^d	

Table 1: Library of *N*-tosyltetrahydro-β-carbolinepyrrolines **7{1–7}**. (continued)

15		**5{15}**	80 **6{15}**	2.3:1	ND[d]	
16		**5{16}**	88 **6{16}**	1.4:1	8 syn-**1{16}**	99%

[a]Isolated yields; [b]dr determined by ^{1}H NMR; [c]purity established by LCMS/ELS; [d]compound **6** detected; [e]compound **6** not detected.

also eased the chromatographic separation of the syn- and anti-isomers for entries 2–7, thus compounds **7{2–7}** were obtained as single diastereomers. Low to moderate yields for this two-step reaction sequence were attributed to a problematic tosylation due to the sterically hindered nature of the indole nitrogen atom. Moreover, unforeseen limitations were encountered for the heteroaromatic and naphthyl-containing β-carboline intermediates (Table 1, entries 8–15). While in some cases the intermediate pyrrolines **1** were observed (Table 1, entries 8, 10, 14, 15), the corresponding tosylated products were not obtained. The heteroaromatic examples (Table 1, entries 9, 11–13), did not undergo cyclization upon treatment with silver nitrate. For these cases, it was assumed that competing coordination of the heteroatom to the silver ion was an issue; however, attempts were not made to alter the reaction conditions for these substrates. Furthermore, conversion of the naphthalene-containing analogues **1{14}** and **1{15}** to their corresponding tosylates was not successful.

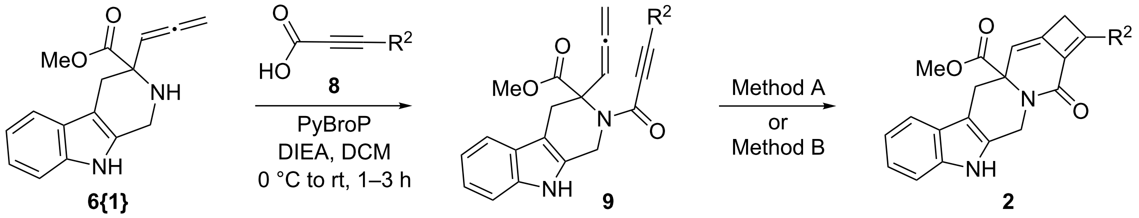
Next, compounds possessing the cyclobutene-fused β-carboline skeleton were assembled from the versatile allenyl intermediate **6**. For this subset of compounds, acylation of the sterically hindered amine of **6{1}** with the ynoic acids **8{1–8}**, by using bromo-tris-pyrrolidino-phosponium hexafluorophosphate (PyBroP), provided the requisite allene-yne substrates **9{1,2}**–**9{1,8}**. For the coupling reaction of the ynoic acids with an aryl group on the terminus of the alkyne **8{5–8}**, the desired allene-ynes **9{1,5}**–**9{1,8}** were afforded along with the [2 + 2] cycloadducts **2{1,5}**–**2{1,8}** (Table 2, entries 5–8). Previous studies with related tryptophan-substituted allene-ynes, required much higher temperatures (225 °C versus rt) to give the [2 + 2] cycloadducts, albeit none of these examples possessed two radical stabilizing groups on the alkyne. Because the calculations performed by Tantillo [6] regarding the thermal [2 + 2] cycloaddition reaction suggest that the energy barrier for this reaction should not be effected by the presence of two radical stabilizing groups over one, it was postulated that this cycloaddition process was facilitated by exposure to incident light [7]. Thus, the mixtures of compounds **2** and **9** were reconstituted in CH_2Cl_2 and placed in front of two 6 W UV lamps for 16 h at rt to afford the desired cyclobutenes (Method B, Table 2, entries 5–8). During optimization of the conditions for the [2 + 2] cycloaddition reaction (Method A), it was found that reducing the reaction temperature from 225 °C to 160 °C afforded cyclobutene **2{1,3}** in 73% yield (Table 2, entry 3). Similarly, allene-yne **9{1,5}** was subjected to the lower reaction temperature (Method A) to produce cyclobutene **2{1,5}** in 57% yield (Table 2, entry 5).

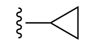
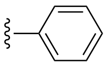
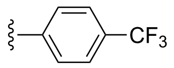
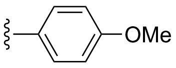
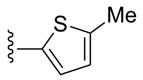
For the final library scaffold, a small subset of α-methylenecyclopentenone-containing tetrahydro-β-carbolines was synthesized. These compounds contain a general substructure that has recently been shown to inhibit DNA damage checkpoints [8]. Allene-ynes **9{1,3}**–**9{1,4}** undergo Pauson–Khand cyclocarbonylation reactions when treated with molybdenum hexacarbonyl in DMSO/toluene solutions (Table 3). Allene-yne **9{1,2}** afforded a mixture of four compounds comprising two diastereomers of **3{1,2}**, the 4-alkylidene cyclopentenone, resulting from the cyclocarbonylation reaction with the distal double of the allene, and a fourth compound, which could not be identified (see spectral data in Supporting Information File 1). Aryl-substituted alkynones **9{1,5}**–**9{1,8}** were not available for the molybdenum-mediated cyclocarbonylation process due to competing [2 + 2] cycloaddition reactions (Table 2).

The majority of these β-carboline-containing products exhibit acceptable calculated physical–chemical properties in accordance with Lipinski's rule of five (Figure 2) [9,10]. These favorable properties and structural novelty make these valuable candidates for deposition in the MLSCN for biological activity evaluation.

Diversity-oriented synthesis (DOS) has been employed to generate thousands of the organic compounds that have been deposited in the NIH molecular repository for medicinal chemistry research. Deciphering the therapeutic potential of this many compounds is a continuing challenge. By combining chemogenomics databases, such as Protein Data Base (PDB) and ChEMBL, it is possible to map new compounds into existing chemical space and to predict protein targets for new compounds, for which there are two complementary strategies that can be implemented. One is a structure-based docking

Table 2: Library of tetrahydro-β-carbolinecyclobutenes **2{1,3}–2{1,8}**.

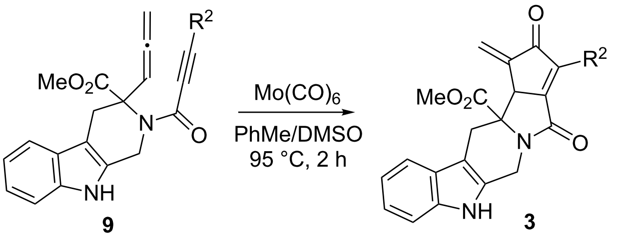


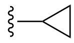
entry	R^2		yield of **9**[a] (%)	method[b]	yield of **2**[a] (%)	purity[c]
1	⌇–H	**8{1}**	0 **9{1,1}**	—	—	—
2	⌇–TMS	**8{2}**	64 **9{1,2}**	A	ND[d]	—
3	⌇–Me	**8{3}**	75[e] **9{1,3}**	A	73 **2{1,3}**	99%
4		**8{4}**	71 **9{1,4}**	A	57 **2{1,4}**	99%
5		**8{5}**	**9{1,5}** **2{1,5}**	A B	57[f] **2{1,5}** 40 **2{1,5}**	99%
6		**8{6}**	**9{1,6}** **2{1,6}**	B	41 **2{1,6}**	99%
7		**8{7}**	**9{1,7}** **2{1,7}**	B	30 **2{1,7}**	99%
8		**8{8}**	**9{1,8}**	B	33 **2{1,8}**	99%

[a]Isolated yield; [b]method A: µW, 160 °C, DMF, 10 min; method B: Placed in front of two 6 W UV lamps (245 nm), CH_2Cl_2, rt, 16 h, no stirring; [c]purity established by LCMS/ELS; [d]ND = not detected; [e]µW, 225 °C, DMF, 7 min, (39%); [f]separated **9{1,5}** (57% yield) from **2{1,5}** (18% yield) after the coupling reaction then submitted **9{1,5}** to method A to give **2{1,5}** in 68% yield. This compound was recombined with the previously isolated **2{1,5}** to afford a combined 57% yield.

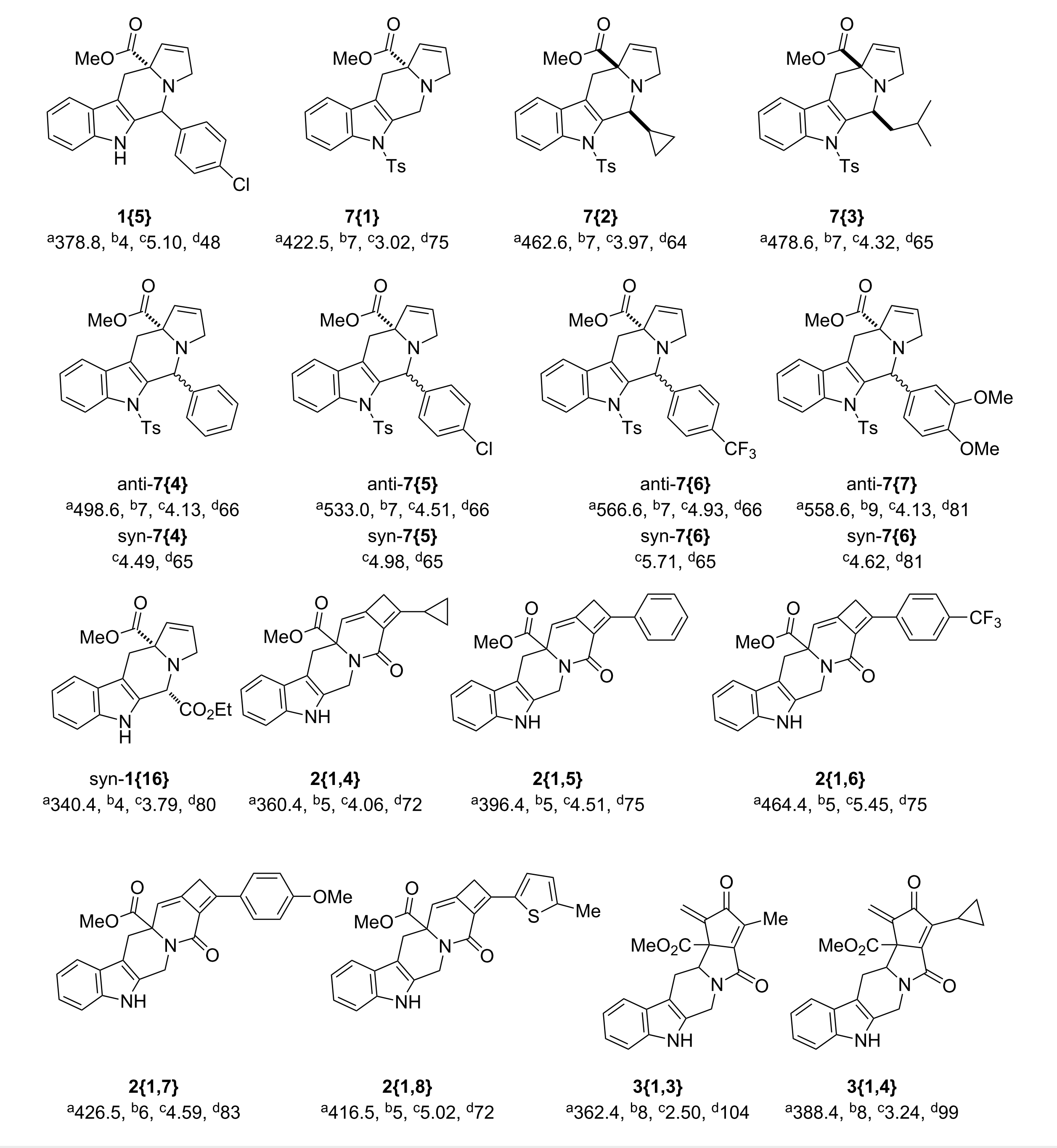
strategy, in which a query compound is fit into a series of protein binding pockets to identify favorable compound–protein interactions. A second approach is a ligand-based strategy in which the structural similarities between a query compound and a collection of bioactive compounds are identified. In the present study, both of these strategies were used to predict potential targets of the newly synthesized library of β-carboline-containing compounds.

Table 3: Synthesis of α-methylenecyclopentenone library **3{1,3}–3{1,4}**.



entry	R^2		yield of **3**[a] (%)	purity[b]
1	⌇–Me	**9{1,3}**	48 **3{1,3}**	99%
2		**9{1,4}**	46 **3{1,4}**	99%

[a]Isolated yields; [b]purity determined by LCMS/ELS.



1{5}
[a]378.8, [b]4, [c]5.10, [d]48

7{1}
[a]422.5, [b]7, [c]3.02, [d]75

7{2}
[a]462.6, [b]7, [c]3.97, [d]64

7{3}
[a]478.6, [b]7, [c]4.32, [d]65

anti-**7{4}**
[a]498.6, [b]7, [c]4.13, [d]66
syn-**7{4}**
[c]4.49, [d]65

anti-**7{5}**
[a]533.0, [b]7, [c]4.51, [d]66
syn-**7{5}**
[c]4.98, [d]65

anti-**7{6}**
[a]566.6, [b]7, [c]4.93, [d]66
syn-**7{6}**
[c]5.71, [d]65

anti-**7{7}**
[a]558.6, [b]9, [c]4.13, [d]81
syn-**7{6}**
[c]4.62, [d]81

syn-**1{16}**
[a]340.4, [b]4, [c]3.79, [d]80

2{1,4}
[a]360.4, [b]5, [c]4.06, [d]72

2{1,5}
[a]396.4, [b]5, [c]4.51, [d]75

2{1,6}
[a]464.4, [b]5, [c]5.45, [d]75

2{1,7}
[a]426.5, [b]6, [c]4.59, [d]83

2{1,8}
[a]416.5, [b]5, [c]5.02, [d]72

3{1,3}
[a]362.4, [b]8, [c]2.50, [d]104

3{1,4}
[a]388.4, [b]8, [c]3.24, [d]99

Figure 2: Library of tetrahydro-β-carboline containing compounds **1–7** and calculated properties ([a]molecular weight; [b]hydrogen-bond donor/acceptors; [c]cLogP; [d]polar surface area (PSA)).

High-throughput docking studies for protein-target prediction of newly synthesized compounds

Molecular docking studies were performed with the 34 newly synthesized compounds, represented by scaffolds **1**, **2**, **3**, and allenyl precursors **4**, **6{1–16}**, **9{1–4}** to identify potential protein targets [11]. Protein structures were downloaded from the PDB [12] and the analysis was limited to a selection of the 607 proteins defined as “druggable” targets, in order to reduce computational time [13]. (The complete listing of these proteins and their PDB IDs are provided in Supporting Information File 2). The Surflex-dock module of the Sybyl software was employed for protein preparation and docking of the β-carboline library [14,15]. Water molecules and ligands were removed from the protein structures and the active site of each protein was defined by the corresponding residues around the cocrystallized ligands. In-house algorithms were used to evaluate ligand-docking efficiency, and docking scores were used to assess and rank the protein targets.

A portion of the protein-scoring matrix is illustrated in Figure 3. Several interesting results emerged from this in silico analysis: (1) Twenty of the new compounds have docking scores greater

PDB ID	**A**	**4**	**7{1}**	**7{7}**	**2{1,3}**	**2{1,4}**	**2{1,5}**	**2{1,6}**	**2{1,7}**	**2{1,8}**
1nuh	7.23	6.45	-4.46	-25.14	3.98	3.49	5.4	3.91	6.17	1.79
1i7b	3.07	7.32	1.74	0.9	4.6	5.28	4.24	3.49	3.84	2.66
2xfo	-0.07	7.29	-4.96	-12.59	-4.95	2.88	1.81	-0.33	0.45	0.99
1d4l	5.78	7.17	3.06	3.08	3.68	3.55	3.31	4.98	3.19	2.29
2vgb	3.13	7.14	-7.1	-17.8	2.7	1.92	0.96	-0.13	-2.08	0.68
2qro	4.7	7.06	-21.42	-51.03	-3.69	-2.23	-2.36	-9.21	-13.18	-7.52
3gqy	4.98	4.96	7.75	0.67	3.66	4.38	3.3	0.84	-1.85	1.54
2vqq	5.24	5.07	1.31	7.14	6.74	7.59	7.69	7.85	7.99	7.03
1s9i	3.99	5.26	3.84	0.35	7.44	5.09	3.03	4.32	3.52	2.15
2q6b	4.76	5.49	5.15	-5.63	7	6.03	7.92	4.47	3.92	2.84
2v3e	4.93	4	2.54	-4.43	5.43	5.3	7.23	7.54	7.46	5.96
2vgq	5.04	6.27	3.42	1.9	3.76	3.87	4.02	7.95	4.35	3.04
3hhm	4.5	4.01	2.4	1.95	3.97	5.42	6.65	7.63	2.71	3.73
3hdn	4.39	4.22	3.63	1.21	2.68	2.86	2.29	7.56	6.14	1.92
3g7w	3.89	5.77	3.31	1.84	4.92	3.97	5.2	7.27	4.8	4.43
3eqc	6.69	5.33	1.59	-0.93	4.39	6.36	5.13	7.08	7.15	6.95
3fwl	5.9	4.39	1.99	1.97	4.03	4.07	6.34	5.18	7.04	3.96
1so2	5.05	6.12	2.3	1.88	6.34	4.21	5	6.2	5.29	7.22

PDB ID	**2{1,8}**	**3{1,4}**	**6{3}**	**6{4}**	**6{6}**	**6{7}**	**6{9}**	**6{10}**	**6{12}**	**6{13}**	**6{15}**
1d4l	2.29	3.02	3.26	3.55	4.55	3.51	5.15	4.83	7.3	5.22	4.1
1so2	7.22	3.84	3.84	6.32	7.25	6.08	8.17	5.78	6.15	5.77	6.43
3ljr	5.45	7.11	3.35	4.66	0.33	3.81	3.33	1.63	4.32	6.29	4.81
2zv2	2.53	3.45	7.37	3.36	2.02	2.83	1.37	4.2	2.05	4.38	1.75
2on3	2.58	2.8	2.13	7	3.02	6.2	4.17	-1.13	3.28	3.84	1.65
3fxw	2.59	3.47	3.09	5.02	5.39	7.65	5.13	4.53	5.69	5.94	3.08
3mhj	-5.26	3.16	3.5	2.03	6.9	7.17	4.23	3.44	6.6	5.53	6.17
1pq6	-1.13	-1.86	6.35	5.8	4.46	6.91	7.57	8.28	6.32	7.02	6.15
1t40	2.37	2.74	2.84	3.52	4.09	5.66	4.64	8.75	6.17	1.69	5.43
3ipq	-9.79	-3.95	5.21	5.47	4.69	6.55	6.9	8.65	5.44	4.37	6
2gvj	4.43	3.1	3.32	4.13	4.67	3.63	3.15	8.47	-7.88	4.49	4.3
1dgh	-1.94	4.06	5.08	4.02	4.75	4.15	6.06	7.74	3	7.17	3.27
3nos	4.35	2.27	3.31	3.84	6.79	6.67	3.47	7.35	7.27	5.18	7.6
1og5	5.8	4.21	3.96	5.08	5.07	5.91	5.92	7.24	5.31	4.78	5.7
1nf7	2.59	3.62	4.63	4.75	-1.19	4.97	0.46	7.21	-5.03	4.8	-1.1
1lpg	3.07	2.38	2	4.86	4.09	2.75	4.45	4.57	5.52	7.01	2.96

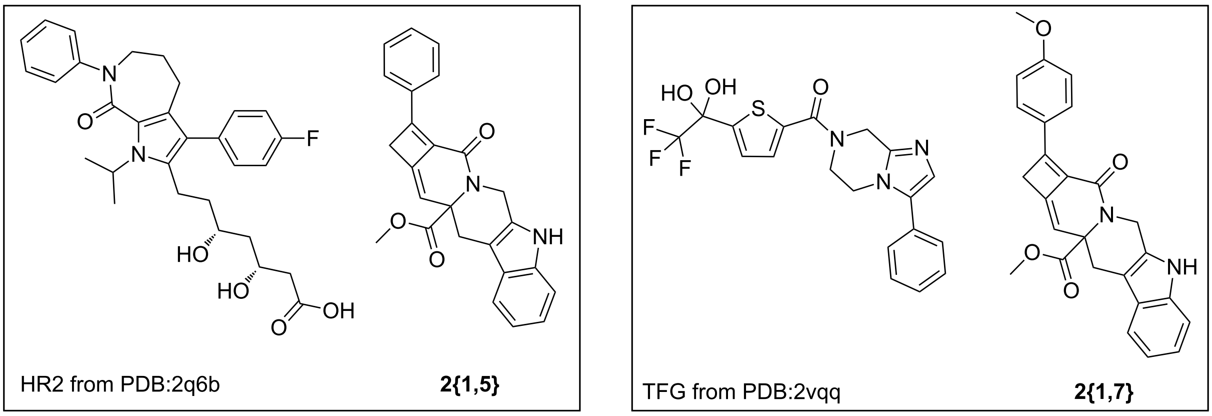


Figure 3: Results of high-throughput docking analysis. Top: A docking-score matrix arranged by compound IDs and PDB IDs; bottom: Structures of known ligands HR2 and TGF and the newly synthesized compounds **2{1,5}** and **2{1,7}**. Docking scores larger than 7.0 are red colored and can be mapped to K_d values less than 100 nM. The corresponding protein names of PDB IDs and the full docking-score matrix are listed in Supporting Information File 1.

than 7.0, a number that can be mapped to K_d values less than 100 nM, for several protein targets; (2) six compounds, **7{7}** and **2{1,4–1,8},** are predicted to be ligands for a single protein, human HDAC4 (PDBID:2vqq); (3) compounds **2{1,5}** and **2{1,7}** are predicted to be high-affinity ligands for 3-hydroxy-3-methylglutaryl-coenzyme A, reductase (PDBID:2q6b) and HDAC4, respectively, even though they are structurally different from the corresponding cocrystallized ligands HR2 and TGF; and (4) compounds **2{1,6}** and **6{10}** are predicted to be ligands for a total of 15 protein targets. This high number of potential protein targets may be due to the electronegative trifluoromethyl group on **2{1,6}** and the effect it would have on the α,β-unsaturated amide and the purported bioactivity of the pyrazole group of **6{10}**.

Ligand-based strategy for target prediction

Ligand-based target prediction algorithms have been developed based upon an established medicinal chemistry principle that structurally similar compounds, with comparable physical properties, should convey related biological properties [16,17]. In this study, structural similarities were calculated between the compounds of the β-carboline library and the bioactive compounds in the well-annotated database, ChEMBL version 13, the largest publicly available compound-target database, containing 1,143,682 distinct compounds, 8,845 targets and 6,933,068 bioactivity entries from 44,682 publications and PubChem bioassays [18,19]. The Openbabel FP2 fingerprint was used as a descriptor to assess similarities between molecules [20]. Tanimoto coefficients were calculated between the compounds of the β-carboline library and the ChEMBL database, and only β-carboline compounds with a Tc greater than 0.60 were considered for bioactivity analysis. A lower Tc threshold was used to identify a larger number of bioactivity targets. Table 4 lists the most promising bioactive targets for the newly synthesized β-carbolines together with the structurally similar lead compounds in ChEMBL along with their reported potency and literature citations. Several interesting results emerge from the comparison study performed, including a number of targets that the compounds should be screened against, such as C–C chemokine receptor type 3, gamma-

Table 4: Potential targets of β-carbolines based upon bioactivity data in ChEMBL.

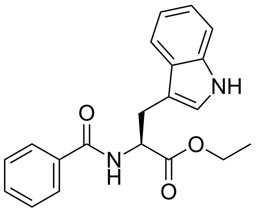
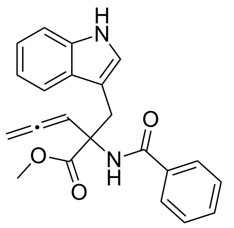
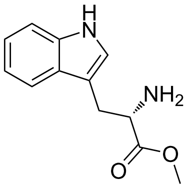
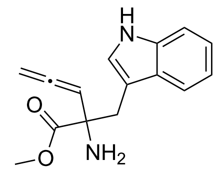
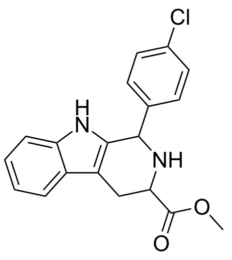
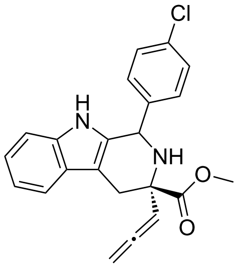
target	CHEMBL compound	bioactivity type and reference	our compound	similarity score
C–C chemokine receptor type 3	 CHEMBL33838	IC_{50} = 325 nM [21]	 **A**	0.79
Leishmania donovani	 CHEMBL55830	IC_{50} = 1.42 μM [22]	 **4**	0.80
Acanthocheilonema viteae	 CHEMBL44573	Activity = 94% [23]	 **6{5}**	0.86

Table 4: Potential targets of β-carbolines based upon bioactivity data in ChEMBL. (continued)

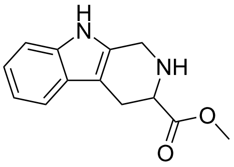
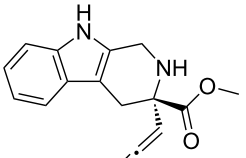
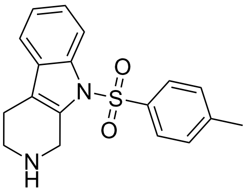
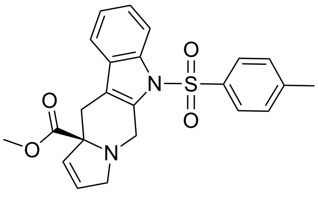
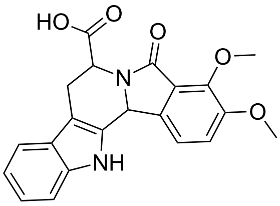
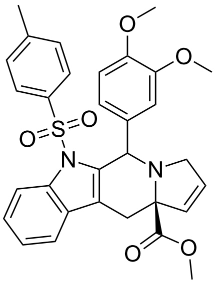
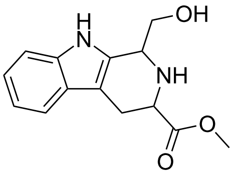
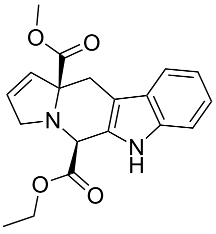
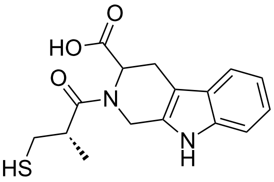
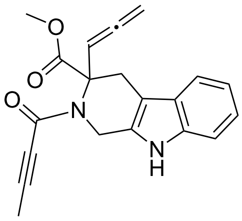
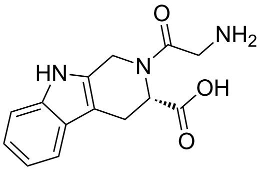
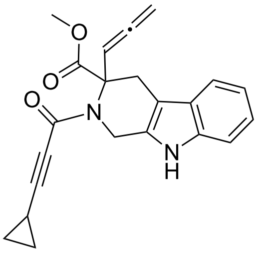
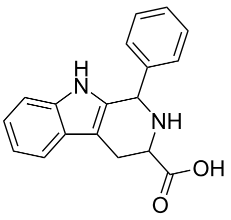
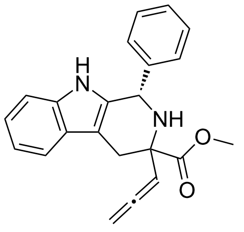
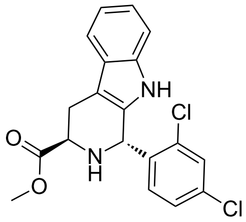
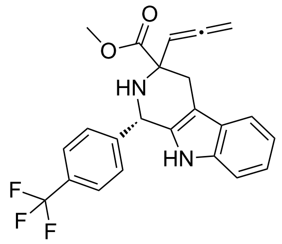
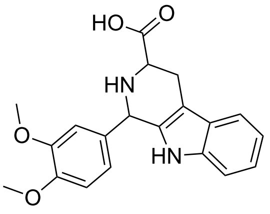
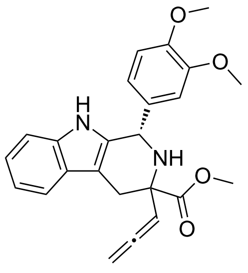
Gamma-aminobutyric acid receptor subunit gamma-2	 CHEMBL358326	IC_{50} = 250 nM [24]	 **6{1}**	0.84
5-Hydroxytryptamine receptor 6	 CHEMBL370935	K_i = 271.3 nM [25]	 **7{1}**	0.69
3-Hydroxyacyl-CoA dehydrogenase type-2	 CHEMBL1382101	Potency = 31.6 µM PubChem AID:893	 **7{7}**	0.64
Benzodiazepine receptors	 CHEMBL11901	K_i = 510 nM [26]	 **1{16}**	0.72
Angiotensin-converting enzyme	 CHEMBL148616	IC_{50} = 500 nM [27]	 **9{1,3}**	0.71
Antithrombotic potency	 CHEMBL1089460	IC_{50} = 8.56 nM [28]	 **9{1,4}**	0.69

Table 4: Potential targets of β-carbolines based upon bioactivity data in ChEMBL. (continued)

Mitogen-activated protein kinase 1	 CHEMBL44295	Potency = 0.794 μM PubChem AID:995	 **6{4}**	0.82
Breast adenocarcinoma cells	 CHEMBL1650665	Inhibition = 78% [29]	 **6{6}**	0.79
DNA polymerase iota	 CHEMBL1360719	Potency = 1.78 μM PubChem AID:588590	 **6{7}**	0.85

aminobutyric acid receptor subunit gamma-2, breast adenocarcinoma cells, 5-hydroxytryptamine receptor 6, angiotensin-converting enzyme, and DNA polymerase iota. Moreover, nine of the twelve compounds are represented by allene precursors, ones that were not originally considered in the diversity analysis.

