Organic LETTERS

Letter

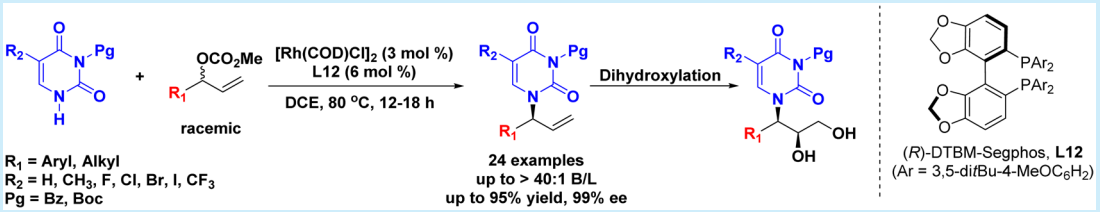
pubs.acs.org/OrgLett

Regio- and Enantioselective Synthesis of Chiral Pyrimidine Acyclic Nucleosides via Rhodium-Catalyzed Asymmetric Allylation of Pyrimidines

Lei Liang,[†] Ming-Sheng Xie,*[,‡] Tao Qin,[‡] Man Zhu,[‡] Gui-Rong Qu,[‡] and Hai-Ming Guo*[,†,‡]

[†]School of Environment and [‡]Henan Key Laboratory of Organic Functional Molecules and Drugs Innovation, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan Province 453007, China

Supporting Information



ABSTRACT: A direct route to branched *N*-allylpyrimidine analogues is herein reported via the highly regio- and enantioselective asymmetric allylation of pyrimidines with racemic allylic carbonates. With $[Rh(COD)Cl]_2$/chiral diphosphine as the catalyst, a range of chiral pyrimidine acyclic nucleosides could be obtained under neutral conditions in good yields (up to 95% yield) with high levels of regio- and enantioselectivities (15:1 to >40:1 B/L and up to 99% ee). Furthermore, chiral pyrimidine acyclic nucleoside bearing two adjacent chiral centers has been successfully synthesized by asymmetric dihydroxylation.

Chiral acyclic nucleosides are currently used as antiviral drugs. (*S*)-Cidofovir, a broad-spectrum antiviral agent, is currently used to treat AIDS-related human cytomegalovirus (HCMV) retinitis and has recognized therapeutic potential for orthopox virus infections.[1] Some other nucleosides and nucleotides with chiral carbons in the acyclic side chain, such as (*S*)-FPMPT, (*S*)-willardiine, (*S*)-HPMPA, and (*R*)-tenofovir, possess various medicinal activities (Figure 1).[2a−d] The absolute configuration of acyclic nucleosides has a significant influence on their biological potency. For example, (1) cidofovir, the *S*-enantiomer, shows high antiviral activity, while its antipode, *R*-enantiomer is devoid of effect.[2e] (2) The *S*-enantiomer of FPMPA has an IC_{50} of 1.85 μM, whereas the *R*-enantiomer is inactive[2f] (Figure 1). Therefore, the synthesis of optical purity acyclic nucleosides seems more valuable, and considerable efforts have been devoted to the construction of chiral pyrimidine acyclic nucleosides.

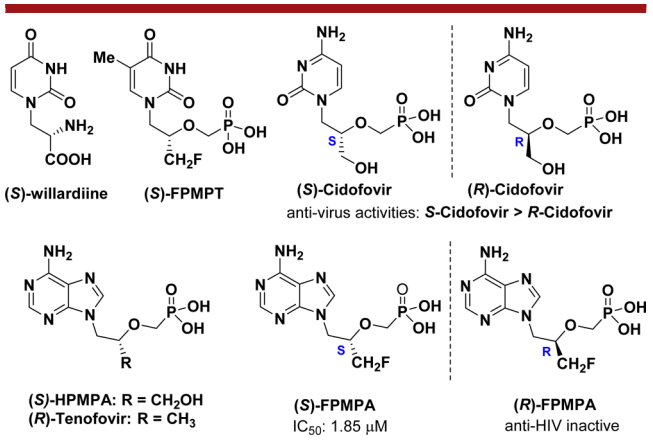


Figure 1. Structures of representative chiral acyclic nucleosides with different biological activities.

