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Kinetic Resolution of Benzylamines via Palladium(II)-Catalyzed C−H Cross-Coupling

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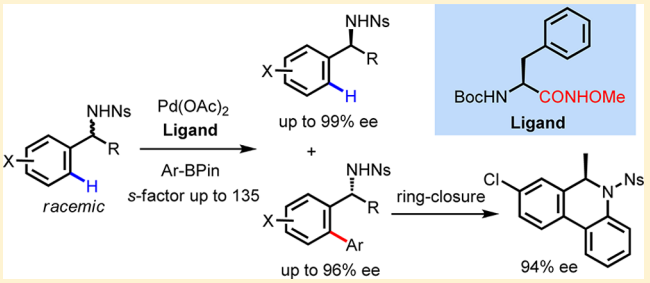
Supporting Information

ABSTRACT: A Pd(II)-catalyzed enantioselective C−H cross-coupling of benzylamines via kinetic resolution has been achieved using chiral mono-*N*-protected α-amino-*O*-methyl-hydroxamic acid (MPAHA) ligands. Both chiral benzylamines and *ortho*-arylated benzylamines are obtained in high enantiomeric purity. The use of a readily removable nosyl (Ns) protected amino group as the directing group is a crucial practical advantage. Moreover, the *ortho*-arylated benzylamine products could be further transformed into chiral 6-substituted 5,6-dihydrophenanthridines as important structural motifs in natural products and bioactive molecules.



1. INTRODUCTION

Enantiopure α-branched amines are highly important structural motifs found prevalent in many natural products and biologically active compounds. In particular, chiral *ortho*-arylated benzylamines are known to be medicinally important motifs with a wide range of biological activities including CYP450 3A inhibition, γ-secretase modulation, and FVIIa inhibition (Figure 1).[1] Consequently, a plethora of methods for

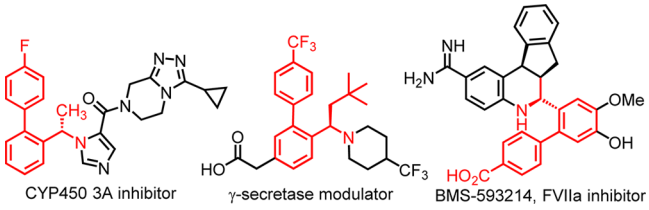
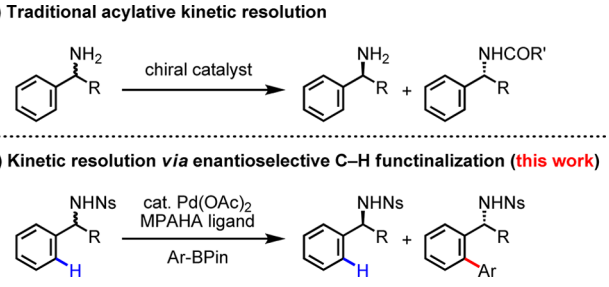


Figure 1. Bioactive compounds containing *ortho*-arylated benzylamines.

the asymmetric synthesis of chiral amines have been developed.[2] Among them, asymmetric addition of carbanions to aldimines/sulfinimines,[3] asymmetric reduction/hydrogenation of ketimines/enamines/enamides,[4] and asymmetric hydroamination of alkenes are most extensively investigated.[5] Despite these impressive advances, the enzymatic kinetic resolution and classical resolution via diastereomeric salt formation are still frequently used in manufacturing.[6] Notably, nonenzymatic kinetic resolution of amines by acylation catalysts remains a significant challenge (Scheme 1a).[7]

Considering the limited success of kinetic resolution of amines via acylation, we envisioned that kinetic resolution of racemic benzylamines via a palladium(II)-catalyzed enantioselective C−H cross-coupling[8] would be appealing, as this approach will give access to both chiral benzylamines and *ortho*-

