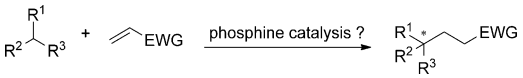
Asymmetric Catalysis

DOI: 10.1002/ange.201208285

Chiral Phosphine Catalyzed Asymmetric Michael Addition of Oxindoles**

*Fangrui Zhong, Xiaowei Dou, Xiaoyu Han, Weijun Yao, Qiang Zhu, Yuezhong Meng, and Yixin Lu**

Asymmetric synthesis through catalysis by nucleophilic phosphines has advanced rapidly in recent years as a powerful and versatile tool for the preparation of chiral organic molecules.[1] Despite the broad scope of reactions that can be catalyzed by nucleophilic phosphines, asymmetric reactions mediated by chiral phosphines are very limited. In a general mode of activation, a tertiary phosphine adds to activated alkenes, allenes, or alkynes to form a zwitterion, which then gets trapped by a suitable electrophile. The (aza)-Morita–Baylis–Hillman (MBH) reaction[2] and various annulations belong to this category. Notably, the 1,3-dipolar nature of the zwitterions derived from allenes and alkynes, in combination with a variety of potential 1,3-dipolarophiles, such as activated alkenes and imines, make annulations highly divergent and synthetically valuable.[3] Kinetic resolution of alcohols is another phosphine-promoted asymmetric reaction that has been relatively well studied.[4] More recently, MBH adducts have been intensively investigated as a reaction partner in the allylic alkylations and cycloadditions.[5] On the other hand, the above-mentioned zwitterion intermediates can also behave as organic bases for the deprotonation of pronucleophiles. In fact, employment of such an in situ generated zwitterion as a base in the Michael addition of 2-nitropropane to electron-deficient olefins was first reported by White and Baizer almost four decades ago.[6] Recently, the utilization of Brønsted basicity of the zwitterionic intermediates in mechanistically relevant γ-additions has drawn much attention.[7] In sharp contrast, very little attention was paid to the conceptually simple Michael addition; only a few sporadic examples were reported,[8] despite the fact that such transformations are synthetically extremely useful.[9] To the best of our knowledge, there is no report on an asymmetric Michael addition mediated by a chiral phosphine (Scheme 1). Herein,

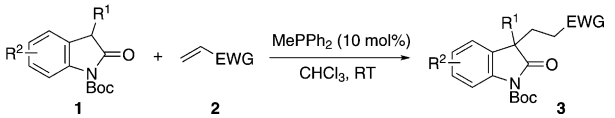


Scheme 1. Phosphine-catalyzed asymmetric Michael addition. EWG = electron-withdrawing group.

we document the first highly enantioselective Michael additions that were mediated by chiral phosphine catalysts derived from amino acids.

To demonstrate the value of chiral phosphines in promoting asymmetric Michael addition, we chose 3-substituted oxindoles[10] as pronucleophiles, as the Michael products of such reactions, 3,3-disubstituted oxindoles, are molecules of great biological importance.[11] To our delight, the reaction between oxindole **1a** and methyl vinyl ketone (MVK) **2a** proceeded smoothly in the presence of methyl diphenylphosphine (10 mol%), and the Michael adduct **3a** was obtained quantitatively within five minutes (Table 1, entry 1). The reaction was found to be applicable to a wide range of 3-aryl- and 3-alkyl-substituted oxindoles (Table 1, entries 2–11). The

Table 1: Michael addition of 3-substitued oxindoles to activated alkenes.[a]



1 2 3

Entry	R^1, R^2	EWG (**2**)	**3**	*t*	Yield [%][b]
1	C_6H_5, H	COMe	**3a**	5 min	98
2	4-F-C_6H_4, H	COMe	**3b**	5 min	97
3	4-Ph-C_6H_4, H	COMe	**3c**	5 min	93
4	3-Me-C_6H_4, H	COMe	**3d**	5 min	90
5	3,5-Me_2-C_6H_3, H	COMe	**3e**	5 min	93
6	2-naphthyl, H	COMe	**3f**	5 min	96
7	benzyl, H	COMe	**3g**	12 h	98
8	C_6H_5, 5-Me	COMe	**3h**	5 min	93
9	C_6H_5, 5-F	COMe	**3i**	5 min	92
10	C_6H_5, 7-Cl	COMe	**3j**	5 min	95
11	C_6H_5, 5,7-Me_2	COMe	**3k**	5 min	94
12	C_6H_5, H	COEt	**3l**	5 min	93
13	C_6H_5, H	COPh	**3m**	10 min	92
14	C_6H_5, H	CHO	**3n**	5 min	88
15[c]	C_6H_5, H	CO_2Et	**3o**	5 h	71
16[c]	C_6H_5, H	CN	**3p**	12 h	63
17	C_6H_5, H	(BocN=NBoc)	**3q**	6 h	85

