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Phosphine-Mediated Regio- and Stereoselective Hydrocarboxylation of Enynes

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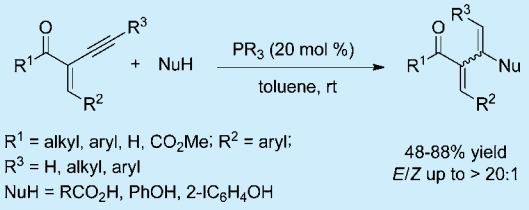
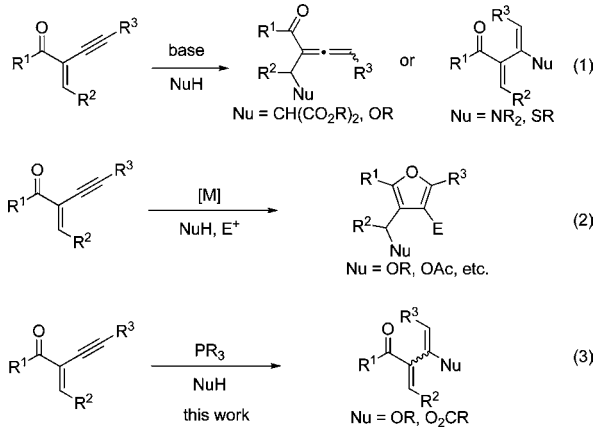
Supporting Information

ABSTRACT: A phosphine-mediated regio- and stereoselective addition reaction of diverse nucleophiles to yne-enones leading to polysubstituted 1,3-diene scaffolds in moderate to good yields has been reported.



Functionalized 1,3-dienes are important building blocks in organic synthesis, which have been successfully employed in Diels–Alder reactions,[1] cycloadditions,[2] and asymmetric hydrogenation reactions.[3] Surprisingly, the stereocontrolled synthesis of functionalized 1,3-dienes has rarely aroused extensive attention, despite the fact that different stereoisomers often have different reactivity and give different stereoisomers in organic reactions.[4] For example, 1,3-alkadien-2-yl carboxylates have been synthesized either by addition of organic carboxylic acids to vinylacetylene[5] or through rearrangement of 2-alkynyl carboxylates[6] or 2,3-allenyl carboxylates.[7] Pu and co-workers found that γ-hydroxyl-α,β-acetylenic esters could be catalyzed by DMAP in acetic anhydride to generate γ-acetoxy dienoates.[8] As an alternative method for the synthesis of 1,3-butadienes, the application of a ring-opening strategy of cyclobutenes at extremely high temperature has been reported.[9] Even though some recent progress[10] has been made in this field, the substitutions are almost limited to the 3,4-position of 1,3-alkadienes with unsatisfied stereoselectivity.

During the past decade, tertiary phosphines have emerged as efficient and mild nucleophilic catalysts for an impressive range of transformations involving activated allenes and alkynes as starting materials.[11,12] Recently, we disclosed the phosphine[13] or base[14]-catalyzed tandem reactions of yne-enones as good Michael acceptors with various nucleophiles to prepare acyclic and cyclic compounds. It is to be noted that the addition reactions of yne-enones and weak nucleophiles such as malonates and 1,3-diketones lead to substituted 1,2-allenes, whereas the addition reactions of yne-enones and heteroatom nucleophiles such as thiols and pyrrolidine produce fuctionalized 1,3-dienes (eq 1). The regioselectivity is controlled by the nature of the nucleophile. Our group[15] and others[16] reported a series of metal-catalyzed cyclizations of yne-enones with various nucleophiles including alcohols or acetic acid, which attach onto an alkene (eq 2). Herein, we describe a novel method for the stereoselective synthesis of functionalized 1,3-butadiene derivatives from yne-enones and various O-based nucleophiles



via regio- and stereoselective addition to the alkyne moiety under the catalysis of phosphine (eq 3).

