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1,2-Diarylethanols by Alternative Regioselective Reductive Ring-Opening of 2,3-Diaryloxiranes

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Dedicated to Professor Carlo Bonini on the occasion of his 60th birthday

Keywords: Epoxides / Ring-opening reactions / Reduction / Alcohols / Enantioselectivity / Regioselectivity

Non-symmetrical *trans*-2,3-diaryloxiranes have been regioselectively opened by catalytic hydrogenation over Pd/C, $NaBH_4$/Pd and $[Cp_2TiCl]/H_2O$. Although in the catalytic hydrogenation reactions the epoxides were mainly opened at the β-carbon with respect to the substituted aryl ring in all cases, with the $[Cp_2TiCl]/H_2O$ system the regioselectivity was affected by the electronic properties of the aryl residues, the epoxides being opened on the carbon bearing the most electron-releasing or the least electron-withdrawing group. With the $NaBH_4$/Pd system different regioisomers were obtained depending on the substituents. Starting from enantioenriched epoxides, no loss of optical purity was observed in the alcohols formed.

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Introduction

The reductive ring-opening of epoxides to the corresponding alcohols has become a powerful tool in organic synthesis due to the rapid development of efficient and practical methods for their preparation in both their racemic and enantiopure form. Various hydrides[1] are frequently employed for this purpose and milder systems have been developed to enhance the chemical yield.[2]

The need for a practical version of this reaction with low environmental impact has generated interest in heterogeneous catalytic systems. In particular, various catalysts based on Ni, Pd and Pt have been developed to increase the chemo- and regioselectivity of such reactions, even with enantiopure epoxides.[3] Different hydrogen sources, such as $HCOONH_4$,[4] and catalysts, such as the ethylenediamine–Pd/C complex,[5] have been used to improve selectivity and to prevent further hydrogenolysis of the alcoholic C–O bond. Nevertheless, solvolysis with methanol remains a problem, particularly in the case of benzyl epoxides. Recently, Pd nanoparticles, microencapsulated in polyurea, have been reported to be very efficient in the reductive ring-opening of different benzyl and alkyl epoxides.[6] Moreover, a magnetically separable palladium catalyst has been synthesized and reported to be active and selective for the hydrogenolysis of different epoxides.[7] Titanocene(III) chloride has been claimed to be one of the best reagents for reductive epoxide ring-opening.[8] The intermediate β-titanoxy radicals were reduced efficiently by different hydrogen atom donors and, in the case of alkyl epoxides, high regioselectivity towards the less substituted alcohol was reported.

During our study on the ring-opening reactions of 2,3-diaryloxiranes,[9] we found that such epoxides were suitable starting materials for the synthesis of 1,2-diarylbromohydrins,[10] acetonides,[11] as well as pyridyl, furyl[12] and anilino alcohols[13] in enantiopure form. These results prompted us to investigate more deeply the reductive ring-opening of non-symmetrical substituted 2,3-diaryloxiranes with the aim of finding a general and efficient method. In this context, such epoxides are challenging substrates in terms of the regioselectivity of the ring-opening due to the small (if

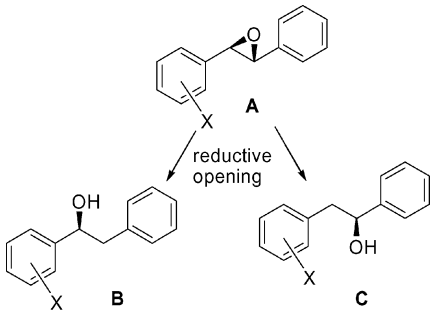

Figure 1. Functionalized diarylethanols from diaryl epoxides.

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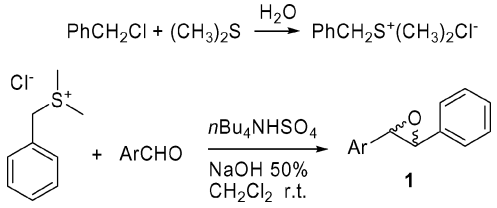
any) difference in reactivity between the benzyl carbon atoms. From a synthetic point of view, they represent useful starting materials because the corresponding diarylethanols can be envisaged as chiral auxiliaries or ligands in asymmetric synthesis, provided the presence of a coordinating heteroatom on the aryl ring[14] (Figure 1).

Results and Discussion

Our recent results on the efficient, alternative and regioselective reduction of *trans*-2-(2-nitrophenyl)-3-phenyloxirane with either the H_2/Pd or $NaBH_4$/Pd system[13] prompted us to investigate various reductive systems with non-symmetrical *ortho*- and *para*-substituted 2,3-diaryloxiranes. Thus, (*E*)-2,3-diaryloxiranes **1** were prepared in good yields in racemic form by the reaction of the dimethylbenzylidenesulfur ylide, generated from the corresponding sulfonium salt under phase-transfer conditions, with the appropriate aryl aldehyde (Scheme 1).[10c,11b]



Scheme 1. Synthesis of (*E*)-2,3-diaryloxirane.

