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

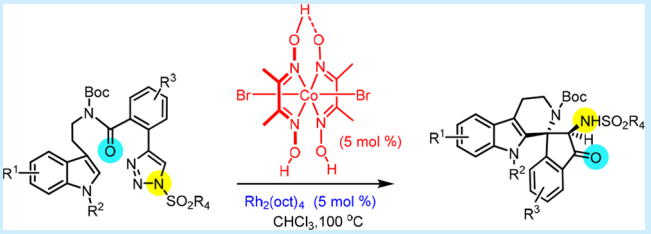
Relay Catalysis of Rh (II) and Cobaloxime: Stereoselective Synthesis of Spiroindanones from N-Sulfonyl-1,2,3-triazoles

Zhao Liu, Qiuchen Du, Hongbin Zhai, and Yun Li*

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, China

Supporting Information

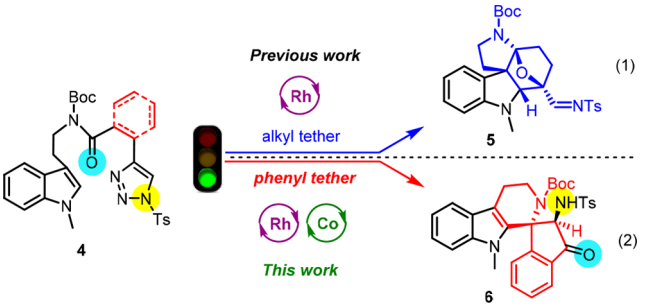
ABSTRACT: A novel relay Rh (II)/cobaloxime (III) dual catalysis strategy has been developed for the stereoselective synthesis of indolyl spiroindanones from readily accessible N-sulfonyl-1,2,3-triazoles. This binary-catalyst system enables an aza-vinyl carbene initiated Pictet-Spengler-type cyclization and sequential cobaloxime promoted intramolecular Mannich-type reaction cascade. The easily accessible reagents, high diastereoselectivity, and operational simplicity make this reaction a method of choice for the preparation of functionalized spiroindanones, which are difficult to access by other classic reactions in one step.



Spiroindanones are privileged substructures owing to the occurrence of many bioactive natural products[1] and the discovery of many medicinally significant compounds.[2] The development of concise methods of synthesizing these heterocyclic compounds is therefore attractive for synthetic organic chemists. Different strategies have been reported for the construction of the indanone framework including intramolecular Friedel−Crafts reaction,[3] Heck cyclization reactions,[4] Nazarov cyclization,[5] carbene involved cyclization,[6] and other methods.[7] In this regard, while much effort has been devoted to the synthesis of such scaffold, an alternative or complementary method with mild reaction conditions and high stereoselectivity, especially from easy-to-assemble substrates, is still of great interest. On the other hand, a cascade transformation provides an ideal platform for the formation of multiple bonds with one single operation. By avoiding protecting group manipulations and tedious purification of the intermediates, desirable time- and cost-saving operations could easily be achieved.

Rh (II)-catalyzed denitrogenative transannulation of N-sulfonyl-1,2,3-triazoles has evolved as a useful synthetic strategy for constructing a wide variety of important heterocycles.[8] The α-imino carbenes derived from the N-sulfonyl 1,2,3-triazoles via a Dimroth-type equilibrium exhibit unique reactivity and have received much attention in recent years.[9] This electrophilic intermediate could be trapped by various nucleophiles leading to a highly reactive ylide and could undergo a variety of subsequent transformations.[10] In a program directed toward the development of cyclization reactions for quick assembly of a natural product scaffold from readily available starting materials, we have recently described the merit of the rhodium-catalyzed denitrogenative [3 + 2] cyclization reaction for the construction of aspidospermidine[11] (Scheme 1, path 1) and montanine-type[12] scaffolds from N-sulfonyl-1,2,3-triazoles. Hence, it was envisioned that extension of this concept to the benzoamide tethered triazole substrate **4** (Scheme 1) might provide new reactivity and lead to the new possibilities for construction of different cyclic scaffolds. Herein, we now describe a rhodium and cobaloxime dual catalyzed denitrogenative cyclization reaction of N-sulfonyl-1,2,3-triazoles for the diastereoselective construction of the biologically important spiroindanones (Scheme 1, path 2).

