ORGANIC LETTERS

2013
Vol. 15, No. 22
5858–5861

Iodobenzene-Catalyzed Oxabicyclo[3.2.1]octane and [4.2.1]Nonane Synthesis via Cascade C–O/C–C Formation

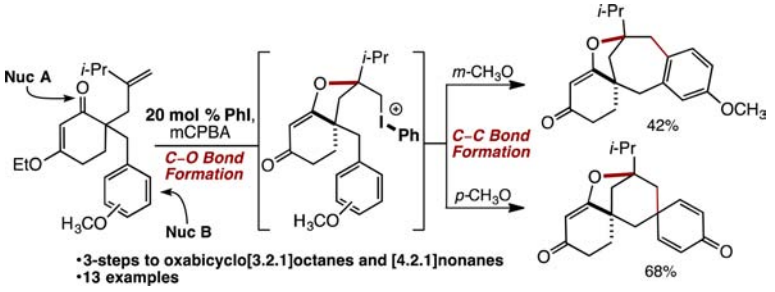
Marsewi Ngatimin,[†] Raphael Frey,[‡] Alison Levens,[†] Yuji Nakano,[†] Marcin Kowalczyk,[†] Kristina Konstas,[‡] Oliver E. Hutt,*[,‡] and David W. Lupton*[,†]

School of Chemistry, Monash University, Clayton 3800, Victoria, Australia, and CSIRO, Clayton South MDC 3169, Victoria, Australia

oliver.hutt@csiro.au; david.lupton@monash.edu

Received October 10, 2013

ABSTRACT



Iodobenzene-catalyzed 1,2-olefin functionalization via C–C and C–O bond formation has been achieved with electron rich aromatic groups and vinylogous esters acting as independent nucleophiles. The reaction provides oxabicyclo[3.2.1]octanes and [4.2.1]nonanes from commercially available 3-alkoxy cycohexen-2-ones in three steps.

The hypervalent iodonium mediated cyclization of heteroatom containing alkenes constitutes a powerful metal-free approach to heterocycles.[1,2] A plausible mechanism[3] for these transformations involves electrophilic activation of the olefin (**1a**, eq 1), followed by nucleophilic addition of the heteroatom providing intermediate **I** that reacts with a second nucleophile, often solvent, to provide heterocycle **2a** (Figure 1).

While intramolecular displacement of the iodonium leaving group within **I** has been shown to provide bicyclic products (i.e., **2b**), to date, this has only been achieved with urea nucleophiles (i.e., **1b**).[4] Furthermore, as a consequence of the bidentate nucleophilicity of the urea this reaction is limited to the formation of ring-fused products (eq 2). We postulated that substrates bearing isolated nucleophilic functionalities (i.e., **3**) should provide access to alternate polycyclic products (i.e., **4**, eq 3). In addition, the modular nature of the nucleophiles should allow the

[†] Monash University.
[‡] CSIRO.

(1) For recent general reviews on hypervalent iodonium chemistry: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (b) Zhdankin, V. V. *ARKIVOC* **2009**, *1*, 1. (c) Brand, J. P.; González, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102. (d) Brown, M.; Farid, U.; Wirth, T. *Synthesis* **2013**, *24*, 424.

(2) Selected examples of cyclizations with oxygen nucleophilies: (a) Boye, A. C.; Meyer, D.; Ingison, C. K.; French, A. N.; Wirth, T. *Org. Lett.* **2003**, *5*, 2157. (b) Serna, S.; Tellitu, I.; Dominguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Lett.* **2003**, *44*, 3483. (c) Vasconcelos, R. S.; Silva, L. F., Jr.; Giannis, A. *J. Org. Chem.* **2011**, *76*, 1499. (d) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353. (e) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053. (f) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, *43*, 1224. (g) Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 1188. (h) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249. (i) Fujita, M.; Yoshida, Y.; Miyata, K.; Wakisaka, A.; Sugimura, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7068. (j) Jang, Y.-B.; Gade, L. H. *J. Am. Chem. Soc.* **2011**, *133*, 3658.

(3) Debate regarding this reaction mechanism remains, particularly as it relates to nitrogen containing compounds. See for example: ref 2g and h.

(4) (a) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 5039. (b) Muniz, K.; Hovelmann, C. H.; Campos-Gomez, E.; Barluenga, J.; Gonzalez, J. M.; Streuff, J.; Nieger, M. *Chem.—Asian J.* **2008**, *3*, 776. (c) Li, H.; Widenhoefer, R. A. *Tetrahedron* **2010**, *66*, 4827. For an enantioselective variant, see: (d) Farid, U.; Wirth, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 3462.

