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Carbon−Sulfur Bond Formation via Iridium-Catalyzed Asymmetric Allylation of Aliphatic Thiols

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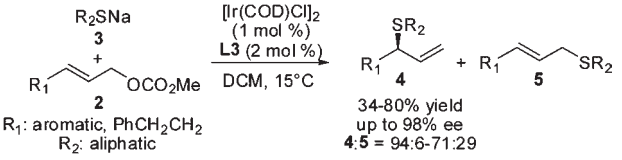
ABSTRACT



An iridium-catalyzed regio- and enatioselective allylation with aliphatic thiols as the nucleophile in dichloromethane has been accomplished; and the branch products were obtained in 34−80% yields with up to 94/6 b/l and 98% ee.

The exploration of transition metal-catalyzed allylations for the construction of carbon−sulfur bonds is of widespread interest due to the growing need for versatile, mild, and selective methods in the preparation of organosulfur compounds.[1] Iridium-catalyzed reactions of this type using an unsymmetrically substituted allylic substrate normally form the branch product along with the linear product, and their enantioselectivity could be controlled by tuning the catalyst system.[2] Since sulfur compounds, particularly aliphatic thiols, are well-known metal catalyst poisons,[3] their use as nucleophiles in this type of transformation remains a considerable challenge. While carbon−sulfur bond formation with aromatic thiols (e.g. 4-chlorothiophenol, 2-pyridinethiol, 2-pyrimidinethiol, and thiophenol) has been investigated in this context,[4] the employment of more basic aliphatic thiols, which failed to conduct an allylation catalyzed by palladium catalyst,[4a] for the

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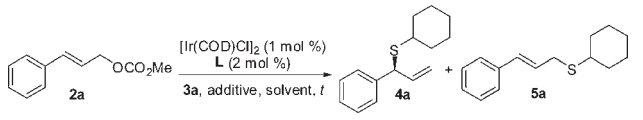
Table 1. Reaction Optimization for the Iridium-Catalyzed Asymmetric Alkylation of Sodium Cyclohexanethiolate **3a**[a]



entry	L	solvent	additive	temp (°C)	yield (%)[b]	4a/5a[c]	ee (%)[d]
1	**L1**	DCM	CsF	15	36	95/5	82
2	**L2**	DCM	CsF	15	NR[e]		
3	**L3**	DCM		15	72	91/9	96
4	**L3**	DCM	CsF	15	78	92/8	98
5	**L4**	DCM	CsF	15	77	93/7	97
6	**L5**	DCM	CsF	15	33	92/8	95
7	**L6**	DCM	CsF	15	NR[e]		
8	**L3**	DCM	CsCl	15	64	88/12	96
9	**L3**	DCM	LiCl	15	77	90/10	96
10	**L3**	DCM	CsF	25	68	88/12	96
11	**L3**	DCM	CsF	0	55	88/12	96
12	**L3**	DCM	CsF	−25	NR[e]		
13	**L3**	THF	CsF	15	trace	66/34	
14	**L3**	PhMe	CsF	15	trace	54/46	

[a] Reaction conditions: 1 mol % of $[Ir(COD)Cl]_2$, 2 mol % of **L**, 200 mol % of **2a**, 100 mol % of **3a**, and 300 mol % of additive. [b] Isolated yields. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Determined by the chiral HPLC analysis. [e] NR = no reaction.

preparation of functionalized allyl alkyl sulfides by iridium catalysis is relatively unexplored.[4]

Our laboratory has started with a program aimed at the development of asymmetric allylation for carbon−sulfur bond formations.[4d] In connection with this program, we envisioned an access to the enantioselective synthesis of allyl alkyl sulfide by iridium-catalyzed allylation. Although allyl alkyl sulfides are key components of bioactive molecules[5] and serve as versatile synthetic intermediates,[6] only direct asymmetric catalytic methods have been identified for their preparation.[4] Herein, we report that chiral monodentate phosphoramidite-ligated iridium complex catalyzes the enantioselective allylation of allylic alcohol derivatives with aliphatic thiols.

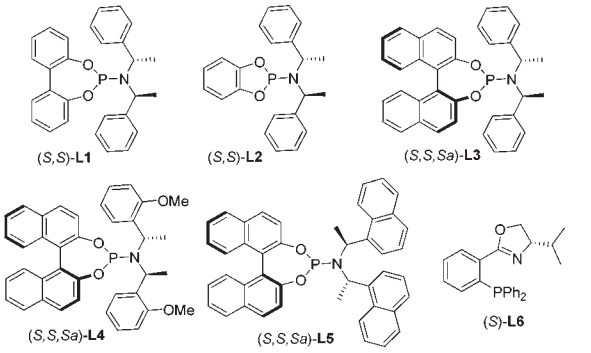


Figure 1. Chiral Ligands **L1**−**L6**.

