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Chiral carbon–sulfur center formation *via* Pd-catalyzed asymmetric allylic thioetherification: synthesis of allylic thioethers†

Junmei Cai,‡ Juewang Cai,‡ Purui Zheng, Xiaorong Wang* and Xiaoming Zhao*

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Pd-catalyzed asymmetric allylic thioetherification reaction of various sodium thiolates was realized, which gave the allylic thioethers in good to high yields with high enantioselectivities. The reaction results considerably depend on the substrates and the bulky sulfur nucleophile led to excellent enantioselectivity as well.

Approximately one-fifth of the 200 most-prescribed drugs in 2011 were organosulfur compounds.[1] More interestingly, the optically active sulfur-containing compounds exhibit excellent biological activity.[2] For example, the popular pharmaceutical products and naturally occurring compounds such as biotin,[3] montelukast,[4] eflucimibe,[5] and mPEES-1 inhibitors contain a chiral center bearing a carbon–sulfur (C–S) bond (Fig. 1).[6] Noticeably, a direct way for the construction of a C–S bond is by palladium-catalyzed allylic substitution.[7] Pd-catalyzed asymmetric allylic substitution has become a powerful tool for the synthesis of chiral compounds.[7,8] To this context, allylic thioetherification reactions have been less reported since sulfur nucleophiles can poison the transition-metal catalyst.[9] Pd-catalyzed allylic substitutions of sulfur nucleophiles revealed that 4-chlorothiophenol,[10] 2-mercaptopyridine,[10] 2-mercaptopyrimidine,[10] *tert*-butylthiol,[10j] tri-*tert*-butyl(*tert*-butylthio)silane,[10j] sulfinates,[10e,10f,11] thiocarbamates,[12] and thioacetates[13] were suitable nucleophiles.

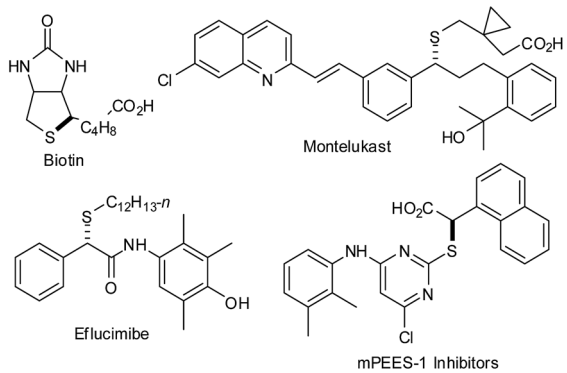

Fig. 1 Four compounds with a chiral C–S center.

Iridium (Ir)-catalyzed asymmetric allylic substitutions of sulfur nucleophiles was contributed by our group[14] and others.[15] To the best of our knowledge, the C–S bond construction by Pd-catalyzed asymmetric allylations is a largely unexplored area in organic synthesis. In this paper, we report an enantioselective Pd-catalyzed allylic substitution of symmetrical allylic acetates with sodium thiolate (NaSR), which afford the allylic thioethers with high enantioselectivities.

An initial thioetherification reaction between (*E*)-1,3-bis(4-chlorophenyl)allyl acetate **1a** and sodium prop-2-ene-1-thiolate **2a** was explored with Pd-complex generated from $Pd_2(dba)_3$, $Pd(OAc)_2$, and $[Pd(C_3H_5)Cl]_2$ with (*R*)-BINAP **L1** (ref. 16) at −10 °C, respectively (Table 1, entries 1–3). To our delight, the allylic thioether **3a** was obtained with a 61% yield and 91% enantiomeric excesses (ee) when $[Pd(C_3H_5)Cl]_2$/**L1** was utilized (Table 1, entry 3). The remaining Pd salts such as $Pd_2(dba)_3$ and $Pd(OAc)_2$ are ineffective for this reaction (entries 1 and 2). Solvent survey indicated that DCM is suitable (Table 1, entry 3) and the other solvents such as THF and toluene gave the poor yields with the moderate ee (Table 1, entries 4 and 5). In contrast, the reaction gave **3a** in a 50% yield with 80% ee in the absence of base (Table 1, entry 6). These results illustrated that the nature of bases has a considerable influence on the enantioselectivities. Thus, a variety of bases including KOAc, NaOAc, KI, trimethylsilyl (*E*)-*N*-(trimethylsilyl)formimidate (BSA), DBACO, and KOAc/BSA was examined. A combination of KOAc and BSA gave rise to a superior result (Table 1, entry 11), whereas other bases led to fair yields with moderate to high ee (Table 1, entries 7–11). A slight excess **2a** was employed and it gave the best result (Table 1, entry 11 *vs.* 12).