Early synthetic approaches to pyrimidine acyclic nucleosides were based mainly on aza-Michael addition, S_N2 reaction, Mitsunobu reaction, or ring opening of epoxides.[3] However, strategies to obtain chiral pyrimidine acyclic nucleosides are still rare. In 2006, Evans and co-workers successfully demonstrated the feasibility of the synthesis of acyclic pyrimidine nucleosides via Rh-catalyzed allylation of thymine.[4] Nevertheless, strong base was required to enhance the nucleophilicity of thymine, and the allylated products were racemic. Furthermore, in order to obtain chiral pyrimidine acyclic nucleosides, a chiral allylic carbonate was necessary as the chiral starting material. In contrast, low-cost and easily accessed achiral allylic electrophiles have never been successfully applied in the synthesis of chiral acyclic pyrimidine nucleosides. The asymmetric synthesis of chiral acyclic pyrimidine nucleosides is still under-developed. As part of our ongoing endeavors on the chemical synthesis of chiral nucleosides,[5] we became interested in addressing this challenge.

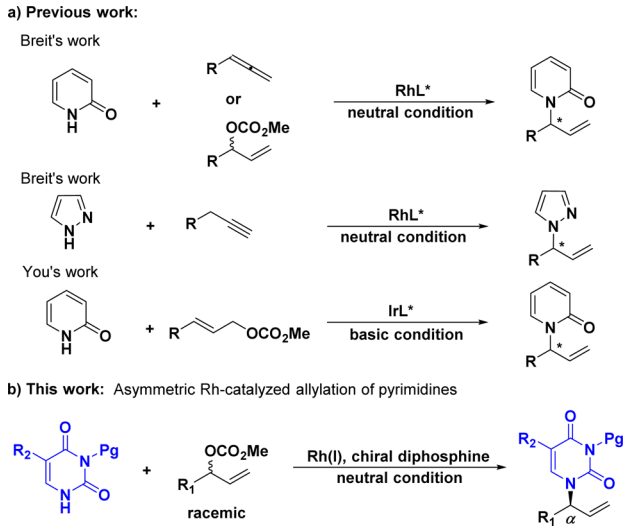
Recently, the asymmetric addition of pronucleophiles to allenes,[6] alkynes,[7] and racemic allylic carbonates[8] catalyzed by

Received: August 10, 2017

DOI: 10.1021/acs.orglett.7b02482
Org. Lett. XXXX, XXX, XXX−XXX

rhodium or iridium has provided a powerful tool to construct a new chiral center (Scheme 1a). Inspired by these previous

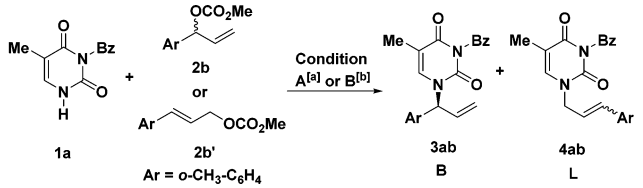
Scheme 1. Synthetic Approaches to *N*-Allylated Products

