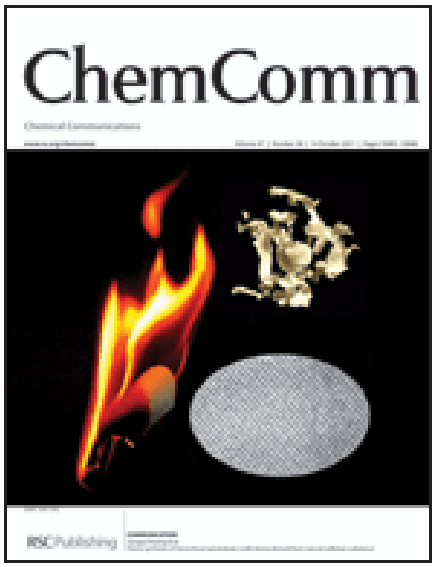

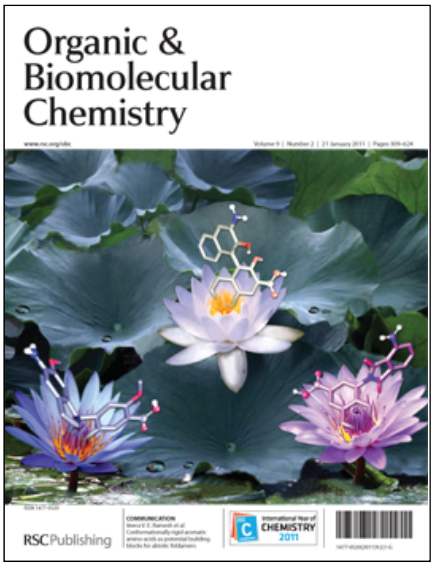

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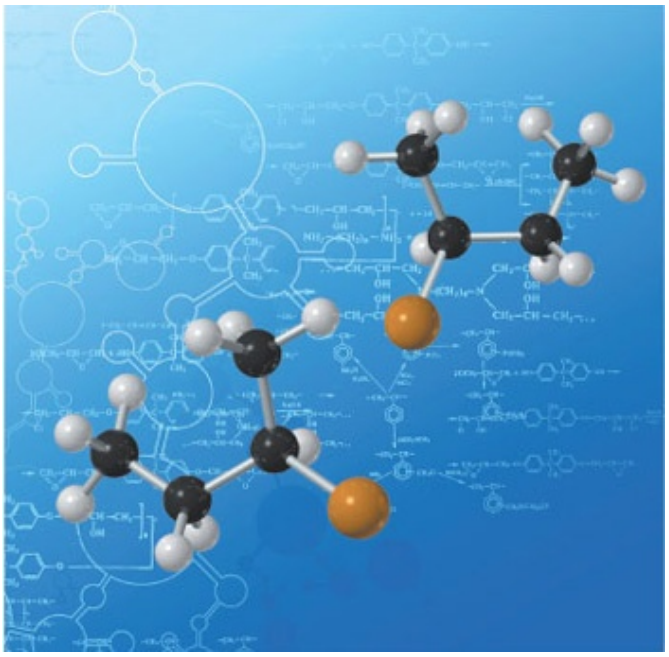

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COMMUNICATION

Transforming terpene-derived aldehydes into 1,2-epoxides *via* asymmetric α-chlorination: subsequent epoxide opening with carbon nucleophiles†‡

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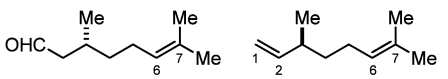
Merging Jørgensen's and MacMillan's organocatalytic aldehyde chlorinations enables the synthesis of chiral vinylcyclopropanes and (−)-*cis*-aerangis lactone *via* terpene-derived 1,2-epoxides.

As an inevitable consequence of the exhaustible nature of fossil resources, an increased utilization of sustainable feedstock from biomass will be one of the major challenges for chemists in the 21st century.[1] We have initiated a research program that is aimed at identifying larger fragments within natural products[2] and fine chemicals[3] that are readily available from renewable resources such as the simple bulk terpenes citronellal or citronellene.



The key challenge in this approach lies in finding efficient ways to functionalize a terpene's hydrocarbon backbone and render these compounds suitable substrates for generally applicable coupling reactions, *e.g.* metal catalyzed cross couplings,[4] metathesis reactions[5] or dithiane linchpin couplings.[6] Organocatalysis[7] has contributed toward this goal by enabling the stereoselective introduction of activating groups in the α-position of carbonyl compounds. In particular, the α-halogenation[8] of aldehydes (Fig. 1) affords valuable and flexible intermediates for follow-up transformations. In the context of a total synthesis campaign, we have recently converted a terpene-derived aldehyde bearing a skipped diene motif into the corresponding terminal epoxide[9] using MacMillan's organo-SOMO methodology[10] and their ready available[11] imidazolidinone **1**. The practical three-step one-pot process[12] involves an enantioselective α-chlorination[13] that is followed by aldehyde reduction and base-promoted intramolecular chloride substitution. Surprisingly, attempts to extend the otherwise successful protocol to a wider set of terpene-derived aldehydes met with little success and led to the decomposition of starting materials. We tentatively attribute