[a] Reactions were performed with **1** (0.1 mmol), **2** (0.3 mmol), and $MePPh_2$ (0.01 mmol) in $CHCl_3$ (1.0 mL). [b] Yields of isolated products. [c] Reaction was performed with PPh_3 (0.01 mmol) in CH_3CN (1 mL) under reflux. Boc = *tert*-butoxycarbonyl.

[*] F. Zhong, X. Dou, X. Han, W. Yao, Q. Zhu, Prof. Dr. Y. Lu
Department of Chemistry & Medicinal Chemistry Program
Life Sciences Institute, National University of Singapore
3 Science Drive 3, Singapore 117543 (Singapore)
E-mail: chmlyx@nus.edu.sg
Prof. Dr. Y. Meng
State Key Laboratory of Optoelectronic Materials and Technologies and the Key Laboratory of Low-Carbon Chemistry & Energy Conservation of Guangdong Province, Sun Yat-Sen University
Guangzhou 510275 (China)

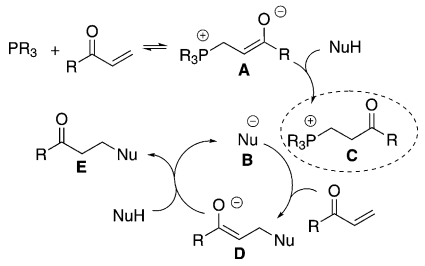
[**] We thank the National University of Singapore and the Ministry of Education (MOE) of Singapore (R-143-000-362-112), the Singapore-Peking-Oxford Research Enterprise (COY-15-EWI-RCFSA/N197-1), and GSK-EDB (R-143-000-491-592) for generous financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201208285.

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

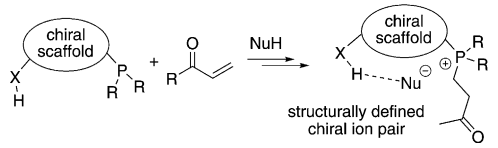
catalytic system also worked well for other activated terminal alkenes, including ethyl vinyl ketone, phenyl vinyl ketone, and acrolein (Table 1, entries 12–14). It is noteworthy that acrylate and acrylonitrile, which are substrates with lower reactivity in Michael addition,[12] were also found to be suitable electrophiles (Table 1, entries 15 and 16). Moreover, amination of oxindole **3a** could be realized with the employment of di-*tert*-butyl azodicarboxylate (DBAD; Table 1, entry 17).

Our next goal was to develop an enantioselective process for the above reaction. A plausible mechanism for a phosphine-mediated Michael addition is illustrated in Scheme 2.



Scheme 2. Phosphine-mediated Michael addition.

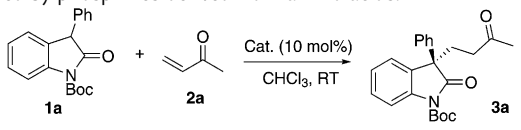
The conjugate addition of phosphine to electron-deficient alkenes generates zwitterion **A**, which deprotonates the incoming nucleophile, resulting in the formation of an ion pair that consists of the anionic form of the nucleophile (**B**) and phosphonium intermediate **C**. Subsequently, addition of **B** to the alkene substrate leads to enolate **D**, which abstracts a proton from the nucleophile to afford the final Michael adduct **E** and complete the catalytic cycle. In order to develop an asymmetric version of this reaction, stereochemical control has to be in place during the addition of **B** to the activated alkene. Apparently, efficient chirality transfer from phosphonium **C** to the addition product in the C–C bond-forming step through ion-pairing interactions is not trivial, which partly explains why there was no literature precedent on phosphine-catalyzed asymmetric Michael addition.[13] We reasoned that bifunctional phosphines may provide a solution to this long-standing problem. We hypothesized that employment of phosphine catalysts that contains an appropriately arranged hydrogen-bond-donating motif may provide constraint to the nucleophile–phosphonium ion pair through hydrogen-bonding interaction with the nucleophile, and such a structurally well-defined ion pair may likely have better stereochemical interactions with the incoming activated alkene (Scheme 3).



