JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Highly Enantioselective Copper-Catalyzed Alkylation of β-Ketoesters and Subsequent Cyclization to Spirolactones/Bi-spirolactones

Qing-Hai Deng, Hubert Wadepohl, and Lutz H. Gade*

Anorganisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

Supporting Information

ABSTRACT: Cu-catalyzed enantioselective alkylation of β-ketoesters using alcohols for *in situ* preparation of alkylating reagents is reported. A number of functionalized β-ketoesters containing a quaternary carbon stereocenter are obtained with up to 99% ee. The alkylation products derived from 2-substituted allylic alcohols or their corresponding iodides can then be converted to spirolactones, bi-spirolactones, and related chiral target products.

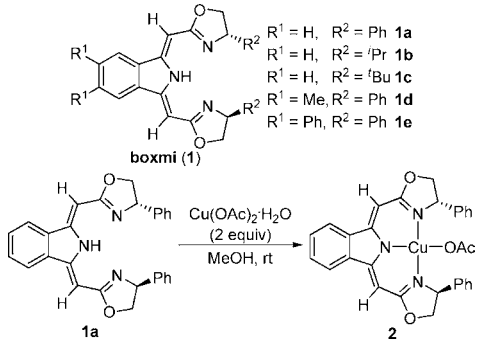
Enantioselective construction of organic target molecules containing all-carbon quaternary stereogenic centers is a challenge in organic synthesis[1] due to steric repulsion between the carbon substituents. Catalytic stereoselective alkylation of β-ketoesters generates chiral quaternary stereocenters with diverse substituents, which themselves offer manifold possibilities for further derivatization.[2] Several methods have been developed, such as Pd-catalyzed asymmetric allylic alkylation with allylic esters or analogues[3,4] and alkylation with halides by phase-transfer catalysis.[5,6] From a conceptual point of view, using alcohols[7,8] to generate alkylating reagents *in situ* is of particular interest because alcohols are among the most abundant and common organic feedstock.

Spirolactone frameworks are present in many biologically active natural products and pharmaceuticals.[9] However, their stereocontrolled synthesis, particularly generating an enantiopure spiro-quaternary stereocenter, poses a challenge.[10] Recently, Marini et al. reported the first organocatalyzed enantioselective synthesis of spirolactones starting from racemic cyclic β-ketoesters[11] and using a vinyl selenone as an alkylating agent.

We recently developed a class of chiral pincer ligands, boxmi (**1**, Scheme 1), which have shown great promise as stereodirecting ligands for transition metal catalysts.[12] Here we report highly enantioselective alkylation of β-ketoesters catalyzed by boxmi-Cu(II) catalysts, using benzylic and allylic alcohols to prepare the corresponding iodides *in situ* as alkylating reagents without further purification. The primary chiral alkylation products are then cyclized in a one-pot procedure to generate spirolactones or bi-spirolactones by adding $BF_3{\cdot}Et_2O$ in the presence of a Cu complex.

Although the Cu(II) catalysts employed in this study were generated *in situ*, Cu complexes bearing the chiral pincer ligand were readily isolable. Direct complexation of the protioligand **1a** with $Cu(OAc)_2{\cdot}H_2O$ in methanol at room temperature gave the corresponding Cu(II) acetato complex **2** (Scheme 1). The

Scheme 1. Chiral Pincer Ligands Boxmi (1) and the Synthesis of Copper Complex 2



molecular structure, established by X-ray diffraction, reveals a planar (rmsd 0.07 Å) T-shape coordination of the Cu(II) by the three N donors, augmented by O(3) of the acetate to a somewhat distorted square planar arrangement (rmsd 0.12 Å) (Figure 1).

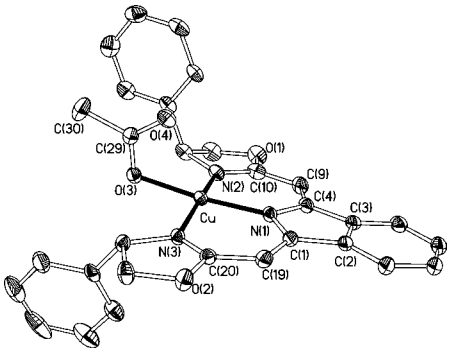


Figure 1. Molecular structure of [Cu(lig)(OAc)] (**2**); hydrogen atoms omitted for clarity.

