Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Ferrocene Derivatives with Planar Chirality via Palladium-Catalyzed Enantioselective C−H Bond Activation

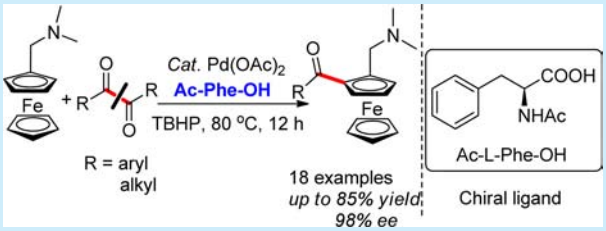
Chao Pi,[†] Xiuling Cui,*[,†,‡] Xiuyan Liu,[†] Mengxing Guo,[†] Hanyu Zhang,[†] and Yangjie Wu*[,†]

[†]Henan Key Laboratory of Chemical Biology and Organic Chemistry, Key Laboratory of Applied Chemistry of Henan Universities, Department of Chemistry, Zhengzhou University, Zhengzhou 450052, P. R. China

[‡]Xiamen Key Laboratory of Ocean and Gene Drugs, School of Biomedical Sciences and Institute of Molecular Medicine of Huaqiao University & Engineering Research Center of Molecular Medicine of Chinese Education Ministry, Xiamen 361021, P. R. China

Supporting Information

ABSTRACT: The first catalytic and enantioselective C−H direct acylation of ferrocene derivatives has been developed. A series of 2-acyl-1-dimethylaminomethylferrocenes with planar chirality were provided under highly efficient and concise one-pot conditions with up to 85% yield and 98% ee. The products obtained could be easily converted to various chiral ligands via diverse transformations.



Ferrocene derivatives with planar chirality as powerful chiral ligands in asymmetric reactions have attracted great attention during the past decades.[1] Chiral 2-acyl-1-dimethylaminomethylferrocenes containing dual functional groups of amino and carbonyl groups are especially valuable due to being readily modified.[2] They could be easily converted to various useful molecules via diverse transformation, such as optically planar ligands in the asymmetric reactions and bioactive compounds. For instance, chiral ferrocenyl amino alcohols were directly obtained through reduction of corresponding chiral 2-acyl-1-dimethylaminomethylferrocenes with lithium reagents, which could promote various asymmetric catalysis, such as enantioselective alkylation of aldehydes with diethylzinc (Figure 1, $_pR$-**2**). Josiphos and PPFA analogs are powerful ligands in a variety of asymmetric transformations, such as allylic alkylations and hydrogenation reactions of C=C and C=N bonds.[3] They could also be accessed from 2-acyl-1-dimethylaminomethylferrocenes. Moreover, chiral 2-acyl-1-dimethylaminomethylferrocenes can serve as useful precursors in the synthesis of chiral ferroquine and ferrocenic mefloquine analogues, both of which are endowed with biological activities in terms of antimalarial (Figure 1, $_pS$-**3**).[4] However, the enantioselective synthesis of 2-acyl-1-dimethylaminomethyl ferrocenes with planar chirality remains rare. To the best of our knowledge, only one procedure was reported, which involved the *ortho*-lithiation of *N*,*N*-dimethylaminomethylferrocene using a stoichiometric amount of lithium reagent and (*R*,*R*)-tetra-methyl-1,2-cyclohexanediamine as a chiral auxiliary, formylation, addition reaction of $_pR$-**4** with phenylithium, and sequential oxidation with manganese dioxide (Scheme 1a).[4,5] This protocol suffers from tedious procedures, low atom economy, less efficiency, narrow substrate scope, relatively harsh reaction conditions, and requirement of excessive organometallic reagents and chiral auxiliaries. Therefore, the development of mild, convenient, and efficient methods to access chiral 2-acyl-1-dimethylaminomethylferrocenes is highly desirable.

