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Regio- and Enantioselective Iridium-Catalyzed Allylation of Thiophenol: Synthesis of Enantiopure Allyl Phenyl Sulfides

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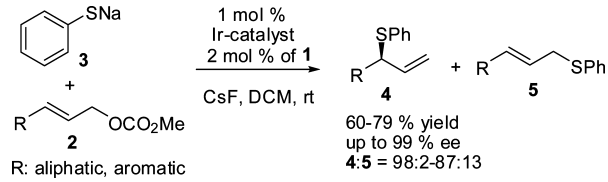
ABSTRACT



A highly regio- and enantioselective allylic alkylation of sodium thiophenoxide has been realized by $[Ir(COD)Cl]_2$/phosphoramidite along with CsF as an additive, producing highly enantioenriched allyl phenyl sulfide compounds with up to 99% ee.

Iridium-catalyzed enantioselective allylic substitutions have been developed as a powerful and general method to synthesize chiral allylic compounds with both high regioselectivity and high enantioselectivity. A wide range of carbo-[1] and heteroatoms[2] (e.g., N, O, and SO_2) nucleophiles has been studied during the past decade, but neither aliphatic nor aromatic thiol nucleophiles have yet been reported. It is well-known that thiols can poison transition-metal catalysts,[3] which imposes a considerable challenge to the study of metal-catalyzed enantioselective allylation substitution reactions. Although the transition-metal-catalyzed allylations of sulfur nucleophiles to form achiral allyl sulfides and sulfones have been extensively investigated,[4] only a few enantioselective allylations of sulfur nucleophiles have been reported; these use Pd catalysis,[5] and the enantioselectivities and product yields varied from poor to excellent depending on reaction conditions and substrates.[5a] Furthermore,

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(1) (a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426–2428. (b) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529–3531. (c) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192–17193. (d) Weix, D. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7720–7721. (e) Helmchen, G.; Dahnz, A.; Duebon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675–691. (f) He, H.; Zheng, X.; Li, Y.; Dai, L.; You, S. *Org. Lett.* **2007**, *9*, 4339–4341. (g) Liu, W.; He, H.; Dai, L.; You, S. *Org. Lett.* **2008**, *10*, 1815–1818. (h) Liu, W.; He, H.; Dai, L.; You, S. *Synthesis* **2009**, 2076–2082. (i) He, H.; Liu, W.; Dai, L.; You, S. *J. Am. Chem. Soc.* **2009**, *131*, 8346–8347. (j) Liu, W.; Zheng, S.; He, H.; Zhao, X.; Dai, L.; You, S. *Chem. Commun.* **2009**, 6604–6607. (k) Spiess, S.; Raskatov, J. A.; Gnamm, C.; Broner, K.; Helmchen, G. *Chem.—Eur. J.* **2009**, *15*, 11087–11090.

(2) (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164–15165. (b) Shu, C. T.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794–4796. (c) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6204–6206. (d) Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949–3951. (e) Ueno, S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1928–1931. (f) Ueda, M.; Hartwig, J. F. *Org. Lett.* **2010**, *12*, 92–94.

(3) (a) Hegedus, L. L.; McCabe, R. W. *Catalyst Poisoning*; Marcel Dekker: New York, 1984. (b) Hutton, A. T. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, U.K., 1984; Vol. 5, p 1151.

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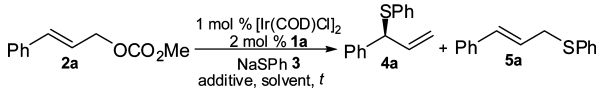
only sulfinates and more acidic aromatic thiols such as 4-chlorothiophenol, 2-mercaptopyridine, and 2-mercaptopyrimidine were effective in these palladium-catalyzed enantioselective systems,[5a,c] and no reactions took place for more basic aliphatic thiols and thiophenol, probably due to competitive coordination to the palladium catalysts between these thiol substrates and chiral ligands.[5a,6]

Herein, we report the formation of chiral allylic phenyl sulfides via iridium-catalyzed enantioselective allylations of sodium thiophenoxide **3**. This represents the first example of the use of transition-metal-catalyzed enantioselective allylations of thiophenol to form allyl phenyl sulfides in good yields and with excellent enantioselectivities. Important potential uses of such products are discussed below.

