Synthesis of [2.2]Paracyclophane-Based Glycidic Amides Using Chiral Ammonium Ylides

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Dedicated to Prof. E. Peter Kündig on the occasion of his 75th birthday.

An ammonium ylide-mediated stereoselective protocol for the synthesis of a series of novel [2.2]paracyclophane-based epoxides starting from racemic 4-formyl[2.2]paracyclophane has been developed. By using achiral ammonium salts as ylide precursors, the corresponding epoxide products were obtained in isolated yields up to 76% and with diastereoselectivities up to d.r. = 9:1. When carrying out the reaction with chiral ammonium salts instead, the products were accessible with e.r. > 93.5:6.5 and d.r. > 3:1, accompanied with a moderately enantioselective kinetic resolution of the racemic starting aldehyde (e.r. = 75:25).

Keywords: ammonium ylides, chiral auxiliaries, cyclophanes, epoxides, paracyclophanes, ylides.

Introduction

Since the pioneering report by Brown and Farthing who first described the isolation of unsubstituted [2.2]paracyclophane (1) in 1949 already, [2.2]paracyclophane derivatives (PCPs) have emerged as interesting and systematically investigated (chiral) scaffolds with unique chemical and physical properties. [2–12] These fascinating planar chiral compounds attracted the interest of material scientists [4–6] and asymmetric synthesis-oriented chemists [7–9] equally and therefore it comes as no surprise that the asymmetric synthesis of novel derivatives still represents a worthwhile task. [10–12] Most classically, the synthesis of enantioenriched PCP-derivatives starts from the unsubstituted parent compound 1, followed by SAr-type functionalization of either one or both aryl rings, followed by different resolution or desymmetrization strategies. [10–12]

Monoformyl and diformyl-substituted PCPs have been known for decades [13–15] and are amongst the most frequently employed PCP building blocks. [16–26]

Utilizing them as starting materials either in racemic or enantioenriched form provides access to unique chiral ligands and organocatalysts, as well as more advanced novel PCP derivatives that may show interesting properties (on a longer term perspective). [3,10,16–26] Importantly, racemic 4-formyl[2.2]paracyclophane 2, [13–15] as well as different diformyl[2.2]paracyclophanes, [19] can easily be obtained from 1 and, given their high synthetic value, it comes as no surprise that the development of robust enantioselective (resolution) approaches to access enantioenriched formyl-containing PCPs has attracted considerable attention over the last decades. [16,17,20–24]

As already stated above, these compounds, i.e. 4-formyl[2.2]paracyclophane 2 (Scheme 1,A), have been utilized for numerous further manipulations. [3,4,10] Surprisingly however, upon closer examination of the reported applications, we realized that compound 2 as well as other formyl-containing PCPs have, to the best of our knowledge, so far not been utilized as a starting material for (asymmetric) epoxidation reactions. Moreover, PCP-based benzyl epoxides have rarely been reported at all [27] which really comes as a surprise considering the generally appreciated high value of (chiral) epoxides for numerous applications and further manipulations. [28–30] Our group has a strong interest in

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FULL PAPER

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ammonium ylide-mediated formal \((n + 1)\)-cyclizations\(^{[31]}\) and some years ago we have shown that (chiral) ammonium ylides can be used to control the relative as well as the absolute configuration of glycic amides \(5\) by reacting simple aryl aldehydes \(3\) with amide-based ammonium salts \(4\) (as ylide precursors) under basic conditions (Scheme 1,B).\(^{[32–34]}\)

Given the potential of this methodology to access valuable (chiral) epoxides from simple aldehydes and considering the lack of PCP-based benzylc epoxides in the literature, we therefore became interested in testing whether an ammonium ylide-mediated epoxidation strategy may allow for the synthesis of the so far unprecedented highly functionalized epoxides \(6\) (Scheme 1,C). Moreover, by using a chiral ammonium salt ylide-precursor,\(^{[32]}\) it may be possible to start from \(\text{rac-2}\) and achieve the simultaneous control of the newly formed epoxide stereocenters as well as the kinetic resolution (KR) of the planar chiral starting material \(2\).

