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Beilstein Journal of Organic Chemistry

Allene chemistry

Kay M. Brummond

Editorial

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Allenes: The changing landscape of C_{sp}

As organic chemists, we continually search for transformations to produce compounds in increasingly efficient and expedient ways, and to synthesize new compounds possessing interesting properties. One particularly appealing strategy is to exploit underutilized functional groups. By using this strategy, novel arrays of atoms that were previously unattainable are made possible. There are hurdles to overcome with this approach, that include, but are not limited to, an incomplete understanding of functional group compatibility issues that may arise during their preparation and/or that may be caused by their presence in subsequent reactions. The focus of this Thematic Series of the *Beilstein Journal of Organic Chemistry* is allenes, which even after decades of use can still be classified as an underutilized functional group. However, great advances in the chemistry of allenes have been made since the time when they were thought to be, "difficult to prepare and very reactive, and not commonly encountered ..." [1].

I first became interested in allenes as a graduate student with Professor Ray Funk at Pennsylvania State University while working on the preparation of ene–diyne systems. Interestingly, I always seemed to isolate allenes instead of the compounds I was hoping to obtain. My interests in allenes continued in my first faculty position at West Virginia University, where my colleagues Professors Bob Moore (of the Doering-Moore-Skattebøl reaction) and Kung Wang (contributor to this issue) contributed greatly to my appreciation and understanding of the allene functional group.

Focusing on a particular functional group at first glance may seem trivial and obvious, but the importance of these types of studies is underscored by the fact that numerous Nobel prizes have been awarded for the study "alkenes in synthesis". More importantly, transformations involving allenes can provide new scaffolds that lead to an expansion of chemical space where currently nearly half of all existing organic compounds can be described by a mere 143 molecular frameworks [2]. This data supports the notion that we tend towards compounds and functionalities with which we are familiar and understand, but this, nevertheless, creates a limitation to our knowledge of our field.

This Thematic Series entitled "Allene chemistry" in the *Beilstein Journal of Organic Chemistry* represents contributions from leading chemists exploring a wide range of reactions

involving allenes as reactants or products. The articles within detail discoveries surrounding the allene group and provide knowledge that chemists need in order to make informed decisions about whether or not to include an allene in a synthetic plan. I would like to thank all the authors for their contributions to this issue.

Kay Brummond

Pittsburgh, April 2011

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CuCl-catalyzed aerobic oxidation of 2,3-allenols to 1,2-allenic ketones with 1:1 combination of phenanthroline and bipyridine as ligands

Shuxu Gao[1], Yu Liu[1] and Shengming Ma*[1,2]

Full Research Paper

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Abstract

A protocol has been developed to prepare 1,2-allenyl ketones using molecular oxygen in air or pure oxygen as the oxidant from 2,3-allenylic alcohols with moderate to good yields under mild conditions. In this reaction CuCl (20 mol %) with 1,10-phenanthroline (10 mol %) and bipyridine (10 mol %) was used as the catalyst. It is interesting to observe that the use of the mixed ligands is important for the higher yields of this transformation: With the monoligand approach developed by Markó et al., the yields are relatively lower.

Introduction

The oxidation of alcohols is one of many fundamental reactions in organic synthesis [1,2]. Usually, stoichiometric oxidants such as MnO_2 [3], PCC [4], PDC [4], etc. were employed for this type of transformation. However, the cost and the byproducts derived from these reagents cause economic and environmental problems [5]. In the past decades, much attention has been paid to catalytic oxidation of alcohols using molecular oxygen as the oxidant with Pd [6-10], Cu [11-13], Ru [14,15] as the catalysts.

1,2-Allenic ketones have become very useful in organic synthesis [16-33]. Current methods for the oxidation of allenic alcohols to ketones include oxidation with MnO_2 [30,34,35], Swern oxidation [17,24] or Dess–Martin oxidation [16,17,24,25,28,31-33]: Catalytic aerobic oxidation has not so far been reported. Due to the synthetic potential of 1,2-allenyl ketones, it is desirable to develop an aerobic oxidation protocol for 2,3-allenols. In this paper we wish to report the CuCl-

catalyzed aerobic oxidation of 2,3-allenols by applying a mixed ligand approach using copper as the catalyst [12,13].

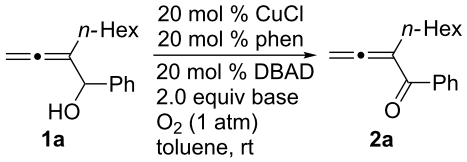
Results and Discussion

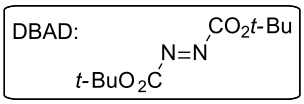
After screening the Pd- [6-10] and Ru-catalyzed [14,15] protocols without success, we began a study of the oxidation of 2-hexyl-1-phenylbuta-2,3-diene-1-ol (**1a**) with O_2 based on the pioneering study of oxidation of normal simple alcohols by Markó et al. [12]. Under the original conditions [12], the expected allenylic ketone **2a** was obtained in 59% yield when CuCl and 1,10-phenanthroline were used (Table 1, entry 1). A series of bases and solvents were then screened for the oxidation of **1a**. The results are summarized in Table 1 and Table 2. We found that (1) K_2CO_3 is the most effective base (Table 1, entry 1) and that organic bases such as NEt_3 and DBU are generally ineffective (Table 1, entries 6 and 7); (2) toluene is the best solvent (Table 2).

In order to improve the yield further, we examined the effect of ligands. When 2,2'-bipyridine, which has a weaker coordinating ability, was used [36], the yield of **2a** was lower (Table 3, entry 2). With 4,7-diphenyl-1,10-phenanthroline the yield was slightly improved to 66% (Table 3, entry 3). These experimental results obviously indicated that the CuCl-catalyzed oxidation of allenic alcohol was influenced by the coordinating ability of nitrogen ligands. Consequently, we carried out the reaction with a mixture of a stronger coordinating ligand together with a relatively weaker coordinating ligand. Indeed, it was interesting to observe that when 4,7-diphenyl-1,10-phenanthroline and 2,2'-bipyridine were mixed in the ratio of 1:1 [37,38], the isolated yield was improved to 82% (Table 3, entry 6). The yield with 1,10-phenanthroline and 2,2'-bipyridine (1:1) was 83% (Table 3, entry 10). However, 4,7-diphenyl-1,10-phenanthroline is relatively expensive (1 g, $ 94, Aldrich), so the cheaper 1,10-phenanthroline (5 g, $ 26.4, Aldrich) was used for further study. The effect of ratio of 1,10-phenanthroline vs 2,2'-bipyridine on the yield was also studied: A ratio of 1:1 proved to be the best (Table 3, entries 7–12). This may be explained by considering that the coordination of 2,2'-bipyridine is important for the formation of the catalytically active species and may be easily replaced with that of the alcohol. We also tried *N*-methylimidazole (NMI), which was used in oxidation of primary aliphatic alcohols reported by Markó et al. [13], however, both the turnover and yield were low (Table 3, entry 14). Both 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline and iPr-Pybox were ineffective in this reaction (Table 3, entries 4 and 5).

Some other Cu(I) catalysts, such as CuBr, CuI, and CuCN were also investigated, but no higher yield was achieved (Table 4). Further studies led to the observation that air (300 psi, 35 °C (oil bath)) could be used instead of pure oxygen

Table 1: Screening of bases for the CuCl-catalyzed oxidation of **1a**[a].

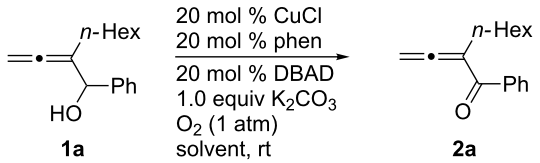




entry	base	time (h)	yield of **2a** (%)[b]
1	K_2CO_3	40	59[c,d]
2	Na_2CO_3	48	22[e]
3	Cs_2CO_3	35	27[d,f,g]
4	$KHCO_3$	45	15[h]
5	KOH[i]	48	39[j]
6	NEt_3	45	NR[k]
7	DBU	45	NR[l]

[a]The reaction was carried out using 0.3 mmol of **1a**, 20 mol % of CuCl, 20 mol % of phen, 20 mol % of DBAD, and 2.0 equiv of base in 3 mL of toluene under 1 atm of oxygen unless otherwise stated. [b]^{1}H NMR yield using CH_2Br_2 as the internal standard. [c]1.0 equiv K_2CO_3 was used. [d]Isolated yield. [e]50% of **1a** was recovered as determined by ^{1}H NMR analysis. [f]15 mol % of catalyst was used. [g]32% of **1a** was recovered by column chromatography. [h]53% of **1a** was recovered as determined by ^{1}H NMR analysis. [i]100 mg of 3 Å MS and 20 mol % of KOH was used. [j]28% of **1a** was recovered as determined by ^{1}H NMR analysis. [k]70% of **1a** was recovered as determined by ^{1}H NMR analysis. [l]72% of **1a** was recovered by column chromatography.

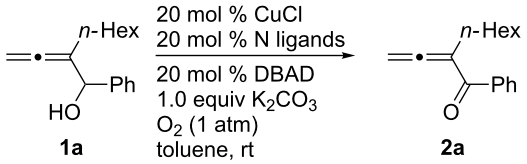
Table 2: Screening of solvents for the CuCl-catalyzed oxidation of **1a**[a].

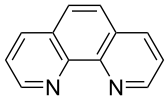
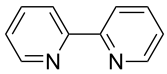
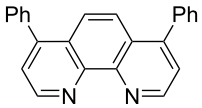
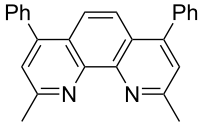
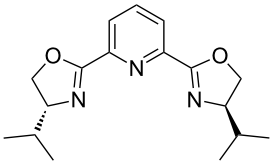
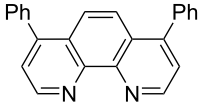


entry	solvent	time (h)	yield of **2a** (%)
1	toluene	40	59[b]
2	CH_3CN	48	NR[c]
3	DCE	47	31[d]
4	$CHCl_3$	47	20[e]
5	DMF	47	NR[f]

[a]The reaction was carried out using 0.3 mmol of **1a**, 20 mol % of CuCl, 20 mol % of phen, 20 mol % of DBAD, and 1.0 equiv of K_2CO_3 in 3 mL of solvent under 1 atm of oxygen. [b]Isolated yield. [c]64% of **1a** was recovered as determined by ^{1}H NMR analysis. [d]^{1}H NMR yield using CH_2Br_2 as the internal standard. [e]78% of **1a** was recovered as determined by ^{1}H NMR analysis. [f]76% of **1a** was recovered as determined by ^{1}H NMR analysis.

Table 3: Screening for different nitrogen ligands in the CuCl-catalyzed oxidation of **1a**[a].



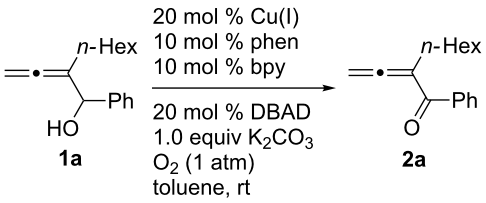
entry	ligand 1 (mol %)	ligand 2 (mol %)	time (h)	yield of **2a** (%)[b]
1	 **L-A**	—	40	61
2	 **L-B**	—	46	43[c]
3		—	14.5	66
4		—	45	NR[d]
5		—	24	NR[e]
6	 (10)	**L-B** (10)	45.5	82
7	**L-A** (17.5)	**L-B** (2.5)	40	79
8	**L-A** (15.0)	**L-B** (5.0)	40	65
9	**L-A** (12.5)	**L-B** (7.5)	40	82
10	**L-A** (10.0)	**L-B** (10.0)	42	83
11	**L-A** (7.5)	**L-B** (12.5)	42	78
12	**L-A** (5.0)	**L-B** (15.0)	40	73
13	**L-A** (2.5)	**L-B** (17.5)	40	68
14[f]	**L-A** (5.0)	**NMI** (7.0)	35	17

[a]The reaction was carried out using 0.3 mmol of **1a**, 20 mol % of CuCl, 20 mol % of nitrogen ligand, 20 mol % of DBAD, and 1.0 equiv of K_2CO_3 in 3 mL of toluene under 1 atm of oxygen. [b]^{1}H NMR yields determined by 300 MHz, ^{1}H NMR analysis using CH_2Br_2 as the internal standard. [c]52% of **1a** was recovered as determined by ^{1}H NMR analysis. [d]87% of **1a** was recovered as determined by ^{1}H NMR analysis. [e]82% of **1a** was recovered as determined by ^{1}H NMR analysis. [f]The reaction was carried out using 0.5 mmol of **1a**, 5 mol % of CuCl, 5 mol % of *t*-BuOK, 5 mol % of DBAD and the indicated ligands in 5 mL of C_6H_5F at 70 °C under 1 atm of oxygen. 52% of **1a** was recovered as determined by ^{1}H NMR analysis.

(1 atm, 15–24 °C) to shorten the reaction time from 40 to 10 hours and the yield was similar (86%) (Table 5, entry 1). Thus, 20 mol % of CuCl, 10 mol % of 1,10-phenanthroline, 10 mol % of 2,2'-bipyridine and 50 mol % of K_2CO_3 in toluene with air (300 psi, 35 °C) as the oxidant were defined as the standard conditions.

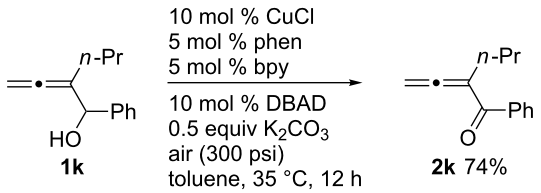
Under the standard conditions a series of 1-aryl-2,3-allenols were oxidized to the corresponding 1,2-allenic aryl ketones: A *para*-nitro group led to a 63% yield of **2e** (Table 5, entry 5); heteroaryl groups such as furanyl and thienyl were also tolerated under the reaction conditions, affording the corresponding allenic ketones **2f** and **2g** in 61% and 73% yields, respectively (Table 5, entries 6 and 7), whilst the reaction of 1-naphthyl-substituted **1h** afforded **2h** in 74% yield (Table 5, entry 8). Trisubstituted allenic alcohol **1j** was also oxidized to the corresponding allenic ketone **2j** in 91% yield (Table 5, entry 10).

Table 4: Screening of other Cu(I) sources.



entry	Cu(I)	time (h)	isolated yield of **2a**
1	CuBr	40	68%
2	CuI	40	49%
3	CuCN	41	45%

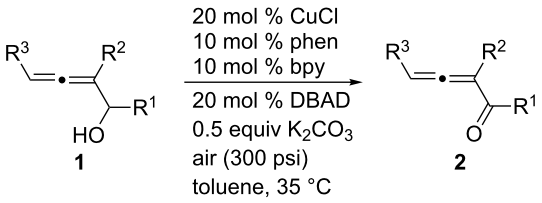
The reaction may be easily carried out on a 1 g scale: the oxidation of allenol **1k** afforded the corresponding allenic ketone **2k** in 74% yield in 12 hours with just 10 mol % of CuCl and 5 mol % each of 1,10-phenanthroline and 2,2'-bipyridine (Scheme 1).



Scheme 1: 1 gram scale reaction of allenol **1k**.

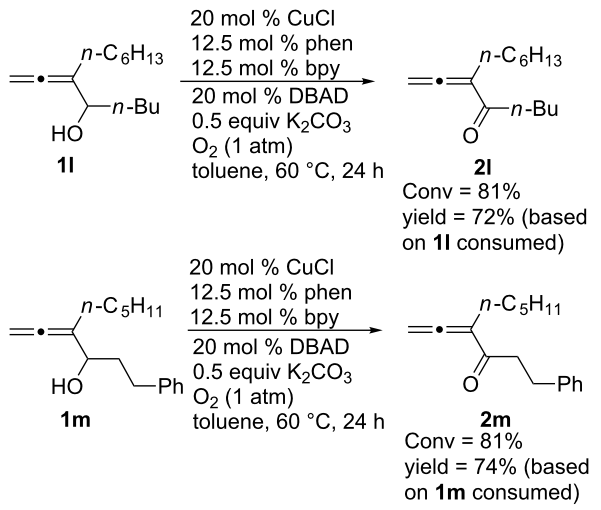
When the reaction of 1-alkyl-substituted-2,3-allenols oxidation was conducted under 1 atm of oxygen at 60 °C, 81% of conversion was observed and the corresponding allenic ketones **2l** and **2m** were obtained in 58% and 60% isolated yields (72% and 74% based on the starting material consumed), respectively (Scheme 2). As a comparison, it should be noted that when **1l** was oxidized with air (300 psi, 60 °C), the allenic ketone **2l** was formed in 43% ^{1}H NMR yield with 73% conversion of **1l** within 10 hours.

Table 5: The CuCl-catalyzed oxidation of allenic alcohols using air as the oxidant[a].



entry	substrate			time (h)	yield (%)[b]
	R^1	R^2	R^3		
1	Ph	*n*-C_6H_{13}	H (**1a**)	10	86 **(2a)**
2	*p*-EtC_6H_4	*n*-Pr	H (**1b**)	10	83 **(2b)**
3	*p*-BrC_6H_4	*n*-Pr	H (**1c**)	6	80 **(2c)**
4	*p*-ClC_6H_4	*n*-C_6H_{13}	H (**1d**)	6	78 **(2d)**
5	*p*-$O_2NC_6H_4$	*n*-C_6H_{13}	H (**1e**)	6	63 **(2e)**
6	3-furanyl	*n*-C_6H_{13}	H (**1f**)	11	61 **(2f)**
7	3-thienyl	*n*-C_5H_{11}	H (**1g**)	8.5	73 **(2g)**
8	1-naphthyl	Me	H (**1h**)	11	74 **(2h)**
9	Ph	allyl	H (**1i**)	11	75 **(2i)**
10	Ph	Bu	*n*-C_5H_{11} (**1j**)	11	91 **(2j)**

[a]The reaction was carried out using 0.3 mmol of **1**, 20 mol % of CuCl, 10 mol % of phen, 10 mol % of bpy, 20 mol % of DBAD, and 0.5 equiv of K_2CO_3 in 3 mL of toluene, air (300 psi, 35 °C (oil bath)). [b]Isolated yields.



Scheme 2: The oxidation of **1l** and **1m** under 1 atm of oxygen.

Conclusion

In conclusion, we have developed a method for the aerobic oxidation of 2,3-allenols, which uses molecular oxygen in air or pure oxygen as the oxidant. In this reaction, CuCl with a 1:1 ratio of 1,10-phenanthroline and bipyridine was used as the catalyst to provide the best results. A series of 1,2-allenic ketones were obtained in moderate to good yields under mild conditions. Compared to the traditional monoligand approach, allenols are obviously unique demanding a mixed ligands approach for better yields probably as a consequence of the coordinating ability of the allene moiety. Further study in this area is being pursued in this laboratory.

Experimental

General experimental methods for starting materials

The starting allenols **1a–e**, **1i**, **1k**, **1l**, **1m** were prepared via the reaction of propargyl bromides and corresponding aldehydes in the presence of $SnCl_2$ and NaI in DMF [39,40]; allenols **1f** [41], **1g** [42], **1h** [43], and **1j** [44] were prepared as reported. These starting allenols were purified by flash chromatography before use.

General experimental procedure for the aerobic oxidation of allenic alcohols

2-Hexyl-1-phenylbuta-2,3-dien-1-one (**2a**)

Typical procedure: 1,10-phenanthroline (5.5 mg, 0.03 mmol), 2,2'-bipyridine (4.7 mg, 0.03 mmol), CuCl (5.9 mg, 0.06 mmol), K_2CO_3 (20.6 mg, 0.15 mmol), and 1.5 mL of dry toluene were added successively into an oven dried reaction vessel (sealed with a stopper to isolate the contents from atmospheric moisture). The resulting mixture was stirred at rt for 0.5 h. Then the stopper was removed to add DBAD (13.7 mg, 0.06 mmol), 2-hexyl-1-phenylbuta-2,3-dien-1-ol (69.6 mg, 0.3 mmol), and 1.5 mL of dry toluene. The reaction vessel was then transferred to an autoclave, which was charged with air to a pressure of 300 psi, and stirred at 35 °C (oil bath). After 10 h, the pressure was carefully released in the hood, the mixture filtered through a short column of silica gel (100–140 mesh) and washed with diethyl ether. Evaporation of the solvent and flash chromatography on silica gel (eluent: petroleum ether/diethyl ether = 30:1) afforded **2a** (59.3 mg, 86%): liquid; ^{1}H NMR (300 MHz , $CDCl_3$) δ 7.76 (d, J = 7.2 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 5.04 (t, J = 2.7 Hz, 2H), 2.46–2.35 (m, 2H), 1.58–1.45 (m, 2H), 1.45–1.20 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 217.0, 194.9, 138.3, 131.9, 129.0, 127.8, 106.9, 79.3, 31.6, 28.9, 27.8, 22.6, 14.0 ppm; MS (m/z) 228 (M^+, 7.25), 105 (100); IR (neat) 2927, 2857, 1933, 1653, 1599, 1450, 1312, 1273 cm^{-1}; HRMS-EI (m/z) calcd for $C_{16}H_{20}O^+$ [M^+]: 228.1514; found: 228.1517.

2-Propyl-1-(4-ethylphenyl)buta-2,3-dien-1-one (**2b**)

The reaction of 1,10-phenanthroline (5.3 mg, 0.03 mmol), 2,2'-bipyridine (4.6 mg, 0.03 mmol), CuCl (5.9 mg, 0.06 mmol), K_2CO_3 (20.8 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (13.7 mg, 0.06 mmol), and 2-propyl-1-(4-ethylphenyl)buta-2,3-dien-1-ol (64.7 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2b** (53.0 mg, 83%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 5.05 (t, J = 2.9 Hz, 2H), 2.69 (q, J = 7.6 Hz, 2H), 2.44–2.32 (m, 2H), 1.63–1.45 (m, 2H), 1.25 (t, J = 7.5 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 216.5, 194.4, 148.8, 135.8, 129.3, 127.3, 106.5, 79.1, 30.1, 28.8, 21.1, 15.1, 13.7 ppm; MS (m/z) 214 (M^+, 1.75), 133 (100); IR (neat) 2964, 2931, 2872, 1933, 1650, 1607, 1458, 1414, 1273, 1182, 1058 cm^{-1}; HRMS-EI (m/z) calcd for $C_{15}H_{18}O^+$ [M^+]: 214.1358; found: 214.1360.

2-Propyl-1-(4-bromophenyl)buta-2,3-dien-1-one (**2c**)

The reaction of 1,10-phenanthroline (5.4 mg, 0.03 mmol), 2,2'-bipyridine (4.6 mg, 0.03 mmol), CuCl (5.9 mg, 0.06 mmol), K_2CO_3 (20.6 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (13.8 mg, 0.06 mmol), and 2-propyl-1-(4-bromophenyl)buta-2,3-dien-1-ol (80.3 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2c** (64.1 mg, 80%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 5.07 (t, J = 2.9 Hz, 2H), 2.41–2.30 (m, 2H), 1.60–1.45 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 217.0, 193.7, 137.0, 131.1, 130.5, 126.7, 106.7, 79.7, 29.7, 21.1, 13.7 ppm; MS (m/z) 266 (M^+ (^{81}Br), 1.68), 264 (M^+ (^{79}Br), 1.76), 185 (100); IR (neat) 2961, 2929, 2870, 1931, 1653, 1585, 1458, 1391, 1270, 1071, 1010 cm^{-1}; HRMS-EI (m/z) calcd for $C_{13}H_{13}O^{81}Br^+$ [M^+]: 266.0129; found: 266.0136.

2-Hexyl-1-(4-chlorophenyl)buta-2,3-dien-1-one (**2d**)

The reaction of 1,10-phenanthroline (5.5 mg, 0.03 mmol), 2,2'-bipyridine (4.8 mg, 0.03 mmol), CuCl (6.0 mg, 0.06 mmol), K_2CO_3 (20.9 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (13.8 mg, 0.06 mmol), and 2-hexyl-1-(4-chlorophenyl)buta-2,3-dien-1-ol (79.6 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2d** (62.0 mg, 78%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 5.06 (t, J = 2.6 Hz, 2H), 2.43–2.32 (m, 2H), 1.55–1.42 (m, 2H), 1.43–1.18 (m, 6H), 0.88 (t, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 217.0, 193.6, 138.2, 136.6, 130.4, 128.1, 106.9, 79.6, 31.6, 28.9, 27.7, 22.5, 14.0 ppm; MS (*m*/*z*) 264 (M^+ (^{37}Cl), 0.76), 262 (M^+ (^{35}Cl), 2.08), 139 (100); IR (neat) 2927, 2857, 1931, 1654, 1590, 1460, 1397, 1274, 1091 cm^{-1}; HRMS-EI (*m*/*z*) calcd for $C_{16}H_{19}O^{35}Cl^+$ [M^+]: 262.1124; found: 262.1130.

