Asymmetric Synthesis

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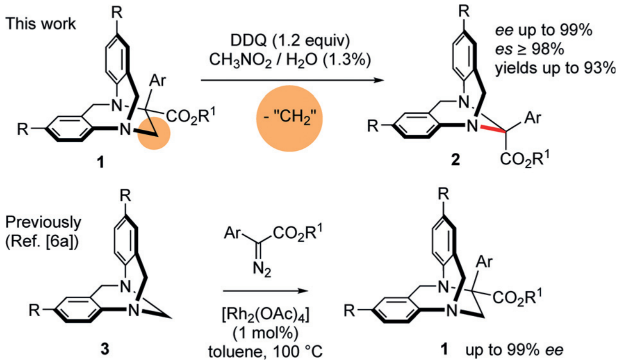
A Mild and Efficient CH_2-Extrusion Reaction for the Enantiospecific Synthesis of Highly Configurationally Stable Tröger Bases**

*Sandip A. Pujari, Céline Besnard, Thomas Bürgi, and Jérôme Lacour**

Dedicated to Professor Volker Schurig on the occasion of his 75th birthday

Abstract: *A novel CH_2-extrusion reaction leading to the transformation of ethano-Tröger bases into disubstituted methano derivatives is reported (yields up to 93 %). Under mild and metal-free oxidative conditions, a loss of CH_2 and a ring contraction are provoked. Despite two bond cleavages at stereogenic nitrogen and carbon centers and a temporary rupture of the bicyclic structure, a very high enantiospecificity ($es \geq 98\,\%$) is observed for this unusual reaction.*

Extrusion reactions, which are formally the reverse of insertion processes, are characterized by the removal of an atom or a group of atoms from a given combination of functional groups and by the reformation of a bond between the atoms to which the departing moiety was attached.[1] Such processes are relatively common in organometallic and chalcogen chemistry.[2,3] With more classical organic substrates, only few CH_2 extrusions are reported using metal-free conditions and activated benzylamines and α-hydroxy carbonyl compounds as substrates.[4] Herein, in the context of nitrogen stereochemistry and Tröger base (TB) derivatives in particular, we report a novel methylene extrusion which sees the enantiospecific transformation of the ethano-TB **1** into the disubstituted methano-TB **2** (Scheme 1, top). Under mild oxidative conditions, the loss of CH_2 occurs with yields of up to 93 %. Importantly, a very high enantiospecificity ($es \geq 98\,\%$) is obtained in this reaction which proceeds with retention of configuration through a ring opening and two bond cleavages at stereogenic nitrogen and carbon centers.



Scheme 1. Extrusion of CH_2 group by concomitant C–C and C–N bond-cleavage reactions (top). Insertion of carbene into a C–N bond (bottom). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Recently, it was shown that Tröger bases of type **3** (Scheme 1, bottom),[5] which are classical chiral molecules as a result of the presence of stereogenic nitrogen atoms, react in a single step with metal carbenes to afford ethano-Tröger bases of type **1**.[6] With donor-acceptor diazo reagents as precursors, the enantiospecificity of the ring expansion is excellent (*es* 97–99 %).[7] The compounds **1**,[8] which are 1,2-diamines, do not racemize under Brønsted- (pH < 1) or Lewis-acidic conditions, which are known to promote the loss of enantiomeric purity of **3**.[9] These ethano-adducts **1** are essentially unknown. We wondered about their global reactivity and decided to use them as substrates in various reactions, including nitrene insertion reactions.[10]

