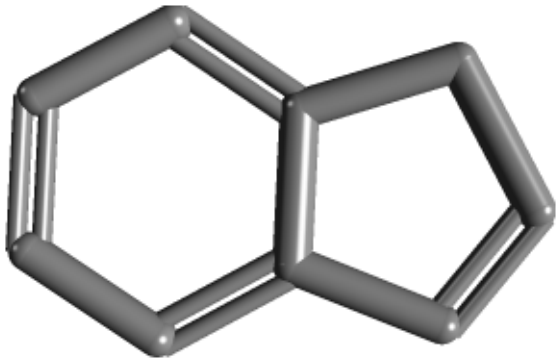
UNIVERSITAT ROVIRA i VIRGILI

Synthesis of Indenes and Indanes by Gold(I)-Catalyzed Decarbenation

Xiang Yin



DOCTORAL THESIS
2018

Xiang Yin

Synthesis of Indenes and Indanes by Gold(I)-Catalyzed Decarbenation

Doctoral Thesis

Supervised by Prof. Antonio M. Echavarren

Institute of Chemical Research of Catalonia (ICIQ)

UNIVERSITAT ROVIRA i VIRGILI

Tarragona 2018

UNIVERSITAT ROVIRA I VIRGILI
SYNTHESIS OF INDENES AND INDANES BY GOLD(I)-CATALYZED DECARBENATION
Xiang Yin

Institut Català d'Investigació Química

UNIVERSITAT ROVIRA I VIRGILI
DEPARTAMENT DE QUIMICA ANALITICA I QUIMICA ORGANICA
C/ Marcel.lí Domingo s/n
Campus Sescelades
43007 Tarragona

I STATE that the present study, entitled "*Synthesis of Indenes and Indanes by Gold(I)-Catalyzed Decarbenation*", presented by Xiang Yin for the award of the degree of Doctor, has been carried out my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, October 8th, 2018

Doctoral Thesis Supervisor

Prof. Antonio M. Echavarren Pablos

To my wife

Acknowledgements

The research documented in this Doctoral Thesis was carried out at the Institute of Chemical Research of Catalonia (ICIQ) under the supervision of Prof. Antonio M. Echavarren. I would like to express my sincere gratitude to Antonio, for his continuous support during the last four years, for his patience, motivation, and immense knowledge.

I would like to thank Sònia Gavaldà. I cannot imagine how can I and my family survive in Spain without her help.

I would also like to thank Imma Escofet for her wonderful efforts, which allowed me to dedicate most of my time on research.

I would like to thank to Dr. Guangwu Zhang, Mauro Mato and Giusseppe Zuccarello, for the pleasant collaboration in some of my projects.

I would like to thank all of my labmates, especially from 2.2, Dr. Bart Herlé, Dr. Oscar Pablo, Dr. Araceli Fernández, Dr. Beatrice Ranieri, Dr. Masha Kirillova, Dr. Hanna Bruss, Dr. Fedor Miloserdov, Dr. Xiao-Li Pei, Giuseppe Zuccarello, Margherita Zanini, Ulysse Caniparoli, Helena Armengol who contributed to give this laboratory a friendly and happy atmosphere.

I would like to thank Dr. Bart Herlé, Dr. Fedor Miloserdov for discussing basic concepts in catalysis, and Sofia Ferrer, Maria Elena de Orbe for valuable suggestion and discussions in DFT calculations.

I would like to thank Dr. Yahui Wang, Zhouting Rong, Xin Huang, Dr. Jinming Yang, Dr. Xiaoli Pei, Dr. Guangwu Zhang, Dr. Zhaofeng Wang, Dr. Xiangwei Liu, Dr. Xueqiang Wang, Dr. Liyin Jiang, Shaofei Ni and the rest of Chinese community in ICIQ for the suggestion and discussion in chemistry and help of my life in Tarragona.

I would like to thank the football, basketball and pingpong players in ICIQ for giving me wonderful breaks.

In addition, I would like to thank the ICIQ Research Support team for their availability and their help during my Thesis.

Thanks to all of the people who gave me help in these years in Tarragona.

Finally, I would like to end up by thanking the most important people: my parents, my wife and my daughters.

The research work developed in the present PhD thesis was carried out with the support of the Spanish Ministry of Economy and Competitiveness (MINECO, projects CTQ2013-42106-P and CTQ2016-75960-P MINECO/AEI/FEDER, UE; FPU grant to S.F., and Severo Ochoa Excellence Accreditation 2014-2018 (SEV-2013-0319)), the CERCA Program/Generalitat de Catalunya, the European Research Council (Advanced Grant No. 321066), the Agency of Management of University and Research Grants (AGAUR, 2014 SGR 818 and 2017 SGR 1257), and the ICIQ Foundation.

At the moment of writing this thesis, the results presented herein have resulted in the following publication:

Gold(I)-Catalyzed Synthesis of Indenes and Cyclopentadienes: Access to (±)-Laurokamurene B and the Skeletons of the Cycloaurenones and Dysiherbols

Yin, X.; Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2017**, *56, 14591-14595*.

Table of contents

Prologue

The manuscript of this Doctoral Thesis has been divided into four main parts: a general introduction and three research chapters. Each chapter contains five sections, including a detailed specific introduction on the research topic, the objectives, the discussion of the results obtained, the conclusions and finally the experimental section. Compounds are numbered independently in each chapter.

The **general introduction** provides an overview of the properties, the applications and the synthesis of indenes and indanes, followed by description of basic concepts and methods for the generation of gold(I) carbenes. Finally, the achievements of gold(I) carbenes generated by retro-Buchner reaction of 7-substituted cycloheptatrienes are summarized.

Chapter 1 discusses the formal (3+2) cycloaddition between allenes and aryl gold(I) carbenes generated by a retro-Buchner reaction of 7-substituted 1,3,5-cycloheptatrienes led to indenes. Part of this work has been described in *Angew. Chem. Int. Ed.* **2017**, *56,* 14591-14595.

Chapter 2 presents the progress towards the total synthesis of cycloaurenones and dysiherbols. Part of this work has also been described in *Angew. Chem. Int. Ed.* **2017**, *56,* 14591-14595.

Chapter 3 describes "Gold carbenes generated from 7-substituted 1,3,5-cycloheptatrienes undergo intramolecular C(sp3)-H functionalization: Reaction development and Mechanistic investigations". This work has not been published yet.

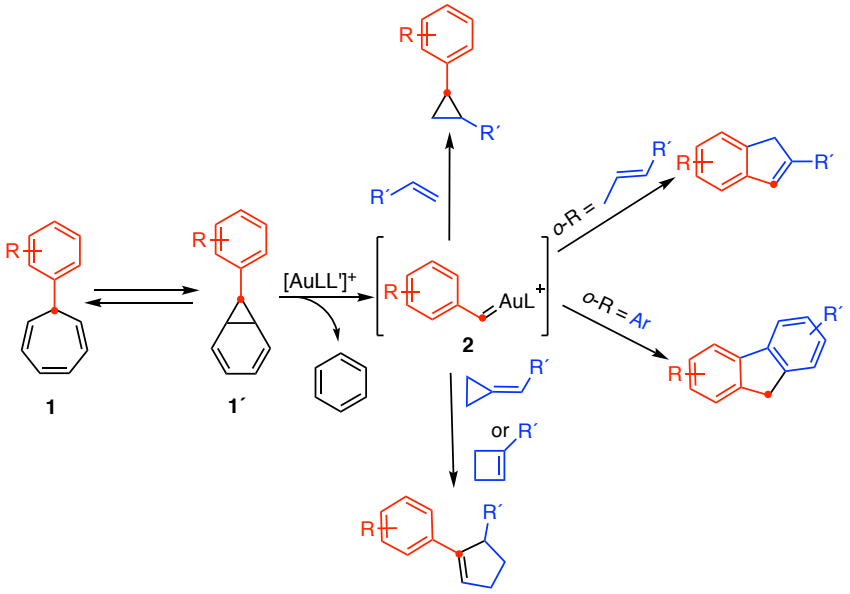
List of Abbreviations and Acronyms

In this thesis, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendations published in the "Guideliness for Authors" of *Journal of Organic Chemistry*. Additional abbreviations and acronyms used in this manuscript are referenced in the list below:

CHT	Cycloheptatriene
NCD	Norcaradiene
APCI	Atmospheric Pressure Chemical Ionization
GOESY	Gradient Enhanced Nuclear Overhauser Effect Spectroscopy
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
L	Ligand
GC-MS	Gas Chromatography-Mass Spectrometry
*t*BuXPhos	2-(di-*tert*-Butylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl-1,1′-biphenyl

Abstract

7-Substituted 1,3,5-cycloheptatrienes **1** (CHT substrates) react with cationic gold(I) catalysts to give gold(I) carbenes (**I**) by a retro-Buchner reaction in which two C-C bonds in norcaradienes **1´** (NCD intermediates) are cleaved by Au(I). This novel strategy obviates the use of shock-sensitive diazo derivatives and generates reactive metal carbenes *in situ* which can undergo further diverse transformations, such as cyclopropanation of external and tethered alkenes and intramolecular Friedel-Crafts-type reactions (Scheme 1). To broaden the range of synthetic methods and applications available for these useful intermediates, in the present Doctoral Thesis we have developed new transformations based on the retro-Buchner reaction leading to the rapid construction of important frameworks and have studied the mechanism of one of the new reactions experimentally and by DFT calculations.



Scheme 1. Transformations of gold (I) carbene generated by retro-Buchner reaction of cycloheptatrienes.

A new gold(I)-catalyzed formal (3+2) cycloaddition reaction between terminal allenes and aryl gold(I) carbenes resulting from CHT substrates was developed. This novel synthetic methodology provides ready access to a variety of highly substituted indenes which are important motifs present in many biologically relevant natural products, and are building blocks in medical chemistry, organic synthesis, organometallic chemistry, and in the field of materials science. A mechanism is proposed involving electrophilic addition of gold carbene to central carbon of the allene leading to an allylic carbocation, followed by intramolecular electrophilic aromatic substitution of this carbocation intermediate, rearomatization, protonolysis of Au-C bond, and migration of *exo*-alkene to give final product.

Cycloaurenones A–C feature a *cis*-decalin moiety, whereas the dysiherbols show *trans*-fusion of the A/B rings. These natural products also differ in their absolute configuration. These compounds are biogenetically related to other natural products isolated from sponges, such as (+)-smenoqualone, ilimaquinone, and smenospongin. Many of these natural products display antimicrobial, anti-HIV, antiinflamatory, antiproliferative, and antisecretory activities. To date, no approach towards the synthesis of the cycloaurenones and the dysiherbols has been reported. As a first approach to their synthesis, the formal (3+2) cycloaddition together with a radical cyclization have been applied to construct the tetracyclic core. Efforts to the total synthesis of cycloaurenones and dysiherbols are undergoing.

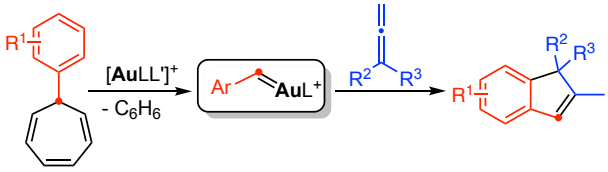
We also developed a novel synthesis of indanes based on the intramolecular insertion of gold(I) carbenes generated by retro-Buchner into C(sp^3)-H bonds. Deuterium-labeling experiments support the hypothesis that the C(sp^3)-H functionalization process takes place through an intramolecular carbon-hydrogen bond transfer to the gold(I) carbene intermediate, while our measured kinetic isotope effect and DFT calculations were consistent with the three-

centered concerted mechanism proposed for these C-H insertions.

General Objectives

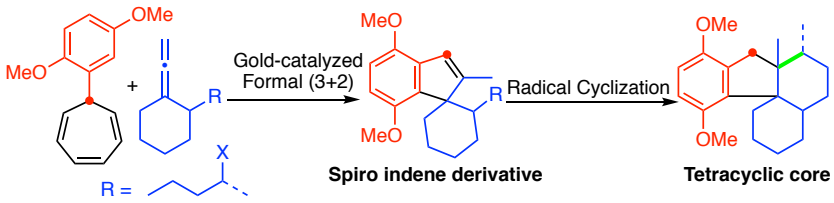
The general objectives of this Doctoral Thesis were exploring the new reactivities of gold(I) carbenes generated by retro-Buchner reaction of 7-substituted 1,3,5-cyclopetatrienes to develop new synthetic methods for the synthesis of useful frameworks and natural products. In parallel, we decided to investigate the mechanism of the new reactions. In particular, our efforts aimed at the following objectives:

Gold(I) carbenes generated by retro-Buchner reaction of 7-aryl-substituted-1,3,5-cycloheptatrienes have emerged as one carbon synthons for the electrophilic cyclization reactions with different alkenes. On the other hand, allenes have been shown to participate in a variety of cycloaddition reactions acting as a 2C or 3C components depending on the substituents. We postulated that gold(I) carbenes raising from 7-aryl-substituted-1,3,5-cycloheptatrienes could be trapped by the π system of allenes leading to highly substituted indene skeletons (Scheme 2).



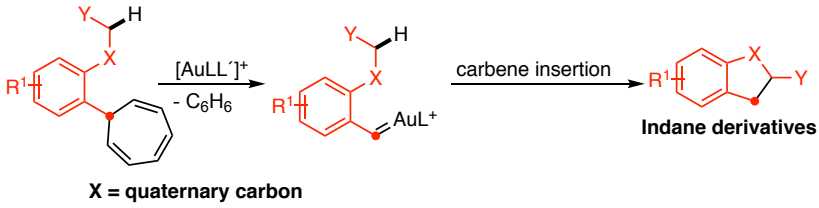
Scheme 2. Proposed cycloaddition of gold(I) carbenes with allenes.

Since a useful strategy for the synthesis of diverse spiro-indene derivatives was developed *via* gold-catalyzed formal (3+2) cyclization of gold carbenes with 1,1-disubstituted terminal allenes, we considered applying this novel cycloaddition reaction together with a radical cyclization as key steps to construct the tetracyclic core structure of cycloaurenones and dysiherbols (Scheme 3).



Scheme 3. Proposal for the synthesis of tetracyclic core of cycloaurenones and dysiherbols.

We also explored the reactivity of the gold(I) carbenes generated from 7-aryl-substituted-1,3,5-cycloheptatrienes in intramolecular C(sp^3)-H functionalization (Scheme 4).



Scheme 4. Proposal for the intramolecular C-H insertion of gold(I) carbenes generated from cycloheptatrienes.

General Introduction

Indenes

Introduction of indene

Indene is a bicyclic hydrocarbon composed of a benzene ring fused with a cyclopentene ring. The double bond of indene can undergo further transformation to give rise to diverse useful building blocks. Thus, hydroxylation reaction can give access to (1*R*,2*S*)-indandiol, an important intermediate in the synthesis of indinavir sulfate (t), a protease inhibitor used in the treatment of AIDS.[1] In analogy to styrene, indene undergoes polymerization. Indeed, the principal industrial use of indene is in the production of indene-coumarone thermoplastic resins by means of polymerization of indene and coumarone.[2] Indene can be thermally isomerized to less stable 2*H*-indene (isoindene), which can act as a diene in Diels-Alder reactions.[3] Indenyl anion generated by deprotonation of indene can be used to prepare indenyl complexes by reactions with metal halides and be trapped by ketones or aldehydes giving rise to benzofulvenes (Figure GI-1).[4]

1. Dorsey, B. D.; Levin, R. B.; Mcdaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I. W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, 37, 3443-3451.
2. Li, G. S.; Rosen, I. **1978**, US05909323.
3. (a) Trost, B. M. *J. Am. Chem. Soc*. **2003**, *125*, 1064–1071. (b) He, Y.; Chen, H.; Hou, J.; Li, Y. *J. Am. Chem. Soc*. **2010**, *132*, 1377-1382. (c) Rigby, S. S.; Stradiotto, M.; Brydges, S.; Pole, D. L.; Top, S.; Bain, A. D.; McGlinchey, M. J. *J. Org. Chem.* **1998**, *63*, 3735-3740.
4. Pauson, P.; Wilkenson, G. *J. Am. Chem. Soc*. **1954**, *76*, 2024-2026.

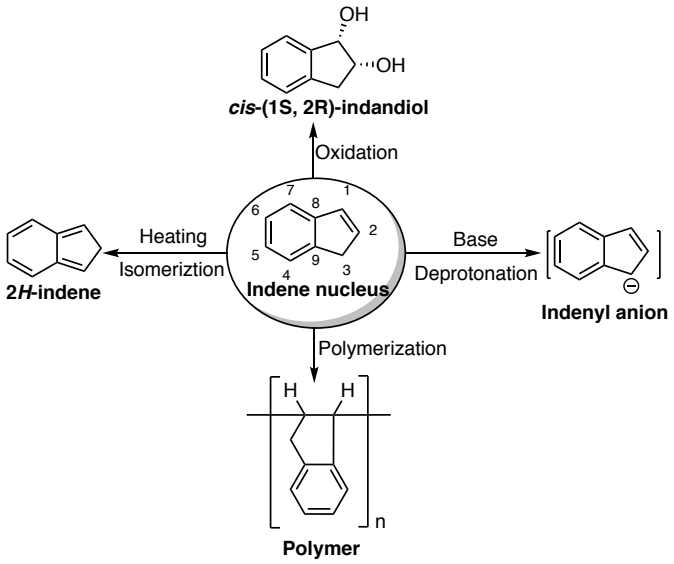


Figure GI-1. Reactivity of indenes.

Indenes are reported to be structural motifs found in many natural products such as taiwaniaquinol,[5] cyanosporaside A/B,[6] biological active molecules such as antipruritic dimetindene,[7] anti-inflammatory sulindac,[8] aldosterone synthase inhibitors,[9] and antitubercular agents[10]. Some of them are market-leading drugs and/or key intermediates for the synthesis of natural products, pharmaceuticals

5. (a) Deng, J.; Zhou, S.; Zhang, W.; Li, J.; Li, R.; Li, A. *J. Am. Chem. Soc*. **2014**, *136*, 8185-8188. (b) Chang, C.; Chien, S.-C.; Lee, S.; Kuo, Y.-H. *Chem. Pharm. Bull*. **2003**, *51*, 1420-1422.
6. (a) Yamada, K.; Lear, M. J.; Yamaguchi, T.; Yamashita, S.; Gridnev, I. D.; Hayashi, Y.; Hirama, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13902-13906. (b) Lane, A. L.; Nam, S.-J.; Fukuda, T.; Yamanaka, K.; Kauffman, C. A.; Jensen, P. R.; Fenical, W.; Moore, B. S. *J. Am. Chem. Soc.* **2013**, *135*, 4171-4174. (c) Jensen, P. R.; Williams, P. G.; Oh, D.-C.; Zeigler, L.; Fenical, W. *Appl. Environ. Microbiol*. **2007**, *73*, 1146-1152.
7. (a) Douros, A.; Bronder, E.; Andersohn, F.; Klimpel, A.; Thomae, M.; Sarganas, G.; Kreutz, R.; Garbe, E. *Br. J. Clin. Pharmacol.* **2015**, *79*, 988-999. (b) Hefner, G.; Stieffenhofer, V.; Gabriel, S.; Palmer, G.; Mueller, K.-M.; Roeschke, J.; Hiemke, C. *Eur. J. Clin. Pharmacol*. **2015**, *71*, 165-172.
8. (a) Femia, A. P.; Soares, P. V.; Luceri, C.; Lodovici, M.; Giannini, A.; Caderni, G. *BMC Cancer* **2015**, *15*, 15:611. (b) Prade, E.; Barucker, C.; Sarkar, R.; Althoff-Ospelt, G.; Lopez, D. A.; Juan, M.; Hossain, S.; Zhong, Y.; Multhaup, G.; Reif, B. *Biochemistry* **2016**, *55*, 1839-1849. (c) Raz, A. *Biochem. Pharmacol*. **2002**, *63*, 343-347.
9. Voets, M.; Antes, I.; Scherer, C.; Vieira, U. M.; Biemel, K.; Oberwinkler, S. M.; Hartmann, R. W. *J. Med. Chem.* **2006**, *49*, 2222-2231.
10. (a) Kahlon, A. K.; Negi, A. S.; Kumari, R.; Srivastava, K. K.; Kumar, S.; Darokar, M. P.; Sharma, A. *Appl. Microbiol. Biotechnol.* **2014**, *98*, 2041-2051. (b) Chanda, D.; Saikia, D.; Kumar, J. K.; Thakur, J. P.; Agarwal, J.; Chanotiya, C. S.; Shanker, K.; Negi, A. S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3966-3969.

and other bioactive compounds, as well as functional materials [11] and metallocene complexes for olefin polymerization (Figure GI-2).[12]

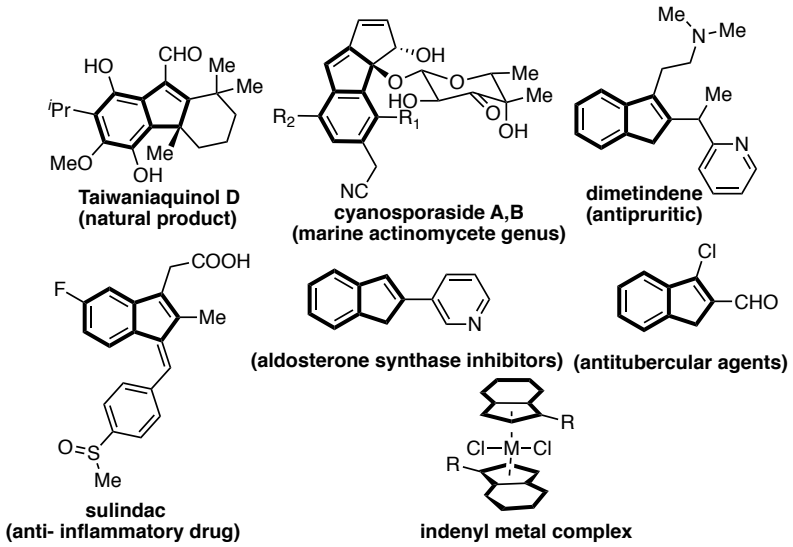


Figure GI-2. Indene moieties in chemistry.

Synthesis of indenes

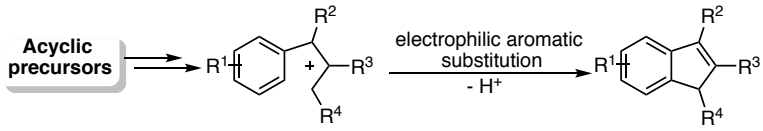
The classical approaches to the synthesis of the indene nucleus include different intramolecular electrophilic substitution reactions, cyclization induced by a nucleophilic attack to a suitable functional group (such as the carbonyl), and cyclization involving metal-catalyzed processes.[13] In next sections, the recent development on the synthesis of indenes by cyclization of acyclic precursors, ring contraction and expansion methods as well as by approaches based on

11. (a) Grimsdale, A. C.; Mullen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5592-5629. (b) Zhu, X.; Tsuji, H.; Nakabayashi, K.; Ohkoshi, S.-I.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 16342-16345. (c) Hu, P.; Lee, S.; Herng,T. S.; Aratani, N.; Gonçalves,T. P.; Qi, Q.; Shi, X.; Yamada, H.; Huang, K.-W.; Ding, J.; Kim, D.; Wu, J. *J. Am. Chem. Soc.* **2016**, *138*, 1065-1077.
12. (a) Alt, H. G.; Koppl, A. *Chem. Rev.* **2000**, *100*, 1205-1222. (b) Ren, S.; Igarashi, E.; Nakajima, K.; Kanno, K.; Takahashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 7492-7493. (c) Zargarian, D. *Coord. Chem. Rev.* **2002**, *233*, 157-176. (d) Leino, R.; Lehmus, P.; Lehtonen, A. *Eur. J. Inorg. Chem.* **2004**, *2004*, 3201-3222.
13. (a) Ivchenko, N. B.; Ivchenko, P. V.; Nifant'ev, I. E. *Russ. J. Org. Chem.* **2000**, *36*, 609-637. (b) Enders, M. Baker, R. W. *Curr. Org. Chem.* **2006**, *10*, 937-953. (c) Gabriele, B.; Mancuso, R.; Veltri, L.; *Chem. Eur. J.* **2016**, *22*, 5056-5094.

subsequent functionalization of cyclic precursors will be briefly reviewed.

Cyclization of acyclic precursors

Intramolecular Friedel–Crafts-type reactions have been widely used for the synthesis of indene derivatives. Ring closure occurs by way of electrophilic aromatic substitution of diverse acyclic precursors, such as allyl alcoholic and propargyl alcoholic derivatives,[14] diene and allene derivative,[15] α, β-unsaturated carbonyl derivatives,[16] benzylic derivatives[17] and other substrates (Scheme GI-1).[18]



Scheme GI-1. Electrophilic aromatic substitution of acyclic precursors for the synthesis of indenes.

14. (a) Guo, S.; Liu, Y.; *Org. Biomol. Chem.* **2008**, *6*, 2064-2070. (b) Wang, J.; Zhang, L.; Jing, Y.; Huang, W.; Zhou, X. *Tetrahedron Lett.* **2009**, *50*, 4978-4982. (c) Zhang, J.; Zhang, J.; Fang, K.; Shu, G.; Xie, M. *Chin. J. Org. Chem.* **2012**, *32*, 1533-1538. (d) Shanmugam, P.; Rajasingh, P. *Chem. Lett.* **2005**, *34*, 1494-1495. (e) Dethe, D. H.; Murhade, G. *Org. Lett.* **2013**, *15*, 429-431. (f) Reddy, B. V.; Reddy, B. B.; Rao, K. V. R.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 5697-5700. (g) Sousa, C.M.; Berthet, J.; Delbaere, S.; Coelho, P. J. *J. Org. Chem.* **2014**, *79*, 5781-5786. (h) Egi, M.; Shimizu, K.; Kamiya, M.; Ota, Y.; Akai, S. *Chem. Commun.* **2015**, *51*, 380-383. (i) Shchukin, A.O.; Vasil'ev, A.V. *Russ. J. Org. Chem.* **2007**, *43*, 784-786. (j) Muthusamy, S.; Sivaguru, M. *Org. Lett.* **2014**, *16*, 4248-4251.

15. (a) Eom, D.; Park, S.; Park, Y.; Ryu, T.; Lee, P. H. *Org. Lett.* **2012**, *14*, 5392-5395. (b) Sun, X.; Izumi, K.-J.; Hu, C.-Q.; Lin, G.-Q. *Chin. J. Org. Chem.* **2006**, *24*, 430-434. (c) Yamazaki, S.; Yamamoto, Y.; Fukushima, Y.; Takebayashi, M.; Ukai, T.; Mikata, Y. *J. Org. Chem.* **2010**, *75*, 5216-5222. (d) Yamakazi, S.; Fukushima, Y.; Ukai, T.; Tatsumi, K. Ogawa, A. *Synthesis* **2012**, 2155-2161.

16. (a) Singh, P. P.; Reddy, P. B.; Sawant, S. D.; Koul, S.; Taneja, S. C.; Kumar, H. M. S. *Tetrahedron Lett.* **2006**, *47*, 7241-7243; (b) Reddy, P. B.; Singh, P. P.; Sawant, S. D.; Koul, S.; Taneja, S. C.; Kumar, H. M. S. *Arkivok* **2006**, *xiii*, 142-146. (c) Womack, G. B.; Angeles, J. G.; Fanelli, V. E.; Indradas, B.; Snowden, R. L.; Sonnay, P. *J. Org. Chem.* **2009**, *74*, 5738-5741. (d) Rulev, A.Y.; Ushakov, I. A.; Nenajdenko, V. G. *Tetrahedron* **2008**, *64*, 8073-8077. (e) Kheira, H.; Li, P.; Xu, J. *J. Mol. Catal. A* **2014**, *391*, 168-174. (f) Vasil'ev, A. V.; Shchukin, A. O. *Russ. J. Org. Chem.* **2006**, *42*, 1239-1241. (g) Dethe, D. H.; Murhade, G. M. *Chem. Commun*. **2013**, *49*, 8051-8053.

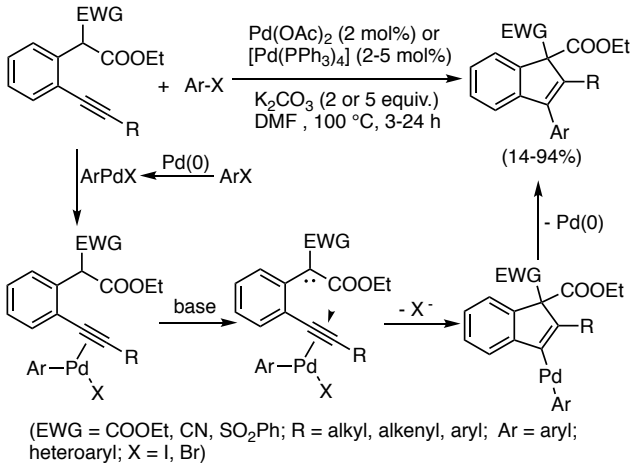
17. (a) Bu, X.; Hong, J.; Zhou, X. *Adv. Synth. Catal.* **2011**, *353*, 2111-2118. (b) Liu, C.-R.; Yang, F.-L.; Jin, Y.-Z.; Ma, X.-T.; Cheng, D.-J.; Li, N.; Tian, S.-K. *Org. Lett.* **2010**, *12*, 3832-3835. (c) Chen, Y.; Li, K.; Liu, X.; Zhu, J.; Chen, B. *Synlett* **2013**, *24*, 130-134.

18. (a) Basavaiah, D.; Reddy, B. S.; Lingam, H. *Tetrahedron* **2013**, *69*, 1994-2003. (b) Boblak, K. N.; Klumpp, D. A. *J. Org. Chem.* **2014**, *79*, 5852-5857.

Alternatively, the construction of indene skeleton can be carried out via transition metal-catalyzed intramolecular annulation or inter/intramolecular cascade protocols, such as rhodium-catalyzed annulation,[19] palladium-catalyzed carboannulation,[20] nickel- or cobalt-catalyzed carbocyclization[21] and gold(I)-catalyzed intramolecular carboalkoxylation.[22]

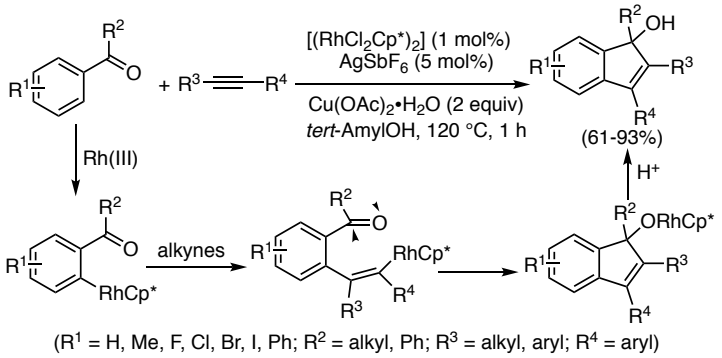
Thus, the oxidative addition of the aryl halide to Pd(0) to give an Ar-Pd-X complex, followed by intramolecular nucleophilic attack of the carbonucleophile to the triple bond coordinated to Ar-Pd-X gives rise to indenes (Scheme GI-2).[20b]

19. (a) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2011**, *50*, 4169-4172. (b) Huang, X.-C.; Yang, X.-H.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* **2014**, *79*, 1025-1031. (c) Shi, X.-Y.; Li, C.-J. *Org. Lett.* **2013**, *15*, 1476-1479.
20. (a) Bi, H.-P.; Liu, X.-Y.; Gou, F.-R.; Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 3527-3529. (b) Zhang, D.; Liu, Z.; Yum, E. K.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 251-262. (c) Zhang, D. H.; Yum, E. K.; Liu, Z. J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4963-4966. (d) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089-4092. (e) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545-3546.
21. (a) Deng, R.; Sun, L.; Li, Z. *Org. Lett.* **2007**, *9*, 5207-5210. (b) Rayabarapu, D. K.; Yang, C.-H.; Cheng, C.-H. *J. Org. Chem.* **2003**, *68*, 6726-6731. (c) Rayabarapu, D. K.; Cheng, C.-H. *Chem. Commun*. **2002**, 942-943. (d) Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 4781-4787. (b) Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.- H. *Org. Lett.* **2003**, *5*, 3963-3966.
22. (a) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062-12063. (b) Zi, W.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 12600-12603. (c) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012-9019. (d) Adcock, H. V.; Langer, T.; Davies, P. W. *Chem. Eur. J.* **2014**, *20*, 7262-7266. (e) Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 4633-4637.



Scheme GI-2. Synthesis of substituted indenes by Pd(0)-catalyzed carboannulation.

In another example, the *ortho*-alkynylation of benzaldehydes and aryl ketones carried out in the presence of [($RhCl_2Cp^*)_2$], AgSbF6 and $Cu(OAc)_2$ in *tert*-amyl alcohol at 120 °C, occurred through triple bond insertion, carbocyclization and protonolysis to form indenols (Scheme GI-3).[19a]



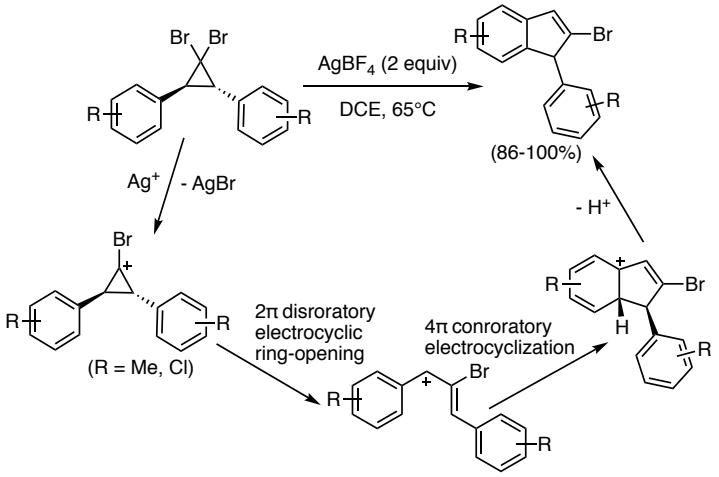
Scheme GI-3. Synthesis of substituted indenes by Rh-catalyzed *ortho* C-H activation.

