Enantioselective Preparation of 2,4-Disubstituted Azetidines

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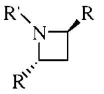
Chiral C_2-symmetric *N*-benzylazetidines have been conveniently prepared from optically pure *anti*-1,3-diols without loss of enantiomeric purity. *N*-Debenzylation led to the corresponding *N*-unsubstituted azetidines, which were then subjected to palladium-catalysed coupling reactions with aryl bromides to afford chiral *N*-arylazetidines. (*R*,*R*)-*N*-Benzyl-2,4-dimethylazetidine has been employed in the synthesis of a new cyclopalladated complex, which can be used, for instance, as a chiral recognition agent for phosphorus ligands.

Introduction

Amongst chiral nitrogen heterocycles, azetidines seem to be the least well studied to date, in terms of both synthetic approaches and applications. This is also the case for chiral 2,4-disubstituted azetidines, as compared to the corresponding aziridines and pyrrolidines. Thus, for instance, C_2-symmetric bis(aziridines)[1] and bis(pyrrolidines)[2] have been prepared and used as bidentate ligands in transition metal catalysed reactions, while *trans*-2,5-disubstituted pyrrolidine moieties find wide application as building blocks for chiral ligands,[3] as chiral bases, and as auxiliaries for asymmetric synthesis.[4] On the other hand, literature reports on optically active symmetrically disubstituted azetidines[5] are largely restricted to azetidine-2,4-dicarboxylic acid derivatives **1a** and azetidine-2,4-dimethanol analogues **1b** derived therefrom. These compounds have only been used as stoichiometric chiral auxiliaries in asymmetric amide alkylations and in catalytic amounts in additions of diethylzinc to aldehydes.



1a R = CO_2R
1b R = CH_2OH

The reason for the lack of progress in the development of the chemistry of optically active azetidines is unclear, but it could be related to synthetic difficulties, given that formation of the four-membered ring from acyclic derivatives is a priori a disfavoured process compared to the analogous construction of five- and even three-membered rings.

A literature survey reveals that optically pure azetidines are generally obtained from racemic mixtures, using stoichiometric amounts of chiral auxiliaries to form diastereomeric pairs.[5a,6] Enzymatic resolutions, such as lipase-catalysed acylation of racemic 2,4-bis(hydroxymethyl)azetidines, have also been considered.[5b,7] Known enantioselective approaches to the four-membered ring are: (a) intramolecular cyclization of 3-amino-1,2-diols (C−N bond formation), which are obtained from chiral epoxy alcohols, in turn obtained from Sharpless epoxidation reactions;[8] (b) photochemical ring closure of α-(*N*-methylamino) ketones (C−C bond formation), prepared from a commercially available, optically pure aminodiol,[9] and (c) reduction of enantiomerically pure β-lactams.[10] As far as we are aware, direct cyclization between primary amines and optically pure 1,3-diol derivatives[11] has hitherto not been developed as a synthetic route to chiral, symmetrically substituted azetidines.

We report herein on a general stereoselective synthesis of new symmetrically 2,4-disubstituted *N*-alkylazetidines from optically pure 1,3-diols. The convenient preparation of *N*-aryl-substituted azetidines through Pd-catalysed coupling reactions is also described.

Results and Discussion

Synthesis of Chiral Azetidines from 1,3-Diols

The general approach to chiral azetidines described here (Scheme 1) is based on the ready availability of optically pure 1,3-diols. Thus, *trans*-2,4-pentanediol is commercially available in optically pure form, while many other diols can conveniently be prepared through catalytic hydrogenation of the corresponding 1,3-diketones, as promoted by (chiral phosphane)ruthenium complexes.[12] In this work, (*R*)- and (*S*)-Binap have been used as chiral ligands in hydrogenation reactions leading to the 1,3-diols **1** shown in Scheme 1. These highly diastereo- and enantioselective hydrogenations − *de* and *ee* values in excess of 95% − have been performed on a scale of up to 10 g in small stainless steel autoclaves using standard laboratory equipment. There is still scope for further scale-up. As a representative example, the synthesis of (*S*,*S*)-4,6-nonanediol (**1c**) is described in the Experimental Section.

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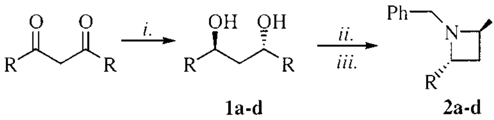
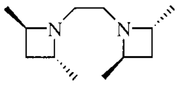


	(*R*,*R*)-2a	(*R*,*R*)-2b	(*R*,*R*)-2c	(*S*,*S*)-2d
R	Me	Et	Pr	CH_2Ph
yield	60%	70%	85%	65%

Scheme 1. Synthesis of chiral *N*-benzylazetidines (R = Me, Et, Pr, CH_2Ph, *i*Pr): (i) H_2, 40–70 bar, r.t. to 80 °C, MeOH, 70 h, catalyst: 0.5% (*R*)- or (*S*)-Binap, (COD)Ru(2-methylallyl)$_2$, HBr (see ref.[13]); (ii) $MeSO_2Cl$, Et_3N; (iii) excess $PhCH_2NH_2$, 45 °C, 60 h

The 1,3-diols were treated with methanesulfonyl chloride in the presence of triethylamine to afford the corresponding bis(methanesulfonates). The crude mesylates were then treated with an excess of benzylamine, according to a procedure previously used for the synthesis of pyrrolidines.[14] The cyclization reactions were found to proceed in moderate to high yields for R = Me, Et, Pr, CH_2Ph. However, the sterically more hindered 2,6-dimethyl-3,5-heptanediyl bis(methanesulfonate) failed to react under analogous conditions. In the synthesis of **2**, ^{1}H-NMR analysis of the crude reaction mixture revealed exclusive formation of the *anti* isomer through a stereospecific substitution reaction,[15] thus we presume that the optical purities of the final azetidines are the same as those of the starting diols.[16] Total inversion at the chiral carbon centres would, of course, be expected on the basis of an S_N2 reaction mechanism. Consequently, the absolute configurations of **2a–c** and **2d** have been assigned as (*R*,*R*) and (*S*,*S*), respectively.

