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# Merging Organocatalysis with an Indium(III)-Mediated Process: A Stereoselective α-Alkylation of Aldehydes with Allylic Alcohols

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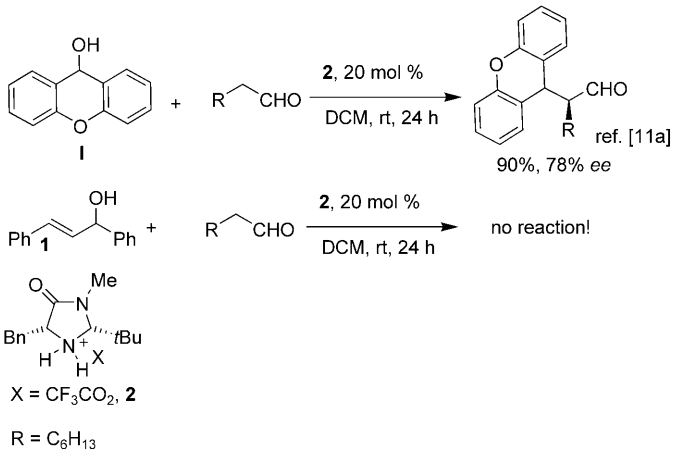
Organocatalysis has grown explosively in the last few years,[1] becoming an exciting area of research, and organocatalytic modes of activation are now considered in the synthetic approach of complex natural products.[2] Activation modes of organocatalysis allow new reactivity, increasing the creativity of organic chemists towards the invention of new reactions.[3] Recently, the combination of organocatalysis with metal catalytic processes produced exciting strategies for the development of innovative transformations and for challenging difficult problems.[4] In particular, Cordova and Ibrahem disclosed the first example of the fusion between transition-metal catalysis and aminocatalysis for the direct catalytic intermolecular α-allylic alkylation of aldehydes and cyclic ketones.[5] However, both his group and that of Saicic[6] were unable to find conditions for performing allylation in an highly enantioselective fashion by the use of an organocatalyst.[7]

Conversely, List and Mukherjee by using Brønsted acid catalysis, reported the first enantioselective allylation of α-branched aldehydes, combining the chiral phosphoric acid (*R*)-TRIP with $Pd^0$ catalysis.[8] Recently, enamine organocatalysis was exploited by Breit and co-workers in a dual Pd/proline-catalyzed α-allylation of aldehydes with alcohols, but no enantiomeric excess was recorded in the reaction.[9]

Herein, we disclose a conceptually new approach towards the organocatalytic allylation of aldehydes with allylic alcohols, by the use of organocatalysts developed by MacMillan and co-workers,[10] and $InBr_3$ as a co-catalyst, avoiding the employment of expensive Pd and Ir metals. Recently, we have focused our attention on the development of α alkylation of aldehydes by $S_N1$-type of reaction with alcohols.[11] Our approach was to combine two powerful concepts, the Mayr's scales[12] of electrophilicity and nucleophilicity with enamine catalysis.[13] We were able to use alcohols, such as xanthol (**I**), capable of forming a relatively stable carbocation as electrophiles in the alkylation of aldehydes. The benzhydrilic carbocations generated in situ in our process were positioned from −7 to −1 of the Mayr's scale. Alcohols leading to carbocations found to be above the mentioned limits, such as 1,3-diphenyl-prop-2-en-1-ol (**1**) (1,3-diphenyl-allyl alcohol), were completely un-reactive in our conditions[14] and only the self condensation of aldehyde was observed by $^1H$ NMR spectroscopy in the crude reaction mixture (Scheme 1).

Generation of allylic carbocations from the corresponding alcohols and their reaction with aldehydes and ketones in the presence of an organocatalyst can be considered an in-




Scheme 1. Stereoselective reaction of activated alcohol **I** with aldehyde promoted by the catalyst **2**.

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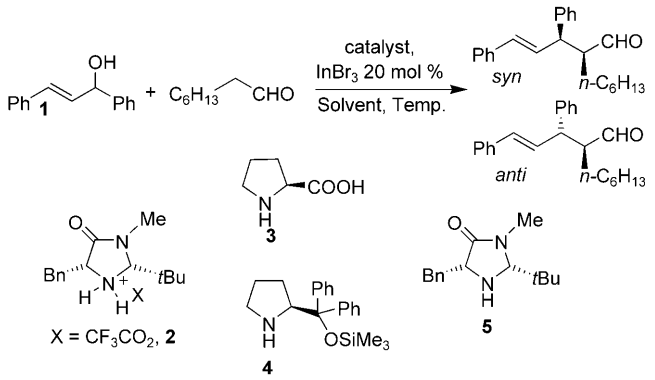
teresting approach for enantioselective allylic alkylation, as the transformation of the allylic alcohol in more reactive species is not required, and the employment of transition metals (Pd, Ir) is avoided. To promote the formation of the allyl carbocation we began to consider the admission of different Lewis acids in catalytic amounts, choosing as model reaction the addition of octanal to **1** (Scheme 2). In fact, the




Scheme 2. Reaction of **1** with octanal in the presence of $InBr_3$ with the organocatalysts **2–5**.

