

Catalytic Enantioselective Stereoablative Alkylation of 3-Halooxindoles: Facile Access to Oxindoles with C3 All-Carbon Quaternary Stereocenters**

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The construction of all-carbon quaternary stereocenters remains one of the most challenging problems in asymmetric catalysis and has been an area of great interest in our laboratories.^[1,2] Over the past several years, significant effort from many research groups has been directed toward the enantioselective synthesis of 3,3-disubstituted oxindoles and derivatives thereof, given the prevalence of this structural motif in biologically active molecules and their interesting molecular architectures (Figure 1).^[3–5] Although a number of catalytic enantioselective approaches to this motif have been developed (Heck reaction,^[6] cyanoamidation,^[7] cycloadditions,^[8] arylation,^[9] alkylation,^[10,11] acyl migration,^[12] Claisen rearrangement,^[13] aldol,^[14] Mannich,^[15] and conjugate addition reactions^[15b]), we pursued an alternative tactic.^[16–18] In all of the reported systems that rely on stereoselective functionalization of an existing oxindole,^[9–15] this unit serves as a nucleophile. In contrast, we present herein an unusual strategy for the enantioselective synthesis of substituted oxindoles with C3 quaternary stereocenters that employs the oxindole moiety as the electrophilic partner for the facile and rapid coupling to malonate nucleophiles.

Despite an early report from Hinman and Bauman in 1964,^[19] the use of 3-halooxindoles as electrophiles in substitution chemistry has been limited. Although the addi-

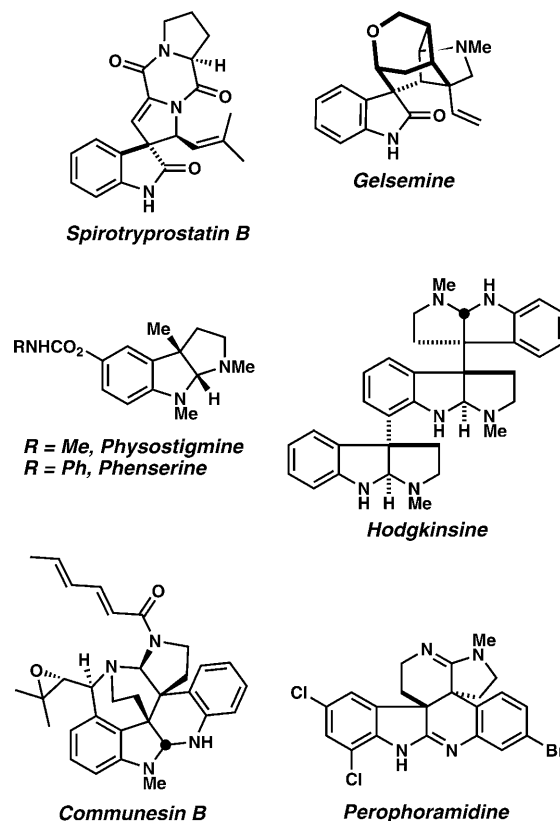


Figure 1. Naturally occurring 3,3-disubstituted oxindoles and indolines bearing all-carbon quaternary stereocenters.

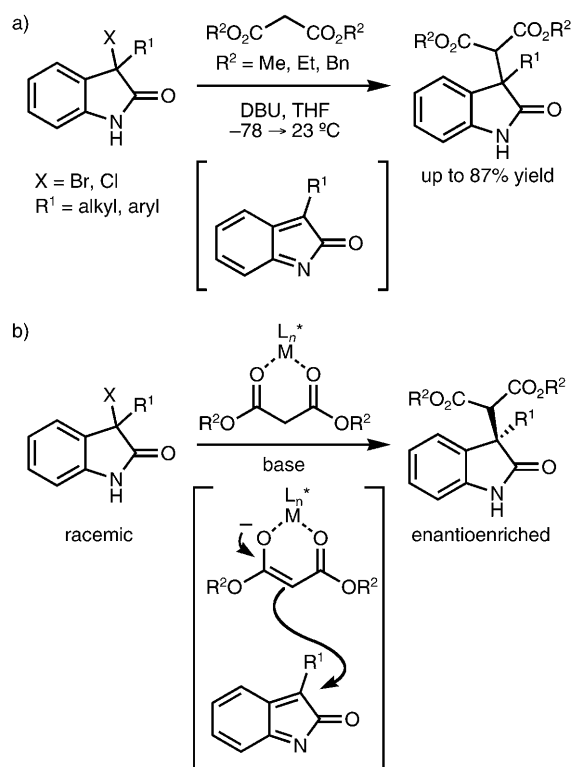
tion of carbon-based π - and heteroatom-nucleophiles to the C3 position of oxindoles has been reported, no enantioselective methods exist.^[20] We recently reported the base-promoted addition of malonate esters to 3-halooxindoles by the in situ formation of a putative *o*-azaxylylene (Scheme 1 a).^[21] In light of these results and our general interest in stereoablative reactions,^[22] we sought to develop a catalytic enantioselective system (Scheme 1 b).^[23] We hypothesized that a Lewis acid could facilitate the base-mediated reaction by lowering the pK_a of the N–H proton of the halooxindole and/or the C_α –H proton of the malonate. Through either pathway, complexation by a chiral Lewis acid could potentially lead to asymmetric induction.