We first aimed at optimizing reaction conditions for the enantioselective iridium-catalyzed allylations of sodium thiophenoxide **3**[7] to form allyl phenyl sulfides. We initially found that the reaction of (*E*)-cinnamyl methyl carbonate **2a** with **3** in the presence of $[Ir(COD)Cl]_2$ and the chiral ligand **1a**[8,9] in CH_2Cl_2 furnished a mixture of **4a** and **5a** in poor yield and regioselectivity, but excellent enantioselectivity for the branched isomer **4a** (entry 1, Table 1). Many additives such as Cs_2CO_3, CsF,[1c] TBAF, CsCl, AgBr, and LiCl were screened (entries 3−8), and only CsF led to a substantial increase in both efficiency and regioselectivity (entry 4 versus entry 1). The use of $ClCH_2CH_2Cl$ as a solvent gave very similar results to those in CH_2Cl_2 but a better yield than $CHCl_3$ (entries 4, 9, and 11). The reactions completely failed when THF and CCl_4 were employed as solvents (entries 10 and 12). The use of a 2-fold amount of **3** led to a significant decrease in yield (entry 15), but a 2-fold amount of **2a** gave the best regioselectivity (94/6) for the branched isomer **4a** without significantly influencing either efficiency or enantioselectivity (entry 13 versus entry 4). Conducting the reaction below ambient temperature proved deleterious to both yields and selectivity (entries 16 and 17).

A variety of chiral ligands **1a**,[8,9] **1b**,[9] **1c**,[8] and **1d**[10] (Figure 1) was evaluated using the optimized conditions listed in entry 13 of Table 1, and **1a** gave the best yield and regio- and enantioselectivity (Table 2). It should be noted that reactions completely failed when **1d** was employed (entry 4).

Table 1. Optimizing Reaction Conditions for Ir-Catalyzed Allylations of NaSPh **3**[a]



entry	additive[b]	solvent	**2a/3**	temp, °C	yield[c] (%)	**4a/5a**[d]	ee[e] (%)
1	none	CH_2Cl_2	1.2/1	25	25	25/75	90
2	none	CH_3CN	1.2/1	25	28	9/91	
3	Cs_2CO_3	CH_2Cl_2	1.2/1	25	67	67/33	
4	CsF	CH_2Cl_2	1.2/1	25	82	89/11	97
5	TBAF	CH_2Cl_2	1.2/1	25	*f*		
6	AgBr	CH_2Cl_2	1.2/1	25	16	94/6	
7	CsCl	CH_2Cl_2	1.2/1	25	38	67/33	
8	LiCl	CH_2Cl_2	1.2/1	25	18	85/15	
9	CsF	$CHCl_3$	1.2/1	25	56	93/7	
10	CsF	CCl_4	1.2/1	25	NR[g]		
11	CsF	$ClCH_2CH_2Cl$	1.2/1	25	78	92/8	
12	CsF	THF	1.2/1	25	NR[g]		
13	CsF	CH_2Cl_2	2/1	25	72	94/6	97
14	CsF	CH_2Cl_2	3/1	25	75	90/10	
15	CsF	CH_2Cl_2	1/2	25	40	80/20	
16	CsF	CH_2Cl_2	2/1	0	20	93/7	
17	CsF	CH_2Cl_2	2/1	−25	trace		

[a] Reaction conditions: 1 mol % of $[Ir(COD)Cl]_2$, 2 mol % of **1a**, 120 mol % of **2a**, and 100 mol % of **3** (0.1 M) at 25 °C. [b] 300 mol % of additive for entries 3−17. [c] Isolated yields. [d] Determined by ^1H NMR of the crude reaction mixture. [e] Determined by chiral HPLC analysis (Phenomenex Celluolose-1). [f] Complex products were observed. [g] NR = no reaction.

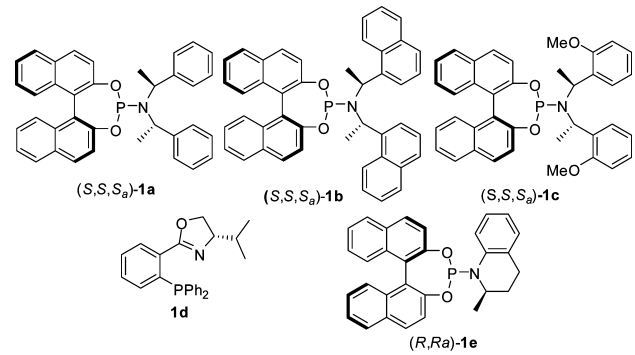


Figure 1. Chiral ligands**1a**−**e**.