2-Hexyl-1-(4'-nitrophenyl)buta-2,3-dien-1-one (**2e**)

The reaction of 1,10-phenanthroline (5.5 mg, 0.03 mmol), 2,2'-bipyridine (4.7 mg, 0.03 mmol), CuCl (5.9 mg, 0.06 mmol), K_2CO_3 (20.8 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (13.9 mg, 0.06 mmol), and 2-hexyl-1-(4-nitrophenyl)buta-2,3-dien-1-ol (82.7 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2e** (51.4 mg, 63%) (eluent: petroleum ether/diethyl ether = 20:1): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 8.7 Hz, 2H), 5.12 (t, J = 2.9 Hz, 2H), 2.44–2.33 (m, 2H), 1.57–1.44 (m, 2H), 1.44–1.20 (m, 6H), 0.89 (t, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 218.0, 193.4, 149.4, 143.6, 129.7, 123.1, 107.6, 80.4, 31.5, 28.8, 27.7, 27.3, 22.5, 14.0 ppm; MS (*m*/*z*) 273 (M^+, 2.56), 150 (100); IR (neat) 2927, 2857, 1930, 1660, 1602, 1526, 1461, 1349, 1272, 1104, 1011 cm^{-1}; HRMS-EI (*m*/*z*) calcd for $C_{16}H_{19}NO_3^+$ [M^+]: 273.1365; found: 273.1367.

2-Hexyl-1-(3-furanyl)buta-2,3-dien-1-one (**2f**)

The reaction of 1,10-phenanthroline (5.4 mg, 0.03 mmol), 2,2'-bipyridine (4.8 mg, 0.03 mmol), CuCl (6.2 mg, 0.06 mmol), K_2CO_3 (21.3 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (13.6 mg, 0.06 mmol), and 2-hexyl-1-(3-furanyl)buta-2,3-dien-1-ol (66.2 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2f** (40.4 mg, 61%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.37 (s, 1H), 6.81 (d, J = 1.2 Hz, 1H), 5.21 (t, J = 2.9 Hz, 2H), 2.39–2.27 (m, 2 H), 1.52–1.38 (m, 2H), 1.38–1.18 (m, 6H), 0.87 (t, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 215.8, 186.4, 147.4, 143.0, 126.7, 110.0, 108.1, 80.0, 31.6, 28.9, 27.8, 27.6, 22.6, 14.1 ppm; MS (*m*/*z*) 218 (M^+, 3.49), 95 (100); IR (neat) 2956, 2928, 2857, 1933, 1724, 1645, 1561, 1509, 1458, 1379, 1311, 1163, 1077, 1009 cm^{-1}; HRMS-EI (*m*/*z*) calcd for $C_{14}H_{18}O_2^+$ [M^+]: 218.1307; found: 218.1305.

2-Pentyl-1-(3-thienyl)buta-2,3-dien-1-one (**2g**)

The reaction of 1,10-phenanthroline (5.5 mg, 0.03 mmol), 2,2'-bipyridine (4.8 mg, 0.03 mmol), CuCl (5.9 mg, 0.06 mmol), K_2CO_3 (20.9 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (13.7 mg, 0.06 mmol), and 2-pentyl-1-(3-thienyl)buta-2,3-dien-1-ol (66.4 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2g** (48.3 mg, 73%) (eluent: petroleum ether/diethyl ether = 50:1): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 1.8 Hz, 1H) 7.53 (d, J = 4.8 Hz, 1H), 7.25 (dd, J_1 = 4.8 Hz, J_2 = 3.3 Hz, 1H), 5.16 (d, J = 2.7 Hz, 2H), 2.41–2.32 (m, 2H), 1.56–1.42 (m, 2H), 1.42–1.24 (m, 4H), 0.90 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 216.0, 187.1, 141.5, 132.2, 128.2, 125.1, 107.6, 79.6, 31.4, 27.9, 27.5, 22.4, 14.0 ppm; MS (*m*/*z*) 220 (M^+, 3.02), 111 (100); IR (neat) 2956, 2927, 2861, 1933, 1641, 1511, 1460, 1411, 1260, 1082 cm^{-1}; HRMS-EI (*m*/*z*) calcd for $C_{13}H_{16}OS^+$ [M^+]: 220.0922; found: 220.0922.

2-Methyl-1-(1-naphthyl)buta-2,3-dien-1-one (**2h**)

The reaction of 1,10-phenanthroline (5.5 mg, 0.03 mmol), 2,2'-bipyridine (4.8 mg, 0.03 mmol), CuCl (6.2 mg, 0.06 mmol), K_2CO_3 (21.4 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (13.5 mg, 0.06 mmol), and 2-methyl-1-naphthylbuta-2,3-dien-1-ol (63.6 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2h** (47.2 mg, 74%, an unknown substance could not be separated via column chromatography and the purity of **2h** is 95%, which was determined by ^{1}H NMR with mesitylene as the internal standard): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11–8.03 (m, 1H), 7.95–7.81 (m, 2H), 7.61–7.39 (m, 4H), 4.80 (q, J = 2.8 Hz, 2H), 2.11 (t, J = 2.7 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 218.6, 197.5, 136.8, 133.5, 130.6, 130.4, 128.2, 126.9, 126.5, 126.1, 125.3, 123.9, 104.8, 78.2, 13.8 ppm; MS (*m*/*z*) 208 (M^+, 63.16), 155 (100); IR (neat) 3059, 1957, 1930, 1650, 1508, 1285, 1251, 1204, 1155, 1080, 1059 cm^{-1}; HRMS-EI (*m*/*z*) calcd for $C_{15}H_{12}O$ [M^+]: 208.0888; found: 208.0887.

2-Allyl-1-phenylbuta-2,3-dien-1-one (**2i**)

The reaction of 1,10-phenanthroline (5.4 mg, 0.03 mmol), 2,2'-bipyridine (4.6 mg, 0.03 mmol), CuCl (6.1 mg, 0.06 mmol), K_2CO_3 (21.5 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (13.7 mg, 0.06 mmol), and 2-allyl-1-phenylbuta-2,3-dien-1-ol (55.1 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2i** (41.1 mg, 75%) (eluent: petroleum ether/diethyl ether = 40:1): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 2H), 7.50 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 5.98–5.82 (m, 1H), 5.22–5.04 (m, 4H), 3.20–3.14 (m, 2H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 217.2, 194.1, 138.0, 134.9, 132.1, 129.0, 127.8, 116.4, 105.3, 79.8, 32.5 ppm; MS (*m*/*z*) 184 (M^+, 2.53), 105 (100); IR (neat) 3081, 3062, 2982, 1956, 1931, 1651, 1598, 1578, 1447, 1422, 1316, 1272 cm^{-1}; HRMS-EI (*m*/*z*) calcd for $C_{13}H_{12}O$ [M^+]: 184.0888; found: 184.0889.

2-Butyl-1-phenylnona-2,3-dien-1-one (**2j**)

The reaction of 1,10-phenanthroline (5.6 mg, 0.03 mmol), 2,2'-bipyridine (4.9 mg, 0.03 mmol), CuCl (6.2 mg, 0.06 mmol), K_2CO_3 (21.5 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (14.1 mg, 0.06 mmol), and 2-butyl-1-phenylnona-2,3-dien-1-ol (82.2 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2j** [43] (74.8 mg, 91%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) 7.71 (d, J = 7.8 Hz, 2H), 7.50–7.42 (m, 1H), 7.40–7.32 (m, 2H), 5.36 (t, J = 7.2 Hz, 1H), 2.48–2.30 (m, 2H), 2.16–1.96 (m, 2H), 1.55–1.11 (m, 10H), 0.93 (t, J = 6.9 Hz, 3H), 0.84 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.3, 195.7, 138.9, 131.5, 128.8, 127.6, 107.4, 95.0, 31.1, 30.2, 28.6, 28.4, 27.8, 22.31, 22.29, 13.89, 13.86 ppm.

2-Propyl-1-phenylbuta-2,3-dien-1-one (**2k**)

The reaction of 1,10-phenanthroline (49.1 mg, 0.27 mmol), 2,2'-bipyridine (42.6 mg, 0.27 mmol), CuCl (54.2 mg, 0.54 mmol), K_2CO_3 (373.8 mg, 2.7 mmol), dry toluene (9 mL), DBAD (124.4 mg, 0.54 mmol), and 2-propyl-1-phenylbuta-2,3-dien-1-ol (1.0141 g, 5.4 mmol)/dry toluene (9 mL) afforded **2k** (0.7512 g, 74%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 5.05 (s, 2H), 2.39 (t, J = 7.2 Hz, 2H), 1.62–1.46 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 217.1, 194.9, 138.3, 131.9, 129.0, 127.8, 106.7, 79.3, 29.9, 21.1, 13.7 ppm; MS (*m*/*z*) 186 (M^+, 6.46), 105 (100); IR (neat) 2961, 2932, 2872, 1933, 1651, 1598, 1578, 1447, 1315, 1271 cm^{-1}; HRMS-EI (*m*/*z*) calcd for $C_{13}H_{14}O^+$ [M^+]: 186.1045; found: 186.1045.

General experimental procedure for the oxidation of allenic alcohols with pure oxygen

3-Hexylocta-1,2-dien-4-one (**2l**)

Typical procedure: 1,10-phenanthroline (6.9 mg, 0.0375 mmol), 2,2'-bipyridine (5.8 mg, 0.0375 mmol), CuCl (5.9 mg, 0.06 mmol), and K_2CO_3 (20.9 mg, 0.15 mmol) were added sequentially to an oven dried Schlenk tube, which was purged with air and refilled with oxygen (twice). Then 1.5 mL of dry toluene was added, the resulting mixture was stirred at rt for 0.5 h which was followed by the sequential addition of DBAD (14.0 mg, 0.06 mmol), 2-hexyl-1-butylbuta-2,3-dien-1-ol (63.8 mg, 0.3 mmol) and 1.5 mL of dry toluene. After stirring at 60 °C for 24 h, the reaction mixture was filtered through silica gel (100–140 mesh) and washed with diethyl ether. Evaporation of the solvent and flash chromatography on silica gel (eluent: petroleum ether/ether = 50:1) afforded **2l** (37.1 mg, 58%) (conv. = 81%, yield = 72% (based on the alcohol consumed)): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (d, J = 2.7 Hz, 2H), 2.62 (t, J = 7.4 Hz, 2H), 2.18–2.09 (m, 2H), 1.60–1.47 (m, 2H), 1.42–1.18 (m, 10H), 0.92–0.78 (m, 6H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 216.2, 201.3, 108.5, 79.3, 38.9, 31.6, 28.8, 27.8, 27.2, 26.2, 22.5, 22.3, 14.0, 13.8 ppm; MS (*m*/*z*) 208 (M^+, 1.00), 85 (100); IR (neat) 2958, 2929, 2862, 1934, 1679, 1461, 1174 cm^{-1}; HRMS-EI (*m*/*z*) calcd for $C_{14}H_{24}O^+$ [M^+]: 208.1827; found: 208.1828.

4-Pentyl-1-phenylhexa-4,5-dien-3-one (**2m**)

The reaction of 1,10-phenanthroline (6.9 mg, 0.0375 mmol), 2,2'-bipyridine (5.9 mg, 0.0375 mmol), CuCl (6.1 mg, 0.06 mmol), K_2CO_3 (21.4 mg, 0.15 mmol), dry toluene (1.5 mL), DBAD (13.9 mg, 0.06 mmol), and 2-pentyl-1-(phenylethyl)buta-2,3-dien-1-ol (72.7 mg, 0.3 mmol)/dry toluene (1.5 mL) afforded **2m** (43.8 mg, 60%) (conv. = 81%, yield = 74% (based on the alcohol consumed)): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.22 (m, 2H), 7.22–7.13 (m, 3H), 5.13 (s, 2 H), 3.02–2.85 (m, 4H), 2.22–2.10 (m, 2H), 1.45–1.20 (m, 6H), 0.88 (t, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 216.3, 200.1, 141.3, 128.3, 126.0, 108.6, 79.7, 40.9, 31.4, 30.9, 27.4, 26.1, 22.4, 14.0 ppm; MS (*m*/*z*) 242 (M^+, 0.87), 105 (100); IR (neat) 2956, 2928, 2861, 1933, 1678, 1496, 1456, 1171, 1100 cm^{-1}; Anal. calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. found: C, 84.16; H, 9.50.

Supporting Information

Supporting Information File 1

^{1}H and ^{13}C NMR spectra of products prepared.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-51-S1.pdf]

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Rh(I)-catalyzed intramolecular [2 + 2 + 1] cycloaddition of allenenes: Construction of bicyclo[4.3.0]nonenones with an angular methyl group and tricyclo[6.4.0.0^{1,5}]dodecenone

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Full Research Paper

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Abstract

The [RhCl(CO)dppp]$_2$-catalyzed intramolecular carbonylative [2 + 2 + 1] cycloaddition of allenenes was developed to prepare bicyclo[4.3.0]nonenones possessing a methyl group at the ring junction, which is difficult to achieve by the Pauson–Khand reaction of the corresponding enynes. This method also provided a new procedure for the construction of the tricyclo[6.4.0.0^{1,5}]dodecenone framework in a satisfactory yield.

Introduction

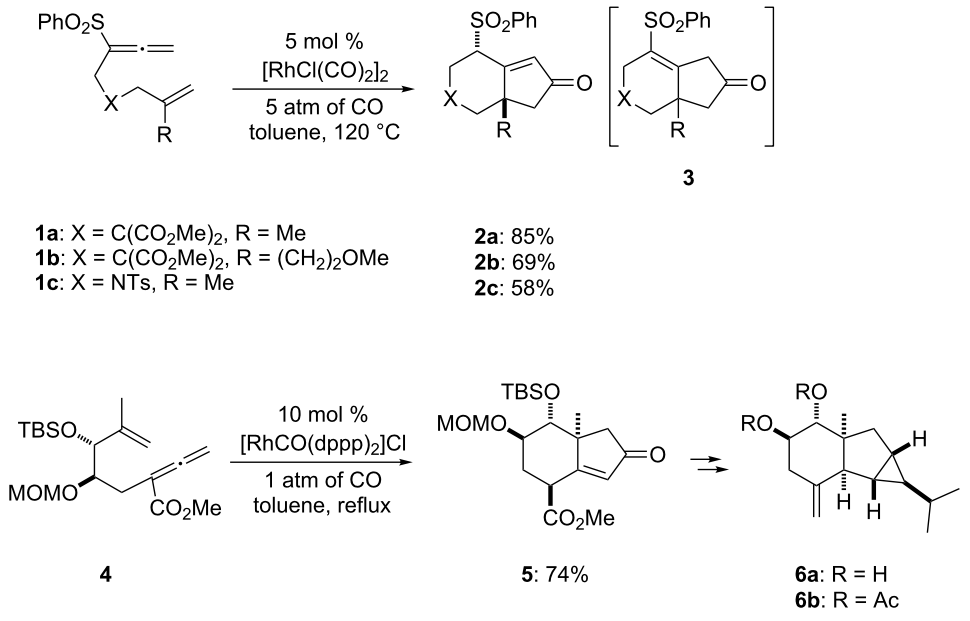
The $Co_2(CO)_8$-mediated Pauson–Khand reaction (PKR) [1,2] is well recognized as a formal [2 + 2 + 1] cycloaddition of three components, the alkyne π-bond, the alkene π-bond and carbon monoxide (CO), for producing cyclopentenone derivatives. The intramolecular PKR [3-9] provides a powerful method for the construction of bicyclo[3.3.0]oct-1-en-3-one and bicyclo[4.3.0]non-1(9)-en-8-one frameworks. In contrast to the fact that the 2-alkyl (or phenyl)-1-hepten-6-ynes also efficiently afford 5-alkyl (or phenyl)bicyclo[3.3.0]oct-1-en-3-ones [10-19], the one-methylene homologated substrates furnish the corresponding bicyclo[4.3.0] skeletons with an angular substituent in rather lower yields [20-22].

Recent efforts in our laboratory have developed the [RhCl(CO)$_2$]$_2$-catalyzed [2 + 2 + 1] cycloaddition of 3-phenylsulfonyl-1,2,7-octatrienes and lead to bicyclo[4.3.0]non-1(9)-

en-8-one derivatives, in which the distal double bond of the allenyl moiety serves exclusively as the π-component [23]. This method could not only be applicable for the construction of the larger bicyclo[5.3.0]dec-1(10)-en-9-one skeleton, but also provides a new entry for the preparation of three types of *trans*-2-phenylsulfonylbicyclo[4.3.0]non-1(9)-en-8-one derivatives **2a**–**c** in moderate to high yields with an alkyl group (Me, $(CH_2)_2OMe$) at the ring junction from 7-alkyl-3-phenylsulfonyl-1,2,7-octatrienes **1a**–**c**. The formation of **2** can be rationalized by the initial formation of the 6-alkyl-2-phenylsulfonylbicyclo[4.3.0]non-1-en-8-one derivative **3**, followed by subsequent isomerization to the α,β-unsaturated ketones **2**. By taking advangage of this newly developed reaction, we have completed the first total syntheses of two tricyclic sesquiterpenes **6a**,**b**, isolated from *Jatropha neopauciflora*, from the methoxycarbonylallenene **4** via the bicyclo[4.3.0]nonenone derivative **5** [24]. The key step in these total syntheses was carried out as follows: The allenene **4**, derived from D-tartrate, was heated under reflux in the presence of 10 mol % of $[RhCO(dppp)_2]Cl$ [25] under a CO atmosphere to produce exclusively the bicyclo[4.3.0]derivative **5** with the desired stereochemistry in 74% yield (Scheme 1). Our continuous interest in this field prompted us to optimize the reaction conditions in order to make our method more useful. This paper describes the Rh(I)-catalyzed [2 + 2 + 1] cycloaddition of allenenes for the facile preparation of the bicyclo[4.3.0]nonenone derivatives possessing an angular methyl group, and for the construction of the tricyclo[6.4.0.$0^{1,5}$]dodecenone skeleton.

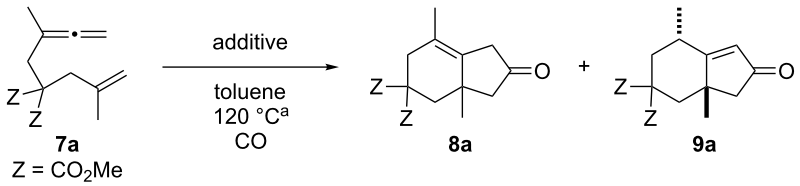
Results and Discussion

In previous studies, we investigated the carbonylative [2 + 2 + 1] cycloaddition reaction of two allenenes **1** and **4** with either a SO_2Ph or CO_2Me substituent on the proximal double bond of the allene group in the presence of several Rh(I) catalysts ($[RhCl(CO)_2]_2$, $[RhCO(dppp)_2]Cl$ or $[RhCl(CO)dppp]_2$). We have now examined the similar ring-closing reaction using an alternative allenene **7a** with a methyl group on the allenyl group for further evaluation of these reactions. According to the conditions described for the formation of **2**, a solution of **7a** in toluene was heated at 120 °C for 4 h in the presence of 5 mol % of $[RhCl(CO)_2]_2$ under 5 atm of CO to afford the desired 4,4-bis(methoxycarbonyl)-2,6-dimethylbicyclo[4.3.0]non-1-en-8-one (**8a**) in 38% yield (Table 1, entry 1). A similar reaction under 1 atm of CO gave **8a** in a better yield (Table 1, entry 2). These results are in sharp contrast to the previous findings, where increasing the CO pressure from 1 to 5 atm led to an improvement in the chemical yield (see reference [23], Table 1). The alternative condition ($[RhCO(dppp)_2]Cl$ (10 mol %) under a CO atmosphere) provided the ring-closing product **8a** in 75% yield (Table 1, entry 3). It has already been shown that the Rh(I)-catalyzed Pauson–Khand type reaction (PKTR) of enynes under a low CO pressure [26,27] leads to better results. Thus, the ring-closing reaction of **7a** was performed under an atmosphere consisting of 0.2 atm of CO and 0.8 atm of Ar, or of 0.05 atm of CO and 0.95 atm of Ar to produce **8a** in 71% and 74% yields, respectively (Table 1, entries 4 and 5). Next, the reaction with $[RhCl(CO)dppp]_2$ in the presence or absence of a silver salt [27-34] was examined



Scheme 1: Rh(I)-catalyzed Pauson–Khand type reaction of **1** and **4**.

Table 1: Rh(I)-catalyzed PKTR of **7a**.



entry	Rh(I) cat. (mol %)	additive (mol %)	CO (atm)	time (h)	yield of **8a** (%)
1	$[RhCl(CO)_2]_2$ (5)	—	5	4	38
2	$[RhCl(CO)_2]_2$ (5)	—	1	16	54
3	$[RhCO(dppp)_2]Cl$ (10)	—	1	17	75[b]
4	$[RhCO(dppp)_2]Cl$ (10)	—	0.2[c]	17	71
5	$[RhCO(dppp)_2]Cl$ (10)	—	0.05[d]	6	74
6	$[RhCl(CO)dppp]_2$ (5)	—	1	19	68
7	$[RhCl(CO)dppp]_2$ (5)	—	0.2[c]	11	79
8	$[RhCl(CO)dppp]_2$ (5)	—	0.1[e]	7	88
9	$[RhCl(CO)dppp]_2$ (5)	—	0.05[d]	8	51[f]
10	$[RhCl(CO)dppp]_2$ (5)	$AgBF_4$ (12)	0.1[e]	1.5	78
11	$[RhCl(CO)dppp]_2$ (5)	$AgBF_4$ (12)	0.05[d]	1.5	93
12	$[RhCl(CO)dppp]_2$ (5)	$AgSbF_6$ (12)	0.05[d]	1.5	79
13	$[RhCl(CO)dppp]_2$ (5)	AgCl (12)	0.05[d]	6	84

[a]Bath temperature. [b]**8a** was obtained in 18% yield under 5 atm of CO. [c]The reaction was conducted under 0.2 atm of CO and 0.8 atm of Ar. [d]The reaction was conducted under 0.05 atm of CO and 0.95 atm of Ar. [e]The reaction was conducted under 0.1 atm of CO and 0.9 atm of Ar. [f]Compound **9a** was obtained in 31%.

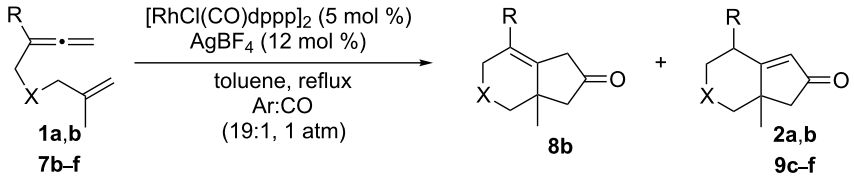
(Table 1, entries 6–13). A significant improvement (**8a**, 93%) was observed when the ring-closing reaction of **7a** was carried out in the presence of 5 mol % of $[RhCl(CO)dppp]_2$ and 12 mol % of $AgBF_4$ under an atmosphere consisting of 0.05 atm of CO and 0.95 atm of Ar at 120 °C (Table 1, entry 11). Almost all of the reactions gave 2,6-dimethylbicyclo[4.3.0]non-1-en-8-one **8a**, and the α,β-unsaturated ketone **9a** could not be detected except for entry 9. This observation obviously differs from the PKTR products **2** and **5** having an electron withdrawing group instead of a methyl group (Scheme 1).

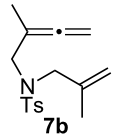
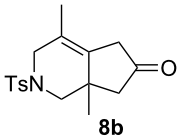
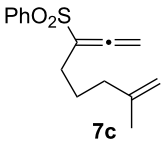
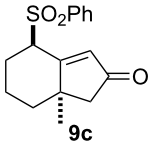
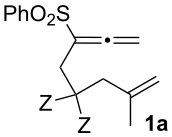
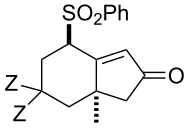
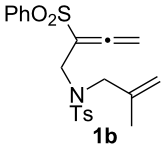
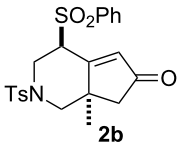
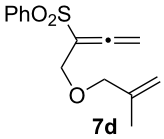
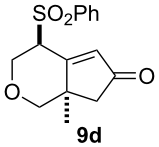
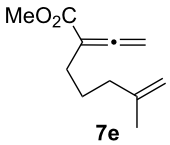
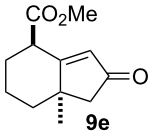
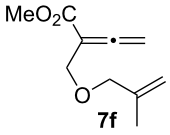
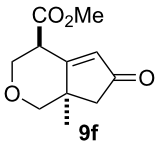
We next investigated the scope of this Rh(I)-catalyzed PKTR using several substrates under the condition of entry 11 in Table 1. The nitrogen congener **7b** produced the corresponding azabicyclic compound **8b** in 56% yield, although a prolonged reaction time was required (Table 2, entry 1). The sulfonylallenene **7c**, which has a simple methylene tether, provided the cyclopentenone derivative **9c** in 55% yield as expected from the results given in Scheme 1 (Table 2, entry 2). As noted above, compounds **2a**,**b** could be obtained in the presence of $[RhCl(CO)_2]_2$: $[RhCl(CO)dppp]_2$ also worked as well as the previous conditions (Table 2, entries 3 and 4). The oxygen congener **7d** produced the corresponding oxabicyclic compound **9d** in 49% yield (Table 2, entry 5). The methoxycarbonyl functionality on the allenyl moiety **7e** was found not to interfere with the ring-closing reaction and afforded **9e** in 63% yield (Table 2, entry 6). On the other hand, **7f** provided the oxabicyclic derivative **9f** in a low yield (Table 2, entry 7). The geminal disubstituent effect (Thorpe–Ingold-type effect) of **1a** and **7a** might be responsible for the high yields of the ring-closed products.

