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Asymmetric [3 + 3] Annulation of Copper−Allenylidenes with Pyrazolones: Synthesis of Chiral 1,4-Dihydropyrano[2,3-*c*]pyrazoles

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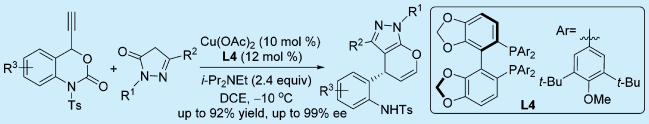
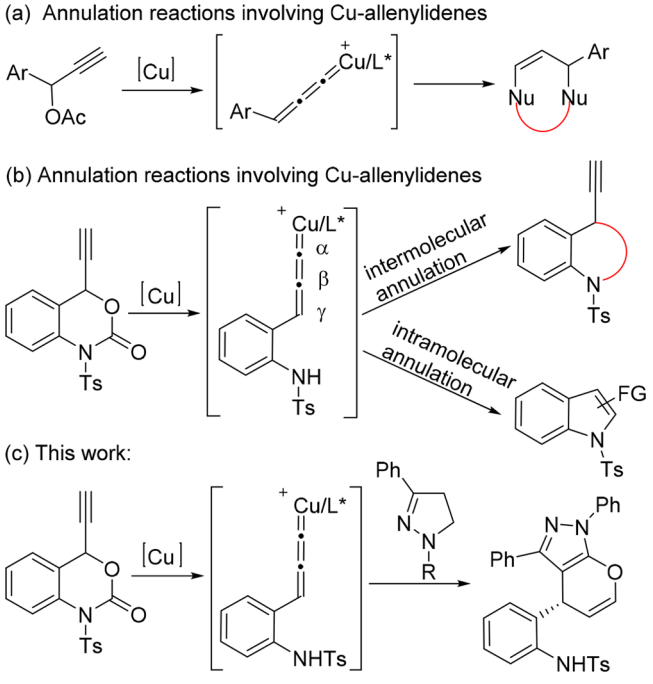
Supporting Information

ABSTRACT: The copper-catalyzed asymmetric [3 + 3] annulation of ethynyl benzoxazinanones with pyrazolones has been achieved, providing simple access to 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives in moderate to excellent yields with excellent enantioselectivities (up to 99% ee). Compared with previous annulation reactions of copper−allenylidenes from ethynyl benzoxazinanones, the current reaction fused the three carbon atoms of the propargyl moiety into a heterocyclic framework.



In the past decades, terminal propargylic compounds having a leaving group, such as ester, have often been used as reaction partners for propargylation and cycloaddition reactions.[1] Generally, in the presence of transition metal catalysts, this type of propargylic compound generates metal−allenylidene intermediates for various reactions.[1,2] Ruthenium-,[3] copper-,[4] or manganese-allenylidenes[5] have shown great potential in cycloaddition reactions with various dipolarophiles.[1f,h] With the use of propargyl acetates as substrate, Hu has developed an extremely excellent catalytic system, accomplishing a series of annulation reactions of copper-allenylidenes with bisnucleophiles (Scheme 1a).[6] In 2016, Xiao and Lu reported a new type of interesting propargylic compounds, ethynyl benzoxazinanones (Scheme 1b).[1h,7] In the presence of a copper catalyst, these compounds produced copper-allenylidene intermediates, which thereupon furnished [4 + 1] annulation with sulfur ylides. With the above copper-allenylidene as key intermediates, Xiao and Lu have developed a series of annulation reactions, for example, the decarboxylative amination/hydroamination sequence giving functionalized indoles;[8] the cascade reaction of ethynyl benzoxazinanones with indoles synthesizing polycyclic indolines;[9] the intramolecular annulation involving a sequence reaction of Friedel−Crafts propargylation/hydroamination/aromatization producing 3,3′-biindoles;[10] and the annulation of phosphonate with Cu-allenylidenes via tandem C−P and C−N bond formations to synthesize 2-phosphorylmethylindoles.[11] Besides the above-mentioned reactions, Gong reported asymmetric [4 + 2] cycloaddition of ammonium enolates with copper-allenylidenes.[12] You presented a [4 + 2] annulation reaction of substituted indole with ethynyl benzoxazinanones for diastereo- and enantioselective synthesis of tetrahydro-5*H*-indolo[2,3-*b*]quinolones.[13] Wu reported asymmetric [4 + 2] annulation of mixed anhydrides with ethynyl benzoxazinanones to synthesize quinolinones[14] and asymmetric[4 + 2] cycloaddition of copper-allenylidene with 5-substituted 2-silyloxyfurans.[15] Song communicated an organo/metal cooperatively catalyzed annulation of ethynyl benzoxazinanones with malononitriles to synthesize indolines.[16] Sun described asymmetric [4 + 2] cycloaddition of