Scheme 1. Kinetic Resolution of Racemic Benzylamines



arylated benzylamines. Despite significant progress in the development of enantioselective C−H functionalization reactions via desymmetrization,[9−12] enantioselective C−H activation reactions through a kinetic resolution process are rare.[13] Recently enantioselective C−H iodination[14] and enantioselective C−H olefination[15] via kinetic resolution were achieved utilizing Pd(II) coordinated with a mono-*N*-protected amino acid (MPAA) ligand as the catalyst.[9,14,15] To the best of our knowledge, kinetic resolution via palladium-catalyzed enantioselective C−H cross-coupling has not been demonstrated to date. The elementary steps of C−H cross-coupling are fundamentally different from those of the C−H iodination[14] and enantioselective C−H olefination,[15] which suggests that the development of a different chiral ligand may be necessary. From the viewpoint of synthetic utility, enantioselective C−H cross-coupling affords highly valuable chiral bis-aryl compounds. Herein, we report a Pd(II)-catalyzed highly enantioselective C−H cross-coupling/kinetic resolution of racemic benzylamines with arylboronic acid pinacol esters using a chiral

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mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligand (Scheme 1b). Notably, the amino moiety protected by the commonly used nosyl (Ns) group is used as the directing group, representing a practical advantage in synthetic applications. In contrast to traditional acylative kinetic resolution, this asymmetric reaction not only separates two enantiomers of racemic benzylamines but also installs a new carbon−carbon bond,[16] thereby providing a valuable method for the preparation of chiral *ortho*-arylated benzylamines.

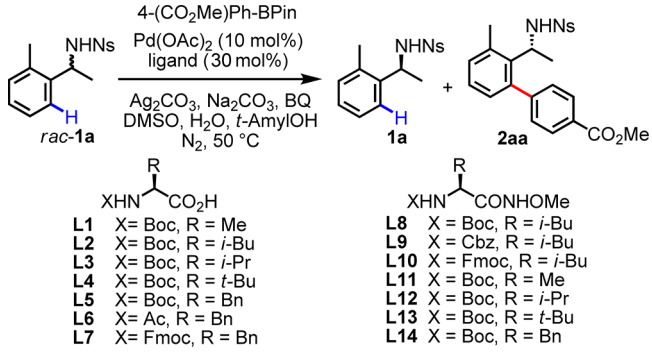
2. RESULTS AND DISCUSSION

We initiated our studies by exploring the enantioselective C−H cross-coupling/kinetic resolution of racemic nosyl (Ns) protected 1-(2-methylphenyl)ethanamine **1a**. Guided by our previous conditions for C−H cross-coupling of triflyl-protected amines,[17] the reaction of **1a** with *para*-methoxycarbonylphenylboronic acid pinacol ester was carried out in the presence of 10 mol% $Pd(OAc)_2$, 30 mol% Boc-L-Ala-OH, 3.0 equiv of Na_2CO_3, 2.0 equiv of Ag_2CO_3, 0.4 equiv of DMSO, and 5.0 equiv of H_2O in *t*-AmylOH at 50 °C. We were pleased to find that the desired cross-coupled product **2aa** and the recovered starting material **1a** were obtained with 58% ee and 93% ee respectively, corresponding to a selectivity factor (*s*)[18] of 12 (Table 1, entry 1). Encouraged by this result, a variety of commercially available Boc protected amino acid ligands with different side chains were screened (entries 2−5). Boc-L-Phe-OH (**L1**) gave the best *s*-factor of 19 (entry 5). However, further tuning of the *N*-protecting group only led to decreased selectivities (entries 6 and 7). Influenced by our previous observation that conversion of the carboxylic acid in MPAA ligand to hydroxamic acid can be beneficial to enantioselective C−H activation reactions,[9e] a series of mono-*N*-protected α-amino-*o*-methylhydroxamic acid (MPAHA) ligands were investigated. This effort led to a significant improvement with Boc-L-Leu-NHOMe (**L8**) giving an excellent *s*-factor of 73 (entry 8). Replacing Boc with Cbz and Fmoc only gave inferior results (entries 9 and 10, *s* = 47 and 29, respectively). Further tuning the side chains revealed that Boc-L-Phe-NHOMe (**L14**) gave the best *s*-factor of 77 (entries 11−14). Notably, increasing the ligand loading to 20 mol% gave a similar *s*-factor albeit a decreased conversion (entry 15). Most likely, excessive ligand can lead to the formation of Pd(II) complexes coordinated to two MPAHA ligands which will prevent substrate binding. When the temperature was raised to 55 °C, the *s*-factor was slightly decreased to 68 (entry 16). The absolute configuration of **2aa** was determined to be *R* by X-ray crystallographic analysis (Figure 2), thus providing important information for the establishment of a stereomodel in the kinetic resolution process through C−H activation.

