Allylic Thioethers

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Enantioselective Allylic Thioetherification: The Effect of Phosphoric Acid Diester on Iridium-Catalyzed Enantioconvergent Transformations**

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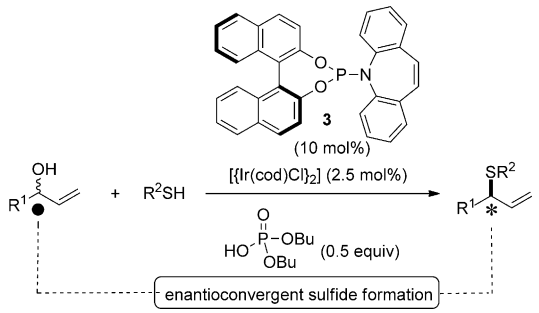
Iridium-catalyzed allylic substitution reactions have established themselves as useful, viable processes for the production of valuable building blocks.[1] The collection of nucleophiles used in this transformation has been expanded dramatically in recent years[2] to include amines,[3] alkoxides and bicarbonates,[4] silyl enol ethers,and malonate diesters.[5] The direct use of a heteroatom nucleophile without prior activation by conversion into a salt has been reported for only a few cases, such as ammonia,[6] alcohols, and phenols.[7] Iridium-catalyzed enantioselective allylations of sulfur nucleophiles[8] are also known, involving thiophenolates,[9] aliphatic thiolates,[10] sodium sulfide,[11] sulfinates,[12] and iPr$_3$SiSNa.[13,14] Herein, we report the direct, enantioselective thioetherification of branched racemic allylic alcohols with thiols to form optically active, secondary allylic thioethers (Scheme 1). We also document our mechanistic findings,



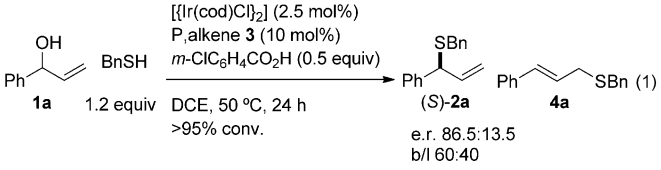
Scheme 1. Direct, enantioconvergent substitution of branched allylic alcohols with thiols.

which implicate a rare example of a direct enantioconvergent transformation (DET), which renders the formation of allylic sulfides from allylic alcohols highly efficient.

We have previously reported the iridium-catalyzed allylic substitution of branched allylic alcohols with sulfamic acid, as an ammonia surrogate, in both enantiospecific[15] and enantioselective[16] syntheses of allylic amines. The approach has been expanded to include alcohols as nucleophiles to provide unsymmetrical ethers.[17] In seeking to further expand the scope and use of allylic alcohols, we have examined the use of thiols directly.[18]

The primary challenge in using racemic electrophiles in enantioselective allylation is the inherent rate difference of the two enantiomers. A variety of approaches to overcome or exploit this rate difference have been developed, such as dynamic kinetic resolution (DKR), dynamic kinetic asymmetric transformation (DYKAT), and parallel kinetic resolution (PKR).[19] A notable example of the latter is the report by Hartwig and co-workers in which the kinetic resolution of racemic branched allylic benzoates leads to substitution products in 37–48% yield based on the allylic substrate, while the other enantiomer is converted to the linear allylic benzoate.[20] A lesser known approach is termed direct enantioconvergent transformation (DET). In this process the substrate enantiomers react by two distinctly different mechanistic pathways to give the same product enantiomer. The criteria for DET are rather difficult to meet, and consequently this transformation has been scarcely reported.[21]

Our investigations into the enantioselective allylic thioetherification commenced with conditions involving the reaction of allylic alcohol **1a** with 1.2 equiv of BnSH, 0.5 equiv of 3-chlorobenzoic acid as a Brønsted acid promoter and [{Ir(cod)Cl}$_2$] with ligand **3** in Cl(CH$_2$)$_2$Cl (DCE) at 50 °C. Complete consumption of **1a** was observed and **2a** was isolated with an e.r. of 86.5:13.5 [Eq. (1)]. In contrast to prior observations with this catalyst in which formation of only the branched product was noted, a 3:2 mixture of thioether products **2a** and **4a** was observed.[22]