Ring expansion and ring contraction

Several ring expansion methods have been developed for the synthesis of indene

derivatives.[23] Most of them are based on the use of three-membered ring systems as starting materials, in particular, methylene- and vinylidene-cyclopropane derivatives.[23b-f] Some recent examples will be illustrated in this section.

The Ag(I)-promoted domino 2π-electrocyclic ring opening/4π-electrocyclization of 1,2-diaryl substituted *gem*-dibromocyclopropanes affords bromoindenes, which could be used as starting materials for the preparation of different indenes. The process, occurring in DCE at 65 °C in the presence of 2 equivalents of $AgBF_4$, led to a mixture of regioisomers when unsymmetrically substituted *gem*-dibromocyclopropanes were used as starting materials (Scheme GI-4).[23b]

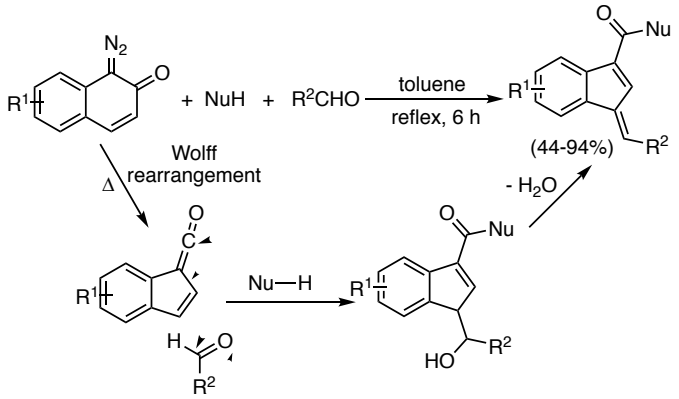


Scheme GI-4. Silver-promoted synthesis of indenes through 2π electrocyclic ring.

23. (a) Rosocha, G.; Batey, R. A. *Tetrahedron* **2013**, *69*, 8758-8768. (b) Nakamura, I.; Kamada, M.; Yamamoto, Y. *Tetrahedron Lett*. **2004**, *45*, 2903-2906. (c) Shao, L.-X.; Xu, B.; Huang, J.-W.; Shi, M. *Chem. Eur. J.* **2006**, *12*, 510-517. (d) Su, C.; Liu, Q. Y.; Ni, Y.; Huang, X. *Tetrahedron Lett.* **2009**, *50*, 4381-4383. (e) Su, C.; Huang, X.; Liu, Q.; Huang, X. *J. Org. Chem.* **2009**, *74*, 8272-8279. (f) Lu, J.-M.; Shi, M. *Org. Lett.* **2006**, *8*, 5317-5320. (g) Stepakov, A. V.; Larina, A. G.; Boitsov, V. M.; Gurzhiy, V. V.; Molchanov, A. P.; Kostikov, R. R. *Tetrahedron Lett*. **2014**, *55*, 2022-2026. (h) Magar, K. B. S.; Lee, Y. R. *Org. Lett.* **2013**, *15*, 4288-4291.

opening/ 4π electrocyclization.

Relatively few methods are known for the synthesis of indenes by ring contraction. An important recent example concerns the thermal decomposition of 1-diazonaphthalen-2(1*H*)-ones in the presence of a nucleophile (a primary or aromatic amine, an alcohol or a phenol) and an aromatic/heteroaromatic aldehyde. The reaction proceeds through a Wolff rearrangement followed by trapping of the ketene intermediate with the nucleophile and simultaneous attack to the aldehyde to give 1-methylene-1*H*-indenes (Scheme GI-5).[23h]



(R^1 = H, OMe, Br; NuH = primary amine, aromatic amine, alcohol, phenol; R^2 = aryl, heteroaryl)

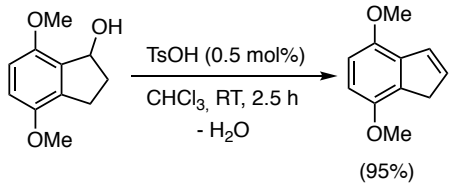
Scheme GI-5. Ring contraction to synthesize indenes by a Wolff rearrangement.

Functionalization of cyclic precursors

Indene derivatives can conveniently be obtained by functionalization of suitable cyclic precursors.[24] The most convenient and frequently used method for the synthesis of indenes is the dehydration of the corresponding indanol in benzene

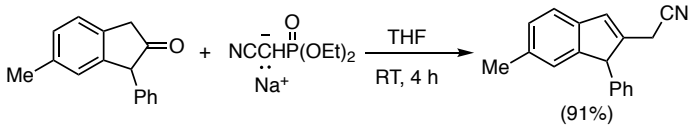
24. (a) Zhang, X.; Thimmaiah, M.; Fang, S. *Synth. Commun.* **2007**, *37*, 1873-1877. (b) Izmer, V. V.; Lebedev, A. Y.; Nikulin, M. V.; Ryabov, A. N.; Asachenko, A. F.; Lygin, A. V.; Sorokin, D. A.; Voskoboynikov, A. Z. *Organometallics* **2006**, *25*, 1217-1229. (c) Deck, L. M.; Greenberg, J. A.; Busby, T. S.; Bright, E. R.; Whalen, L. J.; Jagt, D. L. V.; Royer, R. E. *Tetrahedron Lett.* **2013**, *54*, 6015-6018. (d) Silver, S.; Leppänen, A.-S.; Sjçholm, R.; Penninkangas, A.; Leino, R. *Eur. J. Org. Chem.* **2005**, 1058-1081. (e) Gassman, P. G.; Ray, J. A.; Wenthold, P. G.; Mickelson, J. W. *J. Org. Chem.* **1991**, *56*, 5143-5146. (f) Prugh, J. D.; Alberts, A. W.; Deana, A. A.; Gilfillian, J. L.; Huff, J. W.; Smith, R. L.; Wiggins, J. M. *J. Med. Chem.* **1990**, *33*, 758-765. (g) Tudjarian, A. A.; Minehan, T. G. *J. Org. Chem.* **2011**, *76*, 3576-3581.

or toluene in the presence of *p*-toluenesulfonic acid (TsOH). In a recent example, 4,7-dimethoxy-1*H*-indene was synthesized in 95% yield by dehydration of 4,7-dimethoxy-2,3-dihydro-1*H*-inden-1-ol with TsOH (Scheme GI-6). [24a]



Scheme GI-6. Synthesis of 4,7-dimethoxy-1*H*-indene by acid-catalyzed dehydration of 4,7-dimethoxy-2,3-dihydro-1*H*-inden-1-ol.

Indanones are also useful precursors for the synthesis of indenes by reduction or dehydration.[24e,f] As a representative example, the Horner–Wadsworth–Emmons reaction of the anion of diethyl cyanomethylphosphonate with 6-methyl-1-phenyl-1*H*-inden-2(3H)-one leads to 2-(5-methyl-3-phenyl-1*H*-inden-2-yl)aceto nitrile (Scheme GI-7). [24g]



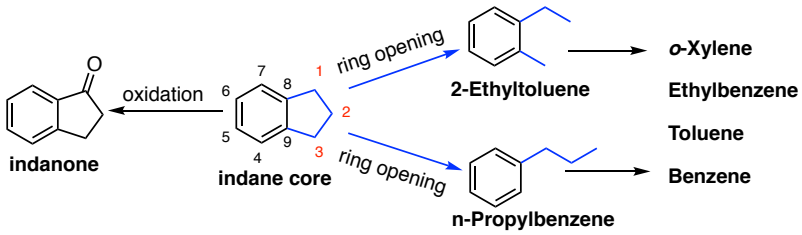
Scheme GI-7. Synthesis of an indene derivative by Horner–Wadsworth–Emmons reaction of indanone.

Indane

Introduction of indane

Indane, also named benzocyclopentane, hydrindene, 2,3-dihydroindene, is a bicyclic hydroncarbon composed of a benzene ring fused with a cyclopentane ring. The benzylic positions of indanes are prone to be oxidized to give indanones which is are useful starting materials for the synthesis of biologically

active compounds.[25] Ring opening takes place at cyclopentane motif under high temperature in the presence of noble metal catalysts supported on boehmite.[26] The ring opening products, if the ring was cleaved only once, are 2-ethyltoluene and *n*-propylbenzene, which can undergo further C-C bond cleavages producing other aromatic compounds (Scheme GI-8).[26a-c]



Scheme GI-8. Reactivity of indanes.

The indanyl core is a common hydrocarbon moiety in organic compound and has been found in many natural products, such as fumarofines[27a] and ochrobirine[27b] were isolated from *Fumaria officinalis* and *Corydalis sibirica (L.)*, respectively, and fredericamycin A,[27c] a unique quinone antitumor antibiotic isolated from a new strain of *Streptomyces griseus* at the Frederick Cancer Research Center (Figure GI-3).[27]

25. (a) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. *J. Med. Chem.* **1984**, *27*, 1508-1515. (b) Lowe, J. A.; Hageman, D. L.; Drozda, S. E.; McLean, S.; Bryce, D. K.; Crawford, R. T.; Zorn, S.; Morrone, J.; Bordner, J. *J. Med. Chem.* **1994**, *37*, 3789-3811.
26. (a) Nylén, U.; Sassu, L.; Melis, S.; Jaras, S.; Boutonnet, M. *Appl. Catal. A* **2006**, *299*, 1-13. (b) Nylén, U.; Delgado, J. F.; Jaras, S.; Boutonnet, M. *Appl. Catal. A* **2004**, *262*, 189-200. (c) Du, H.; Fairbridge, C.; Yang, H.; Ring, Z.; *Appl. Catal. A* **2005**, *294*, 1-21. (d) Ziaei-Azad, H.; Semagina, N. *ChemCatChem* **2014**, *6*, 885-894.
27. (a) Yu, C.K.; Saunders, J. K.; MacLean, D. B. *Can. J. Chem.* **1971**, *49*, 3020-3024. (b) Nalliahq, B.; Ahmed, A.; Manske, R.H.F. *Can. J. Chem.* **1972**, *50*, 1819-1824. (c) Pandey, R. C.; Toussaint, M. W.; Stroshane, R. M.; Kalita, C. C.; Aszalos, A. A.; Garretson, A. L; Wei, T. T.; Byrne, K. M.; Geoghegan, R. F.; White, R. J. *J. Antibiot.* **1981**, *34*, 1389-1401. (d) Wendt, J.; Gauvreau, P. J.; Bach, R. D. *J. Am. Chem. Soc.* **1994**, *22*, 9921-9926. (e) Ahmed, N. Synthetic Advances in the Indane Natural Product Scaffolds as Drug Candidates: A Review. *In Studies in Natural Products Chemistry*; Atta-Ur-Rahman, Ed.; Elsevier, **2016**; *51*, 1-535.

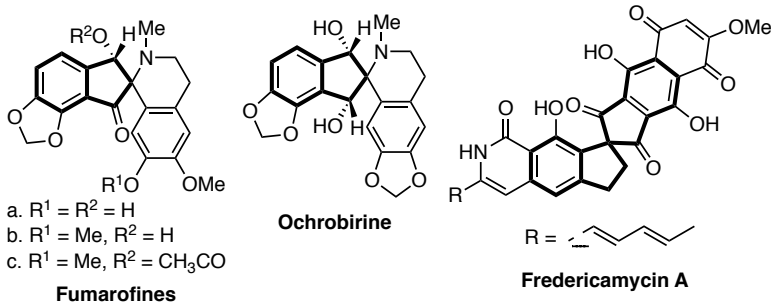


Figure GI-3. Selected examples of indane natural products.

The activity of indane derivatives in biological systems and the wide variety of their actions make them an interesting moiety for medicinal chemistry. Thus, this structural motif is also present in many marketed drugs (Figure GI-4),[28] such as a potent MAO-inhibitor indantadol,[28a] the amine uptake inhibitor indatraline,[28b] the antiinflammatory clidanac,[28c] antiarrhythmic agent indecainide,[28d] diuretic indacrinone,[28e] the anticoagulant hedulin[28f] and Crixivan[1] as mentioned in previous section bearing a enantiopure indane skeleton, an HIV protease inhibitor developed by Merck is one of the best-selling drugs for AIDS treatment. Given the great diversity of targets these drugs act on, one could argue that the indane ring system is a "privileged" substructure.[29]

28. (a) Villetti, G.; Bregola, G.; Bassani, F.; Bergamaschi, M.; Rondelli, I.; Pietra, C.; Simonato, M. *Neuropharmacology*, **2001**, *40*, 866-878. (b) Yu, H.; Kim, I. J.; Folk, J. E.; Tian, X.; Rothman, R. B.; Baumann, M. H.; Dersch, C. M.; Flippen-Anderson, J. L.; Parrish, D.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2004**, *47*, 2624-2634. (c) Juby P. F.; Partyka, R. A.; Hudyma, T. W. **1971**, US3565943. (d) Nestico, P. F.; Morganroth, J.; Horowitz, L. N.; Mulhern, C. *Am. J. Cardiol.* **1987**, *59*, 1332-1336. (e) Woltersdorf, O. W. Jr.; Solms S. J.; Stokker, G. E.; Cragoe, E. J. Jr. *J. Med. Chem.* **1984**, *27*, 840-845. (f) Fisher, M. M.; Wilensky, N. D.; Griffith, R. W.; Drumm, A.; Diefenbach, A. E.; Frankel, G. J. *N. Y. State J. Med.* **1954**, *54*, 778-783.
29. Vilums, M.; Heuberger, J.; Heitman, L. H.; Izerman, A. P. *Med. Res. Rev.* **2015**, *35*, 1097-1126.

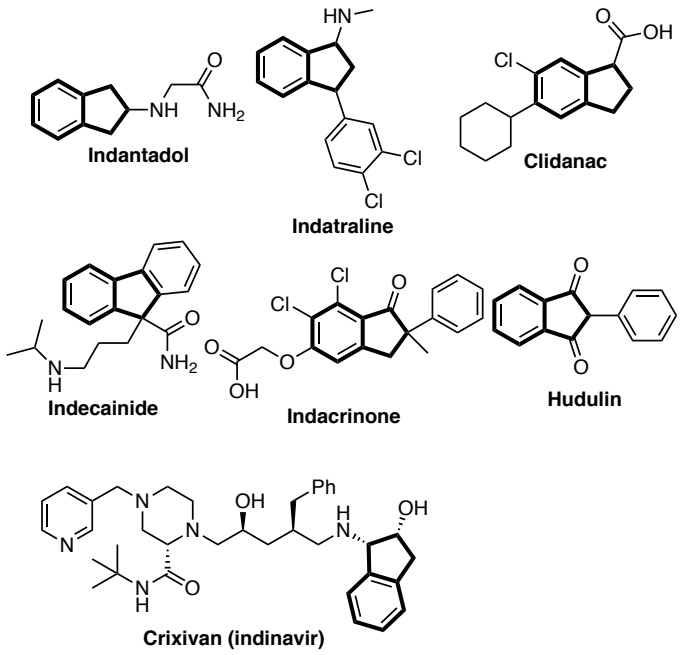


Figure GI-4. Selected examples of indane derivatives as drugs.

In contract with indene, the absence of double bond provides indane two more potential stereogenic centers. Due to this difference, indane derivatives play a more important role in the field of asymmetric catalysis. In addition, the bicyclic structure is a relatively rigid ring system. For these reasons, the indane core has been widely applied in chiral ligands.[30] For instance, a series of spiro bis-indane ligands reported by Zhou have proved their efficiency in a wide range of applications and have even been commercialized.[31] Other chiral indanes have been used as organocatalysts,[32] NHC catalysts,[33] other chiral ligands (Figure GI-5).[34,35]

30. Borie, C.; Ackermann, L.; Nechab, M. *Chem. Soc. Rev.*, **2016**, *45*, 1368-1386.
31. (a) Zhu S.-F.; Zhou, Q.-L. *Acc. Chem. Res,* **2012**, *45*, 1365-1377. (b) Cwiek, R.; Niedziejko, P.; Kałuza, Z. *J. Org. Chem.* **2014**, *79*, 1222-1234.
32. Gao, Y.; Ren, Q.; Wu, H.; Li, M.; Wang, J. *Chem. Commun.* **2010**, *46*, 9232-9234.
33. Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876-8877.
34. Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc*. **2003**, *125*, 12692-12693.
35. Hashimoto, T.; Kawamata Y.; Maruoka, K. *Nat. Chem.* **2014**, *6*, 702-705.

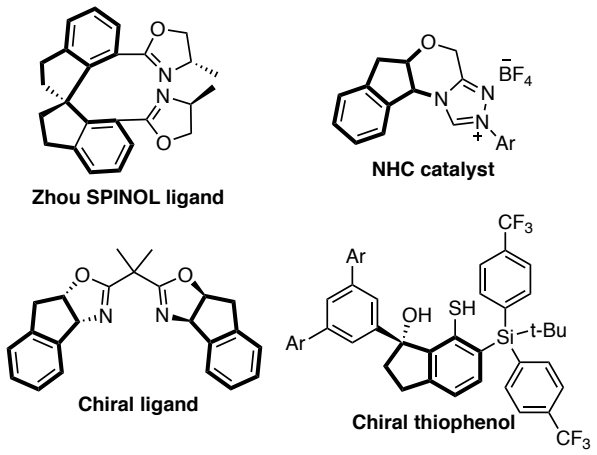


Figure GI-5. Selected examples of chiral indane ligands and catalysts.

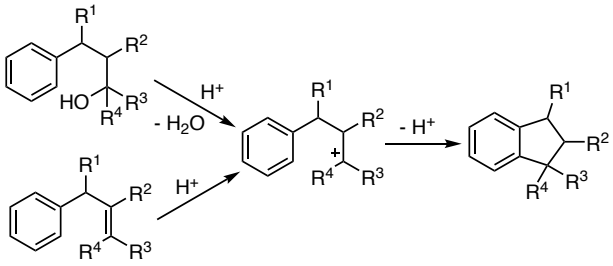
Synthesis of indanes

As summarized above, indanes are important building blocks. Therefore, considerable efforts have been devoted to the development of synthesis of these important structures. In analogy to the synthesis of indenes, the approaches of preparation of indanes will be briefly reviewed according to the following strategies: cyclization of acyclic precursors, ring contraction and expansion as well as by strategies based on the fuctionalization of cyclic precursors.

Cyclization of acyclic precursors

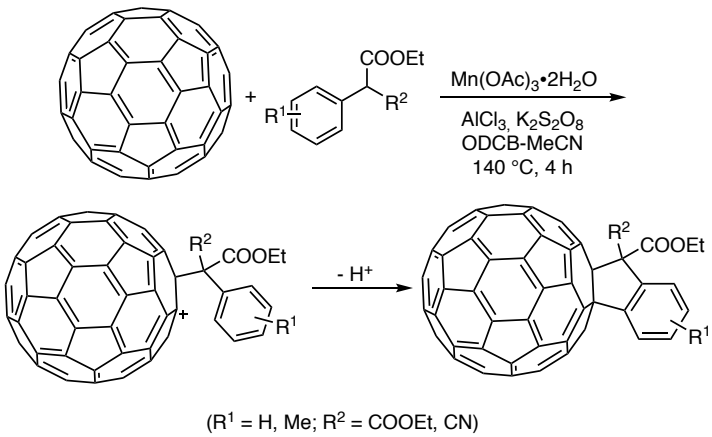
Indanes have been prepared by intramolecular Friedel-Crafts reactions. The formation of carbocation intermediates for the cyclization from a carbinol[36a,b] or a double bond[36c-e] can be promoted by a Lewis or a Brøsted acid, as exemplified in Scheme GI-9.

36. (a) Das, A.; Reddy, A. G. K.; Krishna, J.; Satyanarayana, G.; *RSC Adv.* **2014**, *4*, 26662-26666. (b) Begouin, J.-M.; Capitta, F.; Wu, X.; Niggermann, M. *Org. Lett.* **2013**, *15*, 1370-1373. (c) Wang, Y.; Wu, J.; Xia, P. *Synth. Commun.* **2006**, *36*, 2685-2698. (d) Saito, A.; Umakoshi, M.; Yagyu, N.; Hanzawa, Y. *Org. Lett.* **2008**, *10*, 1783-1785. (e) Lawrence, N. J.; Armitage, E. S. M.; Greedy, B.; Cook, D.; Ducki, S.; McGown, A. T. *Tetrahedron Lett.* **2006**, *47*, 1637-1640.



Scheme GI-9. Synthesis of indane derivatives by intramolecular Friedel-Crafts alkylation.

These facile synthetic methods have been applied for the synthesis of [60]fullerene-fused indane derivatives by the addition of $AlCl_3$ to the acetate-promoted radical reaction of [60]fullerene with 2-arylmalonates and 2-arylcyanoacetates (Scheme GI-10).[37]



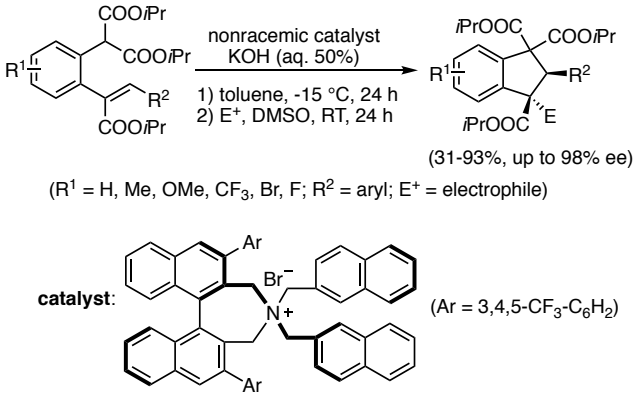
Scheme GI-10. Synthesis of [60]fullerence indane derivatives by intramolecular Friedel-Crafts reaction.

Other methods for synthesis of indanes based on cyclization reactions have been recently reviewed.[27e,30] The main methods have been classified[29] by involving

37. Liu, T.-X.; Li, F.-B.; Wang, G.-W. *Org. Lett.* **2011**, *13*, 6130-6133.

Heck-type reactions,[38] Michael-type addition reactions,[39] cyclizations of acetylenic substrates,[40] and other miscellaneous cyclizations.[41]

Michael additions offer a significant advantage for the efficient construction of various chiral indane moieties. As a representative example, a highly enantioselective and diastereoselective cyclization of malonate derivatives catalyzed by chiral ammonium salts gives substituted indanes (Scheme GI-11).[39a]

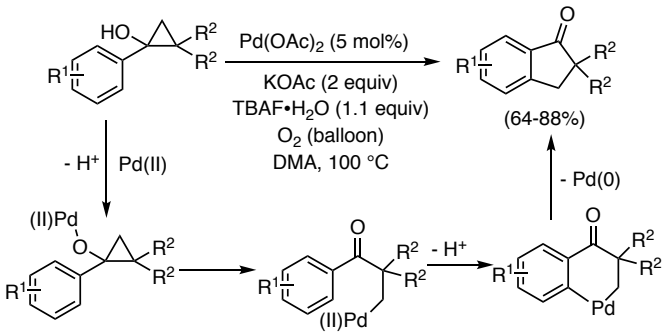


Scheme GI-11. Enantioselective synthesis of indanes by Michael addition.

38. (a) Fan, Y. C.; Kwon, O. *Org. Lett.* **2015**, *17*, 2058-2061. (b) Kesavan, S.; Panek, J. S.; Porco, Jr. J. A. *Org. Lett.* **2007**, *9*, 5203-5206. (c) Mirabdolbaghi, R.; Dudding, T. *Tetrahedron* **2012**, *68*, 1988-1991. (d) Jijy, E.; Prakash, P.; Saranya, S.; Suresh, E.; Radhakrishnan, K. V. *Synthesis* **2013**, 2583-2592.
39. (a) Johnston, C. P.; Kothari, A.; Sergeieva, T.; Okovytyy, S. I.; Jackson, K. E.; Paton, R. S.; Smith, M. D. *Nat. Chem.* **2015**, *7*, 171-177. (b) Fustero, S.; Rodríguez, E.; Herrera, L.; Asensio, A.; Maestro, M. A.; Barrio, P. *Org. Lett.* **2011**, *13*, 6564-6567. (c) Gharpure, S. J.; Reddy, S. R. B.; Sanual, U. *Synlett* **2007**, 1889-1892. (d) Alajarin, M.; Marin-Luna, M.; Vidal, A. *Adv. Synth. Catal.* **2011**, *353*, 557-562. (e) Tang, M.-S.; Zhao, Y.; Cheng, Y. *Synthesis* **2014**, 87-95. (f) Chua, P. J.; Tan, B.; Yang, L.; Zeng, X.; Zhu, D.; Zhong, G. *Chem. Commun.* **2010**, *46*, 7611-7613.
40. (a) Zheng, C.; Fan, R. *Chem. Commun.* **2011**, *47*, 12221-12223. (b) Marchal, E.; Cupif, J.-F. Uriac, P.; van de Weghe, P. *Tetrahedron Lett.* **2008**, *49*, 3713-3715. (c) Auvinet, A.-L.; Ez-Zoubir, M.; Bompard, S.; Vitale, M. R.; Brown, J. A.; Michelet, V.; Ratovelomanana-Vidal, V. *ChemCatChem* **2013**, *5*, 2389-2394. (d) Senaiar, R. S.; Teske, J. A.; Young, D. D.; Deiters, A. *J. Org. Chem.* **2007**, *72*, 7801-7804.
41. (a) Giorgi, G.; Arroyo, F. J.; López-Alvarado, P.; Menéndez, J. C. *Synlett* **2010**, 2465-2467. (b) Pratap, R.; Kumar, B.; Ram, V. J. *Tetrahedron* **2007**, *63*, 10300-10308. (c) Butkevich, A. N.; Ranieri, B.; Meerpoel, L.; Stansfield, I.; Angibaud, P.; Corbu, A.; Cossy, J. *Org. Biomol. Chem.* **2014**, *12*, 728-731.

Ring expansion and ring contraction

As described for indene syntheses, indane derivatives also can be obtained via ring expansion and ring contraction methods, in particular, ring opening of substituted cyclopropanols.[42] Recently, an interesting example based on the strain release of cyclopropanes was reported, including which involved deprotonation of alcohol, ring-opening via Pd-catalyzed cyclopropanol rearrangement reaction, intramolecular *ortho*-metalation, reductive elimination, and reoxidation of Pd(0) (Scheme GI-12).

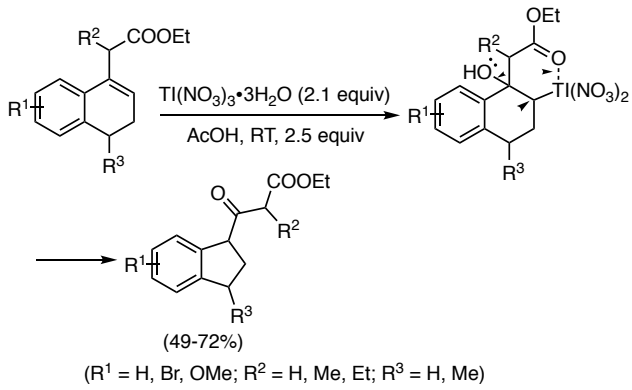


Scheme GI-12. Synthesis of indanes by ring expansion of cyclopropanols.

Thallium(III) compounds are excellent reagents for promoting the ring contraction of 1,2-dihydronaphthalene derivatives into functionalized indanes.[43] In a recent example, the thallium trinitrate mediated oxidative rearrangement of β,γ-unsaturated esters to give indane derivatives was described.[43a] The proposed mechanism begins with the oxythallation of the double bond, favored by the coordination of the oxygen of the ester group, followed by carbonyl formation with simultaneous ring contraction by migration of the aromatic ring to the

42. Rosa, D.; Orellana, A. *Chem. Commun.* **2012**, *48*, 1922-1924.
43. (a) Silva, Jr., L. F.; Pedrozo, E. A.; Ferraz, H. M. C.; Braz. J. *Chem. Soc.* **2006**, *17*, 200-205. (b) Silva, Jr., J. F.; Quintiliano, S. A. P.; Craveiro, M. V.; Vieira, F. Y. M. Ferraz, H. M. C. *Synthesis* **2007**, 355-362. (c) Ferraz, H. M. C.; Carneiro, V. M. T.; Silva, Jr., L. F. *Synthesis* **2009**, 385-388.

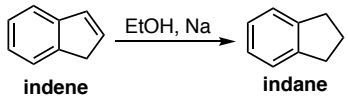
carbon bonded to thallium (Scheme GI-13).



Scheme GI-13. Synthesis of indanes by thallium-promoted ring contraction.

Functionalization of cyclic precursors

As mentioned above, the indane ring system is very common in nature, but before it was identified in natural products, several routes had been developed for the preparation of indanes. Shortly, the synthesis of indane from indene was reported by Kramer and Spilker (Scheme GI-14).[44]



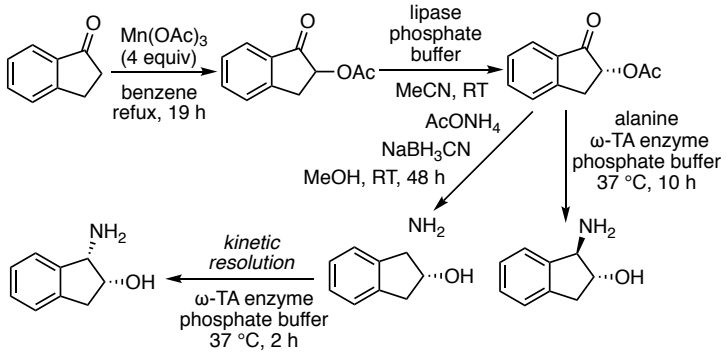
Scheme GI-14. Synthesis of indane from indene.

Many methods have been reported for the synthesis of substituted indanes by functionalization of suitable cyclic precursors.[45] Among them, indanones are excellent starting materials for further diversification of the indane ring. As an example for the synthesis of nonracemic indane derivatives, *trans*-(1*R*,2*R*)-1-

44. Kramer, G.; Spilker, A.; *Ber. Dfsch. Chem. Ges.* **1890**, *23*, 3276-3283.

45. (a) Vial, C.; Bernardinelli, G.; Schneider, P.; Aizenberg, M.; Winter, B.; *Helv. Chim. Acta* **2005**, *88*, 3109-3117. (b) Yun, H.; Kim, J.; Kim, B.-G. *Biotechnol. Bioeng.* **2006**, *93*, 391-395. (c) Nørager, N. G.; Lorentz-Petersen, L. L. R.; Lyngsø, L.O.; Kehler, J.; Juhl, K. *Synlett* **2011**, 1753-1755. (c) Wu, L.; Xie, C.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2014**, *12*, 4620-4627. (d) Xie, C.; Mei, H.; Wu, L.; Soloshonok, V.; Han, J.; Pan, Y. *RSC Adv.* **2014**, *4*, 4763-4768.

amino-2-in-danol and *cis*-(1*S*,2*R*)-1-amino-2-indanol were obtained by oxidation of indan-1-one with $Mn(OAc)_3$ followed by a series of enantioselective enzymatic reactions (Scheme GI-15).[45b]



Scheme GI-15. Enantioselective synthesis of indane derivatives from indanone.

Gold(I) carbenes

Over the past twenty years, homogeneous gold catalysis has contributed significantly to organic chemistry with novel methodologies for the formation of C-C bonds, particularly in the context of the construction of complex architectures.[46] Gold(I) carbenes in which gold is bound to a formally divalent

46. (a) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351-3378. (b) Jiménez-Núñez, E. ; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326-3350. (c) Hashmi, A. S. K.; *Chem. Rev.* **2007**, *107*, 3180-3211. (d) Marion N.; Nolan, S. P. *Angew. Chem., Int. Ed*. **2007**, *46*, 2750-2752. (e) Gorin, D. J.; Toste, F. D. *Nature*, **2007**, *446*, 395-403. (f) Jiménez-Núñez, E. ; Echavarren, A. M. *Chem. Commun.* **2007**, 333-346. (g) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410-3449. (h) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 5703-5705. (i) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239-3265. (j) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266-3325. (k) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395-3442. (l) Corma, A.; Leyva-Pérez, A. Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657-1712. (m) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994-2009. (n) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910-1925. (n) Bandini, M. *Chem. Soc. Rev.* **2011**, *40*, 1358-1367. (o) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448-2462. (p) Liu, L.-P.; Hammond, G. B. *Chem. Soc. Rev.* **2012**, *41*, 3129-3139. (r) Hashmi, A. S. K. *Acc. Chem. Res.* **2014**, *47*, 864-876. (s) Qian, D. Zhang, J. *Chem. Rec.* **2014**, *14*, 280-302. (t) Xie, J.; Pan, C.; Abdukader, A.; Zhu, C. *Chem. Soc. Rev.* **2014**, *43*, 5245-5256.

carbon atom have been invoked in a range of gold-catalyzed transformations,[47,48] whereas their actual structures have been the matter of considerable discussion (Figure GI-7).[49]

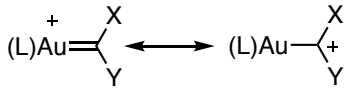


Figure GI-7. Resonance structure of cationic gold complex.

Properties of gold(I) carbene

Gold(I) carbenes can be considered as highly electrophilic Fischer carbenes.[50] To demonstrate the properties of gold carbene, a bonding model was proposed by Goddard and Toste based on a three-center, 4-electron σ-hyperbond formed by the donation of electron density from filled sp^x orbitals of the supporting ligand and carbene carbon atom to the empty 6s orbital on gold, simultaneously with the formation of two π-bonds on the gold center by the donation from perpendicular filled *d*-orbitals into empty π-acceptors on the ligand and carbene carbon(Figure GI-8). [49c]

47. (a) Widenhoefer, R. A.; *Chem. Eur. J.* **2008**, *14*, 5382-5391. (b) Bongers, N.; Krause, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178-2181. (c) Sengupta, S.; Shi, X. *ChemCatChem*. **2010**, *2*, 609-619. (d) Pradal, A.; Toullec, P. Y.; Michelet, V. *Synthesis*, **2011**, 1501-1514. (e) Wang, Y.-M. Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014**, *47*, 889-901.
48. (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754-6756. (b) Echavarren, A. M. *Nat. Chem.* **2009**, *1*, 431-433. (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232-5241. (d) *Modern Gold Catalyzed Synthesis*, ed. Hashmi, A. S. K.; Toste, F. D. Wiley-VCH, Weinheim, **2012**. (e) Obradors, C.; Echavarren, A. M. *Chem. Commun.* **2014**, *50*, 16-28.
49. (a) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030-5033. (b) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2510-2513. (c) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard III, W. A. Toste, F. D. *Nat. Chem.* **2009**, *1*, 482-486. (d) Wang, Y.; Muratore, M. E.; Echavarren, A. M. *Chem. Eur. J.* **2015**, *21*, 7332-7339. (e) Harris, R. J.; Widenhoefer, R. A. *Chem. Soc. Rev.* **2016**, *45*, 4533-4551. (f) Caballero, A.; Pérez, P. J. *Chem. Eur. J.* **2017**, *23*, 14389-14393.
50. (a) Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed.* **1964**, *3*, 580-581. (b) Barluenga, J.; Santamaría, J.; Tomás, M. *Chem. Rev.* **2004**, *104*, 2259-2284.

