OL Organic Letters
Letter
Cite This: *Org. Lett.* XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

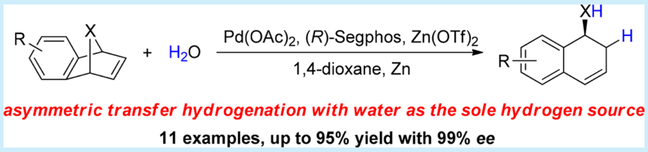
Asymmetric Transfer Hydrogenation of Heterobicyclic Alkenes with Water as Hydrogen Source

Guoli Shen,[†] Jingchao Chen,*[,†] Dandan Xu,[†] Xia Zhang,[†] Yongyun Zhou,[†] and Baomin Fan*[,†,‡]

[†]YMU-HKBU Joint Laboratory of Traditional Natural Medicine, Yunnan Minzu University, Kunming 650500, China
[‡]Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China

Supporting Information

ABSTRACT: The asymmetric transfer hydrogenation of heterobicyclic alkenes was accomplished by using water as the sole hydrogen source. The transformation was co-catalyzed by $Pd(OAc)_2/Zn(OTf)_2$ dual catalyst with metallic zinc as reducing agent. Various azabenzonorbornadienes and oxabenzonorbornadienes were transformed to the corresponding chiral 1,2-dihydronaphthalenes by the asymmetric reductive ring-opening reactions with good to excellent enantioselectivities.

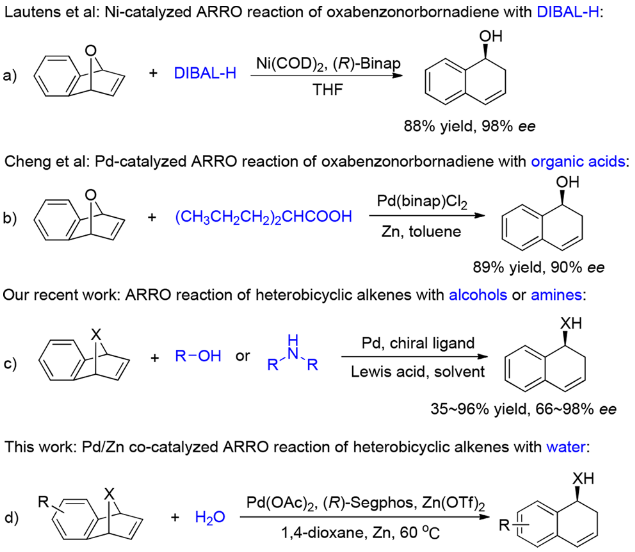


asymmetric transfer hydrogenation with water as the sole hydrogen source

11 examples, up to 95% yield with 99% *ee*

The hydrogenation reaction is one of the most important transformations in organic synthesis, and the asymmetric hydrogenation of prochiral compounds is the most efficient method to produce enantiopure compounds.[1] Studies toward the hydrogenation reactions in this decade has been majorly focused on the development of novel hydrogen sources. The transfer hydrogenation (TH) reaction has been attracting considerable attention, which presents some advantages such of simple manipulation, safety, sustainability, and possible industrial applications.[2] Two general asymmetric transfer hydrogenation (ATH) methodologies have been developed: metal catalysis in the presence of a chiral ligand and organocatalysis using chiral phosphoric acid.[3] As a result, a wide variety of H donors are available for use in both homo- and heterogeneous catalytic TH reactions. The frequently used hydrogen sources in ATH reactions are formic acid,[4] 2-propanol,[5] Hantzsch ester,[6] and some others.[7] Although water is the most cost-efficient and environmentally benign hydrogen source, the application of water as hydrogen source in the ATH reactions remains challenging and less developed. Recently, elegant reduction methods by using stoichiometric water have been illustrated by the groups of Stokes and others.[8] These methodologies feature the employment of a stoichiometric amount of borane reagents to accept the hydroxyl from water. An alternative method was then reported by the groups of Fan and Lloret-Fillol, where they reported the photocatalytic reduction of imines, aldehydes, and ketones with H_2O and an amine as electron donor.[9]

