Organic LETTERS

Letter

pubs.acs.org/OrgLett

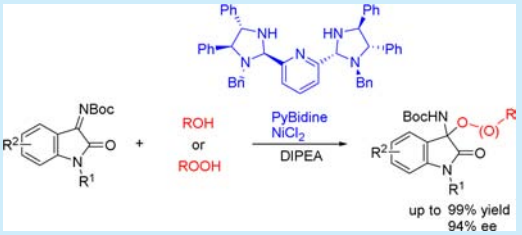
PyBidine–$NiCl_2$-Catalyzed Asymmetric Addition of Alcohols and Peroxides to Isatin-Derived Ketimines

Takayoshi Arai,* Kento Tsuchiya, and Eri Matsumura

Department of Chemistry, Graduate School of Science, Chiba University, 1-33 Yayoi, Inage, Chiba 263-8522, Japan

Supporting Information

ABSTRACT: An (*S*,*S*)-diphenyldiamine-derived bis(imidazolidine)-pyridine (PyBidine)–$NiCl_2$ complex catalyzed the asymmetric addition of methanol and peroxides to isatin-derived *N*-Boc-imines to form chiral quaternary *N*,*O*-acetals at the C3 position of the resulting oxiindoles in up to 99% yield with 94% ee.



The addition of oxygen-based nucleophiles, such as water, alcohols, peroxides, and even oxygen itself, occurs universally in all living organisms to generate highly functionalized natural compounds and to metabolize organic substrates. Examples include the *N*,*O*-acetal (alias *N*,*O*-aminal) groups, obtained by the addition of oxygen-based nucleophiles to imine substrates, to produce numerous biologically significant compounds (Figure 1).

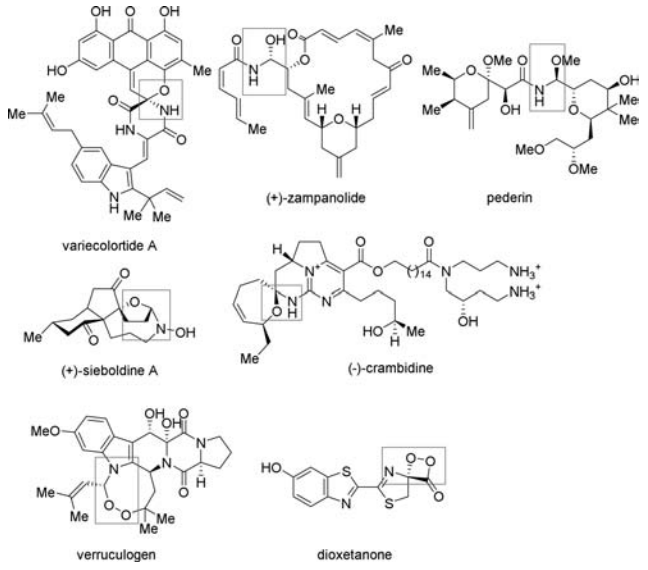


Figure 1. Examples of *N*,*O*-acetal-containing biologically significant compounds.

In variecolortide A, a 9,10-anthraquinone unit and an indol moiety are connected via a spiro *N*,*O*-acetal on the diketopiperazine portion.[1] The anticancer compound (+)-zampanolide[2] and members of the pederin[3] family form *N*,*O*-acetals with simple hydoxy and methoxy functionalities. In addition, verruculogen[4] and dioxeranone[5] are interesting natural products possessing unique α-amino peroxide groups. Finally, the unique compounds (+)-sieboldine A[6] and (−)-crambidine[7] are complex molecules incorporating *N*,*O*-acetals and have become important targets in the total synthesis of pharmaceutical candidates.

A fascinating feature of unsymmetrical *N*,*O*-acetals is their potential to contain chiral stereogenic centers as a result of the addition of oxygen-based nucleophiles to imines. Antilla pioneered the catalytic asymmetric addition of alcohols[8] and peroxides[9] to aldehyde-derived imines (i.e., aldimines) using phosphoric acid, and List reported the synthesis of cyclic *N*,*O*-acetals with a phosphoramide catalyst.[10] With regard to ketone-derived imines (i.e., ketimines), Sha and Wu reported a quinine-based organocatalyst that promotes the enantioselective addition of alcohols to isatin-derived *N*-Boc-ketimines to give the corresponding products with up to 78% ee.[11] Considering the importance of chiral *N*,*O*-acetals in medicinal chemistry, both the general and highly enantioselective catalytic asymmetric addition of alcohols and peroxides to isatin-derived *N*-Boc-ketimines are presented herein.[12−14]