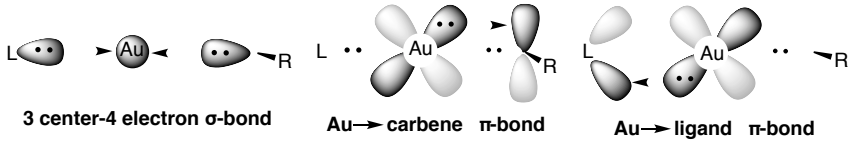
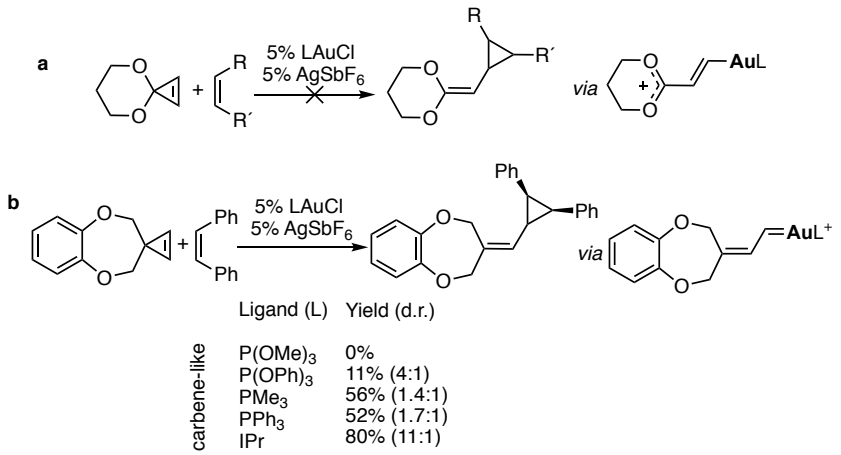


Figure GI-8. Bonding form of gold carbene complex.

The reactivity of gold(I) carbenes, investigated both experimentally in the context of gold(I)-catalyzed cyclopropanation reactions and theoretically by measuring the rotational barriers and bond lengths adjacent to gold by DFT calculations,[49b-c] is highly dependent on carbene substituents and ancillary ligands. Gold-coordinated carbocation intermediates are formed in the gold-catalyzed reactions of the substrates bearing the highly carbocation-stabilizing substituents (like oxygen atom), which are unfavorable to cyclopropanate alkenes (Scheme GI-16a). However, in the presence of less-donating group substituents, the gold-carbon bond possesses more π-character with decreased σ-donation from alkylidene to gold. The gold intermediate performs the reactivity of gold carbene, which proceeds through a cyclopropanation reaction of alkenes (Scheme GI-16b). In terms of ligand, strongly σ-donating and weakly π-acidic ligand that weaken the gold-carbon σ-bonding and strengthen π-donation are expected to increase carbene-like feature (Scheme GI-16b). In conclusion, the reactivity in gold(I) carbenes can be best explained as a continuum ranging from a metal-stabilized singlet carbene to a metal-coordinated carbocation.[49c]



Scheme GI-16. Experimental comparison for the carbene reactivity of the substrate with different substituents and ancillary ligands.

Generation of gold(I) carbenes

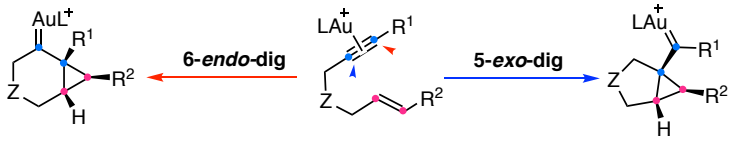
Gold(I) carbenes have been proposed as key intermediates in many transformations. In the following sections, the main transformations proceeding through these intermediates are biefly reviewed.

Gold(I) carbenes from 1,*n*-enynes

1,*n*-Enynes undergo a variety of skeletal rearrangements in the presence of gold catalysts rather than the commonly observed Alder-ene type rearrangements under the catalysis of palladium and rhodium complexes. These skeletal rearrangements often share the formal cyclopropanation step *via* the *endo*/*exo*-dig cyclizations of 1,*n*-enynes (*e.g.*, 1,6-enynes) to form cyclopropyl gold(I) carbene-like intermediates (Scheme GI-17). [51] The mechanism is thought to proceed by initial Z-coordination of the gold to the alkyne followed by the

51. (a) Nieto-Oberhuber, C.; Paz Munoz, M.; Bunuel, E.; Nevado, C.; Cardenas, D. J. Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402-2406. (b) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028-9072. (c) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902-912. (d) Echavarren, A. M.; Muratore, M.; López-Carrillo, V.; Escribano-Cuesta, A.; Huguet, N.; Obradors, C. *Org. React.* **2017**, *92*, 1. (e) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029-6032.

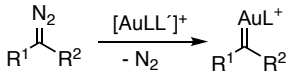
cyclopropanation, leading to reactive gold-carbenes. The pathway followed by a particular enyne is highly influenced by its substitution pattern. DFT calculations[52] support that the formation of 5-membered cyclic compounds is generally kinetically favored for terminal alkynes, while the formation of 6-membered rings becomes preferred for internal alkynes together with the ones with heteroatoms at the tether.



Scheme GI-17. Gold(I) carbenes generated from 1,6-enynes.

Gold(I) carbenes from diazo compounds

Diazo compounds are one of the most important carbene precursors, which decomposed by reaction with transition metals such as Rh, Ru, and Cu giving rise to a various of interesting metallocarbenes.[53] Gold(I) carbenes generated from diazo compounds were first reported by the group of Pérez in 2005 (Scheme GI-18).[54] In the past thirteen years, gold-catalyzed diazo transformations have emerged as useful method in organic synthesis.[55]

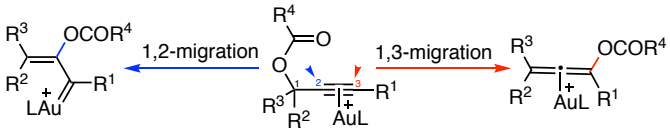


Scheme GI-18. Gold(I) carbenes generated from diazo compounds.

52. Mattalia, J.-M.; Nava, P. *J. Organomet. Chem.* **2014**, *749*, 335-342.
53. (a) Davies, H., Beckwith, R. *Chem. Rev.* **2003**, *103*, 2861-2903. (b) Doyle, M.; Duffy, R.; Ratnikov, M. *Chem. Rev.* **2010**, *110*, 704-724. (c) Gillingham, D.; Fei, N. **2013**, *42*, 4918-4931.
54. Fructos, M. R.; Belderrain, T. R.; Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5284-5288.
55. (a) Qian, D.; Zhang, J. *Chem. Soc. Rev.* **2015**, *44*, 677-698. (b) Wei, F.; Song, C.; Ma, Y.; Zhou, L.; Tung, C.; Xu, Z. *Sci. Bull.* **2015**, *60*, 1479-1492. (b) Prieto, A.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 1790-1793. (c) Rivilla, I.; Gõmez-Emeterio, B. P.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2011**, *30*, 2855-2860. (d) Pérez, P. J.; Díaz-Requejo, M. M.; Rivilla, I. Beilstein *J. Org. Chem.* **2011**, *7*, 653-657. (e) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904-6907.

Gold(I) carbenes from propargyl esters

A variety of vinyl gold(I) carbenes have been obtained by the 1,2-acyloxy migration from readily available propargyl esters in the presence of gold(I) catalysts. [46a,48e,56] 1,3-Migration can also occur to form allene gold(I) complexes (Scheme GI-20).[57]



Scheme GI-19. Gold carbene generated from propargyl esters.

Gold(I) carbenes from cyclopropenes

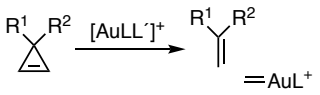
Cyclopropenes are highly strained but readily accessible precursors, which undergo gold-catalyzed ring-opening giving rise to vinyl gold(I) carbenes that can be employed in the cyclopropanation of olefins, self or cross-carbene coupling reactions (Scheme GI-20).[58]

---

56. (a) Mamane, V.; Gress, T. Krause H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654-8655. (b) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802-5803. (c) Gorin, D. J.; Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 14480-14481. (d) Marion, N.; Frémont, P.; Lemière, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, 2048-2050. (e) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736-3737. (f) Moreau, X.; Goddard, J.-P.; Bernard, M.; Lemière, G.; Lòpez-Romero, J. M.; Mainetti, E.; Marion, N.; Mouriès, V.; Thorimbert, S.; Fensterbank, L.; Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43-48. (g) Garayalde, D.; Krüger, K.; Nevado, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 911-915. (h) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002-18003. (i) Petuskova, J.; Bruns, H.; Alcarazo, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3799-3802. (j) Fourmy, K.; Mallet-Ladeira, S.; Dechy-Cabaret, O.; Gouygou, M. *Organometallics*, **2013**, *32*, 1571-1574.

57. (a) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614-12615. (b) Marion, N.; Frémont, P.; Lemière, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, 2048-2050. (c) Marion, N.; Lemière, G.; Correa, A.; Costabile, C.; Ramon, R. S.; Moreau, X.; Frémont, P.; Dahmane, R.; Hours, A. Lesage, D.; Tabet, J.-C.; Goddard, J.-P.; Gandon, V.; Cavallo, L.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Eur. J.* **2009**, *15*, 3243-3260.

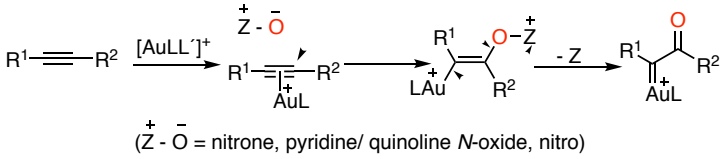
58. (a) Hadfield, M. S.; Bauer, J. T.; Glen, P. E.; Lee, A.-L. *Org. Biomol. Chem.* **2010**, *8*, 4090-4095. (b) Miege, F.; Meyer, C.; Cossy. J. *Beilstein. J. Org. Chem.* **2011**, *7*, 717-734. (c) Bauer, J. T.; Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2008**, 6405-6407. (d) Miege, F.; Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12*, 4144-4147. (e) Miege, F.; Meyer, C.; Cossy, J. *Chem. Eur. J.* **2012**, *18*, 7810-7822.



Scheme GI-20. Vinyl gold(I) carbenes generated from cyclopropenes.

Gold(I) carbenes by oxidation of alkynes

A series of α-oxo gold carbenes can be generated by the oxidation of gold-activated alkynes.[59] The whole process involves the nucleophilic attack of the nucleophilic oxidant to the gold-activated alkyne followed by release of the neutral organic unit (Scheme GI-21). This method provides an efficient and safe alternative to the use of explosive keto diazo compounds.



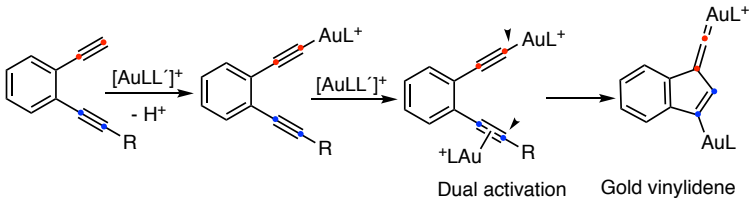
Scheme GI-21. Gold(I) carbenes generated by oxidation of alkynes.

Gold(I) carbenes from 1,2-dialkynylarenes

Gold(I) vinylidenes were proposed as intermediates in cycloisomerization of 1,2-dialkynylarenes (Scheme GI-22). Thus, the gold(I)-promoted nucleophilic σ-activation and electrophilic π-activation of both alkyne units of the diyne system act synergistically. This dual gold-catalyzed pathway was developed independently by the groups of Zhang[60a] and Hashmi and coworkers.[60b,c] The resulting gold(I) vinylidenes can participate in C-H, O-H, N-H insertions as well

59. (a) Vasu, D.; Hung, H.-H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6911-6914. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161. (c) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258–3259. (d) He. W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482–8485. (e) Noey, E. L.; Luo, Y.; Zhang, L.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 1078–1084. (f) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 17412–17415. (g) Ji, K.; Zhao, Y.; Zhang, L. *Angew. Chem. Int. Ed.* **2013**, *52*, 6508–6512. (h) Lu, B.; Li, Y.; Wang, Y.; Aue, D. H.; Luo, Y.; Zhang, L. *J. Am. Chem. Soc.* **2013**, *135*, 8512–8524. (i) Ji, K.; Zhang, L. *Org. Chem. Front.* **2014**, *1*, 34–38. (j) Zhang, L. *Acc. Chem. Res.* **2014**, *47*, 877–888. (k) Yeom, H.-S.; Shin, S. *Acc. Chem. Res.* **2014**, *47*, 966-977.

as cyclopropanations of alkenes.[60]



Scheme GI-22. Gold(I) vinylidene from 1,2-dialkynyarenes.

Gold(I) carbenes by retro-Buchner reaction of 7-substituted-1,3,5-cycloheptatrienes.

Another important method for the generation of gold(I) carbenes precursor was reported by our group and proceeds by the gold(I)-promoted retro-Buchner reaction of 7-substituted-1,3,5-cycloheptatrienes to generate a series of useful aryl and vinyl gold(I) carbenes. Since this reaction it central to the main topic of this Ph Thesis, a brief summary is presented in the next section.

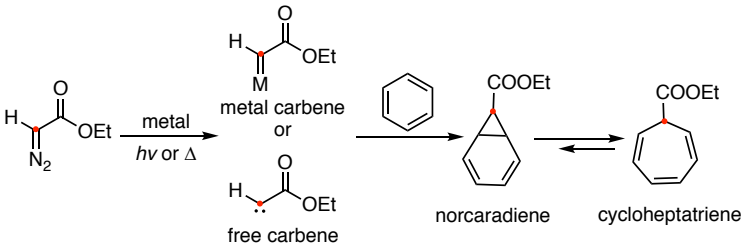
Buchner ring expansion

The Buchner ring expansion is the addition reaction of carbenes to arenes to form cycloheptatrienes.[61] The transformation includes the formation of carbenes via thermal, photochemical or metal-promoted decomposition of diazo compounds, which lead to the cyclopropanation of aromatic rings to form a norcaradiene that undergoes a 6-electron disrotatory electrocyclic opening to form

60. (a) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31-34. (b) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics*, **2012**, *31*, 644-661. (b) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 4456-4460. (c) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Rudolph, M.; Rominger, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10633-10637. (d) Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2013**, *52*, 2593-2598. (e) Braun, I.; Asiri, A. M.; Hashmi, A. S. K. *ACS Catal.* **2013**, *3*, 1902-1907. (f) Mamane, V.; Hannen, P.; Früstner, A. *Chem. Eur. J.* **2004**, *10*, 4556-4575.

61. (a) Dave, V.; Warnhoff, E. W. *Org. React.* **1970**, *18*, 217-401. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091-1160. (c) Reisman, S. E.; Nani, R. R.; Levin, S. *Synlett* **2011**, 2437-2442. (c) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873-876.

cycloheptatrienes. Since the first report of this transformation by E. Buchner and T. Curtius in 1885,[62] this reaction has been applied in several total synthesis as the key step to construct unusual norcaradiene cores or 7-member rings in intramolecular manner (Scheme GI-23).[63]



Scheme GI-23. Buchner ring expansion.

Retro-Buchner reaction

The retro-Buchner reaction is the reverse process of the Buchner reaction, in a transformation in which cycloheptatrienes give rise to arenes unit with concomitant formation of a carbene. The overall process can be considered as a decarbenation, in analogy to other well-known transformations such as the decarbonylation or decarboxylation. The few precedents reported in the literature demonstrate that free carbene or metallocarbenes can be generated by retro-Buchner process under harsh conditions.[64]

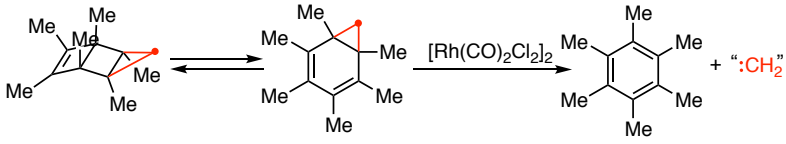
In the presence of catalytic amounts of $[Rh(CO)_2Cl]_2$ the monomethylene adduct of hexamethylbicyclo[2.2.0]hexa-2,5-diene can be quantitatively converted into hexamethylbenzene and a monomethylene carbenoid species; the latter can be

62. Buchner, E.; Curtius, T. *Chem. Ber.* **1885**, *18*, 2371-2377.

63. (a) Kane, J. L.; Shea, K. M.; Crombie, A. L.; Danheiser, R. L. *Org. Lett.* **2001**, *3*, 1081-1084. (b) Levin, S.; Nani, R. R.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774-776.

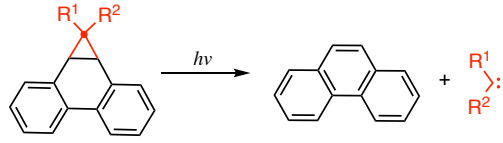
64. (a) Volger, H. C.; Hogeveen, H.; Roobeek, C. F. *Recueil* **1973**, *92*, 1223-1231. (b) Graves, K. S.; Thamattoor, D. M.; Rablen, P. R. *J. Org. Chem.* **2011**, *76*, 1584-1591. (c) Nigam, M.; Platz, M. S.; Showalter, B. M.; Toscano, J. P.; Johnson, R.; Abbot, S. C.; Kirchhoff, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 8055-8059. (d) Glick, H. C.; Likhotvorik, I. R.; Jones, M. *Tetrahedron Lett.* **1995**, *36*, 5715-5718. (e) Richardson, D. B.; Durrett, L. R.; Martin, J. M.; Putnam, W. E.; Slaymaker, S. C.; Dvoretzky, I. *J. Am. Chem. Soc.* **1965**, *87*, 2763-2765. (f) Moore, K. A.; Vidaurri-Martinez, J. S.; Thamattoor, D. M. *J. Am. Chem. Soc.* **2012**, *134*, 20037-20040.

trapped by cyclohexene. The hexamethylbenzene is presumably formed *via* electrocyclic opening of the cyclobutene ring to give coordinated hexamethylnorcaradiene, and extrusion of the carbenoid species (Scheme GI-24).[64a]



Scheme GI-24. Generation of free carbene from hexamethylbicyclo[2.2.0]hexa-2,5-diene.

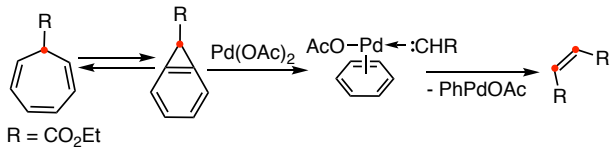
Free carbenes can be formed by irradiation of phenanthrene precursors, which are difficult to be trapped by carbene trapping agent. Instead, these free carbenes undergo the rearrangement reactions to give alkenes[64b-e] or alkynes (Scheme GI-25). [64f]



Scheme GI-25. Free carbenes generated from phenanthrene precursors.

7-Ethoxycarbonyl-1,3,5-cycloheptatriene reacted with an equimolecular amount of $Pd(OAc)_2$ to give diethyl maleate in 14% yield. Cycloheptatrienes have norcaradiene forms as valence isomers, in which the cyclopropane rings can be cleaved to give aromatization products. The formation of this dimer is thought to proceed *via* this type of cyclopropane ring cleavage mechanism. The interaction between the palladium metal and the carbon atom of the cyclopropane ring is considered to yield a carbenoid complex, which then dimerizes to form diethyl maleate (Scheme GI-26).[65]

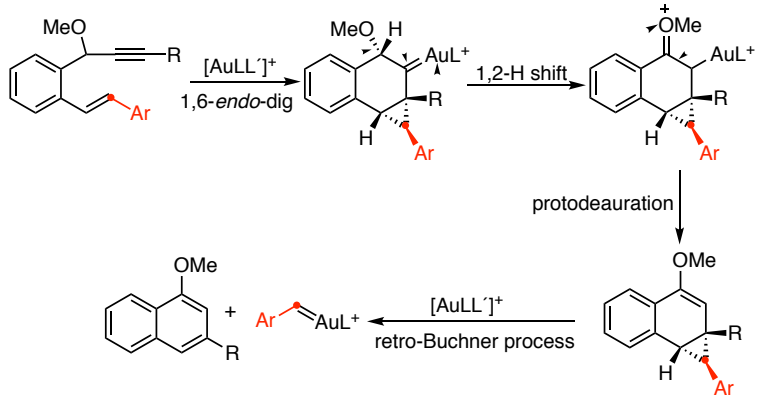
65. Saito, K.; Kozaki, M.; Takahashi, K. *Chem. Pharm. Bull.* **1993**, *41*, 2187-2189.



Scheme GI-26. Palladium induced retro-Buchner reaction of cycloheptatriene.

Gold(I)-promoted retro-Buchner reaction

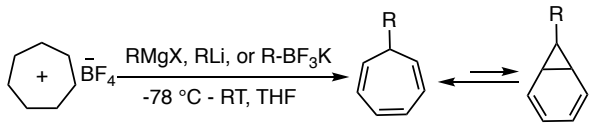
In 2010, our group reported the first gold(I)-promoted retro-Buchner reaction in solution delivering aryl gold(I) carbenes, which can be trapped by alkenes.[66] Thus, reaction of phenyl-linked 1,6-enynes bearing a methoxy group at benzylic position with cationic gold(I) catalysts leads to the formation of cyclopropane intermediates *via* 6-*endo*-*dig* cyclization (Scheme GI-27). Subsequent 1,2-H shift and protodeauration gives rise to dihydro-1*H*-cyclopropa[*a*]naphthalenes, which undergo the decarbenation reaction to release a naphthalene and the aryl gold(I) carbene.



Scheme GI-27. Gold(I) carbenes by retro-Buchner process.

66. (a) Solorio-Alvarado, C. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 11881-11883. A similar process was also proposed in the gas phase: (b) Fedorov, A.; Moret, M.-E.; Chen, P. *J. Am. Chem. Soc.* **2008**, *130*, 8880-8881. (c) Batiste, L.; Fedorov, A.; Chen, P. *Chem. Commun.* **2010**, *46*, 3899-3901. (d) Fedorov, A.; Chen, P. *Organometallics* **2010**, *29*, 2994-3000. (e) Fedorov, A.; Batiste, L.; Bach, A.; Birney D. M.; Chen, P. *J. Am. Chem. Soc.* **2011**, *133*, 12162-12171. (f) Batiste, L.; Chen, P. *J. Am. Chem. Soc.* **2014**, *136*, 9296-9307.

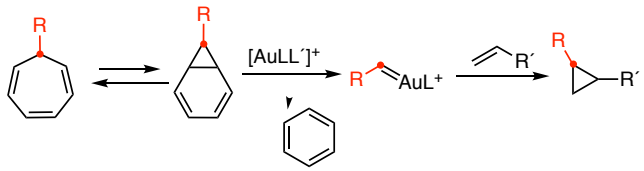
However, this unprecedented gold-promoted retro-Buchner reaction have two obvious drawbacks. Firstly, the carbene precursors, of this process are not readily accessible. The second disadvantage is that the generated gold(I) carbenes react with the intermediate enol ether to form the corresponding cyclopropanes. To overcome this problem, 7-substituted-1,3,5-cycloheptatrienes were chosen as alternative substrates. 7-Aryl-substituted-1,3,5-cycloheptatrienes were synthesized by the nucleophilic attack of organometallic reagents such as organolithium, Grignard reagents or potassium trifluoroborate salts to commercial available tropylium tetrafluoroborate (Scheme GI-28).



Scheme GI-28. Synthesis of 7-substituted-1,3,5-cycloheptatrienes.

Treatment of 7-aryl-substituted-1,3,5-cycloheptatrienes with cationic gold(I) catalysts in 1,2-dichloroethane (DCE) at 120 °C leads to aryl gold(I) carbenes by a retro-Buchner process, which can be trapped by alkenes to give substituted cyclopropanes (Scheme GI-29).[67] DFT calculations showed that the retro-Buchner reaction proceeds by electrophilic cleavage of two C-C bonds of the norcaradiene tautomers in a stepwise manner, in which the first C-C bond cleavage is rate determining step.[68]

67. Solorio-Alvarado, C. R.; Wang, Y.; Echavarren, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 11952-11955.
68. Wang, Y.; McGonigal, P. R.; Herle, B.; Besora, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2014**, *136*, 801-809.



Scheme GI-29. Gold(I) catalyzed retro-Buchner reaction of substituted cycloheptatrienes.

Chapter 1. Formal (3+2) Cycloaddition between Allenes and Aryl Gold(I) Carbenes

Introduction

As discussed in the general introduction, our group found that cationic gold(I) complexes promote the retro-Buchner reaction of 7-substituted 1,3,5-cycloheptatrienes **1**, through their norcaradiene tautomers, leading to relatively simple reactive metal carbenes $[LAu=CHR]^+$ **2** (Figure 1.1),[69] which react with alkenes to give cyclopropanes.[67] The highly electrophilic gold(I) carbenes **2** also can be trapped intramolecularly by alkenes and arenes to form indenes and fluorenes respectively,[68] which can be applied to the synthesis of indenofluorenes used in organic electronics. In these reactions, the gold(I) carbenes **2** displayed reactivity more similar to that of metal carbenes of rhodium or copper or even free carbenes than that of carbocations.

In 2104, an efficient method of constructing aryl substituted cyclopentenes through a formal (4+1) cycloaddition of gold carbenes with methylenecyclopropanes or cyclobutenes was developed by our group, in which gold(I) plays a triple catalytic role including isomerization of methylenecyclopropanes to cyclobutenes, generation of gold(I) carbenes from **1**, ring expansion of the resulting bicyclo[2.1.0]pentanes to cyclopentenes.[70]

69. Jia, M.; Ma, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 9134–9166.
70. Wang, Y.; Muratore, M. E.; Rong, Z.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 14022-14026.

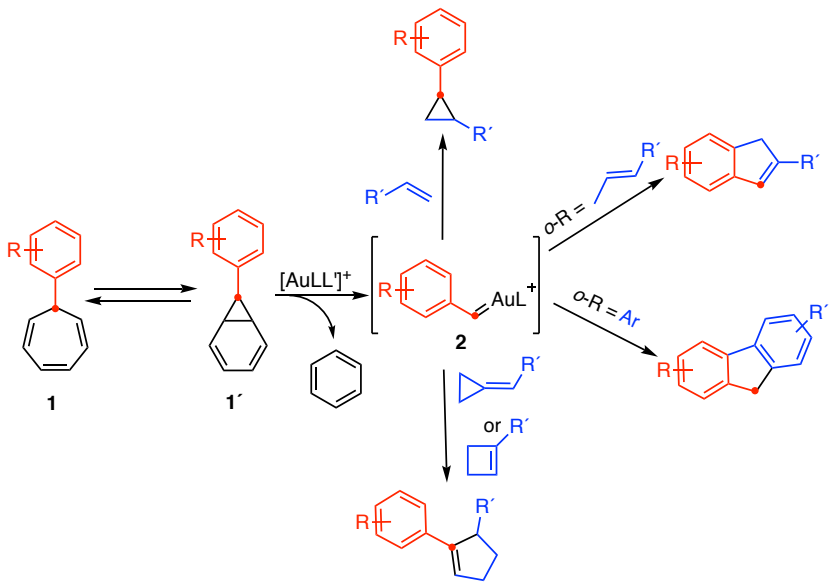
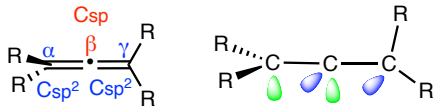


Figure 1.1. Diverse transformations of gold(I) carbene generated *via* retro-Buchner reaction of 7-substituted cycloheptatrienes.

Allenes are cumulated systems including two mutually perpendicular π bonds with the central carbon atom (*sp*-hybridized) joined in a straight line to the two terminal carbon atoms (sp^2-hybridized) (Figure 1.2).[71] A relatively high degree of unsaturation and a readily accessible π-bond system leads to facile addition reactions. The orientation of additions is strongly affected by groups already attached to the cumulene bond.[72] For a long period of time allenes were considered not to be very stable and difficult to make. However, over the last two decades there have been many advances in the development of new synthetic

71. (a) *Allenes in Organic Synthesis*, ed. Schuster, H. F.; Coppola, G. M. *Wiley-Interscience*, *New York*, **1984**. (b) *Modern Allene Chemistry*, ed. Krause, N.; Hashmi, A. S. K. *Wiley-VCH, Weinheim*, **2004**. (c) Soriano, E.; Fernández, I. *Chem. Soc. Rev.* **2014**, *43*, 3041-3105.
72. (a) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679-1688. (b) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067-3125. (c) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994-2009. (d) López, F.; Mascareñas, J. L. *Chem. Eur. J.* **2011**, *17*, 418-428. (e) Ye, J.; Ma, S. *Acc. Chem. Res.* **2014**, *47*, 989-1000. (f) Adams, C. S.; Weatherly, C. D.; Burke, E. G.; Schomaker, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3136-3163. (g) Santhoshkumar, R.; Cheng, C. *Asian J. Org. Chem.* **2018**, *7*,1151-1163.

approaches to prepare different types of allenes.[73] In the meanwhile, allenes have proven to be valuable building blocks for the synthesis of complex molecular targets, revealing novel applications in natural product synthesis, pharmaceutical chemistry and materials science.[74]



IR: antisymetrical streching vibration 1950-1960 cm^{-1}
(*vs*. alkene: 1680 cm^{-1}, alkyne 2200 cm^{-1})
^{1}H NMR: δ = 4.9-4.4 ppm
^{13}C NMR: $\delta_{C\alpha, C\gamma}$ = 120-73 ppm; $\delta_{C\beta}$ = 220-200 ppm

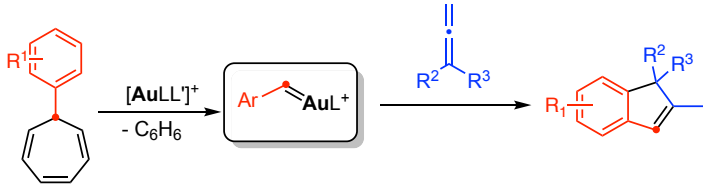
Figure 1.2. Properties of allenes.

Objectives

As summarized in the introduction, gold(I) carbenes generated by retro-Buchner reaction of 7-aryl-substituted-1,3,5-cycloheptatrienes have emerged as one carbon synthons for electrophilic reactions with different alkenes to afford diverse useful moieties. On the other hand, allenes have shown to participate in cycloaddition reactions acting as a 2C or 3C component depending on the substituents. Based on the reactivity of allenes and gold(I) carbenes, we postulated that gold(I) carbenes generated from 7-aryl-substituted-1,3,5-cycloheptatrienes could be trapped by the cumulated π system of allenes leading to highly substituted indenes (Scheme 1.1).

---

73. (a) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133-1150. (b) Krause, N.; Hoffmann-Röder, A. *Tetrahedron*, **2004**, *60*, 11671-11694; (c) Brandsma, L.; *Synthesis of Acetylenes, Allenes and Cumulenes, Elsevier, Oxford*, **2004**. (d) Hammond, G. B. *ACS Symp. Ser.* **2005**, *911*, 204-215. (e) Brummond, K. M.; DeForrest, J. E. *Synthesis*, **2007**, 795-818. (f) Saeeng, R.; Isobe, M. *Chem. Lett.* **2006**, *35*, 552-557. (g) Yu. S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384-5418. (f) Neff, R. K.; Frantz, D. E. *ACS Catal.* **2014**, *4,* 519-528. (g) Chu, W.-D.; Zhang, Y.; Wang, J. *Catal. Sci. Technol.* **2017**, *7*, 4570-4579. (h) l) Wu, S.; Huang, X.; Wu, W.; Li, P.; Fu, C.; Ma, S. *Nat. Commun.* **2015**, *6*, 7946-7960.
74. (a) Ma, S. *Chem. Rev*. **2005**, *105*, 2829-2872. (b) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196-1216. (c) Yu, S.; Ma, S. *Angew. Chem., Int. Ed*. **2012**, *51*, 3074-3112.



Scheme 1.1. Designed cycloaddition of gold carbenes with allenes.

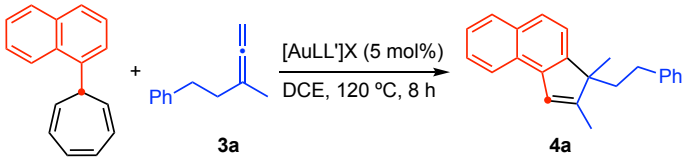
To achieve the proposed cycloaddition of gold(I) carbenes with allenes, we should overcome some obstacles: i. the retro-Buchner process to generate gold(I) carbenes could be slowed down as a result of the coordination of gold(I) to the allenes; ii. The final indenes or the cycloheptatrienes could compete with the allenes in the trapping of the gold(I) carbenes leading to secondary products.

Results and Discussion

Optimization of the model reaction

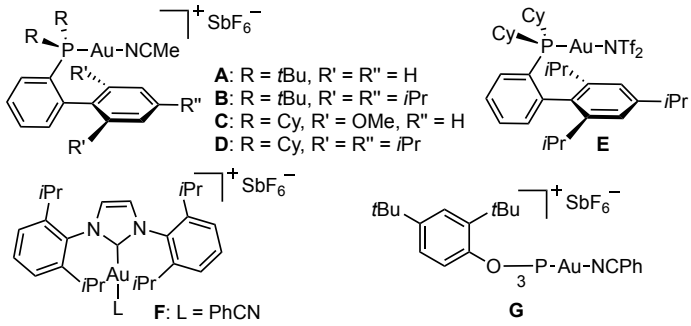
We first studied the reaction of 7-(1-napthyl)-1,3,5-cycloheptatriene (**1a**) with allene **3a** with different gold(I) catalysts (Table 1.1). Reaction of **1a** with 2.0 equiv of **3a** in the presence of 5 mol% of gold(I) complex [(JohnPhos)Au(MeCN)]SbF6 (**A**) in 1,2-dichloroethane at 120 ºC for 8 h gave indene **4a** in 66% isolated yield (Table 1.1, entry 1). Other gold(I) complexes (**B-F**) could also be used in the reaction (Table 1.1, entries 2-6), although none of them outperformed catalyst **A**. Complex **G** bearing a phosphite ligand failed to promote this transformation (Table 1.1, entry 7).

