



Synthesis and optical resolution of 4,5-diaminohomoadamantane: a promising scaffold for chiral ligands and bioactive compounds

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Abstract

Vicinal diamines based on a rigid polycyclic framework such as homoadamantane remain underexplored. We anticipated that the unique steric and lipophilic properties of chiral *trans*-4,5-diaminohomoadamantane could provide the necessary stereoinduction in metal-catalyzed asymmetric reactions. In addition, such structures may serve as a novel scaffold for bioactive compounds. Herein, we report a synthetic approach to this previously inaccessible chiral scaffold. 4,5-Diaminohomoadamantane was prepared as a mixture of *cis*- and *trans*-isomers by reduction of the corresponding vicinal azidoxime with LiAlH_4 . In contrast, the *trans*-isomer was selectively obtained via ring-opening of an *N*-Tf-protected aziridine. The racemic *trans*-4,5-diaminohomoadamantane was resolved with dibenzoyl-*L*-tartaric acid. The absolute (*4R,5R*)-configuration was proposed on the basis of TDDFT calculations of the specific optical rotation using the CAM-B3LYP functional and the 6-311G++(2d,2p) basis set with solvation by CH_2Cl_2 in the SMD model on the base of conformational analysis. Catalytic systems based on (*4R,5R*)-4,5-diaminohomoadamantane derivatives exhibited low to moderate asymmetric induction in Henry and Michael reactions. These results suggest that further molecular design of homoadamantane-based chiral *N,N*-ligands is promising.

Introduction

The chemistry of organic polycyclic cage compounds has been of interest to organic chemists for many years. Such a simple and symmetric structure as adamantane is widely used in phar-

maceutics to obtain drugs with a wide spectrum of action, as well as to improve the properties of drugs currently in use [1-7]. The chemistry of adamantane has been extensively studied

[8-16], while the properties of homoadamantane, its closest homologue, have not been studied so thoroughly. Chemical transformations of homoadamantane both at the bridgehead [17-23] and at the C-4 positions [24-28] are described in the literature. However, compounds of the homoadamantane family with substituents at the C-3 and C-4 [29-38] or at the C-4 and C-5 [39-53] positions have recently attracted more attention. At present, a few examples of homoadamantane derivatives showing pronounced biological activity are known. More than 40 homoadamantane polyprenylated acylphloroglucinols have been isolated from *Hypericum* plants [54-56]. Among them, hyperacmosins **A** and **B** showed a protective effect in paracetamol-induced cell damage [57], and activity against *Staphylococcus aureus* was noted for peroxysampsonone **A** **C** [58]. Basarić and co-workers showed that the replacement of 2-substituted adamantane by a homoadamantane skeleton led to enhanced antiproliferative activity (compound **D**) [59]. Compound **E** showed efficacy against *Staphylococcus aureus* [60]. Fluorobenzohomoadamantanamine **F** proved to be a potent NMDA receptor antagonist with efficacy very close to memantine [61] and compound **G** is approximately two times more potent as an NMDA antagonist than compound **F** [62]. The benzohomoadamantane-based derivative **H** showed high analgesic activity in a mouse model of cystitis (Figure 1) [63].

Vicinal diamines are of interest to chemists not only as precursors for the synthesis of heterocyclic compounds, but also because of their wide range of practical applications. Structures with a 1,2-diamine fragment are widely used in clinical practice [64-66], as well as auxiliaries and ligands in important

asymmetric transformations [67-70]. Bi- and polycyclic vicinal diamines can also be considered as potential ligands for asymmetric catalysis [71-74], but little attention has been paid to methods for obtaining compounds of this type. Vicinal diamines with an adamantyl substituent **I-K** have already been obtained [75-78] and 1,2-diaminoadamantane **L** has been synthesized by different methods [79-81]. For 1,2-diaminonoradamantane **M** there are even fewer data [82]. Polycyclic vicinal diamines **N** and **O** have been prepared recently (Figure 2) [69,83,84].

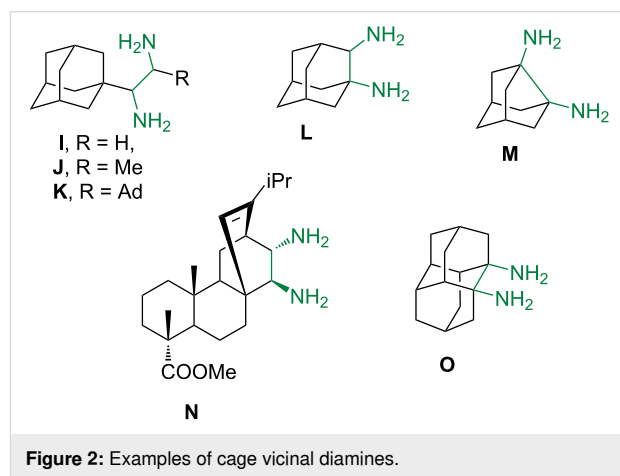


Figure 2: Examples of cage vicinal diamines.

