Allylic Etherification

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Enantioselective Allylic Etherification: Selective Coupling of Two Unactivated Alcohols**

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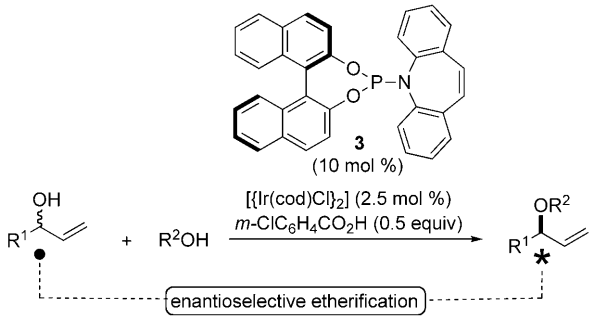
Enantioselective allylic etherification reactions provide efficient methods for the synthesis of enantiomerically enriched, value-added building blocks.[1] Palladium,[2] ruthenium,[3] and iridium[4] catalysts have been developed for this transformation. Iridium and rhodium catalysts are particularly promising because they enable the synthesis of enantioenriched branched products incorporating monosubstituted olefins. The enantioselective approach employing Ir has been documented by the groups of Alexakis, Hartwig, and Helmchen, and the Rh-catalyzed enantiospecific substitution of optically enriched, branched allylic carbonates has been developed by the group of Evans.[5] For the preparation of ethers, all of the methods to date have employed activated electrophiles, for example carbonates or esters, and activated nucleophiles in the form of alkoxides. Optically active allylic ethers may also be prepared through Ir-catalyzed kinetic resolution of racemic allylic alcohol derivatives.[6] Herein, we report the direct, enantioselective substitution of unactivated, branched allylic alcohols to afford branched allylic ethers by a dynamic kinetic resolution process (DKR; Scheme 1).[7] We also document kinetic data on the relative rates of substitution for two enantiomeric alcohols, which also permits kinetic resolution of the substrate in a divergent fashion to provide access to alcohol and ether in enantiopure form. The process is robust, as it can be conducted with technical-grade solvent, with an open flask, employing in situ formed catalyst. To the best of our knowledge, no enantioselective iridium-catalyzed allylic etherification, employing branched substrates, has been reported to date.[6b,8]



Scheme 1. Direct, enantioselective substitution of unactivated, branched allylic alcohols.

In previous work we disclosed the Ir-catalyzed enantiospecific allylic substitution of branched allylic alcohols with sulfamic acid (NH_3SO_3) to form primary allylic amines with high stereospecificity.[9] We have subsequently become interested in expanding the salient features of this process to other nucleophiles. Specifically, we sought the development of a process that would enable direct substitution of the allylic alcohol substrate by an alcohol nucleophile. It is important to note that the processes reported in the literature for the metal-catalyzed preparation of ethers require activated allylic electrophiles (carbonates, esters, and chlorides) and prescribe the use of alcohols as nucleophiles when subjected to prior[4b–d] (ROM: M = Li, Na, Cu, and $(RO)_2Zn$) or in situ[4e–g] (ROH + K_3PO_4 or guanidine or Et_3N) activation as the corresponding alkoxides.

The basis of our investigation was the observation of a side reaction involving condensation of phenyl vinyl carbinol (**1a**) to the corresponding symmetrical ether in the presence of Brønsted acids and Ir complexes incorporating the P,alkene ligand **3**. This suggested the possibility of fashioning a process for the preparation of unsymmetrical ethers derived from the condensation of allylic and aliphatic alcohols. We then proceeded to screen a range of acid additives for activation of the allylic alcohol substrate in the presence of a second alcohol. The results indicate that Brønsted acids with pK_a values in the range of 3.4 to 3.9 (aq) were found to be competent promoters for a range of aliphatic alcohols. The use of weaker acids, such as acetic and benzoic acid, led to negligible conversion (Table 1, entries 1 and 2), and the use of stronger acids, such as camphorsulfonic acid, resulted in decomposition of starting material (entry 3).

