EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300397

Enantioselective One-Pot Catalytic Synthesis of 4,5-Epoxy-3-alkanols and 1-Phenyl-2,3-epoxy-1-alkanols from α,β-Unsaturated Aldehydes

Rebeca Infante,[a] Yulan Hernández,[a] Javier Nieto,*[a] and Celia Andrés*[a]

Keywords: Allylic compounds / Aldehydes / Asymmetric synthesis / Epoxides / Zinc

Conformationally restricted perhydrobenzoxazines have been demonstrated to be good chiral ligands for one-pot asymmetric ethylation/epoxidation, and the unprecedented arylation/epoxidation of trisubstituted α,β-unsaturated aldehydes. The scope of the reaction has been studied and a wide set of substrates with allylic strain of different nature has been explored, obtaining good or total diastereoselectivities in all cases. The enantiocontrol was good or high for the ethylation/epoxidation reaction, whereas it remained at moderate or good levels for the arylation/epoxidation. The reaction is general for trisubstituted enals, and alkylic and aromatic substituents are tolerated at both the α- and β-position of the unsaturated aldehyde; however, disubstituted enals remain challenging substrates. When the one-pot and two-pot protocols were compared, no significant differences concerning the stereocontrol were found, so the advantages of the one-pot procedure are clear.

Introduction

One of the most important transformations in the field of asymmetric synthesis is probably the enantioselective epoxidation of alkenes. In 1965 a low level of stereoinduction was already obtained by Henbest, using (+)-peroxycamphoric acid.[1] However, 15 years later Sharpless and Katsuki developed the first highly enantioselective epoxidation of allylic alcohols. This well-known achievement allowed high stereocontrol to be obtained in the epoxidation of allylic alcohols, including the kinetic resolution (KR) of secondary alcohols.[2,3] Such a discovery caused a revolution in enantioselective synthesis, because chiral epoxy alcohols are one of the most useful building blocks for the preparation of pharmaceutical and natural products.[2,4] The original Sharpless–Katsuki asymmetric epoxidation requires the use of catalytic amounts of titanium isopropoxide and tartrate ester ligands, *tert*-butyl hydroperoxide, and molecular sieves. Nevertheless, many catalytic systems based on transition metals have been developed since that pioneering work, including titanium, vanadium, chromium, manganese, iron, molybdenum or lanthanides, and allylic and homoallylic alcohols or unfunctionalized olefins have been used as substrates.[5,6] More recently, much effort has been devoted to the development of organocatalytic processes that allow metal-free procedures.[7,8]

Despite these excellent findings by Sharpless, nowadays, KR is not the most convenient way to perform the synthesis of chiral secondary epoxy alcohols because low conversions are necessary to obtain good enantioselectivities. For this reason, the synthesis of these compounds have been accomplished in two-step processes involving the isolation and purification of the enantioenriched allylic alcohol, followed by epoxidation employing different transition metals and an oxidant, such as a peracid or a peroxide.[9] Experimental studies have confirmed that the diastereoselectivity of the process relies on both the allylic strain of the olefin and on the nature of the oxidant agent.[10] Consequently, obtaining similar levels of diastereocontrol in the epoxidation of alcohols with different types of allylic strain ($A^{1,2}$ or $A^{1,3}$) with the same oxidant has usually been difficult. In this context, to overcome this weakness, Walsh combined a methodology based on asymmetric alkylation by means of organometallic species to carbonyl compounds, followed by Sharpless epoxidation. This protocol allowed the synthesis of secondary epoxy alcohols with very good yields and enantioselectivities.[11] Curiously, although a set of secondary and tertiary enantio- and diastereoenriched epoxy alcohols were prepared by Walsh's strategy, no examples of directed arylation/epoxidation were included from aldehydes.

Based on the reported excellent results obtained in the arylation, alkylation and alkynylation of aldehydes and α-keto esters promoted by conformationally restricted chiral perhydro-1,3-benzoxazines,[12] we decided to employ this catalytic system as a chirality source to study the preparation of 1-phenyl-2,3-epoxy-1-alkanols employing Walsh's

[a] Centro de Innovación en Química y Materiales Avanzados (CINQUIMA) and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid
Dr. Mergelina s/n, 47011 Valladolid, Spain
Fax: +34-983-423013
E-mail: javiernr@qo.uva.es
celian@qo.uva.es
Homepage: http://sintesisasimetrica.blogs.uva.es/
http://www.uva.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300397.

protocol. We were also interested in studying more extensively the scope and limitations of the ethylation/epoxidation of a broad range of aldehydes using this method.

Results and Discussion

Enantioselective One-Pot Synthesis of 4,5-Epoxy-3-alkanols

Initially, the enantioselective formation of 4,5-epoxy-3-alkanols from aldehydes in the presence of catalytic amounts of perhydrobenzoxazines **1**–**3** (Figure 1) derived from (–)-8-aminomenthol was explored. The first step of this one-pot reaction involves the asymmetric addition of dialkylzinc to the aldehyde, promoted by the chiral ligand, whereas the second step concerns the epoxidation by an oxidant[11,13] with or without titanium isopropoxide.