State Key Laboratory of Pollution Control and Resource Reuse, Department of Chemistry, Tongji University, 1239 Siping Road, 200092 Shanghai, P. R. China. E-mail: xmzhao08@mail.tongji.edu.cn; xrwang@tongji.edu.cn

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‡ The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

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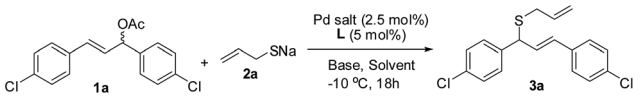
Table 1 Optimization of the reaction conditions[a]



En	Pd salt	L	Sol	Base	Yield[b] [%]	ee[c] [%]
1	$Pd_2(dba)_3$	**L1**	DCM	KOAc	—	—
2	$Pd(OAc)_2$	**L1**	DCM	KOAc	—	—
3	$[Pd(C_3H_5)Cl]_2$	**L1**	DCM	KOAc	61	91
4	$[Pd(C_3H_5)Cl]_2$	**L1**	THF	KOAc	30	85
5	$[Pd(C_3H_5)Cl]_2$	**L1**	Toluene	KOAc	35	75
6	$[Pd(C_3H_5)Cl]_2$	**L1**	DCM	—	50	80
7	$[Pd(C_3H_5)Cl]_2$	**L1**	DCM	NaOAc	60	84
8	$[Pd(C_3H_5)Cl]_2$	**L1**	DCM	KI	50	92
9	$[Pd(C_3H_5)Cl]_2$	**L1**	DCM	BSA	61	92
10	$[Pd(C_3H_5)Cl]_2$	**L1**	DCM	DBACO	60	90
11	$[Pd(C_3H_5)Cl]_2$	**L1**	DCM	KOAc/BSA	73	92
12[d]	$[Pd(C_3H_5)Cl]_2$	**L1**	DCM	KOAc/BSA	81	95
13[d]	$[Pd(C_3H_5)Cl]_2$	**L2**	DCM	KOAc/BSA	Trace	—
14[d]	$[Pd(C_3H_5)Cl]_2$	**L3**	DCM	KOAc/BSA	—	—
15[d]	$[Pd(C_3H_5)Cl]_2$	**L4**	DCM	KOAc/BSA	—	—
16[d]	$[Pd(C_3H_5)Cl]_2$	**L5**	DCM	KOAc/BSA	—	—
17[d,e]	$[Pd(C_3H_5)Cl]_2$	**L1**	DCM	KOAc/BSA	68	83

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (1.0 equiv.), Pd salt (2.5 mmol%), **L1–L5** (5 mmol%), base (1.0 equiv.), and solvent (2.0 mL) at −10 °C under argon. [b] Isolated yield. [c] Determined by HPLC. [d] **2a** = 1.2 equiv. [e] At 0 °C.

The ligands are crucial to Pd-catalyzed asymmetric allylic substitutions.[8] Therefore, the effect of ligands including (*R*)-Tol-BINAP **L2**,[12] Trost **L3**,[17] Josiphos **L4**,[18] and PHOX **L5** (ref. 19) (Fig. 2) on the allylic thioetherification was examined. The allylic thioetherification of **2a** took place with the best enantioselectivity in the presence of the catalyst derived from (*R*)-BINAP **L1** (Table 1, entry 12). Unexpectedly, **L2** structurally similar to **L1** only gave a trace amount of **3a** (Table 1, entry 13). These outcomes indicated that the steric demand of the ligands has great influence on this reaction. Subsequent investigation indicated that the Pd complexes made from **L3–L5** failed to promote this reaction (Table 1, entries 14–16). The reaction was carried out at 0 °C and it afforded a somewhat worse result than that at −10 °C (Table 1, entry 12 *vs.* 17).

Using this procedure, the scope of the thioetherification reactions of a range of allylic acetates **1** with sodium prop-2-ene-1-thiolate **2a** was subsequently explored (Table 2). The allylic substrates **1a–f** with electron-poor group (*e.g.*, *p*-Cl, *p*-F, *p*-Br, *m*-Cl, *m*-F, and *m*-Br) on the phenyl ring gave the corresponding products **3a–f** in moderate to high yields with the high level of the enantioselectivities.

In addition, both (*E*)-1,3-diphenylallyl acetate **1g** and the allylic substrate **1h** with an electron-rich group (*e.g.*, *m*-CH_3) on the phenyl ring offered the allylic thioethers **3g** and **3h** in the acceptable yields with the moderate enantioselectivities. These results suggested that sodium prop-2-ene-1-thiolate **2a** is a somewhat weak nucleophile and the reaction results considerably depend upon the allylic substrates in these cases. The steric demand and nature of sulfur nucleophiles **2** was also investigated. The representative sulfur nucleophiles such as sodium phenylmethanethiolate **2b**, sodium cyclohexanethiolate **2c**, sodium 2-methylpropane-2-thiolate **2d**, and sodium benzenethiolate **2e** were thus examined. **2b** gave the results similar to that of **2a**; and a bulky **2c** resulted in the corresponding **3j** in a 70% yield with 93% ee. Significantly, the more steric hindered **2d** was utilized at −15 °C and it afforded the corresponding **3k** in a 88% yield with 91% ee. Aromatic sulfur nucleophile **2e** also gave rise to the corresponding **3l** in a 70% yield with a lowering ee (Table 2). The allylic substrate **1i** bearing an electron-donating group (*e.g.*, *p*-CH_3) on the phenyl ring provided **3m**