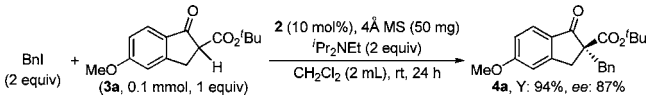
In a first test reaction, the isolated Cu complex **2** catalyzed the enantioselective alkylation of β-ketoester **3a** with benzyl iodide to obtain the product **4a** with 87% ee in 94% yield (Scheme 2).

Since benzyl iodide can be prepared from benzyl alcohol by treatment with CsI and $BF_3{\cdot}Et_2O$ in MeCN,[13] we used benzylic alcohol, converted *in situ* to benzyl iodide and quenched by diisopropylethylamine, without further purification to obtain

Received: December 20, 2011
Published: January 26, 2012

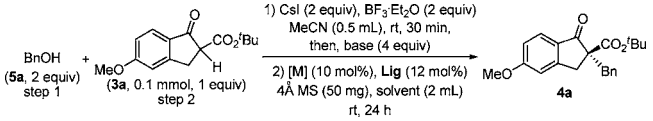
   dx.doi.org/10.1021/ja211859w | *J. Am. Chem. Soc.* 2012, 134, 2946–2949

Scheme 2. Initial Test of Alkylation



the desired alkylation product with the same enantioselectivity (Table 1, entry 1). The same result was obtained upon *in situ*

Table 1. Optimization of Reaction Conditions for the Alkylation of 3a



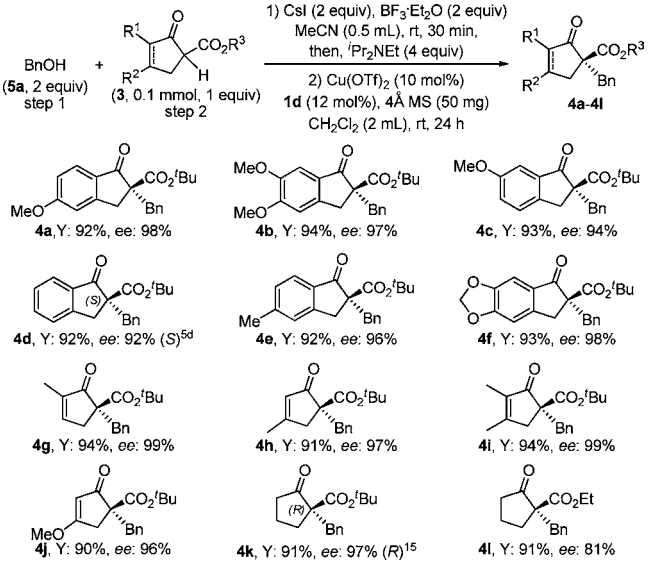
Entry	[M]	Lig.	base	solvent	yield (%)[a]	ee (%)[b]
1	**2**	--	^{i}Pr$_2$NEt	CH_2Cl_2	92	87
2	Cu(OAc)$_2$·H$_2$O	**1a**	^{i}Pr$_2$NEt	CH_2Cl_2	91	89
3	Cu(ClO$_4$)$_2$·6H$_2$O	**1a**	^{i}Pr$_2$NEt	CH_2Cl_2	83	95
4	Cu(OTf)$_2$	**1a**	^{i}Pr$_2$NEt	CH_2Cl_2	92	96
5	Cu(OTf)·0.5tol.	**1a**	^{i}Pr$_2$NEt	CH_2Cl_2	90	96
6	Cu(OTf)$_2$	**1a**	^{i}Pr$_2$NEt	Et_2O	77	93
7	Cu(OTf)$_2$	**1a**	^{i}Pr$_2$NEt	THF	83	28
8	Cu(OTf)$_2$	**1a**	^{i}Pr$_2$NEt	MeCN	76	44
9	Cu(OTf)$_2$	**1a**	Et_3N	CH_2Cl_2	25	87
10	Cu(OTf)$_2$	**1a**	lutidine	CH_2Cl_2	37	96
11	Cu(OTf)$_2$	**1a**	K_2CO_3	CH_2Cl_2	NR[c]	--
12	Cu(OTf)$_2$	**1b**	^{i}Pr$_2$NEt	CH_2Cl_2	91	79
13	Cu(OTf)$_2$	**1c**	^{i}Pr$_2$NEt	CH_2Cl_2	93	43
14	Cu(OTf)$_2$	**1d**	^{i}Pr$_2$NEt	CH_2Cl_2	92	98
15	Cu(OTf)$_2$	**1e**	^{i}Pr$_2$NEt	CH_2Cl_2	90	98