Conclusion

A library of 34 β-carboline-containing compounds was synthesized utilizing a skeletal diversification strategy. High-throughput docking and ligand-based protocols were implemented to predict potential biological targets of the newly synthesized β-carbolines. The docking approach uses a structure-based technology to predict preferred interactions between compounds and protein targets, whereas the ligand-based method uses ligand similarity coefficients to identify potential biological targets. The complementary nature of these two protocols is evidenced by the fact that there was no overlap in the predicted biological targets. Furthermore, the in silico screening of these compounds is intended to add value to the library, by directing them to appropriate biological assays. Such strategies can also be used to explore the mechanisms of a biologically active compound in bioassays whose molecular target is as of yet unidentified.

Supporting Information

Supporting Information File 1

Experimental procedures and spectral data for compounds **1{5}**, **1{16}**, **2{1,3–8}**, **3{1,2–4}**, **4**, **6{1–10}**, **6{12–13}**, **6{15}**, **7{1–7}**, **9{1,2–4}**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-117-S1.pdf]

Supporting Information File 2

The complete listing of the proteins and their PDB IDs (Targets Docking Score Matrix).
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-117-S2.xls]

Acknowledgements

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Synthesis of a library of tricyclic azepinoisoindolinones

Bettina Miller, Shuli Mao, Kara M. George Rosenker, Joshua G. Pierce and Peter Wipf*

Full Research Paper

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Address:
Center for Chemical Methodologies & Library Development (CMLD), Department of Chemistry, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, PA 15260, USA

Email:
Peter Wipf* - pwipf@pitt.edu

* Corresponding author

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Abstract

Hydrozirconation of 1-hexyne, the addition to in situ prepared *N*-acyliminium species, and ring-closing metathesis (RCM) were key steps in the preparation of a tricyclic isoindolinone scaffold. An unusual alkene isomerization process during the RCM was identified and studied in some detail. Chemical diversification for library synthesis was achieved by a subsequent alkene epoxidation and zinc-mediated aminolysis reaction. The resulting library products provided selective hits among a large number of high-throughput screens reported in PubChem, thus illustrating the utility of the novel scaffold.

Introduction

Isoindolinones represent a common scaffold seen in naturally occurring compounds such as magallanesine [1], lennoxamine [2] and clitocybin A [3], or drug candidates such as pagoclone [4] (Figure 1). These heterocycles have demonstrated a variety of pharmacological activities, including anti-inflammatory [5], antihypertensive [6] and vasodilatory [7], antipsychotic [8,9], and anticancer effects [10]. Due to the broad biological properties and the general utility of isoindolinones in the preparation of other synthetic building blocks, a variety of approaches for the preparation of these heterocycles have been explored [11-18]. Previously, we reported on the addition of organometallic reagents to in situ generated *N*-acyliminium ions [19]. This methodology applies to a variety of commercially available or easily prepared starting materials and creates many opportunities for further functionalization and chemical library synthesis. For example, a ring-closing metathesis of the alkene addition product affords structurally novel tricyclic isoindolinones with a newly formed seven-membered ring [19]. We have now developed this concept further toward a library synthesis of functionalized azepino-isoindolinone derivatives.

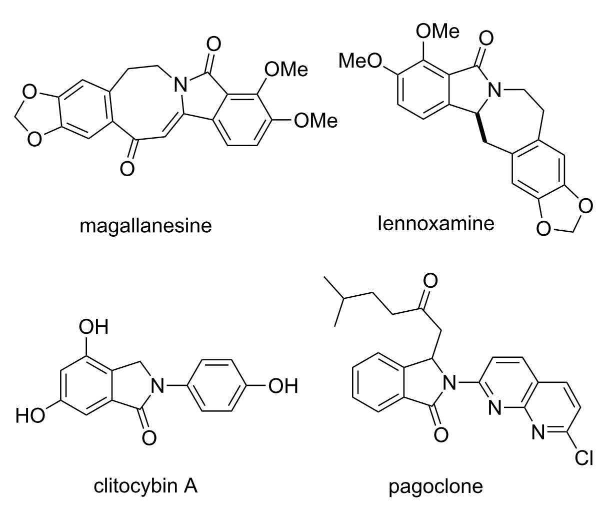


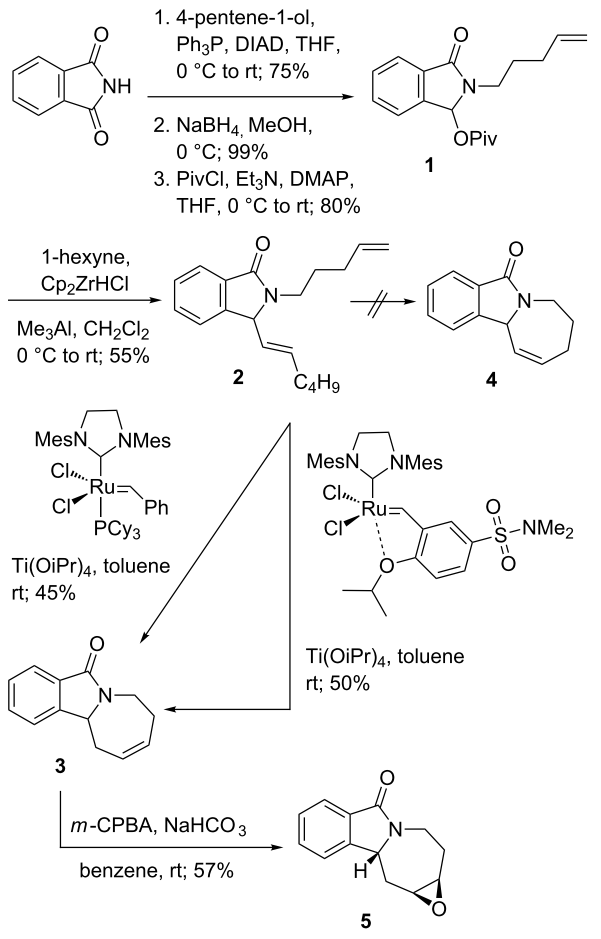
Figure 1: Representative isoindolinone natural products and pharmaceuticals.

Results and Discussion

N-Alkylation of phthalimide with 4-penten-1-ol under Mitsunobu conditions, followed by $NaBH_4$ reduction and pivaloate protection of the intermediate hemiaminal, provided alkene **1** in 59% overall yield (Scheme 1). After hydrozirconation of 1-hexyne with zirconocene hydrochloride [20-23], addition of trimethylaluminium activated the in situ generated alkenylzirconocene and allowed the displacement of the pivaloate on **1** in 55% yield to afford diene **2** [19,24].

Ring-closing metathesis of **2** using Grubbs 2nd generation catalyst [25] in the presence of 1 equiv of $Ti(OiPr)_4$ [26,27] at room temperature provided, surprisingly, a modest 45% yield of the alkene-isomerized homoallylic amide **3** instead of the expected allylic amide **4** (Scheme 1). This result was reproduced with Zhan catalyst-1B [28,29], which gave **3** in 50% yield. The structure of alkene **3** was determined based on the X-ray analysis of epoxide **5** (Figure 2), obtained with $NaHCO_3$-buffered *meta*-chloroperbenzoic acid (*m*-CPBA) in 57% yield [30,31].

The surprising formation of **3** instead of **4** under the metathesis conditions could be explained by a ruthenium-catalyzed double-bond isomerization [32]. The release of ring strain, however, can only be partially responsible for this facile isomerization. DFT calculations of the five possible alkene isomers of **4** indicated a decrease in relative energy from **4** to **3**, but other isomers were even lower in energy (Figure 3). The starting geometries for the alkene isomers prior to DFT optimizations were obtained by a conformational search using the MMFF force field.



Scheme 1: Formation of isomerized azepinoisoindoline **3** and oxirane **5**.

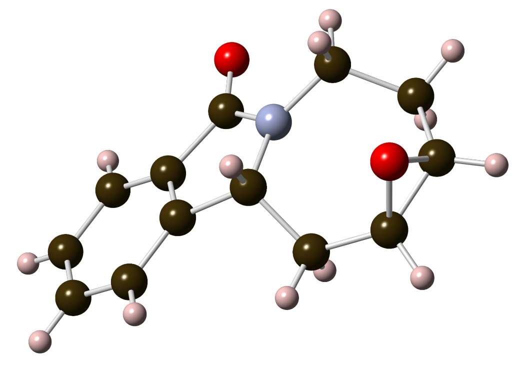


Figure 2: X-Ray structure of epoxide **5**.

In order to investigate the factors influencing the alkene isomerization process, we conducted a ring-closing metathesis in the absence of $Ti(OiPr)_4$ (Scheme 2). The resulting product was different from **3**, based on a TLC analysis, but proved to be quite labile during workup. Therefore, it was immediately subjected to *m*-CPBA epoxidation conditions to give a modest

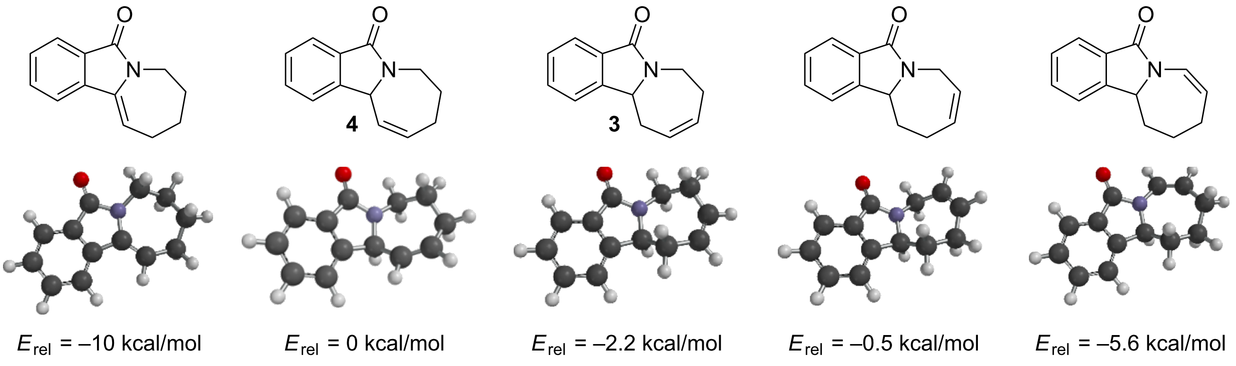
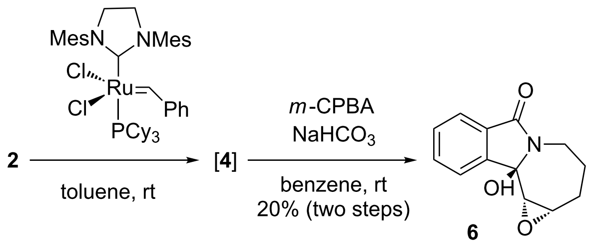


Figure 3: Relative energies of alkene isomers based on RB3LYP/6-311G* calculations with MacSpartan '06.

yield of the further oxidized **6**, which was structurally assigned by X-ray analysis (Figure 4). The formation of **6** implies the intermediate presence of alkene **4**, the product of a regular RCM of diene **2**. Accordingly, the isolation of **6**, and the absence of significant quantities of **5**, confirmed the chelating additive Ti(OiPr)$_4$ as the primary factor responsible for the isomerization of **4** to **3** in the previous reaction sequence. An additional contributing reason for the exclusive formation of **3** in the earlier metathesis reactions could be the decomposition of the acid-labile isomer **4** under the reaction and chromatographic-purification conditions. A possible pathway for decomposition is indicated by the benzylic/allylic methine oxidation product **6**. The ability of Ti(OiPr)$_4$ to induce alkene isomerization during the ring-closing metathesis reaction is noteworthy; while there are a number of additives known to decrease the rate of isomerization in RCM [33-35], we are unaware of any previous report on an alkene-isomerization-promoting effect of an additive in this reaction. We can speculate that the presence of Ti(OiPr)$_4$ stabilizes the ruthenium alkylidene complex and, thus allows product isomerization to take place during and after the RCM reaction (see below).



Scheme 2: Ring-closing metathesis of diene **2** in the absence of Ti(OiPr)$_4$ and isolation of hydroxy epoxide **6** after treatment with *m*-CPBA.

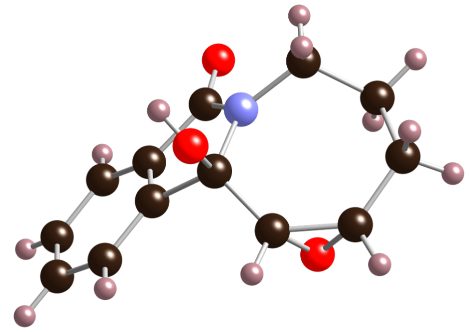
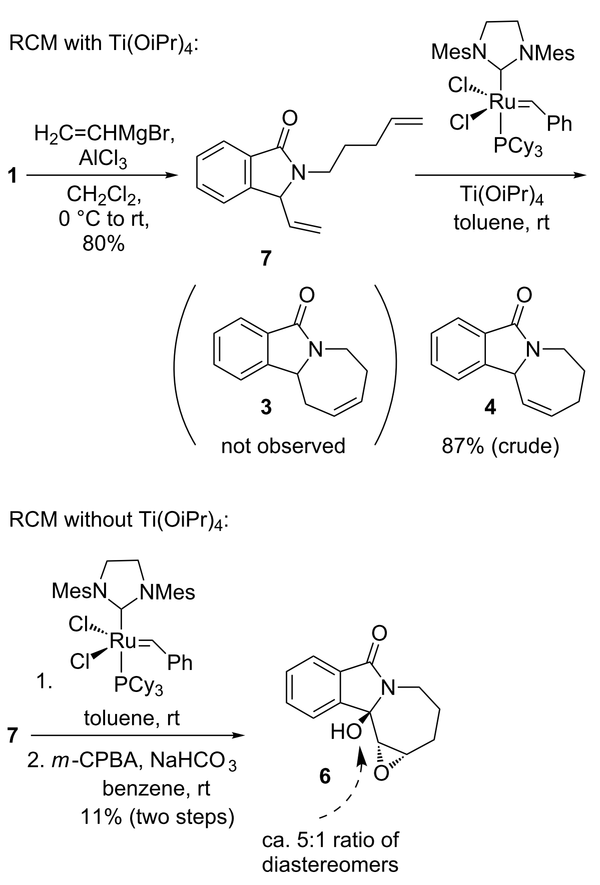


Figure 4: X-Ray structure of epoxyalcohol **6**.

We also briefly studied the influence of the diene substitution pattern on the rate of isomerization from **4** to **3** and the corresponding product distribution (Scheme 3). Addition of in situ prepared vinyl alane to pivaloate **1** provided the diene **7** in 80% yield. RCM with Grubbs second-generation catalyst in the presence of Ti(OiPr)$_4$ led to an exclusive conversion to alkene **4**, i.e., no alkene isomerization was observed in this case, and no homoallylic amide **3** was detected in the reaction mixture. Similarly, in the absence of Ti(OiPr)$_4$, crude **4** was obtained in 77% yield (Supporting Information File 1). The different reaction course with alkenes **2** and **7** indicates a role of the ruthenium carbene intermediate in the isomerization. Metathesis of **2** leads to an alkylidene complex, that could form a ruthenium hydride species. In contrast, metathesis of **7** provides a more reactive methylidene complex that is also likely to decompose more quickly and, thus, be unavailable for isomerization of the kinetic product **4** beyond the time span of the completion of the RCM reaction [36]. It was, however, difficult to purify product **4** due to its chemical instability. When the RCM reaction of **7** was conducted on larger scale in the absence of Ti(OiPr)$_4$, and the crude intermediate was subjected to *m*-CPBA oxidation, epoxy alcohol **6** was isolated in 11% overall yield. LC–MS as well as NMR analyses suggested a 5:1 ratio of epimers at the hemiacetal carbon. Hydroxylation/oxidation at the benzylic position with *m*-CPBA in air in the presence of bicarbonate has been observed previously, and a radical mechanism was proposed [37].

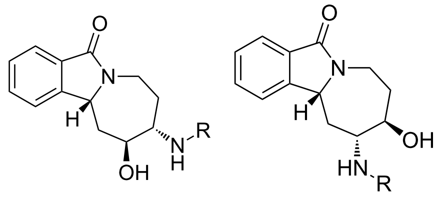


Scheme 3: Preparation and RCM reaction of bis-terminal diene analogue **7**.

In summary, these studies suggest that the alkene isomerization from allylic to homoallylic amides under RCM conditions is both dependent on the presence of the Lewis acidic additive $Ti(OiPr)_4$ as well as the substitution pattern of the α,ω-diene precursor.

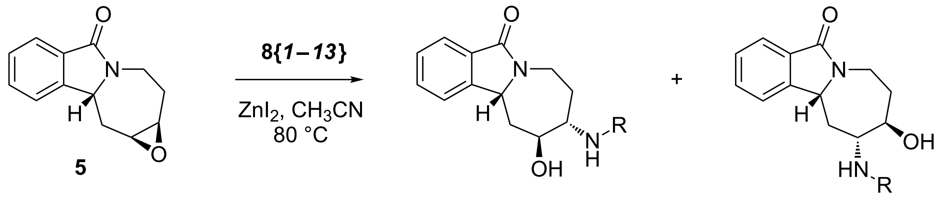
With alkene **3** and the corresponding epoxide **5** in hand, a ZnI_2-mediated amine alkylation protocol could be employed, which introduced a variety of nitrogen nucleophiles **8{*1–13*}** (Scheme 4) [38,39]. $Co(ClO_4)_2$ hexahydrate could also be used in place of ZnI_2, but was generally less efficient (Table 1). Anilines with electron-withdrawing (CF_3, CN, CO_2Et), electron-donating (OCH_3), and halogen substituents (F, Cl, Br) in *ortho*-, *meta*- and *para*-positions were used (Figure 5). Furthermore, aminopyridines **8{*11*}** and **8{*12*}** as well as aliphatic amine **8{*13*}** were compatible with the reaction conditions. With the exception of **8{*13*}**, two regioisomeric products were formed: the major isomer **9{*1–12*}** was obtained by an attack on the distal carbon atom of the epoxide, while the minor isomer **10{*1–13*}** was obtained by proximal ring opening. These isomers were separated by chromatography on SiO_2, and an X-ray analysis confirmed the structural assignment for **10{*7*}** (Figure 6). The remainder of the library products were assigned

Table 1: Library matrix of products **9{*1–13*}** and **10{*1–13*}** [isolated yield (%) and purity by ELSD (%)].



Amine segment R	**9{*1–13*}**	**10{*1–13*}**
8{*1*}	56 (>99)	19 (94)[a]
8{*2*}	81 (95)	15 (>99)
8{*3*}	24 (>99)	10 (99)
8{*4*}	72 (99)	17 (99)
8{*5*}	44 (99)	33 (95)
8{*6*}	69 (>99)	17 (95)
8{*7*}	41 (>99)	12 (>99)
8{*8*}	58 (99)	26 (98)
8{*9*}	85 (99)	15 (99)
8{*10*}	59 (>99)	15 (72)
8{*11*}	59 (>99)	32 (>99)
8{*12*}	20 (99)	–[b]
8{*13*}	–[b]	46 (>99)

[a] $Co(ClO_4)_2 \cdot 6H_2O$ was used in place of ZnI_2; [b] Product was not isolated.



9{*1–13*}, major

10{*1–13*}, minor

Scheme 4: Conversion of epoxide **5** to 1,2-amino alcohols.

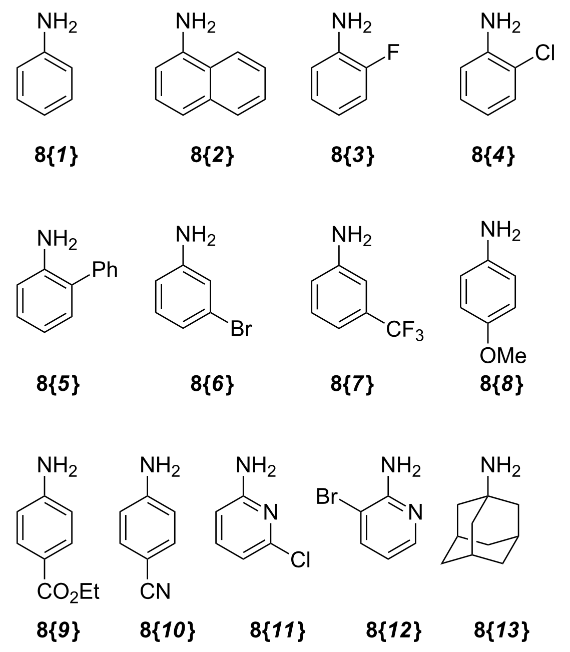


Figure 5: Amine building blocks for library synthesis.

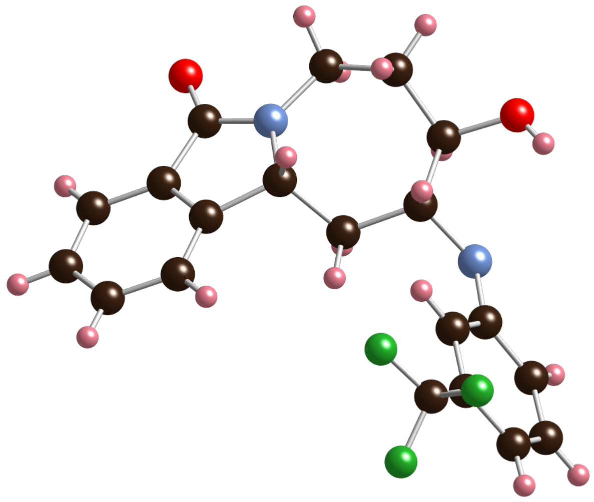


Figure 6: X-ray structure of amino alcohol **10**{*7*}.

based on the characteristic chemical-shift data for **10**{*7*} and its congener **9**{*7*} [40]. Yields and purities of amino alcohols **9**{*1–12*} and **10**{*1–13*} are summarized in Table 1.

The **9**{*1–11*}/**10**{*1–11*} isolated product ratios varied between 5:1 and 1.5:1, with no obvious trends discernable. Interestingly, for adamantyl amine **8**{*13*}, only the corresponding **10**{*13*} was isolated, most likely due to the steric bulk of the adamantyl group: molecular mechanics calculations indicate that the aminolysis of **5** to regioisomer **10** proceeds with minimal isomerization of the seven-membered ring geometry in the lowest-energy product conformer, whereas the formation of **9** requires a substantial ring flip [41].

Conclusion

A library of novel tricyclic isoindolinone amino alcohols was prepared in seven steps from commercially available starting materials. Key transformations include the addition of in situ generated alkenylalanes to an *N*-acyliminium ion derived from pivaloate **1**, a tandem ring-closing metathesis–isomerization sequence and a ZnI_2-mediated epoxide aminolysis. We investigated the factors influencing the alkene isomerization during the RCM process, and identified the presence of the additive $Ti(OiPr)_4$, the substitution pattern on the alkene, and the chemical reactivity of the benzylic allylic methine carbon to be significant contributors. Regioisomeric library products **9** and **10** were submitted to the NIH Small Molecule Repository (SMR) [42], screened in the Molecular Libraries Probe Center Network (MLPCN) [43], and biological results were deposited in PubChem [44]. For example, **9**{*2*} was tested in 188 assays and identified as an active hit (based on the hit criteria in the individual test systems) in 4 assays, including a cell-based assay to identify antagonists of the orexin 1 receptor; an assay to identify inhibitors of Apaf-1 (apoptotic peptidase activating factor 1); a cell-based assay to identify antagonists of the human M1 muscarinic receptor; and a cellular assay to identify human immunodeficiency virus 1 inhibitors. Amino alcohol **9**{*7*} was tested in 185 bioassays reported in PubChem, and found to serve as an inhibitor of human platelet activating factor acetylhydrolase 2 (PAFAH2). It is clear from these and other screening data disclosed for this series in the PubChem database that the tricyclic isoindolinone scaffolds hold strong potential for the development of selective and potent lead structures.

Supporting Information

Supporting information contains experimental procedures for newly synthesized compounds and NMR spectra.

Supporting Information File 1

Experimental procedures and characterization details of synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-120-S1.pdf]

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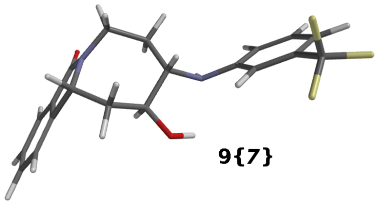
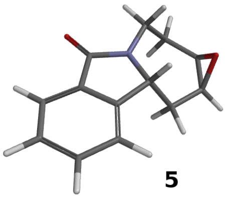
40. The characteristic proton used for assignment of all library products is the benzylic methine proton, which appears between 4.5 and 5.0 ppm as an apparent triplet with *J* ~ 5 Hz in compounds **9{*1–12*}** and as a doublet with *J* ~ 10 Hz in compounds **10{*1–13*}**. These splitting patterns and coupling constants (as a function of the dihedral angles) are confirmed by examination of the X-ray structure of **10{*7*}** (showing dihedral angles of 75.9° and −168.3° for the benzylic methine hydrogen at 4.69 ppm (d, 1H, *J* = 9.9 Hz) and its two vicinal methylene hydrogens). The lowest energy conformer of **9{*7*}** calculated with MMFF in Spartan 10 shows dihedral angles of −36.6° and 77.2° for the benzylic methine hydrogen at 4.85 ppm (t, 1H, *J* = 5.0 Hz) and its two vicinal methylene hydrogens.



9{*7*}

41. Lowest energy conformers calculated with MMFF in Spartan 10:



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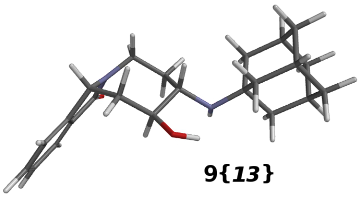
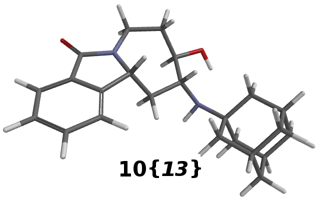


9{*13*}



10{*13*}

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43. MLPCN. http://mli.nih.gov/mli/.
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Synthesis of diverse indole libraries on polystyrene resin – Scope and limitations of an organometallic reaction on solid supports

Kerstin Knepper[1], Sylvia Vanderheiden[2] and Stefan Bräse*[1,2]

Full Research Paper

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Address:
[1]Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT), Fritz-Haber-Weg 6, D-76131 Karlsruhe, Germany and [2]ITG - Complat, Karlsruhe Institute of Technology (KIT), Hermann-von-Helmholtz-Platz 1, D-76344 Eggenstein-Leopoldshafen, Germany

Email:
Stefan Bräse* - braese@kit.edu

* Corresponding author

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Abstract

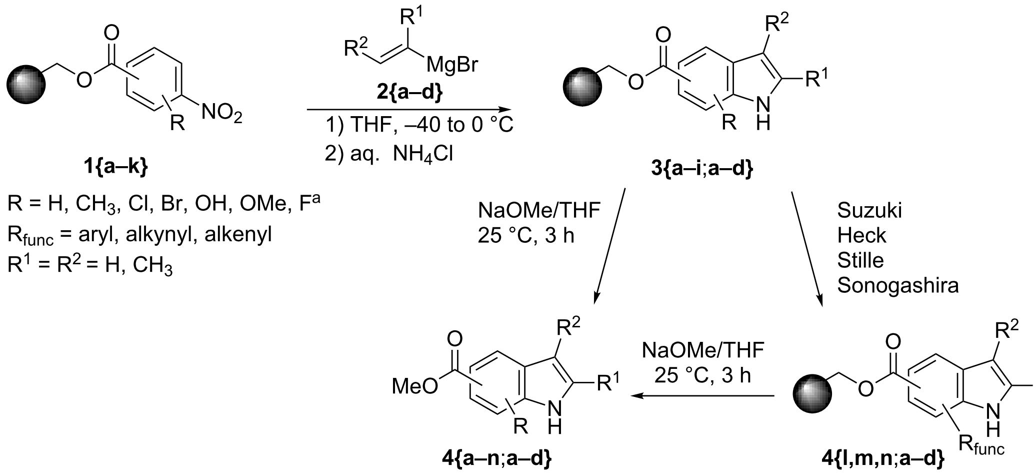
The synthesis of diverse substituted indole structures on solid supports is described. The immobilization of nitrobenzoic acid onto Merrifield resin and the subsequent treatment with alkenyl Grignard reagents delivered indole carboxylates bound to solid supports. In contrast to results in the liquid phase, *ortho*,*ortho*-unsubstituted nitroarenes also delivered indole moieties in good yields. Subsequent palladium-catalyzed reactions (Suzuki, Heck, Sonogashira, Stille) delivered, after cleavage, the desired molecules in moderate to good yields over four steps. The scope and limitations are presented.

Introduction

Indoles are heterocyclic structures of unquestionable importance. It is well recognized that the indole moiety is a privileged structural motif found in numerous natural products, such as alkaloids or peptides, and various synthetic compounds [1,2]. Moreover, a large number of indole-containing compounds show potential as therapeutic agents.

