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Organocatalytic Asymmetric Michael/Hemiketalization/Retro-aldol Reaction of α-Nitroketones with Unsaturated Pyrazolones: Synthesis of 3-Acyloxy Pyrazoles

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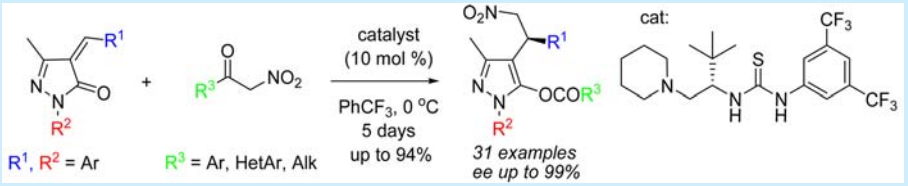
Supporting Information



ABSTRACT: An organocatalytic asymmetric cascade Michael/hemiketalization/retro-aldol reaction between unsaturated pyrazolones and α-nitroketones is described. A bifunctional thiourea catalyst was found to be efficient for this reaction. With 10 mol % of catalyst, high yields as well as excellent enantioselectivities are attained for a variety of 3-acyloxy pyrazoles under mild reaction conditions.

Pyrazoles and pyrazolones are important nitrogen containing heterocylic motifs that are prevalent in a wide range of bioactive compounds having pharmaceutical and agricultural activities.[1] In particular, 3-hydroxypyrazole derivatives that are obtained by aromatization of pyrazolones, have interesting enzyme inhibition[2a−d] and activation[2e] properties, and have been broadly used in antidiabetic,[2a−d] anticancer,[2f−h] anti-inflammatory,[2a] antipsychosis,[2a] insecticidal,[2i] and herbicidal[2j] studies. For instance, some aryl-substituted 3-(3-(dimethylamino)propyloxy)-1*H*-pyrazoles display potent activation of soluble guanylate cyclase and potent inhibition of platelet aggregation (Figure 1).[2e] Similarly, *O*-pyrazole glucopyranoside and galactopyranoside derivatives such as remogliflozin etabonate (Figure 1),[2d] are inhibitors of human sodium-glucose contransporters 1 and 2 (SGLT1 and SGLT2) and may be used for the treatment of diabetes. Thus, the development of efficient methods for the enantioselective construction of 3-hydroxy as well as 3-acyloxy pyrazoles having stereogenic centers is important for the discovery of new chiral drugs and other utilities.

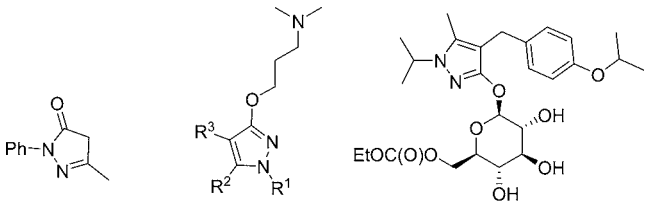
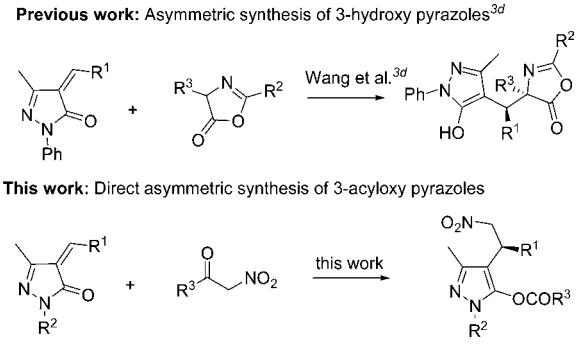


Figure 1. Biologically active 3-hydroxy pyrazole derivatives.

