Organocatalysis

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# Organocatalytic Asymmetric Alkylation of Aldehydes by $S_N1$-Type Reaction of Alcohols**

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The direct nucleophilic substitution of alcohols represents a valuable methodology for the preparation of a variety of derivatives, as water is the only by-product of the transformation.[1,2] We have recently demonstrated the direct substitution of optically active ferrocenyl alcohols[3] and benzylic alcohols[4] with several nucleophiles "on water"[2h] without using Brønsted or Lewis acids. The direct nucleophilic substitution "on water" was possible because of the ability of water to form a hydrogen-bond network,[5] and was driven by the stability of the generated carbocations. On the basis of the electrophilicity parameters introduced by Mayr et al.[6] (see Table 1 in the Supporting Information), we decided to use less reactive carbocations, generated from alcohols, for exploring a direct nucleophilic enantioselective substitution. Mayr et al. have also classified nucleophiles using a related nucleophilicity scale,[6] in which the highly nucleophilic enamines are placed at the top of the list (see Table 2 in the Supporting Information).[7] Notably, chiral enamines[8] are key intermediates in many organocatalytic methodologies which have been explored in recent years.[9] On this basis, we hypothesized that the elusive α-alkylation of an aldehyde might be realized in an effective and simple way by using enamine catalysis coupled with the generation of stabilized carbocations.[10] Recently, the formation of such a stabilized carbocation was invoked by Enders et al.,[11] and by Petrini and Melchiorre et al.[12] in their organocatalytic asymmetric alkylations involving indole derivatives. We report herein a practical, direct asymmetric alkylation of aldehydes realized by nucleophilic substitution of alcohols with aldehydes.

Bis(4-dimethylamino-phenyl)methanol **1**, which can form a stabilized carbocation,[13] was used in the model reaction with *n*-octanal. Different organocatalysts were tested in the model reaction and they were used as either the free amine or as a salt (Figure 1) . Among all the pyrrolidine derivatives tested, only L-proline (**A**) gave the desired product in MeOH, albeit in racemic form. After an extensive survey of various organocatalysts and conditions, we were delighted to find that the MacMillan catalysts,[14] **F, G, H** and **I**, displayed unique and remarkable reactivities in the model reaction performed with *n*-octanal (Table 1).

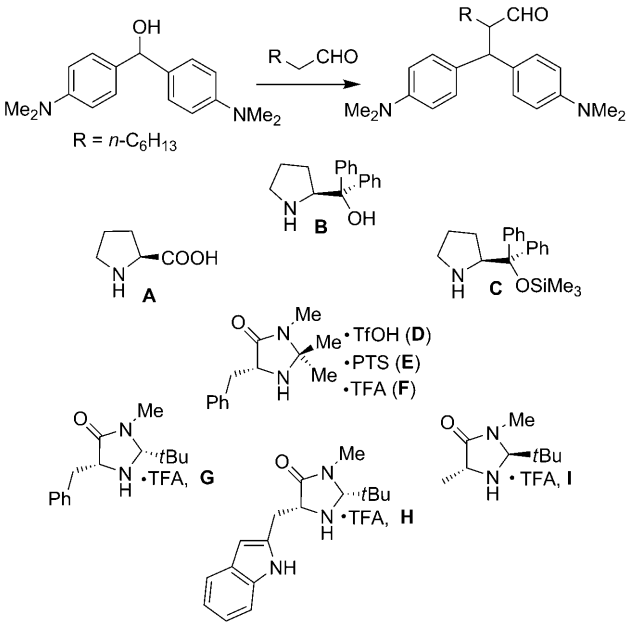


***Figure 1.*** Reaction of *n*-octanal with **1** performed in the presence of different solvents and conditions (R = *n*-$C_6H_{13}$). Tf = trifluorosulfonyl, PTS = *p*-toluenesulfonic acid, TFA = trifluoroacetic acid.

