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Palladium-Catalyzed Asymmetric Benzylic Substitution of Secondary Benzyl Carbonates with Nitrogen and Oxygen Nucleophiles

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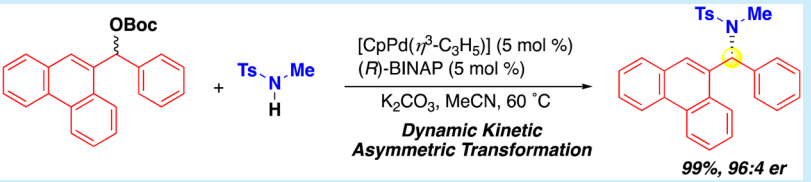
Supporting Information

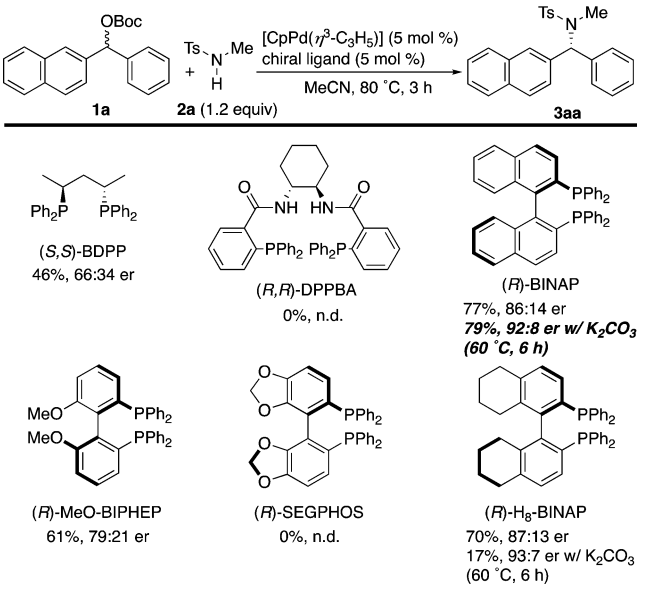


ABSTRACT: A Pd/(*R*)-BINAP-catalyzed asymmetric benzylic substitution of secondary benzyl carbonates with amides and amines proceeds to form the corresponding optically active benzylamines in good yields with a high enantiomeric ratio. The reaction occurs in a dynamic kinetic asymmetric transformation (DYKAT) manner. Additionally, the asymmetric Pd catalysis can also be applicable to phenol nucleophiles, thus delivering chiral ethers with acceptable yields and enantioselectivity.

Transition-metal-catalyzed enantioselective transformation is one of the most powerful and indispensable tools for the preparation of chiral molecules in modern organic chemistry. Particularly, the Pd-catalyzed asymmetric allylic substitution via π-allylpalladium intermediates, known as a Tsuji–Trost reaction, has greatly progressed over the past four decades, and is applied for the synthesis of various chiral molecules including natural products, biologically active compounds, and pharmaceutical agents.[1] On the other hand, its benzylic analogue, namely, asymmetric benzylic substitution via isoelectronic π-benzylpalladium[2] species has been much less explored.[3] Although Trost developed the asymmetric Pd catalysis with prochiral nucleophiles and achiral primary benzylic electrophiles,[4] catalytic control of point chirality at the benzylic position of secondary benzyl electrophiles still remains a challenge.[5] Fiaud, Legros, and co-workers reported the seminal work on the Pd-catalyzed asymmetric substitution of racemic 1-(2-naphthyl)ethyl acetate with malonate anions, but the product yield and enantioselectivity were poor to moderate, probably because of a partial kinetic resolution of the starting secondary benzylic acetate.[6] In this context, we recently developed the first successful example of highly enantioselective Pd-catalyzed benzylic alkylation of secondary benzyl carbonates with active methylene compounds.[7] The reaction occurred in a dynamic kinetic asymmetric transformation (DYKAT)[8] manner to deliver the corresponding alkylated products in good yields and high enantioselectivity. During our continuous interest in this chemistry, we now expand the scope of coupling partner to heteroatom nucleophiles. Herein we report a Pd/(*R*)-BINAP catalyst system for enantioselective benzylic substitution of racemic secondary benzyl carbonates with nitrogen and oxygen nucleophiles to form optically active benzylamines and ethers in good enantiomeric ratios (er).