Scheme 1. Divergent Synthesis of Polycyclic Indole Derivatives from N-Sulfonyl-1,2,3-triazoles

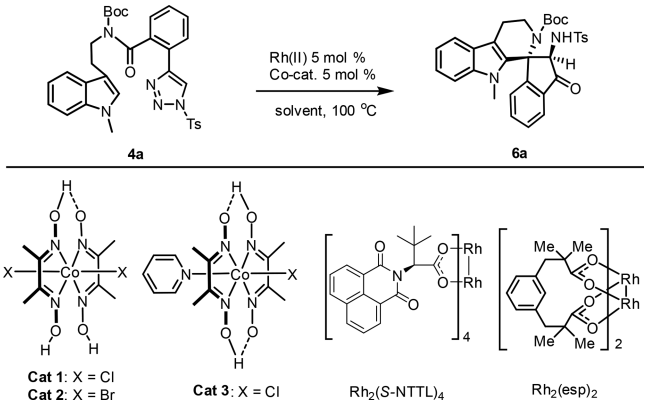


Our research began with evaluation of the N-sulfonyl-1,2,3-triazole-4-yl-benzamide **4a** in the Rh-catalyzed tandem reaction. Initially, **4a** was treated with $Rh_2(oct)_4$ (5 mol %) in chloroform at 100 °C for 12 h; however, only 5% yield of cyclized product **6a** could be isolated as a single isomer (Table 1, entry 1). The full structural information of **6a** was later secured by both NMR spectroscopic data and comparison to the X-ray crystallographic analyses of **6e** (Scheme 2).[13] An extensive condition survey indicated that the yield of **6a** could be improved to 43% when additional $Yb(OTf)_3$ (5 mol %) was employed as a cocatalyst in the reaction (entry 2). This interesting observation prompted us

Received: October 13, 2018

DOI: 10.1021/acs.orglett.8b03275
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Dual Metal Relay Catalyzed Cyclization of 4a[a]



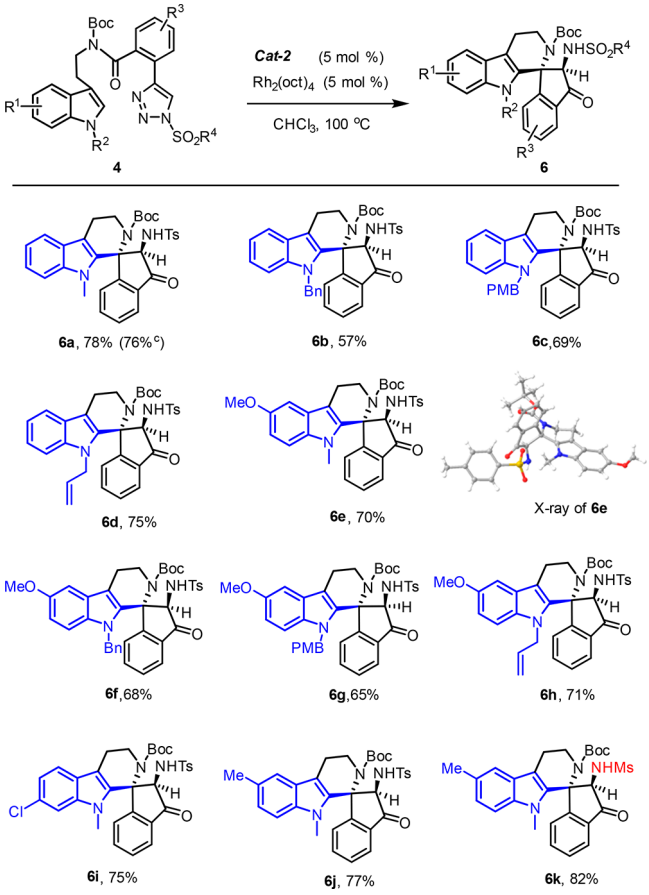
entry	Rh catalyst	Co catalyst	solvent	yield[b] (%)
1	$Rh_2(oct)_4$	none	$CHCl_3$	5
2	$Rh_2(oct)_4$	$Yb(OTf)_3$	$CHCl_3$	34
3	$Rh_2(oct)_4$	$Fe(NO_3)_3$	$CHCl_3$	12
4	$Rh_2(oct)_4$	$CoBr_2$	$CHCl_3$	30
5	$Rh_2(oct)_4$	***Cat 1***	$CHCl_3$	65
6	$Rh_2(oct)_4$	***Cat 2***	$CHCl_3$	81(78)[c]
7	$Rh_2(oct)_4$	***Cat 3***	$CHCl_3$	55
8	$Rh_2(NTTL)_4$	***Cat 2***	$CHCl_3$	0
9	$Rh_2(esp)_4$	***Cat 2***	$CHCl_3$	23
10	$Rh_2(oct)_4$	***Cat 2***	DCE	66
11	$Rh_2(oct)_4$	***Cat 2***	toluene	0
12	none	***Cat 2***	$CHCl_3$	0

