Two-Step Synthesis of Heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}] tetradecane from Norbornadiene: Mechanism of the Cage Assembly and Post-synthetic Functionalization

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Abstract: *A selective and scalable two-step approach to the dimerization of norbornadiene (NBD) into its thermodynamically most stable dimer, heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}] tetradecane, (HCTD) is reported. Calculations indicate that the reaction starts with the Rh-catalyzed stepwise homo Diels–Alder cyclisation of NBD into its exo-cis-endo dimer. Treatment of this compound with acid promotes its evolution to HCTD via a [1,2]-sigmatropic rearrangement. The assemblies of 7,12-disubstituted cages from 7-(alkyl/aryl) NBDs, as well as the selective post-synthetic C−H functionalization of the core HCTD scaffold at position C1, or positions C1 and C4 are described.*

Introduction

The apparently simple structures of cubane,[1] adamantane,[2] dodecahedrane,[3] and other highly symmetric cage hydrocarbons have fascinated chemists since decades and inspired numerous routes, mainly based on rearrangements, to achieve their synthesis in an efficient manner. Probably because of its availability, the most broadly studied cage hydrocarbon from these already mentioned is adamantane **1**. In fact, this architecture has found application in areas as diverse as material science,[4] and medicine.[2a, 5] Adamantane derived amines are approved drugs that display potent antiviral activity. For example, amantadine **2** is used to treat dyskinesia associated with parkinsonism and influenza caused by type A influenzavirus,[6] tromantadine **3** has been identified as an active agent to treat herpes simplex virus infections,[7] and bromantane **4** is an atypical psychostimulant and anxiolytic drug (Scheme 1).[8] Adamantyl substituents have also been strategically used to modulate the lipophilicity of already known pharmaceuticals.[2a]

The chemistry of the second member of the diamandoids series, diamantane **5**, is well studied too.[2b] Although the reduced symmetry of this molecule (D_{3d}) when compared with adamatane makes its selective functionalization a priori more challenging, convenient approaches have been developed over the years, which allow the hydroxylation,[9] halogenation,[10] amination,[11] alkylation,[12] or arylation[10a] of this compound, in some cases even on multi-gram scale. The rigid structure of functionalized diamantanes has also found application as linker for the synthesis of polymers[13] or in the design of mechanochemical devices, such as the molecular gyroscope **6**,[14] among others.

Given the impressive attention attracted by lower diamondoids, it is surprising that the chemistry of HCTD **7**, the D_{2d}-symmetric isomer of diamantane in which all carbon atoms are embedded in fused 5-membered rings, is comparatively unexplored. The reason probably lies in the fact that a practical synthesis able to selectively deliver this highly

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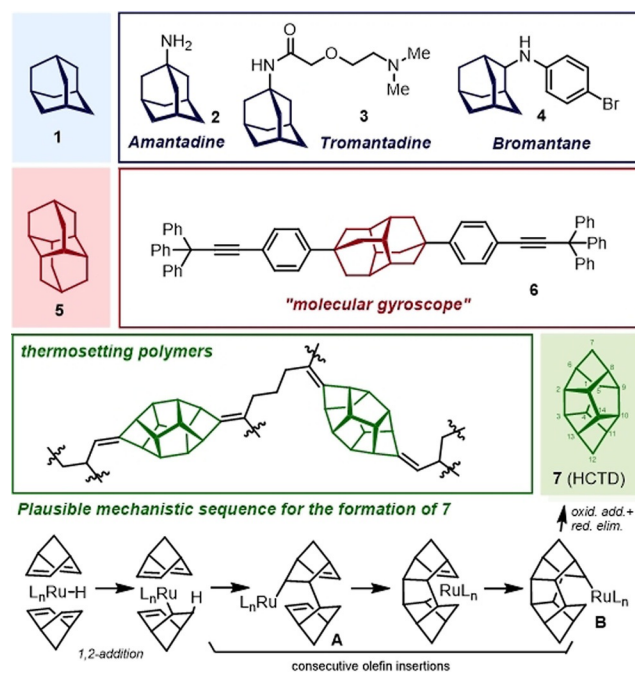Lowell, MA 01854 (USA)
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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.202010766.

