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Tandem Reactions with Chiral Enolates: Preparation of Allylic Alcohols via Trapping with Vinyl Oxiranes

Matthias Welker,[†] Simon Woodward,*[,†] and Alexandre Alexakis*[,‡]

Department of Organic Chemistry, University of Geneva, 30, quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland, and School of Chemistry, University of Nottingham, University Park, NG7 2RD Nottingham, United Kingdom

alexandre.alexakis@chiorg.unige.ch; simon.woodward@nottingham.ac.uk

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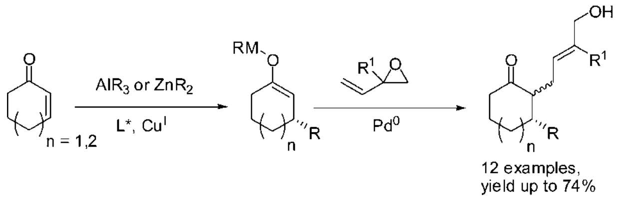
ABSTRACT



An opening of vinyl oxiranes has been accomplished with Zn and Al enolates resulting from asymmetric conjugate addition reactions on cyclic enones. This novel tandem procedure affords the adducts in moderate to good yields, enantioselectivities up to 98%, and moderate to good *cis/trans* selectivities. This provides potentially useful synthetic substrates to prepare complex bicyclic compounds.

Vinyl oxiranes are powerful synthetic substrates to provide allylic alcohols. They have been known to open *via* nucleophilic substitutions. Reports on the use of nonstabilized nucleophiles to perform nucleophilic additions on vinyl oxiranes under Pd^0 catalysis are quite rare, as this transformation usually requires more stabilized nucleophiles. However, Trost et al.[1] noticed that a simple ketone (cyclopentenone) can participate in this reaction despite a low yield. Interestingly, Tsuji et al.[2] described the addition of silyl enol ethers to vinyl oxiranes, however without giving any details. More recently Malacria et al.[3] showed that ester lithium enolates are also suitable reagents to perform those addition reactions.

On another note, advances in Cu-catalyzed asymmetric conjugate addition to enones now enables the preparation of 1,4-addition adducts with ee values up to 99%.[4] This has improved the interest of investigating the reactivity of the enolates formed *in situ*. As a consequence, various examples of novel tandem reactions, leading to the formation of complex products containing several stereogenic centers with high enantio- and diastereoselectivities, have appeared in the literature over the past few years.[5]

This includes for example the use of Zn enolates as nucleophiles for aldol reactions,[6−8] Mannich reactions,[9] *N*-nitroso aldol[10] Dieckmann condensations,[11] alkylation,[12] sillylation,[13] or allylation reactions.[14−17] The use of aluminum enolates is far less developed so far; however, they can

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[†] University of Nottingham.
[‡] University of Geneva.
(1) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969–5972.
(2) Tsuji, J. *Pure Appl. Chem.* **1986**, *58*, 869–878.
(3) Elliott, M. R.; Dimhane, A. L.; Malacria, M. *Tetrahedron Lett.* **1998**, *39*, 8849.
(4) For a recent review in Cu-catalyzed conjugate addition reactions, see: Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823.
(5) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366.
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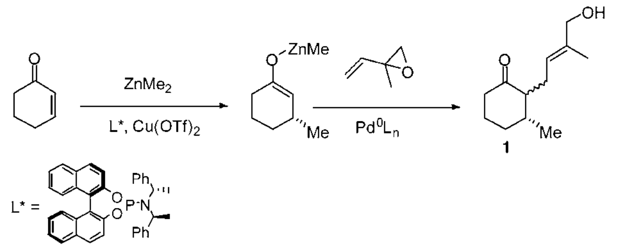
(7) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14977–14985.
(8) Alexakis, A.; Trevitt, G. P.; Bernardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358–4359.
(9) Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **2008**, *49*, 2343–2447. Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 2547–2553.