[a]Isolated yields. [b]Determined by HPLC analysis. [c]No reaction.

generation of the catalyst (entry 2), demonstrating that the catalyst system tolerates a variety of additional components without a significant effect on its performance. Cu(OTf)$_2$ was found to be optimal in terms of yield and enantioselectivity, while solvent screening showed that CH_2Cl_2 gave the best results (entries 4 and 6–8). Other organic bases led to much reduced catalyst activity. Finally, screening of a series of boxmi ligands revealed that higher selectivity was obtained with derivatives that contained 4-phenyloxazolinyl units at the "wing tips" of the pincer ligand (cf. entry 4 with entries 12 and 13). Furthermore, the appropriate substitution pattern in the ligand backbone[14] slightly improved the enantioselectivity (cf. entry 4 with entries 14 and 15). Ligand **1d**, which contained two methyl groups in the backbone, gave the product with the highest enantioselectivity (98% ee) in combination with a high yield (entry 14).

With these optimized reaction conditions we explored the generality of the protocol for different β-ketoesters by reaction with benzyl alcohol **5a**. As summarized in Scheme 3, indanone-derived *tert*-butyl β-ketoesters were found to be suitable for this catalytic transformation and provided products **4a**–**4f** in high yields and excellent enantioselectivities. Cyclopentanone-derived *tert*-butyl β-ketoesters were also successfully employed in the process to generate **4g**–**4k** with high selectivities. In contrast, the corresponding ethyl ester led to a significant decrease in enantioselectivity (**4l**). Substrates with six-

Scheme 3. Enantioselective Alkylation of β-Ketoesters with Benzyl Alcohol[a]

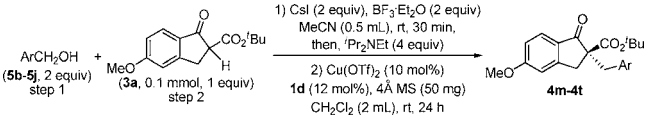


[a]Yields refer to isolated products; ee's were determined by HPLC analysis; absolute configurations of the products were determined by comparison with α_D values reported in the literature.

membered rings and acyclic ketoesters proved to be unreactive under these reaction conditions.

We next investigated the scope with respect to various benzylic alcohols (Table 2, entries 1–6) as well as naphthyl-

Table 2. Enantioselective Alkylation of 3a with Various Benzylic Alcohols



Entry	Ar	product	yield (%)[a]	ee (%)[b]
1	2-MeC$_6$H$_4$	**4m**	92	97
2	3-MeC$_6$H$_4$	**4n**	93	95
3	4-MeC$_6$H$_4$	**4o**	94	97
4	4-MeOC$_6$H$_4$	**4p**	94	98
5	4-BrC$_6$H$_4$	**4q**	92	96
6	4-ClC$_6$H$_4$	**4r**	91	95
7	1-naphthyl	**4s**	93	95
8	2-naphthyl	**4t**	93	97

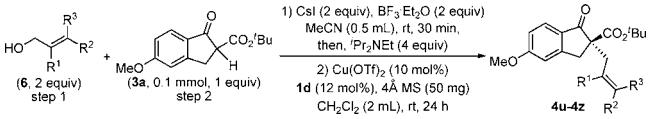
[a]Isolated yields. [b]Determined by HPLC analysis.

derived substrates (entries 7 and 8). All catalytic reactions provided the desired products in high yields and with excellent enantioselectivities.

The catalytic alkylation could also be readily extended to a range of substituted allylic alcohols (Table 3). Thus, treating β-ketoester **3a** with different substituted allylic alcohols yielded the target products **4u**–**4z** again in high yields and with excellent enantioselectivities (up to 99%). It is notable that the configuration of the double bond in products **4y** and **4z** is fully retained (entries 5 and 6) when using Cu complexes, whereas the use of nonligated Cu salts had previously given rise to mixtures resulting from double bond isomerization.[16]