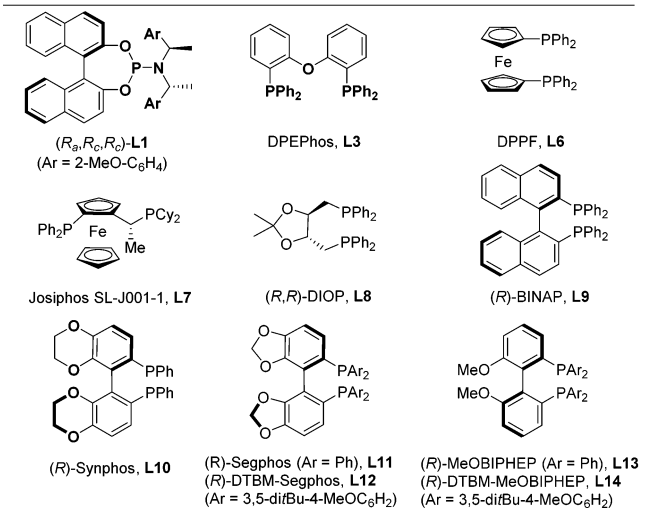


works, we envisioned that the synthesis of chiral acyclic pyrimidine nucleosides might be enabled by asymmetric allylic substitution of less nucleophilic and more complex pyrimidines with achiral allylic electrophiles. Herein, we report a rhodium-catalyzed asymmetric allylation of pyrimidines with achiral allylic electrophiles (easily prepared) for the synthesis of α-chiral acyclic pyrimidine nucleosides (Scheme 1b). Notably, the allylation of pyrimidines proceeded in a highly regio- and enantioselective manner under neutral conditions.

Initially, the reaction between N^3-Bz-protected thymine **1a** and allylic carbonate **2b** or **2b′** was chosen as the model reaction (Table 1). N^1-Allylated product **3ab** was obtained with highly branched regioselectivity in low ee (Table 1, entry 1) when $[Ir(COD)Cl]_2$-**L1** was employed as the catalyst in THF at 50 °C for 12 h. The enantioselectivity of N^1-allylated thymine was hardly controlled by the Ir-catalyst system (see the Supporting Information for details). After that, $[Rh(COD)Cl]_2$/diphosphine catalysts were examined, *rac*-BINAP was first tested for the model reaction, and *N*-allylated **3ab** was isolated in moderate yield and a ratio of 15:1 B/L (Table 1, entry 3). Interestingly, the allylic carbonate **2b′** was not suitable for the allylation reaction, no matter whether an Ir catalyst or Rh catalyst system was selected (Table 1, entries 1−4). Meanwhile, carbonate **2b** was the appropriate reaction partner. A series of achiral ligands were next examined, including $[Rh(COD)Cl]_2$ (3.0 mol %) and DPEPhos (6.0 mol %), and the reaction proceeded smoothly and provided the desired branched product **3ab** with good branched/linear selectivity (Table 1, entries 3−8). With an effective method for the racemic allylation reaction in hand, different types of chiral bidentate phosphine ligands were subsequently screened. Josiphos and (*R*,*R*)-DIOP ligands resulted in moderate to high yields and poor enantioselectivities (Table 1, entries 9 and 10). Biaryl-type bisphosphine ligands were next examined. (*R*)-BINAP-**L9** was not effective at promoting this coupling reaction (Table 1, entry 11). Meanwhile (*R*)-Synphos-L**10** led to moderate yield and ee value. The use of (*R*)-Segphos-**L11** and (*R*)-MeOBIPHEP-**L13** further increased the enantioselectivity of the desired product (Table 1, entries 13 and 15). To our delight, (*R*)-DTBM-

Table 1. Optimization of the Reaction Conditions[b]





entry	ligand	2	B/L[c]	yield[d] (%)	ee[e] (%)
1[a]	**L1**	**2b**	>50:1	92	13
2[a]	**L1**	**2b′**		NR	
3	*rac*-BINAP-**L2**	**2b**	15:1	51	
4	*rac*-BINAP-**L2**	**2b′**		NR	
5	**L3**	**2b**	18:1	73	
6	DPPP-**L4**	**2b**		trace	
7	DPPB-**L5**	**2b**		15	
8	**L6**	**2b**		19	
9	**L7**	**2b**	13:1	52	39
10	**L8**	**2b**	>30:1	88	53
11	**L9**	**2b**	17:1	45	13
12	**L10**	**2b**	20:1	75	51
13	**L11**	**2b**	25:1	83	65
14	**L12**	**2b**	>30:1	85	98
15	**L13**	**2b**	>30:1	79	61
16	**L14**	**2b**	>30:1	83	96