Results and Discussion

Synthetic approaches to cage vicinal diamines are actively studied, as their rigid cage framework makes them promising ligands for asymmetric catalysis. In continuation of the theme

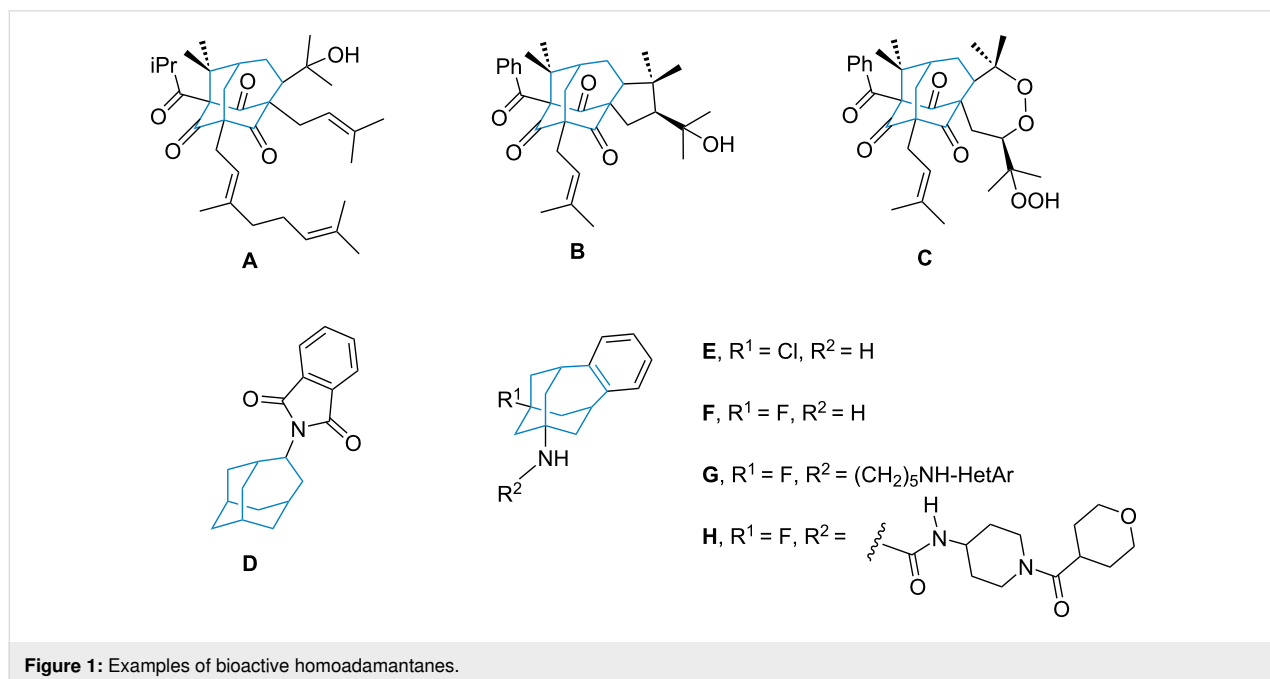
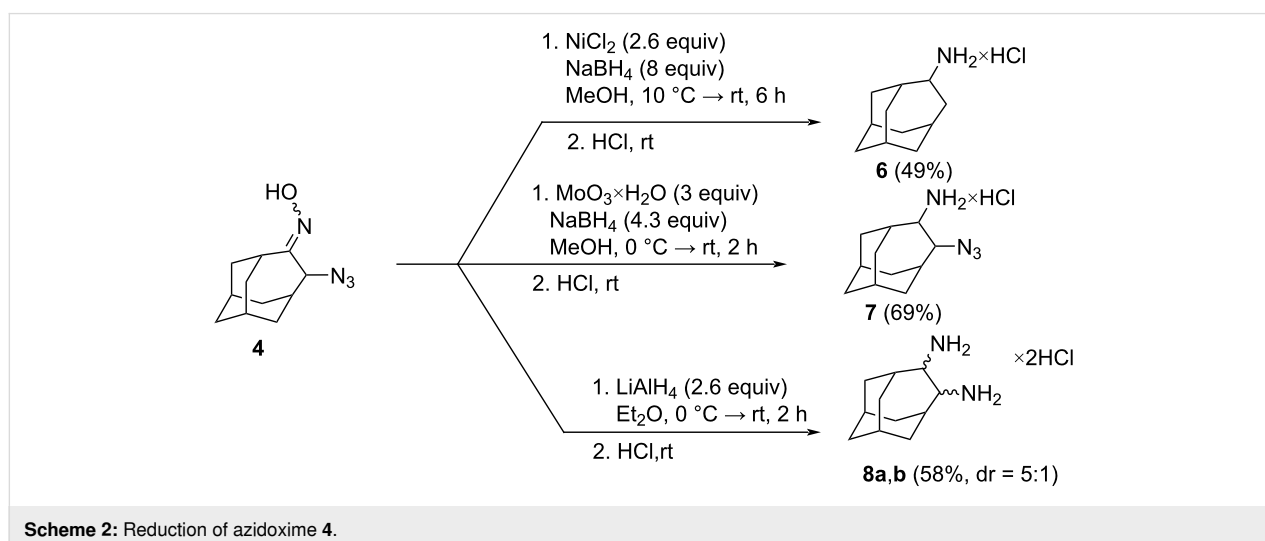
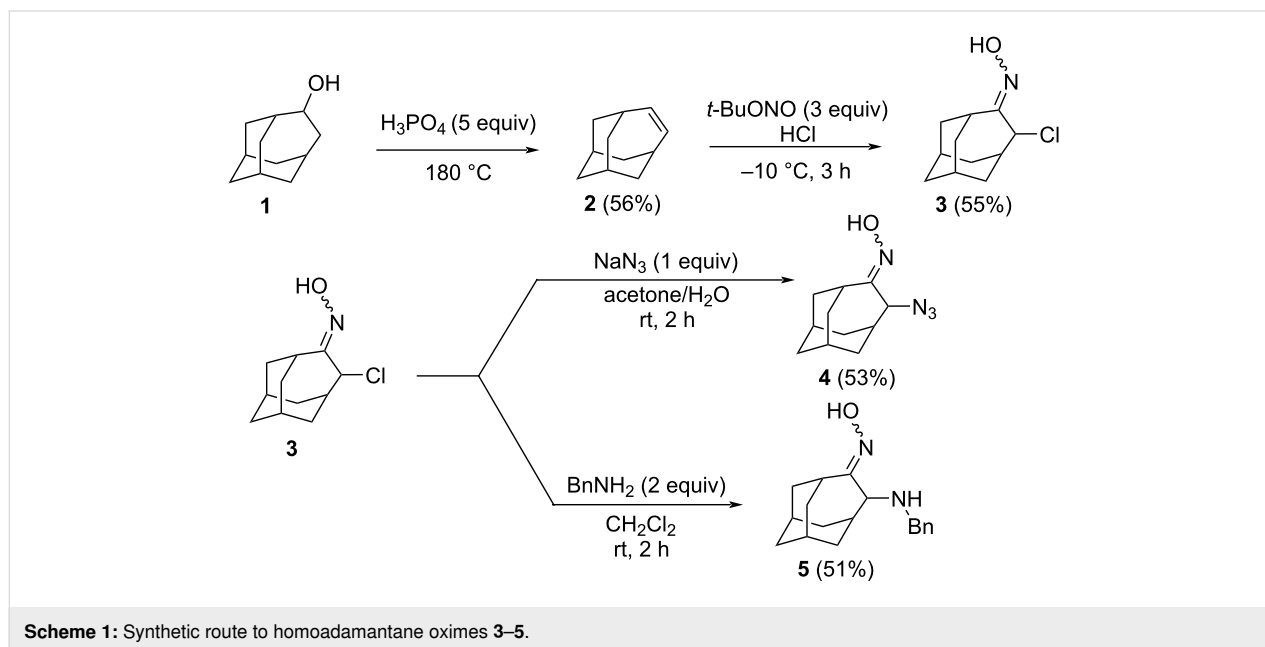