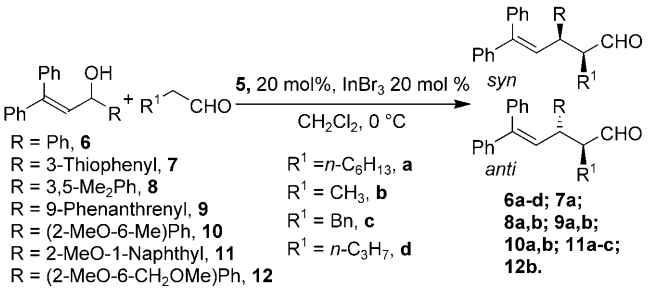
direct substitution of allylic alcohols with many different nucleophiles is easily promoted by the presence of Lewis or Brønsted acids.[15] Unfortunately, in our model reaction, Lewis acids such as $Cu(OTf)_2$, $AuCl_3$, $Ph_3PAuCl$, $Bi(OTf)_3$, $Sc(OTf)_3$, $La(OTf)_3$, and $Zn(OTf)_2$ gave either a complex mixture of products[16] or no reactions. Therefore, we focused our attention on indium salts for this chemistry. Indium salts are able to mediate several organic transformations, in the presence of water,[17] and are not deactivated by water even when present in large excess. Moreover, the dynamic exchange between indium and basic nucleophiles allows Lewis acid catalysis in the presence of basic amines.[18] Therefore the model reaction was studied in the presence of indium salts, and we were pleased to achieve positive results, as shown in Table 1(entries 5, 6, 9–13) in the presence of the MacMillan catalysts **2** and **5**. In the absence of indium salts, no reaction occurred. Different indium salts or indium complexes were tested in the reaction, and on the basis of these results, $InBr_3$ employed in 20 mol% was selected as the co-catalyst. The reaction took place in $CH_2Cl_2$, but other solvents were completely ineffective. Proline (**3**) or proline-derived catalysts such as **4** were also ineffective in promoting the reaction. Quite interestingly, the *ee* improved when the free MacMillan catalyst **5** was used. A major drawback in the reaction was the moderate *ee* and the poor d.r. (1:1) obtained in the reaction of 1,3-diphenyl-prop-2-en-1-ol (**1**) with different linear aldehydes.[19]

Since in the addition of aldehydes to benzhydrols the sterical hindrance of the benzhydrilic carbocation is controlling the d.r. of the reaction,[11] we planned to increase the hindrance of the carbocation generated in the presence of $InBr_3$ (Scheme 3). 1,1,3-Triphenylallyl cations are easily generated[20] and nucleophiles were shown to attack the less hindered position of the allylic cation.[21] Therefore, a series of allyl substrates **6–12** were prepared by addition of lithium or magnesium aryl compounds to β-phenylcinnamaldehyde (see Supporting Information for details).

Table 1. Reaction of **1** with the catalysts **2–5** in different reaction conditions.

| Entry[a] | Catalyst | Temp [°C] | Time [h] | Solvent | *ee* [%][b,c] |
|---|---|---|---|---|---|
| 1 | **2** | rt | 60 | Toluene | [d] |
| 2 | **2** | rt | 60 | *t*BuOMe | [d] |
| 3 | **2** | rt | 60 | $CH_3CN$ | [d] |
| 4 | **2** | rt | 60 | $CH_3NO_2$ | [d] |
| 5 | **2** | rt | 12 | $CH_2Cl_2$ | 50 |
| 6 | **2** | 0 | 12 | $CH_2Cl_2$ | 71 |
| 7 | **3** | 0 | 48 | $CH_2Cl_2$ | [d] |
| 8 | **4** | 0 | 48 | $CH_2Cl_2$ | [d] |
| 9[e] | **5** | 0 | 12 | $CH_2Cl_2$ | 82 |
| 10[f] | **5** | 0 | 72 | $CH_2Cl_2$ | 80 |
| 11[g] | **5** | 0 | 5 | $CH_2Cl_2$ | 80 |
| 12[h] | **5** | 0 | 72 | $CH_2Cl_2$ | 80 |
| 13[i] | **5** | 0 | 5 | $CH_2Cl_2$ | 80 |