By using the selected reaction conditions (catalyst **G**, $Et_2O$ as the reaction solvent), and on the basis of the correlation established between the stability of the carbocations and their reactivities "on water",[4] we selected the alcohols reported in Figure 2 for demonstrating the scope of our alkylation. Alcohol **6** and alcohols that form more reactive carbocations, such as benzhydrol **7**, which are placed at the top of Mayr list (see the Supporting Information), showed no reactivity in our reaction. In contrast, alcohols **2**–**5** smoothly reacted under our reaction conditions with different aldehydes, and the results obtained are reported in Table 2. The enantiomeric excesses obtained the reaction of alcohol **1** with each of the aldehydes tested are in the range of 60 to 78% *ee*. Slightly inferior results in terms of enantiomeric excess were obtained with the alcohols **2** and **3.** Notably, in all cases yields ranging from moderate to excellent were obtained.

Quite remarkable results were obtained with the ferrocenyl alcohol **4**. The reaction performed with the optically active **4** (94% *ee*) and racemic organocatalyst **G** gave the

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***Table 1:*** Reaction of *n*-octanal with **1** performed in the presence of different solvents, conditions, and catalysts (R = *n*-$C_6H_{13}$).

| Entry[a] | Cat. | Solvent | *ee* [%][b] |
|---|---|---|---|
| 1 | **F** | $Et_2O$ | 70 |
| 2 | **F** | $CH_2Cl_2$ | 55 |
| 3 | **F** | DME | 60 |
| 4 | **F** | *t*BuOMe | 66 |
| 5 | **F** | AcOEt | 55 |
| 6 | **G** | $CH_3CN$ | 50 |
| 7[c,d] | **G** | $CH_3CN/H_2O$ | 53 |
| 8[c,e] | **G** | $THF/H_2O$ | 68 |
| 9[c,f] | **F** | $H_2O$ | 70 |
| 7[c] | **D** | $Et_2O$ | 38 |
| 8[c] | **E** | $Et_2O$ | 18 |
| 9[c] | **G** | $Et_2O$ | 70 |
| 10[c] | **G** | toluene | 76 |
| 11[c] | **G** | $Et_2O$ | 80 |
| 12[c,g] | **G** | $Et_2O$ | 80 |
| 13[c,h] | **G** | $Et_2O$ | 80 |
| 14[c,i] | **G** | $Et_2O$ | 80 |
| 15[c] | **G** | toluene | 78 |
| 16[c] | **H** | $Et_2O$ | 54 |
| 17[c] | **I** | $Et_2O$ | 50 |

[a] Reaction conditions: 0.1 mmol scale using 3 equiv of *n*-octanal until complete conversion, which was monitored by TLC (4–24 h). In all the reactions 35 mol% of the catalyst (with respect to the alcohol **1**) and 35 mol% of $CF_3COOH$ were added in sequence to the reaction mixture. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] The reaction was carried out with 35 mol% of the catalyst which was added as the salt. [d] Reaction was performed with 1 mL of $CH_3CN/H_2O$ (1:1). Yield of isolated product after 24 h was 53%. [e] Reaction was performed with 1 mL of $THF/H_2O$ (1:1). Yield of isolated product after 24 h was 73%. [f] Reaction was performed with 1 mL of $H_2O$. Yield of isolated product after 24 h was 78%. [g] The reaction was carried out with 15 mol% of the catalyst which was added as the TFA salt. Yield of the isolated product after 24 h was 90%. [h] The reaction was carried out with 10 mol% of the catalyst which was added as the TFA salt. Yield of isolated product after 24 h was 66%. [i] The reaction was carried out with 5 mol% of the catalyst which was added as the TFA salt. Yield of isolated product after 24 h was 40%.

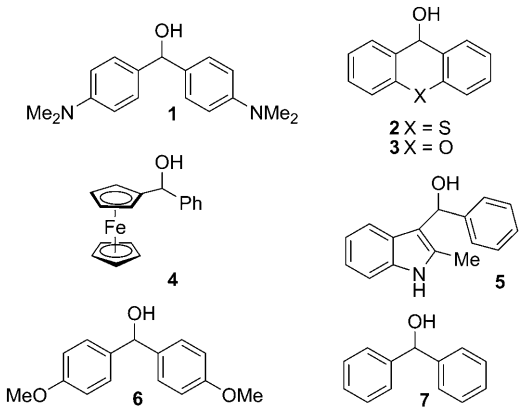
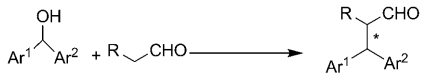



