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Catalytic Cage Formation via Controlled Dimerization of Norbornadienes: An Entry to Functionalized HCTDs (Heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecanes)

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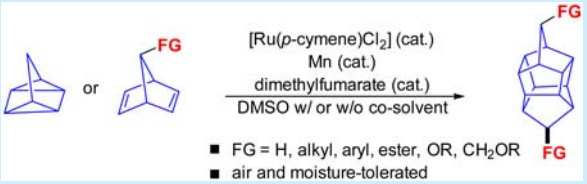
Supporting Information

ABSTRACT: A general and practical catalytic method has been developed for the rapid synthesis of HCTD (heptacyclo-[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecanes) and various new 7,12-disubstituted HCTDs from norbornadienes. Compared to the known approaches, this new protocol avoids stoichiometric metals, utilizes commercially available reagents as catalysts, and affords higher yields and significantly improved selectivity. In addition, quadracyclane was discovered for the first time to undergo a similar *endo,cis,endo* cycloaddition to give HCTD in a good yield. Derivatization of HCTDs led to efficient preparation of a range of novel homo- and heterobifunctional scaffolds that hold potentials for biological and material applications.



With fascinating highly symmetrical structures, carbocyclic cage compounds hold great promise for use as pharmaceuticals (e.g., amino-adamantanes),[1] energetic (e.g., nitrocubanes and CL-20),[2] and photonic/electronic materials (e.g., fullerenes).[3] In particular, HCTD (heptacyclo-[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecane) represents a unique class of cage molecules (Figure 1).[4] Analogous to cubanes and

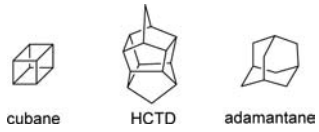
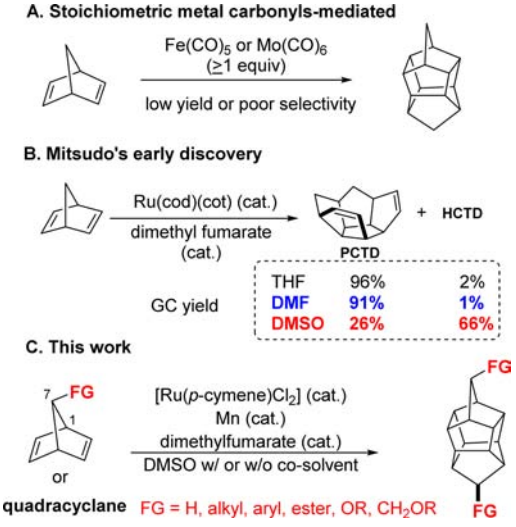


Figure 1. Carbocyclic cage compounds.

adamantanes, HCTD can be considered a distinct repository of cyclopentanes with D_{2d} symmetry. In addition, the rigid, strained, and highly compact scaffold, as well as the unusual overall shape, has made HCTD an attractive moiety for use as energetic materials[2] and energy transfer spacers.[5]

Despite these intriguing features, practical synthesis of HCTD, particularly substituted HCTDs, remains a long-standing challenge. HCTD was first prepared (in 2−3% yield) in 1961 via iron carbonyl [Fe(CO)$_5$]-mediated *endo,cis,endo* cyclodimerization of norbornadiene (NBD) (Scheme 1A).[6] Later, this transformation was also observed using other transition metals, such as rhodium;[7] however, these reactions generally produced a complex mixture with many other isomeric byproducts, and the overall yields of HCTD were low due to the poor selectivity during the NBD-dimerization process (at least 14 pathways to dimerize NBD have been reported to date).[8] A significant improvement was made by Chow and co-workers in 1985; they found that Mo(CO)$_6$ can selectively promote the desired cyclodimerization of NBD to HCTD without forming other observable dimers, although the yield was moderate (26% based on Mo) with excess NBD.[9] Clearly, to thoroughly explore the potential of HCTD or functionalized HCTDs in biomedical or material applications, a practical, efficient, and selective synthesis of HCTD and its derivatives must be developed. Hence, a catalytic approach without the need of stoichiometric metal carbonyls would be highly desirable.

