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Direct Substitution of Primary Allylic Amines with Sulfinate Salts

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Supporting Information

ABSTRACT: The NH_2 group in primary allylic amines was substituted directly by sulfinate salts with excellent regio- and stereoselectivities. In the presence of 0.1 mol % $[Pd(allyl)Cl]_2$, 0.4 mol % 1,4-bis(diphenylphosphino)-butane (dppb), and excess boric acid, a range of α-unbranched primary allylic amines were smoothly substituted with sodium sulfinates in an α-selective fashion to give structurally diverse allylic sulfones in good to excellent yields with exclusive E selectivity. Replacing dppb with 1,1′-bi-2-naphthol (BINOL) allowed unsymmetric α-chiral primary allylic amines to be transformed into the corresponding allylic sulfones in good to excellent yields with excellent retention of ee. Importantly, the reaction complements known asymmetric methods in substrate scope via its unique ability to provide α-chiral allylic sulfones with high optical purity starting from unsymmetric allylic electrophiles.

Allylic sulfones serve as versatile building blocks in a number of carbon−carbon bond-forming reactions, such as fragment coupling and Julia olefination, because of activation of the α-carbon by the sulfonyl group.[1] Additionally, certain allylic sulfones display interesting biological activities, such as anticancer agents,[2] antibacterial agents,[3] TSH receptor antagonists,[4] and weed control herbicides.[5] Thus, much attention has been paid to the preparation of allylic sulfones. While the convergent synthesis of allylic sulfones can be realized through the coupling of allylic nucleophiles with sulfonyl electrophiles,[6] a more frequently used approach is the allylic substitution reaction with sulfonyl nucleophiles.[7] Both sulfinate salts and sulfinic acids have been explored as useful sulfonyl nucleophiles, and in the absence of a catalyst or an additive, the allylic substitution reaction can proceed with reactive allylic electrophiles such as allylic halides.[8]

The use of transition metals, particularly palladium (the Tsuji−Trost reaction),[9] as catalysts dramatically extends the scope of allylic electrophiles used for the synthesis of allylic sulfones. Allylic carboxylates,[10] carbonates,[11] alcohols,[12] and nitro compounds[13] undergo substitution reactions with sulfinate salts to give allylic sulfones with significantly different reactivities and regioselectivities. When sulfinic acids are employed as the sulfonyl nucleophiles, the allylic electrophiles are extended to allylic ethers, sulfides, and secondary and tertiary amines.[14] Notably, the use of an allylic alcohol as the electrophilic component is extremely attractive with regard to atom economy. Nevertheless, the reaction requires excess sodium sulfinate and additive (Et_3B or TMSCl) and ≥5 mol % catalyst loading, and it suffers from a narrow substrate scope.[12]

Although a few catalytic asymmetric allylic substitution reactions with sulfinate salts in the presence of chiral transition-metal catalysts have been developed, they are limited to symmetric (α-substituent = γ-substituent) and α-unbranched allylic electrophiles.[15] In addition, the transfer of chirality when α-chiral allylic electrophiles are used in the synthesis of optically active allylic sulfones has never been disclosed. In this context, we sought to explore new methods to prepare α-chiral allylic sulfones with high optical purity starting from unsymmetric allylic electrophiles (α-substituent ≠ γ-substituent). Clearly, controlling both the regio- and stereoselectivity constitutes a formidable challenge in the asymmetric allylic substitution reaction of unsymmetric allylic electrophiles.

In the course of exploring the synthetic utilities of sp^3 C−N bond cleavage,[16] we recently realized a palladium-catalyzed cross-coupling reaction of primary allylic amines with organoborons wherein the NH_2 group serves as an effective leaving group.[17,18] Prompted by this discovery, we envisioned that it would be possible to develop a direct substitution reaction of primary allylic amines with sulfinate salts by using inexpensive boric acid to activate the NH_2 group, facilitating cleavage of the allylic C−N bond by the palladium catalyst. Sulfinate salts were selected as the sulfonyl nucleophiles because they are more stable and accessible than sulfinic acids. α-Chiral primary allylic amines can be easily prepared in large quantities by resolving the corresponding racemic compounds with inexpensive tartaric acid,[19] and we anticipated that the chiral information would be efficiently transferred during the preparation of optically active allylic sulfones.