We reasoned that the key to implementing a catalytic enantioselective system would be to identify a base that did not promote competitive background reactions in the absence of catalyst. In our initial experiments, we found that exposure of racemic bromooxindole ($\pm$)-**1** to *N,N*-diisopropylethyl-

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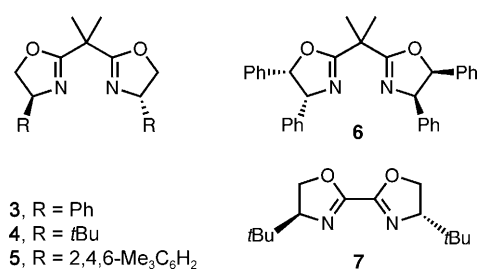
[**] We wish to thank the California TRDRP (postdoctoral fellowships to X.H. and S.K.), Abbott Laboratories, Amgen, Merck, Bristol-Myers Squibb, Boehringer Ingelheim, the Gordon and Betty Moore Foundation, and Caltech for financial support. Lawrence Henling and Dr. Michael Day are gratefully acknowledged for X-ray crystallographic structure determination. Prof. David Horne is thanked for helpful discussions. The Bruker KAPPA APEXII X-ray diffractometer was purchased through an NSF CRIF:MU award to the California Institute of Technology, CHE-0639094. Dr. David VanderVelde and Dr. Scott Ross are acknowledged for NMR assistance.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200902943>.



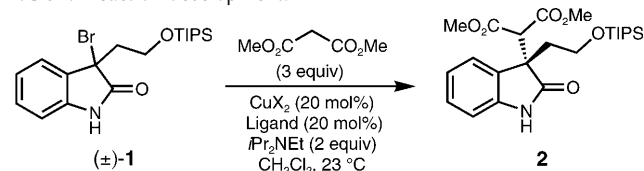
Scheme 1. a) Base-mediated addition of malonates to halooxindoles via a reactive *o*-azaxylylene intermediate.^[21] b) Proposed Lewis acid catalyzed enantioselective alkylation of 3-halooxindoles. Only the malonate activated pathway is shown. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

amine (*i*Pr₂NEt) and dimethyl malonate in the absence of a Lewis acid did not result in formation of adduct **2**.^[24] Encouraged by this finding, we then surveyed a variety of chiral Lewis acids (e.g., Cu^{II}, Mg^{II}, La^{III}, and Ni^{II} complexes) that could potentially promote the asymmetric alkylation. The combination of copper(II) triflate and (*S*)-Ph-box (**3**)



gave the most promising result, producing **2** in 63 % yield and 77 % *ee* (Table 1, entry 1).^[25,26] Related bis(oxazoline) ligands **4–7** resulted in diminished yields and enantioselectivity (Table 1, entries 2–5). Given the strong electronic effects observed in related Lewis acid catalyzed processes, we investigated the effect of less coordinating counterions.^[27] Although imparting only a moderate influence on chemical yield, a more pronounced counterion effect was observed for enantioselectivity. For example, with the hexafluoroantimo-

Table 1: Reaction development.