***Figure 2.*** Alcohols selected for direct organocatalytic alkylation.

desired product in a diastereoisomeric ratio of 3:1 with a slight loss in stereochemical information. However, to accomplish the reaction it was necessary to increase the catalyst loading to 90 mol%. The same reaction performed

***Table 2:*** Reaction of the alcohols **1**–**5** with different aldehydes in the presence of catalyst **G**.



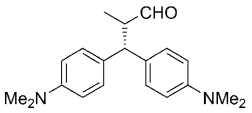
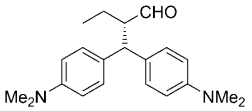
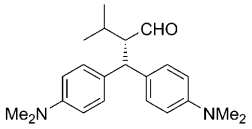
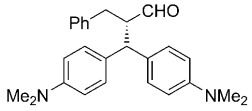
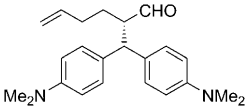
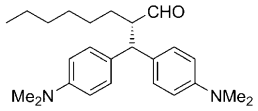
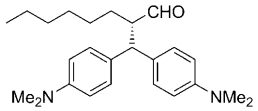
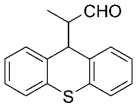
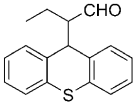
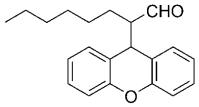
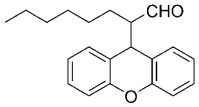
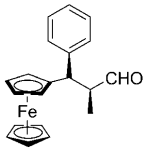
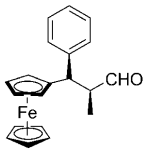
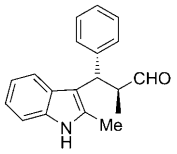
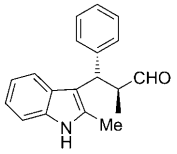
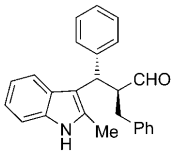

| Entry[a] | *t* [h] | Product | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1[a] | 24 |  | 95 | – | 77 (*S*) |
| 2[a] | 18 |  | 79 | – | 69 |
| 3 | 20 |  | 79 | – | 69 |
| 4 | 4 |  | 77 | – | 77 |
| 5 | 9 |  | 63 | – | 60 |
| 6 | 21 |  | 92 | – | 78 |
| 7[e] | 1 |  | 85 | – | 78 |
| 8 | 24 |  | 73 | – | 74 |
| 9 | 24 |  | 56 | – | 77 |
| 10 | 24 |  | 95 | – | 78 |
| 11[f] | 90 |  | 90 | – | 80 |
| 12[g] | 24 |  | 48 | 1:3 | 90 (2*S*,3*R*) *syn* |
| 13 | 24 |  | 30 | 1:1.3 | 70 (2*S*,3*R*) *syn* 77 (2*S*,3*S*) *anti* |

*Table 2:* (Continued)

| Entry[a] | *t* [h] | Product | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 14 | 2 |  | 80 | 1.5:1 | 88 (2*S*,3*S*) *anti*<br>78 (2*S*,3*R*) *syn* |
| 15[h] | 42 |  | 48 | 2.6:1 | 92 (2*S*,3*S*) *anti*<br>86 (2*S*,3*R*) *syn* |
| 16[h] | 96 |  | 76 | 3:1 | 90 (2*S*,3*S*) *anti*<br>68 (2*S*,3*R*) *syn* |

[a] Reaction conditions: reactions were carried out at room temperature on a 0.1 mmol scale using 3 equivalents of aldehydes and 20 mol% of the catalyst which was added as the trifluoroacetate salt. In the case of reactions in entries 12–16 only the configuration of the major diastereoisomer is indicated. [b] Yield of isolated product after chromatographic purification. [c] Determined by $^1$H NMR or by chiral HPLC analysis on the crude reaction mixture. The ratio indicated is *anti*/*syn*. [d] Determined by chiral HPLC analysis (see the Supporting Information for details). [e] The reaction was carried out without adding solvent. [f] The reaction was carried out at 0 °C. [g] The reaction was carried out using the enantioenriched alcohol (*S*)-**4** (94% *ee*) and 90 mol% of the racemic catalyst **G**. [h] The reaction was carried out at −25 °C.