While no desired reaction was observed between allylic amine **1a** and sulfinate salt **2a** in the presence of 0.2 mol % $Pd(PPh_3)_4$ in dioxane at 100 °C (Table 1, entry 1), the addition of boric acid led to the formation of allylic sulfone **3a** in 35% yield (entry 2). Switching the palladium source to $[Pd(allyl)Cl]_2$ (0.1 mol %) improved the yield to 62% (entry 5). The reaction was significantly affected by the ligand (0.4 mol %), and the use of 1,4-bis(diphenylphosphino)butane (dppb) as the ligand enhanced the yield to 92% (entry 7). Replacing boric acid with a Brønsted acid such as acetic acid or p-toluenesulfonic acid led to a much lower yield (entries 10

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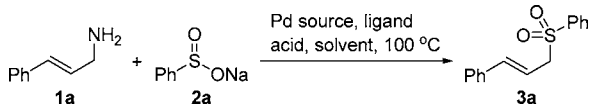
Table 1. Optimization of the Reaction Conditions[a]



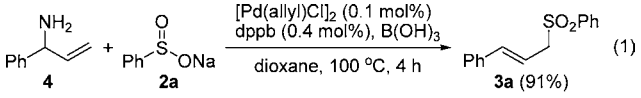
entry	catalyst (mol %)	ligand	acid	solvent	yield (%)[b]
1	$Pd(PPh_3)_4$ (0.2)	none	none	dioxane	0
2	$Pd(PPh_3)_4$ (0.2)	none	$B(OH)_3$	dioxane	35
3	$Pd_2(dba)_3$ (0.1)	none	$B(OH)_3$	dioxane	21
4	$Pd(PPh_3)_2Cl_2$ (0.2)	none	$B(OH)_3$	dioxane	27
5	$[Pd(allyl)Cl]_2$ (0.1)	none	$B(OH)_3$	dioxane	62
6	$[Pd(allyl)Cl]_2$ (0.1)	PPh_3	$B(OH)_3$	dioxane	42
7	$[Pd(allyl)Cl]_2$ (0.1)	dppb	$B(OH)_3$	dioxane	92
8	$[Pd(allyl)Cl]_2$ (0.1)	TMEDA	$B(OH)_3$	dioxane	76
9	$[Pd(allyl)Cl]_2$ (0.1)	BINOL	$B(OH)_3$	dioxane	81
10	$[Pd(allyl)Cl]_2$ (0.1)	dppb	HOAc	dioxane	39
11	$[Pd(allyl)Cl]_2$ (0.1)	dppb	TsOH	dioxane	trace
12	$[Pd(allyl)Cl]_2$ (0.1)	dppb	$B(OH)_3$	diglyme	77
13	$[Pd(allyl)Cl]_2$ (0.1)	dppb	$B(OH)_3$	toluene	9
14	$[Pd(allyl)Cl]_2$ (0.1)	dppb	$B(OH)_3$	DMF	55
15	$[Pd(allyl)Cl]_2$ (0.1)	dppb	$B(OH)_3$	DMSO	50
16	$[Pd(allyl)Cl]_2$ (0.1)	dppb	$B(OH)_3$	water	11
17[c]	$[Pd(allyl)Cl]_2$ (0.1)	dppb	$B(OH)_3$	dioxane	82

[a]Reaction conditions: amine **1a** (0.50 mmol), sulfinate **2a** (0.60 mmol), catalyst (0.1 or 0.2 mol %), ligand (if any, 0.4 mol %), acid (if any, 2.0 mmol), solvent (0.50 mL), 100 °C, 4 h. [b]Isolated yields. [c]The reaction was run at 80 °C.

and 11). In addition, the yield decreased significantly when common solvents other than dioxane were used (entries 12–16) or the reaction was performed at a lower temperature (entry 17).

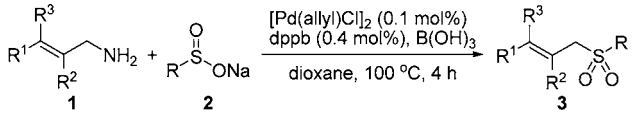
In the presence of 0.1 mol % $[Pd(allyl)Cl]_2$, 0.4 mol % dppb, and excess boric acid, a range of α-unbranched primary allylic amines were smoothly substituted with various sodium sulfinates in an α-selective fashion to give the corresponding allylic sulfones in good to excellent yields (Table 2). Notably, the β- and γ-positions of the allylic amines could bear various substituents such as aryl, heteroaryl, alkenyl, or alkyl groups. While the alkene geometry was retained in reactions with (*E*)-allylic amines (entries 1–9, 11, and 13–20), it was completely inverted in a reaction with a (*Z*)-allylic amine (entry 12). The complete *Z*-to-*E* isomerization could be attributable to the generation of a π-allylpalladium intermediate from the palladium catalyst and the allylic amine (see below), with the reaction preferring to give an (*E*)-allylic sulfone under thermodynamic conditions.