The compound **1a** ($R = R^1 = Me$, Ar = Ph) was thus treated with PhI=NTs under rhodium(II) and copper(II) catalysis. To our surprise, instead of obtaining a product with a higher molecular weight of 169, the derivative **2a** with a loss of a mass of 14 was isolated in good yield (Table 1, entries 1 and 2). This data indicated a probable loss of a CH_2 group, and was confirmed by ^1H and ^{13}C spectroscopic analyses. Only an interesting methano-Tröger base structure with two substituents on the aminal carbon atom was consistent with the data, and the motif was ascertained later by X-ray diffraction analysis (see Table 2).[11] Starting with (+)-**1a** (*ee* 99 %), **2a** was furthermore obtained with an interesting enantiomeric purity of 47 and 69 % (Table 1, entries 1 and 2), thus denoting a rather effective transfer of chirality in this unusual extrusion reaction.[12] Trying to obtain some clues on the reaction mechanism and improve the results, (+)-**1a** was treated separately with an excess of $Cu(OTf)_2$ and PhI=NTs. Importantly, ring-contracted (+)-**2a** was isolated again (entries 3 and 4) and this indicated an oxidative nature for the transformation.[13] Manganese(III) and manganese(IV) complexes, in combination or without $Cu(OTf)_2$, were tested

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[*] Dr. S. A. Pujari, Prof. J. Lacour
Department of Organic Chemistry, University of Geneva
Quai Ernest Ansermet 30, 1211 Geneva 4 (Switzerland)
E-mail: jerome.lacour@unige.ch

Dr. C. Besnard
Laboratory of Crystallography, University of Geneva
Quai Ernest Ansermet 24, 1211 Geneva 4 (Switzerland)

Prof. T. Bürgi
Department of Physical Chemistry, University of Geneva
Quai Ernest Ansermet 30, 1211 Geneva 4 (Switzerland)

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Table 1: Optimization.[a]

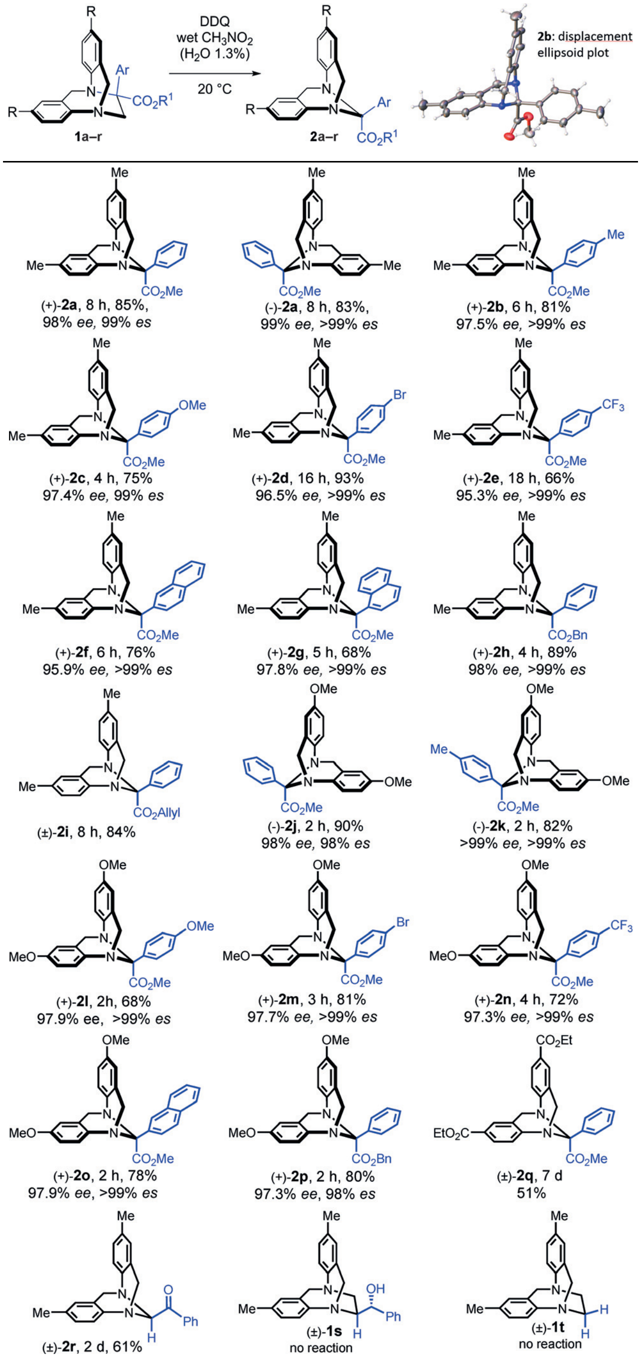
Entry	Oxidant	Solvent	t [h]	**2a** Yield [%][e]	*ee* [%][f]
1	PhINTs/[Rh_2(esp)$_2$]	CH_2Cl_2	24	62	47
2	PhINTs/Cu(OTf)$_2$	CH_3CN	24	75	69
3	Cu(OTf)$_2$	CH_3CN	4	30	83
4	PhINTs	CH_3CN	48	79	46
5	Mn(OAc)$_3$·2 H_2O/Cu(OTf)$_2$	CH_3CN	6	56	70
6	Mn(OAc)$_3$·2 H_2O	CH_3CN	48	trace	–
7[b]	MnO_2	CH_2Cl_2	48	trace	–
8[c]	Iodine	THF	16	77	70
9[c]	NBS	CH_3CN	6	84	83
10[c]	DDQ	CH_3CN	30	77	98
11[c]	DDQ	CH_3NO_2	24	81	98
12[c]	DDQ	CH_3NO_2[d]	8	85	98