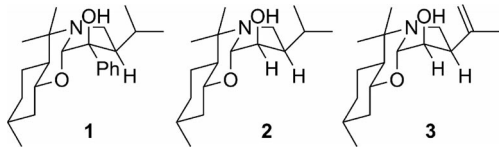


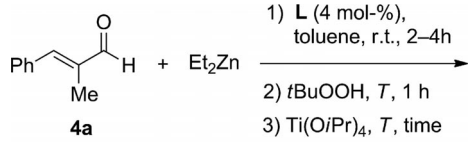
Figure 1. Perhydrobenzoxazines derived from (–)-8-aminomenthol.

The enantioselective ethylation/epoxidation of α-methyl-*trans*-cinnamaldehyde was chosen as a model reaction to examine both the reaction conditions and the efficiency of these ligands.[14] For the ethylation step, the optimal conditions[12a] involved the use of two equivalents of diethylzinc and catalytic amounts of ligand **1** (4 mol-%) at room temperature in toluene. We then focused on the reaction parameters that might affect the diastereo- and enantioselection of the epoxidation step, such as the oxidant, the temperature, the solvent, and the presence or absence of titanium isopropoxide.

Preliminary studies on the nature of the oxidizing agents in the epoxidation step were carried out. In all cases, a solution of α-methyl-cinnamaldehyde in toluene, 4 mol-% of ligand **1**, and 2 equiv. of diethylzinc were reacted at room temperature, and the corresponding oxidant was then added at –20 °C. After one hour, some reaction mixtures were treated with titanium isopropoxide. In this way, the best result was obtained when *tert*-butyl hydroperoxide was used, and the *erythro* epoxy alcohol **6a** could be synthesized quantitatively and diastereoselectively using catalytic amounts of titanium isopropoxide (*dr* 97:3). In the absence of titanium isopropoxide only a small amount of the epoxy alcohol was detected and a significant drop in the diastereoselectivity was perceived (*dr* 67:33).

After determining a suitable combination of *tert*-butyl hydroperoxide and titanium isopropoxide, the influence of the solvent, the temperature of the oxidation step, and the ligand was studied to achieve optimal diastereo- and enantioselectivities; the results are collected in Table 1.

Table 1. One-pot asymmetric ethylation/epoxidation of α-methyl-*trans*-cinnamaldehyde. Optimization of reaction conditions and screening of perhydrobenzoxazine ligands **1**–**3**.[a]



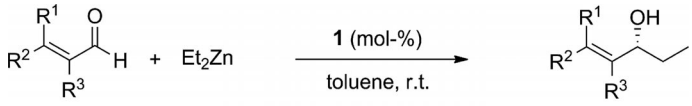
Entry	L	Solvent	*T* [°C]	Time [h]	Yield[b] [%]	*dr*[c] **6a/7a**	*ee*[d] [%]
1	**1**	toluene	25	4	88	87:13	90
2	**1**	toluene	0	12	92	89:11	94
3	**1**	toluene	–20	24	96	97:3	95
4	**1**	hexane	–20	24	92	97:3	93
5	**1**	toluene/hexane (2:1)	–20	24	94	95:5	94
6	**2**	toluene	–20	24	86	93:7	92
7	**3**	toluene	–20	24	90	97:3	71

[a] **L**/Et_2Zn/aldehyde/*t*BuOOH/$Ti(OiPr)_4$ = 0.04:2:1:1:0.1. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined for the major diastereoisomer by HPLC analysis employing a chiral column.

Experiments were carried out at different temperatures for the oxidation step (Table 1, entries 1–3), and a maximal stereoselection was found in the reactions performed at –20 °C. When the reaction was run at 0 °C, the enantiomeric excess remained at the same level, but lower diastereoselectivity was observed (entry 2). In the same way, a higher temperature produced a decrease of both enantio- and diastereoselectivity (entry 1), although the reaction time was significantly reduced. On the other hand, the solvent employed (entries 3–5) did not affect the stereoselection appreciably, and the best results were achieved in toluene (97:3 *dr*, 95% *ee*, entry 3). Concerning the structure of the ligand, the effect of the substituent on the stereogenic center that bears the hydroxyl group was also studied (entries 3, 6 and 7). The secondary alcohol **2** led to the product with good enantioselectivity, albeit with slightly decreased diastereoselection (entry 6). Conversely, replacement of the isopropyl group in **2** by an isopropenyl substituent (**3**, entry 7) produced a significant drop in the enantiocontrol of the process.

With the best reaction conditions established for α-methyl-cinnamaldehyde, our interest turned to an exploration of the scope of the reaction and to an evaluation of the benefits of the one-pot protocol over the corresponding two-step procedure. To this end, a series of diethylzinc addition reactions to a set of unsaturated aldehydes with different substitution patterns were carried out by employing the same chiral inductor; the results are collected in Table 2. It was observed that all substrates afforded the allylic alcohols in very good yields and good or perfect enantioselectivity (entries 1–13).

Table 2. Catalytic asymmetric ethyl transfer to α,β-unsaturated aldehydes in the presence of **1**.