The Rh(I)-catalyzed PKTR of the non-substituted allenene **7g** was investigated as a control experiment under the several conditions (e.g., conditions of entries 3, 6, 10 and 11 in Table 1) but resulted in the formation of the intractable mixtures (Scheme 2). These results in combination with the successful examples shown in Table 2 indicated that the substituent on the proximal double bond of the allene might be mandatory. Removal of the allylic sulfone group in **2a** was achieved by tributyltin hydride in the presence of AIBN to give **9g** in 91% yield [35-41]. Thus, the phenylsulfonyl group of **2a** can be regarded as a hydrogen surrogate and this procedure provides a new method for the preparation of **9g**.

The intramolecular Rh(I)-catalyzed PKTR of allenenes is applicable to the more complex substrate as shown in Table 3 [42-44]. Exposure of the cyclopentene **10** to the standard conditions in Table 2 did not lead to the desired tricyclo[6.4.0.$0^{1,5}$]dodec-7-en-6-one **11**, instead the

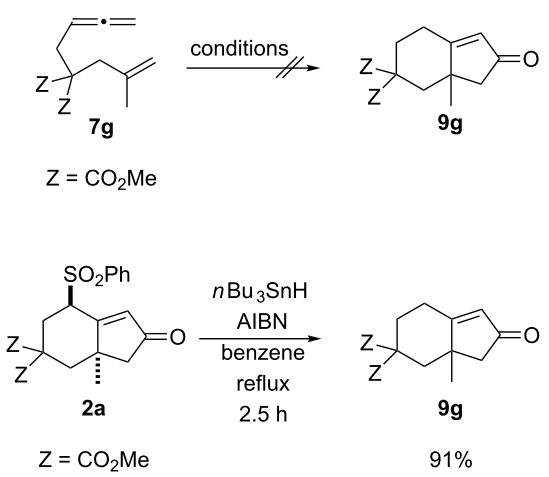
Table 2: Rh(I)-catalyzed PKTR of 7-methyl-1,2,7-trienes.



entry	allenene	product	time (h)	yield (%)
1	 **7b**	 **8b**	6.5	56
2	 **7c**	 **9c**	3	55
3	 **1a** Z = CO_2Me	 **2a**	1	88[a,b]
4	 **1b**	 **2b**	2	66
5	 **7d**	 **9d**	3	49
6	 **7e**	 **9e** (dr = 7:1)	5	63
7	 **7f**	 **9f**	4.5	22

[a]The reaction was carried out without $AgBF_4$ under a CO atmosphere. [b]**2a** was obtained in 68% yield in the presence of 12 mol % of $AgBF_4$.

spiro[4.5]deca-1,6-diene derivative **12** was formed exclusively in 87% yield (Table 3, entry 1). After screening several reaction conditions, the tricyclic derivative **11** was obtained in 73% yield along with **12** (24%) when the reaction was carried out in the absence of $AgBF_4$ under a CO atmosphere (Table 3, entry 2). The $[RhCl(CO)dppp]_2$-catalyzed reaction of **10** under a N_2 atmosphere with or without $AgBF_4$ produced the spiro product **12** in 93% and 91% yield, respectively, whereas no spiro product **12** was obtained under thermal conditions without a Rh(I)-catalyst (Table 3, entries 3–5). Therefore, the formation of **12**



Scheme 2: Formation of 4,4-bis(methoxycarbonyl)-6-methylbicyclo[4.3.0]non-1(9)-en-8-one (**9g**).

must be rationalized by the Rh(I)-catalyzed cycloisomerization. The oxidative addition of the Rh(I)-catalyst to an alkene group and the distal double bond of the allenyl moiety would form a rhodabicyclo[4.3.0]nonene intermediate, which would collapse to the spiro[4.5]deca-1,6-diene system via β-elimination and subsequent reductive elimination [31,32].

In summary, we have developed the intramolecular Rh(I)-catalyzed PKTR between 1,1-disubstituted allene and 1,1-disubstituted alkene functionalities, which leads to the facile formation of bicyclo[4.3.0]nonenone derivatives with an angular methyl group. This method was also successfully applied to the construction of the more complex tricyclo[6.4.0.0^{1,5}]dodecenone skeleton.

Supporting Information

Full experimental details, compound characterization data, ^{1}H NMR spectra and ^{13}C NMR spectra for all new compounds described.

Supporting Information File 1

Experimental, characterization data and spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-52-S1.pdf]

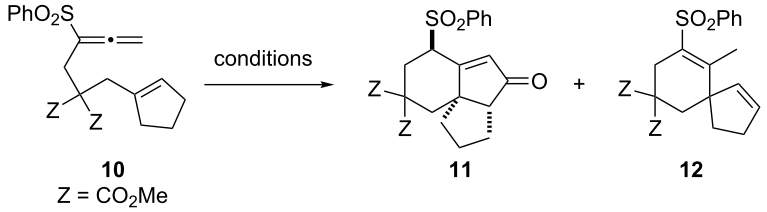
Acknowledgements

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Table 3: Rh(I)-catalyzed cyclization of 6-(cyclopent-1-enyl)-1,2-hexadiene **10**.



entry	Rh(I) cat. (5 mol %)	additive (mol %)	CO or N_2 (atm)	yield of **11** (%)	yield of **12** (%)
1	$[RhCl(CO)dppp]_2$	$AgBF_4$ (12)	CO (0.05)[a]	—	87
2	$[RhCl(CO)dppp]_2$	—	CO (1)	73	24
3	$[RhCl(CO)dppp]_2$	$AgBF_4$ (12)	N_2 (1)	—	93
4	$[RhCl(CO)dppp]_2$	—	N_2 (1)	—	91
5	—	—	N_2 (1)	—	—

[a]The reaction was conducted under 0.05 atm of CO and 0.95 atm of Ar.

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An efficient and practical entry to 2-amido-dienes and 3-amido-trienes from allenamides through stereoselective 1,3-hydrogen shifts

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Full Research Paper

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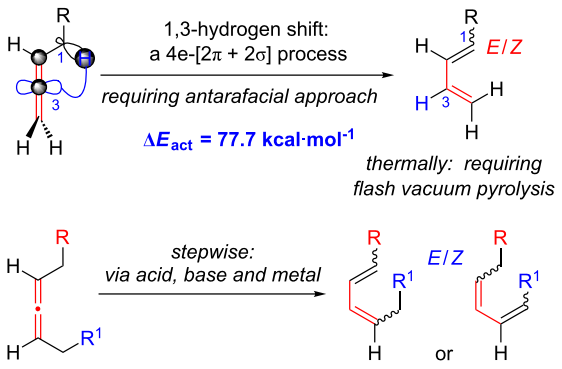
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Abstract

Preparations of de novo acyclic 2-amido-dienes and 3-amido-trienes through 1,3-hydrogen shifts from allenamides are described. These 1,3-hydrogen shifts could be achieved thermally or they could be promoted by the use of Brønsted acids. Under either condition, these processes are highly regioselective in favour of the α-position, and highly stereoselective in favour of the *E*-configuration. In addition, 6π-electron electrocyclic ring-closure could be carried out with 3-amido-trienes to afford cyclic 2-amido-dienes, and such electrocyclic ring-closure could be rendered in tandem with the 1,3-hydrogen shift.

Introduction

While allene isomerization to afford conjugated dienes is a well-known and thermodynamically favourable process, it is not trivial kinetically. A concerted allene isomerization leading to a diene involves a 1,3-hydrogen shift, which constitutes a four-electron ($2\pi + 2\sigma$) process that needs an antarafacial approach to fulfil the anti-Hückel (or Möbius) transition state based upon the Woodward–Hoffman rules [1]. Although there is no experimental precedent in an actual allylic system, it is relatively more feasible for an allenic system due to the presence of orthogonally oriented p-orbitals of the sp-hybridized central allenic carbon (Scheme 1), allowing a formal phase change required for an anti-Hückel transition state (in blue, for references on a

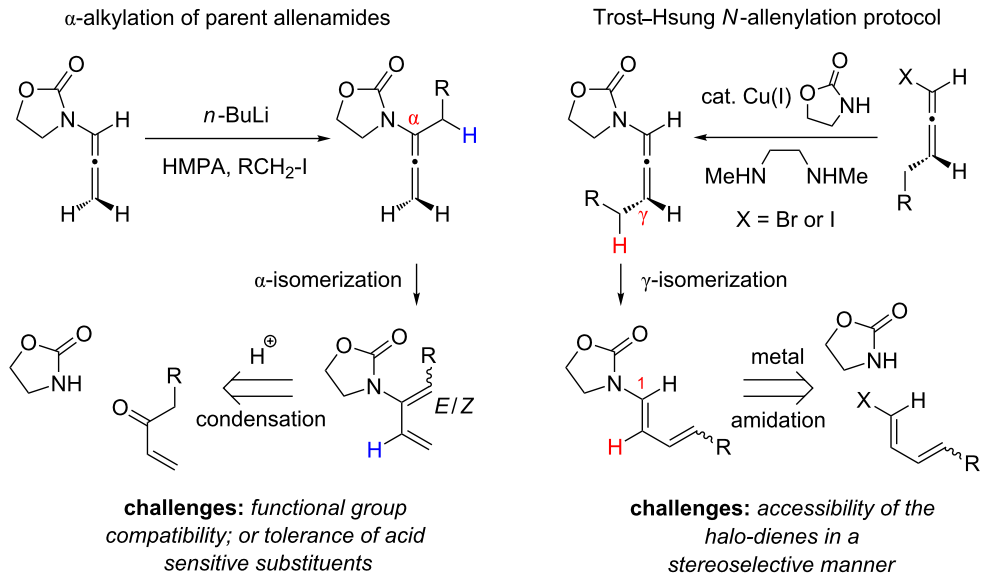


Scheme 1: 1,3-Hydrogen shifts of allenes.

possible radical pathway, see [2]), and a six-electron (2π + 2σ + 2π) process when considering the possible involvement of the second set of allenic π-electrons. Nevertheless, the calculated ΔE_{act} value remains high at 77.7 kcal·mol^{-1} [2]. Whether concerted or not, most thermal isomerizations of allenes require severe reaction conditions (for general reviews on allenes see [3], for some examples of thermal isomerization of exocyclic allenes to dienes via radical intermediates see [4-12]), whereby controlling *E*/*Z* ratios of the resulting diene remains a difficult problem. On the other hand, a stepwise isomerization of allenes via acid-, base-, or metal-mediated conditions seem to be more practical, but known examples have issues in controlling stereo- and regioselectivity [3] (for some examples see [13-20]). Therefore, solving these problems can be highly significant.

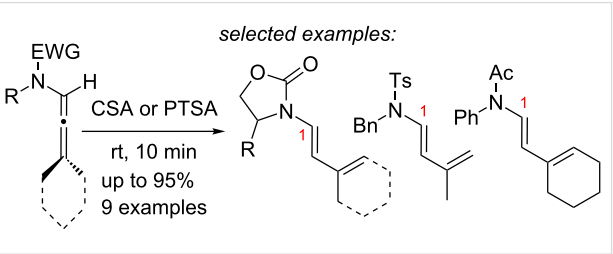
Because of the popularity of dienes as one of the most utilized organic building blocks, a number of stereoselective preparations are known. The major question here is how viable is it to access conjugated dienes from structurally more challenging allenes through a kinetically difficult and stereochemically undistinguished isomerization. It might not seem like a logical approach; however, our justification is that since there are few well established routes for preparing amido-dienes, our allenamide isomerization strategy (for reviews on allenamide chemistry see [21-23], for reports in 2009, 2010 and 2011 see [24-43], for earlier studies on allenamides see [44-46]) can open the door to construct synthetically useful amido-dienes (for a review on the synthesis of enamides see [47], for reviews on the chemistry of dienamides see [48-50], for reviews on the chemistry of 2-amino or 2-amido-dienes see [51,52]). Problems with the two primary approaches to access amido-dienes [47] are that acid-mediated condensations suffer from functional group tolerances, and metal-mediated coupling methods (for reviews on Cu-mediated C–N and C–O bond formations see [53-55], for some examples see [56-58]) suffer from limited access as well as the instability of halo-dienes (Scheme 2).

In contrast, multi-substituted allenamides can be concisely prepared through α-alkylations of a parent allenamide [47,59] (for the synthesis of parent allenamides see [60]) or amidative cross-couplings of allenyl halides [61,62]. Therefore, our allenamide isomerization strategy has a much greater synthetic potential in constructing amido-dienes. While the chemistry of 1-amido-dienes has been explored in some detail (see Scheme 3 for success in preparing 1-amido-dienes via allenamide isomer-



Scheme 2: Synthesizing amido-dienes from allenamides.

izations) [63,64] (for examples see [65-72]), herein, we report details of an efficient entry to synthetically rare 2-amido-dienes [73-77] via a regio- and stereoselective 1,3-hydrogen shift of allenamides.



Scheme 3: Synthesis of 1-amido-dienes from allenamides.

Results and Discussion

As part of our initial screening efforts, both the thermal and acidic conditions were investigated as shown in Table 1. Allenamide **1** smoothly underwent isomerization via a 1,3-hydrogen shift when heated at 115 °C in CH_3CN (sealed tube) to give the desired 2-amido-diene product **2** in 78% isolated yield with a 16:1 *E*/*Z* selectivity (Table 1, entry 1). There appears to be some solvent effect on the *E*/*Z* selectivity with more polar solvents providing the best ratio (Table 1, entries 2–4). In addition to thermal conditions, we screened several Brønsted acids at room temperature in order to investigate a milder condition. While PTSA resulted in poor *E*/*Z* ratio (Table 1, entry 5), a range of Brønsted acids were quite effective in affording the desired 2-amido-diene **2** (Supporting Information File 1 and Supporting Information File 2) with excellent *E*/*Z* selectivity [Table 1, entries 6–9].

After having established the 1,3-hydrogen shift under thermal and protic conditions, a diverse array of 2-amido-dienes was prepared as summarized in Table 2. Some notable features are: (1) a variety of novel chiral 2-amido-dienes **8**–**10** were obtained from chiral allenamides **5**–**7** in synthetically useful yields and with high *E*/*Z* ratios (≥95:5) under both thermal or acidic conditions (Table 2, entries 2–12); (2) unsubstituted 2-amido-dienes **8d** and **9c** could also be prepared in good yields (see R = H in Table 2, entries 7 and 10); (3) even allenamide containing an acyclic carbamate such as **11** underwent an efficient 1,3-hydrogen shift; and (4) the X-ray structure (Supporting Information File 3) of a single crystal of 2-amido-diene **10b** was successfully obtained to assign unambiguously the *E*-configuration (Figure 1).

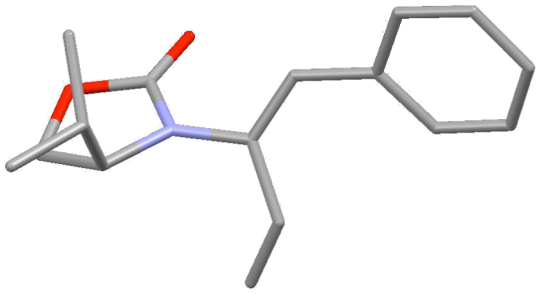
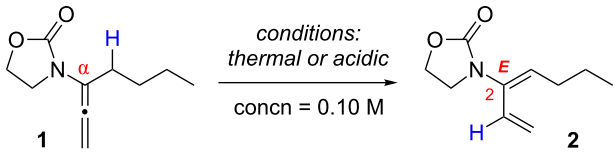


Figure 1: X-ray Structure of **10b**.

Encouraged by this highly stereoselective isomerization, we turned our attention to the possibility of constructing synthetically much more challenging 3-amido-trienes from allenamides through 1,3-hydrogen shifts. As shown in Table 3, to our satis-

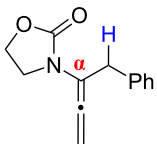
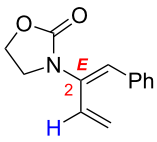
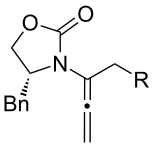
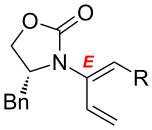
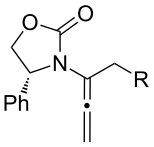
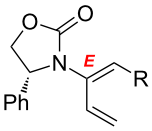
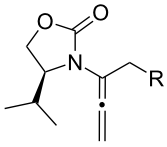
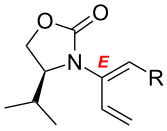
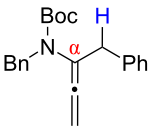
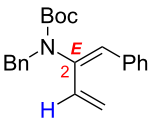
Table 1: 1,3-Hydrogen shift of allenamides.



entry	solvent	acid [10 mol %]	temp [°C]	time [h]	yield [%][a,b]	*E*:*Z*[c]
1	CH_3CN	—	115	16	91 (78)	16:1
2	THF	—	115	16	51	9:1
3	$ClCH_2CH_2Cl$	—	115	16	79	7:1
4	toluene	—	150	16	55	4:1
5	CH_2Cl_2	*p*-toluenesulfonic acid (PTSA)	25	1	66	2:1
6	CH_2Cl_2	*p*-NO_2-$ArCO_2H$	25	16	81	15:1
7	CH_2Cl_2	$PhCO_2H$	25	16	85 (55)	18:1
8	CH_2Cl_2	pyridinium *p*-toluenesulfonate (PPTS)	25	16	77	15:1
9	CH_2Cl_2	camphorsulfonic acid (CSA)	25	10 min	95 (74)	18:1

[a]NMR yields. [b]Isolated yields are shown in brackets. [c]Ratios were determined by ^1H NMR.

Table 2: Synthesis of 2-amido-dienes.

entry	allenamides		conditions (time)[a]	amido-dienes		yield [%][b,c]
1		**3**	115 °C (16 h)		**4**	71
2		**5a:** R = *n*-Pr	115 °C (6 h)		**8a**	77
3		**5a:** R = *n*-Pr	CSA (4 h)[d]		**8a**	87
4		**5b:** R = Ph	115 °C (16 h)		**8b**	74
5		**5b:** R = Ph	CSA (2 h)		**8b**	83
6		**5a:** R = ^{2}Nap[e]	115 °C (16 h)[f]		**8c**	73
7		**5a:** R = H	115 °C (16 h)		**8d**	69
8		**6a:** R = *n*-Pr	CSA (10 min)		**9a**	82
9		**6b:** R = Ph	CSA (10 min)		**9b**	76
10		**6c:** R = H	115 °C (16 h)		**9c**	69
11		**7a:** R = *n*-Pr	115 °C (16 h)		**10a**	62
12		**7b:** R = Ph	115 °C (16 h)		**10b**	82
13		**11**	135 °C (16 h)		**12**	45
14		**11**	CSA[g] (2 h)		**12**	61

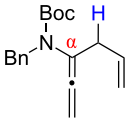
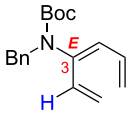
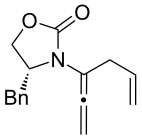
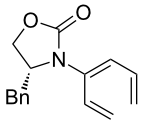
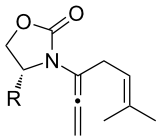
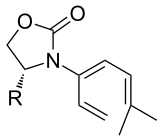
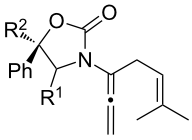
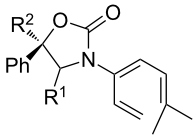
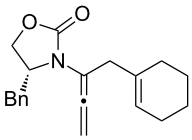
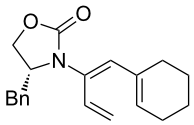
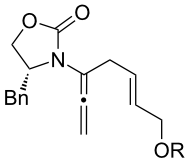
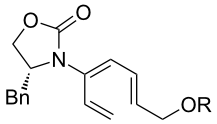
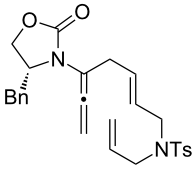
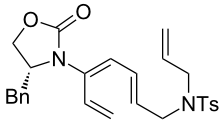
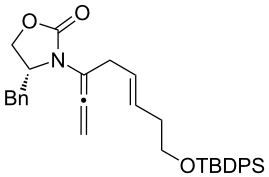
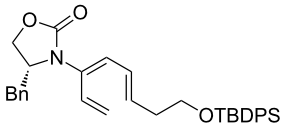
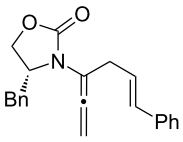
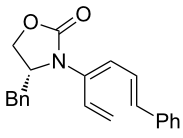
[a]Unless otherwise indicated, CH_3CN was the solvent for thermal conditions and CH_2Cl_2 was the solvent when using 10 mol % of CSA at rt. For all reactions, concn = 0.10 M. [b]All are isolated yields. [c]All 1,3-H shifts were highly *E*-selective [≥95:5] except for entry 1 in which the *E*:*Z* ratio is 6:1 for **4**. Ratios were determined by ^{1}H NMR. [d]Temp started at –78 °C. [e]The group ^{2}Nap stands for 2-naphthyl. [f]$ClCH_2CH_2Cl$ was used. [g]4Å MS was used.

faction, a wide variety of 3-amido-trienes could be readily accessed from corresponding α-allylated allenamides. When using a catalytic amount of CSA, both achiral and chiral 3-amido-trienes were obtained in high yields with exclusive *E*-selectivity, including structurally intriguing examples such as **24**–**28** (Table 3, entries 9–15). Moreover, a protected alcohol or amine in the allenamide did not impede the isomerization process (Table 3, entries 10–14), leading to more functionalized trienes.

To continue elevating the level of complexity, we examined allenamides with both α- and γ-substitutions and hoped to observe regioselectivity during the 1,3-hydrogen shift. Consequently, as shown in Table 4, isomerizations of tetra-substituted allenamides were examined. When heating α- and γ-substituted allenamides **29a** and **30** in CH_3CN at 115 °C in a sealed tube, 1,3-hydrogen shift took place exclusively from the α-position affording highly substituted (*E*)-2-amido-dienes **33a** and **34** in 71% and 79% yields, respectively (Table 4, entries 1 and 3). The *E*-geometry in **33a** and **34** was assigned by NOE (Supporting Information File 2).

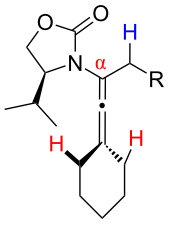
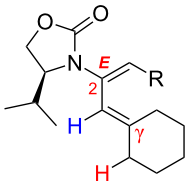
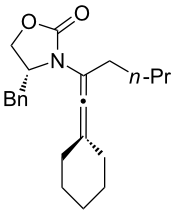
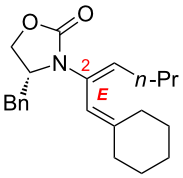
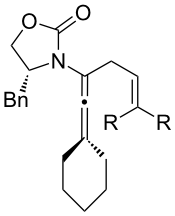
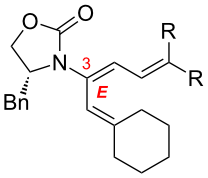
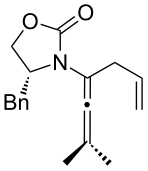
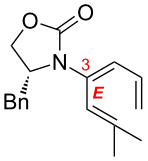
Intriguingly, allenamide **29b** underwent a 1,3-hydrogen shift at room temperature when simply in contact with silica gel during the purification stage; but again, only the 1,3-hydrogen shift was favoured proceeding from the α-position to give (*E*)-2-amido-diene **33b** (Table 4, entry 2). In addition, highly substituted 3-amido-trienes **35a**, **35b**, and **36** were regioselectively synthesized in overall high yields using the CSA-catalyzed conditions (Table 4, entries 4–6). Not only are the products from this regioselective isomerization structurally unique, but also mechanistically intriguing.

Table 3: Synthesis of 3-amido-trienes.[a]

entry	α-allylated allenamides		3-amido-trienes		yield [%][b]
1		**13**		**14**	86
2		**15a**		**22**	79
3		**16a:** R = Bn		**23a**	89
4		**16b:** R = Ph		**23b**	89
5		**16c:** R = iPr		**23c**	91
6		**16d:** R^1 = (*R*)-Me, R^2 = H		**23d**	74
7		**16e:** R^1 = (*S*)-Ph, R^2 = H		**23e**	89
8		**16f:** R^1 = (*R*)-Ph, R^2 = Ph		**23f**	86
9		**17**		**24**	95
10		**18a:** R = TBDPS		**25a**	84
11		**18b:** R = allyl		**25b**	75
12		**18c:** R = cinnamyl		**25c**	54
13		**19**		**26**	62
14		**20**		**27**	72
15		**21**		**28**	72

[a]All reactions were run in CH_2Cl_2 [concn = 0.10 M] with 10 mol % of CSA for 10 min at rt. [b]All were isolated yields.

