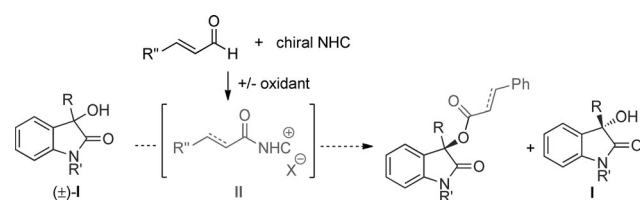


Kinetic Resolution of Tertiary Alcohols: Highly Enantioselective Access to 3-Hydroxy-3-Substituted Oxindoles**

Shenci Lu, Si Bei Poh, Woon-Yew Siau, and Yu Zhao*

In contrast to the well-established kinetic resolution of secondary alcohols,^[1] use of the tertiary alcohol kinetic resolution has remained limited with only a handful of systems reported in the literature including enzymatic and chemical methods.^[2] During our studies, we became interested in the synthesis of 3-hydroxy-3-substituted oxindoles (**I**, Scheme 1), which represent the core structure of a large



Scheme 1. Kinetic resolution of 3-hydroxy-3-substituted oxindoles by NHC-catalyzed esterification.

number of biologically significant natural products and are themselves important targets in medicinal chemistry.^[3] It is shown that the identity of the substituent at the 3-position has significant influence on the biological activity of these natural products.^[4] Not surprisingly, extensive efforts have been focused on their asymmetric synthesis and many successful systems have been developed.^[5] One general catalytic asymmetric method that can tolerate a wide range of 3-substituents, however, remains elusive. We hope to address this issue using an unprecedented and alternative approach, namely the catalytic kinetic resolution of this important class of tertiary alcohols that are readily available in racemic form.^[6]

Considering the strategies applicable to our goal, we were particularly attracted to asymmetric esterification of alcohols employing chiral acyl azolium species (**II**, Scheme 1)^[7] generated from aldehydes catalyzed by a N-heterocyclic carbene (NHC).^[8] This novel catalytic generation of activated carboxylates, either from internal redox reactions of functionalized aldehydes (such as α,β -unsaturated aldehydes or α -

halo aldehydes)^[9] or from simple aldehydes under oxidative conditions,^[10] has added a powerful dimension to NHC catalysis. Application of these new concepts to enantioselective C–C bond formation has met with great success; the use of the chiral acyl azolium to induce asymmetric induction of the alcohol counterpart, however, has lagged behind. In fact, only a few isolated examples for the secondary alcohol kinetic resolution (selectivity *S* up to 7.3)^[9e,10g] or diol desymmetrization (up to 83 % *ee*)^[9b,10b] were reported in the literature.^[11] Simple tertiary alcohols (e.g., *tert*-butanol), on the other hand, showed no reactivity towards the acyl azolium species. Asymmetric induction for tertiary alcohols using NHC catalysis, to the best of our knowledge, is not known.

We initiated our studies by examining the reaction of racemic **1a** with α,β -unsaturated aldehydes catalyzed by triazolium-based NHCs in the absence of an external oxidant (Scheme 1). After extensive experimentation, no significant conversion to the desired saturated ester was obtained and the selectivity remained low (*S* < 5). When MnO₂ was included in the reaction between **1a** and cinnamaldehyde catalyzed by NHC derived from azolium **3**,^[12] 32 % conversion to ester **2a** and a good level of selectivity (*S* = 21) were obtained (entry 1, Table 1). The identity and equivalent of the base turned out to be essential for the reaction (entries 2–4), with 1.0 equiv DBU being the optimal choice (*S* = 30). The screening of different NHC precursors proved azolium **3** as the optimum (entries 2 and 5–7). When quinone **7** was used as the oxidant instead of MnO₂,^[10f–j] low levels of selectivity and reactivity were obtained (entry 8). Other aldehydes including benzaldehyde and hydrocinnamaldehyde were also tested, which proved less efficient and less selective for the reaction as compared to cinnamaldehyde.