4a–m **5a–m**

Entry[a]	Aldehyde	R^1	R^2	R^3	Allylic alcohol	**1** (4 mol-%) Yield [%][b]	*ee* [%][c]	**1** (10 mol-%) Yield [%][b]	*ee* [%][c]
1	**4a**	H	Ph	Me	**5a**	95	90	97	94[d]
2	**4b**	H	Ph	Ph	**5b**	90	98	93	93
3	**4c**	H	Et	Ph	**5c**	89	87	95	98
4	**4d**	H	Me	Ph	**5d**	89	92	91	95
5	**4e**	H	$-(CH_2)_4-$		**5e**	87	96[d,e]	–	–
6	**4f**	Me	Ph	H	**5f**	97	88	96	91
7	**4g**	Ph	Ph	H	**5g**	96	93	97	93
8	**4h**	Me	Me	H	**5h**	84	>99[d,e]	–	–
9	**4i**	H	Ph	H	**5i**	93	89	93	88[d]
10	**4j**	H	*o*-$MeOC_6H_4$	H	**5j**	97	83	99	83
11	**4k**	H	*p*-$MeOC_6H_4$	H	**5k**	96	83	97	86
12	**4l**	H	2-Furyl	H	**5l**	94	89	98	91
13	**4m**	H	Ph	Br	**5m**	86	80	87	81

[a] **1**/Et_2Zn/aldehyde = 0.04/0.1:2:1. [b] Yield of isolated product after purification by flash chromatography. [c] Determined by HPLC analysis employing chiral columns. [d] Absolute configuration was assigned by comparing the sign of specific rotation with literature data. [e] To increase the sensitivity of the UV detection, these compounds were analyzed by chiral HPLC as the corresponding *p*-nitrobenzoates.

The asymmetric ethylation/epoxidation of the above enals was studied, including several previously unexplored acyclic and cyclic unsaturated aldehydes, with a range of alkyl and aryl substituents at the α- and β-positions. The results obtained for these known and unknown compounds are summarized in Table 3. The one-pot ethylation/epoxidation reactions occurred with good to excellent yields and high diastereo- and enantiocontrol, independent of the substitution on the starting enal. Higher diastereoselectivities were achieved for enals that lead to $A^{1,3}$ strain instead of $A^{1,2}$ strain (see entries 6–8 vs. entries 1–5), and an inversion in the diastereoselection of the process was observed. Thus, for enals leading to reaction intermediates with $A^{1,2}$ strain, the major products were the corresponding *erythro* epoxy alcohols (entries 1–5), whereas for enals leading to $A^{1,3}$ strain the principal products were the *threo* isomers (entries 6–8). Formation of the *erythro* or *threo* epoxy alcohol was determined by comparing the ^1H NMR spectroscopic data of known products (entries 1, 5, and 8),[15] and was in agreement with the transition-state structures proposed by Adam and Wirth, which establish a dihedral angle of between 70° and 90° for titanium complexes (Figure 2).[10] The configurations of the new compounds (entries 2–4, 6, and 7) were assigned by taking into account a well-known mechanism of diethylzinc addition[16] promoted by our ligand[12a] and analyzing the allylic interactions in the transition-states of the epoxidation step.

The substitution of a methyl group for a larger group (such as phenyl) in R^3 ($A^{1,2}$ strain) did not influence significantly the diastereo- or enantioselection (Table 3, entries 1 and 2), and both epoxy alcohols **6a** and **6b** could be isolated in high yields and with excellent stereoselection (97:3 *dr*, 95%*ee* and 95:5 *dr*, 93%*ee*, respectively). However, surprisingly, the very bulky bromine atom was not tolerated in the α-position (α-bromo-cinnamaldehyde, **4m**) under the standard conditions, because no trace of the corresponding epoxy alcohol were detected by ^1H NMR spectroscopic analysis, and the only isolated product was the corresponding allylic alcohol (entry 13).

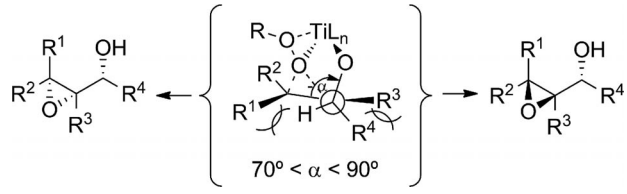
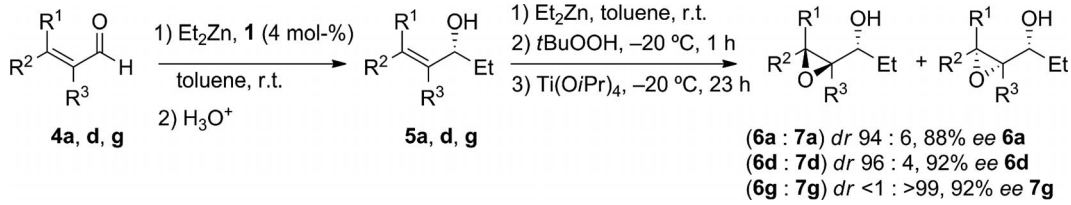


Figure 2. Proposed transition-state structure with the optimal dihedral angles established by Adam and Wirth.

