A Base-Catalyzed Approach for the anti-Markovnikov Hydration of Styrene Derivatives

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The base-catalyzed addition of 1-cyclopropylethanol to styrene derivatives with an acidic reaction workup enables anti-Markovnikov hydration. The use of either catalytic organic superbase or crown ether-ligated inorganic base permits hydration of a wide variety of styrene derivatives, including electron-deficient, *ortho*-substituted and heteroaryl variants. This protocol complements alternative routes to terminal alcohols that rely on stoichiometric reduction and oxidation processes. The utility of this method is demonstrated through multigram scale reactions and its use in a two-step hydration/cyclization process of *ortho*-halogenated styrenes to prepare 2,3-dihydrobenzofuran derivatives.

Introduction

β-Aryl alcohols are an important alcohol subclass that find wide utility in organic chemistry. This substructure is prominently featured in bioactive compounds (Figure 1a)[1] and is a common synthetic intermediate for phenethyl-functionalized compounds, including several pharmaceuticals (Figure 1b).[2] Medicinal chemistry discovery efforts also frequently employ this building block to perform structure activity relationship (SAR) studies on phenethyl units, with three such examples shown in Figure 1c.[3] Two common approaches to β-aryl alcohols are reduction of arylacetic acids[4] and hydroboration/oxidation of styrene derivatives.[5,6] While reliable for simple substrates, these methods have limitations that can prevent rapid access to alcohols with diverse aryl groups. For instance, non-commercial arylacetic acids require separate multistep syntheses.[7] Meanwhile, traditional stoichiometric hydroboration/oxidation protocols[8] are often unselective and low yielding for electron-deficient or *ortho*-substituted styrenes and heteroaryl variants, thus requiring alternative hydroboration methods and reagents.[9] A new approach to β-aryl alcohols from styrene derivatives that does not rely on reduction or oxidation events could therefore improve access to this valuable class of alcohol.[10]

The catalytic anti-Markovnikov hydration of aryl-substituted alkenes has long been desired as a sustainable and complementary alternative to stoichiometric hydroboration/oxidation processes.[11] Several strategies toward this goal have recently been reported for styrenes, including Grubbs' triple relay catalytic process[12], Arnold's and Li's biocatalytic approaches[13], and Lei's photocatalytic alkene oxidation method.[14] While these methods are impressive in their mechanistic strategy for achieving anti-Markovnikov selectivity, they have yet to be applied toward more complex styrene substrates, including vinyl *N*-heteroarenes. Thus, there remains a current challenge to develop catalytic hydration methods that can access densely functionalized β-aryl alcohols to better reflect the structural diversity represented in Figure 1.

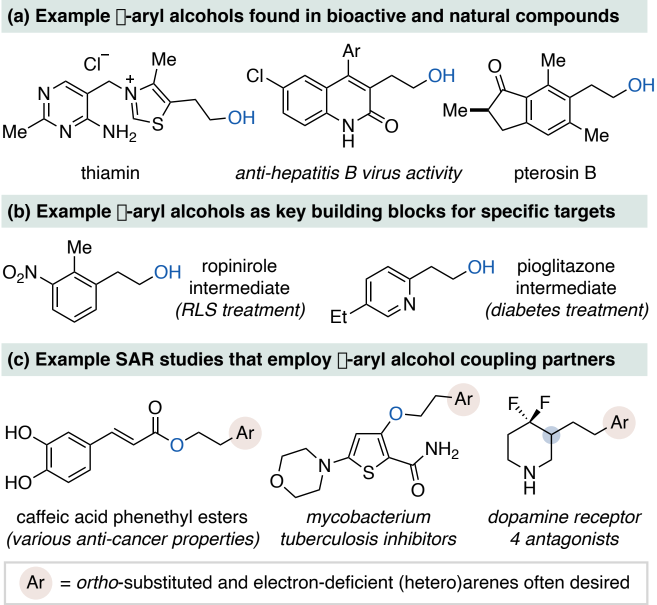

Figure 1. Examples of important of β-aryl substituted alcohols.

We sought to employ base catalysis for the anti-Markovnikov hydration of styrene derivatives as a new approach to β-aryl alcohols. We recently disclosed the use of the phosphazene superbase P_4-*t*-Bu or KO-*t*-Bu with 18-crown-6 as basic catalysts for the nucleophilic addition of alcohols to aryl-substituted alkenes.[15,16] Water does not participate in this reaction, so we instead proposed that a nucleophilic "protected water" source could be identified to achieve formal hydration (Figure 2).[17] Thus, following hydroetherification, facile deprotection could provide straightforward access to β-aryl alcohols with complete regiocontrol. We herein report the discovery of an unconventional nucleophilic water surrogate that enables anti-Markovnikov hydration of styrene derivatives.