In recent years, unsaturated pyrazolones have been exploited as electrophiles in a variety of organocatalytic Michael and cascade reactions.[3] Analogously, pyrazolones have also been found to be suitable nucleophiles in a range of asymmetric reactions.[4] Zhao and co-workers first reported the organocatalytic asymmetric synthesis of 3-hydroxy pyrazole via an aza-Michael addition reaction of pyrazolones to α,β-unsaturated ketones.[4b] Ma and co-workers have shown one example of the synthesis of 3-hydroxy pyrazole in their development of the organocatlytic Michael reaction to nitroolefins followed by a dearomatization reaction.[4g] In contrast, from unsaturated pyrazolones, only a single report for the synthesis of 3-hydroxy pyrazoles has been disclosed by the Wang group (Scheme 1).[3d] However, to the best of our knowledge, a direct asymmetric synthesis of 3-acyloxy pyrazoles is still not known. Herein, we

Scheme 1. Organocatalytic Asymmetric Synthesis of 3-Hydroxy/Acyloxy Pyrazoles from Unsaturated Pyrazolones



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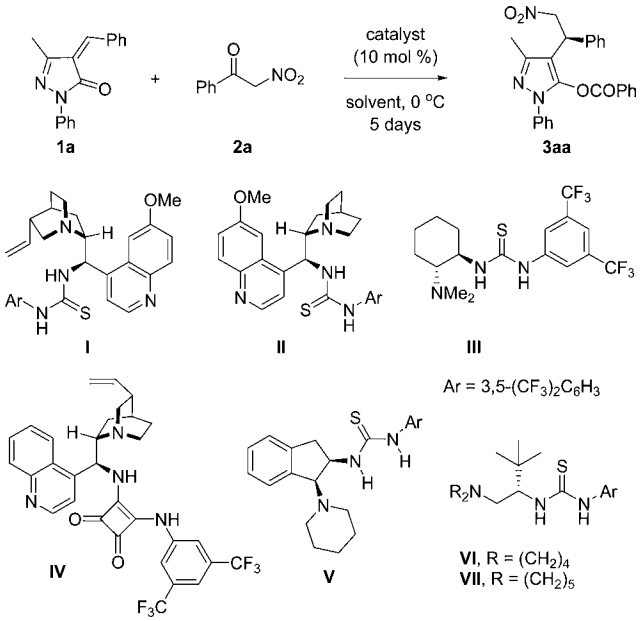
present a method for the synthesis of 3-acyloxy pyrazoles via a Michael/hemiketalization/retro-aldol strategy employing unsaturated pyrazolones and α-nitroketones.

The investigations were initiated by performing a model reaction between alkylidene pyrazolone **1a** and 2-nitro-1-phenylethanone (**2a**) with quininidine derived bifunctional thiourea catalyst **I** in dichloromethane solvent at 0 °C (Table 1, entry 1). Pleasingly a product was isolated in 80% yield and was identified to be **3aa** by ^{1}H and ^{13}C NMR analysis. Previously, only a related kind of Michael-benzoyl transfer reaction was reported in the reaction of α-nitroketone with α,β-unsaturated-α-ketoesters.[5] The enantioselectivity of **3aa** was not improved using hydroquinine derived thiourea catalyst **II** (Table 1, entry 2). Similar kinds of enantioselectivities were achieved with Takemoto catalyst **III** and squaramide catalyst **IV** (Table 1, entries 3–4). A higher enantioselectivity was achieved with catalyst **V** having an Indane moiety (Table 1, entry 5). Then *tert*-leucine derived bifunctional thiourea catalysts **VI** and **VII** were examined. These catalysts were found to be efficient, and in particular, catalyst **VII** having a piperidine motif provided the product **3aa** in 85% yield with 70% ee (Table 1, entry 7). Then the effect of solvent on the yield and enantioselectivity was studied, and delightfully promising results were attained. For example, enhancements in enantioselectivities were observed using chloroform and 1,2-dichloroethane solvent (Table 1, entries 8–9). Nonpolar solvent such as toluene was also efficient and afforded the product **3aa** in 90% ee (Table 1, entry 10). Finally the best solvent was found to be α,α,α-trifluorotoluene, and the product **3aa** was isolated in 91% yield with 99% ee (Table 1, entry 11).

