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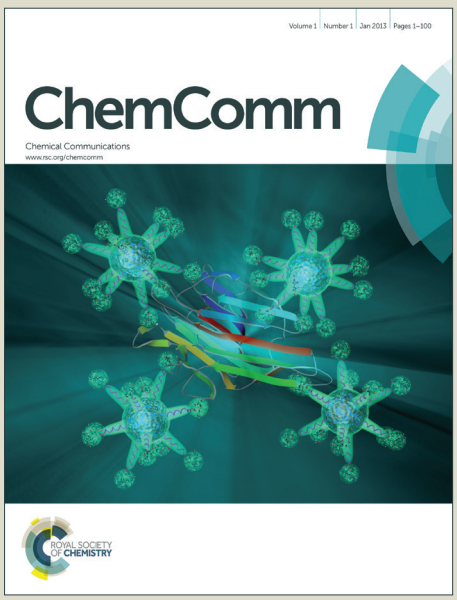

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Enantioselective Synthesis of 3-Fluoro-3-allyl-oxindoles via Phosphine-Catalyzed Asymmetric γ-addition of 3-Fluoro-Oxindoles to 2,3-Butadienoates

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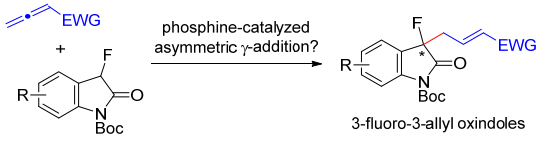
The first phosphine-catalyzed enantioselective γ-addition of 3-fluoro-oxindoles to 2,3-butadienoates has been developed. A range of 3-fluoro-substituted oxindole substrates were employed, and oxindoles containing a 3-fluoro quaternary center were constructed in high yields and with excellent enantioselectivities. The γ-addition products could be converted readily to optically enriched 3-fluoro-3-allyl oxindole derivatives.

Fluorine-containing molecules have captured much attention from synthetic chemists, due to their great importance in medicinal chemistry and pharmaceutical industry.[1] Thus, various synthetic strategies have been devised for efficient preparation of fluorinated compounds in the past years.[2]

Optically enriched 3,3'-disubstituted oxindoles are important structural motifs that commonly present in many natural products and bioactive molecules. In particular, oxindoles bearing a 3-fluoro substituted quaternary stereogenic center are highly interesting.[3] Enantioselective electrophilic fluorination of prochiral oxindoles is the most common and efficient strategy for the construction of such structural motifs.[4] In 2000, Shibata and co-workers first employed cinchona alkaloids and Selectfluor as enantioselective fluorinating reagents.[5] Shortly after, similar strategy was disclosed by the Cahard group.[6] Many catalytic systems for enantioselective fluorination of oxindoles were reported subsequently, including: (*S*)-DM-BINAP-Pd complex, chiral dbfox-Ph-Ni(II), N,N'-dioxide-Sc(III) complex, chiral NHC-Pd, and organo bis-cinchona alkaloids.[7,8] Our group is interested in creating fluorinated chiral molecules, particularly those with quaternary centers. We took indirect approaches to access chiral fluorinated molecules via asymmetric carbon-carbon and carbon-heteroatom bond formation by employing prochiral fluorinated synthons.[9] However, utilization of 3-fluorinated oxindoles is rare, and our early report[10] on amine-catalyzed conjugate addition of 3-fluoro-substituted oxindoles to a vinyl sulfone was the only example. Given the biological importance of 3-fluorinated oxindoles, development of an efficient method to access this type of structural motifs seems to be highly desirable.