dx.doi.org/10.1021/ja211859w | J. Am. Chem. Soc. 2012, 134, 2946–2949

Table 3. Enantioselective Alkylation of 3a with Various Allylic Alcohols

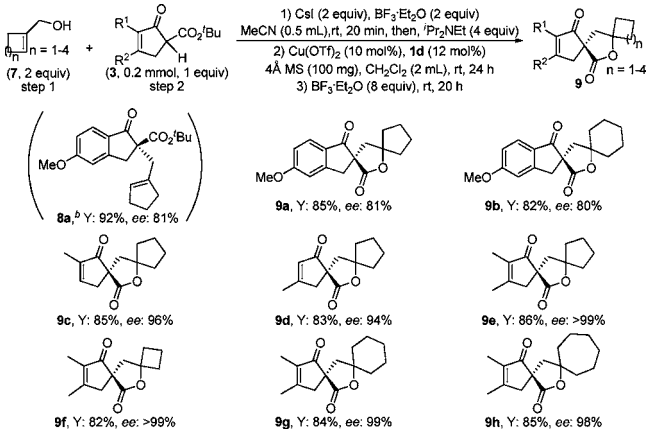


Entry	R^1	R^2	R^3	product	yield (%)[a]	ee (%)[b]
1	H	H	H	**4u**	92	99
2	H	Me	Me	**4v**	93	98
3	H	Ph	H	**4w**	92	98
4	Me	Ph	H	**4x**	94	97
5	H	Et	H	**4y**	93	98
6	H	H	Et	**4z**	91	95

[a]Isolated yields. [b]Determined by HPLC analysis.

The chiral allylation products obtained by using 2-substituted allylic alcohols **7** could be converted to bi-spirolactones **9** by adding 8 equiv of $BF_3{\cdot}Et_2O$[17] in a one-pot procedure (Scheme 4). We found that the Cu complex played a key role in the

Scheme 4. Enantioselective Synthesis of Bi-spirolactones 9[a]

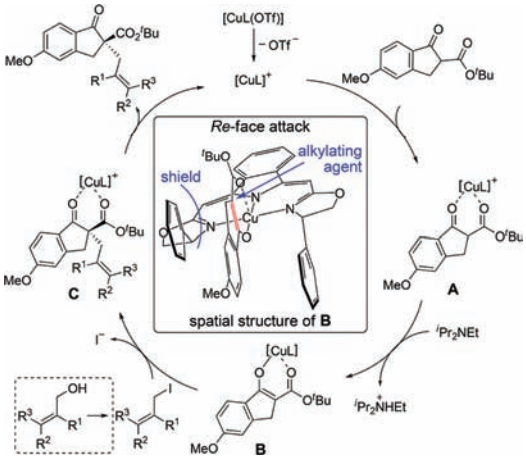


[a]Yields refer to isolated products based on substrate **3**; ee's were determined by HPLC analysis. [b]**8a** was the product of the second step.

cyclization.[18] In a control test without the Cu complex, only trace amounts of **9a** were obtained when the isolated pure alkylation product **8a**[16] was reacted with $BF_3{\cdot}Et_2O$ alone. Indanone-derived *tert*-butyl β-ketoester **3a** yielded products **9a**,**9b** with moderate enantioselectivities; however, cyclopentanone-derived *tert*-butyl β-ketoesters were converted to the corresponding bi-spirolactones **9c**–**9h** with excellent enantioselectivities.

Based on the results described above, a mechanism for this catalytic reaction is proposed in Scheme 5. In the initial step, two carbonyl oxygen atoms of the β-ketoester substrate coordinate to the Cu complex to give intermediate **A**, followed by deprotonation with DIPEA to form the key ester enolate intermediate **B**. This reacts with the benzyl or allyl iodide, generated *in situ* from the alcohol, to give intermediate **C**. Finally, de-coordination from intermediate **C** liberates the product and regenerates the catalyst. Based on the X-ray structure analysis of Cu complex **2**, we assume a molecular structure of intermediate **B** in which the *Si* face of the substrate is blocked by the phenyl group in the oxazolinyl unit and the alkylating agents therefore preferentially approach from the *Re*

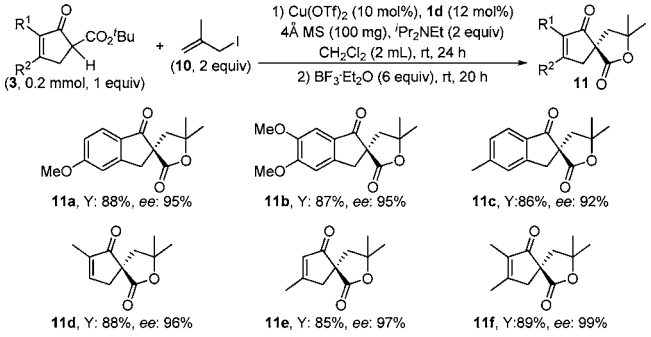
Scheme 5. Proposed Mechanism of the Cu^{II}-Catalyzed Alkylation of Cyclic β-Ketoesters



face of the substrate, consistent with the absolute configuration of products **4d** and **4k** (Scheme 3).

