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Iridium-Catalyzed, Regio- and Enantioselective Allylic Substitution with Aromatic and Aliphatic Sulfinates

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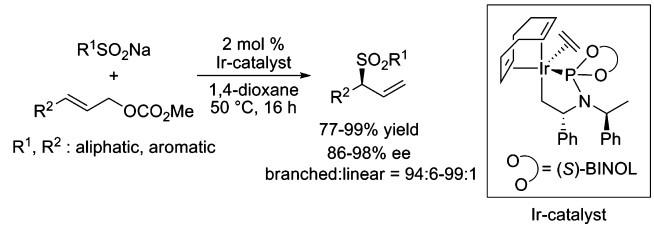
ABSTRACT



The iridium-catalyzed allylation of sodium sulfinate to form branched allylic sulfones is reported. The reactions between various sodium sulfinates and achiral allylic carbonates occur in good yields, with high selectivity for the branched isomer, and high enantioselectivities (up to 98% ee).

Asymmetric allylic substitution catalyzed by transition-metal complexes has become a powerful method for the enantioselective construction of carbon−heteroatom and carbon−carbon bonds.[1] Despite the value of thioethers, sulfoxides, and sulfones as chiral building blocks for the synthesis of natural products and pharmaceutical intermediates,[2] the construction of carbon−sulfur bonds by allylic substitution with high regio- and enantioselectivity has not been well developed.

Sodium *p*-toluenesulfinate is known to serve as a nucleophile in palladium-catalyzed allylic substitution reactions.[3] Moreover, the sulfone product of this reaction is an important building block because it is equivalent to a thioether,[4] and allylic sulfones are known to undergo olefin cross-metathesis.[5] However, few allylations of sulfinates to form chiral, branched products have been reported.[6] Most often, reactions of linear, monosubstituted allylic carbonates form achiral linear sulfonate products.[7]

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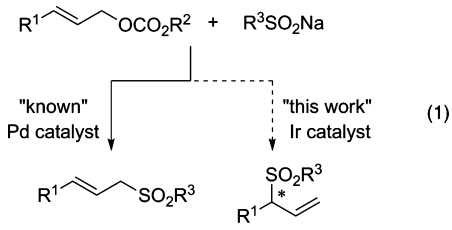
The high regioselectivity of iridium catalysts for formation of branched products, along with the with high enantioselectivity from reactions of heteroatom nucleophiles[8−10] provides the potential that conditions with such a catalyst can be developed for formation of chiral, branched allylic sulfones from reactions of linear allylic esters and alkali metal sulfinates (eq 1). Here, we report highly regio- and enantioselective iridium-catalyzed reactions of a series of allylic carbonates with various sodium sulfinates. These reactions occur with high selectivities and yields with both aliphatic and aromatic methyl carbonates and with both aliphatic and aromatic sulfinates.



(1)

We recently introduced the single-component, metalacyclic iridium complex **1** as an efficient catalyst for enantioselective allylic amination (Figure 1).[9] This complex is an 18-electron

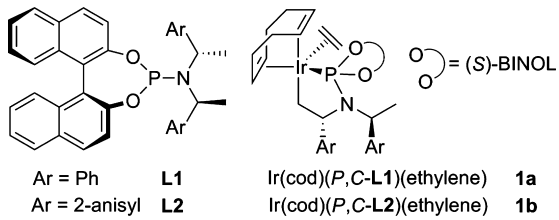
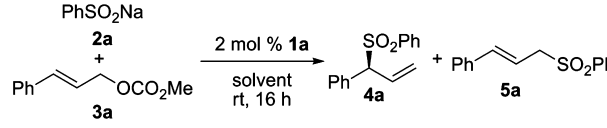


Figure 1. Phosphoramidite ligands and structures of cyclometalated, five-coordinate Ir catalysts.

species, but it contains a labile ethylene ligand that allows initiation of the catalytic cycle by oxidative addition of the allylic ester to the 16-electron species formed by dissociation of this bound olefin.[10] We, therefore, began our investigations of the allylation of sulfinates by testing whether metalacycle **1a** would catalyze the reaction of sodium benzenesulfinate with methyl cinnamyl carbonate to form allylic substitution products. First, we investigated conditions involving an organic and an aqueous phase with tetraoctylammonium bromide as phase transfer agent to address the low solubility of sodium benzenesulfinate in organic solvents. This initial investigation showed that the sulfonated product **4a** forms in 80% yield with 87% ee and 98:2 branched-to-linear ratio (entry 1, Table 1) when the reaction is conducted under biphasic conditions.

