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Iridium-Catalyzed Enantioselective Allylic Substitution of *O*-Allyl Carbamothioates

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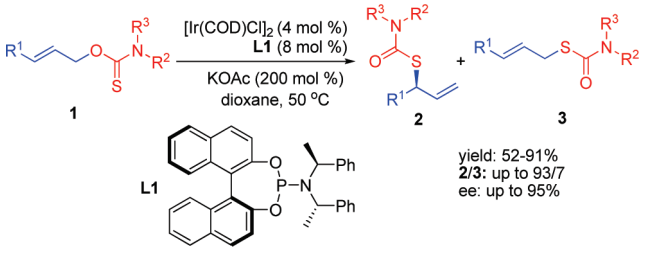

With an $[Ir(COD)Cl]_2$/phosphoramidite ligand system, an allylic substitution of *O*-allyl carbamothioates was developed. The reaction proceeded in the favor of branched products with up to 93:7 branched-to-linear ratio, affording chiral *S*-allyl carbamothioates with up to 95% ee.

Iridium-catalyzed asymmetric allylic substitution has emerged as one of the most efficient methods to form carbon−carbon and carbon−heteroatom bonds, particularly due to its high regioselectivity and excellent enantioselectivity.[1] Studies by Hartwig and Helmchen demonstrated cyclometalated iridium as the active catalytic species, which further provided the basis for asymmetric Ir-catalyzed allylic substitution reactions.[2] Despite the impressive progress to date, the construction of a carbon−sulfur bond in Ir-catalyzed allylic substation reactions is less explored. Several transition metal complexes such as those using Pd,[3] Ru,[4] Rh,[5] Fe,[6] and Ni[7] have been explored as suitable catalysts for allylic substitution in the formation of carbon−sulfur bonds. Notably, Gais and Böhme have reported the enantioselective *O*,*S*-rearrangement of racemic *O*-allylic thiocarbamates, providing enantioenriched allylic sulfur compounds.[3e] Given the successful application of iridium catalysts for the allylic substitution reactions of heteroatom nucleophiles,[8,9] we envisaged that iridium-catalyzed allylic substitution reaction with a sulfur nucleophile would provide an efficient access to chiral sulfur-containing compounds, which are highly important synthetic intermediates.[10] During our recent studies toward this goal using Ir-catalyzed allylic substitution reaction of allyl sulfinates, trisubstituted vinyl sulfones were obtained as a result of the subsequent isomerization.[11] Simultaneously, an elegant protocol, developed by Ueda and Hartwig, afforded the enantioenriched allylic sulfones in excellent yields and ees.[12]

To continue the development of asymmetric synthesis of enantioenriched chiral sulfur compounds, we recently found

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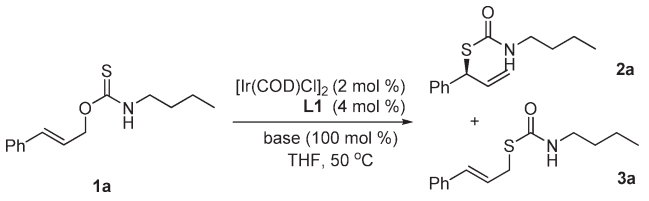
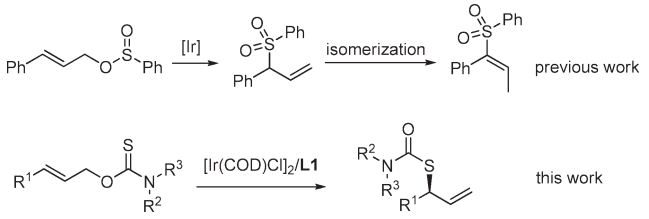
TABLE 1. Optimization of Conditions for Ir-Catalyzed Allylic Substitution of 1a using L1[a]



entry	base	time (h)	conv (%)[b]	**2a**/**3a**[b]	**2a**, yield (%)[c]	ee (%)[d]
1		36	25	80/20		83
2	K_3PO_4	36			NR	
3	Cs_2CO_3	36			NR	
4	DBU	36			NR	
5	DBN	36			NR	
6	BSA	21	20	82/18	12	82
7	Et_3N	23	25	83/17	18	90
8	DIEA	19	20	84/16	17	85
9	DABCO	24	40	62/38	26	90
10	KOAc	23	60	86/14	35	90
11[e]	KOAc	12	54	78/22	25	87
12[f]	KOAc	12	72	85/15	49	92
13[g]	KOAc	36	70	82/18	51	90
14[f,g]	KOAc	12	94	75/25	57	88
15[g,h]	KOAc	12	>95	80/20	50	88

[a]Reaction conditions: 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **L1**, 0.2 mmol of **1a**, and 100 mol % of base in THF (2 mL). [b]Determined by ^1H NMR of the crude reaction mixture. [c]Yield of **2a**. [d]Determined by chiral HPLC analysis. [e]Reflux condition. [f]200 mol % of KOAc was used. [g]4 mol % of $[Ir(COD)Cl]_2$ and 8 mol % of **L1** were used. [h]400 mol % of KOAc was used.

that Ir-catalyzed allylic substitution of *O*-allyl carbamothioates could afford chiral *S*-allyl carbamothioates with up to 95% ee. The reaction proceeded in an atom-economical fashion with moderate to excellent regioselectivities. Herein, we report the detailed studies.