Occasionally, allyl iodides cannot be prepared from the corresponding alcohol by the $CsI/BF_3{\cdot}Et_2O$/MeCN protocol. This is the case for 3-iodo-2-methylpropene (**10**), for which the primary alkylation products were subsequently converted to spirolactones **11** upon addition of 6 equiv of $BF_3{\cdot}Et_2O$ using a one-pot procedure (Scheme 6).

Scheme 6. Enantioselective Synthesis of Spirolactones 11 Using 10 as the Allylating Reagent[a]



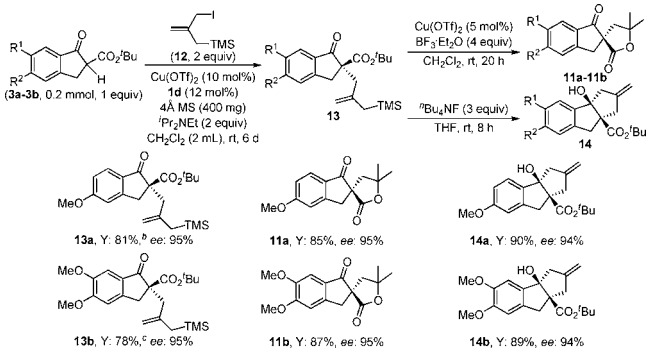
[a]Yields refer to isolated products on the basis of substrates **3**; ee's were determined by HPLC analysis.

This methodology also can be extended to the reaction of **3** with 3-iodo-2-[(trimethylsilyl)methyl]propene (**12**)[19] to provide the corresponding allylsilanes **13** with excellent enantioselectivities. The longer reaction times may be due to the steric hindrance of the bulky trimethylsilyl group in **12**. Combination of **13**, 4 equiv of $BF_3{\cdot}Et_2O$, and 5 mol % of $Cu(OTf)_2$ in dichloromethane at room temperature gave rise to spirolactones **11**, whereas reaction with 3 equiv of tetra-*n*-butylammonium fluoride in THF at room temperature provided the desilylative cyclization products **14** in high yields and enantioselectivities (Scheme 7).[20] Single-crystal X-ray structure analysis of *rac*-**14a** (see Supporting Information) showed that **14** was diastereoselectively generated as a *syn*-diastereomer.

In conclusion, Cu(II) complexes bearing the chiral pincer ligands boxmi (**1**) have been found to be highly efficient for the enantioselective alkylation of cyclic β-ketoesters. Benzyl and

dx.doi.org/10.1021/ja211859w | J. Am. Chem. Soc. 2012, 134, 2946–2949

Scheme 7. Stereoselective Synthesis of Allylsilanes 13 and Their Subsequent Transformations[a]



[a]0.10 mmol of **13** was used in the further transfer. Yields refer to isolated products for the individual step; ee's were determined by HPLC analysis. [b]11% of **3a** was recovered. [c]13% of **3b** was recovered.

allylic alcohols may be employed for the *in situ* preparation of iodides, which then act as alkylating reagents. This strategy has been extended to the one-pot asymmetric synthesis of spirolactones and bi-spirolactones by subsequent cyclization promoted by $BF_3{\cdot}Et_2O$, in which the Cu complex appeared to play a key role in both the alkylation and cyclization steps. Finally, β-ketoester-substituted allylsilanes were converted to spirolactones and bicyclic cyclopentanols with excellent enantioselectivities by subsequent treatment of the primary chiral allylation products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data for all new compounds, and crystallographic results for **2** and **14a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

lutz.gade@uni-hd.de

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Q.-H.D. acknowledges support by the Alexander von Humboldt Foundation. Funding was also provided by the Deutsche Forschungsgemeinschaft (SFB 623, TP B6).

■ REFERENCES

(1) For recent reviews and monograph of catalytic asymmetric synthesis of quaternary carbon centers, see: (a) Kumagai, N. *Chem. Pharm. Bull.* **2011**, *59*, 1. (b) Marco Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (c) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, *2007*, 5969. (d) Trost, B. M.; Jiang, C. *Synthesis* **2006**, *2006*, 369. (e) *Quaternary Stereocenters: Challenges and Solutions in Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley: 2005. (f) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (g) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(2) Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065.