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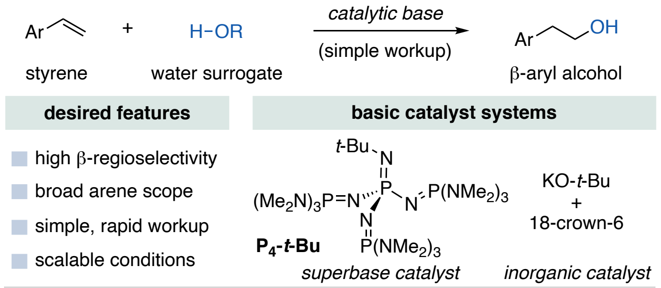
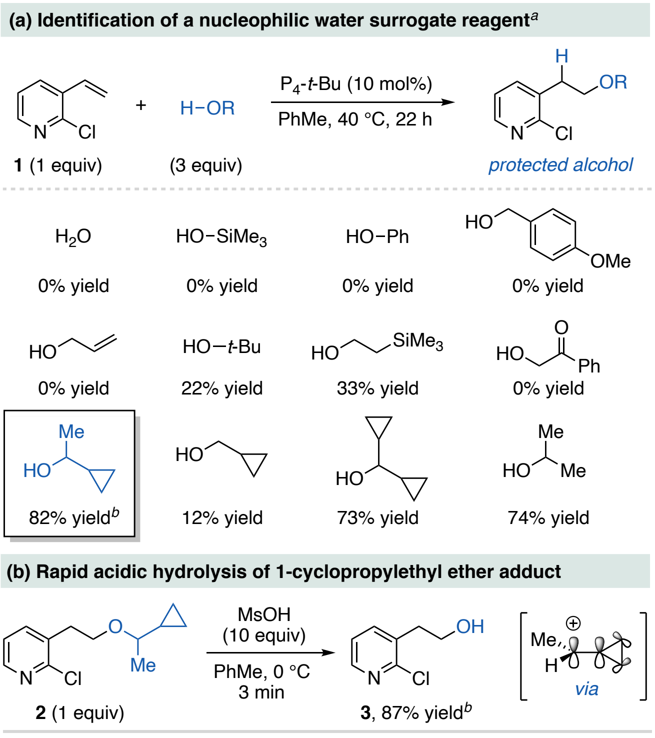


Figure 2. Overview of a base-catalyzed approach to styrene anti-Markovnikov hydration.

Results and Discussion

Base-catalyzed alcohol addition reactions to styrene derivatives are reversible such that the substrate identities and reaction conditions contribute to the observed equilibrium yields. These considerations and the identification of effective catalysts are extensively documented in a recent report from our group that served as the basis for the work described herein.[15b,15d] We began our studies by examining P$_4$-*t*-Bu-catalyzed addition reactions using oxygen pronucleophiles that could potentially serve as water surrogates.[18] These reactions were conducted under our previously optimized reaction conditions with 2-chloro-3-vinylpyridine (**1**) as a model alkene (Scheme 1a).[15d] Water and alcohols comprised of common *O*-protecting groups, such as trimethylsilanol, phenol, *p*-methoxybenzyl alcohol and allyl alcohol do not undergo addition. These results are consistent with our previous studies that revealed alcohol addition to styrenes is both kinetically and thermodynamically challenging, indicating a more nucleophilic water surrogate is necessary for addition.[15,19] However, common aliphatic alcohols devoid of an electron-withdrawing group, such as *tert*-butanol and 2-trimethylsilylethanol, provide low addition yields. Examination of cyclopropyl-substituted alcohols led to the discovery that 1-cyclopropylethanol undergoes addition in 82% isolated yield. The resulting 1-methyl 1'-cyclopropylmethyl (MCPM) ether is a relatively uncommon protecting group developed for oligosaccharide synthesis.[20] For comparison, cyclopropylmethanol, dicyclopropylmethanol and *iso*-propanol all provide lower addition yields. The isolated MCPM ether adduct **2** undergoes high-yielding deprotection in 3 min using methanesulfonic acid, presumably through a cyclopropyl-stabilized carbocation hydrolysis mechanism (Scheme 1b).[21]