Figure 1: Examples of bioactive homoadamantanes.

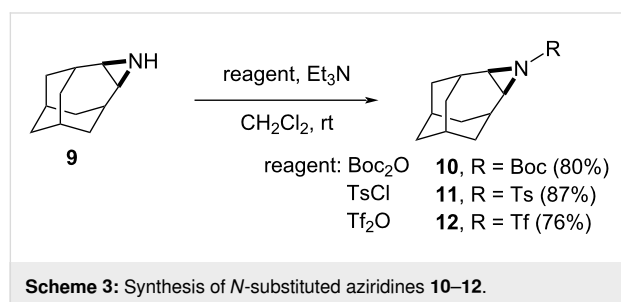
of our studies [75,77,81], we decided to focus on new approaches to the synthesis of 4,5-diaminohomoadamantane, its chiral resolution, and to test its applicability as chirality-inducing ligand in selected model reactions. We commenced the study using a route for the synthesis of 4,5-diaminohomoadamantane from azidoxime **4**. Initially, homoadamantan-4-ene (**2**) was obtained from homoadamantan-4-ol (**1**). In 1969, a method for the preparation of alkene **2** from homoadamantan-4-yl tosylate was proposed [85]. However, the formation of methyl tosylate and the need for purification of the product reduces its usefulness. We herein report an improved method for the synthesis of compound **2** from alcohol **1** using phosphoric acid, affording the target compound in high yield and purity. In the next step, chloronitrosation of alkene **2** led to α -chloroxime **3** in