[a] The reactions were performed at the indicate temperature with 1 equivalent of alcohol **1**, 3 equivalents of octanal, in the presence of 20 mol% of catalyst. 20 mol% of $InBr_3$ (0.33 M solution in $CH_3CN$) was added to the reaction mixture containing the aldehyde, the alcohol **1** and the catalyst. The reactions were run until completion, shown by TLC. [b] For all the reactions the d.r., measured by $^1H$ NMR spectroscopy and HPLC analysis was 1:1. [c] Determined by chiral HPLC analysis. The *syn* and *anti* diastereoisomers had the same enantiomeric excess. [d] No traces of the desired product was detected by $^1H$ NMR analysis and GC-MS analysis of the crude reaction mixture. [e] Yield of purified product was 71%. [f] 5 mol% of $InBr_3$ was used for the reaction. [g] 40 mol% of the catalyst **5** was used in the reaction. [h] 20 mol% of $In(OTf)_3$ added as solid was used for the reaction. [i] 20 mol% of $InBr_3$-BINOL complex was used for the reaction.




Scheme 3. Stereoselective reaction of alcohols **6–12** with aldehydes promoted by catalyst **5**.

We were delighted to verify that these more sterically hindered allyl compounds gave improved selectivity in our reaction, as confirmed by the data collected in Table 2.

Introduction of phenyl substituents in β-position increased the d.r. in the reaction up to 2:1 in favor of the *syn* diastereoisomer.

The reaction catalyzed by the MacMillan catalyst **5** (20 mol%) in combination with 20 mol% of $InBr_3$ as the co-catalyst showed a remarkable enantiocontrol in allylation of aldehydes, with *ee* ranging from 85 to 98% obtained for the major *syn* diasteroisomer. The reactivity of alcohols **6–12**

Table 2. Reaction of **6–12** with the aldehydes **a–d**, in the presence of catalytic amounts of $InBr_3$ and **5**.

| Entry[a] | Product | Yield [%][b] | d.r.[c] | *ee* [%] *syn*[d] | *ee* [%] *anti*[d] |
|---|---|---|---|---|---|
| 1[e] | **6a** | — | — | — | — |
| 2[f] | **6a** | [g] | 2:1 | 87 | 72 |
| 3 | **6a** | 70 | 2:1 | **90** | 75 |
| 4[h] | **6a** | traces | 2:1 | 88 | 72 |
| 5[i] | **6a** | [g] | 2:1 | **90** | 77 |
| 6 | **6b** | 63 | 2:1 | 88(2*S*,3*R*) | 80(2*S*,3*S*) |
| 7 | **6c** | 90 | 2:1 | 89 | 64 |
| 8 | **6d** | 50 | 2:1 | **91** | 77 |
| 9 | **7a** | 56 | 2:1 | 87 | 56 |
| 10 | **8a** | 53 | 2:1 | 85 | 69 |
| 11 | **8b** | 69 | 2:1 | 85 | 73 |
| 12 | **9a** | 66 | 4:1 | 86 | 67 |
| 13 | **9b** | 57 | 4:1 | 88 | 75 |
| 14 | **10a** | 65 | 2:1 | 88 | 79 |
| 15 | **10b** | 50 | 2:1 | **93** | 84 |
| 16 | **11a** | 71 | 3:1 | **91** | 68 |
| 17 | **11b** | 75 | 5:1 | **94** | 87 |
| 18 | **11c** | 77 | 5:1 | **98** | 65 |
| 19[e] | **11b** | 75 | 11:1 | **96** | 85 |
| 20[e] | **11c** | 73 | 20:1 | **99** | 55 |
| 21 | **12b** | 65 | 4:1 | **95** | 81 |

