

MIT Open Access Articles

*Functionalized Metalated Cavitands via
Imidation and Late-Stage Elaboration*

The MIT Faculty has made this article openly available. **Please share**
how this access benefits you. Your story matters.

Citation: Zhao, Yinchuan and Swager, Timothy M. "Functionalized Metalated Cavitands via Imidation and Late-Stage Elaboration." European Journal of Organic Chemistry 2015, no. 21 (June 2015): 4593–4597. © 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

As Published: <http://dx.doi.org/10.1002/ejoc.201500714>

Publisher: Wiley Blackwell

Persistent URL: <http://hdl.handle.net/1721.1/110414>

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

Terms of use: Creative Commons Attribution-Noncommercial-Share Alike





Published in final edited form as:

European J Org Chem. 2015 July 1; 2015(21): 4593–4597. doi:10.1002/ejoc.201500714.

Functionalized Metallated Cavitands via Imidation and Late-Stage Elaboration

Dr. Yanchuan Zhao and Prof. Dr. Timothy M. Swager^[a]

Timothy M. Swager: tswager@mit.edu

^[a]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA, <https://swagergroup.mit.edu/>

Abstract

Efficient methods for the preparation of functionalized metallated cavitands are described. Functional groups can be either introduced by an imidation of metal-oxo complexes or by a late-stage elaboration of the imido ligands. By using diversified iminophosphorane ($\text{PPh}_3=\text{NR}$) reagents, π -conjugated pyrene, redox active ferrocene and polymerizable norbornene moieties were successfully introduced. Furthermore, the iodo and alkynyl groups on the imido ligands are capable of undergoing efficient Sonogashira cross-coupling and copper-catalyzed azide alkyne cycloaddition reactions, thereby providing facile access to complex architectures containing metallated cavitands.

Keywords

calixarene; cavitand; late-stage functionalization; supramolecular

Introduction

Metallated cavitands with endohedral ligand affinity are of interest as a result of their selectivity provided by the precise shape of the cavity.^[1] In comparison to related macrocyclic compounds such as calixarenes, resorcinarenes or cyclodextrins, metallated cavitands often possess enhanced binding capabilities that allow for selective molecular recognition in solution.^[1,2] These receptors make use of strong directional metal-ligand interaction and hence metallated cavitands are appealing candidates for directed self assembly and chemosensing.^[1b] In addition, these systems can be considered as metalloenzyme mimics and can display unique catalytic reactivity as a result of the confined environment defined by the cavity.^[3,4] Given these striking characteristics, methods to functionalize metallated cavitands that are adaptable to construct complex architectures are likely to find utility. Direct late-stage functionalization of metallated cavitands mitigates the synthetic uncertainties in preparing complex ligands. However, this approach is rarely

Correspondence to: Timothy M. Swager, tswager@mit.edu.

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Supporting Information (see footnote on the first page of this article): Full experimental procedures, characterization data and ^1H and ^{13}C NMR spectra.

explored as a consequence of the lability of metallated cavitands and difficulties of their isolation from complex mixtures. Herein, we report a strategy to access a diversity of functionalized metallated cavitands through the formation of metal-imido complexes and subsequent elaborations.

Calixarenes represent an important class of macrocyclic compounds with numerous applications in sensing and supramolecular chemistry.^[5] The multiple phenol groups of this scaffold are capable of chelating early transition metals, and hence calixarenes are supporting ligands for metallated cavitands.^[1a,1d,6] Among the metallated cavitands, tungsten (VI) calix[4]arene complexes have displayed considerable utility as a result of their stability and established coordination chemistry.^[7] Although some tungsten calixarene complexes were synthesized and characterized, the method to introduce these scaffolds to other platforms with various functions are limited. The examples of these compounds have largely leveraged established calixarene chemistries that focus on transformations of phenol groups on the lower rim (Scheme 1, a) or electrophilic reaction *para* to the oxygen groups.^[8] Although these methods can be used to create ligating groups to assemble metallated cavitands, greater diversity is possible by adding functionality independent of the calixarene group. To this end we have targeted direct transformations of tungsten-oxo calixarene complexes as a result of their facile preparation and inherent stability. We envisioned that various imido ligands could be directly introduced through imidation reactions and further elaboration of the imido ligands can produce complex functional architectures (Scheme 1, b).

Results and Discussion

Tungsten calixarene imido complexes were previously prepared from air-sensitive W(VI) ($=\text{NR})_2\text{Cl}_2$ or a calixarene tungsten (IV) olefin adduct, both of which are not readily accessible.^[9] We recently found that simple imido ligands can be incorporated by a direct imidation of the tungsten-oxo calixarene complexes using iminophosphorane reagents.^[7c] A diversity of these reagents were directly prepared from the corresponding anilines using $\text{PPh}_3/\text{iPr}_2\text{Et}_2/\text{C}_2\text{Cl}_6$ (Scheme 2, a) or by reacting arylazides with triphenylphosphine (Scheme 2, b).^[10] We found the two *ortho*-methyl groups on the arylimido ligand are crucial to the success of the transformation, and therefore, various functionalities were installed on the *para*-position of the aniline. In addition to enhancing the stability of the corresponding tungsten-imido complex, methyl groups are proposed to impart sufficient nucleophilicity to the iminophosphorane.^[11,12] It is noteworthy that the two methods in Scheme 2 are complimentary. For instance, anilines **1a–d** have low solubility in acetonitrile and the conversion to arylazides is low, whereas the alkynyl group of **1h** is not compatible with the reaction conditions of method (a). To examine the scope of this method, we selected a series of functional groups that are relevant to various applications. For example, long alkyl chains and pyrene moieties are known to display favourable interactions with carbon-based nanomaterials, such as carbon nanotube and graphene (**2a,b**).^[13] Attachment of redox active ferrocene moieties creates electrochemically responsive materials (**2c,d**).^[14] A polymerizable norbornene moiety was examined with the aim to produce polymers appended with metallated cavitands (**2e**). Additionally, to explore the possible elaboration of