moderate yield. Substitution of chlorine in **3** with azido and benzylamino groups was then carried out to give azidoxime **4** and aminoxime **5** (Scheme 1).

The reduction of azidoxime **4** was carried out using various systems in order to obtain *trans*-4,5-diaminohomoadamantane. Thus, treatment of compound **4** with NaBH₄ in the presence of nickel(II) chloride [86] resulted in the formation of 4-aminohomoadamantane (**6**). The NaBH₄/MoO₃ system [81] led to the selective reduction of only the hydroxyimino group, affording azidoamine **7**. The reduction of azidoxime **4** using LiAlH₄ [75,87] allowed total reduction of both the oxyimino and azido groups, resulting in the formation of isomeric diamines **8a,b** (Scheme 2).

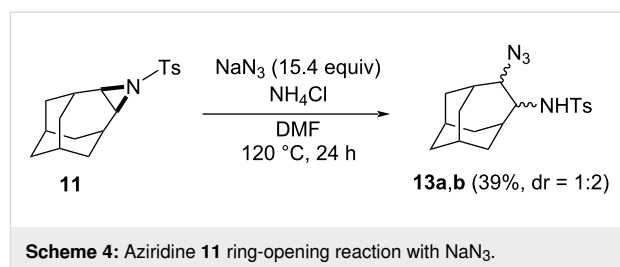


Since 4,5-diaminohomoadamantane was isolated as a mixture of *trans*- and *cis*-isomers **8a,b**, we decided to synthesize *trans*-4,5-diaminohomoadamantane through ring opening of aziridine **9**. This compound was obtained from homoadamantanone oxime by reduction with LiAlH_4 [41]. Since the aziridine ring-opening reaction usually proceeds easily when the aziridine bears an electron-withdrawing group at the *N*-atom, we synthesized *N*-substituted aziridines **10–12** by reactions of **9** with Boc_2O , TsCl , and Tf_2O , respectively (Scheme 3).



Compounds **10–12** were studied in the aziridine ring-opening reaction with sodium azide. Typically, *N*-Boc-substituted aziridines easily give the corresponding ring-opened products [77,88,89], however in our case only the starting compound **10** was isolated. In the reaction of tosylated compound **11** with sodium azide in the presence of ammonium chloride, *trans*- and *cis*-diastereomers of **13a,b** were obtained (Scheme 4).

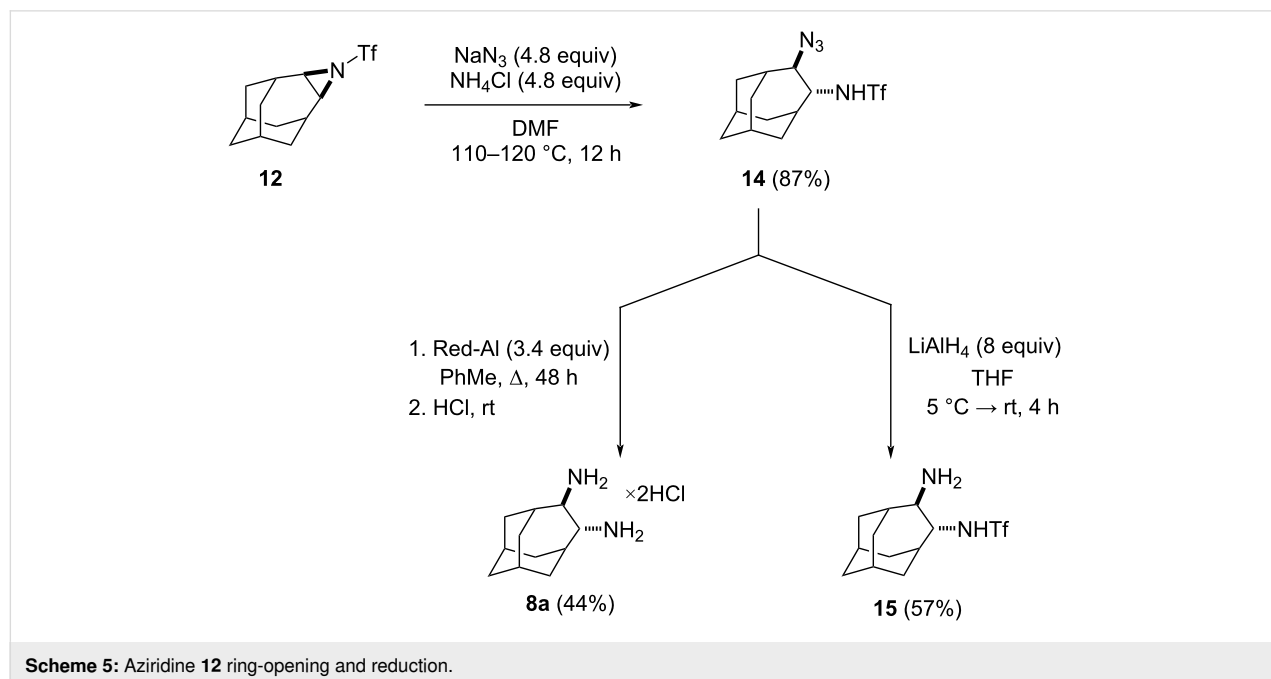
In order to find a more selective method for the synthesis of *trans*-4,5-diaminohomoadamantane (**8a**), aziridine **12** was

