Organic LETTERS

Letter

pubs.acs.org/OrgLett

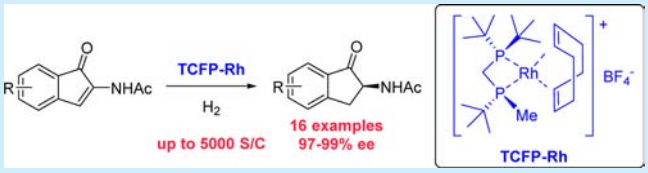
Rh-Catalyzed Asymmetric Hydrogenation of Cyclic α-Dehydroamino Ketones

Zhenfeng Zhang,[†] Qiupeng Hu,[†] Yingjie Wang,[‡] Jianzhong Chen,[‡] and Wanbin Zhang*[,†,‡]

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

Supporting Information

ABSTRACT: Catalyzed by a rhodium complex of P-stereogenic diphosphine trichickenfootphos, five-membered cyclic α-dehydroamino ketones bearing endocyclic acyl and endocyclic vinyl groups were hydrogenated to give chiral α-amino ketones with quantitative conversions and excellent enantioselectivities.



Asymmetric hydrogenation of α-acyl enamides is a practical methodology for the synthesis of chiral α-acyl amines and has been a popular research area for the past half century.[1] However, the hydrogenation of cyclic α-acyl enamides, especially those bearing an endocyclic α-acyl group, remains uncommon (Figure 1, red-colored structures, X = C, N, O, S).[2,3] On the other hand, compared to the extensive research carried out with α-dehydroamino acids, esters, and amides, only one report has been published concerning the asymmetric hydrogenation of α-dehydroamino ketones[4] and none for cyclic substrates, though chiral cyclic α-amino ketones are very useful structural motifs found in a range of bioactive molecules and can be easily derivatized to give versatile chiral cyclic β-amino alcohols and amines.[5] Previously, chiral cyclic α-amino ketones were typically synthesized via intramolecular Friedel−Crafts reactions of chiral α-amino acids and via α-aminations of cyclic ketones or their equivalents.[6−8] In addition to these procedures being inefficient, these methodologies also suffer from problems of partial racemization of the chiral α-amino ketones because of their facile enolization under acidic and alkaline conditions. Therefore, from both theoretical and practical perspectives, synthesis of chiral cyclic α-amino ketones via the asymmetric hydrogenation of cyclic α-dehydroamino ketones with high chemoselectivity (distinguish the reductive C═C and C═O bonds) and enantioselectivity is greatly desired.

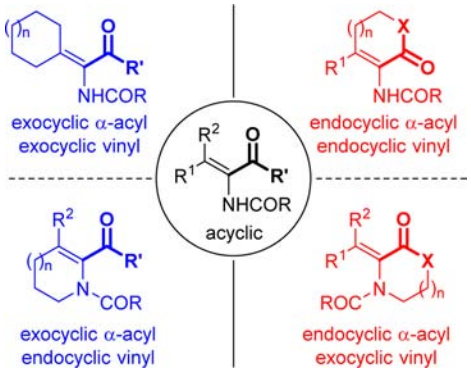


Figure 1. Acyclic and four kinds of cyclic α-acyl enamides.

Recently, we have made encouraging progress in the asymmetric hydrogenation of several types of substrates.[9,10] These include the hydrogenation of five-membered cyclic α,β-unsaturated ketones, esters, amides, and imides bearing endocyclic acyl and exocyclic vinyl groups (Figure 2).[9] Herein,

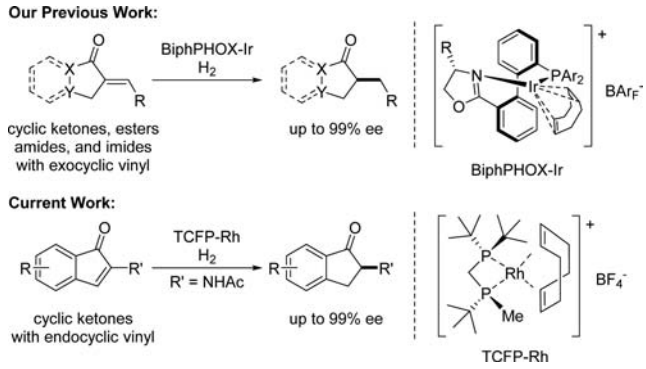


Figure 2. Asymmetric hydrogenation of five-membered cyclic carbonyl compounds with exo- and endocyclic vinyl groups.

