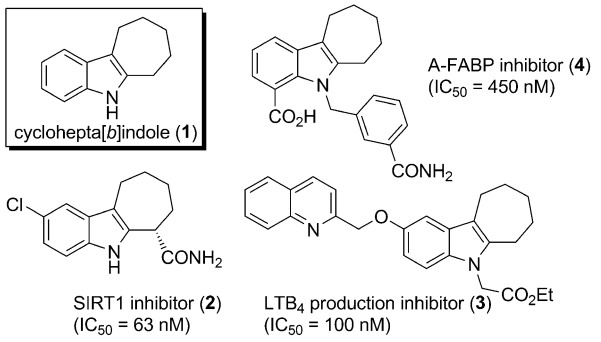
Heterocycles

DOI: 10.1002/ange.201205238

Gallium(III)-Catalyzed Three-Component (4+3) Cycloaddition Reactions**

*Xinping Han, Hui Li, Russell P. Hughes, and Jimmy Wu**

Cyclohepta[*b*]indoles (**1**) exhibit a broad spectrum of biological activity. For instance, compound **2** is a potent inhibitor

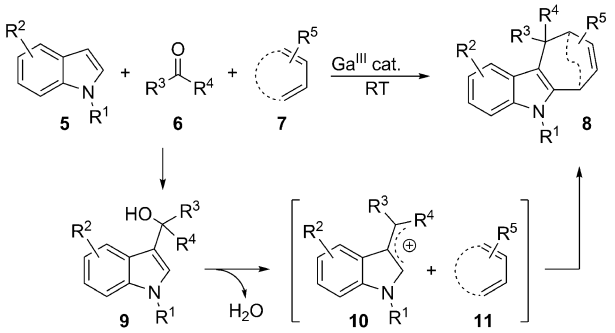


($IC_{50} = 63$ nM) of SIRT1, a member of the class III histone deacetylases (HDAC).[1] SIRT1 can effectively deacetylate p53 and has also been implicated in the regulation of apoptosis. With an IC_{50} of 100 nM, compound **3** inhibits the production of leukotriene B_4 (LTB_4) which is involved in various inflammatory responses.[2] A third molecule, **4**, inhibits the adipocyte fatty-acid binding protein (A-FABP) with an IC_{50} of 450 nM.[3]

The biology of molecules derived from the skeleton of cyclohepta[*b*]indoles, as well as cyclopenta- and cyclohexa-[*b*]indoles, has attracted considerable interest from the pharmaceutical industry as potential therapeutics. In the last decade alone, nearly two dozen patents have been issued on the basis of these structural motifs.[4]

At issue is the synthesis of cyclohepta[*b*]indoles.[3,4] They are most often prepared by means of the Fischer indole synthesis which, while quite useful, possesses certain limitations.[5] These limitations include the need to make the requisite hydrazine and ketone starting materials. Regioselectivity with unsymmetrical ketones can also sometimes be problematic. Finally, electron-withdrawing groups on the aromatic hydrazine can substantially attenuate reactivity. Other methods for preparing cyclohepta[*b*]indoles are known but have not been extensively explored, and are in fact quite different from the work described herein.[6]

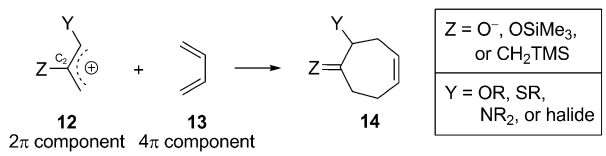
We report herein that gallium(III) salts effectively mediate regio- and diastereoselective three-component (4+3) cycloaddition reactions to furnish cyclohepta[*b*]indoles in high yields (Scheme 1). These reactions occur in a single step



Scheme 1. Proposed three-component (4+3) cycloaddition reaction.

at room temperature without the need for Schlenk techniques, glove boxes, or inert atmosphere. Because each of the three coupling components (i.e., indole, aldehyde/ketone, diene) can be independently varied, this methodology provides rapid access to a diverse library of cyclohepta[*b*]indole derivatives.