Table 2. Screening Chiral Ligands[a]

entry	ligand	time (h)	yield[b] (%)	**4a/5a**[c]	ee[d] (%)
1	**1a**	10	72	94/6	97
2	**1b**	22	62	93/7	95
3	**1c**	12	52	92/8	97
4	**1d**	48	NR[e]		

[a] Reaction conditions: as listed in entry 13, Table 1. [b] Isolated yields. [c] Determined by ^1H NMR of the crude reaction mixture. [d] ee of **4a** was determined by chiral HPLC analysis (Phenomenex Celluolose-1). [e] NR = no reaction.

(4) (a) Kondo, T.; Mitsdo, M. *Chem. Rev.* **2000**, *100*, 3205–3220. (b) Eichelmann, H.; Gais, H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 643–646. (c) Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc.* **1996**, *118*, 6297–6298. (d) Trost, B. M.; Crawley, M. L.; Lee, C. B. *J. Am. Chem. Soc.* **2000**, *122*, 6120–6121. (e) Felpin, F. X.; Landais, Y. *J. Org. Chem.* **2005**, *70*, 6441–6446. (f) Chandrasekhar, S.; Jagadeshwar, V.; Saritha, B.; Narsihmulu, C. *J. Org. Chem.* **2005**, *70*, 6506–6507. (g) Jegelka, M.; Plietker, B. *Org. Lett.* **2009**, *11*, 3462–3465. (h) Alexey, B.; Zaitsev, H. F.; Caldwell, P. S.; Pregosin, L. F. V. *Chem.—Eur. J.* **2009**, *15*, 6468–6477. (i) Kondo, T.; Morisaki, Y.; Uenoyama, S.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **1999**, *121*, 8657–8658.

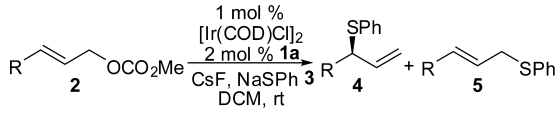
(5) (a) Frank, M.; Gais, H.-J. *Tetrahedron: Asymmetry.* **1998**, *9*, 3353–3357. (b) Gais, H.-J.; Spalthoff, N.; Thomas, J.; Frank, M.; Raabe, G. *Tetrahedron Lett.* **2000**, *41*, 3809–3812. (c) Gais, H.-J.; Thomas, J.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Chem.—Eur. J.* **2003**, *9*, 4202–4221.

(6) (a) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598–11599. (b) Ruiz, J.; Cutillas, N.; Sampedro, J.; López, G.; Hermoso, J. A.; Martínez-Ripoll, M. *J. Organomet. Chem.* **1996**, *526*, 67–72.

(7) Various alkali-metal (Li, Na, and K) salts of thiophenol were tested, and we found that sodium thiophenoxide **3** gave the best result.

Having established the optimized reaction conditions, we turned to a survey of the scope and generality of iridium-catalyzed enantioselective allylations of sodium thiophenoxide. As shown in Table 3, all aromatic and

Table 3. Enantioselective Ir-Catalyzed Allylations of NaSPh with Allyl Methyl Carbonates[a]



entry	R	time (h)	**4**[b] (%)	**4/5**[c]	ee[d] (%)
1[e]	Ph	2	**a**, 72	94/6	97
2	3-MeOC$_6$H$_4$	4	**b**, 68	92/8	99
3	4-MeOC$_6$H$_4$	4	**c**, 79	93/7[e]	95
4	4-MeC$_6$H$_4$	3	**d**, 70	94/6	90
5	4-ClC$_6$H$_4$	4	**e**, 67	91/9	98
6	4-BrC$_6$H$_4$	3	**f**, 73	90/10	96
7	3-CF$_3$C$_6$H$_4$	4	**g**, 69	98/2[e]	97
8	2-thienyl	3	**i**, 72	90/10	99
9	2-ClC$_6$H$_4$	10	**h**, 60	90/10	47
10	*n*-Pr	5	**j**, 70	87/13	91
11	Me	5	**k**, 60	91/9[e]	98

[a] Reaction conditions: 1 mol % of [Ir(COD)Cl]$_2$, 2 mol % of **1a**, 300 mol % of CsF, 200 mol % of **2**, and 100 mol % **3** (0.1 M) in CH_2Cl_2 at 25 °C. [b] Isolated yields. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] ee of **4** was determined by chiral HPLC analysis; see the Supporting Information for details. [e] Determined by GC−MS.

heteroaromatic allyl methyl carbonates **2a**−**i** with either electron-donating groups (e.g., 4-OMe, 3-OMe, and 4-Me) or electron-withdrawing groups (e.g., 4-Cl, 4-Br, and 3-CF_3) on the phenyl ring gave the branched allylic sulfides **4a**−**i** in good yields (67−79%) and with excellent enantioselectivities (90−99% ee, entries 1−8). The reaction also worked well with the aromatic substrate **2h** with an *o*-Cl group on the phenyl ring but with lower enantioselectivity (47% ee, entry 9). The unfavorable ortho substituent effect is in accord with the previously reported iridium-catalyzed asymmetric allylic substitution reactions.[1j] When the same reaction with **2h** was performed using the ligand (*R*,*Ra*)-**1e**[11,1h] rather than **1a**, the result was far inferior; the yield of **4** + **5** was only 5% even after twice the time used in the experiment with ligand **1a**. The aliphatic allylic carbonates **2j**[12] and **2k** are effective substrates as well (entries 10 and 11).