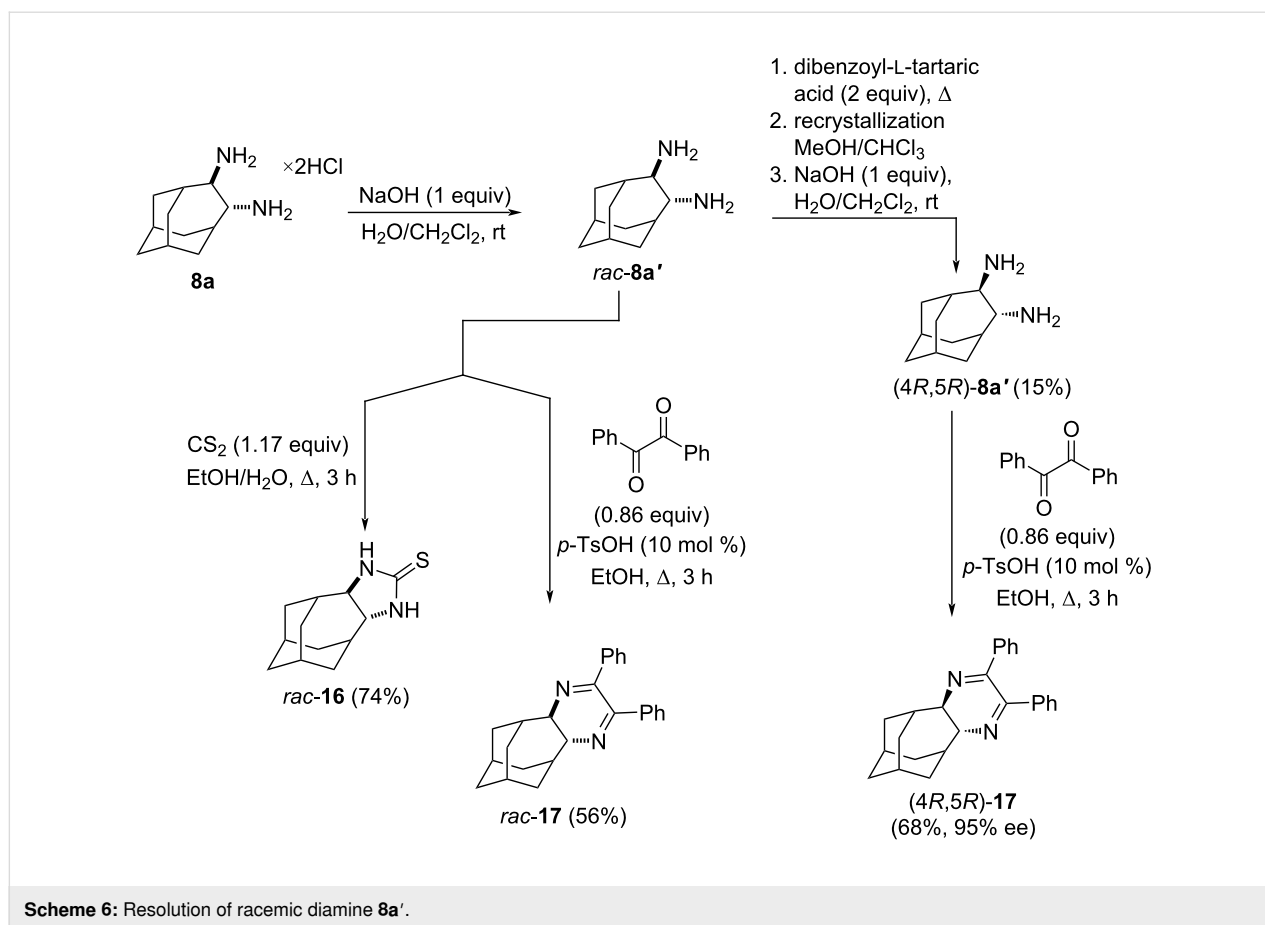


studied. When the tosyl group was replaced with a triflic group (**12**), only the *trans*-diastereomer **14** was formed in the reaction with NaN_3 and NH_4Cl . Upon reduction of the azido group with LiAlH_4 , the *trans*-isomer **15** was isolated. However, the removal of the protecting group in **15** by the known method [90] (sequential action of chloroacetonitrile and Cs_2CO_3) was unsuccessful. Therefore, we decided to use Red-Al [91,92] for simultaneous reduction and deprotection of **14** yielding only the *trans*-diastereomer **8a** (Scheme 5).

At the next stage of the research, we attempted to resolve racemic *trans*-4,5-diaminohomoadamantane (**8a'**) with the use of *L*-tartaric, *L*-malic, (*R*)-mandelic and dibenzoyl-*L*-tartaric acids. The diastereomeric salts derived from the corresponding acids and 4,5-diaminohomoadamantane (**8a'**) in both 2:1 and 1:1 ratios were studied. Successful resolution was achieved by triple crystallization of the bis(dibenzoyl)-*L*-tartrate from a $\text{MeOH}/\text{CHCl}_3$ mixture (Scheme 6).

The attempted determination of the enantiomeric ratio by chiral HPLC of the free amine failed because no optimal analysis





conditions could be identified. Therefore, a preliminary derivatization of diamine **8a**' was required, which was carried out by reactions with carbon disulfide [75] or benzil [77].

However, HPLC analysis was only successful for racemic 2,3-dihydropyrazine **17** (Scheme 6). For *(4R,5R)*-2,3-dihydropyrazine *(4R,5R)*-**17** derived from diamine *(4R,5R)*-**8a**', the enantiomeric excess was determined to be 95%. Multiple attempts to grow a crystal suitable for X-ray analysis were unsuccessful; therefore, the absolute configuration of *(4R,5R)*-**8a**' was proposed on the basis of quantum mechanical calculations. To date, a number of successful determinations of the absolute configuration for both conformationally flexible and rigid molecules have been performed by comparison of experimental and calculated specific rotation values [93–101]. The main difficulty of such a procedure is taking into account all possible conformers of a molecule, especially a flexible one, since specific rotation depends fundamentally on dihedral angles along bonds adjacent to the asymmetric atom. Therefore, the calculation of the specific rotation of rigid molecules is significantly easier since fewer conformers must be taken into account. Recently, it was shown, that calculated optical rotation values may be significantly affected not only by conformers but also by conforma-

tions that are close to them in energy [102,103]. Therefore, to calculate the specific rotation of *(4R,5R)*-**8a**' we applied a methodology that considers optical rotation of conformations that differ from the stable ones by no more than 10 kJ/mol [103]. All calculations were performed with the Gaussian 09 software [104]. Optimization of the molecule's geometry by DFT was performed using the CAM-B3LYP functional and the 6-311G++(2d,2p) basis set with solvation by CH₂Cl₂ in the SMD model. The dihedral scan for the C₄-NH₂ and C₅-NH₂ bonds was performed using the HF method in the 6-31G+(d) basis set. The dihedral angle for C₅-C₄-N-H was set to 50.66, -61.16, and 178.95 degrees that corresponds to staggered conformations and for each of them the dihedral angle for C₄-C₅-N-H was scanned in 15 degrees increments, starting from 171.48 degree. The results of scans are represented in Figure 3.

All in all, 18 conformations, that have energies within 10 kJ/mol from the most stable conformer, were chosen for further computation. The geometry optimization and optical rotation calculations of the chosen conformations were performed using DFT method with the CAM-B3LYP functional and the 6-311G++(2d,2p) basis set with solvation by CH₂Cl₂ in