Scheme 1. Annulation Reactions Involving Copper−Allenylidenes



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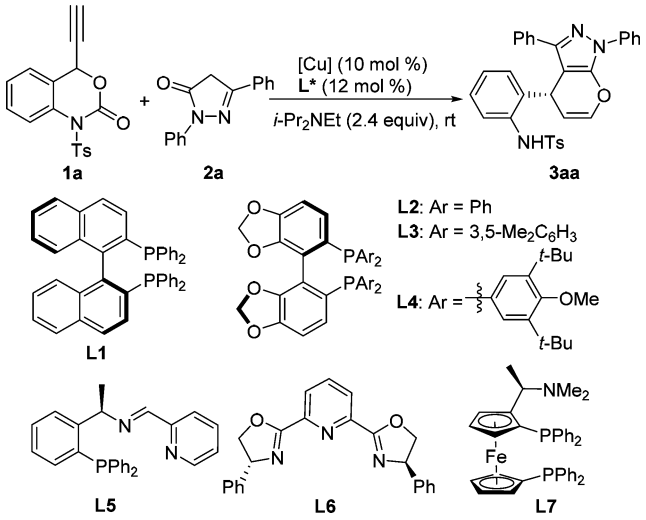
copper-allenylidenes with hexahydro-1,3,5-triazines.[17] In the above-mentioned intermolecular annulation reactions involving copper-allenylidenes from ethynyl benzoxazinanones, ethynyl benzoxazinanones generally worked as a four-membered synthon. The nitrogen atom was fused into the heterocyclic products, and the alkynyl moiety remained intact (Scheme 1b). The cycloaddition reaction of ethynyl benzoxazinanones fusing the three carbon atoms of a propargyl moiety into the heterocyclic framework has not been reported. Herein, we report asymmetric [3 + 3] annulation of pyrazolones with ethynyl benzoxazinanones behaving as a C3 synthon for synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives (Scheme 1c).

We began our studies on the annulation of ethynyl benzoxazinanone **1a** and pyrazolone **2a** with CuOAc as a metal catalyst in the presence of *i*-Pr_2NEt in dichloromethane at room temperature (Table 1). Various chiral ligands were first examined. With the use of (*R*)-BINAP (**L1**) as a chiral ligand, the reaction proceeded smoothly to give the product **3aa** in 65% yield and 23% ee (Table 1, entry 1). Further screening (entries 2−7) indicated that the commercially available SEGPhos **L4** resulted in a good result (entry 4, 61% yield and 67% ee) in terms of yield and ee. Subsequent screening of metal salts (entries 8−11) showed that CuBr was a better catalyst, which provided the product in 70% yield and 68% ee (entry 8). Using CuBr as the catalyst, a solvent screening was performed (entries 12−15), demonstrating that 1,2-dichloroethane (DCE) was the optimal solvent (entry 13). When DCE was used, although only 63% yield and 82% ee was obtained, the ee value was significantly increased, compared with the ee obtained using dichloromethane as the solvent (entry 13 vs 8). In order to further improve the enantioselectivity, with the use of DCE as the solvent, several metal salts were evaluated again (entries 16−18). To our delight, $Cu(OAc)_2$/**L4** led to a 62% yield and 95% ee (entry 18). Lowering the reaction temperature to −10 °C increased the yield to 90% (entry 19). The absolute configuration of the product **3aa** was unambiguously determined to be *S* on the basis of the X-ray crystallographic analysis (CCDC 1844053).