Remarkable progress has been made in nucleophilic phosphine catalysis in the past decade, and now phosphine-catalyzed organocatalytic reactions have been firmly established as powerful tools to access structurally diverse chiral molecules in synthetic organic chemistry.[11] In this context, phosphine-catalyzed γ-addition reactions of γ-substituted allenoates/alkynoates have drawn much attention.[12,13] We recently disclosed[14] the first utilization of 2,3-butadienoates in enantioselective γ-addition reactions catalyzed by our amino acid-based chiral phosphines.[15] To further extend the power of phosphine-catalyzed γ-addition reactions, we became interested in exploring 3-fluoro-substitued oxindoles as potential partners for this type of reaction. Herein, we document a phosphine-catalyzed enantioselective γ-addition of 3-fluoro-oxindoles to allenoates, leading to the formation of novel oxindole derivatives containing a 3-fluorinated quaternary center (Scheme 1).



Scheme 1 Synthesis of oxindoles containing a 3-fluorinated quaternary center.

We chose N-Boc-3-fluoro-oxindole (**5a$_1$**) and allenoate (**6c**) as model compounds to investigate γ-addition reaction. The catalytic effects of a number of amino acid-based bifunctional phosphines were examined, and the results are summarized in Table 1. All the phosphine catalysts were sufficiently effective to promote the projected γ-reaction. L-Valine-derived phosphines containing either a thiourea or sulfonamide functional group led to the formation of the desired γ-addition products in excellent yields, but with poor to moderate enantioselectivities (entries 1–4). Phosphine–amide catalysts were found to be very efficient, furnishing the desired products in very good yields and excellent enantioselectivities (entries 5–10). L-Threonine-derived phosphine-amide **2g** turned out

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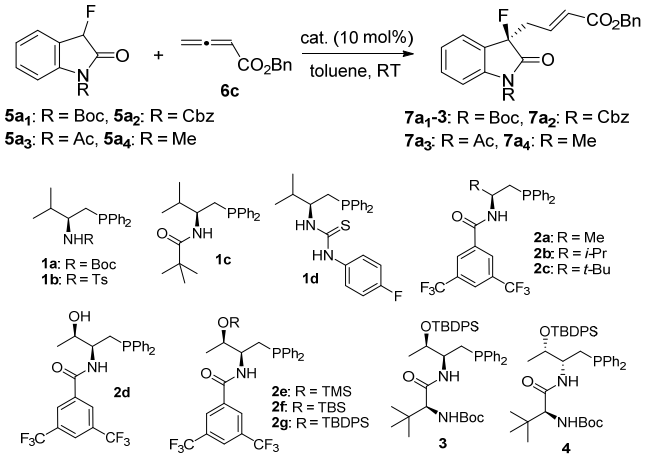
to be the best catalyst, affording the γ-addition product **7a** in 95% yield and with 93% ee (entry 11). The dipeptide phosphines, however, were found to be ineffective (entries 12 and 13). Employing catalyst **2g**, we also examined oxindoles with different *N*-protective groups (entries 14–16), and *N*-Boc group remained the best.

Table 1 Screening of different phosphine catalysts for asymmetric γ-addition of 3-fluoro-oxindole **5a** to 2,3-butadienoate **6c**[a]



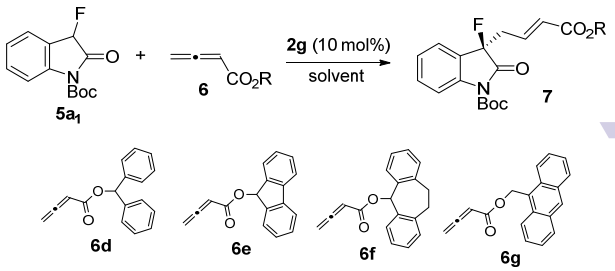
Entry	Cat.	R(**5a**)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**1a**	Boc(**5a$_1$**)	1	88	32
2	**1b**	Boc(**5a$_1$**)	0.5	95	55
3	**1c**	Boc(**5a$_1$**)	1	88	41
4	**1d**	Boc(**5a$_1$**)	0.5	98	77
5	**2a**	Boc(**5a$_1$**)	1	95	90
6	**2b**	Boc(**5a$_1$**)	1	93	90
7	**2c**	Boc(**5a$_1$**)	2	88	88
8	**2d**	Boc(**5a$_1$**)	2	89	64
9	**2e**	Boc(**5a$_1$**)	2	93	93
10	**2f**	Boc(**5a$_1$**)	2	92	92
11	**2g**	**Boc(5a$_1$)**	**2**	**95**	**93**
12	**3**	Boc(**5a$_1$**)	2	90	6
13	**4**	Boc(**5a$_1$**)	2	90	-9
14	**2g**	Cbz(**5a$_2$**)	2	86	93
15	**2g**	Ac(**5a$_3$**)	4	82	83
16	**2g**	Me(**5a$_4$**)	4	<5	--