Entry	X	Ligand	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	OTf	3	63	77
2	OTf	4	45	6
3	OTf	<i>ent</i> - 5	24	–42
4	OTf	6	37	–64
5	OTf	7	49	13
6 ^[a]	PF ₆ ^[d]	3	65	81
7	NTf ₂ ^[d]	3	65	79
8 ^[a]	BF ₄ ^[d]	3	61	76
9	SbF ₆ ^[d]	3	72	84

[a] Performed at –78 → 23 °C. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC. [d] The catalyst was generated by in situ metathesis of [Cu(**3**)Cl₂] with the corresponding AgX salt.^[24]

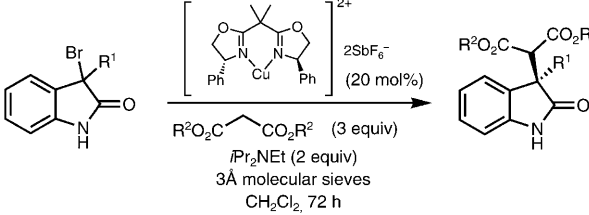
nate (SbF₆[–]) complex, malonate adduct **2** was produced in 72 % yield and 84 % *ee* in less than 10 min (Table 1, entry 9). Ultimately, we found that employing the preformed [Cu(**3**)] (SbF₆)₂ complex at low temperature (i.e., –40 °C) in the presence of 3 Å molecular sieves^[28] produced oxindole **2** in 77 % yield and 88 % *ee* (Table 2, entry 1).

On examining the scope of the transformation, we found that malonate esters could be alkylated with various 3-alkyl and 3-aryl halooxindoles in good yields and high enantioselectivities (Tables 2 and 3).^[29] Methyl, ethyl, and benzyl malonates each added to bromide (±)-**1**, via the putative *o*-azaxylylene, with similar levels of selectivity and yield (Table 2, entries 1–3). Silyl ethers (entries 1–5), benzoate esters (entry 6), and phthalimides (entries 8–10) were all tolerated as substituents on the C3 alkyl chain. Additionally, substituted alkyl chains of various lengths led to alkylation products in high enantioselectivities (entries 1 and 5). Finally, substitution of the bromooxindole core at C5 with a methoxy group produced the malonate addition product in 51 % yield and 91 % *ee* (entry 10).

In addition to the reactions of bromooxindoles, dimethyl malonate reacted smoothly with racemic 3-aryl chlorooxindoles to produce the C3-malonate adducts in good yields and enantioselectivities (Table 3). In these reactions, Et₃N proved to be a better base than *i*Pr₂NEt in both yield and enantioselectivity. Products with phenyl (entry 1), bromophenyl (entry 2), 3,5-dimethylphenyl (entry 3), and naphthyl substitution at C3 (entry 4) were stereoselectively formed with this method. Additionally, methoxy substitution on the oxindole framework at C5 was well tolerated (entry 5).

We proceeded to apply the new method for enantioselective generation of C3-quaternary oxindoles to the synthesis of natural product scaffolds. To construct the pyrrolidinyl-spirooxindole core prevalent in a large family of biologically active alkaloids,^[3] we began with malonate adduct **8** (Table 2, entry 10), which could be recrystallized to 99 % *ee* (Scheme 2). Oxindole malonate **8** was converted to phthali-

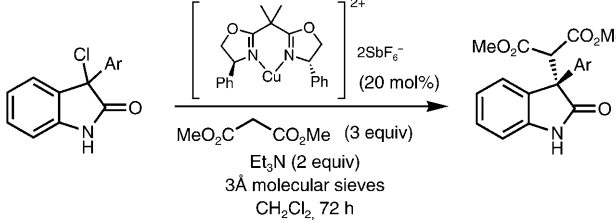
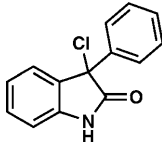
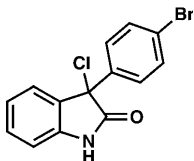
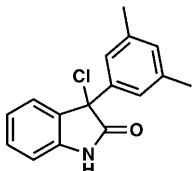
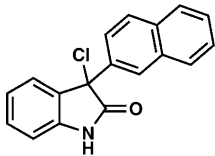
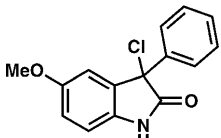
Table 2: Alkyl-substituted oxindoles as substrates in the enantioselective malonate alkylation.