10.1021/ol4029308
Published on Web 11/05/2013

exchange of one nucleophilic component without affecting the other, hence leading to a flexible reaction. To demonstrate these concepts, we recently commenced studies focused on the synthesis of novel bridged oxabicycles. Such materials[5] are well represented in natural products[6] and display significant topological complexity, a property of increasing relevance to fields such as fragment-based drug design.[7] Herein we report the iodobenzene-catalyzed synthesis of oxabicyclo[3.2.1]octanes and [4.2.1]nonanes by cascade 1,2-olefin functionalization (eq 3).

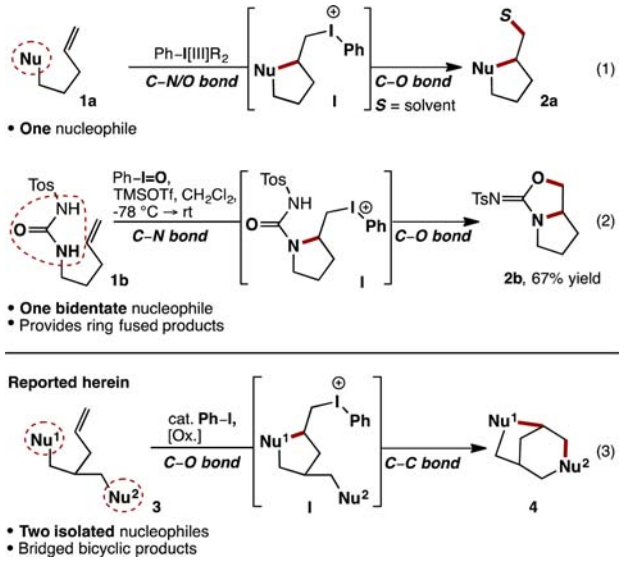
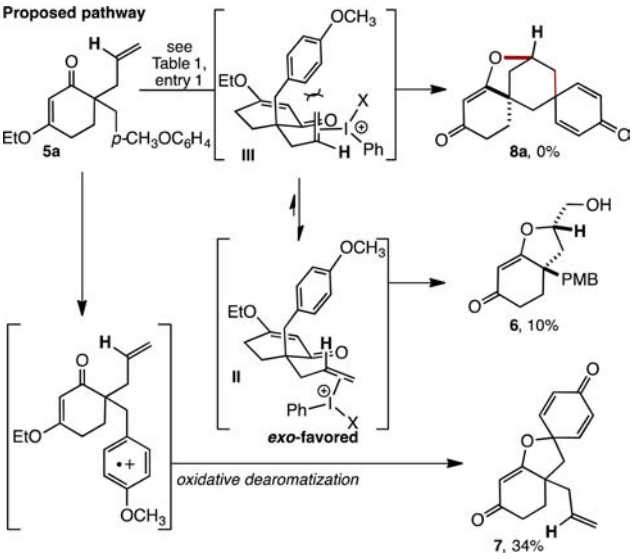


Figure 1. Hypervalent iodonium mediated olefin functionalization.

Olefin functionalization studies commenced with vinylogous ester **5a**, prepared in two steps from commercially available 3-ethoxycyclohexenone.[8,9] This material bears a nucleophilic carbonyl[10] and an electron-rich aromatic for the two cyclization events.[11] When the conversion of **5a** to **8a** was attempted with conditions modified from previous studies[10] the expected product was not observed; instead furans **6** and **7** were isolated (Scheme 1). While the latter arises from direct oxidative dearomatization, formation of the former was rationalized by cyclization with the olefin

Scheme 1



in an *exo* conformation unable to undergo C−C bond formation (i.e., **II**). If this was the case, then favoring conformation **III** should facilitate the desired cyclization. It was postulated that this should be possible by introducing a larger group at the 2-position of the allyl group. To test this hypothesis the cyclization of methallyl **5b** was examined. Gratifyingly, oxabicyclo[3.2.1]octane **8b** now formed in 32% isolated yield (Table 1, entry 1).

Having achieved proof-of-concept, standard reaction optimization was performed. It was found that solvent composition had a significant impact on the reaction, with a 9:1 ratio of HFIP and TFA improving the yield to 77% (Table 1, entry 3). The reaction was moderately sensitive to temperature and concentration, with poorer results obtained at higher temperatures and alternate concentrations (Table 1, entries 4−6). The utility of CH_2Cl_2/TfOH acid mixtures in related transformations has recently been reported.[2j] When TfOH was evaluated as an additive, **8b** failed to form (Table 1, entry 7). However, a HFIP/TfOH mixture gave the expected product in 69% yield (Table 1, entry 8).

