Communication

Superbase-Catalyzed anti-Markovnikov Alcohol Addition Reactions to Aryl Alkenes

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Superbase-Catalyzed anti-Markovnikov Alcohol Addition Reactions to Aryl Alkenes

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Supporting Information Placeholder

ABSTRACT: The organic superbase P_4-*t*-Bu catalyzes the direct anti-Markovnikov addition of alcohols to aryl alkenes to access valuable β-phenethyl ethers. A diverse substrate scope of aryl alkenes and alcohols is demonstrated, including heterocyclic systems and unprotected aminoalcohols. Mechanistic studies reveal that the reaction is under equilibrium control, while extensive comparisons to common inorganic bases indicate that the broad reaction scope is uniquely enabled through the use of the organic superbase.

β-Phenethyl ethers constitute important structural features widely found in pharmaceuticals and natural products and are also useful synthetic intermediates.[1] The most direct synthetic route to ethers of this type would be the anti-Markovnikov addition of alcohols to styrene derivatives, a process for which catalysts have long been desired (Figure 1).[2] Typically, a three-step hydroboration/oxidation/substitution sequence must be followed in order to achieve the formal anti-Markovnikov addition of alcohols to olefins.[3] Despite impressive developments of Brønsted acid-, metal- and photoredox-catalyzed alcohol addition methodologies,[4-6] a general process for the preparation of β-phenethyl ethers remains undeveloped.[7,8] In their pioneering work on photoredox-catalyzed alkenol cyclization, the Nicewicz group reported the anti-Markovnikov addition of methanol to *trans*-anethole, although this intermolecular variant has not been significantly generalized for other substrates.[9]

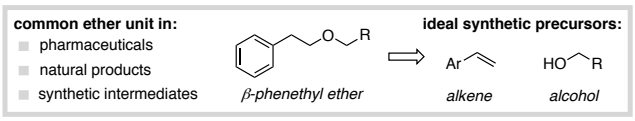
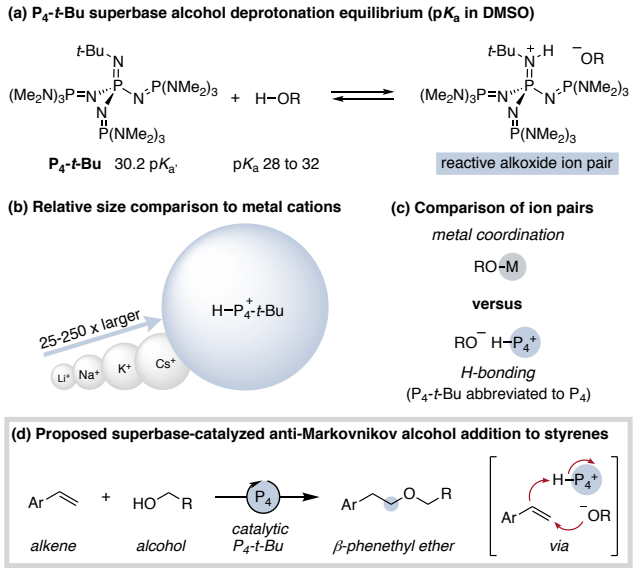


Figure 1. The ideal precursors to valuable β-phenethyl ethers.

In theory, the Brønsted base-catalyzed addition of alcohols to styrenes should proceed with anti-Markovnikov selectivity due to the inherent polarity of the olefin, although almost no reports of this synthetic approach exist. The lack of reactivity of simple styrenes may be attributed to an unfavorable pairing of styrene electrophilicity and the nucleophilicity of common alkoxides.[10] For example, the only reports of base-catalyzed alcohol additions to aryl alkenes involve highly activated systems such as conjugated vinyl *N*-heterocycles.[11] The development of a general base-catalyzed approach has additional challenges, such as the reversibility of the proposed reaction and the propensity for styrene polymerization under basic conditions.[12] We hypothesized that the identity of Brønsted base plays a crucial role in determining the activation energy for alcohol addition and herein report an organic superbase-catalyzed protocol for the anti-Markovnikov addition of alcohols to aryl alkenes.