Scheme 3. Induction of asymmetry in Michael additions through bifunctional chiral phosphines.

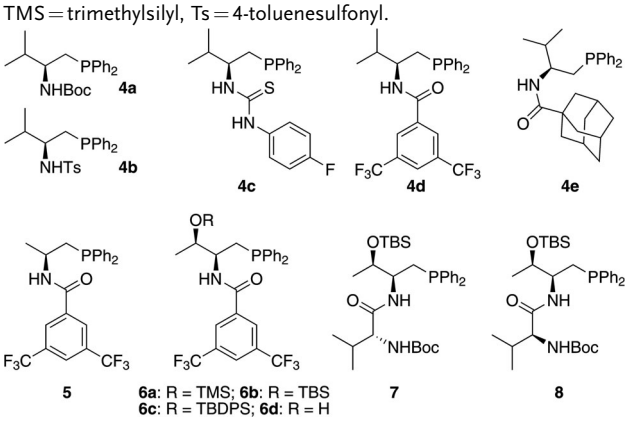
With such a design principle in mind, we investigated the Michael addition of 3-phenyl oxindole **1a** to MVK **2a** mediated by a chiral phosphine (Table 2). A set of bifunctional phosphines derived from amino acids[14] were selected, which have been shown previously to be high effective,

Table 2: Asymmetric Michael addition of oxindole **1a** to MVK **2a** catalyzed by phosphines derived from amino acids.[a]



Entry	Cat.	*t*	Yield [%][b]	*ee* [%][c]
1	**4a**	5 min	95	33
2	**4b**	5 min	94	20
3	**4c**	5 min	96	5
4	**4d**	5 min	97	59
5	**4e**	5 min	93	30
6	**5**	5 min	93	32
7	**6a**	5 min	91	55
8	**6b**	5 min	98	27
9	**6c**	5 min	95	35
10	**6d**	5 min	89	7
11	**7**	5 min	95	5
12	**8**	5 min	94	19
13[d]	**4d**	10 min	95	76
14[e]	**4d**	24 h	96	94

[a] Reactions were performed with **1a** (0.05 mmol), **2a** (0.15 mmol), and the catalyst (0.005 mmol) in $CHCl_3$ (0.75 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was performed at 0 °C. [e] The reaction was performed at −55 °C. TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.



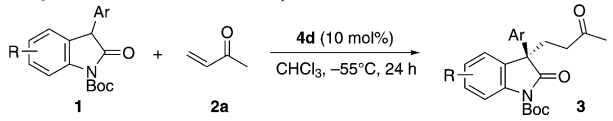
tunable, and versatile in a range of enantioselective organic transformations.[15] We were pleased to discover that valine-based catalysts were effective, the reactions were completed in five minutes and some asymmetric induction was achieved (Table 2, entries 1–5). In particular, phosphine amide **4d**, which bears a 3,5-bistrifluoromethylbenzoyl group, turned out to be a promising catalyst, furnishing the desired product with 59% *ee* (Table 2, entry 4). However, introduction of a sterically more-hindered threonine core[16] into the catalyst structure (**6a–c**) did not lead to further improvement, nor did the employment of less-hindered alanine-based compound **5** or compound **6d**, which contains a free hydroxy group

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

(Table 2, entries 6–10). The dipeptide backbone[3i] also turned out to be ineffective (Table 2, entries 11–12). Solvent screening showed that $CHCl_3$ was the best reaction medium (see the Supporting Information for details). When the reaction was performed at −55 °C, the desired Michael adduct was isolated in 96 % yield and with 94 % *ee* (Table 2, entry 14).

The generality of the reaction was next evaluated by employing various 3-substituted oxindoles (Table 3). Different 3-aryl-substituted oxindoles were well tolerated, and high yields and excellent enantioselectivities were attained (Table 3, entries 1–7). Moreover, the substituents on the oxindole core could also be varied, and high yields and *ee* values were obtained (Table 3, entries 8–12). The absolute configurations of the Michael adducts were determined by comparing the optical rotation of **3a** with the reported value.[10b]

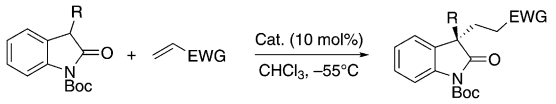
Table 3: Michael addition of 3-aryl-substituted oxindoles **1** to **2a**.[a]