A large number of synthetic approaches have been published over the past hundred years. Recently, versatile and modular organometallic reactions have been used to create the indole core. Among these, the Bartoli reaction is a straightforward route for the generation of the indole moiety starting from nitroarenes. Some limitations of this useful reaction have been reported, e.g., only *ortho*-substituted nitroarenes gave good yields of the indoles. Despite the interest in new indoles [3-5] and in particular for libraries of combinatorial compounds [2,6-17], there has only been one report for the application of the Bartoli reaction [18-23] on solid supports so far [24]. Organometallic reactions on solid supports are always particularly challenging [25].

In the past, indoles were synthesized by using, for example, Fischer indole synthesis [26-30], Bartoli indole synthesis, Nenitzescu synthesis [31], Wittig indole synthesis [32],



Scheme 1: Diverse synthesis of indoles using Bartoli reactions. [a]See [24].

Madelung indole synthesis [33], palladium-catalyzed indole synthesis [34-40], cycloaddition strategies [41], C-arylation of substituted acetonitriles or 1,3-dicarbonyl compounds [42], halocyclization [43,44] and finally, reduction of *ortho*-fluoronitroarenes [42]. The significant biological properties and the distinctive structural features of indole moieties prompted us to investigate the scope and limitations of this reaction. In this paper, we describe our various strategies towards synthesis of the indole core. A solid-phase Bartoli reaction on solid supports is advantageous due to the decreased number of chromatographic steps and the direct use of *ortho*,*ortho*-unsubstituted nitroarenes.

Results and Discussion

Synthetic plan

Based on our initial findings, we attached a variety of nitrobenzoic acids onto solid supports. The resin of choice was Merrifield resin with an initial loading of 0.97 mmol/g. Hence, a number of substituted polymer-bound nitroarenes **1{a–k}** are available (Scheme 1, Figure 1).

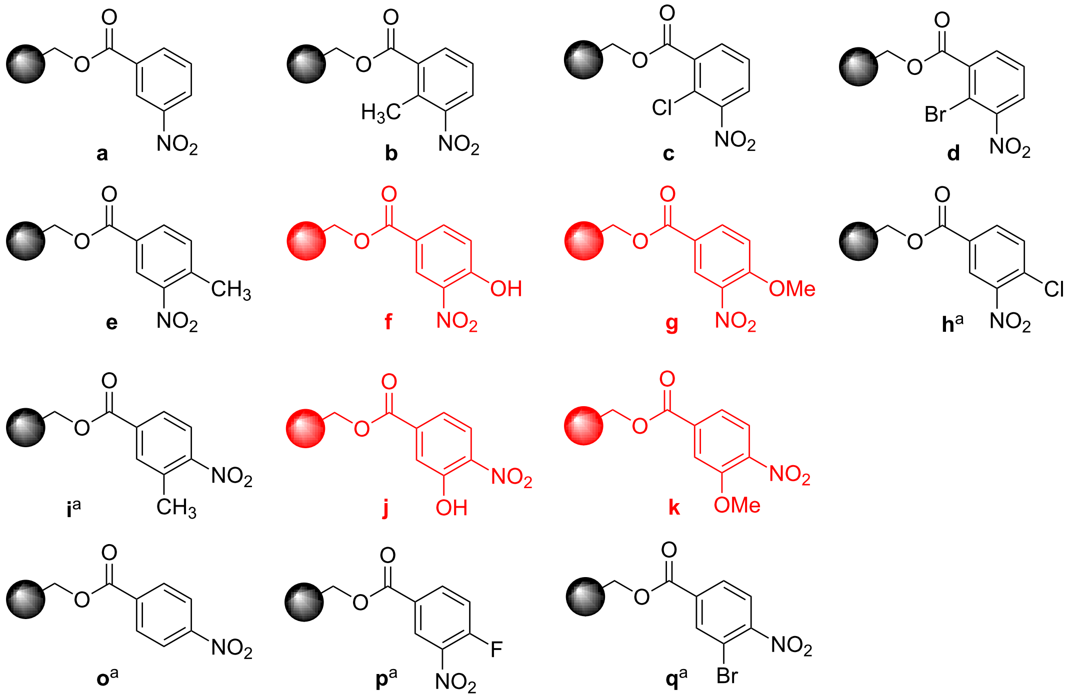


Figure 1: Nitroarenes on solid supports. In red: Nitroarenes failed to give indoles. [a]Resin has been reported before, [24].

Reaction optimization

In order to optimize the reaction conditions, the temperature for the Bartoli reaction on solid supports was systematically changed. For the reaction of (4-chloro-3-nitrophenyl)-carboxymethyl-polystyrene (**1{h}**) with 1-methyl-1-propenyl-magnesiumbromide (**2{b}**), an optimum between −20 and 0 °C was determined (Figure 2). In over 90% of the cases, the purities of the crude material after cleavage were above 80%, and in a few cases even over 90% (according to GC-MS) [24]. Pure material was obtained after thin-layer chromatography.

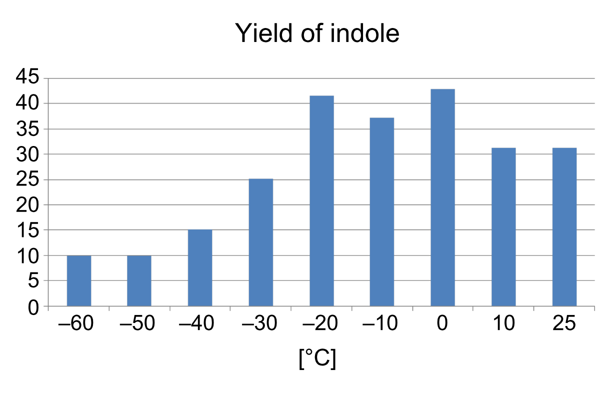


Figure 2: Temperature optimization with Grignard reagent **2{b}**.

A slightly higher temperature was optimal for the reaction of (3-methyl-4-nitrophenyl)carboxymethyl-polystyrene (**1{i}**) with the less active vinyl magnesium bromide **2{a}** (Figure 3).

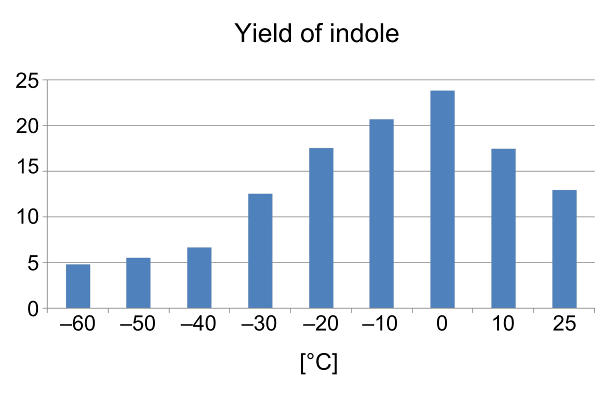


Figure 3: Temperature optimization with Grignard reagent **2{a}**. Isolated yield.

In addition to this, we also varied the amount of Grignard reagent for the reaction of **1{h}** (Figure 4). Interestingly, even with substoichiometric amounts considerable formation of indoles was observed. Very common byproducts are anilines [45-47]. It should be noted at this point that the anilines are more prone to cleavage during the Bartoli reaction, and this led to a high purity (albeit with low yields) of the indole products.

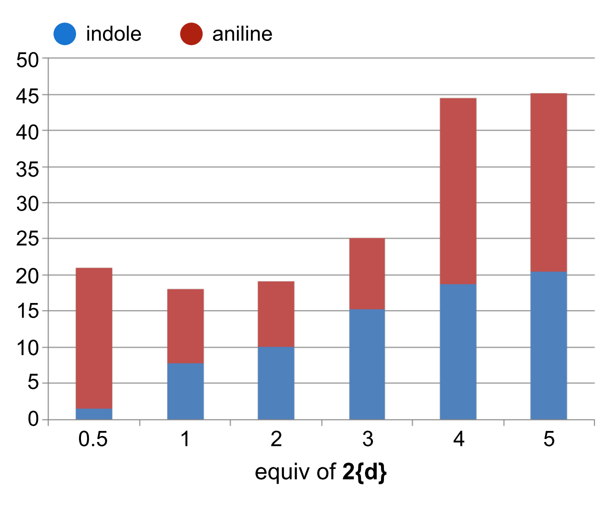


Figure 4: Optimization studies of ester **1{h}** with a Grignard reagent **2{d}** to give indole **3{h,d}** and methyl 3-amino-4-chlorobenzoate (aniline): Isolated yields.

After optimization, we immobilized a number of nitrobenzoic acids onto solid supports. The resulting indoles after reaction with different Grignard reagents and subsequent cleavage are summarized in Table 1.

In general, most of the nitroarenes were successfully converted to the indoles. As yields and purities were found to be higher when −40 °C and 3 equiv of Grignard reagents were used, we adopted these conditions for our library synthesis. Functional groups such as halides were tolerated. Two exceptions were the hydroxycarboxylic acids **1{f}**,**1{j}** and the methoxycarboxylic acids **1{g}**,**1{k}**, which all failed in that very complex mixtures were obtained. Recently, it was reported that methoxynitroarene gave somewhat different products in the presence of Grignard reagent [48].

As reported before, *ortho*,*ortho*-unsubstituted arenes such as **1{a}** were suitable substrates in contrast to their liquid-phase counterparts. However, they gave a mixture of products (Supporting Information File 1).

The next stage is the functionalization by cross-coupling reactions. In our first communication, we employed Suzuki and Heck reactions [24].

Table 1: Cleavage of indoles from solid supports.

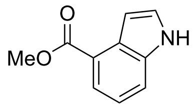
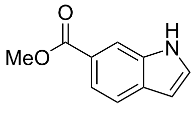
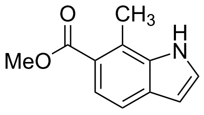
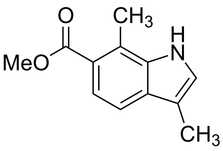
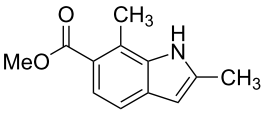
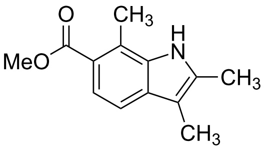
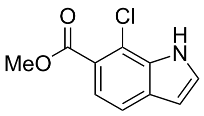
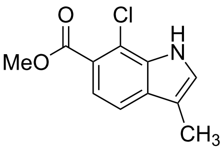
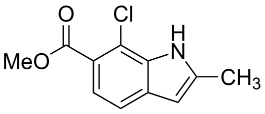
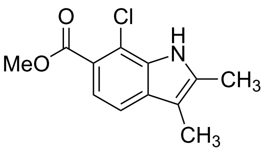
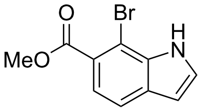
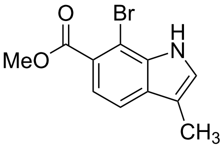
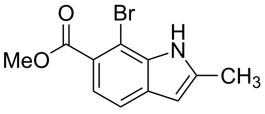
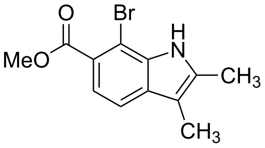
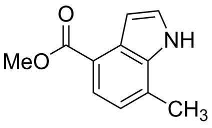
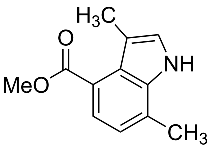
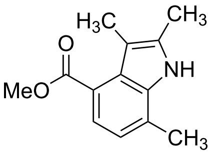
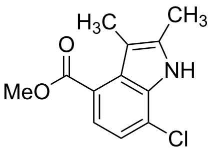
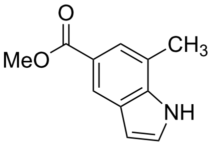
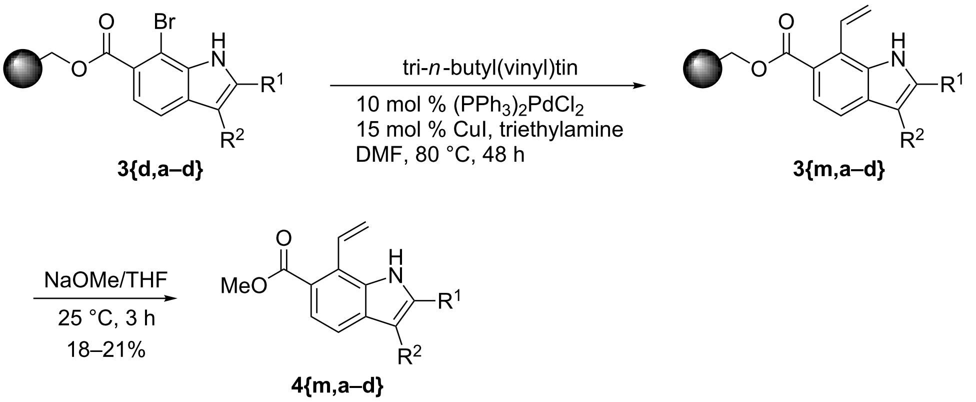
Entry	Resin	Grignard reagent	Indole	Yield over 3 steps (%)
1	**1{a}**	CH_2=CHMgBr (**2{a}**)	 **4{a,a}**	21
			 **4{a,a'}**	21
2	**1{b}**	CH_2=CHMgBr (**2{a}**)	 **4{b,a}**	14
3	**1{b}**	CH_3CH=CHMgBr (**2{b}**)	 **{4b,b}**	16
4	**1{b}**	CH_2=C(CH_3)MgBr (**2{c}**)	 **4{b,c}**	18
5	**1{b}**	CH_3CH=CCH_3MgBr (**2{d}**)	 **4{b,d}**	20
6	**1{c}**	CH_2=CHMgBr (**2{a}**)	 **4{c,a}**	6
7	**1{c}**	CH_3CH=CHMgBr (**2{b}**)	 **{4c,b}**	15
8	**1{c}**	CH_2=C(CH_3)MgBr (**2{c}**)	 **4{c,c}**	6
9	**1{c}**	CH_3CH=CCH_3MgBr (**2{d}**)	 **4{c,d}**	10

Table 1: Cleavage of indoles from solid supports. (continued)

10	**1{d}**	CH_2=CHMgBr (**2{a}**)	 **4{d,a}**	13
11	**1{d}**	CH_3CH=CHMgBr (**2{b}**)	 **4{d,b}**	12
12	**1{d}**	CH_2=C(CH_3)MgBr (**2{c}**)	 **4{d,c}**	7
13	**1{d}**	CH_3CH=CCH_3MgBr (**2{d}**)	 **4{d,d}**	13
14	**1{e}**	CH_2=CHMgBr (**2{a}**)	 **4{e,a}**	14
15	**1{e}**	CH_3CH=CHMgBr (**2{b}**)	 **4{e,b}**	14
16	**1{e}**	CH_3CH=CCH_3MgBr (**2{d}**)	 **4{e,d}**	15
17	**1{h}**	CH_3CH=CCH_3MgBr (**2{d}**)	 **4{h,d}**	25[a]
18	**1{i}**	CH_2=CHMgBr (**2{a}**)	 **4{i,a}**	54[a]

[a]See [25].



Scheme 2: Stille reaction on solid supports.

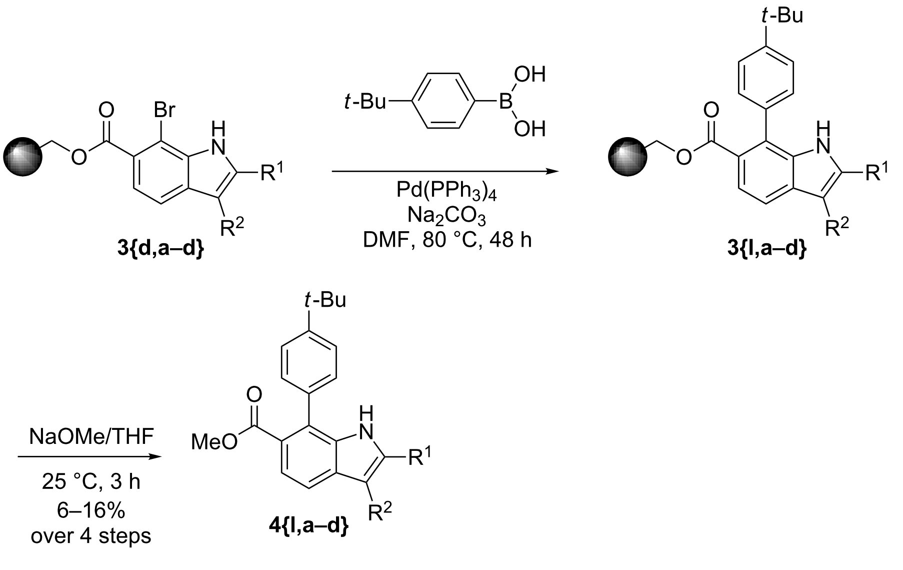
In addition to these reactions, Stille reactions have been used to expand the utility of the Bartoli solid-phase reaction. The reaction with tributyl(vinyl)tin proceeded smoothly and gave the vinylindoles in moderate yields but good purity, in four steps (Scheme 2).

We also performed a couple of Suzuki reactions on solid supports. The details are given in Scheme 3. Again, these reactions proceeded smoothly.

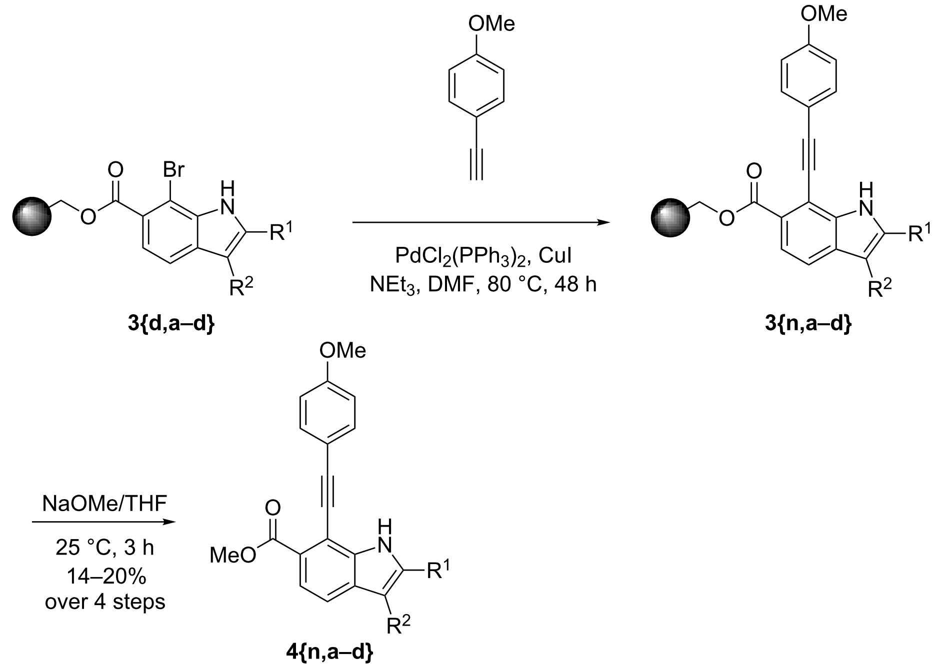
We also performed Sonogashira–Hagihara reactions on solid supports. This reaction gave rise to alkynyl-substituted indoles. It should be noted at this point that the basic cleavable linker prevents the addition of water usually observed under cleavage with acids. The details are given in Scheme 4. It should also be noted that alkynyl-substituted indole carboxylic acids are only reported scarcely [49].

Conclusion

In conclusion, we presented an extension of our Bartoli indole syntheses with application of a diverse set of vinyl Grignard reagents and cross-coupling reactions. Although the overall yield is only moderate, due to the facile solid-phase approach, a small library of highly substituted indoles is readily available.



Scheme 3: Suzuki reaction on solid supports.



Scheme 4: Sonogashira–Hagihara reaction on solid supports.

Experimental

Instrumentation and reagents: ^{1}H NMR spectra were recorded on Bruker DP 300 (300 MHz), Bruker DP 400 (400 MHz). Chemical shifts are expressed in parts per million (δ/ppm) downfield from tetramethylsilane (TMS) and are referenced to chloroform (7.26 ppm), dimethylsulfoxide (2.50 ppm) or methanol (3.31 ppm) as internal standard. All coupling constants are absolute values and J values are expressed in Hertz (Hz). The description of signals include: s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, t = triplet, dd = doublet of doublets, dt doublet of triplets, m = multiplet. The spectra were analyzed according to first order. ^{13}C NMR spectra were recorded on Bruker DP 300 (75 MHz) and Bruker DP 400 (100 MHz). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CDCl_3$ (77.4 ppm), DMSO-d_6 (39.52 ppm) or methanol-d_4 (49.00) as internal standard. Perkin Elmer FT-IR 1750: IR spectra of soluble substances were recorded in distilled dichloromethane; IR spectra of resins were recorded in KBr on Bruker IFS88 IR. EI-MS (electron impact mass spectrometry): Kratos MS 50 (70 eV) and Thermo Quest Finnigan MAT 95 XL (70 eV). The molecular fragments are quoted as the relation between mass and charge (m/z), the intensities as a percentage value relative to the intensity of the base signal (100%). The abbreviation $[M]^+$ refers to the molecular ion. Elemental analysis: Elementar Vario EL. Routine monitoring of reactions was performed by using silica-gel-coated glass plates (Merck, silica gel 60, F_{254}), which were analyzed under UV light at 254 nm and/or dipped into a solution of molybdato phosphate (5% phosphor molybdic acid in ethanol, dipping solution) or potassium permanganate (0.45 g of potassium permanganate and 2.35 g of sodium carbonate in 90 mL of water) and heated with a heat gun. Solvent mixtures are understood as volume/volume. Solid materials were powdered. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, ABCR, Acros, Merck and Lancaster. Solvents, reagents and chemicals were used as purchased unless stated otherwise. Merrifield resin (1–2% cross-linked, 0.97 mmol/g, 200–400 mesh), was purchased from CalBiochem-NovaBiochem.

General washing procedure for resins: After reaction the resins are subsequently washed according to the following procedure: (MeOH, THF, *n*-pentane, CH_2Cl_2) three times, (MeOH, DMF, *n*-pentane, THF) once, (*n*-pentane, CH_2Cl_2, *n*-pentane) twice.

GP 1 - Immobilization of benzoic acids on Merrifield resin: In a three-necked round-bottom flask equipped with a mechanical stirrer, 5 equiv of cesium carbonate are suspended in DMF (mL/mmol) and are stirred for 30 min at 50 °C. Next, 5 equiv of benzoic acid are added and the mixture is stirred for another 30 min. Afterwards, one equiv of Merrifield resin is added and the suspension is stirred for 24 h at 50 °C. After being cooled down to room temperature the resin is filtered off and first washed with water, then treated according to the general washing procedure, and dried in high vacuum. The loading of the resin was calculated according to the nitrogen values of the elemental analysis.

GP 2 - Bartoli-indole synthesis: Under an argon atmosphere, one equiv of the resin is suspended in dry THF (0.1 mmol/mL), cooled down to −40 °C and three equiv of the Grignard reagent are added, while the color of the mixture changes to orange-red. The reaction mixture is allowed to warm to 0 °C, and then a saturated aqueous solution of ammonium chloride is added. The resin is filtered off, and first washed with water, then according to the general washing procedure, and dried in high vacuum. The loading of the resulting resin was calculated as if complete conversion had taken place.

GP 3 - Suzuki reaction: Under an argon atmosphere, one equiv of the respective 7-bromo-1*H*-indole-6-carboxymethyl-polystyrene is suspended in DMF (0.1 mmol/mL) together with 0.10 equiv of tetrakis(triphenylphosphine)palladium and two equiv of boronic acid. An aqueous solution of sodium carbonate (2.5 equiv, 1.5 M) is added and the mixture agitated for two days at 80 °C. After cooling down to room temperature, 10 mL of a 25% aqueous solution of ammonium acetate are added, the resin is filtered off, washed according to the general washing procedure, and dried in high vacuum. The loading of the resulting resin was calculated as if complete conversion had taken place.

GP 4 - Sonogashira–Hagihara reaction: Under an argon atmosphere, one equiv of the respective 7-bromo-1*H*-indole-6-carboxymethyl-polystyrene is suspended in DMF (0.1 mmol/mL) together with 10.0 mol % bis(triphenylphosphine)palladium(II) chloride, 15.0 mol % copper(I) iodide and one equiv of triphenylphosphine. Then, two equiv of triethylamine and 2.5 equiv of 4-ethynylanisole are added and the mixture is agitated for two days at 80 °C. After cooling down to room temperature, 10 mL of a 25% aqueous solution of ammonium acetate are added, the resin is filtered off, washed according to the general washing procedure, and dried in high vacuum. The loading of the resulting resin was calculated as if complete conversion had taken place.

GP 5 - Stille reaction: Under an argon atmosphere, one equiv of the respective 7-bromo-1*H*-indole-6-carboxymethyl-polystyrene is suspended in DMF (0.1 mmol/mL) together with 10.0 mol % bis(triphenylphosphine)palladium(II) chloride, 15.0 equiv of lithium chloride and one equiv of triphenylphosphine. Then, three equiv of tributyl(vinyl)tin are added and the mixture is agitated for two days at 80 °C. After being cooled down to room temperature, 10 mL of a 25% aqueous solution of ammonium acetate are added, and the resin is filtered off, washed according to the general washing procedure, and dried in high vacuum. The loading of the resulting resin was calculated as if complete conversion had taken place.

GP 6 - General cleavage protocol: To one equiv of the resin in dry THF (0.1 mmol/mL), a solution of 30% sodium methoxide in MeOH (2.00 mL/mmol of resin) is added and the mixture is agitated for three hours at room temperature. The resin is filtered off, and the filtrate is hydrolyzed with water and subsequently extracted with ethyl acetate three times. After being dried over magnesium sulfate, the solvent is removed under reduced pressure and the residue is purified by column chromatography by using cyclohexane/ethyl acetate, 3:1 as eluent.

Supporting Information

Supporting Information File 1

Experimental details.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-132-S1.pdf]

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Palladium-catalyzed substitution of (coumarinyl)methyl acetates with C-, N-, and S-nucleophiles

Kalicharan Chattopadhyay[1,2], Erik Fenster[2], Alexander J. Grenning[1] and Jon A. Tunge*[1,2]

Full Research Paper

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Address:
[1]Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045-7528, USA and [2]KU Chemical Methodologies and Library Development Center of Excellence, University of Kansas, 1501 Wakarusa Drive, Lawrence, Kansas 66047, USA

Email:
Jon A. Tunge* - tunge@ku.edu

* Corresponding author

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Abstract

The palladium-catalyzed nucleophilic substitution of (coumarinyl)methyl acetates is described. The reaction proceeds though a palladium π-benzyl-like complex and allows for many different types of C-, N-, and S-nucleophiles to be regioselectively added to the biologically active coumarin motif. This new method was utilized to prepare a 128-membered library of aminated coumarins for biological screening.

Introduction

Coumarins are privileged chemical motifs found in many natural products and drug molecules [1-15]. Because of their biological significance, there have been many classic and modern methods developed for the synthesis of these useful core structures [16-24]. Due to the ambiphilic nature of the heterocyclic ring of coumarin, this core-structure undergoes a diverse array of coupling reactions, such as halogenations [25], cycloadditions [26-32], conjugate additions [33-37] and transition-metal-catalyzed C–H activation/coupling reactions [38-44].

Substituted methylcoumarins, including aminomethylcoumarins are important biologically active motifs (Figure 1) [6-15]. Substitution of methylcoumarins to form compounds akin to **2** typically utilizes the corresponding halomethylcoumarin and highly stabilized nucleophiles or amines [6-15]. Due to the sensitivity and toxicity of related benzyl halides, there has been interest in catalytically activating hydroxymethylarene and heteroarenes (e.g., benzyl alcohol derivatives) toward reactions with nucleophiles [45-55]. In this realm, we [53,55] and others [54] have focused efforts on catalyzing

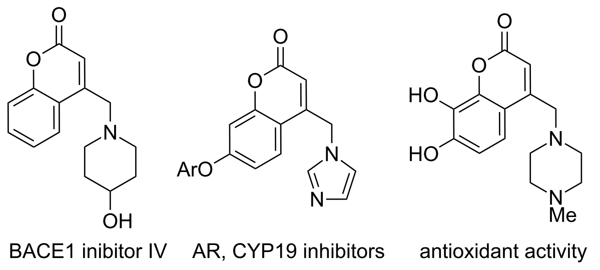
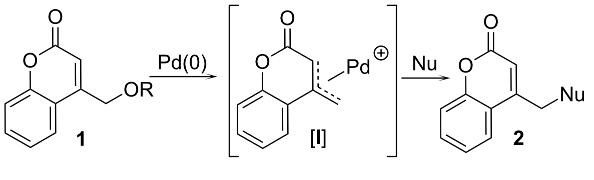


Figure 1: Representative biologically active aminomethylcoumarins.

benzylic substitutions with less-stabilized (DMSO $pK_a \sim 20–30$) nucleophiles through decarboxylative coupling. In the present context, we hypothesized that a broad diversity of nucleophiles could be added to the (coumarinyl)methyl core through palladium-catalyzed couplings of hydroxymethylcoumarin derivatives. Herein we report that hydroxymethylcoumarin derivatives of type-**1** undergo selective nucleophilic substitution at the exo-methyl position with C-, N-, and S-based nucleophiles by using palladium(0) as a catalyst (Scheme 1). In addition, given the known biological activity of aminomethylcoumarins, we prepared a 128-member library of aminated coumarins using rapid automated synthesis.