[a] The reactions were performed at 0 °C with 1 equivalent of alcohol **6–12**, 3 equivalents of aldehyde, in the presence of 20 mol % of catalyst **5**. 20 mol % of $InBr_3$ (0.33 M solution in $CH_3CN$) was added to the reaction mixture containing the aldehyde, the alcohol **6–12** and the catalyst. [b] Yield after chromatographic purification. [c] The d.r. (*syn* vs. *anti*) was measured by $^1$H NMR spectroscopy and HPLC analysis. The relative configuration of *syn* and *anti* product **6b** was established by chemical correlation to known lactones (see text). The relative configuration of all products was established by analogy (the CHO proton of major *syn* diastereoisomer resonates at lower chemical shifts compared to the *anti* for all products). [d] Determined by chiral HPLC analysis (see the Supporting Information for details). The absolute configuration of the product **6b** was established by the TD-DFT calculation of the ECD spectra (see text). The absolute configuration of all the other products was established by analogy. [e] The reaction was performed in absence of $InBr_3$ and in the presence of the catalyst **2**. [f] The reaction was performed at room temperature (rt). [g] Not determined. [h] The reaction was performed at −20 °C in DCM. [i] The reaction was performed at −20 °C in $CHCl_3$.

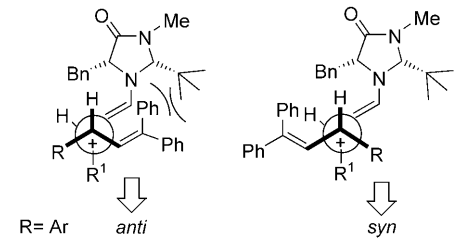
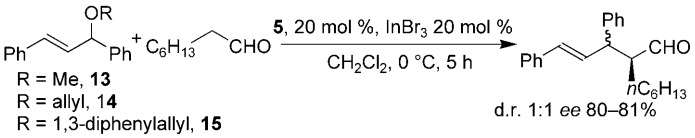



Figure 1. Stereochemical models for the stereoselective allylation of aldehydes.

was dependent on the stability of the corresponding allyl cation.[22] Different aromatic and heteroaromatic groups (Table 2, R = aryl, heteroaryl) were prepared and tested in the optimal reaction conditions. With the substrate **6** (R = Ph) good yields and selectivities (87–91 % *ee*) were obtained with different aldehydes (**a--d**) showing the generality of the process. In all cases, irrespective of the aldehydes employed, a d.r. ratio of 2:1 was recorded. Therefore, the sterical hindrance between the R group and the 1,1-diphenylethenyl chain controls the simple stereoselection of the reaction. We assume that the increased hindrance of the β-position enhances the steric interaction with the *tert*-butyl group of the MacMillan catalyst in the transition state (Figure 1). When the R group and the 1,1-diphenylethenyl chain have a similar sterical hindrance, the simple stereoselection registered for the reaction was quite poor.[23] However, a better control of the simple stereoselection can be realized with allylic substrates in which the R aromatic group is differently substituted in the 2 and 6 positions. With an R group in which the two substituents in position 2 and 6 of the aryl were different as in the substrates **9**, **11**, and **12**, the reaction became more diastereoselective. In fact, with the substrate **11**, a d.r. of 5:1 was obtained. With the substrates **6–10**, and **12** the catalyst **2** was ineffective in promoting the reactions. As a matter of fact, in the case of substrate **11** the reaction is possible even in the absence of $InBr_3$, by the use of the catalyst **2**, as the corresponding carbocation is more stabilized. In this case, a d.r. up to 20:1 with the enantiomeric excess of 99 % was obtained in the reaction.[24]

For gaining some knowledge about the role of the indium salt in the reaction, the ethers **13** and **14** (Scheme 4) were prepared by acid-catalyzed addition of methanol and Williamson etherification, respectively. The substrate **15** was obtained as a 1:1 mixture of diastereoisomers by treating the alcohol **1** with acids.

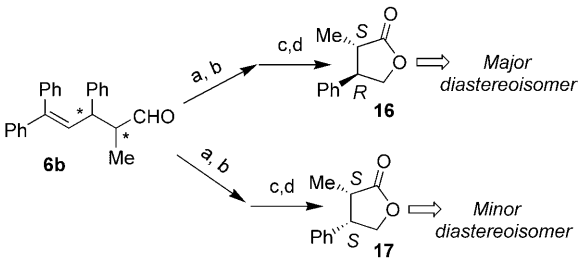



Scheme 4. Reaction of the allyl ethers **13–15** with octanal, in the presence of the catalyst **5**, and $InBr_3$.