For Brønsted acids within the acceptable pK_a window, subtle structural effects on reaction yield and enantioselectivity were observed. Thus, formic acid (pK_a 3.8) performed less effectively than *m*-chlorobenzoic acid (pK_a 3.8) although both have the same pK_a (entries 6 and 8). In this respect, *p*-nitrobenzoic acid (pK_a 3.4), a stronger acid than formic acid, performed almost identically (entry 7). 1,2-Dichloroethane was identified as superior to toluene or tetrahydrofuran (entries 4–6) and optimal as the solvent for the allylic etherification. We have noted that the use of 5 equivalents of aliphatic alcohol co-reactant precludes the formation of the symmetrical diallyl ether and, consequently, provides good yields of the corresponding unsymmetrical allyl alkyl ethers. Interestingly, the use of more than 10 equivalents of alcohol

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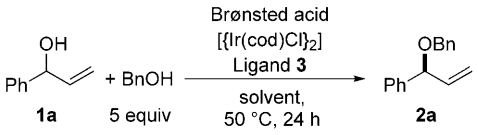
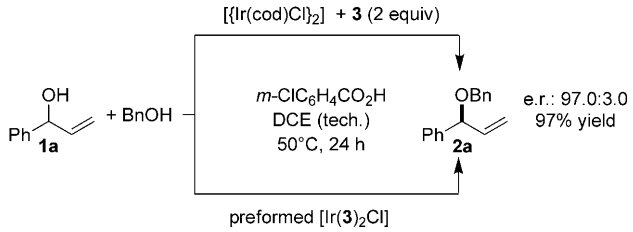
Table 1: Optimization of allylic etherification[a]



Entry	Acid	Solvent	Conv (%)[b]	e.r.
1	$MeCO_2H$	toluene	<10	–
2	$PhCO_2H$	toluene	0	–
3	CSA[c]	toluene	0	–
4	HCO_2H	toluene	60	92.5:7.5
5	HCO_2H	THF	50	81.5:18.5
6	HCO_2H	DCE	73	87.0:13.0
7	p-$NO_2C_6H_4CO_2H$	DCE	74	89.5:10.5
8	***m*-$ClC_6H_4CO_2H$**	**DCE**	**>95**	**98.5:1.5**
9	m-$ClC_6H_4CO_2H$	BnOH, DCE[d]	0	–

[a] General procedure: **1a** (0.10 mmol, 1.0 equiv), BnOH (5.0 equiv), [{Ir(cod)Cl}$_2$] (2.5 mol%), **3** (10 mol%), acid (0.50 equiv), solvent (0.20 mL). [b] Determined by ^{1}H NMR spectroscopy. [c] CSA = camphor sulfonic acid. [d] BnOH (0.2 mL, 20 equiv) and DCE as cosolvent (0.05 mL). DCE = 1,2-dichloroethane.

co-reactant inhibits the reaction (entry 9). The product of linear substitution was not observed, as assayed by ^{1}H NMR spectroscopy. It is important to note that the allylic etherification could be performed under ambient atmosphere with technical-grade solvents with minimal loss in enantioselectivity (Scheme 2), which is a testament to the robustness of the iridium catalyst.[9a]