Table 1. Catalyst Screening and Optimization of Reaction Conditions

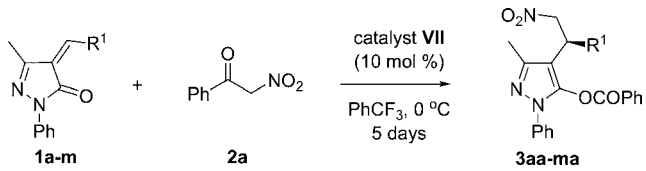


entry[a]	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	**I**	CH_2Cl_2	80	−44
2	**II**	CH_2Cl_2	82	30
3	**III**	CH_2Cl_2	84	−36
4	**IV**	CH_2Cl_2	76	36
5	**V**	CH_2Cl_2	85	61
6	**VI**	CH_2Cl_2	80	70
7	**VII**	CH_2Cl_2	85	70
8	**VII**	$CHCl_3$	89	82
9	**VII**	$(CH_2Cl)_2$	87	87
10	**VII**	$PhCH_3$	88	90
11	**VII**	$PhCF_3$	91	99

[a]Reaction condition: 0.05 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL of solvent using 10 mol % catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

After finding the optimal conditions we examined the scope of the reaction. Initially a variety of pyrazolones **1** having different benzylidene substitutents were tested (Table 2). It was found that a range of electron-withdrawing and -donating groups can be embedded in the *ortho*-, *meta*-, and *para*-position of the aryl group, leading to the synthesis of pyrazoles **3aa**–**3la** in excellent yields and enantioselectivities. A disubstituted aryl group was also tolerated in the reaction, and product **3ma** was obtained in excellent enantioselectivity (Table 2, entry 13).

Table 2. Scope of Pyrazolones with Varied Benzylidene Substituents



entry[a]	R^1	3	yield (%)[b]	ee (%)[c]
1	Ph	**3aa**	91	99
2	4-MeC_6H_4	**3ba**	86	97
3	4-$OMeC_6H_4$	**3ca**	85	97
4	4-$^{t}BuC_6H_4$	**3da**	89	85
5	4-FC_6H_4	**3ea**	65	97
6	4-ClC_6H_4	**3fa**	93	98
7	4-BrC_6H_4	**3ga**	93	94
8	3-MeC_6H_4	**3ha**	88	93
9	3-$OMeC_6H_4$	**3ia**	83	88
10	3-BrC_6H_4	**3ja**	57	88
11	2-MeC_6H_4	**3ka**	93	95
12	2-FC_6H_4	**3la**	80	89
13	2,4-$Me_2C_6H_3$	**3ma**	94	94

[a]Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2a** in α,α,α-trifluorotoluene at 0 °C for 5 days. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

The generality of the reaction was further established by engaging pyrazolones **1** with varied *N*-substitutions (Table 3). Accordingly, a variety pyrazolones **1n**–**r** with different *N*-substitutions were prepared and employed in the reaction. To our delight, the reactions progressed well irrespective of the electronic nature of the aryl group and the products **3na**–**ra** were attained in excellent enantioselectivities (Table 3).

The next phase of experiments included screening different α-nitroketones **1** using this method (Scheme 2). As shown in Scheme 2, a wide range of aryl group containing α-nitroketones **2** could be employed in the reaction, and excellent results were achieved. Initially, different *ortho*-, *meta*-, and *para*-substitutions on the phenyl group were incorporated, and delightfully excellent enantioselectivities (ee = 86–96%) were obtained (**3ab**–**ak**). A heteroaromatic nitroketone **2l** and disubstituted aryl group containing nitroketone **2m** also underwent reactions with pyrazolone **1a** delivering products **3al** and **3am** in excellent enantioselectivities. Finally, α-nitroketone **2n** having a