The generation of a π-allylpalladium intermediate could provide a rationale for the γ-selectivity observed in the reaction with α-substituted allylic amines. For example, the reaction of α-phenyl allylamine (**4**) with sulfinate **2a** gave allylic sulfone **3a** in 91% yield with exclusive *E* selectivity (eq 1). The γ-selectivity probably arises from maximizing conjugation and minimizing steric hindrance prior to sulfinate attack on the π-allylpalladium intermediate (see below).



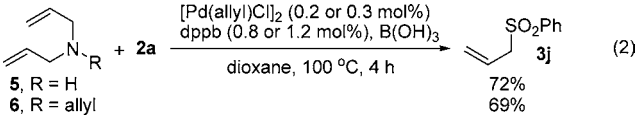
Diallyamine (**5**) and triallylamine (**6**) were also examined (eq 2), and to our delight, each of their allyl groups could be converted to the desired product, allyl sulfone **3j**, in a slightly lower but still good yield relative to that for allylamine (**1j**) (Table 2, entry 10).

Table 2. Direct Substitution of α-Unbranched Primary Allylic Amines with Sodium Sulfinates[a]



entry	**1**, R^1, R^2, R^3	**2**, R	**3**	yield (%)[b]
1	**1a**, Ph, H, H	**2a**, Ph	**3a**	92
2	**1b**, 4-$MeOC_6H_4$, H, H	**2a**, Ph	**3b**	90
3	**1c**, 4-ClC_6H_4, H, H	**2a**, Ph	**3c**	82
4	**1d**, 2-$MeOC_6H_4$, H, H	**2a**, Ph	**3d**	67
5[c]	**1e**, 2-$O_2NC_6H_4$, H, H	**2a**, Ph	**3e**	79
6	**1f**, 2-furyl, H, H	**2a**, Ph	**3f**	84
7	**1g**, (*E*)-MeCH=CH, H, H	**2a**, Ph	**3g**	70
8	**1h**, *n*-hexyl, H, H	**2a**, Ph	**3h**	80
9	**1i**, cyclohexyl, H, H	**2a**, Ph	**3i**	76
10[d]	**1j**, H, H, H	**2a**, Ph	**3j**	79
11	**1k**, Ph, Me, H	**2a**, Ph	**3k**	83
12	**1l**, H, H, Ph	**2a**, Ph	**3a**	84
13	**1a**, Ph, H, H	**2b**, 4-$MeOC_6H_4$	**3l**	94
14	**1a**, Ph, H, H	**2c**, 4-MeC_6H_4	**3m**	94
15	**1a**, Ph, H, H	**2d**, 4-ClC_6H_4	**3n**	86
16[c]	**1a**, Ph, H, H	**2f**, 1-naphthyl	**3o**	64
17	**1a**, Ph, H, H	**2g**, 2-naphthyl	**3p**	80
18	**1a**, Ph, H, H	**2h**, Me	**3q**	75
19	**1a**, Ph, H, H	**2i**, *n*-$C_{16}H_{33}$	**3r**	92
20	**1a**, Ph, H, H	**2j**, $PhCH_2$	**3s**	87

[a]Reaction conditions: amine **1** (0.50 mmol), sulfinate **2** (0.60 mmol), $[Pd(allyl)Cl]_2$ (0.1 mol %), dppb (0.4 mol %), $B(OH)_3$ (2.0 mmol), dioxane (0.50 mL), 100 °C, 4 h. [b]Isolated yields. [c]The reaction was run for 12 h. [d]The reaction was run in a sealed tube.