The single-crystal structure (Figure 2) (see the Supporting Information for details) of compound **4f** in

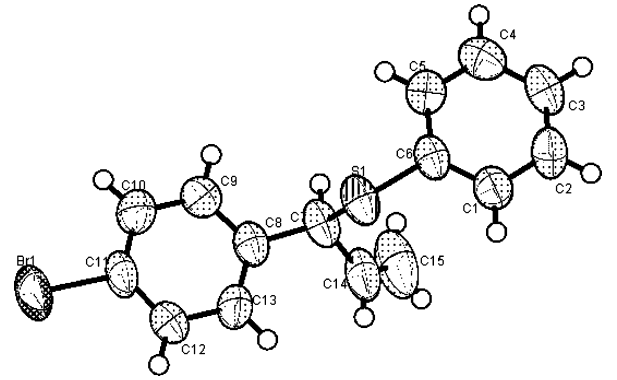
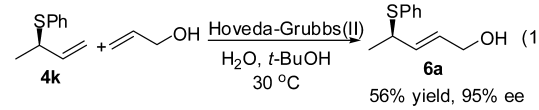


Figure 2. Structure of (*S*)-**4f** (thermal ellipsoids are set at 30% probability).

enantiopure form (**4f** was obtained by recrystallization from isopropyl alcohol) has been determined by X-ray diffraction analysis, which reveals its absolute configuration as *S*. Recently, the origin of enantioselectivity in iridium-catalyzed enantioselective allylic substitutions was described by the Hartwig group based on the single-crystal structure of an elegantly designed allyliridium intermediate complex.[13] The stereochemistry of iridium-catalyzed allylation of sodium thiophenoxide with the chiral phosphoramidite ligand (*S*,*S*,*S*$_a$)-**1a** completely supports their explanation.

We envision very significant synthetic uses of highly enantioenriched allyl phenyl sulfides **4** generated in this way. In order to demonstrate some of these, we have converted the terminally unsubstituted enantioenriched 3-phenylthio-1-butene **4k** into enantioenriched *trans*-4-phenylthio-2-pentene-1-ol **6a** using the metathesis developed by Davis[14] that works particularly well for allyl phenyl sulfides; this representative example is demonstrated in eq 1. Compound **6a** is an apt example since it has been prepared[15] by a considerably longer route from lactic acid and has been converted to *trans*-2-phenythio-3-pentene, demonstrating its potential for conversion to other enantioenriched substrates.



In summary, we report the formation of a variety of allyl phenyl sulfides via the enantioselective iridium-catalyzed allylation of sodium thiophenoxide. To the best of our knowledge, this is the first example in which both good yields and excellent enantioselectivities are simultaneously achieved in the enantioselective transition-metal-catalyzed allylations

(8) Tissot-Croset, K.; Polet, D.; Gille, S.; Hawner, C.; Alexakis, A. *Synthesis* **2004**, 2586–2590.

(9) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865–2878.

(10) (a) Matt, P. v.; Pfaltz, A. *Angew. Chem., Int. Ed* **1993**, *32*, 566–568. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1995**, *34*, 1769–1772.

(11) The ligand (*R*,*Ra*)-**1e** was effective in improving the enantioselectivity of the branched product in the Ir-catalyzed *o*-chlorophenylallylation of indole as indicated in reference **1h**.

(12) Compound **4j** has been prepared in racemic form from **2j** by Pd-catalyzed allylation of thiophenol; the yield was very low due to the unfavorable regioselectivity. Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1994**, *50*, 10321–10330.

(13) Madrahimov, S. T.; Markovic, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 7228–7229.

(14) Lin, Y. A.; Chalker, J. M.; Floyd, N.; Bernardes, G. J. L.; Davis, B. G. *J. Am. Chem. Soc.* **2008**, *130*, 9642–9643.

(15) Bach, T.; Körber, C. *J. Org. Chem.* **2000**, *65*, 2358–2367.

of thiophenol. Some possible important uses of the products are 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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