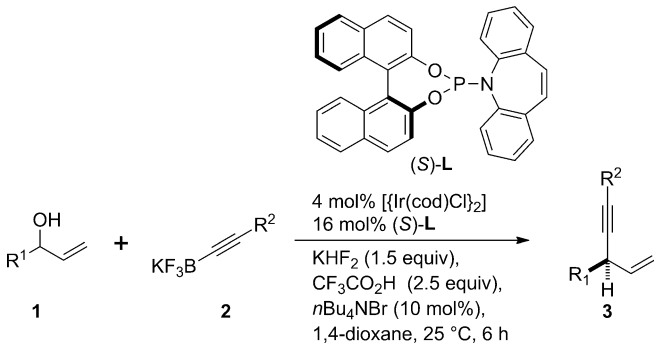
Asymmetric Catalysis

DOI: 10.1002/ange.201302731

Iridium-Catalyzed Enantioselective Allylic Alkynylation**

*James Y. Hamilton, David Sarlah, and Erick M. Carreira**

The development of efficient and enantioselective transformations that lead to new carbon–carbon bonds is at the heart of intense interest in the development of the field of chemical synthesis.[1] Despite significant advances in recent years, the number of existing methods for the enantioselective coupling of terminal alkynes to carbon electrophiles remains relatively small, although such reactions can provide new strategies and building blocks for the synthesis of fine chemicals, pharmaceuticals, and natural products.[2] The low reactivity of alkynylides has limited their use to date to primarily C=O, C=N, and conjugate additions.[3] Additionally, transition-metal-catalyzed, enantioselective hydroalkynylation of unactivated carbon–carbon multiple bonds, has attracted increasing attention.[4] Herein, we present for the first time the direct enantioselective displacement of secondary racemic allylic alcohols with potassium alkynyltrifluoroborates catalyzed by a chiral Ir(P,olefin) complex (Scheme 1). The utility of the method is demonstrated with the rapid construction of a drug candidate for the treatment of type 2 diabetes.



Scheme 1. Direct enantioselective substitution of racemic, branched allylic alcohols with potassium alkynyltrifluoroborates. cod = 1,5-cyclooctadiene.

Allylic substitution is one of the most prominent and effective reactions for enantioselective formation of carbon–carbon bonds.[5] There has been an impressive development of methods that employ transition-metal catalysts and aliphatic carbon nucleophiles, such as malonates, alkyl magnesium, zinc, and boron reagents.[6] However, only Hoveyda and coworkers have previously reported catalytic enantioselective allylic substitutions using alkyne nucleophiles, wherein S_N2'-substitution of allylic phosphates by alkynylaluminum reagents is effected by a copper catalyst.[7] Although this approach provides entry to alkyne-substituted quaternary stereocenters, it does not address the preparation of the corresponding 1,4-enyne products possessing methine stereocenters. In a different approach to such compounds, Alexakis and Li have recently documented the use of alkyl Grignard reagents in Cu-catalyzed asymmetric allylic alkylation of 1-chloro-2-en-4-ynes.[8,9]

We have been interested in expanding the scope of catalytic, enantioselective allylic substitutions using Ir catalysts[10] that are characterized by the direct displacement of allylic alcohols under operationally convenient regimes.[11] As part of our program to extend the synthetic utility of these reactions to carbon nucleophiles, we embarked on an investigation of Ir-catalyzed enantioselective alkynylation reactions.

Our research group recently reported the asymmetric vinylation of allylic alcohols using potassium alkenyltrifluoroborates mediated by an Ir(P,olefin) complex.[11f] We surmised that the direct enantioselective substitution of allylic alcohols might also be possible with the corresponding alkynyltrifluoroborates. Accordingly, our investigation began by subjecting allylic alcohol **1a** and potassium phenylethynyltrifluoroborate (**2a**) to the conditions developed for allylic vinylation. Thus, in the presence of the chiral Ir/(*S*)-**L** catalyst, hydrofluoric acid, and nBu$_4$NHSO$_4$, product **3a** was obtained in 41% yield and 84% *ee* (Table 1, entry 1). Despite low conversion and moderate enantioselectivity, this initial result demonstrated that the Ir(P,olefin) complex is a catalyst with potential in the substitution reaction with alkynes.