the metal cavitands at a late-stage, synthetic handles, such as iodo- and alkynyl groups were installed on the imido ligands (**2f–g**).

With iminophosphorane reagents in hand, we endeavored to prepare functionalized tungsten cavitands. The tungsten-oxo calixarene complex was chosen as a substrate and is readily prepared in situ from *t*-Bu-calixarene and WOCl₄. The subsequent addition of various iminophosphorane reagents (**2a–h**) in refluxing toluene afforded the corresponding tungsten-imido cavitands. As shown in Scheme 3, the tungsten-imido cavitands were produced in good to excellent yields (70–84%) by this one pot procedure. Functional groups, such as alkene (**4e**), alkynyl (**4h**), halide (**4f**, **4g**), and ferrocene (**4c**, **4d**) were tolerated under the reaction conditions, thereby providing access to highly diversified metal cavitands. It is noteworthy that the tungsten cavitands are stable to column chromatography using silica gel and the by product triphenylphosphine oxide is easily separated from the cavitand products. The structures of **4a**, **4c**, and **4d** were unambiguously confirmed by X-ray crystallography (Figure 1).

Bimetallic metal cavitands are appealing building block candidates for constructing self-assembling supramolecular polymers. A molybdenum dinuclear cavitand had been previously reported, its preparation required the use of a dimolybdenum complex precursor.^[15] To enable facile access to dinuclear metallated cavitands, we first prepared iminophosphoranes **2i** and **2g** using method (b) as shown in Scheme 4, and tested their performance in accessing dinuclear cavitands. Although the reaction was sluggish in refluxing toluene at 125 °C, we found that the use of a higher refluxing temperature (155 °C) afforded good yields of dinuclear tungsten cavitands. Both of the linear and the bent cavitands were prepared using this method. It should be mentioned that isolated tungsten-oxo complex (**5**) was employed in this reaction to enable a precise control of the reactant ratio. The X-ray crystal structure confirmed the linear geometry of **4i** (Scheme 4). The well defined coordination chemistry and predictable geometry makes these dinuclear cavitands interesting building blocks to construct supramolecular assemblies with ligands that can fit into the cavitand and coordinate to the tungsten center. We have attempted the construction of supramolecular assembly by mixing **4i** with *N,N'*-(dodecane-1,12-diyl)diformamide. The formation of assembly in both solution and solid state was confirmed by nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy (Figure S1–S5 in SI).

We next examined the feasibility of direct elaboration of the tungsten-imido cavitands. Although these cavitands are thermally stable, they tend to decompose under highly basic or acidic conditions, which poses synthetic challenges for further transformations. We envisioned that the transition-metal catalyzed reactions employing mild reaction conditions might be compatible with these metal cavitands.^[16] However, our initial attempts with palladium-catalyzed Suzuki and Stille coupling reactions failed.^[17] Interestingly, Sonogashira coupling using an organic base was very efficient^[18] and we also found the copper-catalyzed azide alkyne cycloaddition (also known as click reaction) proceeded smoothly in aqueous solution (Scheme 5).^[19] Given the wide applications of these coupling reactions in synthetic chemistry and material science, these late-stage elaborations will allow facile incorporation of metallated cavitands into a variety of platforms.

Considering the availability of diverse methods to modify calixarenes, diversified architectures could be constructed by replacing one of the methylene bridges or by upper-rim functionalization of aromatic rings. To this end, we have introduced a long alkyl group at the *meso* position of calixarene,^[20] and the corresponding product **4m** represents as the first example of metallated calixarene cavitand with a substituent on the methylene bridge. The pyrene-functionalized calixarene was also prepared for potential use as a molecular tweezer.^[21] As illustrated in Scheme 6, these modified calixarenes were smoothly transformed to the corresponding tungsten cavitands under our reaction conditions.

Conclusions

In summary, we have developed an efficient strategy to access functionalized metallated cavitands. The functional groups could be either introduced by a direct imidation of tungsten-oxo calixarene complex using various iminophosphorane reagents or by a late-stage elaboration of the imido ligands of the metallated cavitands. Various moieties, such as π -conjugated pyrene, redox active ferrocene, and polymerizable norbornene were successfully incorporated, demonstrating the broad applicability of the current method. Furthermore, the late-stage elaboration of tungsten cavitands via Sonogashira reaction and copper-catalyzed azide alkyne cycloaddition reaction opens up opportunities for introducing these highly selective endohedral Lewis acidic receptors into various existing platforms. We expect the current strategy will promote the exploitation of new functional materials based on metallated cavitands.