Scheme 1. Controlled Dimerization of NBD



Our research was inspired by the seminal work of Mitsudo and co-workers reported in 1999,[8] in which a novel half-cage

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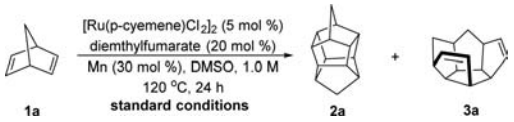
compound (PCTD) was obtained selectively in a Ru-catalyzed NBD-dimerization reaction (Scheme 1B). During the course of this study, an uncommon solvent effect was observed: while THF and DMF gave almost exclusively the PCTD product, the use of DMSO as solvent led to forming a significant amount of HCTD (66−70% GC yield, 45% isolated yield) along with PCTD (23−26% yield). While the selectivity for HCTD is moderate (2.5−3.0:1) and the [Ru(cod)(cot)] catalyst used needs additional preparation, this earlier finding clearly indicated that catalytic formation of HCTD is feasible. However, it was surprising to note that this important discovery has been overlooked for decades with no attention to be advanced for HCTD synthesis. Herein, we describe our development of an improved catalytic method for selective synthesis of HCTD and its derivatives from NBD and 7-substituted NBDs (Scheme 1C). The protocol utilizes commercially available reagents and tolerates air and some moisture; thus it is user-friendly and operationally simple.

The prior mechanistic study[8] suggested that forming the undesired PCTD was initiated by a Ru−H-mediated 1,2-addition of NBD.[10] Thus, it is logical to hypothesize that one key to promote the desired cage formation would be to avoid forming a ruthenium−hydride species, which indicates that choosing an appropriate ruthenium precatalyst would be critical. From a practical viewpoint, the study was initiated by examining a range of commercially available Ru(II) salts in combination with appropriate reductants, e.g., Mn or Zn. To our delight, preliminary screening revealed that, using a catalytic amount of Mn powder as reductant, several Ru(II) chlorides, such as [Ru(cod)Cl_2], [Ru(nbd)Cl_2], and [Ru(benzene)$Cl_2]_2$, afforded HCTD **2a** in good yields (ca. 70%) and high selectivity (8:1−10:1). Ultimately, the [Ru(*p*-cymene)$Cl_2]_2$/Mn combination proved to be optimal, which gave a 75% yield of **2a** with 11:1 selectivity favoring the cage formation (Table 1, entry 1).

Table 1. Selected Reaction Optimization[a]



entry	variations from the standard conditions	2a[b]	3a	2a/3a
1	none	75 (66[c])	7	11:1
2[d]	Mitsudo's conditions	60	31	2:1
3	w/o [Ru(p-cymene)$Cl_2]_2$	-	-	-
4	w/o Mn	-	-	-
5	w/o dimethylfumarate	2	-	-
6	*N*,*N*-dimethylacrylamide instead of dimethylfumarate	23	5	5:1
7	**[Ru] (2.5 mol %)**	73	7	10:1
8	[Ru] (1 mol %)	27	3	9:1
9	**90 °C instead of 120 °C**	73	8	9:1
10	toluene instead of DMSO	-	<5	-
11	THF instead of DMSO	trace	<5	-
12[e]	catalytic use of DMSO (20 mol %) in other solvents	<3	<3	-
13[f]	Zn instead of Mn	72	13	6:1
14	w/air	68	6	11:1
15	under N_2 w/wet DMSO	69	8	9:1
16	**3.0 M instead of 1.0 M**	63	3	21:1

[a]All reactions were run on a 0.3 mmol scale. [b]The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c]Isolated yield. [d]Ru(cod)(cot) (2 mol %) was used instead of [Ru(*p*-cymene)$Cl_2]_2$ and Mn in 1.6 M for 2 h. [e]Common organic solvents including THF, toluene, DMF and 1,4-dioxane were tested. [f]90 mol % Zn was used.