**Results and Discussion**

We started our investigations by reacting the achiral trimethylammonium salts \(4\) with \(\text{rac-2}\) under liquid/liquid or liquid/solid biphasic conditions.\(^{[34]}\) Table 1 gives an overview of the most significant results obtained whereby; trimethylamine was used as an amine leaving group as it was found to be the group of choice for aldehydes \(3\) recently.\(^{[34]}\). First experiments using amide \(4a\) (\(Y = \text{NET}_2\)) with Cs\(_2\)CO\(_3\) as a solid base in different solvents (entries 1–3) showed that the targeted epoxide \(6a\) is indeed accessible by such a strategy, but in low yields only. While toluene did not allow for any product formation (entry 1), \(^1\)PrOH favored the Cannizzaro disproportionation of aldehyde \(2\) and reactions in CH\(_2\)Cl\(_2\) were found to be rather slow with this carbonate base. Changing for liquid/liquid conditions with an excess of a stronger hydroxide base,\(^{[33,34]}\) yield of \(6a\) could be increased significantly. With respect to the relative configuration of product \(6a\), we observed formation of two trans-diastereoisomers, differing in the configuration of the planar chiral paracyclophane unit. Later investigations with chiral ammonium salts (vide infra, Scheme 2) suggest that the major diastereomer has a \((2\text{S},3\text{R},3\text{S})\)-rel-configuration, as depicted in the general structure of compounds \(6\) shown in Table 1. Although KOH and NaOH both gave approximately the same yield and d.r. after one day at 25°C (entries 4 and 5), reactions with KOH gave larger amounts of unidentified side products, while the NaOH-mediated reaction was in general slower in conversion, but also cleaner. Gratifyingly, by prolonging the reaction time to three days and increasing the temperature to 40°C, the yield could be improved significantly (72%) without reducing the diastereoselectivity (d.r. = 9:1; entry 6).

With these conditions at hand, we next investigated the use of different ammonium salts \(4\). Upon testing different amides (entries 6–12), it turned out that secondary amides (like compound \(4f\), entry 11) or the Weinreb amide \(4g\) (entry 12) are not suited, which is in line with the limitations observed previously when using simple aryaldehydes for such reactions.\(^{[33]}\) In contrast, tertiary amides like compounds \(4b–4d\) performed reasonably well (entries 7–9). Interestingly, the dimethylamide-based \(4e\) was found to be rather insoluble and decomposed quickly under the standard conditions and in this case, it was only possible to access traces of the product \(6e\) by using \(^1\)BuOK in DMSO instead (entry 10). Noteworthy however, this class of amide later on performed much better when using a chiral ammonium salt auxiliary (vide infra, \(4\)).

![Scheme 1](image-url)
ylide-precursors were found to be not reactive as they comes as no surprise upon comparison with our own allow for any product formation at all, which again based (Scheme 2). Unfortunately, ester- (entry 13) or ketone-based (entry 14) ammonium salts 4h and 4i did not allow for any product formation at all, which again comes as no surprise upon comparison with our own previous observations for arylaldehydes 3, where these ylide-precursors were found to be not reactive as they form more stable and thus less reactive ammonium ylides.\textsuperscript{[32]}

Having identified suitable conditions for the racemic synthesis of different tert. amide-containing epoxides 6 with reasonable yields and good diastereoselectivities, we next examined whether we could render this reaction enantioselective by using chiral amine-based ammonium salts 4. It should be emphasized that the identification of a suited chiral amine that allows for satisfying yields and enantioselectivities for such ammonium ylide-mediated epoxidations was a major challenge previously,\textsuperscript{[32]} mainly because of the significantly lower leaving group quality of chiral tert. amines like Cinchona alkaloids compared to the simple achiral amines (i.e. trimethylamine).\textsuperscript{[32]} In our inves- tigations of the epoxidation of a variety of benzaldehyde derivatives 3 the chiral bicyclic proline-derived amines \textbf{A} were the only systems that allowed for product 5-formation with good yields and selectivities, while Cinchona alkaloids totally failed.\textsuperscript{[32]}