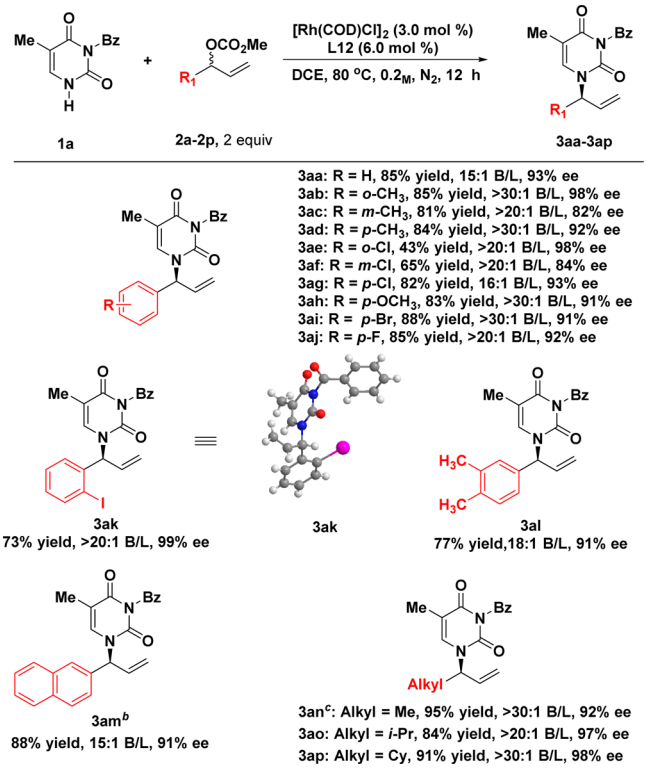
[a]Entries 1−2, conditions A: **1a** (0.2 mmol), **2b** or **2b′** (0.4 mmol), K_3PO_4 (0.2 mmol), $[Ir(COD)Cl]_2$ (2 mol %) and **L1** (4 mol %) in THF (1.0 mL), 50 °C, N_2, 12 h. [b]Entries 3−16, conditions B: **1a** (0.2 mmol), **2b** or **2b′** (0.4 mmol), $[Rh(COD)Cl]_2$ (3 mol %) and **L** (6 mol %), in DCE (1.0 mL), 80 °C, N_2, 12 h. [c]The ratio was determined from the crude ^{1}H NMR. [d]Yields of isolated product. [e]Determined by chiral HPLC analysis. DPPP = 1,3-bis(diphenylphosphino) propane. DPPB = 1,4-bis(diphenylphosphino)butane.

Segphos-**L12** and (*R*)-DTBM-MeOBIPHEP-**L14** (the ligands bearing more bulkier substituent group) led to the desired product in good yield, high regioselectivity, and high enantioselectivity (Table 1, entries 14 and 16). On the basis of these results, we believed that **L12** was the best choice.

Under the optimized reaction conditions, *N*-allylation of thymine with a series of allylic carbonates was evaluated as summarized in Scheme 2. A variety of electron-neutral, electron-rich, or electron-deficient phenyl-substituted allylic carbonates containing *ortho*, *meta*, or *para* substituents gave the corresponding chiral *N*-allylated thymine products in moderate to good yields with good branched regioselectivities and good

DOI: 10.1021/acs.orglett.7b02482
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope of Allylic Carbonates[a]

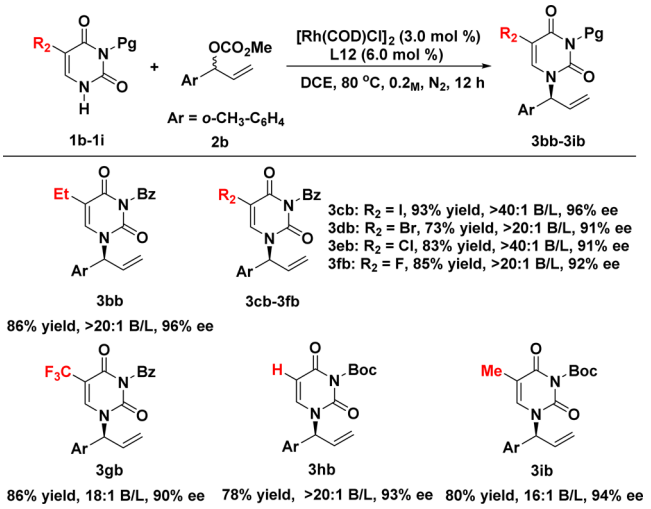


[a]The B/L ratio was determined from crude ^{1}H NMR, and the ee values were determined by chiral HPLC analysis. Yield of isolated branched yield. [b]18 h. [c]$[Rh(COD)Cl]_2$ (1.0 mol %), **L12** (2.0 mol %).