[a] Reaction conditions: the ethano Tröger base (+)-**1a** (1 equiv), oxidant (2 equiv), solvent (0.05 м). [b] 10 equiv of MnO_2 was used. [c] 1.2 equiv of oxidant was used. [d] Nitromethane containing 1.3 % of H_2O. [e] Yield of isolated product. [f] Determined by HPLC using a chiral stationary phase. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, NBS = *N*-bromosuccinimide, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

(entries 5–7).[14] Reactions either did not occur or proceeded with only moderate enantioselectivity (70 % *ee*). Metal-free conditions were attempted. While iodine and NBS provided (+)-**2a** in good yields and interesting levels of chirality transfer (*ee* 70 and 83 % respectively), DDQ (entries 10–12) offered the best results, particularly in wet nitromethane (1.3 % H_2O).[15] Under these reaction conditions, at 20 °C, (+)-**2a** was obtained in 85 % yield and with 98 % *ee*. These optimized reaction conditions were used throughout the study.

The generality of the extrusion reaction was established by using a series of ethano-TB derivatives (**1a–q**). Electron-rich and electron-poor substituents were introduced *para* to the bridgehead nitrogen atoms (Me, OMe and CO_2Et). Care was also taken to prepare substrates with electron-donating and electron-withdrawing substituents on the aromatic group carried by the stereogenic carbon center. Most of these compounds were synthesized in both racemic and enantioenriched forms (96 to > 99 % *ee*; see Table S1 in the Supporting Information).[6a] To our satisfaction, in the 2,8-dimethyl series (**1a–i**) the methylene extrusion proceeded well. Not too surprisingly, reactions were slightly faster with electron-rich substituents on the aromatic ring (e.g., OMe; **1c**). Sterics did not significantly influence the reactivity and stereoselectivity (e.g., **2f** and **2g**).[16] Changing the ester functional group, from methyl to benzyl and allyl, did not affect the outcome of the reaction either. Very similar results were obtained with 2,8-dimethoxy-substituted **1j–p**. The reactions were faster thanks to the electron-donating *p*-MeO substituents (max. 4 h). On the contrary, a seven-day reaction was necessary with **1q** to afford **2q** in moderate yield (51 %).[17] For mechanistic purposes, the benzoyl **1r** and its reduced alcohol derivative **1s** were also tested.[8c] While a slow but effective extrusion occurred with the first derivative, no trace of ring contraction could be detected with **1s**. The necessity of an electron-withdrawing group on the ethano-bridge was confirmed by using **1t**,[8a] which was found to be unreactive.