CCDC 1405018 (for **4a**:CH₃CN), 1405019 (for **4c**:CH₃CN), 1405069 (for **4d**:CH₃CN), and 1405020 (for **4i**:2CH₃CN) contain 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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a National Institutes of Health (NIGMS) grant GM095843. Y.Z. acknowledges Shanghai Institute of Organic Chemistry (SIOC), Zhejiang Medicine and Pharmacology for a joint postdoctoral fellowship. The authors thank Dr. Peter Müller for collecting and solving X-ray crystal structure data.

References

1. a) Gramage-Doria R, Armspach D, Matt D. *Coord Chem Rev.* 2013; 257:776–816. b) Frischmann PD, MacLachlan MJ. *Chem Soc Rev.* 2013; 42:871–890. [PubMed: 23188040] c) Lenthall JT, Steed JW. *Coord Chem Rev.* 2007; 251:1747–1760. d) Kotzen N, Vigalok A. *Supramol Chem.* 2008; 20:129–139.
2. a) Gutsche, CD. *Calixarenes Revisited*. Stoddart, JF., editor. RSC; Cambridge: 1998. b) Kobayashi K, Yamanaka M. *Chem Soc Rev.* 2015; 44:449–466. [PubMed: 24938592] c) Li N, Harrison RG, Lamb JD. *J Incl Phenom Macro.* 2014; 78:39–60. d) Chen G, Jiang M. *Chem Soc Rev.* 2011; 40:2254–2266. [PubMed: 21344115] e) Brouwer EB, Enright GD, Ratcliffe CI, Facey GA, Ripmeester JA. *J Phys Chem B.* 1999; 103:10604–10616. f) Del Valle EMM. *Process Biochem.* 2004; 39:1033–1046.

3. a) Rondelez Y, Duprat A, Reinaud O. *J Am Chem Soc.* 2002; 124:1334–1340. [PubMed: 11841303] b) Rebilly JN, Colasson B, Bistri O, Over D, Reinaud O. *Chem Soc Rev.* 2015; 44:467–489. [PubMed: 25319612] c) Over D, Zeng X, Bornholdt C, Marrot J, Reinaud O. *Inorg Chem.* 2013; 52:14089–14095. [PubMed: 24256339] d) Le Poul N, Douziech B, Zeitouny J, Thiabaud G, Colas H, Conan F, Cosquer N, Jabin I, Lagrost C, Hapiot P, Reinaud O, Le Mest Y. *J Am Chem Soc.* 2009; 131:17800–17807. [PubMed: 19916497] e) Liu JG, Naruta Y, Tani F. *Chem – Eur J.* 2007; 13:6365–6378. [PubMed: 17503416] f) Gout J, Višnjevac A, Rat S, Parrot A, Hessani A, Bistri O, Le Poul N, Le Mest Y, Reinaud O. *Inorg Chem.* 2014; 53:6224–6234. [PubMed: 24901070] g) Rebilly JN, Reinaud O. *Supramol Chem.* 2014; 26:454–479.
4. a) Homden DM, Redshaw C. *Chem Rev.* 2008; 108:5086–5130. [PubMed: 18956902] b) Arnott G, Heaney H, Hunter R, Page PCB. *Eur J Org Chem.* 2004; 5126–5134. c) Gramage-Doria R, Armspach D, Matt D, Toupet L. *Chem – Eur J.* 2012; 18:10813–10816. [PubMed: 22829356] d) Leenders SHAM, Gramage-Doria R, de Bruin B, Reek JNH. *Chem Soc Rev.* 2015; 44:433–448. [PubMed: 25340992] e) Armspach D, Matt D, Peruch F, Lutz P. *Eur J Inorg Chem.* 2003:805–809.
5. a) Guo DS, Uzunova VD, Su X, Liu Y, Nau WM. *Chem Sci.* 2011; 2:1722–1734. b) Diamond, McKervey MA. *Chem Soc Rev.* 1996; 25:15–24. c) Yilmaz M, Erdemir S. *Turk J Chem.* 2013; 37:558–585. d) Nimse SB, Kim T. *Chem Soc Rev.* 2013; 42:366–386. [PubMed: 23032718] e) Guo DS, Liu Y. *Chem Soc Rev.* 2012; 41:5907–5921. [PubMed: 22617955]