we report the first asymmetric hydrogenation of five-membered cyclic α-dehydroamino ketones bearing endocyclic acyl and endocyclic vinyl groups for the synthesis of chiral cyclic α-amino ketones (Figure 2).[11]

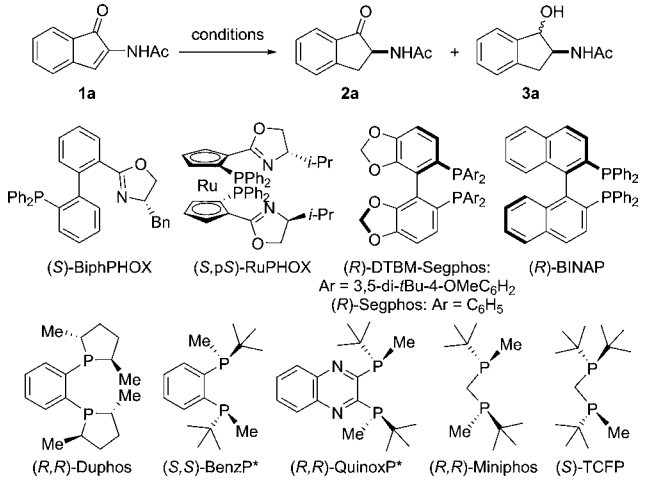
The model substrate *N*-(1-oxo-1*H*-inden-2-yl)acetamide (**1a**) was easily prepared from benzaldehyde by an aldol condensation and an intramolecular Friedel−Crafts reaction[12] and subsequently used in the asymmetric hydrogenation. Under a high H_2 pressure (40 atm) and long reaction time (18 h), Bn-BiphPhox-Ir,[9] DTBM-Segphos-Pd,[10a] and *i*-Pr-RuPhox-Ru[10d] complexes, previously confirmed to be effective for the asymmetric hydrogenation of related substrates, showed low activities and

Received: September 20, 2015
Published: October 26, 2015

DOI: 10.1021/acs.orglett.5b02733
Org. Lett. 2015, 17, 5380−5383

selectivities in the asymmetric hydrogenation of **1a** (see Supporting Information for details). In contrast, BenzP*-Rh was successfully used to give product **2a** (30% ee) and byproduct **3a** in a ratio of 82/18 (Table 1, entry 1). Following a decrease of

Table 1. Ligand and Solvent Screening[a]



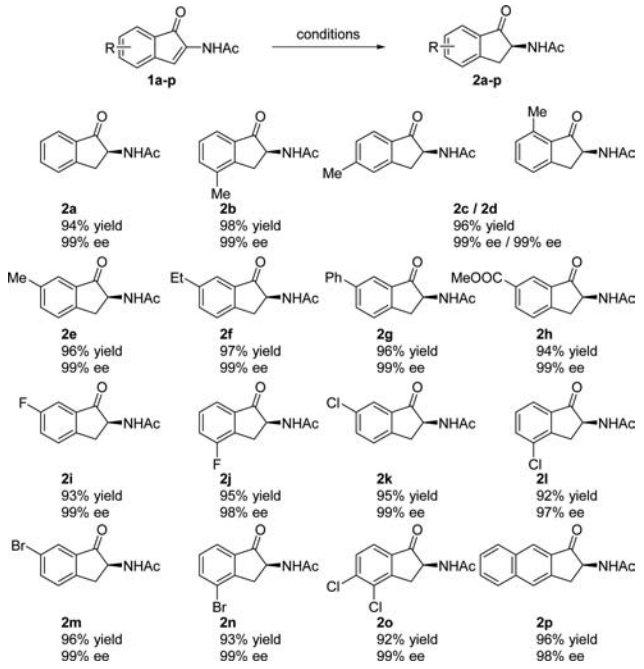
entry	ligand	solvent	conv **2a**/**3a** (%)[b]	ee **2a** (%)[c]
1[d,e]	(*S*,*S*)-BenzP*	MeOH	82/18	30
2	(*S*,*S*)-BenzP*	MeOH	99/0	79
3	(*R*)-Segphos	MeOH	99/0	53
4	(*R*)-BINAP	MeOH	99/0	81
5	(*R*,*R*)-Duphos	MeOH	99/0	65
6	(*R*,*R*)-QuinoxP*	MeOH	99/0	71
7	(*R*,*R*)-Miniphos	MeOH	99/0	92
8	(*S*)-TCFP	MeOH	99/0	98
9	(*S*)-TCFP	CH_2Cl_2	99/0	98
10	(*S*)-TCFP	EtOAc	99/0	99
11	(*S*)-TCFP	THF	99/0	85
12	(*S*)-TCFP	toluene	24/0	20
13[f]	(*S*)-TCFP	MeOH	99/0	95
14[g]	(*S*)-TCFP	MeOH	97/0	91

