A diastereoselective and concise synthesis of functionalised vinyl epoxides with a Morita–Baylis–Hillman backbone†

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Received 18th May 2006, Accepted 26th June 2006
First published as an Advance Article on the web 10th July 2006
DOI: 10.1039/b607040j

A highly diastereoselective organocatalytic synthesis of unique functionalised vinyl epoxides, displaying a Morita–Baylis–Hillman backbone, has been developed by means of an user friendly sulfonium ylide epoxidation of aldehydes from a readily available α-(bromomethyl)acrylamide derivative. The first result in the asymmetric version is discussed.

The construction of useful chiral building blocks from readily available starting materials is a pivotal endeavour in organic synthesis. In this context, the vinyl oxirane architecture has been flourishing in many transformations based on S_N2,[1] S_N2',[2] rearrangements,[3] *etc.*[4] The development of a synthesis towards this challenging target, with the control of the relative and/or the absolute stereochemistry, has motivated many research groups. The two most successful approaches so far are based on the oxidation of alkenes,[5] and the nucleophilic addition of substituted allylic metal reagents to aldehydes.[6] Alternatively, the reaction between an aldehyde and the vinyl sulfonium ylide **2**,[7] generated *in situ* from the corresponding allylic sulfonium salt **1**, provides a connective access to vinyl oxiranes **3** (Fig. 1, path A).[8,9] Despite the first reports, which appeared in the 1970s,[10] the development of this methodology was limited by the relative instability of the allylic sulfonium ylide intermediate **2**, undergoing the competitive 2,3-sigmatropic rearrangement subsequently to a proton transfer (Fig. 1, path B).[11]

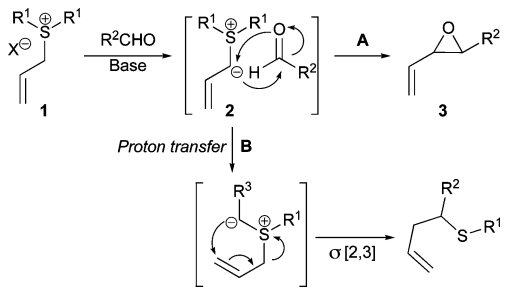

Fig. 1 Vinyl sulfonium ylide chemistry.

Recently, we[12] and others[13] reported on a one pot asymmetric epoxidation of aldehydes to vinyl epoxides (Fig. 2). This process is performed in the presence of a stoichiometric or a catalytic amount of chiral sulfides (as epoxidation mediators) and does not require the pre-formation of the sulfonium salt in a separate step. These studies pointed out that the asymmetric outcome is strongly dependent upon the substitution pattern of the alkene pendant of **4**. For instance, the allylic derivative **4a** (R = H) furnished the vinyl epoxide with low diastereo- and enantioselectivities. In contrast, good enantioselectivities were obtained for the major *trans*-vinyl oxirane constructed from the α-substituted methallylic precursors **4b** (R = Me). Moreover, the yields were markedly dependent on the structure of the targeted epoxide and the amount of sulfide used.[12–14]

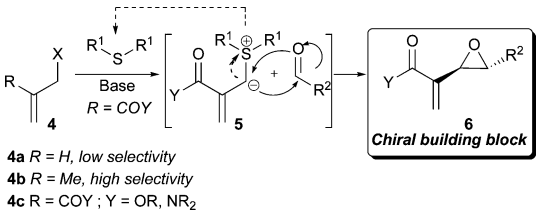

Fig. 2 Strategy.

In order to extend the scope towards the formation of valuable chiral synthetic intermediates, we recently became interested in the reactivity of substituted allylic sulfonium ylides **5** (formed in a catalytic amount *in situ* from the corresponding allyl halide **4c**) towards aldehydes (Fig. 2). Our purpose was to develop a connective synthesis of vinyl epoxides **6** with an acrylic pendant. A literature screen revealed only few studies dealing with these kind of densely functionalised intermediates,[15] although one would recognise the α-methylene-β-hydroxycarbonyl backbone substructure, the so-called Morita–Baylis–Hillman adduct. Together with the vinyl epoxide moiety, this architecture would offer a valuable building block suited for a variety of synthetic transformations.[16] This motif is an element of pharmacologically active molecules.[17] In this context, analogues of epoxide **6** (Y = OH) have also been reported to give, by cyclization, a straightforward access to β-hydroxy-α-methylenelactones, core structures of naturally occurring compounds.[18] With respect to the above-mentioned instability of vinyl sulfonium ylide intermediates such as **5**, a major concern was the integrity of the activated C–C double bond of **4c**, **5** or **6** throughout the epoxidation process. Another issue was the influence of the acrylic moiety connected to the sulfonium ylide species **5** upon the selectivity. This paper will outline our first results towards the diastereoselective synthesis of vinyl oxiranes **6** by means of a catalytic sulfonium ylide epoxidation methodology.