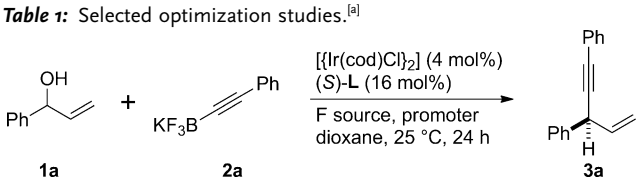
We then turned our attention towards the evaluation of reaction parameters (see the Supporting Information for full details, Tables S1–S8). 1,4-Dioxane proved to be the solvent of choice, and the use of a Brønsted acid as promoter in combination with nBu$_4$NBr[12] resulted in improved conversion and enantioselectivity (entries 2 and 3). In seeking to develop a procedure operationally simpler than the one we had previously employed for vinylation, we looked to identify an alternative to HF[11f] and thus circumvent handling of this hazardous, corrosive mineral acid. In this regard, we observed formation of the alkynylation product when the reaction was performed with a potassium fluoride salt and an excess of an acid promoter (entries 4–6).[13] Thus, the use of trifluoroacetic acid and KHF_2 (in a molar ratio of 2.5:1.5) was identified as optimal for the formation of product (86% yield and 98% *ee*; entry 7). Further optimization revealed that reducing the loading of nBu$_4$NBr and trifluoroborate **2a** had little impact on the overall performance of the Ir-catalyzed process

[*] J. Y. Hamilton, Dr. D. Sarlah, Prof. Dr. E. M. Carreira
ETH Zürich, HCI H335
8093 Zürich (Switzerland)
E-mail: carreira@org.chem.ethz

[**] We are grateful to the ETH Zürich and the Swiss National Science Foundation for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201302731.

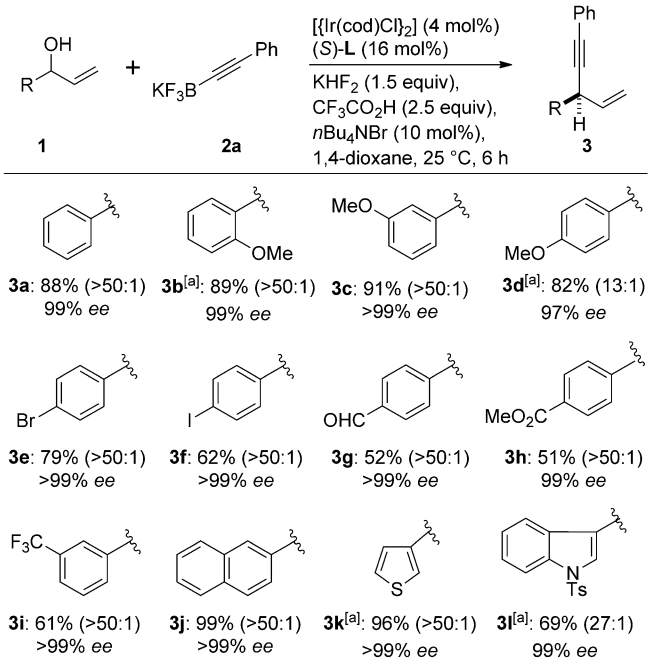
Table 1: Selected optimization studies.[a]



1a 2a 3a

Entry	**2a** [equiv]	F source (equiv)	Promoter (equiv)	PTC (mol%)[b]	Yield [%][c]	*ee* [%][d]
1	2.0	HF (2.0)	–	A (10)	41	84
2	2.0	HF (2.0)	MsOH (0.5)	B (50)	46	96
3	2.0	HF (2.0)	CCl_3CO_2H (0.5)	B (50)	49	95
4	2.0	KF (2.0)	CCl_3CO_2H (3.5)	B (50)	32	96
5	2.0	KF (2.0)	CF_3CO_2H (3.5)	B (50)	52	97
6	2.0	KHF_2 (1.0)	CF_3CO_2H (2.0)	B (50)	65	98
7	2.0	KHF_2 (1.5)	CF_3CO_2H (2.5)	B (50)	86	98
8	2.0	KHF_2 (1.5)	CF_3CO_2H (2.5)	B (10)	88	98
9	1.5	KHF_2 (1.5)	CF_3CO_2H (2.5)	B (10)	91	99
10	1.1	KHF_2 (1.5)	CF_3CO_2H (2.5)	B (10)	83	99