6. Wieser C, Dieleman CB, Matt D. *Coord Chem Rev.* 1997; 165:93–161.
7. a) Vigalok A, Swager TM. *Adv Mater.* 2002; 14:368–371. b) Vigalok A, Zhu Z, Swager TM. *J Am Chem Soc.* 2001; 123:7917–7918. [PubMed: 11493070] c) Zhao Y, Swager TM. *J Am Chem Soc.* 2013; 135:18770–18773. [PubMed: 24299149] d) Zhao Y, Markopoulos G, Swager TM. *J Am Chem Soc.* 2014; 136:10683–10690. [PubMed: 25051051] e) Xu B, Swager TM. *J Am Chem Soc.* 1993; 115:1159–1160. f) Corazza F, Floriani C, Chiesi-Villa A, Rizzoli C. *Inorg Chem.* 1991; 30:4465–4468. g) Arduini A, Massera C, Pochini A, Secchi A, Ugozzoli F. *New J Chem.* 2006; 30:952–958. h) Mongrain P, Douville J, Gagnon J, Drouin M, Decken A, Fortin D, Harvey PD. *Can J Chem.* 2004; 82:1452–1461. i) Xu B, Swager TM. *Angew Chem Int Ed.* 1996; 35:2094–2097.
8. a) Sliwa W, Deska M. *Arkivoc.* 2011:496–551. b) Jain VK, Kanaiya PH. *Russ Chem Rev.* 2011; 80:75–102.
9. a) Radius U, Attner J. *Eur J Inorg Chem.* 1999:2221–2231. b) Guillemot G, Solari E, Floriani C, Rizzoli C. *Organometallics.* 2001; 20:607–615.
10. a) Zeng F, Alper H. *Org Lett.* 2010; 12:1188–1191. [PubMed: 20184348] b) Barral K, Moorhouse AD, Moses JE. *Org Lett.* 2007; 9:1809–1811. [PubMed: 17391043] c) Fresneda PM, Molina P. *Synlett.* 2004:1–17.
11. Tungsten calixarene phenylimido complex is known to be in equilibrium between monomer and dimer in solution. See ref 9b.
12. Axtell JC, Schrock RR, Müller P, Smith SJ, Hoveyda AH. *Organometallics.* 2014; 33:5342–5348. [PubMed: 25328268]
13. a) Zhao YL, Stoddart JF. *Acc Chem Res.* 2009; 42:1161–1171. [PubMed: 19462997] b) Chen RJ, Zhang Y, Wang D, Dai H. *J Am Chem Soc.* 2001; 123:3838–3839. [PubMed: 11457124]
14. a) Sun R, Wang L, Yu H, Abidin Z-u, Chen Y, Huang J, Tong R. *Organometallics.* 2014; 33:4560–4573. b) Szillat F, Schmidt BVKJ, Hubert A, Barner-Kowollik C, Ritter H. *Macromol Rapid Comm.* 2014; 35:1293–1300. c) Wang WY, Ma NN, Sun SL, Qiu YQ. *Organometallics.* 2014; 33:3341–3352.
15. Gibson VC, Redshaw C, Clegg W, Elsegood MRJ. *Chem Commun.* 1998:1969–1970.
16. Negishi, E-i. *J Organomet Chem.* 2002; 653:34–40.
17. a) Miyaura N, Suzuki A. *Chem Rev.* 1995; 95:2457–2483. b) Espinet P, Echavarren AM. *Angew Chem Int Ed.* 2004; 43:4704–4734.
18. a) Chinchilla R, Nájera C. *Chem Rev.* 2007; 107:874–922. [PubMed: 17305399] b) Chinchilla R, Nájera C. *Chem Soc Rev.* 2011; 40:5084–5121. [PubMed: 21655588]
19. a) Liang L, Astruc D. *Coord Chem Rev.* 2011; 255:2933–2945. b) Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. *Angew Chem Int Ed.* 2002; 41:2596–2599.
20. Scully PA, Hamilton TM, Bennett JL. *Org Lett.* 2001; 3:2741–2744. [PubMed: 11506623]