[a] Reactions were performed with **5a** (0.05 mmol), **6c** (0.06 mmol) and catalyst (0.005 mmol) in toluene (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. TBDPS = tert-butyldiphenylsilyl, TBS = tert-butyldimethylsilyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl. Cbz = carboxybenzyl, Ac = acetyl.

Having identified the best catalyst (**2g**), we next attempted to further improve the results by optimizing all the reaction parameters (Table 2). Allenoate **6c** with a benzyl ester group was shown to be the best among all the different allenoates tested (entries 1–8). In addition, α- and γ-substituted allenoates were also examined, and shown to have limited reactivity and selectivity.[1] Subsequently, solvent screening was performed, and toluene remained the best reaction medium (entries 9–13). Furthermore, lowering the reaction temperature was not beneficial (entry 14).

With the optimal reaction conditions in hand, scope of the reaction was then evaluated. Various 3-fluorinated oxin-doles with different substituents and substitution patterns were tested, and the results are summarized in Table 3. Different halide substitutions on the aromatic ring were well tolerated, and the corresponding adducts were obtained in high yields and with excellent enantioselectivities (entries 1–4). The oxindoles with either electron-withdrawing or electron-donating substituents were also suitable substrates (entries 5–7). Moreover, bis-substituted 3-fluoro-oxindole could also be used (entry 8). The absolute configurations of the γ-addition products were determined by comparing the optical rotation of a derivative (**9**) with the value reported in the literature.[7f]

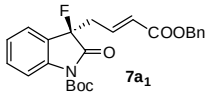
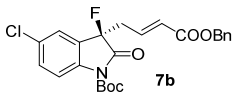
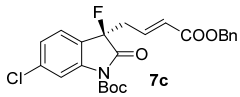
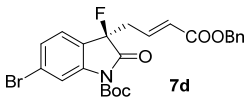
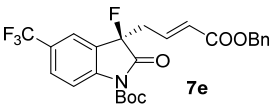
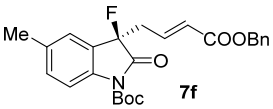
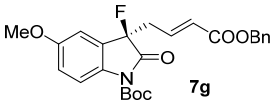
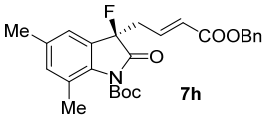
Table 2 Optimization of reaction conditions[a]



Entry	R(**6**)	Solvent	**7**	Yield (%)[b]	Ee (%)[c]
1	Me(**6a**)	toluene	**7a$_1$-1**	92	91
2	*t*-Bu(**6b**)	toluene	**7a$_1$-2**	90	91
3	Bn (**6c**)	toluene	**7a$_1$-3**	95	93
4	**6d**	toluene	**7a$_1$-4**	91	93
5	**6e**	toluene	**7a$_1$-5**	92	93
6	**6f**	toluene	**7a$_1$-6**	89	92
7	**6g**	toluene	**7a$_1$-7**	85	86
8	Ph(**6h**)	toluene	**7a$_1$-8**	88	77
9	Bn(**6c**)	xylene	**7a$_1$-3**	95	90
10	Bn(**6c**)	Et_2O	**7a$_1$-3**	88	73
11[d]	Bn(**6c**)	$CHCl_3$	**7a$_1$-3**	90	88
12[d]	Bn(**6c**)	CH_2Cl_2	**7a$_1$-3**	92	92
13[e]	Bn(**6c**)	EtOAc	**7a$_1$-3**	81	45
14[f]	Bn(**6c**)	toluene	**7a$_1$-3**	83	69