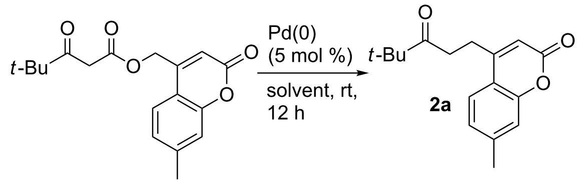


Scheme 1: Approach to diversely substituted coumarins.

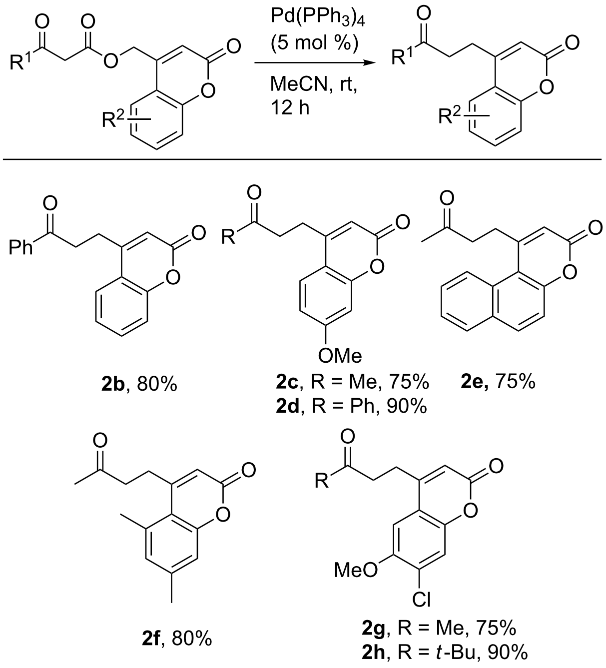
Results and Discussion

To begin investigating the diversification of hydroxymethylcoumarins, we chose to investigate their decarboxylative couplings of enolates. We have previously shown that decarboxylative benzylation (DcB) is a useful method for the addition of less-stabilized enolate anions to a benzyl functionality [46,53-55]. Thus, we envisioned being able to add various ketone enolates to the exo-methyl position of the coumarin core by this method (Table 1). Screening of reaction conditions showed that, in contrast to common decarboxylative benzylation conditions (Table 1,entries 1 and 2) under which nonpolar solvents give the best DcB, the selective mono-alkylation of the enolate proceeds in highest yield in acetonitrile (**2a**, Table 1, entry 3). Bidentate ligated palladium complexes gave mixed results: the Pd/dppf complex (Table 1,entry 4) catalyzed the reaction smoothly, while little product was seen on using the Pd/BINAP complex (Table 1,entry 5). Under the best conditions (5 mol % $Pd(PPh_3)_4$, MeCN, rt, Table 1, entry 3), a variety of enolate nucleophiles could be selectively coupled with coumarin electrophiles (Scheme 2). For example, acetone, acetophenone and 1,1,1-trimethylacetone enolates can all be generated and coupled with the coumarin electrophile. Importantly, selective monobenzylation was achieved for each example. Regarding the coumarin moiety, the decarboxylative coupling was compatible with a variety of simple substitutions, including methoxy (**2c,d,g,h**), chloro (**2g,h**) and naphthyl (**2e**) coumarins.

Table 1: Reaction development for the coupling of in situ generated enolates and coumarin π-benzyl complexes.



Entry	Catalyst	Solvent	Conv. (%)
1	$Pd(PPh_3)_4$	toluene	68
2	$Pd(PPh_3)_4$	THF	70
3	$Pd(PPh_3)_4$	MeCN	95 (88% yield)
4	Pd_2dba_3, dppf	MeCN	88
5	Pd_2dba_3, BINAP	MeCN	10

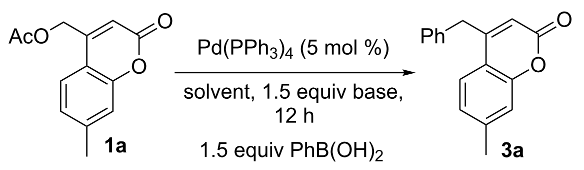


Scheme 2: Scope of the decarboxylative coupling.

While the decarboxylative coupling worked well for the couplings of relatively nonstabilized enolate nucleophiles, we wished to find a more universal starting material that would allow a broader range of nucleophiles to be coupled to the coumarin core in an intermolecular fashion. Such a method was deemed necessary for rapid diversification and chemical library synthesis. Thus, we chose to investigate the Pd-catalyzed benzylic substitution reaction of (coumarinyl)methyl acetates with various nucleophiles. In the forthcoming sections, the coupling of this coumarin template to arylboronic acids [56-61], amines [47] and arylsulfinates is described [62]. Moreover, compared to related methods for palladium-catalyzed benzylic substitution that require specialized ligands [45,47,60-62], we report that coumarin π-benzyl formation is easily achieved with simple PPh_3 ligated palladium.

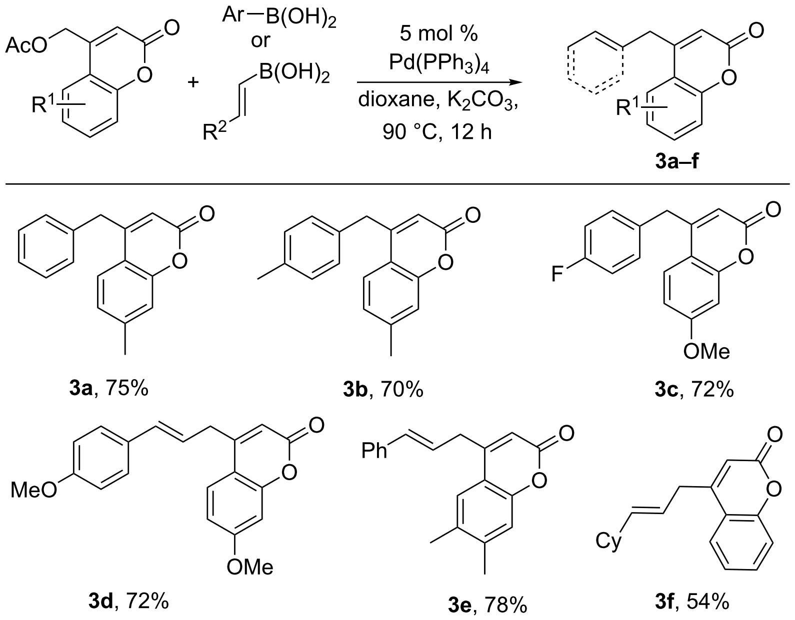
Regarding the development of the Suzuki-like coupling reaction of (coumarinyl)methyl acetate and arylboronic acids, we screened reaction conditions for the coupling of coumarin **1a** with phenylboronic acid (Table 2). We were pleased to find that the reaction progressed reasonably well to **3a** under various conditions. For example, inorganic bases such as K_2CO_3, K_3PO_4, and KF all effected the reaction equally well in methanol. A brief screen of solvents showed that the nonpolar aprotic solvent 1,4-dioxane gave the highest yields of the coupling product (Table 2, entry 6). Lastly, in the absence of added base, the acetate generated upon π-benzyl formation also promoted the desired coupling, albeit in lower yield over the time frame allowed (12 h, Table 2, entry 7).

Table 2: Palladium-catalyzed coupling of coumarinyl acetate and phenylboronic acid.

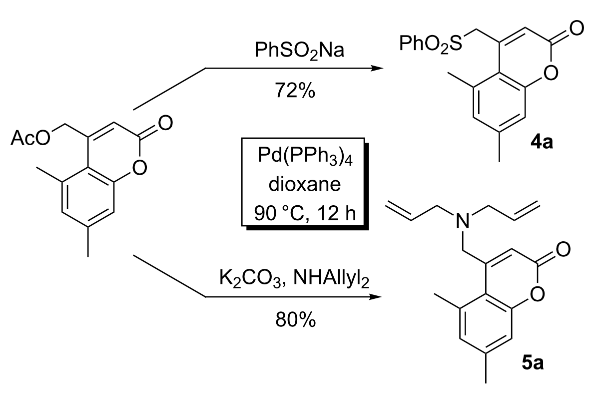


Entry	Solvent	*T* (°C)	Base	Conv. (%)
1	MeOH	65	K_2CO_3	65
2	MeOH	65	KF	59
3	MeOH	65	K_3PO_4	65
4	toluene	90	K_2CO_3	63
5	THF	65	K_2CO_3	63
6	dioxane	90	K_2CO_3	85
7	dioxane	90	–	45

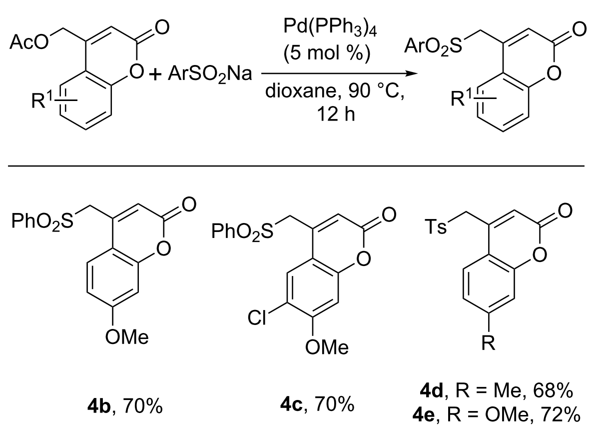
With the optimal conditions in hand, we next tested the scope of the reaction using various boronic acid and coumarinyl acetates (Scheme 3). Regarding the boronic acid coupling partner, modifications including fluoro and alkyl substitution were tolerated. In addition to aryl boronic acids (**3a**–**c**), the reaction was also extended to couplings of vinyl boronic acids having varied electronic properties (**3d**–**e**). As before, various simple substitutions and electronic changes were tolerated on the coumarin core.



Scheme 3: Scope of Suzuki-coupling of coumarinyl acetates.



Scheme 4: Coupling of (coumarinyl)methyl acetates with N- and S-nucleophiles.

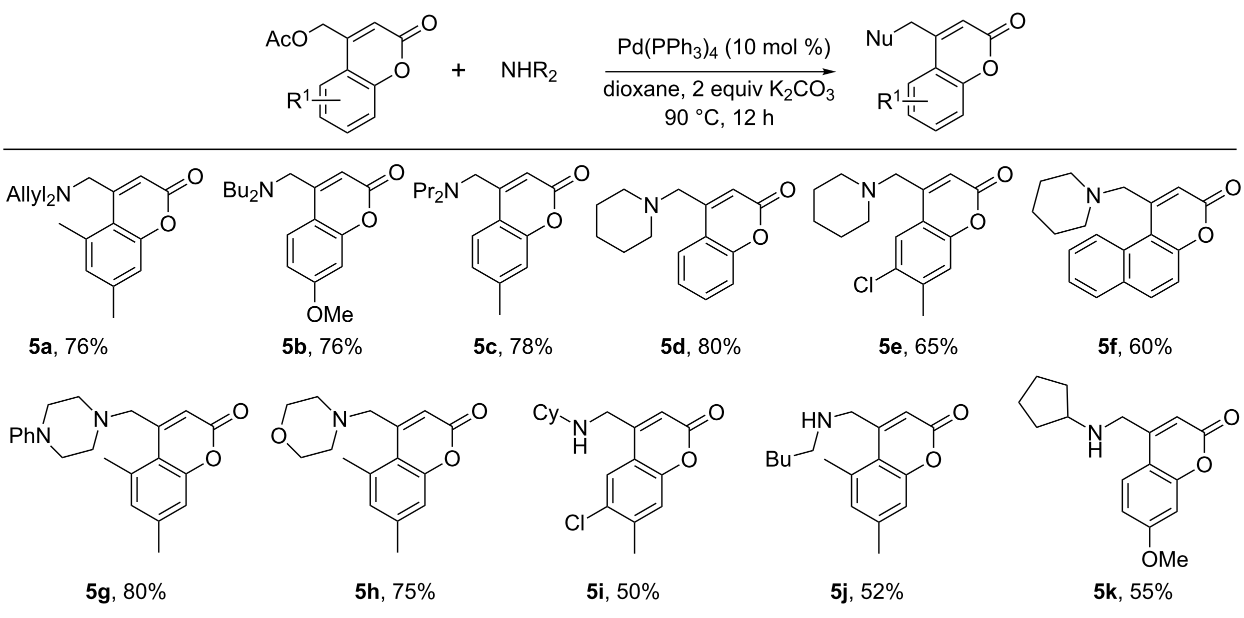


Scheme 5: Scope of the coumarinyl acetate and aryl sulfinate coupling reaction.

In addition to the above Suzuki couplings, acetoxymethylcoumarins were found to undergo palladium-catalyzed substitution with sulfinates and secondary amines under the previously developed palladium-catalysis conditions (Scheme 4). Importantly, related aminomethylcoumarins have been shown to have significant biological activity [6-15].

Regarding the coupling reaction between aryl sulfinates and the coumarinyl acetate, the reaction could be performed without the addition of an external base, since the aryl sulfinate is administered as its anion (Scheme 5). Phenyl (**4a**–**c**) and tolyl (**4d**–**e**) sulfinates were viable coupling partners, giving the product sulfones in good yield. As previously noted, the coumarin core tolerated various simple electronic (**4b**,**c**,**e**) and alkyl (**4a**,**c**,**d**) substitution patterns.

Since (coumarinyl)methylamines are known to possess interesting biological activity, the scope of the amination was investigated in somewhat more detail. Regarding the scope of the amine and coumarinyl acetate coupling reaction, dialkyl (**5a**–**c**) and the cyclic amines pyrrolidine (**5d**–**5f**), pyrazine (**5g**), and morpholine (**5h**) were competent coupling partners (Scheme 6). Primary amines were also compatible coupling partners, although under these conditions, the reaction never went to full conversion (**5i**–**k**).



Scheme 6: Scope of the coumarinyl acetate and amine coupling reaction.

As mentioned previously, we were devising this approach to coumarin substitution not only for the sake of new chemical methodology, but also because this approach could easily lead to rapid library synthesis. As aminomethylcoumarins are a biologically active chemical motif [6-15], we set out to produce a 128-member library of aminated coumarins using our method, with the goal of making unique, biologically active molecules (Figure 2). To begin, an 8 × 16 library (coumarin **C1–8** × amine **A1–16**) of aminomethylcoumarins was devised for preparation by using a Chemspeed SLT100 automated synthesizer. For automated synthesis, the procedure and workflow was modified somewhat for optimal yield. Specifically, the loading of Pd was lowered to 3 mol % and the quantity of amine was raised to 1.5 equivalents to ensure complete conversion. Using the workflow shown in Figure 2 for the reaction of coumarin **C3** with diallylamine **A4**, followed by filtration through a silica SPE, produced product **C3A4** in 74% yield in a test case. In addition, the product was determined to contain 2% PPh_3 impurity. Thus, it was concluded that the entire library should be purified by mass-directed fractionation to ensure high-quality compounds for biological screening.

Regarding the library, coumarins and amines were chosen with diverse structures and properties in order to access the most chemical space within the aminomethylcoumarin family (Figure 2). The coumarins utilized had various electronic properties and substitution patterns. A polyaromatic coumarin was also screened (**C4**). Similarly, a diverse array of amines was chosen. Aside from simple dialkylamines, cyclic and heteroatom-containing amines were utilized. Amines with various functional groups, such as amides, aromatics, olefins, and alkyne substitution patterns, were also incorporated in this library. The automated library synthesis had a success rate of >85%, with the desired products isolated in high purity [63]. Taking center cuts by using mass-directed fractionation ensured that compounds were isolated in >95% purity; however, purity was achieved at some expense to the isolated yields, which were typically lower (5–75%) than those achieved in batch reactions. While most compounds were obtained in sufficient quantity for biological screening, the yields were variable (Figure 3). In particular, coumarins **C6**, **C2** and **C8** provided lower average yields than the other coumarin cores. Thus, it appears that 6,7-substitution of the coumarin core is somewhat problematic. In addition, analysis of the library yields indicates that *N*-arylpiperazines **A8** and **A9** in addition to propargylamine **A15** were the most problematic. Perhaps unsurprisingly, the amine that provided the highest yields and highest success rate was diallyl amine, which was used for initial validation of the Chemspeed method (see above). In addition, piperidine and the simple open-chain dialkyl amines also provided good yields and high success rates.

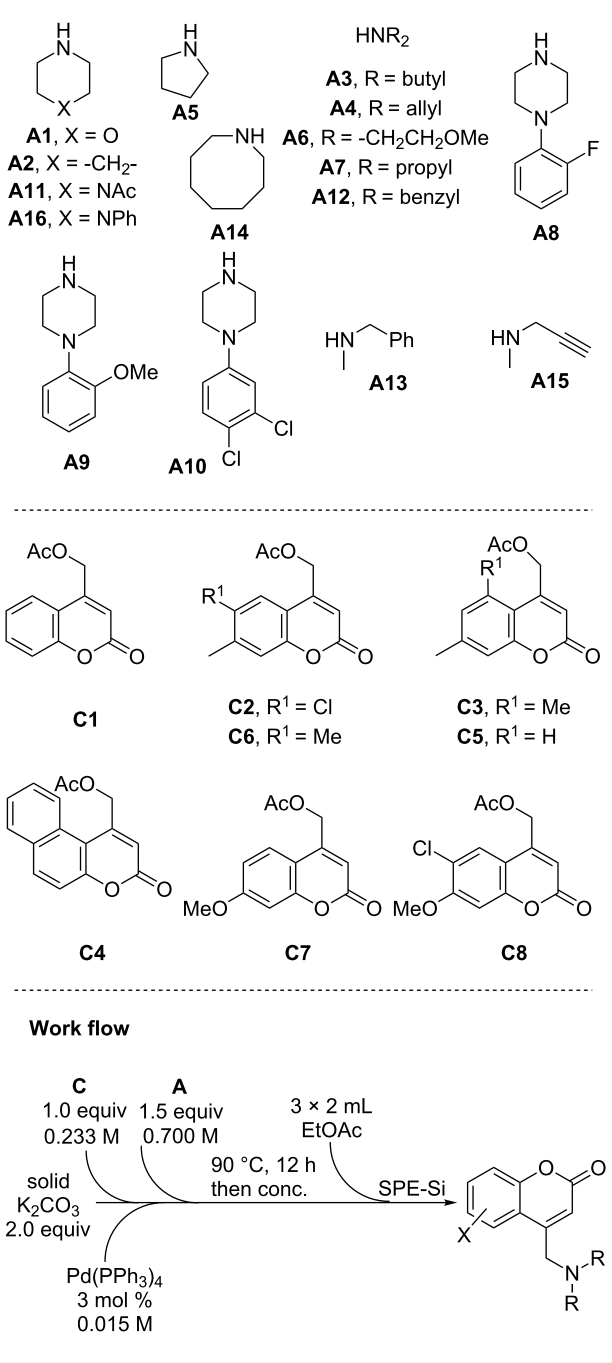


Figure 2: Library planning for amine (**A**) and coumarin (**C**) coupling partners.

Conclusion

In conclusion, we have developed a simple and general strategy for the palladium-catalyzed substitution of coumarins selectively at an exomethyl position. This approach allowed the coupling of various C-,N-, and S-based nucleophiles under mild conditions. We also utilized this approach in the synthesis of a 128-member chemical library appropriate for biological screening.

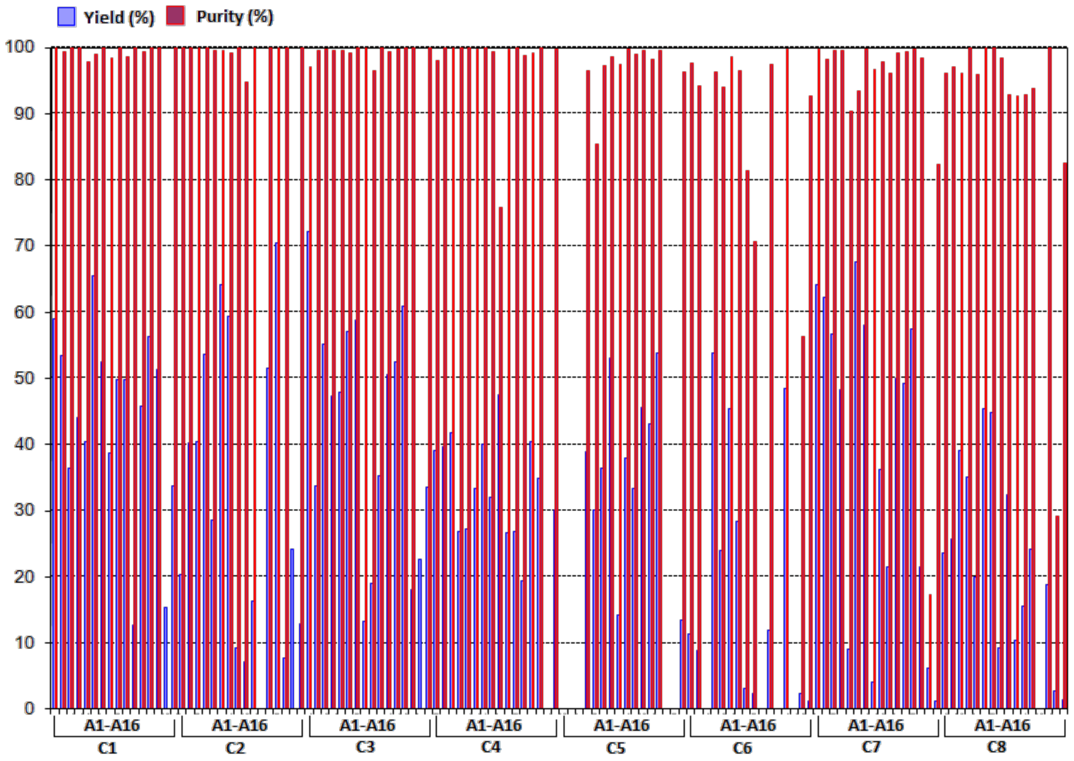


Figure 3: Results for the synthesis of a 128-member library of aminated coumarins by using the Chemspeed SLT100 automated synthesizer. Purified by an automated preparative reverse-phase HPLC (Waters 2767 Mass Directed Fractionation) detected by UV (270 nm). Purity was determined by reverse-phase HPLC (Waters Alliance 2795 system) with peak area (UV) at 214 nm.

Supporting Information

Supporting Information File 1

Experimental data and ^{1}H, ^{13}C, and IR, and HRMS data for new compounds produced in batch.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-133-S1.pdf]

Supporting Information File 2

Detailed results of the library analysis are likewise included.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-133-S2.pdf]

Acknowledgements

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See for related coupling of benzyl acetates with sulfinates.
63. “Success rate” is defined as >10 mg isolated in >95% purity.

License and Terms

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Photochemistry with laser radiation in condensed phase using miniaturized photoreactors

Elke Bremus-Köbberling[1], Arnold Gillner[1], Frank Avemaria[2], Céline Réthoré[2]
and Stefan Bräse*[2,3]

Full Research Paper

Address:
[1]Fraunhofer Institute for Laser Technology, Steinbachstrasse 15, D-52074 Aachen, Germany, [2]Institute of Organic Chemistry, Karlsruhe Institute of Technology, Fritz-Haber-Weg 6, D-76131 Karlsruhe, Germany and [3]Institute of Toxicology and Genetics, Karlsruhe Institute of Technology, Hermann-von-Helmholtz-Platz 1, D-76344 Eggenstein-Leopoldshafen, Germany

Email:
Stefan Bräse* - braese@kit.edu

* Corresponding author

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Abstract

Miniaturized microreactors enable photochemistry with laser irradiation in flow mode to convert azidobiphenyl into carbazole with high efficiency.

Introduction

Classical combinatorial chemistry [1,2] approaches usually aim at the synthesis of multi-milligram amounts of new compounds to extend screening decks used in multiple screening campaigns [3]. An alternative method enabled by the maturing microreaction technology and the use of flow chemistry [4-6] is the integration of synthesis and screening in one integrated lab-on-a-chip approach [7].

Using this methodology we have integrated photochemistry in a miniaturized reaction setup to enable combinatorial flow chemistry in lab-on-a-chip applications.

Photochemical processes are in this case particularly interesting because of their enhanced molecular activation [8]. Photochemistry in microreactors is an emerging research area [9], and especially photocatalytic reactions have been investigated in detail by Matsushita et al. [10,11]. To date there are a couple of reported examples combining miniaturized reaction systems with synthetic laser photochemistry [5,6,9,12-28].

The influence of photons, which are delivered via a suitable light-transparent window, on the processes running in miniaturized photoreactors, is investigated with a focus on increasing the yield and selectivity as well as decreasing the reaction time. Photochemistry with laser radiation is a promising tool to broaden the application spectrum of miniaturized systems, by facilitating a powerful activation step due to a wide range of available wavelengths and energy ranges [29,30]. Moreover, the optical systems can be designed in a way that the reaction initiation by photons and an additional online analysis of the running reaction is feasible.

Results and Discussion

Design and fabrication

In order to realize photochemical synthesis, several reactors and small reactor arrays with reaction volumes of approximately 1 mL down to 35 µL were developed. These reactors were especially designed for the stimulation of photochemical reactions (UV–vis radiation) as well as for demanding reaction conditions, such as the rapid elevation of temperature (with pulsed IR-laser radiation) or pressure pulses (due to the evaporation of the solvent upon the introduction of energy).

Several microstructured reactor types were designed and produced for reactions in the liquid phase. They are equipped with quartz-glass cover plates, transparent to the laser radiation, pressed onto an appropriate sealing material. Moreover, channels suitable for the mixing and reaction of two or more isopycnic solutions were built in a polymer bloc by mechanical treatment [31]. The provision of bubble-free fluid is ensured in this case by microchannels in at least two levels, which are built from corresponding structured layers. These reactors were made of polyether ether ketone (PEEK) and polytetrafluoroethylene (PTFE) [32] to study the influence of side reactions with the reactor material, which could reduce the yield of the desired reaction product. The multilayer system is placed in a stainless-steel frame.

With this type of reactor, it is possible to realize a series of reactions in parallel by arranging the reactor chambers in an (n × m) matrix. The microreactors applied for this study have four reaction chambers with varying volumes of the chambers due to increasing depth, and different connections for the reagent entrance (Figure 1).

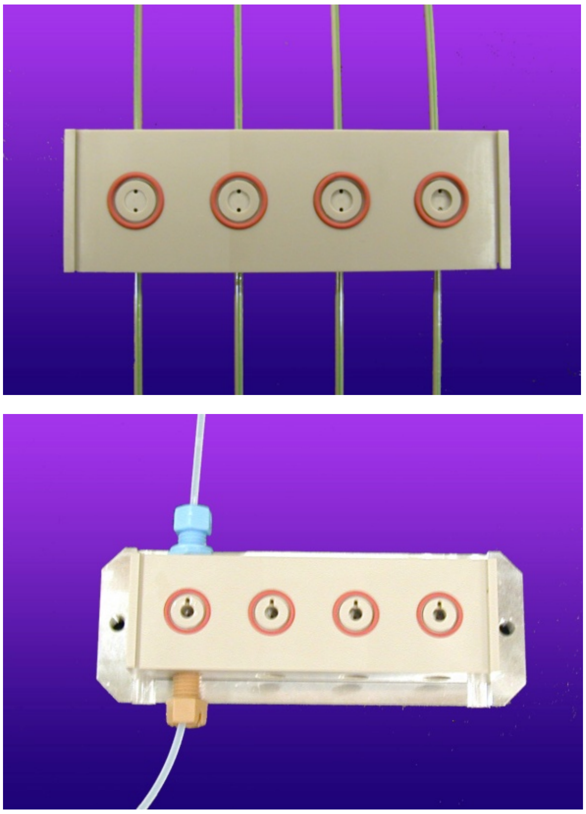
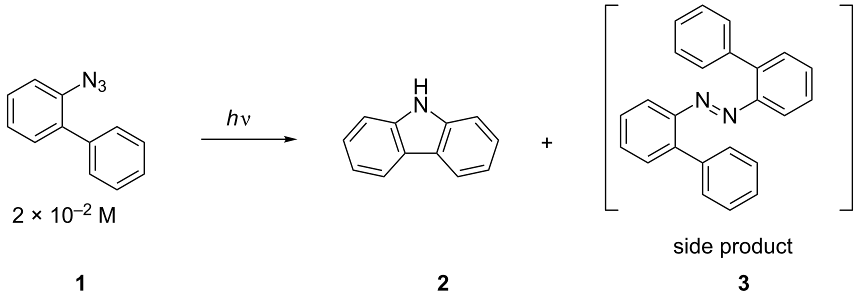


Figure 1: Four-fold PEEK-reactors with increasing chamber depths from left to right and different techniques of fluid connection; top: glued PEEK-capillaries, bottom: ¼ in. screw connections.

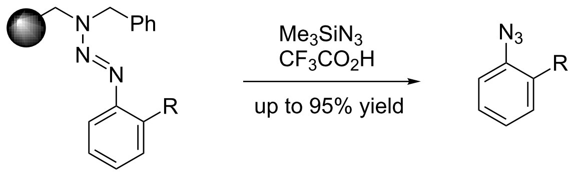
Photochemistry

The combinatorial synthesis of heterocycles and among them of carbazole is of particular interest since they are potential active pharmaceutical compounds [33-35]. The photolysis of 2-azidobiphenyl (**1**) with the help of a conventional UV-lamp has been used for the synthesis of carbazole (**2**) since 1960 (Scheme 1) [36-39].



Scheme 1: Synthesis of carbazole (**2**) by photolysis.