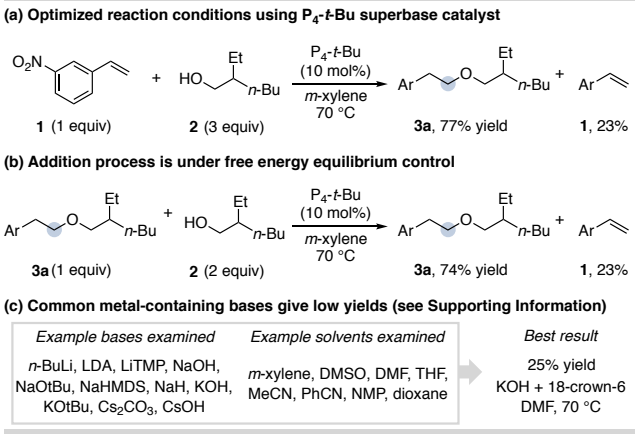
Scheme 1. P_4-*t*-Bu (a) alcohol deprotonation, (b, c) ion pair properties and (d) proposed addition reaction.



We reasoned that the nature of the cation in an alkoxide ion pair, which is derived from the base used for alcohol deprotonation, plays a crucial role in dictating alkoxide reactivity. The commercially available neutral

phosphazene base P_4-*t*-Bu (p$K_{a'}$ 30.2 in DMSO) is predicted to readily deprotonate alcohols (pK_a 28 to 32 in DMSO) in organic solvents to form the alkoxide ion pair shown in Scheme 1a.[13] This base, first reported by Schwesinger in 1987, derives its high basicity from extraordinary electronic donation to a central phosphazene by three flanking phosphazene units.[14] In 2004, Kondo utilized P_4-*t*-Bu to catalyze the addition of alcohols to aryl acetylenes[15], a reaction that inorganic bases also catalyze.[16] We wondered, however, if the unique properties of alkoxide ion pairs derived from P_4-bases could enable other challenging addition reactions (Scheme 1b-d). The large size of the protonated P_4-*t*-Bu cation (500 Å^3, about 25 to 250 times larger volume than common metal cations)[17] has been used to explain the observed "nakedness" and enhanced nucleophilicity of its counteranions.[18] Furthermore, unlike inorganic bases that lead to metal-coordinated alkoxide anions, the P_4-*t*-Bu conjugate acid participates in hydrogen bonding that could rapidly protonate alkoxide addition adducts in either a stepwise or concerted process. Based on this analysis, we hypothesized that the use of P_4-*t*-Bu could overcome the challenges associated with a base-catalyzed approach for the nucleophilic addition of alcohols to aryl alkenes (Scheme 1d).

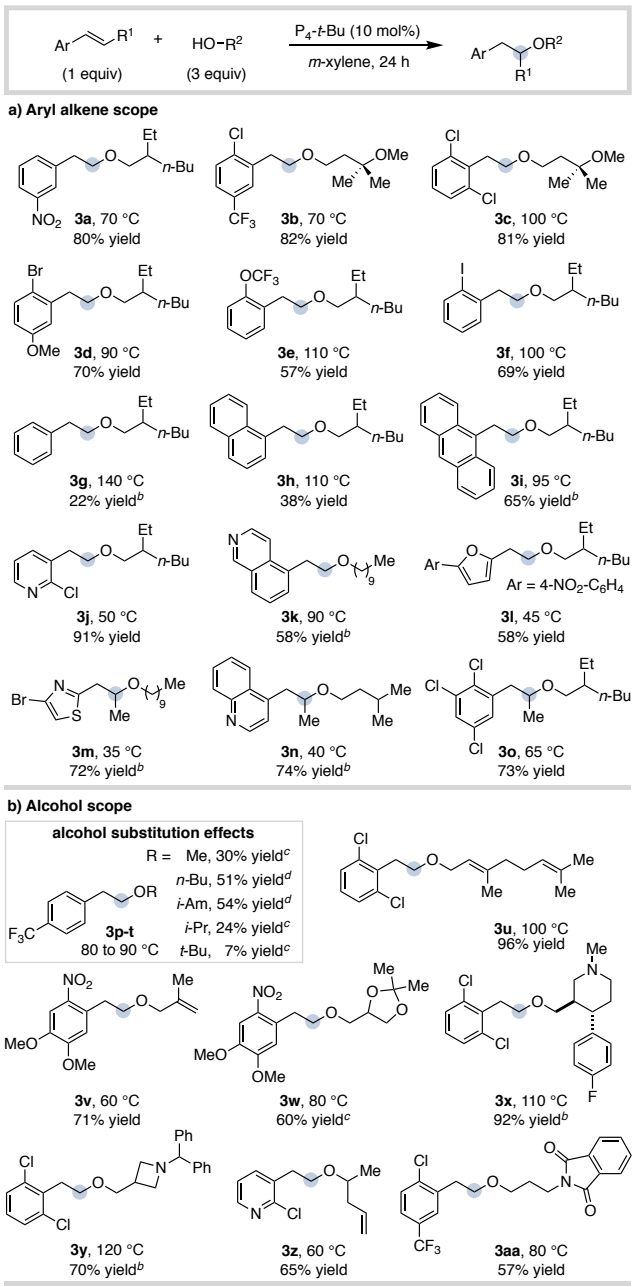
Scheme 2. (a) Optimized and (b) reversible alcohol addition reaction; (c) comparison to inorganic bases.[a]