We began our investigation using (*E*)-2-benzylidene-1-phenylbut-3-yn-1-one (**1a**) and HOAc as a model reaction (Table 1). This test reaction was carried out in the presence of 20 mol % PPh_3 at room temperature to provide 3-benzoyl-4-phenylbuta-1,3-dien-2-yl acetate **2a** in 34% yield (entry 1). With increasing reaction temperature, the better result was obtained at 35 °C to afford the desired product in 62% yield with *E*/*Z* = 6.2:1 (entries 2–3). Other solvents such as DCE, CH_3CN, THF, and CH_2Cl_2 had unfavorable consequences on the reaction yield and stereoselectivity (entries 4–7). Increasing the amount of acetic acid gradually improved the reactivity (entries 8–10). When the reaction was performed using 5 equiv of acetic acid, the desired addition product **2a** was obtained in 72% yield with *E*/*Z* = 7.2:1 (entry 9). The yield improved to 77% by increasing the concentration of the reactants (2 M) (entry 11). Furthermore, the *E*/*Z* ratio increased to 11.0:1 with a slightly lower yield when the reaction

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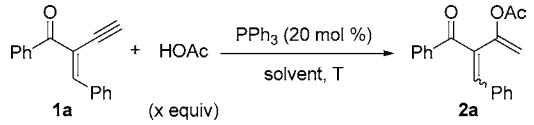
Table 1. Optimization of Reaction Conditions[a]



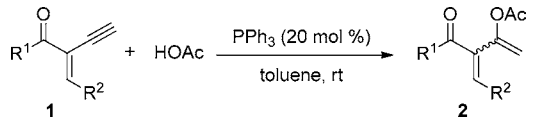
entry	*x* equiv	solvent	*T* (°C)	*t* (h)	yield (%)[b]	*E*/*Z*[c]
1	1.5	toluene	25	36	34	--
2	1.5	toluene	35	36	62	6.2:1
3	1.5	toluene	50	36	38	3.7:1
4	1.5	DCE	35	36	43	4.4:1
5	1.5	CH_3CN	35	36	16	4.3:1
6	1.5	THF	35	36	n.r.	--
7	1.5	CH_2Cl_2	35	36	39	11.0:1
8	3.0	toluene	35	24	68	7.4:1
9	5.0	toluene	35	18	72	7.2:1
10	10.0	toluene	35	18	64	7.8:1
11[d]	5.0	toluene	35	9	77	8.0:1
12[d]	5.0	toluene	25	9	72	11.0:1
13[d]	–	HOAc	25	36	17	>20:1
14[d,e]	5.0	toluene	25	9	n.r.	–

[a]Reaction conditions unless otherwise noted: **1a** (0.25 mmol), HOAc (*x* equiv), PPh_3 (20 mol %), solvent (2.5 mL). [b]Isolated yield. [c]Determined by ^{1}H NMR of crude product. [d]Reaction conditions: **1a** (0.5 mmol), HOAc (*x* equiv), PPh_3 (20 mol %), solvent (2.5 mL). [e]No PPh_3 was added.

was performed at room temperature (entry 12). Reactions using acetic acid as the solvent gave **2a** in only 17% yield as a single *E* isomer after 36 h (entry 13). It was clear that the reaction cannot occur without the PPh_3 catalyst (entry 14).

With the optimal reaction conditions in hand (Table 1, entry 12), we next examined the scope and limitation of this transformation by variation of the terminal yne-enone **1** component (Table 2). It was found that, in addition to aromatic enone, aliphatic enone **1b** could be compatible to finish the addition adduct almost as a single geometrical isomer (entry 1). For terminal yne-enones, both electron-withdrawing and -donating groups on the alkenyl moiety gave good yields

Table 2. Variation of Terminal Yne-Enone 1 Component[a]