However, there are only a few examples of substituted products obtained by this reaction, and several side-products, such as the corresponding azo-derivatives, are usually formed [36,40-44]. During the past few years, we successfully employed triazene resins, such as **4**, which are readily available from aniline in the synthesis of a library of aromatic derivatives [45-48]. Moreover, triazene-resins are perfectly suitable for the synthesis of arylazides **5** (Scheme 2) [49].



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Scheme 2: Synthesis of arylazides **2** by solid-phase synthesis.

The photochemical decomposition of arylazides into carbazoles is appropriate for application in miniaturized photoreactors, since significant results can be observed by an online analysis through HPLC and GC [50]. Because of the miniaturization, online analysis is especially suitable for our setup.

We therefore investigated whether the photoreaction can be realized in miniaturized photoreactors and to what extent the use of a laser as a photon source is advantageous. The irradiation of 2-azidobiphenyl (**1**) in methanol with a conventional xenon lamp (400 W, λ > 345 nm) required 18 h for 50% yield (95% selectivity) in a 10 mm cell with an 8 mm light-exposure diameter (Figure 2).

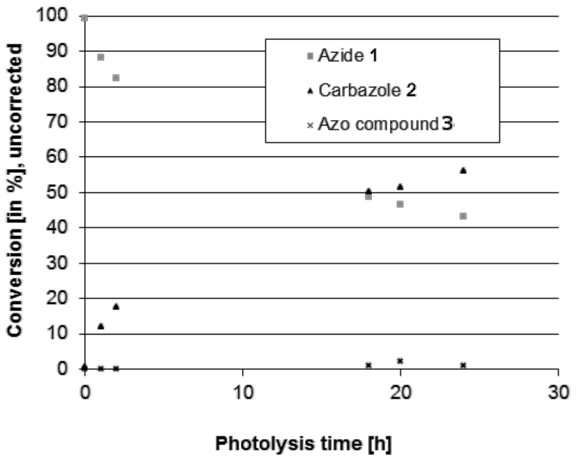

Figure 2: Photolysis results in batch setup (flask) with a xenon lamp (400 W, λ > 345 nm).

Frequency-tripled Nd:YAG laser radiation (λ = 355 nm, 8 kHz pulse frequency; pulse duration 26 ns) was chosen because the wavelength is close to that of the applied UV-lamp, 355 nm is usually within the absorption area of azides, and this laser type is commonly used in most laser labs. We applied a single-pulse power of 0.16 to 3 W resulting in pulse energies between 4 and 87 nJ and energy densities of approximately 0.02 to 0.17 µJ/cm^2 within a defocused laser spot of 0.2 to 0.5 cm^2, to carry out the same reaction (Scheme 1), but carbazole was obtained much faster from 2-azidobiphenyl (**1**). Compared to conventional UV sources, the use of laser irradiation clearly accelerated the reaction: from 18 h (Xe lamp, Figure 2) to 30 s (Nd:YAG laser) for 50% yield and 95% selectivity, calculated from the data presented in Figure 3. This reaction was successfully carried out in a miniaturized photoreactor (Figures 3–6).

The monomolecular reaction can be realized by using laser radiation of 355 nm wavelength as a photon source, in a clean way, avoiding almost completely the formation of the undesired

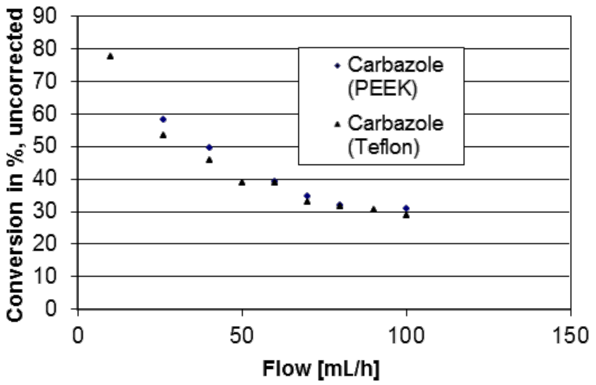

Figure 3: Carbazole synthesis in miniaturized photoreactors Type II (PEEK and Teflon), flow control, P = 0.92 W.

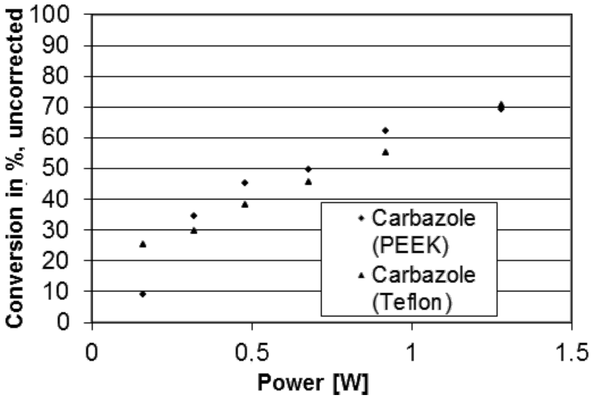

Figure 4: Carbazole synthesis in miniaturized photoreactors Type II (PEEK and Teflon), power control, flow 26 mL/h.

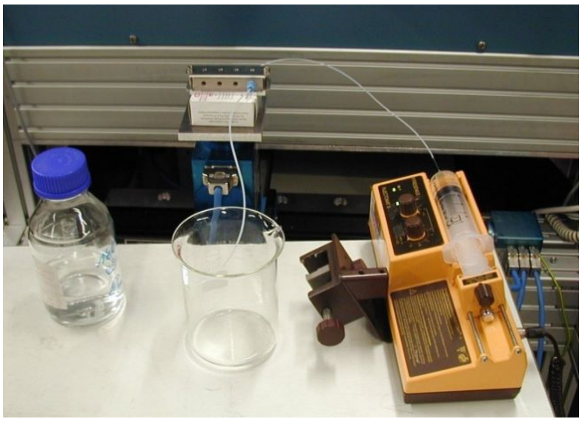

Figure 5: Test setup with continuously operating, miniaturized photoreactor.

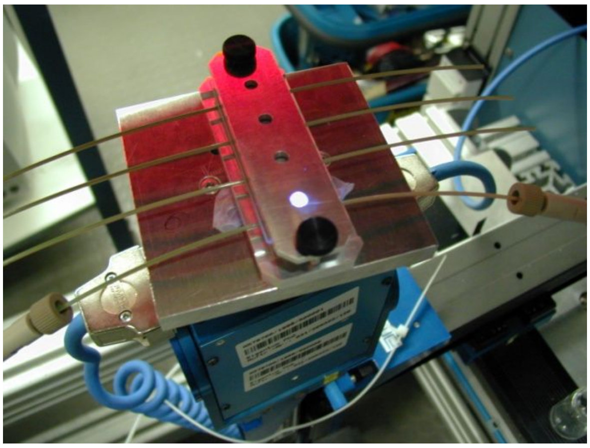

Figure 6: The miniaturized photoreactor (PEEK) during photolysis.

diazo derivatives **3**. The side reaction is supposedly reduced due to a lesser effect of heating owing to the small bandwidth irradiation and minimized exposure time through the miniaturized flow setup.

During these tests, it was shown that a largely better selectivity can be achieved, compared to the one obtained in a standard UV irradiation setup (Figure 2). Experiments were performed in batch as well as flow-injection configuration. The continuous process used allowed us to vary the residence time in the reactor by regulating the flow speed of the reactant solution, with the help of a syringe pump (Figure 5).

For this study, reactors made of PEEK, as well as PTFE reactors were used, leading to similar yields of carbazole (Figure 3 and Figure 4), showing no major influence of the reactor material on the reaction.

The deviations from linearity in the low power area of Figure 4 can be attributed to fluctuations of the laser power. For the high-power area, a correlation between yield, power and reaction time, which can be explained by kinetics, is observed.

Conclusion

The preparation and application of polymeric, miniaturized photoreactors, equipped for the effective use of photons in the reaction chamber, provided by frequency-converted laser sources, was successfully shown.

With these reactors or reactor components, the photonic influence on reactions in miniaturized photoreactors was proven to be useful in parameter studies in which laser power and flow rate were varied.

The advantages of laser chemistry in the condensed phase compared to standard photochemical approaches have been shown in this preliminary study, proving the suitability of laser photochemistry for organic synthesis. Thanks to the further miniaturization and the availability of new moderately priced laser systems even better suited beam sources can be provided for photochemistry.

In the described experiments, laser radiation of 355 nm wavelength (frequency-tripled Nd:YAG) was used. Since the spectral range of interest for most photoreactions ranges from the ultraviolet to the visible region, tunable laser systems (optical parametric oscillators) feature promising properties for use photochemical experiments. Thus, the irradiation wavelength can be adapted to the needs of the reaction (e.g., to a shifted absorption maximum of the reactant due to substitution) facilitating a large range of applications of this technique. Furthermore, IR laser sources (diode laser, Nd:YAG laser, CO_2 laser) could be applied for pulsed temperature and pressure elevation in microreactors, as well as microwave stimulation to accelerate reactions.

Experimental

All starting materials and products were characterized by standard techniques (^1H NMR, ^{13}C NMR, and elemental analysis) and are compared with authentic samples. The products were analyzed by GC–MS (internal standard, dodecane) and/or HPLC.

A solution of 2-azidobiphenyl (**1**) was continuously added to a miniaturized reactor of type II (see Figure 1, dimension of the reactor chamber 3 × 5 mm, 35 µL volume) with a syringe pump. The chamber was continuously irradiated with a Nd:YAG laser (355 nm). At a constant flow of 26 mL/h, the laser-pulse power was varied from 0.16 to 1.28 W. Furthermore, at a constant intermediate power of 0.92 W the flow rate (10 to 100 mL/h) and therefore the dwell time (exposure time) in the reactor was varied. The yield was determined by HPLC.

Supporting Information

Supporting Information File 1

Description of the flow reactor setup, kinetics, experimental procedures and spectroscopic data of all compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-135-S1.pdf]

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Exploring chemical diversity via a modular reaction pairing strategy

Joanna K. Loh[1], Sun Young Yoon[1], Thiwanka B. Samarakoon[1], Alan Rolfe[1], Patrick Porubsky[2], Benjamin Neuenswander[2], Gerald H. Lushington[1,2] and Paul R. Hanson*[1,2]

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Address:
[1]Department of Chemistry, The University of Kansas, 1251 Wescoe Hall Drive, Lawrence, KS 66045-7582, USA and [2]The University of Kansas, Center for Chemical Methodologies and Library Development (KU-CMLD), 2034 Becker Drive, Shankel Structural Biology Center, West Campus, Lawrence, KS 66047-3761, USA

Email:
Paul R. Hanson* - phanson@ku.edu

* Corresponding author

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Abstract

The efficient synthesis of an 80-member library of unique benzoxathiazocine 1,1-dioxides by a microwave-assisted, intermolecular nucleophilic aromatic substitution (S_NAr) diversification pathway is reported. Eight benzofused sultam cores were generated by means of a sulfonylation/S_NAr/Mitsunobu reaction pairing protocol, and subsequently diversified by intermolecular S_NAr with ten chiral, non-racemic amine/amino alcohol building blocks. Computational analyses were employed to explore and evaluate the chemical diversity of the library.

Introduction

The demand for functionally diverse chemical libraries has emerged, as rapid advances in the fields of genomics and proteomics during the “post-genome era” have resulted in an increase in potential therapeutic targets for which there are no known small-molecule modulators [1]. The lack of adequate screening technologies, as well as screening collections of molecules, has hindered these efforts [2,3]. In this regard, recent advances in the construction of chemical libraries that are rich in functional diversity, consisting of appendage, functional group, stereochemical and skeletal diversity, have addressed this challenge and also offer new opportunities [4].

Sultams (cyclic sulfonamides) represent a class of compounds with a non-natural chemotype [5,6] that have gained enormous interest in recent years due to their extensive range of biological activities [7-14]. In particular, benzofused sultams, possessing a rich content of sp^3 amine functionality, have shown a wide biological profile, including antipsychotic activity

[15], modulation of histamine H3-receptor [16], glucokinase activation [17,18] and allosteric modulation of AMPA receptor [19], to name but a few (Figure 1). While there are numerous methodologies being reported in the literature for the synthesis of 5-, 6- and 7-membered benzofused sultams, reports on the generation of 8-membered benzofused sultams have been sparse [20-22]. In this regard, our group has focused on the development of several methodologies and protocols for the generation of diverse sultam collections [23-26]. Recent highlights towards these goals include, "click-click-cyclize" [27,28], complementary ambiphile pairing (CAP) [29], and reagent-based DOS [30,31]. In 2011, we reported the development and application of an efficient reaction pairing strategy utilizing three simple reactions, namely sulfonylation, Mitsunobu alkylation and S_NAr, which when combined in different sequences or with different coupling reagents, give access to skeletally diverse sultams, including the title compounds and the 8-membered bridged, benzofused sultams [32]. Building on this strategy, we herein report the design and synthesis of an 80-member library of benzofused sultams by a microwave-assisted, intermolecular S_NAr diversification of core benzoxathiazocine 1,1-dioxide scaffolds [33-36] (Scheme 1).

Results and Discussion

Initial efforts focused on the synthesis of eight core scaffolds **1**–**8** on multigram scale through the use of three efficient steps, namely sulfonylation, Mitsunobu alkylation and S_NAr, to generate both stereoisomers of each core [37] (Scheme 2). The bridged benzofused sultam scaffolds were prepared by a sulfonylation intramolecular S_NAr protocol, reported previously [32], utilizing 3-hydroxypyrrolidine in combination with 2,4-difluoro- and 2,6-difluorobenzenesulfonyl chloride. The nonbridged scaffolds were also prepared as reported previously by a sulfonylation intermolecular Mitsunobu alkylation/intramolecular S_NAr protocol [32]. 2,4-Difluoro- and 2,6-difluorobenzenesulfonyl chloride were sulfonylated with cyclopropyl amine followed by Mitsunobu alkylation with 3-silyloxybutan-1-ol and subsequent one-pot desilylation intramolecular S_NAr alkoxylation (Scheme 2). Each of the scaffolds **1**–**8** was prepared on a 2.5 g scale.

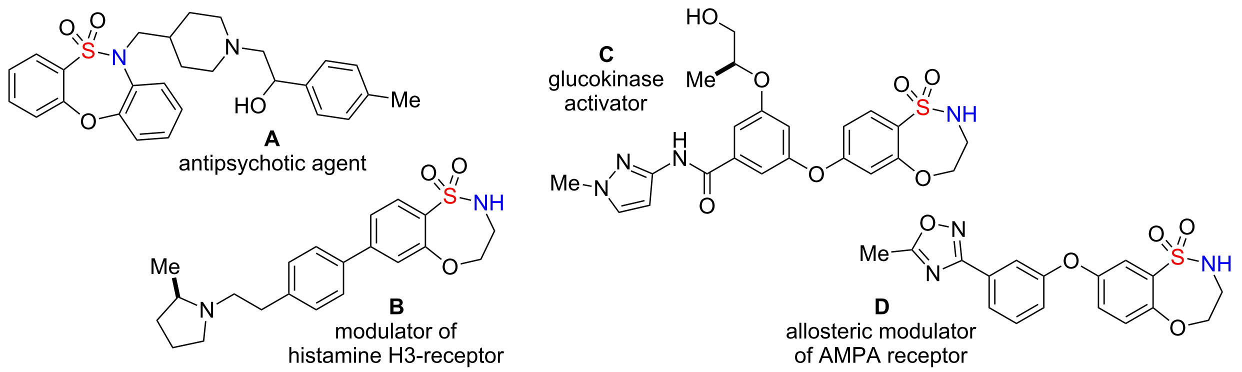
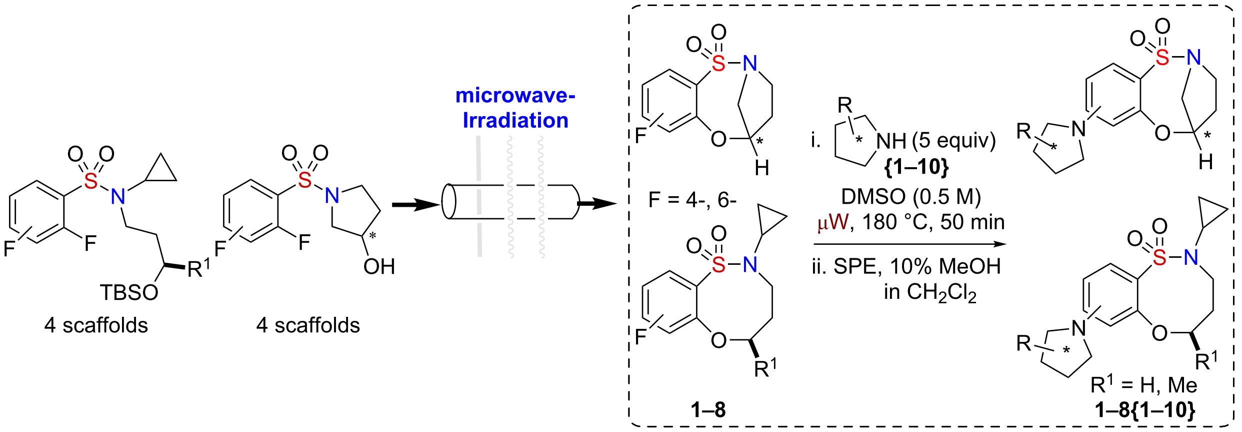
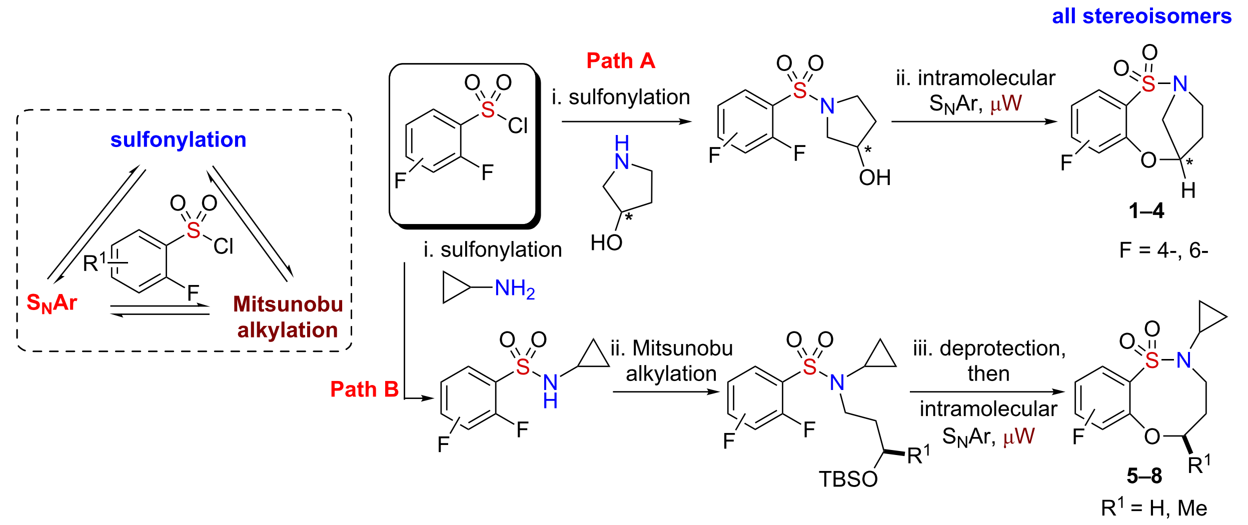


Figure 1: Biologically active benzofused sultams.



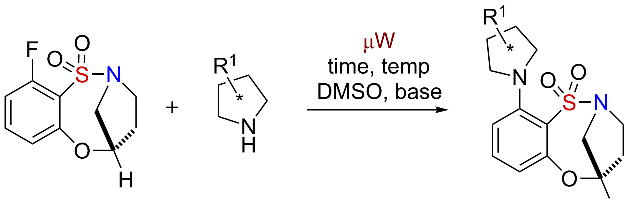
Scheme 1: Proposed library generation by microwave-assisted intermolecular S_NAr diversification reaction.



Scheme 2: Utilization of a reaction pairing strategy for the synthesis of benzoxathiazocine 1,1-dioxides core scaffolds **1–8**.

With scaffolds **1–8** in hand, efforts were focused on the diversification of these core scaffolds with a variety of chiral, non-racemic amines/amino alcohols, by intermolecular S_NAr utilizing benzoxathiazocine 1,1-dioxide **4** as the test substrate (Table 1). A variety of reaction conditions (equiv of amine, presence of base, concentration of solvent, time and temperature) were examined to identify the optimal conditions. Our initial attempt gave a good yield of 94% with 4.4 equiv of amine, an absence of base, at a concentration of 0.1 M of DMSO, and under microwave irradiation at 150 °C for 20 min (Table 1, entry 2). However, when a hindered amine was utilized it resulted in low (29%) or no yield, even when the reaction time was extended (Table 1, entry 3) or when slightly harsher conditions were used (Table 1, entry 4). Thus, more

Table 1: Optimization studies for the S_NAr reaction utilizing sultam **4**.



4 amine **4{1–10}**

Entry	Amine	Equiv	Base	Conc. (M)	Time (min)	Temp (°C)	Yield[a] (%)
1	(*R*)-3-pyrrolidinol	1.3	Cs_2CO_3	0.1	30	150	NA
2	(*R*)-3-pyrrolidinol	4.4	—	0.1	20	150	94
3	(*S*)-2-pyrrolidine methanol	4.4	—	0.1	30	150	29
4	(*S*)-2-methoxymethyl pyrrolidine	4.3	—	0.1	50	180	NA
5	(*S*)-3-dimethylamino pyrrolidine	5.0	—	0.1	50	180	88
6	(*R*)-2-methylpyrrolidine	5.0	—	0.1	30	150	42
7	(*R*)-2-methylpyrrolidine	5.0	—	0.1	40	180	62[b]
8	(*R*)-2-methylpyrrolidine	5.0	—	0.1	50	180	70
9	(*R*)-2-methylpyrrolidine	5.0	—	0.1	60	180	35
10	(*R*)-2-methylpyrrolidine	5.0	—	0.5	50	180	95[b]
11	(*R*)-2-methylpyrrolidine	5.0	—	1.0	50	180	83[b]

[a]Yields are reported after flash column chromatography on silica gel. [b]Crude yield as judged by ^1H NMR.

experiments were performed to investigate other factors, in which the nature and equiv of amine remained the same while the concentration of solvent, temperature and reaction time were increased. Finally, the optimal results were obtained in the absence of base, with 5 equiv of amine, at a concentration of 0.5 M in DMSO, and under 50 min of microwave irradiation at 180 °C (Table 1, entry 10). All reactions were performed under identical conditions, thus attempts were not made to optimize the conditions further for individual substrates.

Library design

An 80-member, full matrix library was designed by using in silico analysis [38]. Eight benzoxathiazocine 1,1-dioxide scaffolds **1**–**8** were designed, of which library **I** (**1**–**4**) was composed of the entire spectrum of possible stereoisomers, and library **II** (**5**–**8**) was composed of two sets of benzofused sultams having an H or Me group at the R^1 position. The use of all possible stereoisomers provides the opportunity to generate stereochemical SAR (SSAR) for each building block combination. With the core sultams in hand, a virtual library incorporating all possible combinations of the building blocks of the secondary amines **{1**–**10}** was constructed for each scaffold (Figure 2). Physico-chemical property filters were applied, guiding the elimination of undesirable building blocks that led to products with undesirable in silico properties (see Supporting Information File 1 for full in silico data and detailed information on the calculations). These metric filters included standard Lipinski's rule of five parameters (molecular weight <500, ClogP <5.0, number of H-acceptors <10, and number of H-donors <5), in addition to consideration of the number of rotatable bonds (<5) and polar surface area. Absorption, distribution, metabolism and excretion (ADME) properties were calculated by using the Volsurf program [39]. Cartesian grid-based chemical diversity analysis was performed according to the method described previously [40], by using standard H-aware 3D BCUT descriptors comparing against the MLSMR screening set (ca. 7/2010; ~330,000 unique chemical structures). Guided by this library design analysis, benzoxathiazocine 1,1-dioxides scaffolds **1**–**8** and amines **{1**–**10}** were chosen to generate the aforementioned 80-member library.

Validation and library generation

With the optimized conditions in hand, a 20-member validation library was prepared by using scaffolds selected from **1**–**5** and amines **{1**–**10}** in DMSO (0.5 M) at 180 °C for 50 min, in 1 dram vials, using the Anton Parr Synthos 3000® platform (Table 2) [41]. Upon completion, the crude reaction mixtures were diluted, filtered through silica SPE, and purified by automated mass-directed HPLC. Library validation was essential to assess both substrate and reaction scope, along with evaluating the application of automated mass-directed HPLC as the final analysis and purification method. Key goals for this compound collection were the synthesis of compounds in >90% purity in 40–50 mg quantities, which would be sufficient for HTS screening in the Molecular Library Probe Center Network (MLPCN) (20 mg), for external biological outreach screening

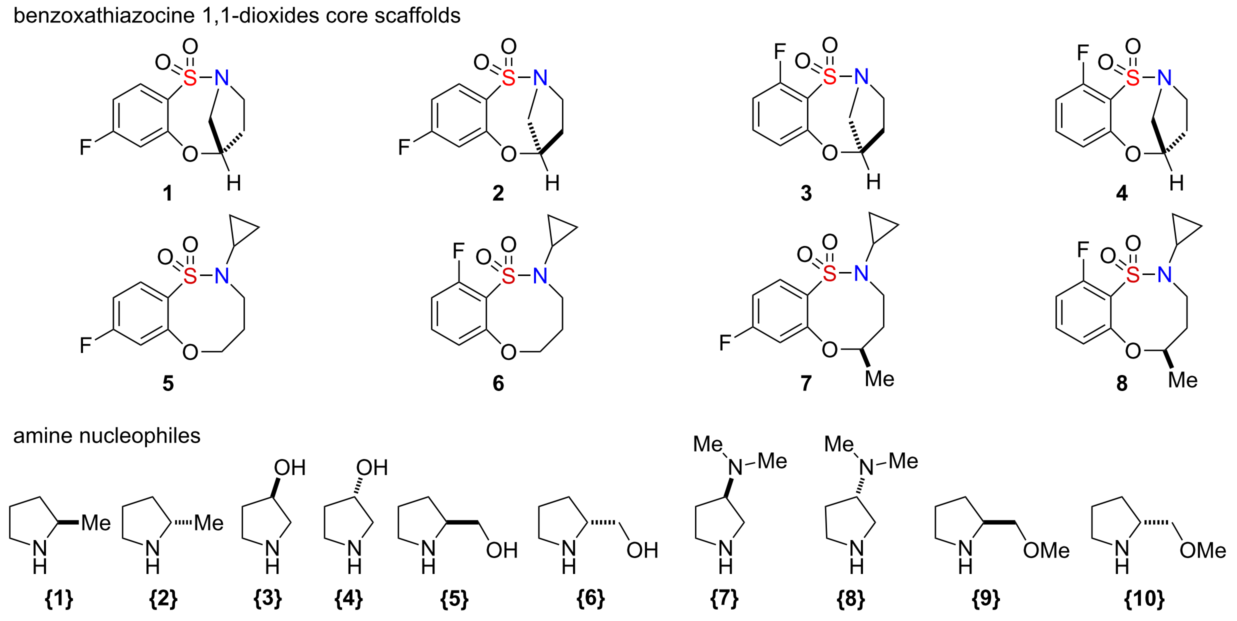
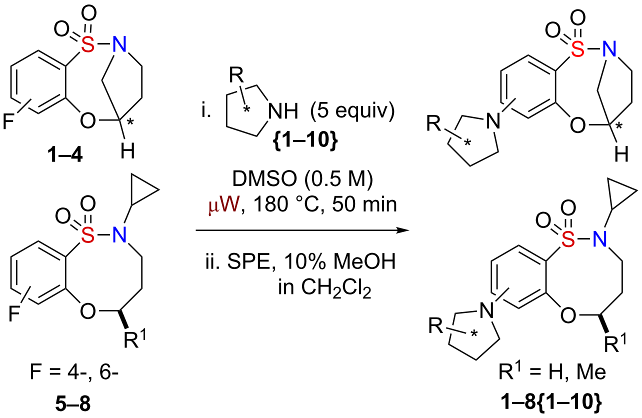


Figure 2: Benzoxathiazocine 1,1-dioxides **1–8** and amine library building blocks **{1–10}**.

Table 2: Use of a 20-member validation library to probe the reaction scope.



Sultam[a]	Purity (%)[b]	Yield (%)[b]	Quantity (mg)	Sultam[a]	Purity (%)[b]	Yield (%)[b]	Quantity (mg)
1{3}	99.8	78	79.5	**5{1}**	100	80	79.8
2{3}	99.4	69	70.0	**5{2}**	100	80	79.4
3{3}	100	48	49.3	**5{3}**	100	76	75.8
4{3}	99.7	53	54.1	**5{4}**	100	79	79.1
1{1}	100	71	71.7	**5{5}**	100	83	85.7
1{2}	100	72	73.4	**5{6}**	100	80	83.1
1{4}	99.8	75	76.7	**5{7}**	98.2	17	18.7[c]
1{5}	99.7	69	73.6	**5{8}**	99.9	46	49.2
1{6}	99.6	85	90.2	**5{9}**	99.1	79	85.3
1{8}	100	86	94.9	**5{10}**	99.1	78	83.7

[a]Reaction conditions: benzoxathiazocine 1,1-dioxides **1–8** (1 equiv, 80 mg), dry DMSO (0.5 M) and amine (5 equiv.); [b]purified by automated preparative reverse phase HPLC (detected by mass spectroscopy); purity was assessed by HPLC (214 nm); [c]the low yield obtained was due to instrumental error (see Supporting Information File 1 for more information).

partners (20 mg), and to retain a sample (10 mg) for follow-up evaluation or to resupply the NIH MLPCN. Evaluation of this validation library demonstrated that all 20 members were successfully prepared (average purity = 99.7%, yield = 70%, quantity = 73.0 mg) in the desired sultam final masses, with all 20 possessing a final purity >98%.