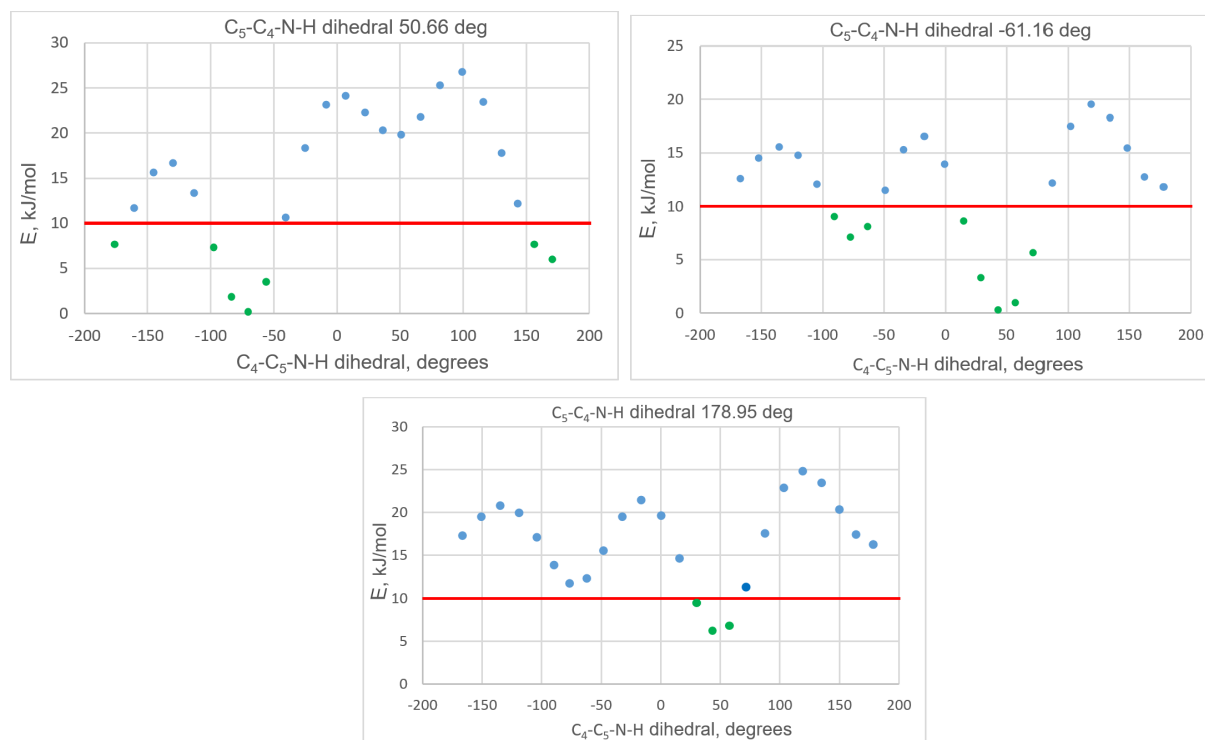


Figure 3: The results of C_4-C_5-N-H dihedrals scan for staggered conformations with C_5-C_4-N-H dihedrals 50.66, -61.16, and 178.95 degrees. Red lines in the graphics represent the energy of 10 kJ/mol. The scans were performed using HF/6-31G(d) method.

SMD model. The distribution of conformations was calculated on the basis of their relative energy with respect to the minimum energy using the Boltzmann law. The overall specific rotation was calculated through weight averaging of all chosen conformations. The results of the specific rotation calculation for six wavelengths, reported in Table 1, agree well with the experimental values of specific rotation, what allows to assign the (4*R*,5*R*)-configuration to compound **8a'**.

Table 1: Predicted and experimental specific rotations for (4*R*,5*R*)-**8a'**.

Wavelength, nm	Average calcd $[\alpha]_D^{25}$, CAM-B3LYP/6-311G++ (2d,2p)/SMD(CH ₂ Cl ₂)	Experimental $[\alpha]_D^{25}$
365	71.89	100.10
405	41.66	60.44
436	36.59	36.78
546	17.98	20.98
589.3	14.48	13.13
633	11.92	8.41