Table 1. Effect of Solvents on the Ir-Catalyzed Allylation of Sodium Benzenesulfinate **2a** at Room Temperature[a]



entry	solvent	yield (%)[b]	**4a**:**5a**[c]	ee (%)[d]
1[e]	CH_2Cl_2/H_2O (3:1)	80	98:2	87
2	DMF	95	>99:1	63
3	THF	89	>99:1	93
4	CH_2Cl_2	89	>99:1	91
5	1,4-dioxane	65	>99:1	94
6	DME	78	>99:1	92

[a] General conditions: 0.6 mmol **2a**, 0.5 mmol **3a**, 0.01 mmol **1a** in 2 mL of solvent. [b] Isolated yield of **4a**. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis, see Supporting Information for details. [e] 6 mol % tetraoctylammonium bromide was added as phase-transfer catalyst.

However, studies of reactions in several organic solvents in the absence of an aqueous phase showed that the aqueous phase and phase-transfer agent are unnecessary to achieve acceptable rates, yields, and selectivities. Reactions conducted in various organic solvents occurred with high enantioselectivity, regioselectivity,[11] and yield within 16 h under mild conditions, despite the low solubility of sodium benzenesulfinate in organic solvents (entry 3−6).

Finally, to improve this process further, we investigated the effects of temperature, the identity of the leaving group on the allylic carbonate, the identity of the aryl groups in the catalyst, and the identity of the solvent on yield and selectivity. Reactions conducted at 50 °C occurred in higher yield than those conducted at room temperature, but the enantioselectivity was lower (entry 1, Table 2). Reactions of isopropyl or *tert*-butyl cinnamyl carbonates (entries 2 and 3) occurred in yields and enantioselectivities that are lower than those of methyl cinnamyl carbonate, and experiments with catalysts containing different aryl groups on the amino substituent showed that reactions conducted with catalyst **1b**

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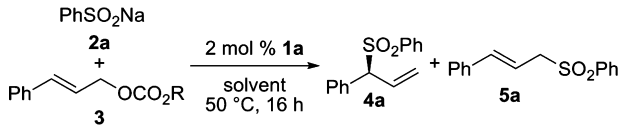
(11) None of the minor isomer from addition to the terminus of the allyl group was observed in the crude NMR spectrum.

Table 2. Effect of Leaving Group and Solvent on the Ir-Catalyzed Allylation of Sodium Benzenesulfinate **2a** at 50 °C[a]



entry	R	solvent	yield (%)[b]	**4a**:**5a**[c]	ee (%)[d]
1	Me	THF	95	97:3	91
2	*i*-Pr	THF	78	94:6	67
3	*t*-Bu	THF	61	93:7	74
4[e]	Me	THF	99	90:10	85
5	Me	toluene	82	97:3	76
6	Me	EtOAc	89	98:2	93
7	Me	MeCN	NR		
8	Me	DME	84	95:5	90
9	Me	1,4-dioxane	92	97:3	94

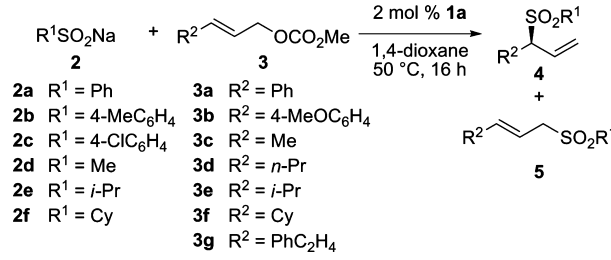
[a] General conditions: 0.6 mmol **2a**, 0.5 mmol **3**, 0.01 mmol **1a** in 2 mL of solvent. [b] Isolated yield of **4a**. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis, see Supporting Information for details. [e] **1b** as catalyst was used.

occurred in excellent yield but with moderate regio- and enantioselectivity (entry 4). High enantioselectivity was maintained at 50 °C when reactions were conducted in dioxane, and they occurred with yields and regioselectivities that were equal or higher than those in other organic solvents (entries 5−9). Thus, reactions conducted in 1,4-dioxane at 50 °C with catalyst **1a** were shown to occur with the best balance of yield, regioselectivity, and enantioselectivity and would allow for the substitutions to be conducted with less reactive aliphatic nucleophiles and electrophiles.