Table 1. Racemic epoxidation using different ammonium salts 4.\textsuperscript{[a]}

| Entry | 4 (Y) | Solvent, T, t | Base | Yield [%]\textsuperscript{[b]} | d.r.\textsuperscript{[c]} |
|-------|-------|---------------|------|-----------------|-----------------|
| 1     | NEt\textsubscript{3} (a) | toluene, 25 \degree C, 1 d | Cs\textsubscript{2}CO\textsubscript{3} (s, 20 equiv.) | – | – |
| 2     | NEt\textsubscript{3} (a) | 'PrOH, 25 \degree C, 1 d | Cs\textsubscript{2}CO\textsubscript{3} (s, 20 equiv.) | < 20\textsuperscript{[da]} | 10:1 |
| 3     | NEt\textsubscript{3} (a) | CH\textsubscript{2}Cl\textsubscript{2}, 25 \degree C, 1 d | Cs\textsubscript{2}CO\textsubscript{3} (s, 20 equiv.) | < 20\textsuperscript{[d]} | 8:1 |
| 4     | NEt\textsubscript{3} (a) | CH\textsubscript{2}Cl\textsubscript{2}, 25 \degree C, 1 d | KOH (50 % aq., 100 equiv.) | 50\textsuperscript{[f]} | 9:1 |
| 5     | NEt\textsubscript{3} (a) | CH\textsubscript{2}Cl\textsubscript{2}, 25 \degree C, 1 d | NaOH (50 % aq., 100 equiv.) | 43\textsuperscript{[g]} | 9:1 |
| 6     | NEt\textsubscript{3} (a) | CH\textsubscript{2}Cl\textsubscript{2}, 40 \degree C, 3 d | NaOH (50 % aq., 100 equiv.) | 72 | 9:1 |
| 7     | N(CH\textsubscript{3})\textsubscript{2} (b) | CH\textsubscript{2}Cl\textsubscript{2}, 40 \degree C, 3 d | NaOH (50 % aq., 100 equiv.) | 57 | 7:1 |
| 8     | Morpholine (c) | CH\textsubscript{2}Cl\textsubscript{2}, 40 \degree C, 3 d | NaOH (50 % aq., 100 equiv.) | 42 | 9:1 |
| 9     | NBn\textsubscript{3} (d) | CH\textsubscript{2}Cl\textsubscript{2}, 40 \degree C, 3 d | NaOH (50 % aq., 100 equiv.) | 76 | 7:1 |
| 10    | NMe\textsubscript{2} (e) | DMSO, 25 \degree C, 1 d | ¹BuOK (1.2 equiv.) | 19 | 6:1 |
| 11    | NHBn (f) | CH\textsubscript{2}Cl\textsubscript{2}, 40 \degree C, 3 d | NaOH (50 % aq., 100 equiv.) | – | – |
| 12    | N(OMe)Me (g) | CH\textsubscript{2}Cl\textsubscript{2}, 40 \degree C, 3 d | NaOH (50 % aq., 100 equiv.) | – | – |
| 13    | OEt (h) | CH\textsubscript{2}Cl\textsubscript{2}, 40 \degree C, 3 d | NaOH (50 % aq., 100 equiv.) | – | – |
| 14    | Ph (i) | CH\textsubscript{2}Cl\textsubscript{2}, 40 \degree C, 3 d | NaOH (50 % aq., 100 equiv.) | – | – |