Table 1.1. Catalyst screening for the reaction of **1a** with allene **3a**.[a]



Entry	Catalyst	**4a** Yield [%][b]
1	**A**	74 (66)[c]
2	**B**	55
3	**C**	61
4	**D**	55
5	**E**	31
6	**F**	57
7	**G**	-[d]

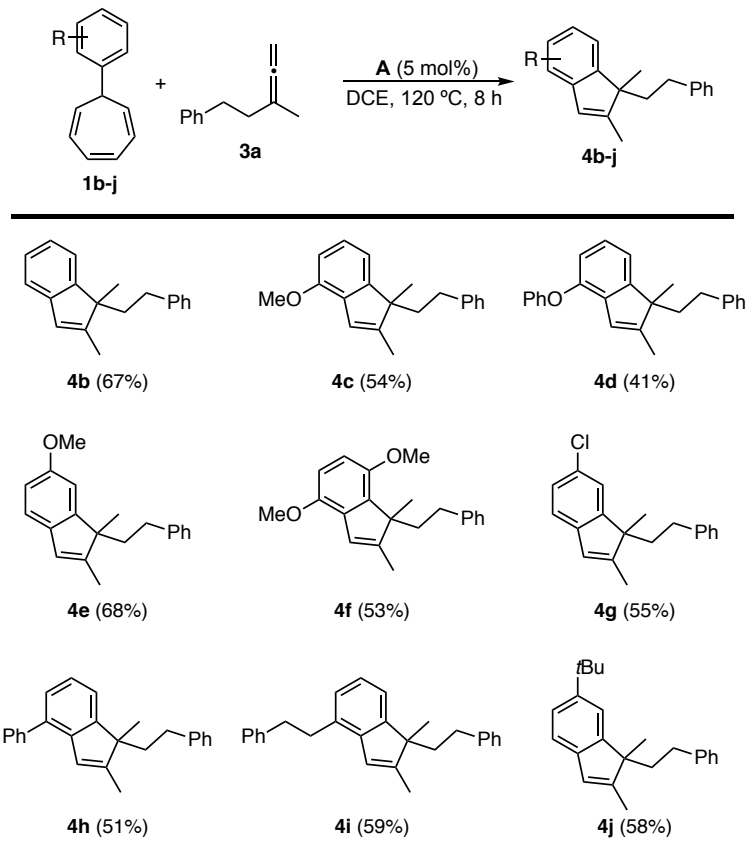
[a] Reaction of **1a** (0.1 M in 1,2-dichloroethane) with 2.0 equiv of **3a**, 5 mol% of catalyst at 120 ºC for 8 h. [b] Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield. [d] Not detected.



Synthesis of indene derivatives

Indenes **4b-j** were synthesized under the standard conditions with 41-67% yield by reaction of (3-methylpenta-3,4-dien-1-yl)benzene **3a** with *ortho*- or *para*-substituted, or *ortho*, *meta*-disubstituted aryl cycloheptatrienes(**1b-j**). Product **4d**, whose structure was confirmed by X-ray diffraction (Figure 1.3), was obtained in a lower yield as a result of the formation of *9H*-xanthene (10% yield) raising from a reported intramolecular Friedel-Crafts-type reaction with the *ortho* position of phenyl of the OPh group.[68] Fluorene generated from intramolecular carbene insertion into *ortho*-benzene of **1h** was observed in less than 5% yield.[68] In addition , we did not observed the formation of products resulting from any intramolecular C(sp^3)-H insertion product from substrate **1i**.[67]

Table 1.2. Gold(I)-catalyzed synthesis of indenes **4b-j**.



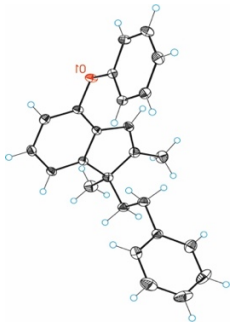
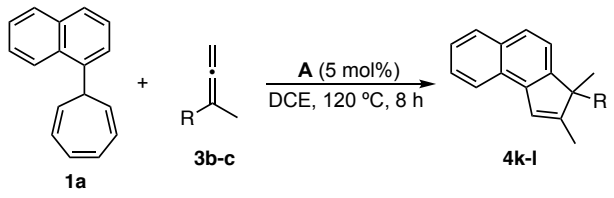


Figure 1.3. X-ray crystal structure of **4d**.

1-Naphtyl cycloheptatriene **1a** reacted satisfactorily with 3-methylbuta-1,2-diene **3b** giving rise to indene **4k** in good yield (71%). However, modification

of the substituents of allene from methyl to the cyclohexyl analogue **3c** provided the corresponding indene **4l** in moderate yield (Table 1.3).

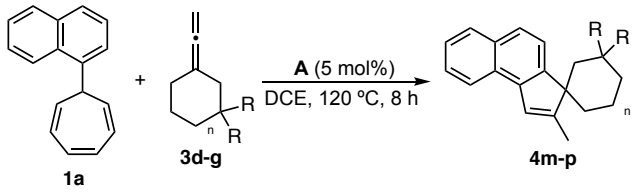
Table 1.3. Gold(I)-catalyzed synthesis of indenes **4k** and **4l**.

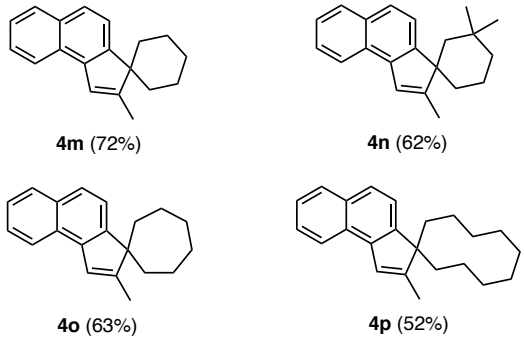


4k (71%) **4l** (49%)

The reaction of cycloheptatriene **1a** with allenes **3m-p** gave rise to several interesting spiro indenes containing six- and seven-membered rings, as well as a cyclodecane in moderate to good yield (Scheme 1.4).

Table 1.4. Gold(I)-catalyzed synthesis of indenes **4m-p**.



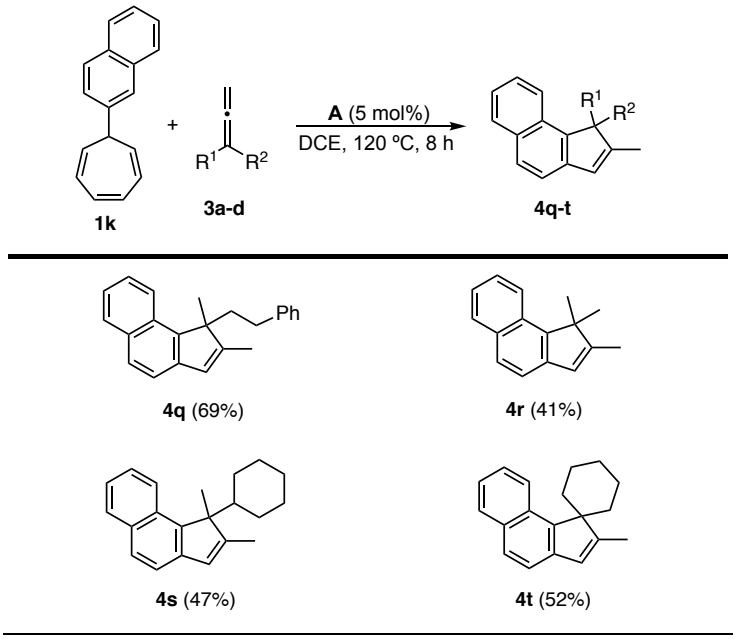


4m (72%) **4n** (62%)

4o (63%) **4p** (52%)

We also focused on 2-naphtyl cycloheptatriene, which could facilitate the ring closure step due to the more reactive α-position of naphthalene. Thus, the reactions of cycloheptatriene **1k** with allenes **3a-d** gave indenes **4q-t**, although in yields similar to those obtained from **1a** (Table 1.5). The X-ray diffraction structure of **4t** (Figure 1.4) confirmed that the ring closing reaction takes place at C-1 of the naphthalene.

Table 1.5. Gold(I)-catalyzed synthesis of indenes **4q-t**.



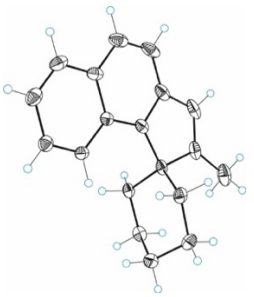
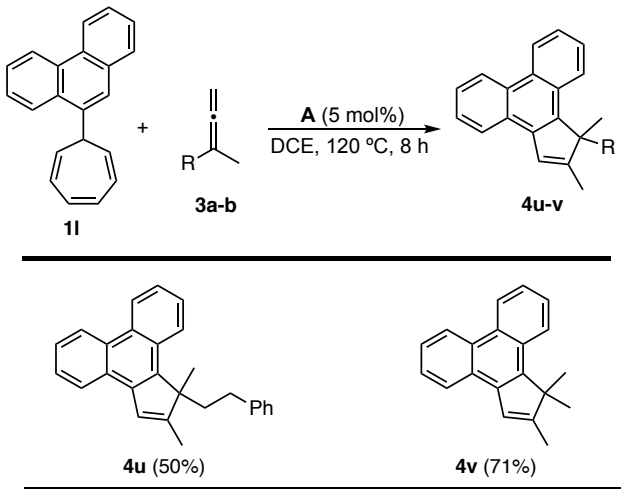


Figure 1.4. X-ray crystal structure of **4t**.

Two benzene-fused indenes **4u** and **4v** were also successfully synthesized by the reaction of phenanthryl substituted cycloheptatriene **1l** with allenes **3a** and **3b** (Table 1.6). The structure of **4v** was confirmed by X-ray diffraction (Figure 1.5).

Table 1.6. Gold(I)-catalyzed synthesis of indenes **4u** and 4**v**.



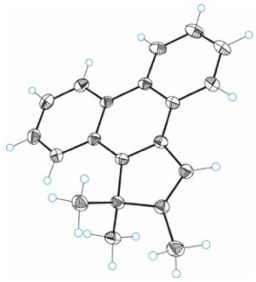
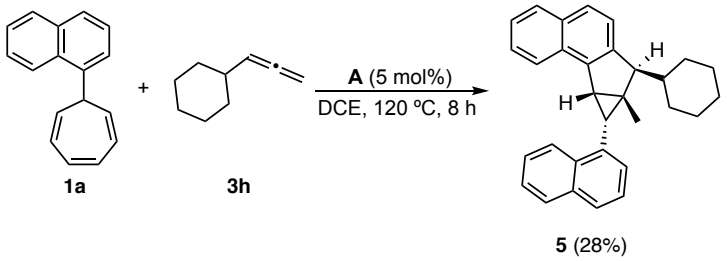


Figure 1.5. X-ray crystal structure of **4v**.

Although the resulting indenes have a reactive double bond, 2:1 adducts were only observed as very minor products in the crude reaction mixtures. In contrast, a 2:1 adduct was obtained in the reaction of **1a** with 1-cyclohexylallene (**3h**), a monosubstituted allene, to form **5** (Scheme 1.2), whose structure and relative configuration was determined by X-ray diffraction (Figure 1.6).



Scheme 1.2. Gold-catalyzed cycloaddition of **1a** with **3h**.

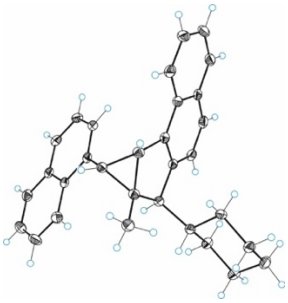
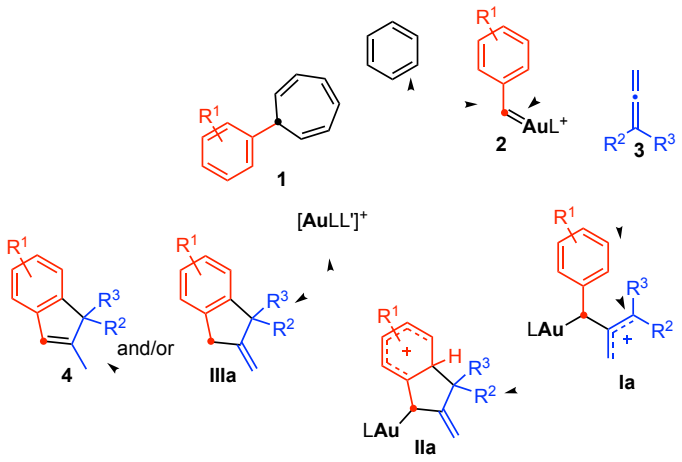


Figure 1.6. X-ray crystal structure of **5**.

A plausible mechanism to rationalize the formation of indenes **4** is proposed in Scheme 1.3. The formal (3 + 2) cycloaddition starts by the gold(I)-promoted retro-Buchner reaction of **1**, releasing benzene and generating gold(I) carbenes **2**, which undergo electrophilic attack to the central carbon of allenes **3** giving rise to allyl cationic species **Ia**. An intramolecular electrophilic aromatic substitution gives intermediates **IIa** that undergo rearomatization and protonolysis of the Au-C bond to form **IIIa**. Finally, isomerization of **IIIa** gives indenes **4**. Alternatively, protonation at the exocyclic double bond of **IIa** with concomitant deauration would furnish directly **4**.



Scheme 1.3. Proposed mechanism for the formal (3 + 2) cycloaddition between allenes and aryl gold(I) carbenes.

Conclusions

In summary, a new gold(I)-catalyzed formal (3 + 2) cycloaddition reaction was developed by reaction of allenes with aryl gold(I) carbenes generated by retro-Buchner reaction of 7-substituted cycloheptatrienes, leading to highly substituted indenes. The X-ray diffraction structures of several cycloadducts provided evidence for a reasonable mechanistic proposal including electrophilic attack of gold(I) carbenes to the central carbon of dialkyl substituted terminal allenes affording allyl cations, intramolecular electrophilic aromatic substitution of resulting cationic species, rearomatization, protonolysis of the Au-C bond and isomerization of exocyclic double bond.

Experimental section

General Information

All gold-catalyzed reactions were performed using HPLC-grade solvents, without a protective inert atmosphere. Unless otherwise stated, the rest of the reactions reported herein were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolvTM Solvent Purification System (SPS, Innovative Technologies, Inc., MA). Yields refer to chromatographically and spectroscopically pure (1H NMR) homogeneous material, unless otherwise stated. Thin layer chromatography was carried out using TLC aluminum sheets coated with 0.2 mm of silica gel (Merck Gf234) using short-wave UV light as visualizing agent and phosphomolybdic acid, KMnO4 or acidic vanillin followed by heat as developing agents. Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-60 μm) as the stationary phase manually, or using a CombiFlash®Rf instrument with normal phase disposable columns of different sizes (Teledyne Isco). Preparative TLC was performed on 20 cm x 20 cm silica gel plates (2.0 mm thick, catalogue number 02015, Analtech or 1.0 mm thick, catalogue number P02013 Analtech). NMR spectra were recorded at 23 oC on a Bruker Avance 300, 400 Ultrashield or Bruker Avance 500 Ultrashield apparatus. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, using the residual undeuterated solvent (CHCl3 at 7.28 ppm 1H NMR, 77.00 ppm 13C NMR) or tetramethylsilane as reference. Coupling constants are reported in hertz (*Hz*). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, br = broad. Mass spectra were recorded on a Waters LCT Premier Spectrometer (ESI and APCI) or on a Autoflex Bruker Daltonics (MALDI and LDI). Melting points were determined using a MP70 Melting Point System (Mettler Toledo). Unless otherwise stated, all reagents were purchased

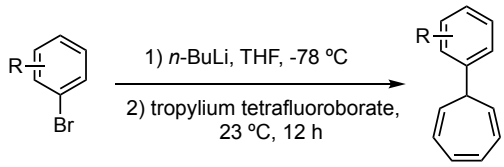
from commercial sources and used without further purification. Tropylium tetrafluoroborate was purchased from Fluorochem.

Handling of Gold(I) Catalysts

All gold complexes were synthesized according to our previously reported procedures[51e,75] or purchased from Sigma Aldrich, such as (acetonitrile)[(2-biphenyl)di-*tert*-butyl-phosphine]gold(I) hexafluoroantimonate (**A**) and (Acetonitrile)[2-di-tert-butyl(2′,4′,6′-triiso-propylbiphenyl)phosphine]gold(I) hexafluoroantimonate (**B**). The bottles were not stored under inert atmosphere.

Preparation of 7-aryl cycloheptatrienes

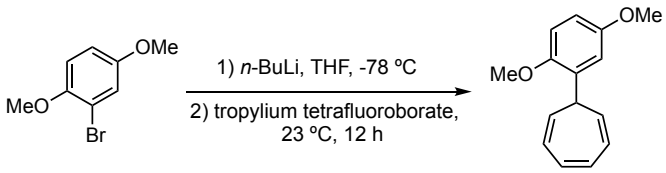
The cycloheptatriene substrates were prepared according to a literature procedure.[67,68,70]



n-BuLi (2.5 M in hexanes, 1.2 equiv) was added dropwise to a solution of the corresponding aryl bromide (1.0 equiv) in dry THF (4 mL/mmol) at −78 ºC under argon. The mixture was stirred for 30 min at −78 ºC, and then tropylium tetrafluoroborate (1.3 equiv) was added in one portion. The cooling bath was removed and the reaction was stirred at room temperature (23 ºC) for 12 h. The reaction was quenched by addition of water. The aqueous phase was extracted with diethyl ether, the combined organic extracts were dried over MgSO4, and the solvent was evaporated. The crude reaction mixture was purified by column chromatography on silica gel with cyclohexane as eluent unless otherwise stated.

75. (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146-6148. (b) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721-7730.

7-(2,5-Dimethoxyphenyl)cyclohepta-1,3,5-triene (1e)



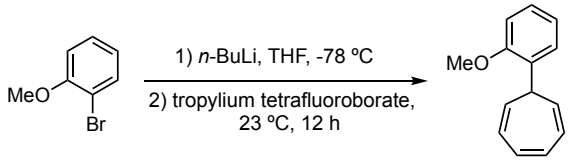
This compound (yellow oil, 2.0 g, yield: 88%) was prepared according to the general procedure from 2-bromo-1,4-dimethoxybenzene (2.2 g, 10 mmol), *n*-BuLi (2.5 M, 4.8 mL, 12 mmol) and tropylium tetrafluoroborate (2.3 g, 13 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, *J* = 3.0 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 6.82 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.74 (dd, *J* = 3.7, 2.7 Hz, 2H), 6.28-6.24 (m, 2H), 5.52-5.34 (m, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.15-3.12 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.73, 151.63, 133.09, 130.79, 126.94, 124.27, 115.26, 112.10, 111.83, 56.15, 55.73, 40.42.

HRMS-APCI: calculated for $C_{15}H_{16}O_2$ $[M+H]^+$: 229.1223; found = 229.1219.

7-(2-Methoxyphenyl)cyclohepta-1,3,5-triene (1f)



This compound (yellow oil, 1.5 g, yield: 76%) was prepared according to the general procedure from 1-bromo-2-methoxybenzene (1.87 g, 10 mmol), *n*-BuLi (2.5 M, 4.8 mL, 12 mmol) and tropylium tetrafluoroborate (2.3 g, 13 mmol).

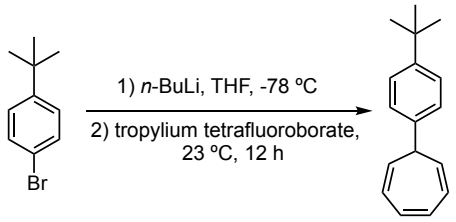
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.34 (m, 1H), 7.33-7.27 (m, 1H), 7.06-6.99 (m, 1H), 6.98-6.94 (m, 1H), 6.79-6.69 (m, 2H), 6.30-6.23 (m, 2H), 5.48-5.41 (m, 2H), 3.83 (d, *J* = 2.0 Hz, 3H), 3.19-3.12 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.36, 131.80, 130.78, 128.92, 127.79, 127.18,

124.14, 120.76, 110.93, 55.40, 40.49.

HRMS-APCI: calculated for $C_{14}H_{15}O[M+H]^+$: 199.1117; found = 199.1114.

7-(4-(*tert*-Butyl)phenyl)cyclohepta-1,3,5-triene (1j)



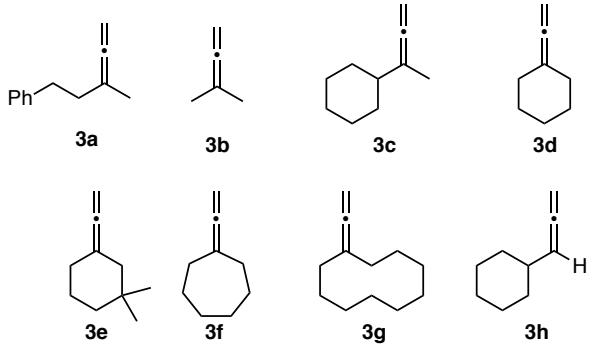
This compound (colourless oil, 1.8 g, yield: 80%) was prepared according to the general procedure from 1-bromo-4-chlorobenzene (2.1 g, 10 mmol), *n*-BuLi (2.5 M, 4.8 mL, 12 mmol) and tropylium tetrafluoroborate (2.3 g, 13 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 0.8 Hz, 2H), 6.77-6.73 (m, 2H), 6.29-6.23 (m, 2H), 5.48-5.39 (m, 2H), 2.72-2.66 (m, 1H), 1.35 (s, 9H).

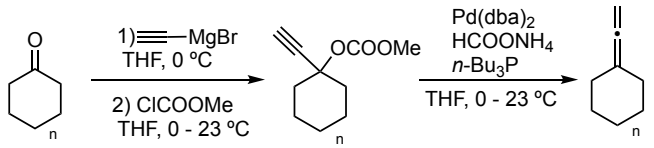
^{13}C NMR (101 MHz, $CDCl_3$) δ 149.43, 140.83, 130.90, 127.19, 126.40, 125.57, 124.28, 44.83, 34.45, 31.41.

HRMS-APCI: calculated for $C_{17}H_{21}$ $[M+H]^+$: 225.1638; found = 225.1635.

Procedure for the preparation of allenes



Allenes **3a**[76a], **3c**[76b], **3f**[76c] were known compounds and those spectral data were in good agreement with literature values. **3b**, **3d**, **3h** were purchased from Aldrich. **3e**, **3g** were prepared according to literature procedure.[76a]



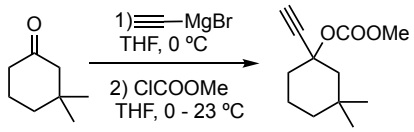
Ethynylmagnesium bromide (0.5 M in THF, 1.1 equiv) was added dropwise to a solution of the corresponding ketone (1.0 equiv) in dry THF (2 mL/mmol) at 0 ºC under argon. The mixture was stirred for 2 hours at 0 ºC, the disappearance of ketone was confirmed by TLC and then methyl chloroformate (1.3 equiv) was added. The cooling bath was removed and the reaction was stirred at room temperature (23 ºC) for 12 h. The reaction was quenched by addition of water. The aqueous phase was extracted with ethyl acetate, the combined organic extracts were dried over MgSO4, and the solvent was evaporated. The crude reaction mixture was purified by column chromatography on silica gel with the mixture of cyclohexane and ethyl acetate as eluent unless otherwise stated to give carbonate.

n-Bu_3P (0.2 equiv) was added dropwise to a stirred mixture of carbonate (1.0 equiv), ammonium formate (2.0 equiv) and $Pd(dba)_2$ (0.05 equiv) in THF (5 mL/mmol) at 0 ºC. After 12 h, the disappearance of carbonate was confirmed by TLC and the reaction mixture was filtered through a short pad of Celite. The solvent was evaporated, the residue was purified by column chromatography on silica gel with pentane as eluent.

1-ethynyl-3,3-dimethylcyclohexyl methyl carbonate (3e´)

---

76. (a) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254-15255. (b) Tani, Y.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2014**, *136*, 17706-17709. (c) Aoki, M.; Izumi, S.; Kaneko, M.; Ukai, K.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2007**, *9*, 1251-1253.



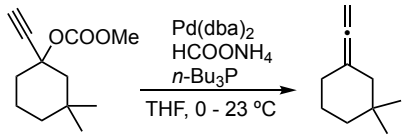
This compound (colorless oil, 1.8 g, yield: 54%) was prepared according to the general procedure from cyclodecanone (2.0 g, 15.9 mmol), ethynylmagnesium bromide (0.5 M in THF, 35 ml, 17.4 mmol) and methyl chloroformate (1.9 g, 1.6 ml, 20.6 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 2.60 (s, 1H), 2.13-1.83 (m, 4H), 1.78-1.57 (m, 2H), 1.39-1.23 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.50, 84.43, 76.66, 73.57, 54.32, 46.95, 38.34, 37.53, 31.08, 30.43, 29.00, 18.59.

HRMS-ESI: calculated for $C_{12}H_{18}NaO_3$ $[M+Na]^+$: 233.1148; found = 233.1155.

1,1-Dimethyl-3-vinylidene cyclohexane (3e)



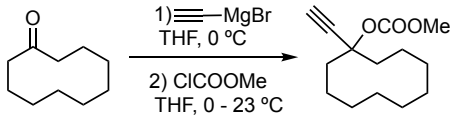
This compound (colorless oil, 800 mg, yield: 82%) was prepared according to the general procedure from **3e´** (2.0 g, 9.5 mmol), *n*-Bu_3P (385 mg, 0.46 ml, 1.9 mmol) and ammonium formate (1.2 g, 19 mmol) and $Pd(dba)_2$ (273 mg, 0.48 mol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61-4.51 (m, 2H), 2.13-2.04 (m, 2H), 1.95-1.88 (m, 2H), 1.66-1.58 (m, 2H), 1.36-1.29 (m, 2H), 0.95 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.47, 99.13, 72.15, 44.23, 38.94, 31.90, 30.63, 28.34, 22.76.

HRMS-APCI: calculated for $C_{10}H_{17}$ $[M+H]^+$: 137.1325; found = 137.1323.

1-Ethynylcyclodecyl methyl carbonate (3g´)



This compound (white solid, 1.7 g, yield: 71%) was prepared according to the general procedure from cyclodecanone (1.54 g, 10 mmol), ethynylmagnesium bromide (0.5 M in THF, 22 ml, 11 mmol) and methyl chloroformate (1.23 g, 1.0 ml, 13 mmol).

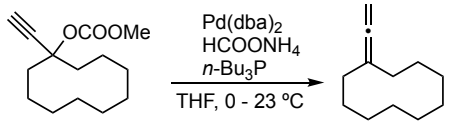
M.p: 59-61 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 2.62 (s, 1H), 2.32 (dt, *J* = 14.6, 7.0 Hz, 2H), 2.08 (dt, *J* = 14.9, 6.5 Hz, 2H), 1.78 – 1.45 (m, 14H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.36, 83.52, 81.01, 74.18, 54.32, 32.64, 26.17, 25.53, 23.54, 20.87.

HRMS-ESI: calculated for $C_{14}H_{22}NaO_3[M+Na]^+$: 261.1461; found = 261.1452.

Vinylidene cyclodecane (3g)



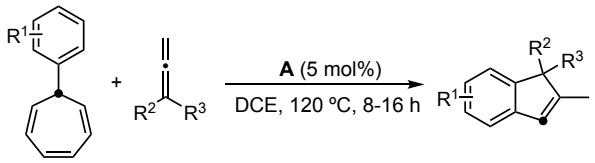
This compound (brown oil, 980 mg, yield: 84%) was prepared according to the general procedure from **3g´** (1.7 g, 7.1 mmol), *n*-Bu_3P (290 mg, 0.35 ml, 1.4 mmol) and ammonium formate (900 mg, 14 mmol) and $Pd(dba)_2$ (205mg, 0.36 mol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65-4.59 (m, 2H), 2.20-2.05 (m, 4H), 1.69-1.36 (m, 14H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 207.31, 101.89, 74.37, 30.69, 25.62, 24.61, 24.48, 24.38.

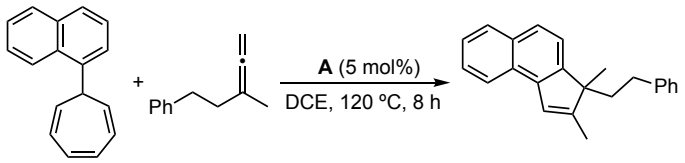
HRMS-APCI: calculated for $C_{12}H_{19}$ $[M-H]^+$: 163.1481; found = 163.1477.

Procedure for gold catalyzed formal (3+2) reactions



A solution of the arylcycloheptatriene substrate (0.2 mmol), allenes (0.4 mmol) and gold complex A (7.7 mg, 0.01 mmol) in 1,2-dichloroethane (DCE, 2 mL) was heated at 120 ºC in a sealed tube until the starting material had been fully consumed (8 h). After the reaction mixture had been allowed to cool to room temperature, the solvent was removed in vacuo and the crude residue was purified by column chromatography on silica gel. The reaction was performed under an air atmosphere with no special precautions taken to exclude water.

2,3-Dimethyl-3-phenethyl-3*H*-cyclopenta[*a*]naphthalene (4a)



The title compound (light yellow oil, 39.5 mg, yield: 66%) was synthesized according to the general procedure from 1-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

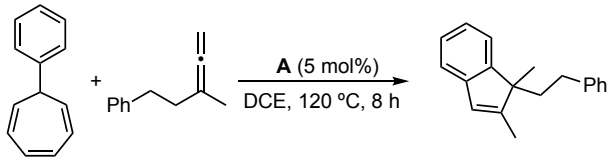
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.61-7.55 (m, 2H), 7.55-7.49 (m, 1H), 7.31 – 7.24 (m, 2H), 7.23-7.16 (m, 1H), 7.14-7.05 (m, 3H), 2.33 (td, *J* = 12.8, 4.6 Hz, 1H), 2.21-2.03 (m, 5H), 1.84 (td, *J* = 13.3, 5.1 Hz, 1H), 1.38 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.37, 148.44, 142.73, 139.73, 133.10, 128.48, 128.25, 128.22, 127.38, 125.61, 125.42, 124.89, 124.39, 124.08, 123.14, 120.16,

54.96, 38.94, 30.34, 23.61, 13.06.

HRMS-APCI: calculated for $C_{23}H_{23}$ $[M+H]^+$: 299.1794; found = 299.1795.

1,2-Dimethyl-1-phenethyl-1*H*-indene (4b)



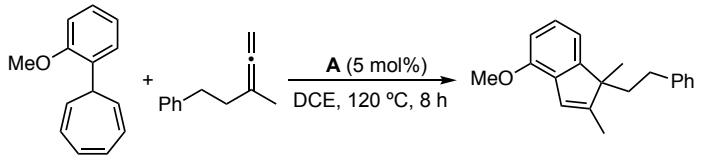
The title compound (colorless oil, 33.4 mg, yield: 67%) was synthesized according to the general procedure from 7-phenylcyclohepta-1,3,5-triene (34 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.12 (m, 7H), 7.07-7.02 (m, 2H), 6.49 (d, *J* = 1.6 Hz, 1H), 2.23-2.12 (m, 1H), 2.09-1.96 (m, 5H), 1.89-1.78 (m, 1H), 1.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.62, 151.36, 143.87, 142.75, 128.20, 128.18, 126.50, 125.77, 125.55, 124.04, 121.25, 119.98, 53.92, 39.31, 30.34, 23.93, 12.69.

HRMS-APCI: calculated for $C_{19}H_{21}$ $[M+H]^+$: 249.1638; found = 249.1641.

4-Methoxy-1,2-dimethyl-1-phenethyl-1*H*-indene (4c)



The title compound (colorless oil, 30 mg, yield: 54%) was synthesized according to the general procedure from 7-(2-methoxyphenyl)cyclohepta-1,3,5-triene (40 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

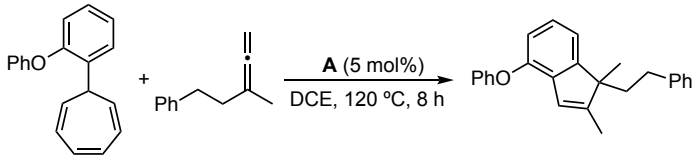
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.22 (m, 2H), 7.21-7.13 (m, 2H), 7.08-7.04 (m, 2H), 6.99 (dt, *J* = 7.4, 0.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 1.6

Hz, 1H), 3.93 (s, 3H), 2.20-2.11 (m, 1H), 2.08-1.97 (m, 5H), 1.90-1.81 (m, 1H), 1.27 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.51, 152.27, 150.95, 142.84, 131.92, 128.20, 125.53, 125.39, 121.70, 114.40, 108.84, 55.39, 54.47, 39.32, 30.35, 23.99, 12.74.

HRMS-APCI: calculated for $C_{20}H_{23}O$ $[M+H]^+$: 279.1743; found = 279.1752.