21. a) Colquhoun HM, Zhu Z, Cardin CJ, Gan Y, Drew MGB. J Am Chem Soc. 2007; 129:16163–16174. [PubMed: 18047339] b) Xu Z, Spring DR, Yoon J. Chem – An Asian J. 2011; 6:2114–2122.

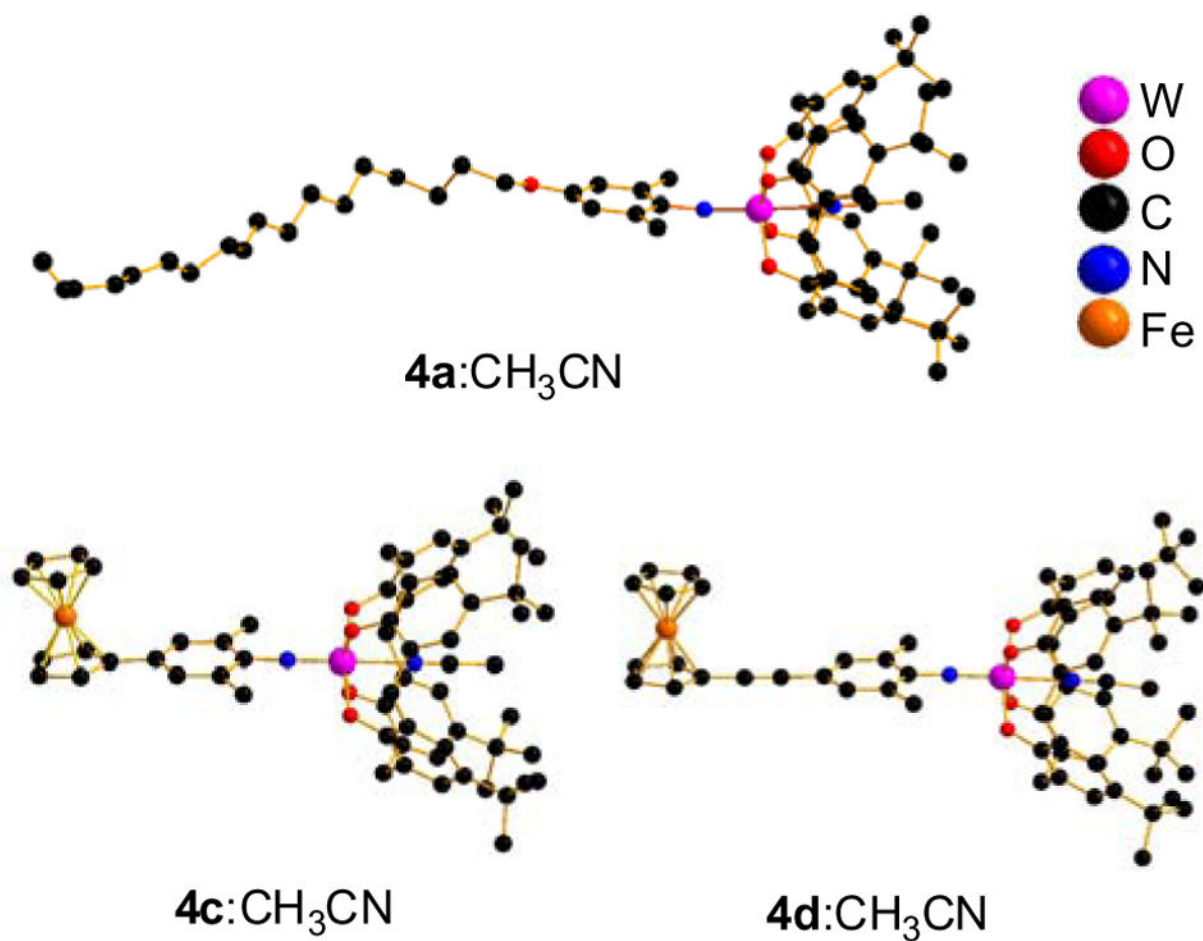
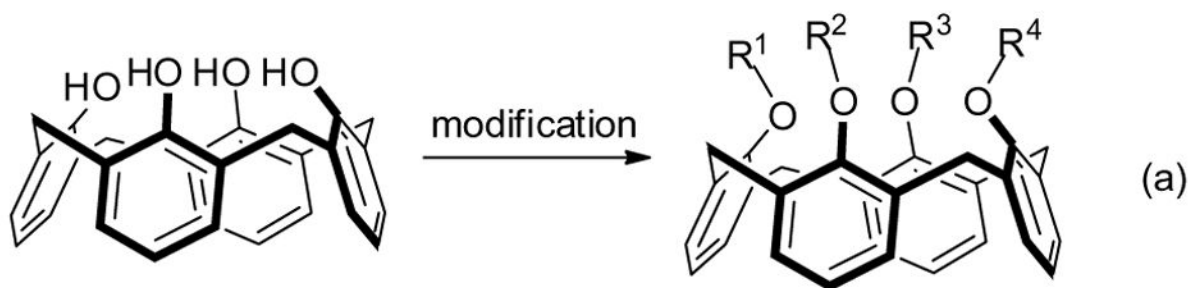
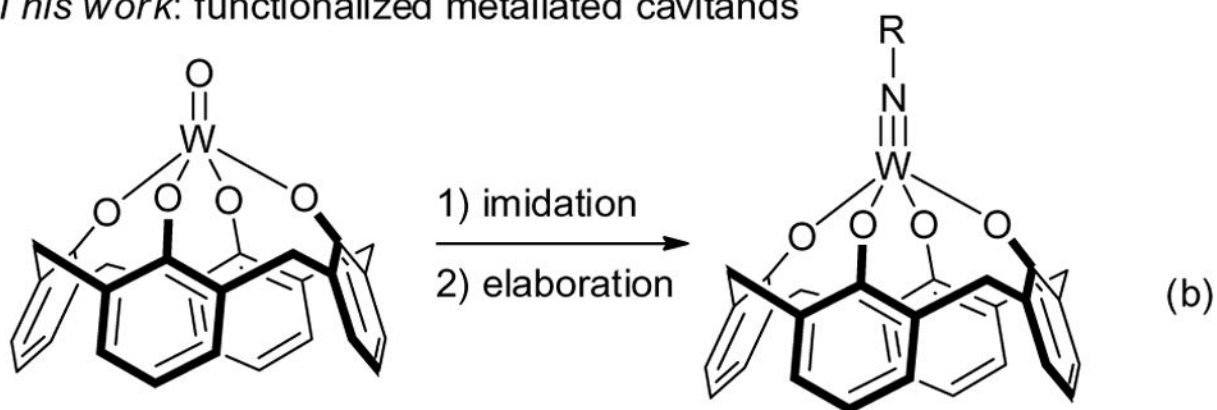


Figure 1.
X-ray crystal structures of tungsten cavitands.