\textsuperscript{[a]} All reactions were carried out using 0.1 mmol 2 and 0.1 mmol 4. \textsuperscript{[b]} Yields of isolated products. \textsuperscript{[c]} Two trans-diastereoisomers were detected, the relative configuration of the major diastereoisomer was assigned to be (2S,3R,\textsubscript{R})-rel through the results obtained with achiral ammonium salts (see Scheme 2 and the corresponding discussion). \textsuperscript{[d]} Estimated yield calculated from the crude product NMR spectrum. \textsuperscript{[e]} Pronounced Cannizzaro disproportionation of 2. \textsuperscript{[f]} Significant amounts of unidentified side products. \textsuperscript{[g]} Around 60\% conversion of 2.
e.r. (i.e. for the major diastereomer). In addition, this approach allowed for the recovery of \((R_p)_2\)-2 (assignment of the absolute configuration was carried out by comparison of the measured \((-\)-rotation with previous reports\footnote{17}) with moderate enantioenrichment (e.r. = 75:25). With these results in hand, the configuration of the major stereoisomer of epoxide 6a formed through this strategy was assigned as follows: Considering the predominant \((R_p)\)-configuration of the recovered aldehyde 2, the [2.2]paracyclophane unit within product 6a has to be \((S_p)\)-configured. In addition, our recent studies revealed that ammonium salts 4\footnote{A} strongly favor the formation of (2\(S\),3\(R\))-epoxides when reacted with arylaldehydes 3. Considering the observed high levels of enantioselectivity controlled by the auxiliary A4 for both, reactions with aldehyde 2 and aldehydes 3, it can therefore be assumed that the major stereoisomer of product 6a isolated herein has \((2S,3R,S_p)\)-configuration, as shown in \textbf{Scheme} 2. Based on the only moderate enantioenrichment of recovered \((R_p)_2\)-2, it can be assumed that the KR is the less-selective process herein (compared to epoxide-formation) and therefore the minor diaster-eomer of epoxide 6a should have \((2S,3R,R_p)\)-configuration instead, which also explains why the d.r. decreases with increasing conversion of \textit{rac}-2.

With this reasonably enantio- and diastereoselective protocol in hand, we finally tested the use of different amide-based ammonium salts 4\footnote{A} (Scheme 2,\B). In contrast to the racemic protocol (and as already stated before), the chiral dimethylamide-based salt 4\footnote{e} performed well in this asymmetric approach, giving product 6e with high selectivity and in good isolated yield. In addition, also the piperidine-based epoxide 6b could be obtained in a similarly efficient manner.

\**Conclusions**

An ammonium ylide-mediated protocol for the formation of novel [2.2]paracyclophane-based epoxides 6 starting from the racemic aldehyde 2 has been developed. When using achiral ammonium salts 4 as ylide precursors, the corresponding amide-containing epoxides 6 were obtained in isolated yields up to 76\% with high diastereoselectivities up to d.r. = 9:1. When carrying out the reaction with the chiral ammonium salts 4\footnote{A} instead, the epoxides 6 were accessible with high enantio- and diastereoselectivities, accompanied with a moderately enantioselective kinetic resolution of the racemic starting aldehyde 2.

\**Experimental Section**

\textit{General Experimental Details}

\(1^H\)- and \(13^C\)-NMR spectra were recorded on a \textit{Bruker Avance III} 300 MHz spectrometer with a broad band observe probe and a sample changer for 16 samples which is property of the Austro Czech NMR Research Center ‘RERI uasb’. NMR Spectra were referenced on the solvent peak and chemical shifts are given in ppm. High resolution mass spectra were obtained using a \textit{Thermo Fisher Scientific LTQ Orbitrap XL} with an \textit{Ion Max API} Source. Analyses were made in the positive ionization mode if not otherwise stated. Purine (exact mass for \([M+H]^+ = 121.050873\)) and 1,2,3,4,5,6-hexakis(2,2,3,3-tetrafluoropropoxy)-1,3,5,2,4,6-triazatrisphosphinane (exact mass for \([M+H]^+ = 922.009798\)) were used for internal mass calibration. HPLC was performed using a \textit{Thermo Scientific Dionex Ultimate 3000} system with diode array detector with a \textit{CHIRAL ART Cellulose-SB} (250 \(\times\) 4.6 mm, 5 \(\mu\)m) chiral stationary phase. Optical rotations were recorded on a \textit{Schmidt + Haensch Polarmeter Model UniPol L1000} at 589 nm. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise
stated. Racemic starting material 2\textsuperscript{[35]} and ammonium salts 4\textsuperscript{[32]} were synthesized as described previously. Dry solvents were obtained from an MBraun-SPS-800 solvent purification system. All reactions were carried out under argon atmosphere, unless stated otherwise.