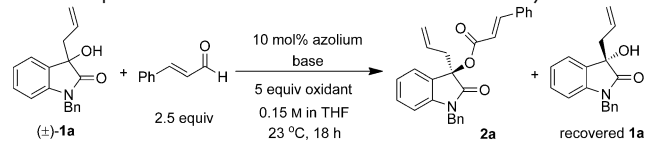
We then focused our attention on improving the reaction rate to recover the unreacted alcohol in high enantiopurity. Solvent screening showed that tetrahydrofuran (THF) was the optimal choice in terms of enantioselectivity, whereas the reaction rate in CH₃CN was higher, which turned out to be important for less reactive substrates later on (see Table 3 and the Supporting Information for details). A higher concentration led to a slight improvement in both reactivity and selectivity (entry 1, Table 2 vs. entry 2, Table 1). Inspired by the recent reports on cooperative catalysis by NHC and Lewis acid pioneered by the Scheidt research group,^[10i,13] we reasoned that the α -hydroxy carbonyl moiety of our substrates may be well-suited for Lewis acid activation. To our satisfaction, although the addition of Sc(OTf)₃ proved futile (entry 2, Table 2), the combination of Mg(OTf)₂ and NHC led to improvement on both selectivity and reaction rate (entry 3). Interestingly, the introduction of NaBF₄ as additive^[10h] further drove the reaction to a higher selectivity (*S* =

[*] Dr. S. Lu, S. B. Poh, W.-Y. Siau, Prof. Y. Zhao
Department of Chemistry, National University of Singapore
3 Science Drive 3, Singapore 117543 (Singapore)
E-mail: zhaoyu@nus.edu.sg
Homepage: <http://zhaoyu.science.nus.edu.sg>

[**] We are grateful for the generous financial support from Singapore National Research Foundation (NRF Fellowship) and National University of Singapore. We thank Dr. Hailong Yan for helpful discussions.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201209043>.

Table 1: Optimization of the kinetic resolution of the tertiary alcohol **1a**.



Entry	Azolium	Base	Oxidant	<i>ee</i> _{2a} ^[a]	<i>ee</i> _{1a} ^[a,b]	Conv. ^[c]	<i>S</i> ^[c]
1	3	0.5 equiv DBU	MnO ₂	87	40	32	21
2	3	1.0 equiv DBU	MnO ₂	88	63	42	30
3	3	1.0 equiv DBU DIPEA ^[d]	MnO ₂	—	—	0	—
4	3	1.0 equiv K ₂ CO ₃	MnO ₂	—	—	0	—
5	4	1.0 equiv DBU	MnO ₂	81	73	47	21
6	5	1.0 equiv DBU	MnO ₂	45	50	44	4
7	6	1.0 equiv DBU	MnO ₂	70	40	36	8
8	3	1.0 equiv DBU	7	52	7	12	3

[a] Determined by HPLC. [b] The absolute configuration of the recovered **1a** was assigned by comparison of the measured optical rotation with the reported value. [c] Conversions and selectivity values were calculated by the methods of Kagan and Fiaud (Ref. [6a]): $\text{Conv.} = ee_1 / (ee_1 + ee_2)$. $S = \ln[(1 - \text{Conv.})(1 - ee_1)] / \ln[(1 - \text{Conv.})(1 + ee_1)]$. See the Supporting Information for details. [d] DIPEA = diisopropylethylamine.

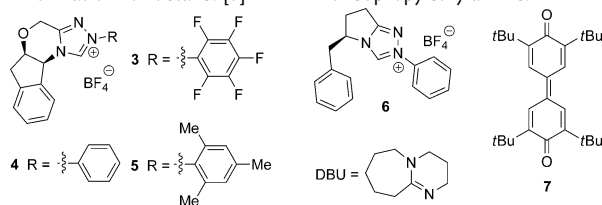
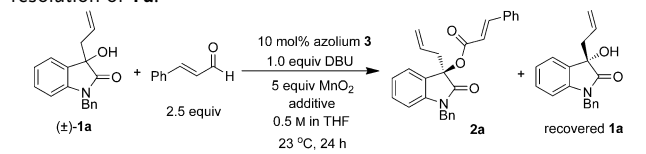


Table 2: Cooperative effect of a Lewis acid and NaBF₄ for the kinetic resolution of **1a**.