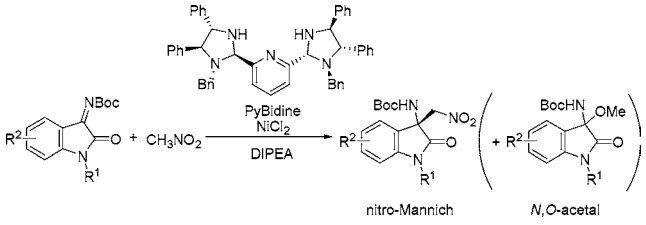
From a program for creating the efficient asymmetric catalyzes, we have previously succeeded in developing a bis-(imidazolidine)pyridine ligand, abbreviated as PyBidine, with applications to metal-catalyzed reactions.[15] PyBidine–metal complexes have been applied to various asymmetric reactions, and a PyBidine–$NiCl_2$ catalyst allowed the first general nitro-Mannich reaction of isatin-derived *N*-Boc-ketimines with nitroalkanes to construct a chiral quaternary aminocarbon center at the C3 positions of oxindoles in yields of up to 99% with 95% ee (Scheme 1).[16]

When this reaction was carried out in methanol, the methanol addition product was obtained in 73% yield with 63% ee in addition to the desired nitro-Mannich adduct (27%, 80% ee). The formation of the chiral *N*,*O*-acetal inspired us to optimize

Received: March 31, 2015
Published: May 1, 2015

DOI: 10.1021/acs.orglett.5b00928
Org. Lett. 2015, 17, 2416–2419

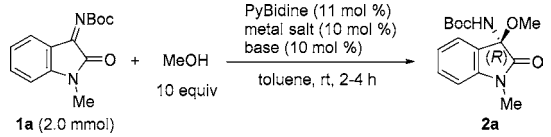
Scheme 1. Asymmetric Nitro-Mannich Reaction Catalyzed by the PyBidine–$NiCl_2$ Complex



in toluene : up to 99% yield, 95% ee for nitro-Mannich
in MeOH (R^1=Me, R^2=H) : 27% yield, 80% ee for nitro-Mannich
73% yield, 63% ee for *N,O*-acetal

the reaction conditions for the addition of methanol to an isatin-derived *N*-Boc-ketamine (**1a**), as shown in Table 1.

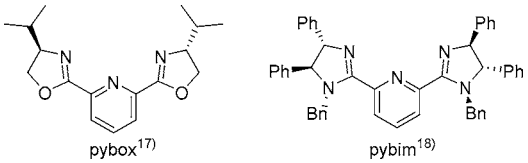
Table 1. Optimization of PyBidine–Metal-Catalyzed Methanol Addition to an Isatin-Derived *N*-Boc-ketimine



1a (2.0 mmol) **2a**

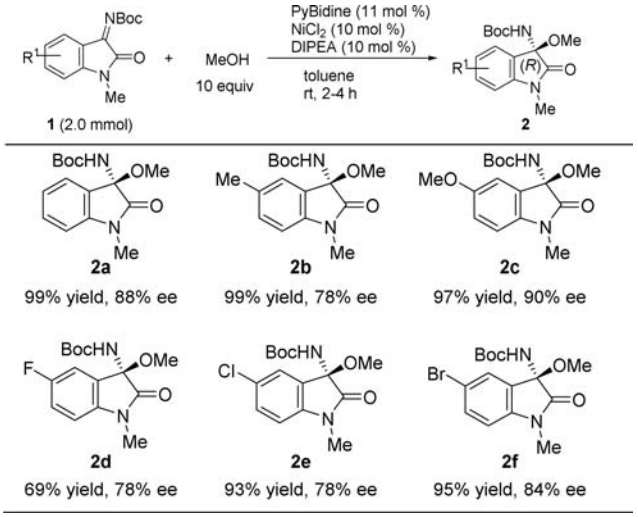
entry	metal salt	solvent	base	yield (%)	ee (%)
1	$NiCl_2$	toluene	DIPEA	99	88
2	$Ni(OAc)_2$[a]	toluene	DIPEA	96	70 (*S*)
3	$Ni(OTf)_2$	toluene	DIPEA	99	22 (*S*)
4	$Ni(ClO_4)_2$[b]	toluene	DIPEA	99	20 (*S*)
5	$CoCl_2$[b]	toluene	DIPEA	87	66
6	$CuCl_2$	toluene	DIPEA	93	8 (*S*)
7	$NiCl_2$	THF	DIPEA	36	64
8	$NiCl_2$	CH_3CN	DIPEA	93	60
9	$NiCl_2$	$CHCl_3$	DIPEA	81	80
10[c]	$NiCl_2$	toluene	DIPEA	47	18
11[d]	$NiCl_2$	toluene	DIPEA	85	46
12	$NiCl_2$	toluene	Et_3N	87	86
13	$NiCl_2$	toluene	K_2CO_3	91	68
14	$NiCl_2$	toluene		trace	