Table 2: Substrate scope.[a]



(+)-**2a**, 8 h, 85%, 98% *ee*, 99% *es*

(-)-**2a**, 8 h, 83%, 99% *ee*, >99% *es*

(+)-**2b**, 6 h, 81% 97.5% *ee*, >99% *es*

(+)-**2c**, 4 h, 75% 97.4% *ee*, 99% *es*

(+)-**2d**, 16 h, 93% 96.5% *ee*, >99% *es*

(+)-**2e**, 18 h, 66% 95.3% *ee*, >99% *es*

(+)-**2f**, 6 h, 76% 95.9% *ee*, >99% *es*

(+)-**2g**, 5 h, 68% 97.8% *ee*, >99% *es*

(+)-**2h**, 4 h, 89% 98% *ee*, >99% *es*

(±)-**2i**, 8 h, 84%

(-)-**2j**, 2 h, 90% 98% *ee*, 98% *es*

(-)-**2k**, 2 h, 82% >99% *ee*, >99% *es*

(+)-**2l**, 2h, 68% 97.9% ee, >99% *es*

(+)-**2m**, 3 h, 81% 97.7% *ee*, >99% *es*

(+)-**2n**, 4 h, 72% 97.3% *ee*, >99% *es*

(+)-**2o**, 2 h, 78% 97.9% *ee*, >99% *es*

(+)-**2p**, 2 h, 80% 97.3% *ee*, 98% *es*

(±)-**2q**, 7 d 51%

(±)-**2r**, 2 d, 61%

(±)-**1s** no reaction

(±)-**1t** no reaction

[a] Reaction conditions: the substrate **1** (1 equiv), DDQ (1.2 equiv), CH_3NO_2/H_2O (1.3 %) (0.05 м), 20 °C. Yield is that for product isolated after chromatography. The *ee* value was determined by CSP-HPLC. Used 4 equiv of DDQ in the case of **2q** and **2r**. Structures of substrates **1** are indicated in the Supporting Information.

Importantly, in all examples performed with enantioenriched substrates, an efficient chirality transfer was observed as enantiospecificity values higher than or equal to 98 % were constantly obtained. To our surprise, the enantiospecificity was high even under Lewis-acidic conditions which are known to promote the racemization of **3** (e.g. $Cu(OTf)_2$, *es* 84%; Table 1, entry 3). The configurational stability of the 13,13′-disubstituted derivatives was thus tested. Solutions in DMF (*N*,*N*-dimethylformamide) of (+)- and (−)-**2a** were treated with camphorsulfonic acid (2 equiv) for 2 hours at 100 °C. To our satisfaction, these samples retained their enantiomeric purity (97–98% *ee*)[18] while, under the same reaction conditions, a complete racemization was observed with the Tröger base (+)-**3** (R = Me, Scheme 1). Also, for these reactions that proceed through bond cleavages at stereogenic nitrogen and carbon atoms, care was taken to determine the absolute configuration of the products **2** with certainty.[19] This configuration was established by vibrational circular dichroism (VCD) in view of the rigidity of the compounds **2**.[20] IR absorption and VCD spectra were measured for solutions (CCl_4) of both (+)- and (−)-**2a** and compared to the averaged spectrum calculated for ($5S_N$,$11S_N$)-**2a** (Figure 1). Overall, a good agreement between the experimental and theoretical spectra was observed, thus allowing the assignment of (+)-**2a** as ($5S_N$,$11S_N$). These results clearly indicate that the methylene extrusion occurs with retention of configuration.[21]