[a]Conditions: **1a** (0.4 mmol), ligand-Rh (1 mol %), H_2 (3 atm), solvent (2 mL), rt, 1 h. [b]Conversions were calculated from ^{1}H NMR spectra. [c]The ee values were determined by HPLC using chiral columns. [d]H_2 (40 atm). [e]18 h. [f]S/C = 2000, 6 h. [g]S/C = 5000, 30 h.

H_2 pressure to 3 atm, complete chemoselectivity was realized with moderate enantioselectivity (79% ee, entry 2). Other diphosphine-Rh complexes also showed excellent chemoselectivities while the P-stereogenic diphosphine ligand TCFP (trichickenfootphos),[13] which is more electron-rich and sterically hindered compared to other ligands, gave the highest enantioselectivity of 98% ee (entries 3−8). Other solvents were tested, and EtOAc was found to give the highest enantioselectivity (99% ee, entries 9−12). This reaction could be carried out on a gram scale using MeOH as the solvent to increase solubility. When the S/C was increased to 2000, 2.2 g of **1a** was completely converted to **2a** with a slightly reduced enantioselectivity of 95% ee (entry 13). When the S/C was further increased to 5000, **2a** was obtained with 97% conversion and 91% ee (entry 14).

With the optimized reaction conditions in hand, we investigated the substrate scope of the hydrogenation reaction catalyzed by the rhodium complex of (*S*)-TCFP (Scheme 1). The chiral α-amido ketones readily racemize under both acidic and basic conditions, even during flash chromatography using

Scheme 1. Substrate Scope[a]



[a]Conditions: **1** (0.4 mmol), TCFP-Rh (1 mol %), H_2 (3 atm), EtOAc (2 mL), rt, 1 h. The ee values were determined by HPLC using chiral columns.

silica gel or neutral aluminum oxide. Since the asymmetric hydrogenation goes to completion and no obvious impurities can be found in the NMR spectra of the reaction mixture, the yields were recorded by weighing the amount of products purified by reslurry. With methyl groups substituted at different positions, all four substrates **1b**−**1e** were converted to **2b**−**2e** with excellent enantioselectivities. Hydrogenation of the substrate **1f** with an ethyl substituent at the 5-position gave **2f** with 99% ee. Attempts to synthesize a more electron-donating 6-OMe-substituted substrate failed because the OMe group is not resistant to $AlCl_3$, which according to the procedure of **1a** is used in the ring-closing step. Changing the alkyl group in the 6-position to aryl and acyl groups did not affect the enantioselectivities of the corresponding products **2g** and **2h**. Substrates **1i**−**1n** bearing halogen substituents at either the 4- or 6-positions were all reduced to their products **2i**−**2n** with satisfactory enantioselectivities. Products bearing electron-withdrawing groups such as F and Cl atoms at the 4-position (**2j** and **2l**) were obtained with slightly lower ee of 98 and 97%, respectively. Furthermore, multisubstituted substrates such as **1o** and **1p** were also amenable to our reaction conditions, affording the corresponding products **2o** and **2p** quantitatively with 99 and 98% ee, respectively.