The asymmetric reductive ring opening (ARRO) reaction of heterobicyclic alkenes has offered a convenient and mild method for the construction of enantiomerically enriched 1,2-dihydronaphthalene structures.[10] The groups of Lautens and Cheng had contributed greatly to the ring-opening reactions of heterobicyclic alkenes. The first example of the ARRO reaction of oxabenzonorbornadiene was reported by the group of Lautens with DIBAL-H, using relative cheap catalyst (Figure 1a).[11] Later, the group of Cheng reported the same reaction with the combination of organic acids and zinc (Figure 1b).[12]


Lautens et al: Ni-catalyzed ARRO reaction of oxabenzonorbornadiene with DIBAL-H:

Cheng et al: Pd-catalyzed ARRO reaction of oxabenzonorbornadiene with organic acids:

Our recent work: ARRO reaction of heterobicyclic alkenes with alcohols or amines:

This work: Pd/Zn co-catalyzed ARRO reaction of heterobicyclic alkenes with water:

Figure 1. Catalytic ARRO reactions of heterobicyclic alkenes.

Our group has a continuous interest toward the ATH reactions with novel hydrogen sources and has previously studied the asymmetric transfer hydrogenation reactions of bicyclic alkenes and imines by using alcohols or amines as hydrogen donors (Figure 1c).[13] Herein, we report an asymmetric transfer hydrogenation reaction of heterobicyclic alkenes with water as sole hydrogen source (Figure 1d).

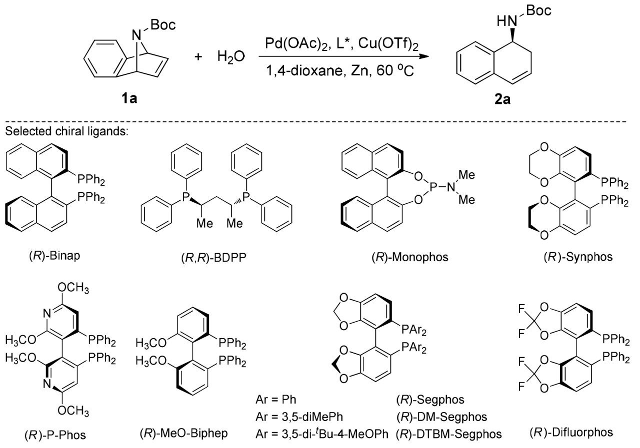
Our study commenced with the ATH reaction of azabenzonorbornadiene **1a** with water, catalyzed by the

Received: January 7, 2019

DOI: 10.1021/acs.orglett.9b00059

combination of palladium and copper. Various chiral ligands were investigated to identify the most suitable chiral catalyst for the present transformation (Table 1). It was pleasing to note that the initial tested biaryl bisphosphine ligand (*R*)-Binap had resulted in the asymmetric reductive ring-opening product **2a** in good yield and enantioselectivity (Table 1, entry 1). A reaction yield with reduced ee was obtained by using (*R*,*R*)-BDPP, which represents the bidentate phosphines bearing point chirality (Table 1, entry 2). The next tested chiral phosphinamine ligand (*R*)-Monophos has failed to promote the current reaction (Table 1, entry 3). Therefore, efforts were dedicated to the screening of other biaryl bisphosphine ligands. The use of (*R*)-Synphos, (*R*)-P-Phos, or (*R*)-MeO-Biphep has delivered **2a** in results comparable to those of (*R*)-Binap (Table 1, entries 4−6 vs 1). It is proposed that (*R*)-Segphos has the narrowest dihedral angle,[14] and it exhibited the best performance among these bisphosphines and afforded **2a** in 98% yield with 93% ee (Table 1, entry 7). The use of sterically more demanding derivatives has decreased the enantioselectivities dramatically (Table 1, entries 8 and 9), and the electron-deficient (*R*)-Difluorphos (Table 1, entry 10) gave inferior results compared with those with (*R*)-Segphos. Therefore, the biaryl bisphosphine ligand (*R*)-Segphos has been identified to be most suitable chiral ligand in current ATH reaction.