1,2-Dimethyl-1-phenethyl-4-phenoxy-1*H*-indene (4d)



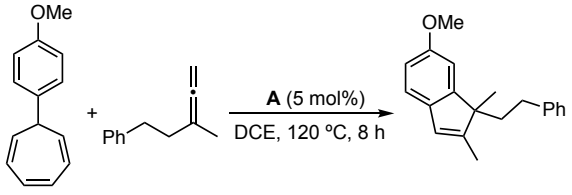
The title compound (yellow oil, 28 mg, yield: 41%) was synthesized according to the general procedure from 7-(2-phenoxyphenyl)cyclohepta-1,3,5-triene (52 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (m, 2H), 7.32-7.25 (m, 2H), 7.24-7.15 (m, 3H), 7.14-7.07 (m, 3H), 7.07-7.02 (m, 2H), 6.93 (dd, *J* = 7.2, 1.7 Hz, 1H), 6.48 (d, *J* = 1.7 Hz, 1H), 2.27-2.17 (m, 1H), 2.14-2.02 (m, 2H), 1.99 (d, *J* = 1.6 Hz, 3H), 1.92 (td, *J* = 14.3, 4.5 Hz, 1H), 1.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.38, 154.26, 152.37, 148.27, 142.66, 135.23, 129.64, 128.29, 128.25, 125.68, 125.55, 122.31, 121.87, 118.04, 117.42, 117.39, 54.57, 39.46, 30.37, 23.97, 12.80.

HRMS-APCI: calculated for $C_{25}H_{25}O$ $[M+H]^+$: 341.1900; found = 341.1902.

6-Methoxy-1,2-dimethyl-1-phenethyl-1*H*-indene (4e)



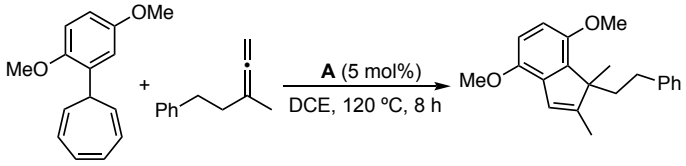
The title compound (colorless oil, 38 mg, yield: 68%) was synthesized according to the general procedure from 7-(4-methoxyphenyl)cyclohepta-1,3,5-triene (40 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.21 (m, 2H), 7.19-7.13 (m, 2H), 7.06 (d, *J* = 7.1 Hz, 2H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.42 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 3H), 2.18-2.00 (m, 3H), 1.97 (d, *J* = 1.6 Hz, 3H), 1.92-1.80 (m, 1H), 1.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.83, 153.61, 150.69, 143.10, 137.27, 128.54, 128.43, 125.88, 125.46, 120.44, 111.42, 109.03, 55.91, 54.32, 39.79, 30.70, 24.56, 12.98.

HRMS-APCI: calculated for $C_{20}H_{23}O$ $[M+H]^+$: 279.1743; found = 279.1749.

4,7-Dimethoxy-1,2-dimethyl-1-phenethyl-1*H*-indene (4f)



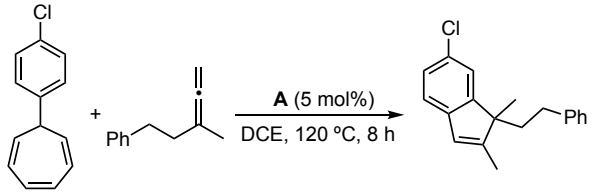
The title compound (colorless oil, 33 mg, yield: 53%) was synthesized according to the general procedure from 7-(2,5-dimethoxyphenyl)cyclohepta-1,3,5-triene (46 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2H), 7.18-7.11 (m, 1H), 7.07-7.03 (m, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.58 (d, *J* = 1.6 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.70-2.62 (m, 1H), 2.03-1.95 (m, 4H), 1.92-1.83 (m, 2H), 1.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.31, 150.39, 146.89, 143.22, 138.70, 133.58, 128.26, 128.08, 125.35, 121.43, 109.78, 107.26, 56.02, 55.56, 55.55, 36.36, 30.73, 21.54, 12.45.

HRMS-APCI: calculated for $C_{21}H_{25}O_2$ $[M+H]^+$: 309.1849; found = 309.1851.

6-Chloro-1,2-dimethyl-1-phenethyl-1*H*-indene (4g)



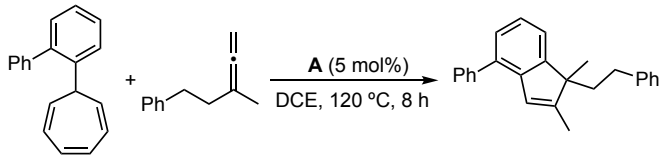
The title compound (colorless oil, 31 mg, yield: 55%) was synthesized according to the general procedure from 7-(4-chlorophenyl)cyclohepta-1,3,5-triene (41 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.21 (m, 4H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.07-7.04 (m, 2H), 6.44 (d, *J* = 1.6 Hz, 1H), 2.18-2.10 (m, 1H), 2.08-1.97 (m, 5H), 1.89-1.81 (m, 1H), 1.26 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.25, 142.33, 142.29, 130.09, 128.74, 128.26, 128.16, 126.67, 125.70, 125.09, 121.89, 120.75, 54.30, 39.08, 30.26, 23.81, 12.71.

HRMS-APCI: calculated for $C_{19}H_{20}Cl$ $[M+H]^+$: 283.1248; found = 283.1248.

1,2-Dimethyl-1-phenethyl-4-phenyl-1*H*-indene (4h)



The title compound (colorless oil, 33.3 mg, yield: 51%) was synthesized according to the general procedure from 2-(cyclohepta-2,4,6-trien-1-yl)-1,1'-biphenyl (49 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

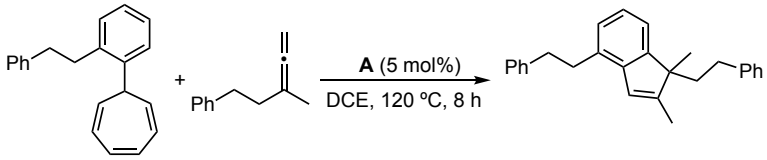
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.55 (m, 2H), 7.53-7.46 (m, 2H), 7.42-7.36

(m, 1H), 7.34-7.22 (m, 5H), 7.20-7.13 (m, 1H), 7.09-7.04 (m, 2H), 6.68 (d, *J* = 1.6 Hz, 1H), 2.27-2.16 (m, 1H), 2.13-1.98 (m, 5H), 1.96-1.86 (m, 1H), 1.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.12, 152.09, 142.74, 141.41, 141.08, 134.16, 128.97, 128.38, 128.23, 127.05, 126.76, 125.60, 124.82, 124.47, 120.30, 54.12, 39.45, 30.43, 24.09, 12.82.

HRMS-APCI: calculated for $C_{25}H_{25}$ $[M+H]^+$: 325.1951; found = 325.1947.

1,2-Dimethyl-1,4-diphenethyl-1*H*-indene (4i)



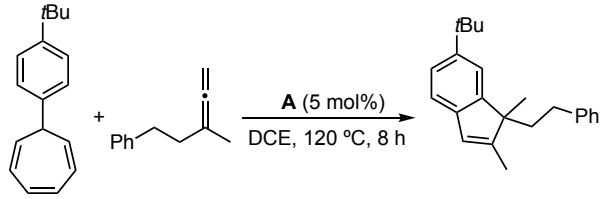
The title compound (colorless oil, 42 mg, yield: 59%) was synthesized according to the general procedure from 7-(2-phenethylphenyl)cyclohepta-1,3,5-triene (54 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.03 (m, 13H), 6.53 (d, *J* = 1.6 Hz, 1H), 3.10-3.03 (m, 2H), 3.02-2.95 (m, 2H), 2.22-2.09 (m, 1H), 2.07-1.95 (m, 5H), 1.90-1.75 (m, 1H), 1.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.16, 151.49, 142.85, 142.23, 142.05, 133.07, 128.52, 128.31, 128.22, 126.79, 125.84, 125.55, 124.27, 123.68, 119.15, 54.04, 39.43, 37.70, 35.24, 30.42, 24.05, 12.79.

HRMS-APCI: calculated for $C_{27}H_{29}$ $[M+H]^+$: 353.2264; found = 353.2262.

6-(*tert*-Butyl)-1,2-dimethyl-1-phenethyl-1*H*-indene (4j)



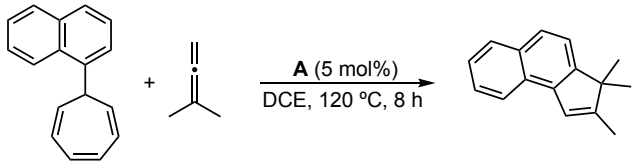
The title compound (colorless oil, 35 mg, yield: 58%) was synthesized according to the general procedure from 7-(4-(*tert*-butyl)phenyl)cyclohepta-1,3,5-triene (45 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.35 (m, 1H), 7.31-7.13 (m, 5H), 7.06-7.01 (m, 2H), 6.46 (d, *J* = 1.5 Hz, 1H), 2.20-2.11 (m, 1H), 2.11-2.01 (m, 2H), 2.00 (d, *J* = 1.6 Hz, 3H), 1.87-1.77 (m, 1H), 1.41 (s, 9H), 1.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.96, 151.21, 147.20, 142.97, 141.28, 128.24, 128.21, 128.18, 125.52, 125.40, 123.27, 119.21, 118.41, 77.35, 77.03, 76.71, 53.91, 39.52, 34.73, 31.80, 30.45, 24.01, 12.72.

HRMS-APCI: calculated for $C_{23}H_{29}$ $[M+H]^+$: 305.2264; found = 305.2268.

2,3,3-Trimethyl-3*H*-cyclopenta[*a*]naphthalene (4k)



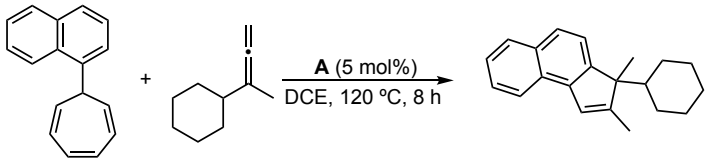
The title compound (colorless oil, 30 mg, yield: 72%) was synthesized according to the general procedure from 1-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and 3-methylbuta-1,2-diene (27 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.56-7.42 (m, 3H), 6.96 (d, *J* = 1.7 Hz, 1H), 2.11 (d, *J* = 1.6 Hz, 3H), 1.32 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.85, 150.73, 138.47, 132.98, 128.41, 127.42, 125.31, 124.76, 124.12, 124.06, 121.08, 120.18, 51.03, 23.40, 12.81.

HRMS-APCI: calculated for $C_{16}H_{17}$ $[M+H]^+$: 209.1325; found = 209.1329.

3-Cyclohexyl-2,3-dimethyl-3*H*-cyclopenta[*a*]naphthalene (4l)



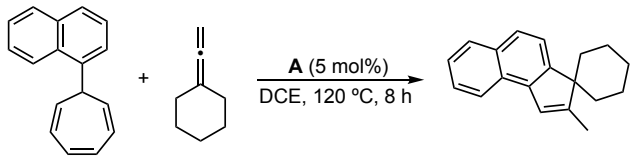
The title compound (colorless oil, 27 mg, yield: 49%) was synthesized according to the general procedure from 1-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and buta-2,3-dien-2-ylcyclohexane (55 mg, 0.4 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.48 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 7.43 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 6.97 (d, *J* = 1.7 Hz, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 2.01-1.94 (m, 1H), 1.85-1.77 (m, 1H), 1.71 (tt, *J* = 12.0, 3.0 Hz, 1H), 1.64-1.54 (m, 2H), 1.44-1.33 (m, 2H), 1.30 (s, 3H), 1.27-1.19 (m, 1H), 1.15 (tt, *J* = 13.0, 3.6 Hz, 1H), 1.02 (tt, *J* = 12.8, 3.7 Hz, 1H), 0.48 (ddd, *J* = 25.3, 13.1, 3.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.09, 148.40, 139.96, 132.77, 128.27, 127.17, 125.14, 124.70, 124.04, 123.34, 122.74, 121.80, 57.91, 44.14, 28.31, 27.40, 27.10, 26.95, 26.55, 20.79, 13.95.

HRMS-APCI: calculated for $C_{21}H_{25}$ $[M+H]^+$: 277.1951; found = 277.1957.

2'-Methylspiro[cyclohexane-1,3'-cyclopenta[*a*]naphthalene] (4m)



The title compound (white solid, 36 mg, yield: 72%) was synthesized according to the general procedure from 1-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and vinylidenecyclohexane (43 mg, 0.4 mmol).

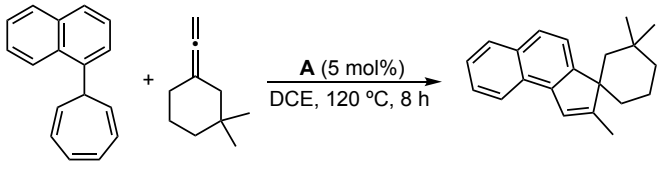
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.91-7.85 (m, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.49 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.44 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 2.18-2.06 (m, 5H), 2.05-1.97 (m, 1H), 1.90-1.77 (m, 4H), 1.58-1.46 (m, 1H), 1.35-1.28 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.08, 150.07, 139.24, 132.56, 128.11, 127.28, 125.14, 124.82, 124.09, 123.23, 122.81, 121.96, 54.63, 31.79, 25.64, 22.60, 13.92.

M.p: 45-47 ºC

HRMS-APCI: calculated for $C_{19}H_{21}$ $[M+H]^+$: 249.1638; found = 249.1638.

2',3,3-Trimethylspiro[cyclohexane-1,3'-cyclopenta[*a*]naphthalene] (4n)



The title compound (colorless oil, 34 mg, yield: 62%) was synthesized according to the general procedure from 1-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and 1,1-dimethyl-3-vinylidenecyclohexane (55 mg, 0.4 mmol).

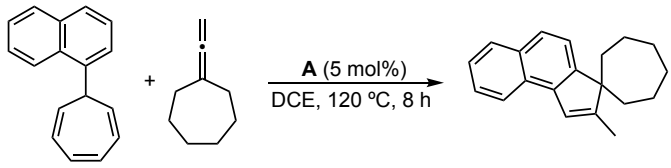
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-7.98 (m, 2H), 7.86-7.82 (m, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.49-7.38 (m, 2H), 6.98-6.94 (m, 1H), 2.22-2.06 (m, 4H), 1.88-1.78 (m, 1H), 1.74-1.63 (m, 3H), 1.48-1.33 (m, 2H), 1.20 (s, 3H), 1.11 (dt, *J* = 14.3, 1.7 Hz, 1H), 1.04 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.60, 150.94, 139.50, 132.43, 127.94, 127.17, 125.11, 124.86, 124.10, 123.36, 122.75, 122.23, 55.62, 43.64, 38.91, 35.42,

30.52, 30.43, 28.73, 20.20, 14.05.

HRMS-APCI: calculated for $C_{21}H_{25}$ $[M+H]^+$: 277.1951; found = 277.1960.

2'-Methylspiro[cycloheptane-1,3'-cyclopenta[*a*]naphthalene] (4o)



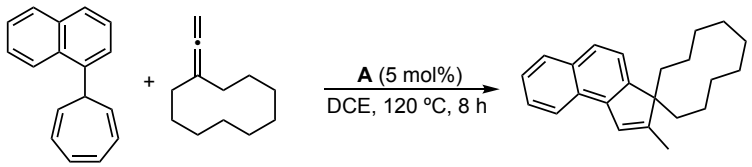
The title compound (colorless oil, 33 mg, yield: 63%) was synthesized according to the general procedure from 1-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and vinylidenecycloheptane (49 mg, 0.4 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.47 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 2.18 (d, *J* = 1.5 Hz, 3H), 2.03-1.90 (m, 2H), 1.89-1.64 (m, 10H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.62, 152.42, 138.34, 132.72, 128.20, 127.26, 125.22, 124.72, 124.07, 123.74, 121.29, 121.10, 57.44, 35.53, 32.32, 25.47, 14.66.

HRMS-APCI: calculated for $C_{20}H_{23}$ $[M+H]^+$: 263.1794; found = 263.1805.

2'-Methylspiro[cyclodecane-1,3'-cyclopenta[*a*]naphthalene] (4p)



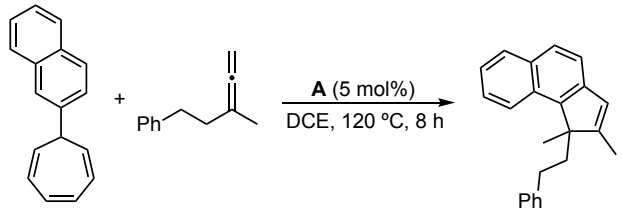
The title compound (colorless oil, 32 mg, yield: 52%) was synthesized according to the general procedure from 1-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and vinylidenecyclodecane (66 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.63-7.53 (m, 2H), 7.48-7.37 (m, 2H), 6.89 (d, *J* = 1.6 Hz, 1H), 2.16 (d, *J* = 1.5 Hz, 3H), 2.09-1.94 (m, 2H), 1.92-1.58 (m, 16H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.33, 150.34, 138.45, 132.69, 128.19, 127.27, 125.14, 124.72, 124.04, 123.26, 121.86, 121.74, 57.91, 29.35, 28.66, 28.13, 23.78, 22.94, 15.86.

HRMS-APCI: calculated for $C_{23}H_{29}$ $[M+H]^+$: 305.2264; found = 305.2268.

1,2-Dimethyl-1-phenethyl-1*H*-cyclopenta[*a*]naphthalene (4q)



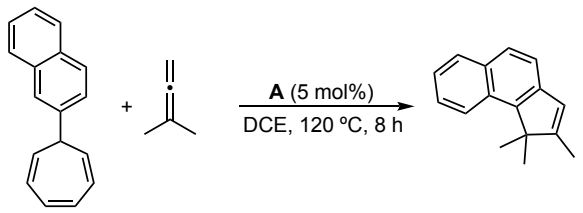
The title compound (colorless oil, 41 mg, yield: 69%) was synthesized according to the general procedure from 2-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.61-7.54 (m, 2H), 7.50-7.44 (m, 1H), 7.22 (tq, *J* = 7.1, 1.2 Hz, 2H), 7.17-7.11 (m, 1H), 6.98 (d, *J* = 7.0 Hz, 2H), 6.67 (s, 1H), 2.69 (td, *J* = 13.1, 5.2 Hz, 1H), 2.28-2.18 (m, 1H), 2.14 (s, 3H), 1.95 (td, *J* = 13.1, 4.5 Hz, 1H), 1.69 (td, *J* = 13.1, 4.8 Hz, 1H), 1.52 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.29, 144.49, 142.66, 141.51, 131.98, 129.68, 129.33, 128.23, 128.16, 127.87, 126.12, 125.89, 125.54, 123.63, 122.43, 120.14, 56.06, 39.37, 30.48, 24.00, 12.60.

HRMS-APCI: calculated for $C_{23}H_{23}$ $[M+H]^+$: 299.1794; found = 299.1799.

1,1,2-Trimethyl-1*H*-cyclopenta[*a*]naphthalene (4r)



The title compound (white soild, 17 mg, yield: 41%) was synthesized according to the general procedure from 2-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and 3-methylbuta-1,2-diene (27 mg, 0.4 mmol).

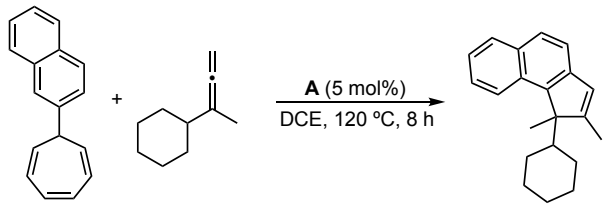
M.p: 73-75 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.57-7.51 (m, 2H), 7.42 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 6.52 (d, *J* = 1.6 Hz, 1H), 2.11 (d, *J* = 1.6 Hz, 3H), 1.49 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.02, 146.88, 140.21, 131.93, 129.58, 128.97, 127.63, 125.58, 123.96, 123.44, 122.81, 120.18, 51.80, 23.51, 12.40.

HRMS-APCI: calculated for $C_{16}H_{17}$ $[M+H]^+$: 209.1325; found = 209.1333.

1-cyclohexyl-1,2-dimethyl-1*H*-cyclopenta[*a*]naphthalene (4s)



The title compound (colorless oil, 26 mg, yield: 47%) was synthesized according to the general procedure from 2-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and buta-2,3-dien-2-ylcyclohexane (55 mg, 0.4 mmol).

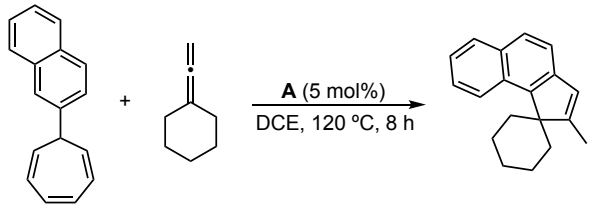
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.1 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.52 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.47 (d, *J* = 8.2 Hz,

1H), 7.40 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 6.55 (d, *J* = 1.7 Hz, 1H), 2.35-2.25 (m, 1H), 2.14 (d, *J* = 1.5 Hz, 3H), 1.91-1.83 (m, 1H), 1.67-1.44 (m, 6H), 1.37-1.24 (m, 2H), 1.14-0.78 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.21, 146.82, 141.33, 132.16, 129.67, 128.94, 127.61, 126.83, 125.25, 123.45, 123.22, 119.76, 59.24, 44.93, 27.85, 27.67, 26.95, 26.64, 20.46, 16.00.

HRMS-APCI: calculated for $C_{21}H_{25}$ $[M+H]^+$: 277.1951; found = 277.1957.

Spiro[cyclohexane-1,1'-cyclopenta[*a*]naphthalene] (4t)



The title compound (yellow solid, 26 mg, yield: 52%) was synthesized according to the general procedure from 2-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol) and vinylidenecyclohexane (44 mg, 0.4 mmol).

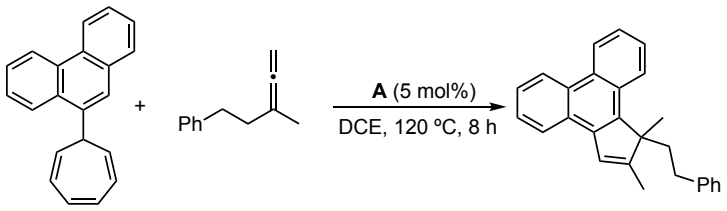
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.55 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.41 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 6.48 (d, *J* = 1.6 Hz, 1H), 2.58 (ddd, *J* = 14.5, 12.8, 6.0 Hz, 2H), 2.43 (d, *J* = 1.6 Hz, 3H), 2.07-1.88 (m, 5H), 1.76-1.63 (m, 1H), 1.49-1.42 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.39, 146.80, 139.96, 132.44, 129.95, 128.01, 125.67, 125.31, 123.19, 122.90, 119.85, 54.77, 31.90, 25.37, 23.01, 19.69.

M.p: 122-124 ºC

HRMS-APCI: calculated for $C_{19}H_{21}$ $[M+H]^+$: 249.1638; found = 249.1647.

1,2-Dimethyl-1-phenethyl-1*H*-cyclopenta[*l*]phenanthrene (4u)



The title compound (white solid, 49.3 mg, yield: 71%) was synthesized according to the general procedure from 9-(cyclohepta-2,4,6-trien-1-yl)phenanthrene (54 mg, 0.2 mmol) and (3-methylpenta-3,4-dien-1-yl)benzene (63 mg, 0.4 mmol).

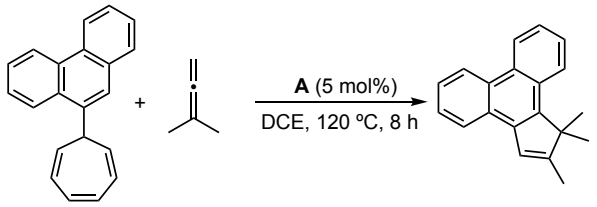
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 8.2 Hz, 1H), 8.85-8.80 (m, 1H), 8.28-8.22 (m, 2H), 7.75 – 7.62 (m, 4H), 7.23-7.16 (m, 3H), 7.15-7.10 (m, 1H), 6.99-6.93 (m, 2H), 2.74 (td, *J* = 13.2, 4.8 Hz, 1H), 2.32-2.17 (m, 4H), 1.97 (ddd, *J* = 13.9, 12.5, 4.5 Hz, 1H), 8.87 (td, *J* = 12.8, 4.9 Hz, 1H), 1.56 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.07, 142.65, 142.32, 138.53, 130.44, 129.16, 129.06, 128.26, 128.20, 127.47, 126.61, 126.45, 125.85, 125.59, 124.67, 124.44, 124.01, 123.27, 123.11, 123.01, 57.28, 39.28, 30.61, 24.01, 12.88.

M.p: 97-99 ºC

HRMS-APCI: calculated for $C_{27}H_{25}$ $[M+H]^+$: 349.1591; found = 349.1596.

1,1,2-Trimethyl-1*H*-cyclopenta[*l*]phenanthrene (4v)



The title compound (white solid, 25.5 mg, yield: 49%) was synthesized according to the general procedure from 9-(cyclohepta-2,4,6-trien-1-yl)phenanthrene (54 mg, 0.2 mmol) and 3-methylbuta-1,2-diene (27 mg, 0.4

mmol).

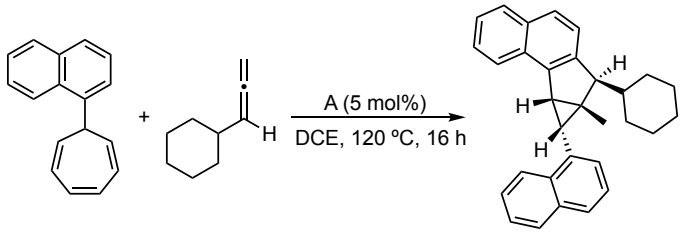
M.p: 125-127 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04-8.59 (m, 2H), 8.40-8.06 (m, 2H), 7.79-7.54 (m, 4H), 7.05 (d, *J* = 1.6 Hz, 1H), 2.20 (d, *J* = 1.6 Hz, 3H), 1.56 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.72, 144.58, 137.06, 130.25, 129.13, 128.73, 127.52, 126.34, 126.27, 125.67, 124.62, 124.17, 123.88, 123.42, 123.16, 120.93, 52.97, 23.45, 12.65.

HRMS-APCI: calculated for $C_{20}H_{19}$ $[M+H]^+$: 259.1481; found = 259.1486.

7-Cyclohexyl-7a-methyl-8-(naphthalen-1-yl)-7,7a,8,8a-tetrahydrocyclo-propa[4,5] cyclopenta[1,2-*a*]naphthalene(5)



A solution of the 1-(cyclohepta-2,4,6-trien-1-yl)naphthalene (44 mg, 0.2 mmol), buta-2,3-dien-2-ylcyclohexane (55 mg, 0.4 mmol) and gold complex A (7.7 mg, 5 mol%) in 1,2- dichloroethane (DCE, 2 mL) was heated at 120 ºC in a sealed tube until the starting material had been fully consumed (16h). After the reaction mixture had been allowed to cool to room temperature, the solvent was removed in vacuo and the crude residue was purified by preparative TLC to give **5** (11 mg, 28% yield) as yellow solid.

M.p: 205-207 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 7.6 Hz, 2H), 7.88-7.81 (m, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.64 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.60-7.38 (m, 5H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.69 (dd, *J* = 8.2, 7.2 Hz, 1H), 6.20 (dt, *J* = 7.3, 1.3 Hz, 1H),

3.32 (dd, J = 7.6, 1.8 Hz, 1H), 2.74 (d, J = 7.5 Hz, 1H), 2.61 (t, J = 2.1 Hz, 1H), 1.93 (s, 4H), 1.79-1.71 (m, 1H), 1.67-1.45 (m, 5H), 1.39-1.17 (m, 2H), 1.08-0.91 (m, 1H), 0.52-0.38 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.93, 139.74, 133.94, 133.43, 132.86, 132.42, 130.89, 128.69, 128.40, 128.02, 125.97, 125.80, 125.69, 125.10, 125.00, 124.84, 124.65, 124.48, 124.39, 123.51, 52.30, 40.65, 35.68, 33.69, 32.85, 32.82, 29.17, 27.61, 26.62, 26.45, 20.85.

HRMS-APCI: calculated for $C_{31}H_{31}$ $[M+H]^+$: 403.2420; found = 403.2417.

Chapter 2. Progress Towards the Total Synthesis of Cycloaurenones and Dysiherbols

Introduction

Cycloaurenones A-C (**1a-c**) were first discovered by Shin and coworkers from a tropical *Dysidea* sp. sponge off the coast of Chuuk Island, Federated States of Micronesia in 2015.[77] On the basis of spectroscopic analysis, cycloaurenones A−C (**1a-c**) were shown to belong to a new class of meroterpenoids with an additional five-membered ring. One year later, dysiherbols A-C (**2a**–**c**) were isolated from South China Sea sponges, Xisha islands of China, by Lin and coworkers. Interestingly, the NF-*κ*B inhibitory and cytotoxic activity evaluation disclosed that dysiherbol A (**2a**) showed potent activity with respective IC50 values of 0.49 and 0.58 μM, which were about 10-fold and 20-fold more potent than those of dysiherbols B (**2b**) and C (**3c**), which feature hydroxy and ketone carbonyl groups at the C-3 position.[78] Structurally, both of cycloaurenones (**1a-c**) and dysiherbols (**2a-c**) possess an interesting 6/6/5/6-fused tetracylic carbon skeleton. However, while the former compounds feature a *cis*-decalin moiety, the dysiherbols show a trans fusion of the A/B rings (Figure 2.1). In addition, they also differ in their absolute configuration. These compounds are biogenetically related to other natural products isolated from sponges, such as (+)-smenoqualone,[79] ilimaquinone,[80] and smenospongin.[81] Many of these natural products display antimicrobial, anti-HIV, anti-inflamatory, antiproliferative, and antisecretory activities and have attracted the interest of synthetic chemists.[82] However, despite all these biological properties, no

77. Kim, C.-K.; Woo, J.-K.; Kim, S.-H.; Cho, E.; Lee, Y.-J.; Lee, H.-S.; Sim, C. J.; Oh, D.-C.; Oh, K.-B.; Shin, J.; *J. Nat. Prod.* **2015**, *78*, 2814-2821.
78. Jiao, W.-H.; Shi, G.-H.; Xu, T.-T.; Chen, G.-D.; Gu, B.-B.; Wang, Z.; Peng, S.; Wang, S.-P.; Li, J.; Han, B.-N.; Zhang, W.; Lin, H.-W. *J. Nat. Prod.* **2016**, *79*, 406-411.
79. Bourguet-Kondracki, M.-L.; Martin, M.-T.; Guyot, M. *Tetrahedron Lett.* **1992**, *33*, 8079-8080.
80. Capon, R. J.; MacLeod, J. K. *J. Org. Chem.* **1987**, *52*, 5059-5060.
81. Kazlauskas, R.; Murphy, P. T.; Warren, R. G.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1978**, *31*, 2685-2697.
82. (a) Bruner, S. D.; Radeke, H. S.; Tallarico, H. S.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114 -1115. (b) Radeke, H. S.; Digits, C. A.; Bruner, S. D.; Snapper, M. L. *J. Org. Chem.* **1997**, *62*, 2823 -2831. (c) Poigny, S.; Guyot, M.; Samadi, M. *J. Org. Chem.* **1998**, *63*, 5890-5894. (d) Ling, T.; Poupon, E.; Rueden, E. J.; Kim, S. H.; Theodorokis, E. A. *J. Am. Chem. Soc.* **2002**,

approach towards the synthesis of the cycloaurenones and the dysiherbols has been reported.

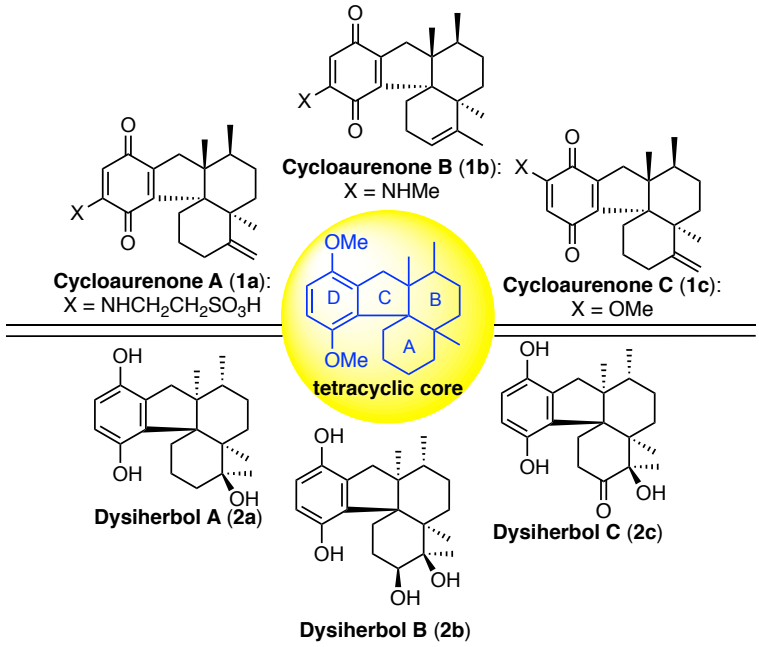
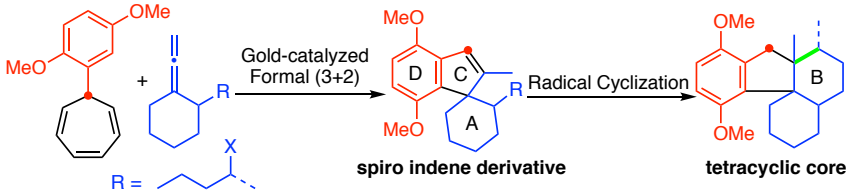


Figure 2.1. Cycloaurenones A-C (**1a-c**) and dysiherbols A-C (**2a-c**).

124, 12261-12267. (e) Ling, T.; Poupon, E.; Rueden, E. J.; Theodorokis, E. A. *Org. Lett.* **2002**, *4*, 819-822. (f) Marcos, I. S.; Conde, A.; Moro, R. F.; Basabe, P.; Díez, D.; Urones, J. G. *Tetrahedron* **2010**, *66*, 8280-8290. (g) Speck, K.; Magauer, T. *Chem. Eur. J.* **2017**, *23*, 1157-1165. (h) Speck, K.; Wildermuth, R.; Magauer, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 14131-14135 (i) Katoh, T.; Atsumi, S.; Saito, R.; Narita, K.; Katoh, T. *Eur. J. Org. Chem.* **2017**, 3837-3849.