Although catalytic hydrogenation over Pd/C is one of the most simple and clean reduction procedures, in terms of the reagents used and subsequent work-up, it is only occasionally described as being efficient with epoxides.[15] Moreover, no systematic study of 2,3-diaryloxiranes is known to have been carried out. Thus the epoxides of type **1** were treated with H_2 at 1 atm in the presence of a catalytic amount of 10% Pd/C in the appropriate solvent. The most significant results are collected in Table 1. As can be seen, all the reactions were highly regioselective, mostly producing only one of the two possible regioisomers[16] in good-to-excellent chemical yields. In the case of the two trifluoromethyl derivatives **1e** and **1f**, considerable amounts of diarylethanes were formed on further hydrogenolysis (entries 6–8). This side-reaction was suppressed in the case of the 2-trifluoromethyl derivative **1e** when the reaction was performed in 1% AcOH/AcOEt solution (entry 5). In the case of the *trans*-β-methylstyrene epoxide, the yield of the expected 3-phenyl-2-propanol was also high (entry 10). The regioselectivity of the reductive ring-opening by the H_2/Pd system appeared independent of the electronic properties of the substituent. In fact, for all oxiranes bearing either an electron-withdrawing (**1a**, **1b**, **1e** and **1f**) or an electron-releasing group (**1c** and **1d**) on one phenyl ring, the regioisomer **2** was obtained as the major product. Even with the weakly electron-releasing *p*-fluoro substituent, the same behaviour was confirmed (entry 9). Such regioselectivity was quite surprising if we consider the classic mechanism of hydrogenolysis with benzyl-type radicals as the key intermediates. In fact, none of the results suggested the preferential formation of a carbon-centred *S*-type benzyl radical in which the term "*S*" refers to the radical stability being affected by the electron-releasing and -withdrawing groups in the same direction.[17] This kind of radical should be the substituted one in all cases and should give the opposite regioisomer. Apart from mechanistic hypotheses, the synthetic value of this reaction is evident, particularly for the preparation of *ortho*-substituted alcohols **2a** and **2c** (Figure 2), which can be envisaged as ligands in the asymmetric synthesis.

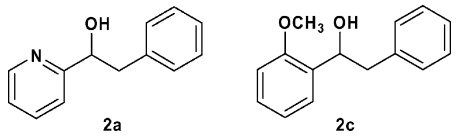
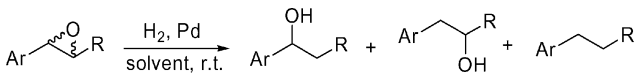


Figure 2. 2-Pyridyl and 2-methoxyphenyl alcohols **2a** and **2c**.

Table 1. Catalytic hydrogenation of *trans* non-symmetrical 2,3-disubstituted oxiranes.



1 2 3 4

Entry[a]	Epoxide	Ar	R	Solvent	Time [h]	**2** [%][b]	**3** [%][b]	**4** [%][b]
1	**1a**	2-pyridyl	Ph	CH_3OH	2	90	–	–
2	**1b**	4-pyridyl	Ph	CH_3OH	2	90	–	–
3	**1c**	2-$CH_3OC_6H_4$	Ph	EtOAc/1% AcOH	12	72[c]	28[c]	–
4	**1d**	4-$CH_3OC_6H_4$	Ph	EtOAc/1% AcOH	7	87[c]	13[c]	–
5	**1e**	2-$CF_3C_6H_4$	Ph	EtOAc/1% AcOH	2	70[d]	–	–
6	**1e**	2-$CF_3C_6H_4$	Ph	CH_3OH	3	60	–	40
7	**1f**	4-$CF_3C_6H_4$	Ph	EtOAc/1% AcOH	2	60	–	40
8	**1f**	4-$CF_3C_6H_4$	Ph	CH_3OH	3	50	–	50
9	**1g**	4-FC_6H_4	Ph	CH_3OH	3	70[d]	–	–
10	**1h**[e]	Ph	CH_3	CH_3OH	2	–	95	–

[a] All reactions were performed by using Pd/C(10%)/substrate, 20 mg/mmol. The conversions were all higher than 99% and were determined by ^1H NMR analysis of the crude product. [b] Isolated yield except for **2c**, **3c**, **2d** and **3d**. [c] The ratio was determined by ^1H NMR analysis of the purified alcoholic mixture. [d] No isolable product was obtained from the rest of the crude. [e] Epoxide **1h** was prepared by oxidation of commercial *trans*-β-methylstyrene with *m*CPBA.

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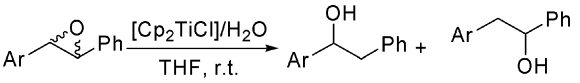
Titanocene(III) chloride represents a valuable reagent for the radical-mediated reductive ring-opening of epoxides.[8] This reaction generally generates the most stable β-titanoxy radical, which can be reduced by a suitable hydrogen-atom donor to an alcohol with the opposite regiochemistry to that expected from the reduction with metal hydrides.[18]

Recently, water was presented as an efficient hydrogen-atom source in such a reaction, working well also with disubstituted and sterically congested epoxides.[19] Thus we decided to explore the synthetic usefulness of such a reaction for the reductive ring-opening of 2,3-diaryloxiranes. We treated epoxides **1** with $[Cp_2TiCl]$ (2.2 equiv.) and H_2O (40 equiv.) in THF at room temperature. The results are summarized in Table 2.

Table 2. Reductive ring-opening of epoxides **1** mediated by $[Cp_2TiCl]/H_2O$.



1 **2** **3**

Entry[a]	Epoxide	Ar	Time [h]	Yield[b] [%] **2**	**3**
1	**1a**	2-pyridyl	24	no reaction	
2	**1b**	4-pyridyl	24	no reaction	
3	**1c**	2-$CH_3OC_6H_4$	2	25	75
4	**1d**	4-$CH_3OC_6H_4$	2	12	88
5	**1e**	2-$CF_3C_6H_4$	2	86	14
6	**1f**	4-$CF_3C_6H_4$	2	75	25
7	**1g**	4-FC_6H_4	2	1	1

[a] The single-electron transfer reagent $[Cp_2TiCl]$ was generated in situ by stirring commercially available $[Cp_2TiCl_2]$ with Mn dust in THF. The conversions were all higher than 99% (except for **1a** and **1b**) and were determined by ^1H NMR analysis of the crude product. [b] The ratio was determined by ^1H NMR analysis of the purified alcoholic mixture.

