Organic LETTERS

Letter

pubs.acs.org/OrgLett

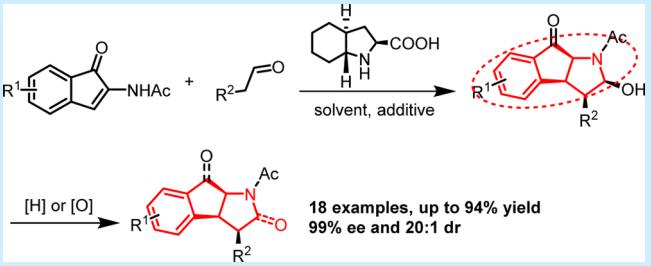
Construction of Chiral-Fused Tricyclic γ-Lactams via a *trans*-Perhydroindolic Acid-Catalyzed Asymmetric Domino Reaction

Qianjin An,[†,§] Jiefeng Shen,[†,§] Delong Liu,*[,†] Yangang Liu,[†] and Wanbin Zhang*[,†,‡]

[†]School of Pharmacy and [‡]School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China

Supporting Information

ABSTRACT: An asymmetric domino reaction was developed utilizing readily available cyclic α-dehydroamino ketones and aldehydes, which when subjected a 2-iodoxybenzoic acid (IBX)-mediated oxidation gives pyrrolidinone-containing tricyclic derivatives. *trans*-Perhydroindolic acid proved to be an efficient organocatalyst in this reaction (up to 94% yield, 99% ee, and >20:1 dr). The product could be conveniently converted to synthetically useful intermediates via simple transformations. A possible stereocontrolled process has been suggested according to X-ray crystallography studies.



Aza-heterocyclic γ-lactams and pyrrolidines are important skeletons and exist in numerous natural products, physiologically active compounds, and catalysts.[1] The construction of such motifs has therefore been intensively investigated. In comparison, even though they can serve as "privileged structures" in medical and pharmaceutical chemistry,[2] γ-lactam and pyrrolidine-containing tricyclic derivatives have received less attention because the synthesis of such functionalized tricycles remains challenging.[3] In 1991, Marson reported a one-pot stereocontrolled synthesis of a few substituted tricyclic γ-lactams via the condensation of 3-alkenamides with benzaldehyde in acidic media (Figure 1, the same below).[4] In 2004,

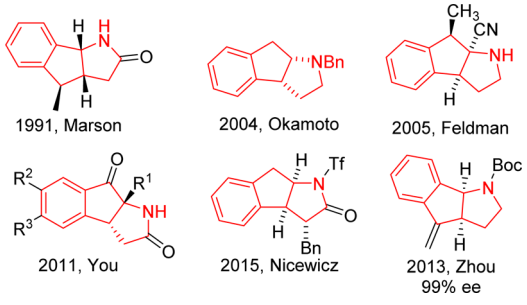
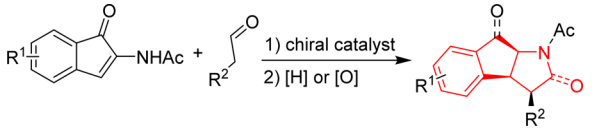


Figure 1. Tricyclic γ-lactams and pyrrolidines.

Okamoto synthesized a pyrrolidine-containing tricycle using a divalent titanium reagent.[5] The following year, Feldman prepared similar products using a cascade cyclization sequence evolving from the thermolyses of allenyl azides.[6] The You group combined a tandem NHC-catalyzed aza-benzoin and Michael reaction to produce dihydroindenones, which can then be transformed to pyrrolidinone-containing tricycles.[7] More recently, Nicewicz realized the only reported example of the synthesis of a tricyclic γ-lactams using a photoredox-mediated approach.[8] Although satisfactory to good yields and excellent regioselectivities could be obtained, the above-mentioned methodologies either utilize substrates that are not readily available or provide somewhat low reaction activities. Furthermore, substrate scope is limited, and only one example of an asymmetric catalytic strategy for the synthesis of enantioenriched pyrrolidine-containing tricycles has been reported by Zhou.[9]

Recently, we reported an efficient Rh-catalyzed asymmetric hydrogenation of cyclic α-dehydroamino ketones for the synthesis of chiral α-amino ketones and *trans*-β-amino alcohols.[10] The cyclic α-dehydroamino ketone substrates can be easily prepared from benzaldehyde via a simple aldol condensation followed by an intramolecular Friedel–Crafts reaction. Furthermore, our group previously disclosed an efficient synthetic route for the preparation of *trans*-perhydroindolic acids, a key intermediate used in the synthesis of trandolapril and its isomeric byproducts.[11] These proline-like molecules subsequently proved to be excellent organocatalysts for several types of asymmetric cascade reactions.[12] Herein, we report the application of *trans*-perhydroindolic acid **IV** to the asymmetric domino reaction of cyclic α-dehydroamino ketones and simple aldehydes for the synthesis of biologically active γ-lactam and pyrrolidine-containing tricyclic derivatives (Scheme 1).

