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Brønsted Acid Catalyzed α-Alkylation of Aldehydes with Diaryl Methyl Alcohols

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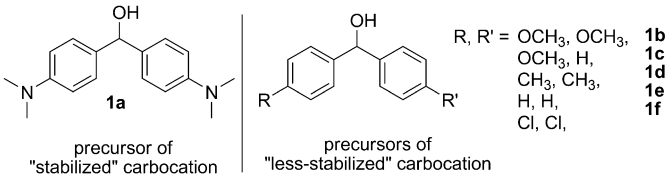
The catalytic α-alkylation of carbonyl compounds is a common approach in organic synthesis. In recent years, many efforts have been directed towards the activation of ketones and aldehydes by means of enamine catalysis to react with a broad range of electrophiles.[1] In 2004, List reported an elegant intramolecular alkylation of aldehydes with alkyl halides using proline-based amine catalysts.[2] While the long-sought intermolecular versions of such enamine-catalytic S_N2-type α-alkylation of aldehydes[3] remain challenging, research by the groups of Melchiorre, Cozzi, Jacobsen and others have pioneered the amine-mediated S_N1-type intermolecular reactions between aldehydes and arylsulfonyl indoles,[4] diaryl alcohols,[5] or halides.[6] In the approach used by Cozzi and others, amine catalysts were used to activate the aldehydes via enamine intermediates, and Brønsted acids were used to mediate the formation of diaryl methyl cations from the corresponding diaryl methanols. Despite the success of this amine/acid co-catalysis approach for diaryl methyl alcohols (e.g., **1a**) that generate highly stabilized carbocations, the scope of the reactions still remains limited: diaryl methyl alcohols (such as **1b–f**) that lead to "less stabilized" diaryl methyl carbocation electrophiles are ineffective substrates in these alkylation reactions.[5b]



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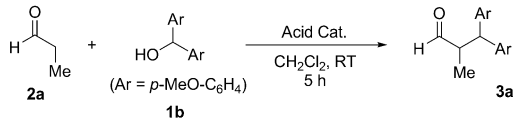
Instead of using enamine catalysis for aldehyde activation, here we disclose the use of Brønsted acids[7] alone to catalyze these S_N1 type aldehyde alkylations. The acid catalyst is believed to facilitate the formation of alcohol-derived carbocations and to accelerate the enolization of aldehydes. A much broader scope of substrates is thereby realized: diaryl methyl alcohols that lead to less stabilized carbocations can be used; aldehydes with α,α-disubstituents react efficiently as well to generate products containing quaternary carbon centers.

Our work began by using diaryl methanol **1b** as a model substrate to develop an acid-catalysis approach. According to the Mayr reactivity scales,[8] such substrates lead to less-stabilized carbocations (e.g., compared to that from **1a**) and were ineffective using the enamine/acid co-catalytic strategies. The results of our initial studies are summarized in Table 1. Weak acids, such as acetic acid, could not mediate

Table 1. Brønsted acid catalyzed alkylation of **2a** with **1b**.[a]



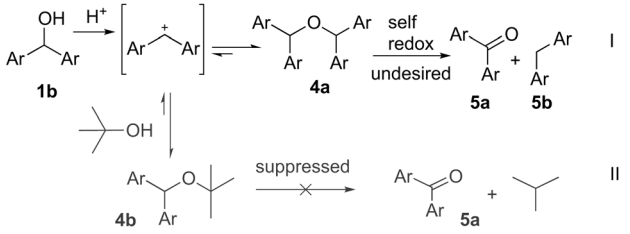
Entry	Acid ([mol%])	Additive	**3a** Yield [%][b]
1	–	–	<1
2	HOAc (10)	–	<1
3	*p*-TSA (10)	–	55
4	DNBA (10)	–	28
5	*p*-TSA (20)	–	63
6	*p*-TSA (10)	*t*BuOH (1.0 equiv)	87(95)[c]

[a] **2a** (1.2 mmol) and **1b** (0.4 mmol) were reacted in CH_2Cl_2 (2 mL). [b] ^1H NMR yield. [c] Yield of isolated compound after 19 h.

this reaction. We then found that by using 10 mol% *p*-toluenesulfonic acid (*p*-TSA) in CH_2Cl_2, the S_N1-type alkylation product **3a** was detected in 55% yield (Table 1, entry 3). Additional studies showed that solvents have dramatic effects on the reaction yield,[9] and CH_2Cl_2 was finally found as an optimal solvent for this reaction. Acids slightly stronger than *p*-TSA, such as 2,4-dinitrobenzenesulfonic acid (DNBA), showed decreased yields under the otherwise identical conditions (Table 1, entry 4).

Further optimizations with respect to typical parameters, such as acid catalysts and reaction temperatures, could not improve the yield to over 70%. We then found that self-

redox reactions[10,11] of the ether intermediate **4a** (formed from **1b** under acid catalysis[5e,10a]) led to a significant consumption of the alcohol substrate to generate undesired products. Finally, by using 1.0 equivalents of *t*BuOH as an additive,[9] the self-redox formation of **5a/b** was almost completely suppressed and the reaction led to quantitative formation of the aldehyde alkylation product (Table 1, entry 6). As intended, *t*BuOH can compete in ether formation, and the resulting cross-ether (**4b**) has a smaller tendency to undergo self-redox reactions (Scheme 1).

