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To be cited as: *Chem. Eur. J.* 10.1002/chem.201800744

Link to VoR: http://dx.doi.org/10.1002/chem.201800744

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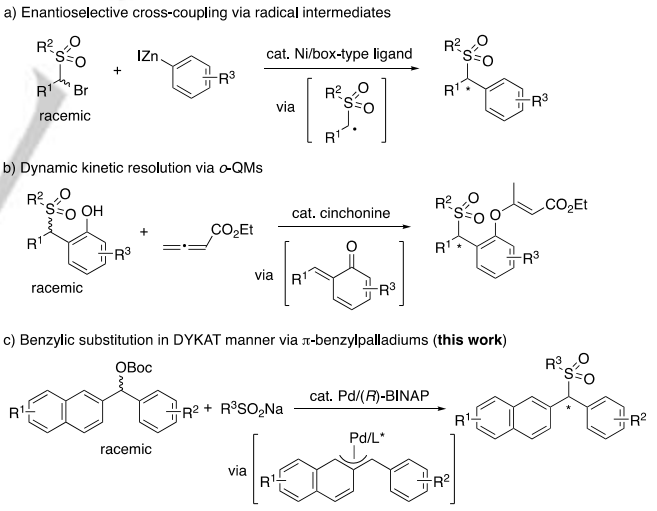
Asymmetric Synthesis of Diarylmethyl Sulfones by Palladium-Catalyzed Enantioselective Benzylic Substitution: A Remarkable Effect of Water

Atifah Najib,[a] Koji Hirano,*[a] and Masahiro Miura*[a]

Dedication ((optional))

Abstract: A Pd/(*R*)-BINAP-catalyzed enantioselective benzylic sulfonation of diarylmethyl carbonates with sodium sulfinates proceeds to deliver the corresponding chiral diarylmethyl sulfones in good yields with high enantioselectivity. The reaction occurs in a dynamic kinetic asymmetric transformation (DYKAT) manner and thus provides convergent access to optically active benzylic sulfones from racemic secondary benzylic carbonates. Additionally, the addition of H_2O is found to be critical for high enantioselectivity.

The sulfonyl group is among representative electron-withdrawing groups and often used as a building block in synthetic organic chemistry.[1] Additionally, it is frequently occurring in biologically active compounds and pharmaceutical agents.[2] Thus, synthetic chemists have developed numerous strategies for preparation of various sulfonyl compounds, including oxidation of sulfides/sulfoxides and classical nucleophilic substitution reactions.[3] However, catalytic synthesis of enantioenriched sulfones has been less developed.[4] Particularly, α-chiral benzylic sulfones still remains challenging targets. In 2016, Yan reported the chiral cation-binding poly ether catalyst for enantioselective elimination of racemic β-sulfonyl ketones. Although the enantioselectivity was excellent, the reaction proceeded in a kinetic resolution manner, thus giving the chiral sulfones in chemical yields theoretically up to 50%.[5] The stereoconvergent approaches to chiral sulfones from racemic starting substrates are more attractive from the viewpoint of atom economy (Scheme 1). Fu developed the nickel/box-type ligand-catalyzed stereoconvergent cross-coupling of α-bromosulfones with arylzinc reagents via radical intermediates to form the corresponding α-chiral benzylic sulfones with yields and enantiomeric ratios (e.r.) up to >99% and 99:1, respectively (Scheme 1a).[6] Additionally, Liu and Li succeeded in a dynamic kinetic resolution of 2-sulfonylalkyl phenols by using cinchonine-derived nucleophilic catalysts and allenoate trapping reagents (Scheme 1b).[7] In this case, the stereoconvergency was induced through the formation of *ortho*-quinone methides (*o*-QMs). Completely different enantioselective conjugate addition of sulfinates across α,β-unsaturated carbonyl compounds was also possible in the presence of chiral NHC/thiourea/amine complex multicatalysts,[8] but there still needs a large demand for further developments of asymmetric benzylic sulfone synthesis. On the other hand, our group recently developed the palladium-catalyzed asymmetric benzylic substitution reactions of secondary benzyl carbonates with carbon, nitrogen, and oxygen nucleophiles.[9] The greatest feature of aforementioned catalysis is stereoconvergency: through the epimerization of two diastereomeric π-benzylpalladium[10] intermediates the racemic secondary benzylic electrophiles are converted into the substitution products in a dynamic kinetic asymmetric transformation (DYKAT)[11] manner, and thus both yield and e.r. can be theoretically reached to 100% and >99:1. Given our previous success and reported asymmetric sulfonation of isoelectronic π-allylpalladiums,[4a,b] we have now found a Pd/(*R*)-BINAP-catalyzed enantioselective benzylic substitution of racemic diarylmethyl carbonates with sodium sulfonates (Scheme 1c).[12] The present asymmetric catalysis occurs again in DYKAT manner and thus provides a new repertoire of stereoconvergent synthesis of chiral benzylic sulfones.