In order to evaluate various acrylic moieties **4c** in the epoxidation reaction (Fig. 2), we needed a robust procedure to synthesize the corresponding 2-(halogenomethyl)-acrylamides **8** and **9** (Scheme 1). We have shown that DABCO was competent

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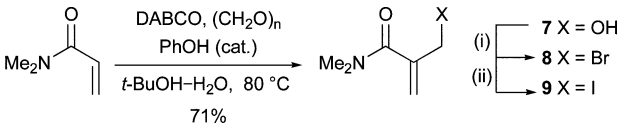
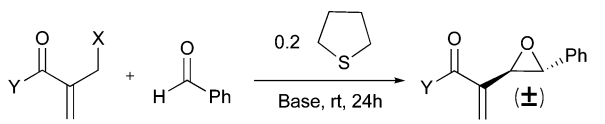
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data for products **7**–**11**. See DOI: 10.1039/b607040j



Scheme 1 (i) PBr_3, DMF, 61%; (ii) NaI, acetone, 89%.

to perform a Morita–Baylis–Hillman reaction (MBH) between dimethylacrylamide and paraformaldehyde to give the allylic alcohol **7** in 1 d, based on Connon's procedure.[19d] Acrylamides are challenging substrates for the MBH reaction,[16] and this outcome with a tertiary acrylamide is noteworthy. In fact, most of the examples in the literature so far deal with the primary derivatives.[19,20] A straightforward bromination and iodination reaction was subsequently carried out on the alcohol **7** to yield the desired allylic halides **8** and **9**.[21] After optimisation, we were able to perform the MBH–bromination sequence on a 6.5 g scale with only one purification step (see the ESI).

At the onset, the epoxidation reactions were carried out in an open vessel with benzaldehyde in the presence of a base (Cs_2CO_3, K_2CO_3, NaOH) and 20% of thiolane as depicted in Scheme 2. In our hands, every attempt to transfer an allyl bromide **10** (with an acrylate backbone) did not lead to any epoxide formation, as detected on the crude product (Table 1, entry 1). It became obvious that the activated C–C double bond was not compatible with the one-pot procedure and instead underwent rapid polymerisation or addition reactions.[22]



8 Y = NMe_2; X = Br
9 Y = NMe_2; X = I
10 Y = OEt; X = Br

11a (Y = NMe_2)

Scheme 2 Optimisation of the epoxidation process.

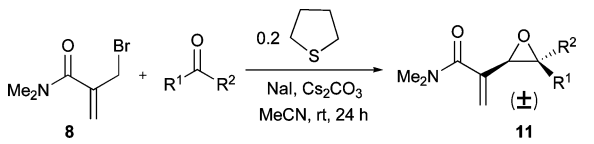
Then, we turned our attention to the allyl iodide **9**, displaying an acrylamide backbone. Pleasingly, this sulfonium ylide precursor effected a complete epoxidation of benzaldehyde in 24 h to give **11a** with a good yield of 76% (entry 2). First of all, this reaction required only 0.2 eq. thiolane. Therefore, an organocatalytic cycle is validated with respect to the sulfide.[23] This methodology allows the synthesis of such vinyl oxiranes with a unique Morita–Baylis–Hillman backbone. Next, this process achieved the formation of the *trans*-epoxide with a diastereoisomeric ratio higher than 95 : 5, as determined on the ^{1}H NMR of the crude product. The more readily available allyl bromide **8** led to a slower reaction rate (entry 3). The addition of 20% sodium iodide allowed the *in situ* formation of the more electrophilic allyl iodide **9**, affording a smooth reaction in 1 d (entry 4).[24] The use of allyl bromide **8** in the presence of NaI also improved the epoxidation yield (entries 2 *vs* 4). We believe that allyl iodide **9** is slightly light-sensitive and somewhat hydrolytically unstable in the reaction media in comparison to its bromide analogue **8**. Nevertheless, in the presence of NaI, only a small quantity of the allylic iodide **9** is generated and consumed in the catalytic cycle before giving any decomposition. Tetrabutylammonium iodide was also used instead of NaI, but a somewhat lower yield was obtained (entry 5). The less soluble potassium carbonate was also effective as a base, but the reaction was not completed after 1 d (entry 6). We carried on the optimisation and observed that the yield of the epoxide decreased with the solvent polarity (entries 7–9). Interestingly, a strong base such as sodium hydroxide in polar protic solvents allowed a smooth epoxidation process, albeit with lower diastereoselectivity (entry 10). This points out the stability of both the substrate **8** and the epoxide **11a** in basic conditions.