Scheme 1. Comparison of the structures of adamantane, diamantane, and HCTD.

compact scaffold has remained a challenge for decades. The available routes invariably produced complex isomeric mixtures of norbornadiene (NBD) dimers,[15] are stoichiometric in metal[16] or simply afforded poor yields. Only recently has a practical protocol for its synthesis based on Ru-catalysis been reported.[17] Although still not studied in detail, cumulative evidence suggests that the cage closure starts with the formation of an *endo-endo* NBD dimer **A**, which evolves through a sequence of consecutive olefin insertion steps into **B**.[16b,18] Final C—H oxidative addition followed by C—C reductive coupling are probably the last steps of the cycle, delivering **7** and regenerating the Ru active species (Scheme 1). This synthetic route has finally paved the way to use the rigid HCTD cage as building block.[19] On the other hand, the efficient post-synthetic functionalization of the naked HCTD skeleton still remains unsolved. Only a handful of methods are reported, and most of them are characterized by exiguous yields or cleavage of the HCTD cage.[20]

Herein, we describe a conceptually different approach to the synthesis of **7** and its derivatives based on an initial asynchronous homo-Diels–Alder dimerization of NBD, followed by the acid-catalyzed isomerization of the intermediate open dimer **8** into **7**. Calculations at the PBE0-D3BJ(PCM)/def2-TZVPP//TPSS-D3BJ/def2-SVP level of theory support this mechanism. Moreover, studies on the post-synthetic functionalization of the core architecture have identified bromination, but specially nitroxylation, as the most efficient entries to 1-substituted HCTDs. The utility of these reactions is illustrated by the regioselective preparation of twelve HCTD derivatives in synthetically relevant yields, which include hydroxy-, amino- and aryl- substituents. Preliminary examples of 1,4-difunctionalized cages are also reported.

Results and Discussion

Initial Work Hypothesis

The difficulties associated with the synthesis of **7** come from the necessity to effectively control the very first C—C bond formation event between the two NBD moieties; a priori it needs to proceed with *endo-endo* diastereoselectivity to afford a direct precursor of **7**. Hence, the metal used as template must hold the two η^4-NBDs ligands that are going to be connected facing each other with their *endo*-sides. The dire consequence of this unique situation is that the usual tool to gain control over stereoselectivity, the use of costumed auxiliary ligands, is quite limited here. Specifically, when using Rh catalysts, the employment of chelating ligands quenches any reactivity towards dimerization,[21] while the imposition of significant steric requirements leads to the wrong hapticity in the NBD ligands. As a consequence, undesired mixtures of dimers, preferentially formed via less sterically demanding *exo*-coupling pathways, are obtained.[15]

At this stage we envisioned that if compound **8**, the *exo-cis-endo* dimer of NBD, could be prepared selectively, it might be used as a precursor for **7**. Under conditions still to be optimized, treatment of **8** with Lewis or Brønsted acid should promote the [1,2]-sigmatropic rearrangement of **8** into **9**;