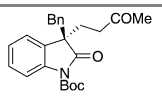
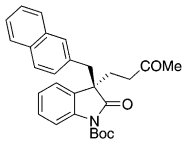
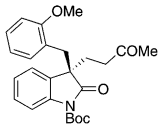
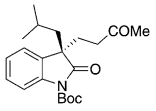
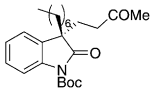
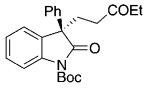
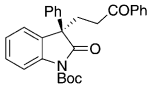
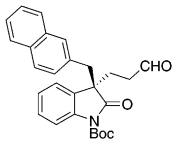


Entry	Ar, R	3	Yield [%][b]	*ee* [%][c]
1	C_6H_5, H	**3a**	96	94
2	4-F-C_6H_4, H	**3b**	93	92
3	4-*t*Bu-C_6H_4, H	**3r**	89	95
4	4-Ph-C_6H_4, H	**3c**	93	94
5	3-Me-C_6H_4, H	**3d**	91	89
6	4-OMe-C_6H_4, H	**3s**	97	94
7	2-naphthyl, H	**3f**	94	90
8	C_6H_5, 5-Me	**3h**	95	95
9	C_6H_5, 5-F	**3i**	91	86
10	C_6H_5, 7-F	**3t**	94	96
11	C_6H_5, 7-Cl	**3j**	90	86
12	C_6H_5, 5,7-Me	**3k**	90	91

[a] Reactions were performed with **1** (0.05 mmol), **2a** (0.15 mmol), and **4d** (0.005 mmol) in $CHCl_3$ (0.75 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase.

Table 4: Michael addition of various 3-alkyl-substituted oxindoles **1** to different alkenes **2**.[a]



Entry	Product	Cat.	*t* [h]	3	Yield [%][b]	*ee* [%][c]
1		**6a**	72	**3g**	87	90
2		**6a**	72	**3u**	75	89
3		**6a**	72	**3v**	81	91
4		**4d**	72	**3w**	78	79
5		**4d**	72	**3x**	73	83
6		**4d**	24	**3l**	92	88
7		**6d**	24	**3m**	93	82
8		**6a**	24	**3y**	83	71

[a] Reactions were performed with **1** (0.05 mmol), **2** (0.15 mmol), and the catalyst (0.005 mmol) in $CHCl_3$ (0.75 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase.

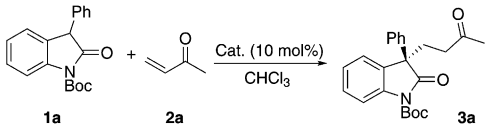
3-Alkyl-substituted oxindoles exhibit much lower reactivity than their aryl-substituted counterparts. Furthermore, stereochemical controls for these two types of substrates may be quite different. In fact, few catalytic systems can work well for both aryl- and alkyl-substituted substrates. Given the efficiency that our catalysts had displayed for 3-aryl-substitued oxindoles, and high tunability of our catalytic systems, we decided to search for a solution by fine-tuning the catalyst structures. For oxindoles with a benzyl-type substituent at the 3-position, a bulkier catalyst **6a** with an OTMS group led to the formation of adducts with excellent enantiomeric excesses (Table 4, entries 1–3). For linear or branched 3-alkyl-substituted oxindole substrates, **4d** was found to be the best catalyst, affording the products with good *ee* values (Table 4, entries 4 and 5). Moreover, other electron-deficient alkenes, including ethyl vinyl ketone, phenyl vinyl ketone, and acrolein, could also be employed, and good results were attained (Table 4, entries 6–8).

The phosphorus species that were involved in the reaction were investigated by ^{31}P NMR spectroscopy.[17] Catalyst **4d** showed a resonance at −22.7 ppm. When **4d** was mixed with MVK, a new resonance at 32.7 ppm appeared, suggesting the presence of a phosphonium enolate.[18] We also took ^{31}P NMR spectra during the reaction progress; two resonances at −22.7 ppm and 32.7 ppm presented in the course of the reaction. These results suggested that the resting state of the catalyst is phosphonium ketone **C**,[19] and there is clearly an equilibrium between the phosphine catalyst and the phosphonium enolate intermediate.