[a] Reaction conditions: **1a** (83.0 μmol, 1.0 equiv), [{Ir(cod)Cl}$_2$] (4.0 mol%), (*S*)-**L** (16.0 mol%), dioxane (0.17 mL), 25 °C for 24 h. [b] Phase-transfer catalyst (PTC): A: nBu_4NHSO_4; B: nBu_4NBr. [c] Determined by ^{1}H NMR integration relative to the internal standard (1,3,5-trimethoxybenzene). Ratio of branched-to-linear products determined by ^{1}H NMR integration and was always >50:1. [d] Determined by SFC on a chiral stationary phase. Absolute configuration determined by correlation.



Scheme 2. Scope of the direct, enantioselective, allylic alkynylation of aromatic allylic alcohols. All reactions were carried out on a 0.25 mmol scale under the standard conditions (see Table 1, entry 9). Yield is of the isolated product after purification by chromatography. Regioselectivity (reported in brackets) was determined by the ^{1}H NMR spectroscopy of the reaction mixture. *ee* values were determined by supercritical fluid chromatography (SFC) on a chiral stationary phase. [a] 1.1 equiv of **2a**, 1.1 equiv of KHF_2 and 1.6 equiv of CF_3CO_2H were used.

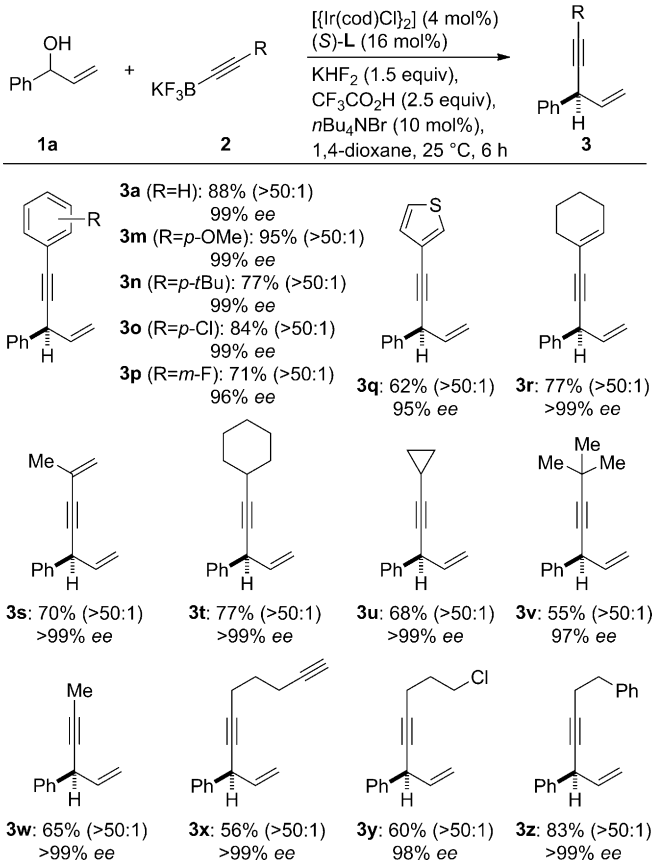
(entries 8–10). Thus, under optimal conditions including the use of 10 mol% of nBu_4NBr and 1.5 equivalents of **2a**, alkynylated product was furnished in 91% yield and 99% *ee* in 6 h (entry 9).