while this last compound is already known to evolve, albeit in poor yield, to the thermodynamic sink **7** by treatment with HI (Scheme 2a).[15a] Hence, with these isomerizations effectively achieved, the synthesis of **7** gets reduced to the selective preparation of **8** via homo-Diels–Alder reaction (Scheme 2b).[22,23]
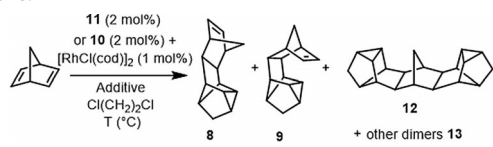
Based on our previous studies employing cationic ancillary ligands,[24] we expect Rh^I complex **11** bearing the chelating phosphine **10** to be a suitable precatalyst for this [2+2+2] cycloaddition.[25] The dicationic nature of **10** makes the Rh atom electron deficient and this facilitates, as shown below, the expansion of the coordination sphere of Rh to a fifth ligand. That is fundamental to assemble the two NBDs with the right hapticity around the metal. Moreover, the steric hindrance created in one side of the metal by the dicationic ligand is expected to favor the now desired *exo*-[2+2+2] cyclization. Precatalyst **11** is prepared by reaction of **10** with [Rh(nbd)Cl]$_2$ in acetone (see the Scheme 2c and the Supporting Information), but as it will be mentioned later, it does not need to be isolated. Identical results were observed when the dimerization experiments were carried out with **10** and [RhCl(cod)]$_2$ mixed in situ.
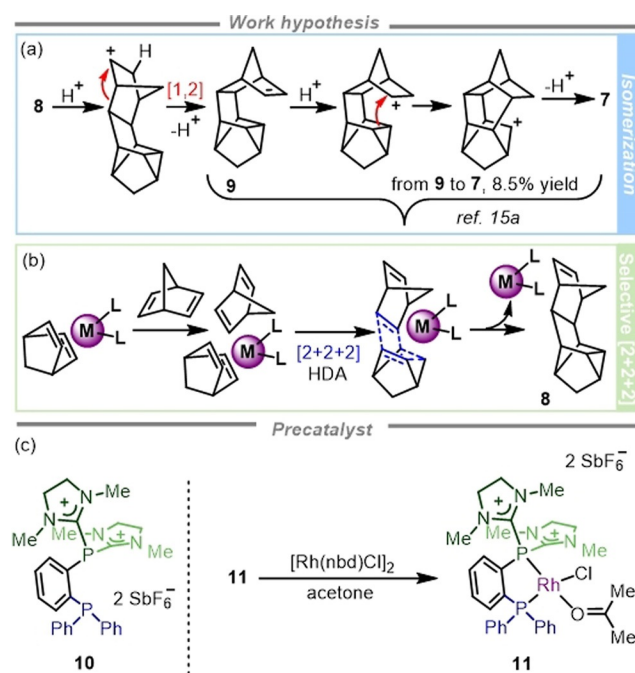
Scheme 2. Working hypothesis and synthesis of precatalyst **11**.

Catalysis

The catalytic performance of **11** (2 mol%) on the desired dimerization was initially tested in 1,2-dichloroethane at 70°C. Under these conditions the desired reaction is not efficient (only 7% conversion); interestingly however, **8** is the major component from the obtained mixture of products (Table 1, entry 1). We were glad to see that addition of NaB(C$_6$F$_5$)$_4$ to the reaction mixture under otherwise identical conditions was enough to improve the overall conversion up

Table 1: Rh-catalyzed dimerization of NBD. Optimization of reaction conditions.


Entry	Additive	T [°C]	Ratio **8:9:12:13** [%]	Conv. [%]
1[a]	–	70	75:10:15:0	7
2[a]	NaB(C$_6$F$_5$)$_4$	70	67:2:22:9	89
3[a]	NaB(C$_6$F$_5$)$_4$	90	76:7:12:5	98
4[b]	NaB(C$_6$F$_5$)$_4$	90	86:10:1:3	97

[a] Experiments carried out with an initial NBD concentration of 0.3 M; [b] initial NBD concentration of 0.2 M.

to 89%. This additive substantially increases the solubility of **11** in 1,2-dichloroethane by anion exchange and probably helps to abstract the chloride ligand from the coordination sphere of Rh. However, considerable amounts of trimer **12** were also formed together with minor amounts of **9** and other dimers (Table 1, entry 2). Having **9** in the reaction mixture is not problematic because this compound is in the route towards **7**; on the other hand, the trimerization of NBD needs to be minimized. Further optimization of the reaction conditions indicated that increasing the working temperature to 90°C was sufficient to achieve complete substrate conversion in 16 h., while working under more diluted conditions ([NBD]$_i$ = 0.2 M) proved to be essential to nearly suppress the formation of undesired **12**. Under the optimized conditions the desired dimer **8** is obtained as a mixture with **9** in a circa 9:1 ratio, respectively, and quantitative yield (Table 1, entry 4). Identical results were observed when these experiments were carried out using a 2:1 mixture of **10** and [RhCl(cod)]$_2$ or [RhCl(nbd)]$_2$ instead of preformed **11**. No reaction was observed when ligand **10** was replaced by 1,2-bis(diphenylphosphino)benzene (dppbz) under otherwise identical conditions.