In our initial investigation, *O*-cinnamyl butylcarbamothioate **1a** was chosen as the model substrate to optimize the reaction conditions. The results are summarized in Table 1. With $[Ir(COD)Cl]_2$ (2 mol %)/**L1** (4 mol %) as the catalyst (Figure 1), the reaction in THF at 50 °C without additional base proceeded in 25% conversion with moderate branched-to-linear ratio (80:20) (entry 1, Table 1). Surprisingly, the addition of K_3PO_4, Cs_2CO_3, DBU, and DBN as bases completely inhibited the reaction (entries 2−5, Table 1). Among a series of other bases tested, KOAc showed a superior result, affording the corresponding product **2a** in 35% yield with 90% ee (entries 6−10, Table 1). Notably, by increasing the catalyst loading and base simultaneously (4 mol % $[Ir(COD)Cl]_2$ and 200 mol % KOAc), the isolated yield of **2a** was improved to 57% with 88% ee (entry 14, Table 1).

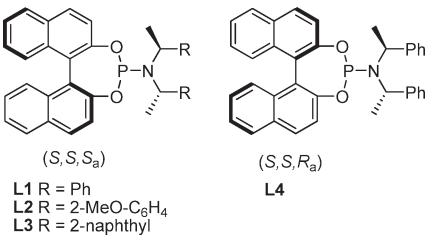


FIGURE 1. Ligands used in the present work.

TABLE 2. Screening Different Solvents and Ligands[a]

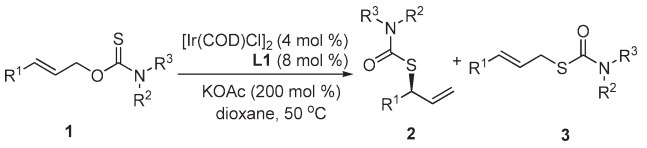
entry	ligand	solvent	conv (%)[b]	**2a**/**3a**[b]	**2a**, yield (%)[c]	ee (%)[d]
1	**L1**	toluene	80	83/17	54	84
2	**L1**	THF	>95	75/25	57	88
3	**L1**	CH_2Cl_2	>95	26/74	19	2
4	**L1**	dioxane	>95	81/19	63	90
5	**L1**	DME		77/23	50	87
6	**L1**	CH_3CN			NR	
7	**L1**	DMF			NR	
8	**L2**	dioxane	>95	79/21	59	87
9	**L3**	dioxane	90	73/27	39	93
10	**L4**	dioxane	71	74/26	30	80

[a]Reactions were conducted under the conditions of entry 14, Table 1. [b]Determined by ^1H NMR of the crude reaction mixture. [c]Yield of **2a**. [d]Determined by chiral HPLC analysis.

Under the above conditions (entry 14, Table 1), further studies on the effect of solvents and ligands were carried out. The results are summarized in Table 2. Various solvents (toluene, CH_2Cl_2, dioxane, and DME) could be tolerated in the reaction (entries 1−5, Table 2), but the regioselectivity is poor in CH_2Cl_2. Moreover, reactions in acetonitrile and DMF failed to give any product (entries 6 and 7, Table 2). The best result was obtained in dioxane in terms of the isolated yield of **2a** (63%) and enantioselectivity (90% ee). In dioxane, different ligands were evaluated (Figure 1). The results suggested that ligands **L2**−**L4** could be employed in the reaction, albeit with relatively lower yields in comparison with **L1** (entries 8−10, Table 2).