Table 1. Chiral Ligands Screening[a]

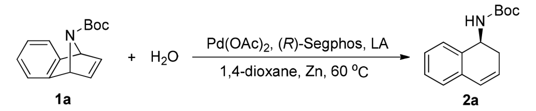


entry	ligand	time (h)	yield[b] (%)	ee[c] (%)
1	(*R*)-Binap	12	87	82
2	(*R*,*R*)-BDPP	12	97	60
3	(*R*)-Monophos	12	ND	
4	(*R*)-Synphos	12	76	80
5	(*R*)-P-Phos	8	90	86
6	(*R*)-MeO-Biphep	15	93	88
7	(*R*)-Segphos	10	98	93
8	(*R*)-DM-Segphos	9	94	70
9	(*R*)-DTBM-Segphos	9	77	48
10	(*R*)-Difluorphos	12	81	86

[a] Reaction conditions: **1a** (0.2 mmol), H_2O (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), chiral ligand (0.012 mmol), $Cu(OTf)_2$ (0.02 mmol), and zinc powder (0.6 mmol) in 1,4-dioxane (2 mL) at 60 °C under an argon atmosphere. [b] Yields were calculated on the basis of ^1H NMR using 1,3-benzodioxole as internal standard. [c] Determined by HPLC with a Chiralcel OJ-H column.

It was proven in our previous studies that the use of Lewis acids has a great effect on the catalytic efficiency of the co-catalytic system in the ATH reactions. Thus, the effects of several Lewis acids in the current reaction were briefly studied (Table 2). All of the tested triflate salts and ZnI_2 had afforded the desired product **2a** in excellent results, and the use of $Zn(OTf)_2$ had given a further promoted enantioselectivity of 96% (Table 2, entries 1−6). The reaction was sluggish in the absence of any Lewis acid and gave **2a** in only 25% yield with 67% ee over 36 h (Table 2, entry 7). Other metallic reducing agents beside zinc were also tested. The use of both manganese and magnesium powder have afforded **2a** in low yields and good ee's, but iron powder was ineffective (Table 2, entries 8−10). Metallic reducing agent was essential as no reaction took place in its absence (Table 2, entry 11). The present reaction also performed well in some other aprotic solvents such as tetrahydrofuran and dichloroethane, but none was more effective than 1,4-dioxane.

Table 2. Screening of Lewis Acids and Additives[a]



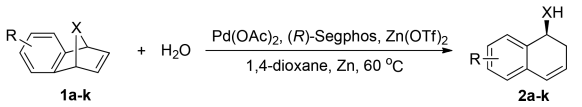
entry	Lewis acid	metallic reducing agent	time (h)	yield[b] (%)	ee[c] (%)
1	$Cu(OTf)_2$	Zn	10	98	93
2	AgOTf	Zn	6	93	94
3	$Zn(OTf)_2$	Zn	6	95	96
4	$Fe(OTf)_2$	Zn	10	94	92
5	$Yb(OTf)_3$	Zn	3.5	95	95
6	ZnI_2	Zn	24	93	88
7		Zn	36	25	67
8	$Zn(OTf)_2$	Mn	36	30	88
9	$Zn(OTf)_2$	Mg	36	25	86
10	$Zn(OTf)_2$	Fe	36	NR	
11	$Zn(OTf)_2$		36	NR	

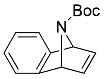
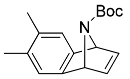
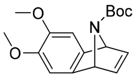
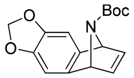
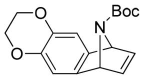
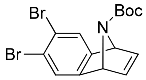
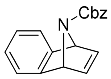
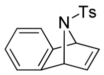
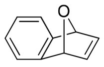
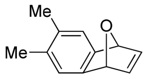
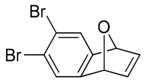
[a] Reaction conditions: **1a** (0.2 mmol), H_2O (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-Segphos (0.012 mmol), Lewis acid (0.02 mmol), and metallic reducing agent (0.6 mmol) in 1,4-dioxane (2 mL) at 60 °C under an argon atmosphere. [b] Yields were calculated on the basis of ^1H NMR using 1,3-benzodioxole as internal standard. [c] Determined by HPLC with a Chiralcel OJ-H column.

With the optimized reaction conditions in hands, we investigated the scope of this transformation for different azabenzonorbornadienes and oxabenzonorbornadienes (Table 3). The azabenzonorbornadienes with electron-donating groups and dibromo substitutions on the phenyl ring participated well in the current ATH reaction, affording **2b−f** in excellent yields and enantioselectivities (Table 3, entries 2−6). Azabenzonorbornadienes **1g** and **1h** with different protecting groups on the nitrogen atoms performed well in the current reaction conditions (Table 3, entries 7 and 8). To our delight, various oxabenzonorbornadienes **1i−k** were successfully transformed into the desired products (Table 3, entries 9−11), but the dimethyl-substituted **1j** was mostly transformed into 6,7-dimethylnaphthalen-1-ol during the reaction. It is noteworthy that the dibromo substitutions on the phenyl ring were well tolerated in the reduction system and allowed further elaboration of the product (Table 3, entries 6 and 11).