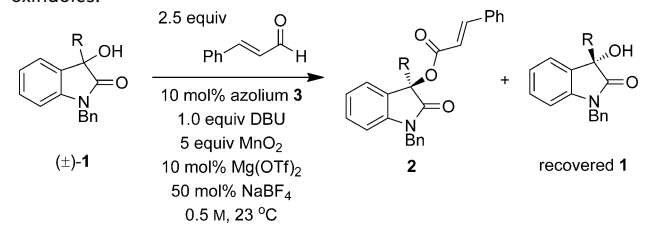
Entry	Lewis acid	NaBF ₄	<i>ee</i> _{2a} ^[a]	<i>ee</i> _{1a} ^[a,b]	Conv. ^[c]	<i>S</i> ^[c]
1	none	none	87	78	47	36
2	10 mol % Sc(OTf) ₃	none	90	47	34	32
3	10 mol % Mg(OTf) ₂	none	89	85	49	48
4	10 mol % Mg(OTf) ₂	50 mol %	88	98	53	70

[a–c] See Table 1.

70) as well as over 50% conversion (entry 4). Under these optimal conditions, unreacted **1a** could be recovered in 45% yield with 98% *ee* (entry 1, Table 3).

The substrate scope of this catalytic system turned out to be remarkably broad (Table 3). The same set of reaction conditions can be used for the successful kinetic resolution of a wide range of 3-hydroxy-3-substituted oxindoles. The selectivities for the 3-alkyl-substituted substrates are uniformly high (*S* > 40, entries 1–5), whereas the selectivities for the alkenyl, alkynyl, and aryl-substituted tertiary alcohols (entries 6–11) are also in a synthetically useful range (*S* > 16). In most cases, the unreacted tertiary alcohols were recovered in high to excellent enantiopurity. As a general trend, increased steric bulk in the 3-substituent led to a reduced

Table 3: Scope of the kinetic resolution of 3-hydroxy-3-substituted oxindoles.^[a]



Entry	Recovered 1	<i>t</i> [h]; Conversion [%]	Yield ₂ [%]; <i>ee</i> ₂ [%]	Yield ₁ [%]; <i>ee</i> ₁ [%]	<i>S</i>
1	1a	24;53	52;87	45;98	70
2 ^[b]	1b	24;55	52;80	39;99	46
3 ^[b]	1c	24;56	53;78	40;99	41
4	1d	24;46	43;92	52;80	59
5	1e	24;27	24;95	69;35	56
6	1f	36;57	53;72	42;98	27
7	1g	24;63	59;58	35;99	18
8 ^[b]	1h	48;60	57;64	32;98	20
9	1i	36;39	34;86	52;55	23
10 ^[b]	1j	36;53	53;80	44;92	29
11	1k	48;34	30;83	60;43	16

[a] Unless stated otherwise, all reactions were carried out in THF for the period of time as indicated. All reagents were used as received from commercial supplier without purification. [b] Reactions were run in CH₃CN. See the Supporting Information for comparing data in THF.

reaction rate. The choice of THF routinely provided the highest level of stereoselectivity. However, for some less reactive substrates reactions in CH₃CN were more efficient as they allowed the reaction to proceed to > 50% conversion so

that the unreacted tertiary alcohols could be recovered in excellent enantiopurity (entries 2, 3, 8 & 10, Table 3). For example, the kinetic resolution of **1b** in THF proceeded to 50% conversion after 24 h with $S=54$, under which conditions both ester product **2b** and unreacted **1b** were isolated with 90% *ee*. The reaction in CH₃CN, in contrast, proceeded to 55% conversion with $S=46$ under otherwise identical conditions and **1b** was recovered with an excellent 99% *ee* (entry 2; see the Supporting Information for more data on comparison of THF and CH₃CN).