In an attempt to gain further knowledge on the nature of the actual catalytic species, the orange oils remaining after extraction of the reaction mixtures with *n*-pentane were combined and dissolved in acetonitrile. Slow evaporation of that solution produced a few crystals of two different Rh complexes **14** and **15**, whose structures were determined by X-ray crystallography (Figure 1).

In **14** the first coordination sphere about the metal center can be described as a distorted square pyramidal environment. The base of the pyramid is formed by the chelating phosphine **11** and a η^4-NBD unit, while a loosely coordinated acetonitrile ligand is accommodated at the apical position. The fact that a d^8 Rh^I coordinates a fifth ligand beautifully illustrates the enhanced electrophilicity at that metal center, which is surely induced by the dicationic ancillary ligand. Moreover, the feasibility of a simultaneous binding of ligand **10** and NBD to the Rh atom is demonstrated. Unfortunately, the extreme insolubility of **14** in common organic solvents once crystallized does not permit its spectroscopic characterization. The structure of **15** is very similar; the only difference being that a chloride anion occupies the apical position at Rh
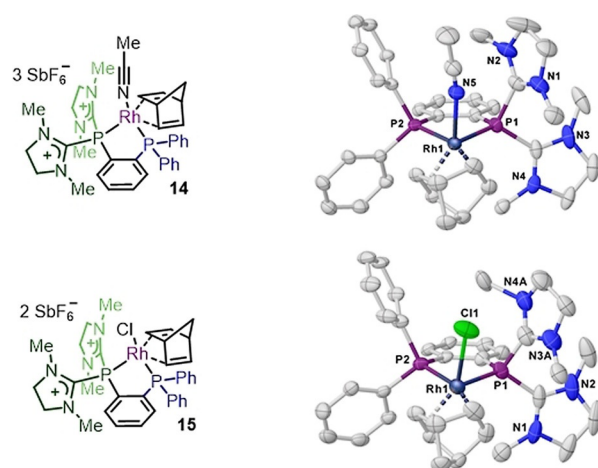
Figure 1. X-ray structures of **14** and **15**. H atoms and SbF$_6$ anions omitted for clarity; ellipsoids set at 50% probability.[26]

instead CH$_3$CN. Both, **14** and **15** are catalytically competent when submitted to the optimized reaction conditions.

At this stage, the interconversion of the obtained **8/9** mixture into **7** was attempted via treatment of the crude dimerization reaction mixtures with acid. A complete series of Lewis and Brønsted acids including BF$_3$, AlCl$_3$, HBF$_4$, HSbF$_6$, and [H(OEt$_2$)$_2$][B(C$_6$F$_5$)$_4$] were tested. Optimal results were achieved when using [H(OEt$_2$)$_2$][B(C$_6$F$_5$)$_4$] (5 mol%) in highly diluted conditions (0.05 M); this minimizes the formation of undesired polymers. Our overall two-step protocol has been scaled up to one gram of NBD and is not only practical for the synthesis of **7** but also for the preparation of 7,12-disubstituted cages **16–20**, from 7-(alkyl/aryl) substituted norbornadienes (Scheme 3).
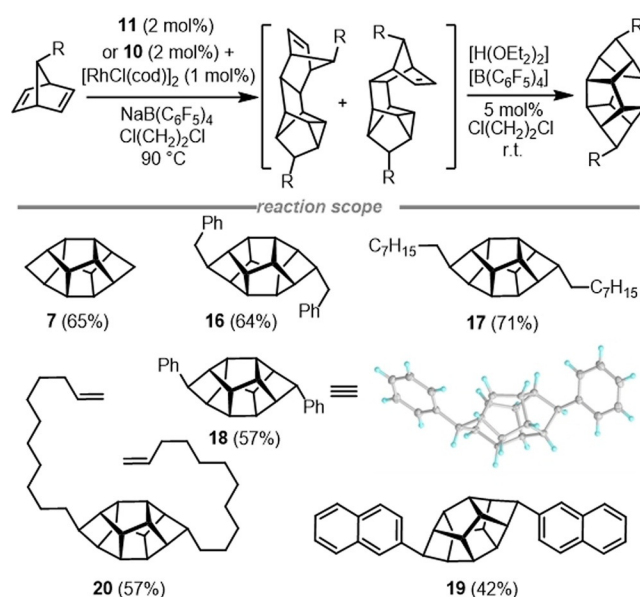
Scheme 3. Substrate scope. Yields are of the isolated products from the corresponding 7-substituted NBD (two steps). X-ray structure of **18**, ellipsoids set at 50% probability.[25]