[a] Yields determined by ^{1}H NMR analysis of crude reaction mixture, see Supporting Information for details; Ar = 3-NO_2-C_6H_4.

Using the addition of 2-ethyl-1-hexanol to 3-nitrostyrene as a model reaction for optimization, we discovered that P_4-*t*-Bu (10 mol%) catalyzes alcohol addition in 77% yield at 70 °C in *m*-xylene, with 23% remaining alkene (Scheme 2a).[19] We observed decreased yields at both lower and higher temperatures, suggesting the addition reaction may be under free energy equilibrium control.[19] This was confirmed when the addition product **3a** was subjected to identical reaction conditions as in Scheme 2a, resulting in a similar ratio of **3a** to 3-nitrostyrene (Scheme 2b). We tested a variety of common inorganic bases in catalytic and stoichiometric quantities under a range of reaction conditions; out of the approximately 125 conditions examined with metal bases, only one gave greater than 20% yield (Scheme 2c).[19] Similar observations to the reversibility experiments and base comparisons shown in Scheme 2 were found using other styrene substrates and are detailed in the Supporting Information. Overall, the comparison to inorganic bases suggests that P_4-*t*-Bu is a more efficient and general catalyst for this transformation, although we cannot rule out that currently unidentified conditions could enable inorganic base catalysis.

Table 1. Substrate scope for the anti-Markovnikov addition of alcohols to aryl alkenes.[a]

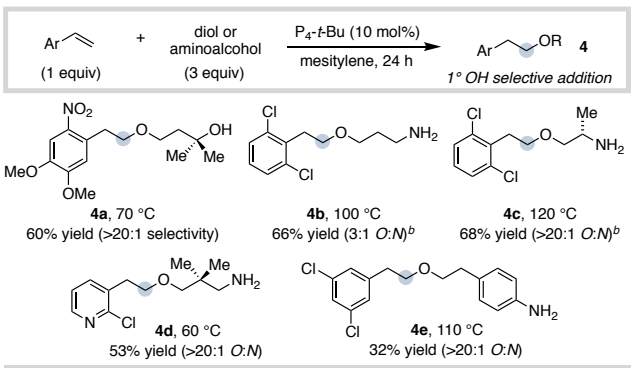


[a] All yields are isolated yields of runs performed with 0.5 to 1 mmol of alkene; [b] mesitylene used as solvent; [c] ^{1}H NMR yield; [d] 5 equiv alcohol used; see Supporting Information for details.

The substrate scope for P_4-*t*-Bu-catalyzed anti-Markovnikov alcohol addition reactions is shown in Table 1. In line with our optimization studies, we found the temperature used for each substrate combination was crucial for obtaining optimal yield, with decreased yields occurring at higher temperatures. First, the scope of aryl alkene was explored using simple alcohols (Table 1a). In general, electron-poor to -neutral styrenes gave moderate to good yields, while highly electron rich styrenes provided trace product. The observed electronic trend is likely both a kinetic and thermodynamic consequence as more electron-rich styrenes require higher temperatures for addition to occur, at which point the equilibrium yield is significantly decreased. Diverse functional groups and substitution patterns were well-tolerated, including *meta*-nitro (**3a**), -trifluoromethyl (**3b**) and -methoxy (**3d**) groups, as well as *ortho*-chloro, -bromo, -trifluoromethoxy and -iodo groups (**3b-f**). Styrene provided 22% product at 140 °C (**3g**), while 1-vinylnaphthalene and 9-vinylanthracene gave increased yields (**3h,i**; 38 and 65% yield, respectively). Heteroaryl alkenes, such as pyridines, quinolines, furans and thiazoles also delivered ethers in high yield (**3j-n**). In product **3j**, the addition process selectively occurred over aromatic substitution at the 2-chloro position. β-substitution is also tolerated on the aryl alkene, yielding secondary ether products **3m-o**. The aryl alkene scope indicates that the reaction does not require resonance-stabilizing functional groups (e.g. nitro, cyano or carbonyl groups) in the 2- or 4-positions.[20]