In addition to a wide range of 3-substituents, different substitutions on the oxindole backbone are also well tolerated by our catalytic system (entries 1–3, Table 4). Substrates bearing both electron-donating and electron-withdrawing groups on the oxindole ring underwent esterification smoothly to produce the recovered starting alcohols in high

Table 4: Scope of the kinetic resolution of 3-hydroxy-3-substituted oxindoles.

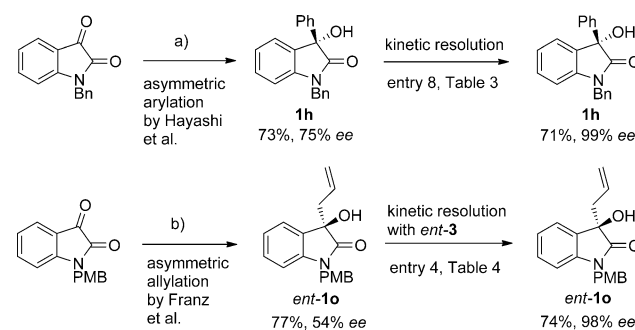
Entry	Recovered 1	t [h]; Conversion [%]	Yield ₂ [%]; <i>ee</i> ₂ [%]	Yield ₁ [%]; <i>ee</i> ₁ [%]	S
1		72;52	51;91	46;98	78
2		72;52	51;83	45;92	34
3		72;54	52;81	44;95	35
4		55;52	50;89	47;97	68
5		55;28	24;80	70;31	12
6		55;29	26;85	67;35	17

enantioselectivity. We have also tested the effect of protecting groups on the nitrogen (entries 4–6). PMB-containing substrate **1o** worked as well as the Bn protected **1a**, whereas methyl containing **1p** proved a less reactive and less selective substrate. Interestingly, the unprotected oxindole derivative

1q provided a synthetically useful level of selectivity ($S=17$, entry 6), albeit with low reaction rate.

The catalytic kinetic resolution is simple to perform at ambient temperature using a readily available catalyst. All the reagents (cinnamaldehyde, DBU, MnO₂, Mg(OTf)₂ and NaBF₄) are used as received without further purification.

Our approach to access enantiopure 3-hydroxy-3-substituted oxindoles complements previous asymmetric syntheses of these molecules nicely. The enantiopurity of the products from a catalytic synthetic method can be easily boosted up to nearly perfect if it is coupled with our kinetic resolution.^[14] This sequential asymmetric catalysis in turn results in an overall more efficient process to access the target compounds. As shown in Scheme 2, following the procedures disclosed by the Hayashi research group^[15] on the Rh-catalyzed arylation of related isatins using the commercially available ligand (*R*)-



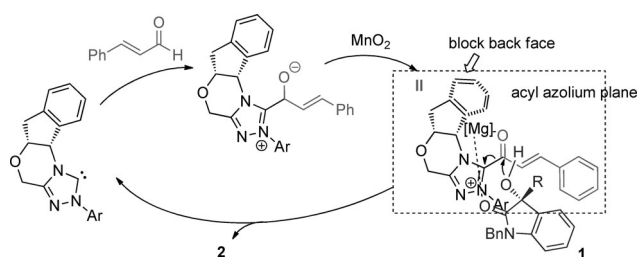
Scheme 2. Sequential catalysis for more efficient synthesis.

a) 2.5 mol % [RhCl(C₂H₄)₂]₂, 5 mol % (*R*)-MeO-MOP, 2 equiv PhB(OH)₂, 15 mol % KOH, THF/H₂O, 50 °C, 24 h. b) 3 equiv allyltributyltin, 5 mol % Sc(OTf)₃, 5 mol % inda-PyBOX, 0.2 M in CH₂Cl₂, 4 Å MS, 23 °C, 16 h.