[a]All reactions were performed with 0.03 mmol of triazole **4a** and 5 mol % of the Rh catalyst and 5 mol % cocatlyst in 1 mL solvent at 100 °C. [b]^{1}H NMR yield (1,3,5-trimethoxybenzene as internal standard). [c]Isolated yield.

to further evaluate more Lewis acids as the cocatalyst in this reaction. It was found that $Fe(NO_3)_3$ and $CoBr_2$ (entry, 3, 4) gave inferior results compared to $Yb(OTf)_3$. On the basis of our previous experience in cobaloxime-catalyzed alkyne hydration reactions,[14] cobaloxime (Table 1, ***Cat 1***−***Cat 3***) that possesses a unique chemical structure could serve as a strong π-acid in alkyne hydration reactions. Thus, we wondered that whether these catalysts could also pay as a strong Lewis acid and promote this cascade reaction; later experimental results proved our hypothesis quite successful. When ***Cat 1*** was employed, the yield of **6a** could be greatly improved to 65% (entry 5). More electronic deficient bromo-complex ***Cat 2*** gave an even better result (entry 6). The desired product could be isolated in 78% yield (81% NMR yield) with a single diastereo isomer. Pyridine coordinated ***Cat 3*** gave lower yield (entry 7). A survey of various Rh (II) catalysts revealed that $Rh_2(oct)_4$ is the optimal catalyst (entry 8, 9). A solvent variation did not further improve the yield of **6a** (entry 10, 11). Notably, the reaction gave none of the desired product when cobaloxime alone was employeded as the catalyst (entry 12), which indicated that both rhodium and cobalt catalysts play critical roles in this transformation.

With the optimal conditions established, we then explored various substituted indole derivatives to examine the substrate scope of this reaction (Scheme 2). Generally, this protocol tolerated a variety of functionalities on the indole moiety and gave synthetically useful yields. Different substituents on the indole N1 such as Me, Bn, PMB, and Allyl (**4a**−**4d**) have little influence on the efficiency of the reaction. Substrates with electron-rich substituent (-OMe) at C5 position of indolyl motif

Scheme 2. Scope Investigation of Spiroindanones Synthesis[a,b]



[a]Reactions were performed (in a sealed tube) with **4** (0.5 mmol, 1 equiv), $Rh_2(oct)_4$ (5 mol %), cobaloxime (5 mol %) in $CHCl_3$ (5 mL) at 100 °C for 10 h. [b]Yield of the isolated product. [c]Isolated yield at 1.4 mmol scale.

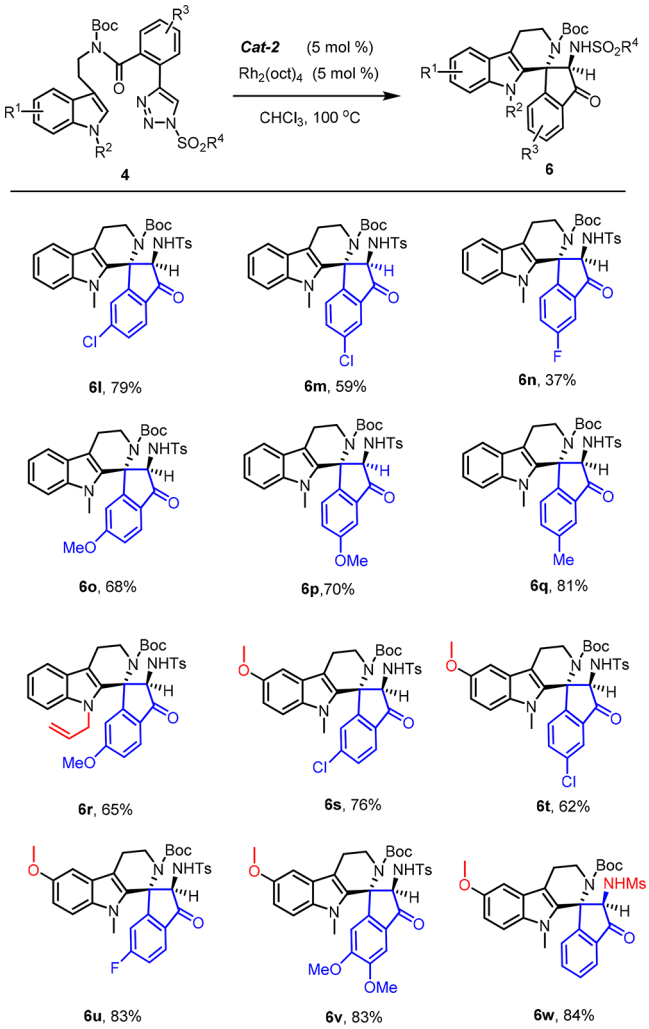
(**4e**−**4h**) gave relative lower yields compared with electron-neutral and deficient ones (**4i**, **4j**). Substrates with N-Mesyl-1,2,3-triazole motif (**4k**) gave relative higher yield of product than corresponding tosyl one (**4j**). In all cases, the antiproducts (respect to two ortho amino groups) were obtained exclusively as determined by ^{1}H NMR spectroscopy.