Scheme 1. Asymmetric Domino Reaction

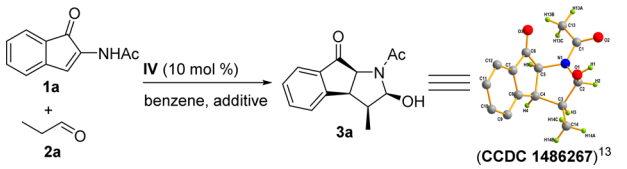


Received: April 17, 2017

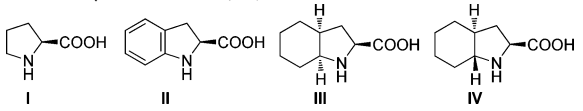
DOI: 10.1021/acs.orglett.7b01160
Org. Lett. XXXX, XXX, XXX–XXX

Initial studies began with the asymmetric domino reaction of cyclic α-dehydroamino ketone **1a** with propanal **2a** in benzene at 25 °C in the presence of DABCO, using different chiral proline-like catalysts **I**–**IV** (Table 1).

Table 1. Screening of Catalysts and Additives[a]



entry	time	additive (equiv)	yield[b] (%)	dr[c]	ee[d] (%)
1[e]	2 h	DABCO (1)	98	89/7/2/2	0
2[f]	7 days	DABCO (1)	70	71/9/19/1	77
3[g]	1.0 days	DABCO (1)	94	86/9/4/1	4
4	1.0 days	DABCO (1)	89	84/5/5/6	93
5	7 days	–	26	52/4/19/25	93
6	7 days	benzoic acid (1)	32	56/8/17/19	87
7	1.5 days	DMAP (1)	86	77/4/8/11	93
8	1.5 days	Et_3N (1)	70	78/5/16/1	91
9	1.5 days	DIPEA (1)	85	74/9/15/2	88
10	1.5 days	TMEDA (1)	90	83/3/13/1	67
11	7 days	Na_2CO_3 (1)	38	67/15/15/3	89
12	1.5 days	DABCO (0.5)	91	86/3/5/6	93
13	2.0 days	DABCO (0.2)	90	88/3/8/1	93

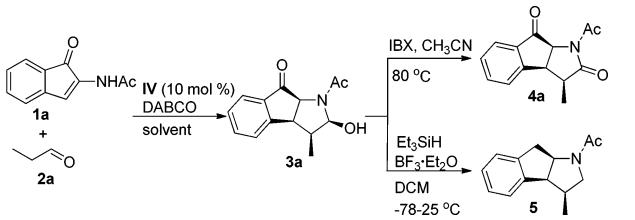


[a]Reactions of **1a** (0.2 mmol) with **2a** (2 mmol) were catalyzed by catalyst **IV** (10 mol %) in the presence of an additive (1 equiv) in benzene (2.0 mL) at 25 °C. [b]Isolated yields of the products containing the major and minor isomers. [c]Determined by chiral HPLC using a chiral IE-H column with products containing four isomers. [d]With the major configuration. [e]Catalyst **I**. [f]Catalyst **II**. [g]Catalyst **III**.

Commonly used proline (**I**) is able to promote smooth reaction, with the desired product being obtained in almost quantitative yield but as a racemic mixture (entry 1). Moderate yield and enantioselectivity were observed when (*S*)-indoline-2-carboxylic acid (**II**) was used as a catalyst (entry 2). Very high yield and low ee were also obtained using *cis*-perhydroindolic acid (**III**) as a catalyst (entry 3). To our delight, when *trans*-perhydroindolic acid (**IV**) was applied in the above reaction, high reaction activity as well as good diastereo- and excellent enantioselectivity were achieved (entry 4). We next investigated the influence of additives on the reaction (entries 5–11). When no additive or an acidic additive such as benzoic acid was added, the reaction proceeded slowly, giving the tricyclic product **3a** with good enantioselectivities but in low yields, even after 7 days (entries 5 and 6). In contrast, organic bases significantly promoted the reaction, with **3a** being obtained in high yields and enantioselectivities (entries 7–10). However, inorganic bases such as Na_2CO_3 were unable to provide high reaction activity, with **3a** being obtained in only 38% yield after 7 days (entry 11). DABCO provided somewhat better catalytic behavior than others and was used for further optimization of the reaction conditions. Finally, the dosage of DABCO was examined. Lowering the amount of DABCO to 0.5 or 0.2 equiv had no obvious effect on the reaction outcome, although reaction activities were slightly lower (entries 12 and 13). Further reducing the dosage of DABCO to 0.1 equiv resulted in a sharp decrease in reaction activity with the reaction failing to go to completion even after 3 days. The ORTEP drawing of the desired product **3a** indicates that a *cis*-fused bicyclic structure bearing four *S*-configuration chiral centers is formed in our reaction.[13]