Scheme 1. Stereoconvergent approaches to α-chiral benzylic sulfones.

Our optimization studies began with *tert*-butyl diarylmethyl carbonate **1a** and sodium *para*-toluenesulfinate hydrate (**2a**•xH_2O) by screening chiral bisphosphine ligands, in conjunction with a [{PdCl(η^3-C_3H_5)}$_2$] catalyst and DMSO solvent, at 60 ˚C (Table 1). Initial investigation of common BINAP-type chiral biarylbisphosphine ligands (entries 1–5) revealed that the parent (*R*)-BINAP was the most promising from the viewpoint of enantioselectivity: the desired chiral benzylic sulfone **3aa** was obtained in 82% with 78:22 e.r. (entry 1). Although BINAP analogues, H_8-BINAP, SEGPHOS, MeO-BIPHEP, and DIFLUOROPHOS, also promoted the reaction with good

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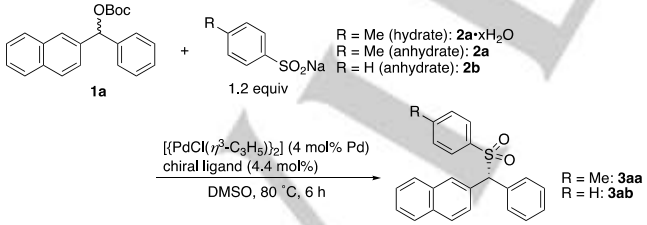
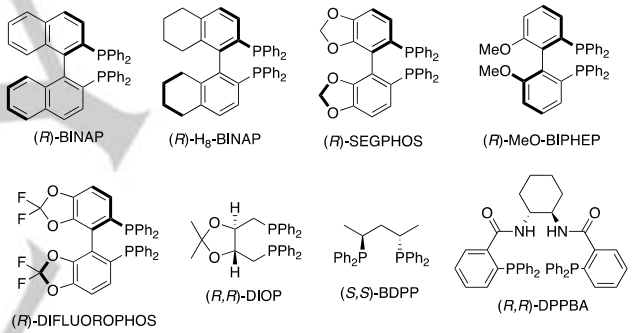
efficiency, but the enantioselectivity was somewhat lower (76–93%, 51:49–74:26 e.r.; entries 2–5). The substitution product **3aa** was formed also in the presence of (*R,R*)-DIOP that bears a similar large bite angle to BINAP, albeit with 67:33 enantioselectivity (entry 6). The (*S,S*)-BDPP ligand, which was employed in seminal work on the asymmetric benzylic substitution reaction of secondary benzyl carbonates by Fiaud and Legros,[13] showed a result comparable to that of (*R*)-BINAP (94%, 79:21 e.r.; entry 7). On the other hand, no reaction occurred with (*R,R*)-DPPBA (entry 8), which was optimal in the asymmetric benzylic substitution of primary benzylic electrophiles with prochiral nucleophiles.[14] We next tested the reaction with anhydrous sulfinate **2a**. However, surprisingly, the enantiomeric ratio dramatically decreased to 56:44 e.r. (entry 9). On the other hand, the addition of H_2O recovered the enantioselectivity (entry 10). Thus, we added other proton sources including MeOH, *t*BuOH, *t*AmOH, AcOH, and HFIP, but almost racemic **3aa** was formed in any cases (see the Supporting Information for details). Thus, such a positive effect on enantioselectivity is unique to H_2O as far as we examined. A similar trend was observed in another sulfinate: anhydrous sodium benzenesulfinate (**2b**) provided the completely racemate of **3ab** (entry 11) while the enantiomeric ratio increased to 89:11 e.r. in the presence of H_2O (entry 12). With benzenesulfinate **2b**, (*R*)-BINAP showed a much better selectivity than (*S,S*)-BDPP (entry 12 vs 13). Finally, the reaction conducted at 60 ˚C further improved the enantioselectivity, and we isolated **3ab** in 98% yield with 91:9 enantiomeric ratio (entry 14). Additional observations are to be noted: no back ground reaction occurred in the absence of any palladium salts and ligands (entry 15); some other palladium sources and polar solvents also work well but a combination of [{PdCl(η^3-C_3H_5)}$_2$] and DMSO was optimal in view of efficiency and selectivity; more bulky substituents on phosphorus in ligands were inferior to the parent Ph group; the use of OPiv leaving group instead of OBoc was detrimental to the enantioselectivity (see the Supporting information for more detailed optimization studies).