Mechanistic Studies

The mechanism for the dimerization of NBD into **8** was investigated using density functional theory (DFT at the PBE0-D3BJ(PCM)/def2-TZVPP//TPSS-D3BJ/def2-SVP level).[27] Questions regarding the mechanism at the outset included 1) what is the lowest energy pathway for formation of product **8**; and 2) why does ligand **10** lead to the unique formation of product **8** in contrast to methods using monodentate phosphine ligands.[15,21]

Multiple pathways were considered in devising the most favorable pathway for product formation. Traditional transition metal catalyzed NBD dimerization using monodentate phosphine ligands involves bis-coordination of two NBD units followed by a reaction sequence of oxidative cyclization, carbometalation, and reductive elimination (Mechanism A; Supporting Information, Scheme S1). This pathway is disfavored when bidentate phosphine ligands are used because they prevent a second NBD from coordinating. In view of the isolation of **14** and **15**, in which the Rh atom is pentacoordinated, this does not seem to be a problem when using **10** as the ancillary ligand.

There are thus two alternative main pathways that can be envisioned; the one that starts with an inner-sphere attack of the second NBD to Rh through only one double bond, or an outer-sphere mechanism in which a non-coordinated NBD attacks an already coordinated NBD. The inner-sphere attack of a NBD can only take place on the unsaturated 16 electron cationic Rh formed from Cl dissociation; the isolation of **14** demonstrates that this happens easily under the reaction conditions applied. An outer-sphere attack can take place on either the Rh-Cl complex **15** or in a tricationic complex resembling **14**. All three mechanisms were explored (Figure 2; Supporting Information, Figures S2 and S3), and the lowest energy pathway (4.3 kcal mol⁻¹ lower than the next

closest one) is discussed here, which is the inner-sphere mechanism.