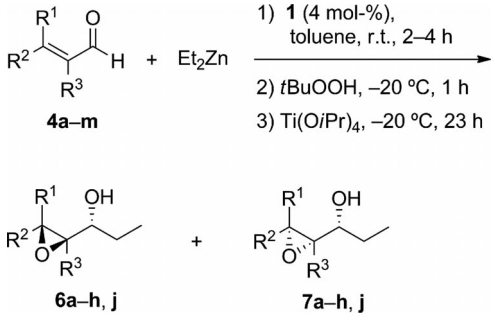
Additionally, no effect in terms of diastereoselectivity was perceived when the phenyl group at the β-position in **4a** (Table 3, entry 1) was replaced by an alkyl substituent in **4c** and **4d** (entries 3 and 4). For example, the epoxy alcohol **6d** was isolated in high yield with 96:4 *dr* and 95%*ee*. Even the *erythro* epoxy alcohol derived from cyclic aldehyde **4e** was isolated in good yield with an excellent 96%*ee* (entry 5). On the other hand, the process was diastereoselective and the enantioselectivity was high for enals leading to $A^{1,3}$ strain (90–94%*ee*), tolerating both alkyl and aryl substituents in R^1 and R^2 (entries 6–8).

In an attempt to further extend the scope of the reaction, we decided to explore the enantio- and diastereoselective one-pot synthesis of disubstituted epoxy alcohols (Table 3, entries 9–12). To this end, a range of *trans*-disubstituted α,β-unsaturated aldehydes that lead to intermediates lacking allylic strains, were subjected to ethylation/epoxidation



Scheme 1. Synthesis of trisubstituted epoxy alcohols in two separate steps. Epoxidation of isolated enantioenriched allylic alcohols.

Table 3. One-pot catalytic asymmetric ethylation/epoxidation to several trisubstituted α,β-unsaturated aldehydes in the presence of **1**.



Entry[a]	4	R^1	R^2	R^3	Yield[b] [%]	*dr* **6**/**7**[c] (*erythro*/*threo*)	*ee*[d] [%]
1	**4a**	H	Ph	Me	96	97:3	95[e]
2	**4b**	H	Ph	Ph	93	95:5	95
3	**4c**	H	Et	Ph	95	97:3	90
4	**4d**	H	Me	Ph	90	96:4	95
5	**4e**	H	$-(CH_2)_4-$		81	90:10	96[e,f]
6	**4f**	Me	Ph	H	80	<1:99	90
7	**4g**	Ph	Ph	H	95	<1:99	94
8	**4h**	Me	Me	H	75	<1:99	91[e,f]
9[g]	**4i**	H	Ph	H	–	–	–
10	**4j**	H	*o*-$MeOC_6H_4$	H	40	52:48	85 (84)
11	**4k**	H	*p*-$MeOC_6H_4$	H	<10	n.d.	n.d.
12	**4l**	H	2-furyl	H	–	–	–
13	**4m**	H	Ph	Br	–	–	–

[a] **1**/Et_2Zn/aldehyde/*t*BuOOH/[$Ti(OiPr)_4$] = 0.04:2:1:1:0.1. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined for the major diastereoisomer by chiral HPLC analysis. The *ee* for the minor diastereoisomer are given in parentheses. [e] Absolute configuration was assigned by comparing the sign of specific rotation with literature data. [f] To increase the sensitivity in the UV detection, these compounds were analyzed by chiral HPLC after transformation into their corresponding benzoates. [g] The only product detected was the corresponding allylic alcohol.

under optimal reaction conditions. Although no epoxidation of *trans*-cinnamaldehyde (**4i**) occurred (entry 9), fortunately, the process took place when *ortho*- and *para*-methoxy-cinnamaldehyde **4j** and **4k** were used as substrates (entries 10 and 11). Whereas *p*-methoxy-cinnamaldehyde was epoxidized in very low yield (< 10%), the preparation of the corresponding epoxy alcohol from the *ortho* counterpart was possible in moderate yield with good enantiomeric excess for both diastereoisomers (**6j** and **7j**), albeit with almost complete absence of diastereoselection (entry 10). Unfortunately, a complex mixture was found when heteroaromatic unsaturated aldehyde **4l** was subjected to the ethylation/epoxidation protocol, and no signal of the desired epoxy alcohol could be identified in the ^1H NMR analysis of the crude reaction mixture.

A comparison of the results summarized in Table 3 (ethylation/epoxidation) and Table 2 (ethylation) indicates that the optical purity of the allylic alcohols and their epoxy analogues remained at similarly high levels, with only slight differences in the *ee* values, mainly in favor of the epoxy alcohols.

In addition, some of these enantioenriched unsaturated alcohols were subjected to epoxidation to compare the diastereo- and enantioselectivities with those obtained by the one-pot approach (Scheme 1). The data revealed that neither the diastereo- nor the enantioselection was substantially modified, so the benefits of the one-pot protocol in terms of operational simplicity are clear.

Enantioselective One-Pot Synthesis of 1-Phenyl-2,3-epoxy-1-alkanols

Although some cyclic and acyclic epoxy alcohols were prepared in a one-pot manner by Walsh et al. using (–)-MIB as chirality source with excellent yields, diastereo- and enantioselection, no precedents of the asymmetric synthesis of 1-phenyl-2,3-epoxy-1-alkanols by one-pot phenylation/epoxidation of unsaturated aldehydes have been reported.