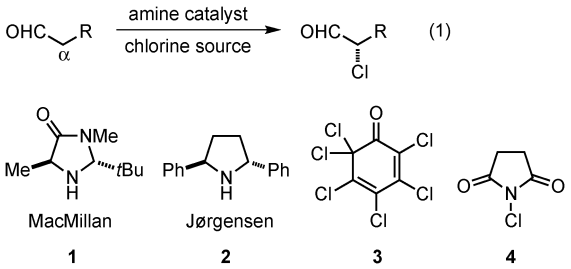


Fig. 1 Asymmetric organocatalytic aldehyde chlorination (1), secondary amine catalysts (**1–2**) and electrophilic chlorine sources (**3–4**).

this to the decomposition of radical intermediates. Other previously reported approaches[14] based on enamine activation were also prohibitive for our intended large-scale operations due to either costly catalysts (**2**) and/or chlorine sources (**3**). After considerable experimentation, we were delighted to find that *N*-chlorosuccinimide **4** (NCS) and imidazolidinone **1** comprise a simple yet effective reagent–catalyst combination.[15] In a typical open-flask experiment, a solution of the aldehyde **5** (0.5 M) in HPLC-grade acetonitrile was treated with the catalyst **1**·TFA (20 mol%) and a slight excess of *N*-chlorosuccinimide (**4**, 1.1–1.3 eq.). The terminal epoxides **7** were obtained in good yields (Table 1) and high selectivities from the corresponding aldehydes **5**. If desired or necessary, the reaction was stopped at the chloroalcohol **6**.

Accordingly, we have prepared a series of homoallylic terminal epoxides (entries 1–6) with trisubstituted *E*- and *Z*-configured double bonds that were subsequently rearranged into chiral cyclopropanes (*vide infra*). The two diastereomeric 1,2-epoxides of citronellene (entries 8 and 10) have not yet been described. In contrast, the 6,7-epoxide[16] has been used as chiral-pool starting material with the idea of transferring the methyl-substituted stereocenter into a given target molecule. The 6,7-epoxide serves as a masked carbonyl group that is released upon periodate cleavage or by direct ozonolysis of the alkene precursor. Starting from citronellal,[17] we now have established a route to the valuable 1,2-epoxides of citronellene (entries 8 and 10) and the respective chloroalcohols (entries 7 and 9) under complete catalyst control.[18] With this robust and reliable route to chiral terpene-derived 1,2-epoxides in hand, we investigated their reactivity profile as well as possible applications in target-oriented synthesis.

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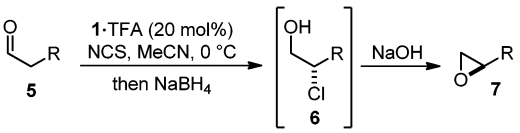
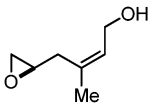
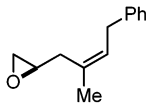
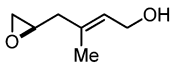
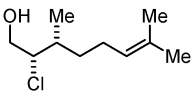
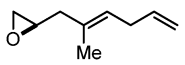
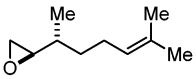
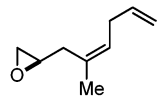
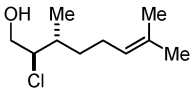
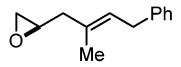
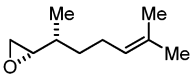
‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cc15173h

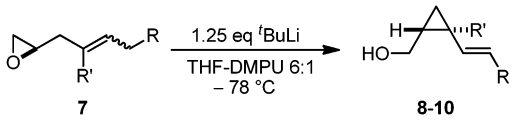
Table 1 Synthesis of terpene-derived chloroalcohols (**6**) and 1,2-epoxides (**7**)

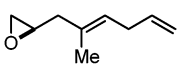
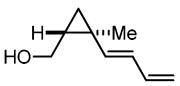
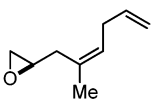
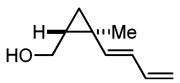
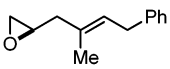
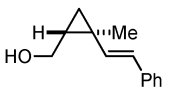
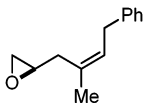
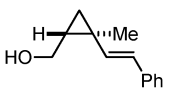
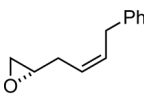
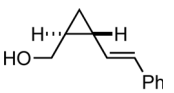


1	 **7a** (64%, 95% *ee*)[a,b]	6	 **7f** (56%,92% *ee*)[a]
2	 **7b** (77%, 95% *ee*)[a,b]	7	 **6g** (73%, >99:1 *dr*)[a]
3	 **7c** (66%, 92% *ee*)[a]	8	 **7g** (98%, >99:1 *dr*)[a,c]
4	 **7d** (56%, 94% *ee*)[a]	9	 **6h** (70%, >99:1 *dr*)[a,d]
5	 **7e** (53%, 91% *ee*)[a]	10	 **7h** (72%, >99:1 *dr*)[a,c]

[a] Isolated yields. Enantiomeric excess and diastereomeric ratio were determined by GC or HPLC. [b] Acetate ester of the primary alcohol was used as starting material. [c] From the corresponding chloroalcohol. [d] Catalyst *ent*-**1**·TFA was used.