The observation of **4a** and the difficulty in improving the selectivity, despite extensive experimentation, led to a study of the mechanism.[23] Our previous work on allylic etherification reactions demonstrated that a Brønsted acid is required to promote alcohol activation and substitution.[17] However, we noted that in the absence of acid catalyst thiols participate in the substitution reaction, albeit conversions above 60% were not observed. The first important mecha-

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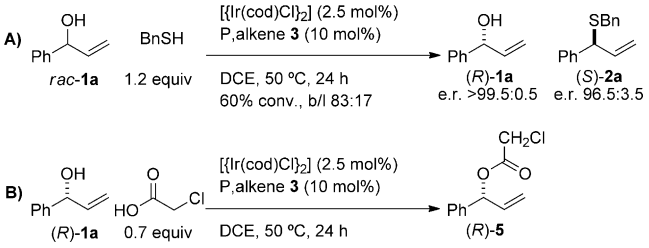
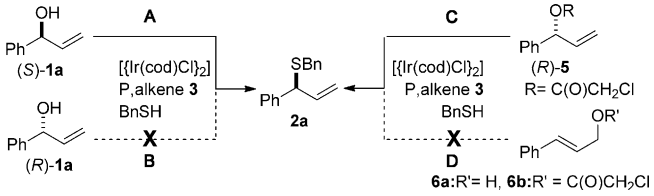
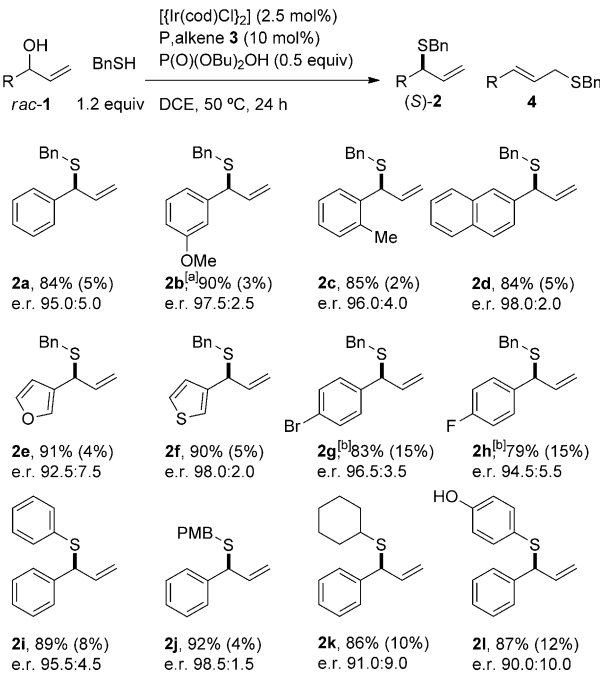


Scheme 2. Key observations for mechanistic investigations. Bn = benzyl.

nistic clue was the observation that the reisolated **1a** displayed an e.r. exceeding 99.5:0.5 (Scheme 2A). These results, the formation of (*R*)-**1a** and (*S*)-**2a** in high optical purity, suggest that kinetic resolution had occurred.[17] This implies that only one substrate enantiomer, namely (*S*)-**1a**, undergoes reaction with the Ir–(P,alkene) complex (Scheme 3, see A and B). A second important observation



Scheme 3. Selected experiments to study the mechanism.[22]



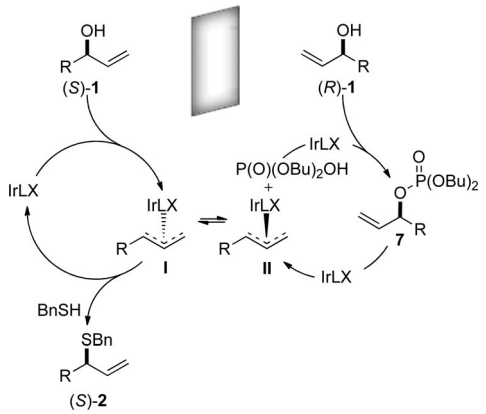
Scheme 4. Enantioselective allylic thioetherification. Yields of isolated product after full consumption of starting material **1**; yield of linear thioether **4** in brackets as measured by ^{1}H NMR analysis; e.r. values determined by SFC on a chiral phase; absolute configuration determined by comparison to $[\alpha]_D$ of known compounds. [a] 23 °C. [b] 80 °C. PMB = *p*-methoxy benzyl; SFC = supercritical fluid chromatography