Table 4: A regioselective 1,3-hydrogen shift.[a]

entry	allenamides		conditions (time)	amido-alkenes		yield [%][b,c]
1		**29a:** R = Ph	115 °C (16 h)		**33a**	71
2		**29b:** R = H	—[d]		**33b**	90
3		**30**	115 °C (16 h)		**34**	79
4		**31a:** R = H	CSA (10 min)		**35a**	68
5		**31b:** R = Me	CSA (10 min)		**35b**	80
6		**32**	CSA (10 min)		**36**	84

[a]Unless otherwise noted, CH_3CN was the solvent for thermal conditions and CH_2Cl_2 was the solvent when using 10 mol % of CSA at rt. For all reactions, concn = 0.10 M. [b]All were isolated yields. [c]All amido-di- and trienes were exclusively *E*-selective [≥95:5]. [d]See text for this isomerization.

One of the probable explanations for the significantly lowered thermal activation barrier of 1,3-hydrogen-shifts of allenamides is that the nitrogen atom can serve to stabilize the biradical intermediate [2,4-12] (for another leading reference on related radical intermediates see [78]) which are presumed to be electron deficient. Based on the model in Figure 2 (left side), stabilization of the biradical intermediate is direct when isomerizations proceed from the α-position, whereas the isomerization from the γ-position is "vinylogous", or remotely stabilized through the olefin. Therefore, thermal isomerizations at the α-position should be faster than at the γ-position.

While under thermal conditions, a biradical intermediate is at play [2,4,24], under acidic conditions, the isomerization clearly proceeds through an *N*-acyl iminium intermediate via protonation of the allenamide (Figure 2, center). Consequently, a similar argument could be used to rationalize the regioselective 1,3-hydrogen shift when acid was used. It is noteworthy that this charged transition state could also be adopted for the thermal isomerization. While still being a neutral transition state, the nitrogen atom could facilitate a polarized transition state through increasing negative charge density at the β-carbon. This action would lead to an *N*-acyl iminium ion-like character with the migrating hydrogen being proton-like with the α-position being favoured. This polarized transition state should also have a lower thermal activation barrier for the 1,3-hydrogen shift than the neutral one.

Lastly, a non-radical proton-transfer like mechanism could also be at play under conditions using protic solvents or owing to the presence of trace of amount of water (Figure 2, right). These last two models also reveal some insight into the *E*-selectivity given the pro-*E* configured transition state (TS) (see the R^1 group). Along the same line, if the reaction proceeds through a

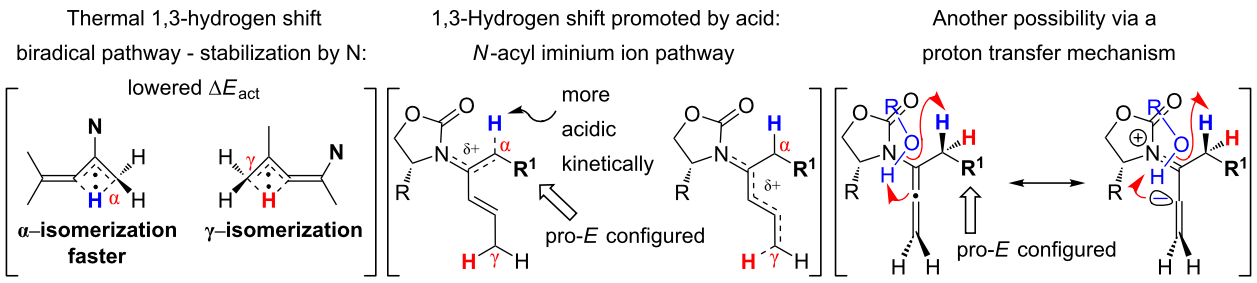
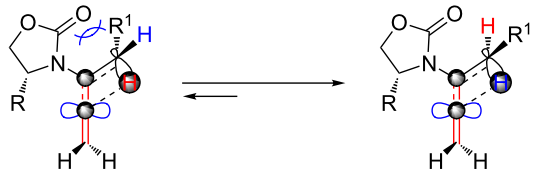


Figure 2: Proposed mechanistic models.

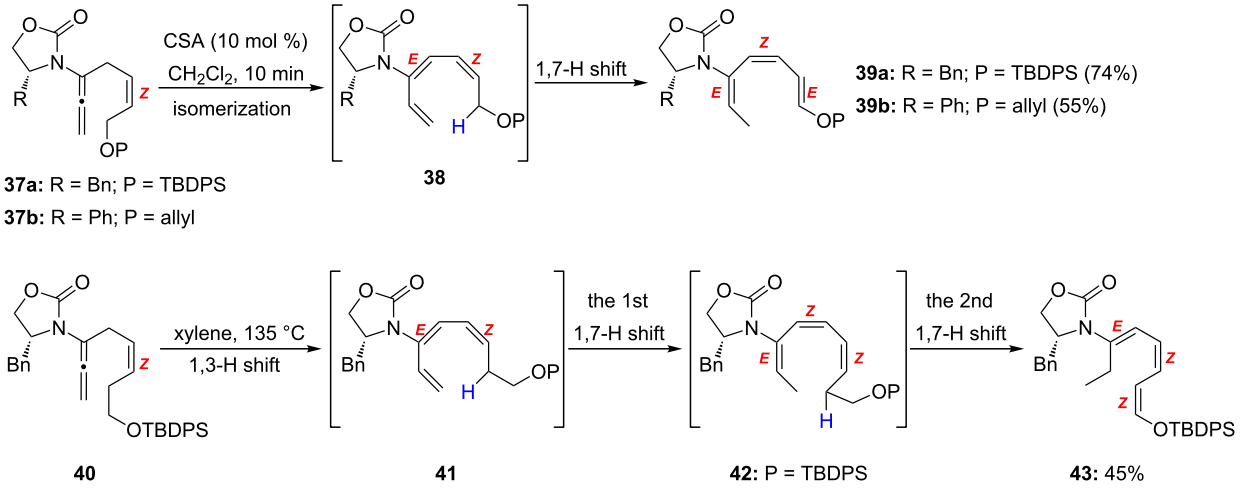
radical pathway, the observed *E*-selectivity in the thermal 1,3-hydrogen shift should be favoured because the pro-*Z* transition state experiences a greater allylic strain compared to the pro-*E* transition state (Scheme 4). A thermodynamically driven equilibration from (*Z*)- to (*E*)-enamide post-isomerization is a real possibility that cannot be ruled out, and the observed solvent effect on the (*E*/*Z*)-selectivity would particularly support this possible notion.



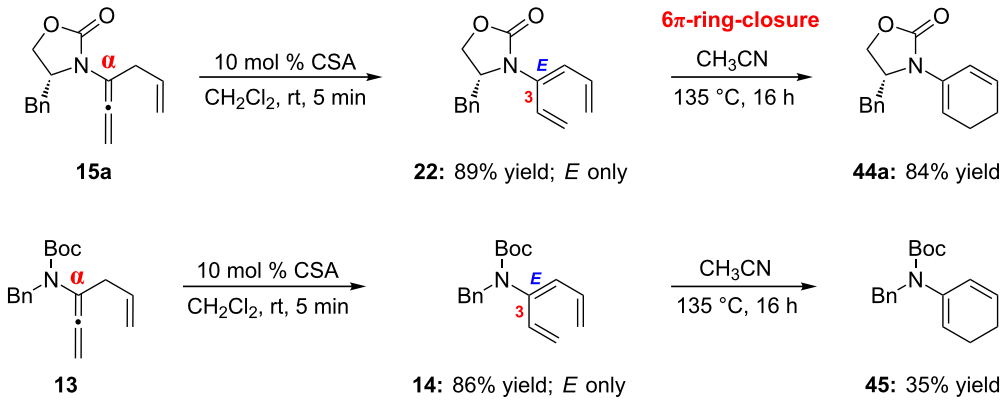
Scheme 4: A favored pro-*E* TS.

An interesting discovery was made during this work. As shown in Scheme 5, when subjected to CSA catalyzed isomerization for protected allyl alcohol-substituted allenamides, the reactions with **37a** and **37b** did not stop at the intermediate **38**, but an unexpected 1,7-H-shift (for some examples of an antarafacial 1,7-H shift see [79-82]) took place at room temperature to afford 5-amido-trienes **39a** and **39b** stereoselectively in good yields. Furthermore, when heating the protected homo-allyl alcohol-substituted allenamide **40**, after the 1,3-hydrogen shift an unprecedented double 1,7-H-shift through intermediate **41** and **42** took place to afford the 6-amido-triene **43** in 45% yield. It is noteworthy that amido-triene **41** could be isolated in 65% yield when using 10 mol % CSA.

The synthesis of 3-amido-trienes from α-isomerization of allenamides allowed us to explore an important pericyclic process for yet another amido-diene synthesis. As shown in Scheme 6, isomerizations of α-allylated allenamides **15a** and **13** under acidic conditions can afford 3-amido-trienes **22** and **14** in excellent yields. Given the *E*-selectivity of this isomerization,



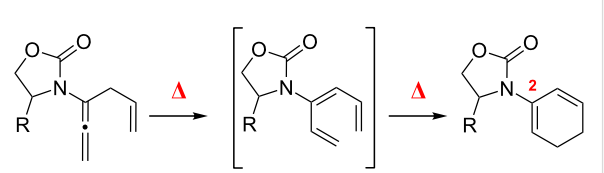
Scheme 5: Unexpected competing 1,7-hydrogen shifts.



Scheme 6: Applications in pericyclic ring-closure.

these 3-amido-trienes are perfectly suited for thermal 6π-electron electrocyclic ring-closure (for reviews on pericyclic ring-closures see [83,84], for reviews on ring-closure in natural product synthesis see [85,86], for recent examples of 6π-electron electrocyclic ring-closure see [87-93], for examples on accelerated ring-closures of 1,3,5-hexatrienes see [94-99]) to access cyclic 2-amido-dienes that are quite rare (for examples see [100-102]). Chiral amido-triene **22** underwent electrocyclization efficiently to give chiral cyclic 2-amido-diene **44a** in 84% yield. Although obtained in only 35% yield, the achiral cyclic 2-amido-diene **45** could also be prepared.

Finally, this overall process was rendered in tandem under thermal conditions to directly prepare cyclic 2-amido-dienes **44a**–**c** from allenamides **15a**–**c**, respectively, in good yields (Scheme 7). Notably these 6π-electron pericyclic ring-closures took place at relatively low temperature (135 °C), thereby implying an accelerated process of electrocyclization. This feature is consistently observed in related ring-closures of 1,3,5-hexatrienes with an electron-donating substituent at the C3 position of the triene [94-99] (for theoretical studies on substituent effects on electrocyclic ring-closures of 1,3,5-hexatrienes see [97,103-105]. It is also noteworthy that while acyclic 2-amido-dienes and 3-amido-trienes are synthetically challenging to make, cyclic amido-dienes are almost inaccessible synthetically [100-102].



15a: R = (*R*)-Bn R = Bn: CH_3CN, 135 °C, 16 h: **44a**: 43% yield
15b: R = H R = H: CH_3CN, 115 °C, 16 h: **44b**: 57% yield
15c: R = (*S*)-iPr R = iPr: CH_3CN, 135 °C, 16 h: **44c**: 54% yield

Scheme 7: Cyclic 2-amido-diene synthesis.

Conclusion

Herein, we have accomplished the preparation of de novo acyclic 2-amido-dienes and 3-amido-trienes through 1,3-hydrogen shifts from allenamides. These 1,3-hydrogen shifts could be achieved under thermal conditions or they could be promoted with Brønsted acids. Under either condition, these processes are highly regioselective in favour of the α-position, and highly stereoselective in favour of the *E*-configuration. Additionally, 6π-electron electrocyclic ring-closure could be carried out from 3-amido-trienes to afford cyclic 2-amido-dienes, and such electrocyclic ring-closure could be rendered in tandem with the 1,3-hydrogen shift, thereby constituting a facile construction of synthetically rare cyclic 2-amido-dienes.

Supporting Information

Supporting Information features detailed information on synthesis, purification and characterization data of all substances given in this article, proton and selected carbon NMR spectra, and X-ray data of compound **10b**.

Supporting Information File 1

Experimental section.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-53-S1.pdf]

Supporting Information File 2

Proton and Carbon NMR spectra, and NOE data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-53-S2.pdf]

Supporting Information File 3

X-Ray structural analysis and information for compound **10b**.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-53-S3.res]

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Synthesis of 5-(2-methoxy-1-naphthyl)- and 5-[2-(methoxymethyl)-1-naphthyl]-11*H*-benzo[*b*]fluorene as 2,2'-disubstituted 1,1'-binaphthyls via benzannulated enyne–allenes

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Full Research Paper

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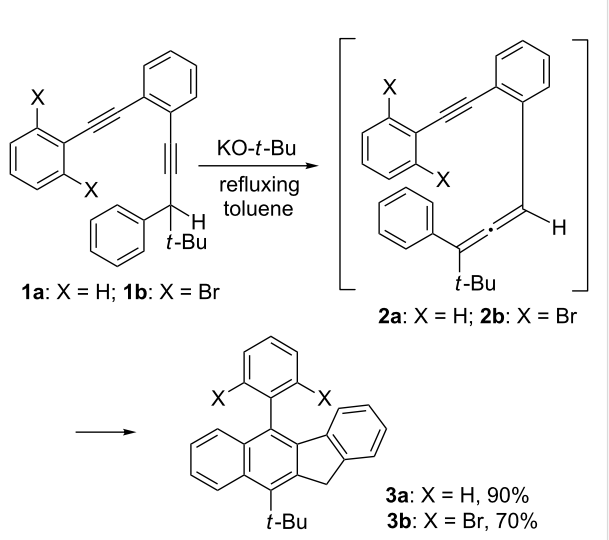
Abstract

5-(2-Methoxy-1-naphthyl)- and 5-[2-(methoxymethyl)-1-naphthyl]-11*H*-benzo[*b*]fluorene were synthesized by treatment of the corresponding benzannulated enediynes with potassium *tert*-butoxide in refluxing toluene to give benzannulated enyne–allenes for the subsequent Schmittel cascade cyclization reactions. The structures of these two 5-(1-naphthyl)-11*H*-benzo[*b*]fluorenes could be regarded as 2,2'-disubstituted 1,1'-binaphthyls with the newly constructed benzofluorenyl group serving as a naphthyl moiety.

Introduction

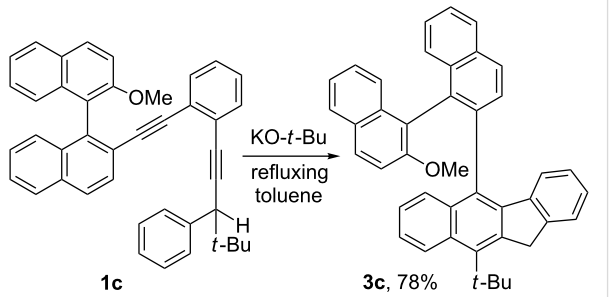
Benzannulated enyne–allenes bearing an aryl substituent at the alkynyl terminus are excellent precursors of 5-aryl-11*H*-benzo[*b*]fluorenes [1-5]. Several synthetic pathways to the benzannulated enyne–allene systems have been reported, including generation in situ from the corresponding benzannulated enediynes. Specifically, treatment of the benzannulated enediyne **1a** with potassium *tert*-butoxide in refluxing toluene for six hours promoted a 1,3-prototropic rearrangement to produce, in situ, the benzannulated enyne–allene **2a**, which in turn underwent a sequence of Schmittel cascade cyclization reactions to form 5-phenyl-11*H*-benzo[*b*]fluorene (**3a**) in a single operation (Scheme 1) [5]. It is interesting to note that the newly formed benzo[*b*]fluorenyl moiety in **3a** could also be regarded as a 1-arylnaphthyl derivative with three additional substituents at the 2, 3, and 4 positions.

The reaction is not sensitive to the steric requirement of the substituent at the alkynyl terminus. The benzannulated enediyne



Scheme 1: Synthesis of 5-aryl-11*H*-benzo[*b*]fluorenes via benzannulated enyne–allenes.

1b with a sterically demanding 2,6-dibromophenyl substituent was also smoothly converted to **3b** [6]. With **1c** having a 1,1'-binaphthyl substituent, a 1:1 mixture of the *syn* and the *anti* atropisomers of **3c** was likewise obtained (Scheme 2) [7].



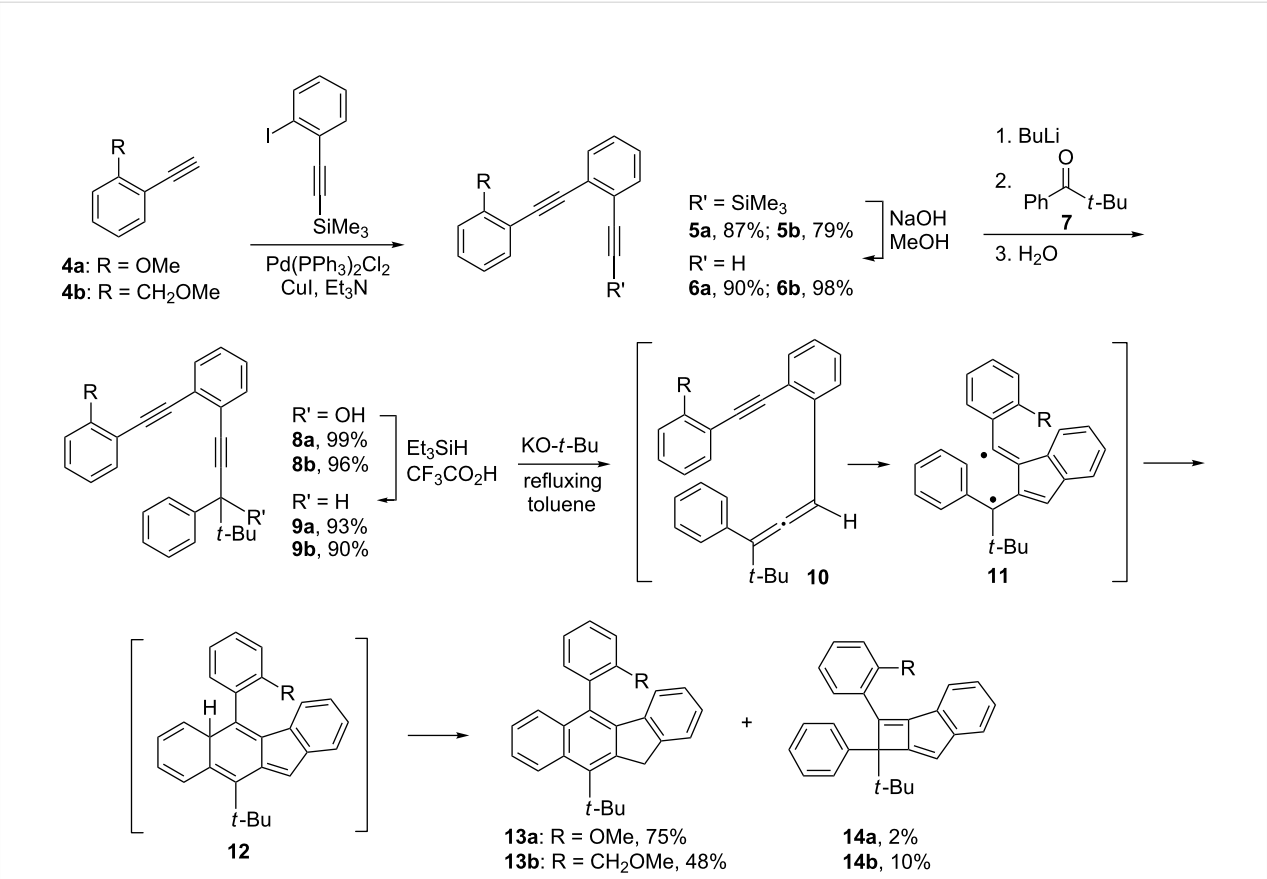
Scheme 2: Synthesis of 1,1'-binaphthyl-substituted 11*H*-benzo[*b*]fluorene **3c**.

We now have successfully extended the cascade sequence to the synthesis of other sterically congested analogues with an ortho-methoxy or an ortho-methoxymethyl group on the phenyl substituent. In addition, by placing a 2-methoxy-1-naphthyl or a 2-(methoxymethyl)-1-naphthyl group at one of the alkynyl termini of the benzannulated enediyne system, the resulting naphthyl-substituted benzo[*b*]fluorenes could be regarded as 2,2'-disubstituted 1,1'-binaphthyls with two additional substituents at the 3 and 4 positions. The versatility of 1,1'-binaphthyl-2,2'-diol (BINOL) and BINOL derivatives as reagents in asymmetric synthesis has stimulated the development of new synthetic methods for 2,2'-disubstituted 1,1'-binaphthyls [8-16]. However, the great majority of the reported methods involved coupling of two properly substituted 1-naphthyl derivatives. Construction of a new 1-naphthyl ring as an essential step toward 1,1'-binaphthyls is rare [17-19].

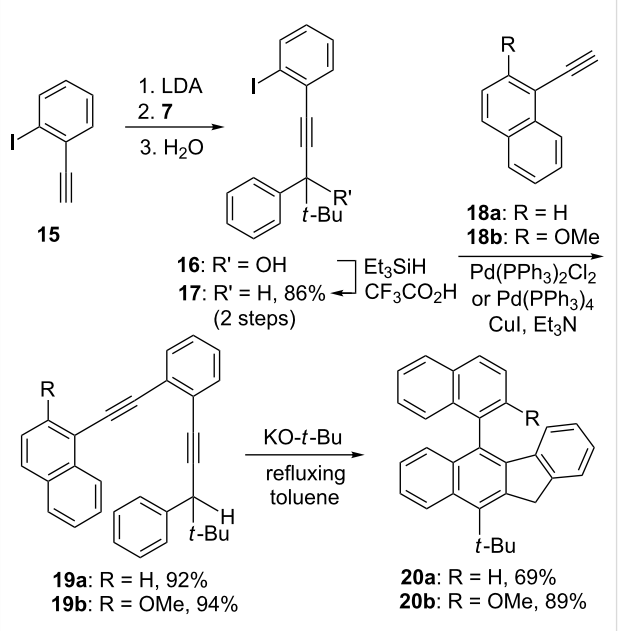
Results and Discussion

The Sonogashira reaction between 1-ethynyl-2-methoxybenzene (**4a**) and 1-iodo-2-[2-(trimethylsilyl)ethynyl]benzene produced **5a**, which was desilylated to give **6a** (Scheme 3). Condensation between **6a** and pivalophenone (**7**) then furnished the benzannulated enediynyl alcohol **8a**. Subsequent reduction with triethylsilane in the presence of trifluoroacetic acid afforded the benzannulated enediyne **9a**. Similarly, the benzannulated enediyne **9b** was synthesized from 1-ethynyl-2-(methoxymethyl)benzene (**4b**). On exposure to potassium *tert*-butoxide in refluxing toluene for five hours, **9a** was transformed to 5-(2-methoxyphenyl)-11*H*-benzo[*b*]fluorene **13a** along with a small amount (ca. 2%) of **14a** in a single operation. Presumably, the cascade sequence involved an initial 1,3-protropic rearrangement to form the corresponding benzannulated enyne–allene **10a**. A Schmittel cyclization reaction [1-4] generates biradical **11a,** which then undergoes an intramolecular radical–radical coupling to afford **12a**. This is followed by a second prototropic rearrangement to restore the aromaticity to furnish **13a** as proposed previously [5]. An intramolecular [2 + 2] cycloaddition reaction of **10a** or a direct radical–radical coupling of **11a** could account for the formation of **14a** [5]. From **9b**, 5-[2-(methoxymethyl)phenyl]-11*H*-benzo[*b*]fluorene **13b** and the [2 + 2] cycloaddition adduct **14b** were produced in a 5:1 ratio. The presence of the carbon–carbon double bonds in **14b** allows easy removal of **14b** by treatment of the resulting mixture with BH_3·THF followed by silica gel column chromatography. The presence of a benzofluorenyl moiety and a methoxy or a methoxymethyl group in **13a** and **13b** could allow these compounds to serve as hetero-bidentate ligands for complex formation with transition metals [20].

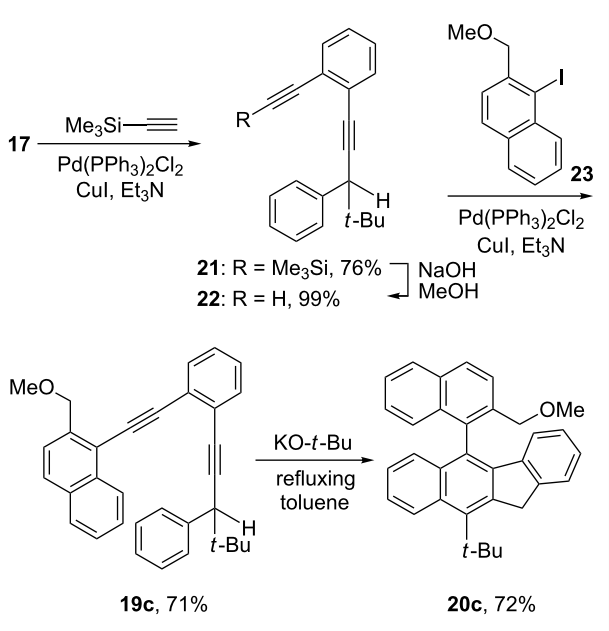
We also investigated the possibility of using the benzannulated enediynes bearing a 1-naphthyl, a 2-methoxy-1-naphthyl, or a 2-(methoxymethyl)-1-naphthyl substituent at one of the alkynyl termini for the cascade cyclization reaction. Using a slightly different synthetic sequence from that shown in Scheme 3 but reminiscent of a sequence developed for the synthesis of 4,5-diheteroarylphenanthrenes [21], the benzannulated enediynes **19a** and **19b** were obtained (Scheme 4). It was gratifying to observe that on treatment with potassium *tert*-butoxide, **19a** and **19b** were smoothly converted to **20a** and **20b**, respectively. Similarly **20c** was obtained via the synthetic sequence outlined in Scheme 5. It is worth noting that the synthetic sequences outlined in Scheme 4 and Scheme 5 represent new routes to 2,2'-disubstituted 1,1'-binaphthyls with the newly constructed benzofluorenyl serving as one of the naphthyl groups.