We selected the benzylic amination of racemic *tert*-butyl (2-naphthyl)(phenyl)methyl carbonate (**1a**; 0.25 mmol) with *N*-methyltosylamide (**2a**; 0.30 mmol) in MeCN at 80 °C as the model reaction and commenced optimization studies by screening chiral bisphosphine ligands in the presence of the [CpPd(η^3-C_3H_5)] catalyst (5 mol %; Scheme 1). The reaction with (*S,S*)-BDPP showed moderate enantioselectivity (66:34 er) whereas (*R,R*)-DPPBA, which was a promising chiral ligand

Scheme 1. Optimization Studies for Pd-Catalyzed Asymmetric Benzylic Amination of *tert*-Butyl (2-Naphthyl)(phenyl)methyl Carbonate (1a) with *N*-Methyltosylamide (2a)



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in related benzylic substitutions,[4] gave no desired product. Similar to our previous work,[7] better chiral induction (79:21–87:13 er) was observed when chiral biarylbisphosphines such as (*R*)-BINAP, (*R*)-H_8-BINAP, and (*R*)-MeO-BIPHEP were employed. Exceptionally, (*R*)-SEGPHOS did not catalyze the reaction at all. Additional fine-tuning with (*R*)-BINAP revealed that addition of K_2CO_3 and a lower reaction temperature (60 °C) increased the enantiomeric ratio, and **3aa** was obtained in 79% yield with 92:8 er.[9] The absolute configuration was assigned to be *R* by the X-ray crystallographic analysis.[10] Additionally notable is that the asymmetric reaction was uniquely catalyzed by [CpPd(η^3-C_3H_5)]; other Pd salts such as $Pd(OAc)_2$ were totally ineffective.

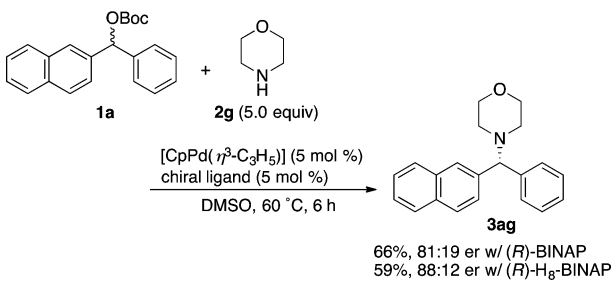
With good conditions in hand, we initially performed the Pd-catalyzed asymmetric benzylic amination of **1a** with several sulfonamides **2** (Table 1). In addition to **2a** (entry 1), electron-donating methoxy and electron-withdrawing chloro substituents at the para position as well as a bulky mesityl group were tolerated, and the corresponding chiral benzylamines **3ab**–**3ad** in 47–71% yields with 90:10–91:9 er (entries 2–4). The heteroaromatic thienylsulfonamide **2e** also underwent the reaction in DMSO to provide **3ae** in 79% yield with 93:7 er (entry 5). Additionally, aliphatic sulfonamide **2f** was a viable substrate, and the desired substitution product **3af** was formed with comparable enantioselectivity (entry 6). Moreover, morpholine (**2g**) also worked well as the nitrogen nucleophile (Scheme 2); in this case K_2CO_3 was not necessary, and (*R*)-H_8-BINAP gave better enantioselectivity. Unfortunately, attempts to apply phthalimide and primary tosylamides remained unsuccessful to the extent we tested (data not shown).