With the optimal conditions in hand, we examined the scope of pyrazolones for this cycloaddition reaction (Table 2). A broad range of 2-arylpyrazolones, bearing either electron-withdrawing or -donating substituents on the benzene ring, were tolerated to furnish the corresponding products in moderate to excellent yield with excellent enantioselectivities (entries 2−16). The position of the substituent on the phenyl

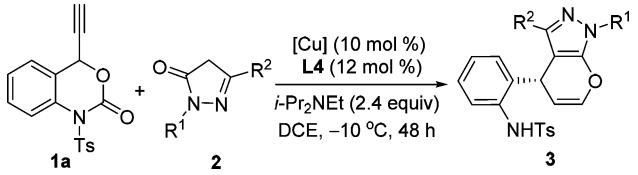
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	L	solvent	yield (%)[b]	ee (%)[c]
1	CuOAc	**L1**	CH_2Cl_2	65	23
2	CuOAc	**L2**	CH_2Cl_2	58	−53
3	CuOAc	**L3**	CH_2Cl_2	80	34
4	CuOAc	**L4**	CH_2Cl_2	61	67
5	CuOAc	**L5**	CH_2Cl_2	39	−49
6	CuOAc	**L6**	CH_2Cl_2	10	0
7	CuOAc	**L7**	CH_2Cl_2	45	3
8	CuBr	**L4**	CH_2Cl_2	70	68
9	$Cu(MeCN)BF_4$	**L4**	CH_2Cl_2	69	61
10	$CuOTf(MeCN)_4$	**L4**	CH_2Cl_2	57	65
11	$Cu(OAc)_2$	**L4**	CH_2Cl_2	61	65
12	CuBr	**L4**	$CHCl_3$	51	53
13	CuBr	**L4**	DCE	63	82
14	CuBr	**L4**	THF	19	43
15	CuBr	**L4**	toluene	0	–
16	CuOAc	**L4**	DCE	54	95
17	$Cu(OTf)_2$	**L4**	DCE	38	86
18	$Cu(OAc)_2$	**L4**	DCE	62	95
19[d]	$Cu(OAc)_2$	**L4**	DCE	90	92

[a]Unless noted, reactions were performed with **1a** (0.12 mmol), **2a** (0.1 mmol), Cu salt (10 mol %), **L*** (12 mol %), and *i*-Pr_2NEt (2.4 equiv) at rt. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]At −10 °C.

Table 2. Scope of Pyrazolones[a]



entry	R^1 in **2**	R^2 in **2**	**3**	yield (%)[b]	ee (%)[c]
1	**2b**: 2-MeC_6H_4	Ph	**3ab**	90	97
2	**2c**: 3-MeC_6H_4	Ph	**3ac**	87	95
3	**2d**: 4-MeC_6H_4	Ph	**3ad**	48	94
4	**2e**: 4-$OMeC_6H_4$	Ph	**3ae**	67	92
5	**2f**: 2,4-$Me_2C_6H_3$	Ph	**3af**	46	96
6	**2g**: 2-FC_6H_4	Ph	**3ag**	48	>99
7	**2h**: 3-FC_6H_4	Ph	**3ah**	75	>99
8	**2i**: 4-FC_6H_4	Ph	**3ai**	52	91
9	**2j**: 2-ClC_6H_4	Ph	**3aj**	46	99
10	**2k**: 3-ClC_6H_4	Ph	**3ak**	75	>99
11	**2l**: 4-ClC_6H_4	Ph	**3al**	59	90
12	**2m**: 2-BrC_6H_4	Ph	**3am**	79	96
13	**2n**: 3-BrC_6H_4	Ph	**3an**	69	93
14	**2o**: 4-BrC_6H_4	Ph	**3ao**	77	95
15	**2p**: 4-$CF_3C_6H_4$	Ph	**3ap**	90	92
16[d]	**2q**: 2-naphthyl	Ph	**3aq**	62	91
17	**2r**: Bn	Ph	**3ar**	29	>99
18	**2s**: Me	Ph	**3as**	0	–
19	**2t**: Ph	4-MeC_6H_4	**3at**	62	87
20	**2u**: Ph	4-$OMeC_6H_4$	**3au**	76	80

[a]Unless noted, reactions were performed with **1a** (0.12 mmol), **2** (0.1 mmol), $Cu(OAc)_2$ (10 mol %), **L4** (12 mol %), and *i*-Pr_2NEt (2.4 equiv) in DCE at −10 °C for 48 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Reaction time was 72 h.