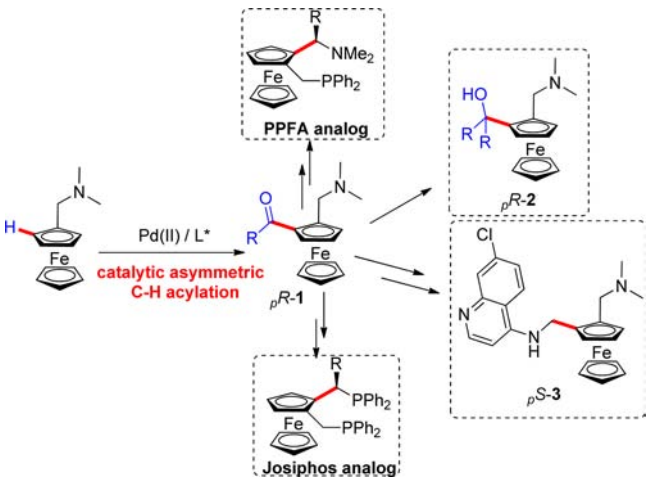
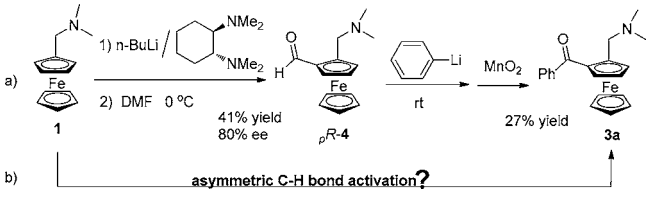


Figure 1. Synthetic method and general applications.

Scheme 1. Synthesis of ($_pR$)-2-Benzoyl-1-*N*,*N*-dimethylaminomethylferrocene

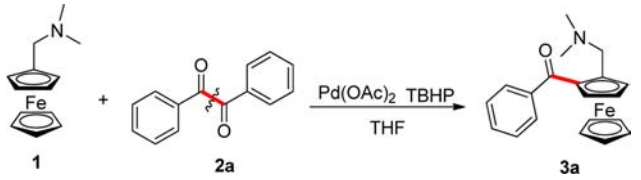


Received: August 26, 2014
Published: September 23, 2014

dx.doi.org/10.1021/ol502509f | *Org. Lett.* 2014, 16, 5164−5167

Very recently, You, Gu, and our group independently accessed ferrocene derivatives with planar chirality based on Pd-catalyzed C−H bond activation using an amino acid or BINAP as ligands.[6] Shibata and co-workers reported an iridium-catalyzed enantioselective alkylation of ferrocenes with alkenes using chiral diene as ligands.[7] Encouraged by these results obtained, we envisaged that 2-acyl-1-dimethylaminomethylferrocenes with planar chirality could be directly accessed by transition-metal-catalyzed asymmetric C−H acylation (Scheme 1b).

Table 1. Screening of Protected Amino Acids[a]



1 2a 3a

entry	ligand	yield (%)[b]	ee (%)[c]
1	Boc-L-Phe-OH	43	86
2	Boc-L-Ala-OH	50	71
3	Boc-L-Val-OH	49	81
4	Boc-L-Leu-OH·H_2O	52	79
5	Boc-L-Ile-OH·0.5H_2O	52	80
6	Boc-L-tLeu-OH	48	79
7	Boc-L-Abu-OH	41	74
8	Boc-L-Cys(Trt)-OH	23	77
9	Fmoc-L-Phe-OH	n.r.[d]	–
10	Ac-L-Phe-OH	62	90
11	Ac-L-Ile-OH	60	87
12[e]	Ac-L-Phe-OH	45	91
13[f]	Ac-L-Phe-OH	36	88
14[g]	Ac-L-Phe-OH	54	90
15[h]	Ac-L-Phe-OH	79	96
16[i]	Ac-L-Phe-OH	70	97
17[h,j]	Ac-L-Phe-OH	45	95

[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), ligand (20 mol %), TBHP (70% aqueous solution) (3 equiv), K_2CO_3 (0.3 equiv), and TBAB (0.5 equiv) in THF (2.0 mL) at 80 °C (oil bath) under air. [b]Isolated yields based on **1**. [c]Determined by HPLC analysis. [d]n.r. = No reaction. [e]60 °C. [f]100 °C. [g]20 h. [h]K_2CO_3, 1.0 equiv. [i]K_2CO_3, 1.5 equiv. [j]$Pd(OAc)_2$, 5 mol %.

To achieve this goal, a variety of carbonyl sources, including benzaldehyde, benzyl alcohol, benzoylformic acid, benzoic acid, benzyl amine, and diphenyl diketone, were initially tested. The results indicated that diphenyl diketone was an effective starting material (see Table S1 in the SI). Then the reaction of *N*,*N*-dimethylaminomethylferrocene (**1**) with diphenyl diketone (**2a**) was chosen as a model reaction. The desired product **3a** was afforded in 43% isolated yield with 86% ee in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % Boc-L-Phe-OH, 30 mol % K_2CO_3, 50 mol % TBAB, and 3 equiv TBHP in THF at 80 °C under air for 12 h. The absolute configuration of product was assigned from the cyclopalladated complex described in the literature.[8] Further, the reaction parameters, including the catalyst, oxidant, and solvent, were examined (for details, see Table S2 in the Supporting Information).