Scheme 3: Synthesis of 5-(2-methoxyphenyl)- and 5-[2-(methoxymethyl)phenyl]-11*H*-benzo[*b*]fluorene **13a** and **13b**.



Scheme 4: Synthesis of 5-(1-naphthyl)- and 5-(2-methoxy-1-naphthyl)-11*H*-benzo[*b*]fluorene **20a** and **20b**.

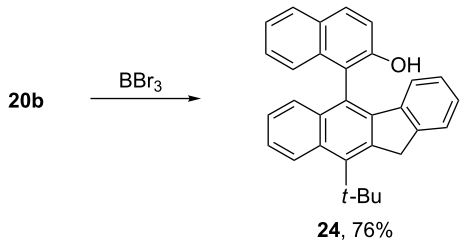


Scheme 5: Synthesis of 5-[2-(methoxymethyl)-1-naphthyl]-11*H*-benzo[*b*]fluorene **20c**.

The ^{1}H NMR spectrum of **13a** in C_6D_6 recorded on a 600 MHz NMR spectrometer exhibited an AB system with signals at δ 4.21 (J = 21.0 Hz) and 4.13 (J = 21.0 Hz), attributable to the methylene hydrogens on the five-membered ring. AB systems from the methylene hydrogens were also observed in other similar 11*H*-benzo[*b*]fluorenyl structures [7,22-24]. The AB pattern remained unchanged at 70 °C, suggesting a relatively slow rate of rotation, on the NMR time scale, around the carbon–carbon single bond connecting the 2-methoxyphenyl substituent to the C5 of the benzofluorenyl moiety. The rotational barrier was calculated to be at least 16.7 kcal/mol at 70 °C on the basis of the lack of coalescence of signals at this temperature. This lowest possible rotational barrier is significantly higher than that of 1-phenylnaphthalene, which was calculated by MM2' to be 12.4 kcal/mol [25,26]. Similarly, the ^{1}H NMR spectrum of **13b** taken in $CDCl_3$ showed a clear AB system at δ 4.07 (J = 13.8 Hz) and 4.04 (J = 13.8 Hz), attributable to the methylene hydrogens on the carbon attached to the methoxy group. The signals of the methylene hydrogens on the five-membered ring could barely be discerned as an AB system with the two inner signals overlapped at δ 4.51 and two small outer signals at δ 4.55 and 4.47.

The rotational barrier of the parent 1,1'-binaphthyl in *N*,*N*-dimethylformamide was determined to be 23.5 kcal/mol at 50 °C, corresponding to a half-life of 14.5 minutes for racemization [27,28]. Because the structure of **20a** could be regarded as a 2,3,4-trisubstituted 1,1'-binaphthyl, the rate of rotation can be expected to be even slower. Again, in C_6D_6 recorded on a 600 MHz NMR spectrometer, the signals of the methylene hydrogens on the five-membered ring could be discerned as an AB system at δ 4.27 (J = 21 Hz) and 4.25 (J = 21 Hz).

The rotational barrier of BINOL as a member of the 2,2'-disubstituted 1,1'-binaphthyls was determined to be 37.2 kcal/mol at 195 °C in naphthalene, corresponding to a half-life of 4.5 hours for racemization [28]. The high stability of the configuration even at such an elevated temperature allows BINOL to be used in a variety of synthetic applications. The configurational stability of **20b** and **20c**, which could be regarded as 2,2'-disubstituted 1,1'-binaphthyls with two additional substituents at the 3 and 4 positions, could also be expected to be high. AB patterns were observed for the methylene hydrogens on the five-membered ring of **20b** and on the carbon bearing the methoxy group of **20c**.



Scheme 6: Demethylation of **22b** to form 5-(2-hydroxy-1-naphthyl)-11*H*-benzo[*b*]fluorene **24**.

Treatment of **20b** with boron tribromide converted the methoxy group to the hydroxy group, providing a handle for resolution of **24** with (1*S*)-(−)-camphanoyl chloride (Scheme 6) [29]. It was possible to achieve partial separation of a small fraction of the two diastereomeric (1*S*)-camphanates in a 5:1 ratio by silica gel column chromatography.

Conclusion

In conclusion, the use of benzannulated enediynes as precursors to 2,2'-disubstituted 1,1'-binaphthyls represents a new synthetic approach to these sterically hindered molecules. The assembly of the enediynyl precursors from three separate aromatic fragments allows the possibility of placing a variety of functional groups at various positions of the 1,1'-binaphthyl system. Transformation of the methoxy group in **20b** to a hydroxy group provides a handle for resolution with optically active reagents.

Experimental

General information

All organometallic reactions were conducted in oven-dried (120 °C) glassware under a nitrogen atmosphere. Diethyl ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl prior to use. 1-Ethynyl-2-methoxybenzene (**4a**), pivalophenone (**7**), *n*-butyllithium (1.6 M) in hexanes, 1-bromo-2-[2-(trimethylsilyl)ethynyl]benzene, triethylsilane, trifluoroacetic acid, potassium *tert*-butoxide (1.0 M) in 2-methyl-2-propanol, lithium diisopropylamide (LDA, 2.0 M) in heptane/THF/ethylbenzene, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, copper(I) iodide, triethylamine, 1.0 M BH_3·THF solution in THF, 1-ethynylnaphthalene (**18a**), 2-methoxy-1-naphthaldehyde, 1-bromo-2-(methoxymethyl)naphthalene, (trimethylsilyl)acetylene, boron tribromide, and (1*S*)-(−)-camphanoyl chloride were purchased from chemical suppliers and were used as received. 1-Iodo-2-[2-(trimethylsilyl)ethynyl]benzene was prepared by treatment of 1-bromo-2-[2-(trimethylsilyl)ethynyl]benzene in THF with *n*-butyllithium at −78 °C followed by treatment with iodine [7]. 1-Ethynyl-2-iodo-benzene (**15**) [30] was prepared in quantitative yield by desilylation of 1-iodo-2-[2-(trimethylsilyl)ethynyl]benzene with sodium hydroxide in methanol. 1-Ethynyl-2-(methoxymethyl)benzene (**4b**) [31] and dimethyl (1-diazo-2-oxopropyl)phosphonate [32] were prepared according to the reported procedures.

1-Iodo-2-(4,4-dimethyl-3-phenyl-1-pentynyl)benzene (17). To 1.032 g (4.528 mmol) of **15** in 10 mL THF under a nitrogen atmosphere at 0 °C, was added 3.77 mL of a 2.0 M solution of LDA (7.55 mmol) in THF. After stirring for 30 min, a solution of 0.616 g of **7** (3.774 mmol) in 10 mL of THF was introduced via cannula, and the reaction mixture allowed to warm to room temperature. After an additional 3 h, 20 mL of water was introduced, and the reaction mixture extracted with diethyl ether. The combined organic extracts were washed successively with brine and water, dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography (silica gel/10% diethyl ether in hexanes) to afford 1.476 g of crude **16** as a light yellow liquid. Crude **16** without any further purification was treated with 0.810 g of triethylsilane (6.983 mmol) and 2.1 g of trifluoroacetic acid (18.4 mmol) to afford 1.382 g (3.699 mmol, 86% for 2 steps) of **17** as a colorless liquid: IR 2966, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.83 (1H, dd, J = 7.9, 1.2 Hz), 7.47–7.41 (3H, m), 7.36–7.23 (4H, m), 6.96 (1H, td, J = 7.7, 1.7 Hz), 3.69 (1H, s), 1.09 (9H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 138.9, 138.6, 132.9, 130.5, 129.9, 128.8, 127.6, 126.7, 100.5, 95.5, 85.5, 50.6, 35.7, 27.9.

Benzannulated enediyne 19b. To a mixture of 0.307 g of **17** (0.822 mmol), $Pd(PPh_3)_4$ (0.040 g, 0.035 mmol), and copper(I) iodide (0.015 g, 0.080 mmol) in 10 mL of toluene, was added via cannula a solution of 0.150 g of **18b** (0.824 mmol) in 5 mL of triethylamine. After stirring at 120 °C for 12 h, 15 mL of a saturated ammonium chloride solution and 15 mL of diethyl ether were added. The organic layer was separated and the aqueous layer back extracted with diethyl ether. The combined organic layers were washed successively with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/30% methylene chloride in hexanes) afforded 0.331 g of **19b** (0.773 mmol, 94%) as a colorless liquid: IR 2207, 1271, 1078 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.43–8.39 (1H, m), 7.85 (1H, d, J = 9.2 Hz), 7.82–7.77 (1H, m), 7.70–7.65 (1H, m), 7.56–7.52 (1H, m), 7.43–7.25 (7H, m), 7.10–7.00 (3H, m), 4.00 (3H, s), 3.66 (1H, s), 0.95 (9H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 158.9, 139.0, 134.5, 132.3, 130.2, 129.7, 128.4, 127.9, 127.8, 127.3, 127.2, 126.4, 126.3, 126.0, 125.7, 124.1, 112.6, 106.5, 97.8, 95.5, 87.3, 82.6, 56.6, 50.5, 35.5, 27.7; HRMS m/z $[M + H]^+$ calcd for $C_{32}H_{29}O$, 429.2218; found, 429.2217.

Benzannulated enediyne 19c. To a mixture of 0.242 g of **23** (0.812 mmol), $Pd(PPh_3)_2Cl_2$ (0.030 g, 0.043 mmol), and copper(I) iodide (0.015 g, 0.080 mmol) in 6 mL of triethylamine, was added via cannula a solution of 0.265 g of **22** (0.974 mmol) in 2 mL of triethylamine. After stirring at 60 °C for 12 h, 15 mL of a saturated ammonium chloride solution and 15 mL of diethyl ether were added. The organic layer was separated and the aqueous layer back extracted with diethyl ether. The combined organic layers were washed successively with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/5% methylene chloride in hexanes) afforded 0.255 g of **19c** (0.577 mmol, 71%) as a colorless liquid: ^1H NMR ($CDCl_3$, 270 MHz) δ 8.51 (1H, d, J = 7.7 Hz), 7.88–7.83 (2H, m), 7.67–7.57 (3H, m), 7.53–7.42 (2H, m), 7.38–7.32 (4H, m), 7.12–7.05 (3H, m), 4.92 (1H, d, J = 13.1 Hz), 4.83 (1H, d, J = 12.9 Hz), 3.69 (2H, s), 3.41 (3H, s), 0.97 (9H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 139.1, 138.9, 133.2, 132.5, 132.1, 129.6, 128.7, 128.1, 128.0, 127.4, 126.8, 126.6, 126.3, 126.2, 125.5, 125.0, 119.0, 98.3, 96.0, 88.4, 82.7, 72.8, 58.3, 50.5, 35.5, 27.7.

5-(2-Methoxy-1-naphthyl)-10-(1,1-dimethylethyl)-11*H*-benzo[*b*]fluorene (20b). To 0.295 g of **19b** (0.689 mmol) in 10 mL of anhydrous toluene under a nitrogen atmosphere, was added 0.77 mL of a 1.0 M solution of potassium *tert*-butoxide (0.77 mmol) in 2-methyl-2-propanol. The reaction mixture was then heated under reflux for 6 h. After the reaction mixture was allowed to cool to room temperature, 10 mL of water and 40 mL of methylene chloride were introduced. The organic layer was separated, dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (silica gel/5% methylene chloride in hexanes) to provide 0.263 g of **20b** (0.614 mmol, 89%) as a light yellow liquid: IR 1267, 1250, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 8.66 (1H, d, J = 9.0 Hz), 8.11 (1H, d, J = 9.6 Hz), 7.92 (1H, d, J = 8.4 Hz), 7.53 (1H, d, J = 9.0 Hz), 7.44 (1H, d, J = 7.2 Hz), 7.40 (1H, ddd, J = 8.4, 6.6, 1.8 Hz), 7.35 (1H, d, J = 9.0 Hz), 7.31 (1H, td, J = 6.6, 1.2 Hz), 7.18 (1H, t, J = 7.8 Hz), 7.13–7.05 (3H, m), 6.77 (1H, t, J = 7.8 Hz), 6.08 (1H, d, J = 7.8 Hz), 4.55 (2H, s), 3.68 (3H, s), 1.97 (9H, s); ^1H NMR (C_6D_6, 600 MHz) δ 8.67 (1H, d, J = 9.0 Hz), 7.90 (1H, d, J = 9.6 Hz), 7.79 (1H, d, J = 8.4 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.42 (1H, d, J = 8.4 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.23 (1H, d, J = 7.2 Hz), 7.17 (1H, d, J = 6.6 Hz), 7.12 (1H, t, J = 7.5 Hz), 7.06 (1H, t, J = 7.5 Hz), 6.98 (1H, t, J = 7.2 Hz), 6.89 (1H, t, J = 7.8 Hz), 6.72 (1H, t, J = 7.5 Hz), 6.53 (1H, d, J = 7.8 Hz), 4.25 (1H, d, J = 21.6 Hz), 4.19 (1H, d, J = 21.6 Hz), 3.13 (3H, s), 1.77 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.8, 144.2, 141.0, 140.3, 139.3, 137.9, 134.7, 133.9, 131.8, 129.8, 129.5, 128.1, 127.8, 127.2, 127.0, 126.7, 126.6, 126.4, 125.2, 124.1, 123.9, 123.7, 123.3, 122.8, 122.2, 114.4, 56.9, 40.3, 38.9, 34.5; MS m/z 428 (M^+), 413, 400, 371; HRMS m/z calcd for $C_{32}H_{28}O$, 428.2140; found, 428.2126.

Recrystallization from a mixture of isopropyl alcohol and methylene chloride produced a crystal for X-ray structure analysis. Although the weakly diffracting crystal limited the amount of

observed data, the analysis of these data supports the structural assignment of **20b**.

5-[2-(Methoxymethyl)-1-naphthyl]-10-(1,1-dimethylethyl)-11*H*-benzo[*b*]fluorene (20c). The same procedure as described for **20b** was repeated except that 0.142 g of **19c** (0.321 mmol) was treated with 0.48 mL of a 1.0 M solution of potassium *tert*-butoxide (0.48 mmol) in 2-methyl-2-propanol to afford 0.102 g of **20c** (0.231 mmol, 72%) as a light yellow liquid: IR 2943, 1273, 1248, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.67 (1H, d, *J* = 8.9 Hz), 8.12 (1H, d, *J* = 8.7 Hz), 7.97 (1H, d, *J* = 8.2 Hz), 7.91 (1H, d, *J* = 8.6 Hz), 7.47–7.39 (3H, m), 7.28–7.08 (5H, m), 6.75 (1H, t, *J* = 7.7 Hz), 5.89 (1H, d, *J* = 7.9 Hz), 4.56 (2H, s), 4.16 (1H, d, *J* = 13.4 Hz), 4.10 (1H, d, *J* = 13.3 Hz), 3.09 (3H, s), 1.98 (9H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 144.1, 141.5, 139.7, 139.2, 137.7, 135.3, 134.3, 134.0, 133.2, 132.7, 131.6, 128.4, 128.1, 127.9, 126.95, 126.91, 126.6, 126.4, 126.0, 125.9, 124.9, 124.5, 123.8, 123.6, 122.9, 71.9, 58.4, 40.3, 39.0, 34.5; MS *m*/*z* 442 (M^+), 427, 395; HRMS *m*/*z* calcd for $C_{33}H_{30}O$, 442.2297; found, 442.2283.

Supporting Information

Supporting Information File 1

Experimental procedures, spectroscopic data, and ^1H and/or ^{13}C NMR spectra of **5a**,**b**, **6a**,**b**, **8a**,**b**, **9a**,**b**, **13a**,**b**, **17**, **18b**, **19a**–**c**, **20a**–**c**, **21**–**24**, and the (1*S*)-camphanates of **24**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-58-S1.pdf]

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Synthesis of cross-conjugated trienes by rhodium-catalyzed dimerization of monosubstituted allenes

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Full Research Paper

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Abstract

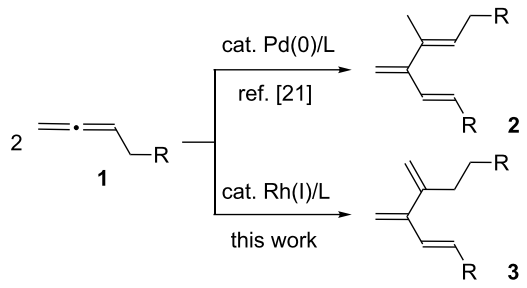
A rhodium(I)/dppe catalyst promoted dimerization of monosubstituted allenes in a stereoselective manner to give cross-conjugated trienes, which are different from those obtained by a palladium catalyst.

Introduction

Cross-conjugated trienes, known as [3]dendralenes [1], are attractive synthetic precursors used for consecutive double [4 + 2] cycloaddition reactions [2-4] to provide a rapid access to polycyclic carbon frameworks. Thus, a number of methods for the preparation of the parent 3-methylenepenta-1,4-diene [5] and its substituted derivatives [6-17] has been developed. Among these, transition-metal-catalyzed dimerization of allenes presents a unique entry to substituted cross-conjugated trienes. For example, a nickel(0)/triphenylphosphine complex catalyzes a dimerization reaction of 3-methylbuta-1,2-diene to afford 2,5-dimethyl-3,4-bismethylenehex-1-ene [18,19]. The nickel-catalyzed reaction, however, leads to a complex mixture of products when monosubstituted allenes such as penta-1,2-diene and 1-phenylpropa-1,2-diene are employed [20]. On the other hand, a palladium-catalyzed dimerization reaction of monosubstituted allenes produces substituted cross-conjugated trienes **2** in high yield (Scheme 1) [21]. We report here that dimerization of monosubstituted allenes is also catalyzed by a rhodium(I)/dppe complex to form cross-conjugated trienes **3**, which are different from those obtained with the palladium catalyst.

Results and Discussion

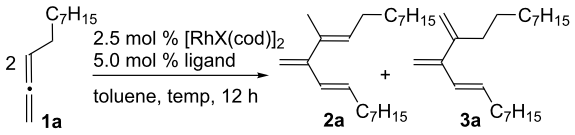
We initiated our study using undeca-1,2-diene (**1a**) as the model substrate and a rhodium(I) complex as the catalyst (Table 1). When **1a** was treated with a catalytic amount of $[RhCl(cod)]_2$ (2.5 mol %, cod = cycloocta-1,5-diene) in toluene at 130 °C for 12 h, **2a** was formed in 40% NMR yield along with another minor dimerized product (13% NMR yield) and unidentified



Scheme 1: A new entry to substituted cross-conjugated trienes.

compounds (Table 1, entry 1). The structure of the minor dimerized product was determined to be (*E*)-10,11-dimethyleneicos-8-ene (**3a**) by ^{1}H and ^{13}C NMR spectroscopy. Thus, the two isomeric dimers, one identical to the isomer obtained by the palladium-catalyzed reaction and the other a different isomer, were produced by the rhodium-catalyzed reaction. Next, several phosphine ligands were examined (Table 1, entries 2–5). To our delight, the use of the dppe ligand suppressed the formation of **2a** and the unidentified compounds, and increased the NMR yield of **3a** to 96% (86% isolated yield, Table 1, entry 4). A complex mixture of products was obtained when the reaction temperature was lowered from 130 °C to 90 °C (Table 1, entry 6). Moreover, the use of $[Rh(OH)(cod)]_2$ and Rh(acac)(cod) as the precatalyst resulted in a decrease of the reaction rate (Table 1, entries 7 and 8).

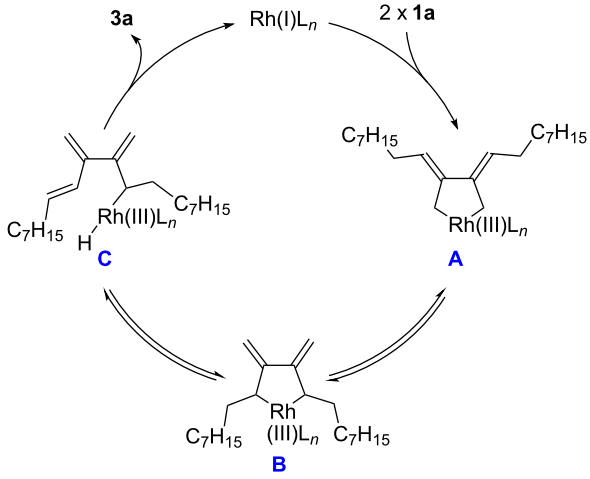
Table 1: Optimization of reaction conditions[a].



Entry	X	Ligand[b]	*T* (°C)	Yield of **2a** (%)[c]	Yield of **3a** (%)[c]
1	Cl	none	130	40	13
2	Cl	PPh_3[d]	130	24	18
3	Cl	dppm	130	24	37
4	Cl	dppe	130	<5	96 (86)
5	Cl	dppp	130	17	50
6	Cl	dppe	90	38	24
7	OH	dppe	130	40	10
8	acac[e]	dppe	130	44	<5

[a]Reactions conducted on a 0.4 mmol scale.
[b]dppm = 1,1-bis(diphenylphosphino)methane, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane.
[c]NMR yield using mesitylene as an internal standard. Isolated yield given in parenthesis.
[d]Using 10 mol % of PPh_3.
[e]Using 5.0 mol % of Rh(acac)(cod).

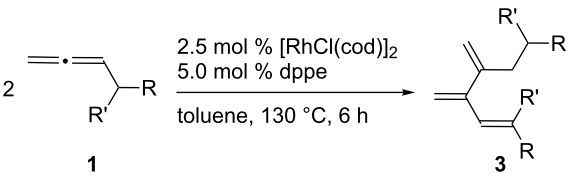
We propose that the dimerization reaction proceeds through the pathway outlined in Scheme 2. Initially, two molecules of **1a** coordinate to a rhodium(I) center at the terminal carbon–carbon double bonds from their sterically less-hindered sides. Oxidative cyclization occurs in a head-to-head manner to form the five-membered rhodacyclic intermediate **A** [22-25], which is in equilibrium with another rhodacyclic intermediate **B** via σ–π–σ isomerization. Then, β-hydride elimination takes place with **B** to form rhodium hydride **C** stereoselectively. Finally, reductive elimination from **C** yields **3a** together with the catalytically active rhodium(I) complex. It is also conceivable, however, that oxidative cyclization of two molecules of **1a** occurs in a tail-to-tail manner to directly furnish **B**. The other isomer **2a** could be formed through allylic 1,3-migration of rhodium from **C** and subsequent reductive elimination.



Scheme 2: A proposed reaction pathway.

Under the optimized reaction conditions using dppe as the ligand, various monosubstituted allenes **1b**–**j** were subjected to the catalytic dimerization reaction (Table 2). In most cases, essentially one isomer **3** was formed, and the other isomer **2** was barely detectable in the ^{1}H NMR spectrum of the crude reaction mixture (<5%). Allenes **1b**–**i** possessing a primary alkyl group reacted well to afford the corresponding products **3b**–**i** in yields ranging from 63% to 90% (Table 2, entries 1–8). Functional groups such as benzyloxy, siloxy, hydroxy and cyano groups were tolerated in the alkyl chain under the reaction conditions. Cyclohexylpropa-1,2-diene (**1j**) possessing a secondary alkyl group also participated in the dimerization reaction (Table 2, entry 9). On the other hand, 1,1-disubstituted allenes such as 3-methylbuta-1,2-diene and 3-pentylocta-1,2-diene failed to undergo the dimerization reaction, in contrast to the nickel-catalyzed reaction [18,19].

Table 2: Synthesis of cross-conjugated trienes by the allene dimerization reaction[a].



1 **3**

Entry	1	R	R'	3	Yield (%)[b]
1	**1b**	C_5H_{11}	H	**3b**	85
2	**1c**	CH_2Ph	H	**3c**	78[c]
3	**1d**	Cy	H	**3d**	83[d]
4	**1e**	CH_2OBn	H	**3e**	70
5	**1f**	$(CH_2)_3OBn$	H	**3f**	78
6	**1g**	$(CH_2)_3OSiMe_2t$-Bu	H	**3g**	90
7	**1h**	$(CH_2)_3OH$	H	**3h**	63
8	**1i**	$(CH_2)_3CN$	H	**3i**	75
9	**1j**	$-(CH_2)_5-$		**3j**	60[d]

[a]Reactions conducted on a 0.4 mmol scale.
[b]Isolated yield unless otherwise noted.
[c]The product was accompanied by a small amount of an unidentified impurity.
[d]NMR yield using mesitylene as an internal standard.