					
Entry	Racemic substrate	R ²	T [°C]	Yield ^[a] [%]	ee ^[b] [%]
1		Me	−40	77	88
2		Et	−40	73	84
3		Bn	−40	78	88
4		Me	−40	78	88
5		Me	−20	47	86
6		Me	−20	51	83
7		Me	−40	44	84
8		Me	−20	63	94
9		Me	−20	42	81
10		Me	−20	51	91

[a] Yield of isolated product. [b] Determined by chiral-phase HPLC.

midoester **9** by Krapcho decarboxylation.^[30] Cleavage of phthalimide **9** with hydrazine resulted in rapid formation of spirocyclic bis(lactam) **10**. Double alkylation of oxindole **10** produced bis(*p*-bromobenzyl)lactam **11**, a crystalline compound amenable to single crystal X-ray analysis and determination of absolute configuration.^[31]

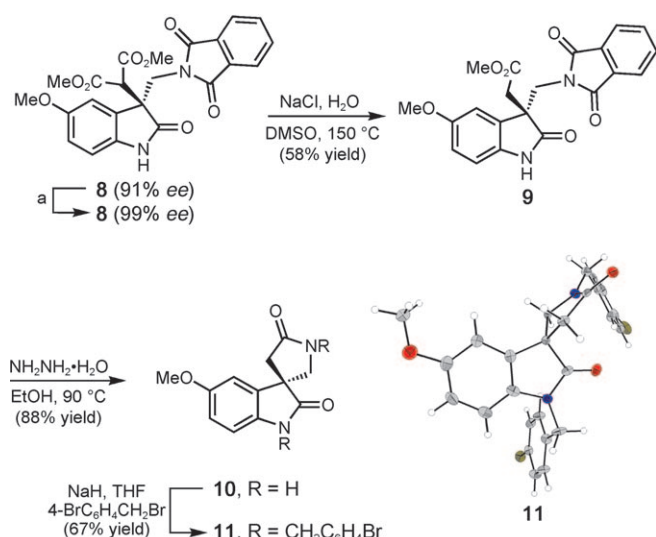
Table 3: Aryl-substituted oxindoles as substrates in the enantioselective malonate alkylation.

				
Entry	Substrate	T [°C]	Yield ^[a] [%]	ee ^[b] [%]
1		−20	76	−76 ^[c]
2		0	84	81
3		−40	69	84
4		0	74	74
5		−20	76	84

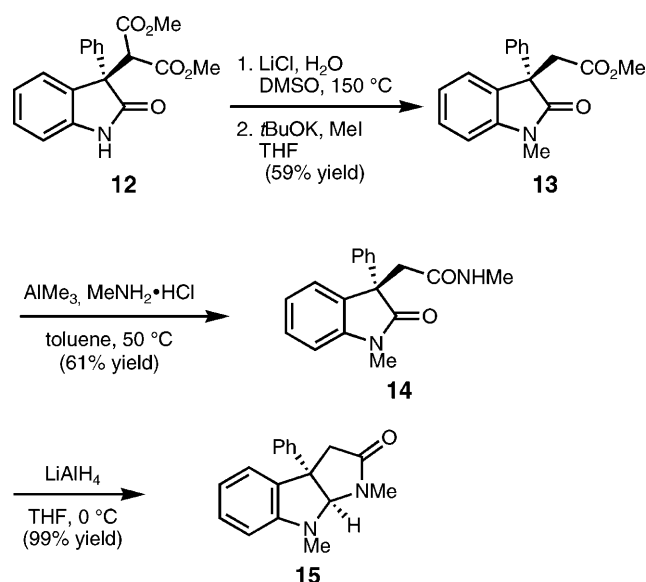
[a] Yield of isolated product. [b] Determined by chiral-phase HPLC. [c] (*R,R*)-**3** was employed as ligand.

In addition to spirocyclic motifs, fused pyrrolidinooxindoles are also a key moiety found in many natural products. To access this family, quaternary C3-aryl oxindole malonate adduct **12** was subjected to Krapcho decarboxylation^[30] and N-alkylation to give methyl ester **13** (Scheme 3). Finally, ester **13** was converted to methyl amide **14** and reduced with LiAlH₄, providing lactam **15** with the pyrrolidinooxindole core.

In summary, we have discovered a unique copper-catalyzed enantioselective synthesis of C3-quaternary oxindoles. This stereoablative transformation most likely involves the in situ formation of a highly reactive *o*-azaxylylene from C3-halo oxindoles followed by enantioselective malonate addition. Finally, we have demonstrated that our method is



Scheme 2. The synthesis of a pyrrolidinone-spirooxindole. a) Recrystallization from CH_2Cl_2 /hexanes (3.5:1), 92% yield.^[24]



Scheme 3. The synthesis of a fused indolinopyrrolidinone.

useful for the rapid and stereoselective construction of the core structures of important biologically active alkaloids. Mechanistic studies and further synthetic applications of our method are underway.