Finally, commercially available N-Boc-protected L-amino acids as ligands were systematically examined. The results were summarized in Table 1. The desired product was obtained in yields ranging from 23% to 52% with enantioselectivity ranging from 71% ee to 86% ee (Table 1, entries 1−8). No desired product was observed when the boc group was replaced by a larger protecting group [fmoc, (9*H*-fluoren-9-yl) acetate] (Table 1, entry 9). Reducing the bulk of the protecting group from boc to acetyl resulted in a higher yield and enantioselectivity (Table 1, entries 10 and 11). Ac-L-Phe-OH proved to be the most efficient chiral ligand in term of enantioselectivity and reactivity, providing the desired product in 62% yield with 90% ee (Table 1, entry 10). By elevating and reducing the reaction temperature, the yield was reduced to 45% and 36% respectively (Table 1, entries 12 and 13). The yield was reduced to 54% prolonging the reaction time to 20 h. According to our previous work,[6a] it was envisioned that benzoic acid might be produced in the reaction process and participated in competition with the chiral amino acid, which would affect the enantioselective C−H bond activation of the ferrocene ring. With this motivation in mind, the base was increased to 1.0 equiv. To our great delight, the reaction proceeded smoothly and afforded the desired product in 79% yield with 96% ee (Table 1, entry 15). The yield slightly decreased by adding 1.5 equiv of K_2CO_3 (Table 1, entry 16) and dramatically decreased to 45% when reducing the catalyst loading to 5 mol % (Table 1, entry 17). The optimized reaction conditions were identified as follows: $Pd(OAc)_2$ (10 mol %), Ac-L-Phe-OH (20 mol %), 1.0 equiv of K_2CO_3, 50 mol % TBAB, and 3 equiv of TBHP in THF at 80 °C under air for 12 h (Table 1, entry 15).

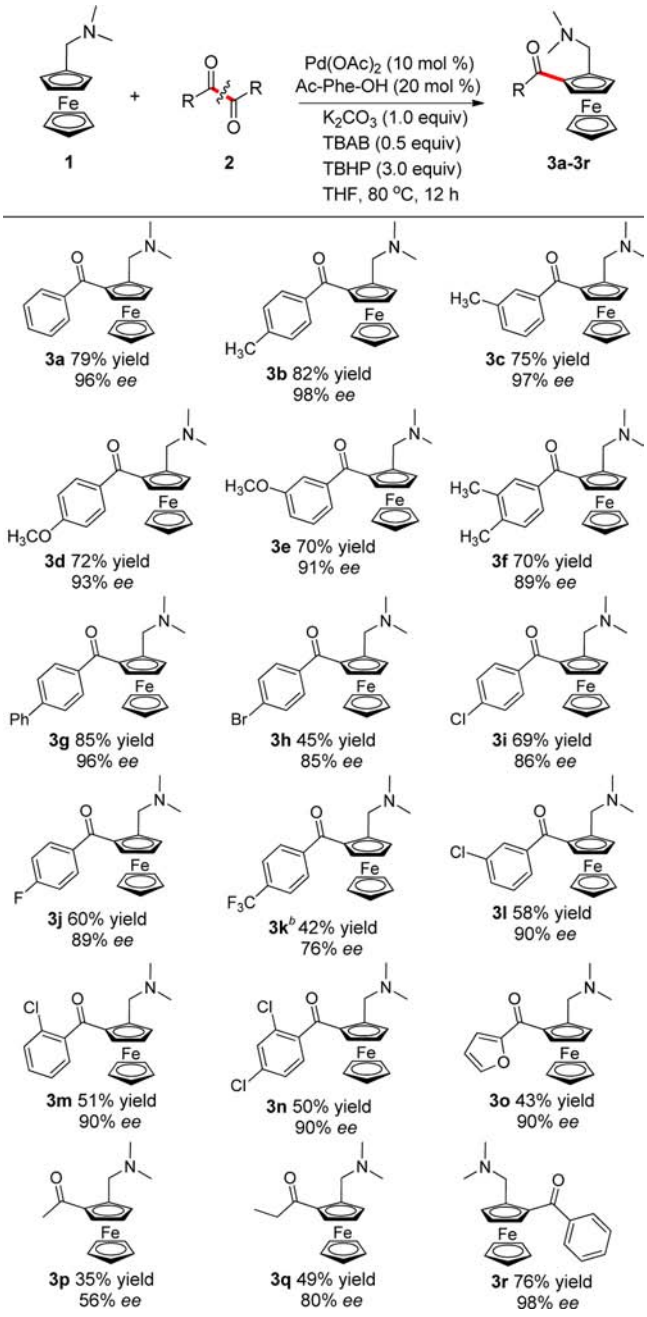
Under the optimized reaction conditions, the scope of substrates for this asymmetric transformation was investigated. The results were summarized in Scheme 2. Generally, various diaryl diketones bearing either electron-donating or -withdrawing groups were well-tolerated and converted into the corresponding products in moderate to good yields with excellent enantioselectivity. Moreover, the enantioselectivity was not affected significantly by the steric hindrance and electronic effect of substrates **2**. Diaryl diketones with electron-donating groups afforded the acylated products **3b**−**3g** in 70−85% yields with 89−98% ee's. Meanwhile, diaryl diketones bearing electron-withdrawing substituents, such as F, Cl, Br, and CF_3, also led to the corresponding products **3h**−**3n** in 42−69% yields and 76−90% ee's. It is noteworthy that furil also reacted smoothly with *N*,*N*-dimethylaminomethylferrocene (**1**), giving the product **3o** in 43% yield and 90% ee. In addition, we were delighted to find that dialiphatic diketones also proceeded smoothly. For example, 2,3-butanedione and 3,4-hexanedione offered acceptable yields of the corresponding products **3p** and **3q**, which provided an efficient route to introduce an aliphatic carbonyl group to the ferrocene ring. As expected, the enantiomer **3r** was obtained in good yield (76%) and excellent enantioselectivity (98%) when Ac-L-Phe-OH was replaced by Ac-D-Phe-OH.

