

Tandem Ir-Catalyzed Allylic Substitution Reaction of Allyl Sulfonates and Isomerization

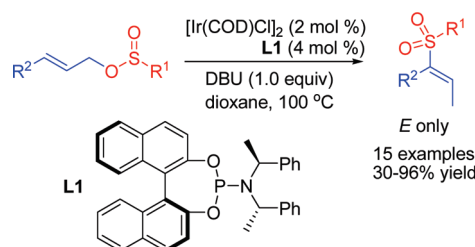
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Received December 13, 2009

ABSTRACT



An efficient method for the synthesis of trisubstituted vinyl sulfones is reported. Using the $[\text{Ir}(\text{COD})\text{Cl}]_2$ /phosphoramidite ligand (**L1**)/DBU, trisubstituted vinyl sulfones could be synthesized from allyl sulfonates in high yields as exclusively *E* isomers.

Sulfones have received much attention in both organic and medicinal chemistry because of their versatile synthetic utilities and interesting biological activities.^{1–3} Particularly, substituted vinyl sulfones are known for biological activities such as being potent inhibitors for many types of cysteine proteases.² Synthetically, substituted vinyl sulfones are widely used as Michael acceptors or dienophiles in cycloaddition reactions.⁴ More recently, there have been several reports on the utilization of substituted vinyl sulfones in catalytic enantioselective processes, providing efficient syntheses of optically active sulfones.^{5–7} Consequently, the development of efficient synthesis of substituted vinyl sulfones has attracted considerable attention in both organic

synthesis and the pharmaceutical industry. To date, there have been many reports on the synthesis of vinyl sulfones,^{1,8}

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however, the synthesis of multisubstituted vinyl sulfones in a stereoselective manner is still challenging and highly desirable.⁹

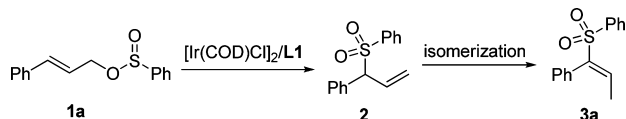


Figure 1. Ir-catalyzed allylic substitution reaction of allyl sulfinate.

As part of our research program to develop Ir-catalyzed allylic substitution reactions,¹⁰ we recently attempted the synthesis of optically pure allyl sulfones via Ir-catalyzed allylic substitution of allyl sulfonates (Figure 1). However, when the reaction of allyl sulfinate **1a** and [Ir(COD)Cl]₂/ligand **L1** (Figure 2) was carried out,¹¹ surprisingly, the substituted vinyl sulfone **3a** was obtained in good yield exclusively as an *E* isomer. The formation of **3a** is likely through the isomerization of the desired allyl sulfone **2** (Figure 1). Given the importance for the stereoselective synthesis of trisubstituted vinyl sulfones, we report our results on this subject here.

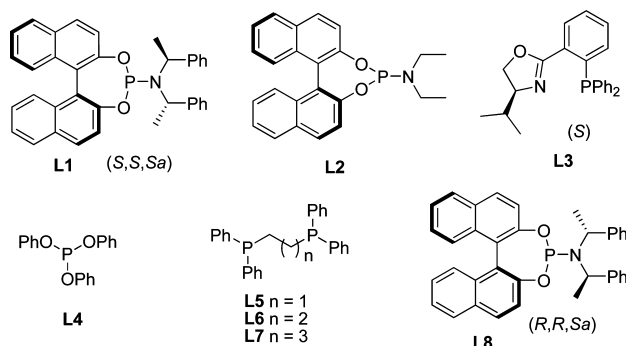


Figure 2. Different ligands used in the reaction.

We began our study by examining different bases, and DBU (1 equiv) was found to be the optimal base, affording **3a** in 82% yield (entry 1, Table 1). Reducing the loading of DBU led to a significant decrease of the conversion, and no product was formed in the absence of DBU (entries 6 and 7, Table 1). Various solvents such as THF, toluene, CH₃CN, ether, CH₂Cl₂, and dioxane were all tolerated in the reaction,

and the highest yield (92%) was obtained in dioxane at 100 °C (entries 8–12, Table 1).