With the optimized reaction conditions in hand, we next investigated the scope of the arylboronic acid coupling partner. To our delight, the enantioselective C−H cross-coupling of racemic benzylamine **1a** with a variety of arylboronic acid pinacol esters proceeded smoothly to provide the desired products with excellent *s*-factor values (Table 2). The reaction with *para*-methoxycarbonylphenylboronic acid pinacol ester provided a 47% yield of the arylated product **2aa** in 91% ee, accompanied by a 46% yield of recovered **1a** in 96% ee (*s* = 77). Fluoro- and trifluoromethyl-substituted phenylboronic acid pinacol esters were also suitable coupling partners, affording the corresponding products with *s*-factor values ranging from 96 to 107 (**2ab**−**2ad**). Functional groups such as aryl chlorides (**2ae**, *s* = 100), nitriles (**2af**, *s* = 67), and ketones (**2ag**, *s* = 73) were well tolerated. Coupling partners containing electron-donating methyl and methoxy groups also performed well and gave the cross-coupled products in excellent selectivity factors (**2ah** and **2ai**, *s* = 103 and 98, respectively). In general, the structures of the organoboronic acids do not have a significant impact on the *s*-factor, which is consistent with the enantioselectivity being determined by the C−H activation step.

We then examined the amine scope of the kinetic resolution process. We were pleased to find that our protocol was tolerant of a variety of substituents on the phenyl ring, giving the corresponding products in high enantioselectivities (Table 3). Both electron-withdrawing (**2b**−**2f**) and electron-donating

Table 1. Reaction Optimization[a]



entry	L	ligand	conv (%)[b]	ee (%)[c] 1a	ee (%)[c] 2aa	s[d]
1	L1	Boc-L-Ala-OH	62	93	58	12
2	L2	Boc-L-Leu-OH	45	51	62	7
3	L3	Boc-L-Val-OH	73	96	36	7
4	L4	Boc-L-Tle-OH	66	96	50	10
5	L5	Boc-L-Phe-OH	60	97	65	19
6	L6	Ac-L-Phe-OH	43	74	44	5
7	L7	Fmoc-L-Phe-OH	24	80	74	17
8[e]	L8	Boc-L-Leu-NHOMe	51	95	90	73
9[e]	L9	Cbz-L-Leu-NHOMe	37	55	93	47
10[e]	L10	Fmoc-L-Leu-NHOMe	39	57	88	29
11[e]	L11	Boc-L-Ala-NHOMe	30	41	93	40
12[e]	L12	Boc-L-Val-NHOMe	37	55	93	45
13[e]	L13	Boc-L-Tle-NHOMe	51	89	86	39
14[e]	L14	**Boc-L-Phe-NHOMe**	**51**	**96**	**91**	**77**
15[f]	L14	Boc-L-Phe-NHOMe	41	66	95	77
16[e,g]	L14	Boc-L-Phe-NHOMe	54	99	85	68

[a]Reaction conditions: *rac*-**1a** (0.1 mmol), 4-(CO_2Me)Ph-BPin (1.0 equiv), $Pd(OAc)_2$ (10 mol%), ligand (30 mol%), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (3.0 equiv), BQ (0.5 equiv), H_2O (5.0 equiv), DMSO (0.4 equiv), *t*-AmylOH (0.5 mL), N_2, 50 °C, 15 h. [b]Calculated conversion, $C = ee_{SM}/(ee_{SM} + ee_{PR})$. [c]Determined by chiral HPLC analysis. [d]Selectivity $(s) = \ln[(1 - C)(1 - ee_{SM})]/\ln[(1 - C)(1 + ee_{SM})]$. [e]Using 15 mol% ligand. [f]Using 20 mol% ligand. [g]Run at 55 °C.

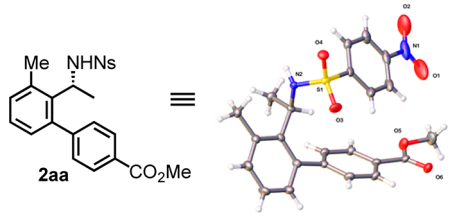


Figure 2. X-ray crystal structure of **2aa**.