The (4+3) cycloaddition reaction has been known for some time.[7–8] A stabilizing group is nearly always present at C2 of the 2π component (Scheme 2). Heteroatom substitution[9] with either sulfur, oxygen, or a halide at the terminal ends of the allylic cation are also known. However, reactions utilizing substrates with nitrogen-based substituents, such as those described in this report, are relatively underexplored. Recently Hsung and co-workers have made considerable progress with respect to this variant.[9a–c] To the best of our knowledge, (4+3) cycloaddition reactions in which the 2π component is derived from indole, one of nature's most ubiquitous heterocycles, have not been described before.



Scheme 2. Prior art. TMS = trimethylsilyl.

[*] X. Han, H. Li, Prof. Dr. R. P. Hughes, Prof. Dr. J. Wu
Department of Chemistry, Dartmouth College
6128 Burke Laboratories, Hanover, NH (USA)
E-mail: jimmy.wu@dartmouth.edu

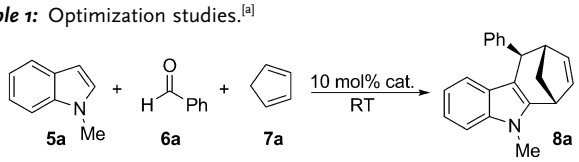
[**] J.W. acknowledges the financial support provided by an NSF CAREER Award (CHE-1052824), Dartmouth College. R.P.H. acknowledges the NSF for generous support through an operating grant which supported the acquisition of computational hardware and software used in this study.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201205238.

We were intrigued by recent reports published by Winne and Pattenden.[10] They treated 2-furfuryl alcohols with a stoichiometric amount of $TiCl_4$ to promote the formation of furfuryl cations for (4+3) cycloaddition reactions. We surmised that nucleophilic addition of the C3 of an indole to either an aldehyde or ketone would furnish the alcohol **9** (Scheme 1). In the presence of an appropriate Lewis acid, water would be ejected to generate the indolyl cation **10** for (4+3) reactions analogous to those reported by Winne et al.[10] Our group has recently been interested in developing gallium(III)-catalyzed processes.[11] Because gallium(III) salts, and in particular $Ga(OTf)_3$,[12] are stable to air and moisture, we hypothesized that they could be used in a catalytic fashion despite the fact that an equivalent of water would be generated in the proposed three-component (4+3) cycloaddition.

As is evident from Table 1, both $Ga(OTf)_3$ and $GaBr_3$ were effective in promoting the desired reaction. $Ga(OTf)_3$ was qualitatively the more reactive catalyst. But because it also generated a by-product (not formed with the use of $GaBr_3$) which was difficult to separate from **8a**, we decided to explore the scope of the transformation using $GaBr_3$. $InBr_3$ was effective as well but several other Lewis acids (entries 6 and 8–10) resulted in either diminished yields or varying amounts of the alcohol **9**.

Table 1: Optimization studies.[a]



Entry	Catalyst	Yield [%]	Comments[e]
1[b]	$Ga(OTf)_3$	91	by-product hard to separate
2	$GaBr_3$	94	
3[c]	$GaBr_3$	84	
4[d]	$GaBr_3$	–	only **9** observed
5	$GaCl_3$	–	only **5a** and **9** observed
6	$In(OTf)_3$	54	substantial decomposition
7	$InBr_3$	92	
8	$InCl_3$	32	mostly **9** observed
9	$Sc(OTf)_3$	14	slow reaction
10	$Cu(OTf)_2$	–	only **9** observed
11	TFA	–	only **9** observed
12	TsOH	52	slow reaction
13[b]	TfOH	83	by-product hard to separate

[a] 10 mol% catalyst, 2 equiv **6a**, 5 equiv **7a**, RT, CH_2Cl_2 (all rxns stopped at 2 h). [b] Reaction time 35 min. [c] Toluene as solvent. [d] THF or Et_2O as solvent. [e] Diastereoselectivities were 3:1 to 5:1 for all reactions in which product was observed (as determined by ^1H NMR spectroscopy). TFA = trifuoroacetic acid, Tf = trifluoromethanesufonyl, Ts = 4-toluenesulfonyl.