(*S*,*S*)-2,4-Pentanediyl bis(methanesulfonate) was also treated with 0.5 equivalents of ethylenediamine in the presence of triethylamine to afford 1,2-bis(2,4-dimethylazetidino)ethane (**3**), albeit in low yield (25%).



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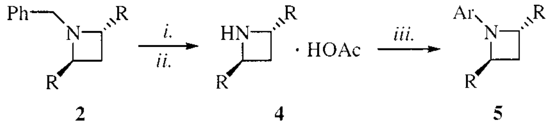
The C_2-symmetric diamine **3** can be expected to find application as a chiral ligand in several transition metal catalysed reactions, as already shown for the aziridine and pyrrolidine analogues.[1,2]

The aforementioned direct cyclization route to azetidines is somewhat less efficient than the analogous synthesis of pyrrolidines,[14] probably due to ring strain[17] and unfavourable entropy factors in the ring-closing step.[18] However, this synthetic approach remains highly convenient from a preparative point of view, given the ready availability of the chiral starting materials.

Synthesis of *N*-Arylazetidines through Palladium-Promoted Coupling Reactions

The synthetic approach to *N*-alkylazetidines shown in Scheme 1 is much less efficient for the preparation of chiral *N*-phenylazetidines, e.g. from aniline and (*R*,*R*)-2,4-pentanediyl bis(methanesulfonate). In this reaction, the use of *n*BuLi as a strong base is required and the desired *N*-phenyl-2,4-dimethylazetidine is obtained in low yield along with several side-products. It has already been shown that harsh conditions (130 °C in HMPA) are required for analogous azetidine syntheses from aniline, even when the starting materials are primary 1,3-diol derivatives.[19] An alternative, convenient approach to arylazetidines can be devised, based on palladium-catalysed coupling of secondary amines with aryl halides, as independently described by Hartwig and by Buchwald.[20] *N*-Unsubstituted chiral azetidines can be expected to be suitable substrates for this coupling reaction, provided that their optical purities are not affected during the catalytic reaction. The reaction sequence is shown in Scheme 2.

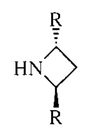


Scheme 2. Synthesis of chiral *N*-arylazetidines (R = Me, Et): (i) 7 bar H_2, $Pd(OH)_2$ cat., MeOH; (ii) HOAc; (iii) ArBr, catalyst: $Pd_2(dba)_3$/*rac*-Binap, NaO*t*Bu, toluene, 70–100 °C, 3–6 h

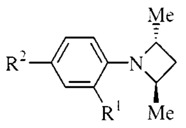
The *N*-unsubstituted azetidines required for the arylation reaction were conveniently prepared by hydrogenation of the corresponding benzylazetidines **2a–c** under standard reaction conditions using 20% $Pd(OH)_2$ as a catalyst. In small-scale experiments, the *N*-unsubstituted azetidines are difficult to recover from the reaction mixtures owing to their low boiling points.[21] They are more easily isolated and characterized as their acetic acid salts, **4**, obtained by addition of acetic acid to the crude reaction mixtures. Attempted debenzylation of azetidine **2d** (R = CH_2Ph) led mainly to the ring-opened product, 1,5-diphenyl-2-pentylamine.

The azetidinium acetates are themselves suitable starting materials for the synthesis of *N*-arylazetidines through palladium-catalysed coupling reactions with aryl bromides. These reactions require the presence of a base, usually *t*BuOK, which also serves to generate the free azetidine from its acetic acid adduct. The results of these coupling reactions are summarized in Table 1. The reaction conditions used in this work were those recommended by Buchwald for the coupling of optically active amines.[22] Most notably, the use of *rac*-Binap and moderate reaction temperatures seem to be crucial features for suppressing racemization of the starting amines. According to the proposed mechanism, racemization results from a reversible β-elimination process; when azetidines **4** are involved, this should lead to the corresponding *cis*-azetidine derivatives. The formation of *cis*-azetidines was never observed in this work, even in reactions performed at high temperature (100 °C). It would therefore appear that the carbon stereochemistry is fully retained during the catalytic process. This is also demonstrated by the optical purity of the azetidine **5a** obtained in this way, which was found to be the same as that

Table 1. Palladium-catalysed coupling of azetidines with aryl bromides

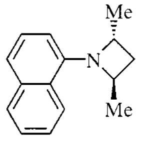


4a R=Me
4b R=Et

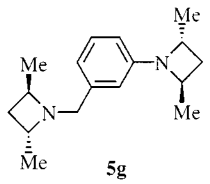


5a-d, **5f**

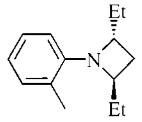
	R^1	R^2
5a	H	H
5b	Me	H
5c	OMe	H
5d	Br	H
5f	H	CF_3



5e



5g



5h

Entry	Aryl halide	Amine	Product	Yield
1	bromobenzene	**4a**	**5a**	75%
2	*o*-tolyl bromide		**5b**	85%
3	2-bromoanisole		**5c**	83%
4	1,2-dibromobenzene		**5d**	95%
5	1-bromonaphthalene		**5e**	80%
6	1-bromo-4-(trifluoromethyl)benzene		**5f**	96%
7	3-bromobenzyl bromide		**5g**	32%
8	2-bromotoluene	**4b**	**5h**	58%

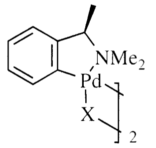
of the product derived from aniline by the direct cyclization route.

As shown in Table 1, a variety of aryl bromides were found to be effective coupling partners. Azetidines were successfully arylated with *ortho*-substituted halides, although in some cases a high reaction temperature was required (e.g. 100 °C in Entries 4 and 8). Use of 3-bromobenzyl bromide furnished the unsymmetrical bis(azetidine) **5g** in moderate yield (Entry 7), while reaction with 1,2-dibromobenzene gave exclusively the mono(azetidine) **5d**, even after prolonged heating with excess azetidine (Entry 4).