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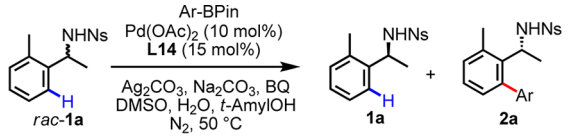
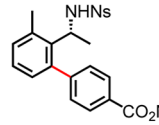
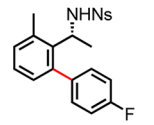
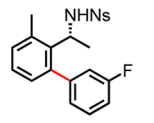
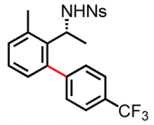
Table 2. Scope of Arylboronic Acid Coupling Partners[a,b]

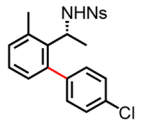


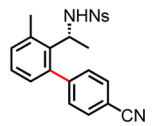

2aa: 47% yield, 91% ee
1a: 46% yield, 96% ee
C = 51%, *s* = 77

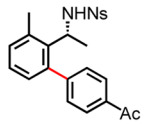

2ab: 46% yield, 92% ee
1a: 44% yield, 97% ee
C = 51%, *s* = 103

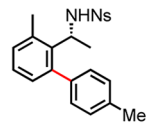

2ac: 46% yield, 92% ee
1a: 45% yield, 97% ee
C = 51%, *s* = 107

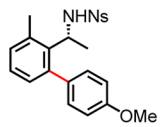

2ad: 47% yield, 91% ee
1a: 44% yield, 98% ee
C = 52%, *s* = 96


2ae: 49% yield, 91% ee
1a: 43% yield, 98% ee
C = 52%, *s* = 100


2af: 41% yield, 93% ee
1a: 50% yield, 76% ee
C = 45%, *s* = 67

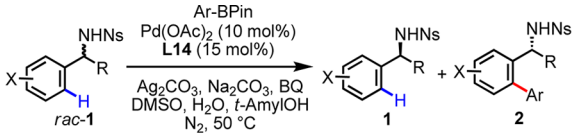

2ag: 42% yield, 94% ee
1a: 51% yield, 77% ee
C = 45%, *s* = 73

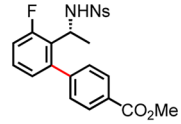

2ah: 46% yield, 89% ee
1a: 43% yield, 99% ee
C = 53%, *s* = 103

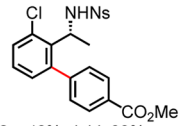

2ai: 51% yield, 89% ee
1a: 40% yield, 99% ee
C = 53%, *s* = 98

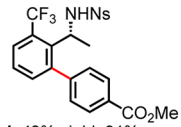
[a]Reaction conditions: *rac*-**1a** (0.2 mmol), Ar-BPin (1.0 equiv), $Pd(OAc)_2$ (10 mol%), **L14** (15 mol%), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (3.0 equiv), BQ (0.5 equiv), H_2O (5.0 equiv), DMSO (0.4 equiv), *t*-AmylOH (0.5 mL), N_2, 50 °C, 15 h. [b]Isolated yield; Calculated conversion, $C = ee_{SM}/(ee_{SM} + ee_{PR})$. Enantiomeric excess (ee) was determined by chiral HPLC analysis; Selectivity (s) = $\ln[(1 - C)(1 - ee_{SM})]/\ln[(1 - C)(1 + ee_{SM})]$.

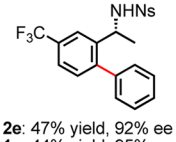
Table 3. Scope of Benzylamine Substrates[a,b]