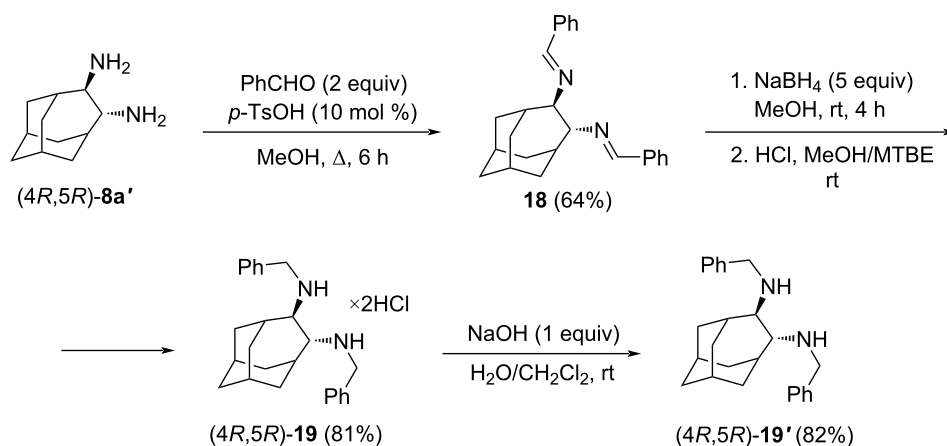
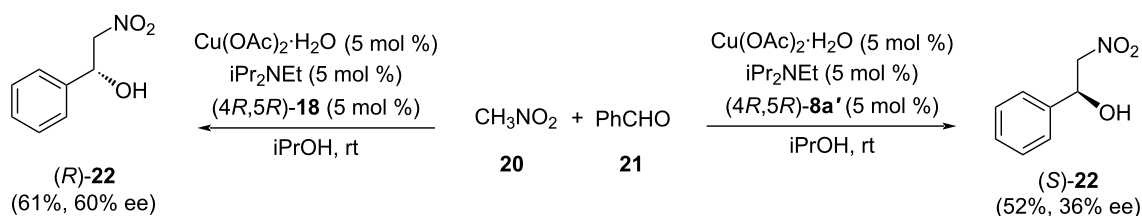
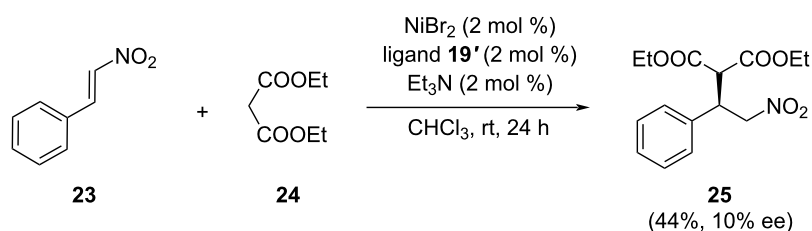
Since the chiral resolution of *trans*-4,5-diaminohomoadamantane was successful, we decided to study metal complexes of

ligands based on (4*R*,5*R*)-**8a'** in model reactions. Ligand **18** was obtained by the reaction of diamine (4*R*,5*R*)-**8a'** with benzaldehyde and the *N,N'*-dibenzyl-substituted ligand (4*R*,5*R*)-**19'** was synthesized by reduction of diimine **18** (Scheme 7).

Ligands (4*R*,5*R*)-**8a'** and **18** were studied as chiral inducers in a Henry reaction. The reaction of benzaldehyde with nitromethane was carried out in *i*PrOH in the presence of copper(II) acetate hydrate, ligand **8a'** or **18**, and diisopropylethylamine (5 mol % each) (Scheme 8).

When diamine (4*R*,5*R*)-**8a'** was used, the reaction mixture was enriched in the (*S*)-isomer (36% ee), while diimine ligand **18** promoted the formation of mainly the (*R*)-isomer (60% ee). The formation of products with different configurations when using ligands of similar structure indicates an enantiodivergent effect [105].

The ligand **19'** was studied in a model Michael reaction. The reaction of nitrostyrene with diethyl malonate was conducted in chloroform in the presence of ligand **19'**, NiBr₂, and NEt₃ (2 mol % each). This reaction does not proceed in the absence of triethylamine, as evidenced by the quantitative recovery of the starting materials (Scheme 9).

Scheme 7: Synthesis of ligands **18** and **19'**.Scheme 8: Enantiodivergent Henry reaction when using ligands **8a'** and **18**.Scheme 9: Catalysis of the Michael reaction using the complex $(4R,5R)\text{-}19'\text{-NiBr}_2$.

A slight enantiomeric enrichment in the (*S*)-enantiomer (10% ee) was observed with the *N,N'*-dibenzyl-substituted diamine **19'** based complex.

Conclusion

In conclusion, a new route for the synthesis of *trans*-4,5-diaminohomoadamantane and its subsequent optical resolution has been proposed. This compound is a valuable chiral scaffold for the construction of bioactive molecules and chiral ligands. In this work, chiral imine and amine ligands based on *trans*-4,5-diaminohomoadamantane were obtained. Catalytic systems based on them have been studied in the asymmetric Michael

and Henry reactions. Low enantioselectivity (up to 60% ee) was observed, but an enantiodivergent effect was noted in the Henry reaction.

Supporting Information

Supporting Information File 1

Experimental section.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-22-80-S1.pdf>]

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Author Contributions

Polina A. Man'kova: investigation; writing – original draft. Vadim A. Shiryaev: formal analysis; investigation. Olga S. Podlipnova: investigation. Marat M. Khisyamov: investigation. Dmitry S. Nikerov: investigation; visualization; writing – original draft. Alexander N. Reznikov: investigation; writing – original draft. Yuri N. Klimochkin: conceptualization; supervision.

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information of this article.

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