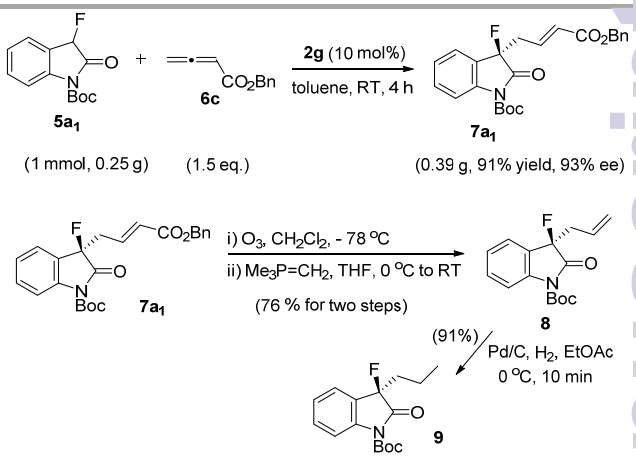
[a] Reactions were performed with **5a$_1$** (0.05 mmol), **6** (0.06 mmol) and **2g** (0.005 mmol) in the solvent (0.2 mL) specified at room temperature for 2 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction time was 4 h. [e] The reaction time was 6 h. [f] Performed at 0 °C for 12 h.

Table 3 Scope of asymmetric γ-addition of 3-fluoro-oxindoles **5** to allenoate **6c**[a]

Entry	7	Time (h)	Yield (%)[b]	Ee (%)[c]
1	 **7a$_1$**	2	95	93
2	 **7b**	0.5	93	83
3	 **7c**	0.5	95	94
4	 **7d**	2	95	94
5	 **7e**	2	95	92
6	 **7f**	2	94	90
7	 **7g**	2	92	94
8	 **7h**	2	88	90

[a] Reactions were performed with **5** (0.05 mmol), **6c** (0.06 mmol) and **2g** (0.005 mmol) in toluene (0.2 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

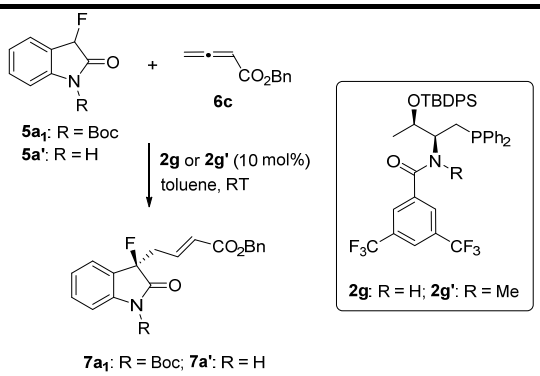
Although the reactions were generally performed in small scales, scale-up could be done easily. When the reaction was performed with 1 mmol of oxindole **5a$_1$**, the desired quaternary 3-fluoro-oxindole **7a$_1$** was obtained in essentially same chemical yield and enantioselectivity. The γ-addition product could be converted to a 3-allyl substituted oxindole **8** in high yield through a few trivial steps. Saturation of the double bond yielded 3-fluoro-3-alkyl substituted oxindole derivative **9** in good yield (Scheme 2).



Scheme 2 Elaboration of γ-addition products.

At this stage, we have not performed detailed mechanistic studies[17] to elucidate the origin of stereochemical outcome. It is intuitive to correlate hydrogen bonding interactions between N-Boc of substrates and the amide moiety of the catalyst with observed asymmetric induction. This hypothesis was supported experimentally; employment of the methylated catalyst **2g'**, or utilizing oxindole **5a'** without N-Boc group led to dramatically decreased enantioselectivity (Table 4).