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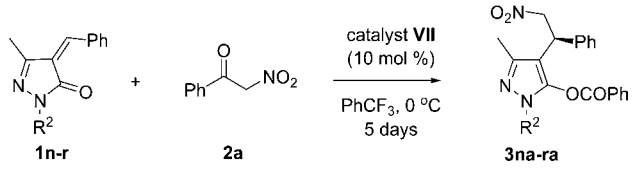
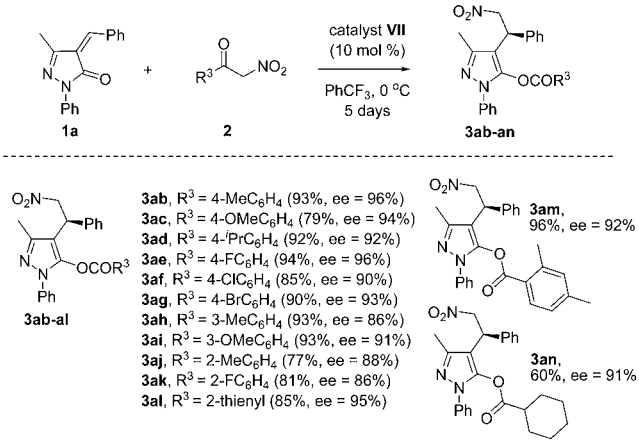
Table 3. Scope of Pyrazolones with Varied *N*-Substituents



entry[a]	R^2	3	yield (%)[b]	ee (%)[c]
1	4-MeC_6H_4	**3na**	82	96
2	4-ClC_6H_4	**3oa**	83	96
3	4-BrC_6H_4	**3pa**	81	92
4	4-CNC_6H_4	**3qa**	82	89
5	2-MeC_6H_4	**3ra**	93	99

[a]Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2a** in α,α,α-trifluorotoluene at 0 °C for 5 days. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

Scheme 2. Scope of α-Nitroketones[a,b]

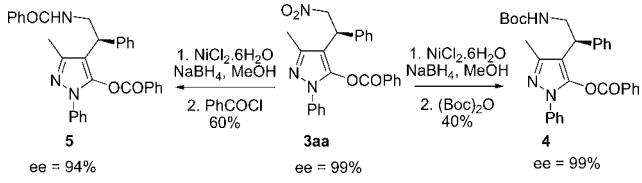


[a]Reactions were carried out with 0.1 mmol of **1a** and 0.1 mmol of **2** in α,α,α-trifluorotoluene at 0 °C for 5 days. [b]Isolated yield after silica gel column chromatography and ee was determined by HPLC.

cyclohexyl moiety was screened, and gratifyingly excellent enantioselectivity was maintained.

To demonstrate the synthetic utility of our method, few reactions were carried out on **3aa** (Scheme 3). Nickel

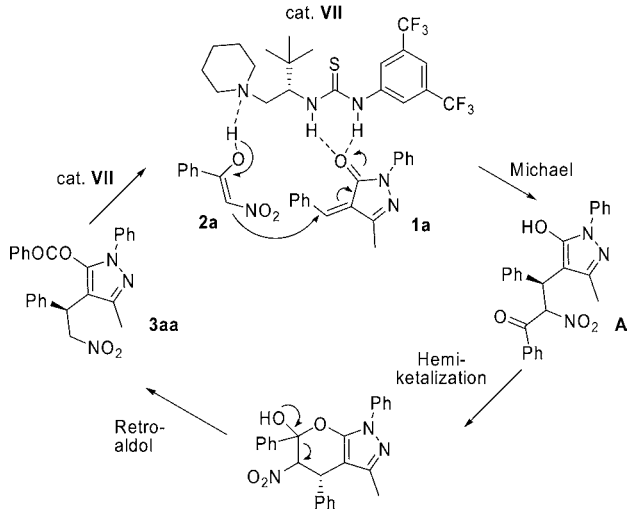
Scheme 3. Synthetic Transformations of 3aa



chloride–sodium borohydride treatment followed by a reaction with Boc anhydride resulted in the formation of compound **4** in moderate yield while preserving the excellent enantioselectivity. A similar reaction with nickel chloride–sodium borohydride and benzoyl chloride provided amide **5** in an acceptable yield although a slight erosion in enantioselectivity was detected.