with optically active organocatalyst **G** gave the product in low yield with an enantiomeric excess of 70%.[15] The reaction of ferrocenyl racemic alcohols with aldehydes represents a new and effective way to prepare optically active ferrocene building blocks.[16] In addition, alcohol **5** is a representative of a class of useful starting materials for easy access to relevant indolyl derivatives.[17] Alcohol **5** smoothly reacted in a fast reaction at room temperature to afford the desired product (Table 2, entry 14) in high enantiomeric excess, but with low control of the diastereoselection. Performing the reaction at low temperature (−25 °C, Table 2, entry 15) provided better control of the stereoselection at the expense of the yield.

The absolute configuration of the products derived from alcohol **1** was established by correlation to known derivatives obtained by using a methodology reported by Paras and MacMillan[18,19] (see the Supporting Information). The absolute configuration of the products derived from alcohol **5** was assigned by comparison of the elution order of the products from a chiral phase HPLC column to those reported in the literature.[20] The absolute configuration of the products obtained can be explained by a model in which a carbocation attacks the less hindered face of the *E* enamine obtained in situ by the reaction of the aldehyde with the amine catalyst (see the Supporting Information). In the catalytic cycle illustrated in Figure 3 the formation of the free acid (HX) is probably responsible for the generation of the carbocation. Notably, the iminium ion formed in the first step of the

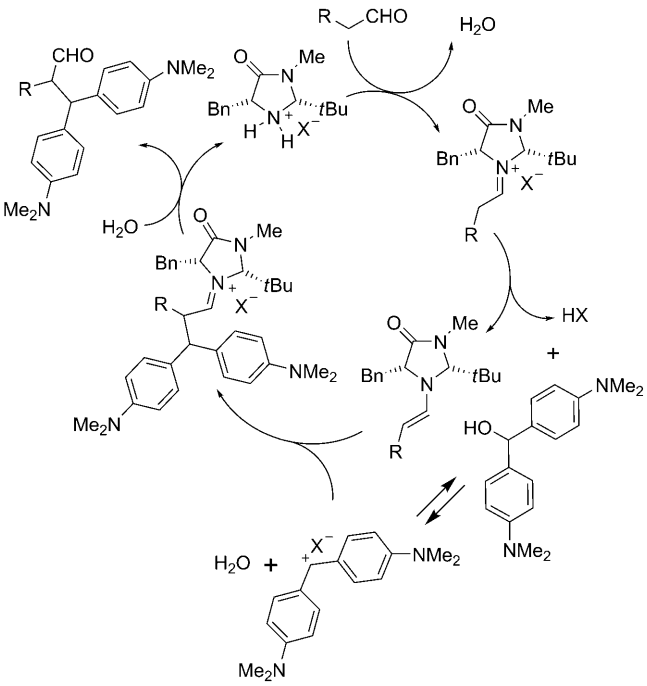


***Figure 3.*** Proposed catalytic cycle for the organocatalytic transformation.

catalytic cycle is placed at $E = -7$ on the Mayr scale.[21] The equilibrium established between the enamine and the carbocation might be possible with alcohols that are able to generate relatively stable carbocations of the same or slightly higher electrophilicity relative to enamine.

In summary, we have reported an effective and very simple method to effect the enantioselective direct alkylation of aldehydes with unfunctionalized alcohols.[22] This methodology opens several opportunities for realizing cascade, consecutive, and multicomponent organocatalytic reactions that include benzylic alcohols in their synthetic design. The scope of the present reaction, as well as the use of ketones and other nucleophiles in the organocatalytic, enantioselective direct nucleophilic substitution of alcohols, is presently under active investigation in our laboratory.

## *Experimental Section*

Organocatalyst **G** (20 mol%), alcohol **1** (1 equiv), and the aldehyde (3 equiv) were placed in a vial and dissolved in $Et_2O$ (0.1M). The solution immediately turned deep blue, and the reaction mixture was stirred until the disappearance of the blue color, indicating complete reaction. The mixture was evaporated and purified by column chromatography (eluent hexane/$Et_2O$ 8:2).

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**Keywords:** alcohols · aldehydes · carbocations · enamines · organocatalysis

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