Table 4 Asymmetric γ-addition promoted by different phosphines: investigating the importance of H-bond[a]



Entry	5	2	t(h)	7/Yield (%)[b]	Ee (%)
1	**5a$_1$**	**2g**	2	7a/95	93
2	**5a$_1$**	**2g'**	4	7a/85	37
3	**5a'**	**2g**	2	7a'/81	43

[a] Reaction conditions: oxindole (0.05 mmol), **6c** (0.12 mmol), and catalyst (0.005 mmol) in toluene (0.5 mL). [b] Isolated yield. Determined by HPLC analysis on a chiral stationary phase.

In conclusion, we have developed the phosphine-catalyzed asymmetric γ-addition of 3-fluorinated oxindoles to allenoate for the first time. The desired quaternary 3-fluoro

substituted oxindoles were obtained in high yields and with excellent enantioselectivities. Given the importance of oxindole compounds and fluorinated molecules in medicinal chemistry, the products derived via our method may be biologically very useful. Evaluation of bioactivities of molecules synthesized and theoretical studies to understand stereochemical origin of the reaction are underway.

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Notes and references

1 For general reviews on fluorinated compounds in medicinal chemistry, see: (*a*) K. Muller, C. Faeh, F. Diederich, *Science*, 2007, **317**, 1881; (*b*) K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305; (*c*) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. 2008, **37**, 320; (*d*) D. O'Hagan, *Chem. Soc. Rev.* 2008, **37**, 308.

2 For reviews, see: (*a*) H. Ibrahim and A. Togni, *Chem. Commun.*, 2004, 1147; (*b*) K. Mikami, Y. Itoh, M. Yamanaka, *Chem. Rev.*, 2004, **10**, 1; (*c*) M. Oestreich, *Angew. Chem., Int. Ed.*, 2005, **44**, 2324; (*d*) P. M. Pihko, *Angew. Chem., Int. Ed.*, 2006, **45**, 544; (*e*) G. K. S. Prakash, P. Beier, *Angew. Chem., Int. Ed.*, 2006, **45**, 2172; (*f*) V. A. Brunet, D. O'Hagan, *Angew. Chem., Int. Ed.*, 2008, **47**, 1179; (*g*) J.-A. Ma, D. Cahard, *Chem. Rev.*, 2008, **108**, 1; (*h*) C. Hollingworth, V. Gouverneur, *Chem. Commun.*, 2012, **48**, 2929.

3 (*a*) V. K. Gribk ff , J. E. Starrett Jr., S. L. Dworetzky, P. Hewawasam, C. G. Boissard, D. A. Cook, S. W. Frantz, K. Heman, J. R. Hibbard, K. Huston, G. Johnson, B. S. Krishnan, G. G. Kinney, L. A. Lombardo, N. A. Meanwell, P. B. Molinoff, R. A. Myers, S. L. Moon, A. Ortiz, L. Pajor, R. L. Pieschl, D. J. Post-Munson, L. J. Signor, N. Srinivas, M. T. Taber, G. Thalody, J. T. Trojnacki, H. Wiener, K. Yeleswaram and S. W. Yeola, *Nat. Med.*, 2001, **7**, 471; (*b*) P. Hewawasam, V. K. Gribko ff, Y. Pendri, S. I. Dworetzky, N. A. Meanwell, E. Martinez, C. G. Boissard, D. J. Post-Munson, J. T. Trojnacki, K. Yeleswaram, L. M. Pajor, J. Knipe, Q. Gao, R. Perrone and J. E. Starrett Jr., *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1023.

4 (*a*) J.-A. Ma, D. Cahard, *Chem. Rev.*, 2004, **104**, 6119; (*b*) K. Muñiz, *Angew. Chem., Int. Ed.*, 2001, **40**, 1653.

5 (*a*) N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc.*, 2001, **123**, 7001; (*b*) N. Shibata, T. Ishimaru, E. Suzuki and K. L. Kirk, *J. Org. Chem.*, 2003, **68**, 2494; (*c*) N. Shibata, E. Suzuki, and Y. Takeuchi, *J. Am. Chem. Soc.* 2000, **122**, 10728.