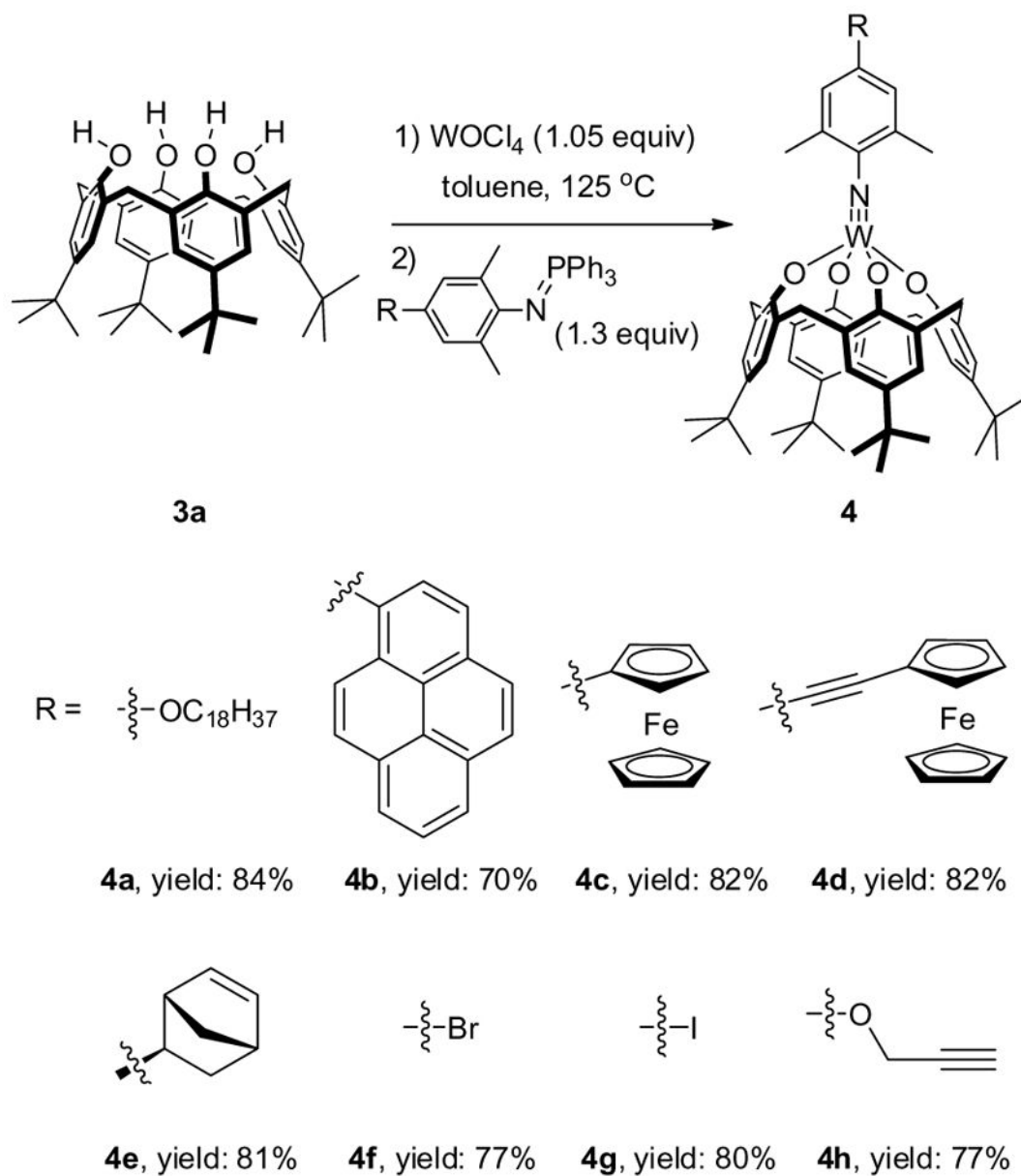
Previous work: functionalized calixarenes