Received: June 1, 2009

Published online: September 18, 2009

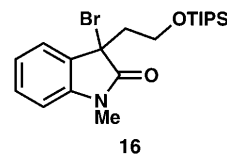
Keywords: alkylation · asymmetric catalysis · copper · enantioselectivity · umpolung

- [1] For reviews of catalytic asymmetric construction of all-carbon quaternary stereocenters, see: a) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; b) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (Eds.: J. Christoffers, A. Baro), Wiley, Weinheim, **2005**; c) J. Christoffers, A. Baro, *Adv. Synth.*

Catal. **2005**, 347, 1473–1482; d) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, 101, 5363–5367; e) D. J. Ramon, M. Yus, *Curr. Org. Chem.* **2004**, 8, 149–183; f) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969–5994.

- [2] a) K. V. Petrova, J. T. Mohr, B. M. Stoltz, *Org. Lett.* **2009**, 11, 293–295; b) S. R. Levine, M. R. Krout, B. M. Stoltz, *Org. Lett.* **2009**, 11, 289–292; c) J. A. Enquist, Jr., B. M. Stoltz, *Nature* **2008**, 453, 1228–1231; d) D. E. White, I. C. Stewart, R. H. Grubbs, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, 130, 810–811; e) D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2007**, 119, 4155–4158; *Angew. Chem. Int. Ed.* **2007**, 46, 4077–4080; f) R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, 128, 7738–7739; g) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem.* **2005**, 117, 7084–7087; *Angew. Chem. Int. Ed.* **2005**, 44, 6924–6927; h) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, 126, 15044–15045.
- [3] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, 119, 8902–8912; *Angew. Chem. Int. Ed.* **2007**, 46, 8748–8758; b) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209–2219; c) J. A. May, B. Stoltz, *Tetrahedron* **2006**, 62, 5262–5271.
- [4] For selected recent examples, see: a) L. E. Overman, M. D. Rosen, *Angew. Chem.* **2000**, 112, 4768–4771; *Angew. Chem. Int. Ed.* **2000**, 39, 4596–4599; b) A. Lerchner, E. M. Carreira, *J. Am. Chem. Soc.* **2002**, 124, 14826–14827; c) H. Lin, S. J. Danishefsky, *Angew. Chem.* **2003**, 115, 38–53; *Angew. Chem. Int. Ed.* **2003**, 42, 36–51; d) P. Siengalewicz, T. Gaich, J. Mulzer, *Angew. Chem.* **2008**, 120, 8290–8296; *Angew. Chem. Int. Ed.* **2008**, 47, 8170–8176; e) T. Kawasaki, M. Shinada, D. Kamimura, M. Ohzono, A. Ogawa, *Chem. Commun.* **2006**, 420–422; f) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, 101, 5482–5487; g) B. M. Trost, Y. Zhang, *J. Am. Chem. Soc.* **2006**, 128, 4590–4591; h) T. Matsuura, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, 120, 6500–6503; i) A. Huang, J. J. Kodanko, L. E. Overman, *J. Am. Chem. Soc.* **2004**, 126, 14043–14053; j) C. Marti, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, 127, 11505–11515; k) T. Onishi, P. R. Sebahar, R. M. Williams, *Org. Lett.* **2003**, 5, 3135–3137; l) B. M. Trost, D. T. Stiles, *Org. Lett.* **2007**, 9, 2763–2766; m) F. Y. Miyake, K. Yakushijin, D. A. Horne, *Org. Lett.* **2004**, 6, 4249–4251; n) F. Y. Miyake, K. Yakushijin, D. A. Horne, *Angew. Chem.* **2004**, 116, 5471–5474; *Angew. Chem. Int. Ed.* **2004**, 43, 5357–5360; o) M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, 126, 16077–16086; p) T. D. Bagul, G. Lakshmaiah, T. Kawabata, K. Fuji, *Org. Lett.* **2002**, 4, 249–251; q) S. Edmondson, S. J. Danishefsky, L. Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.* **1999**, 121, 2147–2155; r) P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc.* **2000**, 122, 5666–5667.
- [5] J. T. Mohr, M. R. Krout, B. M. Stoltz, *Nature* **2008**, 455, 323–332.
- [6] a) A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. Eur. J.* **2007**, 13, 961–967; b) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, 103, 2945–2964, and references therein; c) A. Ashimori, B. Bachand, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, 120, 6477–6487; d) A. Ashimori, T. Matsuura, L. E. Overman, D. J. Poon, *J. Org. Chem.* **1993**, 58, 6949–6951; e) C. A. Busacca, D. Grossbach, R. C. So, E. M. O'Brien, E. M. Spinelli, *Org. Lett.* **2003**, 5, 595–598.
- [7] Y. Yasui, H. Kamisaki, Y. Takemoto, *Org. Lett.* **2008**, 10, 3303–3306.
- [8] B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, 129, 12396–12397.
- [9] a) E. P. Kündig, T. M. Seidel, Y.-x. Jia, G. Bernardinelli, *Angew. Chem.* **2007**, 119, 8636–8639; *Angew. Chem. Int. Ed.* **2007**, 46, 8484–8487; b) S. Lee, J. F. Hartwig, *J. Org. Chem.* **2001**, 66, 3402–3415.