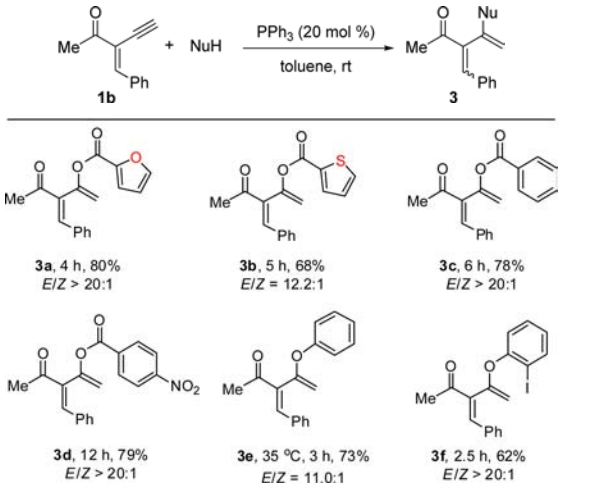
entry	R^1/R^2 (**1**)	time (h)	yield (%)[b]	**2**, *E*/*Z*[c]
1	Me/Ph (**1b**)	5	83	**2b**, 18.0:1
2	Me/4-MeC_6H_4 (**1c**)	12	71	**2c**, >20:1
3	Me/4-$MeOC_6H_4$ (**1d**)	48	74	**2d**, >20:1
4	Me/4-ClC_6H_4 (**1e**)	8	73	**2e**, >20:1
5	Me/4-NCC_6H_4 (**1f**)	4	79	**2f**, 14.0:1
6	4-$MeOC_6H_4$/Ph (**1g**)	24	81	**2g**, 10.0:1
7	4-ClC_6H_4/Ph (**1h**)	12	83	**2h**, 2.7:1[e]
8	Ph/1-naphthyl (**1i**)	88	66	**2i**, >20:1
9	Ph/styryl (**1j**)	48	50	**2j**, 2.9:1[d]
10	H/Ph (**1k**)	5	48	**2k**, 6.3:1[e]
11	CO_2Me/Ph (**1l**)	1	62	**2l**, 11.9:1

[a]Reaction conditions: **1** (0.5 mmol), HOAc (2.5 mmol), PPh_3 (20 mol %), toluene (2.5 mL) at room temperature. [b]Isolated yield. [c]Determined by ^{1}H NMR of crude product. [d]Reaction performed at 50 °C, recovery of 20% **1j**. [e]Isolated ratio of two isomers.

with perfect stereoselectivity (entries 2–5 and 8). Reactions of substrates bearing an electron-withdrawing substituent were faster than those of substrates bearing an electron-donating substituent. Compounds **1g** and **1h** were transformed into the corresponding dienes **2g** and **2h** in 81% and 83% yield, respectively, whereas the *E*/*Z* ratio of **2h** was somewhat lower (2.7:1) (entries 6 and 7). Surprisingly, besides dienes, triene **2j** could be synthesized using this method in 50% yield as a mixture of *E*/*Z* stereoisomers along with 20% unreacted substrate **1j** (entry 9). It is also noteworthy that the reaction of enyne **1k** with a formyl group could give the desired product **2k** in 48% yield with moderate *E*/*Z* (entry 10). Finally, we expanded the reaction to (*E*)-methyl 3-benzylidene-2-oxopent-4-ynoate **1l**, which afforded the corresponding product **2l** in 62% yield after 1 h (entry 11).

Next, other weak nucleophiles were examined, and the results are listed in Table 3. Besides acetic acid, arylcarboxylic

Table 3. Scope of Nucleophile Component 3[a]



[a]Reaction conditions: **1a** (0.5 mmol), NuH (1.5 mmol), PPh_3 (20 mol %), toluene (2.5 mL) at room temperature. *E*/*Z* was determined by ^{1}H NMR of crude product.

acids such as 2-furoic acid, 2-thenoic acid, benzoic acid, and 4-nitrobenzoic acid also turned out to be viable substrates for the S_N2' reaction of terminal yne-enones, producing the corresponding dienes **3a–3d** in good yields and excellent stereoselectivites. Excitingly, the addition of phenols to enynes can be also achieved under the standard conditions. Phenol and 2-iodophenol reacted with yne-enone **1b** to provide the corresponding dienes **3e–3f** in moderate yields,[17] as *E* isomers exclusively.

To our delight, a wide variety of internal yne-enones were well tolerated in the addition reaction, providing reaction products **5** in good yields and selectivitites using a more nucleophilic phosphine catalyst (Table 4). The reaction of (*E*)-3-benzylidene-5-phenylpent-4-yn-2-one (**4a**) with acetic acid proceeded smoothly to produce tetrasubstituted diene (1*E*,3*E*)-**5a** in 70% yield as a single geometrical isomer after 5 h at room temperature (entry 1). Not only aromatic but also aliphatic-substituted yne-enones on the alkynyl moiety were tolerated even if a 3.6:1 mixture of stereoisomers was observed in the case of the *n*-butyl-substituted yne-enone **4d** (entries 2–4). Yne-enones containing electron-donating and -withdrawing aryl substituents on the alkenyl moiety provided products **5e–5g** as a single isomer in good yields in only 1–3 h (entries 5–7). The