was the isolation of allylic ester **5** from the reaction mixtures in the absence of thiol (Scheme 2B).[24] Whether allylic ester **5** could be an intermediate in the allylic thioetherification was then investigated. When **5** was independently prepared and subjected to the reaction conditions without an acid promoter, full conversion of (*R*)-**5** to **2a** with improved enantioselectivity (e.r. 86.0:14.0) and regioselectivity (b/l 92:8) occurred (Scheme 3C). Control experiments showed that alcohol **6a** and ester **6b** were not substrates for the reaction (Scheme 3D).

These observations prompted us to examine whether it would be possible to utilize the divergent reactivity of allylic alcohols in an enantioconvergent transformation, in which an acid serves as a promoter for a pathway enabling the conversion of the second substrate enantiomer to product. The in-depth study by Helmchen and You on allylic substitution reactions of *o*-aminostyrenes decisively demonstrated that allyl phosphates are superior nucleofuges in allylation reactions.[25] Consequently, we sought to form an allyl phosphate intermediate in situ that would subsequently be converted to thioether product **2a**. After some optimization with various phosphoric acids, optimal conditions were identified.[22] The use of 0.5 equiv of di-*n*-butylphosphoric acid furnished **2a** in 84% yield at full conversion, with an e.r. of 95.0:5.0 and vastly improved regioselectivity of 96:4 (b/l) (Scheme 4, **2a**). Investigations of the substrate scope revealed that electron-rich allylic alcohols participated in the thioetherification at 23 °C (Scheme 4, **2b**), while electron-deficient substrates required a higher reaction temperature of 80 °C (Scheme 4, **2g** and **2h**).

Sterically hindered (Scheme 4, **2c**) and heteroaromatic (Scheme 4, **2e**, **2f**) thioethers could be formed from BnSH in good yields and enantioselectivity. Thiophenol gave thioether **2i** in good yield, e.r. 95.5:4.5, and b/l selectivity of 92:8 (Scheme 4, **2i**). *p*-Methoxy benzyl mercaptan formed the protected allyl thiol in e.r. 98.5:1.5 and 92% yield (Scheme 4, **2j**). Aliphatic cyclohexanethiol could also be employed, albeit with lower enantioselectivity (e.r. 91.0:9.0; Scheme 4, **2k**). 4-Mercaptophenol gave only product substituted at sulfur (Scheme 4, **2l**).

The initial observations delineated above in the allylic thioetherification (Scheme 3) in combination with additional studies involving phosphoric acid[22] led us to postulate the operation of an enantioconvergent mechanism,[26] where each enantiomeric alcohol undergoes reaction through independent mechanistic pathways (Scheme 5). Thus, (*S*)-**1** enters the catalytic cycle directly upon its conversion to a putative allyl–iridium intermediate **I** to give product enantiomer (*S*)-**2** with overall retention of configuration. The other substrate enantiomer, (*R*)-**1**, first is transformed to its allyl phosphoric ester **7**, leading to allyl–iridium intermediate **II**. The latter is presumably in equilibrium with **I** and subsequently undergoes conversion to thioether (*S*)-**2** with overall inversion of configuration. Although the precise nature of the allyl–iridium intermediate is not yet known, the interconversion between the π-allyl iridium complexes **I** and **II** has been

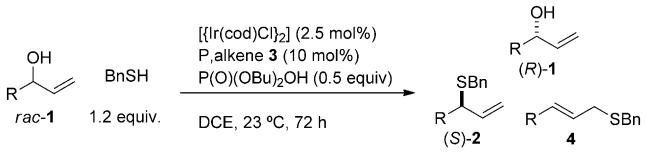


Scheme 5. Mechanistic proposal for the enantioconvergent allylic thioetherification.[22]

postulated by Helmchen and Bartels in a related system.[27] In this respect, we have independently prepared allylic phosphate esters (*S*)-**7** and (*R*)-**7** (R = Ph) and have shown by ^{1}H NMR spectroscopy that under standard conditions with BnSH (2.5 mol% [{Ir(cod)Cl}$_2$], 10 mol% **3**, 50 °C) each furnished the same *S* product **2a**.