Table 1. Optimization studies for palladium-catalyzed enantioselective benzylic substitution of *tert*-butyl diarylmethyl carbonate **1a** with sodium sulfinates **2**.[a]



Entry	**2**	Chiral ligand	**3**, Yield [%][b], e.r.[c]
1	**2a**•xH_2O	(*R*)-BINAP	**3aa**, 82, 79:21
2	**2a**•xH_2O	(*R*)-H_8-BINAP	**3aa**, 76, 51:49
3	**2a**•xH_2O	(*R*)-SEGPHOS	**3aa**, 93, 63:37
4	**2a**•xH_2O	(*R*)-MeO-BIPHEP	**3aa**, 92, 74:26
5	**2a**•xH_2O	(*R*)-DIFLUOROPHOS	**3aa**, 91, 74:26
6	**2a**•xH_2O	(*R,R*)-DIOP	**3aa**, 87, 67:33
7	**2a**•xH_2O	(*S,S*)-BDPP	**3aa**, 94, 79:21
8	**2a**•xH_2O	(*R,R*)-DPPBA	**3aa**, 0, n.d.
9	**2a**	(*R*)-BINAP	**3aa**, 79, 56:44
10[d]	**2a**	(*R*)-BINAP	**3aa**, 92, 72:28
11	**2b**	(*R*)-BINAP	**3ab**, 71, 50:50
12[d]	**2b**	(*R*)-BINAP	**3ab**, 86, 89:11
13[d]	**2b**	(*S,S*)-BDPP	**3ab**, 83, 76:24
14[d,e]	**2b**	(*R*)-BINAP	**3ab**, 98, 91:9
15[f]	**2a**•xH_2O	none	**3aa**, 0, n.d.

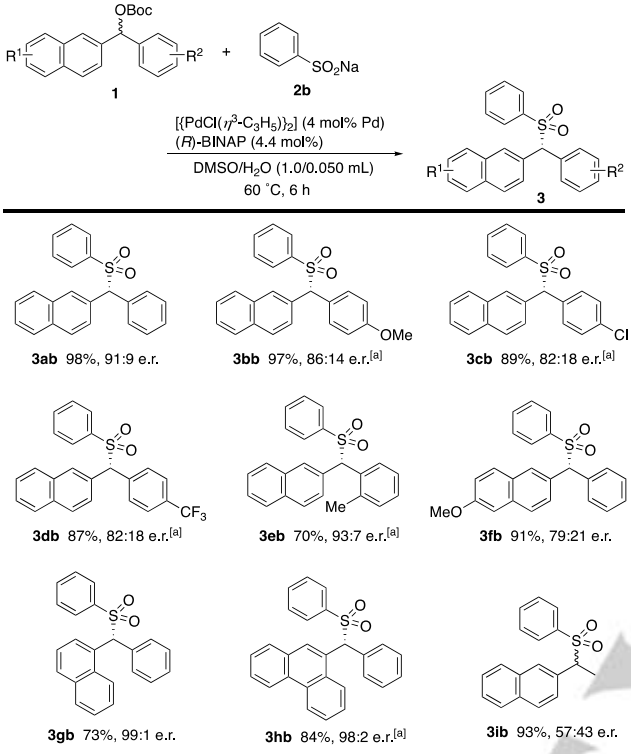
[a] Conditions: **1a** (0.25 mmol), **2** (0.30 mmol), [{PdCl(η^3-C_3H_5)}$_2$] (0.0050 mmol), ligand (0.011 mmol), DMSO (1.0 mL), 80 ˚C, 6 h, N_2. [b] Yields of the isolated product are given. [c] Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral stationary phase. [d] In DMSO/H_2O (1.0/0.050 mL). [e] At 60 ˚C. [f] Without Pd and ligand. Boc = *tert*-butoxycarbonyl. n.d. = not determined.