The planar-chiral N,O-ligand **L1** has been applied successfully in the catalytic asymmetric ethylation of benzaldehyde by Et_2Zn.[3a,9] Starting from compound **3a** obtained in our methodology, **L1** was prepared by treatment with phenyllithium in 82% yield (Scheme 3). In comparison, the current study provided a more simple and efficient entry to various N,O-ligand analogues, which could also be modified further into other kinds of useful ligands in asymmetric reactions.

To gain insight into the mechanism of this transformation, the reaction was performed in the presence of a radical scavenger (TEMPO).[10] The target product was not detected, which indicates that the reaction proceeds via a radical pathway. Based on the result obtained above and previous literature,[6a,8,11] the reaction mechanism was proposed and shown in Figure 2. First,

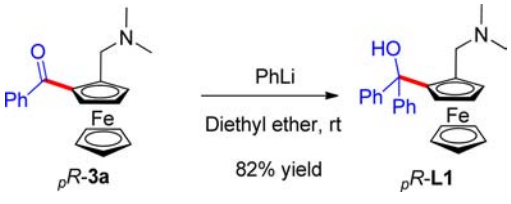
dx.doi.org/10.1021/ol502509f | *Org. Lett.* 2014, 16, 5164−5167

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (10 mol %), Ac-L-Phe-OH (20 mol %), TBHP (70% aqueous solution) (3 equiv), K_2CO_3 (1.0 equiv), and TBAB (0.5 equiv) in THF (2.0 mL) at 80 °C (oil bath) under air. Isolated yields based on **1**. [b] Boc-L-Phe-OH as the ligand.

Scheme 3. Transformation of Acylated Product



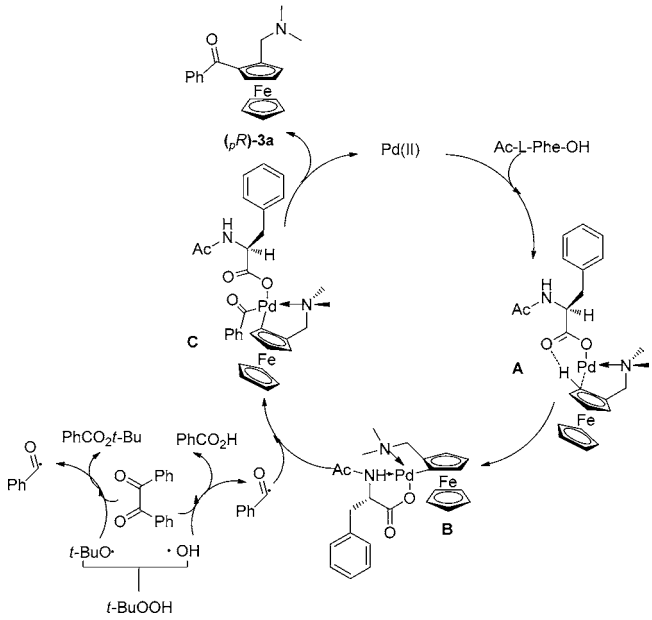


Figure 2. Proposed reaction mechanism.