We next investigated the influence of solvent on the reaction (Table 2). The reaction proceeded smoothly in the protic alcohol

Table 2. Screening of Solvents[a]



entry	time (days)	solvent	yield[b] (%)	dr[c]	ee[d] (%)
1	0.5	CH_3OH	77	61/21/11/7	68
2	7	THF	69	71/11/14/4	88
3	2.0	DCM	90	62/9/19/10	86
4	2.0	benzene	90	88/3/8/1	93
5	2.0	bromobenzene	81	72/6/15/7	91
6	2.0	toluene	94	82/6/9/3	93
7	2.0	*m*-xylene	94	87/4/6/3	92
8	2.0	mesitylene	95	90/4/5/1	96
9[e]	2.0	mesitylene	93	90/10	94
10[f]	2.0	mesitylene	88	88/12	94

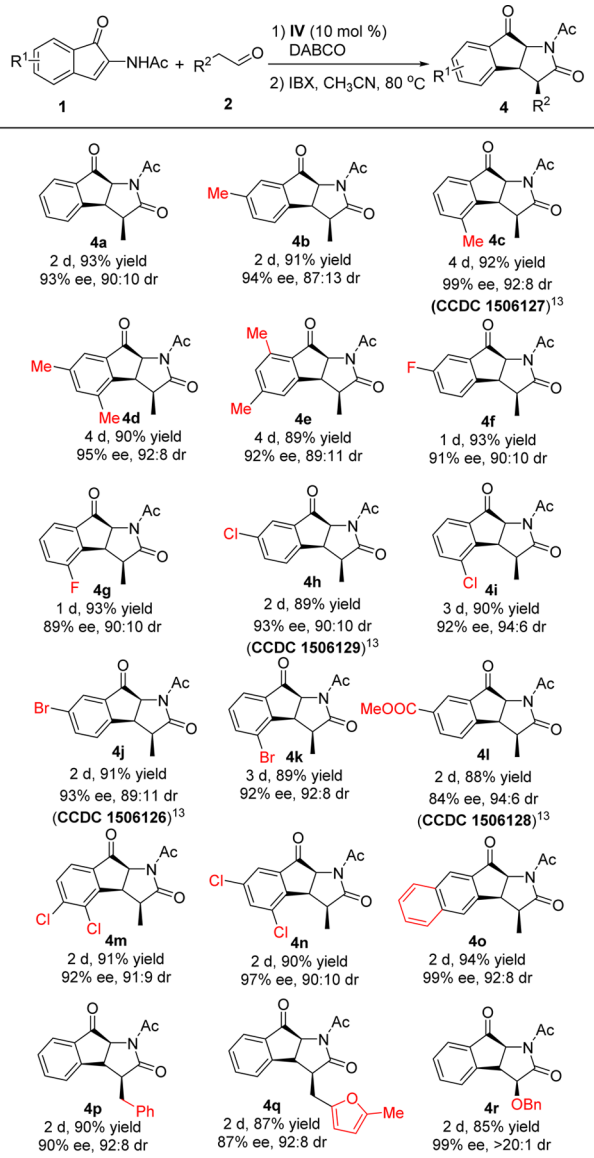
[a]Using the optimal reaction conditions shown in Table 1 (entry 13) in different solvent. [b]Isolated yields of the products **3a** containing the major and minor isomers. [c]Determined by chiral HPLC using a chiral IE-H column with products containing four isomers. [d]With the major configuration. [e]Product **4a**; IBX, CH_3CN, 80 °C. [f]Product **5**; Et_3SiH/$BF_3{\cdot}Et_2O$, DCM, −78 to 25 °C.