6 (a) D. Cahard, C. Audouard, J.-C. Plaquevent, N. Roques, *Org. Lett.*, 2000, **2**, 3699; (*b*) L. Zoute, C. Audouard, J.-C. Plaquevent, D. Cahard, *Org. Biomol. Chem.* 2003, **1**, 1833.

7 For metal-catalytic enantioselective fluorination of oxindoles, see: (*a*) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.,* 2005, **127**, 10164; (*b*) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem., Int. Ed.*, 2005, **44**, 4204; (*c*) Q.-H. Deng, H. Wadepohl, L. H. Gade, *Chem.–Eur. J.*, 2011, **17**, 14922; (*d*) J. Li, Y. Cai, W. Chen, X. Liu, L. Lin, X. Feng, *J. Org. Chem.*, 2012, **77**, 9148; (*e*) K. Shen, X. H. Liu, L. L. Lin, X. M. Feng, *Chem. Sci*. 2012, **3**, 327; (*f*) Z. Wang, Z. L. Zhang, Q. Yao, X. H. Liu, Y. F. Cai, L. L. Lin, X. M. Feng, *Chem.–Eur. J.* 2013, **19**, 8591; (*g*) L. Wu, L. Falivene, E. Drinkel, S. Grant, A. Linden, L. Cavallo, R. Dorta, *Angew. Chem., Int. Ed.*, 2012, **51**, 2870; (*h*) X. Gu, Y. Zhang, Z.-J. Xu, C.-M. Che, *Chem. Commun.,* 2014, **50**, 7870.

8 For organocatalytic asymmetric synthesis of 3-fluoro-3-a… oxindoles, see: T. Ishimaru, N. Shibata, T. Horikawa, N… Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem., In… Ed.*, 2008, **47**, 4157.

9 For examples reported by us, see: (*a*) Kwiatkowski, J.; Lu, … *Org. Biomol. Chem.* 2015, **13**, 2350; (*b*) Kwiatkowski, J.; Lu, … *Eur. J. Org. Chem.* 2015, 320; (*c*) Kwiatkowski, J.; Lu, Y. … *Chem. Commun.* 2014, **50**, 9313; (*d*) Kwiatkowski, J.; Lu, … *Asian J. Org. Chem.* 2014, **3**, 458; (*e*) Luo, J.; Wu, W.; Xu, L. … W.; Meng, Y.; Lu, Y. *Tetrahedron Lett.* 2013, **54**, 2623; (*f*) Liu … C.; Dou, X.; Lu, Y.; *Org. Lett.* 2011, **13**, 5248; (*g*) X. Han, … Zhong, Y. Lu, *Adv. Synth. Catal.* 2010, **352**, 2778; (h) Han, X.; Luo, J.; Liu, C.; Lu, Y. *Chem. Commun.* 2009, 2044; (*i*) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int… Ed.* 2009, **48**, 7604.

10 X. Dou, Y. Lu, *Org. Biomol. Chem*., 2013, **11**, 5217.

11 For selected 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. Voitur… *Synlett* 2010, 174; (*f*) S.-X. Wang, X. Han, F. Zhong, Y. Li, *Synlett* 2011, 2766; (*g*) Q.-Y. Zhao, Z. Lian, Y. Wei, M. …, *Chem. Commun.* 2012, **48**, 1724; (*h*) Y. C. Fan, O. Kwon, *Chem, Commun.,* 2013, **49**, 11588; (*i*) Z. Zhang, X. Xu, O. Kwon, *Chem. Soc. Rev.*, 2014, **43**, 2927; (*j*) Y. Xiao, Z. Sun, … Guo, O. Kwon, *Beil. J. Org. Chem.,* 2014, **10**, 2089.