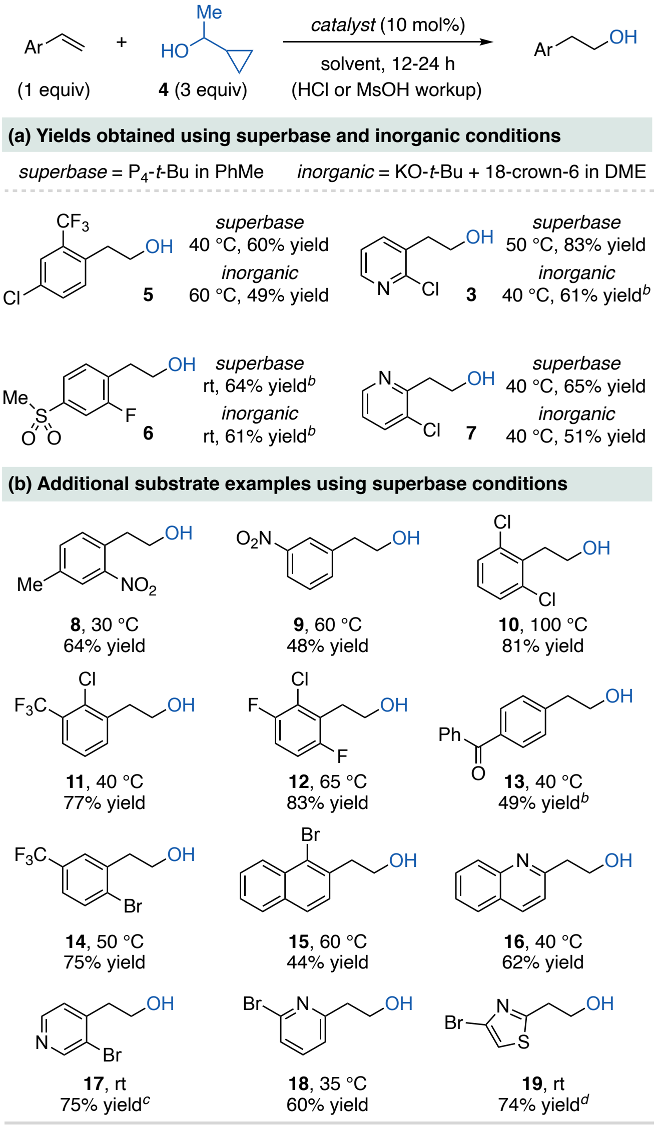


Scheme 1. Optimization studies for (a) superbase-catalyzed alcohol addition and (b) ether hydrolysis. [a] Yields determined by ^{1}H NMR spectroscopy. [b] Isolated yield of purified product.

We next investigated the substrate scope for anti-Markovnikov hydration using 1-cyclopropylethanol (**4**) and an *in situ* acidic workup procedure (Table 1). First, in Table 1a, a comparison of superbase (P$_4$-*t*-Bu in PhMe) and inorganic (KO-*t*-Bu/18-crown-6 in DME) catalysts is shown for two styrene derivatives (**5** and **6**) and two chlorinated vinyl pyridines (**3** and **7**). The inorganic conditions were selected based on our prior extensive screening of effective bases for hydroetherification reactions[15b], with additional information provided in the Supplementary Information. As seen in Table 1a, the inorganic conditions enable synthetically useful alcohol yields (49-61% yields) while the use of P$_4$-*t*-Bu generally provides higher yields (60-83% yields). The yield differences between the superbase and inorganic conditions are likely a solvent equilibrium effect, as we previously measured alcohol addition to be more favorable in PhMe than in DME.[15b] While P$_4$-*t*-Bu is an efficient catalyst in both solvents, the KO-*t*-Bu/18-crown-6 system is most active in DME and typically does not catalyze the reaction in PhMe to its equilibrium position.[15d]