MeO-MOP and the Franz research group^[16] on allylation of *N*-methyl isatins catalyzed by Sc(OTf)₃-inda-PyBOX complex, respectively, alcohols **1h** and **ent-1o** were obtained in good yields with moderate *ee* of 75% and 54% (see the Supporting Information for more details). The kinetic resolution of these moderately enantioenriched compounds following the conditions listed in Tables 3 and 4 then provided the alcohols in nearly enantiopure form, and more importantly, with 71 and 74% isolated yields, which compared favorably with the < 50% yield in the kinetic resolution of the corresponding racemates. Alcohol **ent-1o** has served as a key intermediate for the preparation of the natural product CPC-1, which was previously reported with only 85% *ee*.^[17]

The proposed reaction pathway is illustrated in Scheme 3. The formation of acyl azolium **II** under oxidative NHC catalysis and its conformation were well-documented.^[7,10] The tertiary alcohol presumably attacks **II** from the opposite side of the catalyst chiral backbone. The Lewis acid additive may activate the substrate in a cooperative fashion. Secondary interactions between the aryl ring of the substrate and the styrenyl moiety on **II** may be involved to secure the substrate conformation during the esterification.

Preliminary studies on substrate modification suggested that the oxindole structure is important for this system to



Scheme 3. Proposed reaction pathway.

work, as simple tertiary alcohol such as 1-methyl-1-indanol lacking the amide moiety showed no reactivity under similar conditions. Further studies are underway to better understand the substrate requirement to expand the scope of this catalytic system.

Received: November 12, 2012

Revised: December 6, 2012

Published online: January 7, 2013

Keywords: asymmetric catalysis · enantioselectivity · kinetic resolution · oxindoles