Next, we examined the consecutive double [4 + 2] cycloaddition reaction of the cross-conjugated trienes obtained in the present study. Triene **3a** was treated with 4-phenyl-1,2,4-triazoline-3,5-dione (**4**, PTAD), a highly reactive dienophile, in toluene at 0 °C (Scheme 3). The conversion of **3a** was complete within 1 h, and after chromatographic isolation, bisadducts **5a** and **5a'** were obtained in 75% and 6% yields, respectively. The major bisadduct **5a** resulted from initial addition to the more congested diene moiety of **3a** (site β). When tetracyanoethylene (**6**, TCNE), which was a less reactive dienophile than **4**, was used, [4 + 2] cycloaddition also occurred preferentially at site β, but only once on heating at 60 °C for 24 h.

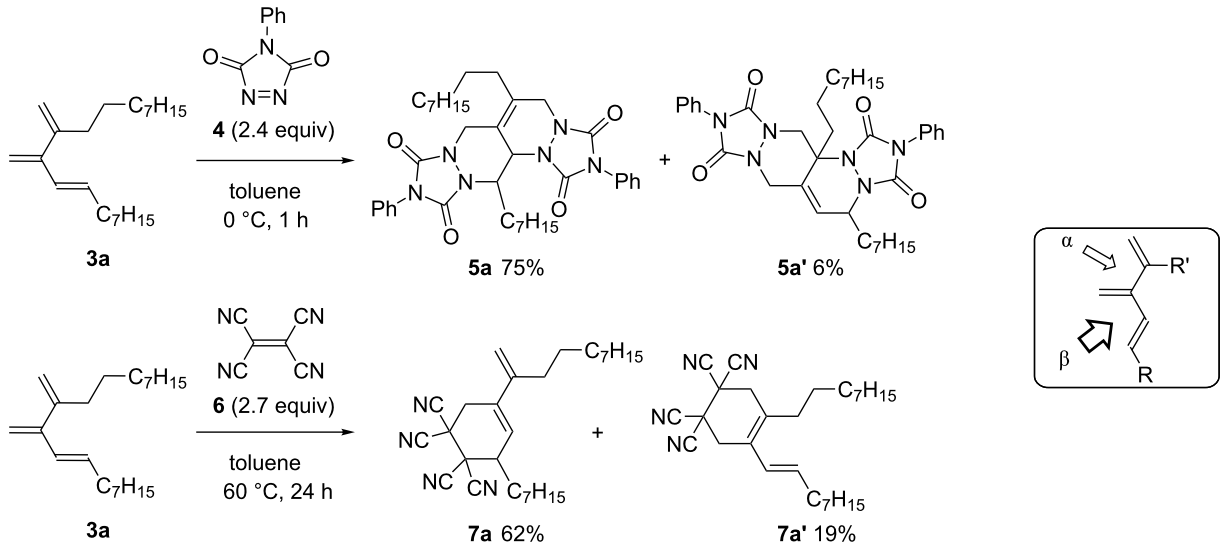
Conclusion

In summary, we have developed a new dimerization reaction of monosubstituted allenes catalyzed by a rhodium(I)/dppe complex, allowing the stereoselective formation of substituted cross-conjugated trienes. It is interesting that the rhodium catalyst and the palladium catalyst gave different types of cross-conjugated trienes.

Experimental

General procedure for rhodium-catalyzed dimerization of monosubstituted allenes

To a side-arm tube equipped with a stirrer bar, was added $[RhCl(cod)]_2$ (4.9 mg, 2.5 mol %) and dppe (7.7 mg, 5 mol %). The tube was evacuated and refilled with argon three times. Then, toluene (4 mL) and substrate **1** (0.4 mmol) were added via syringe and the tube was closed. After heating at 130 °C for 6 h, the reaction mixture was cooled to room temperature, passed through a pad of Florisil® and eluted with ethyl acetate (≈ 90–100 mL). The filtrate was concentrated under reduced pressure and the residue purified by preparative thin-layer chromatography to give product **3**. Although the isolated **3** was relatively labile, it could be kept at −30 °C for days without any detectable decomposition or polymerization.



Scheme 3: [4 + 2] cycloaddition reaction of **3a** with PTAD and TCNE.

Supporting Information

Supporting Information File 1

Experimental details and spectroscopic data for new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-67-S1.pdf]

Acknowledgements

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Gold-catalyzed regioselective oxidation of terminal allenes: formation of α-methanesulfonyloxy methyl ketones

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Full Research Paper

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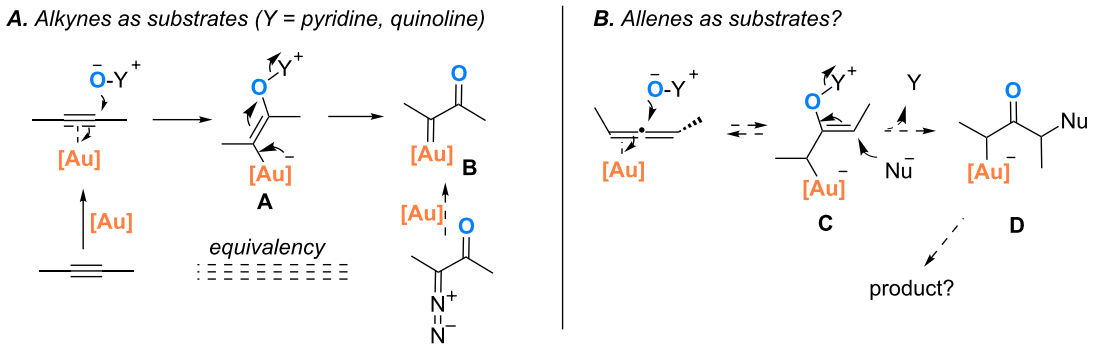
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Abstract

Synthetically useful α-methanesulfonyloxy methyl ketones are readily prepared in one-step from terminal allenes in fair to good yields. The chemistry relies on a gold-catalyzed intermolecular oxidation of the 1,2-diene unit using 3,5-dichloropyridine *N*-oxide as the oxidant. The reaction tolerates a range of functional groups and shows excellent regioselectivity.

Introduction

While alkynes are the most studied substrates in homogeneous gold catalysis [1-9], allenes [10] occupy a not-so-distant second place, and many versatile transformations have been developed either using allenes as substrates [11-17] or via allenes generated in situ [18-21]. We have recently shown that highly reactive gold carbenes can be generated from alkynes via gold-promoted intermolecular oxidation by pyridine/quinoline *N*-oxides [22-25], making benign alkynes effective surrogates of toxic and potentially explosive α-diazo ketones (Scheme 1A). Synthetically useful structures such as oxetan-3-ones [22], dihydrofuran-3-ones [23], azetidin-3-ones [24] and α,β-unsaturated ketones [25] are readily accessed via these gold carbene intermediates. This led us to consider whether or not allenes could also be oxidized by these *N*-oxides in the presence of gold catalysts. As shown in Scheme 1B, intermediate **C**, likely formed via an initial nucleophilic attack of a gold-activated allene, cannot undergo elimination in the same way as intermediate **A**, hence gold carbene intermediate **B** would not be formed. While **C** may revert back to the allene substrate, we suspect that a S_N2'-type reaction by an external nucleophile could facilitate the fragmentation of the O–Y bond, ultimately leading to useful products via intermediate **D**. Herein we report our preliminary studies, which led to a facile synthesis of α-methanesulfonyloxy methyl ketones.



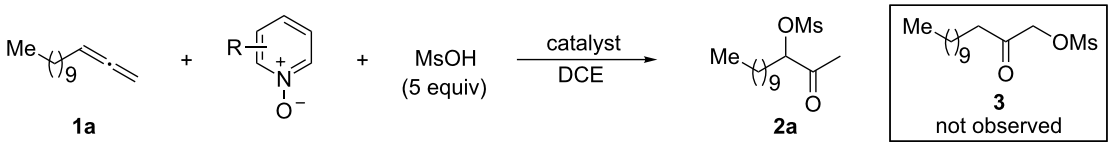
Scheme 1: Gold-catalyzed intermolecular oxidation of alkynes and allenes.

Results and Discussion

Initially, trideca-1,2-diene (**1a**) was treated with commercially available pyridine *N*-oxide in the presence of MsOH (5 equiv) and $Ph_3PAuNTf_2$ (5 mol %) in DCE at room temperature. Consumption of **1a** was initially observed and was complete in two days. A relatively polar compound was detected and subsequently isolated (Table 1, entry 1). NMR and MS analysis showed it to be the α-methanesulfonyloxy ketone **2a**. Interestingly, its regioisomer (i.e., **3**) was not observed, suggesting excellent regioselectivity in terms of the MsO delivery. The reaction time was shortened to 8 h by increasing the reaction temperature (entry 2). Attempts to increase the reaction efficiency by varying the *N*-oxide (entries 3–5) revealed that 3,5-dichloropyridine *N*-oxide was a superior oxidant, and **2a** was formed in 75% NMR yield. While less reactive but bulky gold catalysts, such as $IPrAuNTf_2$ (entry 6) and Cy-JohnPhosAuNTf$_2$ (entry 7), did not fare as well as $Ph_3PAuNTf_2$, the more Lewis acidic $(4\text{-}CF_3Ph)_3PAuNTf_2$ was better, and **2a** was formed in 77% isolated yield (entry 8). A decrease in the amount of MsOH was counterproductive (entry 9), whilst no desired product was observed in the absence of a gold catalyst (entry 10).

With the optimized reaction conditions established (Table 1, entry 8), the scope of this chemistry was studied. As shown in Table 2, remote functional groups were readily tolerated. For example, good yields were obtained in the presence of a distal acetoxy (entry 1) or benzoyloxy (entry 2) group; moreover, reactive tosyloxy and mesyloxy groups were also tolerated (entries 3 and 4). A chloro (entry 5), a benzyloxy (entry 6), a

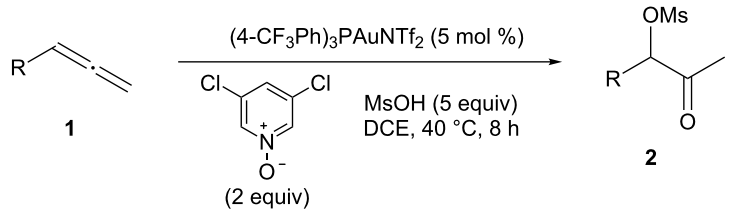
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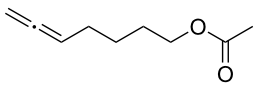
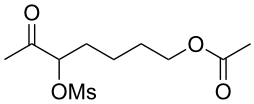
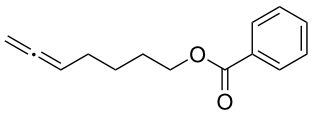
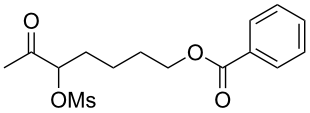
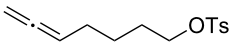
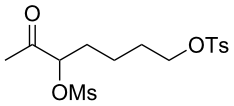
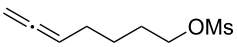
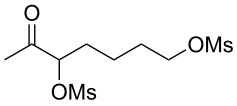
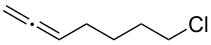
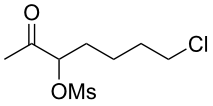
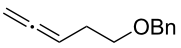
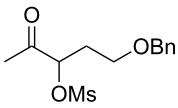
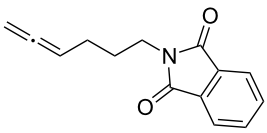
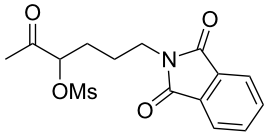
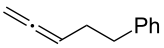
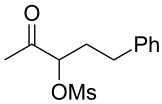
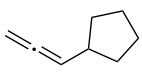
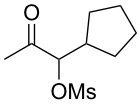
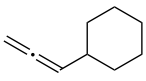
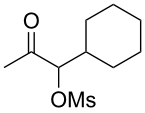


Entry	Catalyst (5 mol %)	*N*-Oxide (2 equiv)	Reaction conditions	Yield[b] (%)
1	$Ph_3PAuNTf_2$	pyridine *N*-oxide	rt, 2 d	46
2	$Ph_3PAuNTf_2$	pyridine *N*-oxide	40 °C, 8 h	52
3	$Ph_3PAuNTf_2$	quinoline *N*-oxide	40 °C, 8 h	51/6[c]
4	$Ph_3PAuNTf_2$	2-bromopyridine *N*-oxide	40 °C, 8 h	44/10[c]
5	$Ph_3PAuNTf_2$	3,5-dichloropyridine *N*-oxide	40 °C, 8 h	75
6	$IPrAuNTf_2$	3,5-dichloropyridine *N*-oxide	40 °C, 8 h	10/53[c]
7	Cy-JohnPhosAuNTf$_2$	3,5-dichloropyridine *N*-oxide	40 °C, 8 h	47/7[c]
8	$(4\text{-}CF_3Ph)_3PAuNTf_2$	3,5-dichloropyridine *N*-oxide	40 °C, 8 h	80(77[d])
9[e]	$(4\text{-}CF_3Ph)_3PAuNTf_2$	3,5-dichloropyridine *N*-oxide	40 °C, 8 h	55/13[c]
10	—	3,5-dichloropyridine *N*-oxide	40 °C, 8 h	—

[a]**[1a]** = 0.05 M; [b]determined by ^{1}H NMR using diethyl phthalate as the external standard; [c]unreacted starting material; [d]isolated yield; [e]2.5 equiv of MsOH.

Table 2: Reaction scope[a].

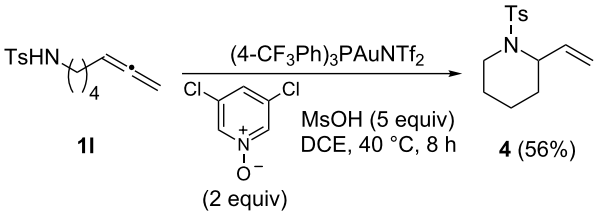


Entry	Allene		Products		Yield[b]
1		**1b**		**2b**	79%
2		**1c**		**2c**	75%
3		**1d**		**2d**	80%
4		**1e**		**2e**	73%
5		**1f**		**2f**	63%
6		**1g**		**2g**	61%
7		**1h**		**2h**	76%
8		**1i**		**2i**	60%
9		**1j**		**2j**	72%
10		**1k**		**2k**	59%

[a][**1**] = 0.05 M; [b]isolated yield.

protected amino (entry 7) and a phenyl group (entry 8) were also allowed, and the corresponding α-functionalized ketones were isolated in useful yields. Besides linear allenes, exocyclic allenes such as **1j** and **1k** were also suitable substrates and gave mesylates **2j** and **2k** in 72% and 59% yield, respectively (entries 9 and 10).

Some substrates, however, did not participate in this reaction effectively. For example, allenes derived by replacing the acetoxy group of **1b** with a free OH or an OTBS group did not lead to the desired products. Presumably, the nucleophilic OH group in the substrate, or one generated via acidic desilylation, interfered with the reaction. This reasoning was supported by the isolation of piperidine **4** upon subjecting **1l** to the optimized reaction conditions (Scheme 2). In addition, allenylbenzene was not a good substrate, and <10% of the desired ketone was detected by NMR. Somewhat surprisingly, pentadeca-7,8-diene [26], an internal allene, did not participate in the reaction.



Scheme 2: A side reaction from **1l**.

It is of note that α-methanesulfonyloxy ketones are versatile synthetic intermediates that can undergo various reactions [27], including substitution [28], elimination [29], the formation of zinc homoenolates [30], the formation of cyclopropane rings under photo-irradiation [31-33], the formation of aminoimidazoles [34], the generation of cyclopropanone–oxyallyl intermediates [35], and ring contraction [36]. Their direct synthesis from corresponding ketones can be realized via oxidation by using either CuO/MsOH [37,38] or PhI(OH)OMs [39]. However, the former method uses stoichiometric amounts of copper, whilst the latter suffers from low regioselectivities. This gold-catalyzed approach offers an attractive alternative that is highly regioselective, catalytic on gold and takes place under relatively mild reaction conditions.

The mechanism of this highly regioselective gold-catalyzed oxidation of allenes is proposed in Scheme 3. The first step, as in the case of alkyne oxidation [22,23,25], is probably an attack by the pyridine *N*-oxide on the gold-activated allene. Selective reaction at the terminal C–C double bond should occur due to steric preference. The allyl gold intermediate **E** can then undergo protonation to form intermediate **F** with MsO^- as the counter anion. An S_N2'-type substitution by the anion would afford the observed product. This substitution is facilitated by the fragmentation of the weak N–O bond and the annihilation of the charges.

Conclusion

We have successfully realized the first gold-catalyzed intermolecular oxidation of allenes. With 3,5-dichloropyridine *N*-oxide as the oxidant and in the presence of MsOH, α-methanesulfonyloxy methyl ketones are formed in one step in fair to good yield with excellent regioselectivities under relatively mild reaction conditions. The reaction tolerates a wide range of functional groups. Studies to explore the synthetic potential of this allene oxidation strategy are currently underway.

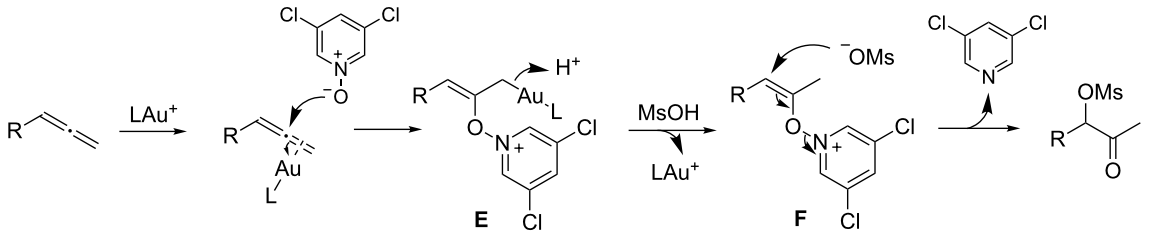
Supporting Information

Supporting Information File 1

Experimental procedures and characterization data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-69-S1.pdf]

Supporting Information File 2

NMR spectra of compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-69-S2.pdf]



Scheme 3: A proposed reaction mechanism.

Acknowledgements

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Beilstein Journal of Organic Chemistry

Complete transfer of chirality in an intramolecular, thermal [2 + 2] cycloaddition of allene-ynes to form non-racemic spirooxindoles

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Letter

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Abstract

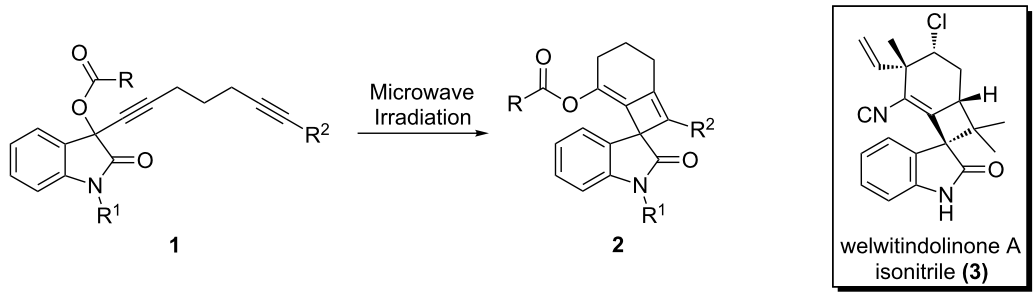
A thermal [2 + 2] cycloaddition reaction of allene-ynes has been used to transform chiral non-racemic allenyl oxindoles into chiral non-racemic spirooxindoles containing an alkylidene cyclobutene moiety. The enantiomeric excesses were determined by chiral lanthanide shift NMR analysis and the transfer of chiral information from the allene to the spirooxindole was found to be greater than 95%.

Introduction

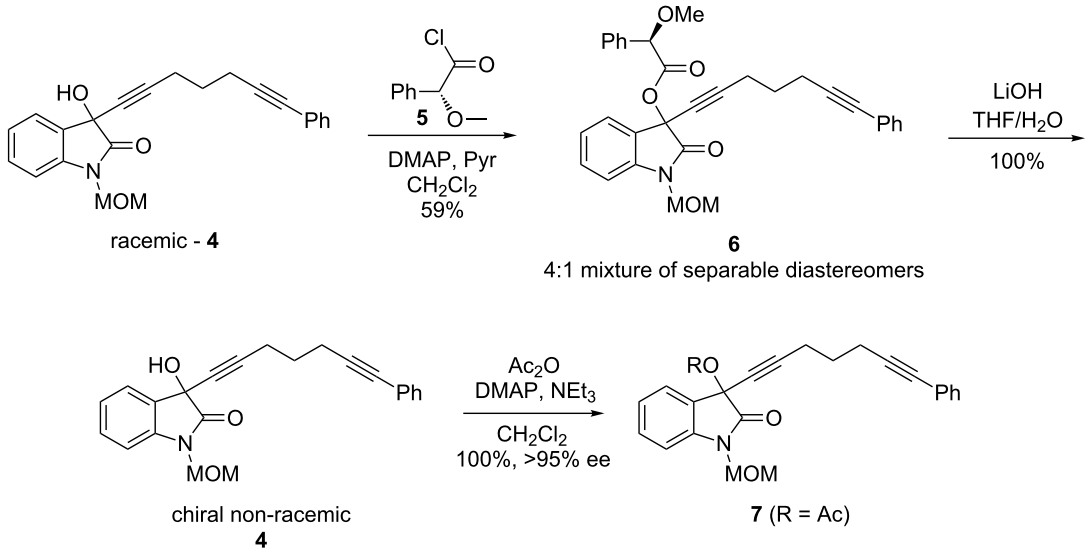
The [2 + 2] cycloaddition reaction of allenes and alkynes provides rapid entry into synthetically challenging alkylidene cyclobutene ring systems. We, along with others, have demonstrated the intramolecular variant of this reaction under thermal conditions [1,2]. This thermally forbidden process is believed to proceed via a biradical intermediate mechanism, a conclusion supported by both computational and experimental studies [3]. Recently, the scope of this method has been expanded to the synthesis of spirooxindole-containing skeletons **2** in a two-step one-pot process from propargyl acetates **1** [4] (Scheme 1). Inspired by this rapid entry into the molecularly complex substructure **2**, and the structural similarity to welwitindolinone A isonitrile (**3**), we became interested in the synthesis of chiral non-racemic spirooxindoles for application to natural product synthesis [5-7]. Herein, we disclose preliminary results demonstrating a complete transfer of chiral information from a chiral non-racemic allene-yne to form an enantiomerically enriched spirooxindole in a [2 + 2] cycloaddition reaction.

Findings

This study commenced with the preparation of the enantiopure propargyl acetate **7** [8]. Treatment of racemic propargyl alcohol **4** with the (*R*)-acid chloride **5**, DMAP, and pyridine resulted in propargyl ester **6** as a separable 4:1 mixture of diastereomers.



Scheme 1: Conversion of propargyl acetate **1** to spirooxindole **2** containing the core framework of welwitindolinone A isonitrile (**3**).



Scheme 2: Preparation of enantiopure propargyl acetate **7** (R = Ac).

Saponification of the major diastereomer of **6**, followed by acylation provided the propargyl acetate **7** in quantitative yield (Scheme 2).

The enantiomeric purity of propargyl acetate **7** was determined based on treatment of the compound with the chiral shift reagent (+)-Eu(hfc)$_3$. Figure 1 shows the ^{1}H NMR of the racemic as well as the enantiomerically enriched propargyl acetate upon treatment with the chiral shift reagent. Treating racemic acetate **7** with the chiral shift reagent enabled resolution of the resulting diastereomeric complexes, which was evidenced by the resonances for the aromatic proton labeled H$_a$ in the spectrum shown below. The spectrum of racemic acetate **7** contains two doublets at δ 7.54 and 7.52, while the spectrum of enantiomerically enriched **7** shows only a single doublet at δ 7.54. Based on this result, the enantiomeric excess of enantiomerically enriched acetate **7** is greater than 95%.