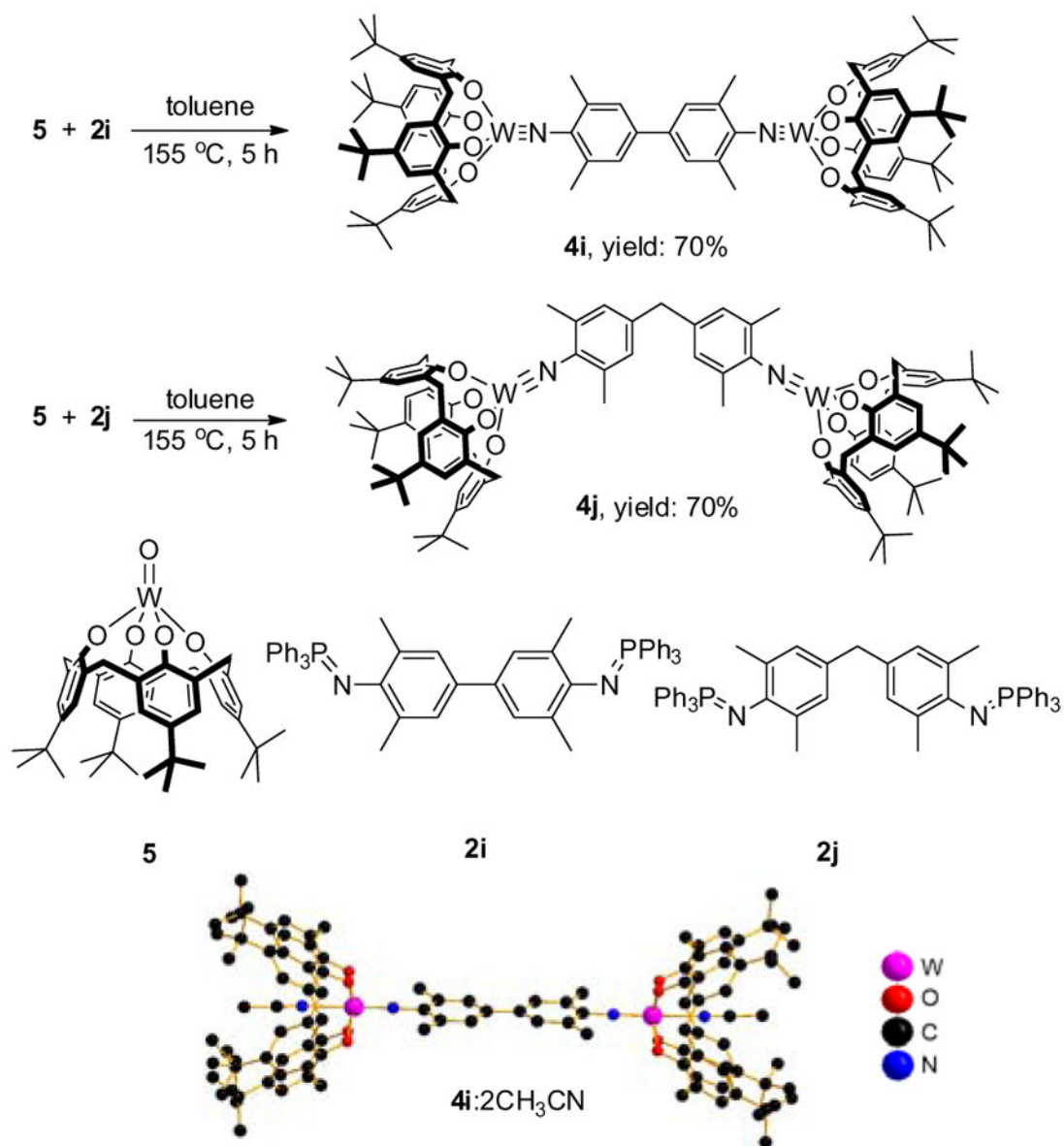
This work: functionalized metallated cavitands



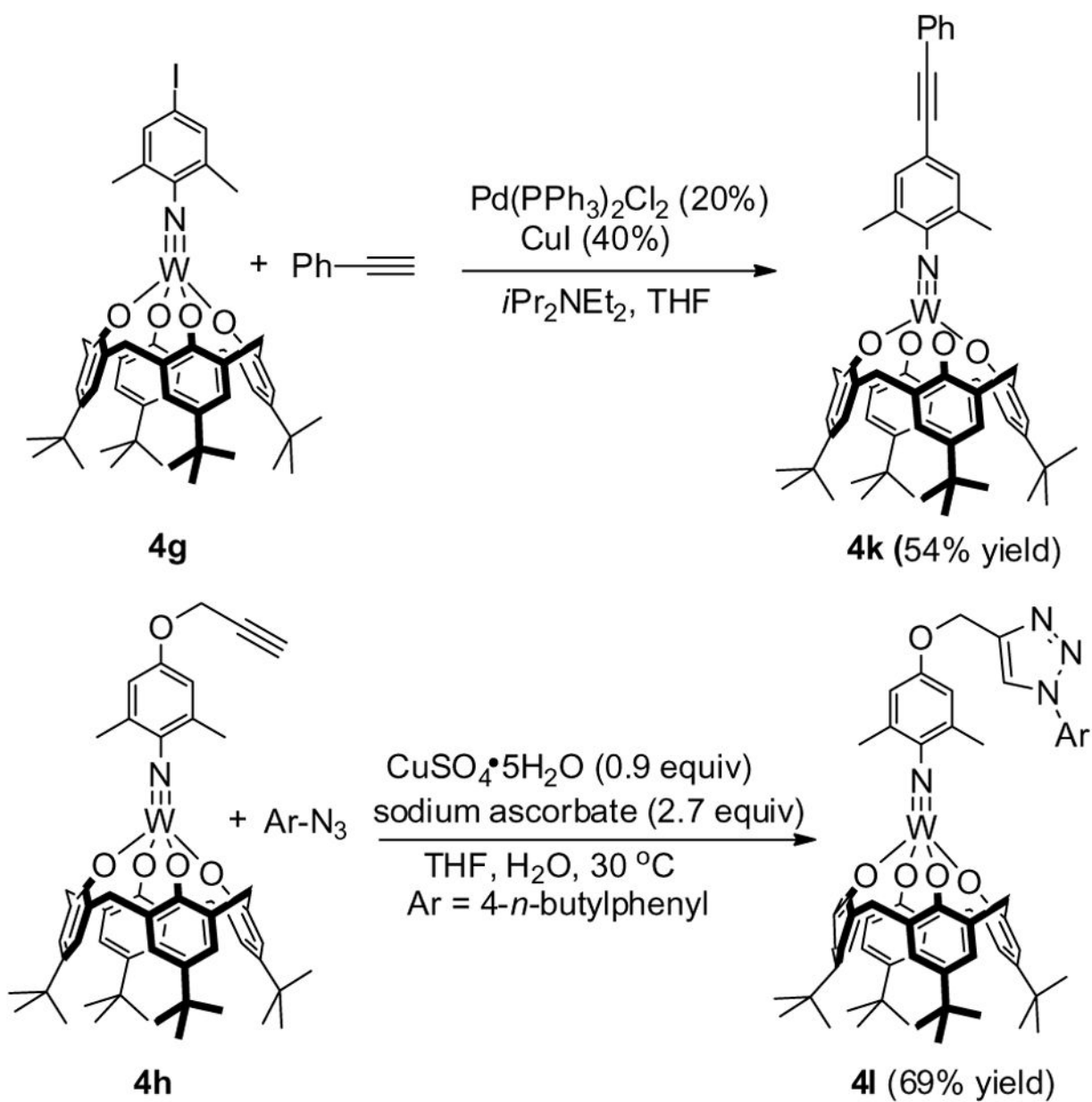
Scheme 1.
Functionalized calixarenes and metallated cavitands.