- [10] a) T. B. K. Lee, G. S. K. Wong, EP 438796A2, **1991** 19910731 US 90-46992; b) T. B. K. Lee, G. S. K. Wong, *J. Org. Chem.* **1991**, *56*, 872–875.
- [11] a) B. M. Trost, Y. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 14548–14549; b) B. M. Trost, M. K. Brennan, *Org. Lett.* **2006**, *8*, 2027–2030; c) B. M. Trost, Y. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591; d) B. M. Trost, M. U. Frederiksen, *Angew. Chem.* **2004**, *116*, 312–314; *Angew. Chem. Int. Ed.* **2004**, *43*, 308–310.
- [12] a) I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051–4054; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921–3924; b) S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va, E. Vedejs, *J. Am. Chem. Soc.* **2006**, *128*, 925–934; c) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369.
- [13] E. C. Linton, M. C. Kozlowski, *J. Am. Chem. Soc.* **2008**, *130*, 16162–16163.
- [14] S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2007**, *119*, 8820–8823; *Angew. Chem. Int. Ed.* **2007**, *46*, 8666–8669.
- [15] a) X. Tian, K. Jiang, J. Peng, W. Du, Y.-C. Chen, *Org. Lett.* **2008**, *10*, 3583–3586; b) R. He, C. Ding, K. Maruoka, *Angew. Chem.* **2009**, *121*, 4629–4631; *Angew. Chem. Int. Ed.* **2009**, *48*, 4559–4561.
- [16] For enzymatic desymmetrization methods, see: a) S. Akai, T. Tsujino, E. Akiyama, K. Tanimoto, T. Naka, Y. Kita, *J. Org. Chem.* **2004**, *69*, 2478–2486; b) K. Nakazawa, M. Hayashi, M. Tanaka, M. Aso, H. Suemune, *Tetrahedron: Asymmetry* **2001**, *12*, 897–901; c) S. Akai, T. Tsujino, T. Naka, K. Tanimoto, Y. Kita, *Tetrahedron Lett.* **2001**, *42*, 7315–7317.
- [17] For catalytic enantioselective methods that produce C3-quaternary oxindoles after additional functionalization steps, see: a) K. Nagata, D. Sano, T. Itoh, *Synlett* **2007**, 547–550; b) M. Bella, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 3670–3671.
- [18] Catalytic asymmetric fluorinations and hydroxylations have also been reported for the syntheses of fully substituted tertiary stereocenters at the C3-position of the oxindole core, see: a) T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2008**, *120*, 4225–4229; *Angew. Chem. Int. Ed.* **2008**, *47*, 4157–4161; b) Y. Hamashima, M. Sodeoka, *Synlett* **2006**, 1467–1478; c) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165; d) D. Sano, K. Nagata, T. Itoh, *Org. Lett.* **2008**, *10*, 1593–1595; e) J.-R. Chen, X.-P. Liu, X.-Y. Zhu, L. Li, Y.-F. Qiao, J.-M. Zhang, W.-J. Xiao, *Tetrahedron* **2007**, *63*, 10437–10444; f) R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem.* **2006**, *118*, 3431–3434; *Angew. Chem. Int. Ed.* **2006**, *45*, 3353–3356; g) T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa, *J. Am. Chem. Soc.* **2006**, *128*, 16488–16489; h) P. Y. Toullec, R. B. C. Jagt, J. G. de Vries, B. L. Feringa, A. J. Minnaard, *Org. Lett.* **2006**, *8*, 2715–2718; i) G. Luppi, P. G. Cozzi, M. Monari, B. Kaptein, Q. B. Broxterman, C. Tomasini, *J. Org. Chem.* **2005**, *70*, 7418–7421.
- [19] R. L. Hinman, C. P. Bauman, *J. Org. Chem.* **1964**, *29*, 2431–2437.