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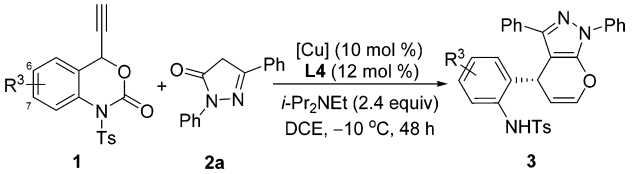
ring seems to have a significant influence on the reactivity of the substrates. For example, the pyrazolone **2d** having a *para*-methyl substituted phenyl group led to a lower yield than that for the substrates bearing an *ortho*- and a *meta*-methyl substituted phenyl (entry 3 vs entries 1 and 2). For the substrates with halides including fluorine and chlorine, the *meta*-substituted phenyl group afforded higher yields than the *ortho*- or *para*-substituted phenyl group (entry 7 vs entries 6 and 8, entry 10 vs entries 9 and 11). Interestingly, although the position of the substituent on the phenyl group remarkably influenced the reactivity of pyrazolones, it had not impact on the enantioselectivity and excellent enantioselectivities were obtained in all cases (entries 1−17). Additionally, 2-naphthylpyrazolone (**2q**) also underwent the annulation reaction to give the 1,4-dihydropyrano[2,3-*c*]pyrazole derivative in 62% yield with 91% ee (entry 16). Particularly, 2-benzyl-substituted pyrazolone **2r** performed the annulation with ethynyl benzoxazinanone **1a** to give the product in 99% ee, albeit in 29% yield (entry 17). Unfortunately, 2-alkyl-substituted pyrazolone **2s** did not work under the standard reaction conditions (entry 18). In addition, 5-arylpyrazolones **2t** and **2u** were also examined under the optimal conditions, affording the corresponding products in high yields with good enantioselectivities (entries 19 and 20).

Next, we explored the generality of the reaction for various ethynyl benzoxazinanones (Table 3). It was observed that the

Table 3. Scope of Ethynyl Benzoxazinanones[a]



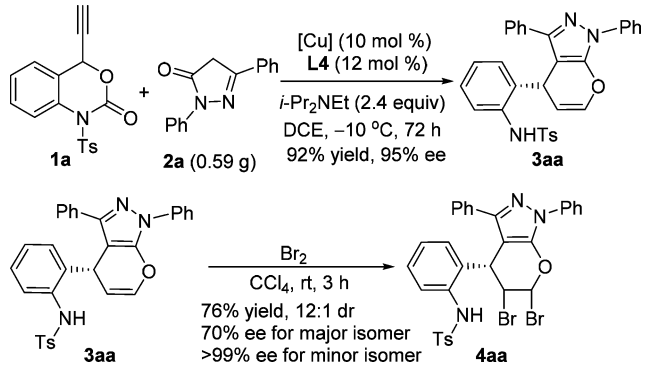
entry	R^3 in **1**	**3**	yield (%)[b]	ee (%)[c]
1	**1b**: 6-Me	**3ba**	79	90
2[d]	**1c**: 6-F	**3ca**	82	91
3	**1d**: 7-F	**3da**	62	95
4[d]	**1e**: 6-Cl	**3ea**	78	91
5	**1f**: 7-Cl	**3fa**	68	95
6[d]	**1g**: 6-Br	**3ga**	76	92

[a]Unless noted, reactions were performed with **1a** (0.12 mmol), **2** (0.1 mmol), $Cu(OAc)_2$ (10 mol %), **L4** (12 mol %), and *i*-Pr_2NEt (2.4 equiv) in DCE at −10 °C for 72 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Reaction for 72 h.

benzoxazinanones with both electron-withdrawing and -donating groups on the benzene ring were compatible substrates, providing the desired products in satisfactory yields with excellent enantioselectivities (entries 1−6). The 6-Me-substituted benzoxazinanone **1b** produced the desired heterocyclic product **3ba** in 79% yield and 90% ee (entry 1). With the use of ethynyl benzoxazinanones bearing an electron-withdrawing group, such as fluoro, chloro, and bromo groups as the substrates, the corresponding products were obtained in 62−82% yields and 91−95% ee (entries 2−6). The position of halide on the benzene ring has a certain effect on the reactivity of the substrates. The 6-substituted benzoxazinanones led to better yield than 7-substituted substrates (entry 2 vs 3, 4 vs 5).