Next, the effect of the R^2-substituents on the benzene ring of the benzoamide fragment was explored for the reaction (Scheme 3). The substrates bearing a chloride at the *para*- or *meta*-position (**4l**−**4m**) afforded the desired products in reasonable yields (59−79%), whereas switching to more electron-deficient fluorine group furnished the corresponding cyclization in quite lower yield (37%). Both electron donating (**4o, 4p**) and neutral groups (**4q**) at the *para*- or *meta*-position led to preparative yields. It should be mentioned that the electron-rich group (such as methyl or allyl) on the indolic nitrogen N1 position was essential for the cyclization (**4a**−**4r**), while the carbomethoxy derivative did not give any of the desired product. When the tryptamine fragment was changed to 5-methoxyl tryptamine in the substrate (**4s**−**4w**), only negligible influence was observed for the cyclization. The replacement of indole fragment in the substrates by benzene and benzofuran failed to deliver the desired products.[15]

A mechanistic rationale for the formation of the spiroindanone is provided in Scheme 4. Heating the triazole **4** in the

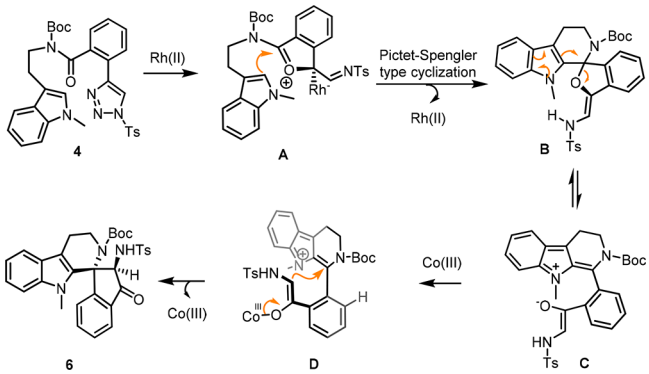
DOI: 10.1021/acs.orglett.8b03275
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Continued Scope Investigation[a,b]



[a]Reactions were performed (in a sealed tube) with **4** (0.5 mmol, 1 equiv), $Rh_2(oct)_4$ (5 mol %), cobaloxime (5 mol %) in $CHCl_3$ (5 mL) at 100 °C for 10 h. [b]Yield of the isolated product.

Scheme 4. Proposed Reaction Mechanism



presence of the dirhodium catalyst generates the imino carbene-intermediate and is then trapped by an internal amide carbonyl group affording ylide intermediate **A**. The following Pictet-Spengler-type cyclization of **A** provides spiroaminal intermediate **B**. Cobaloxime might facilitate a quick equilibrium from **B** to zwitterion **C**. After the formation of the corresponding cobalt enolate **D**, the following stereoselective intramolecular Mannich-type cyclization yielded the desired spiroindanone **6**.

In conclusion, we have demonstrated that the Rh (II)/cobaloxime binary-catalyst system enables relay cascade cyclization with steadily available N-sulfonyl-1,2,3-triazoles as the precursor. This reaction showed excellent stereoselectivity and expeditious access to indoly spiroindanones. A wide range of substrates are tolerated in this transformation, and various products can be obtained in good yields. The operational simplicity coupled with the mild reaction conditions of the present approach has established a new entry to a diverse set of valuable spiroindanones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03275.