- [1] a) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, 103, 2985–3012; b) G. C. Fu, *Acc. Chem. Res.* **2004**, 37, 542–547; c) E. R. Jarvo, S. J. Miller in *Comprehensive Asymmetric Catalysis, Suppl. 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2004**, pp. 189–206.
- [2] a) B. List, D. Shabat, G. Zhong, J. M. Turner, A. Li, T. Bui, J. Anderson, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **1999**, 121, 7283–7291; b) E. R. Jarvo, C. A. Evans, G. T. Copeland, S. J. Miller, *J. Org. Chem.* **2001**, 66, 5522–5527; c) M. C. Angione, S. J. Miller, *Tetrahedron* **2006**, 62, 5254–5261; d) R. Kourist, S. Bartsch, U. T. Bornscheuer, *Adv. Synth. Catal.* **2007**, 349, 1393–1398; e) R. Shintani, K. Takatsu, T. Hayashi, *Org. Lett.* **2008**, 10, 1191–1193; f) B. Karatas, S. Rendler, R. Fröhlich, M. Oestreich, *Org. Biomol. Chem.* **2008**, 6, 1435–1440; g) D. J. Schipper, S. Rousseaux, K. Fagnou, *Angew. Chem.* **2009**, 121, 8493–8497; *Angew. Chem. Int. Ed.* **2009**, 48, 8343–8347; h) I. Čorić, S. Müller, B. List, *J. Am. Chem. Soc.* **2010**, 132, 17370–17373.
- [3] S. Peddibhotla, *Curr. Bioact. Compd.* **2009**, 5, 20–38.
- [4] P. Hewawasam, M. Erway, S. L. Moon, J. Knipe, H. Weiner, C. G. Boissard, D. J. Post-Munson, Q. Gao, S. Huang, V. K. Gribkoff, N. A. Meanwell, *J. Med. Chem.* **2002**, 45, 1487–1499.
- [5] For reviews, see: a) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, 352, 1381–1407; b) G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, 112, 6104–6155.
- [6] a) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, 18, 249–330; b) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, 343, 5–26; c) E. Vedejs, M. Jure, *Angew. Chem.* **2005**, 117, 4040–4069; *Angew. Chem. Int. Ed.* **2005**, 44, 3974–4001.
- [7] J. Mahatthananchai, P. Zheng, J. W. Bode, *Angew. Chem.* **2011**, 123, 1711–1715; *Angew. Chem. Int. Ed.* **2011**, 50, 1673–1677.
- [8] a) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, 119, 3046–3058; *Angew. Chem. Int. Ed.* **2007**, 46, 2988–3000; b) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, 107, 5606–5655; c) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta* **2009**, 42, 55–66; d) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, 44, 1182–1195; e) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, 40, 5336–5346; f) P. C. Chiang, J. W. Bode in *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools* (Ed.: S. Díez-González), RSC, Cambridge **2011**, pp. 399–435.
- [9] a) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, 126, 8126–8127; b) N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, 126, 9518–9519; c) C. Burstein, F. Glorius, *Angew. Chem.* **2004**, 116, 6331–6334; *Angew. Chem. Int. Ed.* **2004**, 43, 6205–6208; d) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, 126, 14370–14371; e) A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, 7, 905–908; f) K. Zeitler, *Org. Lett.* **2006**, 8, 637–640; g) Y.-M. Zhao, Y. Tam, Y.-J. Wang, Z. Li, J. Sun, *Org. Lett.* **2012**, 14, 1398–1401.
- [10] a) S. Tam, L. Jimenez, F. Diederich, *J. Am. Chem. Soc.* **1992**, 114, 1503–1505; b) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Org. Lett.* **2007**, 9, 371–374; c) B. E. Maki, A. Chan, E. M. Phillips, K. A. Scheidt, *Tetrahedron* **2009**, 65, 3102–3109; d) C. Noonan, L. Baragwanath, S. J. Connon, *Tetrahedron Lett.* **2008**, 49, 4003–4006; e) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem.* **2008**, 120, 8855–8858; *Angew. Chem. Int. Ed.* **2008**, 47, 8727–8730; f) S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, 132, 1190–1191; g) S. De Sarkar, A. Biswas, C. H. Song, A. Studer, *Synthesis* **2011**, 1974–1983; h) Z.-Q. Rong, M.-Q. Jia, S.-L. You, *Org. Lett.* **2011**, 13, 4080–4083; i) J. Mo, X. Chen, Y. R. Chi, *J. Am. Chem. Soc.* **2012**, 134, 8810–8813; j) A. G. Kravina, J. Mahatthananchai, J. W. Bode, *Angew. Chem.* **2012**, 124, 9568–9572; *Angew. Chem. Int. Ed.* **2012**, 51, 9433–9436.
- [11] For the kinetic resolution of cyclic secondary amines using the combination of an achiral NHC catalyst and a chiral hydroxamic acids, see: M. Binanzer, S.-Y. Hsieh, J. W. Bode, *J. Am. Chem. Soc.* **2011**, 133, 19698–19701.
- [12] H. U. Vora, S. P. Lathrop, N. T. Reynolds, M. S. Kerr, J. R. de Alaniz, T. Rovis, *Org. Synth.* **2010**, 87, 350–361.
- [13] a) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, 2, 766–771; b) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, 132, 5345–5347; c) D. T. Cohen, B. Cardinal-David, K. A. Scheidt, *Angew. Chem.* **2011**, 123, 1716–1720; *Angew. Chem. Int. Ed.* **2011**, 50, 1678–1682; d) D. T. Cohen, B. Cardinal-David, J. M. Roberts, A. A. Sarjeant, K. A. Scheidt, *Org. Lett.* **2011**, 13, 1068–1071; e) D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, 3, 53–57; f) X. Zhao, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, 133, 12466–12469.
- [14] a) C. E. Aroyan, M. M. Vasbinder, S. J. Miller, *Org. Lett.* **2005**, 7, 3849–3851; b) A. Gansäuer, C.-A. Fan, F. Keller, J. Keil, *J. Am. Chem. Soc.* **2007**, 129, 3484–3485; c) J. M. Rodrigo, Y. Zhao, A. H. Hoveyda, M. L. Snapper, *Org. Lett.* **2011**, 13, 3778–3781.
- [15] R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem.* **2006**, 118, 3431–3434; *Angew. Chem. Int. Ed.* **2006**, 45, 3353–3356.
- [16] N. V. Hanhan, A. H. Sahin, T. W. Chang, J. C. Fetting, A. K. Franz, *Angew. Chem.* **2010**, 122, 756–759; *Angew. Chem. Int. Ed.* **2010**, 49, 744–747.
- [17] D. Sano, K. Nagata, T. Itoh, *Org. Lett.* **2008**, 10, 1593–1595.