12 For pioneering studies on phosphine-mediated γ-additions… see: (*a*) B. M. Trost, C.-J. Li, *J. Am. Chem. Soc.* 1994, **11**… 10819; (*b*) B. M. Trost, C.-J. Li, *J. Am. Chem. Soc.* 1994, **116**, 3167; (*c*) B. M. Trost, G. R. Dake, *J. Org. Chem.* 1997, **6**… 5670; (*d*) C. Zhang, X. Lu, *synlett.* 1995, 645; (*e*) Z. Chen, … Zhu, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Org. Chem.* 199… **63**, 5631; (*f*) C. Zhang, X. Lu, *synlett.* 1995, 645.

13 For selected asymmetric γ-additions, see: (*a*) Y. K. Chung, … C. Fu, *Angew. Chem. Int. Ed.* 2009, **48**, 2225; (*b*) S. W. Smith, G. C. Fu, *J. Am. Chem. Soc.* 2009, **131**, 14231; (*c*) R. Sinisi, … Sun, G. C. Fu, *Proc. Natl. Acad. Sci*. USA 2010, **107**, 20652; (… J. Sun, G. C. Fu, *J. Am. Chem. Soc.* 2010, **132**, 4568; (*e*) Y. Fujiwara, J. Sun, G. C. Fu, *Chem. Sci.* 2011, **2**, 2196; (*f*) R. … Lundgren, A. Wilsily, N. Marion, C. Ma, Y. K. Chung, G. C. Fu, *Angew. Chem. Int. Ed.* 2013, **52,** 2525; (*g*) J. Chen, Y. Cai, G. Zhao, *Adv. Synth. Catal.* 2014, **356**, 359.

14 T. Wang, W. Yao, F. Zhong, G. H. Pang, Y. Lu, *Angew. Chem. Int. Ed.* 2014, *53*, 2964.

15 (*a*) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* 2011, **133**, 1726; (*b*) X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* 2012, **51**, 767; (*c*) F. Zhong, X. Han, Y. Wang, … Lu, *Chem. Sci.* 2012, **3**, 1231; (*d*) F. Zhong, X. Han, Y. Wang, … Lu, *Angew. Chem. Int. Ed.* 2011, **50**, 7837; (*e*) F. Zhong, G.-Y… Chen, X. Han, W. Yao, Y. Lu, *Org. Lett.*, 2012, **14**, 3764; (*f*) … Han, W. Yao, T. Wang, Y. R. Tan, Z. Yan, J. Kwiatkowski, Y. L…, *Angew. Chem. Int. Ed.* 2014, **53**, 5643; (*g*) X. Han, S.-X. Wan… F. Zhong, Y. Lu, *Synthesis* 2011, 1859; (*h*) F. Zhong, J. Luo, G… Y. Chen, X. Dou, Y. Lu, *J. Am. Chem. Soc.* 2012, **134**, 10222; … F. Zhong, X. Dou, X. Han, W. Yao, Q, Zhu, Y. Meng, Y. Lu, *Angew. Chem. Int. Ed.* 2013, **52**, 943; (*j*) W. Yao, X. Dou, Y. …u, *J. Am. Chem. Soc.* 2015, **137**, 54; (*k*) X. Han, S.-X. Wang, F. Zhong, Y. Lu, *Synthesis* 2011, 1859.

16 See the ESI (Scheme S2) for details.

17 See our proposed mechanism in ESI. For examples of recently mechanistic studies, see: (a) Y. Xia, Y. Liang, Y. Che…, M. Wang, L. Jiao, F. Huang, S. Liu, Y. Li, Z.-X. Yu, *J. Am. Chem… Soc.* 2007, **129**, 3470; (*b*) Y. Liang, S. Liu, Y. Xia, Y. Li, Z.-X. Yu, *Chem.–Eur. J.* 2008, **14**, 4361; (*c*) Y. Liang, S. Liu, Z.-X. Yu, *Synlett* 2009, 905; (*d*) T. Dudding, O. Kwon, E. Mercier, *Org. Lett.* 2006, **8**, 3643.