With the validation completed, the remaining 60 compounds of both libraries **I** and **II** were synthesized by the diversification of core benzoxathiazocine 1,1-dioxides scaffolds **1**–**8** and amine {**1**–**10**}. Under the optimal S_NAr reaction conditions, libraries **I** and **II** were generated and purified by automated mass-directed HPLC. A total of 80 compounds were prepared and isolated in good yields (average yield 65%), and all compounds had purities greater than 95% after automated purification (see Supporting Information File 1 for all compounds with full numeric data). Final assessment of both libraries **I** and **II** demonstrated that the primary objectives set out in the library design were achieved; final masses ranged between 18–127 mg and the average final mass was 68 mg (original target being 50 mg).

In silico analysis of chemical diversity and drug-likeness

In silico analysis of the molecular library was performed to achieve enhanced drug-like and lead-like properties, as well as to assess the molecular diversity. In order to assess diversity, five computational analyses were performed, including

1. Cartesian grid-based chemical diversity analysis [40]
2. Overlay analysis
3. Principal moments of inertia (PMI) analysis [42]
4. Conformational analysis
5. Quantitative estimate of drug-like (QED) values [43]

Cartesian grid-based chemical diversity analysis

The grid-based diversity analysis protocol, described previously in the Library Design section, provides a simple measure of the relative novelty of a compound. By computing the position of a compound within the molecular property space defined by a large reference set of other interesting compounds, chemical novelty can be estimated from the density of reference compounds in close proximity to the compound of interest.

This analysis suggests that our compounds consistently occupy regions of chemical space that are under-represented within the MLSMR reference set. Specifically, all 80 compounds were located in regions with local compound densities of less than the mean value, with compounds **3{3}**, **4{3}**, **4{4}**, **5{3}** and **5{4}** occupying a particularly sparse region of space (all colocating within a cell whose density was 3.5% of the mean density experienced by the reference compounds), while the least unique eight compounds (**5{5}**, **5{6}**, **7{3}**, **7{4}**, **7{5}**, **7{6}**, **8{3}** and **8{4}**) all colocated in a cell with density equal to 78.9% of the mean density experienced by the reference compounds. The mean local density experienced by the 80 compounds reported herein was only 31.7% of the mean density experienced by the reference compounds. All related information can be found in Supporting Information File 1.

Overlay analysis

The overlay produced for the 80 compounds reported herein is depicted in Figure 3 and provides a rudimentary indication of the shape distribution and diversity evident in this library. Orientations 3iv and 3v collectively suggest that the library generally tends toward elongated (rod-like) structures, while the apparent distribution of functional substituents across angles spanning the better part of the whole sphere surrounding the conserved core, suggests that the library as a whole achieves a reasonable level of shape-based diversity.

Principal moments of inertia (PMI) analysis

The rudimentary information gleaned from overlay analysis can be quantified more rigorously via principal moments of inertia (PMI) analysis, which was also employed herein to assess the molecular diversity [42]. PMI analysis utilizes shape-based descriptors: The minimum energy conformation of each library member is determined, PMI ratios are calculated and normalized, and a subsequent triangular plot depicts the shape diversity of the library. The analysis reveals that the 80 compounds generally mirror the shape distribution of the set of 771 known drugs (Figure 4), thus demonstrating the potential drug-likeness of our scaffold. In contrast, some of the compounds are located in the unpopulated region of chemical space, illustrating the novel nature of some of our compounds from the perspective of molecular shape.

Conformational analysis

While overlay and PMI analysis tend to focus on the shape diversity of libraries as a function of the combined structure of

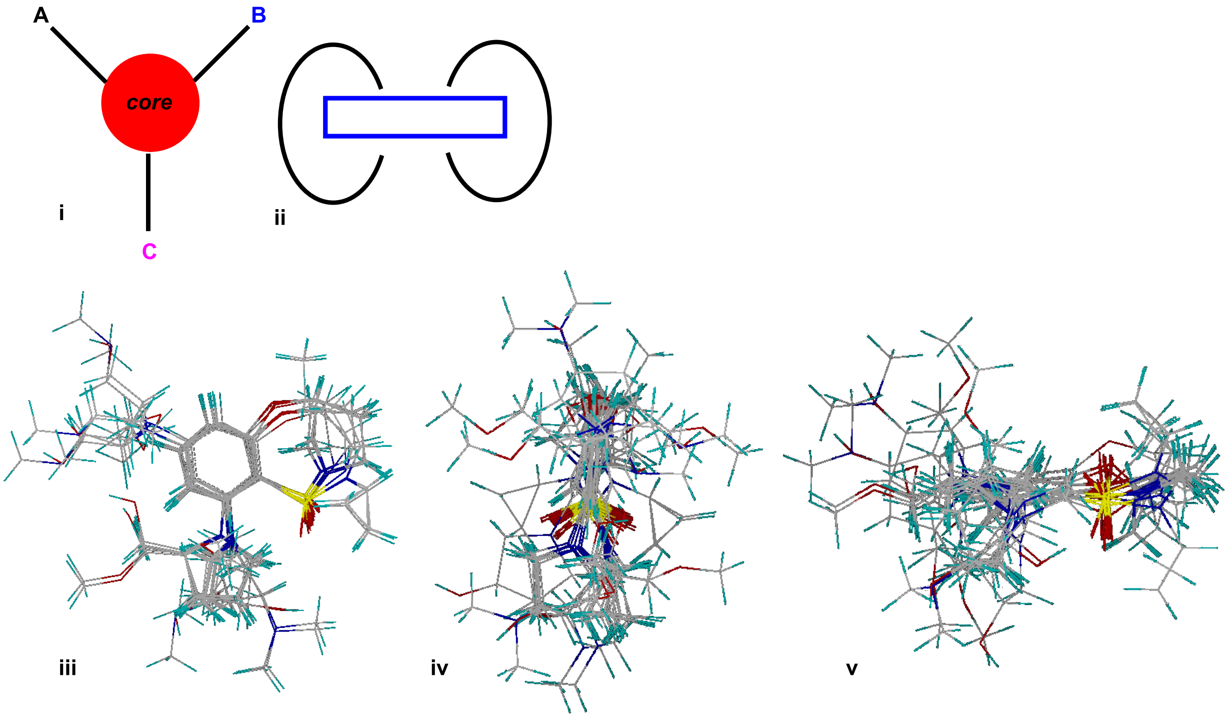


Figure 3: (i) Simple cartoon of the library compounds, with a core of MW ~ 80, based on Lipinski's rules (MW < 500), and comprising three substituents, each having MW < 140, to establish different functional groups. (ii) This cartoon demonstrates that the substituents extend out of the core in a circular motion. (iii) Overlay images exhibiting the common core in these 80 compounds. (iv) and (v) both overlay images revealing that the substituents are extending outwards in the circular motion as mentioned in (ii).

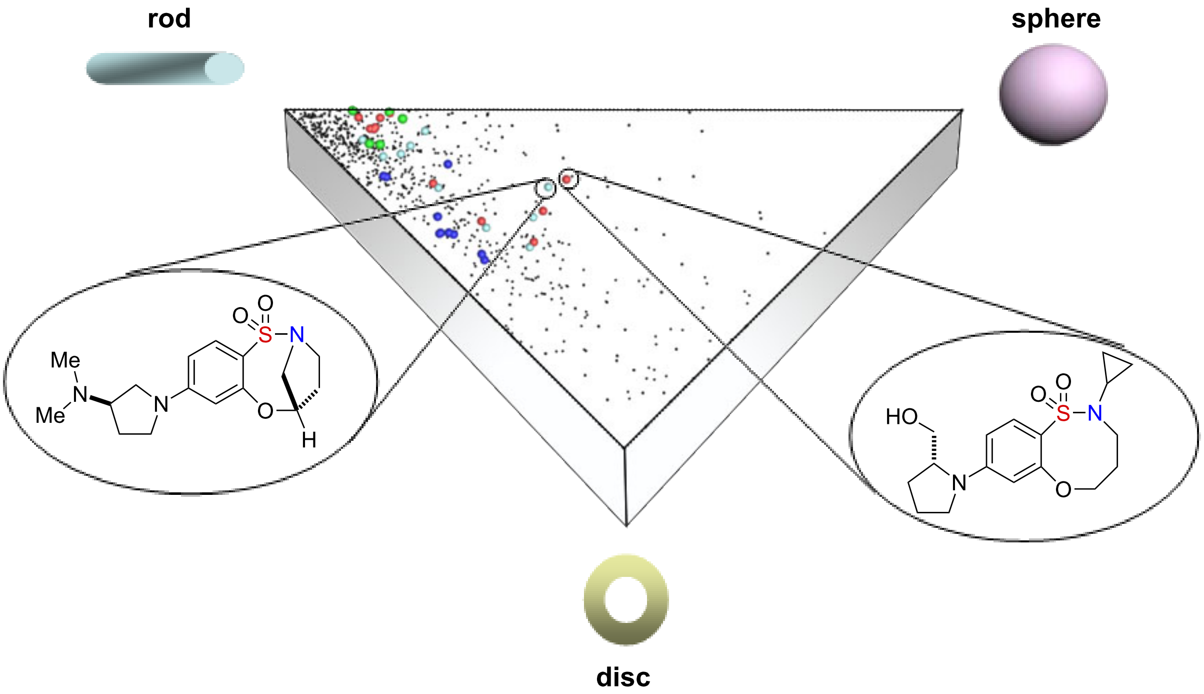


Figure 4: Distribution of 80 compounds (colored spheres) relative to the set of 771 known orally available drugs (black dots) [43].

the core scaffold and all known substituents, it is useful to quantify the conformational diversity of the core alone, since this provides additional insight into the prospects for sampling new diversity space as a function of hitherto untested substituents. To quantify this, computations were generated for the mean pairwise atomic root-mean-squared distance (RMSD) using a small set of representative products from the library that was synthesized and compared this value with similar pairwise RMSD calculations for other analogous libraries (Figure 5). In all cases, the structures have been sketched and optimized in SYBYL [44], according to default molecular mechanics settings, and the resulting optimized structures were then all mutually aligned in order to minimize the total pairwise RMSD among conserved scaffold core atoms. The pairwise RMSD values reported in Figure 5 also only correspond to conserved core atoms. The fact that the highlighted core scaffold achieves

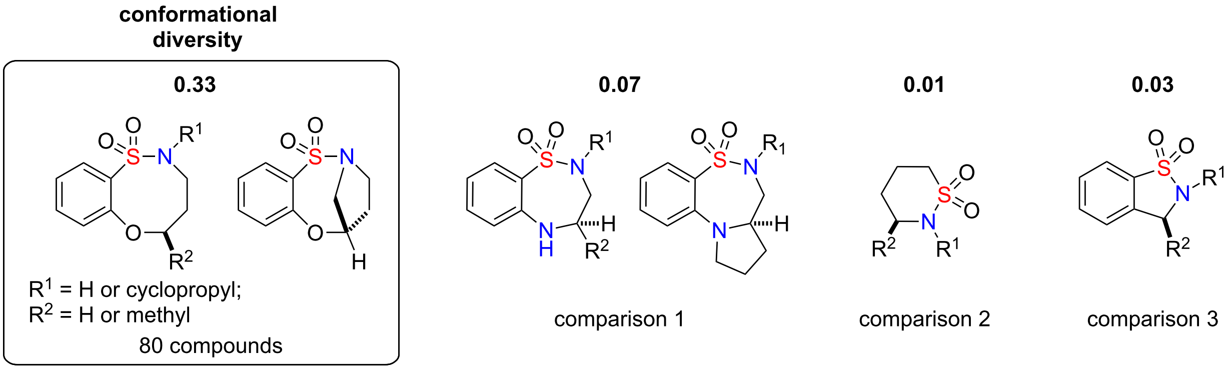


Figure 5: Comparison of a small set of our representative compounds versus two sultams synthesized by our group as well as a biological active compound [11].

a much higher RMSD than the other libraries suggests that the scaffold conformation is more sensitive to the choice of substituents, whereas the other libraries exhibit little variation as a function of different substituents. This greater sensitivity on the part of the highlighted library should correspond to greater conformational diversity, which implies sampling of a broader range of property and pharmacophore space than those libraries with lesser conformational diversity.

Quantitative estimate of drug-like (QED) values and *Z*-scores

While molecular diversity is in itself a topic of intellectual value, in applied sciences it is important to balance this intellectual aspect with suitability toward the intended application. In other words, if one intends to synthesize novel compounds for potential pharmacological applications it is critical that the compounds not only be unique but also be drug-like. Quantifying drug-likeness is one of the numerous methods that are regularly utilized as useful guidelines for early stage drug discovery. A measure of drug-likeness based on the concept of desirability called the quantitative estimate of drug-likeness (QED) has been proposed [43]. The QED concept is a simple approach to multicriteria optimization whereby compound desirability is defined as a function of eight molecular properties, i.e., molecular weight, ALogP, polar surface area, H-bond donor, acceptor, rotatable bond and aryl ring counts, and the presence of structural alerts. The weighted QED values were calculated based on the equation provided by Hopkins et al., mapping compounds to a range from 0 to 1, in which a value of 1 indicates that all properties are within a favorable range. Based on this measure, the 80 compounds reported herein may have elevated prospects for interesting chemical biology: the lowest QED values among these 80 compounds (QED = 0.819 for **1{3}** and **1{4}**) are actually significantly above the mean value (QED = 0.615) for the 771 known drugs analyzed by Hopkins et al., while several distinct scaffolds within our library produced QED values of greater than 0.90 (Figure 6).

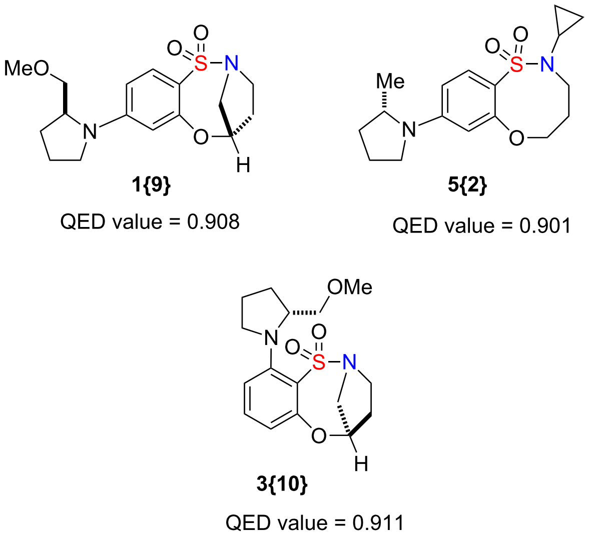


Figure 6: Three representative compounds with high QED values.

To characterize the QED scores of our scaffolds relative to the reference set of 771 known drugs, we computed mean *Z*-scores for each scaffold and plotted them in Figure 7. Since *Z*-scores of 1.64 and 1.0 correspond to percentile rankings of 95 and 84.1, respectively, it is apparent that all of the reported scaffolds contain compounds with QED values in the upper 80th to lower 90th percentile. The 80 compounds exhibited an average *Z*-score of 1.29, which corresponds to a mean percentile ranking of 90.

Conclusion

In conclusion, an efficient microwave-assisted intermolecular-S_NAr protocol for the synthesis of an 80-member library of amino benzoxathiazocine 1,1-dioxides has been developed. Employing a variety of commercially available chiral, non-racemic amines, the 80-member library of bridged, benzofused, bicyclic sultams was generated by the microwave assisted-S_NAr diversification at 4-F and 6-F positions. A series of computational analyses was performed in order to provide pertinent information that guided the second part of the reaction pairing strategy, which will be reported in due course. Further computational analysis revealed that the compounds reported herein generally occupy underrepresented chemical space relative to the MLSMR screening set, but are drug-like both in terms of their distribution in shape space (as compared to a collection of 771 known orally available drugs depicted according to molecular PMI profiles) and according to the QED measure (by which all of this library of compounds are predicted to be significantly more drug-like than the average real drug). Structural overlays and PMI analysis suggest that the highlighted compounds tend to sample a reasonable array of shape space within the range between rod-like and disk-like compounds. RMSD comparisons of a selection of representative structures from this library suggest that the core scaffold has a greater inherent flexibility than comparable products from other related libraries. This flexibility can produce libraries with greater molecular diversity as a function of a fixed number of substituents than is observed for comparably sized libraries arising from more rigid scaffolds. It is our hope that the combination of drug-likeness and inherent molecular diversity evident in this library will produce products that demonstrate interesting behavior in biological screening. To gauge these prospects rigorously, these compounds have been submitted for evaluation of their biological activity in high-throughput screening assays at the NIH MLPCN and the results will be reported in due course.

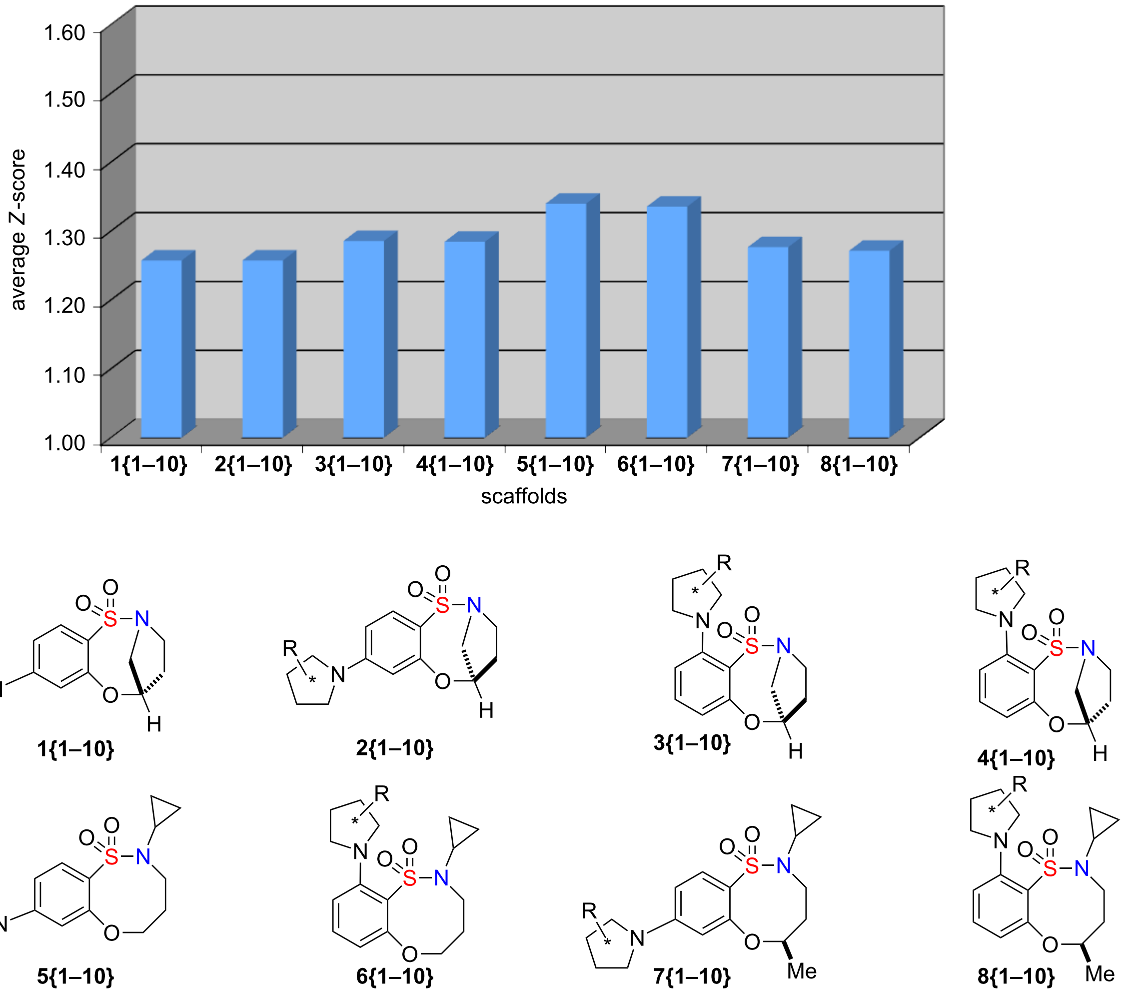


Figure 7: Representation of *Z*-scores for the 80 compounds.

Supporting Information

Supporting Information File 1

Experimental procedures, tabulated results for all libraries, and full characterization data for 20 representative compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-147-S1.pdf]

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Synthesis of a novel chemotype via sequential metal-catalyzed cycloisomerizations

Bo Leng, Stephanie Chichetti, Shun Su, Aaron B. Beeler
and John A. Porco Jr.*

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Address:
Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, USA

Email:
John A. Porco Jr.* - porco@bu.edu

* Corresponding author

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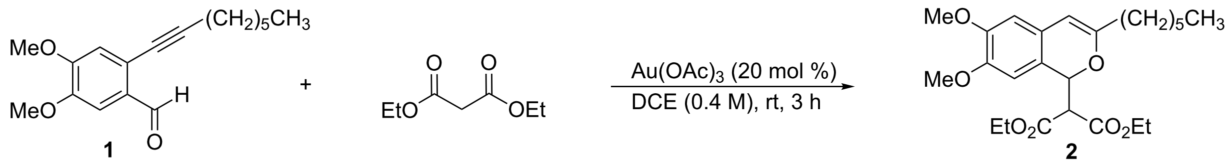
Abstract

Sequential cycloisomerizations of diynyl *o*-benzaldehyde substrates to access novel polycyclic cyclopropanes are reported. The reaction sequence involves initial Cu(I)-mediated cycloisomerization/nucleophilic addition to an isochromene followed by diastereoselective Pt(II)-catalyzed enyne cycloisomerization.

Introduction

Our laboratory has an ongoing interest in discovering transformations that afford novel chemotypes [1-4]. To this end, we have developed a reaction screening paradigm that enables the discovery of new reaction processes and chemotypes [5]. For example, we have conducted multidimensional reaction screens using alkynyl *o*-benzaldehyde scaffolds, which revealed a number of reactions affording novel polycyclic scaffolds, including Au(III)-catalyzed addition of diethyl malonate to **1** to afford isochromene **2** (Scheme 1). The chemotypes discovered in initial pilot studies have been further developed into library



Scheme 1: Cycloisomerization/nucleophilic addition of alkynyl benzaldehyde **1** to isochromene **2**.

scaffolds and identified as biologically interesting structures [6]. Herein, we report the expanded utility of alkynyl *o*-benzaldehydes through a sequential metal-catalyzed cycloisomerization process to afford a novel polycyclic cyclopropane chemotype.

Results and Discussion

In an effort to further explore the utility of alkynyl *o*-benzaldehydes as scaffolds for reaction screening, we designed a focused reaction screen with diynyl benzaldehyde [7] substrate **3**. Based on the cycloisomerization/addition reactions previously studied (Scheme 1), it was not clear at the outset of our study whether an *o*-alkynyl benzaldehyde containing an additional alkynyl moiety (**3**) would react to form an isochromene derivative or whether additional polycyclization would occur [8]. Accordingly, a reaction screen was conducted, evaluating a number of metal catalysts in the presence of diethyl malonate. From this focused reaction screen we identified three types of reactivity: (1) no reaction; (2) alkyne hydration (**4**); and (3) cycloisomerization leading to isochromene (**5**) (Figure 1). Many catalysts resulted in no reaction, including ones that might have been expected to catalyze cycloisomerization, such as AgOTf. Two catalysts, Cu(OTf)$_2$ and Pd(MeCN)$_2$Cl$_2$, afforded only hydration of the alkyne. Interestingly, hydration was regioselective, which is possibly due to direction from the ether oxygen. We were most interested in metal catalysts that effected cycloisomerization of **3** to alkynyl isochromene **5**, which is an interesting enyne substrate with potential for further reactivity [9,10]. In the reaction screen of alkynyl benzaldehyde substrate **3**, we found that in the absence of optimization Cu(MeCN)$_4$PF$_6$ [11-13] afforded the highest isolated yield of **5** (60%) (Scheme 2).

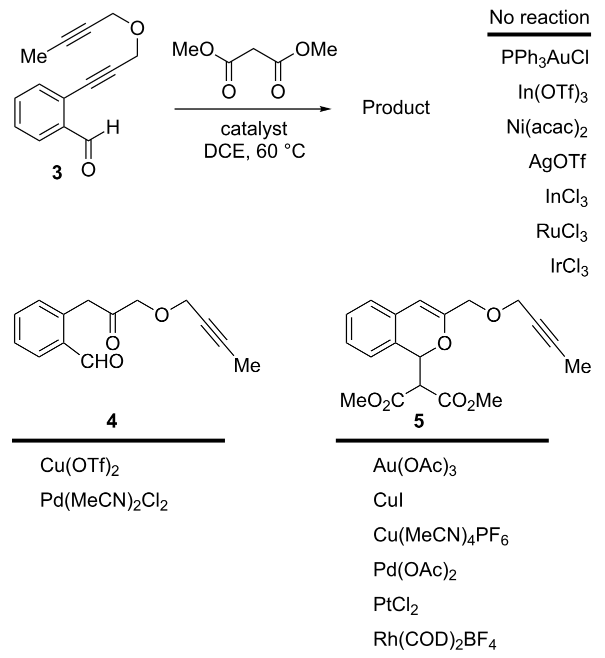
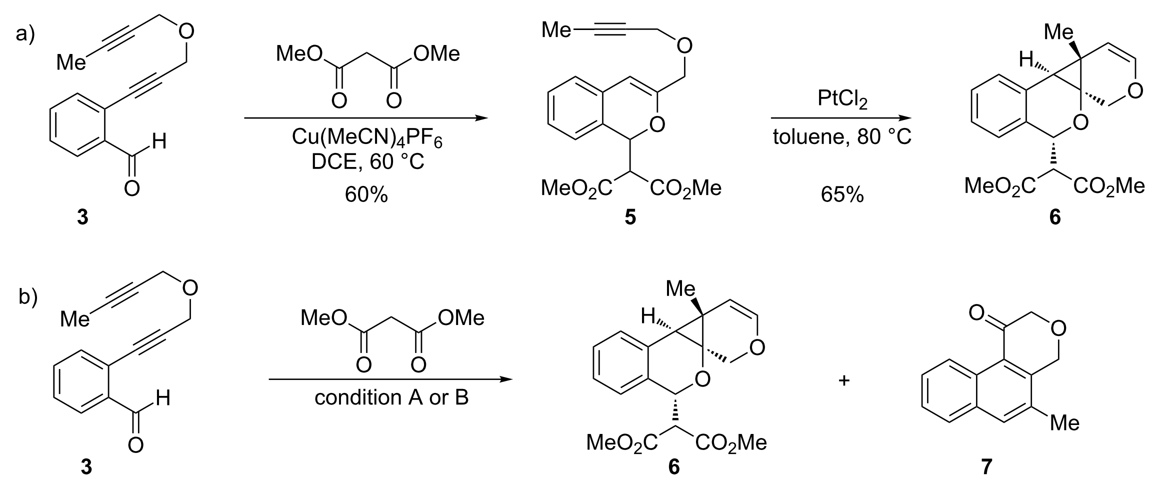


Figure 1: Reaction screen with diynyl benzaldehyde **3**.

As the production of isochromene **5** offered a unique opportunity for additional cycloisomerization processes, we elected to explore this manifold of reactivity. Based on reports by Echavarren and co-workers [14,15], we treated enyne **5** with PtCl$_2$ at 80 °C in toluene [16,17]. The reaction afforded polycyclic cyclopropane **6** in good yield (65%) as a single diastereomer (Scheme 2a). Interestingly, reaction of **3** in the presence of only PtCl$_2$ afforded exclusively isochromene **5** in low yield. Further studies revealed that a multicatalytic reaction system [18] utilizing both Cu(I) and Pt(II) [19] catalysts afforded the desired cyclopropane **6** in moderate yield (40%) along with ketone **7** (45%), derived from [4 + 2] cycloaddition of the benzopyrylium intermediate with the pendent alkyne [20]

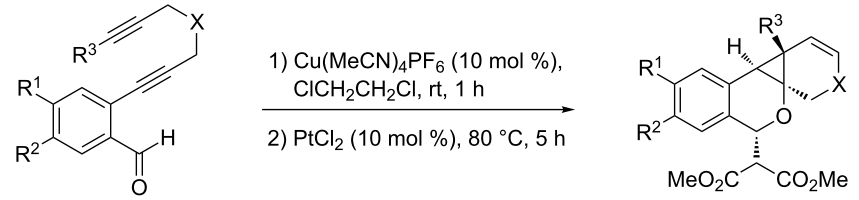


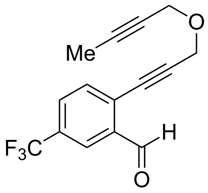
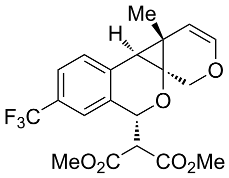
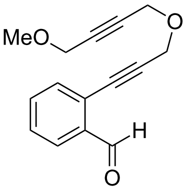
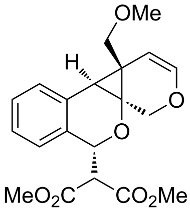
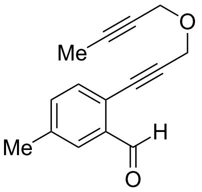
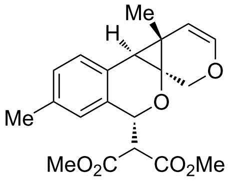
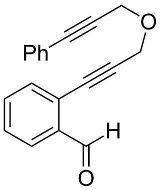
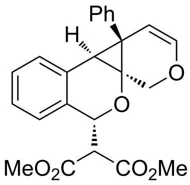
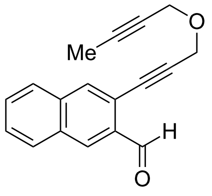
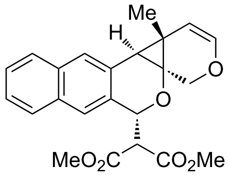
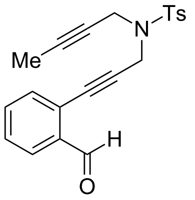
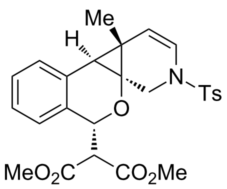
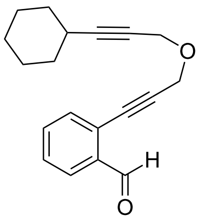
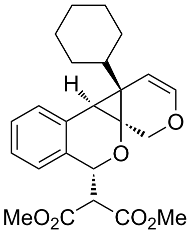
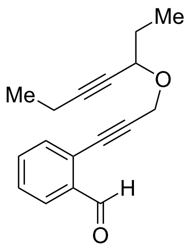
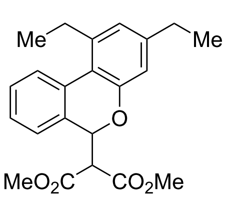
Scheme 2: Sequential cycloisomerizations of substrate **3**. Condition A: PtCl$_2$ (10 mol %), Cu(MeCN)$_4$PF$_6$ (10 mol %), toluene, 80 °C, 8 h (40%). Condition B: Step 1: Cu(MeCN)$_4$PF$_6$ (10 mol %), rt, 1 h. Step 2: PtCl$_2$ (10 mol %), 80 °C, toluene, 5 h (89%).