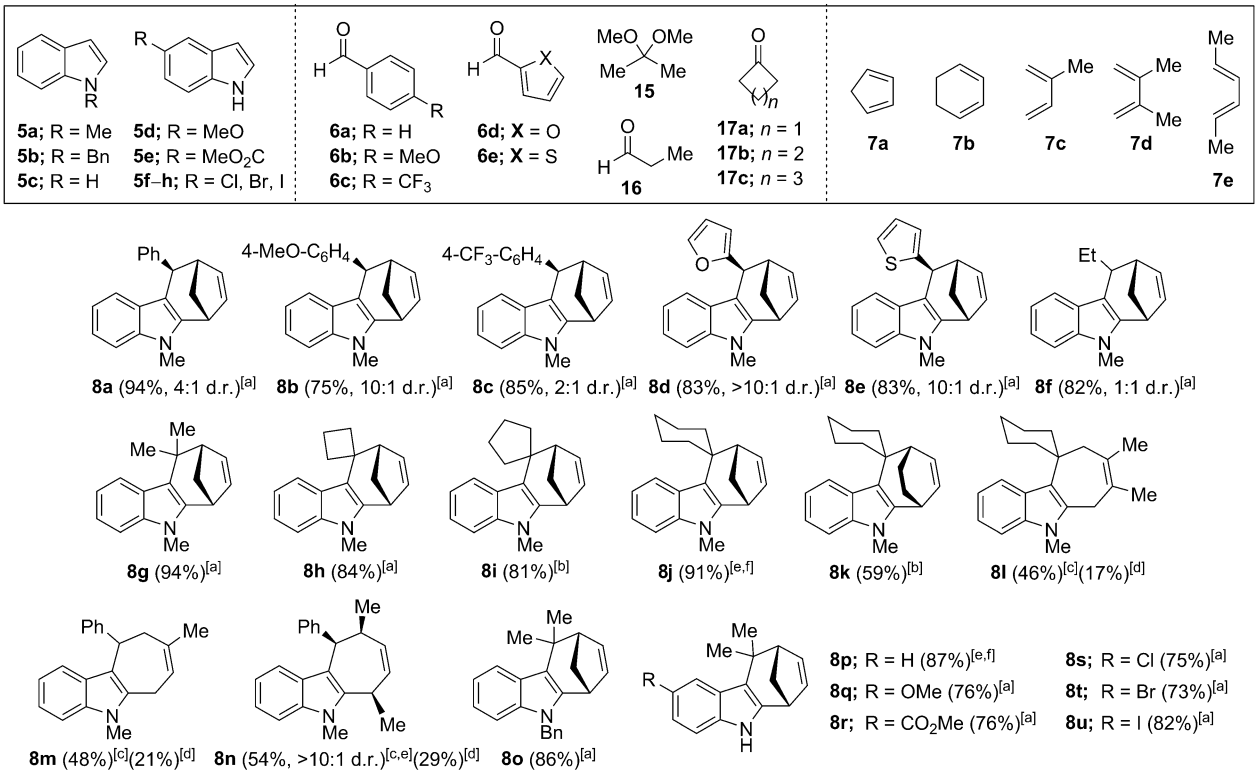
Presently, we cannot conclusively rule out the possibility that small amounts of adventitious Brønsted acid, resulting from hydrolysis of the catalyst, may at least be partially responsible for promoting the reactions in the entries using Lewis acids.[13] However, several reports by Olah, Prakash, and co-workers describing the hydrolytic stability of gallium(III) salts[12] lead us to consider such a scenario to be unlikely.

The scope of the three-component (4+3) reaction appears to be quite broad (Scheme 3). We surveyed a variety of combinations involving the indoles **5a–h**, aldehydes **6a–e** and **16**, ketal **15**, ketones **17a–c**, and dienes **7a–e**. The reaction is tolerant to N–H indoles as well as indoles having an alkyl group on the nitrogen atom. Electron-withdrawing or electron-donating groups on either the indole or carbonyl components are compatible. Electron-rich substrates such as **5d**, **6b**, and **6d**,**e** appear to accelerate the reaction rate. With less reactive substrates the use of $Ga(OTf)_3$ was beneficial for achieving higher yields and shorter reaction times (**8i**, **8k–n**). The presence of halides in **8s–u**, offers a convenient handle for additional elaboration of the indole core through transition metal-catalyzed cross-coupling reactions.