CH_3OH to give the desired product **3a** in only moderate yield and enantioselectivity (entry 1). When aprotic solvents such as THF, DCM, benzene, bromobenzene, toluene, *m*-xylene, and mesitylene were used, good to excellent yields and enantioselectivities were obtained (entries 2–8). Mesitylene was found to be the best solvent according to a combination of chemical yield and enantioselectivity (entry 8). To obtain the terminal tricyclic γ-lactam product, **3a** was oxidized using 2-iodoxybenzoic acid (IBX) to give the desired product **4a** in 93% yield, 94% ee, and 90/10 dr (entry 9). Additionally, the hydroxyl group and the carbonyl group of **3a** could be removed in the presence of $Et_3SiH/BF_3{\cdot}Et_2O$, affording the reduced product **5** in high yield and with good diastereoselectivity and excellent enantioselectivity (entry 10).

With the optimal reaction conditions in hand, the substrate scope of the reaction between different cyclic α-dehydroamino ketones **1** with several aldehydes **2** was explored (Scheme 2). Cyclic α-dehydroamino ketones bearing one or two Me groups on the phenyl ring were first examined. We were pleased to discover that asymmetric catalytic behavior was mostly unaffected, and all reactions proceeded smoothly with the desired products being obtained in more than 90% yield and ee and 90/10 dr (**4b**–**4e**). The effect of different electron-withdrawing substituents on the phenyl ring was next examined (**4f**–**4n**). Excellent asymmetric catalytic behavior was still observed and **4n** was obtained in 97% ee. When the phenyl ring was replaced by a naphthalene group, the tetracyclic γ-lactam

DOI: 10.1021/acs.orglett.7b01160
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Scope of Substrates[a]

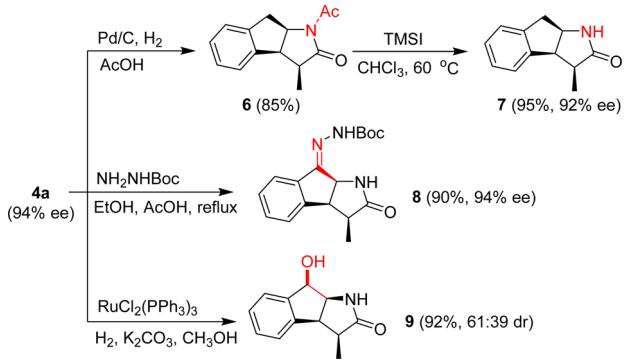


[a]Using the optimal reaction conditions shown in Table 2 (entry 9) followed by treatment with IBX in CH_3CN at 80 °C. Yields of isolated products of the major and minor isomers are presented. The diastereomeric ratio was determined by ^1H NMR of the crude product; ee values were determined by chiral HPLC.

product **4o** was obtained in 94% yield and with 99% ee. Finally, several aldehydes **2** were investigated, and good to excellent results were also obtained (**4p**–**4r**). A BnO-substituted aldehyde gave its corresponding product (**4r**) with 99% ee and more than 20/1 dr. The reaction was also carried out with other aliphatic aldehydes, such as *n*-butyl aldehyde and *iso*-pentaldehyde; however, no reaction occurred.

The tricyclic γ-lactam products have the potential to participate in a variety of transformations (Scheme 3). For example, the carbonyl group of **4a** can be removed using a Pd/C and H_2 system in AcOH to give the corresponding lactam **6**. N-Deprotection of **6** with trimethylsilyl iodide (TMSI) in chloroform affords **7**.[14] Structures such as **7** not only are medicinally interesting but also represent a synthetically challenging family of intermediates owing to the presence of three stereogenic centers.[3] Alternatively, the carbonyl group can

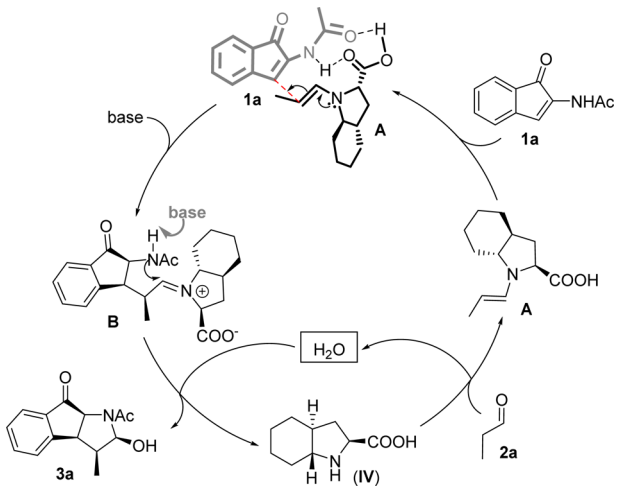
Scheme 3. Transformation of 4a



also be simply converted to give hydrozone **8** in 90% yield with no effect on enantioselectivity.[15] The carbonyl group can also be partially reduced in the presence of a $RuCl_2(PPh_3)_3$ catalyst under 40 bar H_2 at room temperature to give the corresponding chiral cyclic β-amino alcohol **9** in good yield. Alcohol **9** is a potentially important building block for the synthesis of several biologically active molecules and chiral catalysts.[10b]