Table 1. Optimization of the Conditions for Ir-Catalyzed Allylic Substitution of **1a** and Isomerization with Ligand **L1**^a

entry	base	solvent	time (h)	convn (%) ^b	yield (%) ^c
1	DBU	THF	38	>95	82
2	Et ₃ N	THF	48		NR
3	K ₃ PO ₄	THF	48		NR
4	Cs ₂ CO ₃	THF	48	28	
5	BSA	THF	48		trace
6 ^d	DBU	THF	36	33	
7	-	THF	25		NR
8	DBU	toluene	36		77
9	DBU	CH ₃ CN	60		82
10	DBU	Et ₂ O	20		87
11	DBU	CH ₂ Cl ₂	36		67
12 ^e	DBU	dioxane	9	>95	90

^a Reaction conditions: 2 mol % of [Ir(COD)Cl]₂, 4 mol % of **L1**, 0.2 mmol of **1a** in 2 mL of solvent. ^b Determined by ¹H NMR of the crude reaction mixture. ^c Isolated yields. ^d 20 mol % of DBU was used. ^e At 100 °C. BSA = *N,O*-Bis(trimethyl)acetamide.

Under the above conditions (entry 12, Table 1), different ligands were evaluated, and the results are summarized in Table 2. Most ligands could be used in this reaction but with relatively low conversion. The reaction with ligand **L8**, the diastereomer of **L1**, led to the formation of **3a** in 85% yield (entry 8, Table 2). Notably, the reaction in the presence of DBU only without Ir catalyst also proceeded slowly, affording 10% conversion.

Under the optimized reaction conditions [2 mol % of [Ir(COD)Cl]₂, 4 mol % of **L1**, 1.0 equiv of DBU, dioxane, 100 °C], various substrates were carried out to test the generality of the reaction. As summarized in Table 3, both aryl (phenyl, tolyl) and aliphatic (*tert*-butyl) sulfonates could be used in the reaction. For the phenyl sulfinate, aryl-bearing

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Table 2. Screening Different Ligands^a

entry	ligand	convn (%)	yield (%)
1	L1	>95	90
2	L2	33	
3	L3	43	
4	L4	33	
5	L5	25	
6	L6	30	
7	L7	20	
8	L8	>95	85
9 ^b	none	10	

^a Reactions were conducted under the conditions of entry 12, Table 1.^b Reaction with DBU only in the absence of Ir catalyst.

electron-withdrawing substituents and aliphatic allyl alcohol derived sulfonates could all be tolerated, generally in good to excellent yields (entries 1–6, Table 3). However, when electron-donating groups containing aryl allyl sulfonates were attempted, the pure substrates were difficult to obtain due to the instability of these substrates on the silica gel column. Therefore, the intermolecular reaction between allyl carbonates and sodium sulfonates was explored to access these products.

Table 3. Substrate Scope for Tandem Ir-Catalyzed Allylic Substitution of Allyl Sulfonates and Isomerization^a

entry	1	R ¹	R ²	yield (%) ^b
1	1a	Ph	Ph	3a , 92
2	1b	Ph	<i>n</i> -Pr	3b , 92
3	1c	Ph	<i>p</i> -BrC ₆ H ₄	3c , 90
4	1d	Ph	<i>p</i> -CF ₃ C ₆ H ₄	3d , 82
5	1e	Ph	Et	3e , 73
6	1f	Ph	<i>p</i> -FC ₆ H ₄	3f , 93
7	1g	<i>p</i> -MeC ₆ H ₄	Ph	3g , 92
8	1h	<i>p</i> -MeC ₆ H ₄	<i>n</i> -Pr	3h , 30
9	1i	<i>p</i> -MeC ₆ H ₄	<i>p</i> -BrC ₆ H ₄	3i , 90
10	1j	<i>p</i> -MeC ₆ H ₄	<i>p</i> -FC ₆ H ₄	3j , 96
11	1k	<i>t</i> -Bu	Ph	3k , 96
12	1l	<i>t</i> -Bu	<i>n</i> -Pr	3l , 91
13	1m	<i>t</i> -Bu	<i>p</i> -BrC ₆ H ₄	3m , 78

^a Reaction conditions: 2 mol % of [Ir(COD)Cl]₂, 4 mol % of **L1**, 0.2 mmol of **1** in 2 mL of dioxane. ^b Isolated yields.