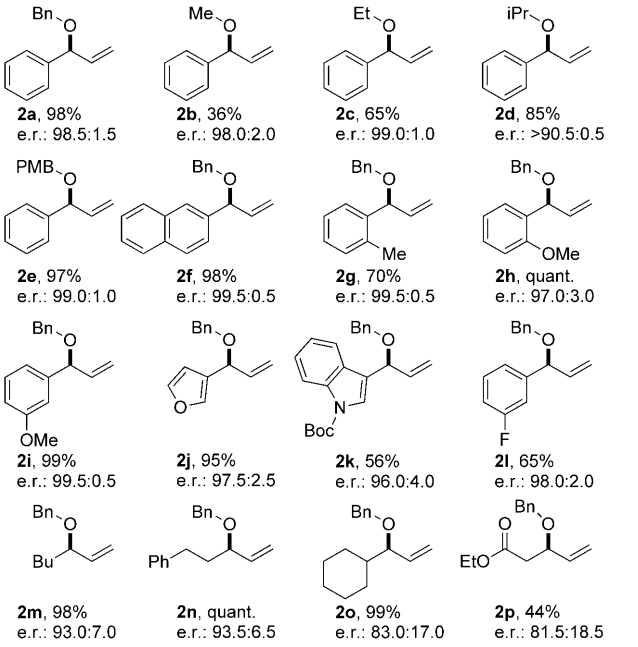


Scheme 2. Substitution reactions in techical-grade solvent with catalyst prepared in situ (top) and with preformed and purified catalyst [Ir(**3**)$_2$Cl] (bottom).

Moreover, the Ir(**3**)$_2$Cl complex prepared and crystallized beforehand was found to be catalytically competent: its use in the allylic etherification provided product in identical yield and enantioselectivity, as that of reactions in which [{Ir(cod)Cl}$_2$] (cod = 1,5-cyclooctadiene) and ligand (**3**) were added sequentially to the reaction vessel prior to addition of substrates (Scheme 2; compare Table 1, entry 8). This result also suggests that the cod ligand is not a participant in the active catalyst. The reaction time can be shortened by heating the reaction mixture to 80 °C, which leads to completion of the reaction in 5 hours but with decreased enantioselectivity (e.r.: 80:20).[10]

With the optimal conditions at hand (Table 1, entry 9) the substrate scope of the allylic etherification reaction was investigated. A variety of both aliphatic and allylic alcohol substrates were evaluated. In addition to benzyl alcohol (Table 2, **2a**), other common alcohols, such as methanol (**2b**), ethanol (**2c**), and 2-propanol (**2d**), serve as nucleophiles in the reaction of *rac*-**1a**. The corresponding ether derived from

Table 2: Stereoselective allylic etherification.[a]



[a] Yield of isolated product after full consumption of starting material **1**; e.r. values determined by SFC on a chiral phase; absolute configuration determined by comparison with $[\alpha]_D$ of known compounds.[10]

p-methoxy benzyl alcohol was obtained in 97% yield and an e.r. of 99.0:1.0 (**2e**). It is important to note that the yields listed in Table 2 correspond to the yields of products isolated at full consumption, or conversion, of starting material. Thus, the reaction that leads to the formation of product **2k** was allowed to proceed until all alcohol starting material had been observed to be consumed.

Using benzyl alcohol as the common nucleophile, it was found that aromatic (**2f**, **2g**), heteroaromatic (**2j**, **2k**), and electron-deficient (**2l**) allylic alcohols were competent substrates. In general, however, the highest yields and enantioselectivities were achieved in reactions utilizing arene vinyl carbinols. Interestingly, *rac*-ethyl 3-hydroxypent-4-enoate serves as a substrate and affords ether **2p**. To the best of our knowledge such allylic alcohols have not been investigated as substrates before and their use in the allylic etherification reaction provides an alternate direct route to protected acetate aldol adducts of acrolein.

In order to demonstrate that both substrate enantiomers are transformed to the same ether enantiomer, highly enantioenriched samples of either (*R*)- or (*S*)-**1a** were separately subjected to the catalytic etherification reaction conditions as described above. (*S*)-**2a** was formed in >99.5:0.5 e.r. from (*S*)-**1a** and in 97.0:3.0 e.r. from (*R*)-**1a** (Figure 1). When the reactions were monitored by ^{1}H NMR spectroscopy, it was found that the rate for the reaction of (*S*)-**1a** exceeds that for the reaction using (*R*)-**1a**.