The Brønsted acid moiety of the chiral phosphines was conceivably crucial for the asymmetric induction. Accordingly, we prepared the *N*-methylated phosphine **9** and compared its catalytic effects with those of catalyst **4d** (Table 5). The presence of the amide NH in **4d** was shown to be crucial for both reactivity and enantioselectivity of the reaction; in the presence of *N*-methylated **9**, the Michael

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

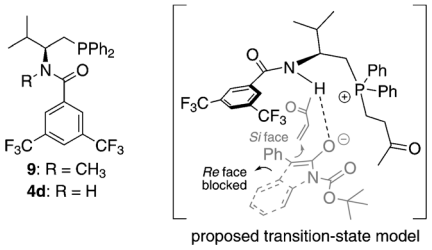
Table 5: Michael additions promoted by different phosphines and the proposed transition-state model.[a]



1a **2a** **3a**

Entry	Cat.	*T*	*t*	Yield [%][b]	*ee* [%][c]
1	**9**	−55 °C	24 h	trace	–
2	**9**	RT	5 h	94	13
3	**4d**	RT	5 min	97	59

[a] Reactions were performed with **1a** (0.05 mmol), **2a** (0.15 mmol), and the catalyst (0.005 mmol) in $CHCl_3$ (0.75 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase.



addition did not proceed at −55 °C (entry 1), and furnished the addition product with only 13 % *ee* at room temperature (entry 2). In comparison, 59 % *ee* was attained when **4d** was used as the catalyst under otherwise identical conditions (Table 5, entry 3). On the basis of these experimental results, a plausible transition-state model was presented. We propose that the hydrogen-bonding interaction between the amide NH and the enolate oxygen atom of the nucleophile facilitates formation of the nucleophile–phosphonium ion pair,[20] and makes the latter more structurally defined. The presence of the 3,5-CF_3-substituted phenyl ring blocks the *Re* face and makes the approach of the incoming electrophile from the *Si* face more favorable.

In summary, we have reported the first highly enantioselective Michael addition of oxindoles catalyzed by chiral phosphines. It is noteworthy that the asymmetry induced by the nucleophilic bifunctional phosphine in the Michael addition is unprecedented, and we believe that this novel mode of asymmetric induction will extend the scope of phosphine-mediated asymmetric catalysis and open up new avenues to the design of enantioselective organic processes. Currently, we are extending the concept demonstrated in this report to other important organic transformations, and theoretical studies to fully understand the origin of the observed enantioselectivity are also in progress.

Received: October 15, 2012
Published online: December 7, 2012

Keywords: alkenes · amino acids · bifunctional phosphines · Michael addition · oxindoles

[1] For reviews, see: a) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535; b) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035; c) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140; d) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102; e) A. Marinetti, A. Voituriez, *Synlett* **2010**, 174; f) S.-X. Wang, X. Han, F. Zhong, Y. Lu, *Synlett* **2011**, 2766; g) Q.-Y. Zhao, Z. Lian, Y. Wei, M. Shi, *Chem. Commun.* **2012**, *48*, 1724; for related examples, see: h) A. Sakakura, A. Ukai, K. Ishihara, *Nature* **2007**, *445*, 900; i) A. Sakakura, M. Sakuma, K. Ishihara, *Org. Lett.* **2011**, *13*, 3130.

[2] For reviews on (aza)-MBH reactions, see: a) D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447; b) P. Langer, *Angew. Chem.* **2000**, *112*, 3177; *Angew. Chem. Int. Ed.* **2000**, *39*, 3049; c) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811; d) G. Masson, C. Housseman, J. Zhu, *Angew. Chem.* **2007**, *119*, 4698; *Angew. Chem. Int. Ed.* **2007**, *46*, 4614; e) D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev.* **2007**, *36*, 1581; f) Y.-L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 2905; g) G.-N. Ma, J.-J. Jiang, M. Shi, Y. Wei, *Chem. Commun.* **2009**, 5496; h) V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1; i) Y. Wei, M. Shi, *Acc. Chem. Res.* **2010**, *43*, 1005.