This organocatalytic epoxidation protocol offers operational simplicity, does not require exclusion of air and offers mild reaction conditions.‡ Thus, we evaluated the addition of this original vinyl sulfonium ylide reagent, generated from **8**, onto various aldehydes in the presence of 0.2 equivalent of thiolane and Cs_2CO_3 in 24 h (Scheme 3). A smooth diastereoselective epoxidation took place with benzaldehyde derivatives bearing an electron-withdrawing group (Table 2, entries 1–2). These conditions were also successful with the electron-rich *para*-anisaldehyde but the reaction needed 2 d for completion (entry 3). We were able to form the *trans*-epoxide **11e** from furylaldehyde with a good diastereoselectivity and purity according to the ^{1}H NMR spectra of the crude product. As expected, this oxirane was highly unstable on column chromatography (alumina or silica gel) and could not be purified thereby.[25] Interestingly, this method allowed the formation of the bis-vinyl oxirane **11f** by effecting the chemoselective addition of the vinyl sulfonium ylide to cinnamaldehyde (entry 5). This epoxide is flanked by two alkene moieties with different electronic properties, and would allow further selective functionalisations.[3] This example sheds light on one advantage of the sulfonium ylide epoxidation over the electrophilic epoxidation of alkenes, which would have to select between three types of C–C double bonds to

Table 1 Optimisation of the epoxidation process[a]

Entry	Y	X (1.3 eq.)	Solvent	RI (0.2 eq.)	Base (1.8 eq.)	Yield (%)	dr (*trans* : *cis*)
1	OEt	Br	MeCN	—	Cs_2CO_3	—[b]	
2	NMe_2	I	MeCN	—	Cs_2CO_3	76	>95 : 5
3	NMe_2	Br	MeCN	—	Cs_2CO_3	63[c]	>95 : 5
4	NMe_2	Br	MeCN	NaI	Cs_2CO_3	90	>95 : 5
5	NMe_2	Br	MeCN	*n*-Bu_4NI	Cs_2CO_3	79[d]	>95 : 5
6	NMe_2	Br	MeCN	NaI	K_2CO_3	51[d]	>95 : 5
7	NMe_2	Br	CH_2Cl_2	NaI	Cs_2CO_3	65	93 : 7
8	NMe_2	Br	THF	NaI	Cs_2CO_3	14	>95 : 5
9	NMe_2	Br	Toluene	NaI	Cs_2CO_3	16	>95 : 5
10	NMe_2	Br	*t*-BuOH[e]	NaI	NaOH	62[f]	85 : 15

[a] General reaction conditions: benzaldehyde (0.5 M), allylic derivative (1.3 eq.), thiolane (0.2 eq.), base (1.8 eq.), iodide (0.2 eq.), rt. [b] Polymerisation. [c] A conversion of 77%. [d] NMR yield with an internal standard. [e] *t*-BuOH–H_2O (9 : 1). [f] A conversion of 80%.