We envisioned that the use of α-chiral primary allylic amines would enable the generation of chiral allylic sulfones by a chirality transfer mechanism. Thus, the aforementioned conditions were applied to chiral amine **7a**, whose optical purity was 99% ee. Whereas the reaction proceeded in an α-selective fashion to give chiral sulfone **8a** in 97% yield with exclusive *E* selectivity, the ee decreased to 82% (Table 3, entry 1). To achieve an effective transfer of chirality, we surveyed a few ligands that significantly affected the stereoselectivity. To our delight, the use of racemic BINOL as the ligand dramatically reduced the deterioration of the ee and led to the formation of sulfone **8a** with 96% ee (entry 4). (*R*)-BINOL was examined for comparison, and the reaction gave the same stereoselectivity.[20] Moreover, a lower ee and yield were obtained when BINOL was replaced with one of its derivatives, ethylene glycol, or phenol (entries 5–8).

In the presence of 0.1 mol % $[Pd(allyl)Cl]_2$, 0.4 mol % BINOL, and excess boric acid, a range of enantioenriched α-chiral primary allylic amines ($R^1 \neq R^3$) were smoothly substituted with sodium sulfinates in an α-selective fashion to give various α-chiral allylic sulfones in good to excellent yields

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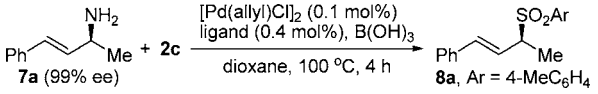
Table 3. Survey of Ligands[a]

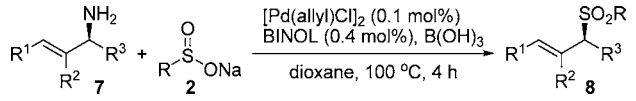


entry	ligand	ee (%)[b]	yield (%)[c]	entry	ligand	ee (%)[b]	yield (%)[c]
1	dppb	82	97	5[d]	3,3′-Ph_2-BINOL	94	45
2[d]	BINAP	91	96	6[d]	6,6′-Br_2-BINOL	95	63
3	TMEDA	84	87	7	$HOCH_2CH_2OH$	95	86
4[d]	BINOL	96	93	8	PhOH	93	90

[a]Reaction conditions: amine **7a** (0.50 mmol), sulfinate **2c** (0.60 mmol), $[Pd(allyl)Cl]_2$ (0.1 mol %), ligand (0.4 mol %), $B(OH)_3$ (2.0 mmol), dioxane (0.50 mL), 100 °C, 4 h. [b]Determined by HPLC analysis on a chiral stationary phase. [c]Isolated yields. [d]The racemic ligand was used.

with excellent retention of ee (Table 4).[21] Importantly, the reaction complements known asymmetric methods[15] in regard

Table 4. Direct Substitution of α-Chiral Primary Allylic Amines with Sodium Sulfinates[a]

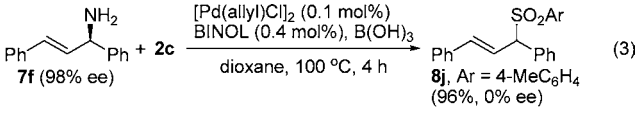


entry	7, R^1, R^2, R^3	2, R	8	ee (%)[b] 7	ee (%)[b] 8	yield (%)[c]
1	**7a**, Ph, H, Me	**2c**, 4-MeC_6H_4	**8a**	99	96	93
2	**7b**, 2-naphthyl, H, Me	**2c**, 4-MeC_6H_4	**8b**	93	92	86
3	**7c**, cyclohexyl, H, Me	**2c**, 4-MeC_6H_4	**8c**	99	98	82
4	**7d**, Ph, Me, Me	**2c**, 4-MeC_6H_4	**8d**	98	97	92
5	**7e**, Ph, H, Et	**2c**, 4-MeC_6H_4	**8e**	96	95	95
6	**7a**, Ph, H, Me	**2a**, Ph	**8f**	99	94	93
7	**7a**, Ph, H, Me	**2d**, 4-ClC_6H_4	**8g**	99	96	90
8	**7a**, Ph, H, Me	**2h**, Me	**8h**	99	92	78
9	**7a**, Ph, H, Me	**2j**, $PhCH_2$	**8i**	99	95	88

[a]Reaction conditions: amine **7** (0.50 mmol), sulfinate **2** (0.60 mmol), $[Pd(allyl)Cl]_2$ (0.1 mol%), BINOL (0.4 mol%), $B(OH)_3$ (2.0 mmol), dioxane (0.50 mL), 100 °C, 4 h. [b]Determined by HPLC analysis on a chiral stationary phase. [c]Isolated yields.

to substrate scope as a result of its unique ability to provide α-chiral allylic sulfones with high optical purity starting from unsymmetric allylic electrophiles.