Examination of the reaction scope began with vinylogous esters **5c**−**d** and thioester **5e**. While the reaction was insensitive to the type of vinylogous ester (Table 2, entries 1−3), thioester **5e** gave only a trace of oxabicyclo[3.2.1]octane **8b** (Table 2, entry 4), presumably as a consequence of oxidation

(5) For access to related materials using palladium catalysis, see: Matsuura, B. S.; Condie, A. G.; McBee, I. A.; Buff, R. C.; Karahalis, G. J.; Stephenson, C. R. J. *Org. Lett.* **2012**, *13*, 6320 and references cited therein.

(6) For selected examples of bridged bicycle containing natural products, see: For platensimycin: (a) Saleem, M.; Hussain, H.; Ahmed, I.; van Ree, T.; Krohn, K. *Nat. Prod. Rep.* **2011**, *28*, 1534. For futoenone: (b) Ogiso, A.; Kurabayashi, M.; Mishima, H.; Woods, M. C. *Tetrahedron Lett.* **1968**, *9*, 2003. For nidifocene: (c) Waraszkiewicz, S. M.; Erickson, K. L. *Tetrahedron Lett.* **1976**, *17*, 1443.

(7) For a recent review, see: O'Connor, C. J.; Beckmann, H. S. G.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 4444.

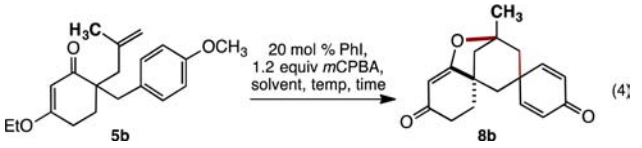
(8) For general procedures for the synthesis of such structures, see: Stork, G.; Danheiser, R. *J. Org. Chem.* **1973**, *38*, 1775.

(9) Studies herein exploit (±)-**5**; for the enantioenriched variant, see: Trost, B. M.; Bream, R. N.; Xi, J. *Angew. Chem., Int. Ed.* **2006**, *118*, 3181.

(10) Ngatimin, M.; Frey, R.; Andrews, C.; Lupton, D. W.; Hutt, O. E. *Chem. Commun.* **2011**, *47*, 11778.

(11) For examples of electron rich aromatic functionality in hypervalent iodonium mediated reactions, see: (a) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797 and references cited therein. (b) Tamura, Y.; Yakura, T.; Haruta, J.-i.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (c) Hata, K.; Hamamoto, H.; Shiozaki, Y.; Kita, Y. *Chem. Commun.* **2005**, *41*, 2465. For an account on phenolic cyclizations, see (d) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, *4*, 467. With olefinic nucleophiles, see: (e) Desjardins, S.; Andrez, J.-C.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406. (f) Zheng, C.; Wang, L.; Li, J.; Wang, L.; Wang, D. Z. *Org. Lett.* **2013**, *15*, 4046 and references cited therein. (g) Andrez, J.-C.; Giroux, M.-A.; Lucien, J.; Canesi, S. *Org. Lett.* **2010**, *12*, 4368. For a novel double annulation, see: (h) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394.

Table 1. Selected Optimization



(4)

entry	temp	solvent	M	time	% yield **8b**[a]
1	−10 °C	1:1 HFIP:TFA	0.1	1 h	32
2	−10 °C	19:1 HFIP:TFA	0.1	1 h	46
3	**−10 °C**	**9:1 HFIP:TFA**	**0.1**	**1 h**	**77**
4	0 °C	9:1 HFIP:TFA	0.1	0.5 h	72
5	−10 °C	9:1 HFIP:TFA	0.2	1 h	53
6	−10 °C	9:1 HFIP:TFA	0.05	4 h	66
7	rt	99:1 CH_2Cl_2:TfOH	″	1 h	–
8	−10 °C	4:1 HFIP:TfOH	″	–	69

[a] Isolated yield following column chromatography.

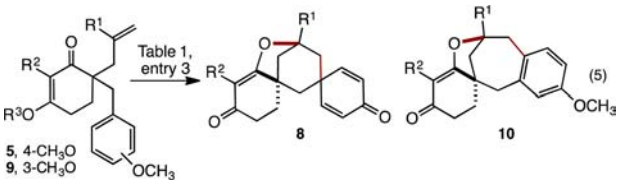
at sulfur. The nature of the olefin was probed initially by reexamining allyl substrate **5a**. Even using the optimized reaction conditions it was only possible to form **8a** in 47% isolated yield, the structure of which was confirmed by single crystal X-ray analysis (Table 2, entry 5).[12] Alkyl substitution about the allyl group was well tolerated with ethyl containing **5f** and isopropyl containing **5g** providing **8f** and **g** in 71 and 68% yield (Table 2, entries 6 and 7). Finally the reaction was sensitive to alkyl substituents in the 2-position of the vinylogous ester with a modest 34% yield of **8h** obtained from **5h** (Table 2, entry 8).