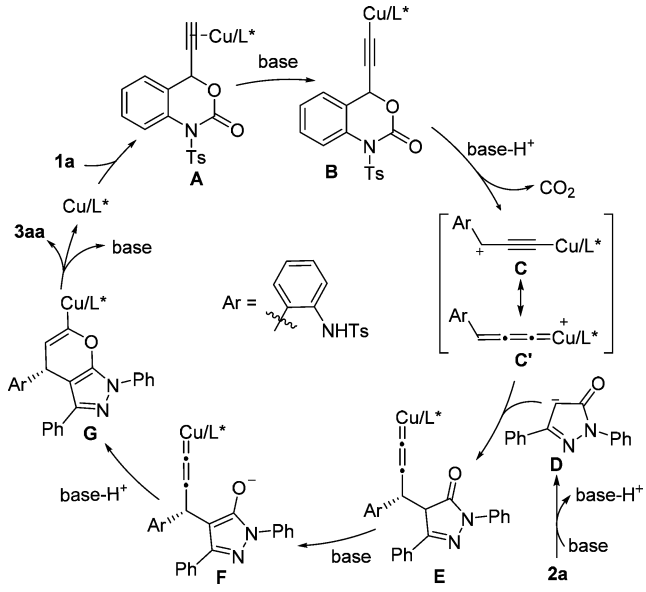
To demonstrate the utility of this method, a gram-scale reaction was performed with 0.98 g of **1a** and 0.59 g of **2a** in DCE at −10 °C for 3 days, giving the product **3aa** in 92% yield with 95% ee (Scheme 2). Treatment of the product **3aa** with Br_2 in CCl_4 at rt for 3 h led to the derivative **4aa** in 76% yield with good stereoselectivity.

Scheme 2. Scaled-up Synthesis and Further Transformations of the Cycloadduct



According to previous reports,[6a,7] a plausible mechanism was proposed in Scheme 3. First, the ethynyl benzoxazinanone **1a**

Scheme 3. A Plausible Reaction Mechanism and Transition-State Mode for Chiral Induction



is activated by a copper complex to form a π complex. Deprotonation of **A** with a base generates Cu-acetylide intermediate **B**, which eliminates CO_2 to generate a copper−allenylidene intermediate **C′** stabilized by its resonance form **C**. The anion intermediate **D**, from deprotonation of **2a**, nucleophilically attacks the intermediate **C′** at the C_γ atom, producing the corresponding Cu-acetylide complex **E**. Subsequent deprotonation followed by tautomerization gives the intermediate **F**, which performed an intramolecular nucleophilic attack to furnish the annulation intermediate **G**. After protonation, the product **3aa** is produced with simultaneous regeneration of the copper catalyst.

In conclusion, we have successfully developed an asymmetric [3 + 3] annulation of copper−allenylidenes with pyrazolones. The reaction worked under mild conditions to afford optically active 1,4-dihydropyrano[2,3-*c*]pyrazole de-

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rivatives in moderate to excellent yields with excellent enantioselectivities. In sharp contrast to previously reported intermolecular annulation reactions of copper−allenylidenes from ethynyl benzoxazinanone working as a quaternary synthon, ethynyl benzoxazinanones act as a C3 synthon in the current annulation reaction and three carbon atoms of propargyl moiety were fused into the heterocyclic framework.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02214.

Experimental procedures, characterization data, HPLC analysis dada, NMR spectra and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1844053 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. (b) Bruce, M. I. *Chem. Rev.* **1998**, *98*, 2797. (c) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176. (d) Cadierno, V.; Gimeno, J. *Chem. Rev.* **2009**, *109*, 3512. (e) Detz, R. J.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2009**, *2009*, 6263. (f) Hu, X.-P.; Hu, X.-H.; Liu, Z.-T.; Shao, L. *Synthesis* **2015**, *47*, 913. (g) Sakata, K.; Nishibayashi, Y. *Catal. Sci. Technol.* **2018**, *8*, 12. (h) Li, T.-R.; Wang, Y.-N.; Xiao, W.-J.; Lu, L.-Q. *Tetrahedron Lett.* **2018**, *59*, 1521.