Under the optimized reaction conditions [4 mol % of $[Ir(COD)Cl]_2$, 8 mol % of **L1**, 200 mol % of KOAc, dioxane, 50 °C], a wide range of substrates were tested to examine the scope of this reaction. The results are shown in Table 3. Various *O*-allyl carbamothioates derived from aryl allyl alcohols bearing either electron-withdrawing groups (*p*-CF_3, *p*-Br) or electron-donating groups (*p*-Me, *p*-OMe) could react well, affording the desired products in up to 90% yield and 90% ee for **2** (entries 1−8, Table 3). It is worth noting that the enantioselectivity of bulky 1-naphthyl-substituted carbomothioate **1i** sharply decreased, and only 20% ee was obtained (entry 9, Table 3). When *O*-allyl carbamothioates derived from alkyl allyl alcohols, the substitution products were obtained in up to 91% yield but with decreased regioselectivity (entries 10−12, Table 3). As to substituents attached to the nitrogen, both phenyl and aliphatic (*n*-butyl, Bn) groups could be tolerated in the reaction. Notably, substrate **1m** featuring dialkylated nitrogen group could also give rise to its desired product in 85% yield and 95% ee (entry 13, Table 3). Although only moderate regioselectivities were obtained, all of the branched products could be easily separated from their linear isomers using column chromatography except **2m**.

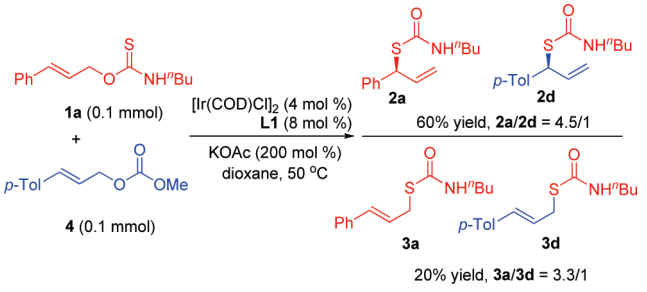
TABLE 3. Substrate Scope for Ir-Catalyzed Allylic Substitution of *O*-Allyl Carbamothioates[a]



entry	1	2/3[b]	yield (%)[c]	ee (%)[d]
1	**1a**: R^1 = Ph, R^2 = *n*-Bu, R^3 = H	81/19	90	90
2	**1b**: R^1 = *p*-$CF_3C_6H_4$, R^2 = *n*-Bu, R^3 = H	74/26	68	90
3	**1c**: R^1 = *p*-BrC_6H_4, R^2 = *n*-Bu, R^3 = H	62/38	80	85
4	**1d**: R^1 = *p*-MeC_6H_4, R^2 = *n*-Bu, R^3 = H	93/7	52	93
5	**1e**: R^1 = *p*-$MeOC_6H_4$, R^2 = *n*-Bu, R^3 = H	61/39	61	64
6	**1f**: R^1 = Ph, R^2 = Bn, R^3 = H	86/14	66	89
7	**1g**: R^1 = *p*-MeC_6H_4, R^2 = Bn, R^3 = H	65/35	80	86
8	**1h**: R^1 = Ph, R^2 = Ph, R^3 = H	78/22	62	63
9	**1i**: R^1 = 1-naphthyl, R^2 = *n*-Bu, R^3 = H	82/18	74	20
10	**1j**: R^1 = *n*-Pr, R^2 = *n*-Bu, R^3 = H	61/39	79	89
11	**1k**: R^1 = *n*-Pr, R^2 = Ph, R^3 = H	61/39	91	56
12	**1l**: R^1 = *n*-Pr, R^2 = Bn, R^3 = H	60/40	89	84
13	**1m**: R^1 = Ph, R^2, R^3 = -$(CH_2)_5$-	70/30	85	95

[a]General conditions: 4 mol % of $[Ir(COD)Cl]_2$, 8 mol % of **L1**, 0.2 mmol of **1**, and 200 mol % of KOAc in dioxane (2 mL). [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Yields of **2** and **3**. [d]Determined by chiral HPLC analysis.

SCHEME 1. Crossover Experiment of 1a and 4

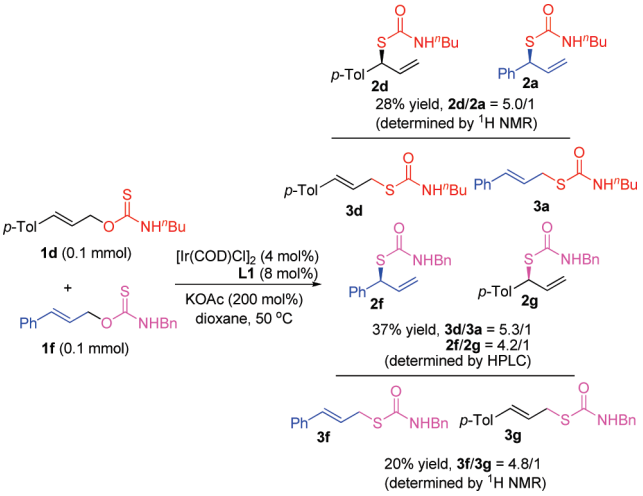


To determine the absolute configuration of the product, an X-ray crystallographic analysis of enantiopure bromine-containing compound **2c** showed the configuration as *S* (see the Supporting Information for details).