Full experimental procedures; characterization data, and NMR spectra data (PDF)

Accession Codes

CCDC 1866860 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, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liyun@lzu.edu.cn.

ORCID

Hongbin Zhai: 0000-0003-2198-1357

Yun Li: 0000-0003-2236-9880

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (21572089), the Program for Changjiang Scholars and the Innovative Research Team in University (PCSIRT: IRT_15R28), the FRFCU (lzujbky-2018-61), and the Gansu Provincial Sci. and Tech. Department (2016B01017).

■ REFERENCES

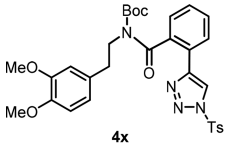
(1) (a) Baisheva, K. S.; Fesenko, D. A.; Rostotskii, B. K.; Perel'son, M. E. *Chem. Nat. Compd.* **1970**, *6*, 465. (b) Manske, R. H. F.; Rodrigo, R.; MacLean, D. B.; Gracey, D. E. F.; Saunders, J. K. *Can. J. Chem.* **1969**, *47*, 3585. (c) Yu, C. K.; MacLean, D. B. *Can. J. Chem.* **1971**, *49*, 3025. (d) Hanaoka, M.; Kohzu, M.; Yasuda, S. *Chem. Pharm. Bull.* **1985**, *33*, 2621. (e) Hughes, D. W.; Nalliah, B. C.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1977**, *55*, 3304.

(2) (a) Lv, B.; Feng, Y.; Dong, J.; Xu, M.; Xu, B.; Zhang, W.; Sheng, Z.; Welihinda, A.; Seed, B.; Chen, Y. *ChemMedChem* **2010**, *5*, 827. (b) Ramesh, E.; Manian, R. D. R. S.; Raghunathan, R.; Sainath, S.; Raghunathan, M. *Bioorg. Med. Chem.* **2009**, *17*, 660. (c) Frankish, N.; Sheridan, H. *J. Med. Chem.* **2012**, *55*, 5497.

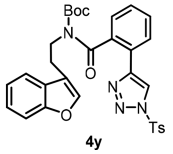
(3) (a) Wang, J.; Zhou, Y.; Zhang, L.; Li, Z.; Chen, X.; Liu, H. *Org. Lett.* **2013**, *15*, 1508. (b) Ou-yang, J.; Zhang, W.; Qin, F.; Zuo, W.; Xu, S.; Wang, Y.; Qin, B.; You, S.; Jia, X. *Org. Biomol. Chem.* **2017**, *15*, 7374. (c) Yin, W.; Ma, Y.; Xu, J.; Zhao, Y. *J. Org. Chem.* **2006**, *71*, 4312.