(Scheme 2b). However, better yields were observed when the initial cycloisomerization was carried out in the presence of $Cu(MeCN)_4PF_6$ followed by the addition of $PtCl_2$ to the reaction mixture (Scheme 2b). Optimization of the one-pot conditions afforded exclusively **6** in good yield (89%). X-ray crystal analysis confirmed the structure and relative stereochemistry of polycyclic cyclopropane **6** (Figure 2, Supporting Information File 1).

We next focused on an evaluation of the general scope of the reaction with regard to aryl and alkyne substitution. Reaction utilizing an electron-poor trifluoromethyl-substituted diynyl benzaldehyde **8** was successful, producing product **9** in moderate yield (Table 1, entry 1). *m*-Methyl- and naphthyl-containing substrates **10** and **12** afforded polycyclic cyclopropanes **11** and **13** in 48 and 51% yields, respectively (Table 1, entries 2 and 3).

Table 1: Sequential cycloisomerizations of diynyl benzaldehyde substrates.



entry	aldehyde	product	yield	entry	aldehyde	product	yield
1	 **8**	 **9**	53%	5	 **16**	 **17**	62%
2	 **10**	 **11**	48%	6	 **18**	 **19**	59%
3	 **12**	 **13**	51%	7	 **20**	 **21**	82%
4	 **14**	 **15**	60%	8	 **22**	 **23**	65%

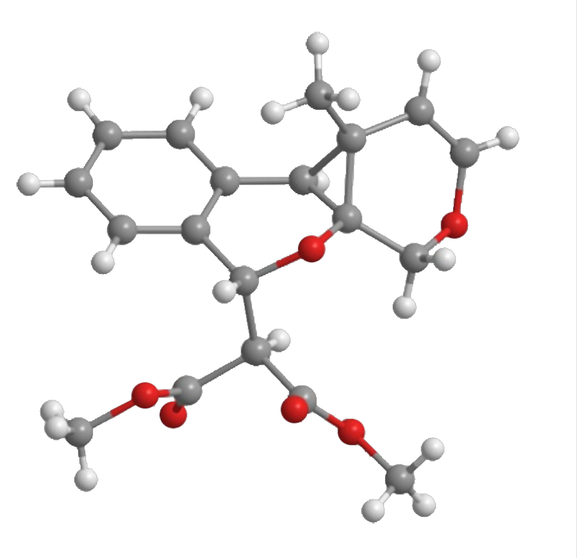


Figure 2: X-ray crystal structure of cyclopropane **6**.

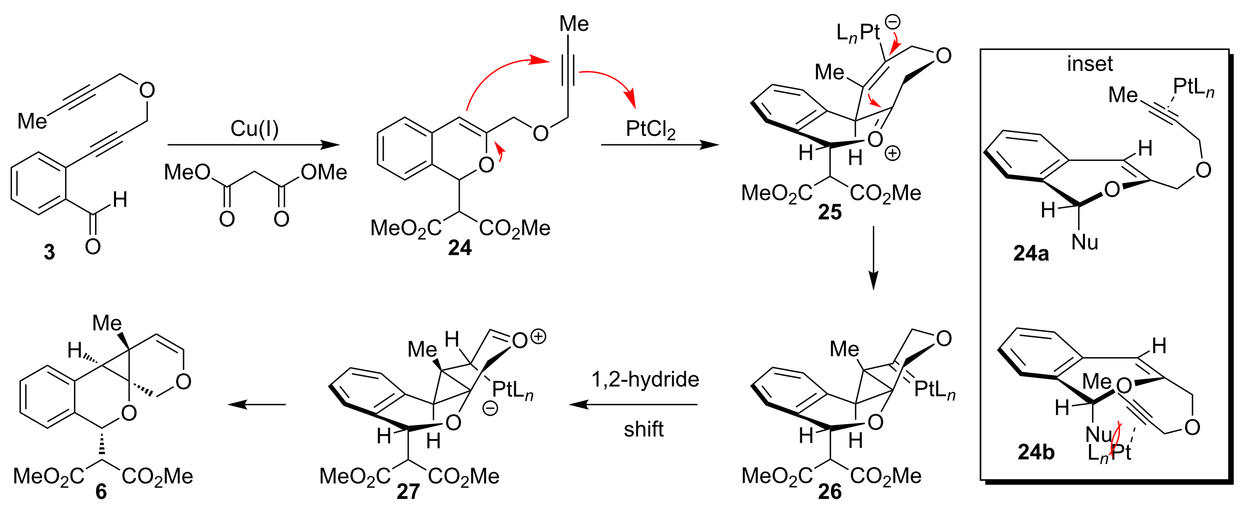
We next explored substitution of the pendant alkyne. Reaction with cyclohexane diyne **14** afforded the fused cyclopropane **15** in moderate yield (60%), while methyl ether **16** afforded cyclopropane **17** in 62% yield. Phenyl substitution (**18**) also resulted in a moderate yield (59%, Table 1, entry 6). Substituting the oxygen with *N*-tosyl (**20**) afforded *N*-tosyl cyclopropane **21** in good yield (82%). Substitution at the internal methylene (**22**) resulted in a diverted reaction pathway (vida infra) affording product **23** exclusively in moderate yield (65%).

A proposed mechanistic pathway for diastereoselective, sequential cycloisomerizations is shown in Scheme 3. We propose the initial cycloisomerization and nucleophilic addition of diynyl benzaldehyde **3** and dimethyl malonate is catalyzed by Cu(I) to afford isochromene **24** [20-22]. Pt(II) π-coordination of the pendant alkyne of **24** followed by cyclization of the enol ether affords the seven-membered-ring metal-“ate” intermediate **25**. The cyclization occurs at the face opposite the malonate substituent (Nu, **24a**) to minimize steric interactions relative to **24b**, leading to the observed diastereoselectivity (Scheme 3, inset) [23,24]. Subsequent cyclopropane formation through addition of the vinyl metal to the oxonium intermediate affords metallocarbenoid **26**, which may then undergo a 1,2-hydride shift to intermediate **27** followed by elimination of the metal catalyst [25] to afford the observed cyclopropane product **6**.

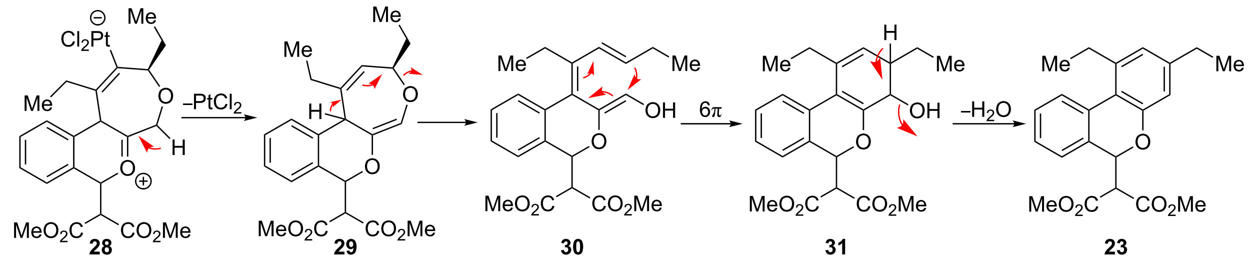
An alternative reaction pathway may be invoked for the ethyl-substituted substrate **22** leading to product **23** (Scheme 4). After initial cyclization of the enol ether with the Pt-activated alkyne, the resulting metal-“ate” intermediate **28** may undergo preferential elimination and proto-demetallation to afford 1,5-diene **29**. A second elimination results in the ring-opened triene **30**. Subsequent 6π-electrocyclization affords alcohol **31**, which aromatizes through loss of water to afford the observed isochromane **23**.

Conclusion

We have described sequential cycloisomerizations of diynyl *o*-benzaldehyde substrates to access novel polycyclic cyclopropanes. The reaction sequence involves initial Cu(I)-mediated cycloisomerization/nucleophilic addition to an isochromene followed by diastereoselective Pt(II)-catalyzed enyne cycloisomerization. The chemistry reported herein illustrates the power of sequential cycloisomerization processes to provide access to novel chemotypes and chemical diversity



Scheme 3: Proposed reaction pathway for diastereoselective, sequential cycloisomerization.



Scheme 4: Proposed alternative reaction pathway affording **23**.

from readily accessible building blocks [26]. Further transformations of the novel polycyclic cyclopropanes as well as additional studies employing reaction screening for metal-mediated processes is ongoing and will be reported in future publications.

Experimental

General Information: All nuclear magnetic resonance spectra were recorded on either a Varian or Bruker spectrometer. ^{1}H NMR spectra were recorded at 400 MHz at ambient temperature with $CDCl_3$ as solvent, unless otherwise stated. ^{13}C NMR spectra were recorded at 100.0 MHz at ambient temperature with $CDCl_3$ as solvent, unless otherwise stated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.27; ^{13}C, δ 77.0) and acetone-d_6 (^{1}H, δ 2.05; ^{13}C, δ 30.8). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, m = multiplet), coupling constant in hertz, and integration. All ^{13}C NMR spectra were recorded with complete proton decoupling. Analytical LC was performed on a 2.1 × 50 mm, 1.7 μM C18 column. Analytical thin-layer chromatography was performed by using 0.25 mm silica gel 60-F plates. Otherwise, flash chromatography was performed by using 200–400 mesh silica gel. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Acetonitrile, CH_2Cl_2, THF, and toluene were purified by passing through two packed columns of neutral alumina. All reactions were performed under an argon atmosphere in oven-dried or flame-dried glassware.

General procedure for the synthesis of alkynyl *o*-benzaldehydes: 2-(3-(but-2-ynyloxy)prop-1-ynyl)benzaldehyde. To a solution of 2-bromobenzaldehyde (2.0 g, 10.8 mmol) and 1-(prop-2-ynyloxy)but-2-yne (1.4 g, 13 mmol) in Et_3N (68 mL), was added tetrakis(triphenylphosphine)palladium(0) (0.38 g, 0.32 mmol). The reaction mixture was stirred at room temperature for 5 min. Copper(I) iodide (0.075 g, 0.4 mmol) was added, and the mixture was heated to 60 °C overnight. The mixture was concentrated in vacuo and purified by flash chromatography (SiO_2, petroleum ether/EtOAc 4:1) to afford diynyl benzaldehyde **3** (1.5 g, 7.1 mmol, 66%) as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.57 (m, 2H), 7.46 (m, 1H), 4.54 (s, 2H), 4.29 (q, J = 2.4 Hz, 2H), 1.89 (t, J = 2.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 136.2, 133.8, 133.6, 129.0, 127.3, 126.1, 91.9, 83.7, 82.2, 74.2, 57.6, 57.1, 3.7; IR (thin film) ν_{max}: 2920, 2852, 1697, 1594, 1477, 1450, 1350, 1274, 1244, 1193, 1138, 1076, 765 cm^{-1}.

General one-pot procedure for sequential cycloisomerization: To a flame-dried round-bottom flask was added **3** (10 mg, 0.046 mmol), dimethyl malonate (5.8 μL, 0.05 mmol) and toluene (1.0 mL). To the reaction mixture was added tetrakis(acetonitrile)copper(I) hexafluorophosphate (1.7 mg, 0.005 mmol), and the reaction mixture was stirred at room temperature for 1 h. Platinum(II) chloride (1.2 mg, 0.005 mmol) was added and the reaction mixture was heated to 80 °C for 5 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography (SiO_2, petroleum ether/EtOAc 9:1 to 4:1) to afford the desired cycloisomerization product **6** (14 mg, 0.041 mmol, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.08 (m, 1H), 6.98 (d, J = 4.2 Hz, 1H), 6.11 (d, J = 5.6 Hz, 1H), 5.28 (d, J = 10.4 Hz, 1H), 5.07 (d, J = 5.6 Hz, 1H), 4.33 (d, J = 10.0 Hz, 1H), 3.92 (d, J = 10.8 Hz, 1H), 3.83 (s, 3H), 3.66 (d, J = 10.0 Hz, 1H), 3.49 (s, 3H), 2.51 (s, 1H), 0.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.4, 141.0, 135.8, 133.7, 130.8, 130.3, 128.9, 126.2, 111.1, 75.0, 63.9, 62.7, 59.4, 53.2, 52.7, 30.5, 26.4, 12.2; IR (thin film) ν_{max}: 2953, 2926, 2870, 1761, 1741, 1679, 1639, 1493, 1435, 1341, 1253, 1194, 1144, 1073, 1018, 912, 774, 749 cm^{-1}; HRMS–ESI$^+$ (*m*/*z*): [M + Na]$^+$ calcd for $C_{19}H_{20}O_6$, 367.1158; found, 367.1189.

Supporting Information

Supporting Information File 1

Characterization data, spectra, and crystal structure data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-153-S1.pdf]

Acknowledgements

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    See for an illustrative recent application of cycloisomerizations in diversity-oriented synthesis (DOS).

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Automated three-component synthesis of a library of γ-lactams

Erik Fenster[1], David Hill[1], Oliver Reiser[2] and Jeffrey Aubé[*1]

Full Research Paper

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Address:
[1]Center of Excellence in Chemical Methodologies and Library Development, the University of Kansas, 2034 Becker Drive, Lawrence Kansas, 66047, USA and [2]Institut für Organische Chemie, Universität Regensburg, Universitätsstrasse 31, 93053, Regensburg, Germany

Email:
Jeffrey Aubé[*] - jaube@ku.edu

* Corresponding author

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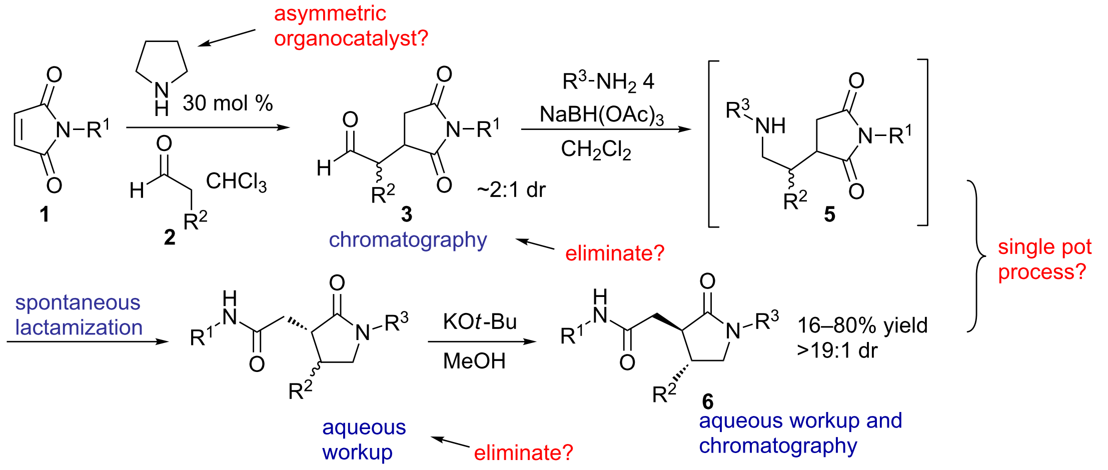
Abstract

A three-component method for the synthesis of γ-lactams from commercially available maleimides, aldehydes, and amines was adapted to parallel library synthesis. Improvements to the chemistry over previous efforts include the optimization of the method to a one-pot process, the management of by-products and excess reagents, the development of an automated parallel sequence, and the adaption of the method to permit the preparation of enantiomerically enriched products. These efforts culminated in the preparation of a library of 169 γ-lactams.

Introduction

In recent years, the rapid access to structurally diverse and complex small molecules has grown in importance within the context of high-throughput screening of biologically relevant targets. The need for such compounds, both as pharmacological probes and as starting points for drug-discovery campaigns, has primarily fuelled this interest, while enabling technologies, such as diversity-oriented synthesis (DOS), have improved access to small-molecule libraries [1-5].

Compounds containing a γ-lactam moiety have been significant in the treatment of epilepsy [6,7], HIV [8,9], neurodegenerative disease and depression [10,11]. Having identified the lactam ring as a target of opportunity in chemical-screening efforts, we previously reported a method to prepare γ-lactams from readily available maleimides, aldehydes and amines [12]. The method involved a three-step stepwise sequence involving an organocatalyzed Michael addition, a reductive amination/intramolecular lactamization, and an epimerization step (Scheme 1). It culminated in the preparation of a 43-member library. Although this method permitted relatively easy access to highly substituted racemic γ-lactams, it required manual manipulations of the intermediate products in each step in the form of workups and purifications. Accordingly, we wished to develop a streamlined approach that would provide access to



Scheme 1: Three-step sequence for the preparation of γ-lactams from maleimides, aldehydes and amines. Potential improvements are indicated in red.

larger numbers and quantities of diverse γ-lactams, preferentially in enantiomerically pure form. Ideally, this would take the form of a single-pot process utilizing automation. We now report improvements to this process, which (1) generates enantiomerically enriched compounds, (2) eliminates the need for intermediate purifications, (3) simplifies the method to a three-step one-pot sequence, and (4) allows for the magnification of the library scale through the use of automation.

Results and Discussion

We began by probing the potential for the above-mentioned improvements to our previously reported method by (a) exploring the possibility for an asymmetric organocatalyzed reaction in the Michael addition step, (b) combining the individual three steps, and (c) automating the process to produce a demonstrative 256 member γ-lactam library.

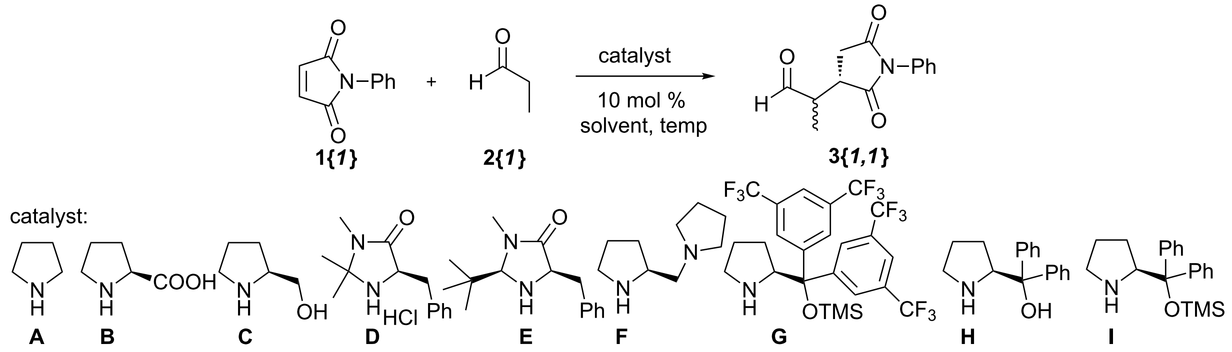
Asymmetric organocatalyzed Michael addition

The success of pyrrolidine as the organocatalyst for the Michael addition of enolizable aldehydes to maleimides in the original method suggested the possibility of producing chiral γ-lactams through the use of a chiral proline-like organocatalysts. In fact, Córdova and co-workers have previously established a protocol for such a process [13]. Based on this initial protocol, we explored the use of various chiral amines in the conjugate addition reaction of propionaldehyde (**2**{*1*}) to *N*-phenylmaleimide (**1**{*1*}) (Table 1). Although the achiral pyrrolidine was found to be an efficient catalyst in the reaction [12], this led to a ~1:1 mixture of racemic succinimide diastereomers **3**{*1,1*}, even at lowered temperatures (Table 1, entries 1 and 2). While a number of chiral amines failed to produce any significant amounts of the desired succinimide product (Table 1, entries 3–9), we were pleased to find that the use of protected diphenylprolinol catalyst **I** at room temperature produced **3**{*1,1*} in high yields and with high enantioselectivity, albeit with low diastereoselectivity. Such a low diastereoselectivity was of no concern in the originally reported procedure since the final potassium *tert*-butoxide promoted epimerization step produced a racemic mixture of a single diastereomer. In the case of an asymmetric synthesis, however, the initial diasteromeric ratio would be reflected in the enantiomeric ratio of the final products when the downstream epimerization step is taken into account; this is illustrated for the limiting case of high facial selectivity with respect to the maleimide component in Scheme 2. Consequently, higher diastereoselectivity was required for the synthesis of enantioenriched γ-lactams. Indeed, **3**{*1,1*} could be produced with moderate diastereoselectivity when the reaction was performed at 0 °C over a prolonged length of time (Table 1, entry 11) [14]. The use other solvents (THF, acetonitrile) failed to either produce any product (Table 1, entry 12) or lead to higher diastereoselectivity (Table 1, entry 13). We considered that lowering reaction temperatures in chloroform may lead to increased diastereoselectivities, but concluded that the lengthy reaction times necessitated under these conditions would have made the overall process inefficient. Although future work will explore additional catalysts and reaction conditions to improve this diastereoselectivity, we elected at this point to explore the additional steps to produce γ-lactams with the modest enantiomeric enrichment in hand.

Combination of three discrete steps into a single-pot process

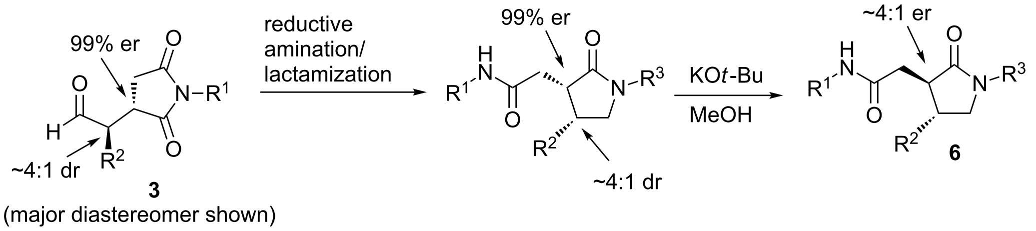
We next turned our attention to combining the initial Michael addition step with the remaining reductive amination/lactamiza-

Table 1: Asymmetric organocatalytic addition of propionaldehyde (**2{*1*}**) to *N*-phenylmaleimide (**1{*1*}**).



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)	dr	ee (%)[a]
1	**A**[b]	$CHCl_3$	61	2	74	1:1.1	—
2	**A**	$CHCl_3$	rt	16	72	1:1.2	—
3	**B**	$CHCl_3$	61	12	trace	—	—
4	**C**	$CHCl_3$	61	12	NR	—	—
5	**D**	$CHCl_3$	61	12	NR	—	—
6	**E**	$CHCl_3$	61	12	NR	—	—
7	**F**	$CHCl_3$	rt	24	30	1:2.0	60
8	**G**	$CHCl_3$	61	12	NR	—	—
9	**H**	$CHCl_3$	61	12	trace	—	—
10	**I**	$CHCl_3$	rt	12	88	1:2.0	96
11	**I**	$CHCl_3$	0	36	90	1:4.2	99
12	**I**	THF	61	12	NR	—	—
13	**I**	CH_3CN	0	36	72	1:2.5	90

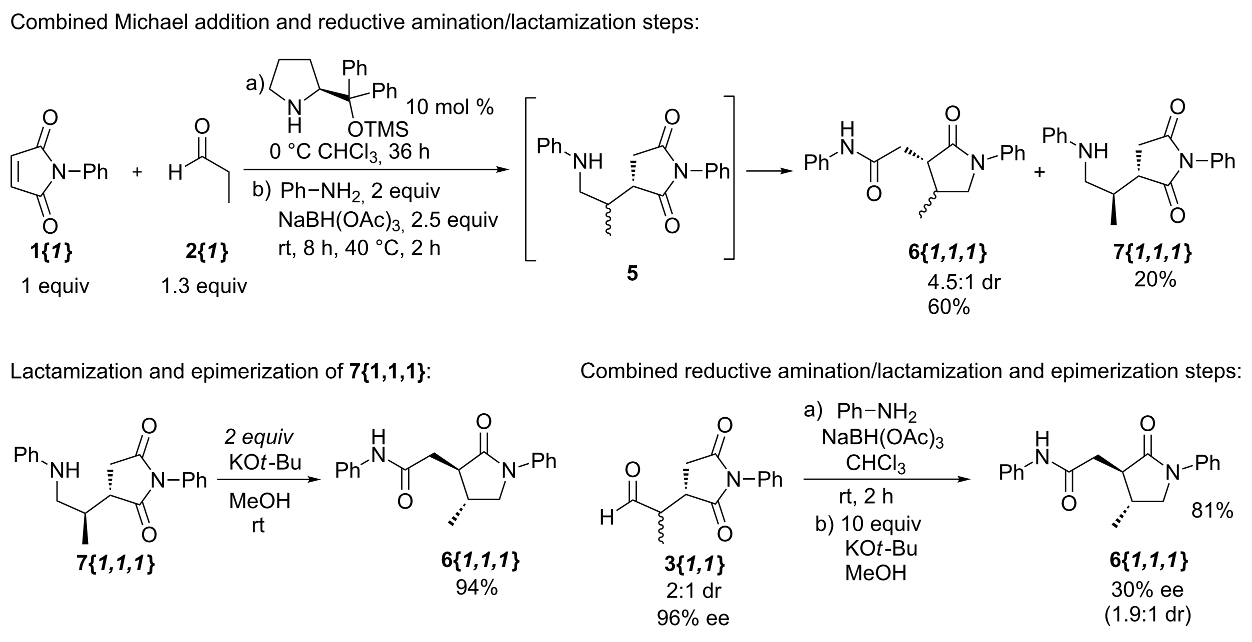
[a] Determined by chiral phase HPLC analysis. [b] 30 mol % of the catalyst was used.



Scheme 2: The transfer of the diastereoselective ratio of **3** to the enantioselectivity of the overall process in the synthesis of γ-lactams **6**.

tion and epimerization steps. In the original procedure, the reductive amination/lactamization reaction was performed in methylene chloride [12]. However, in order to combine this step with the previous Michael addition step, we thought to perform the reaction in chloroform (Scheme 3). In fact, when the Michael addition reaction between propionaldehyde (**2**{*1*}) and *N*-phenylmaleimide (**1**{*1*}) was performed in chloroform at 0 °C (using the protected diphenylprolinol catalyst **I**), followed by addition of aniline (**4**{*1*}) and sodium triacetoxyborohydride after 36 h, the desired γ-lactam **6**{*1,1,1*} was obtained in 60% yield (as a 4.5:1 mixture of diastereomers). However, 20% of the succinimide product **7**{*1,1,1*} was also isolated as a single diastereomer, resulting from incomplete transamidation.

Although the reductive amination occurred readily at room temperature, the lactamization appeared to occur more slowly than we had anticipated. In investigating individually the reductive amination/lactamization step using **3**{*1,1*} with aniline (**4**{*1*}) (Table 2), we found that the reaction required heating at 40 °C for at least 8 h for complete lactamization to be achieved



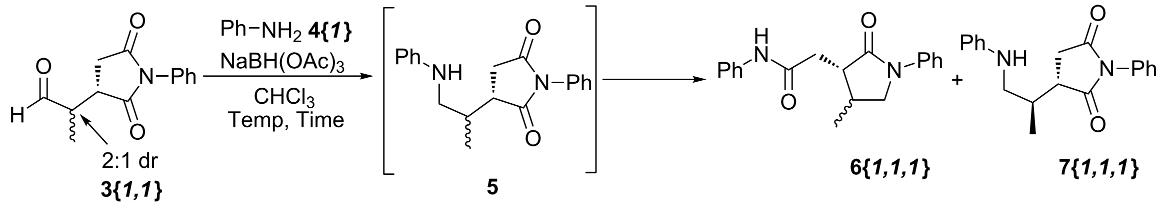
Scheme 3: Combination of the Michael addition step with the reductive amination/lactamization step and of the reductive amination/lactamization step with the epimerization step.