Subsequently, two deuterium-labeling experiments were carried out to identify the hydrogen source in the current asymmetric transfer hydrogenation (Figure 2). When D_2O was used instead of water, deuterium was found in the 1,2-

Table 3. Reaction Scope of Heterobicyclic Alkenes[a]



entry	1	time (h)	yield (%)[b]	ee (%)[c]
1	 **1a**	6	95	96
2	 **1b**	7	95	94
3	 **1c**	8	91	92
4	 **1d**	9	94	94
5	 **1e**	8	91	99
6	 **1f**	14	76	89
7	 **1g**	5	94	91
8	 **1h**	5	60	86
9[d]	 **1i**	24	72[e]	84
10	 **1j**	4.5	30	82
11	 **1k**	12	85[e]	84

[a]Reaction conditions: **1** (0.2 mmol), H_2O (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), (*R*)-Segphos (0.012 mmol), $Zn(OTf)_2$ (0.02 mmol), and zinc powder (0.6 mmol) in 1,4-dioxane (2 mL) at 60 °C under an argon atmosphere; [b]Yields were calculated on the basis of ^1H NMR using 1,3-benzodioxole as internal standard. [c]Determined by HPLC with a Daicel AD-H, AS-H, OJ-H or OD-H chiral column. [d]Reacted at 40 °C. [e]Isolated yield after column chromatography.

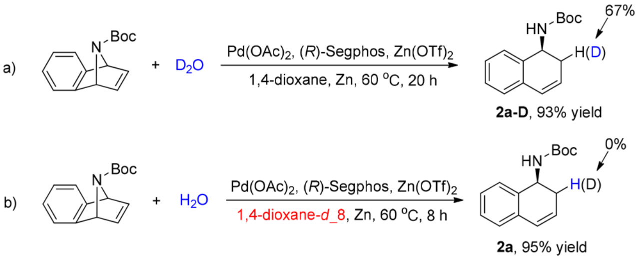


Figure 2. Deuterium-labeling experiments.

dihydronaphthalene moiety of the product **2a-D** with 67% incorporation (Figure 2, a). The hydrogen may come from the reaction environment, as the reaction without addition of water still gave **2a** in 40% yield, leaving 58% of **1a** unreacted. The other experiment employing 1,4-dioxane-d_8 instead of 1,4-dioxane resulted **2a** in 95% yield without any deuterium incorporation (Figure 2, b). This result has ruled out the possibility that the solvent provide hydrogen. Therefore, it can be concluded that water serves as the sole hydrogen source in the present asymmetric transfer hydrogenations.

On the basis of the deuterium-labeling experiments and reported literature,[15] the mechanism of the present ATH reaction was proposed as illustrated in Figure 3. The catalytic cycle would be initiated by the coordination of (*R*)-Segphos to $Pd(OAc)_2$ to generate chiral palladium catalyst **A**. Subsequently, the oxidative addition of water to complex **A** generates palladium complex **B**, and **C** is formed by the further coordination of **B** with azabenzonorbornadiene **1a** and zinc ion. The subsequent insertion of alkene to the Pd−H bond affords intermediate **D**. Next, the *β*-elimination of nitrogen opens the pyrrolidine ring and gives the ring-opened species **E**. Then the hydration of **E** by water gives the final product **2a**. Finally, the reduction of **F** by zinc metal regenerates the chiral palladium catalyst **A**.

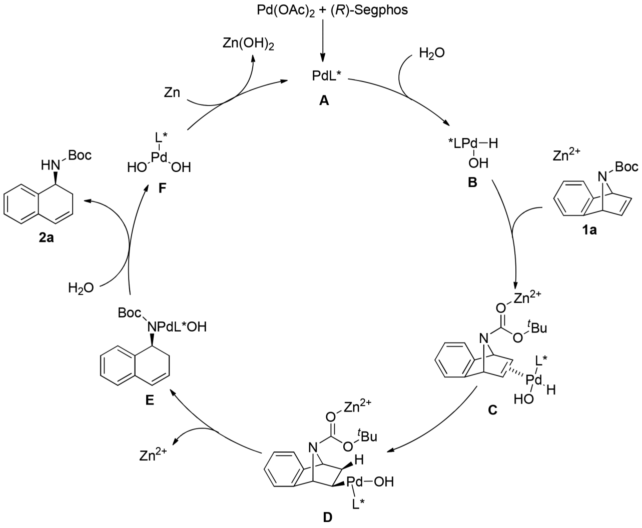


Figure 3. Proposed mechanism of ATH reaction.