For the products **8a–f**, diastereoselectivities were observed in the range from greater than 10:1 to 1:1. Electron-rich aldehydes appear to provide products with the highest selectivities while electron-poor and linear alkyl substrates exhibited lower levels of selectivity. The use of an unsymmetrical diene, isoprene (**7c**), furnished the desired product **8m** as a single regioisomer. The structures of **8j**, **8n**, and **8p** were confirmed by single-crystal X-ray analysis.

Unfortunately, neither dimethoxymethane nor formaldehyde were suitable substrates. Attempts to extend the diene scope to include pyrrole (and several N-protected derivatives), furan, thiophene, Danishefsky's diene, or Rawal–Kozmin's diene were not successful. What we observed in most cases was the addition of the diene (i.e. formation of a single C–C bond) to the indolyl cation rather than the desired cycloaddition products.

To gain insight into the mechanism of this reaction, DFT calculations were performed using the M06 functional[14] and the 6-311G**++ basis set,[15] as implemented in the Jaguar program.[16] For the reaction of cyclopentadiene (**7a**) with the indolyl cation derived from indole (**5c**) and the ketal **15**, the lowest energy pathway was identified as a two-step process. Rather than a concerted pericyclic reaction, an intermediate is formed by initial C–C bond formation between the terminal carbon atom of the indolyl cation and a terminal diene carbon atom, with subsequent closure to the seven-membered ring. Transition states for both steps were located, and an overall reaction free-energy profile is depicted in Figure 1 (full details are provided in the Supporting Information). A stepwise mechanism is in agreement with what Winne et al. proposed for the related (4+3) reaction of furfuryl cations.[10a] We also explored an alternative pathway in which an initial (4+2) cycloaddition might be followed by ring expansion, by 1,2-migration, to the observed product. No low-energy synchronous (4+2) pathway was located; the formation of the intermediate in Figure 1 is the lowest energy initial step. Closure of the same intermediate to give the formal (4+2) product proceeds via a transition state that is higher in energy



Scheme 3. Scope of the three-component (4+3) reaction. [a] Indole (1 equiv), electrophile (2 equiv), diene (5 equiv), $GaBr_3$ (10 mol%), RT. [b] Indole (1 equiv), electrophile (2 equiv), diene (5 equiv), $Ga(OTf)_3$ (10 mol%), RT. [c] Indole (1 equiv), electrophile (1.1 equiv), diene (5 equiv), $Ga(OTf)_3$ (20 mol%), RT. [d] Yield with 20% TfOH. [e] Structure confirmed by single-crystal X-ray analysis. [f] 2 mmol scale, 5 mol% $GaBr_3$; all else same.

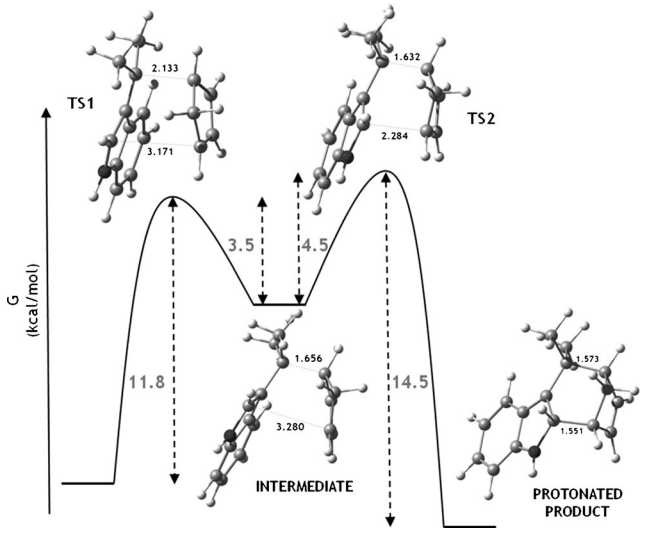


Figure 1. DFT (M06/6-311G**++) calculated free-energy profile for reaction of dimethylindolyl cation with cyclopentadiene to give the protonated precursor to product **8k**.

than TS2, thus illustrating that the stepwise (4+3) pathway is kinetically favored in this system.