**Scheme 3.**

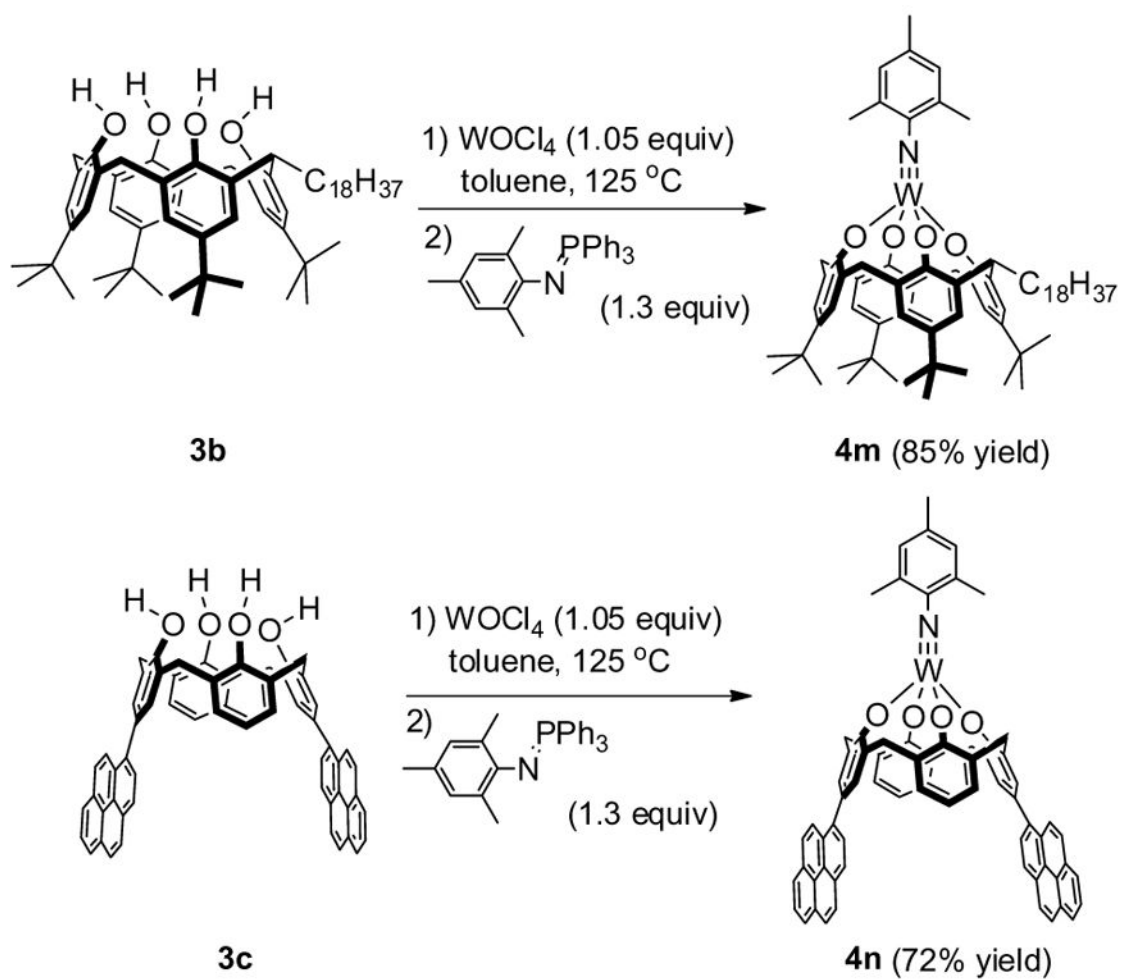
Preparation of functionalized tungsten cavitands through imidation.



Scheme 4.
Preparation of dinuclear tungsten cavitands and X-ray crystal structure of **4i**:2CH₃CN.



Scheme 5.
Late-stage elaboration of tungsten-imido cavitands.



Scheme 6.
Late-stage elaboration of tungsten imido cavitands.