To understand the role of each reaction parameter, a number of control experiments were carried out (Table 1). First, Mitsudo's protocol with Ru(cod)(cot) was successfully reproduced,[11] which gave a 2:1 mixture of HCTD **2a** and PCTD **3a** (Table 1, entry 2). In the absence of the ruthenium complex or the reductant, neither **2a** nor **3a** was formed (Table 1, entries 3 and 4), suggesting that the reaction was catalyzed by a low-valent Ru complex. The use of an electron-deficient olefin ligand is also critical, as in the absence of dimethylfumarate or use of *N*,*N*-dimethylacrylamide instead, the yields were considerably lower (Table 1, entries 5 and 6). *Nearly the same results were obtained using 2.5 mol % of [Ru(p-cymene)*$Cl_2]_2$ (Table 1, entry 7); further reducing of the loading to 1 mol % led to a much slower reaction albeit with the same selectivity (Table 1, entry 8). Gratifyingly, the reaction temperature can be lowered to 90 °C without much influence on the yield and selectivity (Table 1, entry 9). It is worthy to note that, when other solvents, such as toluene and THF, were used, no significant conversion was observed (Table 1, entries 10 and 11) suggesting a major difference between Mitsudo's[8] and this catalytic system, in which the former gave more than 90% conversion to PCTD in the absence of DMSO (Scheme 1B). Nevertheless, both systems affirmed the indispensable role of DMSO, although the exact reason remained to be defined. In addition, attempts to use a catalytic amount of DMSO were unsuccessful (Table 1, entry 12). Zn was found less reactive than Mn; however, a similar yield can be obtained when more Zn was used (Table 1, entry 13). Furthermore, in contrast to the [Ru(cod)(cot)]-based procedure that requires argon atmosphere,[8] this [Ru(*p*-cymene)$Cl_2]_2$ system tolerated air and moisture (Table 1, entries 14 and 15). Interestingly, under a higher concentration (3.0 M), the selectivity was remarkably increased to 21:1 (Table 1, entry 16).

With the optimal conditions in hand, the scope of using various 7-substituted NBDs was explored (Scheme 2).[12] First, C_7−O*t*-Bu and OTBS substituted NBDs (**1b** and **1c**) smoothly underwent the *endo*,*cis*,*endo* cyclodimerization to furnish the oxygenated HCTDs (**2b** and **2c**) in good yields. The structure of **2c** was unambiguously confirmed by X-ray crystallography. In contrast, the reaction of the OBn-substituted substrate **1d** was much less selective,[13] wherein formation of HCTD was likely hampered by an undesired intramolecular coordination of the aryl group with the Ru-catalyst. We hypothesized that use of an aromatic cosolvent should minimize chelation of the aryl group in the NBD substrate with the catalyst; indeed, with the use of a toluene/DMSO (1:1) mixed solvent, improved yield for the cage formation was achieved. The same trend was also found when using C_7-aryl- and benzyl-substituted NBDs (**1h**−**1l**). On the other hand, a THF/DMSO (7:1) mixed solvent was found more effective for alkyl-substituted NBDs (**2e** and **2f**) than pure DMSO. In addition to alkoxy, siloxy, alkyl, benzyl, and aryl groups, acetals (i.e., MEM ether, **2f**) and esters **2g** were also proved compatible. Notably, in this study, a range of new $C_{7,12}$-diarylated HCTDs were made available in moderate but synthetically useful yields, which were not achieved previously with other methods.

To understand the kinetic profile of this transformation, the reaction progress was monitored by ^{1}H NMR with substrate **1b**. As depicted in Figure 2, the reaction exhibited a short or no induction period, indicating a fast reduction of the Ru(II) precatalyst. In addition, a high initial rate was observed for the cage-compound formation, as during the first hour HCTD **2b** was produced in 63% yield, and thereafter the rate was