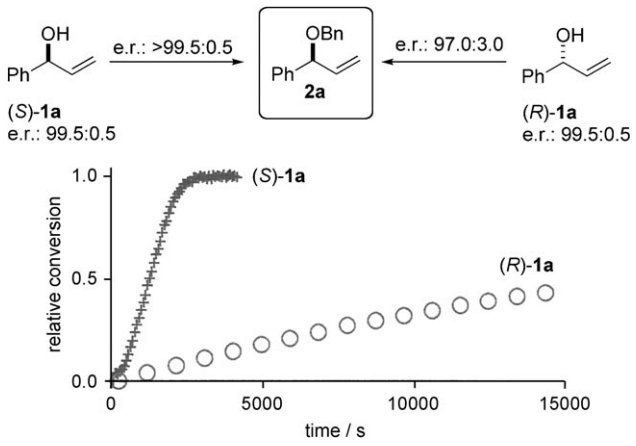
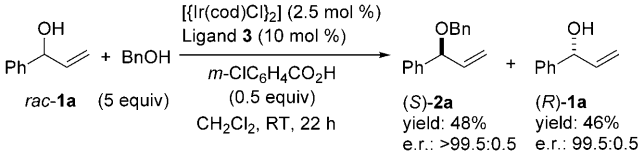


Figure 1. Profile for the allylic etherification for both substrate enantiomers, (*S*)-**1a** (+) and (*R*)-**1a** (○), monitored by ^{1}H NMR spectroscopy at 52 °C. Full conversion of (*R*)-**1a** was observed after 1 day.[10]

The observed rate difference prompted us to investigate the possible kinetic resolution of the allylic alcohol substrate.[8c] At room temperature the allylic alcohol *rac*-**1a** was successfully resolved to its *R* enantiomer by selective allylic etherification of (*S*)-**1a** with benzyl alcohol following the (P,alkene)Ir-catalyzed allylic etherification protocol described (Scheme 3). The use of 5 equivalents of benzyl alcohol as the nucleophile posed no problem to the resolution and both products were recovered in good yield (46–48 %) and excellent enantioselectivity (e.r.: 99.5:0.5 or better).



Scheme 3. Kinetic resolution at room temperature.

In summary, we have developed a robust enantioselective allylic etherification reaction that employs two alcohols, with allylic alcohols as electrophiles and commercially available aliphatic alcohols as nucleophiles. As part of a preliminary mechanistic study, we have noted a difference involving the rate of the reaction of the enantiomeric substrates, as demonstrated by ^{1}H NMR spectroscopic studies. This should enable the development of a modified protocol for the kinetic resolution of an allylic alcohol, allowing isolation of unreacted alcohol and the corresponding benzyl ether in high optical purity, as showcased for a test substrate. The results we have described underscore the unique aspects of the Ir complex incorporating the P,alkene ligand, leading to considerable simplification in the preparation of optically active allyl alkyl ethers. Moreover, the Ir catalyst is able to accept allylic alcohols directly as substrates because of the ability of a Brønsted acid to serve as co-catalyst. This considerably expands the activation options for these substrates beyond those previously described by us and others. Additional studies are underway, and results will be reported as they become available.

Experimental Section

A round-bottom flask under argon was charged with [{Ir(cod)Cl}$_2$] (8.40 mg, 13.0 μmol, 2.50 mol %), ligand **3** (25.4 mg, 50.0 μmol, 10.0 mol %), and *m*-chlorobenzoic acid (39.1 mg, 250 μmol, 0.50 equiv). Dichloroethane (1.00 mL, 0.5 M with respect to allylic alcohol) was added, and the reaction mixture was stirred at 23 °C for 15 min. Benzyl alcohol (260 μL, 2.50 mmol, 5.00 equiv) was added by syringe, followed by allylic alcohol **1a** (67.1 mg, 0.500 mmol, 1.00 equiv). The resulting reaction mixture was stirred at 50 °C for 1 day. The reaction mixture was washed with sodium carbonate (10.0 mL). The aqueous layer was extracted with dichloromethane (2 × 5.00 mL), and the combined organic fractions 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 as eluent afforded allylic ether **2a** as a clear oil in 98 % yield (110 mg, 0.49 mmol). e.r.: 98.5:1.5 (OJ-H; flow: 3.00 mL min^{-1}; 24.5 min (major), 26.4 min (minor); 100 % CO_2 at 100 bar, 25 °C) $[\alpha]_D^{22.9} = -2.19$ ($c = 0.1$ in $CHCl_3$).

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[10] See the Supporting Information for further details.