Objectives

In above chapter, we summarized our efforts on the development of a useful strategy for the synthesis of diverse spiro indene derivatives by gold-catalyzed formal (3+2) cyclization of gold carbenes with 1,1-disubstituted terminal allenes. As a first approach to the synthesis of these natural products, we considered applying this novel cycloaddition reaction together with a radical cyclization as key steps to construct the tetracyclic core structure of **1a–c** and **2a–c** (Scheme 2.1).



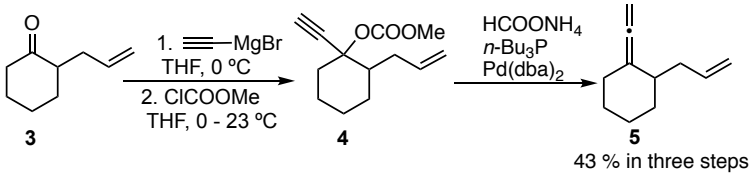
Scheme 2.1. Proposal of tetracyclic core syntheses.

According to the proposal, the A/C skeleton could be efficiently built in a single step by the gold(I)-catalyzed cycloaddition reaction. Moreover, the targeted spiro indene derivative would be obtained as a 1:1 mixture of two diastereomers, each with the relative configuration of cycloaurenones and dysiherbols. Once the synthesis of this crucial sprio compound were achieved, a radical cyclization would be conducted to form B ring of the tetracyclic core. Meanwhile, several challenges of this proposed strategy should be kept in mind: i. the allene substrate bearing a functional group substituted side chain could undergo an undesired cyclization in the presence of cationic gold(I) catalyst; ii. the separation and structure confirmation of the two diastereomers generated in the gold(I)-catalyzed step could be a technical difficulty.

Results and Discussion

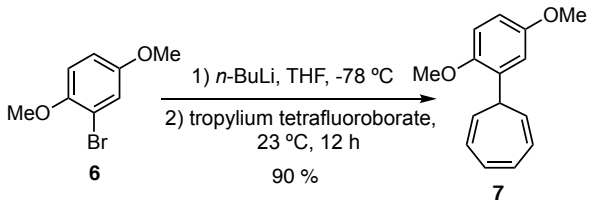
Attempt to synthesize spiro-indene skeleton

We chose ketone as a precursor for synthesis of allene moiety. On the other hand, the halogen required for the radical cyclization could be installed from alkene group. Thus, the synthesis of allene **5** started with 2-allylcyclohexan-1-one **3**, which is commercial available. Treatment of ketone **3** with ethynylmagnesium bromide, followed by addition of methyl chloroformate gave crude product **4** as a 1:1 mixture of diastereomers, which underwent palladium-catalyzed reduction with ammonium formate to give allene **5** bearing allyl group at α-position. Allene **5** was thus formed in 43% overall yield in three steps as a colorless oil (Scheme 2.2).



Scheme 2.2. Synthesis of allene substrate **5**.

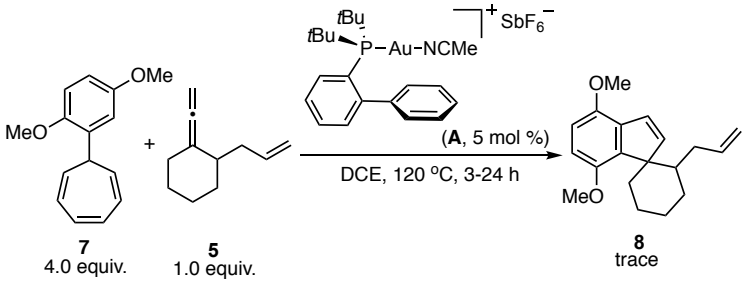
7-(2,5-Dimethoxyphenyl)cyclohepta-1,3,5-triene **7** was obtained in 90% yield by lithium-halogen exchange of 2-bromo-1,4-dimethoxybenzene **6** and nucleophilic attack of tropylium tetrafluoroborate (Scheme 2.3).



Scheme 2.3. Synthesis of cycloheptatriene **7**.

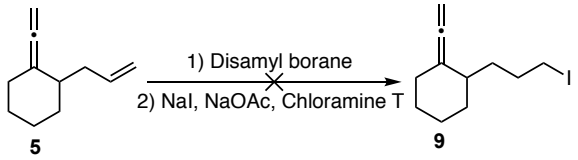
With the allene and cycloheptatriene in hand, we performed the (3+2) cycloaddition reaction in the presence of gold(I) catalyst **A** at 120 °C in DCE.

Unfortunately, just trace of spiro indene product was observed by GC-MS. In this reaction, the allene was decomposed probably because of isomerization to the 1,3-diene or alkyne or the intramolecular reaction of allene with alkene promoted by gold(I). The gold(I) catalyst was also decomposed resulting in the formation of gold mirror after 1 h (Scheme 2.4).



Scheme 2.4. Gold-catalyzed formal (3+2) reaction of **7** with **5**.

We were considering modification of terminal alkene into the alkyl halide to avoid side reactions. A hydroboration-iodination sequence[83] transformation of **5** to the corresponding alkyl iodide **9** failed (Scheme 2.5). Due to their similar reactivity, [71] it was difficult to functionalize the alkene in the presence of the allene.



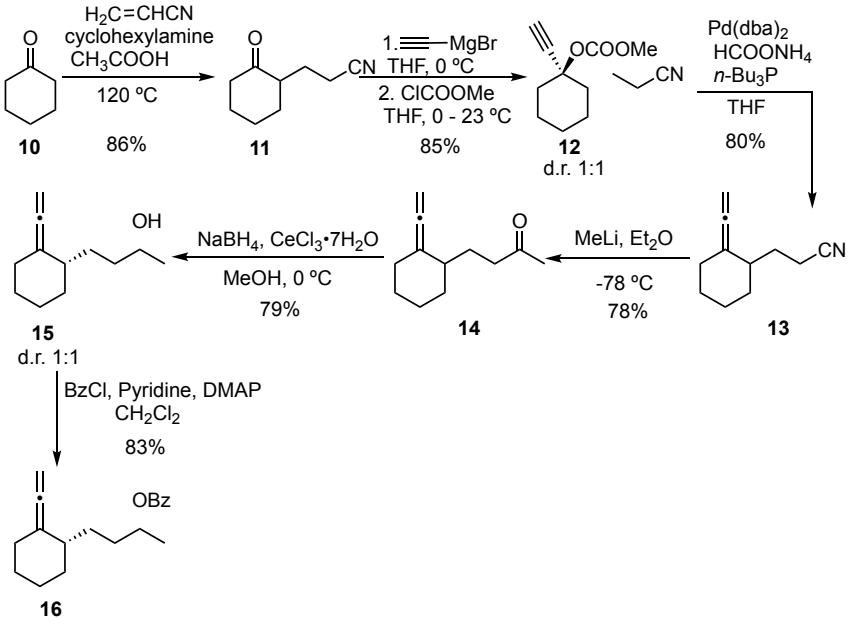
Scheme 2.5. Attempt on modification of terminal alkene to iodine.

New strategy for construction of spiro-indene skeleton

In order to solve the problem with the functionalization of the side chain, we decided to install a protected alcohol as the precursor which was regarded as a tolerated functional group for gold-catalyzed retro-Buchner process.

83. (a) Kabalka, G. W.; Gooch, E. E. *J. Org. Chem.* **1981**, *46*, 2582-2584. (b) Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 6712-6724.

3-(2-Oxocyclohexyl)propanenitrile (**11**) was obtained by the Michael addition of cyclohexanone to acrylonitrile in 86% yield.[84] The allene was constructed by a sequence involving the addition of ethynylmagnesium bromide to the carbonyl, activation of the alcohol with methyl chloroformate, Pd(0)-catalyzed reduction of the carbonate as we described above to give **13** with 68% overall yield for three steps. Treatment of the nitrile **13** with methyllithium followed by acidic quenching led to the ketone **14** in 78% yield. The carbonyl group of **14** was reduced to the alcohol under Luche conditions to give allenol **15** as a 1:1 mixture of diastereomers in 79% yield as a colorless oil. Benzoate protection of the alcohol of **15** yielded **16** in 83% yield as a stable yellow oil in gram scale (Scheme 2.6).



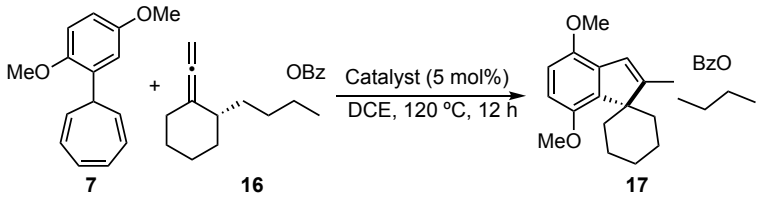
Scheme 2.6. Synthesis of substrate **16**.

With compound **16** in hand, we conducted the (3+2) cycloaddition in the

84. Woodmansee, D. H.; Muller, M.-A.; Neuburger, M.; Pfaltz, A. *Chem. Sci.* **2010**, *1*, 72-78.

presence of JohnPhos gold(I) catalyst **A** at 120 °C in DCE using 2 equivalents of allene substrate **16** leading to the cycloadduct **17** in a low yield (Table 2.1, entry 1). Since allene **16** was prepared in seven steps with 30% overall yield from commercial available cyclohexanone whereas cycloheptatriene **6** was accessed in one step with 90% yield, we changed the ratio of cycloheptatriene and allene from 1:2 to 2:1, although the improvement of the yield was modest (Table 2.1, entry 2). To avoid oxidation of gold(I) carbene by oxygen,[85] the reaction was set up in glove box and was performed in a sealed tube giving **17** in 25% yield (Table 2.1, entry 3). Treatment of the reaction with [IPrAu(PhCN)]SbF_6 (**B**) gave **17** in moderate yield (Table 2.1, entry 4) and this transformation could be conducted in 1 mmol scale with a comparable yield (Table 2.1, entry 5).

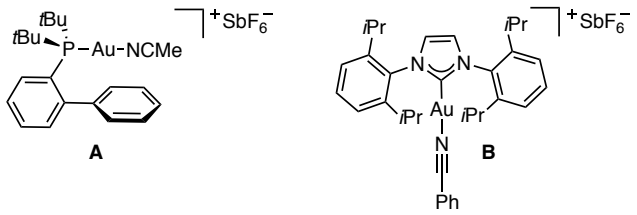
Table 2.1. Optimization of the key (3 + 2) cycloaddtion.



Entry	Catalyst (5%)	Ratio of **7** and **16**	Yield (%) [a]
1	**A**	1:2	15
2	**A**	2:1	21
3 [b]	**A**	2:1	25
4 [b]	**B**	2:1	41(59) [c]
5 [d]	**B**	2:1	39 (55) [c]

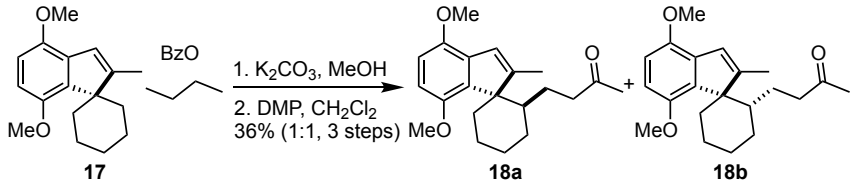
[a] Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [b] Reaction under Argon. [c] The yield based on recovered starting material is given in the parentheses. [d] 1 mmol scale.

85. (a) Zhou, Y.; Trewyn, B. G.; Angelici, R. J.; Woo, L. K. *J. Am. Chem. Soc.* **2009**, *131*, 11734-11743. (b) Zhan, H.; Zhao, L.; Liao, J.; Li, N.; Chen, Q.; Qiu, S.; Cao, H. *Adv. Synth. Catal.* **2015**, *357*, 46-50.



Synthesis of tetracyclic skeletons

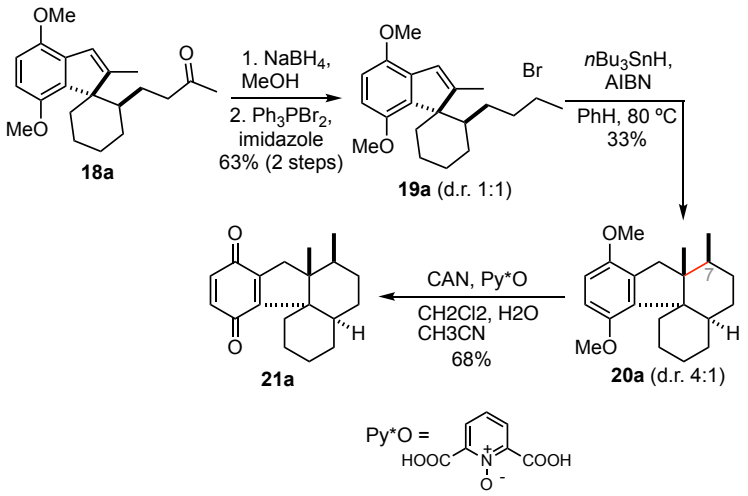
Treatment of crude cycloadduct **17** with potassium carbonate gave free alcohol that was oxidized by Dess–Martin periodinane delivering ketones **18a** and **18b** in a 1:1 ratio. 36% isolated yield was achieved over three steps from allene **16** after only one purification by preparative TLC, which allowed obtaining each product as single stereoisomers (Scheme 2.7).



Scheme 2.7. Synthesis of ketones **18a** and **18b**.

Ketone **18a** was reduced to the corresponding alcohol and then treated with triphenylphosphine dibromide to give alkyl bromide **19a** in 63% yield over two steps (Scheme 2.8). Treatment of **19a** with *n*Bu_3SnH in the presence of AIBN triggered a radical cyclization delivering the corresponding tetracyclic product **20a** in 33% yield (4:1 mixture of epimers at C-7). The major isomer displays the configuration of cycloaurenones, as shown by X-ray diffraction (Figure 2.2). Finally, oxidative deprotection of the methoxy groups with cerium ammonium nitrate and 2,6-pyridinedicarboxylic acid *N*-oxide[86] led to quinone **21a**.

86. (a) Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, 521-522. (b) Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D.-H.; Chen, J.; Starr, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 7448-7451.



Scheme 2.8. Synthesis of tetracyclic skeleton of **21a**.

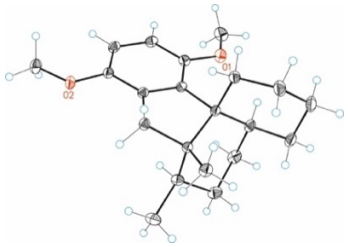
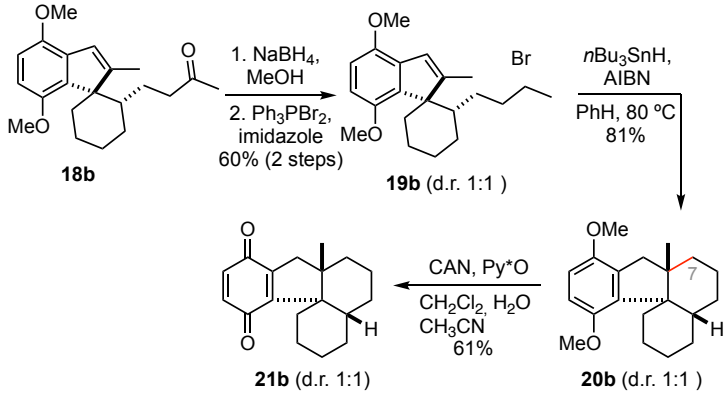


Figure 2.2. X-ray of compound **20a**.

Following the same sequence of reactions, **20b**, corresponding to the tetracyclic carbon skeleton of the dysiherbols, was obtained as a 1:1 mixture of epimers via a remarkably efficient radical cyclization of bromide **19b** (81% yield) (Scheme 2.9). Oxidation of **20b** as before provided quinone **21b**.



Scheme 2.9. Synthesis of tetracyclic skeleton of **21b**.

Conclusions

The synthesis of tetracyclic core of cycloaurenones A-C and disherbols A-C was achieved *via* two key reactions: the cyclization of a gold(I) carbene generated from a cycloheptatriene with a terminal allene and an AIBN-promoted radical cyclization. The gold(I)-catalyzed cyclization resulted in the formation of a 1:1 mixture of two diastereomers, which could be separated at a later stage in the synthesis, leading to a stereodivergent approach to the synthesis of these families of natural products, which displayed the corresponding relative configuration of cycloaurenones and dysiherbols, respectively. Subsequently, B ring was constructed by a radical cyclization to furnish the tetracyclic core.

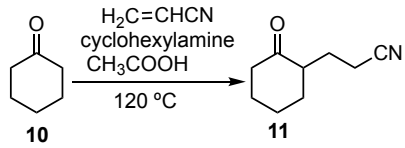
Experimental Section

General Information

The general information has been described in the experimental section of the first chapter.

Procedure for the synthesis of sprio-indene compounds 18a and 18b

3-(2-Oxocyclohexyl)propanenitrile (11)



The title compound was synthesized according to a literature procedure.[87] To a stirred mixture of cyclohexanone (35g, 37 mL, 0.36 mol) and acrylonitrile (28 g, 35 mL, 0.54 mol) was added cyclohexylamine (3.5 g, 4.1 mL, 36 mmol) and acetic acid (214 mg, 0.2 mL, 3.6 mmol). The reaction mixture was heated at 120 ºC for 3 h. The resulting liquid was purified by column chromatography on silica gel (eluent cyclohexane/ethyl acetate 90/10) to result in a colorless oil (46.5 g, 86% yield).

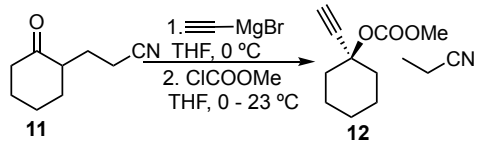
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56-2.27 (m, 5H), 2.18-2.01 (m, 3H), 1.94-1.85 (m, 1H), 1.79-1.60 (m, 2H), 1.56-1.46 (m, 1H), 1.45-1.32 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.75, 119.72, 48.87, 42.25, 34.30, 28.00, 25.61, 25.18, 15.26.

HRMS-ESI: calculated for $C_9H_{13}NNaO$ $[M+Na]^+$: 174.0895; found: 174.0889.

2-(2-Cyanoethyl)-1-ethynylcyclohexyl methyl carbonate (12)

87. D. H. Woodmansee, M.-A. Muller, M. Neuburger, A. Pfaltz, *Chem. Sci.* **2010**, *1*, 72-78.



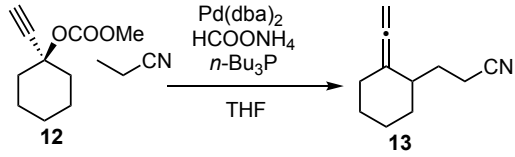
Ethynylmagnesium bromide (32 mL, 15.9 mol, 0.5 M in THF) was added dropwise to a solution of 3-(2-oxocyclohexyl)propanenitrile **11** (2 g, 13.2 mmol) in dry THF (30 mL) at 0 ºC under argon. The mixture was stirred for 2 h at 0 ºC, the disappearance of ketone was confirmed by TLC and then methyl chloroformate (1.6 g, 1.3 mL, 17.2 mmol) was added. The cooling bath was removed and the reaction was stirred at room temperature (23 ºC) for 12 h. The reaction was quenched by the addition of water. The aqueous phase was extracted with ethyl acetate, the combined organic extracts were dried over MgSO4, and the solvent was evaporated. The crude reaction mixture was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 90:10) to give carbonate **12** (2.65g, 85% yield, *d.r.* = 1:1) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (d, *J* = 4.2 Hz, 6H), 2.92-2.78 (m, 2H), 2.70 (s, 1H), 2.66 (s, 1H), 2.55-2.14 (m, 6H), 1.85-1.18 (m, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.26, 153.13, 119.73, 119.55, 82.69, 81.45, 79.54, 78.14, 77.62, 74.97, 54.50, 54.42, 45.20, 45.15, 35.95, 34.73, 28.59, 26.83, 26.24, 25.63, 24.73, 24.24, 23.10, 20.57, 15.53, 15.35.

HRMS-ESI: calculated for $C_{13}H_{17}NNaO_3$ $[M+Na]^+$: 258.1101; found: 258.1099.

3-(2-Vinylidene cyclohexyl)propanenitrile (13)



n-Bu_3P (340 mg, 0.4 ml, 1.7 mmol) was added dropwise to a stirred mixture of carbonate **12** (2.0 g, 8.5 mmol), ammonium formate (1.1 g, 17 mmol) and

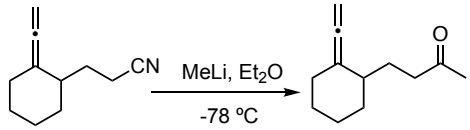
$Pd(dba)_2$ (244 mg, 0.4 mmol) in THF (50 mL) at 0 ºC under argon. After 12 h, the disappearance of carbonate **12** was confirmed by TLC and the reaction mixture was filtered through a short pad of Celite. The solvent was evaporated, the residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 50:1) to give allene **13** (1.1 g, 80% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75-4.68 (m, 2H), 2.46-2.39 (m, 2H), 2.35-2.27 (m, 1H), 2.09-1.72 (m, 6H), 1.69-1.58 (m, 1H), 1.48-1.35 (m, 2H), 1.25-1.12 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.42, 120.05, 104.25, 75.83, 38.32, 33.45, 31.34, 29.29, 27.20, 25.43, 15.17.

HRMS-ESI: calculated for $C_{11}H_{15}NNa$ $[M+Na]^+$: 184.1102; found: 184.1099.

4-(2-Vinylidene cyclohexyl)butan-2-one (14)



13 **14**

MeLi (30 mL, 48 mmol, 1.6 M in Et_2O) was added dropwise to a stirred solution of **13** (2.2 g, 13.6 mmol) in Et_2O (90 mL) at -78 ºC under argon. The mixture was allowed to warm to 0 ºC during 4 h. Thereafter, a saturated solution of NH_4Cl (20 mL) was added dropwise while stirring at 0 ºC. The aqueous phase was extracted with Et_2O, the combined organic extracts were dried over MgSO4. The solvent was evaporated, the residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 50:1) to give ketone **14** (1.9 g, 78% yield) as a colorless oil.

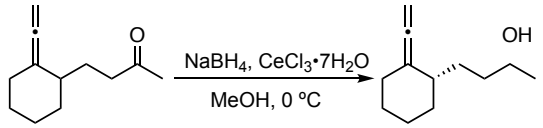
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (t, J = 3.3 Hz, 2H), 2.58-2.39 (m, 2H), 2.31-2.22 (m, 1H), 2.13 (s, 3H), 2.01-1.68 (m, 6H), 1.61-1.51 (m, 1H), 1.48-1.28 (m,

2H), 1.23-1.12 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.40, 199.94, 102.10, 72.03, 38.86, 35.99, 30.72, 28.36, 26.97, 24.53, 24.41, 22.42.

HRMS-ESI: calculated for $C_{12}H_{18}NaO$ $[M+Na]^+$: 201.1250; found: 201.1254.

4-(2-Vinylidene cyclohexyl)butan-2-ol (15)



14 **15**

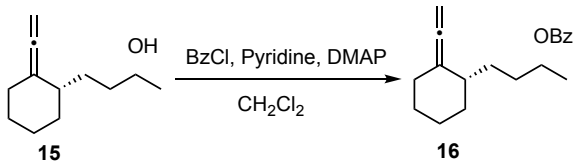
Cerium(III) chloride heptahydrate (12.5 g, 33.7 mmol) was added to a solution of **14** (1.5 g, 8.4 mmol) in MeOH (100 mL) at 0 ºC. The mixture was stirred 10 min and then $NaBH_4$ (350 mg, 9.3 mmol) was added. After 1 h, the disappearance of ketone was confirmed by TLC and MeOH was removed. To the residue was added water and it was extracted with ethyl acetate, the combined organic extracts were dried over MgSO4. The solvent was evaporated, the residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 10:1) to give alcohol **15** (1.2 g, 79% yield, *d.r.* = 1:1) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63-4.62 (m, 2H), 3.81-3.73 (m, 1H), 2.34-2.21 (m, 1H), 2.04-1.10 (m, 16H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.06, 203.03, 105.68, 105.57, 74.79, 74.76, 68.46, 68.38, 39.40, 39.26, 37.19, 37.10, 33.66, 33.64, 31.50, 31.44, 29.68, 29.50, 27.43, 25.56, 25.51, 23.50, 23.46.

HRMS-APCI: calculated for $C_{12}H_{21}O$ $[M+H]^+$: 181.1587; found: 181.1582.

4-(2-Vinylidene cyclohexyl)butan-2-yl benzoate (16)



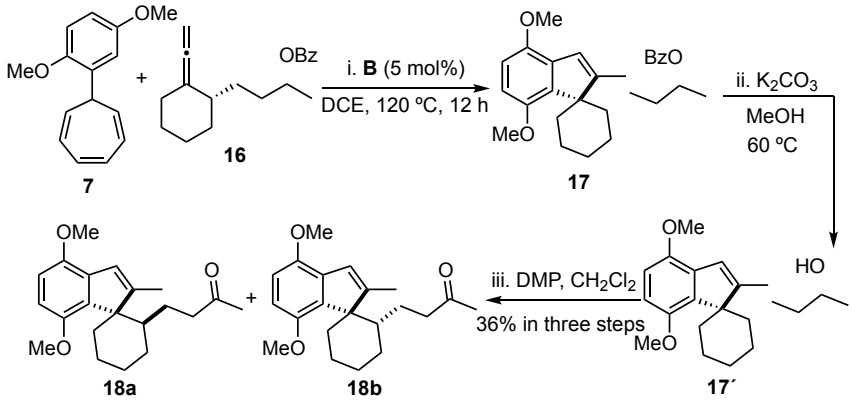
To a solution of **15** (1.0 g, 5.6 mmol) in CH_2Cl_2 (60 mL) was added pyridine (1.3 mL, 16.6 mmol) at 0 °C. The mixture was kept at 0 °C for 10 min and then benzoyl chloride (1.0 mL, 8.3 mmol) was added dropwise. After stirring for 24 h at 23 °C and **15** was no longer detected by TLC, water (50 ml) was added. The residue was extracted with CH_2Cl_2, the combined organic extracts were dried over MgSO4. The solvent was evaporated, the residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 20:1) to give compound **16** (1.3 g, 83% yield, *d.r.* = 1:1) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16-8.02 (m, 2H), 7.62-7.53 (m, 1H), 7.51-7.41 (m, 2H), 5.26-5.04 (m, 1H), 4.71-4.54 (m, 2H), 2.29 (dd, *J* = 13.4, 4.6 Hz, 1H), 2.08-1.52 (m, 8H), 1.51-1.26 (m, 6H), 1.25-1.08 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.91, 166.22, 132.64, 130.98, 129.51, 128.24, 105.45, 105.42, 74.93, 72.08, 71.90, 39.35, 39.16, 33.93, 33.81, 33.77, 33.72, 31.50, 31.48, 29.33, 29.20, 27.42, 25.57, 25.55, 20.06.

HRMS-ESI: calculated for $C_{19}H_{24}NaO_2$ $[M+Na]^+$: 307.1669; found: 307.1672.

Procedure for synthesis of compounds 18a and 18b.



Step i:

A solution of the 7-(2,5-dimethoxyphenyl)cyclohepta-1,3,5-triene (**7**) (913 mg, 4 mmol), 4-(2-vinylidene cyclohexyl)butan-2-yl benzoate (284 mg, 1 mmol) and gold complex **B**, [IPrAu(PhCN)]SbF_6, (46 mg, 0.05 mmol) in 1,2-dichloroethane (DCE, 20 mL) was heated at 120 ºC in a sealed tube under nitrogen. After 12 h, the reaction mixture was allowed to cool to room temperature, the solvent was removed in vacuum and the crude residue was passed through a short pad of silica to provide crude product **17** with all four isomers together, which was used directly for the next step.

Step ii:

To a solution of crude **17** in MeOH (40 mL) was added K_2CO_3 (276 mg, 2 mmol). The reaction mixture stirred for 18 h at 50 ºC and was quenched by saturated aqueous solution of NH_4Cl. The residue was extracted with ethyl acetate and the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated to provide the crude deprotected alcohol **17´**, which was used directly for the next step.

Step iii:

To a solution of crude product **17´** in CH_2Cl_2 (50 mL) was added DMP (466 mg, 1.1 mmol) at 0 ºC. The reaction mixture stirred for 2 h and was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) at 0 ºC. The layers were separated and aqueous layer was extracted with CH_2Cl_2 (3×25 mL), the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated, the residue was purified by preparative TLC (pentane/ethyl ether 10:1) to give alcohol **18a** (60 mg, 18% for 3 steps) as colorless oil and **18b** (60 mg, 18% for 3 steps) as a colorless oil as well.

4-((1*R,2*S**)-4',7'-Dimethoxy-2'-methylspiro[cyclohexane-1,1'-inden]-2-yl)butan-2-one (18a)**

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (d, *J* = 8.7 Hz, 1H), 6.57 (d, *J* = 8.7 Hz, 1H), 6.52-6.47 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.67-2.53 (m, 2H), 2.29-2.19 (m, 4H), 2.07 (ddd, *J* = 16.0, 8.7, 7.3 Hz, 1H), 1.95-1.66 (m, 7H), 1.56-1.44 (m, 2H), 1.36-1.27 (m, 1H), 1.21-1.10 (m, 1H), 1.05-0.96 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.76, 153.09, 149.64, 146.47, 140.49, 133.08, 123.86, 109.67, 107.67, 59.27, 55.91, 55.30, 42.43, 37.31, 31.26, 29.08, 27.70, 25.90, 25.78, 22.53, 20.56.

HRMS-ESI: calculated for $C_{21}H_{28}NaO_3$ $[M+Na]^+$: 351.1931; found: 351.1936.

4-((1*R,2*R**)-4',7'-Dimethoxy-2'-methylspiro[cyclohexane-1,1'-inden]-2-yl)butan-2-one (18b)**

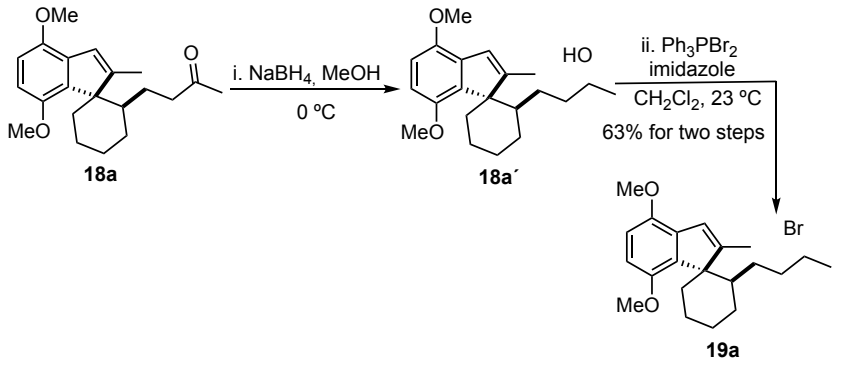
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 6.55-6.54 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.35-2.06 (m, 4H), 2.01 (s, 3H), 1.97-1.91 (m, 4H), 1.77-1.56 (m, 4H), 1.46-1.32 (m, 1H), 1.21-1.15 (m, 1H), 1.11-1.02 (m, 1H), 0.95-0.86 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.65, 153.48, 150.23, 147.05, 138.34, 135.07, 121.48, 109.75, 107.45, 61.45, 55.94, 54.83, 41.71, 38.42, 34.35, 29.62, 26.84, 26.26, 25.59, 22.64, 13.65.

HRMS-APCI: calculated for $C_{21}H_{28}NaO_3$ $[M+Na]^+$: 351.1931; found: 351.1933.

Procedure for the synthesis of tetracyclic skeleton of cycloaurenones

(1*R,2*S**)-2-(3-Bromobutyl)-4',7'-dimethoxy-2'-methylspiro[cyclohexane-1,1'-indene] (19a).**



Step i:

To a solution of the **18a** (60 mg, 0.18 mmol) in MeOH (10 mL) was added $NaBH_4$ (10.3 mg, 0.27 mmol) at 0 ºC. After 30 min, the disappearance of the ketone was confirmed by TLC and MeOH was removed. To the residue was added water and it was extracted with ethyl acetate, the combined organic extracts were dried over MgSO4. The solvent was evaporated to provide crude alcohol **18a´**, which was used directly for the next step.

Step ii:

To a mixture of alcohol **18a´** and imidazole (15 mg, 0.22 mmol) in CH_2Cl_2 (4 mL) was added Ph_3PBr_2 (92 mg, 0.22 mmol) in the glove box. The reaction was stirred for 12 h and the solvent was removed, the residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 20:1) to give compound **19a** (45 mg, 63% yield for two steps, *d.r.* = 1:1) as a colorless oil.

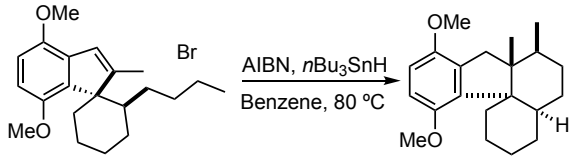
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.58 (dd, *J* = 8.7, 4.4 Hz, 1H), 6.52-6.47 (m, 1H), 4.01-3.81 (m, 7H), 2.72-2.48 (m, 2H), 2.26 (dd, *J* = 4.8, 1.6 Hz, 3H), 1.97-1.31 (m, 13H), 1.11-0.89 (m, 1H), 0.86-0.74 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.23, 153.20, 149.75, 149.63, 146.48, 146.43, 140.58, 140.56, 133.13, 133.10, 123.75, 123.74, 109.69, 109.64, 107.79, 107.70, 59.41, 59.36, 55.96, 55.42, 55.37, 52.08, 51.30, 39.67, 39.51, 37.36, 36.83, 31.30, 31.27, 29.29, 28.93, 28.03, 27.67, 26.67, 26.03, 26.02, 25.34, 22.62, 22.57, 20.61,

20.60.

HRMS-APCI: calculated for $C_{21}H_{30}BrO_2$ $[M+H]^+$: 393.1424; found: 393.1422.

(4a*S,7*R**,7a*S**,12b*R**)-9,12-Dimethoxy-7,7a-dimethyl-1,2,3,4,4a,5,6,7,7a,8 decahydrobenzo[*d*]fluorine (20a).**



19a **20a**

d.r 4:1

To a refluxing solution of **19a** (45 mg, 0.11 mmol) and AIBN (3.8 mg, 0.02 mmol) in benzene (8 mL) was added over 2 h a solution of nBu$_3$SnH (0.154 ml, 0.57 mmol) in benzene (8 mL). The resulting solution was heated at reflux for 2 h, then the solvent was evaporated under vacuum. The residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 20:1) to give compound **20a** (12 mg, 33% yield, *d.r.* = 4:1) as a yellow solid.