We next conducted a series of experiments to investigate the scope of allylic alcohols with potassium phenylethynyltrifluoroborate (**2a**), as summarized in Scheme 2. A wide range of alkoxy-substituted (products **3b**–**3d**) and halogenated (products **3e** and **3f**) aromatic substrates afforded the corresponding alkynes in good yields with high regio- and stereoselectivity. Although substrates bearing electron-withdrawing substituents (products **3g**–**3i**) were less reactive than the former, the observed selectivity was nonetheless excellent. In the case of highly electron-rich aromatics (products **3b**, **3d**, **3k**, and **3l**), high efficiency and enantiocontrol was achieved even when using reduced amounts of **2a**, KHF_2, and trifluoroacetic acid. It is noteworthy that allylic alcohol **1g**, containing a carbaldehyde, reacted exclusively at the allylic position to afford the corresponding aldehyde **3g**. In addition, other aromatics and heteroaromatics, such as naphthyl, thiophene, and indole (products **3j**–**3l**) proved to be good substrates for the reaction.

Subsequently, a range of potassium alkynyltrifluoroborates were evaluated to examine the generality of the method with respect to this substrate (Scheme 3). In this regard, allylic phenylalkynylation proceeded smoothly with methoxy-, alkyl-, and halogen-substituted benezenetrifluoroborates (products **3m**–**3p**). Furthermore, other aromatic systems can be successfully employed, as exemplified by 3-thienyl-substituted alkyne (product **3q**). In addition to aromatic alkynes, conjugated enynes (products **3r** and **3s**) were also tolerated, and the corresponding alkynes were obtained in good yields with excellent regio- and enantioselectivity. Finally, we tested the catalytic system with a series of aliphatic alkynes. A number of cycloalkyl- (products **3t** and **3u**) and alkyl-substituted alkynyltrifluoroborates (products **3v**–**3z**) proved to be good substrates for the substitution reaction. Importantly, various functional groups, such as a terminal alkyne (product **3x**) or chloride (product **3y**), are chemically inert in this Ir-catalyzed process, thus providing opportunities for further elaboration of the products.

To showcase the synthetic utility of the process, we applied the alkynylation chemistry to the synthesis of AMG 837 (**6**), a potent GPR40 receptor agonist developed by Amgen for the treatment of type 2 diabetes (Scheme 4).[14] Along these lines, allylic alcohol **4** was subjected to the substitution reaction under the optimized conditions using potassium 1-propynyltrifluoroborate (**2w**) and provided enyne **5** in 72% yield and excellent selectivity (40:1 branched/linear, >99% *ee*). Next, we tested the practicability and robustness of the described process by conducting the reaction on a larger scale (1.54 g, 4.0 mmol of **4**), applying lower Ir/(*S*)-**L** catalyst loadings (3/12 mol%), in technical grade solvent, and open to air. Gratifyingly, only a slight decrease in yield and selectivity was observed (67%, 98% *ee*). Subsequent chemoselective hydroboration of enyne **5**, followed by Jones oxidation of the corresponding alcohol, furnished **6** in 74% yield (>99% *ee*).[15]

In summary, we have developed an Ir-catalyzed alkynylation that allows the direct and highly enantioselective



Scheme 3. Scope of the potassium alkynyltrifluoroborates for the direct, enantioselective allylic alkynylation. All reactions were carried out on a 0.25 mmol scale under the standard conditions (see Table 1, entry 9). Yield is of the isolated product after purification by chromatography. Regioselectivity (reported in brackets) was determined by the ^{1}H NMR spectroscopy of the reaction mixture. *ee* values determined by SFC on a chiral stationary phase.