[3] For selected examples on phosphine-catalyzed annulation reactions, see: a) C. Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906; b) G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836; c) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1454; *Angew. Chem. Int. Ed.* **2006**, *45*, 1426; d) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988; e) Y. Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660; f) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *J. Am. Chem. Soc.* **2008**, *130*, 14030; g) M. Sampath, T.-P. Loh, *Chem. Sci.* **2010**, *1*, 739; h) H. Xiao, Z. Chai, C.-W. Zheng, Y.-Q. Yang, W. Liu, J.-K. Zhang, G. Zhao, *Angew. Chem.* **2010**, *122*, 4569; *Angew. Chem. Int. Ed.* **2010**, *49*, 4467; i) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726; j) Y. Fujiwara, G. C. Fu, *J. Am. Chem. Soc.* **2011**, *133*, 12293; k) H. Guo, Q. Xu, O. Kwon, *J. Am. Chem. Soc.* **2009**, *131*, 6318; l) R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard III, H. Guo, O. Kwon, *J. Am. Chem. Soc.* **2011**, *133*, 13337; m) Q. Zhang, L. Yang, X. Tong, *J. Am. Chem. Soc.* **2010**, *132*, 2550; n) X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem.* **2012**, *124*, 791; *Angew. Chem. Int. Ed.* **2012**, *51*, 767.

[4] a) E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430; b) E. Vedejs, O. Daugulis, *J. Am. Chem. Soc.* **1999**, *121*, 5813; c) E. Vedejs, O. Daugulis, J. A. MacKay, E. Rozners, *Synlett* **2001**, 1499; d) E. Vedejs, O. Daugulis, N. Tuttle, *J. Org. Chem.* **2004**, *69*, 1389.

[5] For a review, see: a) T.-Y. Liu, M. Xie, Y.-C. Chen, *Chem. Soc. Rev.* **2012**, *41*, 4101; for selected examples with phosphine catalysis, see: b) Y.-Q. Jiang, Y.-L. Shi, M. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 7202; c) C.-W. Cho, J.-R. Kong, M. J. Krische, *Org. Lett.* **2004**, *6*, 1337; d) Q.-G. Wang, S.-F. Zhu, L.-W. Ye, C.-Y. Zhou, X.-L. Sun, Y. Tang, Q.-L. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1914; e) B. Tan, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 4672; f) F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem.* **2011**, *123*, 7983; *Angew. Chem. Int. Ed.* **2011**, *50*, 7837; g) H.-P. Deng, Y. Wei, M. Shi, *Adv. Synth. Catal.* **2012**, *354*, 783; h) F. Zhong, G.-Y. Chen, X. Han, W. Yao, Y. Lu, *Org. Lett.* **2012**, *14*, 3764; i) F. Zhong, J. Luo, G.-Y. Chen, X. Dou, Y. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 10222.

[6] D. A. White, M. M. Baizer, *Tetrahedron Lett.* **1973**, *14*, 3597.

[7] a) B. M. Trost, C.-J. Li, *J. Am. Chem. Soc.* **1994**, *116*, 3167; b) C. Zhang, X. Lu, *Synlett* **1995**, 645; c) B. M. Trost, G. R. Dake, *J. Org. Chem.* **1997**, *62*, 5670; d) B. M. Trost, C.-J. Li, *J. Am. Chem. Soc.* **1994**, *116*, 10819; e) Y. K. Chung, G. C. Fu, *Angew. Chem.* **2009**, *121*, 2259; *Angew. Chem. Int. Ed.* **2009**, *48*, 2225; f) S. W.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Smith, G. C. Fu, *J. Am. Chem. Soc.* **2009**, *131*, 14231; g) J. Sun, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 4568; h) R. Sinisi, J. Sun, G. C. Fu, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20652; i) Y. Fujiwara, J. Sun, G. C. Fu, *Chem. Sci.* **2011**, *2*, 2196.

[8] a) T. Yoshida, S. Saito, *Chem. Lett.* **1982**, 1587; b) R. B. Grossman, D. S. Pendharkar, B. O. Patrick, *J. Org. Chem.* **1999**, *64*, 7178; c) I. C. Stewart, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 8696; d) G.-L. Zhao, M. Shi, *Tetrahedron* **2005**, *61*, 7277; e) C. Gimbert, M. Lumbierres, C. Marchi, M. Moreno-Mañas, R. M. Sebastián, A. Vallribera, *Tetrahedron* **2005**, *61*, 8598; f) V. Sriramurthy, G. A. Barcan, O. Kwon, *J. Am. Chem. Soc.* **2007**, *129*, 12928; g) X. Wang, F. Fang, C. Zhao, S.-K. Tian, *Tetrahedron Lett.* **2008**, *49*, 6442; h) D. Bhuniya, S. Mohan, S. Narayanan, *Synthesis* **2003**, 1018; i) O. Baslé, S. Porcel, S. Ladeira, G. Bouhadir, D. Bourissou, *Chem. Commun.* **2012**, *48*, 4495.