Scheme 3 Epoxidation of various carbonyl derivatives.

give this oxirane. The softness of these conditions was exemplified, with cesium carbonate as a base, by the epoxidation of a long chain enolisable aldehyde such as valeraldehyde, albeit with a slight decrease in diastereoselectivity (entry 6). Eventually, we tested an acetophenone derivative. A moderate yield of the corresponding epoxide was obtained, even after a prolonged reaction time, and a poor diastereoselective induction in favor of the *cis* isomer was measured (entry 7).[26] This more-hindered carbonyl group would deserve further optimisation. The stability of the vinyl epoxides is also an important issue.[2b] In our hands, these epoxides were rather air stable, and could be stored for weeks in the fridge. The ^{1}H NMR of crude products hardly showed any impurities and most of them could be purified on silica gel. When the oxirane ring was substituted with an electron-rich aryl group (**11d**), or another vinyl substituent (**11f**), these structures turned out to be acid-sensitive and had to be purified on neutral alumina with a somewhat decreased yield.

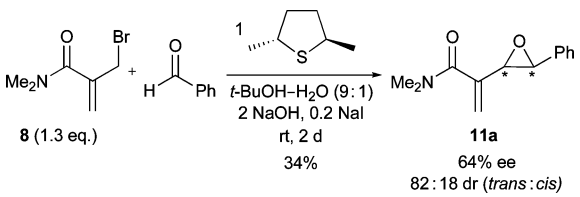
Table 2 Epoxidation of various carbonyl derivatives[a]

Entry	R^1	R^2	Product	dr (*trans* : *cis*)	Yield[b] (%)
1	H	4-$CF_3C_6H_4$	**11b**	93 : 7	92
2	H	4-$NO_2C_6H_4$	**11c**	94 : 6	83
3	H	4-$MeOC_6H_4$[c]	**11d**	>95 : 5	73[d] (33[e])
4	H	2-Furyl	**11e**	95 : 5	75[d]
5	H		**11f**	92 : 8	85[d] (67[e])
6	H	*n*-Butyl	**11g**	77 : 23	78
7	Me	4-$NO_2C_6H_4$	**11h**	41 : 59	32

[a] General reaction conditions: 0.25 mmol of benzaldehyde (0.5 M), allylbromide (1.3 eq.), thiolane (0.2 eq.), Cs_2CO_3 (1.8 eq.), NaI (0.2 eq.), MeCN, rt, 24 h. [b] Isolated yield after column chromatography on silica gel. [c] After 48 h. [d] NMR yield with a internal standard. [e] Purification on neutral alumina.

The presence of the amide group in alkene **8**, and its derivatives, was crucial to the success of this epoxidation without any damage of the acrylic moiety. On one hand, we assume that the amine pair of electrons conjugates with the carbonyl group preventing any activation of the alkene part, leading to further polymerisation events. On the other hand, the robustness of these structures could be explained by the known non-planarity of the methacrylamides.[27] For steric reasons, the amide group is out of the plane of the alkene, and, therefore, minimises the overlapping between the orbitals of the C=O and the C=C bonds. Moreover, the amide group on the alkene **8** allowed a good diastereoselectivity. Its origin would require more studies, but it might be explained by the model proposed recently by Aggarwal and Harvey in the stilbene oxide series.[28] The nucleophilic addition of the ylide reagent onto an aldehyde leads to the formation of both an *anti*-betaine and a *syn*-betaine. Then, the *anti*-betaine cyclises to provide the *trans*-epoxide. The *syn*-betaine, instead of leading to the *cis*-epoxide, tends to reverse to the starting sulfonium ylide, which subsequently moves on towards the formation of the *trans*-epoxide. This equilibrium is influenced by the steric and electronic properties of the substrates.[28] In our case, the reversibility of the *syn*-betaine to the starting material would be favored by the increased steric hindrance of the acrylamide moiety with respect to a simple vinyl moiety (allyl iodide gives a 71 : 29 *trans* : *cis* ratio in these epoxidation conditions).