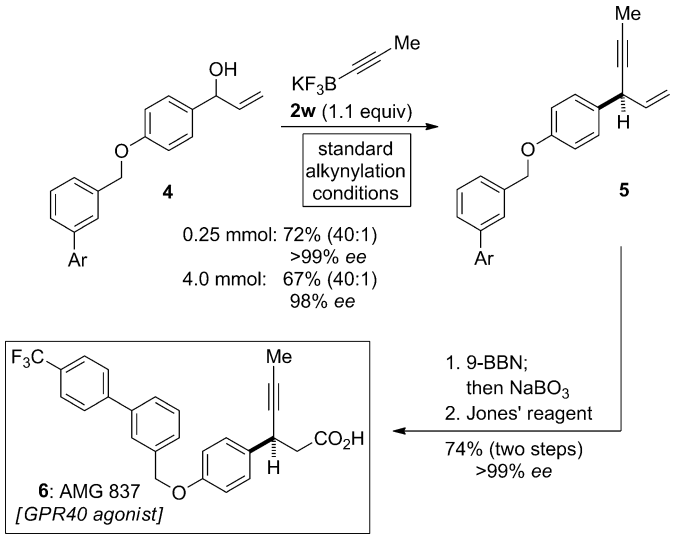
substitution of racemic allylic alcohols with potassium alkynyltrifluoroborates. Salient features of the process are excellent branched-to-linear selectivity and enantioselectivity. The use of alkynyltrifluoroborates expands the scope of reacting partners that can be used in Ir-catalyzed allylic substitutions well beyond the more traditional collection of carbon nucleophiles used to date. In addition, the value of this operationally simple protocol, which relies on the use of readily available and bench-stable reagents, has been highlighted in the enantioselective synthesis of medicinal agent AMG 837. Further investigations into the mechanism and applications of this transformation are ongoing and will be reported in due course.

Experimental Section

General procedure for asymmetric allylic alkynylation: [{Ir(cod)Cl}$_2$] (6.7 mg, 10.0 μmol, 4.0 mol%) and ligand (*S*)-**L** (20.3 mg, 40.0 μmol, 16.0 mol%) were placed in a polypropylene screw-capped vial (2.0 mL) with a magnetic stir bar. Then 1,4-dioxane (0.50 mL) was added, and the reaction mixture was vigorously stirred for 15 min, during which time the solution turned dark red. Allylic alcohol **1** (0.25 mmol, 1.0 equiv), potassium alkynyltrifluoroborate **2** (0.375 mmol, 1.5 equiv), nBu$_4$NBr (8.1 mg, 25.0 μmol, 10 mol%), KHF_2 (29.3 mg, 0.375 mmol, 1.5 equiv), and trifluoroacetic acid (47.8 μL, 0.625 mmol, 2.5 equiv) were added in the respective order, and the reaction vessel was purged with nitrogen. The resulting heterogeneous yellow/orange mixture was stirred at 25 °C for 6 h. Triethylamine (0.10 mL) and hexane (1.0 mL) were added, and the resulting mixture was directly subjected to flash chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the product.

Received: April 3, 2013
Published online: May 27, 2013

Keywords: alkynes · alkynyltrifluoroborates · allylic substitution · enantioselectivity · iridium



Scheme 4. Enantioselective synthesis of AMG 837 (**6**). Ar = 4-CF_3-C_6H_4, 9-BBN = 9-borabicyclo[3.3.1]nonane.

[1] a) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, A. H. Yamamoto), Springer, Berlin, **1999**, and *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, A. H. Yamamoto), Springer, Berlin, **2003** (For Supplement I); b) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley, New York, **2000**; c) *New Frontiers in Asymmetric Catalysis* (Eds.: K. Mikami, K. Lautens), Wiley, Hoboken, **2007**.

[2] a) *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**; b) *Acetylene Chemistry: Chemistry, Biology, and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), VCH, Weinheim, **2005**.

[3] For recent reviews, see: a) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963; b) G. Lu, Y. M. Li, X. S. Li, A. S. C. Chan, *Coord. Chem. Rev.* **2005**, *249*, 1736; c) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095; d) L. Pu, *Tetrahedron* **2003**, *59*, 9873.

[4] For examples, see: a) T. Nishimura, X.-X. Guo, T. Hayashi, *Chem. Asian J.* **2008**, *3*, 1505; b) M. Shirakura, M. Suginome, *Angew. Chem.* **2010**, *122*, 3915; *Angew. Chem. Int. Ed.* **2010**, *49*, 3827; c) B.-M. Fan, Q.-J. Yang, J. Hu, C.-L. Fan, S.-F. Li, L. Yu, C. Huang, W.-W. Tsang, F.-Y. Kwong, *Angew. Chem.* **2012**, *124*, 7941; *Angew. Chem. Int. Ed.* **2012**, *51*, 7821; for sequential hydroalkynylation/asymmetric 1,4-reduction, see: d) B. M. Trost, B. R. Taft, J. T. Masters, J.-P. Lumb, *J. Am. Chem. Soc.* **2011**, *133*, 8502.