the cyclopalladated complex **B** was formed through bicycle-intermediate **A**, which was formed from the coordination of the palladium atom to the N-atom and subsequent enantioselective electrophilic attack at the 2-position C-atom. Then, the reaction of the cyclopalladated complex **B** with a benzoyl radical provided Pd^{III} or Pd^{IV} intermediate **C**.[12] The benzoyl radical was generated by the reaction of diphenyl diketone with TBHP.[13] Finally a carbon−carbon bond was formed via reductive elimination of **C**, delivering the acylated product and regenerating the Pd^{II} species for the next cycle.

In summary, we have developed a novel and convenient protocol to achieve the 2-acyl-1-dimethylaminomethylferrocene with planar chirality. Various 2-acyl-1-dimethylaminomethyl-ferrocene derivatives were prepared in moderate to good yields with excellent enantioselectivities via Pd-catalyzed asymmetric C−H bond activation using commercially available and cheap monoprotected amino acids as a chiral ligand under mild reaction conditions. Further mechanistic investigations and applications of the chiral products as ligands in organic synthesis are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra copies. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: cuixl@zzu.edu.cn.
*E-mail: wyj@zzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSF of China (Nos. 21102133 and 21172200) and the NSF of Henan (082300423201).

REFERENCES

(1) (a) *Chiral Ferrocenes in Asymmetric Catalysis*; Dai, L.-X., Hou, X.-L., Eds.; Wiley-VCH: Weinheim, 2010. (b) Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965. (c) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (d) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659. (e) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101. (f) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (g) Fu, G. C. *Acc. Chem. Res.* **2006**, *39*, 853. (h) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475. (i) Arae, S.; Ogasawara, M. *J. Synth. Org. Chem.* **2012**, *70*, 593. (j) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (k) Duan, Z.-C.; Hu, X. P.; Zhang, C.; Wang, D. Y.; Yu, S. B.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 9191. (l) Thiesen, K. E.; Maitra, K.; Olmstead, M. M.; Attar, S. *Organometallics* **2010**, *29*, 6334. (m) Chang, M.-X.; Li, W.; Hou, G.-H.; Zhang, X.-M. *Adv. Synth. Catal.* **2010**, *352*, 3121. (n) Weiss, M.; Frey, W.; Peters, R. *Organometallics* **2012**, *31*, 6362. (o) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Chem. Sci.* **2013**, *4*, 97. (p) Hokoshi, R. *Coord. Chem. Rev.* **2013**, *257*, 621.

(2) (a) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421. (b) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160. (c) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062. (d) Naud, F.; Malan, C.; Spindler, F.; Ruggeberg, C.; Schimidt, A. T.; Blasé, H.-U. *Adv. Synth. Catal.* **2006**, *348*, 47. (e) Enders, D.; Peters, R.; Lochtman, R.; Raabe, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 2421. (f) Ierland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212.

(3) (a) *Ferrocenes*; Togni, A., Hayashi, T., Eds.; Wiley-VCH: Weinheim, 1995; p 105. (b) *Trivalent Phosphorus Compounds in Asymmetric Catalysis: Synthesis and Applications*; Borner, A., Ed.; Wiley-VCH: Weinheim, 2008; pp 345 and 359. (c) Delacroix, O.; Picart-Goetgheluck, S.; Maciejewski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4417. (d) Bolm, C.; Muniz, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491. (e) Schuecker, R.; Weissensteiner, W. *Organometallics* **2010**, *29*, 6443. (f) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180. (g) Babaro, P.; Bianchini, C.; Giambastiani, G.; Parisel, S. L. *Coord. Chem. Rev.* **2004**, *248*, 2131. (h) Jia, X.; Li, X. L.; Lam, W. S.; S. Kok, H. L.; Xu, L.; Lu, G.; Yeung, C. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 2273. (i) Tang, Z. Y.; Lu, Y.; Hu, Q. S. *Org. Lett.* **2003**, *5*, 297. (j) Tappe, K.; Knochel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 91.

