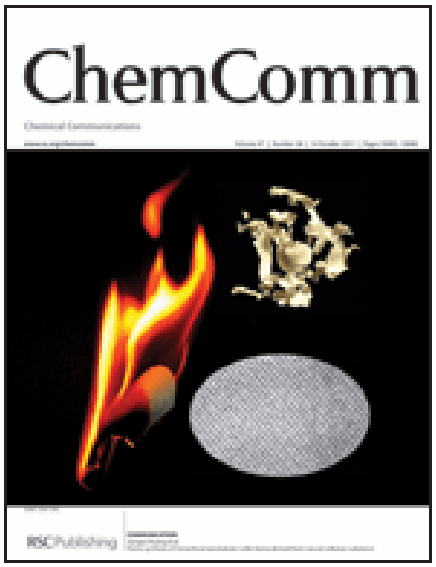

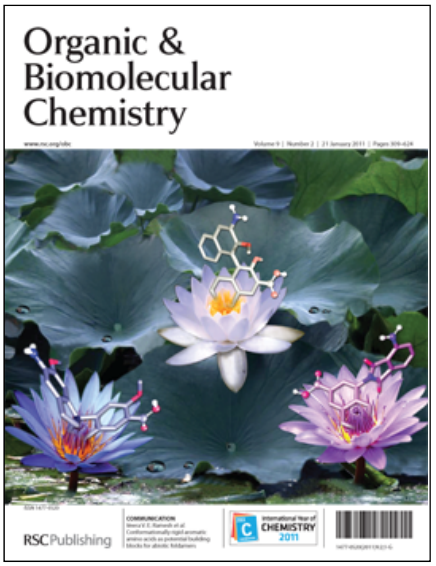

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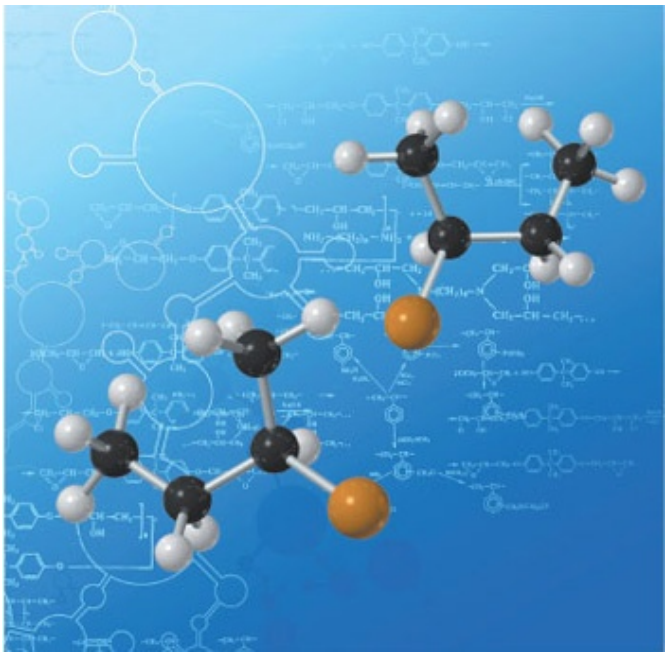

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COMMUNICATION

Asymmetric oxidative Lewis base catalysis—unifying iminium and enamine organocatalysis with oxidations†‡

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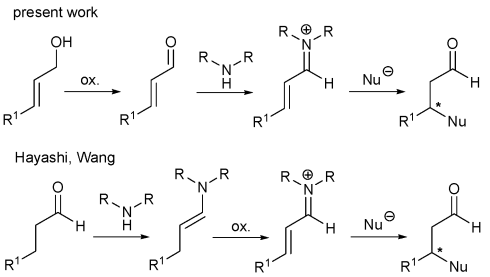
Enantioselective oxidative domino reactions of allylic alcohols to functionalized aldehydes have been developed. The one pot domino oxidation-iminium activation represents a convenient strategy for the enantioselective addition of malonates to allylic alcohols and the asymmetric formation of formyl cyclopropanes.

Oxidation reactions are of fundamental importance in chemistry and a lot of research effort has been devoted to the development of mild and efficient reactions.[1] One-pot domino oxidation procedures, in which the oxidized intermediate is further elaborated, are highly desirable not only because they offer a potential one-flask-access to demanding and highly functionalized molecules in higher oxidation states but also because of their inherent benefits in terms of time, cost and environmental savings.[2,3] Aldehydes in particular are challenging substrates as they are sensitive to storage and degrade in time. Recently, one-pot oxidation procedures involving their *in situ* generation have been developed.[4–6]