10.1021/ol9027682

react with acetic anhydride to provide the corresponding acetates.[18]

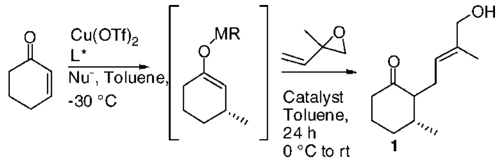
This led us to consider the possibility of combining the asymmetric conjugate addition (ACA) of dialkylzinc reagents to enones with enolate trapping with isoprene monoxide in a one pot procedure, as shown in Scheme 1. Pd should enhance the reactivity of the vinyl oxirane through the formation of a π-allyl-Pd complex.

Scheme 1. Tandem ACA/Vinyl Oxirane Opening



Early optimization results are outlined in Table 1. We were pleased to notice that Zn enolate reacted with isoprene monoxide even in the absence of Pd^0 catalyst, albeit in low yield. The addition of $Pd(PPh_3)_4$ seemed to have a positive effect on the reaction, leading to improved yields (entry 3).

Table 1. Conditions Optimization



entry	nucl. (equiv)	equiv E^+	catalyst	yield	*trans/cis* ratio[b]; *E:Z* (ee[c])
1	$ZnMe_2$ (1.2)	1.5	/	30%	2/1; 4:1 (96%)
2	$ZnMe_2$ (1.2)	1.5	$Ni(OAc)_2$ 5%	33%[a]	2.5/1; n.d.
3	$ZnMe_2$ (1.2)	1.1	$Pd(PPh_3)_4$ 5%	61%	2/1; 4:1
4	$ZnMe_2$ (1.2)	1.5	$Pd(PPh_3)_4$ 5%	55%[d]	2/1; 4:1 (98%)
5	$ZnMe_2$ (1.2)	1.5	$Pd(PPh_3)_4$ 5%	74%	2/1; 4:1
6	$AlMe_3$ (1.2)	1.5	$Pd(PPh_3)_4$ 5%	40%	2/1; 4:1. (91%)
7	MeMgBr (1.2)	5	$Pd(PPh_3)_4$ 5%	/	/

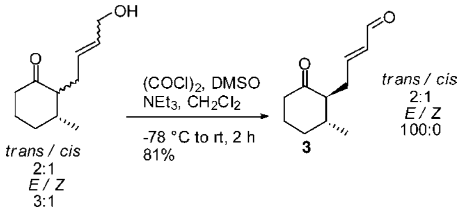
[a] All yields presented in the table are isolated yield after column chromatography; [b] Determined by ^1H NMR; [c] Determined by GC. [d] Reaction performed in Et_2O.

Although Et_2O gave also an acceptable yield (entry 4, 55%), we noticed that toluene gave slightly superior results. Increasing the excess of vinyl oxirane leads to an increase of the yield, which could be explained by competing Me transfer from the Zn alkoxide to the vinyl oxirane, although this product could not be isolated.

More interestingly, aluminum enolates also proved to be effective, albeit in slighlty lower yield. Magnesium enolates led to a complex mixture from which not even traces of product were obtained.

However, despite excellent enantioselectivities on the ACA reaction, the reaction lead to an approximately *trans/cis* 2:1 mixture of diastereomers which cannot be driven to the *trans* product through epimerization with DBU. This result is however consistent with results obtained by Caine et al.[19] on 2-allyl-3methylcyclohexanone who found out the thermodynamic mixture is composed of 65% of *trans* and 35% of *cis* isomers. The reaction also showed moderate *E/Z* selectivity with 4:1 ratios. Interestingly a Swern oxidation of alcohol **2** led to a 2:1 mixture of *cis/trans* aldehyde and only one geometric isomer. This could also serve as a potentially useful synthon for further functionnalisation (Scheme 2).

Scheme 2. Oxidation of the Allylic Alcohol



Vinyl oxiranes are readily available materials which can be obtained either by epoxidation of diene precursors or by olefination of the corresponding aldehydes.[20] Cyclic vinyl oxiranes are available in two steps from the corresponding cyclic enones.[21,22]

We therefore decided to prepare some of these substrates (Scheme 3) and investigate the scope of the reaction by changing the Michael acceptors and the α,β-unsaturated oxiranes (Table 2).