Table 1. Pd-Catalyzed Asymmetric Benzylic Amination of *tert*-Butyl (2-Naphthyl)(phenyl)methyl Carbonate (1a) with Several Sulfonamides 2[a]

entry	R (2)	3, yield (%),[b] er[c]
1	4-MeC_6H_4 (**2a**)	**3aa**, 79, 92:8
2	4-$MeOC_6H_4$ (**2b**)	**3ab**, 47, 90:10
3	4-ClC_6H_4 (**2c**)	**3ac**, 56, 90:10
4[d]	2,4,6-$Me_3C_6H_2$ (**2d**)	**3ad**, 71, 91:9
5[e]	2-thienyl (**2e**)	**3ae**, 79, 93:7
6	Me (**2f**)	**3af**, 51, 90:10

[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.30 mmol), [CpPd(η^3-C_3H_5)] (0.013 mmol), (*R*)-BINAP (0.013 mmol), K_2CO_3 (0.50 mmol), MeCN (3.0 mL), N_2, 60 °C, 6 h. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]At 80 °C for 3 h. [e]In DMSO.

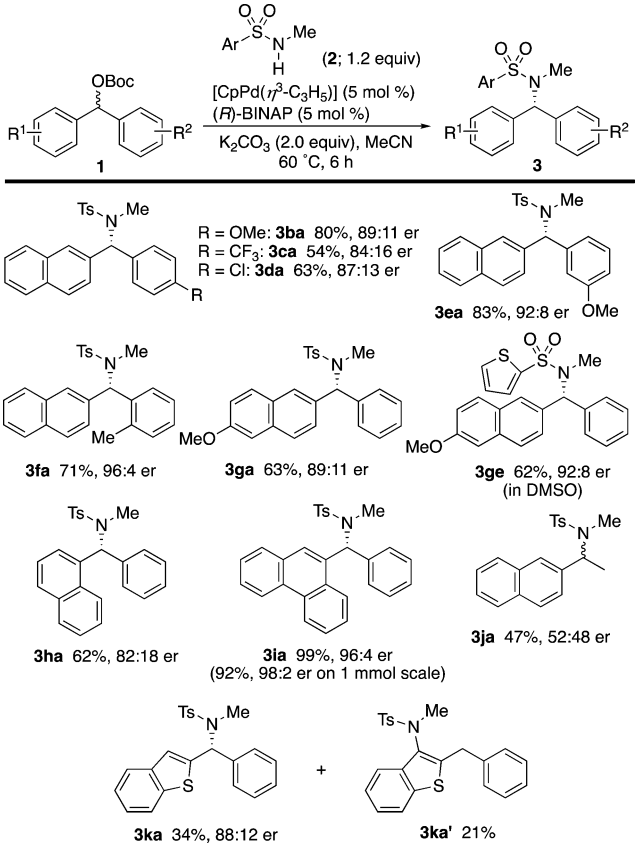
Scheme 2. Pd-Catalyzed Asymmetric Benzylic Amination of 1a with Morpholine (2g)



We next investigated the scope of secondary benzyl carbonates **1** with tosylamide **2a** (Scheme 3). The asymmetric Pd catalysis was compatible with electronically diverse functions, including methoxy, trifluoromethyl, and chloro groups, at the para position on the benzene ring of the parent **1**, and the corresponding amines **3ba**, **3ca**, and **3da** were obtained with synthetically useful levels of yield (54–80%) and enantioselectivity (84:16–89:11 er). The substituents at the ortho and meta positions somewhat positively impacted the enantiomeric ratio to furnish **3ea** and **3fa** with 92:8 and 96:4 er, respectively. The replacement of the 2-naphthyl group with 6-methoxy-2-naphthyl and 1-naphthyl substituents was also possible (**3ga**, **3ge**, and **3ha**); in the former case the reaction with thienylsulfonamide **2e** conducted in DMSO uniquely gave better enantioselectivity (**3ga**; 89:11 er vs **3ge**; 92:8 er). The higher fused phenanthrene-substituted carbonate underwent the reaction smoothly to form **3ia** in 99% yield with 96:4 er. The reaction could also be conducted on a 1.0 mmol scale without any difficulties (92%, 98:2 er). On the other hand, the (2-naphthyl)ethyl carbonate formed the nearly racemic **3ja** (52:48 er), indicating the current limitation of the Pd/(*R*)-BINAP catalyst system.[11] It should be noted that the (benzothienyl)methyl carbonate provided a mixture of usual benzylic amination product **3ka** (34%, 88:12 er) and rearranged 3-aminated benzothiophene **3ka′** (21%), thus suggesting the intermediacy of π-benzylpalladium species (vide infra).[12]