enantioselectivities (Scheme 2, **3aa**–**ak**). The reactions with phenyl-substituted allylic carbonates containing diverse electronic properties at the *para* position furnished the products in moderate to high yields, and the results were similar to the phenyl allylic carbonate **2a** (Scheme 2, **3ad**, **3ag**–**aj**). The highest selectivities were observed with the *o*-I phenyl-substituted allylic carbonate (Scheme 2, **3ak**). Notably, the yields of desired products were decreased when a chlorine atom was present at the *ortho* or *meta* position of the phenyl (Scheme 2, **3ae**, **3af**). However, the reaction of the corresponding allylic carbonate **2b** gave the branched allylation product **3ab** in good yield (85%) and regioselectivity (>30:1) with high enantioselectivity (98% ee). Both 3,4-dimethylphenyl and 2-naphthyl allylic carbonates reacted selectively with thymine, and the reaction time of **2m** was prolonged to 18 h (Scheme 2, **3al**, **3am**). Alkyl-substituted allylic carbonates were also reacted to provide allylated products **3an**–**ap**. Methyl allylic carbonate **2n** furnished the corresponding product in high yield (95%) with a relatively good enantioselectivity (92% ee), whereas α-branched isopropyl **2o** and α-branched cyclohexyl **2p** allylic carbonates afforded the desired substitution products in good yields with excellent enantioselectivities (Scheme 2, **3ao**, **3ap**). Notably, in all cases, the allylated products were obtained with >10:1 branched-to-linear selectivity. The absolute configuration of the chiral allylic thymine analogue **3ak** was determined to be *S* by single-crystal X-ray diffraction analysis.

Subsequently, a series of pyrimidine derivatives with different substituents at the C5 position were investigated (Scheme 3). 5-Ethyl- and 5-halo-substituted pyrimidines (**1b**–**f**) reacted smoothly to provide the allylic pyrimidine derivatives **3bb**–**fb** in 73–93% yields, >15:1 B/L, and 90–96% ee. In addition,

Scheme 3. Substrate Scope of Pyrimidine Derivatives[a]

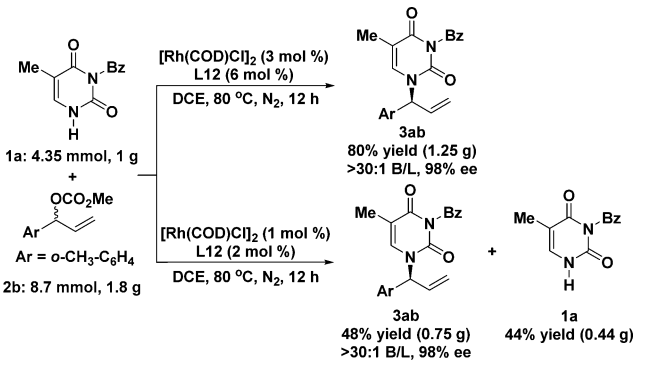


[a]The B/L ratio was determined from crude ^{1}H NMR, and the ee values were determined by chiral HPLC analysis. Yield of isolated branched yield.

strong electron-withdrawing group such as −F and $-CF_3$ were also tolerated well in this reaction, delivering the corresponding products in good ee values (**3fb**, **3gb**). After that, N^3-Boc-protected pyrimidine derivatives were examined. When Boc-protected uracil (**1h**) and Boc-protected thymine (**1i**) were used, the intermolecular asymmetric allylic reaction smoothly afforded the branched products in good results (**3hb**, **3ib**).