Aliphatic and some electron-poor allylic alcohols did not participate in enantioconvergent thioetherifications. Instead, in these cases a phosphate-promoted kinetic resolution process was observed (Table 1). To optimize the enantio-

Table 1: Resolution of aliphatic and electron-poor secondary allylic alcohols.



Entry	R	Conv. [%][a]	Yield **2** [%][b]	**2**/**4**[c]	e.r.[d]
1	4-$CF_3C_6H_4$	49	45	97:3	96.5:3.5
2	2-BrC_6H_4	51	47	97:3	99.0:1.0
3	$PhCH_2CH_2$	50	48	>99:1	96.5:3.5
4	Bu	52	46	>99:1	87.0:13.0

[a] Determined by ^{1}H NMR analysis. [b] Yields of isolated product. [c] Determined by ^{1}H NMR analysis. [d] e.r. values determined by SFC on a chiral phase; absolute configuration determined by comparison to $[\alpha]_D$ of known compounds.

and regioselectivity, the resolution reactions of electron-poor and aliphatic allylic alcohols were performed at room temperature over 4 days. The resolution reaction stopped at about 50% conversion even with 1.2 equivalents of thiol. The high yields and enantioselectivity make this kinetic resolution protocol a viable procedure for these challenging substrates.[28,29]

In conclusion we have developed an enantioselective allylic thioetherification reaction of racemic branched allylic alcohols employing thiols in the presence of an Ir–(P, alkene) catalyst and dibutyl phosphate as a promoter. Allylic thioethers are synthesized with good yields and good to excellent enantioselectivity. For some electron-deficient and aliphatic allyl alcohols a kinetic resolution protocol with high selectivity was developed. A collection of observations suggest the operation of an underlying enantioconvergent mechanism for the transformation of racemic starting materials into one product enantiomer. The use of a phosphate diester has been identified as the key to enabling the enantioconvergent pathways. The effect of phosphate as a catalyst in combination with its properties as a leaving group as observed by You and Helmchen opens up new avenues for the development of new enantioselective transformations of racemic substrates. Additional investigations are ongoing and will be reported as the results become available.

Experimental Section

A round-bottom flask under Argon was charged with [{Ir(cod)Cl}$_2$] (16.8 mg, 25.0 μmol, 2.50 mol%) and the phosphorus–alkene **3** (50.8 mg, 100 μmol, 10.0 mol%). Dichloroethane (2.00 mL, 0.5 M) was added and the reaction mixture was stirred at 23 °C for 15 min. Benzyl mercaptan (141 μL, 1.20 mmol, 1.20 equiv) and dibutyl phosphate (105 mg, 0.500 mmol, 0.500 equiv) were added by syringe, followed by allylic alcohol **1a** (134 mg, 1.00 mmol, 1.00 equiv). The resulting reaction mixture was stirred at 50 °C for 24 h. Conversion was monitored by disappearance of the starting material on TLC. The reaction mixture was washed with sodium carbonate (2.00 mL). The aqueous layer was extracted with dichloromethane (2 × 2.50 mL) and the combined organic fractions were dried with magnesium sulfate. The solvent was removed in vacuo and purification of the residue by flash chromatography on silica gel using hexanes/ethyl acetate (100:1) as eluent afforded allylic thioether **2a** as a clear oil in 84% yield (201 mg, 0.836 mmol). e.r. 95.1:4.9.

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[24] The formation of ester **5** was accompanied by the formation of its linear isomer $\mathbf{6_{[c]}}$; see Table S4, entries 5 and 6 in the Supporting Information. Ester $\mathbf{6_{(c)}}$ could be formed from **5** by [3,3]-sigmatropic rearrangement since the styrene residue is more stable.

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