The plausible mechanism of Pd-catalyzed asymmetric benzylic amination is basically the same as that of our previous asymmetric alkylation with active methylene compounds

Scheme 3. Pd-Catalyzed Asymmetric Benzylic Amination of Various Secondary Benzyl Carbonates 1 with Sulfonamides 2



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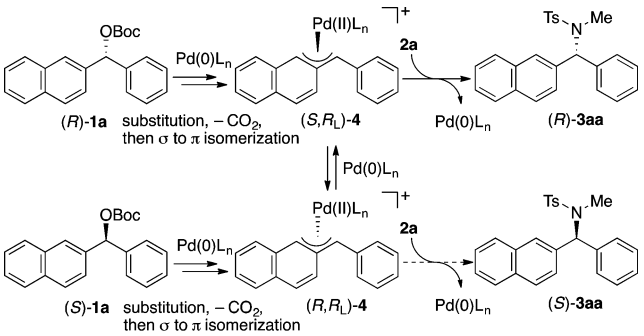
(Scheme 4).[7] Initial S_N2-type substitution of the secondary benzyl carbonates (*R*)-**1a** and (*S*)-**1a** with [Pd(0)L_n] [L = (*R*)-BINAP] is followed by decarboxylation and σ-to-π isomerization[13] to form the corresponding diastereomeric π-benzyl intermediates (S,R_L)-**4** and (R,R_L)-**4**, respectively (R_L means the absolute configuration of the ligand L). They then undergo the interconversion probably by the attack of additional [Pd(0)L_n] species.[14,15] During this process, the stereochemical information on the starting carbonate at the benzylic position is lost and DYKAT thus is accessible. The asymmetric induction stems from a selective backside attack of tosylamide **2a** with one (S,R_L)-**4** isomer to produce the observed major enantiomer (*R*)-**3aa**.

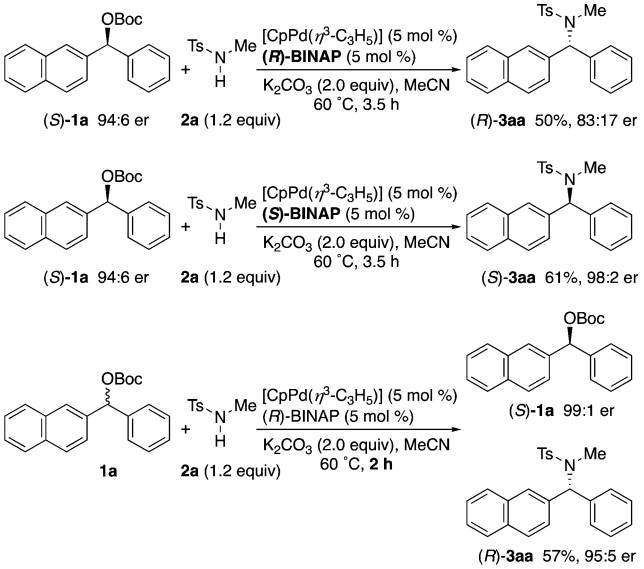
Scheme 4. Proposed Mechanism for Pd-Catalyzed Asymmetric Benzylic Amination of 1a with 2a[a]



[a]L = (*R*)-BINAP. The descriptor R_L means the absolute configuration of the ligand L.