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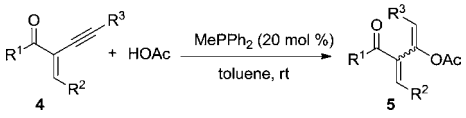
Table 4. Variation of Internal Yne-Enone 4 Component[a]



entry	$R^1/R^2/R^3$ (4)	t (h)	5, yield (%)[b]
1	Me/Ph/Ph (**4a**)	5	**5a**, 70
2	Me/Ph/4-MeOC$_6$H$_4$ (**4b**)	2	**5b**, 76
3	Me/Ph/4-MeOCC$_6$H$_4$ (**4c**)	3	**5c**, 74
4	Me/Ph/*n*-C$_4$H$_9$ (**4d**)	2	**5d**, 66 (3.6:1)[c]
5	Me/4-MeOC$_6$H$_4$/Ph (**4e**)	3	**5e**, 77
6	Me/4-ClC$_6$H$_4$/Ph (**4f**)	1	**5f**, 67
7	Me/4-NCC$_6$H$_4$/Ph (**4g**)	1	**5g**, 64
8	Ph/Ph/Ph (**4h**)	2	**5h**, 84[d]
9	4-MeOC$_6$H$_4$/Ph/Ph (**4i**)	2	**5i**, 67 (2.6:1)[c]
10	4-ClC$_6$H$_4$/Ph/Ph (**4j**)	2	**5j**, 88 (3.7:1)[c]
11	H/Ph/Ph (**4k**)	2	**5k**, 55 (3.3:1)[c]

[a]Reaction conditions: **4** (0.3 mmol), HOAc (1.5 mmol), MePPh$_2$ (20 mol %), toluene (2.5 mL) at room temperature. [b]Isolated yield. No other isomers were found unless otherwise noted. [c]Isolated ratio of two major isomers. [d]Trace amounts of two other isomers were detected by ^{1}H NMR analysis of the crude product.

substrate **4h**, which has a phenyl group on the α-position of ketone, was converted to buta-1,3-diene **5h** in 84% isolated yield for the major stereoisomer (entry 8). Notably, electron-rich and halide-substituted groups on the phenyl ring of R^1 were compatible, and the reactions gave compounds **5i** and **5j** in good to excellent yields as mixtures of two stereoisomers (entries 9−10). To our delight, even the reaction of enyne **4k** with an aldehydyl group also proceeded to afford the corresponding diene **5k** in 55% yield, albeit as a 3.3:1 mixture of two stereoisomers (entry 11). The relative configuration of **5g** was confirmed via X-ray crystallographic analysis to be (1*E*, 3*E*) (Figure 1).[18] Moreover, treatment of (*E*)-3-(4-chlorobenzylidene)-4-oxopent-1-en-2-yl acetate **2e** with Selectfluor generated the corresponding fluorinated ketone **6** in 64% yield.[7c] Notably, the reaction of diene **2e** with hydrazine hydrate in DMA under air was complete within 1 h to give the corresponding pyrazole **7** in 62% yield (Scheme 1).

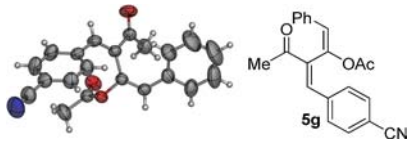
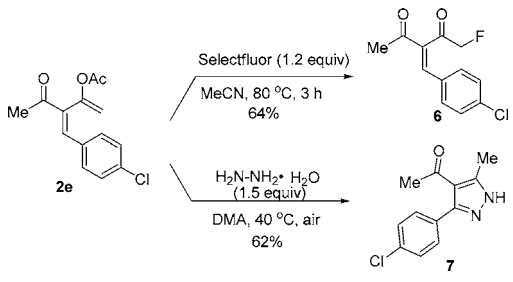


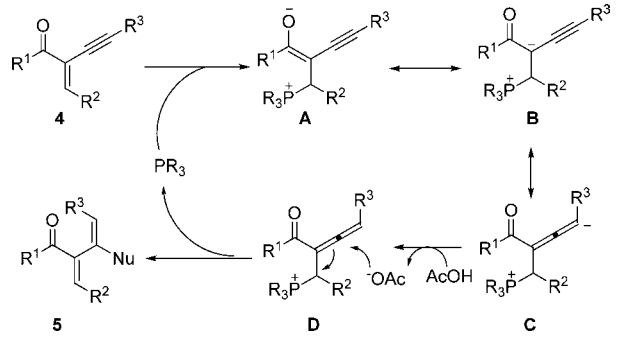
Figure 1. X-ray crystallographic analysis of 1,3-diene **5g**.

