ORGANIC LETTERS

2010
Vol. 12, No. 4
800−803

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

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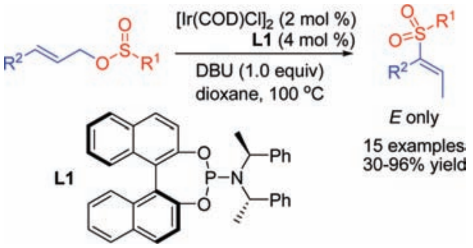
Received December 13, 2009

ABSTRACT



An efficient method for the synthesis of trisubstituted vinyl sulfones is reported. Using the [Ir(COD)Cl]$_2$/phosphoramidite ligand (L1)/DBU, trisubstituted vinyl sulfones could be synthesized from allyl sulfinates 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]

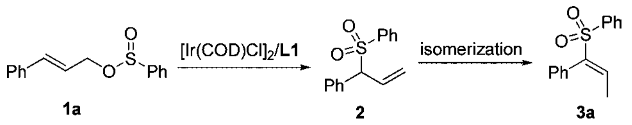


Figure 1. Ir-catalyzed allylic substitution reaction of allyl sulfinate.

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 sulfinates (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.

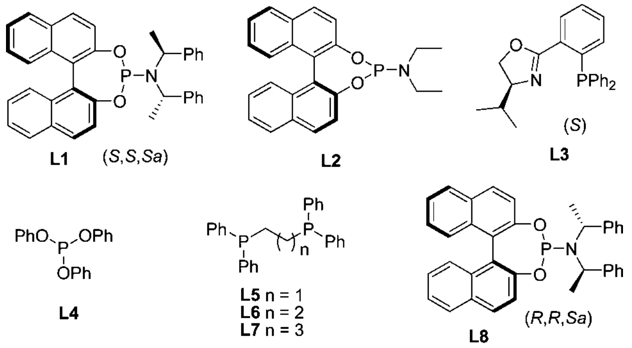
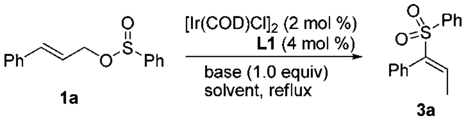


Figure 2. Different ligands used in the reaction.

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, CH_3CN, ether, CH_2Cl_2, 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_3N	THF	48		NR
3	K_3PO_4	THF	48		NR
4	Cs_2CO_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_3CN	60		82
10	DBU	Et_2O	20		87
11	DBU	CH_2Cl_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) sulfinates could be used in the reaction. For the phenyl sulfinate, aryl-bearing

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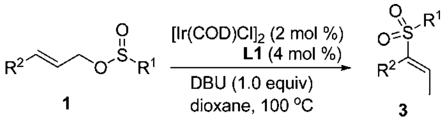
Table 2. Screening Different Ligands[a]

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 sulfinates could all be tolerated, generally in good to excellent yields (entries 1−6, Table 3). However, when electron-donating groups containing aryl allyl sulfinates 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 sulfinates was explored to access these products.

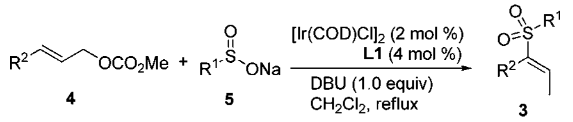
Table 3. Substrate Scope for Tandem Ir-Catalyzed Allylic Substitution of Allyl Sulfinates and Isomerization[a]



entry	1	R^1	R^2	yield (%)[b]
1	**1a**	Ph	Ph	**3a**, 92
2	**1b**	Ph	*n*-Pr	**3b**, 92
3	**1c**	Ph	*p*-BrC$_6$H$_4$	**3c**, 90
4	**1d**	Ph	*p*-CF$_3$C$_6$H$_4$	**3d**, 82
5	**1e**	Ph	Et	**3e**, 73
6	**1f**	Ph	*p*-FC$_6$H$_4$	**3f**, 93
7	**1g**	*p*-MeC$_6$H$_4$	Ph	**3g**, 92
8	**1h**	*p*-MeC$_6$H$_4$	*n*-Pr	**3h**, 30
9	**1i**	*p*-MeC$_6$H$_4$	*p*-BrC$_6$H$_4$	**3i**, 90
10	**1j**	*p*-MeC$_6$H$_4$	*p*-FC$_6$H$_4$	**3j**, 96
11	**1k**	*t*-Bu	Ph	**3k**, 96
12	**1l**	*t*-Bu	*n*-Pr	**3l**, 91
13	**1m**	*t*-Bu	*p*-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.

Table 4. Ir-Catalyzed Allylic Substitution of Sodium Arylsulfinates and Isomerization[a]



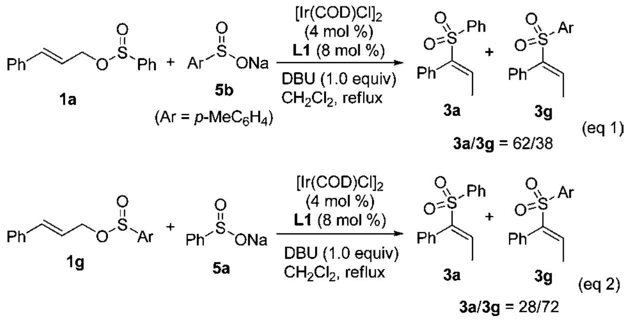
entry	R^1	R^2	yield (%)[b]
1	**5a**, Ph	**4a**, Ph	**3a**, 92
2	**5a**, Ph	**4b**, *p*-MeOC$_6$H$_4$	**3n**, 96
3	**5a**, Ph	**4c**, 1-thienyl	**3o**, 65
4	**5a**, Ph	**4d**, *p*-CF$_3$C$_6$H$_4$	**3d**, 75
5	**5a**, Ph	**4e**, *n*-Pr	**3b**, 94
6	**5b**, *p*-MeC$_6$H$_4$	**4a**, Ph	**3g**, 85

[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 CH$_2$Cl$_2$. [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 sulfinates but also the electron-withdrawing groups bearing aryl and aliphatic ones. Both sodium benzenesulfinate and sodium *p*-methylbenzenesulfinate 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 62/38, determined by ^{1}H 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*-methylbenzensulfinate. 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).

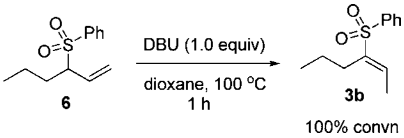
Scheme 1. Cross Experiments



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 sulfinate and isomerization allows ready access to trisubstituted vinyl

Scheme 2. DBU-Catalyzed Isomerization



sulfones either from an intramolecular reaction of allyl sulfinates or from the intermolecular reactions between allyl carbonates and sodium sulfinates. 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