In conclusion, we have developed gallium(III)-catalyzed three-component (4+3) cycloaddition reactions which generate cyclohepta[*b*]indole derivatives in a single step. To the best of our knowledge, this is the first instance of a (4+3) cycloaddition in which the 2π component is derived from indole. DFT calculations support a stepwise cyclization process. The versatility of the title reaction provides quick and convenient access to a diverse library of cyclohepta[*b*]-indole analogues.

Received: July 3, 2012
Published online: September 11, 2012

Keywords: annulation · cycloaddition · heterocycles · gallium · multicomponent reactions

[1] A. D. Napper, J. Hixon, T. McDonagh, K. Keavey, J.-F. Pons, J. Barker, W. T. Yau, P. Amouzegh, A. Flegg, E. Hamelin, R. J. Thomas, M. Kates, S. Jones, M. A. Navia, J. O. Saunders, P. S. DiStefano, R. Curtis, *J. Med. Chem.* **2005**, *48*, 8045.

[2] C. Kuehm-Caubère, P. Caubère, B. Jamart-Grégoire, B. Pfeiffer, B. Guardiola-Lemaître, D. Manechez, P. Renard, *Eur. J. Med. Chem.* **1999**, *34*, 51.

[3] T. Barf, F. Lehmann, K. Hammer, S. Haile, E. Axen, C. Medina, J. Uppenberg, S. Svensson, L. Rondahl, T. Lundbäck, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1745.

[4] a) M. R. Schrimpf, C.-H. Lee, T. Li, G. A. Gfesser, K. H. Mortell, R. Faghih, D. L. Nersesian, K. B. Sippy, W. H. Bunnelle, M. Scanio, Shi, L. M. Gopalakrishnan, D. Donnelly-Roberts, M. Hu, WO 2010/036998A2, April 1, **2010**; b) L. Shi, W. H. Bunnelle, M. J. Scanio, M. R. Schrimpf, C.-H. Lee, US 2011/0152306A1, June 23, **2011**; c) K. Gudmundsson, US 2009/0170923A1, July 2, **2009**; d) K. Gudmundsson, US 2009/0156621A1, June 18, **2009**;

e) T. Barf, K. Hammer, M. Luthman, F. Lehmann, R. Ringom, WO 2004/063156A1, July 29, **2004**; f) R. Curtis, P. Distefano, WO 2010/054382A1, May 14, **2010**; g) Z. Sui, X. Zhang, X. Li, WO 2006/047017A1, May 4, **2006**; h) Z. Sui, X. Zhang, X. Li, WO 2006/034090A1, March 30, **2006**; i) G. Balasubramanian, L. Gharat, A. Lakdawala, X. Bedekar, WO 2004/069831A1, Aug. 19, **2004**; j) N. Nishikawa, M. Sugai, K. Aoki, M. Suzuki, A. Ikegawa, EP 1 184 373A1, March 6, **2002**; k) D. T. Hung, A. A. Protter, S. Chakravarty, R. P. Jain, WO 2009/120720A1, Oct. 1, **2009**; l) S. D. Boggs, J. G. Catalano, K. S. Gudmundsson, L. D. Richardson, P. R. Sebahar, WO 2005/023245A1, March 17, **2005**; m) S. D. Boggs, K. S. Gudmundsson, L. D. Richardson, P. R. Sebahar, WO 2004/110999A1, Dec. 23, **2004**; n) K. Hajela, A. K. Jha, M. M. Singh, G. K. Jain, A. K. Balapure, A. Dwivendy, B. Agarwal, P. Murthy, WO 2005/094833A1, Oct. 13, **2005**; o) H. Gao, G. P. Stack, A. L. Sabb, WO 03/091257A1, Nov. 6, **2003**; p) M. A. Wilson, G. S. Welmaker, E. J. Trybulski, R. L. Magolda, US 2008/0027090A1, Jan. 31, **2008**; q) P. R. Guzzo, A. J. Henderson, K. Nacro, M. L. Isherwood, A. Ghosh, K. Xiang, WO 2011/044134A1, April 14, **2011**; r) P. R. Guzzo, M. D. Surman, A. J. Henderson, M. Hadden, E. E. Freeman, US 2011/0003737A1, Jan. 6, **2011**; s) C. Coburn, J. A. McCauley, S. W. Ludmerer, K. Liu, J. P. Vaca, H. Wu, B. Hu, R. Soll, F. Sun, X. Wang, M. Yah, C. Zhang, M. Zheng, B. Zhong, J. Zhu, WO 2010/111483A1, Sept. 20, **2010**; t) T. Rawson, B. Safina, J. Dotson, A. Zhou, I. Aliagas-Martin, J. Halladay, M. Rueth, B.-Y. Zhu, US 2007/0037791A1, Feb. 15, **2007**; u) N. Tanimoto, Y. Hiramatsu, S. Mitsumori, M. Inagaki, EP 1 505 061A1, Feb. 9, **2005**; v) W. Ying, D. James, S. Zhang, T. Przewloka, J. Chae, D. Manamada, C.-W. Lee, E. Kostik, H. P. Ng, K. Foley, Z. Du, J. Barsoum, WO 2006/055760A1, May 26, **2006**; w) W. Ying, K. Foley, WO 2008/021364A2, Feb 21, **2008**.