[9] For reviews, see: a) D. Almaşi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701.

[10] For selected examples on the Michael additions of 3-substituted oxindoles, see: a) T. Bui, S. Syed, C. F. Barbas III, *J. Am. Chem. Soc.* **2009**, *131*, 8758; b) R. He, C. Ding, K. Maruoka, *Angew. Chem.* **2009**, *121*, 4629; *Angew. Chem. Int. Ed.* **2009**, *48*, 4559; c) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9168; d) R. He, S. Shirakawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 16620; e) X. Li, B. Zhang, Z.-G. Xi, S. Luo, J.-P. Cheng, *Adv. Synth. Catal.* **2010**, *352*, 416; f) T. Zhang, L. Cheng, S. Hameed, L. Liu, D. Wang, Y.-J. Chen, *Chem. Commun.* **2011**, *47*, 6644; g) C. Wang, X. Yang, D. Enders, *Chem. Eur. J.* **2012**, *18*, 4832.

[11] For reviews, see: a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209; b) R. M. Williams, R. J. Cox, *Acc. Chem. Res.* **2003**, *36*, 127; c) H. Lin, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 38; *Angew. Chem. Int. Ed.* **2003**, *42*, 36; d) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; e) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003; f) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381; for our work on constructing chiral oxindole cores, see: g) Q. Zhu, Y. Lu, *Angew. Chem.* **2010**, *122*, 7919; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753; h) F. Zhong, G.-Y. Chen, Y. Lu, *Org. Lett.* **2011**, *13*, 82; i) F. Zhong, X. Han, Y. Wang, Y. Lu, *Chem. Sci.* **2012**, *3*, 1231; j) X. Dou, X. Han, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 85.

[12] Michael additions of 3-substituted oxindoles to acrylates and acrylonitrile are unknown; employment of one equivalent of DIPEA or DBU did not give the desired adduct.

[13] R. B. Grossman, S. Comesse, R. M. Rasne, K. Hattori, M. N. Delong, *J. Org. Chem.* **2003**, *68*, 871.

[14] For reviews on asymmetric catalysis mediated by amino acids and peptides, see: a) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807; b) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047; c) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759.

[15] For our recent account, see reference [1f]; for examples reported by us, see: a) F. Zhong, Y. Wang, X. Han, K.-W. Huang, Y. Lu, *Org. Lett.* **2011**, *13*, 1310; b) X. Han, Y. Wang, F. Zhong, Y. Lu, *Org. Biomol. Chem.* **2011**, *9*, 6734; c) X. Han, S.-X. Wang, F. Zhong, Y. Lu, *Synthesis* **2011**, 1859; d) Q. Zhao, X. Han, Y. Wei, M. Shi, Y. Lu, *Chem. Commun.* **2012**, *48*, 970; also see references [3i,n, 5f,h,i, 11i]; for other examples, see: e) K. Ishihara, Y. Kosugi, M. Akakura, *J. Am. Chem. Soc.* **2004**, *126*, 12212; f) Y. Kosugi, M. Akakura, K. Ishihara, *Tetrahedron* **2007**, *63*, 6191; g) K. Ishihara, Y. Kosugi, S. Umemura, A. Sakakura, *Org. Lett.* **2008**, *10*, 3191; h) A. Sakakura, S. Umemura, K. Ishihara, *Synlett* **2009**, 1647.

[16] a) L. Cheng, X. Han, H. Huang, M. W. Wong, Y. Lu, *Chem. Commun.* **2007**, 4143; b) L. Cheng, X. Wu, Y. Lu, *Org. Biomol. Chem.* **2007**, *5*, 1018; c) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812; d) Q. Zhu, Y. Lu, *Chem. Commun.* **2010**, *46*, 2235; e) X. Dou, F. Zhong, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 13945; also see references[3i,n, 5f,h,i, 11i,j, 15a–d].

[17] See the Supporting Information for ^{31}P NMR spectra.

[18] H. G. Alt, H. I. Hayen, *J. Organomet. Chem.* **1986**, *316*, 301.

[19] This result is consistent with an observed phosphonium ketone intermediate, see [8c].

[20] A. Sakakura, R. Kondo, Y. Matsumura, M. Akakura, K. Ishihara, *J. Am. Chem. Soc.* **2009**, *131*, 17762.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim