

Expanding the chemical diversity of spirooxindoles via alkylative pyridine dearomatization

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

Letter

Open Access

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

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

* Corresponding author

Keywords:
chemical diversity; 1,3-dicarbonyl compounds; Diels–Alder reaction; molecular diversity; pyridine dearomatization; spirooxindole

Beilstein J. Org. Chem. **2012**, *8*, 986–993.
doi:10.3762/bjoc.8.111

Received: 18 March 2012
Accepted: 31 May 2012
Published: 02 July 2012

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

Guest Editor: J. A. Porco Jr.

© 2012 Dai et al; licensee Beilstein-Institut.
License and terms: see end of document.

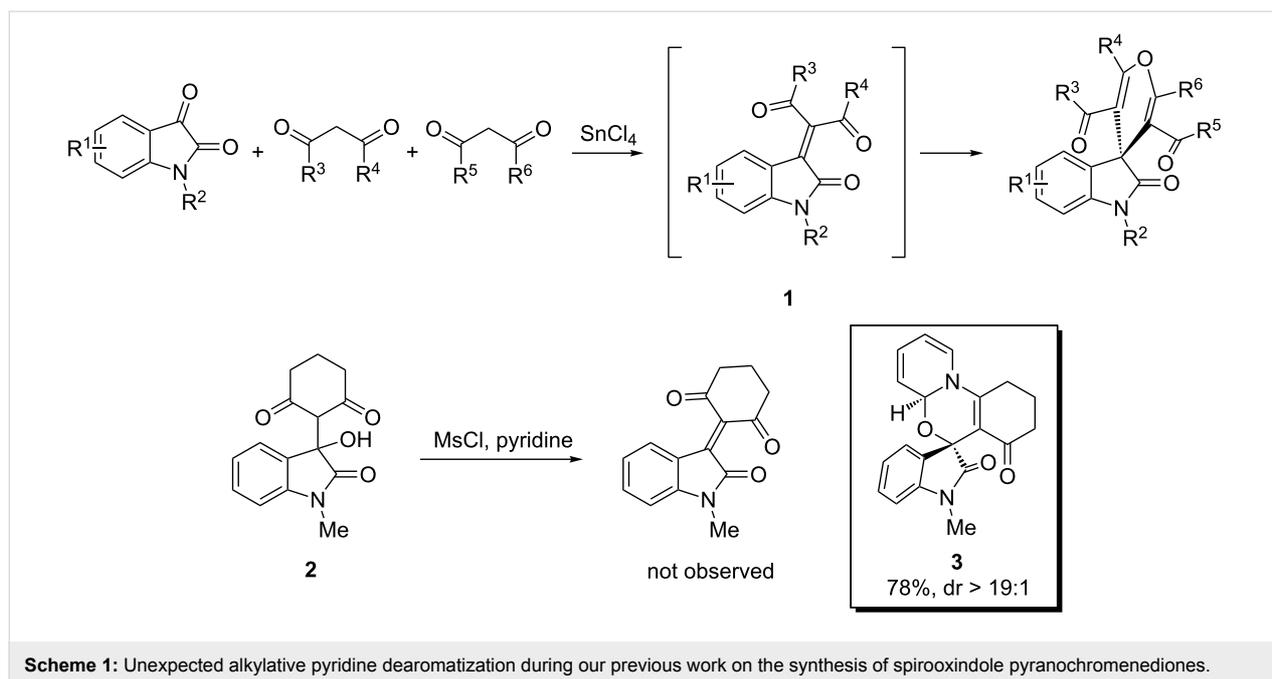
Abstract

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

Introduction

The spirooxindole is a common structural motif found in a variety of complex alkaloids [1]. Many compounds that possess a spirooxindole moiety exhibit significant biological activity, thus exemplifying their role in drug development [2-8]. Moreover, the challenging molecular architecture of spirooxindoles is appealing to chemists because it evokes novel synthetic strategies that address configurational demands and provides platforms for further reaction development [9-11]. To our knowledge, most studies of these types of molecules focus on spirooxindoles bearing a pyrrolidine ring at the 3-position of the oxindole core, while few reports expand to formulate the syntheses of other spiro rings. As part of our ongoing reaction-

screening objective [12,13], we previously reported a Lewis acid catalyzed, three-component synthesis of spirooxindole pyranochromenedione derivatives using isatin and two 1,3-dicarbonyl compounds (Scheme 1) [14]. Mechanistically, we believed this reaction to proceed through an intermediate isatylidene **1** [15-17]. As a means to support our mechanistic hypothesis, we attempted to prepare and isolate the isatylidene; however, our attempts were unsuccessful. Interestingly, treatment of **2** with methanesulfonyl chloride (MsCl) in pyridine provided the dearomatized alkylation product **3** in 78% yield. In the context of developing novel and practical methods for the preparation of diverse heterocyclic compounds, herein, we



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

Results and Discussion

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

Based on preliminary results, we commenced with the reaction of *N*-substituted isatins **4** and 1,3-dicarbonyl compounds **5** in pyridine. After addition of the reagents, the mixture was

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

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

entry ^a	R ¹	R ²	5	product	yield (%) ^b
1	H	H			31

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

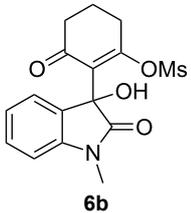
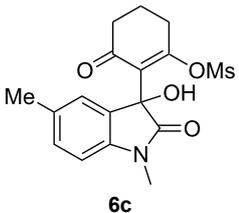
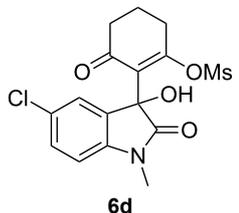
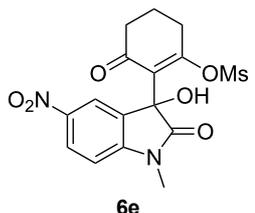
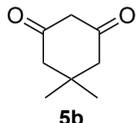
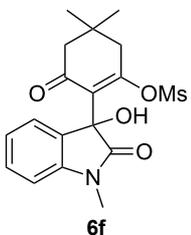
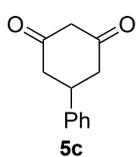
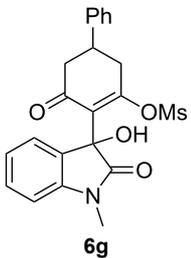
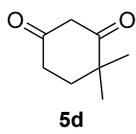
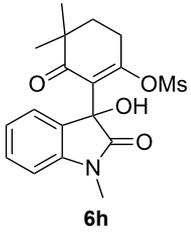
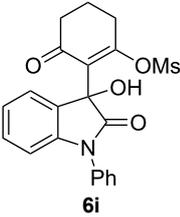
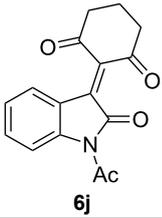
2	Me	H	5a	 6b	80
3	Me	5-Me	5a	 6c	57
4	Me	5-Cl	5a	 6d	84
5	Me	5-NO ₂	5a	 6e	89
6	Me	H	 5b	 6f	87
7	Me	H	 5c	 6g	61
8	Me	H	 5d	 6h	71

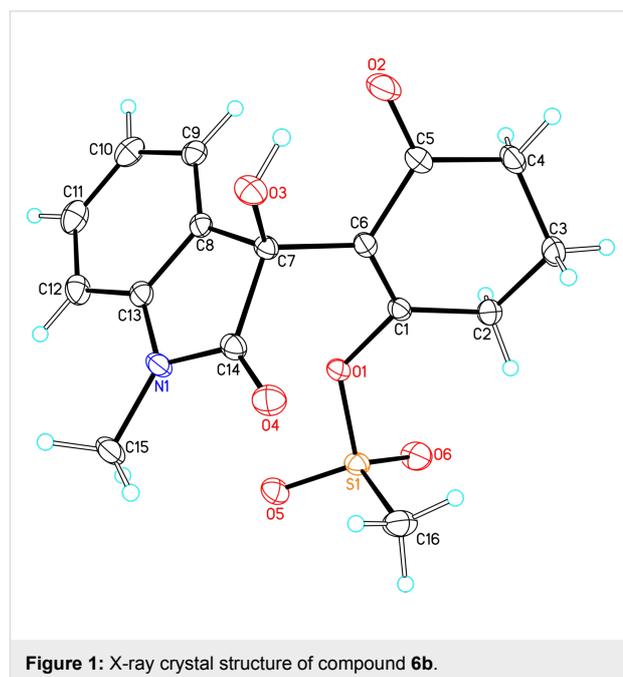
Table 1: Reaction of isatins **4** and 1,3-dicarbonyl compounds **5** in pyridine. (continued)

9	Ph	H	5a	 6i	73
10 ^c	Ac	H	5a	 6j	74

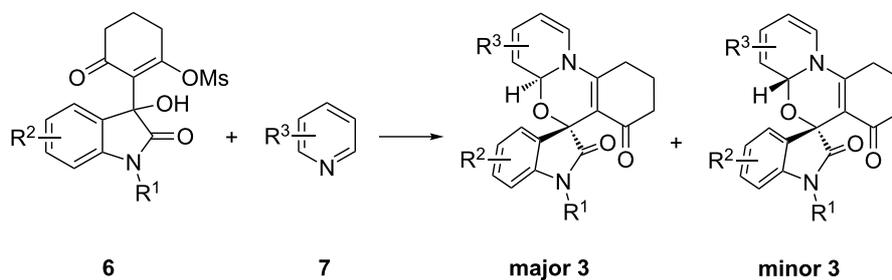
^aReactions were carried out on a 10 mmol scale in pyridine (8.0 mL) with 1.0 equiv of isatins **4** and 1,3-dicarbonyl compounds **5** at room temperature for 2 h, followed by the addition of 1.5 equiv of MsCl at 0 °C over 1 h and another 2 h stirring at the same temperature. ^bIsolated yield. ^cThe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

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

Having established a facile route to our desired vinylogous sulfonyl esters **6**, we next examined their reactivity towards alkylative pyridine dearomatization reactions (Table 2). During optimization studies, we discovered that the reaction performed



best at 45 °C using pyridine as the solvent. The substituent groups on the isatin moiety did not have a great effect on the reactivity of compounds **6**. Generally, the reaction was complete in 12 h and provided inseparable diastereoisomers with good to excellent yields (Table 2, entries 1–5). 4-Picoline (**7b**) gave a lower yield after 12 h at 45 °C (Table 2, entry 6). 4-Methoxypyridine (**7c**) provided the desired product **3g** in 78% isolated yield in only 6 h at room temperature (Table 2, entry 7). Isoquinoline (**7d**) and 4-acetylpyridine (**7e**) also underwent the reaction to provide the desired products in moderate yields

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

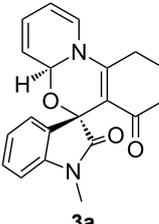
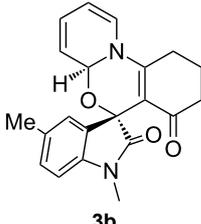
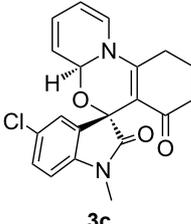
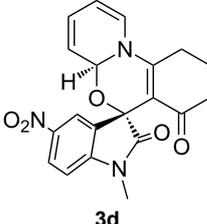
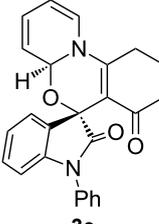
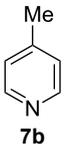
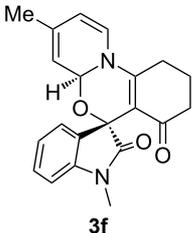
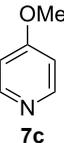
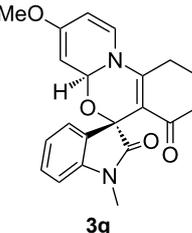
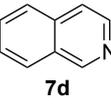
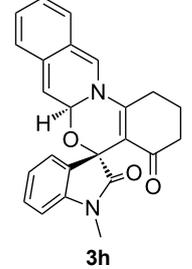
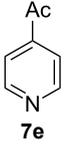
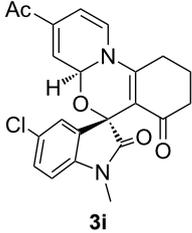
entry ^a	6	7	T (°C)	h	product 3	dr ^b	yield (%) ^c
1	6b	 7a	45	12	 3a	5:1	90
2	6c	7a	45	12	 3b	9:1	83
3	6d	7a	45	12	 3c	7:1	90
4	6e	7a	45	12	 3d	5:1	91
5	6i	7a	45	12	 3e	5:1	74

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

6	6b		45	12		8:1	48
7	6b		23	6		3:1	78
8	6b		60	18		2:1	65
9	6d		60	18		8:1	67

^aReactions were conducted with vinylogous sulfonyl esters **6** (1.0 mmol) and pyridine derivatives **7** (1.0 mL) at 23–60 °C. Reaction time varied from 6–18 h. ^bDetermined by ¹H NMR integration. ^cIsolated yield.

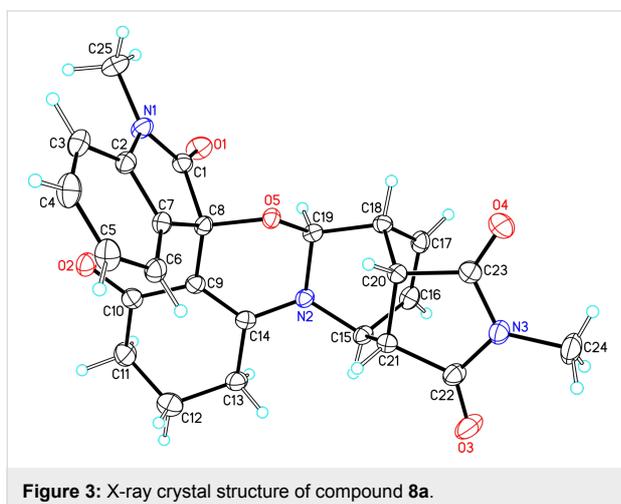
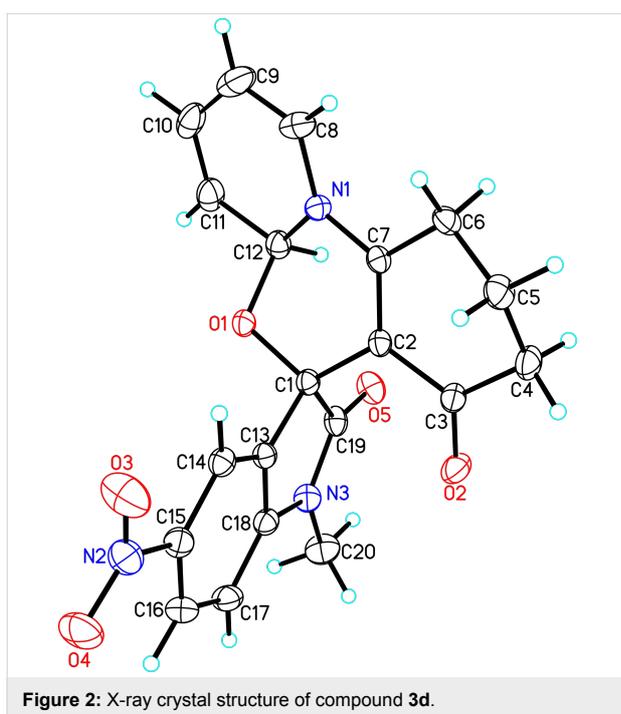
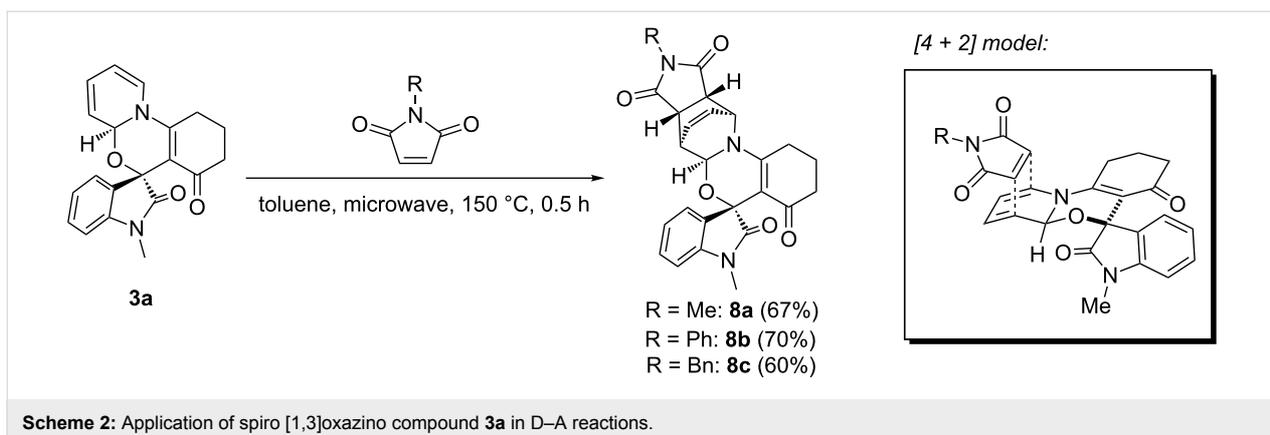
(Table 2, entries 8–9), but required an elevated temperature (60 °C) and a longer reaction time (18 h). On the basis of the results in Table 2, we speculate that the unexpected formation of compound **3** in Scheme 1 was due to the evaporation of solvent after the reaction at elevated temperature (45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

Further plans to expand the molecular diversity of these compounds utilizing available functionalities are currently underway. As an illustrative example, spiro [1,3]oxazino compounds having a diene moiety within their molecular framework are susceptible to Diels–Alder (D–A) reactions [22].

Scheme 2 highlights three examples in which compound **3a** was exposed to *N*-substituted maleimides in toluene at 150 °C under microwave irradiation for 0.5 h, and D–A products **8a–c** were isolated in moderate yields. Finally, the structure of compound **8a** was established by single-crystal X-ray analysis (Figure 3).

Conclusion

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



Supporting Information

Supporting Information File 1

Full experimental details and analytical data and crystallographic information.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-111-S1.pdf>]

Acknowledgements

Financial support for this research from the NIH-NIGMS (P50-GM067041), NSF (CHE-1056568), the Alfred P. Sloan Foundation, Amgen, Boehringer Ingelheim, and Boston University is gratefully acknowledged. C.D. thanks AstraZeneca for a graduate fellowship. NMR (CHE-0619339) and MS (CHE-0443618) facilities at BU are supported by the NSF. The authors are grateful to Professor John Porco (Boston University) for helpful discussions.

References

- Bindra, J. S. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, pp 84–121.
- Onishi, T.; Sebahar, P. R.; Williams, R. M. *Tetrahedron* **2004**, *60*, 9503–9515. doi:10.1016/j.tet.2004.07.047
- Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137. doi:10.1021/ol0351910
- Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667. doi:10.1021/ja001133n
- Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186–3189. doi:10.1002/(SICI)1521-3773(19991102)38:21<3186::AID-ANIE3186>3.0.CO;2-E
- Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155. doi:10.1021/ja983788i
- Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503. doi:10.1021/ja980788+
- Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487. doi:10.1021/ja980786p
- Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *18*, 3003–3025. doi:10.1055/s-0029-1216975

10. Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748–8758. doi:10.1002/anie.200701342
11. Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219. doi:10.1002/ejoc.200300050
12. Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413–1419. doi:10.1021/ja0674744
13. Balthaser, B. R.; Maloney, M. C.; Beeler, A. B.; Porco, J. A., Jr.; Snyder, J. K. *Nat. Chem.* **2011**, *3*, 969–973. doi:10.1038/nchem.1178
14. Liang, B.; Kalidindi, S.; Porco, J. A., Jr.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 572–575. doi:10.1021/ol902764k
15. Yin, X.-G.; Liu, X.-Y.; Hu, Z.-P.; Yan, M. *Org. Biomol. Chem.* **2012**, *10*, 1506–1509. doi:10.1039/C2OB06995D
16. Deng, H.-P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348–3351. doi:10.1021/ol201094f
17. Hari Babu, T.; Joseph, A. A.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 994–996. doi:10.1016/j.tetlet.2009.12.082
18. Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068–4093. doi:10.1002/anie.201006017
19. Nair, V.; Devipriya, S.; Suresh, E. *Tetrahedron* **2008**, *64*, 3567–3577. doi:10.1016/j.tet.2008.01.106
20. Yavari, I.; Mokhtarporiani-Sanandaj, A.; Moradi, L. *Tetrahedron Lett.* **2007**, *48*, 6709–6712. doi:10.1016/j.tetlet.2007.07.135
21. Nair, V.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T.; Devi, B. R.; Menon, R. S.; Rath, N. P.; Srinivas, R. *Synthesis* **2003**, 1895–1902. doi:10.1055/s-2003-41000
22. Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98–122. doi:10.1002/jlac.19284600106

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (<http://www.beilstein-journals.org/bjoc>)

The definitive version of this article is the electronic one which can be found at:
[doi:10.3762/bjoc.8.111](https://doi.org/10.3762/bjoc.8.111)