DOI: 10.1021/acs.orglett.8b03275
Org. Lett. XXXX, XXX, XXX−XXX

(d) Rendy; Zhang, Y.; McElrea, A.; Gomez, A.; Klumpp, D. A. *J. Org. Chem.* **2004**, *69* (69), 2340.
(4) (a) Brekan, J. A.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 1472. (b) Taylor, J. G.; Ribeiro, R. d. S.; Correia, C. R. D. *Tetrahedron Lett.* **2011**, *52*, 3861. (c) Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 9253.
(5) (a) Zheng, H. J.; Xie, X. G.; Yang, J.; Zhao, C. G.; Jing, P.; Fang, B. W.; She, X. G. *Org. Biomol. Chem.* **2011**, *9*, 7755. (b) Nie, J.; Zhu, H. W.; Cui, H. F.; Hua, M. Q.; Ma, J. A. *Org. Lett.* **2007**, *9*, 3053. (c) Cui, H. F.; Dong, K. Y.; Zhang, G. W.; Wang, L.; Ma, J. A. *Chem. Commun.* **2007**, 2284. (d) Teske, J.; Plietker, B. *Org. Lett.* **2018**, *20*, 2257.
(6) (a) Yuan, H.; Gong, J.; Yang, Z. *Chem. Commun.* **2017**, *53*, 9089−9092. (b) Shen, H.; Fu, J.; Gong, J.; Yang, Z. *Org. Lett.* **2014**, *16*, 5588. (c) Sun, R.; Jiang, Y.; Tang, X.-Y.; Shi, M. *Chem. - Eur. J.* **2016**, *22*, 5727. (d) Yu, Y.; Zhu, L.; Liao, Y.; Mao, Z.; Huang, X. *Adv. Synth. Catal.* **2016**, *358*, 1059.
(7) (a) Chanda, T.; Singh, M. S. *Org. Biomol. Chem.* **2016**, *14*, 8895. (b) Duan, Y. J.; Liu, J. L.; Wang, C. L. *Chin. J. Org. Chem.* **2010**, *30*, 988.
(8) (a) Pal, K.; Hoque, A.; Volla, C. M. R. *Chem. - Eur. J.* **2018**, *24*, 2558. (b) Bosmani, A.; Guarnieri-Ibanez, A.; Goudedranche, S.; Besnard, C.; Lacour, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 7151. (c) Yang, Y.; Yu, J.-X.; Ouyang, X.-H.; Li, J.-H *Org. Lett.* **2017**, *19*, 3982. (d) Chuprakov, S.; Kwok, S. W.; Fokin, V. V. *J. Am. Chem. Soc.* **2013**, *135*, 4652. (e) Lee, D. J.; Han, H. S.; Shin, J.; Yoo, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 11606. (f) Parr, B. T.; Green, S. A.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 4716. (g) Shang, H.; Wang, Y.; Tian, Y.; Feng, J.; Tang, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5662.
(9) For recent reviews, see: (a) Anbarasan, P.; Yadagiri, D.; Rajasekar, S. *Synthesis* **2014**, *46*, 3004. (b) Jiang, Y.; Sun, R.; Tang, X. Y.; Shi, M. *Chem. - Eur. J.* **2016**, *22*, 17910. (c) Wang, Y.; Lei, X.; Tang, Y. *Synlett* **2015**, *26*, 2051. (d) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151. (e) Li, Y.; Yang, H.; Zhai, H. *Chem. - Eur. J.* **2018**, *24*, 12757.
(10) (a) Li, Y.; Zhang, R.; Ali, A.; Zhang, J.; Bi, X.; Fu, J. *Org. Lett.* **2017**, *19*, 3087. (b) Guarnieri-Ibanez, A.; Medina, F.; Besnard, C.; Kidd, S. L.; Spring, D. R.; Lacour, J. *Chem. Sci.* **2017**, *8*, 5713. (c) Zhang, L.; Sun, G.; Bi, X. *Chem. - Asian J.* **2016**, *11*, 3018. (d) Yuan, H.; Gong, J.; Yang, Z. *Org. Lett.* **2016**, *18*, 5500. (e) Man, Z.; Dai, H.; Shi, Y.; Yang, D.; Li, C.-Y *Org. Lett.* **2016**, *18*, 4962. (f) Lu, X.-L.; Liu, Y.-T.; Wang, Q.-X.; Shen, M.-H.; Xu, H.-D. *Org. Chem. Front.* **2016**, *3*, 725. (g) He, J.; Shi, Y.; Cheng, W.; Man, Z.; Yang, D.; Li, C.-Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 4557. (h) Zhang, W.-B.; Xiu, S.-D.; Li, C.-Y. *Org. Chem. Front.* **2015**, *2*, 47. (i) Xu, H.-D.; Jia, Z.-H.; Xu, K.; Zhou, H.; Shen, M.-H. *Org. Lett.* **2015**, *17*, 66.
(11) Li, Y.; Zhang, Q.; Du, Q.; Zhai, H. *Org. Lett.* **2016**, *18*, 4076.
(12) Yang, H.; Hou, S.; Tao, C.; Liu, Z.; Wang, C.; Cheng, B.; Li, Y.; Zhai, H. *Chem. - Eur. J.* **2017**, *23*, 12930.
(13) CCDC 1866860 (**6e**) contains the supplementary crystallographic data for this paper. Data can be obtained free of charge from the Cambridge Crystallographic Data Centre.
(14) Hou, S.; Yang, H.; Cheng, B.; Zhai, H.; Li, Y. *Chem. Commun.* **2017**, *53*, 6926.
(15) The following two substrates (**4x**, **4y**) were also evaluated under the standard condition; however, none of the cyclized product was isolated.



4x



4y

DOI: 10.1021/acs.orglett.8b03275
Org. Lett. XXXX, XXX, XXX−XXX