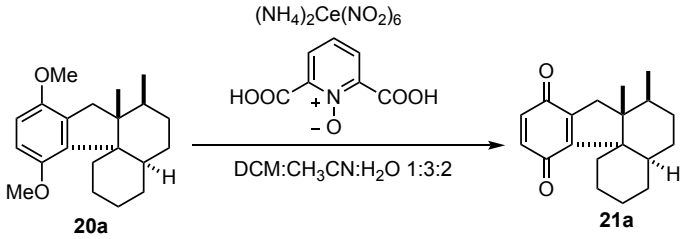
M.p.: 102-104 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67-6.64 (m, 1H), 6.61 (d, J = 8.7 Hz, 1H), 3.78 (s, 6H), 3.16 (d, J = 12.9 Hz, 1H), 2.78 (d, J = 15.8 Hz, 1H), 2.53 (dd, J = 15.8, 0.9 Hz, 1H), 1.92-1.33 (m, 12H), 1.23 (s, 3H), 1.19-1.12 (m, 1H), 0.87 (d, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.98, 150.48, 141.47, 131.18, 110.14, 108.16, 55.84, 55.52, 55.16, 49.06, 39.94, 37.25, 35.60, 33.11, 30.86, 29.10, 26.27, 26.20, 24.12, 19.51, 18.13.

HRMS-APCI: calculated for $C_{21}H_{31}O_2$ $[M+H]^+$: 315.2319; found: 315.2317.

(4a*S,7*R**,7a*S**,12b*R**)-7,7a-Dimethyl-1,2,3,4,4a,5,6,7,7a,8-decahydro-benzo[*d*] fluorene-9,12-dione (21a).**



20a **21a**

An ice-cold solution of cerium ammonium nitrate (87 mg, 0.16 mmol) in 1:1 MeCN/water (0.4 mL) was added slowly to a stirred and cooled (0 ºC) solution of **20a** (10 mg, 0.032 mmol) in 1:2:1 CH_2Cl_2/MeCN/water (0.8 mL) containing 2,6-dicarboxypyridine 1-oxide (14.6 mg, 0.08 mmol). After 40 min, the mixture was diluted with water (5 mL), and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by preparative TLC (pentane/ethyl ether 10:1) to give compound **21a** (6.2 mg, 68% yield) as a yellow oil.

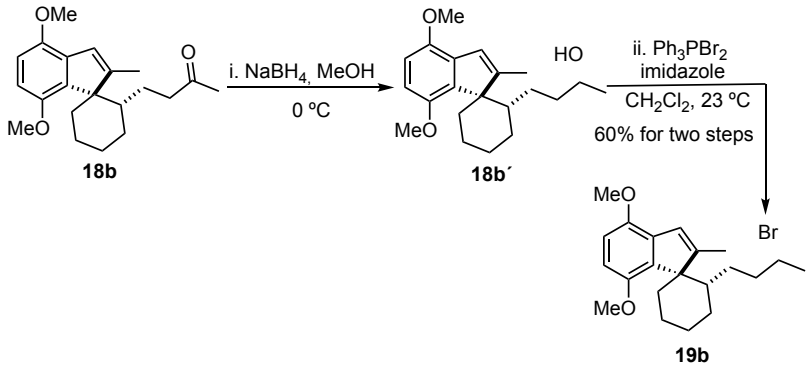
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (d, *J* = 10.0 Hz, 1H), 6.57 (d, *J* = 10.0 Hz, 1H), 2.94 (d, *J* = 12.8 Hz, 1H), 2.62 (d, *J* = 18.0 Hz, 1H), 2.38 (d, *J* = 18.0 Hz, 1H), 1.82- 1.75 (m, 2H), 1.71-1.56 (m, 4H), 1.50-1.34 (m, 7H), 1.21 (s, 3H), 0.88 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 187.14, 186.83, 153.77, 147.55, 138.11, 135.14, 56.02, 48.33, 39.85, 37.81, 34.50, 31.46, 31.36, 28.60, 25.55, 25.47, 23.38, 18.76, 17.94.

HRMS-ESI: calculated for $C_{19}H_{24}NaO_2$ $[M+H]^+$: 307.1699; found: 307.1676.

Procedure for the synthesis of tetracyclic skeleton of dysiherbols

(1*R,2*R**)-2-(3-Bromobutyl)-4',7'-dimethoxy-2'-methylspiro[cyclohexane-1,1'-indene] (19b).**



Step i:

To a solution of the **18b** (60 mg, 0.18 mmol) in MeOH (10 mL) was added $NaBH_4$ (10.3 mg, 0.27 mmol) at 0 ºC. After 30 min, the disappearance of ketone was confirmed by TLC and MeOH was removed. To the residue was added water and extracted with ethyl acetate, the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated to provide crude product **18b´**, which was used directly for the next step.

Step ii:

In a glovebox, to a mixture of **18b´** and imidazole (15 mg, 0.22 mmol) in CH_2Cl_2 (4 mL) was added Ph_3PBr_2 (92 mg, 0.22 mmol). The reaction stirred for 12 h and the solvent was removed, the residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 20:1) to give compound **19b** (43 mg, 60% yield for two steps, *d.r.* = 1:1) as a colorless oil.

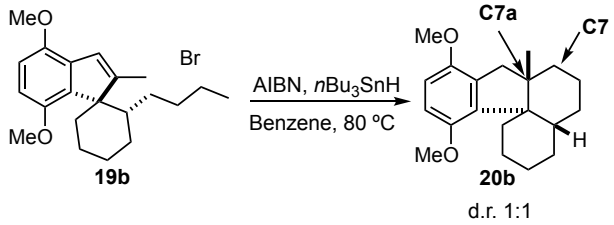
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 8.7 Hz, 1H), 6.63 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.57-6.53 (m, 1H), 3.94-3.75 (m, 7H), 2.23-2.06 (m, 2H), 1.95 (dd, *J* = 7.7, 1.5 Hz, 3H), 1.86-1.50 (m, 10H), 1.49-1.26 (m, 1H), 1.24-1.13 (m, 1H), 0.98-0.63 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ δ 153.46, 153.39, 150.29, 150.27, 147.02, 147.00, 138.54, 138.49, 135.10, 135.07, 121.46, 121.40, 109.72, 109.70, 107.56, 107.49, 61.53, 55.97, 55.95, 54.95, 54.90, 51.92, 51.85, 39.67, 39.18, 39.00, 38.34, 34.38,

34.32, 29.05, 28.92, 27.11, 26.86, 26.54, 26.37, 26.36, 26.00, 22.68, 22.66, 13.75, 13.68.

HRMS-APCI: calculated for $C_{21}H_{30}BrO_2$ $[M+H]^+$: 393.1424; found: 393.1425.

(4a*R,7a*S**)-9,12-Dimethoxy-7,7a-dimethyl-1,2,3,4,4a,5,6,7,7a,8-decahydro -benzo [*d*]fluorine (20b).**



To a refluxing solution of **19b** (43 mg, 0.11 mmol) and AIBN (3.6 mg, 0.02 mmol) in benzene (8 mL) was added over 2 h a solution of Bu_3SnH (0.147 mL, 0.55 mmol) in benzene (8 mL). The resulting solution was heated at reflux for 2 h, then the solvent was evaporated under vacuum. The residue was purified by column chromatography in silica gel (cyclohexane/ethyl acetate 20:1) to give compound **20b** (28 mg, 81% yield, *d.r.* = 1:1) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80-6.59 (m, 4H), 3.84-3.74 (m, 12H), 2.92 (d, *J* = 16.5 Hz, 1H), 2.77 (d, *J* = 15.9 Hz, 1H), 2.54-2.40 (m, 3H), 2.32 (qd, *J* = 12.6, 5.1 Hz, 1H), 1.85-1.61 (m, 3H), 1.57-1.23 (m, 22H), 1.14 (s, 3H), 1.02 (s, 3H), 0.95-0.82 (m, 1H), 0.79 (d, *J* = 6.2 Hz, 3H), 0.65 (d, *J* = 7.1 Hz, 3H).

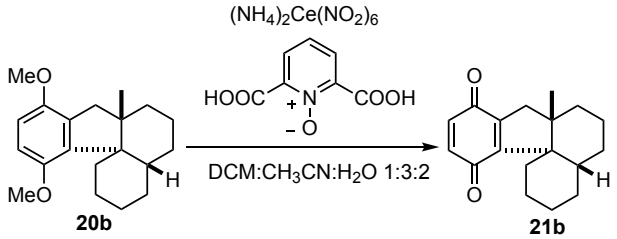
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.10, 151.06, 150.24, 149.69, 140.36, 139.73, 133.66, 132.84, 109.82, 109.62, 108.86, 108.64, 59.35, 56.86, 55.68, 55.65, 55.05, 54.88, 50.46, 49.85, 38.73, 38.40, 37.31, 36.22, 35.98, 35.45, 35.29, 32.24, 31.25, 29.64, 28.96, 27.79, 26.80, 26.73, 23.65, 22.53, 22.14, 18.45, 17.98, 13.30.

HRMS-APCI: calculated for $C_{21}H_{31}O_2$ $[M+H]^+$: 315.2319; found: 315.2324.

Note: The title compound was obtained as 1:1 mixture of diastereoisomers at **C7**.

The configuration at **C7a** was assumed based on simple structure modelling and geometry considerations, as the radical cyclization is expected to occur much easier from the same face of the substituent than from the opposite one.

(4a*R,7a*S**)-7,7a-Dimethyl-1,2,3,4,4a,5,6,7,7a,8-decahydrobenzo[*d*]fluorene-9,12-dione (21b).**



An ice-cold solution of cerium ammonium nitrate (87 mg, 0.16 mmol) in 1:1 MeCN/water (0.4 mL) was added slowly to a stirred and cooled (0 ºC) solution of **20b** (10 mg, 0.032 mmol) in 1:2:1 CH_2Cl_2/MeCN/water (0.8 mL) containing 2,6-dicarboxypyridine 1-oxide (14.6 mg, 0.08 mmol). After 40 min, the mixture was diluted with water (5 mL), and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by preparative TLC (pentane/ethyl ether 10:1) to give compound **21b** (5.5 mg, 61% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 4H), 4.49-3.66 (m, 1H), 2.89 (d, J = 19.2 Hz, 1H), 2.74-2.58 (m, 2H), 2.45-2.27 (m, 3H), 1.90-1.75 (m, 2H), 1.68-1.04 (m, 27H), 1.01 (s, 3H), 0.83 (dd, J = 6.7, 4.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 187.21, 186.93, 186.74, 156.25, 155.29, 151.42, 151.17, 138.74, 138.58, 134.34, 134.22, 61.30, 58.85, 49.67, 48.68, 38.96, 38.04, 37.80, 36.01, 35.77, 35.59, 35.43, 35.03, 31.69, 29.38, 29.31, 27.95, 27.78, 26.40, 26.17, 23.35, 23.11, 22.43, 18.33, 17.88, 12.99.

HRMS-ESI: calculated for $C_{19}H_{24}NaO_2$ $[M+H]^+$: 307.1699; found: 307.1671.

Chapter 3. Gold-Catalyzed Intramolecular C(sp^3)-H Functionalization: Reaction Development and Mechanistic Investigations

Introduction

Compared with sp and sp^2 C-H bonds, sp^3 C-H bond possesses a smaller s-orbital contribution, larger dissociation energy and lower proton acidity. Thus, the direct functionalization of C(sp^3)-H bond is much more challenging. Metal-carbene insertion into C(sp^3)-H bond, one of the typical reactions of carbene species, have attracted great attentions.[88] Mechanistically, this reaction is considered to proceed by a concerned pathway with *via* a three-center transition state (Figure 3.1).[89]

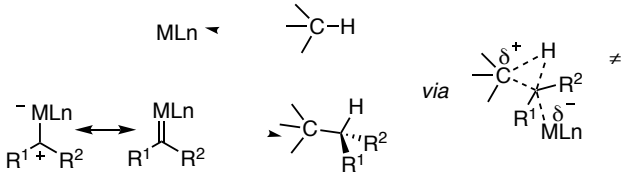


Figure 3.1. Three-center transition state for the C-H insertion of metal carbenes into sp^3 C-H bond.

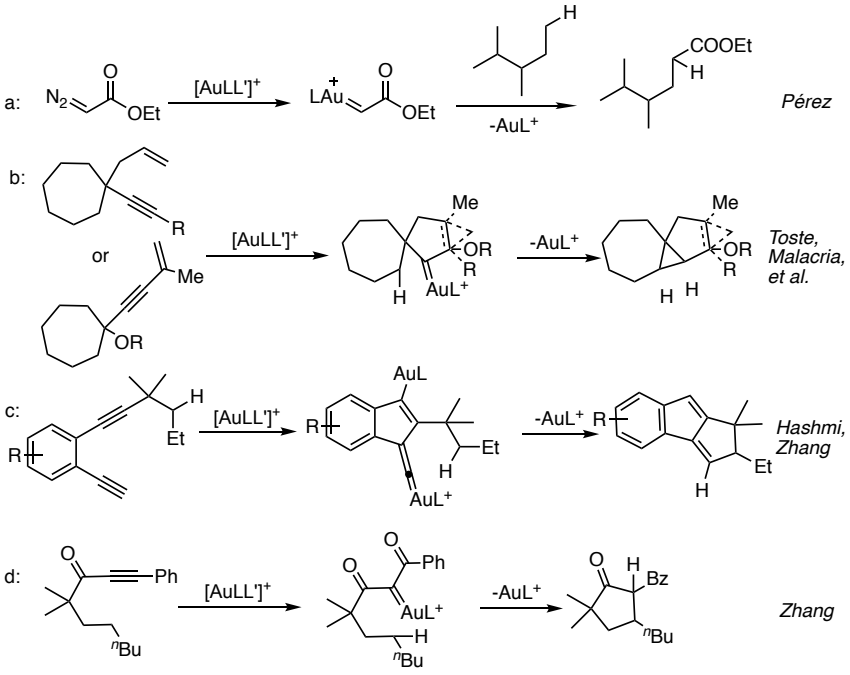
In the case of gold(I), the functionalization of C(sp^3)-H bond was much less explored than with other metals.[90] The first gold carbene insertion of C(sp^3)-H

88. (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861-2904. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704-724. (c) Taber, D. F.; Stiriba, S.-E. *Chem. Eur. J.* **1998**, *4*, 990-992. (d) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009**, *38*, 3061-3071. (e) Egger, J.; Carreira, E. M. *Nat. Prod. Rep.* **2014**, *31*, 449-455. (f) Lombard, F. J.; Coster, M. *J. Org. Biomol. Chem.* **2015**, *13*, 6419-6431. (g) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950-1975. (h) Caballero, A.; Díaz-Requejo, M. M.; Fructos, M. R.; Olmos, A.; Urbano, J.; Pérez, P. J. *Dalton Trans.* **2015**, *44*, 20295-20307. (i) Olmos, A.; Gava, R.; Noverges, B.; Bellezza, D.; Jacob, K.; Besora, M.; Sameera, W. M. C.; Etienne, M.; Maseras, F.; Asensio, G. Caballero, A.; Pérez, P. J. *Angew. Chem. Int. Ed.* **2018**, *57*,13848-13852.

89. (a) Wang, J.; Chen, B.; Bao, J. *J. Org. Chem.* **1998**, *63*, 1853-1862. (b) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958-964. (c) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063-3070. (d)

90. (a) Bhunia, S.; Liu, R. S. *J. Am. Chem. Soc.* **2008**, *130*, 16488-16489. (b) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2809-2811. (c) Zhou, G.; Zhang, J. *Chem. Commun.* **2010**, *46*, 6593-6595. (d) Zhang, Y.; Peng, H.; Zhang, M.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2011**, *47*, 2354-2356. (e) Xie, J.; Li, H.; Xue, Q.; Cheng, Y.; Zhu, C. *Adv. Synth. Catal.* **2012**, *354*, 1646-1650. (f) Xie, J.; Pan, C.; Abdukaer, A.; Zhu, C. *Chem. Soc. Rev.* **2014**, *43*, 5245-5256.

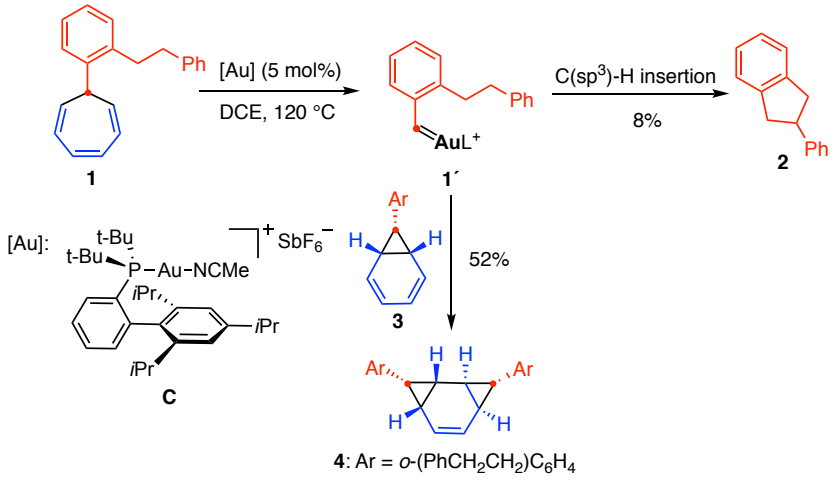
bond was reported in 2006 from ethyl diazoacetate by Pérez and coworkers.[91] After that, the C(sp^3)-H functionalization through the insertion of gold carbenes derived from enyne cycloisomerization,[90b, 92] dual-gold catalysis,[60a,b] and oxidation of alkynes[59j,93] has been studied and have achieved great progress (Scheme 3.1).[46n,94]



Scheme 3.1. Examples of gold-catalyzed insertion of carbene into C(sp^3)-H bond.

91. (a) Fructos, M. R.; Frémont, P.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics*, **2006**, *25*, 2237-2241. (b) Rivilla, I.; Gómez-Emeterio, B. P.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics*, **2011**, *30*, 2855-2860. (c) Delgado-Rebollo, M.; Beltrán, Á.; Prieto, A.; Díaz-Requejo, M. M.; Echavarren, A. E.; Pérez, P. J. *Eur. J. Inorg. Chem.* **2012**, 1380-1386.
92. Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993-3006.
93. Wang, Y.; Zheng, Z.; Zhang, L. *J. Am. Chem. Soc.* **2015**, *137*, 5316–5319.
94. Rivews see: (a) Skouta, R.; Li, C. J. *Tetrahedron*, **2008**, *64*, 4917-4938. (b) Haro, T.; Nevado, C. *Synthesis*, **2011**, 2530-2539. (c) Gaillard, S.; Cazin, C. S. J.; Nolan, S. P. *Acc. Chem. Res.* **2012**, *45*, 778-787. (d) Liu, L.; Zhang, J. *Chem. Soc. Rev.* **2016**, *45*, 506-516. (e) Liu, L.; Zhang, J. *Chin. J. Org. Chem.* **2017**, *37*, 1117-1126. (f) Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.* **2016**, *52*, 7326-7335. (g) Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Pérez, P. J. *Dalton Trans.*, **2006**, 5559-5566.

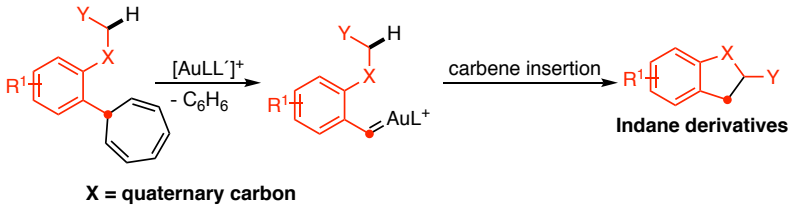
As mentioned in the previous chapters, gold(I) species generated by retro-Buchner reaction of 7-aryl-stubstituted-1,3,5-heptatrienes participate in cyclopropantion of alkenes, electrophilic addition of allenes and arenes leading to a various of useful moieties, which displayed reactivity more similar to that of metal carbenes of rhodium or copper or even free carbenes than that of carbocations. Thus, we envisioned that a gold(I) carbene formed by retro-Buchner process could undergo intramolecular C-H insertion. Indeed, treatment of cycloheptatriene **1** with gold catalyst **A** in DCE at 120 °C, indane product **2** was obtained albeit in very low yield.[67] The major product was the unsymmetrical biscyclopropane **4**, which was formed by trapping of gold(I) carbene **1´** with *endo*-norcaradiene **3** (Scheme 3.2).



Scheme 3.2. Gold(I) carbene generated from cycloheptatriene leading to intramolecular C(sp^3)-H insertion.

Objectives

To explore the reactivity of gold(I) carbene generated from 7-aryl-substituted-1,3,5-cycloheptatrienes in the field of C(sp^3)-H functionalization, we postulated that this transformation would take place by modification of the substrate to push the C(sp^3)-H bonds closer to carbene center. Inspired by the application of Thorpe-Ingold effect in increasing reaction rate and/or equilibrium constant of cyclization reactions, we designed a series of substrates bearing quaternary carbons at the *ortho*-benzylic position, which could favor the insertion of gold(I) carbenes into C(sp^3)-H bond giving rise to indane derivatives (Scheme 3.3).



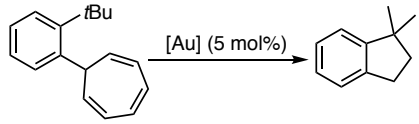
Scheme 3.3. Proposal of gold(I) carbene generated from cycloheptatriene induced intramolecular C(sp^3)-H insertion.

Results and Discussion

Optimization of gold-catalyzed intramolecular C(sp^3)-H functionalization reaction

We first studied the reaction of 7-(2-(*tert*-butyl)phenyl)cyclohepta-1,3,5-triene (**5a**) with different gold(I) catalysts (Table 3.1). Reaction of **5a** in the presence of 5 mol% of NHC gold(I) catalyst (**F**) in 1,2-dichloroethane (DCE) at 120 ºC for 7 h gave indane **6a** in 86% yield (Table 3.1, entry 6). Although other gold(I) complexes (**A-E**) could also be used in the reaction (Table 3.1, entries 1-5), none of them outperformed catalyst **F** after 7 h or longer time. Complex **G** failed to promote this transformation, presumably due to its instability at the temperature required for the retro-Buchner reaction (Table 3.1, entry 7). When the reaction was performed at 100 °C and 80 °C, indane **6a** was obtained in 93% and 72% yield, respectively, after 7 h (Table 3.1, entries 8-9). The reaction yield was significantly lower in other solvents such as toluene, ethyl acetate, and 1,4-dioxane (Table 3.1, entries 10-12).

Table 3.1. Optimization of the intramolecular reaction of **5a**.[a]

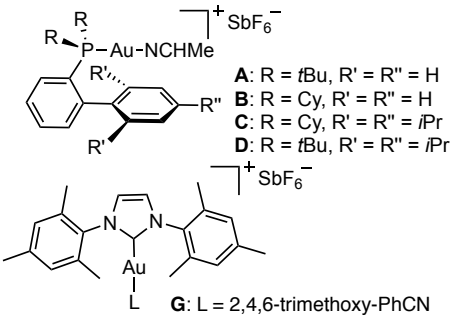


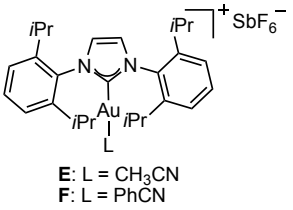
5a **6a**

Entry	Solvents	Catalysts	T (°C)	Time(h)	Conv.(%)[b]	Yield(%)[b]
1	DCE	**A**	120	7/18	63/75	51/52
2	DCE	**B**	120	7/18	80/86	55/60
3	DCE	**C**	120	7/18	33/40	18/22
4	DCE	**D**	120	7/18	32/36	15/15
5	DCE	**E**	120	7	100	80
6	DCE	**F**	120	7	100	86
7	DCE	**G**	120	7	20	trace

8	DCE	**F**	100	7	100	93(85)[c]
9	DCE	**F**	80	7	80	72
10	Toluene	**F**	100	7	55	44
11	EA	**F**	100	7	100	50
12	1,4-dioxane	**F**	100	7	35	30

[a] Reaction of 0.2 mmol **5a** (0.025 M in 1,2-dichloroethane) in sealed tube. [b] Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c] The yield of the isolated product is given in parentheses. DCE = 1,2-dichroloethane, EA = ethyl acetate.

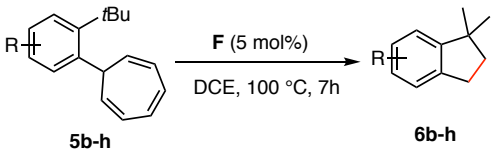


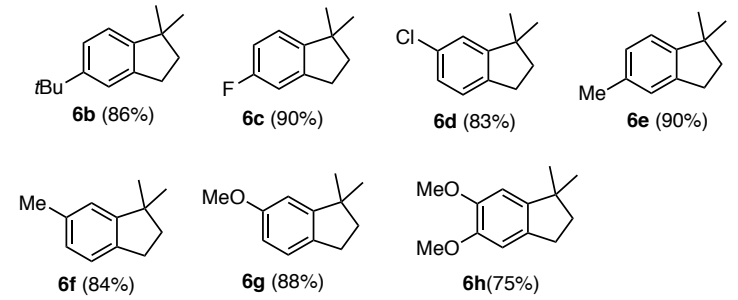


Synthesis of indane derivatives

With the optimized conditions in hand, indanes **6b-h** were obtained in excellent isolated yields (83-90%) by reaction of *ortho*, *meta*-, *para*-substituted aryl (**5b-h**) cycloheptatrienes (Table 3.2). 4,5-Dimethoxyl substituted cycloheptatrienes **5h** resulted in a decrease in the yield on account of the intermolecular reaction of the resulting carbenes with the cycloheptatriene starting material.

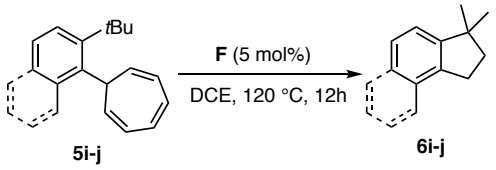
Table 3.2. Synthesis of indane derivatives **6b-h**.

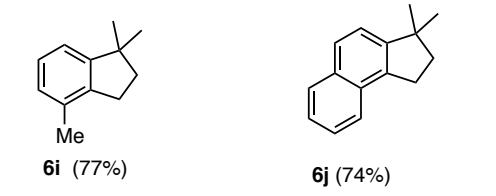




Indanes **6i** and **6j** were obtained in the presence of NHC gold(I) catalyst **F** at 120 °C after 12 h in DCE with 77% and 74% yield, respectively (Table 3.3). These two reactions were performed at higher temperature and needed longer reaction time, which was probably due to the higher steric repulsion induced by the *ortho*-substitution.

Table 3.3. Synthesis of indane derivatives **6i-j**.

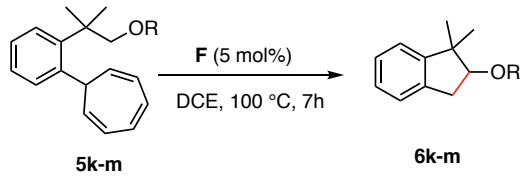




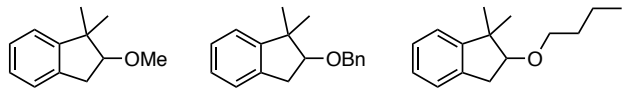
The resulting gold(I) carbenes generated from **5k-m** underwent exclusively insertion of the more reactive C(sp^3)-H bonds adjacent to oxygen to give indanes **6k-6m** under the standard conditions in 72-81% yield (Table 3.4). Although there are two more active distal C(sp^3)-H bonds adjacent to oxygen and benzene, the corresponding seven-member ring product derived from the carbene

insertion at those positions was not observed.[88b,95]

Table 3.4. Synthesis of indane derivatives **6k-m**.



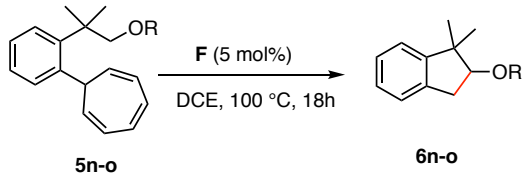
5k-m **6k-m**



6k (81%) **6l** (77%) **6m** (72%)

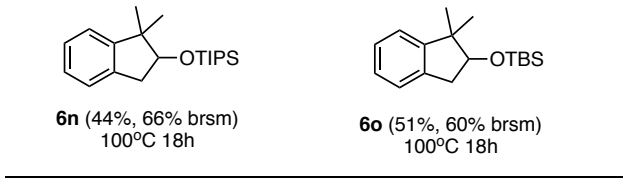
Indanes **6n** and **6o** were obtained in the presence of NHC gold(I) catalyst **F** at 100 °C in DCE after 18 h with 44% and 51% isolated yield, respectively (Table 3.5). Longer reaction time and higher reaction temperature led to lower yields, which can be due to the partial cleavage of the silyl protecting groups in the presence of the acidic catalyst.

Table 3.5. Synthesis of indane derivatives **6n-o**.



5n-o **6n-o**

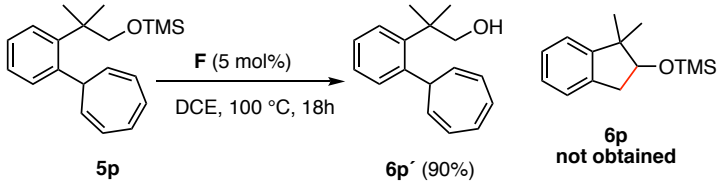
95. Metal catalyzed intramolecular C-H insertion reactions predominantly afford five-membered rings. See: (a) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron Asymmetry* **1998**, *9*, 3145-3169. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417-424. (c) Taber, D. F.; Ruckle Jr., R. E. *J. Am. Chem. Soc.* **1986**, *108*,7686-7693.



6n (44%, 66% brsm)
100°C 18h

6o (51%, 60% brsm)
100°C 18h

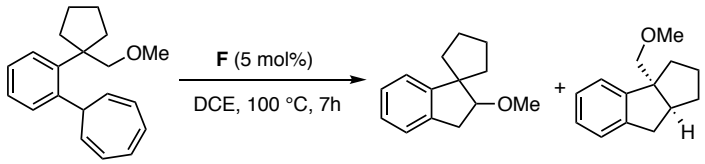
Treatment of less sterically hindered TMS of cyclohetatriene protected derivative **5p** under the standard conditions led to product **6p´** instead of **6p**, as a consequence of the deprotection of the TMS group (Scheme 3.4).



5p **6p´** (90%) **6p** not obtained

Scheme 3.4. Gold acted as Lewis acid to deprotect TMS.

Indanes **6q** and **6q´** were isolated as a 1.4:1 mixture under the standard conditions in 77% overall yield (Scheme 3.5). In this transformation, the low selectivity observed between cyclopentane and α-methylene of oxygen for C(sp3)-H insertion because the electronic effects were outweighed by steric and conformational factors.



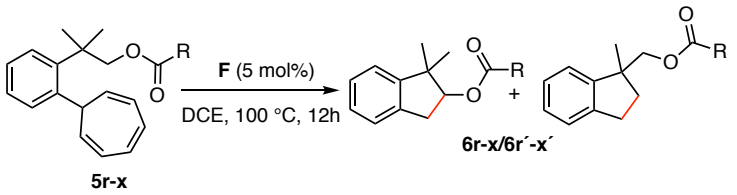
5q **6q/6q´** (77%, 1.4 : 1)

Scheme 3.5. Synthesis of indanes **6q**/**6q´**.

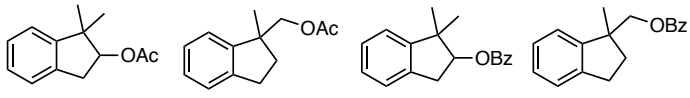
Cycloheptatrienes **5r-x** that incorporate electron-withdrawing esters reacted with gold catalyst **F** at 100 °C in DCE to give indanes **6r-x** and **6r´-x´** in 75-86% overall yield (Table 3.6). The regioselectivity was lower in the cyclization of substrates **5t** and **5u** containing electron-donating substituents in the aromatic

ring of the ester. On the other hand, cycloheptatrienes **5v-x** with more electron-deficient esters favor insertion at the methyl groups.[96]

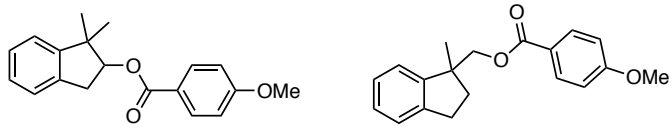
Table 3.6. Synthesis of indane derivatives **6r-x** and **6r´-x´**.



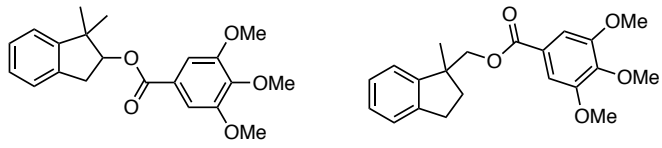
5r-x **6r-x/6r´-x´**



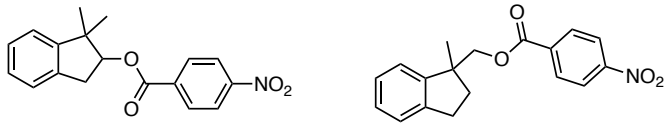
6r/6r´ (86%, 1 : 1.5) **6s/6s´** (85%, 1 : 1.2)



6t/6t´ (83%, 1.7 : 1)

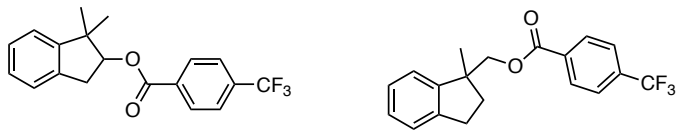


6u/6u´ (81%, 1 : 1)

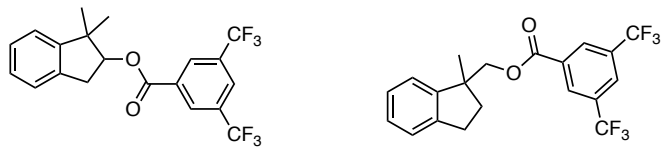


6v/6v´ (78%, 1 : 5)

96. Stork, G.; Nakatani, K. *Tetrahedron Lett*. **1988**, *29*, 2283-2286.

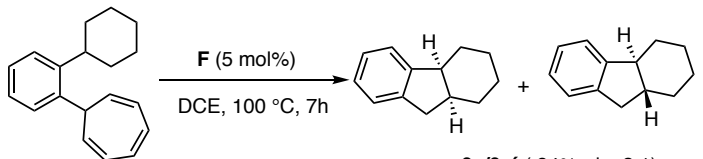


6w/6w´ (75%, 1 : 3)



5x/5x´ (82%, 1 : 7)

Interestingly, hexahydrofluorenes **6y** and **6y´** were isolated in 84% overall yield as a 2:1 mixture under the standard conditions (Scheme 3.6).