After optimizing the reaction conditions, we found that the intermolecular reactions proceeded smoothly in refluxing dichloromethane, leading to sulfones **3** in good yields. As summarized in Table 4, the intermolecular reaction is suitable for not only the electron-donating groups bearing aryl allyl sulfonates but also the electron-withdrawing groups bearing

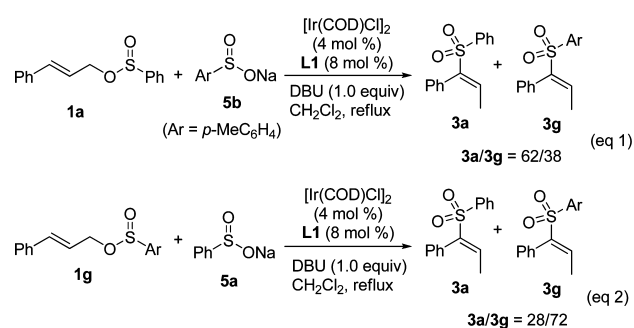
Table 4. Ir-Catalyzed Allylic Substitution of Sodium Arylsulfonates and Isomerization^a

entry	R ¹	R ²	yield (%) ^b
1	5a , Ph	4a , Ph	3a , 92
2	5a , Ph	4b , <i>p</i> -MeOC ₆ H ₄	3n , 96
3	5a , Ph	4c , 1-thienyl	3o , 65
4	5a , Ph	4d , <i>p</i> -CF ₃ C ₆ H ₄	3d , 75
5	5a , Ph	4e , <i>n</i> -Pr	3b , 94
6	5b , <i>p</i> -MeC ₆ H ₄	4a , Ph	3g , 85

^a Reaction conditions: 2 mol % of [Ir(COD)Cl]₂, 4 mol % of **L1**, 0.3 mmol of **4** and 0.2 mmol of **5** in 2 mL of CH₂Cl₂. ^b Isolated yields.

aryl and aliphatic ones. Both sodium benzenesulfonate and sodium *p*-methylbenzenesulfonate were tolerated in the reaction.

To gain insight into the reaction mechanism, cross experiments have been carried out by subjecting an equimolar amount of **1a** and **5b** to the reaction conditions (eq 1, Scheme 1). Two products **3a** and **3g** were obtained with the ratio

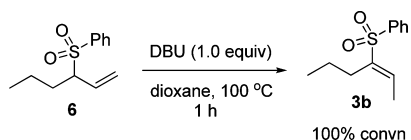
Scheme 1. Cross Experiments

62/38, determined by ¹H NMR of the crude reaction mixture. These results exclude the rearrangement pathway for the current reaction. The different distribution of the two products is likely due to the poor solubility of sodium *p*-methylbenzenesulfonate. To test this hypothesis, the reaction of **1g** and **5a** was carried out under the same reaction conditions. As expected, two products **3a** and **3g** (**3a/3g** = 28/72) were obtained with the reversed ratio (eq 2, Scheme 1).

In addition, when sulfone **6** and DBU were heated at 100 °C in dioxane for 1 h, complete isomerization to **3b** was observed (Scheme 2). These results suggest that DBU is responsible for the isomerization process.

In summary, we have found an efficient stereoselective synthesis of trisubstituted vinyl sulfones. The tandem reaction involving Ir-catalyzed allylic substitution of allyl sulfonate and isomerization allows ready access to trisubstituted vinyl

Scheme 2. DBU-Catalyzed Isomerization



sulfones either from an intramolecular reaction of allyl sulfonates or from the intermolecular reactions between allyl carbonates and sodium sulfonates. The ready availability of the starting materials, mild conditions, and atom-economical

process make the current reaction potentially useful in organic synthesis.

Acknowledgment. We thank the NSFC (20872159, 20821002, 20932008) and National Basic Research Program of China (973 Program 2009CB825300) for generous financial support.

Supporting Information Available: Experimental procedures and characterization of the products **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>. OL902873Q