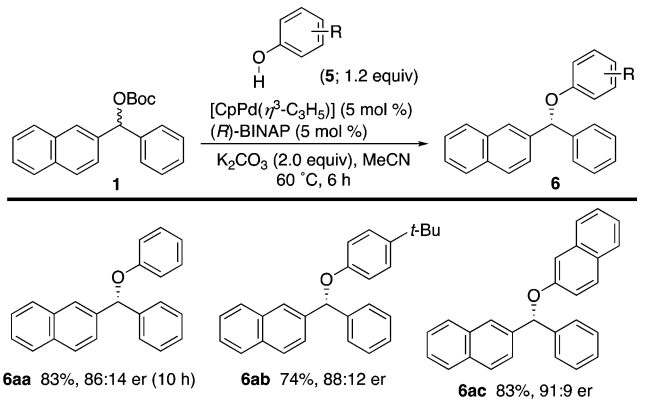
To gain more insight into the mechanism, some experiments with enantioenriched (*S*)-**1a** (94:6 er) were carried out (Scheme 5). Different from our previous benzylic alkylation reaction,[7] small but significant match/mismatch phenomena about the enantioselectivity were observed: the reaction with Pd/(*R*)-BINAP gave (*R*)-**3aa** with 83:17 er whereas (*S*)-**3aa** was formed in higher enantiomeric purity (98:2 er) in the presence of Pd/(*S*)-BINAP. These outcomes indicate that the interconversion between (S,R_L)-**4** and (R,R_L)-**4**, which is racemization at the benzylic position, is not much more rapid than amination, and a partial enantiospecific pathway (probably a net retention process via double inversion) is competitive. Actually, at an early stage of the enantioselective reaction (2 h), the enantiomeric ratio of **3aa** (95:5 er) was higher than that under the standard conditions (6 h, 92:8 er; Table 1, entry 1), and the recovered starting carbonate is the nearly enantiomerically pure (*S*)-enantiomer (99:1 er). Thus, the present asymmetric amination catalysis generally showed somewhat lower enantioselectivity than the previous asymmetric alkylation.[7]

Scheme 5



We finally applied the enantioselective Pd catalyst to the reaction with oxygen nucleophiles. While still preliminary, the asymmetric etherification with several phenols was possible under identical conditions, affording optically active benzyl ethers **6aa**–**6ac** in 74–83% yield with 86:14–91:9 er (Scheme 6).

Scheme 6. Pd-Catalyzed Asymmetric Benzylic Etherification of *tert*-Butyl (2-Naphthyl)(phenyl)methyl Carbonate (1a) with Phenols 5



In conclusion, we have developed a Pd-catalyzed enantioselective benzylic substitution of secondary benzyl carbonates with amides and phenols. The reaction proceeds via a DYKAT manner to form the corresponding optically active benzylamines and ethers from racemic starting materials. Although the enantioselectivity still requires improvement, this is the first successful application of heteroatom nucleophiles in the Pd-catalyzed DYKAT process with secondary benzylic electrophiles, to the best of our knowledge. Further development of related DYKAT and attempts to overcome the "naphthalene problem"[11] are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01022.

^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR spectra, chiral HPLC charts for products, and ORTEP drawing (PDF)
Crystallographic data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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(9) See the Supporting Information for more detailed optimization studies.

(10) Crystallographic data for the structure has been deposited with the Cambridge Crystallographic Data Centre (CCDC 1536820). See the Supporting Information for details. The absolute configuration of other products was tentatively assigned by analogy.

(11) Other unsuccessful substrates included (phenyl)(2-furyl)methyl, (phenyl)(4-trifluoromethylphenyl)methyl, and (4-biphenylyl)-(phenyl)methyl carbonates, which apparently suggest the "naphthalene problem". The better reactivity of naphthalene and related higher fused aromatics can be associated with their lower aromaticity. Similar trends are often observed in metal-catalyzed cross-coupling reactions with C−O electrophiles. See: (a) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717. (b) Correa, A.; Léon, T.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 1062. (c) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. And refs 2a, b, and 3d−g.

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(15) We performed the reaction in the presence of 2.5, 5, and 7.5 mol % of Pd catalyst and checked the enantiomeric ratio (er). However, the er was less dependent on the concentration of Pd. Thus, further studies are essential for clarification of the detailed racemization mechanism.

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