These reactions are particularly useful as they avoid the isolation of potentially unstable aldehydes. However, these methodologies are mainly restricted to reactions where the oxidized intermediate is further reacted with a stabilized ylide in the oxidation–Wittig reaction.[4a–g] In this context, Taylor and co-workers have developed a number of elegant MnO_2 mediated domino oxidations starting from allylic alcohols.[2,5] More recently, Scheidt and co-workers presented an oxidation protocol where benzylic and allylic alcohols were converted to esters employing a NHC-catalyst.[6]

Asymmetric Lewis base catalyzed reactions involving the *in situ* oxidation of alcohols have not been reported. Due to our interest in Lewis base organocatalysis[7] and the plethora of domino reactions in the field,[8] we became interested in an oxidation protocol where the allylic alcohol is converted *in situ* into the corresponding aldehyde which can then be manipulated with asymmetric amine-catalysis (Scheme 1, top). A related strategy which involves stoichiometric oxidation of the enamine intermediate derived from an aldehyde and subsequent reaction



Scheme 1 Oxidative-iminium domino reactions.

with a nucleophile was reported independently by Hayashi[9a] and Wang[9b] during our investigations (Scheme 1, bottom). In these reactions aldehydes which are often sensitive to air and moisture were applied. Additionally, rather expensive oxidants were used which needed to be separated by column chromatography.

We decided to start from stable allylic alcohols and prepare the aldehydes *in situ*, thus avoiding the cumbersome purification of aldehydes by distillation or column chromatography. It should be noted that in iminum catalysis yields as well as selectivities are typically considerably lower if the aldehyde is not freshly prepared. This is due to aldehyde decomposition products, including acids which unfavourably interact with the Lewis base catalyst.[10]

Herein, we report the first domino oxidative iminium strategy towards the asymmetric synthesis of formyl cyclopropanes and the enantioselective addition of malonates to *in situ* generated α,β-unsaturated aldehydes from allylic alcohols.

In order to develop a most simple and economic procedure we decided to evaluate cheap, non-toxic, heterogeneous oxidizing reagents as they could be easily separated by filtration. Thus we were delighted to see that MnO_2 could be used as a cheap and readily available oxidant in the presence of an amine and that no oxidation of the catalyst could be detected. Furthermore, with the application of the chiral TMS-prolinol ether the first asymmetric formation of formyl cyclopropanes from allylic alcohols (Table 1) could be developed. Full conversion was reached over night at room temperature.[11,12] Evaluation of temperature, solvent, base, and catalyst allowed the identification of a reaction protocol which affords the corresponding formyl cyclopropanes in good yields and high enantiomeric excesses (Table 1). For example, the diphenylprolinol TMS-ether **4a**[13] catalyzes the oxidative iminium–enamine domino addition of diethyl bromomalonate to cinnamyl alcohol, affording cyclopropane **3a** in 78% yield with 96% ee (Table 1, entry 1).

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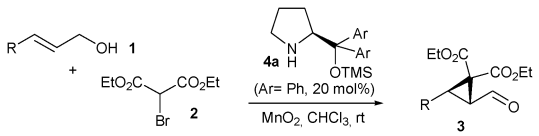
‡ Electronic supplementary information (ESI) available: Experimental details and spectra. See DOI: 10.1039/c2cc16447g

Table 1 One-pot enantioselective cyclopropanation of allylic alcohols



Entry[a]	Product	R	Yield[b] (%)	ee[c] (%)
1	**3a**	Ph	78	96
2	**3b**	*o*-NO_2–C_6H_4	88	94
3	**3c**	*p*-NO_2–C_6H_4	84	93
4	**3d**	*o*-Br–C_6H_4	78	98
5	**3e**	*m*-Br–C_6H_4	68	93
6	**3f**	*p*-Br–C_6H_4	66	93
7	**3g**	*p*-F–C_6H_4	67 (78)[d]	95 (93)[d]
8	**3h**	*p*-Cl–C_6H_4	67	93
9	**3i**	*p*-Me–C_6H_4	72	95
10	**3j**	*p*-CF_3–C_6H_4	69	94

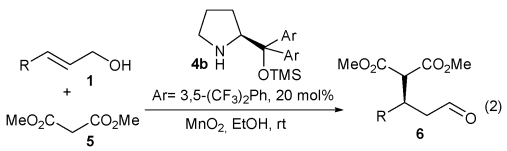
[a] Reaction conditions: allylic alcohol **1**, diethyl bromomalonate **2** (1.3 equiv.), MnO_2 (10.0 equiv.), NEt_3 (0.7 equiv.) and TMS-prolinol **4a** (20 mol%) at 0.2 M concentration in $CHCl_3$, rt, 18 h. [b] Yield after column chromatography. [c] Enantiomeric excess was determined by HPLC. [d] Reaction run at 0 °C with 2,6-lutidine (1.0 equiv.).