To gain insights into the reaction mechanism, a crossover experiment has been carried out by subjecting an equimolar amount of **1a** and **4** to the standard reaction conditions (Scheme 1). As determined by ^{1}H NMR, the branched products **2a**/**2d** were isolated in 60% yield with the ratio 4.5:1, and the linear products **3a**/**3d** were isolated in 20% yield with the ratio 3.3:1. The formation of products **2d** and **3d** excludes the rearrangement pathway, while the dominant formation of **2a** (**3a**) over **2d** (**3d**) indicates the existence of coordination between the Ir−allyl complex and sulfur-containing nucleophile. This likely contributes to the relatively low regioselectivity and enantioselectivity of the current reaction.

In addition, a crossover experiment between **1d** and **1f** has been carried out (Scheme 2). As determined by ^{1}H NMR or HPLC, all possible eight products could be obtained. The products derived from the same *O*-allyl carbamothioate were favorably formed. This experiment also excludes the rearrangement pathway and suggests the existence of

SCHEME 2. Crossover Experiment of 1d and 1f



coordination between the Ir−allyl complex and sulfur-containing nucleophile.

In summary, we have developed an iridium-catalyzed allylic substitution reaction that affords branched *S*-allyl carbamothioates with moderate to excellent yields, enantioselectivities, and regioselectivities. The readily available catalyst, facile transformation of the products, and the atom-economical process make the current methodology potentially useful in organic synthesis.

Experimental Section

General Procedure for Ir-Catalyzed Allylic Substitution of *O*-Allyl Carbamothioates. To a dry Schlenk tube filled with argon were added $[Ir(COD)Cl]_2$ (5.4 mg, 0.008 mmol), phosphoramidite ligand **L1** [*O*,*O*′-(*S*)-(1,1′-dinaphthyl-2,2′-diyl)-*N*,*N*′-di-(*S*,*S*)-[phenylethylphosphoramidite] (8.6 mg, 0.016 mmol), THF (1 mL), and propylamine (0.7 mL) were added. The reaction mixture was heated at 50 °C for 30 min, and then the volatile solvents were removed under vacuum to give a yellow solid. Then, *O*-allyl carbamothioate **1** (0.20 mmol), KOAc (39.2 mg, 0.40 mmol), and 1,4-dioxane (2.0 mL) were added. The reaction mixture was heated at 50 °C until the carbamothioate was fully consumed (monitored by TLC). Then the crude reaction mixture was filtrated with Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to give the desired products. The ratio of regioisomers (branched to linear **2**/**3**) was determined by ^{1}H NMR of the crude reaction mixture. For **1a**, 90% yield, **2a**/**3a** = 81:19. **Data for 2a**: 72% yield, clear oil, 90% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); *n*-hexane/2-propanol = 90:10; flow rate = 0.7 mL/min; detection wavelength = 214 nm; t_R = 16.70 (minor), 21.50 (major) min]. $[\alpha]^{20}_D$ = −240.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.22 (m, 5H), 6.15 (ddd, *J* = 6.6, 9.9, 16.8 Hz, 1H), 5.29−5.16 (m, 4H), 3.30−3.24 (m, 2H), 1.52−1.42 (m, 2H), 1.37−1.25 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 140.1, 137.5, 128.6, 128.1, 127.3, 116.5, 51.3, 41.1, 31.6, 19.9, 13.6; IR (film) ν_{max} (cm^{-1}) 3308, 3030, 2960, 2933, 2874, 1654, 1521, 1494, 1206, 986, 921, 840, 698; EI-MS (*m*/*z*) 249 (M^+, 1), 150 (37), 117 (100), 115 (35), 91 (10), 77 (2); HRMS (EI) exact mass calcd for $C_{14}H_{19}NOS$ $[M]^+$ 249.1187, found: 249.1191. **Data for 3a**: 18% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.18 (m, 5H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.23 (dt, *J* = 7.2,

16.0 Hz, 1H), 5.52 (br s, 1H, NH), 3.73 (d, J = 7.2 Hz, 2H), 3.28 (m, 2H), 1.52−1.45 (m, 2H), 1.37−1.28 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 136.6, 132.4, 128.4, 127.5, 126.3, 125.5, 41.2, 32.5, 31.6, 19.8, 13.6; IR (film) ν_{max} (cm^{-1}) 3290, 2961, 2938, 2873, 1662, 1633, 1525, 1398, 1214, 968, 744, 692; EI-MS (m/z) 249 (M^+, 14), 150 (18), 117 (100), 115 (26), 91 (8), 57 (8). Anal. Calcd. for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68; N, 5.62. Found: C, 67.29; H, 7.50; N, 5.51. Mp 100−102 °C.

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Supporting Information Available: Experimental procedures and characterization of the products **2** and **3**, including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.