(3) For Pd-catalyzed asymmetric allylic alkylation of β-ketoesters, see: (a) Trost, B. M.; Schäffner, B.; Osipov, M.; Wilton., D. A. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3548. (b) Nemoto, T.; Fukuda, T.; Matsumoto, T.; Hitomi, T.; Hamada, Y. *Adv. Synth. Catal.* **2005**, *347*, 1504. (c) Trost, B. M.; Sacchi, K. L.; Schroeder, G. M.; Asakawa, N. *Org. Lett.* **2002**, *4*, 3427. (d) Brunel, J. M.; Tenaglia, A.; Buono, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3585. (e) Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236. (f) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879.

(4) For recent reviews of Pd-catalyzed asymmetric allylic alkylation, see: (a) Guerrero Rios, I.; Rosas-Hernandez, A.; Martin, E. *Molecules* **2011**, *16*, 970. (b) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. (c) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (d) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (e) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. For Pd-catalyzed asymmetric benzylation of oxindoles, see: (f) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2010**, *132*, 15534.

(5) For phase-transfer catalyzed asymmetric alkylation of β-ketoesters, see: (a) Tari, S.; Chinchilla, R.; Nájera, C.; Yus, M. *ARKIVOC* **2011**, *vii*, 116. (b) Hashimoto, T.; Sasaki, K.; Fukumoto, K.; Murase, Y.; Ooi, T.; Maruoka, K. *Synlett* **2009**, *4*, 661. (c) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897. (d) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796.

(6) For recent reviews of asymmetric phase transfer catalysis, see: (a) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679. (b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (c) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222.

(7) For nonasymmetric alkylation of β-ketoesters with allylic alcohols, see: (a) Tao, Y.; Wang, B.; Wang, B.; Qu, L.; Qu, J. *Org. Lett.* **2010**, *12*, 2726. (b) Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241. (c) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. (d) Bergbreiter, D. E.; Weatherford, D. A. *J. Chem. Soc., Chem. Commun.* **1989**, 883.

(8) For asymmetric allylation of other nucleophiles with allylic alcohols, see: (a) Jiang, G.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471. (b) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508. (c) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314.

(9) (a) Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 7562. (b) Bister, B.; Bischoff, D.; Ströbele, M.; Riedlinger, J.; Reicke, A.; Wolter, F.; Bull, A. T.; Zähner, H.; Fiedler, H.-P.; Süssmuth, R. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2574. (c) Elger, W.; Beier, S.; Pollow, K.; Garfield, R.; Shi, S. Q.; Hillisch, A. *Steroids* **2003**, *68*, 891. (d) Wood, C. A.; Lee, K.; Vaisberg, A. J.; Kingston, D. G. I.; Neto, C. C.; Hammond, G. B. *Chem. Pharm. Bull.* **2001**, *49*, 1477. (e) Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, *3*, 1925.

(10) Bartoli, A.; Rodier, F.; Commeiras, L.; Parrain, J.-L.; Chouraqui, G. *Nat. Prod. Rep.* **2011**, *28*, 763 and references therein.

(11) Sternativo, S.; Calandriello, A.; Costantino, F.; Testaferri, L.; Tiecco, M.; Marini, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 9382.

(12) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *Chem.—Eur. J.* **2011**, *17*, 14922.

(13) Hayat, S.; Rahman, A.-U.; Khan, K. M.; Choudhary, M. I.; Maharvi, G. M.; Ullah, Z.; Bayer, E. *Synth. Commun.* **2003**, *33*, 2531.

(14) Langlotz, B.; Wadepohl, H.; Gade, L. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4670.

(15) Kei, M. *Tetrahedron* **1998**, *54*, 14465.

(16) Racemates of products were obtained by using racemic ligand.

(17) (a) Sünnemann, H. W.; Hofmeister, A.; Magull, J.; De Meijere, A. *Chem.—Eur. J.* **2007**, *13*, 3739. (b) Papanikos, A.; Meldal, M. *J. Comb. Chem.* **2004**, *6*, 181.

(18) Adrio, L. A.; Quek, L. S.; Taylor, J. G.; Hii, K. K. M. *Tetrahedron* **2009**, *65*, 10334.

(19) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 5032.

(20) Molander, G. A.; Andrews, S. W. *Tetrahedron Lett.* **1986**, *27*, 3115.