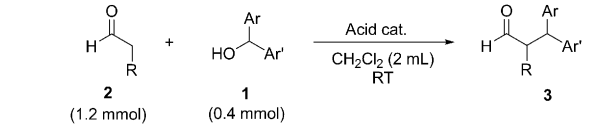


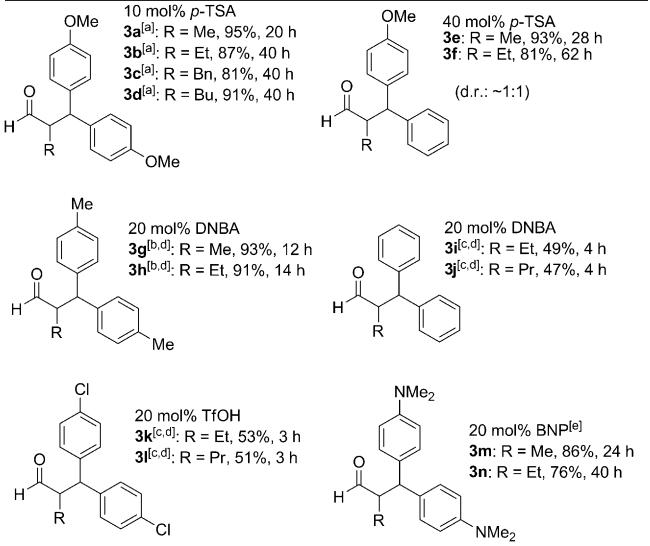
Scheme 1. Proposed self-redox pathway and its suppression pathway.

We then examined the scope of the reaction. In particular, we focused on alcohols that led to the challenging less-stabilized diaryl carbocations (Table 2). Due to the different reactivities (including the undesired reactivities) of the diaryl methyl alcohols, it was difficult to find a "universal" catalyst or condition that is optimal for different substrates. Thus, we slightly tuned the conditions for each substrate. For diaryl alcohol **1c**, which will generate an even less-stabilized carbocation (than that from **1b**), a higher loading of the *p*-TSA catalyst and longer reaction time were needed to generate product **3e** and **3f**. DNBA was used for diaryl methanol **1d** and **1e** (Table 2, products **3g–j**). The carbocation generated from bis(4-chlorophenyl)methanol (**1f**) was listed as the least stabilized diaryl cation of this series in Mayr's scale.[8] By using triflic acid as the catalyst, the alkylation products (Table 2, **3k** and **3l**) were obtained in moderate yields. Further pushing the limits to diaryl alcohols with strong electron-withdrawing groups, such as a CF_3 group on the benzene ring, resulted in complicated reactions without isolable amounts of the desired product under a range of conditions. Although it was not the focus of this study, we also tested diaryl alcohol **1a**, which was previously used in the enamine/acid catalysis. As expected, this less-challenging alcohol also worked well under the acid catalysis.

We next investigated the use of α,α-disubstituted aldehydes as the nucleophilic substrate (Table 3). In all cases, the reactions proceeded cleanly to afford the products in excellent yields. The acid catalysis approach was also extended to allylic alcohols[12] that can generate allylic carbocations, as exemplified in Table 4.

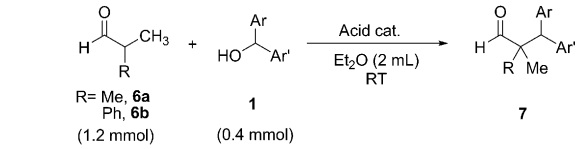
Table 2. Scope of diaryl alcohols and aldehydes.

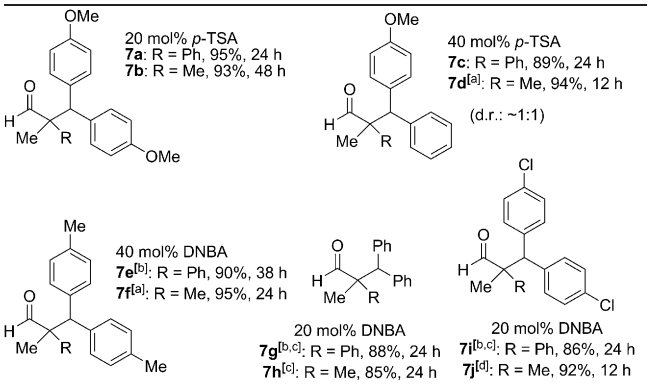




[a] With 1 equiv *t*BuOH as additive. [b] Reaction at 50 °C. [c] Reaction at 80 °C in $MeNO_2$. [d] Isolated after reduction to the corresponding alcohol. [e] BINOL-derived phosphoric acid.