Based on the absolute configuration of **3a** and detailed reaction results, we believe that the reaction may undergo the following stereocontrolled process (Scheme 4). First, an enamine **A** is

Scheme 4. Proposed Reaction Pathway



generated in situ via the reaction of *trans*-perhydroindolic acid **VI** with one molecule of propanal **2a**. A H-bond interaction between the amide (**1a**) and carboxyl group (**A**) directs the attack of the enamine moiety of **A** from the top side of **1a** due to the steric hindrance of the six-membered fused ring system of the catalyst; intermediate **B** is subsequently formed. In the presence of a base, **B** undergoes a nucleophilic addition via back surface attack of the acetyl amino group to the aldehyde group. The desired tricyclic product **3a** is obtained after a further hydrolysis, and the chiral catalyst is released.

To summarize, we have developed an efficient asymmetric domino reaction of readily available cyclic α-dehydroamino ketones and aldehydes for the synthesis of chiral γ-lactam-containing tricyclic derivatives. The previously synthesized *trans*-perhydroindolic acid proved to be an efficient organocatalyst for this reaction. Under the optimal reaction conditions, the reaction provided the desired products in up to excellent yield (up to 94%), with excellent diastereoselectivities (up to >20:1) and

DOI: 10.1021/acs.orglett.7b01160
Org. Lett. XXXX, XXX, XXX−XXX

enantioselectivities (up to 99%). A stereocontrolled process has been proposed, and the tricyclic products could be converted to structurally useful scaffolds using simple transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01160.

Experimental procedures and characterization details (PDF)
X-ray data for **3a** (CIF)
X-ray data for **4c** (CIF)
X-ray data for **4h** (CIF)
X-ray data for **4j** (CIF)
X-ray data for **4l** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: dlliu@sjtu.edu.cn.
*E-mail: wanbin@sjtu.edu.cn.

ORCID

Wanbin Zhang: 0000-0002-4788-4195

Author Contributions

§Q.A. and J.S. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by the National Natural Science Foundation of China (Nos. 21372152, 21402117, 21672142, and 21232004), Program of Shanghai Subject Chief Scientists (Nos. 14XD1402300 and 15JC1402200), and the Instrumental Analysis Center of SJTU for characterization.

■ REFERENCES

(1) For selected reviews, see: (a) Alonso, D. A.; Almasi, D.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (c) Li, J. L.; Liu, T. Y.; Chen, Y.-C. *Acc. Chem. Res.* **2012**, *45*, 1491. (d) Han, M.-Y.; Jia, J.-Y.; Wang, W. *Tetrahedron Lett.* **2014**, *55*, 784. (e) Ye, L. W.; Shu, C.; Gagosz, F. *Org. Biomol. Chem.* **2014**, *12*, 1833. (f) Zhang, Z.; Butt, N. A.; Zhang, W. *Chem. Rev.* **2016**, *116*, 14769.

(2) For selected papers, see: (a) Crooks, P. A.; DeSimone, F.; Ramundo, E. *J. Heterocycl. Chem.* **1982**, *19*, 1433. (b) Crooks, P. A.; Deeks, T.; DeSimone, F. *J. Heterocycl. Chem.* **1989**, *26*, 1113. (c) Chen, Y. L.; Nielsen, J.; Hedberg, K.; Dunaiskis, A.; Jones, S.; Russo, L.; Johnson, J.; Ives, J.; Liston, D. *J. Med. Chem.* **1992**, *35*, 1429. (d) Qiao, L.; Zhao, L.-Y.; Rong, S.-B.; Wu, X.-W.; Wang, S.; Fujii, T.; Kazanietz, M. G.; Rauser, L.; Savage, J.; Roth, B. L.; Flippen- Anderson, J.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 955. (e) Gavuzzo, E.; Pomponi, M. *J. Biochem. Mol. Toxicol.* **2002**, *16*, 64. (f) Huck, B. R.; Llamas, L.; Robarge, M. J.; Dent, T. C.; Song, J.; Hodnick, W. F.; Crumrine, C.; Stricker-Krongrad, A.; Harrington, J.; Brunden, K. R.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4130. (g) Fu, X.; Chen, J.; Li, G.; Liu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5500. (h) Xing, J.; Wang, X.-R.; Yan, C.-X.; Cheng, Y. *J. Org. Chem.* **2011**, *76*, 4746. (i) Luo, Y.; Wu, J. *Org. Lett.* **2012**, *14*, 1592. (j) Lachia, M.; Wolf, H. C.; Jung, P. J. M.; Screpanti, C.; De Mesmaeker, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2184.