**General Procedure for the Racemic Epoxidation**

The achiral ammonium salt 4 (0.1 mmol, 1 equiv.) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (1 mL, 0.1 m) followed by the addition of NaOH (50% aq., 550 \mu L, 100 equiv.) and rac-2 (25 mg, 1 equiv.). The mixture was heated to 40°C and stirred for 3 d. After cooling to room temperature, the mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} and the combined organic phases dried over Na\textsubscript{2}SO\textsubscript{4}. The crude product was purified by column chromatography (elution of the recovered aldehyde with heptanes/AcOEt 10:1 and of the epoxides with heptanes/AcOEt 2:1).

**General Procedure for the Asymmetric Epoxidation**

The chiral ammonium salt 4 (0.1 mmol, 1 equiv.) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (1 mL, 0.1 m) followed by the addition of NaOH (50% aq., 550 \mu L, 100 equiv.) and rac-2 (25 mg, 1 equiv.) and stirred at 25°C for 2 d. The mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} and the combined organic phases dried over Na\textsubscript{2}SO\textsubscript{4}. The crude product was purified by column chromatography (elution of the recovered enantioenriched aldehyde with heptanes/AcOEt 10:1 and of the enantioenriched epoxides with heptanes/AcOEt 2:1).

**Analytical Details**

**Data of epoxide 6b**: Prepared either according to the General Racemic Procedure (57%; d.r.=7:1) or according to the General Asymmetric Procedure (40%; e.r.$\text{major}=96.5:3.5$, e.r.$\text{minor}=98:2$; d.r.=6:1). \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}, 298.0 K): 6.82 (d, J = 7.8, 1 H); 6.53–6.44 (m, 5 H); 6.33 (d, J = 1.6, 1 H); 4.06 (d, J = 1.9, 1 H); 3.68–3.38 (m, 5 H); 3.35 (d, J = 1.9, 1 H); 3.25–2.85 (m, 7 H); 1.69–1.51 (m, 6 H). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}, 298.0 K): 165.2; 141.0; 140.0; 139.1; 138.6; 135.1; 135.0; 133.4; 132.9; 132.8; 131.5; 129.2; 57.1; 56.0; 46.1; 43.3; 35.4; 35.2; 34.7; 33.0; 26.6; 25.5; 24.6. HR-ESI-MS: 362.2116 ([C\textsubscript{24}H\textsubscript{24}NO\textsubscript{2} + H]+; calc. 362.2115). HPLC: YMC Chiral ART Cellulose-SB, hexane/PrOH 1:1, 1 mL/min, 10°C; t\textsubscript{R}=8.5, 12.8, 14.2, 21.9 min.

**Data of epoxide 6c**: Prepared according to the General Racemic Procedure (42%; d.r.=9:1). \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}, 298.0 K): 6.80 (d, J = 7.8, 1 H); 6.54–6.45 (m, 5 H); 6.31 (d, J = 1.6, 1 H); 4.08 (d, J = 1.9, 1 H); 3.75–3.63 (m, 4 H); 3.56–3.44 (m, 1 H); 3.34 (d, J = 1.9, 1 H); 3.22–2.85 (m, 7 H). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}, 298.0 K): 165.7; 141.0; 139.5; 139.0; 138.7; 135.0; 134.7; 133.4; 133.1; 132.9; 132.8; 131.5; 129.1; 66.8; 66.7; 56.7; 56.2; 45.5; 42.5; 35.4; 35.2; 34.8; 33.0. ESI-MS: 364.05 ([C\textsubscript{25}H\textsubscript{25}NO\textsubscript{3} + H]+; calc. 364.19).