The absolute configuration of the hydrogenated products was assigned by comparison of the HPLC spectra with compound **2a**, which was synthesized via an intramolecular Friedel−Crafts reaction of (*S*)-*N*-acetyl-L-phenylalanine. The favored and unfavored transition states are shown in Figure 3.[14] Less steric hindrance between the Rh-chelate ring containing the NHAc group of the substrate and the methyl group of the ligand is observed in the favored transition state, thus leading to products with the *S*-configuration.

To demonstrate the practicality of this methodology, several transformations were performed (see Supporting Information for details). Product **2a** was reduced by Pd/C-catalyzed

DOI: 10.1021/acs.orglett.5b02733
Org. Lett. 2015, 17, 5380−5383

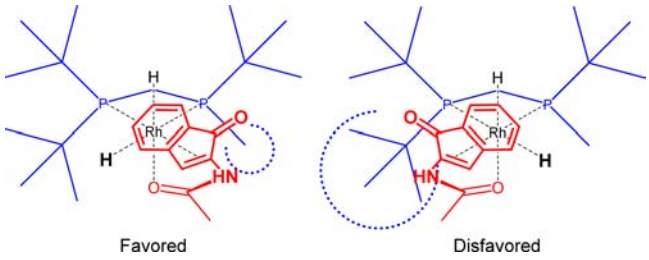
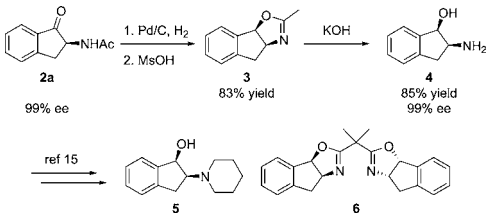


Figure 3. Proposed stereochemical model for the asymmetric hydrogenation of cyclic α-dehydroamino ketones catalyzed by TCFP-Rh. The red-colored ketone is positioned on top of the blue-colored TCFP-Rh complex.

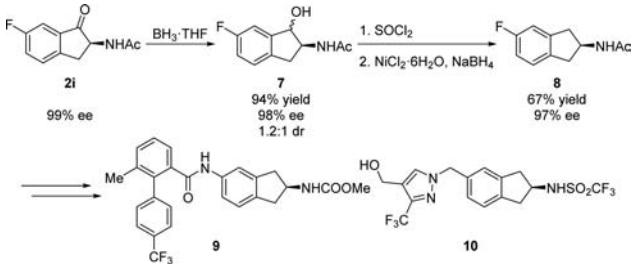
hydrogenation and further derivatized to cyclic oxazoline intermediate **3** in 83% yield. After a simple hydrolysis, chiral cyclic β-amino alcohol **4** was obtained in 85% yield, and only the *cis*-isomer was detected with 99% ee (Scheme 2). A similar

Scheme 2. Preparation of a Key Intermediate for the Synthesis of Useful Ligands



reduction of product **2i** using borane-THF afforded the β-amido alcohol **7** in 94% yield with 98% ee and 1.2:1 dr. The OH group was removed to afford the chiral cyclic amide **8** in 67% yield and with 97% ee (Scheme 3). According to previously reported

Scheme 3. Preparation of a Key Intermediate for the Synthesis of Bioactive Compounds



procedures, compound **4** could be readily converted to two types of useful ligands **5** and **6** (Scheme 2).[15] Compound **8** has the potential to be used as a key intermediate for the synthesis of important bioactive compounds **9** and **10** (Scheme 3).[16] This represents the first time such types of products have been prepared via asymmetric hydrogenation.

In conclusion, five-membered cyclic α-dehydroamino ketones bearing endocyclic acyl and endocyclic vinyl groups have been hydrogenated for the first time to give chiral α-amino ketones quantitatively with 97−99% ee. The reaction could be carried out on a gram scale, and the catalyst loading could be increased to 5000 S/C. This methodology was further applied to the asymmetric synthesis of several useful ligands and bioactive compounds via simple derivatization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02733.

Synthetic details for substrates, procedures for hydrogenation reactions, NMR spectra, and HPLC data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

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

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by the National Natural Science Foundation of China (Nos. 21172143, 21202096, 21232004, and 21472123), Science and Technology Commission of Shanghai Municipality (No. 14XD1402300), China Postdoctoral Science Foundation (No. 2014M551397), and Shanghai Jiao Tong University. We gratefully acknowledge Prof. Tsuneo Imamoto and Dr. Masashi Sugiya from Nippon Chemical Industrial Co., Ltd. for helpful discussions. We also thank the Instrumental Analysis Center of SJTU for characterization.