In contrast, when the putative π-allylpalladium intermediate was symmetric, the product was observed as a racemic mixture, but still with excellent yield (eq 3). Taken together, this

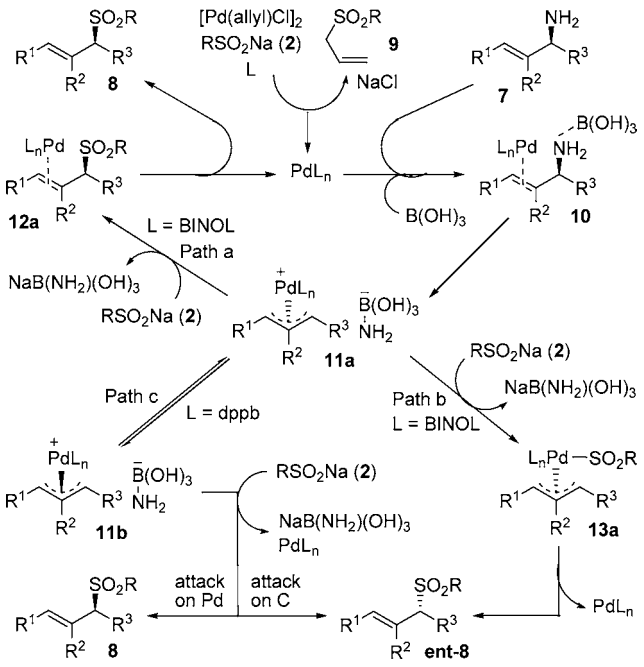


(3)

stereoerosion, the *Z*-to-*E* isomerization (Table 2, entry 12), and the γ-selectivity with an α-substituted allylamine (eq 1) substantially support the intermediacy of a π-allylpalladium species.

According to our results and the general mechanism of the Tsuji–Trost reaction,[9] we propose the following reaction pathways for the substitution reaction of α-chiral primary allylic amines with sulfinate salts (Scheme 1). Nucleophilic attack of

Scheme 1. Proposed Reaction Pathways



sulfinate **2** on $[Pd(allyl)Cl]_2$ leads to the formation of allyl sulfone **9** and the palladium(0) catalyst (PdL_n). The NH_2 group in chiral amine **7** is activated by boric acid, and the allylic C–N bond is cleaved by the palladium(0) catalyst with inversion of configuration to give π-allylpalladium **11a**.[17] When BINOL is used as the ligand, the allylic carbon of complex **11a** is attacked by sulfinate **2** with inversion of configuration to give chiral sulfone **8** and regenerate the palladium(0) catalyst (path a). Alternatively, the palladium atom of complex **11a** is attacked by sulfinate **2** to form palladium-*S*-sulfinate **13a**,[22] which undergoes reductive elimination to give the minor enantiomer **ent-8** (path b). The regioselectivity is determined by the steric and electronic properties of the R^1 and R^3 groups in complexes **11a** and **13a**. If $R^1 = R^3$, the reaction loses optical purity completely because of symmetry. It is noteworthy that racemization of complex **11a** takes place when a phosphine is used as the ligand,[9] and consequently, a portion of chiral amine **7** is transformed into chiral sulfone **ent-8** (path c).

In summary, we have developed for the first time a highly efficient direct substitution reaction of primary allylic amines with sulfinate salts. In the presence of 0.1 mol % $[Pd(allyl)Cl]_2$, 0.4 mol % dppb, and excess boric acid, a range of α-unbranched primary allylic amines are smoothly substituted with sodium sulfinates in an α-selective fashion to give structurally diverse allylic sulfones in good to excellent yields with exclusive *E*

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selectivity. Replacing dppb with BINOL allows α-chiral primary allylic amines to be transformed into the corresponding allylic sulfones in good to excellent yields with excellent retention of ee. Importantly, the reaction complements known asymmetric methods in substrate scope via its unique ability to provide α-chiral allylic sulfones with high optical purity starting from unsymmetric allylic electrophiles.

■ ASSOCIATED CONTENT

Supporting Information

General information, experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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