In summary, the asymmetric reductive ring-opening reaction of heterobicyclic alkenes was accomplished via asymmetric transfer hydrogenation with water as sole hydrogen source. The catalytic system was constituted by the combination of $Pd(OAc)_2$/(*R*)-Segphos and $Zn(OTf)_2$. A wide range of azabenzonorbornadienes and oxabenzonorbornadienes were transformed to the corresponding chiral 1,2-dihydronaphthalenes smoothly with good to excellent enantioselectivities. Further applications of this co-catalytic system in other asymmetric transfer hydrogenation reactions are in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00059.

Experimental procedures and characterization data (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: chenjingchao84@163.com.
*E-mail: adams.bmf@hotmail.com.

ORCID

Baomin Fan: 0000-0003-1789-3741

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully thank the National Natural Science Foundation of China (21572198), the Applied Basic Research Project of Yunnan Province (2018FB021, 2017FA004), and Yunnan Provincial Key Laboratory Construction Plan Funding of Universities for their financial support.

REFERENCES

(1) Selected reviews of asymmetric hydrogenation: (a) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713−1760. (b) Etayo, P.; Vidal-Ferran, A. *Chem. Soc. Rev.* **2013**, *42*, 728−754. (c) Chen, Q.-A.; Ye, Z.-S.; Duan, Y.; Zhou, Y.-G. *Chem. Soc. Rev.* **2013**, *42*, 497−511. (d) Zhang, Z.-F.; Butt, N. A.; Zhang, W.-B. *Chem. Rev.* **2016**, *116*, 14769−14827. (e) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998−2007. (f) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008−2022. (g) Ager, D. J.; de Vries, A.; de Vries, J. G. *Chem. Soc. Rev.* **2012**, *41*, 3340−3380.

(2) Selected reviews of asymmetric transfer hydrogenation: (a) Zassinovich, G.; Mestroni, G. *Chem. Rev.* **1992**, *92*, 1051−1069. (b) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621−6686. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102. (d) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498−2518. (e) Muzart, J. *Eur. J. Org. Chem.* **2015**, *2015*, 5693−5707. (f) Roszkowski, P.; Czarnocki, Z. *Mini-Rev. Org. Chem.* **2007**, *4*, 190−200.

(3) (a) Foubelo, F.; Yus, M. *Chem. Rec.* **2015**, *15*, 907−924. (b) Wang, C.; Wu, X.; Xiao, J. *Chem. - Asian J.* **2008**, *3*, 1750−1770. (c) Saito, K.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 11740−11743. (d) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781−3783.

(4) (a) Xu, H.-Y.; Yang, P.; Chuanprasit, P.; Hirao, H.; Zhou, J.-R. *Angew. Chem., Int. Ed.* **2015**, *54*, 5112−5116; *Angew. Chem.* **2015**, *127*, 5201−5205. (b) Roszkowski, P.; Maurin, J. K.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2013**, *24*, 643−650. (c) Zuo, W.-W.; Lough, A. J.; Li, Y. F.; Morris, R. H. *Science* **2013**, *342*, 1080−1083.

(5) (a) Zhou, S.-L.; Fleischer, S.; Junge, K.; Das, S.; Addis, D.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8121−8125. (b) Menéndez-Pedregal, E.; Vaquero, M.; Lastra, E.; Gamasa, P.; Pizzano, A. *Chem. - Eur. J.* **2015**, *21*, 549−553. (c) Pablo, Ó.; Guijarro, D.; Yus, M. *Eur. J. Org. Chem.* **2014**, *2014*, 7034−7038. (d) Landwehr, A.; Dudle, B.; Fox, T.; Blacque, O.; Berke, H. *Chem. - Eur. J.* **2012**, *18*, 5701−5714.

(6) (a) Werkmeister, S.; Fleischer, S.; Junge, K.; Beller, M. *Chem. - Asian J.* **2012**, *7*, 2562−2568. (b) Marcelli, T.; Hammar, P.; Himo, F. *Chem. - Eur. J.* **2008**, *14*, 8562−8571.