Having this working hypothesis in mind, we moved on towards an asymmetric process in the presence of the bulkier C_2 symmetrical (*R*,*R*)-2,5-dimethylthiolane (Scheme 4).[24,29] As expected, a slower reaction took place and, pleasingly, we obtained a promising 64% enantiomeric excess for the *trans*-epoxide.[30] However, this result is puzzling. One would have expected that a sterically more-hindered chiral sulfide would enhance the reversibility of the *syn*-betaine formation step, and hence, the overall diastereoselectivity. We obtained a 82 : 18 (*trans* : *cis*) diastereoisomeric ratio instead. Furthermore, we previously showed, in similar conditions,[12] that methallyl iodide furnished the corresponding *trans*-vinyl oxirane with 84% ee and 98 : 2 dr. Obviously, the measured 64% ee accounts for a completely different behaviour of allyl bromide **8**, displaying an acrylamide moiety, in comparison with methallyl iodide. In fact, one can take into account the presence of an axis of chirality along the bond between the amide group and the alkene moiety of **8** (Scheme 4), and hence on the ylide **5** (Fig. 2). We assume a mismatch effect between the orientation of the amide group and the chiral sulfide part, which would influence the stability of betaine intermediates (upon diastereoselectivity), and the accessibility of the ylide reagent faces (upon enantioselectivity).[7b] Therefore, the control of this extra element of chirality is an issue, which would require the use of other chiral sulfides for a successful asymmetric epoxidation.



Scheme 4 Asymmetric epoxidation.

In summary, we have disclosed a straightforward and user-friendly access to functionalized vinyl epoxide displaying a unique Morita–Baylis–Hillman backbone. These polyfunctionalised structures are expected to be useful chiral building blocks in organic synthesis. This racemic sulfonium ylide epoxidation of aldehydes, from an allylic bromide derivative, provides a connective synthesis of such oxiranes with good to excellent diastereoselectivities with a catalytic amount of thiolane. The success of this method is based on the original use of allylic precursors displaying an acrylamide moiety, whose amide group does protect the alkene against any side reactions. The development of an asymmetric process by means of enantiopure sulfides is currently under investigation.

Acknowledgements

We gratefully acknowledge financial support from the "Ministère de la Recherche", CNRS (Centre National de la Recherche Scientifique), the "Région Basse-Normandie" and the European Union

(FEDER funding). We also warmly thank Hélène Colombel for her contribution in the synthesis of the acrylamide precursors.

Notes and references

‡ General experimental epoxidation procedure. To a solution of the allylic bromide **8** (62 mg, 0.33 mmol, 1.3 eq.), aldehyde (0.25 mmol) and sodium iodide (7.5 mg, 0.05 mmol, 0.2 eq.) in acetonitrile (0.5 mL) was added tetrahydrothiophene (4.5 μL, 0.05 mmol, 0.2 eq.). The reaction mixture was stirred for 5 min, then cesium carbonate (147 mg, 0.45 mmol, 1.8 eq.) was added. The resulting mixture was vigorously stirred at 20 °C for 24 h. Water (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated *in vacuo.* Purification by column chromatography afforded the desired epoxide as an inseparable mixture of *trans* and *cis* diastereoisomers.

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24 (*a*) M. Davoust, J.-F. Brière, P.-A. Jaffrès and P. Metzner, *J. Org. Chem.*, 2005, **70**, 4166; (*b*) J. Zanardi, C. Leriverend, D. Aubert, K. Julienne and P. Metzner, *J. Org. Chem.*, 2001, **66**, 5620.

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26 The relative stereochemistry was proven by NOE between the methyl and the proton on the oxirane of the major *cis* isomer.

27 For general discussions on acrylamide conformations, see: (*a*) N. A. Poster, B. Giese and D. P. Curran, *Acc. Chem. Res.*, 1991, **24**, 296; (*b*) W. Adam and A. Zhang, *SYNLETT*, 2005, 1047.

28 V. K. Aggarwal, J. N. Harvey and J. Richardson, *J. Am. Chem. Soc.*, 2002, **124**, 5747. See ref. 7*b* for excellent discussions about the mechanism of sulfonium ylide epoxidation.

29 The (*R*,*R*)- or (*S*,*S*)-2,5-dimethylthiolanes are synthesized in two steps from the commercially available chiral 1,4-diols, which are available in bulk from JFC-Juelich Fine Chemicals GmbH company, see: J. Haberland, W. Hummel, T. Daussmann and A. Liese, *Org. Process Res. Dev.*, 2002, **6**, 458.

30 The use of this chiral sulfide with other conditions optimised in Table 1 led to lower enantioselectivities.