- [20] a) C.-M. Cheung, F. W. Goldberg, P. Magnus, C. J. Russell, R. Turnbull, V. Lynch, *J. Am. Chem. Soc.* **2007**, *129*, 12320–12327; b) D. B. England, G. Merey, A. Padwa, *Org. Lett.* **2007**, *9*, 3805–3807; c) P. Magnus, R. Turnbull, *Org. Lett.* **2006**, *8*, 3497–3499; d) J. R. Fuchs, R. L. Funk, *Org. Lett.* **2005**, *7*, 677–680; e) F. W. Goldberg, P. Magnus, R. Turnbull, *Org. Lett.* **2005**, *7*, 4531–4534; f) J. R. Fuchs, R. L. Funk, *J. Am. Chem. Soc.* **2004**, *126*, 5068–5069; g) I. Fejes, L. Toke, M. Nyerges, C. S. Pak, *Tetrahedron* **2000**, *56*, 639–644; h) W. G. Rajeswaran, R. B. Labroo, L. A. Cohen, *J. Org. Chem.* **1999**, *64*, 1369–1371; i) E. M. Beccalli, A. Marchesini, T. Pilati, *J. Chem. Soc. Perkin Trans. 1* **1994**, 579–587; j) R. B. Labroo, V. M. Labroo, M. M. King, L. A. Cohen, *J. Org. Chem.* **1991**, *56*, 3637–3642; k) M. J. Kornet, A. P. Thio, *J. Med. Chem.* **1976**, *19*, 892–898.
- [21] S. Krishnan, B. M. Stoltz, *Tetrahedron Lett.* **2007**, *48*, 7571–7573.
- [22] For a review of catalytic enantioselective stereoablative reactions, see: J. T. Mohr, D. C. Ebner, B. M. Stoltz, *Org. Biomol. Chem.* **2007**, *5*, 3571–3576.
- [23] For select recent examples of malonate alkylation catalyzed by chiral Lewis acids, see: a) D. A. Evans, S. Mito, D. Seidel, *J. Am. Chem. Soc.* **2007**, *129*, 11583–11592; b) M. Watanabe, A. Ikagawa, H. Wang, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149; c) K. Majima, R. Takita, A. Okada, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 15837–15845; d) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105; e) Y. S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohsima, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6506–6507.
- [24] See the Supporting Information for details.
- [25] For reviews on the use of bis(oxazoline) ligands in asymmetric catalysis, see: a) I. Atodiresei, I. Schiffrers, C. Bolm, *Tetrahedron: Asymmetry* **2006**, *17*, 620–633; b) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651; c) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; d) D. A. Evans, T. Rovis, J. S. Johnson, *Pure Appl. Chem.* **1999**, *71*, 1407–1415; e) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45; f) A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339–345; g) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151–4202.
- [26] For an example of bis(oxazoline)-mediated MeLi additions to electrophiles and an excellent discussion of the use of bisoxazolines in general, see: S. E. Denmark, C. M. Stiff, *J. Org. Chem.* **2000**, *65*, 5875–5878.
- [27] D. A. Evans, J. A. Murry, P. von Matt, R. D. Norcross, S. J. Miller, *Angew. Chem.* **1995**, *107*, 864–867; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798–800, and references therein.
- [28] Exposure of racemic bromooxindole ($\pm$)-**1** to preformed [Cu(3)](SbF₆)₂ in the presence of *i*Pr₂NEt at –40°C without molecular sieves gave malonate adduct **2** in 68% yield and 86% ee.
- [29] Consistent with our proposal of an *o*-azaxylylene intermediate, exposure of *N*-methyl bromooxindole **16** to our reaction conditions (see Table 2) failed to give any detectable amount of the malonate adduct.



- [30] a) A. P. Krapcho, *Synthesis* **1982**, 893–914; b) A. P. Krapcho, *Synthesis* **1982**, 805–822.
- [31] The absolute configuration depicted for all products in Tables 2 and 3 is derived by analogy from the X-ray analysis of **11**.