[a]Tetrahydrate was used. [b]Hexahydrate was used. [c]pybox was used as the ligand. [d]pybim was used as the ligand.



When 10 equiv of methanol (relative to the isatin-derived *N*-Boc ketamine) was used, the PyBidine–$NiCl_2$ complex smoothly catalyzed the *N,O*-acetal formation in toluene to give the product in 99% yield with 88% ee. Interestingly, varying the metal salts showed that the PyBidine–$Ni(OAc)_2$ complex gave the (*S*)-enriched product in 70% ee, while the PyBidine–$CoCl_2$ complex gave the (*R*)-enriched product in 66% ee. Reactions using $CoCl_2$ and $CuCl_2$, elements on either side of Ni in the periodic table, resulted in lower enantiomeric excess values. In contrast, the PyBidine–$NiCl_2$-catalyzed reaction in a less polar solvent gave both a higher yield and a greater ee value. The application of an amine base gave superior results compared to the use of an inorganic base, while the reaction without a base resulted in only a trace of the desired product. The use of the analogous ligands pybox[17] and pybim[18] generated lower enantiomeric inductions in the case of the $NiCl_2$-catalyzed reactions (entries 10 and 11). PyBidine–$NiCl_2$ in toluene with DIPEA as the base was selected as the best catalyst system, giving the product with the highest enantioselectivity in the (*R*)-enriched form. Using the optimized conditions, the generality of the PyBidine–metal-catalyzed alcohol addition to isatin-derived *N*-Boc-ketimines was examined, with the results presented in Scheme 2. Both electron-enriched and -deficient isatin-derived *N*-Boc-ketimines were readily converted, and the 5-methoxy product **2c** was obtained with 90% ee.

Scheme 2. Asymmetric Addition of Methanol to an Isatin-Derived *N*-Boc-ketimine Catalyzed by a PyBidine–$NiCl_2$ Complex



Among the typical alcohols we examined, the smallest methanol showed the highest reactivity during *N,O*-acetal formation. Under the reaction conditions for entry 1 in Table 1, the reaction using ethanol gave a 53% yield with 68% ee (20 h), while the reaction with *i*-PrOH resulted in only a trace of the product.

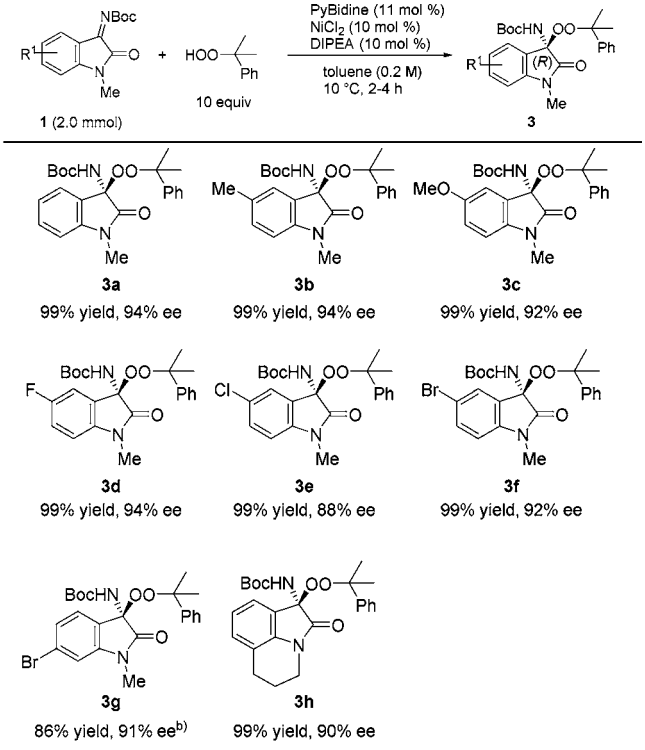
Subsequently, peroxides were examined as analogues for the smallest oxygen-based nucleophile (methanol) but with higher nucleophilicity.[19,20] Under similar reaction conditions to entry 1 in Table 1, *tert*-butyl hydroperoxide (TBHP) showed good reactivity to give the corresponding adduct in 93% yield with 84% ee following reaction at rt over 2 h. Cumene hydroperoxide (CMHP) gave improved results with 90% ee (99% yield at rt over 2 h), while the reaction at 10 °C over 4 h generated the product with up to 94% ee. The PyBidine-$NiCl_2$-catalyzed asymmetric addition of CMHP to isatin-derived *N*-Boc-ketimines was examined under the optimized conditions, and the results are shown in Scheme 3. *N*-Methylisatins containing not only electron-withdrawing but also electron-donating substituents on the benzene ring reacted successfully to give the *N,O*-acetal **3** with ee values ranging from 88% to 94%. From 1 g of **1a**, **2a** was quantitatively obtained with 89% ee.