Next, the focus turned to the conversion of enantiomerically enriched propargyl acetate **7** to an enantiomerically enriched allene **8**. It has been previously shown that delivery of an alkyl group from an organocuprate in an S$_N$2' fashion occurs with retention of chiral information in the resulting allene [9]; thus we began by screening cuprate conditions to form the desired allenyloxindole **8** (Table 1). In order to generate the allene, we examined various leaving groups (OMs, OMe, OAc), solvents (THF, Et$_2$O), and cuprates (lower and higher order cyanocuprates). The reaction incorporating a mesylate as a leaving group was problematic due to substrate instability issues, even at low temperatures (Table 1, entry 1) and the substrates containing –OMe and –OAc leaving groups were unreactive toward the lower order cuprates (Table 1, entries 2–5). The optimal conditions were found using the propargylic acetate and the higher order cuprate, *t*-Bu$_2$Cu(CN)Li$_2$ at −78 °C which gave compound **8** (R' = *tert*-butyl) in 49% yield (Table 1,

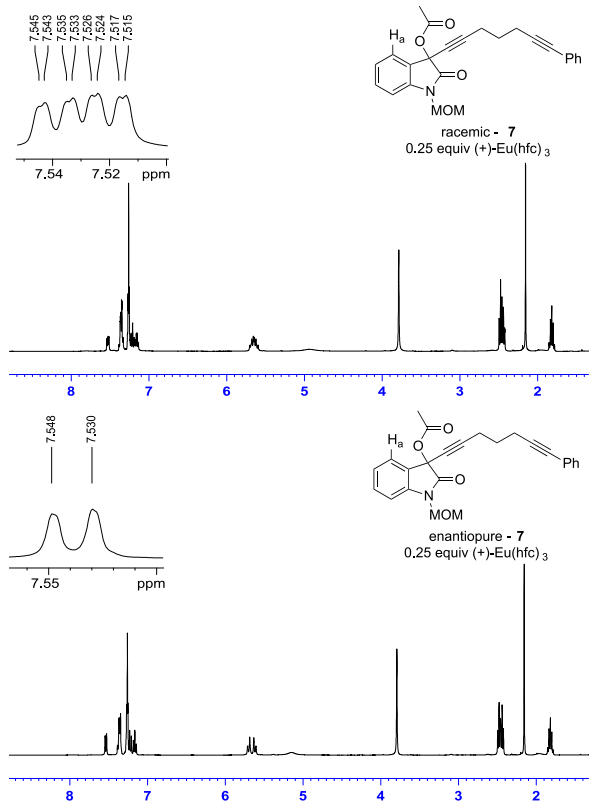


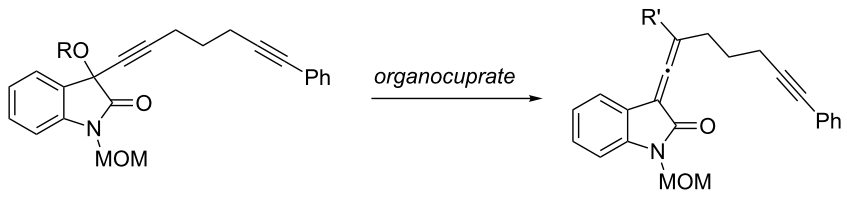
Figure 1: Chiral NMR shift analysis of propargyl acetate **7**.

entry 6). As a prelude to this proposed synthetic route, our attempts to thermally rearrange the chiral non-racemic propargyl acetate to form an enantiomerically enriched allenyl acetate followed by tandem [2 + 2] cycloaddition to provide directly a structure resembling compound **2**, gave the racemic spirooxindole product. This finding will be discussed in detail in a full account of this work.

To examine the chiral transfer from the propargylic acetate **7** to the allenyloxindole **8**, a chiral ^{1}H NMR shift analysis was performed using (+)-Eu(hfc)$_3$. The NMR spectra of the racemic compound **8** as well as the enantiomerically enriched compound **8** are shown in Figure 2. In the case of the racemic compound, the resonances for the *tert*-butyl groups of the diastereomeric complexes are split into two distinct signals in the presence of the shift reagent; one singlet at δ 1.23 ppm and a second singlet at δ 1.20 ppm. The enantiomerically enriched compound **8** shows one singlet, corresponding to the resonance for the *tert*-butyl group at δ 1.22 ppm; thus the enantiomeric excess of allenyloxindole **8** is greater than 95%.

With the enantiomerically enriched allene-yne **8** in hand, we were poised to test the transfer of chiral information under thermal [2 + 2] reaction conditions. Irradiation of **8** in *o*-dichlorobenzene with microwaves for 5 min at 225 °C provided the desired spirooxindole **9** in 44% yield (Scheme 3). Despite the somewhat low yield, the reaction is clean as judged by TLC with the exception of some baseline material.

Table 1: Screening conditions for the formation of allenyloxindole **8**.



7 **8**

Entry	R	Solvent	Temp	Cuprate	R'	Yield
1	Ms	THF	−45 °C	MeCu(CN)Li	Me	0%[a]
2	Me	Et_2O	0 to 35 °C	MeCu(CN)Li	Me	0%[b]
3	Ac	Et_2O	0 °C	MeCu(CN)Li	Me	0%[b]
4	Ac	THF	−78 °C to rt	MeCu(CN)Li	Me	0%[c]
5	Ac	Et_2O	−78 °C	*t*-BuCu(CN)Li	*t*-Bu	0%[b]
6	Ac	THF	−78 °C	*t*-Bu_2Cu(CN)Li_2	*t*-Bu	49%[d]

[a]Complete decomposition of the mesylate (generated in situ) was observed prior to cuprate addition. [b]Complete recovery of starting material. [c]Starting material was recovered in addition to the deacylation product. [d]The product of a second addition of the tert-butyl group to the central carbon of the allene was also isolated in 21% yield.

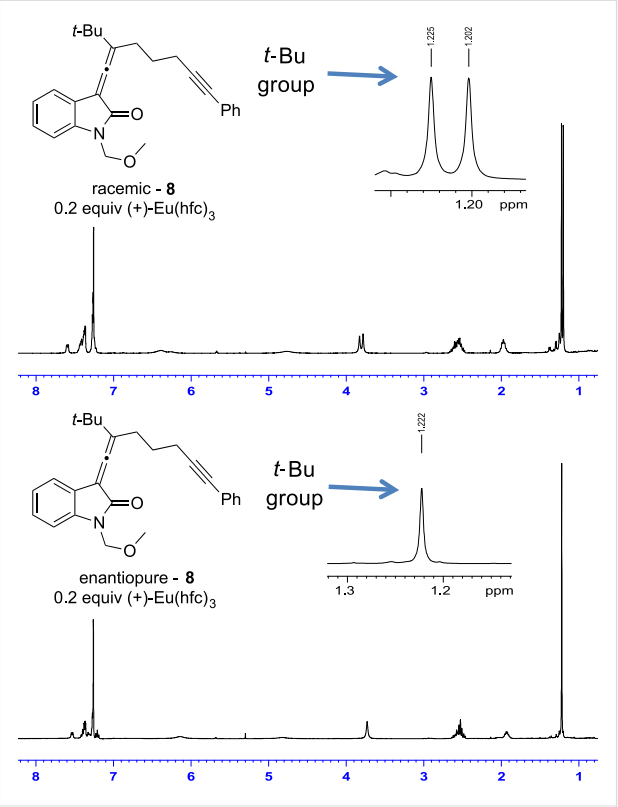


Figure 2: Chiral NMR shift analysis of allenyloxindole **8**.

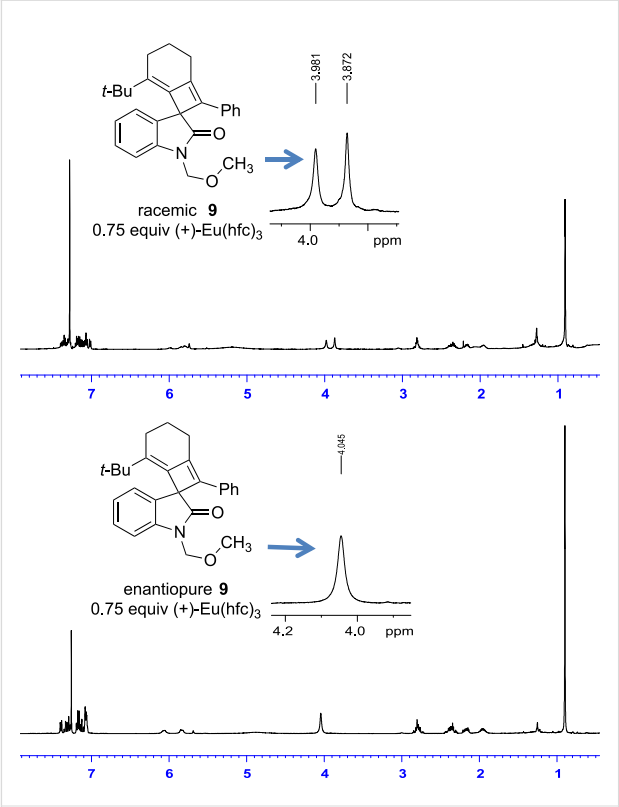
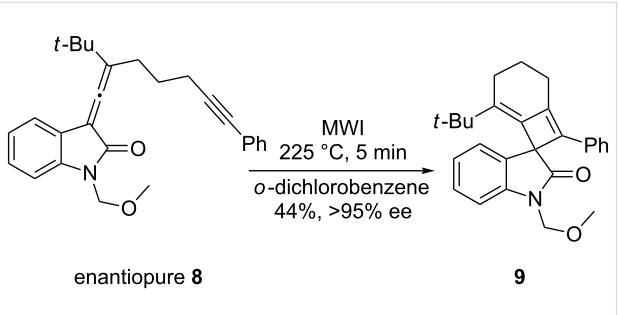


Figure 3: Chiral NMR shift analysis of spirooxindole **9**.

Spirooxindole **9** was purified by column chromatography and the transfer of chiral information was determined using chiral ^{1}H NMR shift analysis.



Scheme 3: Microwave irradiation of allenyloxindole **8**.

Spirooxindole **9** was treated with 0.75 equiv of (+)-Eu(hfc)$_3$ in $CDCl_3$. The resulting diastereomeric complexes were resolved based upon the resonances at δ 3.98 and δ 3.87 ppm, which are peaks that correspond to the methyl in the MOM group on the oxindole nitrogen. For the enantiomerically enriched compound **9**, only a single resonance is observed at δ 4.05 ppm in the presence of the chiral shift reagent. Based on this analysis, the product was formed with greater than 95% enantiomeric excess (Figure 3).

Our working hypothesis for the mechanism for transfer of chiral information from the allene to the spirooxindole-containing cyclobutene is that the reaction still proceeds through the thermally generated biradical intermediate, but the *tert*-butyl group hinders rotation around the carbon–carbon bond as shown in Figure 4, thus slowing racemization of the resulting radical containing carbon. This hypothesis is supported by a report by Pasto, where transfer of chiral information was incomplete in a thermal, intermolecular [2 + 2] cycloaddition reaction between 2,3-pentadiene and methyl propiolate [10].

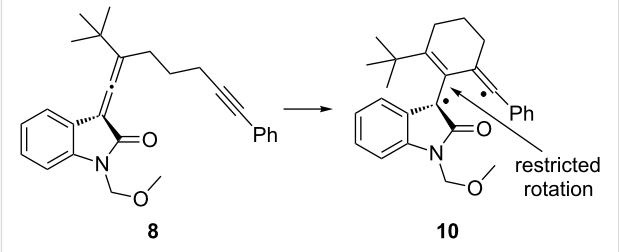


Figure 4: Thermally generated biradical intermediate **10**.

In summary, there are only a few general methods to prepare carbocyclic spirooxindoles non-racemically [11-14]; we have demonstrated the first thermal, intramolecular [2 + 2] cycload-

dition reaction of an allene-yne that generates a chiral non-racemic spirooxindole from a chiral non-racemic allene. Furthermore, this reaction could also be applicable in the enantioselective synthesis of natural products that contain a spirooxindole core, such as welwitindolinone A isonitrile. We are currently working to expand the scope of this chirality transfer to other allenyl systems possessing less bulky and/or traceless groups.

Supporting Information

Supporting Information File 1

General methods, experimental and spectral data for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-70-S1.pdf]

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Beilstein Journal of Organic Chemistry

Homoallylic amines by reductive inter- and intramolecular coupling of allenes and nitriles

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Full Research Paper

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Keywords:
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Abstract

The one-pot hydrozirconation of allenes and nitriles followed by an in situ transmetalation of the allylzirconocene with dimethylzinc or zinc chloride provides functionalized homoallylic amines. An intramolecular version of this process leads to 3-aminotetrahydrofurans and 3-aminotetrahydropyrans.

Introduction

The reversible addition of zirconocene hydrochloride ($Cp_2Zr(H)Cl$, Schwartz's reagent) to π-bonds usually leads predominantly to σ-complexes, and the resulting organozirconocene complexes are valuable reactive intermediates for the formation of carbon–halogen and carbon–carbon bonds [1-6]. The reaction of Schwartz's reagent with allenes occurs at low temperature and provides a ready access to σ-bound allylzirconocenes [7]. These species can be added diastereoselectively to aldehydes and ketones to yield homoallylic alcohols, but they are generally not sufficiently reactive towards many other electrophiles [8,9]. Similar to the related alkyl- and alkenylzirconocenes [1-3,6], this limitation of sterically hindered allylzirconocene complexes can be overcome by selective transmetalation of zirconium to other metals. Suzuki and co-workers treated allylzirconocenes with methylaluminoxane (MAO) in order to achieve the carbalumination of 1-alkynes [10], internal alkynes [11], conjugated enynes [12], and 1-iodoalkynes [13]. Huang and Pi found that allylzirconocenes underwent conjugated addition to enones in the presence of $CuBr{\cdot}SMe_2$ [14]. Wipf and Pierce demonstrated that, upon the addition of a zinc reagent to allylzirconocenes, transient allylzinc intermediates can be successfully added to phosphoryl- and sulfonylimines to provide homoallylic amines in good yields and diastereoselectivities [15]. Of particular interest was the reaction of tin- or silicon-substituted allenes that furnish bis-metallic reagents that could potentially serve as dianion equivalents and provide (*E*)-vinylsilanes and (*E*)-vinylstannanes in good yields [15].

N-Metalloimines are reactive intermediates that represent masked imine derivatives of ammonia, which are often unstable

and difficult to prepare. A common method for the preparation of these species is the addition of various metal hydrides to nitriles [16-20], including aluminium [21-24], niobium [25], samarium [26] and iron hydrides [27]. Zirconocene hydrochloride can also be added to nitriles to provide *N*-zirconoimines, which can be trapped with a range of electrophiles to form imine derivatives [28-30]. Floreancig and co-workers developed a method for the preparation of α-functionalized amides by trapping *N*-zirconoimines with acyl chlorides, followed by the addition of nucleophiles to the intermediate acyl imines [31-33]. Furthermore, the utility of the hydrozirconation of nitriles can be enhanced by using Lewis acids to engage nitrile-derived acylimines in Friedel–Crafts reactions, generating indanyl or tetrahydronaphthyl derivatives [34,35].

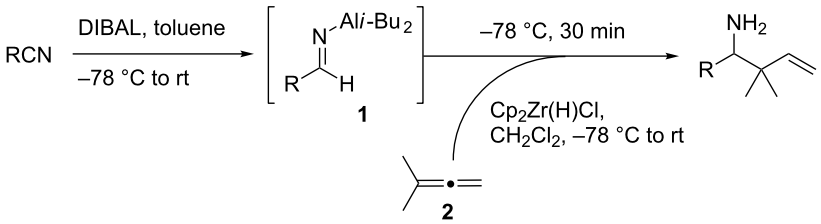
Previous work in our group had concentrated on the transmetalation of alkenyl- and allylzirconium species to give zinc organometallics, which were added to phosphoryl- and sulfonylimines to obtain homoallylic amines [15,36]. The preparation of phosphoryl- and sulfonylimines as well as the subsequent removal of these activating groups was often low-yielding. Because of that, as well as limited functional group compatibility in this methodology, we sought to develop a new approach for the protective group-free synthesis of homoallylic amines. The ease of synthesis of *N*-metalloimines by hydrometalation of nitriles could potentially provide suitable intermediates for this synthetic strategy. In this article, we report a one-pot hydrozirconation of allenes and nitriles that facilitates the reductive coupling to yield *N*-unprotected homoallylic amines.

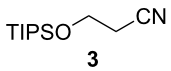
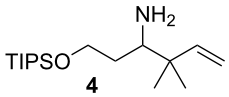
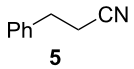
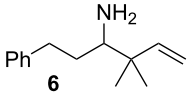
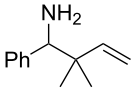
Results and Discussion

We first investigated the addition of allylzirconocenes to *N*-aluminoimines. *N*-aluminoisobutyroimine **1** was prepared in situ by the reduction of nitrile **3** with DIBAL (1 equiv) in toluene. The resulting mixture was cannulated at −78 °C into a solution of allylzirconocene (1.4 equiv), prepared by the hydrozirconation of 3-methyl-1,2-butadiene (**2**). After stirring for 30 min, the desired product **4** was isolated in 76% yield as a single regioisomer. Other aliphatic nitriles were also good substrates for this reaction; however, *N*-aluminoimines obtained from aromatic nitriles were unreactive towards allylzirconocenes, and the desired product was not detected from these substrates (Table 1).

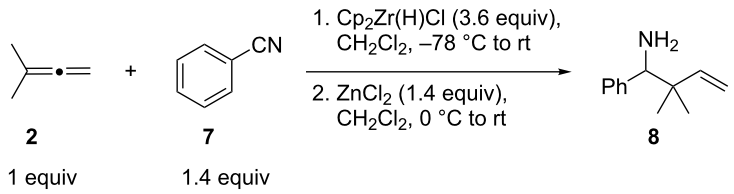
We also investigated the one-pot hydrozirconation of allenes and nitriles, aiming to explore the in situ formation-addition of allylzirconocenes to *N*-zirconoimines (Scheme 1). Exposure of benzonitrile (**7**) and 3-methyl-1,2-butadiene (**2**) to an excess of Schwartz's reagent in CH_2Cl_2 at −78 °C led to the formation of a bright red solution after gradual warming to room temperature. However, upon aqueous work-up, none of the desired amine was obtained, even when the more Lewis acidic $Cp_2Zr(H)Cl$ prepared in situ by the Negishi protocol [37] was used. In contrast, adding 1.4 equiv of $ZnCl_2$ to the hydrozir-

Table 1: Reaction of *N*-aluminoimines with allylzirconocene derived from allene **2**.



Entry	Nitrile	Product	Yield (%)
1	 **3**	 **4**	76
2	 **5**	 **6**	69
3	PhCN **7**	 **8**	—[a]

[a]None of the desired product was detected in this reaction; instead, a mixture of high molecular weight byproducts was observed.



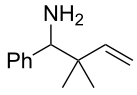
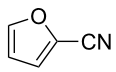
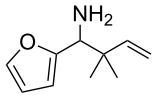
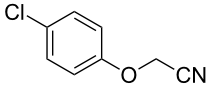
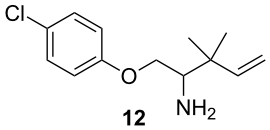
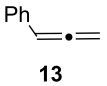
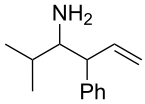
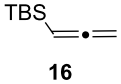
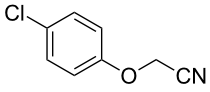
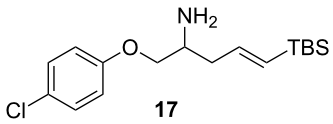
Scheme 1: One-pot hydrozirconation-reductive coupling of allene **2** and nitrile **7**.

conation reaction mixture, according to Suzuki's protocol for the reductive coupling of allenes and alkynes [38], led to the formation of homoallylic amine **8** in 75% yield after stirring at room temperature for 3 h.

Under the optimized conditions for the reaction of benzonitrile (**7**), we further explored the scope of the reaction of nitriles with **2** (Table 2). Both aromatic (Table 2, entries 1 and 2) and aliphatic (Table 2, entries 3 and 4) *N*-zirconoimines derived from the corresponding nitriles reacted smoothly with allylzirconocene in the presence of a slight excess of $ZnCl_2$ (1.4 equiv) to give homoallylic amines in moderate to good yields. The phenylallene **13** yielded exclusively the terminal alkene product **15** in good yield as a single diastereoisomer. In all of these examples, the γ-adduct was isolated as the sole regioisomer, and no internal alkene was detected. This regioselectivity is consistent with the allylzincation of imines [15] and opposite to that of the zinca-Claisen reaction observed by Suzuki and co-workers [38]. Analogous to the previous work in our group [15], the silyl-substituted allene **16** produced the (*E*)-vinylsilane **17** as the sole product in this reaction.

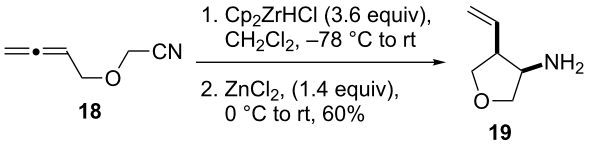
Given the success of the one-pot intermolecular reductive coupling of allenes and nitriles, we sought to expand our methodology to an intramolecular variant. For this purpose, we synthesized substrate **18** by *O*-alkylation of allenylmethanol

Table 2: Reductive coupling of allenes and nitriles in the presence of $Cp_2Zr(H)Cl$ and $ZnCl_2$.[a]

Entry	Allene	Nitrile	Product	Yield (%)
1	 **2**	PhCN **7**	 **8**	75 (78)[b]
2	 **2**	 **9**	 **10**	55 (67)[b]
3	 **2**	 **11**	 **12**	80 (81)[b]
4	 **13**	 **14**	 **15**	65 (71)[b,c]
5	 **16**	 **11**	 **17**	67 (70)[b,d]

[a]All reactions were carried out by hydrozirconation of a mixture of allene (1.4 equiv) and nitrile (1 equiv) in CH_2Cl_2 at −78 °C, followed by the addition of a 1 M solution of $ZnCl_2$ in ether (1.4 equiv) at 0 °C. [b]Yields in parentheses correspond to the reaction in which transmetalation was performed using Me_2Zn (1.4 equiv) in toluene. [c]Only one diastereoisomer was observed by ^1H NMR analysis of the crude reaction mixture. [d]Alkene geometry was assigned by coupling constant analysis.

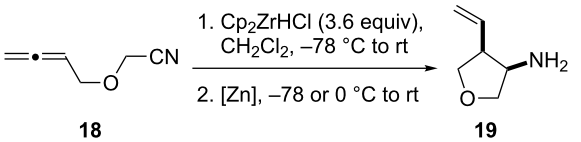
[39] with bromoacetonitrile (Supporting Information File 1). We were pleased to see that treatment of substrate **18** with 3.6 equiv of Schwartz's reagent in CH_2Cl_2 followed by the addition of 1.4 equiv of $ZnCl_2$ led to the formation of the desired tetrahydrofuran product **19** as a single diastereoisomer in 60% yield (Scheme 2). Surprisingly, however, we found that repeating this reaction gave variable yields. Because the reaction mixture was heterogeneous after the addition of the zinc salt, we argued that decreasing the amount of $Cp_2Zr(H)Cl$ or a lower substrate concentration might help to address this problem. Unfortunately, these studies were inconclusive, and 3.6 equiv of Schwartz's reagent were generally needed for a satisfactory reaction progress.



Scheme 2: Cyclization of allenylnitrile **18**.

To address the reproducibility issue, we also investigated different zinc sources (Table 3). The presence of zinc halides and triflates ($ZnCl_2$, $Zn(OTf)_2$) in a range of solvents always resulted in the formation of a precipitate. Therefore, we turned our attention to dialkylzincs. We were pleased to see that the addition of a 1 M solution of diethylzinc to the hydrozirconated **18** at −78 °C produced a homogeneous red solution; however, only traces of the desired product **19** were detected. Switching the solvent from CH_2Cl_2 to toluene before the addition of the dialkylzinc reagent resulted in the desired product formation in good yield and provided a single diastereoisomer. This observation is in agreement with previous work in our group that showed the transmetalation from zirconium to zinc to occur faster in toluene than in CH_2Cl_2 [15]. Furthermore, we also repeated some earlier examples of the intermolecular reaction using dimethylzinc in toluene for the transmetalation step. These new experiments produced results similar to the reactions in the presence of zinc chloride (Table 2).

Table 3: Optimization of the intramolecular reductive coupling of allene and nitrile to give tetrahydrofuran **19**.

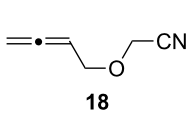
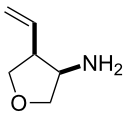
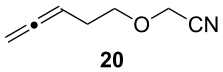
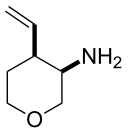
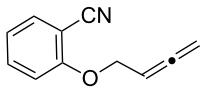
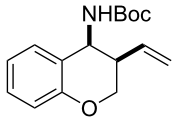


Entry	Zinc source	Solvent	Yield (%)
1	$ZnCl_2$[a]	CH_2Cl_2	53
2	$ZnCl_2$[b]	CH_2Cl_2	50
3	$Zn(OTf)_2$[b]	CH_2Cl_2	17
4	$ZnCl_2$[a]	DCE	55
5	Et_2Zn[c]	CH_2Cl_2	<5
6	Et_2Zn[d]	CH_2Cl_2/Toluene	68
7	Me_2Zn[d]	CH_2Cl_2/Toluene	69

[a]1 M solution in Et_2O. [b]Neat salt was added. [c]1 M solution in CH_2Cl_2. [d]1 M solution in toluene.

Next, we investigated the scope of the intramolecular reaction (Table 4). Both tetrahydrofuran and tetrahydropyran products were obtained in moderate to good yields as single diastereomers, as determined by ^1H NMR analysis. The conversion of substrate **22** was good, but met with difficulties in isolating the free amine product. Accordingly, treatment of the crude reaction mixture with Boc_2O and Et_3N for 2 h at room temperature improved the reaction workup and provided compound **23** in 60% yield.

Table 4: Cyclative reductive couplings.[a]

Entry	Substrate	Product	Yield
1	 **18**	 **19**	69%[b]
2	 **20**	 **21**	53%[c]
3	 **22**	 **23**	60%[b,d]

[a]All reactions were carried out by hydrozirconation of a mixture of allene (1.4 equiv) and nitrile (1 equiv) in CH_2Cl_2 at −78 °C, followed by a solvent switch to toluene and addition of 1 M $ZnMe_2$ (entries 1 and 2) or 1 M $ZnEt_2$ (entry 3) in toluene (1.4 equiv) at −78 °C. [b]Relative configuration was assigned in analogy to **21**. [c]Relative configuration was determined by coupling constant analysis (Figure 1). [d]Compound **23** was isolated as a Boc-protected amine upon treatment of the crude reaction mixture with Boc_2O (1 equiv) and Et_3N (6 equiv) in THF/CH_2Cl_2.