This mechanism may lead to up to four different NBD dimers depending on the diastereoselectivity of the attack; we only show in Figure 2 the calculated pathways leading to products **8** (**Prod$_{exo}$**) and **9** (**Prod$_{endo}$**). The mechanism initiates through association of the second NBD to the Rh atom using one of its π-systems to form the corresponding 18 electron complexes in either an *exo* (**INT1$_{exo}$**) or *endo* (**INT1$_{endo}$**) configuration, with *exo* association being favored by 2.3 kcal mol⁻¹. This energetic preference is reflected structurally in a shorter distance between the Rh center and C atoms of the associating π-system in **INT$_{exo}$** (2.41 Å; 2.50 Å) than in the **INT$_{endo}$** (2.59 Å; 2.68 Å), indicating a stronger interaction and suggesting that *endo* association is sterically more hindering than the *exo*. The subsequent oxidative cyclisation, which is calculated to be the rate determining step of the mechanism, takes place with the *exo* pathway maintaining the energetic preference by 2.5 kcal mol⁻¹ (compare **TS1$_{exo}$** and **TS1$_{endo}$**). While the initial intermediates after **TS1** can be considered 16 electron complexes, the second π-system of the *endo* pathway, **INT2′$_{endo}$**, weakly coordinates to the Rh center to form **INT2$_{endo}$** resulting in a higher stabilization for the *endo* over *exo* intermediate (Figure 2). The participation of the second π-system is geometrically restricted from coordinating in **INT2$_{exo}$** and thus, the Rh atom in **INT2$_{exo}$** remains unsaturated. The second C−C bond is next formed through carborhodation leading to **INT3**. **INT3$_{endo}$** is substantially lower in energy than **INT3$_{exo}$** due to the stabilization provided by coordination of the olefin π-bond, which cannot be compensated by the weaker σ C−H agostic interaction in **INT3$_{exo}$**. The products are then formed through reductive elimination in the final step forming the cyclopropane ring. From this analysis it can be concluded that even though the second, nonreactive π-system in the *endo* pathway helps with
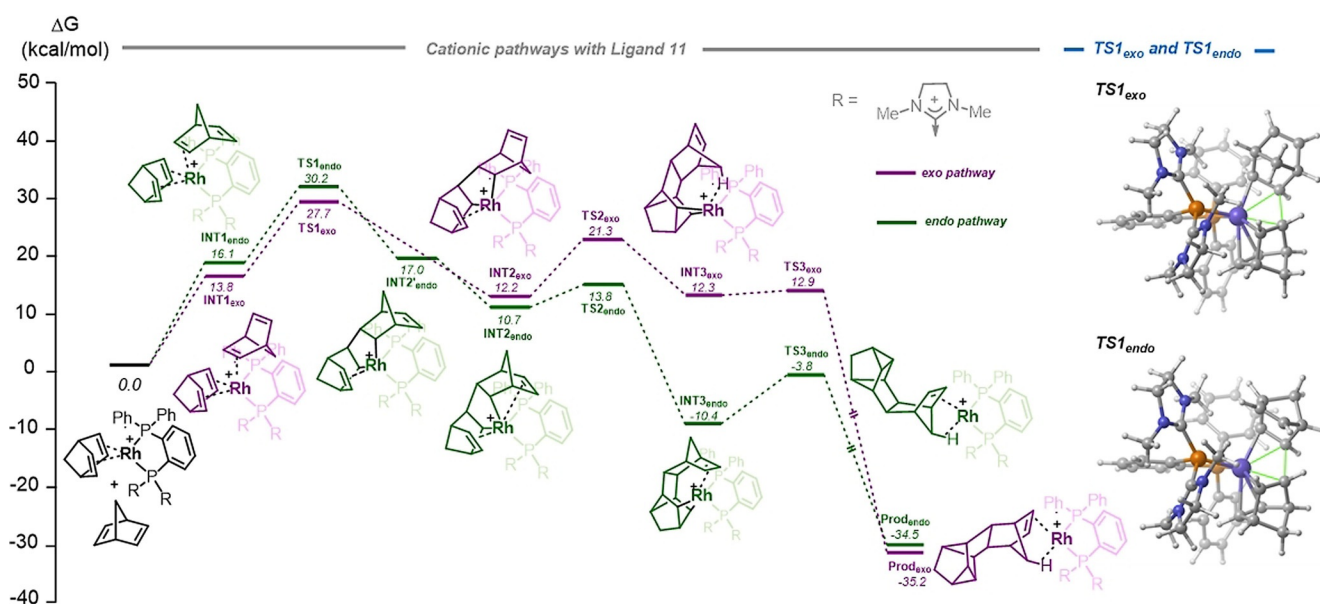
Figure 2. Gibbs free-energy profile computed at the PBE0-D3BJ(PCM)/def2-TZVPP//TPSS-D3BJ/def2-SVP level of DFT. The green pathway corresponds to the *endo* pathway and magenta the *exo* pathway relating to NBD approach. The "=" between TS3 and Prod symbolizes the presence of a higher-energy, shallow intermediate.
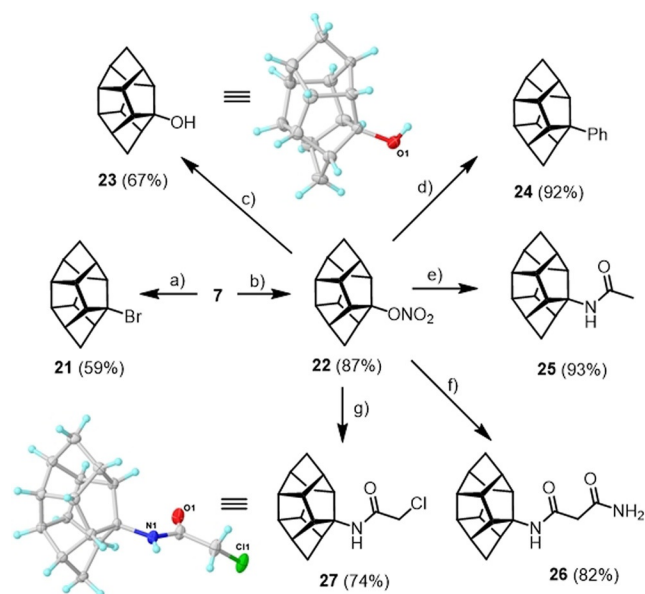
stabilization through coordination, this assistance only takes place after the rate determining step **TS1**; as consequence, the formation of **8** over **9** is favored. Moreover, it is clear how trimer **12** may be formed through the association of a third NBD unit to **Prod**ₑₓₒ.