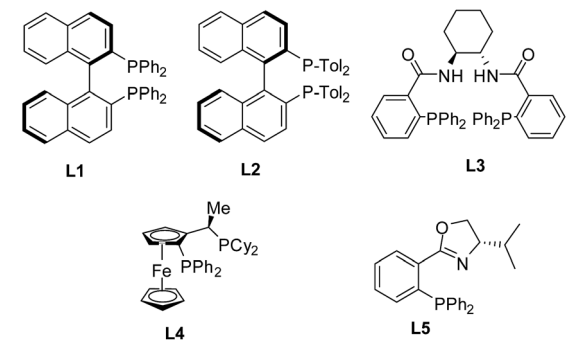
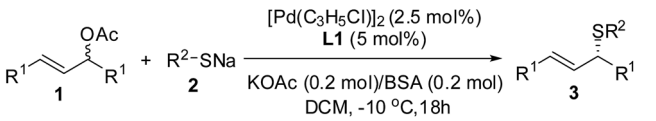
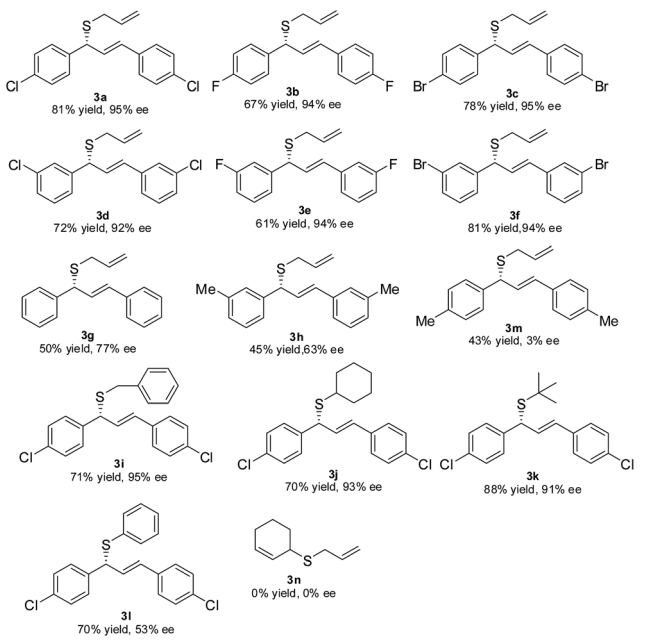


Fig. 2 Chiral ligands **L1–L5** used in this allylic sulfane.

Table 2 The scope of the allyl acetates **1** and sodium thiolates **2**[a,b,c,d]





[a] Reaction conditions: **1** (0.20 mmol), **2** (1.2 equiv.), $[Pd(C_3H_5Cl)]_2$ (2.5 mmol), **L1** (5 mmol), KOAc (1.0 equiv.), BSA (1.0 equiv.) and solvent (2.0 mL) at −10 °C under argon. [b] Isolated yield. [c] Determined by HPLC. [d] At −15 °C.

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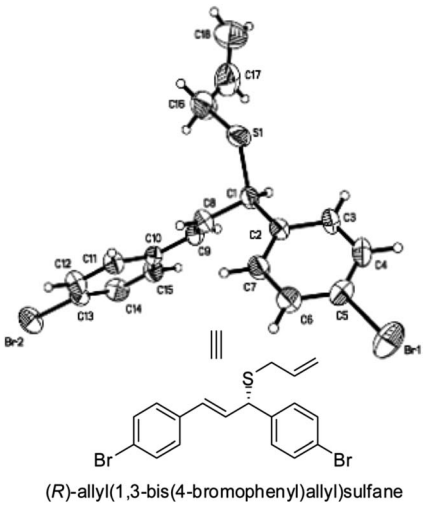

Fig. 3 X-ray structure of (*R*)-**3c**.

with a 43% yield with 3% ee. The aliphatic substrate such as cyclohex-2-enyl acetate **1j** was also examined and the corresponding product **3n** were not observed (Table 2).

A single-crystal X-ray diffraction analysis of **3c**[20] (Fig. 3) illustrates the absolute configuration of **3c** as *R* (see ESI† for details).

Conclusions

In conclusion, we developed a practical method for the formation of C–S bond *via* Pd-catalyzed asymmetric allylic thioetherifications, which gives the allylic thioethers in good to high yields with high enantioselectivities. This method allows the use of bulky sulfur nucleophiles, illustrates good tolerance of the aryl-substituted allyl acetates, and offers a new way to chiral allylic thioethers.

Acknowledgements

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