To demonstrate the modularity of the reaction the cascade was examined with the *m*-methoxybenzyl replacing the *p*-methoxy group, thereby potentially providing access to oxabicyclo[4.2.1]nonanes. While ethyl and isopropyl substituted vinylogous esters **9a** and **9b** provided [4.2.1]nonanes **10a** and **10b** (Table 2, entries 9 and 10), the standard conditions gave undesired materials from unsubstituted or methallyl substituted substrates (*vide infra*). Finally, as with oxabicyclo[3.2.1]octane formation the [4.2.1]nonane synthesis was sensitive to substituents in the 2-position, with **10c** formed in 28% yield from **9c** (Table 2, entry 11).

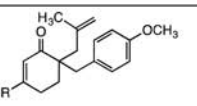
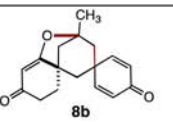
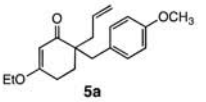
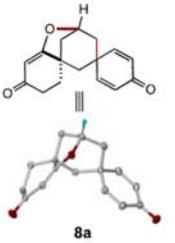
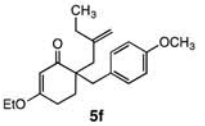
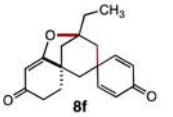
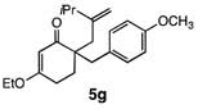
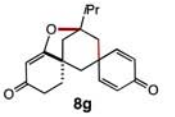
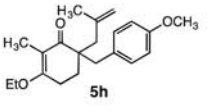
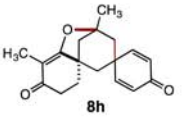
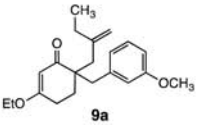
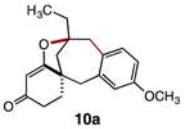
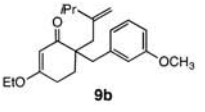
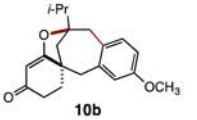
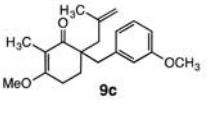
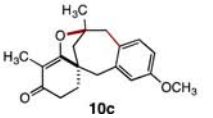
Olefin functionalization with vinylogous ester **9d** under the standard conditions provided pyran **11** (Figure 2).[10] In contrast, with methylallyl substituted **9e** decomposition occurred; however, at 0 °C the dearomatized epoxide **10e** was isolated. Single crystal X-ray analysis was used to provide evidence for this structure.[12] Formation of the ethyl variant of **10e**, namely **10a′**, could also be achieved in comparable yield from vinylogous ester **9a** at 0 °C. While the yields of these products are modest the transformation generates significant molecular complexity, with three new C−O bonds, one new C−C bond, and three rings formed.

(12) CCDC 961140 and 961141 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Synthesis of Oxabicyclo[3.2.1]octanes (**8**) and [4.2.1]Nonane (**10**)



(5)

entry	starting material	product	%yield[a]
			
		8b	
1	**5b**, R = OEt		77
2	**5c**, R = OCH_3		71
3	**5d**, R = O*i*-Pr		70
4	**5e**, R = SEt		*trace*[b]
5			47
	5a	8a	
6			71
	5f	8f	
7			68
	5g	8g	
8			34
	5h	8h	
9			43
	9a	10a	
10			42
	9b	10b	
11			28
	9c	10c	

[a] Isolated yield following column chromatography. [b] From 400 MHz ^{1}H NMR analysis in $CDCl_3$.

Formation of these compounds may occur via the *para*-quinone methide that is subsequently epoxidized.