**Data of epoxide 6d**: Prepared according to the General Racemic Procedure (76%; d.r.=7:1). \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}, 298.0 K): 7.36–7.10 (m, 10 H); 6.81 (d, J = 7.8, 1 H); 6.51–6.40 (m, 5 H); 6.25 (d, J = 1.6, 1 H); 4.66 (s, 2 H); 4.45 (s, 2 H); 4.16 (d, J = 1.9, 1 H); 3.45 (d, J = 1.9, 1 H); 3.45–3.37 (m, 1 H); 3.16–2.82 (m, 7 H). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}, 298.0 K): 167.6; 140.8; 139.5; 139.1; 138.7; 136.6; 135.9; 134.9; 134.6; 133.4; 133.3; 133.0; 132.9; 132.8; 131.6; 129.2; 129.8; 128.6; 128.0; 127.9; 126.8; 56.8; 56.5; 49.3; 48.7; 35.4; 35.2; 34.8; 32.9. ESI-MS: 374.15 ([C\textsubscript{33}H\textsubscript{34}NO\textsubscript{2} + H]+; calc. 374.24).

**Data of epoxide 6e**: Prepared either in racemic manner by using \textsuperscript{1}BuOK (1.2 equiv.) in DMSO at 25°C for 24 h (19%; d.r.=6:1) or according to the General Asymmetric Procedure (55%; e.r.$\text{major}=94.5:5.5$, e.r.$\text{minor}>99.5:0.5$; d.r.=4:1). \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}, 298.0 K): 6.81 (d, J = 7.8, 1 H); 6.53–6.44 (m, 5 H); 6.33 (d, J = 1.6, 1 H); 4.07 (d, J = 1.9, 1 H); 3.50–3.47 (m, 1 H); 3.38 (d, J = 1.9, 1 H); 3.20–2.77 (m, 7 H); 3.03 (s, 3 H); 3.02 (s, 3 H). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}, 298.0 K): 167.0; 141.0; 139.5; 139.2; 138.7; 135.0; 135.0; 133.4; 133.0; 132.9; 132.8; 131.6; 129.2; 129.8; 126.7; 56.7; 56.1; 36.5; 35.8; 35.4; 35.2; 34.7; 33.0. HR-ESI-MS: 322.1804 ([C\textsubscript{21}H\textsubscript{23}NO\textsubscript{2} + H]+; calc. 322.1802). HPLC: YMC Chiral ART Cellulose-SB.
hexane/PrOH 1:1, 1 mL/min, 10°C; t<sub>R</sub> = 11.7, 15.2, 16.4, 20.1 min.

Recovered (R<sub>p</sub>)-2: e.r. = 75:25. [α]<sub>D</sub> = −73.4 (c = 1, CHCl<sub>3</sub>).<sup>17</sup> 1H-NMR (300 MHz, CDCl<sub>3</sub>; 298.0 K): 9.95 (s, 1 H); 7.02 (d, J = 1.9, 1 H); 6.73 (dd, J = 7.8, 1.9, 1 H); 6.60–6.36 (m, 5 H); 4.16–4.05 (m, 1 H); 3.31–2.90 (m, 7 H). HPLC: YMC Chiral ART Cellulose-SB, hexane/PrOH 1:1, 1 mL/min, 10°C; t<sub>R</sub> = 9.2, 10.5 min.

Supplementary Material

Supporting information (copies of NMR spectra and HPLC traces) for this article is available on the WWW under https://doi.org/10.1002/hlca.202100073.

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Author Contribution Statement

D. W. carried out all the experimental work. M. W. conceived the project and wrote the manuscript.

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