The procedure appeared in general to be efficient (mass balance generally exceeding 90%) with the exception of the two pyridyl epoxides **1a** and **1b** (entries 1 and 2) in which the Ti complex is likely poisoned by the pyridyl ring. The reaction also showed considerable regioselectivity in all cases and was strongly affected by the electronic properties of the aryl residues. In the oxiranes with Ar bearing an electron-releasing OCH_3 group (entries 3 and 4), the main reaction product was regioisomer **3**, whereas in the presence of an electron-withdrawing CF_3 group, regioisomer **2** was formed preferentially (entries 5 and 6).

Thus, all epoxides were ring-opened at the carbon atom bearing the most electron-releasing (or the least electron-withdrawing) group, which indicates that of the two alternative benzylic β-titanoxy radicals that can be formed as intermediates, **7** is the most favoured (that is, the most stable) (Figure 3).

With these results in hand, we were also interested in testing the reductive ring-opening of diaryl epoxides with hydrides to observe a possible reverse of the regioselectivity.

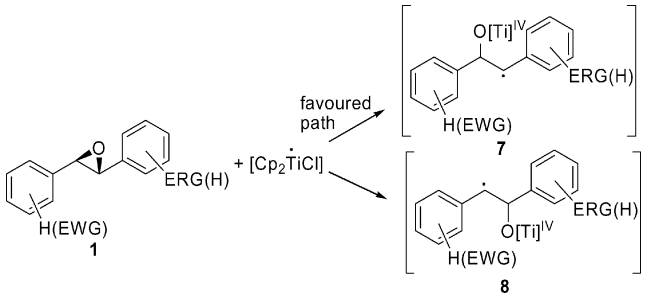
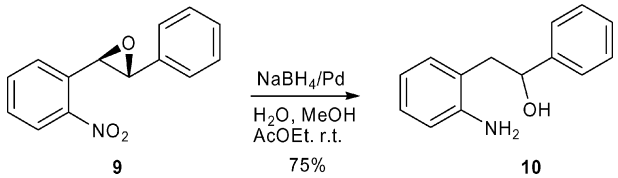


Figure 3. Alternative formation of the benzyl β-titanoxy radicals **7** and **8**.

Of the various hydrides that are efficient in the reductive ring-opening of epoxides, $LiAlH_4$ is the most common[20] and the milder borohydrides often require the presence of a Lewis acid, which activates the epoxide towards nucleophilic attack. Indeed, the $NaBH_4/ZrCl_4$[21] and $Zn(BH_4)_2/SiO_2$[22] systems are reported to be efficient and, recently, $NaCNBH_3$ in the presence of ZnI_2 was found to effect regioselective ring-opening of benzylic epoxides.[23]

It is known that $NaBH_4$ is capable of reducing palladium salts to metallic palladium and that the latter catalyses the slow release of hydrogen from the borohydride. This system has been used for selective nitro reduction[24] and its behaviour was proven to be highly dependent upon the reaction conditions, fluctuating between a simple source of hydrogen (like in catalytic hydrogenation) and a more "hydridic" reagent. No example of oxiranyl ring-opening with this system was known before our recent results with *trans*-2-(2-nitrophenyl)-3-phenyloxirane.[13] This encouraged us to test the $NaBH_4$/Pd system with the above-mentioned diaryl epoxides, looking for a complementary method with respect to catalytic hydrogenation and the $[Cp_2TiCl]/H_2O$ system. Thus, we first optimized the reaction conditions for the reduction of *trans*-2-(2-nitrophenyl)-3-phenyloxirane (**9**), obtaining the corresponding amino alcohol **10** in high yield (75%) by modifying the procedure of Neilson et al.[25] (see the Exptl. Sect.) by adding 10% AcOEt to the solvent mixture to solubilize the substrate (Scheme 2).



9 **10**

Scheme 2. Reductive ring-opening of the *o*-nitrophenyl epoxide **9**.

Then the epoxides **1** were treated with the $NaBH_4$/Pd system under the same reaction conditions, apart from the use of AcOEt, which was not necessary for the solubilization of the substrates. The most significant results are collected in Table 3.

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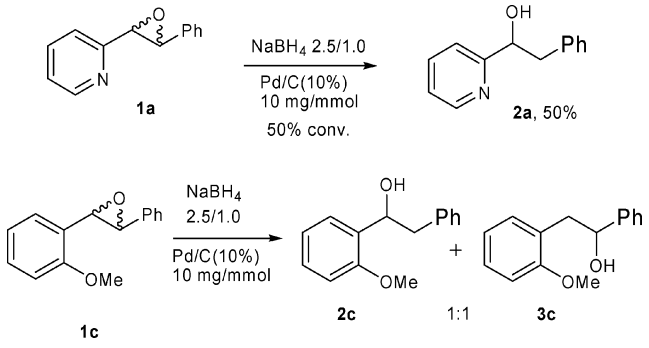
Table 3. Reductive ring-opening of the epoxides by the $NaBH_4$/Pd system.

Entry[a]	Epoxide	Ar	R	Time [h]	Yield [%][b] 2	3
1	**1a**	2-pyridyl	Ph	4	–	80
2	**1b**	4-pyridyl	Ph	4	–	75
3	**1c**	2-$CH_3OC_6H_4$	Ph	2	33[c]	67[c]
4	**1d**	4-$CH_3OC_6H_4$	Ph	2	15[c,d]	60[c,d]
5	**1e**	2-$CF_3C_6H_4$	Ph	2	90	–
6	**1f**	4-$CF_3C_6H_4$	Ph	3	65[d]	–
7	**1h**	Ph	CH_3	–	–	90

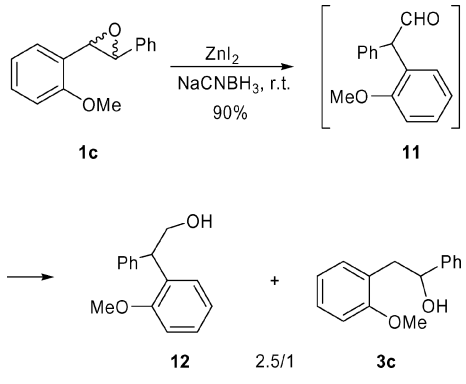
[a] All the reactions were performed at room temp. with a $NaBH_4$/substrate ratio of 7.5:1.0 and Pd/C(10%)/substrate, 50 mg/mmol. The conversions were all higher than 99% and were determined by ^1H NMR analysis of the crude product. [b] Isolated yield except for **2c**, **3c**, **2d** and **3d**. [c] The ratio was determined by ^1H NMR analysis of the purified alcoholic mixture. [d] No isolable product was obtained from the rest of the crude.

As can be seen, the $NaBH_4$/Pd system showed a high efficiency in the reductive ring-opening in terms of conversion and regioselectivity. The chemical yields were good in all cases. *trans*-β-Methylstyrene epoxide **1h** was regioselectively opened at the benzylic carbon atom to afford the corresponding alcohol **3h** as the only product, which confirms the higher reactivity of the aryl position with respect to the alkyl one. In the case of non-symmetrical diaryl epoxides, the regioselectivity was highly affected by the electronic properties of the substituents in combination with the unique characteristics of the reagent. Steric effects, if present, were negligible as *ortho*- and *para*-substituted substrates gave the same type of regioisomer in similar chemical yield. For substrates with the strong electron-withdrawing group CF_3 (entries 5 and 6), only the regioisomers **2** were detected in the reaction mixtures, the hydrogen exclusively attacking the β-carbon with respect to the substituted phenyl ring. These results account for an electron-deficient acyclic intermediate, which has already been postulated for the ring-opening reaction with LiBr/Amb. 15 system.[10c] Accordingly, in the case of **1c** and **1d**, which possess an electron-releasing group on the phenyl ring, regioisomers **3** (α opening) were the major products observed (entries 3 and 4). On the other hand, this mechanism can hardly explain the results for pyridyl epoxides **1a** and **1b** (bearing an electron-withdrawing heteroaryl group) for which only alcohols **3** (α opening) were the only product formed (entries 1 and 2). These results indicate that, in these cases, the activated epoxide is more likely the reactive species in which the electrophilicity of the two oxiranyl carbon atoms drives the nucleophilic attack. As the sensitivity of the system to the reaction conditions is well known, we also explored the effect of changing different reaction parameters, that is, the borohydride/substrate and Pd/substrate ratios. The critical role of Pd was evident by the complete inertness of epoxides **1** in the presence of $NaBH_4$ alone at room temp. for 24 h. Although different Pd/substrate ratios influenced only the reaction times, different $NaBH_4$/substrate ratios gave rise to different reaction mixtures. As an example, with a $NaBH_4$/substrate ratio of 2.5:1.0, pyridyl epoxide **1a** gave, at low conversions, only alcohol **2a**, whereas **1c** afforded an equimolar mixture of the regioisomers **2c** and **3c** (Scheme 3). The formation of **2a** suggests that with a lower $NaBH_4$/substrate ratio, a hydrogen species with properties closer to those of catalytic hydrogenation was operative.



Scheme 3.

These results suggest that a high $NaBH_4$/substrate ratio (at a given Pd/substrate ratio) not only favours reductive ring-opening over side-reactions, but also influences the regioselectivity of the reaction. Under these conditions, $NaBH_4$ likely produces a more "hydridic" reducing reagent with properties different to those of H_2 in catalytic hydrogenation reactions. To support this hypothesis and to show that a mechanism involving an acyclic cationic type intermediate was not operating in the case of **1c**, we treated it with ZnI_2/$NaCNBH_3$, which is known to proceed by Lewis acid activation of the epoxide towards nucleophilic attack. In this case the main reaction product was 2,2-diarylethanol **12** (together with the expected **3c**), likely derived from the reduction of aldehyde **11**, which was initially formed by rearrangement of the starting epoxide (Scheme 4).[26]



Scheme 4.

Finally, we tried to apply the most efficient procedures to enantiopure 2-pyridyl epoxide (*R*,*R*)-**1a** and *o*-methoxyphenyl epoxide (*R*,*R*)-**1c** (Scheme 5) to obtain valuable ligands that would be useful in asymmetric synthesis.

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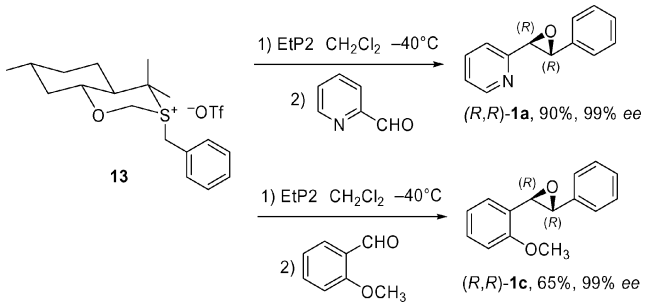
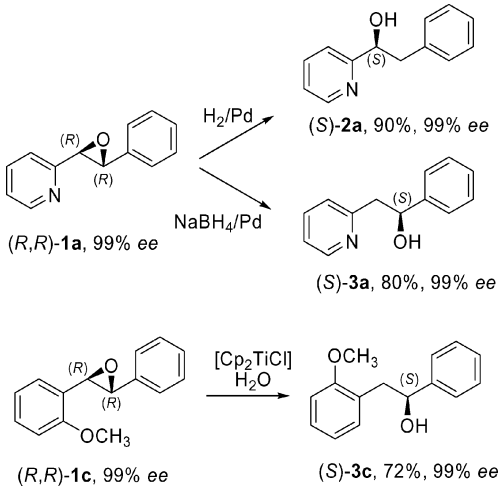


Scheme 5. Synthesis of enantiopure (*R*,*R*)-**1a** and (*R*,*R*)-**1c**.

Both epoxides (*R*,*R*)-**1a** and -**1c** were prepared in good yields and *ee* values following the literature procedure[11b,12] starting from 2-pyridinecarbaldehyde and 2-methoxybenzaldehyde, respectively, and 1 equiv. of a sulfur ylide, which was preformed in situ by deprotonation of the sulfonium salt **13**, derived from Eliel's oxathiane.

Epoxide (*R*,*R*)-**1a** was also submitted to Pd-catalysed hydrogenation and reduction with $NaBH_4$/Pd to afford two regioisomeric pyridyl alcohols (*S*)-**2a** and (*S*)-**3a**, respectively, as the main products. Analogously, (*R*,*R*)-**1c** was treated with the [Cp_2TiCl] system, which afforded the corresponding alcohol (*S*)-**3c** (Scheme 6). In all cases no loss of optical purity was observed,[27] proving that no epimerization occurred during the oxiranyl ring-opening, irrespective of the method used.



Scheme 6. Reductive ring-opening of enantiopure (*R*,*R*)-**1a** and (*R*,*R*)-**1c**.

Beyond mechanistic considerations, the synthetic value of the three different reductive ring-opening methods is unquestionable. They represent powerful tools for enantiospecific access to functionalized chiral 1,2-diarylethanols from easy-to-make diaryl epoxides.

Conclusions

We have developed a new regio- and enantioselective approach to 1,2-diarylethanols from the corresponding parent 2,3-diaryloxiranes by the use of suitable reductive systems. Different regioisomers were obtained by using the H_2/Pd, [Cp_2TiCl]/H_2O or $NaBH_4$/Pd/C systems. Application of these procedures to enantiopure epoxides resulted in no loss of optical purity in the corresponding products.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. Mass spectra were recorded with a Hewlett–Packard 6890 chromatograph equipped with a HP 5973 mass detector. Commercially available reagents were used without further purification. All reactions were monitored by TLC on silica gel coated plates. Column chromatography was carried out by using 60–240 mesh silica gel at atmospheric pressure.

(*E*)-3-Phenyl-2-(2-pyridyl)oxirane (1a): Oxirane **1a** was obtained in 67% yield (247 mg from 200 mg of picolinecarbaldehyde) after chromatographic purification ($CHCl_3$/Et_2O, 7:3). The ^1H and ^{13}C NMR spectra were consistent with literature data.[12]

(2*R*,3*R*)-3-Phenyl-2-(2-pyridyl)oxirane [(*R*,*R*)-1a]: Oxirane (*R*,*R*)-**1a** was prepared in 82% yield (302 mg from 200 mg of picolinecarbaldehyde) and 99% *ee* (CHIRALCEL ODH, *n*-hexane/2-propanol, 90:10, flow rate: 1.0 mL min^{-1}) according to a literature procedure.[12]

(*E*)-3-Phenyl-2-(4-pyridyl)oxirane (1b): Oxirane **1b** was obtained in 95% yield (350 mg from 200 mg of picolinecarbaldehyde) after chromatographic purification ($CHCl_3$/Et_2O, 7:3). The ^1H and ^{13}C NMR spectra were consistent with literature data.[28]

(*E*)-2-(2-Methoxyphenyl)-3-phenyloxirane (1c), (*E*)-2-(4-Methoxyphenyl)-3-phenyloxirane (1d), (*E*)-3-Phenyl-2-(4-trifluoromethylphenyl)oxirane (1f), (*E*)-2-(4-Fluorophenyl)-3-phenyloxirane (1g) and (*E*)-1-Phenylpropylene Oxide (1h): Oxiranes **1c**,**d**,**f**–**h** were obtained according to literature procedures.[10c]

(2*R*,3*R*)-2-(2-Methoxyphenyl)-3-phenyloxirane [(*R*,*R*)-1c]: Oxirane (*R*,*R*)-**1c** was prepared in 65% yield (216 mg from 200 mg of 2-methoxybenzaldehyde) and 99% *ee* (CHIRALCEL OJ, *n*-hexane/2-propanol, 99:1, flow rate: 0.5 mL min^{-1}) according to a literature procedure.[11b]

(*E*)-3-Phenyl-2-(2-trifluoromethylphenyl)oxirane (1e): Oxirane **1e** was obtained in 90% yield (273 mg from 200 mg of 2-trifluorobenzaldehyde) after chromatographic purification (petroleum ether/CH_2Cl_2, 4:1) as a colourless oil. R_f = 0.65. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.76 (d, ^3J = 2.0 Hz, 1 H), 4.23 (d, ^3J = 2.0 Hz, 1 H), 7.37–7.46 (m, 6 H), 7.62 (AB system, J_{AB} = 7.5 Hz, 2 H), 7.68 (d, ^3J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 59.1, 62.6, 124.2 (q, $^1J_{CF}$ = 273 Hz), 125.4, 125.5, 125.6, 127.8, 128.1 (q, $^2J_{CF}$ = 32 Hz), 128.5, 128.6, 132.3, 135.8, 136.3 ppm. MS: *m*/*z* (%) = 264 (100) $[M]^+$, 246 (21), 235 (58), 215 (46), 195 (37), 167 (41), 90 (92), 89 (78). $C_{15}H_{11}F_3O$ (264.08): calcd. C 68.18, H 4.20; found C 68.20, H 4.18.

General Procedure for Pd/C Catalytic Hydrogenation: A mixture of epoxide (1 mmol), 10% Pd/C (60 mg) in CH_3OH (20 mL; or 1%AcOH in AcOEt) was stirred at room temperature under H_2 (1 atm.). At the end of the reaction the catalyst was removed by filtration and the mixture was evaporated under vacuum. The products were isolated by chromatographic purification of the crude product on silica gel.

General Procedure for Reductive Ring-Opening Mediated by [Cp_2TiCl]/H_2O: A mixture of [Cp_2TiCl_2] (1.1 mmol) and Mn dust (4 mmol) in THF (25 mL) was stirred at room temp. until the red colour turned green (about 5 min) and then a deoxygenated solu-

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tion of the corresponding epoxide (0.5 mmol) and H_2O (20 mmol) in THF (3 mL) was added and the mixture stirred for 6 h. The reaction was quenched with 5% aqueous NaH_2PO_4 and extracted with *t*BuOMe. The organic layer was washed with brine, dried with anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The products were isolated by chromatographic purification of the crude product on silica gel.

General Procedure for Reduction with the $NaBH_4$/Pd/C System: A mixture of $NaBH_4$ (7.5 equiv.) in H_2O (7 mL) was poured into a suspension of 10% Pd/C (50 mg) in CH_3OH (5 mL) under argon and the mixture was cooled to 0 °C. A solution of epoxide (1 mmol) in CH_3OH (10 mL) was added dropwise. At the end of the reaction the catalyst was removed by filtration, the methanol evaporated under vacuum and the resulting mixture extracted with EtOAc. The organic phase was washed with brine, dried on anhydrous Na_2SO_4 and the solvents evaporated under vacuum. The products were isolated by chromatographic purification of the crude product on silica gel.

2-Phenyl-1-(2-pyridyl)ethanol (2a): Alcohol **2a** was obtained in 90% yield (91 mg from 100 mg of **1a**) by Pd/C catalytic hydrogenation after chromatographic purification ($CHCl_3/Et_2O$ = 7:3). The ^1H and ^{13}C NMR spectra were consistent with literature data.[12]

1-Phenyl-2-(2-pyridyl)ethanol (3a): Alcohol **3a** was obtained in 80% yield (81 mg from 100 mg of **1a**) by reduction with the $NaBH_4$/Pd system after chromatographic purification ($CHCl_3/Et_2O$ = 7:3). The ^1H and ^{13}C NMR spectra were consistent with literature data.[12]

(1*S*)-2-Phenyl-1-(2-pyridyl)ethanol [(*S*)-2a]: Alcohol (*S*)-**2a** was obtained in 90% yield [91 mg from 100 mg of (*R*,*R*)-**1a**] by Pd/C catalytic hydrogenation after chromatographic purification ($CHCl_3/Et_2O$ = 7:3) and with 90% *ee* (CHIRALCEL ODH, *n*-hexane/2-propanol, 80:20, flow rate: 1.0 mL min^{-1}). The optical rotation and ^1H and ^{13}C NMR spectra were consistent with literature data.[12]

(2*S*)-1-Phenyl-2-(2-pyridyl)ethanol [(*S*)-3a]: Alcohol (*S*)-**3a** was obtained in 80% yield [81 mg from 100 mg of (*R*,*R*)-**1a**] by reduction with the $NaBH_4$/Pd system after chromatographic purification ($CHCl_3/Et_2O$, 7:3) and with 90% *ee* (CHIRALCEL ODH, *n*-hexane/2-propanol, 80:20, flow rate 1.0 mL min^{-1}). The optical rotation and ^1H and ^{13}C NMR spectra were consistent with literature data.[12]

2-Phenyl-1-(4-pyridyl)ethanol (2b): Alcohol **2b** was obtained in 90% yield (81 mg from 100 mg of **1b**) by Pd/C catalytic hydrogenation after chromatographic purification ($CHCl_3/Et_2O$, 7:3) as a colourless oil. R_f = 0.15. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.87 (A part of ABX system, $^2J_{AB}$ = 13.5, $^3J_{AX}$ = 8.5 Hz, 1 H), 2.95 (B part of ABX system, $^2J_{AB}$ = 13.5, $^3J_{AX}$ = 5.0 Hz, 1 H), 3.11 (br. s, 1 H), 4.81 (X part of ABX system, dd, $^3J_{AX}$ = 8.5, $^3J_{BX}$ = 5.0 Hz, 1 H), 7.08 (d, ^3J = 7.5 Hz, 2 H), 7.15–7.18 (m, 3 H), 7.22 (dd, $J_1 = J_2$ = 7.5 Hz, 2 H), 8.37 (d, ^3J = 5.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.7, 73.6, 120.9, 126.9, 128.6, 129.5, 137.0, 149.5, 152.9 ppm. MS: *m*/*z* (%) = 199 (5) $[M]^+$, 180 (6), 108 (69), 92 (100), 91 (72). $C_{13}H_{13}NO$ (199.10): calcd. C 78.36, H 6.58, N 7.03; found C 78.39, H 6.61, N 7.10.

1-Phenyl-2-(4-pyridyl)ethanol (3b): Alcohol **3b** was obtained in 75% yield (76 mg from 100 mg of **1b**) by reduction with the $NaBH_4$/Pd system after chromatographic purification ($CHCl_3/Et_2O$, 7:3) as a colourless oil. R_f = 0.21. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.91 (A part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{AX}$ = 5.0 Hz, 1 H), 2.97 (B part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{BX}$ = 8.0 Hz, 1 H), 4.85 (X part of ABX system, $^3J_{AX}$ = 5.0, $^3J_{BX}$ = 8.0 Hz 1 H), 7.02 (d, ^3J = 5.5 Hz, 2 H), 7.18–7.28 (m, 5 H), 8.36 (d, ^3J = 5.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.0, 74.5, 124.9, 125.8, 128.0, 128.6, 143.3, 147.4, 149.5 ppm. MS: *m*/*z* (%) = 199 (0.2) $[M]^+$, 181 (7.5), 107 (28), 93 (100). $C_{13}H_{13}NO$ (199.10): calcd. C 78.36, H 6.58, N 7.03; found C 78.52, H 6.48, N 7.12.

1-(2-Methoxyphenyl)-2-phenylethanol (2c) and 2-(2-Methoxyphenyl)-1-phenylehanol (3c): Alcohols **2c** and **3c** were obtained as mixture in 95% yield (96 mg from 100 mg of **1c**) by reduction by Pd/C catalytic hydrogenation, the $[Cp_2TiCl]/H_2O$ system or the $NaBH_4$/Pd system after chromatographic purification (petroleum ether/Et_2O, 3:2) and were analysed by ^1H NMR spectroscopy. ^1H NMR (500 MHz, $CDCl_3$): 72:28 mixture of **2c** and **3c**: δ = 2.50 (br. s, 1 H), 2.98 (A part of ABX system, $^2J_{AB}$ = 13.0, $^3J_{AX}$ = 8.0 Hz, 1 H, 72%), 3.08 (A part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{AX}$ = 9.0 Hz, 1 H, 28%), 3.15 (B part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{BX}$ = 4.0 Hz, 1 H, 28%), 3.17 (B part of ABX system, $^2J_{AB}$ = 13.0, $^3J_{BX}$ = 3.0 Hz, 1 H, 72%), 3.84 (s, 3 H, 72%), 3.87 (s, 3 H, 28%), 5.00 (X part of ABX system, $^3J_{AX}$ = 9.0, $^3J_{BX}$ = 4.0 Hz, 1 H, 28%), 5.17 (X part of ABX system, $^3J_{AX}$ = 8.0, $^3J_{BX}$ = 3.0 Hz, 1 H, 72%), 6.90 (m, 2 H, 28%), 6.98 (m, 2 H, 72%), 7.10 (d, ^3J = 8.0 Hz, 1 H), 7.22–7.27 (m, 2 H), 7.32–7.39 (m, 2 H), 7.62–7.68 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): characteristic signals of **2c**: δ = 44.2, 55.3, 71.5 ppm.

(2*S*)-2-(2-Methoxyphenyl)-1-phenylethanol [(*S*)-3c]: Alcohol (*S*)-**3c** was obtained in 72% yield [73 mg from 100 mg of (*R*,*R*)-**1c**] by reduction with the $[Cp_2TiCl]/H_2O$ system after chromatographic purification (petroleum ether/toluene/diethyl ether, 7:2:1) as a colourless oil (R_f = 0.35) and with 90% *ee* (CHIRALCEL OJ, *n*-hexane/2-propanol, 90:10, flow rate: 1.0 mL min^{-1}). $[\alpha]_D^{25}$ = +8.8 (*c* = 0.25, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.50 (br. s, 1 H), 3.08 (A part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{AX}$ = 9.0 Hz, 1 H), 3.15 (B part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{BX}$ = 4.0 Hz, 1 H), 3.87 (s, 3 H), 5.00 (X part of ABX system, $^3J_{AX}$ = 9.0, $^3J_{BX}$ = 4.0 Hz 1 H), 6.90 (m, 2 H), 7.10 (d, ^3J = 8.0 Hz, 1 H), 7.22–7.27 (m, 2 H), 7.32–7.39 (m, 2 H), 7.62–7.68 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.2, 55.4, 74.3, 110.4, 120.7, 125.7, 127.2, 128.0, 128.2, 131.5, 144.5, 157.6 ppm. MS: *m*/*z* (%) = 228 (2) $[M]^+$, 122 (100), 107 (35), 91 (22). $C_{15}H_{16}O_2$ (228.12): calcd. C 78.92, H 7.06; found C 78.83, H 7.12.