(7) (a) Jagadeesh, R. V.; Wienhöfer, G.; Westerhaus, F. A.; Surkus, A.-E.; Pohl, M.-M.; Junge, H.; Junge, K.; Beller, M. *Chem. Commun.* **2011**, *47*, 10972−10974. (b) Li, J.; Hua, R.; Liu, T. *J. Org. Chem.* **2010**, *75*, 2966−2970.

(8) (a) Cummings, S. P.; Le, T.-N.; Fernandez, G. E.; Quiambao, L. G.; Stokes, B. J. *J. Am. Chem. Soc.* **2016**, *138*, 6107−6110. (b) Ojha, D. P.; Gadde, K.; Prabhu, K. R. *Org. Lett.* **2016**, *18*, 5062−5065. (c) Zhou, Y.-M.; Zhou, H.-F.; Liu, S.-S.; Pi, D.-W.; Shen, G.-S. *Tetrahedron* **2017**, *73*, 3898−3904. (d) Xuan, Q.-Q.; Song, Q.-L. *Org. Lett.* **2016**, *18*, 4250−4253. (e) Wang, D.-W.; Wang, D.-S.; Chen, Q.-A.; Zhou, Y.-G. *Chem. - Eur. J.* **2010**, *16*, 1133−1136. (f) Flinker, M.; Yin, H.-F.; Juhl, R. W.; Eikeland, E. Z.; Overgaard, J.; Nielsen, D. U.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2017**, *56*, 15910−15915; *Angew. Chem.* **2017**, *129*, 16126−16131.

(9) (a) Wang, R.; Ma, M.-Y.; Gong, X.; Panetti, G. B.; Fan, X.-Y.; Walsh, P. J. *Org. Lett.* **2018**, *20*, 2433−2436. (b) Call, A.; Casadevall, C.; Acuña-Parés, F.; Casitas, A.; Lloret-Fillol, J. *Chem. Sci.* **2017**, *8*, 4739−4749.

(10) (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58. (b) Rayabarapu, D. K.; Cheng, C.-H. *Acc. Chem. Res.* **2007**, *40*, 971−983.

(11) (a) Lautens, M.; Rovis, T. *Tetrahedron* **1998**, *54*, 1107−1116. (b) Lautens, M.; Chiu, P.; Ma, S.-H.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532−533. (c) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 11090−11091.

(12) Li, L.-P.; Rayabarapu, D. K.; Nandi, M.; Cheng, C.-H. *Org. Lett.* **2003**, *5*, 1621−1624.

(13) (a) Yang, F.; Chen, J.-C.; Xu, J.-B.; Ma, F.-J.; Zhou, Y.-Y.; Shinde, M. V.; Fan, B.-M. *Org. Lett.* **2016**, *18*, 4832−4835. (b) Ma, F.-J.; Chen, J.-C.; Yang, F.; Shinde, M. V.; Zhou, Y.-Y.; Fan, B.-M. *Org. Biomol. Chem.* **2017**, *15*, 2359−2362. (c) Yang, F.; Chen, J.-C.; Shen, G.-L.; Zhang, X.-X.; Fan, B.-M. *Chem. Commun.* **2018**, *54*, 4963−4966. (d) Pu, D.-D.; Zhou, Y.-Y.; Yang, F.; Shen, G.-L.; Gao, Y.; Sun, W.-Q.; Khan, R.; Fan, B.-M. *Org. Chem. Front.* **2018**, *5*, 3077−3082.

(14) (a) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264−267. (b) Hu, A.-G.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W.-B. *Adv. Synth. Catal.* **2006**, *348*, 2051−2056.

(15) (a) Zhang, X.-J.; Xie, X.; Liu, Y.-H. *J. Am. Chem. Soc.* **2018**, *140*, 7385−7389. (b) Sato, T.; Watanabe, S.; Kiuchi, H.; Oi, S.; Inoue, Y. *Tetrahedron Lett.* **2006**, *47*, 7703−7705. (c) Campaña, A. G.; Estévez, R. E.; Fuentes, N.; Robles, R.; Cuerva, J. M.; Buñuel, E.; Cárdenas, D.; Oltra, J. E. *Org. Lett.* **2007**, *9*, 2195−2198.

DOI: 10.1021/acs.orglett.9b00059
Org. Lett. XXXX, XXX, XXX−XXX