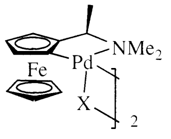
Generally speaking, the flexible synthetic method shown in Schemes 1 and 2 allows access to a number of C_2-symmetric azetidines, which constitute a new class of readily available chiral amines. Their efficiencies as chiral auxiliaries in catalytic and stoichiometric reactions will be explored in due course. Nevertheless, a first application involving the use of a palladium complex of the *N*-benzylazetidine **2a** as a ^{31}P-NMR probe in determining enantiomeric excesses is presented in the following section.

Synthesis and Use of a Cyclopalladated Azetidine Complex

Optically active cyclopalladated compounds derived from N-donor ligands are well known as valuable reagents in enantioselective synthesis, in the resolution of chiral substrates, as well as in the determination of enantiomeric excesses of chiral phosphanes by NMR.[23] Moreover, recent work has shown that they also display interesting catalytic properties in enantioselective transformations.[24] Chiral benzylamines and ferrocenylmethylamines afford the most commonly used cyclopalladated complexes, such as **6**[25] and **7**[26,24] (X = Cl, $MeCO_2$). The *N*-benzylazetidines **2** can be expected to represent alternative sources of chiral palladacycles, as we show in the following.



6



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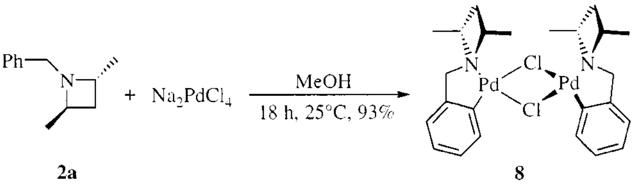
Reaction of (*R*,*R*)-1-benzyl-2,4-dimethylazetidine (**2a**) with Na_2PdCl_4 in methanol at room temperature led to a yellow precipitate, the spectral data of which were consistent with the expected dimeric complex **8**. A single isomer possessing two non-equivalent azetidine moieties was formed, which corresponds to a *cis* arrangement of these ligands across the dimer, as shown in Scheme 3.



Scheme 3. Synthesis of a cyclopalladated *N*-benzylazetidine

An analogous *cis* arrangement has been established for **7** on the basis of X-ray crystal studies,[27] while **6** has been shown to adopt mainly a *trans* geometry. Compared to **6** and **7**, complex **8** displays peculiar structural features, in as much as its chiral centres are located on the nitrogen substituents, outside the palladacycle. The effect of this unprecedented arrangement on the efficiency of chiral discrimination by **8** is difficult to predict and thus merits examination.

Complex **8** was thus tested as a chiral recognition reagent for optically active phosphanes by means of ^{31}P-NMR measurements[23b,23d,23h,23j] using (±)-Binap as a model substrate. A mixture of (±)-Binap and **8** (2:1 ratio) was stirred at room temperature in $CDCl_3$. The ^{31}P-NMR spectrum of the crude mixture showed rather broad signals, which were, however, converted into two well-defined AB signals following the addition of one equivalent of $AgPF_6$: $\delta = 13.68$ and 36.53, $J_{PP} = 42.4$ Hz for (−)-Binap; $\delta = 13.15$ and 39.95, $J_{PP} = 48.8$ Hz for (+)-Binap.[28] The low-field signals in particular give an excellent diastereomeric peak separation ($\Delta\delta = 3.4$) and would allow the evaluation of enantiomeric excesses within the limits of NMR detection. The use of **8** as a resolving agent for chiral phosphanes can also be envisaged.

In summary, we have developed a short, stereoselective preparation of C_2-symmetric azetidines, starting from readily available 1,3-diols. Moreover, the efficient coupling of *N*-unsubstituted azetidines with aryl bromides considerably widens the scope of this synthetic approach. These azetidines represent a new series of potentially useful chiral auxiliaries and synthons.

Experimental Section

(*S,S*)-4,6-Nonanediol (1c, R = Pr): The synthesis of the catalyst was carried out under argon. (*S*)-Binap (72 mg, 0.12 mmol) and (COD)(2-methylallyl)$_2$Ru (32 mg, 0.10 mmol) were first suspended in anhydrous acetone (5 mL). A methanolic HBr solution (1.5 mL, 0.16 N) was then added and the resulting mixture was stirred at room temperature for 30 min. The solvent was subsequently removed in vacuo and the residual yellow solid was used directly as the catalyst for the hydrogenation reaction. Methanol (15 mL) and 4,6-nonanedione (20 mmol) were added to the reaction vessel, which was then placed in a stainless steel autoclave under argon. The argon was replaced by hydrogen and the autoclave was pressurized to 50 bar. The reaction was allowed to proceed at 50 °C for 70 h. Complete conversion into the *anti*-diol **1c** was confirmed by NMR spectroscopy. The final product was crystallized from a cyclohexane/diethyl ether mixture as a colourless solid. Yield 2.8 g (86%). − ^{1}H NMR (CDCl$_3$): δ = 0.92 (t, *J* = 6.6 Hz, Me), 1.2−1.4 (m, 8 H, CH$_2$), 1.58 (t, *J* = 5.4 Hz, CHC*H*$_2$CH), 3.96 (m, 2 H, CHO). − $[\alpha]_D$ = +6 (*c* = 1, CHCl$_3$). − The enantiomeric excess of **1c** was shown to be higher than 95% by ^{1}H NMR (OMe signal: δ = 3.60) and GC analysis of the corresponding Mosher ester (DB 1701 column, J. W. Scientific, 200−250 °C, retention time = 33.5 min). For comparison, the (*R,R*) enantiomer of **1c** was prepared by hydrogenation of 4,6-nonanedione using (*R*)-Binap as the chiral ligand. The corresponding Mosher ester showed a ^{1}H-NMR signal at δ = 3.54 due to the OMe group and a GC retention time of 33.0 min. The absolute configuration of **1c** was assumed to be (*S,S*) by analogy with ref.[11]

Diols (*S,S*)-**1a** and (*S,S*)-**1b**[29] were prepared according to the same procedure as above, using (*S*)-Binap as the chiral ligand. Diol (*R,R*)-**1d** was obtained by [(*R*)-Binap]ruthenium-promoted hydrogenation.