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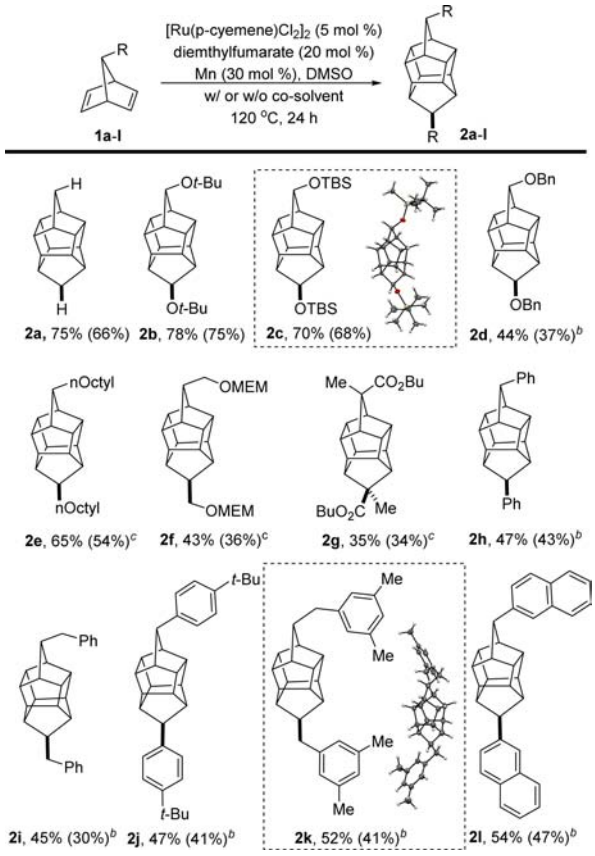
Scheme 2. Substrate Scope[a]



[a]All reactions were run on a 0.2 mmol scale; NMR yields are presented due to the difficulty of fully purifying these nonpolar compounds; the numbers in parentheses are isolated yields of the pure fractions. [b]DMSO:toluene (1:1) mixed solvent was used. [c]DMSO:THF (7:1) mixed solvent was used.

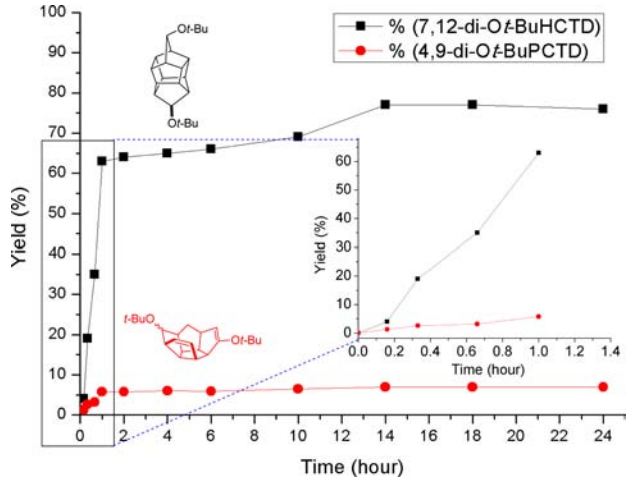
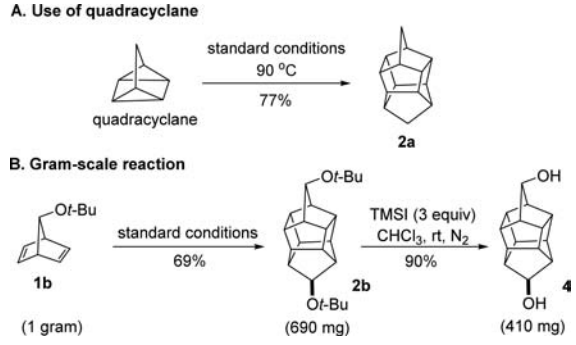


Figure 2. Kinetic profile of forming 7,12-di-O*t*-BuHCTD (**2b**) and 4,9-di-O*t*-BuPCTD (**3b**).

significantly diminished. In contrast, the rate of forming PCTD was much lower throughout the reaction.