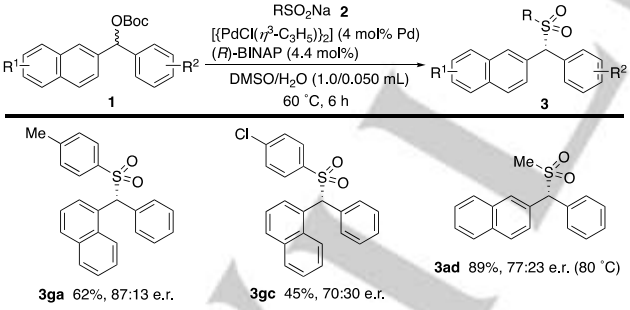
With the conditions in entry 14 of Table 1, we performed the asymmetric benzylic sulfonation of several secondary benzylic carbonates **1** with **2b**. The representative products are illustrated in Scheme 2. In addition to **3ab**, the methoxy-, chloro-, and trifluoromethyl-substituted chiral benzylic sulfones **3bb**–**3db** were obtained in good yields with 82:18–86:14 e.r. while the reaction should be conducted at 40 ˚C.[15] The asymmetric catalysis was compatible with the sterically demanding *ortho*-methyl group, giving the desired **3eb** with a good enantiomeric ratio (93:7 e.r.). Although the introduction of methoxy substituent at the 2-naphthalene ring somewhat decreased the enantioselectivity (**3fb**), 1-naphthylmethy carbonate provided the substitution product **3gb** with excellent enantioselectivity (99:1 e.r.). The higher fused phenanthrene derivative could also be employed, and the corresponding sulfone **3hb** was obtained with a high enantiomeric ratio (98:2 e.r.). On the other hand, similar in our previous work,[9] 1-(2-naphthyl)ethyl carbonate gave nearly racemate (**3ib**).[16] The absolute configuration of **3gb** was determined to be *R* by single crystallographic X-ray analysis, and others are tentatively assigned by analogy.[17]

Several sodium sulfinates **2** were also tested (Scheme 3). The *para*-toluenesulfinate (**2a**) could be coupled with **1g** to form the chiral benzylic sulfone **3ga** with a good enantiomeric ratio

(87:13 e.r.). On the other hand, electron-withdrawing chloro-substituted sulfinate **2c** and aliphatic methanesulfinate **2d** were also reactive, but somewhat lower enantioselectivity was observed (**3gc** and **3ad**).