(*S,S*)-4,6-Nonanediyl Bis(methanesulfonate): To a solution of (*S,S*)-4,6-nonanediol (**1c**) (2.5 g, 16 mmol) in CH$_2$Cl$_2$ (60 mL) was added triethylamine (50 mL, 36 mmol). The resulting mixture was cooled to 0 °C, whereupon methanesulfonyl chloride (2.7 mL, 35 mmol) was added dropwise over a period of 10 min. After completion of the addition, the mixture was stirred at 0 °C for 1 h and then poured into 40 mL of cold 1 N HCl. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 30 mL) and the combined organic phases were washed with saturated NaHCO$_3$ solution, dried with MgSO$_4$, filtered, and concentrated. The bis(methanesulfonate) was obtained in quantitative yield (5.0 g) as a colourless oil and was used without further purification. − ^{1}H NMR (CDCl$_3$): δ = 0.95 (t, *J* = 7.2 Hz, Me), 1.3−1.5 (m, 4 H, CH$_2$), 1.6−1.9 (m, 4 H, CH$_2$), 1.97 (dd, *J* = 5.5 and 6.7 Hz, CHC*H*$_2$CH), 2.98 (MeSO$_2$), 4.06 (m, 2 H, CHO).

The same procedure was employed for the syntheses of the bis(mesylates) of diols **1a**, **1b**, and **1d**.

General Procedure for the Synthesis of *N*-Benzylazetidines 2: The synthesis of **2a** is described here as a representative case. The bis(methanesulfonate) of (*R,R*)-**1a** (50 mmol) was dissolved in benzylamine (32 mL, 0.30 mol) and the resulting solution was heated at 45 °C for 60 h. A cyclohexane/diethyl ether (1:1) mixture was then added to the cooled reaction mixture so as to cause precipitation of benzylammonium methanesulfonate. After filtration and concentration of the filtrate to dryness, the residual azetidine was chromatographed on a basic alumina column using cyclohexane/ethyl acetate (95:5) as eluent (R_f = 0.2) in order to separate the excess benzylamine. Azetidine **2a** was obtained in 60% yield (5.3 g) as a colourless oil. In small-scale experiments, the final azetidine could be purified by TLC on silica gel plates eluting with cyclohexane/ethyl acetate (90:10). Where necessary, the azetidines were distilled under reduced pressure in a kugelrohr apparatus.

(*R,R*)-*N*-Benzyl-2,4-dimethylazetidine (2a): ^{1}H NMR (CDCl$_3$): δ = 1.12 (d, *J* = 5.8 Hz, Me), 1.89 (t, *J* = 6.4 Hz, CHC*H*$_2$CH), 3.59 (*A*B, *J* = 13.5 Hz, 1 H, NCH$_2$), 3.65 (m, NCH), 3.76 (A*B*, 1 H, NCH$_2$), 7.2−7.4 (m, Ph). − ^{13}C NMR (CDCl$_3$): δ = 18.2 (Me), 33.3 (CH$_2$), 54.0 (NCH$_2$Ph), 56.8 (NCH), 126.4, 128.0, 128.4 (CH), 139.7 (C). − MS: *m/z* (%) = 175 [M$^+$] (25), 91 (100). − $[\alpha]_D^{25}$ = −45 (*c* = 1, CHCl$_3$).

(*R,R*)-*N*-Benzyl-2,4-diethylazetidine (2b): ^{1}H NMR (CDCl$_3$): δ = 0.80 (t, *J* = 7.4 Hz, 6 H, Me), 1.47−1.61 (m, 4 H, CH$_2$), 1.88 (t, *J* = 6.5 Hz, 2 H, CHC*H*$_2$CH), 3.33−3.47 (m, 2 H, NCH), 3.61 (*A*B, *J* = 13.8 Hz, 1 H, NCH$_2$), 3.85 (A*B*, 1 H, NCH$_2$), 7.2−7.4 (m, Ph). − ^{13}C NMR (CDCl$_3$): δ 9.6 (Me), 25.3 (CH$_2$), 29.0 (CH$_2$), 54.4 (NCH$_2$Ph), 63.1 (NCH), 126.5, 128.2, 128.3 (CH), 140.5 (C). − MS: *m/z* (%) = 203 [M$^+$] (8), 174 [M$^+$ − C$_2$H$_5$] (54), 91 (100). − $[\alpha]_D^{25}$ = −88 (*c* = 1, CHCl$_3$).

(*R,R*)-*N*-Benzyl-2,4-dipropylazetidine (2c): ^{1}H NMR (CDCl$_3$): δ = 0.87 (t, *J* = 7.1 Hz, 6 H, Me), 1.1−1.3 (m, 4 H, CH$_2$), 1.49 (m, 4 H, CH$_2$), 1.88 (t, *J* = 6.5 Hz, 2 H, CHC*H*$_2$CH), 3.33−3.47 (m, *J* = 6.5 Hz, 2 H, NCH), 3.58 (*A*B, *J* = 13.9 Hz, 1 H, NCH$_2$), 3.82 (A*B*, 1 H, NCH$_2$), 7.2−7.3 (m, Ph). − ^{13}C NMR (CDCl$_3$): δ = 14.3 (Me), 18.8 (CH$_2$), 30.1 (CH$_2$), 34.7 (CH$_2$), 54.2 (NCH$_2$Ph), 61.6 (NCH), 126.4, 128.1, 128.2 (CH), 140.0 (C). − MS: *m/z* (%) = 231 [M$^+$] (5), 188 [M$^+$ − C$_3$H$_7$] (66), 91 (100). − $[\alpha]_D^{25}$ = −92 (*c* = 1, CHCl$_3$).

(*S,S*)-*N*-Benzyl-2,4-dibenzylazetidine (2d): ^{1}H NMR (CDCl$_3$): δ = 1.93 (t, *J* = 6.4 Hz, 2 H, CHC*H*$_2$CH), 2.76 (*A*B, J_{AB} = 12.8 Hz, $^3J_{HH}$ = 9.4 Hz, 2 H, CH$_2$Ph), 2.85 (A*B*, $^3J_{HH}$ = 5.2 Hz, 2 H, CH$_2$Ph), 3.64 (*A*B, *J* = 13.8 Hz, 1 H, NCH$_2$), 3.8 (m, 2 H, NCH), 3.89 (A*B*, 1 H, NCH$_2$), 7.1−7.4 (m, Ph). − ^{13}C NMR (CDCl$_3$): δ = 29.2 (CH$_2$), 38.9 (PhCH$_2$), 54.2 (NCH$_2$Ph), 62.5 (NCH). − MS: *m/z* (%) = 327 [M$^+$] (<5), 236 [M$^+$ − CH$_2$Ph] (57), 91 (100). − $[\alpha]_D^{25}$ = +112 (*c* = 1, CHCl$_3$).