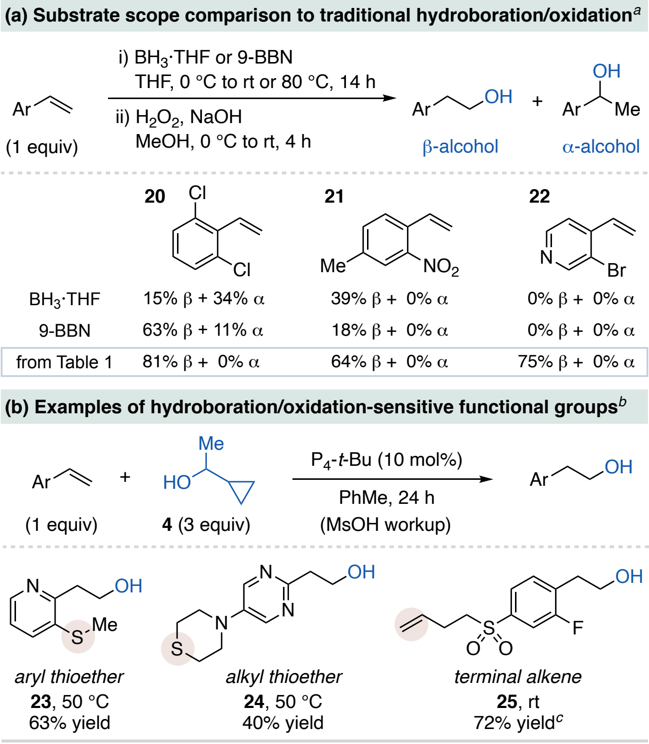
Table 1b shows hydration products of other vinyl arenes using the superbase conditions, while a full comparison to inorganic conditions is provided in the Supplementary Information. Styrenes featuring diverse substitution patterns with nitro (**8** and **9**), fluoro (**6** and **12**), chloro (**5**, **10** and **11**), bromo (**14** and **15**), sulfonyl (**6**), trifluoromethyl (**5**, **11** and **14**) and benzoyl (**13**) substituents undergo hydration in good yields. A notable feature of this scope is that *ortho*-substituents are well tolerated. Vinyl heteroarenes are also excellent substrates, including those with halogens that could be prone to nucleophilic aromatic substitution. Thus, halogenated 2-, 3-, and 4-vinyl pyridine derivatives (**3**, **7**, **17** and **18**) undergo hydration in high yields. Beyond pyridines, quinoline (**16**) and thiazole (**19**) derivatives are also hydrated in good yield. Although 1-cyclopropylethanol (**4**) will add to electron-neutral styrenes and 1,1-disubstituted variants, only low equilibrium yields are observed under these conditions.[15b] Representative substrates documenting the electronic limitations of this method are shown in the Supplementary Information.

Table 1. Product scope for anti-Markovnikov hydration.[a]



[a] Yields are of purified alcohol product; reactions performed on 0.5 to 1.0 mmol scale. [b] 5 equiv of **4** used. [c] 1 h reaction time. [d] 4 equiv of **4** used.

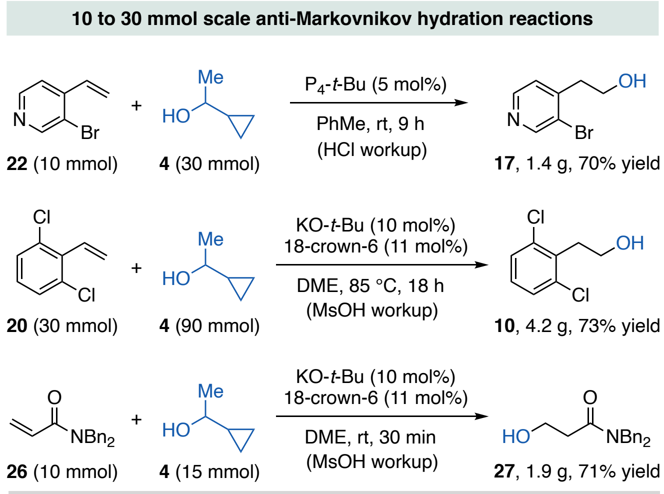
We next compared the hydration yields of several substrates from Table 1 to traditional hydroboration/oxidation protocols using BH_3·THF and 9-BBN. Although use of these boranes results in high yields of β-phenethyl alcohols from electron-neutral styrenes, decreased yields and selectivities are common for electron-deficient and heteroaryl variants.[8] Hydroboration/oxidation of 2,6-dichlorostyrene (**20**) leads to mixtures of α- and β-phenethyl alcohols while 2-nitro-4-methylstyrene (**21**) results in low yields of β-phenethyl alcohol (Scheme 2a). An even greater limitation is observed for 3-bromo-4-vinylpyridine (**22**), in which only over-reduction (i.e. hydrogenation) occurs with no alcohol formation. In contrast, base-catalyzed hydration gives high yields with exclusive β-regioselectivity for these substrates.