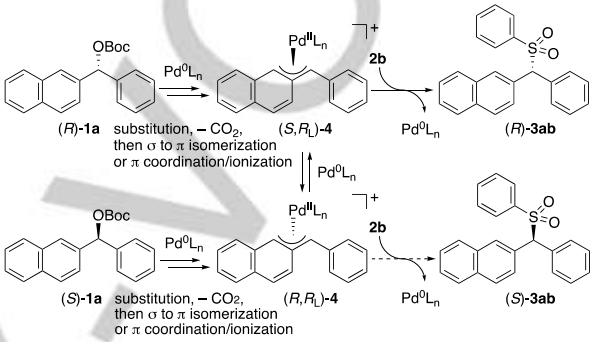


Scheme 2. Palladium-catalyzed enantioselective benzylic substitution of *tert*-butyl diarylmethyl carbonate **1** with sodium benzenesulfinate **2b**. Conditions: **1** (0.25 mmol), **2b** (0.30 mmol), [{PdCl(η^3-C_3H_5)}$_2$] (0.0050 mmol), (*R*)-BINAP (0.011 mmol), DMSO/H_2O (1.0/0.050 mL), 60 ˚C, 6 h, N_2. Yields of the isolated product are given. Enantiomeric ratio (e.r.) was determined by HPLC analysis on a chiral stationary phase. [a] At 40 ˚C.



Scheme 3. Palladium-catalyzed enantioselective benzylic substitution of **1a** and **1g** with several sodium sulfinate **2**. Conditions: see the footnote of Scheme 2.

On the basis of our previous findings and literature information, we are tempted to assume the reaction mechanism of **1a** with **2b** as follows (Scheme 4). Initial S_N2-type substitution of the secondary benzyl carbonates (*R*)-**1a** and (*S*)-**1a** with [Pd^0L_n] [L = (*R*)-BINAP] is followed by decarboxylation and σ-to-π isomerization 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).[18] An alternative mechanism includes initial π-coordination/ionization,[10,14] which can explain better reactivity of naphthalene substrates.[16] They then undergo the epimerization probably by the attack of additional [Pd(0)L_n] species.[19] During this process, the stereochemical information on the starting carbonate at the benzylic position is lost and DYKAT thus is accessible. A related process is proposed in the isoelectronic π-allylpalladium chemistry.[20] The asymmetric induction arises from a selective backside attack of sulfinate **2b** with one (*S,R*$_L$)-**4** isomer to produce the observed major enantiomer (*R*)-**3ab**.



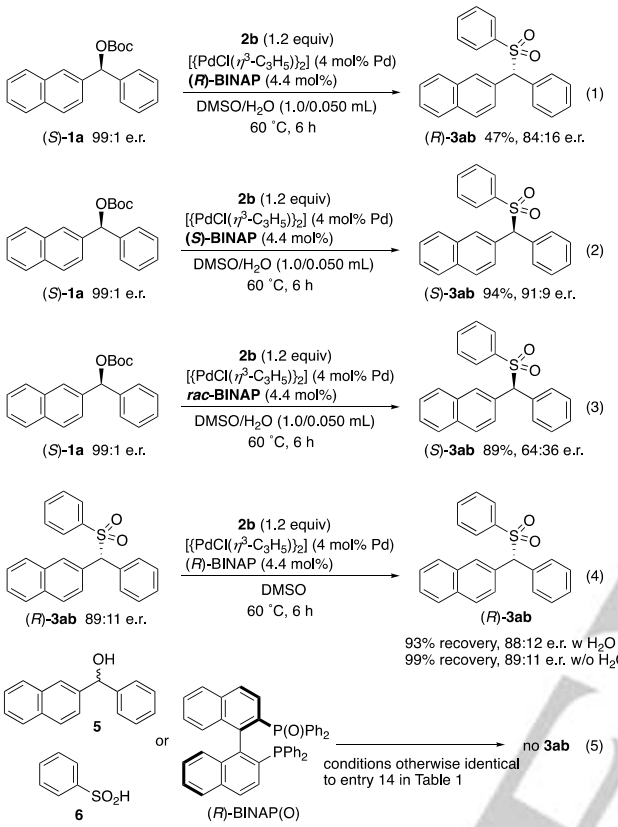
Scheme 4. Plausible mechanism. L = (*R*)-BINAP. The descriptor R_L means the absolute configuration of the ligand L.