(2*R*,2′*R*,4*R*,4′*R*)-1,1′-(1,2-Ethanediyl)-2,2′,4,4′-tetramethylbis(azetidine) (3): A mixture of the bis(methanesulfonate) of **1a** (1.0 g, 4 mmol), triethylamine (1.7 mL, 12 mmol), and freshly distilled ethylenediamine (0.14 mL, 2 mmol) was heated at 45 °C for 60 h. A diethyl ether/MeOH (1:1) mixture was then added to the cooled reaction mixture. The resulting precipitate was filtered off and the filtrate was concentrated to dryness. The residual azetidine was chromatographed on a basic alumina column using an ethyl acetate/methanol (95:5) mixture as eluent (R_f = 0.3) to afford 0.10 g (25%) of a colourless oil. − ^{1}H NMR (CDCl$_3$): δ = 1.18 (d, *J* = 6.3 Hz, Me), 1.84 (t, *J* = 6.4 Hz, CHC*H*$_2$CH), 2.4−2.6 (m, 4 H, NCH$_2$), 3.53 (m, *J* = 6.4 Hz, NCH). − ^{13}C NMR (CDCl$_3$): δ = 18.4 (Me), 33.2 (CH$_2$), 49.0 (NCH$_2$), 56.7 (NCH). − MS: *m/z* = 196 [M$^+$] (5), 98 (100).

Synthesis of *N*-Unsubstituted Azetidines: The procedure for the synthesis of **4a** is described here as a representative example.

(*R,R*)-2,4-Dimethylazetidinium Acetate (4a): *N*-Benzylazetidine **2a** (2.0 g, 11 mmol) was dissolved in methanol (20 mL) and then 20% Pd(OH)$_2$ on carbon (0.5 g) was added. The reaction vessel was placed in a stainless steel autoclave, pressurized to 7 bar with H$_2$, and heated to 50 °C for 20 h. After cooling to room temperature, the mixture was filtered and acetic acid (0.75 mL) was added to the filtrate. The solvent was then evaporated, the residue was taken up in ethyl acetate, and this solution was filtered through Celite to afford pure **4a**. − ^{1}H NMR ($CDCl_3$): δ = 1.50 (d, J = 6.8 Hz, Me), 1.99 (s, Me), 2.24 (t, J = 7.6 Hz, $CHCH_2CH$), 4.32 (m, NCH). − ^{13}C NMR ($CDCl_3$): δ = 19.2 (Me), 23.4 (MeCO), 33.1 (CH_2), 51.7 (NCH), 177.5 (CO_2). − MS (DCI/NH_3): m/z (%) = 103 [$C_5H_{12}N$ + NH_3] (10), 86 [$C_5H_{12}N$] (100). − $[\alpha]_D^{25}$ = −8 (c = 1, $CHCl_3$).

(*R*,*R*)-2,4-Diethylazetidinium Acetate (4b): ^{1}H NMR ($CDCl_3$): δ = 0.97 (t, J = 7.4 Hz, Me), 1.9 (m, 4 H, CH_2), 2.06 (s, Me), 2.26 (t, J = 7.8 Hz, $CHCH_2CH$), 4.25 (m, NCH). − ^{13}C NMR ($CDCl_3$): δ = 9.3 (Me), 21.0 (MeCO), 26.8 (CH_2), 29.2 (CH_2), 58.4 (NCH), 176.0 (CO_2). − MS (DCI/NH_3): m/z (%) = 156 [$C_7H_{16}N$ + NH_3] (10), 114 [$C_7H_{16}N$] (100). − $[\alpha]_D^{25}$ = −23 (c = 1, $CHCl_3$).

(*R*,*R*)-2,4-Dipropylazetidinium Acetate (4c): ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, J = 7.1 Hz, Me), 1.3 (m, 4 H, CH_2), 1.8 (m, 4 H, CH_2), 2.01 (s, Me), 2.24 (t, J = 7.7 Hz, $CHCH_2CH$), 4.22 (m, J = 7.7 Hz, NCH). − ^{13}C NMR ($CDCl_3$): δ = 13.5 (Me), 18.3 (CH_2), 30.1 (CH_2), 35.5 (CH_2), 56.4 (NCH). − MS (DCI/NH_3): m/z (%) = 142 ($C_9H_{20}N$). − $[\alpha]_D^{25}$ = −24 (c = 1, $CHCl_3$).

General Procedure for the Palladium-Catalysed Coupling Reactions: A mixture of the aryl bromide (1 mmol), azetidinium acetate **4** (1.2 mmol), $Pd_2(dba)_3$ (9 mg, 2 mol-% Pd), and NaO*t*Bu (0.35 g, 3.6 mmol) in toluene (5 mL) was heated at 70 °C for 6−9 h. After cooling to room temperature, the mixture was diluted with diethyl ether and filtered through Celite. After evaporation of the solvent from the filtrate, the residue was purified by chromatography on alumina eluting with cyclohexane or cyclohexane/AcOEt mixtures. The azetidines **5** were recovered as colourless oils in the yields listed in Table 1. In the syntheses of **5d** and **5h**, the reaction mixtures were heated at 100 °C for 18 h.

(*R*,*R*)-2,4-Dimethyl-*N*-phenylazetidine (5a): ^{1}H NMR ($CDCl_3$): δ = 1.33 (d, J = 6.1 Hz, Me), 2.08 (t, J = 6.4 Hz, $CHCH_2CH$), 4.30 (m, J = 6.2 Hz, NCH), 6.48 (d, J = 8.4 Hz, CH-*ortho*), 6.70 (t, J = 7.3 Hz, CH-*para*), 7.20 (m, CH-*meta*). − ^{13}C NMR ($CDCl_3$): δ = 19.5 (Me), 33.0 (CH_2), 55.5 (NCH), 113.1, 116.8, 128.8 (CH), 148.2 (NC). − MS: m/z (%) = 161 [M^+] (67), 146 [M^+ − Me] (57), 104 [PhNCH] (100). − $[\alpha]_D$ = −186 (c = 1, $CHCl_3$).