The substrates **13–15** were tested in the reaction with octanal, in the presence of 20 mol % the MacMillan catalyst **5** and 20 mol % of $InBr_3$ (Scheme 4). In all the three cases the product **1a** was isolated with same d.r. and *ee* (1:1 and 80 %). On the other hand, when the reaction of **1** with octanal in the presence of the MacMillan catalyst was stopped after 20 min, **1** was completely consumed and the bis-allyl-ether product **15**, present as a 1:1 mixture of diastereoisomers, was observed in the reaction mixture by $^1$H NMR spectroscopy and TLC analysis. In a quite fast reaction the catalytic amount of $InBr_3$ promotes the formation of the allylic ether by the reaction of the allylic alcohol **1** with the allylic carbocation. The same behavior was generally observed with the different allylic substrates **6–12** by checking the reaction mixture by TLC. When the substrates **6–12** were treated with a catalytic amount (20 mol %) of $InBr_3$ in $CH_2Cl_2$, a rapid red coloration of the solution was observed. $^1$H NMR spectroscopy of the crude reaction mixture showed the formation of the corresponding ethers, obtained as a mixture of diastereoisomers. Although the conversion of the

allylic starting alcohol is complete, the yields of the reactions are moderate given the rapid formation of the dimeric ether. The allylic carbocations are slowly generated in the reaction mixture from the allylic ethers by the Lewis acid activation with $InBr_3$.[25] Apparently, just one molecule of the MacMillan catalyst is involved in the stereo-determining step.[26] The relative configurations of *syn* and *anti* products were assigned by chemical transformation of the product **6b** to the corresponding lactones (Scheme 5). The aldehyde **6b**




Scheme 5. Reagents and conditions: a) $NaClO_2$, $H_2O_2$ 35%; $CH_3CN$–$KH_2PO_4$ buffer, 10°C. b) $TMSCHN_2$; $Et_2O$, 0°C. c) $O_3$, MeOH. d) $NaBH_4$, MeOH, 42% (over four steps).

was oxidized to the acid,[27] which was esterified with trimethylsilyldiazomethane. The ozonolysis of the double bond[28] followed by reduction with $NaBH_4$ and lactonization gave the lactones **16** and **17**, separated by flash chromatography. The chemical shifts and the $^3J$ coupling constant of the separated products were compared to those reported in the literature for assigning the *syn*/*anti* relative configurations.[29] The lactones **16** and **17** were also obtained by the same reaction sequence performed on the product **1b**. The absolute configuration of the lactone derivatives was assigned on the basis of the time-dependent density functional theory (TD-DFT) calculation of the electronic circular dichroism (ECD) spectra (see the Supporting Information for details).[30] The *S* absolute configuration of the stereocenters in the α-position was in complete agreement with our previous work with stabilized carbocations,[11] and in general, with the diastereofacial selection obtained with the MacMillan catalyst **5** in organocatalytic reactions.

In conclusion, we have described the first catalytic stereoselective addition of aldehydes to allylic alcohols promoted by a combination of organocatalysis and a metal-catalyzed process.[31] In this innovative transformation, a stereoselective reaction of stabilized carbocations is realized[13] by the employment of a chiral nucleophile. The exploitation of such a strategy for the selective construction of C–C bonds, by the merger of organometallic and organocatalytic processes is under further development in our laboratory.

## Experimental Section

To a solution of the compounds **6**–**12** (0.1 mmol, 1 equiv) in $CH_2Cl_2$ (1 mL) were added MacMillan catalyst **5** (0.02 mmol, 20 mol%) and aldehyde ( 0.3 mmol, 3 equiv) at 0°C. The mixture was stirred for 5 min at the same temperature and then a solution of $InBr_3$ (20 mol%, 0.33 M in acetonitrile) was added slowly. The mixture was stirred until no further conversion took place (monitored by TLC) at the same temperature. Then the reaction was quenched with water. The organic layer was separated, and the aqueous layer was extracted twice with $Et_2O$. The combined organic layer was washed with water, dried over $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography ($SiO_2$; cyclohexane: diethyl ether).

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**Keywords:** aldehydes · allylic alcohols · indium · MacMillan catalysts · organocatalysis

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[22] 4,4-Dimethyl-1,1-diphenyl-pent-1-en-3-ol and 1,4,4-triphenyl-but-3-en-2-ol are completely unreactive substrates under the standard reaction conditions.

[23] In fact, when 3,3-diphenyl-1-(2,4,6-trimethylphenyl)-prop-2-en-1-ol (3-mesityl-1,1diphenylallyl alcohol) was allowed to react with octanal, the corresponding product was obtained in 88 % *ee* but in a d.r. of 1:1.

[24] The carbocation derived from **11** is more stabilized then the carbocation derived from **6**. Replacement of the benzhydryl hydrogen in benzhydrylium ions by a styryl group reduces the electrophilicity by 2 to 5 orders of magnitude For a discussion of stability of carbocations in relation to the Mayr scale see references [11] and [12].

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