(Table 2, entry 3). Furthermore, the isolation of succinimide **7**{*1,1,1*} as a single diastereomer at reduced temperatures (Table 2, entry 1) or reaction times (Table 2, entry 2) seemed to indicate that the lactamization in forming the *syn*-diastereomer of **6**{*1,1,1*} occurs at a slower rate than that for the *anti*-diastereomer.

However, we found that subjecting succinimide **7**{*1,1,1*} by itself to potassium *tert*-butoxide in methanol promoted the lactamization at room temperature in addition to the final epimerization to produce **6**{*1,1,1*} as a single diastereomer (Scheme 3). Consequently, it became clear that complete lactamization in the previous step would not necessarily be required if the reductive amination/lactamization and epimerization steps were combined. Thus, subjecting **3**{*1,1,1*} to the reductive amination conditions for 2 h at room temperature, followed by addition of potassium *tert*-butoxide (after a solvent change from $CHCl_3$ to MeOH) provided the γ-lactam **6**{*1,1,1*} in 81% (Scheme 3) [15].

Having demonstrated the ability to combine the first two steps as well as the last two steps, our attention was turned to combine all three steps in a single-pot process (Scheme 4). At this stage, we also investigated the possibility for removal of

Table 2: Reductive amination/lactamization of **3**{*1*} with aniline (**4**{*1*}).

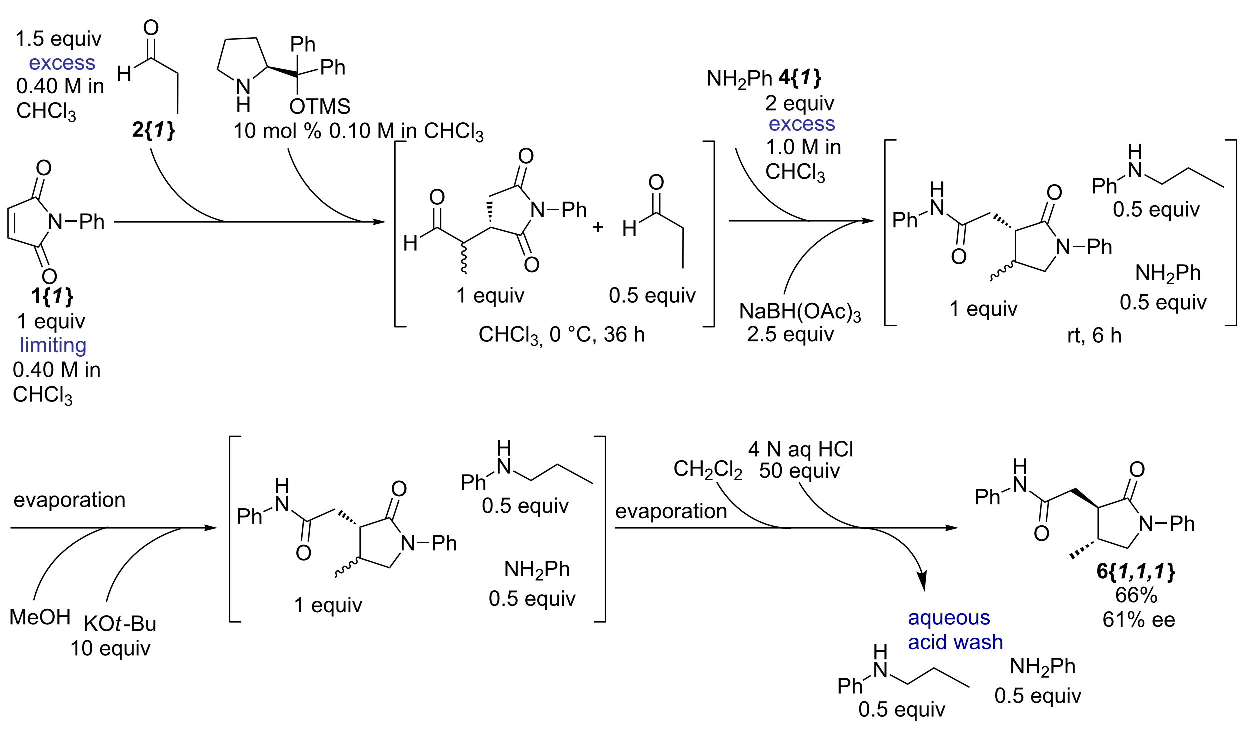


Entry	Temp (°C)	Time (h)	**6**{*1,1,1*} Yield (%)	**6**{*1,1,1*} dr	**7**{*1,1,1*} Yield (%)
1	rt	8	45	1.1:1	40
2	40	2	60	1.6:1	22
3	40	8	76	2.0:1	—

excess reagents and byproducts in order to render the overall process more efficient for parallel synthesis. If *N*-phenylmaleimide (**1**{*1*}) was to be used as a limiting reagent and propionaldehyde (**2**{*1*}) and aniline (**4**{*1*}) were used (with **4**{*1*} in excess relative to **2**{*1*}), then at the end of the one-pot process we should be left with the desired γ-lactam **6**{*1,1,1*} and with only amines (aniline and *N*-propylaniline) as excess byproducts, which could be removed with a simple aqueous acid wash along with the remaining catalyst, borate salts, and potassium *tert*-butoxide. Thus, *N*-phenylmaleimide (**1**{*1*}) (1 equiv) was stirred with an excess of propionaldehyde (**2**{*1*}) (1.5 equiv) in the presence of the silylated diphenylprolinol catalyst (10 mol %) for 36 h at 0 °C, after which an excess of aniline (2 equiv) and sodium triacetoxyborohydride (2.5 equiv) were added to the reaction mixture. After being stirred for 6 h at room temperature, the chloroform solvent was removed in vacuo, replaced with methanol, and potassium *tert*-butoxide (10 equiv) was added. After 12 h at room temperature, the methanol solvent was evaporated in vacuo, the resulting residue was redisolved in methylene chloride, and the solution was washed with 4 N HCl. Following simple filtration through a plug of silica gel, the γ-lactam **6**{*1,1,1*} was obtained in 66% yield (with 80% es; % es = % major enantiomer, corresponding to 60% ee). Overall, the above-mentioned one-pot sequence, in which both workups and purifications are minimized, proved serviceable in the desired parallel-synthesis sequence.

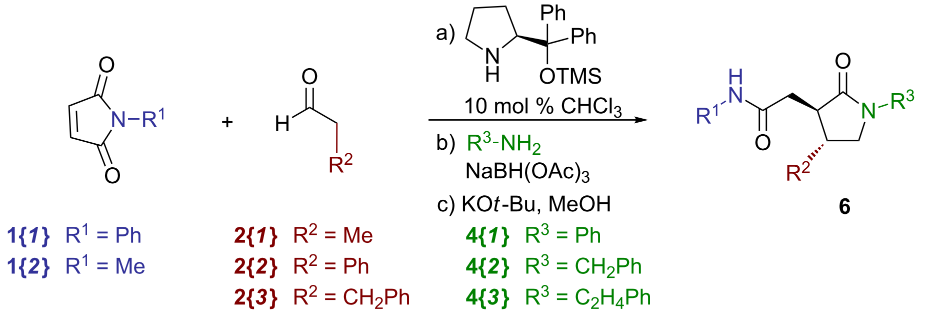
Parallel library synthesis

The combined sequence was next attempted as a rehearsal 2 × 3 × 3 validation library by using a Chemspeed Accelerator SLT-100 synthesizer (Table 3). In general, substrates which varied in their steric and electronic nature were chosen (alkyl and aryl groups). By using the three-step single-pot sequence described above on the Chemspeed platform (0.400 mmol scale), the resulting 18 crude γ-lactams **6** were subjected to preparative HPLC purification. In general, yields in the range of 35–58% were obtained, with the exception of those reactions that used phenylacetaldehyde **2**{*2*} (yields in the range of 4–12%). Although in our previous work aryl acetaldehydes were found to produce decent yields with pyrrolidine [12], similar results were not obtained when the protected diphenylprolinol catalyst **I** was used. Except for the experiment in Table 3, entry 4, chemical purities >85% were observed for all of the isolated products. Although most of the reactions proceeded with high diastereoselectivities following the epimerization step (>19:1), this was not the case for all library products prepared during the production run described in the following section, as evident from small impurities (ca. ≤10%) observable in the ^{13}C NMR spectra of the final products (Supporting Information File 1). Such products were deemed suitable for screening purposes. Finally, enantiomeric purity measurements were obtained for six selected γ-lactam products, which ranged between 62 and 84% es.



Scheme 4: Combination of the Michael addition, the reductive amination/lactamization, and the epimerization step in a single-pot process.

Table 3: Chemspeed rehearsal 2 × 3 × 3 library of γ-lactams **6**.



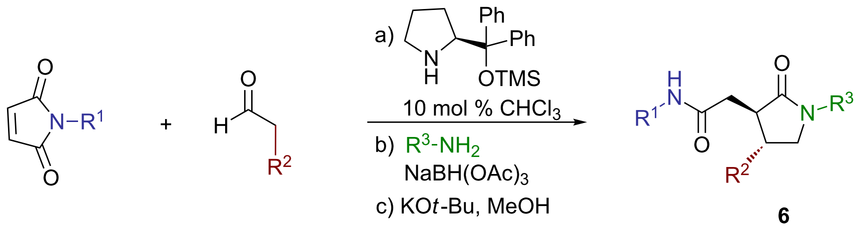
Entry	Maleimide	Aldehyde	Amine	Product	Yield (%)[a]	Purity (%)[b]	es (%)[c,d]
1	**1{*1*}**	**2{*1*}**	**4{*1*}**	**6{*1,1,1*}**	45	100	62
2	**1{*1*}**	**2{*1*}**	**4{*2*}**	**6{*1,1,2*}**	50	100	n.d.
3	**1{*1*}**	**2{*1*}**	**4{*3*}**	**6{*1,1,3*}**	59	100	66
4	**1{*1*}**	**2{*2*}**	**4{*1*}**	**6{*1,2,1*}**	10	83.1	n.d.
5	**1{*1*}**	**2{*2*}**	**4{*2*}**	**6{*1,2,2*}**	10	100	n.d.
6	**1{*1*}**	**2{*2*}**	**4{*3*}**	**6{*1,2,3*}**	12	100	n.d.
7	**1{*1*}**	**2{*3*}**	**4{*1*}**	**6{*1,3,1*}**	58	100	75
8	**1{*1*}**	**2{*3*}**	**4{*2*}**	**6{*1,3,2*}**	52	96.6	84
9	**1{*1*}**	**2{*3*}**	**4{*3*}**	**6{*1,3,3*}**	58	93.7	n.d.
10	**1{*2*}**	**2{*1*}**	**4{*1*}**	**6{*2,1,1*}**	50	85.0	n.d.
11	**1{*2*}**	**2{*1*}**	**4{*2*}**	**6{*2,1,2*}**	52	85.4	n.d.
12	**1{*2*}**	**2{*1*}**	**4{*3*}**	**6{*2,1,3*}**	43	95.7	71
13	**1{*2*}**	**2{*2*}**	**4{*1*}**	**6{*2,2,1*}**	5	90.6	n.d.
14	**1{*2*}**	**2{*2*}**	**4{*2*}**	**6{*2,2,2*}**	4	100	n.d.
15	**1{*2*}**	**2{*2*}**	**4{*3*}**	**6{*2,2,3*}**	8	91.7	n.d.
16	**1{*2*}**	**2{*3*}**	**4{*1*}**	**6{*2,3,1*}**	35	100	n.d.
17	**1{*2*}**	**2{*3*}**	**4{*2*}**	**6{*2,3,2*}**	39	100	n.d.
18	**1{*2*}**	**2{*3*}**	**4{*3*}**	**6{*2,3,3*}**	42	100	74

[a]Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). [b]Purity was determined by HPLC with peak area (UV) at 214 nm. [c]30 mol % of the catalyst was used. [d]Determined by chiral phase HPLC analysis.

Overall, the results of the validation efforts demonstrated both the success of the one-pot automated method, as well as the scope of substrates suitable for a larger library set. With these considerations, we planned for a 4 × 8 × 8 = 256 member library of γ-lactams **6** on the Chemspeed platform with the conditions evaluated in the rehearsal library. A number of maleimides **1**, aldehydes **2** and amines **3** were chosen (Scheme 5) based on differences in their structure and polarity. Using the validated conditions, the Chemspeed was programmed to run four sets of 4 maleimides × 2 aldehydes × 8 amines (64 compounds each) for a total of 256 attempted syntheses. Upon completion of the four 64-compound runs, the reaction mixtures were purified by preparative HPLC, which afforded 169 compounds that met our goals of quantities >20 mg and purities >90%, in each case starting with 0.400 mmol of maleimides **1** [16]. Further analysis of the results showed that the arylacetaldehydes (**2{*2*}**, **2{*6*}** and **2{*7*}**) produced either lowered or zero amounts of material in the reactions for which these were utilized, with no discrepancy of the substitution on the aryl ring. Additionally, 3-pycolylamine **4{*8*}** yielded little or no material in the reactions for which it was used. With these exceptions, the process, in general, yielded products in the 15–70% range.

Conclusion

In summary, our previously reported method for the three-component preparation of γ-lactams from commercially available maleimides, aldehydes and amines was improved and adapted to automated parallel library synthesis. Improvements to the chemistry over the previous method include the introduction of asymmetry in the form of an organocatalyzed Michael addition, the removal of the main by-products and excess reagents by using an aqueous acid wash, and the optimization for a one-pot process. These efforts allowed the efficient use of



6

1{*1*} R^1 = Ph
1{*2*} R^1 = Me
1{*3*} R^1 = *p*-OMe-Ph
1{*4*} R^1 = *p*-Br-Ph

2{*1*} R^2 = Me
2{*2*} R^2 = Ph
2{*3*} R^2 = CH_2Ph
2{*4*} R^2 = C_3H_7
2{*5*} R^2 = CH_2SMe
2{*6*} R^2 = *p*-OMe-Ph
2{*7*} R^2 = *p*-Br-Ph
2{*8*} R^2 = $CH(CH_3)_2$

4{*1*} R^3 = Ph
4{*2*} R^3 = CH_2Ph
4{*3*} R^3 = C_2H_4Ph
4{*4*} R^3 = *p*-OMe-Ph
4{*5*} R^3 = *p*-Br-Ph
4{*6*} R^3 = Cy
4{*7*} R^3 = C_4H_9
4{*8*} R^3 = CH_2-3-Py

Scheme 5: Chemspeed 4 × 8 × 8 library of γ-lactams **6**.

automation for parallel library synthesis, culminating in the preparation of a library of 169 γ-lactams.

Experimental

General

All single-vessel reactions were performed under an argon atmosphere in flame-dried glassware. The glass syringes and stainless-steel needles used for handling anhydrous solvents and reagents were oven dried, cooled in a desiccator, and flushed with dry nitrogen prior to use. Plastic syringes were flushed with dry nitrogen before use. Thin-layer chromatography (TLC) was performed on Analtech Uniplate Silica Gel GHLF 250 µm precoated TLC plates. All library syntheses using automated technology were performed by using a Chemspeed Accelerator SLT-100 Automated Synthesizer under an argon atmosphere in vacuum dried (50 °C, 9 mmHg) 13 mL reactor vessels. Parallel evaporations were performed by using a GeneVac EZ-2 plus evaporator. Automated preparative reverse-phase HPLC purification was performed by using a Waters 2767 Mass Directed Fractionation system (2767 sample manager, 2525 Binary Pump, 515 Make-up pump) with a Waters ZQ quadrapole spectrometer and detected by UV (270 nm, Waters Xterra MS C-18 column, 19 × 150 mm, elution with the appropriate gradient of acetonitrile in pH 9.8 buffered aqueous ammonium formate at 18 mL·min^{-1} flow rate). Purity was determined by reverse-phase HPLC with peak area (UV) at 214 nm by using a Waters Alliance 2795 system (Waters Xterra MS C-18 column, 4.6 × 150 mm, elution with a linear gradient of 5% acetonitrile in pH 9.8 buffered aqueous ammonium formate to 100% acetonitrile at 1.0 mL·min^{-1} flow rate). Purity was determined by reverse-phase HPLC with peak area (UV) at 214 nm by using a Waters Alliance 2795 system (Waters Xterra MS C-18 column, 4.6 × 150 mm, elution with a linear gradient of 5% acetonitrile in pH 9.8 buffered aqueous ammonium formate to 100% acetonitrile at 1.0 mL·min^{-1} flow rate). Methylene chloride, acetonitrile, methanol and tetrahydrofuran were purified by using an Innovative Technology Pure-Solv 400 solvent purification system. Chloroform was purified by distillation over calcium hydride. The maleimides **1**, the aldehydes **2**, the amines **3** and the chiral amine organocatalyst (**A–I**) were purchased from the Aldrich Chemical Co. and used without further purification. Melting points were performed by using an Optimelt (MPA100) automated melting-point system (Sanford Research Systems) and are uncorrected. Optical rotations of samples were performed by using a Rudolph Research Analytical Autopol IV automatic polarimeter at 589 nm. Infrared (IR) spectra were obtained using a Perkin-Elmer Spectrum 100 FT-IR spectrometer with a UATR application. Chiral HPLC measurements were performed on a Shimadzu SCL-10A system with a SPD-10AV UV–vis detector and hexane/isopropanol as the solvent mobile phase. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform by using a Bruker AV-400 or a Bruker DRX-500. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of deuterochloroform (δ 7.24 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). Coupling constants are given in hertz (Hz). Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on a Waters LCT Premier TOF spectrometer for electrospray ionization (ESI).

General procedure for the asymmetric organocatalyzed Michael addition of aldehyde **2{*1*}** to maleimide **1{*1*}** to produce **3{*1,1*}** (Table 1)

Propionaldehyde (**2**{*1*}) (31.2 µL, 0.433 mmol, 1.5 equiv) was added to a solution of *N*-phenylmaleimide (**1**{*1*}) (50.0 mg, 0.289 mmol, 1.0 equiv) in chloroform (3 mL) at 0 °C, followed by the appropriate chiral amine (**A–I**) (0.0289 mmol, 0.1 equiv) and the reaction mixture was stirred at the appropriate temperature for the appropriate length of time listed in Table 1. Water was added upon completion of the reaction and the resulting mixture was extracted with methylene chloride (3 × 5 mL). The methylene chloride extracts were combined, dried over sodium sulfate and concentrated in vacuo to yield a yellow liquid. The crude liquid was purified by column chromatography (2/3 ethyl acetate–hexane) to yield the succinimide **3{*1,1*}** as a clear colorless liquid composed of a mixture of two diastereomers, which were separated by further chromatographic purification.

(*R*)-2-((*S*)-2,5-Dioxo-1-phenylpyrrolidin-3-yl)propanal (3{*1,1*}) (major diastereomer): $[\alpha]_D^{25}$ +74.0 (*c* 1.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.47 (m, 2H), 7.39 (m, 1H), 7.35–7.23 (m, 2H), 3.36 (m, 1H), 3.13 (m, 1H), 2.98 (dd, *J* = 18.5, 9.7 Hz, 1H), 2.51 (m, 1H), 1.30 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 177.5, 175.0, 131.8, 129.1, 128.6, 126.4, 46.9, 39.4, 31.5, 9.7; IR (neat): 2971, 2940, 1774, 1701 cm^{-1}; MS (ESI^+) *m*/*e* 232.1 $[M + H]^+$; HRMS (ESI^+) calcd for $C_{13}H_{14}NO_3$ $[M + H]^+$: 232.0974; found: 232.0988.

(*S*)-2-((*S*)-2,5-Dioxo-1-phenylpyrrolidin-3-yl)propanal (3{*1,1*}) (minor diastereomer): $[\alpha]_D^{23}$ +43.3 (*c* 0.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.47 (m, 2H), 7.39 (m, 1H), 7.28 (m, 2H), 3.26–3.15 (m, *J* = 13.0, 6.5 Hz, 1H), 3.10–3.00 (m, 1H), 2.87 (dd, *J* = 18.1, 9.6 Hz, 1H), 2.54 (dd, *J* = 18.1, 5.6 Hz, 1H), 1.33 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 177.6, 175.1, 132.0, 129.0, 128.5, 126.5, 46.8, 40.6, 31.5, 11.2; IR (neat): 2973, 2941, 1773, 1701 cm^{-1}; MS (ESI^+) *m*/*e* 232.1 $[M + H]^+$; HRMS (ESI^+) calcd for $C_{13}H_{14}NO_3$ $[M + H]^+$: 232.0974; found: 232.0985.

General procedure for the reductive amination/lactamization of **3{*1,1*}** with aniline (**4{*1*}**) (Table 2)

Aniline (**4**{*1*}) (38.4 μL, 0.422 mmol, 1.5 equiv) and sodium triacetoxyborohydride (119 mg, 0.562 mmol, 2.0 equiv) were added to a solution of succinimide **3**{*1,1*} (65.0 mg, 0.281 mmol, 1.0 equiv) in chloroform (3 mL) and the reaction mixture was stirred at the appropriate temperature for the appropriate length of time listed in Table 2. A 1 N aqueous solution of sodium hydroxide (3 mL) was added and the reaction mixture was extracted with methylene chloride (3 × 2 mL). The methylene chloride extracts were combined, dried over sodium sulfate and concentrated in vacuo to yield a yellow liquid. The crude liquid was purified by column chromatography (1/1 ethyl acetate-hexane) to yield **6**{*1,1,1*} as a clear colorless liquid composed of a mixture of two diastereomers and **7**{*1,1,1*} as a clear colorless liquid.

2-((3*S*,4*R*)-4-Methyl-2-oxo-1-phenylpyrrolidin-3-yl)-*N*-phenylacetamide (6{*1,1,1*}) (major syn diastereomer): ^1H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.62–7.53 (m, 4H), 7.42–7.36 (m, *J* = 8.0 Hz, 2H), 7.32–7.24 (m, 2H), 7.22–7.16 (m, *J* = 9.2, 5.5 Hz, 1H), 7.10–7.03 (m, *J* = 7.4 Hz, 1H), 4.05 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.43 (dd, *J* = 9.7, 0.9 Hz, 1H), 3.29–3.22 (m, *J* = 7.8, 5.4 Hz, 1H), 3.00–2.93 (m, 1H), 2.82–2.74 (m, 1H), 2.51 (dd, *J* = 15.3, 5.3 Hz, 1H), 1.09 (d, *J* = 3.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 170.0, 139.2, 138.4, 129.0, 128.9, 125.2, 123.9, 120.3, 119.8, 54.9, 44.7, 35.1, 30.7, 14.9; IR (neat): 3465, 3263, 2932, 2855, 1660 cm^{-1}; MS (ESI^+) *m*/*e* 309.2 $[M + H]^+$; HRMS (ESI^+) calcd for $C_{19}H_{21}N_2O_2$ $[M + H]^+$: 309.1603; found: 309.1606.

2-((3*S*,4*S*)-4-Methyl-2-oxo-1-phenylpyrrolidin-3-yl)-*N*-phenylacetamide (6{*1,1,1*}) (minor anti diastereomer): ^1H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.62–7.51 (m, 4H), 7.41–7.33 (m, 2H), 7.30–7.22 (m, *J* = 10.3, 5.5 Hz, 2H), 7.22–7.12 (m, *J* = 7.4 Hz, 1H), 7.10–6.98 (m, *J* = 7.4 Hz, 1H), 3.79 (dd, *J* = 9.4, 8.0 Hz, 1H), 3.42 (t, *J* = 9.5 Hz, 1H), 2.85 (dd, *J* = 14.7, 7.7 Hz, 1H), 2.72–2.61 (m, *J* = 12.6, 11.2, 8.8 Hz, 1H), 2.55 (dd, *J* = 14.7, 3.9 Hz, 1H), 2.33–2.14 (m, 1H), 1.22 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 169.4, 138.7, 138.3, 128.8, 128.7, 125.0, 123.7, 120.1, 119.6, 54.1, 48.1, 37.7, 33.7, 16.6; IR (neat): 3460, 3265, 2932, 2855, 1657 cm^{-1}; MS (ESI^+) *m*/*e* 309.2 $[M + H]^+$; HRMS (ESI^+) calcd for $C_{19}H_{21}N_2O_2$ $[M + H]^+$: 309.1603; found: 309.1590.

(*S*)-1-Phenyl-3-((*R*)-1-(phenylamino)propan-2-yl)pyrrolidine-2,5-dione (7{*1,11*}): ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.33 (m, 3H), 7.24–7.08 (m, 4H), 6.79–6.67 (m, *J* = 7.3 Hz, 1H), 6.67–6.52 (m, *J* = 7.5 Hz, 2H), 3.82 (s, 1H), 3.42–3.26 (m, 1H), 3.26–3.09 (m, 2H), 2.92 (dd, *J* = 18.5, 9.6 Hz, 1H), 2.63 (dd, *J* = 18.5, 5.0 Hz, 1H), 2.63–2.50 (m, *J* = 5.0 Hz, 1H), 1.09 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 175.6, 147.8, 131.8, 129.3, 129.1, 128.6, 126.6, 117.9, 112.9, 46.9, 42.4, 34.3, 31.3, 15.0; IR (neat): 3380, 2974, 2950, 1775 cm^{-1}; MS (ESI^+) *m*/*e* 309.2 $[M + H]^+$; HRMS (ESI^+) calcd for $C_{19}H_{21}N_2O_2$ $[M + H]^+$: 309.1603; found: 309.1595.

General procedure for the combination of the Michael addition, the reductive amination/lactamization, and the epimerization step in a single-pot process to produce γ-lactam **6{*1,1,1*}** (Scheme 4)

A 0.400 M solution of propionaldehyde (**2**{*1*}) in chloroform (1.50 mL, 0.600 mmol, 1.5 equiv) was added to a 0.400 M solution of *N*-phenylmaleimide (**1**{*1*}) in chloroform (1.00 mL, 0.400 mmol, 1.0 equiv) at 0 °C, followed by a 0.100 M solution of (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (0.40 mL, 0.040 mmol, 0.10 equiv), and the reaction mixture was stirred at 0 °C for 36 h. A 1.00 M solution of aniline (**4**{*1*}) (0.80 mL, 0.800 mmol, 2.0 equiv) was added followed by sodium triacetoxyborohydride (212 mg, 1.00 mmol, 2.5 equiv) and the reaction mixture was stirred at room temperature for 6 h. The chloroform solvent was removed in vacuo, methanol (10 mL) was added followed by potassium *tert*-butoxide (449 mg, 4.00 mmol, 10.0 equiv), and the reaction mixture was stirred at room temperature for 12 h. The methanol solvent was removed in vacuo, a 4.0 N aqueous solution of hydrochloric acid (5.0 mL, 20 mmol, 50.0 equiv) was added, and the reaction mixture was extracted with methylene chloride (3 × 2 mL). The methylene chloride extracts were combined, dried over sodium sulfate and concentrated in vacuo to yield a yellow liquid. The crude liquid was purified by column chromatography (1/1 ethyl acetate-hexane) to yield 81.4 mg (66%) of a single diastereomer of **6**{*1,1,1*} as a clear colorless liquid. The ee of the product was determined by chiral HPLC analysis to be 80% (Chiralpak AD column, 80/20 hexane/isopropanol).

General procedure for the single-pot parallel synthesis of γ-lactams **6** by using an automated synthesizer (Scheme 5)

Using a Chemspeed Accelerator SLT-100 automated synthesizer with 64 individual 13 mL reactor vessels, 0.400 M solutions of the maleimides **1** in chloroform (1.00 mL, 0.400 mmol, 1.0 equiv) were added to the appropriate reactor vessels, and the reactors were cooled to 0 °C. Solutions (0.400 M) of the aldehydes **2** in chloroform (1.50 mL, 0.600 mmol, 1.5 equiv) were added to the appropriate reactor vessels followed by a 0.100 M solution of (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (0.40 mL, 0.040 mmol, 0.10 equiv), and the reaction mixtures were subjected to vortex mixing at 0 °C for 36 h. 1.00 M solutions of the amines **4** (0.80 mL, 0.800 mmol, 2.0 equiv) were then added to the appropriate reactor vessels followed by sodium triacetoxyborohydride (212 mg, 1.00 mmol, 2.5 equiv) and the reaction mixtures were subjected to vortex mixing at room temperature for 6 h. The reaction mixtures were concentrated in vacuo within the reactor vessels (30 °C, 6 mmHg), methanol (10 mL) was then added followed by potassium *tert*-butoxide (449 mg, 4.00 mmol, 10.0 equiv), and the reaction mixtures were subjected to vortex mixing at room temperature for 12 h. The reaction mixtures were concentrated in vacuo within the reactor vessels (40 °C, 6 mmHg), followed by the addition of 4.0 N aqueous solution of hydrochloric acid (5.0 mL, 20 mmol, 50.0 equiv) to the resulting residues. The mixtures were extracted with methylene chloride (3 × 2 mL) and each of the extracts were gravity filtered through a silica gel 500 mg SPE-Si cartridge followed by washing the SPE with ethyl acetate (2 × 2 mL). The resulting solutions were then further purified by using preparative HPLC.

Supporting Information

Supporting Information File 1

Results for the four 4 × 2 × 8 libraries using an automated synthesizer, full characterization data for representative compounds, and copies of ^{1}H and ^{13}C NMR spectra for representative compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-206-S1.pdf]

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14. This should ultimately produce lactams with ~80% es.
15. We observed a decrease in the enantiomeric purities, reflective of the diastereomeric ratio of the succinimide, as we had anticipated (Scheme 3).

16. The standards for compound purity and quantity are based on those requested from the National Institutes of Health's Molecular Library Small Molecule Repository (http://mlsmr.glpg.com/MLSMR_HomePage/submitcompounds.html).

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