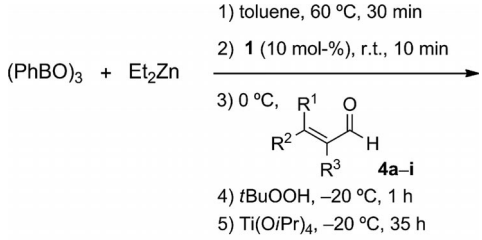
Recently, we have reported excellent results for the enantioselective arylation of an extensive set of aldehydes employing diethylzinc, 10 mol-% of ligand **1**, and triarylboroxins as the aryl source. This process involves two steps: the preparation of the arylating reagent in situ and the addition to the carbonyl component.[12b] One important feature of this arylation method is that both enantiomeric forms are accessible with the same chiral ligand by means of the appropriate combination of arylboronic acid or triarylboroxin and aromatic aldehyde.

With these precedents in mind, we decided to extend this study to the one-pot arylation/epoxidation of α,β-unsaturated aldehydes to synthesize the challenging 1-phenyl-2,3-epoxy-1-alkanols. First, the preparation of the phenylethylzinc species in situ was performed in toluene by using triphenylboroxin and diethylzinc at 60 °C for 30 min.[12b] Next, addition of the chiral ligand and aldehyde was carried out at 0 °C, and finally the epoxidation was run under the previously described standard conditions. This initial experiment demonstrated that no epoxidation occurred for α-methyl-*trans*-cinnamaldehyde under such conditions, and that the only isolated product was the allylic alcohol. How-

ever, to our delight, an increase in the amount of the oxidizing agent (to 3 equiv.) and titanium isopropoxide (0.3 equiv.) led to formation of product **8a** in good yield (88%), with excellent diastereoselection (94:6 *dr*) and good enantioselectivity (87%*ee*). This result is noteworthy because removal of boron species from the reaction medium before the epoxidation step is not necessary with this protocol.

To evaluate the scope of the one-pot phenylation/epoxidation reaction, additional acyclic α,β-unsaturated aldehydes were tested; the results are summarized in Table 4. All compounds successfully underwent the phenylation/epoxidation process (entries 1–4 and 6), with the only exception being aldehyde **4g**, which, in agreement with previous reports,[17] suffered decomposition during the epoxidation step and only a small amount of the epoxy alcohol could be isolated (entry 5). The diastereocontrol was excellent for all trisubstituted enals (entries 1–4), similar to the ethylation/epoxidation process, although the enantioselectivities were not as high as those obtained for the corresponding ethylated compounds.

Table 4. One-pot catalytic asymmetric phenylation/epoxidation to α,β-unsaturated aldehydes in the presence of **1** and triphenylboroxin as aryl source.[a]



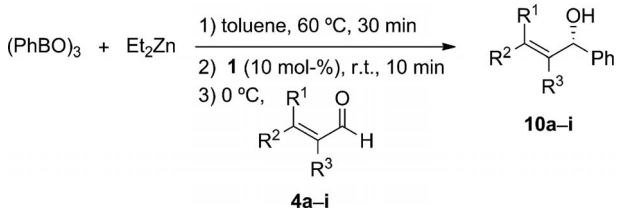
Entry	**4**	R^1	R^2	R^3	Yield[b] [%]	*dr* **8**/**9**[c] (*erythro*/*threo*)	*ee*[d] [%]
1	**4a**	H	Ph	Me	88	94:6	87 (84)
2	**4b**	H	Ph	Ph	83	>99: 1	79
3	**4c**	H	Et	Ph	80	98:2	79
4	**4d**	H	Me	Ph	74	96:4	73[e]
5	**4g**	Ph	Ph	H	15[f]	n.d.	n.d.
6	**4i**	H	Ph	H	77	71:29	80 (86)[e]

[a] **1e**/$(PhBO)_3$/Et_2Zn/aldehyde/*t*BuOOH/$[Ti(OiPr)_4]$ = 0.1:0.6:2.4:1:3:0.3. [b] Yield of product isolated after purification by flash chromatography. [c] Determined by ^1H NMR analysis (n.d.: not determined). [d] Determined for major diastereoisomer by HPLC analysis employing chiral columns. The *ee* for the minor diastereoisomer is given in parentheses (n.d.: not determined). [e] Configuration was assigned by comparing ^1H NMR spectroscopic analysis and the sign of specific rotation with literature data. [f] Decomposition of the product was observed.