Table 3 summarizes the scope of the reactions conducted under the optimized conditions described in entry 9 of Table 2. The reaction of electron-rich carbonate **3b** occurred in high yield (entry 2). Likewise, the reactions of the more electron-rich of the aromatic sulfinates **2b** occurred in higher yield than those of the electron-neutral sodium benzenesulfinate **2a** (entry 3). Most striking, the reaction of aliphatic allylic carbonates occurred with complete regioselectivities and high enantioselectivities (entry 4−8). Often iridium-catalyzed allylic substitutions of aliphatic allylic carbonates in the presence of catalyst **1a** occur with regioselectivities that are good but not as high as that observed with the sulfinate nucleophile.

The reactions of allylic carbonates with a variety of sodium sulfinates were also investigated. The reactions of electron-poor sodium aromatic sulfinates **2c** and **3b** occurred with somewhat lower regio- and enantioselectivity than reactions of sodium benzene sulfonate. However, the sodium salts of aliphatic sulfinates **2d**−**2f** reacted with the *p*-methoxy-substituted cinnamyl carbonate **3b** with exceptionally high regioselectivity, high yield, and high enantioselectivity. These reactions of sulfinates **2d**−**f** required 2.0 equiv of sulfinates, perhaps because of the low reactivity of aliphatic sulfinates as nucleophile (entries 10−12).

Table 3. Ir-Catalyzed Allylation of Various Sodium Sulfinates[a]



entry	R^1	R^2	**4**	yield (%)[b]	**4**:**5**[c]	ee (%)[d]
1	Ph	Ph	**4a**	92	97:3	94
2	Ph	4-$MeOC_6H_4$	**4b**	95	99:1	89
3	4-MeC_6H_4	Ph	**4c**	95	94:6	92
4	4-MeC_6H_4	Me	**4d**	92	99:1	94
5	4-MeC_6H_4	*n*-Pr	**4e**	77	99:1	93
6	4-MeC_6H_4	*i*-Pr	**4f**	86	99:1	97
7	4-MeC_6H_4	Cy	**4g**	99	99:1	98
8	4-MeC_6H_4	PhC_2H_4	**4h**	91	99:1	91
9[e]	4-ClC_6H_4	4-$MeOC_6H_4$	**4i**	85	95:5	86
10[e]	Me	4-$MeOC_6H_4$	**4j**	95	>99:1	92
11[e]	*i*-Pr	4-$MeOC_6H_4$	**4k**	99	>99:1	93
12[e]	Cy	4-$MeOC_6H_4$	**4l**	91	>99:1	95

[a] General conditions: 0.6 mmol **2**, 0.5 mmol **3**, 0.01 mmol **1a** in 2 mL of dioxane. Results are an average of two runs. [b] Isolated yield of **4**. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis, see Supporting Information for details. [e] 1.0 mmol of **2** was used.

The absolute configurations of the reaction products **4e** and **4f** were determined by comparison of the specific rotations of the products with literature data.[6a,12] Reactions conducted with the catalyst derived from the (*S*,*S*,*S*)-phosphoramidite generate the (*R*)-sulfonate. The stereochemistry of these reactions parallels that of the reactions of amine nucleophiles[9] in the presence of the same Ir catalysts.

In summary, we have developed regio- and enantioselective iridium-catalyzed allylations of sodium sulfinates to produce branched substitution products. Notable features of these reactions include high regio- and enantioselectivity of the process with a broad range of allylic carbonates and sodium sulfinates. We are currently investigating applications of this process that would exploit the unique features of chiral, nonracemic, allylic sulfones.

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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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