Scheme 2. Comparison of base-catalyzed hydration to hydroboration/oxidation methods. [a] Yields and regioselectivities determined by ^1H NMR spectroscopy of the crude reaction mixture; yields from Table 1 represent isolated yields. [b] Yields are of purified alcohol product. [c] 5 equiv of **4** used.

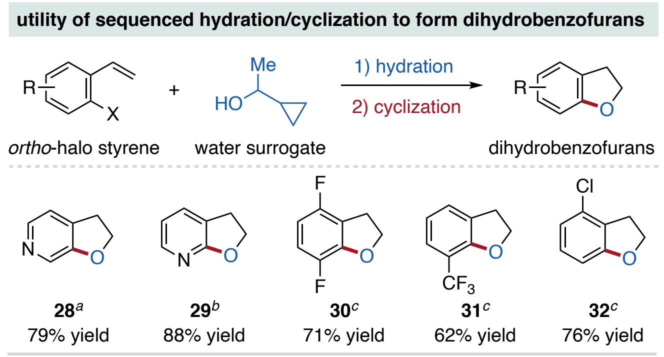
Base-catalyzed hydration is also likely to have complementary reactivity and functional group tolerance to hydroboration/oxidation protocols. This is illustrated in Scheme 2b, where substrates with an aryl thioether (**23**) and a thiomorpholine (**23**) that are sensitive to oxidizing conditions undergo P_4-*t*-Bu-catalyzed hydration in moderate yields.[22] Substrate **25**, featuring a terminal alkene that is reactive toward traditional hydroboration, illustrates the chemoselectivity of this method for styrene hydration.[23]

Scheme 3 demonstrates the scalability of this protocol through three hydration reactions conducted on 10 mmol scale or greater. Hydration of 3-bromo-4-vinylpyridine (**22**) is best accomplished using P_4-*t*-Bu and thus 5 mol% catalyst loading provided access to 1.4 grams of alcohol **17**.[24] The hydration of 2,6-dichlorostyrene (**20**, 30 mmol) is achieved in 73% yield using catalytic KO-*t*-Bu, exemplifying the practicality of the inorganic conditions. Although the highest styrene hydration yields are obtained using 3 equiv of 1-cyclopropylethanol (**4**), we also identified conditions that allow for only moderately decreased addition yields using 1.2 equiv of **4**. This finding, shown in Table S3 of the Supplementary Information, exploits our previous discovery of a negative alcohol rate order for base-catalyzed hydroetherification reactions.[15b] Thus, reactions can be run at lower temperatures when less alcohol is used, therefore decreasing the entropic penalty of addition to counteract Le Chatelier's principle. This effect was extended to a challenging oxa-Michael addition process for acrylamide **26**, where just 1.5 equiv of **4** and 30 min are required for a high-yielding KO-*t*-Bu-catalyzed hydration process at room temperature.[25]



Scheme 3. Examples of preparative scale anti-Markovnikov hydration reactions; yields are of isolated alcohol product.

Given that this method is suitable for *ortho*-halogenated vinyl (hetero)arenes, we reasoned hydration could be sequenced with a cyclization reaction to prepare 2,3-dihydrobenzofuran derivatives.[26] Thus, employing substrates from Table 1, base-promoted or metal-catalyzed cyclization reactions produce **28-32** in high yields (Scheme 4). This approach should improve access to this important heterocycle class[27], especially functionalized and aza variants where there is limited availability of the corresponding benzofuran compounds.[28]



Scheme 4. Utility of Table 1 alcohol products for dihydrobenzofuran derivative synthesis; yields are of isolated product from the cyclization step using given conditions. [a] CuI (10 mol%), 8-quinolinol (15 mol%), Cs_2CO_3 (1.5 equiv), PhMe, 110 °C, 16 h. [b] NaH (1.5 equiv), THF, 70 °C, 16 h. [c] $Pd(OAc)_2$ (3 mol%), JohnPhos (4 mol%), Cs_2CO_3 (1.5 equiv), PhMe, 80 °C, 22 h.

Conclusions

In conclusion, base-catalyzed addition of 1-cyclopropylethanol to styrene derivatives provides a convenient method for preparing β-aryl substituted alcohols. The use of catalytic P_4-*t*-Bu superbase allows for superior yields to inorganic bases, although KO-*t*-Bu/18-crown-6 may be a more practical catalyst system for achieving hydration on larger scale. In the broader context, analogous application of the nucleophilic yet easily deprotected 1-cyclopropylethanol water surrogate can likely enable other challenging hydration processes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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