Scheme 1. Synthetic Application of the Diene 2e



We proposed a mechanism for this phosphine-mediated regioselective addition reaction as shown in Scheme 2. The

Scheme 2. Possible Mechanism



nucleophilic addition of phosphine to the yne-enone gives the corresponding zwitterionic intermediate, enolate **A**, and its resonance form progargylic carbanion **B** and allenyl carbanion **C**.[13b] Subsequent protonation by the acetic acid would produce the allenyl ketone type intermediate **D** and acyloxy anion. Nucleophilic addition followed by β'-elimination of the phosphine or S_N2' type substitution of the phosphine by the acyloxy anion would afford the highly functionalized 1,3-diene and regenerate the phosphine catalyst.

In conclusion, we have described a phosphine-mediated regioselective addition reaction between yne-enones and various nucleophiles (carboxylic acids, phenols), furnishing highly functionalized 1,3-dienes in good to excellent yields with high levels of selectivity for the olefin geometry. The transformation is general with respect to a broad range of substrates including terminal and internal yne-enones, with the latter requiring a more nucleophilic phosphine catalyst. Further studies focusing on extending the scope of substrates and synthetic applications will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For examples, see: (a) Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; John Wiley & Sons: New York, 1990. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (c) Pollini, G. P.; Bianchi, A.; Casolari, A.; Risi, C.; Zanirato, V.; Bertolasi, V. *Tetrahedron: Asymmetry* **2004**, *15*, 3223. (d) Kobayashi, S.; Furuya, T.; Otani, T.; Saito, T. *Tetrahedron* **2008**,

64, 9705. (e) Kobayashi, S.; Semabs, T.; Takahashi, T.; Yoshida, S.; Dai, K.; Otani, T.; Saito, T. *Tetrahedron* **2009**, *65*, 920. (f) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658.

(2) (a) *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, 1993; Vol. 3. (b) Roversi, E.; Vogel, P. *Helv. Chim. Acta* **2002**, *85*, 761.

(3) Boaz, N. W. *Tetrahedron Lett.* **1998**, *39*, 5505.

(4) (a) Wilker, S.; Erker, G. *J. Am. Chem. Soc.* **1995**, *117*, 10922. (b) Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, *16*, 2841.

(5) (a) Werntz, J. H. *J. Am. Chem. Soc.* **1935**, *57*, 204. (b) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230. (c) Zhao, Y.-L.; Liu, Q.; Zhang, Y.-F.; Sun, S.-G.; Li, Y.-N. *Synlett* **2006**, 231.

(6) For examples, see: (a) Miki, K.; Fujita, M.; Uemura, S.; Ohe, K. *Org. Lett.* **2006**, *8*, 1741. (b) Wang, S.; Zhang, L. *Org. Lett.* **2006**, *8*, 4585. (c) Li, G.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 3740. (d) Cho, E. J.; Lee, D. *Adv. Synth. Catal.* **2008**, *350*, 2719. (e) Bray, C. V.-L.; Dérien, S.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1439. (f) Wang, Y.; Lu, B.; Zhang, L. *Chem. Commun.* **2010**, *46*, 9179. (g) Cho, E. J. *Chem.—Eur. J.* **2012**, *18*, 4495.

(7) For examples, see: (a) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 985. (b) Zhang, X.; Fu, C.; Ma, S. *Org. Lett.* **2011**, *13*, 1920. (c) Jin, Z.; Hidinger, R. S.; Xu, B.; Hammond, G. B. *J. Org. Chem.* **2012**, *77*, 7725.

(8) Yue, Y.; Yu, X.-Q.; Pu, L. *Chem.—Eur. J.* **2009**, *15*, 5104.

(9) Murakami, M.; Miyamoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6441.