(4) (a) Biot, C.; Chavain, N.; Dubar, F.; Pradines, B.; Trivelli, X.; Brocard, J.; Forfar, I.; Dive, D. *J. Organomet. Chem.* **2009**, *694*, 845. (b) Biot, C.; Delhaes, L.; Maciejewski, L. A.; Mortuaire, M.; Camus, D.; Dive, D.; Brocard, J. S. *Eur. J. Med. Chem.* **2000**, *35*, 707. (c) Maguene, G. M.; Jakhlal, J.; Ladyman, M.; Vallin, A.; Ralambomanana, D. A.; Bousquet, T.; Maugein, J.; Lebibi, J.; Pelinski, L. *Eur. J. Med. Chem.* **2011**, *46*, 31. (d) Domarle, O.; Blampain, G.; Agnaniet, H.; Nzadiyabi, T.; Lebibi, J.; Brocard, J.; Maciejewski, L.; Biot, C.; Georges, A. J.; Millet, P. *Antimicrob. Agents Chemother.* **1998**, *42*, 540.

(5) (a) Nishibayashi, Y.; Arikawa, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1996**, *61*, 1172. (b) Delacroix, O.; Picart-Goetgheluck, S.; Maciejewski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1999**, *10*, 4417. (c) Delacroix, O.; Andriamihaja, B.; Picart-Goetgheluck, S.; Brocard, J. *Tetrahedron* **2004**, *60*, 1549. (d) Malfait, S.; Pelinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2207. (e) Picart- Goetgheluck, S.; Delacroix, O.; Maciejewski, L.; Brocard, J. *Synthesis* **2000**, *10*, 1421.

(6) (a) Pi, C.; Li, Y.; Cui, X.-L.; Zhang, H.; Han, Y.-B.; Wu, Y.-J. *Chem. Sci.* **2013**, *4*, 2675. (b) Gao, D.-W.; Shi, Y.-C.; Gu, Q.; Zhao, Z.-L.; You, S.-L. *J. Am. Chem. Soc.* **2013**, *135*, 86. (c) Shi, Y.-C.; Yang, R.-F.; Gao, D.-W.; You, S.-L. *Beilstein J. Org. Chem.* **2013**, *9*, 1891. (d) Deng, R.-X.; Huang, Y.-Z.; Ma, X.-N.; Li, G.-C.; Zhu, R.; Wang, B.; Kang, Y.-B.; Gu, Z.-H. *J. Am. Chem. Soc.* **2014**, *136*, 4472. (e) Gao, D.-W.; Yin, Q.; Gu, Q.; You, S.-L. *J. Am. Chem. Soc.* **2014**, *136*, 4841.

(7) Shibata, T.; Shizuno, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 5410.

(8) (a) Dendele, N.; Bisaro, F.; Gaumont, A. C.; Perriob, S.; Richards, C. J. *Chem. Commun.* **2012**, *48*, 1991. (b) Gunay, M. E.; Richards, C. J. *Organometallics* **2009**, *28*, 5833.

(9) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

(10) (a) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A.-W. *J. Am. Chem. Soc.* **2010**, *132*, 16737. (b) Warren, J. J.; Mayer, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 7784. (c) Chan, C.-W.; Zhou, Z.; Chan, A. S. C.; Yu, W. Y. *Org. Lett.* **2010**, *12*, 3926.

(11) Sokolov, V. I.; Troitskaya, L. L.; Khrushchova, N. S. *J. Organomet. Chem.* **1983**, *250*, 439.

(12) (a) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. (c) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945. (d) Rosewall, C. F.; Sibbald, P. A.; Liskin, D. V.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 9488. (e) Basle, O.; Bidange, J.; Shuai, Q.; Li, C. J. *Adv. Synth. Catal.* **2010**, *352*, 1145. (f) Li, C. L.; Wang, L.; Li, P.-H.; Zhou, W. *Chem.—Eur. J.* **2011**, *17*, 1020.

(13) (a) Bentrude, W. G.; Darnall, K. R. *J. Am. Chem. Soc.* **1968**, *90*, 3588. (b) Adam, W.; Oestrich, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 3455. (c) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991. (d) Zhou, W.; Li, H.; Wang, L. *Org. Lett.* **2012**, *14*, 4594.