Furthermore, allylic alcohols **1b–j** bearing aromatic residues with different substitution patterns and electronic properties are tolerated in this reaction (entries 2–10). Halo-containing allylic alcohols were subjected to this one pot procedure yielding *o*-, *m*- and *p*-substituted halo-cyclopropanes in good yields with high enantiomeric excesses (entries 3–8).

To further expand the scope of the oxidative domino-iminium protocol other nucleophiles such as malonates were investigated (Table 2).[14] It turned out that dimethyl malonate **5** is a suitable nucleophile for this oxidative domino protocol and cinnamyl alcohol could be converted to the chiral aldehyde **6a** in 78% yield and 90% ee (Table 2, entry 1).

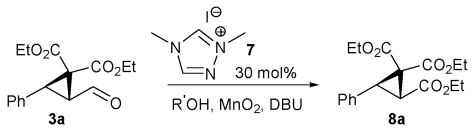
Furthermore, dimethyl malonate is added to the *in situ* generated *o*- and *p*-nitro cinnamic aldehydes (entries 2 and 3) to give the desired products **6b** and **6c** in good yields with high enantioselectivities (91 and 90% ee respectively). A slightly lower selectivity was observed in the case of allylic alcohols bearing methyl electron donating groups (entries 4 and 6).

Table 2 Enantioselective addition of malonates to allylic alcohols



Entry[a]	Product	R	Yield[b] (%)	ee[c] (%)
1	**6a**	Ph	78	90
2	**6b**	*o*-NO_2–C_6H_4	70	91
3	**6c**	*p*-NO_2–C_6H_4	74	90
4	**6d**	*p*-Me–C_6H_4	86	87
5	**6e**	*p*-Br–C_6H_4	63	88
6	**6f**	*o*,*p*-Me_2–C_6H_3	78	83

[a] Reaction conditions: allylic alcohol **1**, dimethylmalonate **5** (1.3 equiv.), MnO_2 (10.0 equiv.) and TMS-prolinol **4b** (20 mol%) at 0.2 M concentration in $CHCl_3$, rt, 72 h. [b] Yield after column chromatography. [c] Enantiomeric excess was determined by HPLC.



Scheme 2 Oxidative esterification of formyl cyclopropane **3a**.

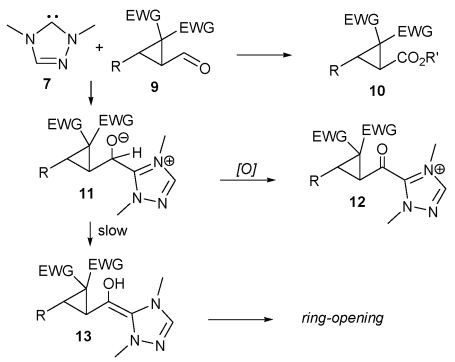
Earlier reports have demonstrated that formyl cyclopropanes undergo ring-opening[11a,15] in the presence of a NHC-catalyst.[16] We envisioned that the selectivity of these reactions could be changed in the presence of MnO_2 allowing the conversion of the aldehyde to the ester[6,17] without affecting the cyclopropane ring. We found that, upon treating **3a** with MnO_2 in the presence of carbene **7** in ethanol, indeed no ring opening was observed and that cyclopropane ester **8a** could be isolated in 78% yield with 95% ee (Scheme 2).

Regarding the mechanism of the reaction, addition of carbene **7** to the cyclopropane derivative **9** yields intermediate **11** which is oxidized to the acyl azolium intermediate **12** which subsequently reacts with the alcohol (R′OH) to give the appropriate cyclopropane ester derivative **10**. In this case the oxidation is fast enough, preventing thus the potential ring opening pathway (Scheme 3).

In summary, we have developed an enantioselective oxidative domino reaction pathway. The newly developed procedure prevents the necessary purification or distillation step associated with the use of aldehydes in asymmetric organocatalysis. The procedure allows the use of allylic alcohols, together with the cheap and readily available oxidant MnO_2 which can be simply separated by filtration. Thus, the newly developed protocol represents a valuable alternative to recently reported oxidative procedures which employ aldehydes and more expensive or difficult to handle oxidizing reagents, such as IBX and DDQ.[9]

The domino oxidative iminium reaction is viable for the enantioselective formation of formyl cyclopropanes and addition of malonates to allylic alcohols. The corresponding valuable chiral aldehydes have been isolated in good yields with high enantioselectivities. In contrast to earlier reports, we were also able to demonstrate for the first time that cyclopropane aldehydes can further be manipulated to their corresponding esters in a highly chemoselective manner by using a carbene catalyst.

The generally mild reaction conditions of the oxidative processes together with the operational simplicity and practicability render this approach not only a useful procedure for the synthesis of optically active chiral aldehydes and esters but, additionally,



Scheme 3 Proposed mechanism for the oxidative carbene-catalyzed esterification of aldehydes.

expands further the repertoire of enantioselective covalent catalysis.

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