(*R*,*R*)-2,4-Dimethyl-*N*-(*o*-tolyl)azetidine (5b): ^{1}H NMR ($CDCl_3$): δ = 1.19 (d, J = 6.2 Hz, Me), 2.05 (t, J = 6.4 Hz, $CHCH_2CH$), 2.15 (Me), 4.32 (m, J = 6.3 Hz, NCH), 6.61 (d, J = 8.2 Hz, CH-*ortho*), 6.80 (t, CH-*para*), 7.10 (m, CH-*meta*). − ^{13}C NMR ($CDCl_3$): δ = 19.1 (Me), 19.3 (Me), 32.6 (CH_2), 56.1 (NCH), 114.3, 119.5, 126.2 (CH), 127.1 (C), 131.0 (CH), 146.7 (NC). − MS: m/z (%) = 175 [M^+] (50), 160 [M^+ − Me] (40), 118 [ArNCH] (100). − $[\alpha]_D$ = −101 (c = 1, $CHCl_3$).

(*R*,*R*)-*N*-(*o*-Anisyl)-2,4-dimethylazetidine (5c): ^{1}H NMR ($CDCl_3$): δ = 1.20 (d, J = 6.2 Hz, Me), 2.05 (t, J = 6.5 Hz, $CHCH_2CH$), 3.81 (OMe), 4.33 (m, NCH), 6.6 (m, 1 H), 6.8−6.9 (m, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 19.4 (Me), 33.2 (CH_2), 55.0 (NCH), 56.7 (OMe), 110.3, 114.2, 119.4, 120.9 (CH), 137.7 (C), 149.8 (NC). − MS: m/z (%) = 191 [M^+] (63), 176 [M^+ − Me] (57), 134 [ArNCH] (100). − $[\alpha]_D$ = −139 (c = 1, $CHCl_3$).

(*R*,*R*)-*N*-(*o*-Bromophenyl)-2,4-dimethylazetidine (5d): ^{1}H NMR ($CDCl_3$): δ = 1.21 (d, J = 6.2 Hz, Me), 2.06 (t, J = 6.5 Hz, $CHCH_2CH$), 4.55 (m, NCH), 6.64 (dd, J = 8.1 Hz, 1 H), 6.71 (td, J = 7.7 Hz, 1 H), 7.18 (td, J = 8.1 Hz, 1 H), 7.43 (dd, J = 7.8 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 19.3 (Me), 32.0 (CH_2), 56.7 (NCH), 111.8 (C), 116.3, 120.5, 127.6, 133.7 (CH), 146.3 (NC). − MS: m/z (%) (^{81}Br) = 241 [M^+] (50), 226 [M − Me] (43), 199 [ArNCHMe] (93), 184 [ArNCH] (100). − $[\alpha]_D$ = −166 (c = 1, $CHCl_3$).

(*R*,*R*)-2,4-Dimethyl-*N*-(1-naphthyl)azetidine (5e): ^{1}H NMR ($CDCl_3$): δ = 1.21 (d, J = 6.2 Hz, Me), 2.19 (t, J = 6.5 Hz, $CHCH_2CH$), 4.64 (m, NCH), 6.65 (m, 1 H), 7.3−7.5 (m, 4 H), 7.8 (m, 1 H), 7.9 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 19.1 (Me), 32.8 (CH_2), 57.9 (NCH), 109.7, 119.9, 123.7, 124.4, 125.6, 126.0 (CH), 126.7 (C), 128.3 (CH), 134.6 (C), 145.0 (NC). − MS: m/z (%) = 211 [M^+] (90), 196 [M^+ − Me] (43), 169 [ArNCHMe] (100), 154 [ArNCH] (100). − $[\alpha]_D$ = −222 (c = 1, $CHCl_3$).

(*R*,*R*)-2,4-Dimethyl-*N*-[*p*-(trifluoromethyl)phenyl]azetidine (5f): ^{1}H NMR ($CDCl_3$): δ = 1.35 (d, J = 6.2 Hz, Me), 2.11 (t, J = 6.4 Hz, $CHCH_2CH$), 4.36 (m, NCH), 6.43 (d, J = 8.4 Hz, 2 H), 7.40 (d, J = 8.4 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 19.6 (Me), 33.0 (CH_2), 55.6 (NCH), 111.6 (CH), 126.2 (CH), 150.3 (NC). − MS: m/z (%) = 229 [M^+] (27), 214 [M^+ − Me] (47), 172 [ArNCH] (100). − $[\alpha]_D$ = −115 (c = 1, $CHCl_3$).

(*R*,*R*)-*N*-{3-[(*R*,*R*)-2,4-Dimethyl-1-azetidinylmethyl]phenyl}-2,4-dimethylazetidine (5g): ^{1}H NMR ($CDCl_3$): δ = 1.12 (d, J = 6.4 Hz, Me), 1.31 (d, J = 6.4 Hz, Me), 1.85 (t, J = 6.4 Hz, $CHCH_2CH$), 2.05 (t, J = 6.4 Hz, $CHCH_2CH$), 3.47 (*A*B, J_{AB} = 13.3 Hz, 1 H, NCH_2Ph), 3.59 (m, 2 H, NCH), 3.66 (A*B*, 1 H, NCH_2Ph), 4.28 (m, 2 H, NCH), 6.33 (dd, J = 8.0 Hz, 1 H), 6.45 (s, 1 H), 6.67 (d, J = 7.5 Hz, 1 H), 7.10 (t, J = 7.8 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 18.4 (Me), 19.6 (Me), 33.0 (CH_2), 33.3 (CH_2), 54.5 (NCH_2Ph), 55.5 (NCH), 56.9 (NCH), 111.4, 113.4, 117.4, 128.6 (CH), 140.4 (C), 148.1 (NC). − MS: m/z (%) = 258 [M^+] (18), 175 (100).

(*R*,*R*)-2,4-Diethyl-*N*-(*o*-tolyl)azetidine (5h): ^{1}H NMR ($CDCl_3$): δ = 0.83 (t, J = 7.4 Hz, Me), 1.3−1.5 (m, CH_2), 2.02 (t, J = 6.1 Hz, $CHCH_2CH$), 2.12 (Me), 4.07 (m, NCH), 6.61 (d, J = 8.1 Hz, 1 H), 6.76 (t, J = 7.3 Hz, 1 H), 7.02−7.11 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 9.0 (Me), 19.2 (Me), 26.0 (CH_2), 27.8 (CH_2), 61.8 (NCH), 114.1, 119.4, 126.1 (CH), 130.8 (CH). − MS: m/z (%) = 203 [M^+] (33), 174 [M^+ − Et] (100), 118 [ArNCH] (77).

Synthesis of the Cyclopalladated Complex 8: According to the procedure described by Cope and Friedrich,[30] a mixture of Na_2PdCl_4 (0.29 g, 1 mmol) and (*R*,*R*)-*N*-benzyl-2,4-dimethylazetidine (**2a**) (0.21 g, 1.2 mmol) in methanol (10 mL) was stirred at room temperature for 16 h, which led to the deposition of a yellow precipitate. The product was filtered off, washed with MeOH, and dried in vacuo. It was redissolved in chloroform and the resulting solution was filtered through Celite to afford pure **8** as a pale-yellow powder. Yield: 0.29 g (93%). − ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.43 (d, J = 7.0 Hz, Me), 1.45 (d, J = 7.1 Hz, Me), 1.78 (d, J = 6.6 Hz, Me), 1.81 (d, J = 6.6 Hz, Me), 2.0−2.1 (m, 2 H, CH_2), 2.35 (dt, J = 10.6 Hz, J = 7.5 Hz, 1 H, CH_2), 2.45 (dt, J = 10.9 Hz, J = 8.2 Hz, 1 H, CH_2), 3.58 (m, 2 H, CH), 3.73 (*A*B, J = 13.3 Hz, 1 H, NCH_2Ph), 3.74 (*A*B, J = 13.3 Hz, 1 H, NCH_2Ph), 4.58 (A*B*, 1 H, NCH_2Ph), 4.60 (A*B*, 1 H, NCH_2Ph), 4.73 (m, 2 H, NCH), 6.8−6.9 (m, 6 H, Ph), 7.13 (d, J = 7.7 Hz, 2 H, Ph). − ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.8 (Me), 15.9 (Me), 25.9 (Me), 26.0 (Me), 32.4 (CH_2), 32.5 (CH_2), 60.9 (NCH), 62.0 (NCH), 65.7 (NCH_2Ph), 65.8 (NCH_2Ph), 69.0 (NCH), 69.3 (NCH), 121.2, 124.3, 125.0, 125.1, 132.7, 133.1 (CH), 142.8, 143.0, 145.9, 146.1 (C). − $[\alpha]_D^{25}$ = −115 (c = 0.5, $CHCl_3$).

---

[1] D. Tanner, P. G. Andersson, A. Harden, P. Somfai, *Tetrahedron Lett*. **1994**, *35*, 4631. P. G. Andersson, A. Harden, D. Tanner, P.-O. Norrby, *Chem. Eur. J.* **1995**, *1*, 12. P. G. Andersson, F. Johansson, D. Tanner, *Tetrahedron* **1998**, *54*, 11549. D. Tanner,

F. Johansson, A. Harden, P. G. Andersson, *Tetrahedron* **1998**, *54*, 15731.

[2] H. Kubota, M. Nakajima, K. Koga, *Tetrahedron Lett*. **1993**, *34*, 8135.

[3] L. A. Van de Kuil, Y. S. J. Veldhuizen, D. M. Grove, J. W. Zwikker, L. W. Jenneskens, W. Drenth, W. J. J. Smeets, A. L. Spek, G. van Koten, *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 267. M. Shi, Y. Satoh, T. Makihara, Y. Masaki, *Tetrahedron: Asymmetry* **1995**, *6*, 2109. J. A. Sweet, J. M. Cavallari, W. A. Price, J. W. Ziller, D. V. McGrath, *Tetrahedron: Asymmetry* **1997**, *8*, 207. J. P. Cahill, F. M. Bohnen, R. Goddard, C. Krüger, P. J. Guiry, *Tetrahedron: Asymmetry* **1998**, *9*, 3831. J. P. Cahill, P. J. Guiry, *Tetrahedron: Asymmetry* **1998**, *9*, 4301. J. P. Cahill, A. P. Lightfoot, R. Goddard, J. Rust, P. J. Guiry, *Tetrahedron: Asymmetry* **1998**, *9*, 4307.

[4] For selected recent references, see: J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581. J. K. Whitesell, S. W. Felman, *J. Org. Chem.* **1977**, *42*, 1663. J.-E. Bäckvall, C. Löfström, M. Maffei, V. Langer, *Tetrahedron Lett*. **1992**, *33*, 2417. V. S. M. Dankwardt, J. W. Dankwardt, R. H. Schlessinger, *Tetrahedron Lett*. **1998**, *39*, 4971. T. J. Donohoe, M. Helliwell, C. A. Stevenson, T. Ladduwahetty, *Tetrahedron Lett*. **1998**, *39*, 3071. J. M. Chong, I. S. Clarke, I. Koch, P. C. Olbach, N. J. Taylor, *Tetrahedron: Asymmetry* **1995**, *6*, 409 and references therein.

[5] [5a] J. Hoshino, J. Hiraoka, Y. Hata, S. Sawada, Y. Yamamoto, *J. Chem. Soc., Perkin Trans. 1* **1995**, 693. − [5b] G. Guanti, R. Riva, *Tetrahedron: Asymmetry* **1995**, *6*, 2921. − [5c] M. Shi, K. J. Jiang, *Tetrahedron: Asymmetry* **1999**, *10*, 1673.

[6] Selected examples: A. V. R. Rao, M. K. Gurjar, V. Kaiwar, *Tetrahedron: Asymmetry* **1992**, *3*, 859. W. A. J. Starmans, R. W. A. Walgers, L. Thijs, R. de Gelder, J. M. M. Smits, B. Zwanenburg, *Tetrahedron* **1998**, 54, 4991.

[7] W. A. J. Starmans, R. G. Doppen, L. Thijs, B. Zwanenburg, *Tetrahedron: Asymmetry* **1998**, *9*, 429.

[8] M. Poch, X. Verdaguer, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron Lett*. **1991**, *32*, 6935.

[9] P. Wessig, J. Schwarz, *Helv. Chim. Acta* **1998**, *81*, 1803.

[10] I. Ojima, M. Zhao, T. Yamato, K. Nakahashi, *J. Org. Chem.* **1991**, *56*, 5263. G. V. Shustov, A. Rauk, *J. Am. Chem. Soc.* **1995**, *117*, 928. J. K. Lynch, M. W. Holladay, K. B. Ryther, H. Bai, C.-N. Hsiao, H. E. Morton, D. A. Dickman, W. Arnold, S. A. King, *Tetrahedron: Asymmetry* **1998**, *9*, 2791.

[11] The synthesis of racemic 2,4-diphenylazetidines from *anti*-1,3-diphenyl-1,3-propanediol has recently been mentioned: G. H. P. Roos, A. R. Donovan, *Tetrahedron: Asymmetry* **1999**, *10*, 991.

[12] M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1988**, *11*, 629. D. Blanc, V. Ratovelomanana-Vidal, A. Marinetti, J.-P. Genêt, *Synlett* **1999**, *4*, 480 and references therein.

[13] J.-P. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, L. Bischoff, M. C. Cano de Andrade, S. Darses, C. Galopin, J. A. Laffitte, *Tetrahedron: Asymmetry* **1994**, *5*, 675.

[14] R. P. Short, R. M. Kennedy, S. Masamune, *J. Org. Chem.* **1989**, *54*, 1755.

[15] The ^{1}H-NMR spectra of the *syn* and *anti* isomers have been reported: J. P. Freeman, P. J. Mondron, *Synthesis* **1974**, 894.

[16] The enantiomeric purity of **2a** (*e.e.* > 95% − within the ^{1}H-NMR detection limit) was established by ^{1}H-NMR analysis (400 MHz) of its Mosher acid salt: Separate NCH_2 signals are observed for the (*S*,*S*)-**2a**-(*R*)-$F_3CC(OMe)(Ph)CO_2H$ and (*R*,*R*)-**2a**-(*R*)-$F_3CC(OMe)(Ph)CO_2H$ adducts at $\delta = 3.83$ (*A*B, $J_{AB} = 12.6$ Hz) and $\delta = 3.81$ (*A*B, $J_{AB} = 12.6$ Hz), respectively.

[17] T. Dudev, C. Lim, *J. Am. Chem. Soc.* **1998**, *120*, 4450.

[18] D. E. Davies, R. C. Starr, in: *Comprehensive Heterocyclic Chemistry* (Ed.: W. Lwowski), Pergamon, Oxford, **1984**, vol. 7, part 5, p. 237 and references therein.

[19] E. Juaristi, J. D. Reyna, *Tetrahedron Lett.* **1984**, *25*, 3521. E. Juaristi, D. Madrigal, *Tetrahedron* **1989**, *45*, 629.

[20] For recent reviews, see: J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2047. J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805.

[21] The reported boiling point of 2,4-dimethylazetidine is 84−86 °C: J. P. Freeman, D. G. Pucci, G. Binsch, *J. Org. Chem.* **1972**, *37*, 1894.

[22] S. Wagaw, R. A. Rennels, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 8451.

[23] A few selected examples are: [23a] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932. − [23b] E. P. Kyba, S. P. Rines, *J. Org. Chem.* **1982**, *47*, 4800. − [23c] P. H. Leung, A. C. Willis, S. B. Wild, *Inorg. Chem.* **1992**, *31*, 1406. − [23d] J. L. Bookham, W. McFarlane, *J. Chem. Soc., Chem. Commun.* **1993**, 1352. − [23e] H. B. Aw, H. P. Leung, *Tetrahedron: Asymmetry* **1994**, *5*, 1167. − [23f] J.-M. Valk, T. D. W. Claridge, J. Brown, D. Hibbs, M. B. Hursthouse, *Tetrahedron: Asymmetry* **1995**, *6*, 2597. − [23g] V. V. Dunina, E. B. Golovan, N. S. Gulyunina, A. V. Buyevich, *Tetrahedron: Asymmetry* **1995**, *6*, 2731. − [23h] J. Albert, J. Granell, G. Muller, D. Sainz, M. Font-Bardia, X. Solans, *Tetrahedron: Asymmetry* **1995**, *6*, 325. − [23i] A. V. C. Lopez, R. Bosque, D. Sainz, X. Solans, M. Font-Bardia, *Organometallics* **1997**, *16*, 3261. − [23j] V. V. Dunina, L. G. Kuz'mina, M. Yu. Kazakova, K. Grishin, Yu. A. Veits, E. I. Kazakova, *Tetrahedron: Asymmetry* **1997**, *8*, 2537.

[24] T. K. Hollis, L. E. Overman, *Tetrahedron Lett.* **1997**, 38, 8837. F. Cohen, L. E. Overman, *Tetrahedron: Asymmetry* **1998**, 9, 3213. Y. Donde, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 2933.

[25] Commercially available from Aldrich Chemical Company.

[26] V. I. Sokolov, L. L. Troitskaya, J. Reutov, *J. Organomet. Chem.* **1977**, *133*, C28.

[27] C. Lopez, R. Bosque, X. Solans, M. Font-Bardia, *Tetrahedron: Asymmetry* **1996**, 7, 2527.

[28] Assignments were made by treating **8** with (*R*)- and (*S*)-Binap in separate experiments.

[29] An alternative approach to the optically active diols **1b** and **1d** has been reported: S. D. Rychnovsky, G. Griesgraber, S. Zeller, D. J. Skalitzky, *J. Org. Chem.* **1991**, *56*, 5161.

[30] A. C. Cope, E. C. Friedrich, *J. Am. Chem. Soc*. **1968**, *90*, 909.

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