The structure of peroxide adduct was confirmed by a single X-ray crystallographic analysis of racemic product **3f** (Figure 2).

The proposed catalytic cycle for the PyBidine–$NiCl_2$-catalyzed asymmetric addition of CMHP to isatin-derived *N*-Boc-ketimines is provided in Scheme 4. When the PyBidine–$NiCl_2$ was mixed with **1a**, HRMS analysis found a peak at m/z =

DOI: 10.1021/acs.orglett.5b00928
Org. Lett. 2015, 17, 2416–2419

Scheme 3. Asymmetric Addition of CMHP to Isatin-Derived *N*-Boc-ketimines Catalyzed by a PyBidine−$NiCl_2$ Complex[a,b]



[a]Absolute structure was provided by analogy of **2a**. [b]At 0 °C.

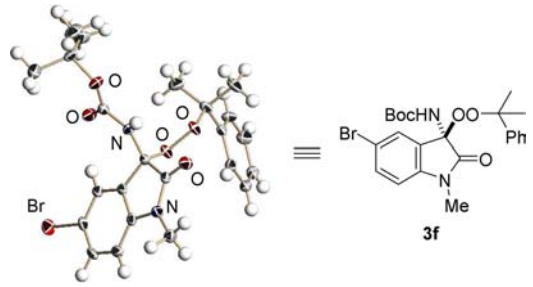
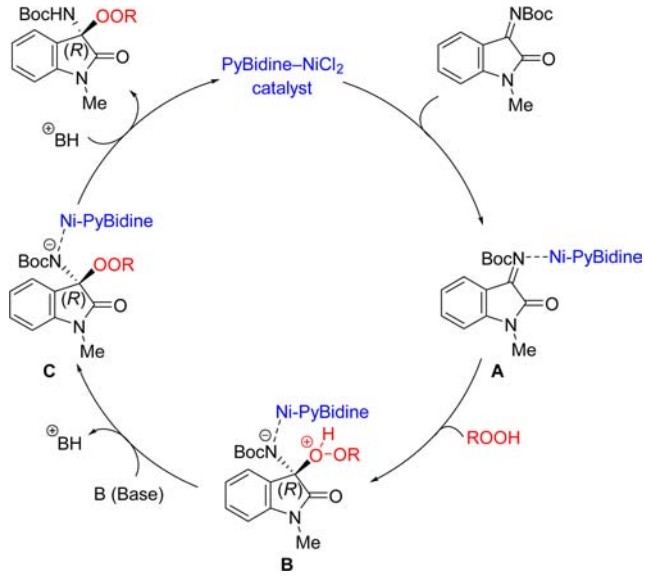


Figure 2. X-ray crystallographic analysis of racemic product **3f**.

1056.3870, corresponding to [PyBidine−NiCl + **1a**]$^+$. Thus, the reaction starts with the activation of the isatin-derived *N*-Boc-ketimine by the PyBidine−$NiCl_2$ catalyst to give **A**. The peroxide (pK_a = ca. 12.17) then attacks the activated *N*-Boc-ketamine in an enantioselective manner to form **B**, following which the basic additive (pK_a of DIPEA = ca. 10.75) abstracts a proton to give the nickel-bound amide intermediate **C**. Subsequent protonation of **C** produces the *N*,*O*-acetal with regeneration of the PyBidine−$NiCl_2$ catalyst.