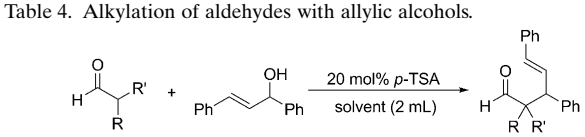
Table 3. Alkylation of α,α-disubstituted aldehydes.

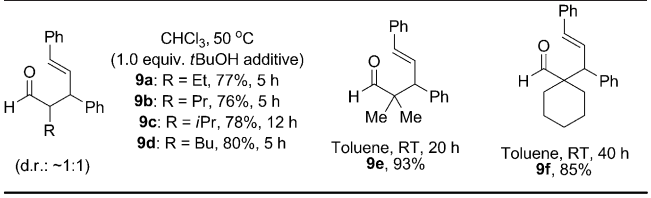




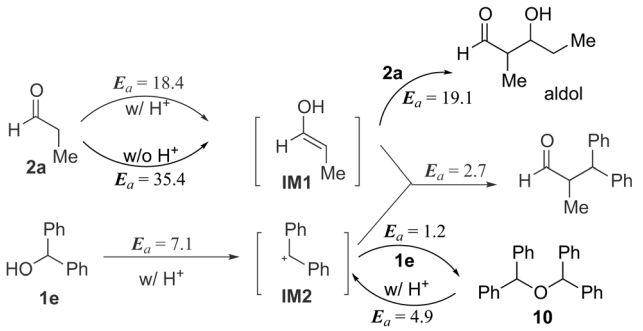
[a] Reaction in Bu_2O at 50 °C. [b] Isolated after reduction to the corresponding alcohol. [c] Reaction in $MeNO_2$. [d] Reaction in $MeNO_2$ at 50 °C.

Table 4. Alkylation of aldehydes with allylic alcohols.





The reaction pathways were briefly explored by means of DFT calculations using the reaction between aldehyde **2a** and alcohol **1e** in CH_3NO_2 as a model reaction (Scheme 2).



Scheme 2. Proposed reaction pathways studied by DFT calculations. All activation barriers [kcal mol^{-1}] were calculated relative to the infinitely separated reactants.

The enolization of aldehyde **2a** was found to be the rate-determining step in this acid-catalyzed alkylation reaction. The activation energy for the aldehyde enolization was calculated to be 18.36 and 35.96 kcal mol^{-1} in the presence and absence of the acid catalyst, respectively, indicating the important role of the acid catalyst in this step.[14] The acid-catalyzed formation of diphenyl methyl cation **IM2** has an energy barrier of 7.1 kcal mol^{-1}, and the aldehyde alkylation starting from enol **IM1** and carbocation **IM2** appears to be facile, with an energy barrier of 2.7 kcal mol^{-1}. The pathways for two major side reactions were also investigated. The self-aldol reaction[13,15] of the aldehyde (activation energy: 19.1 kcal mol^{-1}) is hard to eliminate under these reaction conditions, since the aldehyde enolization has a similar energy barrier (18.4 kcal mol^{-1}). Experimentally, self-aldol reactions were observed to different extents in nearly all the reactions, although high yields of the desired products could still be obtained after optimizations. The interconversion of the diphenyl methyl cation intermediate **IM2** and the ether side product **10** is facile, requiring relatively low activation energies. This agrees with the experimental results that the reversible ether formation itself does not affect the reaction outcome.[16]

In summary, we have introduced the use of Brønsted acids as the sole catalyst to mediate the S_N1-type alkylation of aldehydes with diaryl alcohols. In this acid catalysis, the challenging diaryl alcohols that generate less-stable carbocation intermediates are effective substrates. The α,α-disubstituted aldehydes can also be employed to give highly efficient reactions. Mechanistic studies by means of DFT calculations have also been performed. Ongoing work in our lab includes the development of an asymmetric version of this reaction,[17] and the expansion of substrates to simpler alcohols that generate highly unstable carbocations.

Experimental Section

General procedures: Diaryl alcohol (0.4 mmol), aldehyde (1.2 mmol) and acid catalyst in solvent (2 mL) as indicated were placed in a 5 mL vial equipped with a magnetic stir bar. The mixture was stirred at the indicated conditions. The reaction progress was monitored by means of ^{1}H NMR analysis of the crude reaction mixture. When the reaction neared completion, the reaction mixture was directly subjected to SiO_2 column chromatography purification eluting with EtOAc/hexane to give the desired product.

Acknowledgements

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Keywords: alcohols · aldehydes · alkylation · Brønsted acid · carbocations

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[16] It is the self-redox reaction of the ether that leads to unproductive consumption of the alcohol substrate.

[17] It is worth noting that our attempts to develop an enantioselective version of this reaction using the recently reported chiral BINOL-based phosphoric acid catalysts (ref. [7]) were unsuccessful at this point. The addition of diarylprolinol ethers as chiral amine catalysts (ref. [5]) to acid-catalyzed reactions with less-stabilized carbocations did not lead to any enantioselectivity either. Thereby, the amine catalysts were consumed through reactions with the alcohol substrates.

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