The absolute configuration of the product **3af** was determined to be (*S*) by X-ray crystallography.[6] The absolute configuration of other products was expected to be the same by analogy. Based on the absolute configuration a plausible mechanism has been depicted in Scheme 4. It is expected

Scheme 4. Proposed Mechanism



that nitroketone **2a** is activated by the piperidine moiety of the catalyst **VII** whereas a thiourea motif binds with pyrazolone **1a**.[5a] Since the *Re* face of **1a** is blocked by catalyst **VII**, addition takes place from the *Si* face to provide intermediate **A**. Then **A** is converted to **B** via hemiketalization. Finally a retro-aldol reaction of **B** delivers product **3aa**.

In conclusion, we have developed a mild and operationally simple Michael–hemiketalization–retro-aldol reaction between unsaturated pyrazolones and α-nitroketones. This reaction furnished diverse 3-acyloxypyrazoles in high yields and with excellent enantioselectivities. Given the high pharmaceutical and agricultural importance of 3-alkoxypyrazoles, our method will be useful for the rapid preparation of these compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03823.

Experimental procedures, characterization data of all the products (PDF)

Crystallograhic data for compound **3af** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Sondhi, S. M.; Dinodia, M.; Singh, J.; Rani, R. *Curr. Bioact. Compd.* **2007**, *3*, 91. (b) Varvounis, G. *Adv.*

DOI: 10.1021/acs.orglett.6b03823
Org. Lett. 2017, 19, 662–665

Heterocycl. Chem. **2009**, *98*, 143. (c) Schmidt, A.; Dreger, A. *Curr. Org. Chem.* **2011**, *15*, 1423. (d) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984.

(2) (a) Cuberes-Altisent, R.; Holenz, J. PCT Int. Appl. WO2007098953, 2007; *Chem. Abstr.* **2007**, *147*, 301168. (b) Teranishi, H.; Fushimi, N.; Yonekubo, S.; Shimizu, K.; Shibazaki, T.; Isaji, M. PCT Int. Appl. WO2004014932, 2004; *Chem. Abstr.* **2004**, *140*, 199632. (c) Washburn, W. N. Pct Int. Appl. WO2003020737, 2003; *Chem. Abstr.* **2003**, *138*, 221784. (d) Shiohara, H.; Fujikura, H.; Fushimi, N.; Ito, F.; Isaji, M. PCT Int. Appl. WO 2002098893, 2002; *Chem. Abstr.* **2003**, *138*, 24917. (e) Selwood, D. L.; Brummell, D. G.; Budworth, J.; et al. *J. Med. Chem.* **2001**, *44*, 78. (f) Baraldi, P. G.; Nunez, M. d. C.; Tabrizi, M. A.; De Clercq, E.; Balzarini, J.; Bermejo, J.; Estevez, F.; Romagnoli, R. *J. Med. Chem.* **2004**, *47*, 2877. (g) Brana, M. F.; Gradillas, A.; Ovalles, A. G.; Lopez, B.; Acero, N.; Llinares, F.; Mingarro, D. M. *Bioorg. Med. Chem.* **2006**, *14*, 9. (h) Alterico, D.; Jereczek-Fossa, B. A.; Fiore, M. R.; Piperno, G.; Ansarin, M.; Orecchia, R. *Anticancer Res.* **2007**, *27*, 1105. (i) Hughes, K. A.; Lahm, G. P.; Selby, T. P. PCT Int. Appl. WO2004046129, 2009; *Chem. Abstr.* **2004**, *141*, 23526. (j) Ohno, R.; Watanabe, A.; Matsukawa, T.; Ueda, T.; Sakurai, H.; Hori, M.; Hirai, K. *J. Pestic. Sci.* **2004**, *29*, 15. For a review, see: Washburn, W. N. *J. Med. Chem.* **2009**, *52*, 1785.