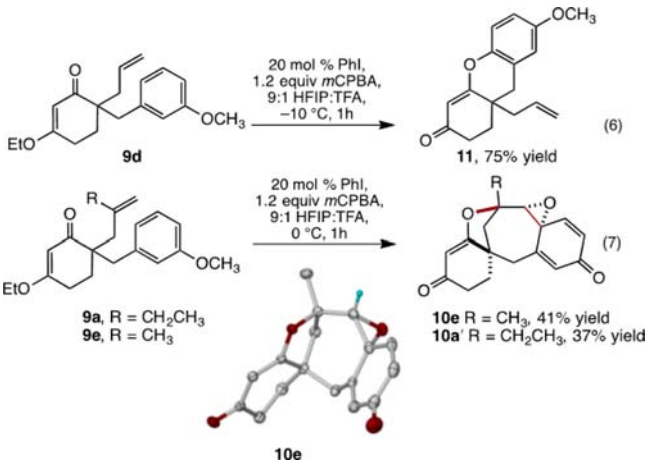


Figure 2. Alternate cyclizations with *m*-methoxybenzyl substrates.

To examine the preferred bridged bicycle formation vinylogous ester **12** was prepared and subjected to the optimized reaction conditions. In this case, a modest yield of the [4.2.1]nonane **10f** was isolated without [3.2.1]octane **8i** (Figure 3, eq 8), indicating that when both cyclization modes are possible, seven membered ring formation is favored. Supporting observations regarding the reaction's sensitivity to the conformation of the allyl group dimedone derived substrate **13** failed to provide the expected cyclization product **14** (eq 9). Unfortunately, the reaction's sensitivity to conformation could not be exploited. For example, using prenyl substrate **15** it was postulated that *endo* cyclization should be favored, providing access to oxabicyclo[3.3.1]nonanes (i.e., **16**). In the event the reaction failed with starting materials decomposed (eq 10).

In summary, a concise method to oxabicyclo[3.2.1]-octanes and [4.2.1]nonanes has been developed via a 1,2-olefin functionalization cascade using two distinct nucleophiles. The strategy is flexible, with the second cyclization event achieved using two alternate electron rich aromatic groups, providing a range of carbocycles. Mechanistically olefin activation followed by nucleophilic attack from

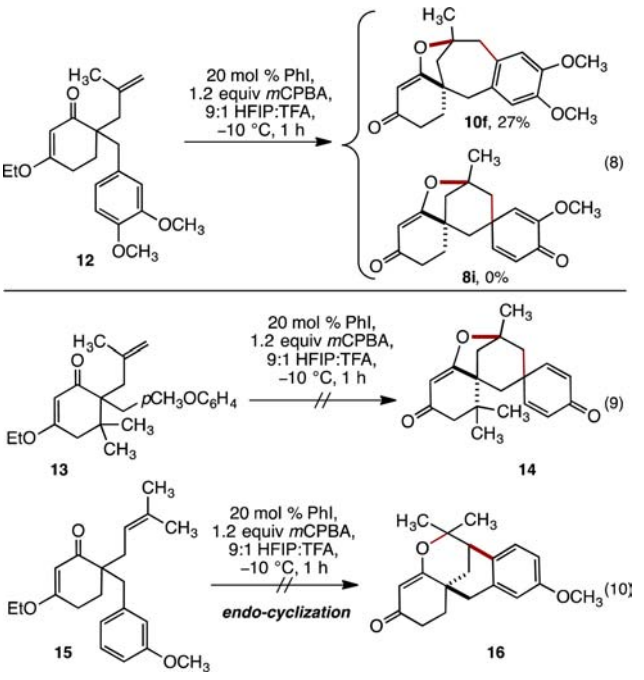


Figure 3. Preliminary mechanistic studies.

the vinylogous ester,[13] then the aromatic group, provides an explanation for the outcome. Although in a number of cases yields are modest, this sequence defines a concise 3-step strategy to complex polycyclic furans. In addition, the transformation is performed under catalytic conditions, enhancing efficiency, and adding to a growing family of aryl iodonium catalyzed reactions.[14] Ongoing studies are focused on the design of new catalysts for these types of transformation and application of the polycyclic furans in diversity, and target oriented synthesis.

Acknowledgment. O.E.H. and D.W.L. dedicate this manuscript to Professor Lewis N. Mander (Australian National University) for his achievements in synthesis. D.W.L. thanks the ARC for financial support through Future Fellowship and Discovery programs. O.E.H. thanks CSIRO Australian Biotechnology Growth Partnerships.

Supporting Information Available. Experimental procedures, characterization of all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) From ^{1}H NMR monitoring experiments there is no evidence for the formation of 1,3-dicarbonyl intermediates.

(14) For early examples of aryl iodide catalysis, see: (a) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 6193. (b) Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244. For reviews on catalytic hypervalent iodine chemistry, see: (c) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (d) Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem.* **2008**, 4229. (e) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (f) Ngatimin, M.; Lupton, D. W. *Aust. J. Chem.* **2009**, *63*, 653. (g) Liang, H.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11849.