Besides NBDs, quadracyclane was also discovered to be a competent substrate to give HCTD, although the exact mechanism is unclear. For example, under the standard conditions except at 90 °C in the absence of light (to avoid any light-mediated formation of NBD from quadracyclane), dimerization of quadracyclane provided HCTD in 77% yield, which, to the best of our knowledge, was unknown previously (Scheme 3A).[14] Moreover, our method proved to be readily

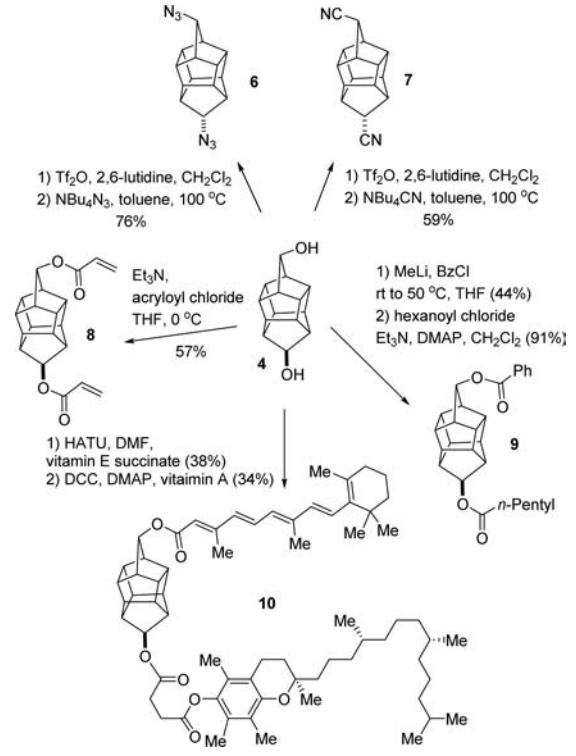
Scheme 3. Further Exploration



scalable; **2b** was isolated in 69% yield on a gram scale, and subsequent removal[5a] of the *t*-butyl group with TMSI provided HCTD-diol **4** in an excellent yield (Scheme 3B).

Preparation of further functionalized cage compounds was exemplified using diol **4** as a platform (Scheme 4). A diverse

Scheme 4. Derivatization of the HCTD−Diol



range of functional moieties can be introduced through simple derivatizations of the alcohol groups. For example, azide-and cyano-substituted HCTDs **6** and **7** were efficiently synthesized via S_N2-type approaches,[15] which offers opportunities for subsequent "Click" couplings,[16] or access of the corresponding amino and carbonyl compounds.[17] Diacrylate **8** was prepared simply by acylation of diol **4** using excess acryloyl chloride, which can potentially be used as a distinct cross-linker for polymer synthesis. Heterodiester **9** was synthesized by a two-

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step sequence, offering an approach to access unsymmetrical HCTDs. In particular, two biologically relevant molecules, such as vitamins A and E, can be installed at each end of the HCTD **10**, in which the rigid cage core serves as a unique linker holding the two vitamins in nearly orthogonal directions.

In conclusion, a practical catalytic method to prepare HCTD and 7,12-disubstituted HCTDs was developed.[18] Compared to the traditional alternatives, this method provides improved yield and selectivity, uses commercially available reagents as catalysts, and tolerates air/moisture. In addition, quadracyclane, an isomer of NBD, was discovered for the first time to undergo a similar *endo,cis,endo* cycloaddition in a good yield. Detailed mechanistic investigation to advance our understanding for further reaction improvement is ongoing. Finally, more functionalized HCTDs can be rapidly accessed through derivatization of a diol intermediate. Exploring the potential of these resulting novel scaffolds in biomedical and material applications is now underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00207.

Full experimental and characterization data for all compounds (PDF)

X-ray data for compound **2c** (CIF)

X-ray data for compound **2k** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) In our hand, use of commercially available $Ru_3(CO)_{12}$ provided considerably lower yield (26%) for **2a** than the reported one (66%) in ref 8; however, the possibility that this reaction is highly sensitive to the purity of $Ru_3(CO)_{12}$ cannot be excluded.

(12) Attempts to use C1 or C2-substituted NBDs remain unsuccessful, which is likely due to the steric hindrance of the substrates.

(13) In addition to the HCTD product, several inseparable isomers including *endo* and *exo*-PCTDs were observed in the crude ^{1}H NMR spectra.

(14) For a stepwise conversion of quadracyclane to NBD and then to HCTD, see: Marchand, A. P.; Dave, P. R. *J. Org. Chem.* **1989**, *54*, 2775−2777.

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(18) The mechanistic pathway of forming HCTD remains unclear. Efforts on investigating the catalytic cycle are ongoing.

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