[5] a) S. Y. Ambekar, *Curr. Sci.* **1983**, *52*, 578; b) B. Robinson, *Chem. Rev.* **1969**, *69*, 227; c) M. Inman, C. J. Moody, *Chem. Commun.* **2011**, *47*, 788.

[6] a) M. C. Willis, G. N. Brace, I. P. Holmes, *Angew. Chem.* **2005**, *117*, 407; *Angew. Chem. Int. Ed.* **2005**, *44*, 403; b) J. Barluenga, A. Jiménez-Aquino, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 1551; *Angew. Chem. Int. Ed.* **2007**, *46*, 1529; c) K. Sun, S. Liu, P. M. Bec, T. G. Driver, *Angew. Chem.* **2011**, *123*, 1740; *Angew. Chem. Int. Ed.* **2011**, *50*, 1702; d) C. Liu, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 10250; e) J. R. Ragains, J. D. Winkler, *Org. Lett.* **2006**, *8*, 4437; f) A. C. Silvanus, S. J. Heffernan, D. J. Liptrot, G. Kociok-Köhn, B. I. Andrews, D. R. Carbery, *Org. Lett.* **2009**, *11*, 1175; g) M. Ishikura, H. Kato, *Tetrahedron* **2002**, *58*, 9827.

[7] a) M. Harmata, *Chem. Commun.* **2010**, *46*, 8886; b) M. Harmata, *Acc. Chem. Res.* **2001**, *34*, 595; c) M. Harmata, *Adv. Synth. Catal.* **2006**, *348*, 2297; d) M. A. Battiste, P. M. Pelphrey, D. L. Wright, *Chem. Eur. J.* **2006**, *12*, 3438; e) I. V. Hartung, H. M. R. Hoffman, *Angew. Chem.* **2004**, *116*, 1968; *Angew. Chem. Int. Ed.* **2004**, *43*, 1934; f) M. Harmata, *Tetrahedron* **1997**, *53*, 6235; g) W. K. Chung, S. K. Lam, B. Lo, L. L. Liu, W.-T. Wong, P. Chiu, *J. Am. Chem. Soc.* **2009**, *131*, 4556; h) M. Harmata, S. Elomari, C. L. Barnes, *J. Am. Chem. Soc.* **1996**, *118*, 2860; i) M. G. Nilson, R. L. Funk, *J. Am. Chem. Soc.* **2011**, *133*, 12451; j) F. Yu, G. Li, P. Gao, H. Gong, Y. Liu, Y. Wu, B. Cheng, H. Zhai, *Org. Lett.* **2010**, *12*, 5135; k) L. L. Liu, P. Chiu, *Chem. Commun.* **2011**, *47*, 3416; l) J. C. Lee, S.-J. Jin, J. K. Cha, *J. Org. Chem.* **1998**, *63*, 2804; m) J. C. Lee, J. K. Cha, *Tetahedron* **2000**, *56*, 10175; n) H. M. L. Davies, X. Dai, *J. Am. Chem. Soc.* **2004**, *126*, 2692.