Table 2 Transformation of epoxides (**7**) into cyclopropanes (**8–10**)



Entry	Substrate	Product
1	 **7c**	 **8** (90%, 1:1 *dr*)[a]
2	 **7d**	 **8** (97%, 10:1 *dr*)[a]
3	 **7e**	 **9** (61%, 1:1 *dr*)[a]
4	 **7f**	 **9** (69%, 8:1 *dr*)[a]
5	 **7i**	 **10** (74%, 6:1 *dr*)[a]

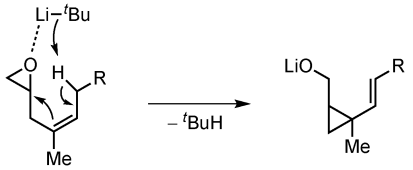
[a] Isolated yields. Diastereomeric ratio was determined by ^{1}H-NMR.

There are two major strategies for the transformation of epoxyalkenes into cyclopropanes. While Hodgson *et al.*[19] have devised an efficient protocol for the intramolecular cyclopropanation[20] *via* epoxide lithiation featuring a carbenoid–alkene-addition, an alternative pathway involves allylic deprotonation and intramolecular S_N2-epoxide opening.[21] The latter route has been largely neglected due to a lack of diastereocontrol in the absence of functional groups.[22] In line with previous observations, the cyclization of **7c** afforded cyclopropane **8** bearing a quaternary stereocenter[23] as a 1 : 1-mixture of *cis–trans*-isomers (Table 2, entry 1). However, when we changed the configuration of the trisubstituted double bond from *E* to *Z*, the cyclization of **7d** gave **8** with an improved 10 : 1 *trans*-selectivity (entry 2). In the optimized protocol, treatment of epoxides **7c–f** and **7i**[24] with *t*-BuLi in the presence of a disaggregating additive (DMPU) at low temperature (−78 °C) furnishes the chiral vinylcyclopropanes[25] **8–10** in good to excellent yields. The relative configuration of the vinylcyclopropanes was established using 1D-NOE experiments and the absolute configuration was deduced from the epoxide (assuming an intramolecular S_N2 opening) or by comparison of the optical rotation (**10**) to that reported in the literature.[26]

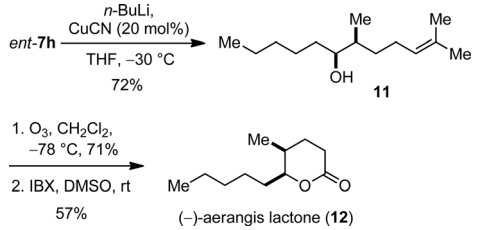
We speculate that the *Z*-configuration of the shifting double bond allows for a concomitant coordination of the lithium atom to the epoxide oxygen during the deprotonation of the methylene group. In our mechanistic rationale shown in Scheme 1, a possibly diastereoselective deprotonation is followed by a rapid intramolecular epoxide opening in which the lithium atom activates the epoxide and accepts the evolving negative charge on oxygen. Further experiments will be necessary to narrow down the complex mechanistic possibilities and the stereochemical details of this reaction.

Terminal epoxides are extremely useful intermediates in total synthesis. Classical synthetic applications were dominated by dithiane or cuprate openings, but nowadays metal catalyzed reductive openings[27] are quickly advancing. Following our interest in semiochemicals,[28] we were excited to showcase the utility of 1,2-epoxycitronellene **7h** as a chiral building block in a short synthesis of volatile constituent responsible for the lovely scent of *Aerangis kirkii*.[29] As shown in Scheme 2, a copper(I)-catalyzed nucleophilic epoxide opening of **7h** with *n*-butyl lithium afforded alcohol **11** in 72% yield. Subsequent ozonolysis (71%) and *in situ* oxidation of the somewhat labile lactol with IBX (57%) provided the fragrant (−)-*cis*-aerangis lactone **12** in three steps from **7h**.[30]

In conclusion, we have developed a practical protocol for the conversion of aldehydes into terminal epoxides *via* an organocatalytic asymmetric enamine chlorination. The required MacMillan catalyst (**1**) is easily available on the multigram scale rendering this approach viable for total synthesis. In addition,



Scheme 1 Proposed mechanism of the vinylcyclopropane formation.



Scheme 2 Synthesis of (−)-*trans*-aerangis lactone **12**.

we found a useful stereoselective rearrangement of 1,2-epoxy-4*Z*-alkenes into cyclopropanes and we used 1,2-epoxycitronellene in a short synthesis of (−)-aerangis lactone.

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