The generation of an (*R*)-enriched *N*,*O*-acetal by the (*S*,*S*)-diphenylethylene-derived PyBidine−$NiCl_2$ catalyst can be explained on the basis of the reaction model depicted in Figure 3. Examining the catalytic cycle above, together with the results of previous studies of the PyBidine−$NiCl_2$-catalyzed asymmetric nitro-Mannich reaction,[16] it is believed that the PyBidine−$NiCl_2$ complex acts as a Lewis acid to activate the isatin-derived *N*-Boc-ketimines. Due to the affinity of nickel for nitrogen atoms, the isatin-derived *N*-Boc-ketimines coordinate to the nickel center through the lone electron pair of the imine unit. The alcohol and peroxide then attack the isatin-derived *N*-Boc-ketimines

Scheme 4. Proposed Catalytic Cycle for the PyBidine−$NiCl_2$-Catalyzed Asymmetric Addition of a Peroxide to an Isatin-Derived *N*-Boc-ketimine



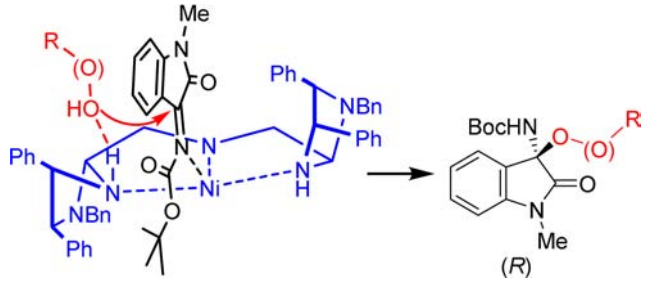


Figure 3. Proposed reaction mechanism for the PyBidine−$NiCl_2$-catalyzed asymmetric *N*,*O*-acetal formation.

coordinated to the nickel center from the second quadrant. In this scenario, the NH functionality of the imidazolidine ring of the PyBidine moiety guides the attack of the nucleophile through hydrogen bonding, since the reaction using the PyBidine−$NiCl_2$ catalyst gave superior results to the reactions using either pybox−$NiCl_2$ or pybim−$NiCl_2$. The successful and highly enantioselective synthesis of **3h**, with a sterically hindered 6-membered ring, agrees with the coordination scenario for the (*R*)-enriched product presented in Figure 3.

In conclusion, a bis(imidazolidine)pyridine (PyBidine)−$NiCl_2$ catalyst enabled the highly enantioselective addition of methanol and peroxides to isatin-derived *N*-Boc-ketimines. The cooperation between the metal−Lewis acid and the imidazolidine−NH through hydrogen bonding during this catalysis works general to promote the asymmetric nucleophilic addition reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of products, NMR spectra, and X-ray data for **3f**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00928.

DOI: 10.1021/acs.orglett.5b00928
Org. Lett. 2015, 17, 2416−2419

AUTHOR INFORMATION

Corresponding Author

*E-mail: tarai@faculty.chiba-u.jp.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Mr. T. Tosaka in the Department of Chemistry, Graduate School of Science, Chiba University, for a scale-up experiment. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by the Workshop on Chirality at Chiba University (WCCU).