(10) (a) Potman, R. P.; Kleef, F. J.; Scheeren, H. W. *J. Org. Chem.* **1985**, *50*, 1955. (b) Seltzer, S. *J. Org. Chem.* **1995**, *60*, 1189. (c) Kalita, B.; Bezbarua, M. S.; Barua, N. C. *Synth. Commun.* **2002**, *32*, 3181. (d) Kumar, N. N. B.; Reddy, M. N.; Swamy, K. C. K. *J. Org. Chem.* **2009**, *74*, 5395. (e) Geary, L. M.; Hultin, P. G. *J. Org. Chem.* **2010**, *75*, 6354. (f) Xu, S.; Chen, R.; He, Z. *J. Org. Chem.* **2011**, *76*, 7528. (g) Yang, Y.-L.; Wei, Y.; Xu, Q.; Shi, M. *Tetrahedron* **2013**, *69*, 3593.

(11) For recent reviews, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Valentine, D. H.; Hillhouse, J. H. *Synthesis* **2003**, 317. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (d) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (e) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520. (f) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (g) Ye, L.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140.

(12) For some pioneering examples, see: (a) Martin, T. J.; Vakhshori, V. G.; Tran, Y. S.; Kwon, O. *Org. Lett.* **2011**, *13*, 2586. (b) Szeto, J.; Sriramurthy, V.; Kwon, O. *Org. Lett.* **2011**, *13*, 5420. (c) Zhao, Q.; Han, X.; Wei, Y.; Shi, M.; Lu, X. *Chem. Commun.* **2012**, *48*, 970. (d) Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 767. (e) Zhong, F.; Dou, X.; Han, X.; Yao, W.; Zhu, Q.; Meng, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 943. (f) Li, E.; Huang, Y.; Liang, L.; Xie, P. *Org. Lett.* **2013**, *15*, 3138. (g) Zheng, J.; Huang, Y.; Li, Z. *Org. Lett.* **2013**, *15*, 5064.

(13) (a) Chen, Z.; Zhang, J. *Chem.—Asian J.* **2010**, *5*, 1542. (b) Yu, X.; Cao, Z.; Zhang, J. *Org. Biomol. Chem.* **2010**, *8*, 5059.

(14) (a) Yu, X.; Ren, H.; Xiao, Y.; Zhang, J. *Chem.—Eur. J.* **2008**, *14*, 8481. (b) Xiao, Y.; Zhang, J. *Chem. Commun.* **2009**, 3594. (c) Li, W.; Xiao, Y.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 3083. (d) Yu, X.; Du, B.; Wang, K.; Zhang, J. *Org. Lett.* **2010**, *12*, 1876. (e) Yu, X.; Zhang, J. *Adv. Synth. Catal.* **2011**, *353*, 1265. (f) Yu, X.; Zhou, G.; Zhang, J. *Chem. Commun.* **2012**, *48*, 4002. (g) Yu, X.; Zhang, J. *Chem.—Eur. J.* **2012**, *18*, 12945.

(15) (a) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903. (b) Liu, R.; Zhang, J. *Chem.—Eur. J.* **2009**, *15*, 9303. (c) Xiao, Y.; Zhang, J. *Adv. Synth. Catal.* **2011**, *353*, 36. (d) Xiao, Y.; Zhang, J. *Chem. Commun.* **2010**, *46*, 752. (e) Li, W.; Zhang, J. *Chem. Commun.* **2010**, *46*, 8839. (f) Liu, R.; Zhang, J. *Chem.—Asian J.* **2012**, *7*, 294.

(16) (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (b) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (c) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609. (d) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679. (e) Oh, C. H.; Reddy, V. R.; Kim, A.; Rhim, C. Y. *Tetrahedron Lett.* **2006**, *47*, 5307. (f) Cho, C.-H.; Larock, R. C. *ACS Comb. Sci.* **2011**, *13*, 272.

(17) (a) Olsen, R. K.; Feng, X.; Campbell, M.; Shao, R.; Math, S. K. *J. Org. Chem.* **1995**, *60*, 6025. (b) Geary, L. M.; Hultin, P. G. *J. Org. Chem.* **2010**, *75*, 6354.

(18) CCDC 967650 (**5g**) contains the supplementary crystallographic data for this paper. www.ccdc.cam.ac.uk/data_request/cif.