Surprisingly, in contrast to the ethylation/epoxidation process, the phenylated/epoxidized products derived from *trans*-cinnamaldehyde (**8i** and **9i**) could be reached with reasonable stereoselection, despite the absence of allylic strain in the transition state (Table 4, entry 6). The configurations of alcohols **8d**, **8i** and **9i** were assigned according to reported data.[18] Analogously, the configurations of all new epoxy alcohols were assigned with regard to the allylic strain in the models proposed by Adam and Wirth,[10] and taking into account the stereochemistry of the arylation step for ligand **1**.[12b]

In search of the origin of the moderate enantiocontrol, the phenylation of the previous α,β-unsaturated aldehydes was carried out under the same conditions; the results obtained are collected in Table 5. All products were isolated in good yields with moderate or good enantiocontrol. The trisubstituted allylic alcohols **10a**–**d** were isolated with enantioselectivities ranging between 66 and 80%*ee* (entries 1–4). In this case, allylic alcohol **10g** derived from β-phenylcinnamaldehyde was stable and could be analyzed by HPLC, although its enantiomeric excess reached just 52% (entry 5). In addition, the disubstituted *trans*-cinnamaldehyde was phenylated in 94% yield and 82%*ee* (entry 6). In general, no significant differences in terms of *ee* were found between the epoxides and the allylic alcohols, with some exceptions in which the epoxy alcohols are afforded with higher selectivities (see Table 4, entries 1 and 4, and Table 5). The evolution of the conversion and enantioselectivity along reaction time for the epoxidation step of **4a** showed a constant value for the enantioselectivity, showing that the difference between the *ee* value of allyl alcohol and the corresponding epoxy alcohol did not arise from kinetic resolution during the epoxidation.

Table 5. Catalytic asymmetric phenyl transfer to α,β-unsaturated aldehydes in the presence of **1** and triphenylboroxin as aryl source.[a]



Entry	**4**	R^1	R^2	R^3	Allylic alcohol	Yield[b] [%]	*ee*[c] [%]
1	**4a**	H	Ph	Me	**10a**	93	73
2	**4b**	H	Ph	Ph	**10b**	95	80
3	**4c**	H	Et	Ph	**10c**	91	82
4	**4d**	H	Me	Ph	**10d**	87	66
5	**4g**	Ph	Ph	H	**10g**	90	52
6	**4i**	H	Ph	H	**10i**	94	82

[a] **1e**/$(PhBO)_3$/Et_2Zn/aldehyde = 0.1:0.6:2.4:1. [b] Yield of product isolated after purification by flash chromatography. [c] Determined by HPLC analysis employing chiral columns (AS-H, OD, AD and AD-H).

The greater simplicity of the one-pot protocol makes it the preferred procedure for the synthesis of this kind of compounds.

Conclusions

A wide range of known and unknown 4,5-epoxy-3-alkanols could be prepared by one-pot ethylation/epoxidation of cyclic and acyclic α,β-unsaturated aldehydes employing perhydrobenzoxazine **1** as chiral inductor. An extensive study was carried out to elucidate the scope and limitations of this reaction. Several aldehydes possessing $A^{1,2}$ and $A^{1,3}$ strain showed complete tolerance for this methodology and very high diastereo- and enantioselectivities were reached. Disubstituted unsaturated aldehydes have been studied in the one-pot ethylation/epoxidation and the reaction proceeded with good enantiocontrol, although with the absence of diastereoselection, for *o*-methoxycinnamaldehyde. In addition, the unprecedented asymmetric one-pot phenylation/epoxidation has been reported, involving the preparation of the arylating species in situ, further addition to the unsaturated aldehyde, followed by epoxidation to yield chiral 1-phenyl-2,3-epoxy-1-alkanols. With the objective of comparing the results obtained for all epoxy alcohols with respect to their corresponding allylic alcohols, an extensive list of new enantioenriched compounds were isolated in high or excellent yields and with moderate to total enantioselectivity by using ligand **1**.

Experimental Section

General Information: All reactions were carried out in anhydrous solvents under an argon atmosphere in flame-dried glassware by means of Schlenk techniques. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts for protons are reported in ppm from tetramethylsilane, with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbon atoms are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br. = broad), coupling constants (Hz), and integration. Specific rotations were measured using a 5-mL cell with a 1-dm path length, and a sodium lamp, and concentration is given in g/100 mL. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to pure isolated substances. TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F_{254} indicator, and visualized by either UV irradiation or by staining with I_2 or phosphomolybdic acid solution. Chiral HPLC analysis was performed using a Daicel Chiralcel OD Column, Chiralpak AD-H or Chiralpak AS-H. UV detection was monitored at 220 or 254 nm. HRMS were performed with a quadrupole spectrometer and TOF analyzer.

Unless otherwise indicated, all compounds were purchased from commercial sources and used as received. Aldehydes **4b**[19] and **4f**[20] were synthesized from commercially available (2Z)-2,3-diphenyl-2-propenoic acid and ethyl *trans*-β-methylcinnamate, respectively, by reduction with $LiAlH_4$ followed by Swern oxidation of the corresponding alcohol. Racemic allylic alcohols were prepared by addition of Grignard reagents to the corresponding aldehydes. Racemic epoxy alcohols were synthesized from the corresponding racemic allylic alcohols by employing *m*CPBA and CH_2Cl_2 as solvent at –20 °C. Triphenylboroxin was freshly prepared by heating phenylboronic acid for 8 h at 110 °C in a conventional oven and used without further purification.[21] Ligands **1**–**3** were prepared according to reported procedures.[12a,14]

Supporting Information (see footnote on the first page of this article): Synthetic procedures, copies of ^{1}H and ^{13}C NMR spectra, and HPLC data are included.