The formation of the other two diasteromeric NBD dimers was also considered (Supporting Information, Figure S1); the corresponding **TS1** for each are calculated to be higher in energy than the lowest energy *exo* pathway discussed here.

Post-synthetic Functionalization of the HCTD Cage

The C−H functionalization of adamantane and related structures is well developed; hence, we decided to make use of these already existing protocols to attempt the derivatization of **7**.[28] Initially, the bromination of the HCTD cage was targeted. Direct treatment with Br₂ under a variety of conditions resulted to be completely inefficient and **7** was re-isolated from the reaction mixtures untouched. Hence, we turned our attention to the functionalization of **7** employing Schreiner's protocol using [Br₃C]• radicals generated under phase transfer catalytic conditions. To our delight, bromine derivative **21** bearing the Br-substituent in position 1 could be obtained using this method, albeit in moderate yield.[29] Importantly, although **7** contains two non-equivalent tertiary C−H bonds, the 6-Br derivate was not detected under these conditions (Scheme 4).
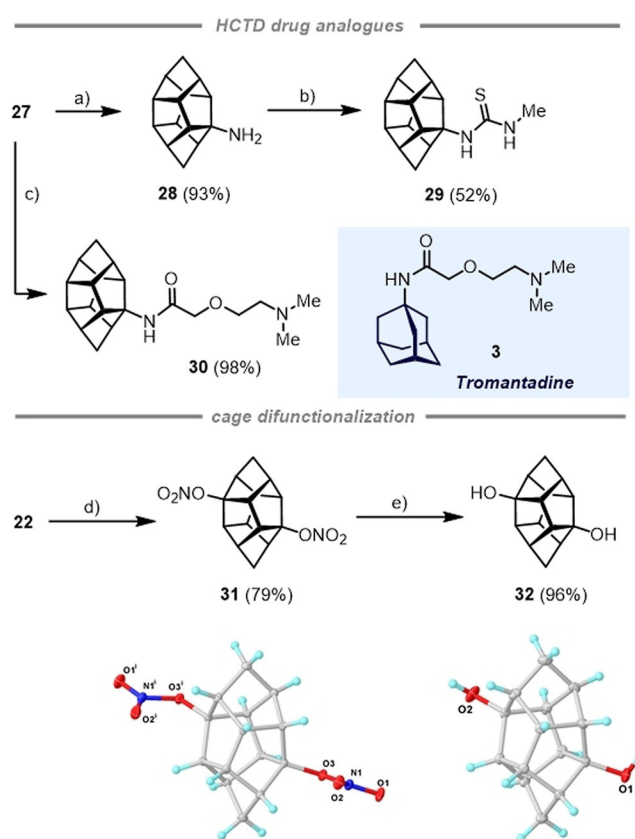
A more general approach however for the preparation of functionalized HCTDs is nitroxylation, which we carried out in neat HNO₃ under identical conditions to those employed to