The zinc enolates resulting from the highly stereoselective methyl additions were treated with various oxirane electrophiles. Not suprisingly, butadiene and isoprene monoxide gave the best results. However, although no noticeable amount of the branched addition adduct was isolated, the

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(11) Agapiou, K.; Cauble, D. F; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4528–4529.

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Scheme 3. Preparation of α,*β*-Unsaturated Oxiranes

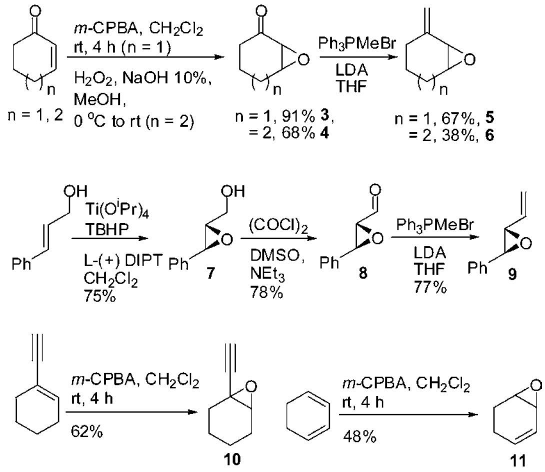
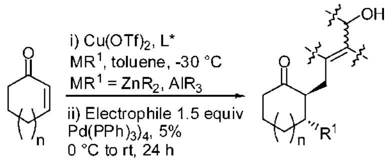
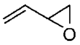
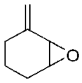
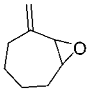
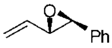
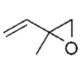
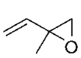
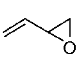
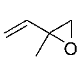
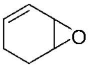
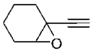
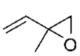
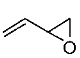
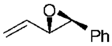
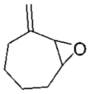
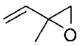


Table 2. Scope of the Reaction



Entry	n	MR^1_x	E$^+$	Product yield^a	*trans/cis*^{b} *E*:*Z*^{c} (ee^h)
1	1	ZnMe$_2$		**2** 68%	*2 / 1* 3:1 (96%)
2	1	ZnMe$_2$		**12** 42%^{d}	*2.4 / 1*^{g}
3	1	ZnMe$_2$		**13** 56%^{e}	*1.9:1* OH epim.: 3:1^c
4	1	ZnMe$_2$		**14** 61%^{f}	*2.5 / 1* E only
5	1	ZnEt$_2$		**15** 52%	*2 / 1* 3:1 (98%)
6	1	ZnPh$_2$		**16** 64%	*>10 / 1* 3:1 (94%)
7	1	AlMe$_3$		**2** 30%	*2 / 1* 3:1
8	1	AlEt$_3$		**1** 37%	*2 / 1* 3:1 (87%)
9	1	ZnMe$_2$		0%	/
10	1	ZnMe$_2$		0%	/
11	2	ZnMe$_2$		**17** 52%^{d}	*12 / 1* 3.5:1
12	2	ZnMe$_2$		**18** 47%^{d}	*>10 / 1* 3:1 (94%)
13	2	ZnMe$_2$		**19** 46%^{d}	*3 / 1* E only
14	2	ZnMe$_2$		**20** 49%^{d}	*9 / 1*^{e} OH epim: 1.3:1
15	2	ZnEt$_2$		**21** 50%	6 / 1 3:1 (98%)