Acknowledgments

The authors acknowledge financial support from the Spanish Ministerio de Ciencia e Innovación (MICINN) (project number CTQ2011-28487/BQU) and the Junta de Castilla y León (GR168). R. I. thanks the Junta de Castilla y León for a predoctoral fellowship.

[1] H. B. Henbest, *Biochem. Soc. Spec. Publ.* **1965**, *19*, 83–92.
[2] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; b) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240; c) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780; d) S. S. Woodard, M. G. Finn, K. B. Sharpless, *J. Am. Chem. Soc.* **1991**, *113*, 106–113.
[3] For reviews, see: a) T. Katsuki, V. S. Martín, *Org. React.* **1996**, 1–300; b) T. Katsuki, in: *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, vol. 2, p. 621–648; c) R. A. Johnson, K. B. Sharpless, in: *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**.
[4] A. Riera, M. Moreno, *Molecules* **2010**, *15*, 1041–1073.
[5] For reviews, see: a) K. A. Jørgensen, *Chem. Rev.* **1989**, *89*, 431–458; b) E. N. Jacobsen, *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **1993**; c) A. H. Li, L. X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341–2372; d) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, in: *Comprehensive Asymmetric Catalysis I–III*, Springer, Berlin, **1999**, vol. 2; e) C. Bonini, G. Righi, *Tetrahedron* **2002**, *58*, 4981–5021; f) B. S. Lane, K. Burgess, *Chem. Rev.* **2003**, *103*, 2457–2473; g) H. Adolfsson, Y. Shi, in: *Modern Oxidation Methods* (Ed.: J.-E. Bäckvall), Wiley-VCH, Weinheim, Germany, **2004**, p. 21–49; h) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu, K.-X. Su, K.-X. Su, *Chem. Rev.* **2005**, *105*, 1603–1662; i) D. J. Ramón, M. Yus, *Chem. Rev.* **2006**, *106*, 2126–2208; j) D. Díez, M. G. Núñez, A. B. Antón, P. García, R. F. Moro, N. M. Garrido, I. S. Marcos, P. Basabe, J. G. Urones, *Curr. Org. Synth.* **2008**, *5*, 186–216; k) K. Matsumoto, Y. Sawada, T. Katsuki, *Pure Appl. Chem.* **2008**, *80*, 1071–1077; l) O. A. Wong, Y. Shi, *Chem. Rev.* **2008**, *108*, 3958–3987; m) K. Matsumoto, T. Katsuki, in: *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2010**, p. 839–890; n) G. de Faveri, G. Ilyashenko, M. Watkinson, *Chem. Soc. Rev.* **2011**, *40*, 1722–1760.
[6] For recent and selected examples, see: a) W. Zhang, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 286–287; b) C. P. Burke, Y. Shi, *Org. Lett.* **2009**, *11*, 5150–5153; c) K. Matsumoto, T. Kubo, T. Katsuki, *Chem. Eur. J.* **2009**, *15*, 6573–6575; d) K. Matsumoto, T. Oguma, T. Katsuki, *Angew. Chem.* **2009**, *121*, 7568; *Angew. Chem. Int. Ed.* **2009**, *48*, 7432–7435; e) H. Egami, T. Oguma, T. Katsuki, *J. Am. Chem. Soc.* **2010**, *132*, 5886–5895; f) Z. Li, H. Yamamoto, *J. Am. Chem. Soc.* **2010**, *132*, 7878–7880; g) X. Zou, X. Fu, Y. Li, X. Tu, S. Fu, Y. Luo, X. Wu, *Adv. Synth. Catal.* **2010**, *352*, 163–170; h) S. Liao, B. List, *Angew. Chem.* **2010**, *122*, 638; *Angew. Chem. Int. Ed.* **2010**, *49*, 628–631; i) K. Matsumoto, C. Feng, S. Handa, T. Oguma, T. Katsuki, *Tetrahedron* **2011**, *67*, 6474–6478; j) D. Xiong, X. Hu, S. Wang, C.-X. Miao, C. Xia, W. Sun, *Eur. J. Org. Chem.* **2011**, 4289–4292; k) Y. Nishikawa, H. Yamamoto, *J. Am. Chem. Soc.* **2011**, *133*, 8432–8435; l) M.-C. Lamas, M. Malacria, S. Thorimbert, *Eur. J. Org. Chem.* **2011**, 2777–2780; m) R. V. Otten-