(2) For selected examples, see: (a) Pilette, D.; Ouzzine, K.; Lebozec, H.; Dixneuf, P. H.; Rickard, C. E. F.; Roper, W. R. *Organometallics* **1992**, *11*, 809. (b) Godfrey, J. D.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405. (c) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S. *J. Org. Chem.* **1994**, *59*, 2282. (d) Esteruelas, M. A.; Gomez, A. V.; Lopez, A. M.; Modrego, J.; Onate, E. *Organometallics* **1997**, *16*, 5826. (e) Cadierno, V.; Conejero, S.; Gamasa, M. P.; Gimeno, J.; Falvello, L. R.; Llusar, R. M. *Organometallics* **2002**, *21*, 3716. (f) Ljungdahl, N.; Kann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 642. (g) Hattori, G.; Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3781. (h) Shao, W.; Li, H.; Liu, C.; Liu, C. J.; You, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 7684. (i) Han, F. Z.; Zhu, F. L.; Wang, Y. H.; Zou, Y.; Hu, X. H.; Chen, S.; Hu, X. P. *Org. Lett.* **2014**, *16*, 588. (j) Zhang, D. Y.; Zhu, F. L.; Wang, Y. H.; Hu, X. H.; Chen, S.; Hou, C. J.; Hu, X. P. *Chem. Commun.* **2014**, *50*, 14459. (k) Zhu, F. L.; Zou, Y.; Zhang, D. Y.; Wang, Y. H.; Hu, X. H.; Chen, S.; Xu, J.; Hu, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 1410. (l) Zou, Y.; Zhu, F.-L.; Duan, Z.-C.; Wang, Y.-H.; Zhang, D.-Y.; Cao, Z.; Zheng, Z.; Hu, X.-P. *Tetrahedron Lett.* **2014**, *55*, 2033. (m) Shao, L.; Hu, X. P. *Chem. Commun.* **2017**, *53*, 8192.

(3) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 7900.

(4) Pan, Y.-M.; Zhao, S.-Y.; Ji, W.-H.; Zhan, Z.-P. *J. Comb. Chem.* **2009**, *11*, 103.

(5) Lu, Q.; Cembellin, S.; Gressies, S.; Singha, S.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2018**, *57*, 1399.

(6) For selected examples, see: (a) Zhang, C.; Hu, X. H.; Wang, Y. H.; Zheng, Z.; Xu, J.; Hu, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 9585. (b) Zhu, F. L.; Wang, Y. H.; Zhang, D. Y.; Xu, J.; Hu, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 10223. (c) Li, Q.; Hou, C.-J.; Hui, Y.-Z.; Liu, Y.-J.; Yang, R.-F.; Hu, X.-P. *RSC Adv.* **2015**, *5*, 85879. (d) Zhang, D.-Y.; Shao, L.; Xu, J.; Hu, X.-P. *ACS Catal.* **2015**, *5*, 5026. (e) Liu, Z. T.; Wang, Y. H.; Zhu, F. L.; Hu, X. P. *Org. Lett.* **2016**, *18*, 1190. (f) Shao, L.; Wang, Y. H.; Zhang, D. Y.; Xu, J.; Hu, X. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 5014. (g) Zhou, Y.; Zhu, F. L.; Liu, Z. T.; Zhou, X. M.; Hu, X. P. *Org. Lett.* **2016**, *18*, 2734.

(7) Wang, Q.; Li, T. R.; Lu, L. Q.; Li, M. M.; Zhang, K.; Xiao, W. J. *J. Am. Chem. Soc.* **2016**, *138*, 8360.

(8) Li, T. R.; Cheng, B. Y.; Wang, Y. N.; Zhang, M. M.; Lu, L. Q.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 12422.

(9) Li, T. R.; Lu, L. Q.; Wang, Y. N.; Wang, B. C.; Xiao, W. J. *Org. Lett.* **2017**, *19*, 4098.

(10) Li, T. R.; Zhang, M. M.; Wang, B. C.; Lu, L. Q.; Xiao, W. J. *Org. Lett.* **2018**, *20*, 3237.

(11) Wang, B. C.; Wang, Y. N.; Zhang, M. M.; Xiao, W. J.; Lu, L. Q. *Chem. Commun.* **2018**, *54*, 3154.

(12) Song, J.; Zhang, Z. J.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 5212.

(13) Shao, W.; You, S. L. *Chem. - Eur. J.* **2017**, *23*, 12489.

(14) Lu, X.; Ge, L.; Cheng, C.; Chen, J.; Cao, W.; Wu, X. *Chem. - Eur. J.* **2017**, *23*, 7689.

(15) Chen, H.; Lu, X.; Xia, X.; Zhu, Q.; Song, Y.; Chen, J.; Cao, W.; Wu, X. *Org. Lett.* **2018**, *20*, 1760.

(16) Zhang, Y. C.; Zhang, Z. J.; Fan, L. F.; Song, J. *Org. Lett.* **2018**, *20*, 2792.

(17) Ji, D.; Wang, C.; Sun, J. *Org. Lett.* **2018**, *20*, 3710.

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