■ REFERENCES

(1) Recent representative papers: (a) Imamoto, T.; Tamura, K.; Zhang, Z.; Horiuchi, Y.; Sugiya, M.; Yoshida, K.; Yanagisawa, A.; Gridnev, I. D. *J. Am. Chem. Soc.* **2012**, *134*, 1754. (b) Molinaro, C.; Scott, J. P.; Shevlin, M.; Wise, C.; Ménard, A.; Gibb, A.; Junker, E. M.; Lieberman, D. *J. Am. Chem. Soc.* **2015**, *137*, 999.

(2) Papers on substrates with an exocyclic α-acyl group: (a) Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, *60*, 2656. (b) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635. (c) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614. (d) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534. (e) Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 2560. (f) Baeza, A.; Pfaltz, A. *Chem. - Eur. J.* **2010**, *16*, 2036.

(3) Only two special substrates with an endocyclic α-acyl group were hydrogenated with moderate enantioselectivities: (a) Buser, H. P.; Pugin, B.; Spindler, F.; Sutter, M. *Tetrahedron* **1991**, *47*, 5709. (b) Armstrong, J. D.; Eng, K. K.; Keller, J. L.; Purick, R. M.; Hartner, F. W., Jr.; Choi, W.-B.; Askin, D.; Volante, R. P. *Tetrahedron Lett.* **1994**, *35*, 3239.

(4) Sun, T.; Hou, G.; Ma, M.; Zhang, X. *Adv. Synth. Catal.* **2011**, *353*, 253.

(5) (a) Nordlander, J. E.; Payne, M. J.; Njoroge, F. G.; Vishwanath, V. M.; Han, G. R.; Laikos, G. D.; Balk, M. A. *J. Org. Chem.* **1985**, *50*, 3619. (b) Draper, R. W.; Hou, D.; Iyer, R.; Lee, G. M.; Liang, J. T.; Mas, J. L.; Vater, E. J. *Org. Process Res. Dev.* **1998**, *2*, 186. (c) Jindal, D. P.; Piplani, P.; Fajrak, H.; Prior, C.; Marshall, I. G. *Eur. J. Med. Chem.* **2001**, *36*, 195. (d) Glansdorp, F. G.; Thomas, G. L.; Lee, J. K.; Dutton, J. M.; Salmond, G. P. C.; Welch, M.; Spring, D. R. *Org. Biomol. Chem.* **2004**, *2*, 3329. (e) Waykole, L. M.; McKenna, J. J.; Bach, A.; Prashad, M.; Repič, O.; Blacklock, T. J. *Synth. Commun.* **2007**, *37*, 1445. (f) Guo, H.; Zhang, G.; Zhang, T.; He, X.; Wu, Z.; Xiao, Y.; Pan, Y.; Qiu, G.; Liu, P.; Hu, X. *Eur. J. Med. Chem.* **2011**, *46*, 3662.

(6) By intramolecular Friedel−Crafts reaction of chiral α-amino acids: (a) McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1981**, *46*, 2431. (b) Kurokawa, M.; Watanabe, T.; Ishikawa, T. *Helv. Chim. Acta* **2007**, *90*, 574.

DOI: 10.1021/acs.orglett.5b02733
Org. Lett. 2015, 17, 5380−5383

(7) By α-amination of cyclic ketones: (a) Yamashita, Y.; Ishitani, H.; Kobayashi, S. *Can. J. Chem.* **2000**, *78*, 666. (b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (c) Hayashi, Y.; Aratake, S.; Imai, Y.; Hibino, K.; Chen, Q.-Y.; Yamaguchi, J.; Uchimaru, T. *Chem. - Asian J.* **2008**, *3*, 225.