1-(4-Methoxyphenyl)-2-phenylethanol (2d) and 2-(4-Methoxyphenyl)-1-phenylethanol (3d): Alcohols **2d** and **3d** were obtained as a mixture in 95% yield (96 mg from 100 mg of **1d**) by Pd/C catalytic hydrogenation and reduction with the $[Cp_2TiCl]/H_2O$ system and in 75% yield by reduction with the $NaBH_4$/Pd system after chromatographic purification (petroleum ether/Et_2O, 3:2). The ^1H NMR spectra were consistent with literature data.[29] ^1H NMR (500 MHz, $CDCl_3$): 87:13 mixture of **2d** and **3d**: δ = 1.85 (br. s, 1 H), 2.90 (m, 2 H), 3.71 (s, 3 H, 13%), 3.73 (s, 3 H, 87%), 4.78 (m, 1 H), 6.77 (d, ^3J = 7.5 Hz, 2 H, 13%), 6.81 (d, ^3J = 7.5 Hz, 2 H, 87%), 7.03 (d, ^3J = 7.5 Hz, 2 H, 13%), 7.11 (d, ^3J = 7.5 Hz, 2 H, 87%), 7.20 (m, 5 H) ppm.

2-Phenyl-1-(2-trifluoromethylphenyl)ethanol (2e): Alcohol **2e** was obtained in 70% yield (71 mg from 100 mg of **1e**) by catalytic hydrogenation (in 1%AcOH/AcOEt) and in 90% yield by reduction with the $NaBH_4$/Pd system after chromatographic purification (petroleum ether/Et_2O, 3:2) as a colourless oil. R_f = 0.45. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.84 (A part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{AX}$ = 10.0 Hz, 1 H), 3.10 (B part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{BX}$ = 2.4 Hz, 1 H), 5.33 (X part of ABX system, $^3J_{AX}$ = 10.0, $^3J_{BX}$ = 2.5 Hz, 1 H), 7.20–7.30 (m, 5 H), 7.33 (dd, $^3J_1 = J_2$ = 7.5 Hz, 1 H), 7.54 (dd, $^3J_1 = {}^3J_2$ = 7.5 Hz, 1 H), 7.58 (d, ^3J = 7.5 Hz, 1 H), 7.80 (d, ^3J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 46.2, 70.7, 124.4 (q, $^1J_{CF}$ = 251 Hz), 125.4 (q, $^3J_{CF}$ =

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6.0 Hz), 126.5 (q, $^2J_{CF}$ = 30 Hz), 126.8, 127.5, 127.6, 128.7, 129.5, 132.3, 138.1, 143.0 ppm. MS: *m/z* (%) = 266 (2) $[M]^+$, 155 (64), 127 (28), 92 (100). $C_{15}H_{13}F_3O$ (266.09): calcd. C 67.66, H 4.92; found C 67.52, H 5.03.

1-Phenyl-2-(2-trifluoromethylphenyl)ethanol (3e): Alcohol **3e** was obtained as a mixture with **2e** (**2e**/**3e** = 86:14) from **1e** by reduction with the $[Cp_2TiCl]/H_2O$ system and identified by characteristic ^1H NMR signals. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.16 (A part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{AX}$ = 8.5 Hz, 1 H), 3.26 (B part of ABX system, $^2J_{AB}$ = 14.0, $^3J_{BX}$ = 3.0 Hz, 1 H), 4.95 (X part of ABX system, $^3J_{AX}$ = 8.5, $^3J_{BX}$ = 3.0 Hz 1 H) ppm.

2-Phenyl-1-(4-trifluoromethylphenyl)ethanol (2f): Alcohol **2f** was obtained in 60% yield (60 mg from 100 mg of **1f**) by catalytic hydrogenation (in 1%AcOH/AcOEt) and 65% yield (65 mg from 100 mg of **1f**) by reduction with the $NaBH_4$/Pd system after chromatographic purification (petroleum ether/Et_2O, 3:2). The ^1H and ^{13}C NMR spectra were consistent with literature data.[30]

1-(4-Fluorophenyl)-2-phenylethanol (2g): Alcohol **2g** was obtained in 70% yield (71 mg from 100 mg of **1g**) by catalytic hydrogenation after chromatographic purification (petroleum ether/Et_2O, 4:1). The ^1H and ^{13}C NMR spectra were consistent with literature data.[30]

3-Phenyl-2-propanol (3h): Alcohol **3h** was obtained in 95% yield (96 mg from 100 mg of **1h**) by catalytic hydrogenation and 90% yield by reduction with the $NaBH_4$/Pd system after chromatographic purification (petroleum ether/Et_2O, 4:1). The ^1H and ^{13}C NMR spectra were consistent with literature data.[30]

Supporting Information (see also the footnote on the first page of this article): Experimental procedures for the synthesis of compounds **1a**–**g** and **12**. ^1H NMR spectra of compounds **1a**–**h**, **2a**–**g**, **3a**–**d**, **3h** and **12**. ^{13}C NMR spectra of compounds **1e**, **2b**, **2e**, **3b**, **3c** and **12**.

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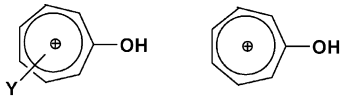
[16] The regiochemistries of the products were determined by comparison of ^1H NMR spectra with known compounds (**2a**, **2d**, **2f**, **2g**, **3d** and **3h**) or by MS identification of characteristic fragments of type **5** for regioisomer **2** (**2b** and **2e**) and of type **6** for regioisomer **3** (**3b**, **3e** and **3f**).



5 **6**

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