REFERENCES

(1) Wang, W.-L.; Zhu, T.-J.; Tao, H.-W.; Lu, Z.-Y.; Fang, Y.-C.; Gu, Q.-Q.; Zhu, W.-M. *Chem. Biodiversity.* **2007**, *4*, 2913.
(2) Smith, A. B., III; Safanov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 12426.
(3) Jewett, J. C.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6502.
(4) Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55.
(5) Chung, L. W.; Hayashi, S.; Lundberg, M.; Nakatsu, T.; Kato, H.; Morokuma, K. *J. Am. Chem. Soc.* **2008**, *130*, 12880.
(6) Hirasawa, Y.; Morita, H.; Shiro, M.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 3991.
(7) Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E. *J. Nat. Prod.* **1993**, *56*, 1007.
(8) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216.
(9) Zheng, W.; Wojtas, L.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6589.
(10) Vellalath, S.; Coric, I.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 9749.
(11) Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *Tetrahedron* **2013**, *69*, 7314.
(12) Other examples for catalytic asymmetric synthesis of *N,O*-acetals on isatin derivatives: (a) Liu, Z.; Feng, X.; Du, H. *Org. Lett.* **2012**, *14*, 3154. (b) Zhou, F.; Zeng, X.-P.; Wang, C.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2013**, *49*, 2022.
(13) For selected methods for the *N,O*-acetal construction, see: (a) Rech, J. C.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 1495. (b) Ko, C.; Hsung, R. P. *Org. Biomol. Chem.* **2007**, *5*, 431. (c) Huang, X.; Shao, N.; Palani, A.; Aslanian, R. *Tetrahedron Lett.* **2007**, *48*, 1967. (d) Kiren, S.; Shangguan, N.; Williams, L. J. *Tetrahedron Lett.* **2007**, *48*, 7456. (e) Wan, S.; Green, M. E.; Park, J.-H.; Floreancig, P. E. *Org. Lett.* **2007**, *9*, 5385.
(14) For recent examples for catalytic asymmetric nucleophilic addition to *N*-Boc-ketimines, see: (a) Liu, Y.-L.; Zhou, F.; Cao, J.-J.; Ji, C.-B.; Ding, M.; Zhou, J. *Org. Biomol. Chem.* **2010**, *8*, 3847. (b) Hashimoto, T.; Yamamoto, K.; Maruoka, K. *Chem. Lett.* **2011**, *40*, 326. (c) Lv, H.; Tiwari, B.; Mo, J.; Xing, C.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 5412. (d) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512. (e) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem.—Eur. J.* **2012**, *18*, 9276. (f) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003. (g) Hu, F.-L.; Wei, Y.; Shi, M.; Pindic, S.; Li, G. *Org. Biomol. Chem.* **2013**, *11*, 1921. (h) Chen, X.; Chen, H.; Ji, X.; Jiang, H.; Yao, Z.-J.; Liu, H. *Org. Lett.* **2013**, *15*, 1846. (i) Nakamura, S.; Hyodo, K.; Nakamura, M.; Nakane, D.; Masuda, H. *Chem.—Eur. J.* **2013**, *19*, 7304. (j) Chauhan, P.; Chimni, S. S. *Tetrahedron: Asymmetry* **2013**, *24*, 343. (k) Liu, Y.-L.; Zhou, J. *Chem. Commun.* **2013**, *49*, 4421. (l) Wang, D.; Liang, J.; Feng, J.; Wang, K.; Sun, Q.; Zhao, L.; Li, D.; Yan, W.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 548. (m) Wang, Y.-H.; Liu, Y.-L.; Cao, Z.-Y.; Zhou, J. *Asian J. Org. Chem.* **2014**, *3*, 429. (n) Wang, Y.; Cao, Z.; Niu, Y.; Zhao, X.; Zhou, J. *Acta Chim. Sinica* **2014**, *72*, 867. (o) Xu, J.; Mou, C.; Zhu, T.; Song, B.-A.; Chi, Y. R. *Org. Lett.* **2014**, *16*, 3272. (p) Nakamura, S.; Takahashi, S.; Nakane, D.; Masuda, H. *Org. Lett.* **2015**, *17*, 106. (q) Zhao, K.; Shu, T.; Jia, J.; Raabe, G.; Enders, D. *Chem.—Eur. J.* **2015**, *21*, 3933. (r) Beceno, C.; Chauhan, P.; Rembiak, A.; Wang, A.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 672.
(15) (a) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338. (b) Arai, T.; Mishiro, A.; Matsumura, E.; Awata, A.; Shirasugi, M. *Chem.—Eur. J.* **2012**, *18*, 11219. (c) Arai, T.; Matsumura, E. *Synlett* **2014**, *25*, 1776.
(16) Arai, T.; Matsumura, E.; Masu, H. *Org. Lett.* **2014**, *16*, 2768.
(17) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846.
(18) Bhor, S.; Anilkumar, G.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevendt, A.; Beller, M. *Org. Lett.* **2005**, *7*, 3393.
(19) Sala, G. D.; Lattanzi, A. *ACS Catal.* **2014**, *4*, 1234.
(20) (a) Schulz, M.; Kluge, R.; Gelalcha, F. G. *Tetrahedron: Asymmetry* **1998**, *9*, 4341. (b) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134. (c) Reisinger, C. M.; Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 8112. (d) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677. (e) Russo, A.; Lattanzi, A. *Adv. Synth. Catal.* **2008**, *350*, 1991. (f) Feng, X.; Yuan, Y.-Q.; Cui, H.-L.; Jiang, K.; Chen, Y.-C. *Org. Biomol. Chem.* **2009**, 3660. (g) Ratnikov, M. O.; Farkas, L. E.; Doyle, M. P. *J. Org. Chem.* **2012**, *77*, 10294. (h) Pramanik, S.; Ghorai, P. *Org. Lett.* **2013**, *15*, 3832. See also refs 9 and 11.

DOI: 10.1021/acs.orglett.5b00928
Org. Lett. 2015, 17, 2416−2419