The alcohol scope for this process is highlighted in Table 1b. First, using 4-(trifluoromethyl)styrene, we found that the alcohol addition equilibrium favors ether to a greater degree for longer chain primary alcohols compared to methanol (**3p-r**). Isopropanol (**3s**) and *tert*-butanol (**3t**) also provided product, albeit in decreased yields.[21] A range of diverse and densely functionalized primary alcohols provided ethers in high yield. Geraniol (**3u**), solketal (**3w**), a paroxetine derivative (**3x**), and alcohols featuring olefin (**3v**), azetidine (**3y**) and phthalimide (**3aa**) functional groups were compatible with this protocol. A secondary homoallylic alcohol also coupled to 2-chloro-3-vinylpyridine in good yield (**3z**).

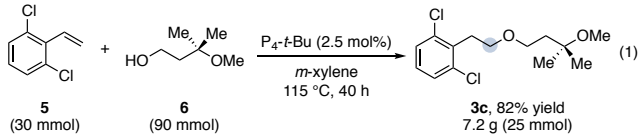
Table 2. Highly selective anti-Markovnikov addition reactions of unprotected diols and aminoalcohols.[a]



[a] Yields represent isolated yields of shown product; selectivity determined by ^{1}H NMR analysis of crude reaction mixture. [b] ^{1}H NMR yield of *O*-addition product; **4b** isolated as Boc-protected amine in 58% yield and **4c** isolated as Fmoc-protected amine in 49% yield; see Supporting Information for details.

We sought to extend this protocol toward the selective functionalization of alcohols containing multiple nucleophilic heteroatoms, such as unprotected diols and aminoalcohols (Table 2).[22] We found selective addition of primary alcohols occurred over a tertiary alcohol (**4a**), primary amines (**4b-d**) and an aniline (**4e**). This selectivity is promising for developing selective reactions of more complex molecules and leaves unprotected heteroatoms available for further functionalization.

Finally, we show that the anti-Markovnikov addition reaction is scalable using low P_4-*t*-Bu catalyst loadings. Thus, using 2.5 mol% catalyst, 7.2 g of ether product **3c** was isolated from the 30 mmol scale reaction in Equation 1.



The described catalytic protocol dramatically streamlines the preparation of simple and complex β-phenethyl ethers through the direct anti-Markovnikov addition of alcohols to styrene derivatives. The addition reaction is governed by equilibrium control, and further mechanistic studies could reveal important thermodynamic parameters required to enable other challenging alcohol addition reactions.[23] This work, and the development of other reactions enabled by organic superbases, are currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization data for all compounds (PDF).

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Notes

The authors declare no competing financial interest.

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(19) See Supporting Information for details.

(20) Activated aryl alkenes, such as 4-nitrostyrene and 4-vinylpyridine, undergo efficient addition, while electron-deficient α-substituted styrenes provide moderate yields; see Supporting Information.

(21) Under the current reaction conditions, water and trimethylsilanol do not react to provide the desired β-phenethyl alcohol or protected alcohol, respectively.

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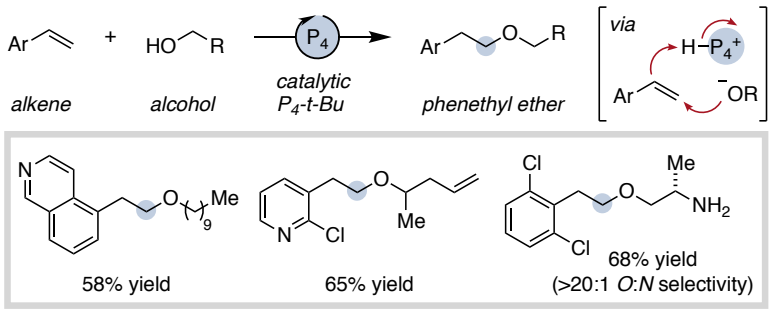
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phenethyl ether
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58% yield
O
N
Cl
Me
65% yield
Cl
Me
O
NH2
Cl
68% yield
(>20:1 O:N selectivity)