[5] "Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis": *Topics in Organometallic Chemistry*, *Vol. 38* (Ed.: U. Kazmaier), Springer, Heidelberg, **2012**.
[6] For recent reviews, see: a) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824; b) Z. Lu, S. Ma, *Angew. Chem.* **2008**, *120*, 264; *Angew. Chem. Int. Ed.* **2008**, *47*, 258; c) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pamies, M. Dieguez, *Chem. Rev.* **2008**, *108*, 2796; d) C. A. Falciola, A. Alexakis, *Eur. J. Org. Chem.* **2008**, 3765; for allylic substitution with alkylboranes, see: e) Y. Shido, M. Yoshida, M. Tanabe, H. Ohmiya, M. Sawamura, *J. Am. Chem. Soc.* **2012**, *134*, 18573.
[7] J. A. Dabrowski, F. Gao, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 4778.
[8] H. Li, A. Alexakis, *Angew. Chem.* **2012**, *124*, 1079; *Angew. Chem. Int. Ed.* **2012**, *51*, 1055.
[9] For other asymmetric allylic alkylation reports employing enyne electrophiles, see: a) B. M. Trost, S. Hildbrand, K. Dogra, *J. Am. Chem. Soc.* **1999**, *121*, 10416; b) M. A. Kacprzynski, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 10676.
[10] For seminal contributions, see: a) R. Takeuchi, M. Kashio, *Angew. Chem.* **1997**, *109*, 268; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 263; b) J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025; c) T. Ohmura, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 15164.
[11] a) C. Defieber, M. A. Ariger, P. Moriel, E. M. Carreira, *Angew. Chem.* **2007**, *119*, 3200; *Angew. Chem. Int. Ed.* **2007**, *46*, 3139; b) M. Lafrance, M. Roggen, E. M. Carreira, *Angew. Chem.* **2012**, *124*, 3527; *Angew. Chem. Int. Ed.* **2012**, *51*, 3470; c) M. Roggen, E. M. Carreira, *Angew. Chem.* **2011**, *123*, 5683; *Angew. Chem. Int. Ed.* **2011**, *50*, 5568; d) M. Roggen, E. M. Carreira, *Angew. Chem.* **2012**, *124*, 8780; *Angew. Chem. Int. Ed.* **2012**, *51*, 8652; e) M. Schafroth, D. Sarlah, S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2012**, *134*, 20276; f) J. Y. Hamilton, D. Sarlah, E. M. Carreira, *J. Am. Chem. Soc.* **2013**, *135*, 994.
[12] For use of tetrabutylammonium salts in phase-transfer catalysis, see: a) A. N. Thadani, R. A. Batey, *Tetrahedron Lett.* **2003**, *44*, 8051; b) A. N. Thadani, R. A. Batey, *Org. Lett.* **2002**, *4*, 3827.
[13] For an example of the generation of HF in the organic phase when using a solid fluoride source, acid, and phase-transfer catalysis, see: G. Rothenberg, M. Royz, O. Arrad, Y. Sasson, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1491.
[14] M. Akerman, J. Houze, D. C. H. Lin, J. Liu, J. Luo, J. C. Medina, W. Qiu, J. D. Reagan, R. Sharma, S. J. Shuttleworth, Y. Sun, J. Zhang, L. Zhu, Int. Appl. PCT, WO 2005086661, **2005**.
[15] For previous enantioselective approaches, see: a) S. Cui, S. D. Walker, J. C. S. Woo, C. J. Borths, H. Mukherjee, M. J. Chen, M. M. Faul, *J. Am. Chem. Soc.* **2010**, *132*, 436; b) J. C. S. Woo, S. Cui, S. D. Walker, M. M. Faul, *Tetrahedron* **2010**, *66*, 4730; c) R. Yazaki, N. Kumagai, M. Shibasaki, *Org. Lett.* **2011**, *13*, 952.