(3) For selected examples, see: (a) Zea, A.; Alba, A. N. P.; Mazzanti, A.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2011**, *9*, 6519. (b) Liu, L.; Zhong, Y.; Zhang, P.; Jiang, X.; Wang, R. *J. Org. Chem.* **2012**, *77*, 10228. (c) Chen, Q.; Liang, J.; Wang, S.; Wang, D.; Wang, R. *Chem. Commun.* **2013**, *49*, 10228. (d) Geng, Z.-C.; Chen, X.; Zhang, J.-X.; Li, N.; Chen, J.; Huang, X.-F.; Zhang, S.-Y.; Tao, J.-C.; Wang, X.-W. *Eur. J. Org. Chem.* **2013**, *2013*, 4738. (e) Chauhan, P.; Mahajan, S.; Loh, C. C. J.; Raabe, G.; Enders, D. *Org. Lett.* **2014**, *16*, 2954. (f) Li, J.-H.; Du, D.-M. *Chem. - Asian J.* **2014**, *9*, 3278. (g) Han, B.; Huang, W.; Ren, W.; He, Gu.; Wang, J-h.; Peng, C. *Adv. Synth. Catal.* **2015**, *357*, 561. (h) Li, J.-H.; Feng, T.-F.; Du, D.-M. *J. Org. Chem.* **2015**, *80*, 11369. (i) Wang, H.-X.; Wu, L.-L.; Wang, Y. M.; Zhou, Z.-H. *RSC Adv.* **2015**, *5*, 42836. (j) Li, J.-H.; Wen, H.; Liu, L.; Du, D.-M. *Eur. J. Org. Chem.* **2016**, *2016*, 2492. (k) Wang, S.; Rodriguez-Escrich, C.; Pericás, M. A. *Org. Lett.* **2016**, *18*, 556. For a review, see: (l) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Commun.* **2015**, *51*, 12890.

(4) For selected reports, see: (a) Gogoi, S.; Zhao, C.-G. *Tetrahedron Lett.* **2009**, *50*, 2252. (b) Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249. (c) Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2010**, *352*, 827. (d) Yang, Z.; Wang, Z.; Bai, S.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 596. (e) Mazzanti, A.; Calbet, T.; Font-Bardia, M.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2012**, *10*, 1645. (f) Enders, D.; Grossmann, A.; Gieraths, B.; Düzdemir, M.; Merkens, C. *Org. Lett.* **2012**, *14*, 4254. (g) Li, F.; Sun, L.; Teng, Y.; Yu, P.; Zhao, J. C.-G.; Ma, J.-A. *Chem. - Eur. J.* **2012**, *18*, 14255. (h) Šimek, M.; Remeš, M.; Veselý, J.; Rios, R. *Asian J. Org. Chem.* **2013**, *2*, 64. (i) Yetra, S. R.; Mondal, S.; Suresh, E.; Biju, A. T. *Org. Lett.* **2015**, *17*, 1417. (j) Hack, D.; Chauhan, P.; Deckers, K.; Mizutani, Y.; Raabe, G.; Enders, D. *Chem. Commun.* **2015**, *51*, 2266. (k) Vila, C.; Amr, F. i.; Blay, G.; Muňoz, M. C.; Pedro, J. R. *Chem. - Asian J.* **2016**, *11*, 1532. (l) Kumarswamyreddy, N.; Kesavan, V. *Org. Lett.* **2016**, *18*, 1354. For a review, see ref 3k.

(5) (a) Gao, Y.; Ren, Q.; Siau, W.-Y.; Wang, J. *Chem. Commun.* **2011**, *47*, 5819. (b) Lu, R.-J.; Yan, J.-Y.; Wang, J.-J.; Du, Q.-S.; Nie, S.-Z.; Yan, M. *J. Org. Chem.* **2011**, *76*, 6230. (c) Li, P.; Chan, S. H.; Chan, A. S. C.; Kwong, F. Y. *Org. Biomol. Chem.* **2011**, *9*, 7997.

(6) CCDC 1523176 contains the crystallographic data for **3af**.

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Org. Lett. 2017, 19, 662−665