(3) For selected papers, see: (a) Marson, C. M.; Grabowska, U. *J. Org. Chem.* **1994**, *59*, 284. (b) Behler, F.; Habecker, F.; Saak, W.; Kluener, T.; Christoffers, J. *Eur. J. Org. Chem.* **2011**, *2011*, 4231. (c) Zhou, W.; An, G.; Zhang, G.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2011**, *9*, 5833. (d) Wang, S.; Yang, Q.; Dong, J.; Li, C.; Sun, L.; Song, S.; Chang, J. *Eur. J. Org. Chem.* **2013**, *2013*, 7631. (e) Zhou, P.; Hao, W. J.; Zhang, J. P.; Jiang, B.; Li, G. G.; Tu, S. J. *Chem. Commun.* **2015**, *51*, 13012.

(4) Marson, C. M.; Grabowska, U. *J. Org. Chem.* **1991**, *56*, 2603.

(5) Uchikawa, W.; Matsuno, C.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 9037.

(6) Feldman, K. S.; Iyer, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 4590.

(7) Wu, K.-J.; Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2011**, *47*, 493.

(8) Gesmundo, N. J.; Grandjean, J. M. M.; Nicewicz, D. A. *Org. Lett.* **2015**, *17*, 1316.

(9) Hu, J.; Hirao, H.; Li, Y.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 8676.

(10) (a) Zhang, Z.; Hu, Q.; Wang, Y.; Chen, J.; Zhang, W. *Org. Lett.* **2015**, *17*, 5380. (b) Hu, Q.; Chen, J.; Zhang, Z.; Liu, Y.; Zhang, W. *Org. Lett.* **2016**, *18*, 1290.

(11) (a) Shen, J.; Liu, D.; An, Q.; Liu, Y.; Zhang, W. *Adv. Synth. Catal.* **2012**, *354*, 3311. (b) Shi, T.; Shen, J.; An, Q.; Liu, D.; Liu, Y.; Zhang, W. *Youji Huaxue* **2013**, *33*, 1573.

(12) (a) Zhao, L.; Shen, J.; Liu, D.; Liu, Y.; Zhang, W. *Org. Biomol. Chem.* **2012**, *10*, 2840. (b) Shen, J.; An, Q.; Liu, D.; Liu, Y.; Zhang, W. *Chin. J. Chem.* **2012**, *30*, 2681. (c) An, Q.; Shen, J.; Liu, D.; Butt, N.; Liu, Y.; Zhang, W. *Synthesis* **2013**, *45*, 1612. (d) An, Q.; Shen, J.; Butt, N.; Liu, D.; Liu, Y.; Zhang, W. *Org. Lett.* **2014**, *16*, 4496. (e) An, Q.; Li, J.; Shen, J.; Butt, N.; Liu, D.; Liu, Y.; Zhang, W. *Chem. Commun.* **2015**, *51*, 885. (f) An, Q.; Shen, J.; Butt, N.; Liu, D.; Liu, Y.; Zhang, W. *Adv. Synth. Catal.* **2015**, *357*, 3627.

(13) CCDC 1486267, 1506126, 1506127, 1506128, and 1506129 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) (a) Miller, R. D.; Goelitz, P. *J. Org. Chem.* **1981**, *46*, 1616. (b) Chen, Y. L.; Nielsen, J.; Hedberg, K.; Dunaiskis, A.; Jones, S.; Russo, L.; Johnson, J.; Ives, J.; Liston, D. *J. Med. Chem.* **1992**, *35*, 1429.

(15) Cranwell, P. B.; Russell, A. T. J. *J. Chem. Educ.* **2016**, *93*, 949.

DOI: 10.1021/acs.orglett.7b01160
Org. Lett. XXXX, XXX, XXX−XXX