[8] For examples of [3+2] cycloaddition reactions of indolyl cations, see: a) C.-A. Harrison, R. Leineweber, C. J. Moody, M. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1127; b) J. McNulty, D. Mcleod, *Synlett* **2011**, 717.

[9] a) H. Xiong, J. Huang, S. K. Ghosh, R. P. Hsung, *J. Am. Chem. Soc.* **2003**, *125*, 12694; b) A. G. Lohse, R. P. Hsung, *Chem. Eur. J.* **2011**, *17*, 3812; c) A. G. Lohse, R. P. Hsung, M. D. Leider, S. K. Ghosh, *J. Org. Chem.* **2011**, *76*, 3246; d) M. Harmata, *Chem. Commun.* **2010**, *46*, 8904; e) C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff, C. R. Carson, *J. Am. Chem. Soc.* **2011**, *133*, 7688; f) J. C. Lee, J. K. Cha, *J. Am. Chem. Soc.* **2001**, *123*, 3243; g) R. A. Aungst, Jr., R. L. Funk, *Org. Lett.* **2001**, *3*, 3553; h) M. Harmata, S. Wacharasindhu, *Org. Lett.* **2005**, *7*, 2563; i) K. Lee, J. K. Cha, *Org. Lett.* **1999**, *1*, 523; <*lit* j> C. Blackburn, R. F. Childs, R. A. Kennedy, *Can. J. Chem.* **1983**, *61*, 1981; k) M. Harmata, M. Kahraman, G. Adenu, C. L. Barnes, *Heterocycles* **2004**, *62*, 583; l) M. Harmata, C. B. Gamlath, *J. Org. Chem.* **1988**, *53*, 6154; m) S. A. Hardinger, C. Bayne, E. Kantorowski, R. McClellan, L. Larres, M.-A. Nuesse, *J. Org. Chem.* **1995**, *60*, 1104; n) T. Sasaki, Y, Ishibashi, M. Ohno, *Tetrahedron Lett.* **1982**, *23*, 1693.

[10] a) J. M. Winne, S. Catak, M. Waroquier, V. Van Speybroeck, *Angew. Chem.* **2011**, *123*, 12196; *Angew. Chem. Int. Ed.* **2011**, *50*, 11990; b) G. Pattenden, J. M. Winne, *Tetrahedron Lett.* **2009**, *50*, 7310.

[11] a) A. M. Lauer, F. Mahmud, J. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 9119; b) X. Han, J. Wu, *Org. Lett.* **2010**, *12*, 5780; c) F. J. Robertson, J. Wu, *Org. Lett.* **2010**, *12*, 2668.

[12] a) G. A. Olah, O. Farooq, S. M. F. Farnia, J. A. Olah, *J. Am. Chem. Soc.* **1988**, *110*, 2560; b) G. K. S. Prakash, T. Mathew, G. A. Olah, *Accts. Chem. Res.* **2012**, *45*, 565; c) G. K. S. Prakash, T. Mathew, C. Panja, S. Alconcel, H. Vaghoo, C. Do, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 3703; d) G. K. S. Prakash, T. Mathew, C. Panja, H. Vaghoo, K. Venkataraman, G. A. Olah, *Org. Lett.* **2007**, *9*, 179; e) G. K. S. Parakash, P. Yan, B. Török, I. Bucsi, M. Tanaka, G. A. Olah, *Catal. Lett.* **2003**, *85*, 1; f) P. Yan, P. Batamack, G. K. S. Prakash, G. A. Olah, *Catal. Lett.* **2005**, *103*, 165.

[13] S. Kobayashi, C. Ogawa, *Chem. Eur. J.* **2006**, *12*, 5954.

[14] a) Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157; b) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.

[15] a) R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, *J. Chem. Phys.* **1980**, *72*, 650; b) A. D. McLean, G. S. Chandler, *J. Chem. Phys.* **1980**, *72*, 5639; c) T. Clark, J. Chandrasekhar, G. W. Spitznagel, P. v. R. Schleyer, *J. Comput. Chem.* **1983**, *4*, 294; d) M. J. Frisch, J. A. Pople, J. S. Binkley, *J. Chem. Phys.* **1984**, *80*, 3265.

[16] *Jaguar, versions 7.0–7.7*, Schrödinger, LLC, New York, NY, **2007–2011**.