To further evaluate the prospect of using the methodology in synthesis, a gram-scale synthesis of N^1-allylthymine **3ab** was performed. As shown in Scheme 4, **3ab** was obtained in 80%

Scheme 4. Gram-Scale Synthesis of 3ab



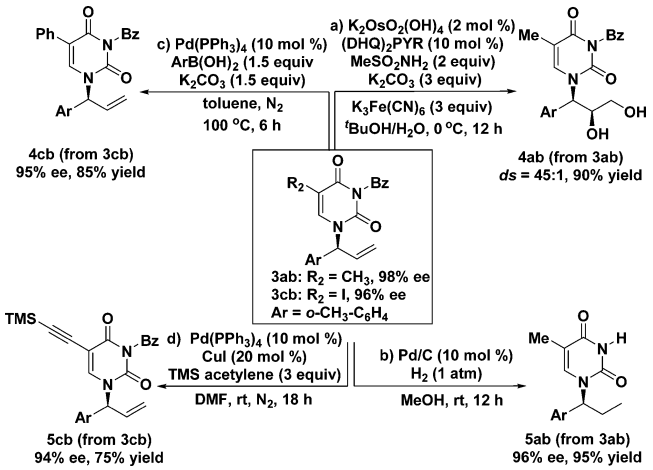
yield (1.25 g), >30:1 B/L, and 98% ee by treatment of 4.35 mmol of Bz-protected thymine **1a** with allylic carbonate **2b** in the presence of 3 mol % of $[Rh(COD)Cl]_2$ and 6 mol % of (*R*)-DTBM-Segphos-**L12**. When the reaction was performed with 1 mol % of $[Rh(COD)Cl]_2$, 2 mol % of **L12**, the allylate ion product **3ab** was obtained in 48% yield along with the recovery of the starting material **1a** in 44% yield.

In order to highlight its synthetic utility, the transformations of *N*-allylated pyrimidine derivatives were next examined. The acylic nucleoside analogue **4ab** was successfully synthesized with good selectivity (ds = 45:1) by the Sharpless asymmetric dihydroxylation[9] of **3ab**. Hydrogenation of **3ab** provided *N*-alkylpyrimidine **5ab** in 95% yield with 96% ee. A broader range of products could be obtained through the modification of the

DOI: 10.1021/acs.orglett.7b02482
Org. Lett. XXXX, XXX, XXX−XXX

pyrimidine skeleton via Suzuki and Sonogashira coupling reactions which performed well and delivered the corresponding products **4cb** and **5cb** in good yields (Scheme 5, c and d).

Scheme 5. Synthesis of Acyclic Nucleoside Analogue and the Transformations of *N*-Allylated Pyrimidine Derivatives



In summary, we have reported a rhodium/chiral-diphosphine catalyst entry to chiral *N*-allylation pyrimidine analogues via the highly enantioselective allylation reactions of pyrimidines with racemic allylic carbonates for the first time (up to 95% yields, 15:1 → 40:1 B/L and up to 99% ee). A series of chiral *N*-allylation pyrimidine analogues were successfully obtained, which could be employed for the synthesis of acyclic pyrimidine nucleoside analogues via Sharpless asymmetric dihydroxylation. In addition, the intermolecular allylation reaction could be performed on a gram scale, affording the desired adduct in excellent results. To our knowledge, this is the first report about Rh-catalyzed asymmetric allylation of aryl-substituted allylic carbonates with nitrogen heterocyclic rings in which the electronic and steric effects were examined.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02482.

Experimental procedures, the synthesis method of the starting materials, and compound characterization data (PDF)

X-ray data for compound **3ak** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xiemingsheng@htu.edu.cn.

*E-mail: ghm@htu.edu.cn.

ORCID

Hai-Ming Guo: 0000-0003-0629-4524

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the National Natural Science Foundation of China (Nos. U1604283 and 21402041), the Plan for Scientific Innovation Talent of Henan Province (164200510008), and Program for Innovative Research Team in Science and Technology in University of Henan Province (15IRTSTHN003).

■ REFERENCES

(1) Eriksson, U.; Peterson, L. W.; Kashemirov, B. A.; Hilfinger, J. M.; Drach, J. C.; Borysko, K. Z.; Breitenbach, J. M.; Kim, J. S.; Mitchell, S.; Kijek, P.; McKenna, C. E. *Mol. Pharmaceutics* **2008**, *5*, 598.