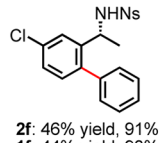


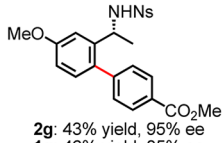

2b: 44% yield, 94% ee
1b: 46% yield, 91% ee
C = 49%, *s* = 109

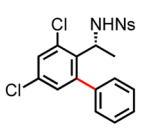

2c: 46% yield, 93% ee
1c: 42% yield, 98% ee
C = 51%, *s* = 135

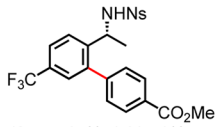

2d: 48% yield, 91% ee
1d: 41% yield, 99% ee
C = 52%, *s* = 100

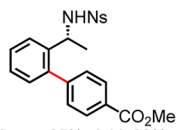

2e: 47% yield, 92% ee
1e: 44% yield, 95% ee
C = 51%, *s* = 92

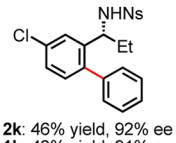

2f: 46% yield, 91% ee
1f: 44% yield, 98% ee
C = 52%, *s* = 99

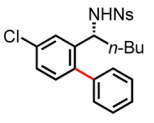

2g: 43% yield, 95% ee
1g: 46% yield, 85% ee
C = 51%, *s* = 102

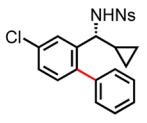

2h: 41% yield, 95% ee
1h: 52% yield, 71% ee
C = 43%, *s* = 75

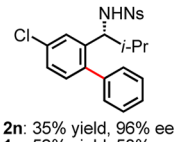

2i$_{mono}$: 27% yield, 52% ee
2i$_{di}$: 11% yield, 99% ee
1i: 48% yield, 85% ee
C[c] = 48%, *s* = 87

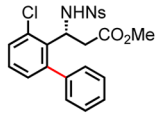

2j$_{mono}$: 25% yield, 22% ee
2j$_{di}$: 17% yield, 99% ee
1j: 49% yield, 78% ee
C[c] =45%, *s* = 72

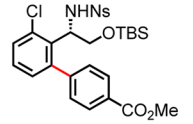

2k: 46% yield, 92% ee
1k: 42% yield, 91% ee
C = 50%, *s* = 72


2l: 47% yield, 92% ee
1l: 43% yield, 99% ee
C = 52%, *s* = 122


2m: 44% yield, 93% ee
1m: 46% yield, 96% ee
C = 51%, *s* = 100


2n: 35% yield, 96% ee
1n: 52% yield, 58% ee
C = 38%, *s* = 93


2o: 42% yield, 87% ee
1o: 45% yield, 75% ee
C = 46%, *s* = 34


2p: 46% yield, 90% ee
1p: 45% yield, 99% ee
C = 52%, *s* = 95

[a]Reaction conditions: *rac*-**1** (0.2 mmol), Ar-BPin (1.0 equiv), $Pd(OAc)_2$ (10 mol%), **L14** (15 mol%), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (3.0 equiv), BQ (0.5 equiv), H_2O (5.0 equiv), DMSO (0.4 equiv), *t*-AmylOH (0.5 mL), N_2, 50 °C, 15 h. [b]Isolated yield; Calculated conversion, $C = ee_{SM}/(ee_{SM} + ee_{PR})$. Enantiomeric excess (ee) was determined by chiral HPLC analysis; Selectivity (s) = $\ln[(1 - C)(1 - ee_{SM})]/\ln[(1 - C)(1 + ee_{SM})]$. [c]Conversion was determined by crude ^1H NMR.

(**2g**) benzylamines were reactive. The chloride-containing substrates were also suitable for this enantioselective cross-coupling (**2c**, **2f**, and **2h**), although the 2,4-dichlorinated substrate gave a slightly decreased conversion of 43% (**2h**, s = 75). While the reaction with *ortho*- and *meta*-substituted substrates provided only the monoarylated products, the reaction of *para*-substituted and unsubstituted substrates gave a mixture of mono- and diarylated products (**2i** and **2j**, s = 87 and 72, respectively). A series of different alkyl-substituted amines were also subjected to the reaction conditions. Primary alkyl-substituted substrates afforded excellent *s*-factor values (**2k** and **2l**, s = 72 and 122, respectively). The secondary cyclopropyl-substituted amine **1m** proceeded smoothly with an *s*-factor of 100, but bulkier isopropyl-substituted substrate **1n** led to a decrease in conversion (C = 38%, s = 93). The results obtained with substrates **1k**–**n** containing the same *meta*-chloro phenyl group suggests that the size of alkyl chain has a moderate effect on enantioselectivity with the longest chain butyl group affording the highest *s*-factor. This trend is consistent with the stereomodel proposed for kinetic resolution via C–H olefination enabled by an analogous chiral MPAA ligand.[15] The reaction with racemic β-amino acid **1o** also produced the arylated product in high enantioselectivity, albeit with a reduced *s*-factor of 34. Importantly, this enantioselective C–H activation method can also be applied to prepare chiral β-amino alcohols (**2p**, s = 95), an important class of molecules with broad applications as chiral synthons and chiral auxiliaries in asymmetric synthesis.[19] Comparison between substrates **1o** and **1p** containing the same *ortho*-chloro phenyl group indicates that a sterically hindered alkyl chain gives better enantioselectivity.