substitute diamantanes.[9] Once obtained, the nitroxyl derivative **22** can be hydrolyzed to produce alcohol **23** in much better yield than previously reported.[30] Additionally, treatment of **22** with H₂SO₄ generates the transient carbocation intermediate that can be trapped either with an arene following a Friedel–Crafts alkylation mechanism, such as in the case of **24**, or with nitriles in a typical Ritter-type reaction. Amides **25–27** are obtained in good to excellent yields following this method; the structures of **25** and **27** being confirmed by X-ray diffraction (Scheme 4 and the Supporting Information). Functionalization of **7** at position 1 destroys the symmetry of the original cage and as a consequence; compounds **21–27** are chiral even though they are obtained as racemates.

Following the methodology already described, HCTD analogues to adamantane derived clinically approved drugs have been prepared as well. For example, hydrolysis of **27** under acidic conditions delivers amine **28**, which can be considered an amantadine analogue; while reaction of the same compound with deprotonated 2-(dimethylamino)ethanol affords **30**, the HCTD version of Tromantadine **3**. Finally, re-subjection of **22** to nitroxylation conditions affords the dinitroxyl derivative **31**. The relative 1,4-disposition of the two -ONO₂ units was initially suspected by NMR spectros-

Scheme 4. Preparation of 1-substituted HCTD. Reagents and conditions: a) CBr₄ (1 equiv), [BnNEt₃]Cl (7 mol%), 50% NaOH (aq.)/CH₂Cl₂, 70°C for 18 h; b) HNO₃/CH₂Cl₂, r.t.; c) H₂SO₄ and then H₂O; d) H₂SO₄/C₆H₆, 50°C; e) H₂SO₄/CH₃CN, 50°C; f) H₂SO₄/NCCH₂CN, 50°C; g) H₂SO₄/ClCH₂CN, 50°C. X-ray structures of **23** and **27**, ellipsoids set at 50% probability.[25]

Scheme 5. Preparation of HCTD analogues to adamantane-derived drugs and dinitroxylation of the cage. Reagents and conditions: a) thiourea (1.2 equiv), 10 h. and then aq. NaOH solution; b) MeNCS (1.0 equiv), EtOH, r.t. 12 h; c) Me₂NCH₂CH₂OH (1.5 equiv), NaH (1.5 equiv), THF, reflux, 3 h.; d) HNO₃, 16 h. r.t. 16 h; e) H₂SO₄ and then H₂O. X-ray structure of **31** and **32**, ellipsoids set at 50% probability and solvent molecules omitted for clarity.[25]

copy, which indicated the formation of a C_2-symmetric product, and later confirmed by X-ray crystallography. Hydrolysis of **31** cleanly delivers diol **32**. The isolation of these two compounds represents a first milestone for the preparation of di-functionalized HCTD cages (Scheme 5).

Conclusion

We have presented an efficient two-steps protocol for the synthesis of HCTD **7**. For the first one a Rh-catalyzed homo Diels–Alder dimerization is utilized. The dicationic ancillary ligand that the Rh center bears makes possible this reaction by both, activation of the π-system, and limiting formation of undesired products of *trans*-dimerization, as supported by DFT. Subsequently, the initial dimers obtained are readily transformed into **7** via acidic treatment. Making use of the chemistry already developed for the C−H functionalization of adamantanes, a series of HCTD derivatives have been prepared in synthetically useful yields. Ongoing research in our group is focused on the development of protocols allowing the asymmetric mono- and di-functionalization of **7**.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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