(2) (a) Luo, M.; Groaz, E.; Andrei, G.; Snoeck, R.; Kalkeri, R.; Ptak, R. G.; Hartman, T.; Buckheit, R. W., Jr.; Schols, D.; De Jonghe, S.; Herdewijn, P. *J. Med. Chem.* **2017**, *60*, 6220. (b) Dolman, N. P.; More, J. C. A.; Alt, A.; Knauss, J. L.; Troop, H. M.; Bleakman, D.; Collingridge, G. L.; Jane, D. E. *J. Med. Chem.* **2006**, *49*, 2579. (c) Webb, R. R.; Martin, J. C. *Tetrahedron Lett.* **1987**, *28*, 4963. (d) Doláková, P.; Dračínský, M.; Masojídková, M.; Šolínová, V.; Kašička, V.; Holý, A. *Eur. J. Med. Chem.* **2009**, *44*, 2408. (e) Pack, E. J., Jr.; Bleiberg, B.; Rosenberg, I. E. *Chirality* **1990**, *2*, 275. (f) Kiesewetter, D. O.; Knudson, K.; Collins, M.; Srinivasula, S.; Lim, E.; Di Mascio, M. *J. Labelled Compd. Radiopharm.* **2008**, *51*, 187.

(3) (a) Xie, M.-S.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *Tetrahedron Lett.* **2014**, *55*, 7156. (b) Prunier, A.; Calata, C.; Legros, J.; Maddaluno, J.; Pfund, E.; Lequeux, T. *J. Org. Chem.* **2013**, *78*, 8083. (c) Swamy, K. C. W.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551. (d) Zhang, L.; Peritz, A.; Meggers, E. *J. Am. Chem. Soc.* **2005**, *127*, 4174. (e) Guo, H.-M.; Wu, Y.-Y.; Niu, H.-Y.; Wang, D.-C.; Qu, G.-R. *J. Org. Chem.* **2010**, *75*, 3863.

(4) Evans, P. A.; Lai, K. W.; Zhang, H.-R.; Huffman, J. C. *Chem. Commun.* **2006**, 844.

(5) (a) Sun, H.-L.; Chen, F.; Xie, M.-S.; Guo, H.-M.; Qu, G.-R.; He, Y.-M.; Fan, Q.-H. *Org. Lett.* **2016**, *18*, 2260. (b) Guo, H.-M.; Yuan, T.-F.; Niu, H.-Y.; Liu, J.-Y.; Mao, R.-Z.; Li, D.-Y.; Qu, G.-R. *Chem. - Eur. J.* **2011**, *17*, 4095. (c) Xie, M.-S.; Zhou, P.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *Org. Lett.* **2016**, *18*, 4344.

(6) (a) Koschker, P.; Breit, B. *Acc. Chem. Res.* **2016**, *49*, 1524. (b) Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2017**, *56*, 1520. (c) Haydl, A. M.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 7149. (d) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 2162. (e) Li, C.-K.; Kähny, M.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 13780. (f) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 10876. (g) Parveen, S.; Li, C.; Hassan, A.; Breit, B. *Org. Lett.* **2017**, *19*, 2326.

(7) (a) Haydl, A. M.; Hilpert, L. J.; Breit, B. *Chem. - Eur. J.* **2016**, *22*, 6547. (b) Koschker, P.; Kahny, M.; Breit, B. *J. Am. Chem. Soc.* **2015**, *137*, 3131.

(8) (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (b) Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8971. (c) Pouy, M. J.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11312. (d) Zhang, X.; Yang, Z.-P.; Huang, L.; You, S.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 1873. (e) Li, C.-K.; Breit, B. *Chem. - Eur. J.* **2016**, *22*, 14655.

(9) Johnson, R. A.; Sharpless, K. B. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 6, p 357.

DOI: 10.1021/acs.orglett.7b02482
Org. Lett. XXXX, XXX, XXX−XXX