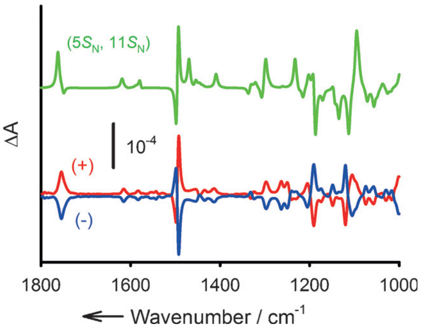
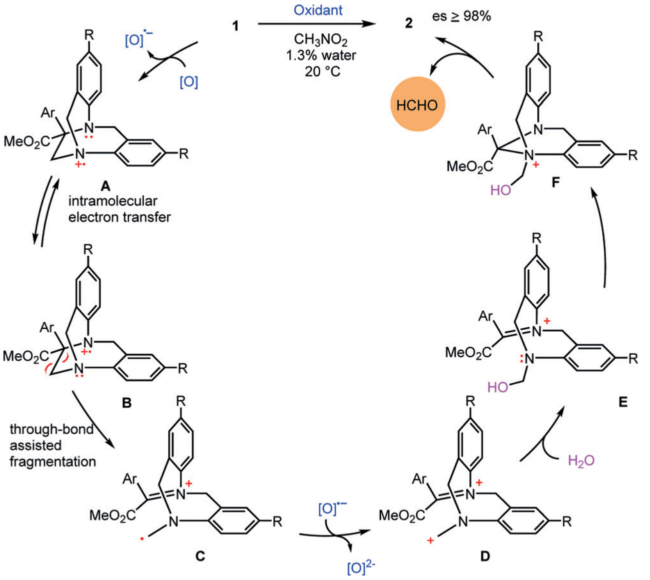


Figure 1. Calculated spectrum of ($5S_N$, $11S_N$)-**2a** (green). Experimental VCD spectra (CCl_4, 298 K) of (+)-**2a** (red) and (−)-**2a** (blue). The calculated spectrum represents a weighted average of the VCD spectra of two conformers (see the Supporting Information for details).

At that stage, the fate of the extruded CH_2 group was determined. Careful ^1H NMR monitoring of the oxidation process was performed with a catalytic amount of DDQ (10 mol%) and an excess of MnO_2 (10 equiv).[22] It revealed a significant amount of formaldehyde in the crude reaction mixture [up to 15 mol%, Eq. (1)].[23] With that information in hand, several mechanistic proposals can be considered, the most likely being that detailed in Scheme 2.

$$\mathbf{1j} \xrightarrow[\substack{\text{MnO}_2\text{ (10 equiv)}\\ \text{CD}_2\text{Cl}_2\text{, 48 h}\\ 20\,^{\circ}\text{C}}]{\text{DDQ (10 mol\%)}} \mathbf{2j} + \underset{\substack{\text{up to}\\ \text{15 mol\%}}}{\text{HCHO}} \qquad (1)$$

First, compounds of type **1** react in one-electron oxidations to generate nitrogen-centered radical cations of type **A**. These intermediates are formed from the more-electron-rich and sterically accessible bridgehead nitrogen atom. Then, an intramolecular electron-transfer reaction[24] occurs to generate the intermediate **B** which undergoes a homolytic C–C cleavage[25] favored by the alignment of the nitrogen orbitals and the C–C bond.[26] This through-bond-promoted fragmentation creates the intermediate **C**, which is characterized by the presence of an iminium ion and a radical stabilized by the adjacent nitrogen lone pair (two-center three-electron "half-bond").[26] Then, rapid oxidation of the α-aminomethyl radical forms the cationic intermediate **D** which is trapped by a water molecule (→**E**). Intramolecular nucleophilic attack of the tertiary nitrogen atom onto the iminium ion leads to the ring closure (**E**→**F**). Hydrolysis of the carbinol-ammonium group leading to the release of the methylene group as formaldehyde and to the formation of the ring-contracted products **2**. Finally, it is essential to stress the importance of the aryl and ester-substituted iminium moiety (**C**→**E**) which is conformationally locked and forbids a relaxation of the azocine ring. This restraint leads to the high level of enantiospecificity and retention of configuration.



Scheme 2. Proposed reaction mechanism.

In conclusion, a highly enantiospecific methylene extrusion reaction is reported and requires only mild oxidative conditions. Interestingly, the products of ring contraction are significantly more configurationally stable than regular Tröger bases. Applications of these derivatives in asymmetric synthesis and catalysis are looked for.

CCDC 1040107 (**2b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Keywords: configuration determination · enantioselectivity · heterocycles · ring contraction · stereochemistry

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[15] Water content was determined using a Karl Fischer instrument.

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[17] In this particular case, reaction is particularly sluggish as, after seven days with 4 equivalents of DDQ, traces of unreacted starting material remained.

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