bacher, K. P. Bryliakov, E. P. Talsi, *Adv. Synth. Catal.* **2011**, *353*, 885–889.
[7] For reviews, see: a) K. M. Weiß, S. B. Tsogoeva, *Chem. Rec.* **2011**, *11*, 18–39; b) O. A. Wong, Y. Shi, *Chem. Rev.* **2008**, *108*, 3958–3987; c) A. Lattanzi, *Curr. Org. Synth.* **2008**, *5*, 117–133; d) W. Adam, C. R. Saha-Möller, P. A. Ganeshpure, *Chem. Rev.* **2001**, *101*, 3499–3548.
[8] For recent examples, see: a) C. Zheng, Y. Li, Y. Yang, H. Wang, H. Cui, J. Zhang, G. Zhaoa, *Adv. Synth. Catal.* **2009**, *351*, 1685–1691; b) P. C. B. Page, B. R. Buckley, M. M. Farah, A. J. Blacker, *Eur. J. Org. Chem.* **2009**, 3413–3426; c) C. Sparr, W. B. Schweizer, H. M. Senn, R. Gilmour, *Angew. Chem.* **2009**, *121*, 3111; *Angew. Chem. Int. Ed.* **2009**, *48*, 3065–3068; d) R. Novikov, J. Lacour, *Tetrahedron: Asymmetry* **2010**, *21*, 1611–1618; e) A. Russo, A. Lattanzi, *Org. Biomol. Chem.* **2010**, *8*, 2633–2638; f) J. Li, N. Fu, L. Zhang, P. Zhou, S. Luo, J.-P. Cheng, *Eur. J. Org. Chem.* **2010**, 6840–6849; g) B. P. Bondzic, T. Urushima, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2010**, *12*, 5434–5437; h) M. Nagano, M. Doi, M. Kurihara, H. Suemune, M. Tanaka, *Org. Lett.* **2010**, *12*, 3564–3566; i) O. Lifchits, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2010**, *132*, 10227–10229; j) B.-S. Li, E. Zhang, Q.-W. Zhang, F.-M. Zhang, Y.-Q. Tu, X.-P. Cao, *Chem. Asian J.* **2011**, *6*, 2269–2272; k) J. M. Vega-Perez, M. Vega-Holm, I. Perinan, C. Palo-Nieto, F. Iglesias-Guerra, *Tetrahedron* **2011**, *67*, 364–372; l) C. De Fusco, C. Tedesco, A. Lattanzi, *J. Org. Chem.* **2011**, *76*, 676–679.
[9] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307–1370.
[10] W. Adam, T. Wirth, *Acc. Chem. Res.* **1999**, *32*, 703–710.
[11] M. M. Hussain, P. J. Walsh, *Acc. Chem. Res.* **2008**, *41*, 883–893.
[12] a) C. Andrés, R. Infante, J. Nieto, *Tetrahedron: Asymmetry* **2010**, *21*, 2230–2237; b) R. Infante, J. Nieto, C. Andrés, *Org. Biomol. Chem.* **2011**, *9*, 6691–6699; c) R. Infante, J. Nieto, C. Andrés, *Synthesis* **2012**, *44*, 1343–1348; d) R. Infante, J. Nieto, C. Andrés, *Chem. Eur. J.* **2012**, *18*, 4375–4379; e) R. Infante, A. Gago, J. Nieto, C. Andrés, *Adv. Synth. Catal.* **2012**, *354*, 2797–2804.
[13] a) D. Enders, J. Ahu, G. Raabe, *Angew. Chem.* **1996**, *108*, 1827; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1725–1728; b) H.-B. Yu, X.-F. Zheng, Z.-M. Lin, Q.-S. Hu, W.-S. Huang, L. Pu, *J. Org. Chem.* **1999**, *64*, 8149–8155; c) H. van der Deen, R. M. Kellogg, B. L. Feringa, *Org. Lett.* **2000**, *2*, 1593–1595; d) M. J. Porter, J. Skidmore, *Chem. Commun.* **2000**, 1215–1225; e) D. Seyferth, *Organometallics* **2001**, *20*, 2940–2955; f) J. Lewinski, Z. Ochal, E. Bojarski, E. Tratkiewicz, I. Justyniak, J. Lipkowski, *Angew. Chem.* **2003**, *115*, 4791; *Angew. Chem. Int. Ed.* **2003**, *42*, 4643–4646.
[14] a) R. Pedrosa, C. Andrés, C. D. Rosón, M. Vicente, *J. Org. Chem.* **2003**, *68*, 1852–1858; b) C. Andrés, I. González, J. Nieto, C. D. Rosón, *Tetrahedron* **2009**, *65*, 9728–9736.
[15] a) A. E. Lurain, A. Maestri, A. R. Kelly, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 13608–13609; b) K. A. Rowley, A. E. Lurain, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 14668–14674; c) L. Salvi, S.-J. Jeon, E. L. Fisher, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2007**, *129*, 16119–16125.
[16] L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824.
[17] E. P. Kohler, E. M. Nygaard, *J. Am. Chem. Soc.* **1933**, *55*, 310–314.
[18] a) G. H. P. Roos, A. R. Donovan, *Tetrahedron: Asymmetry* **1999**, *10*, 991–1000; b) V. Capriati, S. Florio, R. Luisi, I. Nuzzo, *J. Org. Chem.* **2004**, *69*, 3330–3335.
[19] J. Cotter, A.-M. L. Hogan, D. F. O'Shea, *Org. Lett.* **2007**, *9*, 1493–1496.
[20] R. Pedrosa, C. Andrés, J. Nieto, *J. Org. Chem.* **2002**, *67*, 782–789.
[21] X. Wu, X. Liu, G. Zhao, *Tetrahedron: Asymmetry* **2005**, *16*, 2299–2305.

Received: March 15, 2013
Published Online: June 25, 2013