In order to determine the relative configuration of pyran **21**, the amine was protected as the *t*-butyl carbamate (Supporting Information File 1). Signals for both hydrogen atoms H_b and H_c were doublets of doublets with one large and one small coupling constant. The large coupling constant, J_{bc} = 11.4 Hz, corresponds to the geminal coupling between H_b and H_c, while

the small coupling constants, J_{ab} = 1.8 Hz and J_{ac} = 2.7 Hz, correspond to the coupling between $H_{b/c}$ and H_a. This analysis implies that hydrogen atom H_a is in the equatorial position, placing the electronegative carbamate substituent and the C–O bond in the tetrahydropyran ring into a gauche orientation (Figure 1).

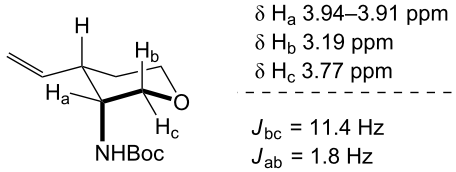
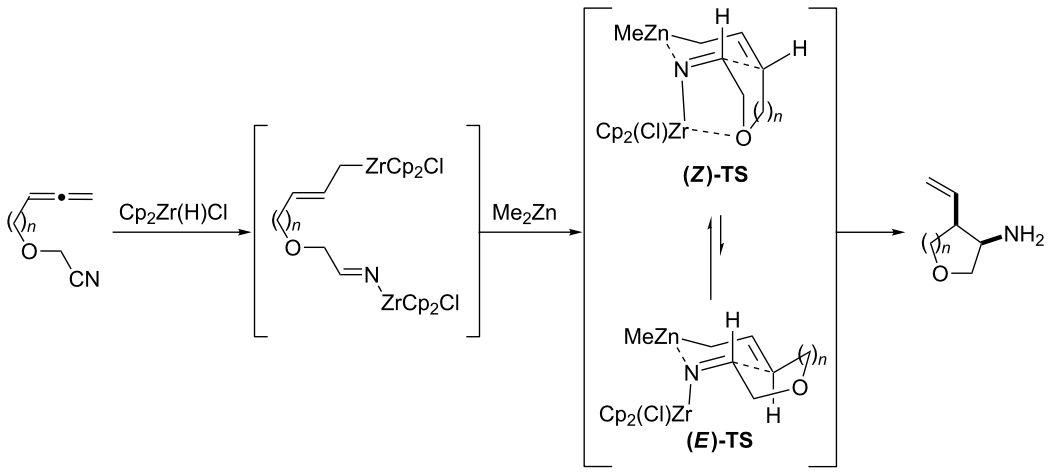


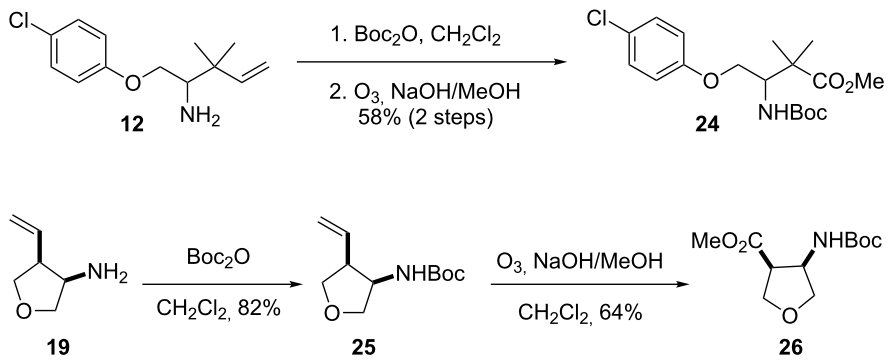
Figure 1: Coupling constant analysis of the Boc-protected aminopyran ring in **21**.

We propose a chelated transition state for the formation of **19**, **21**, and **23** (Scheme 3). After the initial hydrozirconation and transmetallation with dimethylzinc, both (*E*)- and (*Z*)-allylzinc species can exist in the solution. The chelation of the zirconocene to the ether oxygen and the imine nitrogen leads to a preference for the **(*Z*)-TS** species, paving the way for the formation of the observed *cis*-product.

To further elaborate on the utility of this methodology, we demonstrated that the homoallylic amine products could be readily converted to synthetically useful building blocks, such as β-amino acids (Scheme 4). *N*-Boc-protection of the primary amine **12** followed by ozonolysis under Marshall's conditions [40] yielded the β-amino acid derivative **24**. The cyclic amine **19** was subjected to analogous reaction conditions to form the tetrahydrofuran β-amino acid derivative **26**.



Scheme 3: Proposed chelated transition state model.



Scheme 4: Conversion of homoallylic amines to β-amino acid derivatives.

Conclusion

We have developed a method for the one-pot simultaneous hydrozirconation of allenes and nitriles to yield allylic zirconocenes and *N*-zirconoimines, respectively. These intermediates can be transmetalated in situ with dimethylzinc or zinc chloride, which facilities the cross-coupling process to give *N*-unprotected homoallylic amines after aqueous workup. All products were isolated as single regio- and diastereoisomers, and the regioselectivity of the allylation step was shown to depend on the allene substitution. The intramolecular variant of this reaction was used to prepare 3-aminotetrahydrofurans and 3-aminotetrahydropyrans, and these addition products can subsequently be transformed into synthetically valuable β-amino acid building blocks.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization details of synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-94-S1.pdf]

Acknowledgements

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Toward an integrated route to the vernonia allenes and related sesquiterpenoids

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Letter

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Abstract

The synthesis of a model endocyclic allene related to the vernonia allenes is described. Fragmentation of a suitable decalin derivative gave the simplified germacrane scaffold. Computational analysis of this and related substrates provides insight into the stereoelectronic requirements of C–C fragmentation. The overall strategy to access these and other sesquiterpenes and the key steps in the present sequence are also discussed.

Introduction

Well over 150 allene-containing natural products are known [1-5]. Among these, intriguing complex structures were assigned by Bohlmann and co-workers to isolates from the aerial parts of *Vernonia* species collected mainly from northern Brazil about 30 years ago (**1**–**3**, Figure 1) [6-8]. These bicyclic germacranolides are the only known endocyclic allene-containing natural products. Interestingly, no synthetic studies of these complex natural products have been reported, perhaps in part due to the limited number of routes for cyclic allene construction that are sufficiently mild to effect allene formation in complex settings [9-16].

Our interest in the vernonia allenes was motivated in part by a desire to identify, and to simplify access to, useful bioactive compounds with these sequiterpenoid structures, examples of which are given in Figure 1 (**4**–**12**) [17-23]. Although many of these isolates have not been characterized with regard to their biological function, there is a rich variety of germacranes from terrestrial plants, algae, and insect pheromones that purportedly have anticancer, antifungal, and antibiotic activity, among others. For example, parthenolide (**6**) has anti-inflammatory and anti-hyperalgesic effects and induces apoptosis of human acute myelogenous leukemia stem and progenitor cells [24]; eupaheliangolide A (**7**) is cytotoxic to human oral epidermoid (KB), cervical epitheloid (Hela), and liver (hepa59T/VGH) carcinoma cells [21]; sinugibberodiol (**10**) exhibits beneficial multidrug resistance properties in mammalian tumor cells [25]; eleganolactone B (**11**) inhibits the proliferation of the HL-60

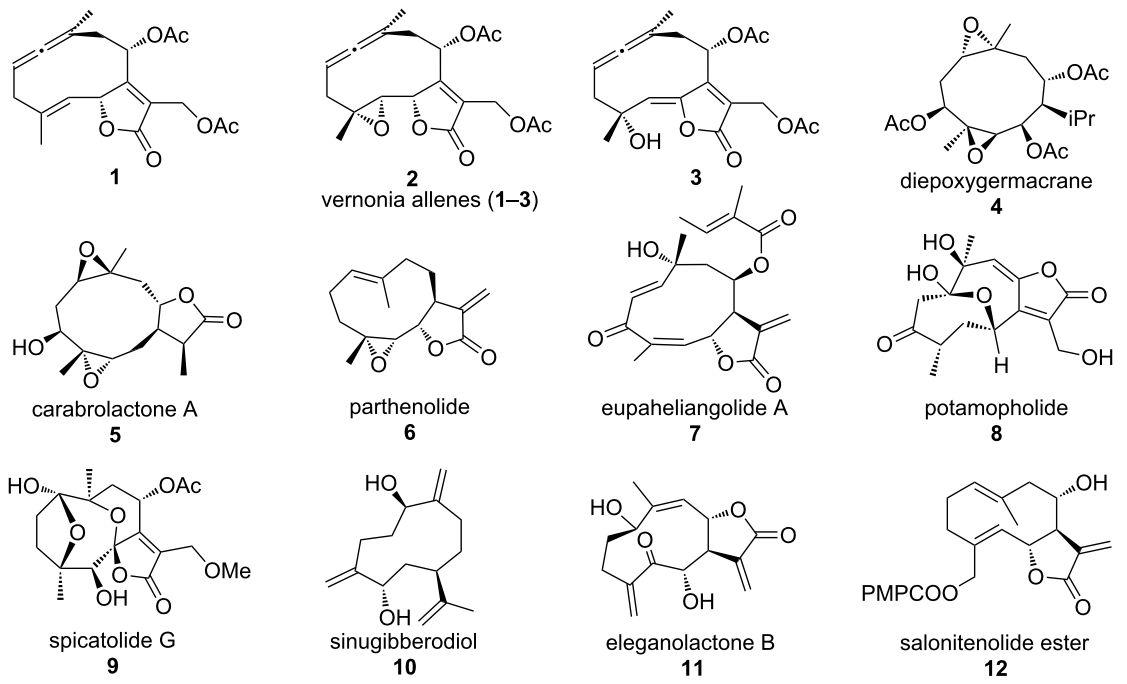


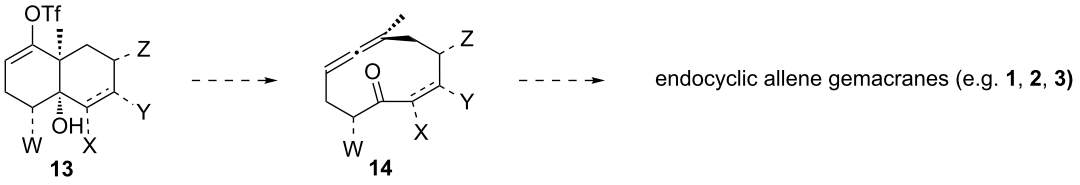
Figure 1: Known natural endocyclic allenes and related germacranes.

human promyelocytic leukemia cell line in a dose-dependent manner [26], and ester derivatives of salonitenolide **12** show promising antibacterial activity [27].

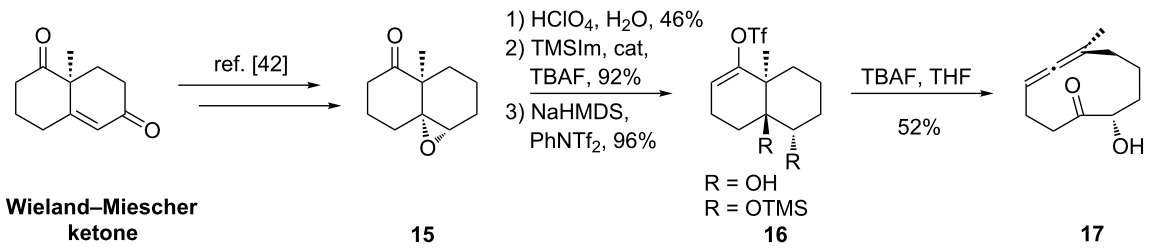
We have initiated a study that aims to integrate the chemical syntheses of compounds in this structure space into a single, late-stage-divergent, route [28]. A pluripotent route that would enable direct access to a broad range of these targets would be useful and would offer advantages over single-target routes, especially in terms of overall step economy. Given the difficulties associated with the stereoselective preparation of endocyclic allenes, and the fact that such structures are largely unexplored, we focused on the vernonia allenes. Moreover, we expected that such allenes contain the coded reactivity to access many sesquiterpenoid variants, especially in light of new methods of transforming allenes to diverse motifs [29-37]. Herein we report our efforts toward this goal with a short synthesis of a model 10-membered endocyclic allene of type **14** (Scheme 1).

Results and Discussion

Advanced intermediates with a high degree of unsaturation have greater potential use in an integrated routing strategy than more highly oxidized products, since not all targets in the group of compounds of interest share identical oxidation states or patterns. Recently, we reported the synthesis of 9- and 10-membered cyclopolyenes [28,38], including a new stereospecific allene synthesis via C–C fragmentation. This transformation appears well-suited for access to the vernonia targets and related compounds [15]. The method relies on suitably functionalized vinyl triflates [39-41]. In general, C–C fragmentation reactions appear to be sensitive to the precise structure of the cyclic system involved, and small, apparently minor, structural changes may severely retard the reaction [38]. For



Scheme 1: C–C fragmentation strategy to yield endocyclic allenes.



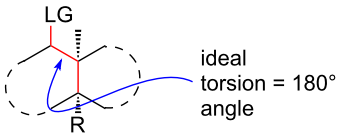
Scheme 2: Endocyclic allene **17**.

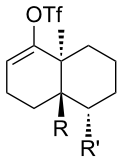
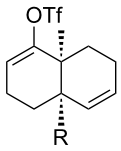
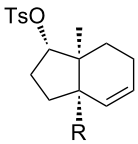
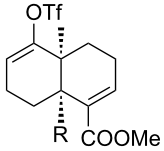
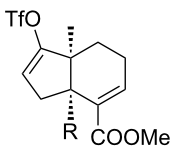
example, in our original disclosure, endocyclic allene **17** was formed from *trans*-decalin derivative **16** by way of the known compound **15** (Scheme 2) [42]. However, the vinyl triflate (**16**, R = OH) resisted fragmentation under standard basic conditions, whereas, the silyl ether (**16**, R = OTMS) underwent smooth fragmentation upon exposure to TBAF.

The ideal orientation for the two bonds that cleave in a C–C fragmentation reaction is antiperiplanar [43-46]. However, to our knowledge, the minimum torsion angle required for fragmentation is not known, and no computational mechanistic study on these reactions has appeared as a guide in this regard. Admittedly, there are distinct differences between fragmentation and substitution; nevertheless, by analogy to S_N2 reactions, C–C fragmentation substrates with angles significantly less than 180° may fail due to inadequate relative orientation [47,48]. For our purposes, we aimed to identify a scaffold that would readily adopt the ideal, or near-ideal, stereoelectronic arrangement necessary for C–C fragmentation, and yet, would have the potential to accept further structural modification without intrinsic change, should that become necessary or desirable.

Table 1 summarizes the ground state computational modeling of several C–C fragmentation substrates. The Gaussian suite of programs, with the B3LYP functional and the 6-31G(d,p) basis set, was used to generate these data [49-60]. The hydroxy derivatives (R/R' = OH) and the corresponding alkoxides in vacuum were taken together to approximate the torsion angle of the anion fragmentation precursors. The *trans*-decalin system of entry 1 (c.f. Scheme 2) is highly constrained. The relevant torsion angles are around 155°, thus deviate significantly from 180°. This is true for the mono anions **II** and **III** as well as the diol **I**. Interestingly however, the dianion does not represent a stable structure, and instead gives the endocyclic allene via fragmentation, as observed experimentally. Entry 2 shows a *cis*-decalin system. Low energy conformers were identified for these species [59]. The lowest energy conformer gave the greatest torsion angles (~175°) for both the alcohol **V** and the alkoxide **VI**, and these approach 180°. For comparison purposes, the *cis*-hydrindane derivative in entry 3 was also studied [38]. Analogous to entry 2, this system contains an unsaturated site adjacent to the hydroxy/alkoxide. The torsion angles of the scissile bonds for this entry are approximately 163°. Importantly, this compound is known to undergo base-

Table 1: Computed torsion angles for potential C–C fragmentation substrates.[a]



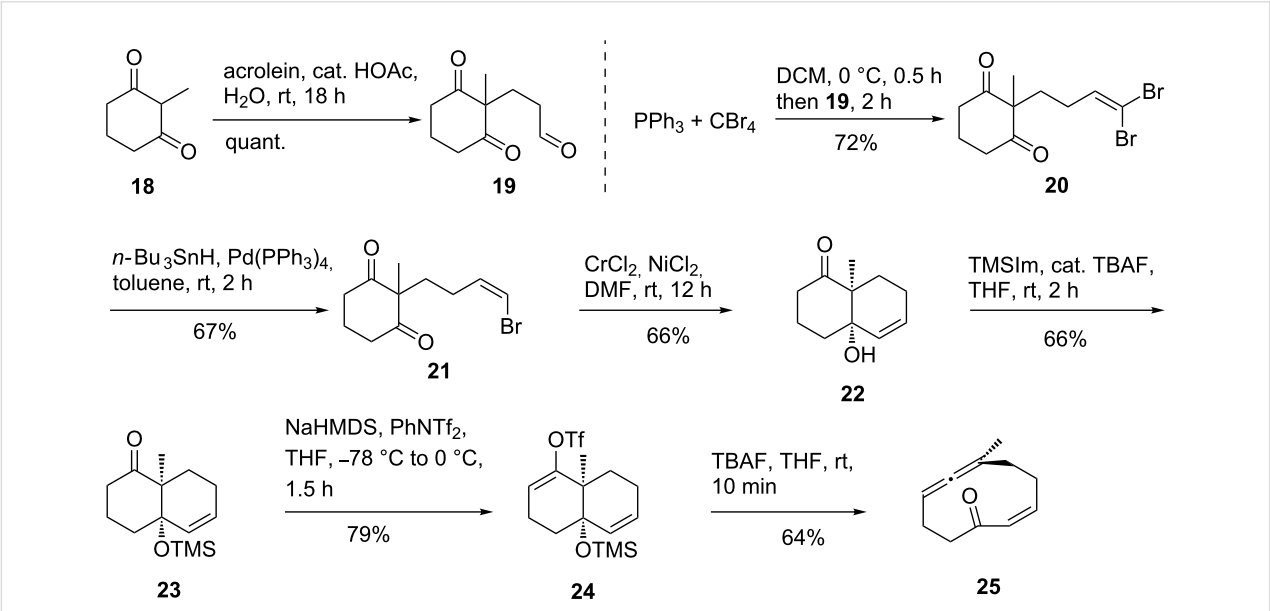
entry	Substrate	R (R')	torsion angle
1		**I**: OH (OH) **II**: OH (O^-) **III**: O^- (OH) **IV**: O^- (O^-)	153° 155° 156° see text
2		**V**: OH **VI**: O^-	175° 176°
3		**VII**: OH **VIII**: O^-	164° 162°
4		**IX**: OH **X**: O^-	174° 177°
5		**XI**: OH **XII**: O^-	171° 170°

[a]DFT: B3LYP functional, 6-31G(d,p) basis set.

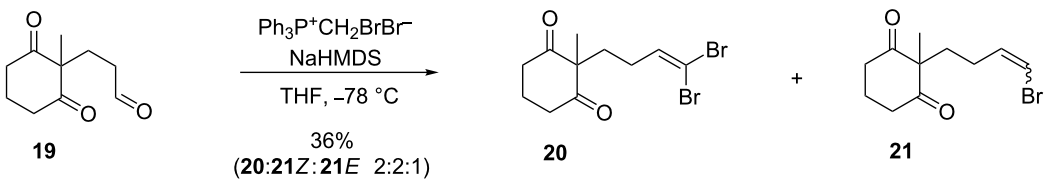
induced fragmentation to give the (*E*)-alkene in excellent yield [61]. Among the substituted variants we considered, we were intrigued by the *cis*-decalin derivative of entry 4. The ester functionality was taken as a prototype for substitution at this position and represents the potential for both steric and electronic effects. In this case, although both compounds exhibit similar torsion angles (~175°), there appears to be a significant difference between the orientation of the ester relative to the adjacent C–C double bond. For the neutral (R = OH) compound, the ester is coplanar with the double bond, whereas the ester is twisted out of planarity for the alkoxide (R = O^-). This appears to be an electrostatic influence. The behavior noted in entry 4 was not unique to the *cis*-decalin system and the analogous *cis*-hydrindane exhibits similar behavior (entry 5): The ester group of the hydroxy entry 5 is coplanar with the alkene, whereas the ester is twisted out of planarity for the alkoxide (R = O^-) [62].

In light of the above data, we targeted compound **24** (c.f. **14**, Scheme 1) to extend the C–C fragmentation to *cis*-decalins and to provide an important model for our synthetic studies. This substrate should be able to adopt conformers with the proper orientation for fragmentation and may well tolerate substitution. Given the uncertainties associated with the computational analysis and the precise requirements for fragmentation, it was not clear that even this model compound would undergo C–C fragmentation to give the corresponding endocyclic allene. Consequently, we aimed to prepare **24** by a direct and modular route.

Scheme 3 depicts a concise route to **24** and **25**. Beginning with the commercially available diketone **18**, acid promoted Michael addition with acrolein gave aldehyde **19**. A two step procedure, via **20**, was employed to obtain the (*Z*)-bromoolefin **21**. Initially, we examined the direct formation of **21** via bromomethyltriphenylphosphonium bromide (Scheme 4). This reaction was inefficient and gave both the (*E*)- and (*Z*)-bromoolefins as well as dibromoolefin **20**. Bromo group scrambling under basic Wittig reaction conditions is known [63], and the usual procedure for Wittig reagent formation with slow addition of **19** (1 h) gave **21** with the desired olefin geometry but with low selectivity and yield (see below). Rapid addition of **19**



Scheme 3: Preparation of endocyclic allene **25**.



Scheme 4: Bromo-olefination products from diketone aldehyde **19**.

(1 min), gave the desired product in 26% yield. The use of HMPA and/or iodomethyltriphenylphosphorane [64,65] was examined and failed to improve the reaction profile, as did varying the ratio of Wittig reagent relative to aldehyde (1–3 equiv), solvent (THF and toluene), and aldehyde concentration (0.035–0.09 M). The yield of the reaction was low under all the conditions examined (13–26%) [66]. The known behavior of bromomethyltriphenylphosphonium bromide under these strongly basic conditions, and the poor solubility of reactive species in THF, account for these results [63].

Alternatively, the *Z*-vinyl bromide **21** was readily obtained via dibromo-olefination of the aldehyde followed by selective removal of the (*E*)-bromide with *n*-Bu_3SnH and catalytic Pd(0) (**19**→**21**, Scheme 3). A simple sequence was utilized to furnish allene precursor **24**: Thus **21** was converted to bicycle **22** under Nozaki–Hiyama–Kishi conditions [67,68], followed by silyl ether formation (→**23**) [69] and triflation to produce the desired decalin **24**. There is little precedent for Nozaki–Hiyama–Kishi addition to ketones [67,68], but the reaction proceeded without problems in serviceable yield. Brief exposure of **24** to anhydrous fluoride conditions effected clean C–C fragmentation to give the functionalized 10-membered endocyclic allene **25** in good yield.

Conclusion

These studies demonstrate a concise modular preparation of endocyclic allene **25** under mild reaction conditions. This seven step route gives access to a model system for a synthetic strategy that aims to access the structure space represented by a variety of germacrane natural products, including the vernonia isolates. Computational studies suggest that the diene scaffold may be suitable for further structural modification and adopt the stereoelectronic arrangement necessary for C–C fragmentation. Further studies will be reported in due course.

Experimental

Preparation of endocyclic allene **25**: In a 25 mL flame-dried flask, vinyl triflate **24** (157 mg, 0.408 mmol, azeotroped with toluene) was suspended in dry THF (13 mL). TBAF (0.4 mL, 0.4 mmol, 1.0 M in THF, stored over molecular sieves for >24 h) was added dropwise. After 10 min, the reaction was quenched by satd. NH_4Cl (aq) (15 mL) and partitioned against and washed with ethyl acetate (3 × 15 mL). The organic fractions were combined, washed with satd. NaCl (aq) (15 mL), dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by FCC (5% ethyl acetate/hexane) to give **25** (43 mg, 64%) as a colorless oil. R_f 0.08 (1% ethyl acetate/hexane); IR (neat) ν_{max}: 2975, 2903, 2851, 1964, 1693, 1440, 1400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (dd, *J* = 11.9, 2.2 Hz, 1H), 5.70 (td, *J* = 11.7, 4.2 Hz, 1H), 4.95–4.85 (m, 1H), 2.70–2.57 (m, 2H), 2.42–2.15 (m, 5H), 1.76 (ddt, *J* = 14.7, 12.1, 2.2 Hz, 1H), 1.63 (d, *J* = 2.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.90, 202.06, 140.21, 132.05, 97.82, 89.33, 41.94, 32.71, 26.71, 26.05, 19.93; ESIMS *m*/*z*: $[M + Na]^+$calcd for $C_{11}H_{14}NaO$, 185.1; found, 185.0.

Supporting Information

Supporting Information File 1

General experimental methods and analytical data, ^1H and ^{13}C NMR spectra of compounds **18**–**25** and computed structural coordinates for entries 1–5 in Table 1.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-104-S1.pdf]

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