To demonstrate the synthetic utility of this enantioselective C–H activation reaction, a gram-scale experiment was carried out using racemic **1f** under the optimal reaction conditions. The cross-coupled product **2f** was obtained in 45% yield with 94% ee, and the recovered starting material **1f** was isolated in 42% yield with 91% ee (Scheme 2a). Importantly, the nosyl protecting group was readily removed under mild conditions (Scheme 2b). Moreover, the arylated product **2f** was further transformed into 6-substituted 5,6-dihydrophenanthridine **4** without loss of optical activity by an NIS-mediated ring closure (Scheme 2c). It should be noted that 6-substituted 5,6-dihydrophenanthridines are important structural units in natural products and biologically active molecules.[20]

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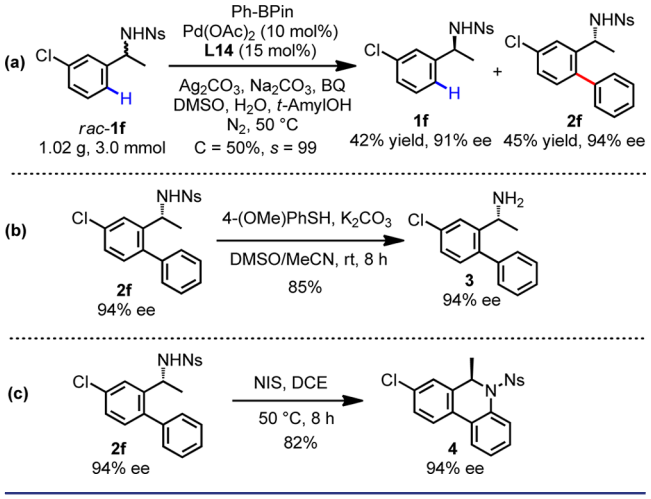
Scheme 2. Synthetic Applications



3. CONCLUSION

In conclusion, we have developed an unprecedented kinetic resolution process for nosyl-protected benzylamines via Pd(II)-catalyzed enantioselective C−H cross-coupling. This approach allows for rapid preparation of both chiral benzylamines and *ortho*-arylated benzylamines in high enantioselectivities. The use of Ns-protected amines as substrates is an important practical advantage for synthetic applications. In addition, NIS-mediated ring closure of enantioenriched *ortho*-arylated benzylamines provides a convenient access to the highly valuable chiral 6-substituted 5,6-dihydrophenanthridines. Currently, the incompatibility of this reaction with heterocyclic substrates is a limitation that remains to be overcome.

4. EXPERIMENTAL SECTION

General Procedure for Kinetic Resolution of Benzylamines via Palladium(II)-Catalyzed C−H Cross-Coupling. Substrate *rac*-**1** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), **L14** (0.15 equiv), Ar-BPin (1.0 equiv), Ag_2CO_3 (2.0 equiv), Na_2CO_3 (3.0 equiv), BQ (0.5 equiv), DMSO (0.4 equiv), H_2O (5.0 equiv), and *t*-AmylOH (1.0 mL) were added into a 10 mL sealed tube. The reaction vessel was evacuated and backfilled with nitrogen (×3). The reaction mixture was heated to 50 °C for 15 h under vigorous stirring. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite, eluting with EtOAc. The filtrate was concentrated under vacuum, and the resulting residue was purified by preparative TLC using EtOAc/hexanes as the eluent to produce the desired product. The ee value was determined on a Hitachi LaChrom HPLC system using commercially available chiral columns.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b04660.

Detailed experimental procedures, characterization of new compounds (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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