In the first instance, we began with a study on aliphatic thiols as the nucleophile. Thus, an allylation of (*E*)-cinnayl methyl carbonate **2a** with sodium cyclohexanethiolate **3a** as the model reaction in the presence of $[Ir(COD)Cl]_2$ (1 mol %), ligand **L1**[7] (2 mol %), and cesium fluoride (CsF) in dichloromethane (DCM) was performed at 15 °C. To our delight, the corresponding products were obtained in 36% yield with 95:5 **4a**:**5a** and 82% ee (entry 1), indicating that the chiral amine of **L1** alone could induce the good ee value of the branch product **4a**. Inspired by these results, a range of the varying ligands such as **L2**,[8] **L3**,[9,10] **L4**,[9] **L5**,[10] and PHOX ligand **L6**[11] (see Figure 1) were further evaluated and the preliminary results were illustrated in Table 1. The reactions with ligands **L3** and **L4** afforded the branch product **4a** in 72−78% yields with excellent regio- and enatioselectivity (entries 3−5). However, the iridium complex generated from either a stereochemically simpler ligand **L2** or PHOX ligand **L6** totally failed to promote this allylation (entry 2 vs entry 7). In addition, the use of a sterically hindered ligand **L5** in this allylation led to the desired products in poor yield (entry 6). Finally, **L3** was chosen as the optimal ligand for further exploration. In our previous study on the iridium-catalyzed allylation of thiophenol, we found that CsF has strong influences on the efficiency and regioselectivity.[4d] As a result, we investigated the effect of additives, solvents, and temperature on this allylation. As shown in Table 1, the use of additives including CsF, CsCl, and LiCl merely had slight influences on both yield and regioselectivity (entries 4, 8, and 9). Interestingly, the desired products were also obtained in 72% yield with 91:9 **4a**:**5a** and 96% ee without the use of any additive (entry 3 vs entry 4). Changing the temperature had a dramatic effect on the

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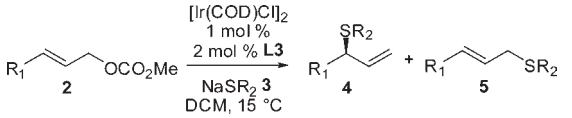
Table 2. Ir-Catalyzed Asymmetric Allylation of Sodium Aliphatic Thiolates [a]



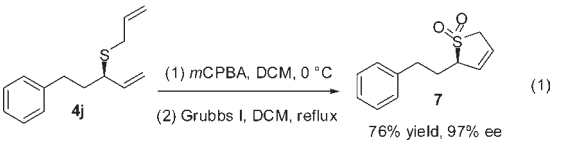
entry	R_1	R_2	time (h)	**4** (%)[b]	**4**/**5**[c]	ee (%)[d]
1	Ph	C_6H_{11}	12	**a**, 72	91/9	96
2	3-$MeOC_6H_4$	C_6H_{11}	12	**b**, 78	84/16 (91/9)[e]	96
3	4-$MeOC_6H_4$	C_6H_{11}	12	**c**, 71	94/6	98
4	4-MeC_6H_4	C_6H_{11}	36	**d**, 74	93/7	97
5	4-ClC_6H_4	C_6H_{11}	36	**e**, 71	88/12 (92/8)[e]	95
6	4-BrC_6H_4	C_6H_{11}	12	**f**, 80	86/14 (90/10)[e]	98
7	2-thienyl	C_6H_{11}	12	**g**, 74	86/14	98
8	$PhCH_2CH_2$	C_6H_{11}	12	**h**, 56	71/29[f]	95
9	4-BrC_6H_4	allyl	12	**i**, 60	94/6	94
10	$PhCH_2CH_2$	allyl	12	**j**, 34	77/23[f]	95

[a] Reaction conditions: 1 mol % of $[Ir(COD)Cl]_2$, 2 mol % of **L3**, 200 mol % of **2**, and 100 mol % **3** (0.10 M) in DCM at 15 °C. [b] Isolated yields. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Determined by a chiral HPLC analysis. [e] 300 mol % of CsF was used in this case. [f] Determined by GC−MS.

efficiency and regioselectivity (entries 4 and 10−12). Furthermore, the survey of solvents indicated that DCM is the optimal solvent (entries 3 and 4). Other solvents such as THF and toluene were not effective (entries 13 and 14).

The scope and generality of this method for a diversity of allylic substrates and aliphatic thiols was further explored under the optimized reaction conditions described in entry 3 of Table 1. As demonstrated in Table 2, the phenyl and aryl allyl methyl carbonates **2a**−**f** with either electron-poor groups (e.g., 4-Cl and 4-Br) or electron-rich groups (e.g., 4-OMe, 3-OMe, and 4-Me) on the phenyl ring using sodium cyclohexanethiolate **3a** afforded the corresponding products in 71−80% yields with both excellent regio- and enantioselectivities (entries 1−6). In contrast, the reaction in the presence of CsF led to 4−7% improvement of the regioselectivity with a slight influence on the yield and anitioselectivity (entries 2, 5, and 6). Using 2-thienyl allyl methyl carbonate **2g** resulted in the desired products in 74% yield and 98% ee with slightly lower regioselectivity (86/14) (entry 7). Notably, the reaction of the aliphatic carbonate **2h** or **2j** (entry 8 vs entry 10) occurred in good yield with high enantioselectivity, although the regioselectivity was lower (71:29 to 77:23). Sodium prop-2-ene-1-thiolate **3b** is an effective nucleophile as well (entries 9 and 10).

The branch products **4** generated in this way are highly useful intermediates for the synthesis of biologically active sulfur compounds,[5] especially biotin analogues.[12] To demonstrate the synthetic potential of **4**, a representative example for the preparaton of compound **7** with a biotin core is illustrated in eq 1. The ring-closing metathesis (RCM) of (3-(allylsulfonyl)pent-4-enyl)benzeneacyclic sulfone with Grubbs' catalyst, which was made from the enantioenriched allyl(5-phenylpent-1-en-3-yl)sulfane **4i**[13] by the oxidation with *m*CPBA, afforded the cyclic sulfone **7**[12g,14], in two steps with 76% yield and 97% ee.



In summary, we have developed an asymmetric iridium-catalyzed allylic alkylation of aliphatic thiols. The allyl alkyl sulfides were achieved in 34−80% yields with up to 94:6 b:l and 98% ee. To the best of our knowledge, this is the first example that good yields and excellent regio- and enantioselectivities are simultaneously realized in the enantioselective transition metal-catalyzed allylations of aliphatic thiols. An important use of the branch product was discussed.

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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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