To support the proposed mechanism, some additional experiments were implemented. When the enantiomerically pure (*S*)-**1a** was subjected to conditions with (*R*)-BINAP or (*S*)-BINAP-ligated palladium catalyst, the obtained major enantiomer of **3ab** was dependent on the absolute configuration of ligand: (*R*)-BINAP and (*S*)-BINAP mainly provided (*R*)-**3ab** and (*S*)-**3ab**, respectively, thus suggesting operation of DYKAT [Eqs. (1) and (2)]. However, a significant match/mismatch phenomenon was also observed. This is probably because the epimerization between (*S,R*$_L$)-**4** and (*R,R*$_L$)-**4** is not much more rapid than the sulfonation with **2b**, and thus enantiospecific pathway competitively occurs. Actually, the reaction of (*S*)-**1a** with **2b** in the presence of Pd/*rac*-BINAP catalyst resulted in a partial but significant chirality transfer likely through double inversion process (net retention) [Eq. (3)].

Finally, we performed some control studies to get insight into the role of H_2O. One possibility is to suppress the racemization of initially formed enantioenriched product, however, this is unlikely since the independently prepared (*R*)-**3ab** (89:11 e.r.) underwent no racemization in the presence or absence of H_2O [Eq. (4)]. Others are in situ conversions of starting reagents and catalysts to truly active and selective species, but any attempts with the free carbinol **5**, sulfinic acid **6**, or (*R*)-BINAP monoxide (*R*)-BINAP(O)[21] did not furnish the substitution product **3ab** at all [Eq. (5)]. Thus, although details are still unclear, H_2O may play a pivotal role in the sulfonation step to increase the difference of reaction rates between (*S,R*$_L$)-**4** and (*R,R*$_L$)-**4** with **2b** (Scheme 4).

In conclusion, we have developed a palladium-catalyzed asymmetric benzylic substitution of diarylmethyl carbonates with sodium sulfinates in a DYKAT manner to form the α-chiral

benzylic sulfones, which are difficult to prepare by the conventional methods. The present asymmetric catalysis can provide an additional stereoconvergent approach to chiral sulfones from racemic starting substrates. Further elucidation of mechanism, particularly role of H_2O, and development of other types of DYKAT process are now ongoing in our laboratory.



Acknowledgements ((optional))

This work was supported by JSPS KAKENHI Grant Nos. JP 15H05485 (Grant-in-Aid for Young Scientists (A)) to K.H. and JP 17H06092 (Grant-in-Aid for Specially Promoted Research) to M.M. We thank Misaki Terada, Kazutaka Takamatsu, and Dr. Yuji Nishii for their assistance with X-ray analysis.

Keywords: asymmetric catalysis • benzylic substitution • DYKAT • palladium • sulfones

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[15] We confirmed the racemization by subjection of isolated **3db** (64:36 e.r.) to standard conditions (60 °C), giving the recovered **3db** with 52:48 e.r. However, other products hardly underwent the racemization as far as we tested.

[16] As far as we tested, the present catalyst system did not address the "naphthalene problem": diphenylmethyl and (4-biphenylyl)(phenyl)methyl carbonates gave no desired products. Such a reactivity difference can be associated with weaker aromaticity of naphthalene and related fused aromatics, which accelerates the formation of π-benzyl intermediates. Similar trends are often observed in metal-catalyzed cross-coupling reactions with C–O electrophiles. See: a) M. Tobisu, N. Chatani, *Acc. Chem. Res.* **2015**, *48*, 1717; b) S. N. Mendis, J. A. Tunge, *Org. Lett.* **2015**, *17*, 5164.

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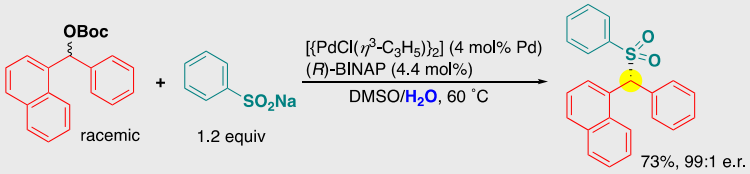

Dynamic road to sulfones: A Pd/(*R*)-BINAP-catalyzed enantioselective benzylic sulfonation of diarylmethyl carbonates with sodium sulfinates proceeds in a dynamic kinetic asymmetric transformation (DYKAT) manner to deliver the corresponding chiral diarylmethyl sulfones in good yields with high enantioselectivity. The key to success is addition of H_2O as well as judicious choice of ancillary chiral ligand.

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