(8) By other tactics: (a) Phukan, P.; Sudalai, A. *Tetrahedron: Asymmetry* **1998**, *9*, 1001. (b) Hurt, C. R.; Lin, R.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 225. (c) Adam, W.; Roschmann, K. J.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **2000**, *2000*, 557. (d) Liang, J.-L.; Yu, X.-Q.; Che, C.-M. *Chem. Commun.* **2002**, 124. (e) Li, W.; Liu, X.; Hao, X.; Hu, X.; Chu, Y.; Cao, W.; Qin, S.; Hu, C.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2011**, *133*, 15268. (f) Frongia, A.; Secci, F.; Capitta, F.; Piras, P. P.; Sanna, M. L. *Chem. Commun.* **2013**, *49*, 8812.

(9) For our papers on asymmetric hydrogenation of five-membered substrates with endocyclic acyl and exocyclic vinyl groups, see: (a) Tian, F.; Yao, D.; Liu, Y.; Xie, F.; Zhang, W. *Adv. Synth. Catal.* **2010**, *352*, 1841. (b) Liu, Y.; Yao, D.; Li, K.; Tian, F.; Xie, F.; Zhang, W. *Tetrahedron* **2011**, *67*, 8445. (c) Liu, Y.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 2203. (d) Liu, Y.; Gridnev, I. D.; Zhang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 1901.

(10) For our recent papers on asymmetric hydrogenation of other substrates, see: (a) Chen, J.; Liu, D.; Butt, N.; Li, C.; Fan, D.; Liu, Y.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 11632. (b) Li, C.; Chen, J.; Fu, G.; Liu, D.; Liu, Y.; Zhang, W. *Tetrahedron* **2013**, *69*, 6839. (c) Yu, K.; Zhang, Z.; Huo, X.; Wang, X.; Liu, D.; Zhang, W. *Youji Huaxue* **2013**, *33*, 1932. (d) Wang, J.; Liu, D.; Liu, Y.; Zhang, W. *Org. Biomol. Chem.* **2013**, *11*, 3855. (e) Wang, Y.; Wang, J.; Liu, D.; Zhang, W. *Youji Huaxue* **2014**, *34*, 1766. (f) Hu, Q.; Zhang, Z.; Liu, Y.; Imamoto, T.; Zhang, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 2260.

(11) Cyclic α,β-unsaturated ketones and esters with endocyclic acyl and endocyclic vinyl groups but without an α-amino/amido substituent: (a) Massonneau, V.; Le Maux, P.; Simonneaux, G. *Tetrahedron Lett.* **1986**, *27*, 5497. (b) Massonneau, V.; Le Maux, P.; Simonneaux, G. *J. Organomet. Chem.* **1987**, *327*, 269. (c) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1992**, *33*, 635. (d) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357. (e) Huang, K.; Guan, Z.-H.; Zhang, X. *Tetrahedron Lett.* **2014**, *55*, 1686.

(12) (a) Awad, W. I.; Hafez, M. S. *J. Org. Chem.* **1961**, *26*, 2055. (b) Rostami, M.; Khosropour, A. R.; Mirkhani, V.; Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S. *Synlett* **2011**, *2011*, 1677. (c) Rostami, M.; Khosropour, A. R.; Mirkhani, V.; Moghadam, M.; Tangestaninejad, S.; Mohammadpoor-Baltork, I. *Tetrahedron Lett.* **2011**, *52*, 7149.

(13) (a) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966. (b) See ref 2e.

(14) Similar mechanism for the transition state: (a) Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 7183. (b) See ref 2e. (c) Gridnev, I. D.; Imamoto, T. *Chem. Commun.* **2009**, 7447.

(15) Rodríguez-Escrich, S.; Solà, L.; Jimeno, C.; Rodríguez-Escrich, C.; Pericàs, M. A. *Adv. Synth. Catal.* **2008**, *350*, 2250.

(16) (a) Prashad, M.; Hu, B.; Har, D.; Repic, O.; Blacklock, T. J.; Acemoglu, M. *Adv. Synth. Catal.* **2001**, *343*, 461. (b) Jamieson, C.; Maclean, J. K. F.; Brown, C. I.; Campbell, R. A.; Gillen, K. J.; Gillespie, J.; Kazemier, B.; Kiczun, M.; Lamont, Y.; Lyons, A. J.; Moir, E. M.; Morrow, J. A.; Pantling, J.; Rankovic, Z.; Smith, L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 805.

DOI: 10.1021/acs.orglett.5b02733
Org. Lett. 2015, 17, 5380−5383