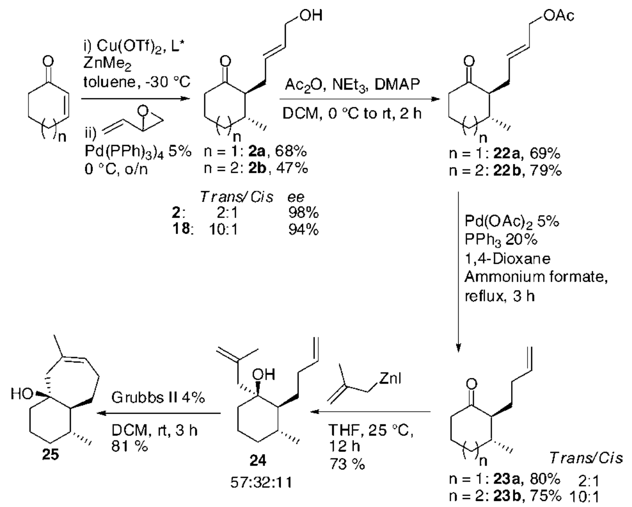
[a] Isolated yield as a mixture of isomers. [b] Estimated by ^{1}H NMR. [c] Estimated by ^{13}C NMR. [d] Performed with 2 equiv of electophile. [e] Performed with 3 equiv of electrophile. [f] Performed with 5 equiv of electrophile. [g] Ratio of epimer at the newly formed C−OH position could not be determined. [h] Determined by chiral GC.

reaction proceeded in moderate *E:Z* and *trans/cis* selectivities. Cyclic oxiranes were also reactive leading to a similar mixture of *trans* and *cis* isomers. An enantiomerically pure oxirane derived from cinnamaldehyde (entries 4, 13) reacted with no loss of diastereoselectivity and an improved *E/Z* selectivity.

Interestingly the enolate derived from ACA of ZnPh$_2$ proved also to be efficient, and led to what appeared to be an improved *trans/cis* mixture of isomers. Aluminum enolates (entries 7−8) proved to be reactive as well, albeit in lower yields. It is also noticeable that the use of 2-cycloheptenone as Michael acceptor led to increased *trans/cis* selectivities (entries 11−15), although the products were isolated in slightly lower yields. Cyclic oxiranes used in large excess (entries 3, 14), lead to a mixture of epimers at the newly created C−OH chiral center with an excess of one epimer.

Finally, propargylic oxiranes (entry 10) are known to react with high selectivity with ZnMe$_2$ under Cu^I catalysis,[23] but in this case we could not observe the expected allene. Nonterminal α,*β*-unsaturated oxiranes proved to be unreactive with Zn enolates (entry 9).

Scheme 4. Application to Synthesis



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This tandem reaction was applied to the synthesis of complex [6,7]-bicyclic homoallylic alcohol **25** (Scheme 4). Cyclohexanone was sujected to the described ACA/vinyl oxiranes trapping to provide **2** in acceptable yield, as a mixture of *cis/trans* and *E/Z* isomers. Acetylation provide **22** which is then subjected to Pd catalyzed hydrogenolysis which provide **23**, as a mixture of *trans* and *cis* isomers. Coumpound **23b** is a known precursor[12] in the synthesis of anticancer agent *Clavularin B*. Noticeably, this is also to the best of our knowledge only the second exemple of the introduction of an homoallyl group using Zn enolates.[12] Precedents[14] persuaded us that a Grignard addition should proceed to give selectively the adduct with a *trans* relationship between the homoallyl and the newly introduced methallyl groups, but in our hands it led to a 3/2.4/1 mixture of 3 isomers. The selectivity was improved to 5.7/3.2/1.1 using the more sterically hindered methallyl zinc iodide. Cyclisation with Grubbs second generation catalyst afforded the bicyclic homoallylic alcohol **25** as a *ca.*2:1 separable mixture of diastereomers.

In conclusion,we successfully developed a novel reactivity for zinc and aluminum enolates through a tandem reaction involving highly enantioselective ACA reactions. Moderate diastereoselectivity was achieved for the trapping of enolates with various vinyl oxiranes, and the resulting allylic alcohols were then used in the synthesis of [6,7]-bicyclic adducts and in a formal synthesis of *clavularin B*.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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