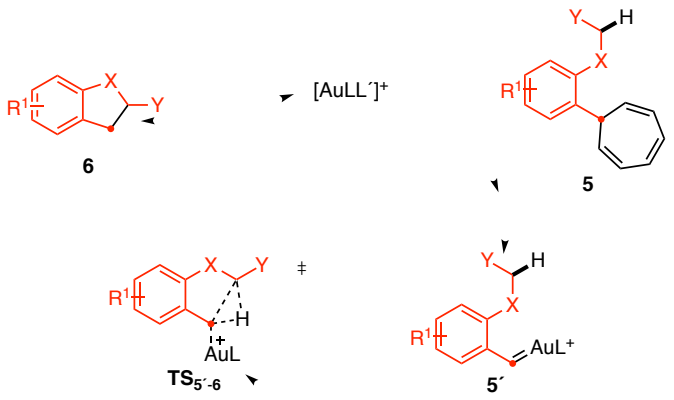
5y

6y/6y´ (84%, d.r. 2:1)

Scheme 3.6. Synthesis of indane derivatives **6y** and **6y´**.

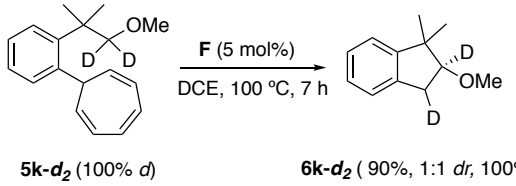
Mechanistic study

A mechanism for the C-H insertion is proposed in Scheme 3.7. The gold(I) carbenes **5´** generated by gold(I)-catalyzed retro-Buchner reaction of cycloheptatrienes **5** insert into the C(sp^3)-H bond by a three-center transition state leading to indanes **6**. This electron-deficient transition state is assisted by an electron-donating group, which is in agreement with our observation that the preference for insertion into C(sp^3)-H bonds adjacent to groups that stabilize a partial positive charge in the transition state.



Scheme 3.7. Mechanistic proposal for the gold(I)-catalyzed C(sp^3)-H functionalization.

To gain insight into the mechanism of the C(sp^3)-H functionalization, we determined the kinetic isotope effects (KIE) and performed deuterium labelling studies. Firstly, the double-deuterium substituted cycloheptatriene **5k-*d*$_2$** was synthesized and submitted to the gold(I)-catalyzed C(sp^3)-H functionalization reaction. Both of the deuterium atoms were transferred to the indane **6k-*d*$_2$**, which was obtained a 1:1 mixture of stereoisomers (Scheme 3.8). This result demonstrates that the C(sp^3)-H insertion takes place through an intramolecular C-H (or C-D) bond transfer to the gold(I) carbene intermediate **5´**.



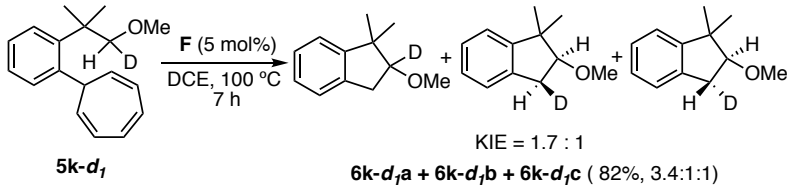
5k-*d*$_2$ (100% *d*) **6k-*d*$_2$** (90%, 1:1 *dr*, 100% *d*)

Scheme 3.8. Deuterium labelling experiment from **5k-*d*$_2$**.

We also prepared monodeuterated cycloheptatriene **5k-*d*$_1$** to directly measure the kinetic isotope effect of the C-H insertion step.[97] Treatment of **5k-*d*$_1$** under the standard reaction conditions led to three isomers **6k-*d*$_1$a**, **6k-*d*$_1$b**, and **6k-*d*$_1$c** as a 3.4:1:1 mixture, which corresponds to a KIE value of 1.7:1 (Scheme 3.9),

97. Simmons, E. M.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072

consistent with the three-centered concerted mechanism for most metal-carbene species that usually show k_H/k_D = 1-2.5.[98] Moreover, since significant KIE are generally observed for the C-H bond undergoing hydride transfer to a carbocation,[99] our measured kinetic isotope effect for the C(sp^3)-H insertion strongly suggests that a simple hydride transfer to a carbocation-like species could be excluded in our case.



Scheme 3.9. Kinetic isotope effect determined in the reaction of **5k-*d*$_1$**.

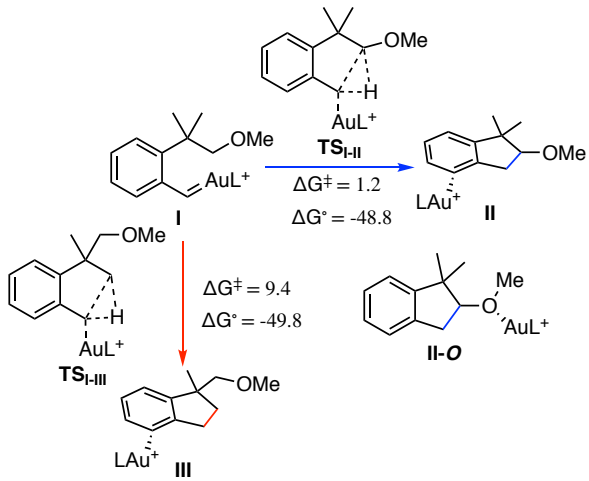
The insertion of gold(I) carbenes into C(sp^3)-H bonds was also investigated theoretically by performing DFT calculations (M06, 6-31G(d) (C, H, N, O) and SDD (Au), SMD = 1,2-dichloroethane, L = IPr).

In these calculations we examine the detailed reaction mechanisms starting with optimized gold(I) carbenes.[100] We selected ether **5k** and ester derivatives **5r-s** and **5t** as the substrates, which possess both electron donating and withdrawing groups adjacent to the reacting C-H bond.

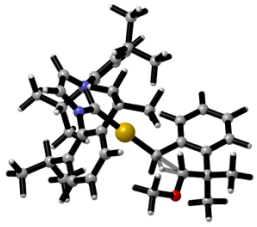
We first studied the highly selective formation of indane **6k** from cycloheptatriene **5k** by DFT calculations. After the retro-Buchner reaction, highly reactive gold(I) carbene **I** could insert intramolecularly into carbon-

98. (a) Sulikowski, G. A.; Lee, S. *Tetrahedron Lett.* **1999**, *40*, 8035-8038. (b) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296-3305. (c) Ishii, S.; Zhao, S.; Helquist, P. *J. Am. Chem. Soc.* **2000**, *122*, 5897-5898. (d) Mbuvi, H. M.; Woo, L. K. *Organometallics* **2008**, *27*, 637-645, and For the insertion of a gold carbenoid into an C(sp3)-H bond see: (e) Bhunia,S.; Ghorpade, S.; Huple, D. B.; Liu, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 2939-2942, and references therein.
99. (a) Mayr, H.; Lang, G.; Ofial, A. R. *J. Am. Chem. Soc.* **2002**, *124*, 4076-4083, and references therein. For a theoretical analysis, see: (b) Gronert, S.; Keeffe, J. R. *J. Org. Chem.* **2006**, *71*, 5959-5968.
100. The formation of gold carbene was investigated by DFT in our previous work: see reference 68.

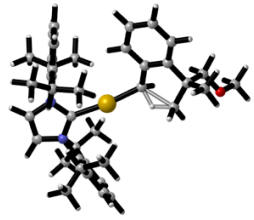
hydrogen bonds adjacent to oxygen and/or C-H bonds in the methyl groups through the three-centered transition states $\mathbf{TS_{I\text{-}II}}$ and $\mathbf{TS_{I\text{-}III}}$, respectively. Due to the donation of electron density from OMe to the electron-deficient carbon center in the transition state, as expected, the calculated free energy of activation to reach $\mathbf{TS_{I\text{-}II}}$ (only 1.2 kcal/mol) is much lower than that for $\mathbf{TS_{I\text{-}III}}$ (9.4 kcal/mol) (Scheme 3.10). This result fully agrees with the observed formation of indane **6k** from **5k** by carbene C-H insertion. In addition to **II**, which was found as the absolute minimum (-48.8 kcal/mol) in the reaction coordinate, other relative minima such as **II-*O***, with gold(I) coordinated to oxygen (-47.4 kcal/mol) or other positions of indane ring were also found in the DFT calculations. It is important to note that structures similar to that of **II**, in which gold(I) coordinates in a η^1-fashion with one the carbons of the aromatic ring, have been found experimentally in previous work of our group.[101]



101. (a) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455-5459. (b) Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324-5332.



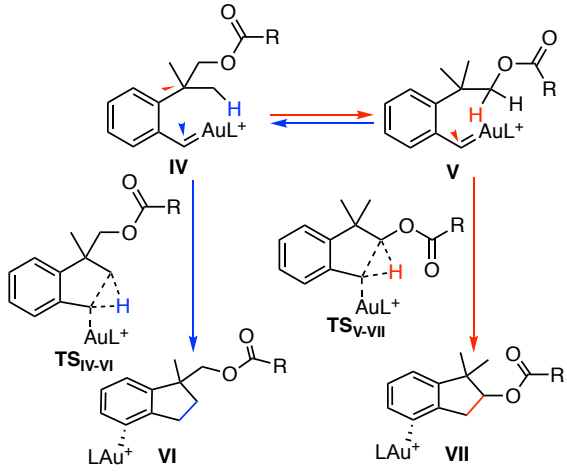
$TS_{I\text{-}II}$[a]



$TS_{I\text{-}III}$

Scheme 3.10. DFT calculations on the gold(I) carbene insertion reaction of **5k** (free energies in kcal/mol). [a] The energy of $TS_{I\text{-}II}$ was calculated by freezing the following distance: d(C23−H22), the value of this distance was taken from the optimized geometry using scan of the distance of d(C23-H22).

Next, we extended our study to the substrates **5r-t** and **5v** bearing ester groups, which delivered the corresponding indanes as the mixture of **6r-t**, **6v** by carbene insertion into methylene adjacent to ester group, and **6´r-t**, **6´v**, by carbene insertion into the C-H of the methyl groups. Gold(I) carbenes **IV** or their rotamers **V** could evolve through intramolecular carbene insertion into the corresponging CH bonds to afford (η^1-indane)gold(I) complexes **VI** *via* $TS_{IV\text{-}VI}$ or **VII** through $TS_{V\text{-}VII}$ (Scheme 3.11).



Scheme 3.11. Gold(I) carbene insertion into C(sp^3)-H bonds of the substrates containing

ester groups.

According to our calculations, it was found that the nature of the R group of the ester has an effect on the relatively stabilities of the two transition states. Table 3.7 summaries the calculated free energy barriers for the carbene insertions involved in four related cyclization reactions. The relative free energy barriers of C-C bond rotation (ΔG_1) to the suitable geometries were found to be small (from 1.8 to 3.6 kcal/mol). For the OAc group substitution (R = Me), the free energy barrier for the carbene insertion on at the methyl group (ΔG_2 = 10.6 kcal/mol) is similar to that for insertion at the methylene (ΔG_3 = 11.3 kcal/mol). In the case of the benzoate (R = Ph), the barriers for these two pathways are almost the same (10.6 vs. 10.4 kcal/mol). When the R group is *p*-methoxyphenyl, ΔG_3 became lower than ΔG_2. Conversely, for *p*-nitrobenzoate, the barrier for the insertion at the methyl is lower than that the barrier for the insertion at the methylene (10.6 vs. 11.4 kcal/mol). It can be seen that the barriers for **TS$_{V\text{-}VII}$** increase with the electron withdrawing substitution, whereas those for **TS$_{IV\text{-}VI}$** are almost the same. These theoretical results are consistent with experimental observation that electron withdrawing groups reduced the reactivity of adjacent C(sp^3)-H bonds in the gold(I) carbene insertion reaction.

Table 3.7. Calculated free energy barriers (in kcal/mol) of gold carbene insertion reactions.

R	ΔG_1[a]	ΔG_2[b]	ΔG_3[c]
Me	3.4	10.6	11.3
Ph	1.8	10.6	10.4
p-MeOPh	3.6	11.0	9.8
p-NO_2Ph	2.6	10.6	11.4

[a] Free energy barriers for the C-C bond rotation step. [b] Free energy barriers for the carbene insertion into CH bonds of methyl group (**TS$_{IV\text{-}VI}$**). [c] Free energy barriers for the carbene insertion into CH bonds of the methylene adjacent to ester group (**TS$_{V\text{-}VII}$**).

Conclusions

A novel method for the synthesis of indanes based on the intramolecular insertion of gold(I) carbenes generated by retro-Buchner process from 7-aryl-substituted-1,3,5-cycloheptatrienes into C(sp^3)-H bonds has been developed. The indanes are made through a well-accepted three-centered concerned mechanism in moderate to excellent yields. Deuterium-labeling experiments, studies of the kinetic isotope effects, and DFT calculations strongly support the hypothesis that the C(sp^3)-H functionalization proceeds through an intramolecular C-H bond transfer to the electrophilic gold(I) carbene intermediate.

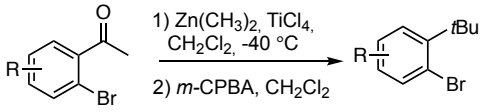
Experiment section

General Information

The general information has been described in the experimental section of the first chapter.

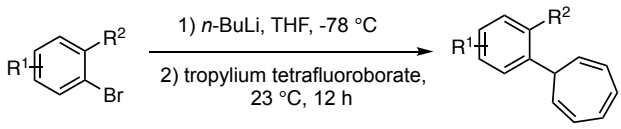
Synthesis of starting materials

General procedure (A) for the synthesis of 1-bromo-2-(*tert*-butyl)-substituted benzene



Under nitrogen atmosphere, a solution of $TiCl_4$ (2.2 equiv) in anhydrous CH_2Cl_2 was dropwise added Me_2Zn (1M in toluene, 2.2 equiv) at -40 °C. After stirring for 15 minutes, a solution of the aryl ketone (1.0 equiv) in anhydrous CH_2Cl_2 was dropwise added. The reaction was stirred overnight at 0 °C. The mixture was poured on an ice/water bath, extracted with Et_2O (x3) and washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude was dissolved in CH_2Cl_2, *m*-CPBA (3.0 equiv) was added at 0 °C and the mixture was stirred overnight at room temperature (23 °C). The crude was filtered through Celite, washed with $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated. The product was purified on silica gel chromatography with pentane 100%.

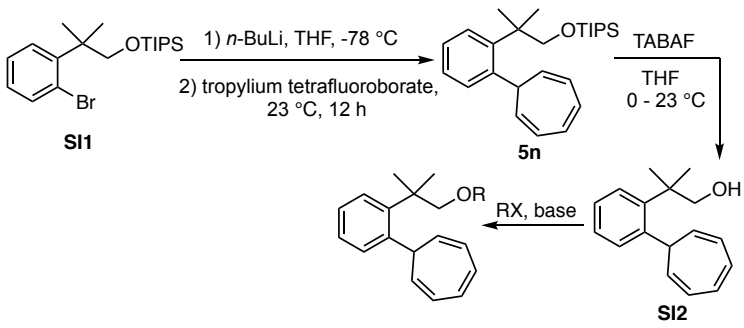
General Procedure (B) for the synthesis of arylcycloheptatrienes



n-BuLi (2.5 M in hexanes, 1.0 equiv) was added dropwise to a solution of the corresponding aryl bromide (1.0 equiv) in dry THF (0.4 M) at −78 °C under

argon. The mixture was stirred for 30 min at −78 °C, and then tropylium tetrafluoroborate (1.2 equiv) was added in one portion. The cooling bath was removed and the reaction was stirred at room temperature (23 °C) for 12 h. The reaction was quenched by the addition of water. The aqueous phase was extracted with diethyl ether, the combined organic extracts were dried over MgSO4, and the solvent was evaporated. The crude reaction mixture was purified by column chromatography on silica gel with cyclohexane and ethyl acetate as eluent unless otherwise stated.

General Procedure (C) for the Synthesis of 2-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropan ether



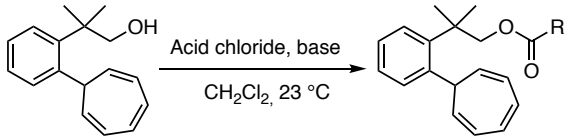
Step 1: *n*-BuLi (2.5 M in hexanes, 1.0 equiv) was added dropwise to a solution of **SI1**[102] (1.0 equiv) in dry THF (0.4 M) at −78 °C under argon. The mixture was stirred for 30 min at −78 °C, and then tropylium tetrafluoroborate (1.2 equiv) was added in one portion. The cooling bath was removed and the reaction was stirred at room temperature (23 °C) for 12 h. The reaction was quenched by the addition of water. The aqueous phase was extracted with diethyl ether, the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. The crude reaction mixture was purified by column chromatography on silica gel with pentane as eluent to get **5n**.

102. Gutiérrez-Bonet, Á.; Juliá-Hernández, F.; Luis, B.; Martin, R. *J. Am. Chem. Soc.* **2016**, *138*, 6384−6387.

Step 2: TBAF (1 M in THF, 1.2 equiv) was added dropwise to **5n** (1.0 equiv) in dry THF (0.4 M) at 0 °C under argon. The cooling bath was removed and the reaction was stirred at room temperature (23 °C) for 6 h. The reaction was quenched by the addition of water. The aqueous phase was extracted with diethyl ether, the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. The crude reaction mixture was purified by column chromatography on silica gel with cyclohexane and ethyl acetate as eluent to get **SI2**.

Step 3: To a solution of **SI2** (1 equiv) in dry CH_2Cl_2 or THF (0.2 M), corresponding base was added portionwise at 0 °C. After 0.5 h, corresponding alkyl or silicon halides were added dropwise. The reaction mixture was stirred overnight at room temperature (23 °C). The reaction was quenched by the addition of water. The aqueous phase was extracted with diethyl ether, the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. The crude reaction mixture was purified by column chromatography on silica gel with pentane as eluent unless otherwise stated.

General procedure (D) for the synthesis of 2-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropan ester.



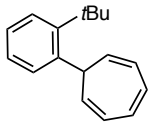
SI2

To a solution of **SI2** (1 equiv) in dry CH_2Cl_2 (0.2 M), corresponding base was added portionwise at 0 °C. After 0.5 h, corresponding acid chloride was added dropwise. The reaction mixture was stirred overnight at room temperature (23 °C). The reaction was quenched by the addition of water. The aqueous phase was extracted with diethyl ether, the combined organic extracts were dried over MgSO4, and the solvent was evaporated. The crude reaction mixture was

purified by column chromatography on silica gel with cyclohexane and ethyl acetate as eluent unless otherwise stated.

Compound Characterization

7-(2-(*tert*-Butyl)phenyl)cyclohepta-1,3,5-triene (5a)



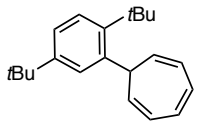
The title compound (colorless oil, 510 mg, 73% yield) was prepared according to the general procedure (**B**) from 1-bromo-2-(*tert*-butyl)benzene[102] (660 mg, 3.1 mmol), *n*-BuLi (2.5 M, 1.2 mL, 3.1 mmol) and tropylium tetrafluoroborate (660 mg, 3.7 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.33 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29-7.20 (m, 1H), 6.81-6.73 (m, 2H), 6.33-6.23 (m, 2H), 5.41-5.34 (m, 2H), 3.52-3.25 (m, 1H), 1.28 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.88, 144.04, 130.63, 130.10, 129.60, 126.72, 126.14, 125.63, 124.16, 43.35, 35.32, 31.75.

HRMS-APCI: calculated for $C_{17}H_{21}$ $[M+H]^+$: 225.1638; found: 225.1639.

7-(2,5-di-*tert*-Butylphenyl)cyclohepta-1,3,5-triene (5b)



The title compound (white solid, 1.6 g, 77% yield) was prepared according to the general procedure (**B**) from 2-bromo-1,4-di-*tert*-butylbenzene[103] (2.0 g, 7.4

103. Yap, J.; Ding, Y.; Yang, X.; Wong, J.; Li, Y.; Pullarkat, S.; Leung, P. *Eur. J. Inorg. Chem.* **2014**, 5046-5052.

mmol), *n*-BuLi (2.5 M, 3.0 mL, 7.4 mmol) and tropylium tetrafluoroborate (1.6 g, 8.9 mmol).

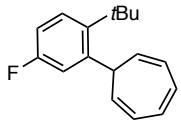
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.3 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.75 (dd, *J* = 3.7, 2.7 Hz, 2H), 6.33-6.21 (m, 2H), 5.43-5.30 (m, 2H), 3.43-3.33 (m, 1H), 1.35 (s, 9H), 1.25 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.15, 144.81, 143.45, 130.58, 130.02, 127.13, 125.28, 124.09, 122.86, 43.48, 34.87, 34.37, 31.77, 31.37.

HRMS-APCI: calculated for $C_{21}H_{29}$ $[M+H]^+$: 281.2264; found: 281.2269.

M.p.: 118-120 °C.

7-(2-(*tert*-Butyl)-5-fluorophenyl)cyclohepta-1,3,5-triene (5c)



The title compound (white solid, 680 mg, 78% yield) was prepared according to the general procedure (**B**) from 2-bromo-1-(*tert*-butyl)-4-fluorobenzene (830 mg, 3.6 mmol), *n*-BuLi (2.5 M, 1.4 mL, 3.6 mmol) and tropylium tetrafluoroborate (770 mg, 4.3 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.9, 6.0 Hz, 1H), 7.30 (dd, *J* = 10.3, 2.9 Hz, 1H), 6.95 (ddd, *J* = 8.9, 7.7, 2.9 Hz, 1H), 6.84-6.79 (m, 2H), 6.37-6.31 (m, 2H), 5.41- 5.32 (m, 2H), 3.47-3.34 (m, 1H), 1.31 (s, 9H).

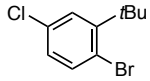
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.11, 160.68, 146.79 (d, *J* = 6.2 Hz), 144.07 (d, *J* = 3.1 Hz), 131.14, 129.00, 127.79 (d, *J* = 7.7 Hz), 124.92, 116.84 (d, *J* = 20.8 Hz), 113.02 (d, *J* = 19.9 Hz), 43.74 (d, *J* = 1.6 Hz), 35.44, 32.26.

^{19}F NMR (376 MHz, $CDCl_3$) δ -117.53 (s).

HRMS-APCI: calculated for $C_{17}H_{20}F$ $[M+H]^+$: 243.1544; found: 243.1538.

M.p.: 66-68 °C.

1-Bromo-2-(*tert*-butyl)-4-chlorobenzene (5d´)



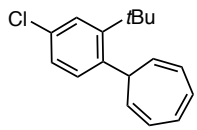
The title compound (colorless oil, 980 mg, 37% yield) was prepared according to the general procedure (**A**) from 1-(2-bromo-5-chlorophenyl)ethan-1-one (2.5 g, 10.7 mmol), $TiCl_4$ (2.6 mL, 23.6 mmol), $ZnMe_2$ (1.2 M, 19.6 mL, 23.6 mmol), and *m*-CPBA (5.5 g, 32 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 2.6 Hz, 1H), 7.02 (dd, *J* = 8.4, 2.6 Hz, 1H), 1.50 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.07, 137.10, 133.68, 128.74, 127.71, 120.83, 37.18, 29.85.

HRMS-APCI: calculated for C_9H_9BrCl $[M\text{-}CH_3]^+$: 230.9571; found: 230.9572.

7-(2-(*tert*-Butyl)-4-chlorophenyl)cyclohepta-1,3,5-triene (5d)



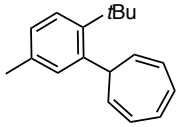
The title compound (colorless oil, 230 mg, 61% yield) was prepared according to the general procedure (**B**) from 1-bromo-2-(*tert*-butyl)-4-chlorobenzene (360 mg, 1.45 mmol), *n*-BuLi (2.5 M, 0.6 mL, 1.45 mmol) and tropylium tetrafluoroborate (311 mg, 1.75 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.29-7.26 (m, 1H), 6.82-6.66 (m, 2H), 6.32-6.18 (m, 2H), 5.34-5.21 (m, 2H), 3.33-3.27 (m, 1H), 1.23 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.97, 142.55, 131.75, 131.41, 130.69, 128.97, 126.61, 126.02, 124.40, 42.86, 35.43, 31.45.

HRMS-APCI: calculated for $C_{17}H_{21}Cl$ $[M+H]^+$: 259.1248 ; found: 259.1257.

7-(2-(*tert*-Butyl)-5-methylphenyl)cyclohepta-1,3,5-triene (5e)



This compound (orange solid, 600 mg, 57% yield) was prepared according to the general procedure (**B**) from 2-bromo-1-(*tert*-butyl)-4-methylbenzene[104] (1.0 g, 4.4 mmol), *n*-BuLi (2.5 M, 1.8 mL, 4.4 mmol) and tropylium tetrafluoroborate (0.94 g, 5.3 mmol).

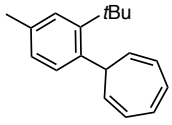
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 2.0 Hz, 1H), 7.28 (dd, J = 8.2, 1.3 Hz, 2H), 7.13-6.97 (m, 1H), 6.74 (ddd, J = 3.7, 2.6, 1.0 Hz, 2H), 6.36-6.13 (m, 2H), 5.46-5.23 (m, 2H), 3.42-3.25 (m, 1H), 2.36 (d, J = 1.0 Hz, 3H), 1.24 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.34, 144.26, 136.43, 131.22, 130.99, 130.12, 127.27, 126.05, 124.49, 43.58, 35.34, 32.18, 21.21.

HRMS-APCI: calculated for $C_{18}H_{23}$ $[M+H]^+$: 239.1794; found: 239.1802 .

M.p.: 58-60 °C.

7-(2-(*tert*-Butyl)-4-methylphenyl)cyclohepta-1,3,5-triene (5f)



This compound (white solid, 510 mg, 66% yield) was prepared according to the general procedure (**B**) from 1-bromo-2-(*tert*-butyl)-4-methylbenzene (740 mg,

104. Wu, Z.; Ma, D.; Zhou, B.; Ji, X.; Ma, X.; Wang, X.; Zhang, Y. *Angew. Chem. Int. Ed.* **2017**, *56,* 12288-12291.

3.3 mmol), *n*-BuLi (2.5 M, 1.3 mL, 3.3 mmol) and tropylium tetrafluoroborate (700 mg, 3.9 mmol).

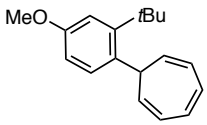
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.8 Hz, 1H), 7.25-7.20 (m, 1H), 7.19-7.12 (m, 1H), 6.83-6.66 (m, 2H), 6.34-6.17 (m, 2H), 5.41-5.26 (m, 2H), 3.37-3.29 (m, 1H), 2.39 (s, 3H), 1.27 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.14, 141.44, 135.82, 131.05, 130.53, 130.25, 127.83, 126.90, 124.50, 43.47, 35.62, 32.19, 21.84.

HRMS-APCI: calculated for $C_{18}H_{23}$ $[M+H]^+$: 239.1794; found: 239.1792.

M.p.: 94-96 °C.

7-(2-(*tert*-Butyl)-4-methoxyphenyl)cyclohepta-1,3,5-triene (5g)



This compound (orange oil, 230 mg, 73% yield) was prepared according to the general procedure (**B**) from 1-bromo-2-(*tert*-butyl)-4-methoxybenzene[105] (300 mg, 1.2 mmol), *n*-BuLi (2.5 M, 0.5 mL, 1.2 mmol) and tropylium tetrafluoroborate (260 mg, 1.5 mmol).

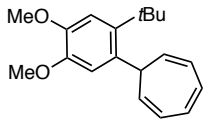
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.2 Hz, 1H), 6.99 (d, *J* = 2.7 Hz, 1H), 6.89 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.8-6.71 (m, 2H), 6.33-6.20 (m, 2H), 5.40-5.28 (m, 2H), 3.85 (d, *J* = 0.7 Hz, 3H), 3.36-3.21 (m, 1H), 1.27 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.05, 150.06, 136.72, 131.54, 131.16, 130.44, 124.53, 113.14, 111.30, 55.71, 43.20, 35.91, 32.09.

HRMS-APCI: calculated for $C_{18}H_{23}O$ $[M+H]^+$: 255.1743; found: 255.1732.

7-(2-(*tert*-Butyl)-4,5-dimethoxyphenyl)cyclohepta-1,3,5-triene (5h)

105. Samanta, R.; Yamamoto, H. *Chem. Eur. J.* **2015**, *21*,11976-11979.



The title compound (yellow solid, 300 mg, 61% yield) was prepared according to the general procedure (**B**) from 1-bromo-2-(*tert*-butyl)-4,5-dimethoxybenzene[106] (470 mg, 1.7 mmol), *n*-BuLi (2.5 M, 0.7 mL, 1.7 mmol) and tropylium tetrafluoroborate (370 mg, 2.1 mmol).

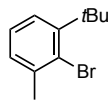
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.94 (s, 1H), 6.80-6.67 (m, 2H), 6.32-6.23 (m, 2H), 5.44-5.33 (m, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.38-3.30 (m, 1H), 1.26 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.41, 146.48, 140.64, 136.09, 130.79, 129.71, 124.29, 113.18, 110.05, 56.07, 43.01, 35.11, 31.98.

HRMS-APCI: calculated for $C_{19}H_{25}O_2$ $[M+H]^+$: 285.1849; found: 285.1842.

M.p.: 69-71 °C.

2-Bromo-1-(*tert*-butyl)-3-methylbenzene (5i´)



The title compound (colorless oil, 410 mg, 37% yield) was prepared according to the general procedure (**A**) from 1-(2-bromo-3-methylphenyl)ethan-1-one (1.05 g, 4.9 mmol), $TiCl_4$ (1.2 mL, 10.7 mmol), $ZnMe_2$ (1.2 M, 9.0 mL, 10.7 mmol), and *m*-CPBA (2.5 g, 14.6 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (m, 1H), 7.18-7.11 (m, 2H), 2.47 (s, 3H), 1.57 (s, 9H).

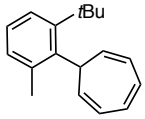
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.36, 140.21, 128.93, 126.81, 126.04, 125.72,

106. Talipov, M.; Navale, T.; Hossain, M.; Shukla, R.; Ivanov, M.; Rathore, R. *Angew. Chem. Int. Ed.* **2017**, *56*, 266-269

37.28, 30.21, 25.60.

HRMS-APCI: calculated for $C_{10}H_{12}Br$ $[M\text{-}CH_3]^+$: 211.0117; found: 211.0116.

7-(2-(*tert*-Butyl)-6-methylphenyl)cyclohepta-1,3,5-triene (5i)



The title compound (White solid, 500 mg, 70% yield) was prepared according to the general procedure (**B**) from 2-bromo-1-(*tert*-butyl)-3-methylbenzene (680 mg, 3.0 mmol), *n*-BuLi (2.5 M, 1.2 mL, 3.0 mmol) and tropylium tetrafluoroborate (640 mg, 3.6 mmol).

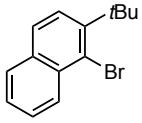
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 1H), 7.19-7.12 (m, 2H), 6.71-6.52 (m, 2H), 6.26-6.12 (m, 2H), 5.49-5.31 (m, 2H), 4.02-3.91 (m, 1H), 2.45 (s, 3H), 1.29 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.90, 140.81, 138.26, 132.44, 131.05, 130.71, 126.33, 124.32, 123.89, 42.24, 35.80, 32.30, 23.38.

HRMS-APCI: calculated for $C_{18}H_{23}$ $[M+H]^+$: 239.1794; found: 239.1784.

M.p.: 72-74 °C.

1-Bromo-2-(*tert*-butyl)naphthalene (5j´)



The title compound (colorless oil, 690 mg, 33% yield) was prepared according to the general procedure (**A**) from 1-(2-bromo-5-chlorophenyl)ethan-1-one (2.0 g, 8.0 mmol), $TiCl_4$ (1.9 mL, 17.7 mmol), $ZnMe_2$ (1.2 M, 14.7 mL, 17.7 mmol), and *m*-CPBA (4.2 g, 24.1 mmol).

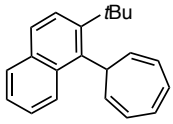
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 8.7, 0.9 Hz, 1H), 7.82-7.73 (m, 2H),

7.65 (d, J = 8.8 Hz, 1H), 7.61-7.54 (m, 1H), 7.52-7.44 (m, 1H), 1.67 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.38, 134.16, 133.58, 128.23, 128.15, 127.94, 127.68, 126.46, 126.28, 123.67, 38.05, 30.88.

HRMS-APCI: calculated for $C_{14}H_{15}Br$ $[M]^+$: 262.0352; found: 262.0340.

2-(*tert*-Butyl)-1-(cyclohepta-2,4,6-trien-1-yl)naphthalene (5j)



The title compound (white solid, 310 mg, 43% yield) was prepared according to the general procedure (**B**) from 1-bromo-2-(*tert*-butyl)naphthalene (690 mg, 2.6 mmol), *n*-BuLi (2.5 M, 1.0 mL, 2.6 mmol) and tropylium tetrafluoroborate (560 mg, 3.2 mmol).

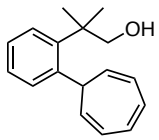
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42-8.33 (m, 1H), 7.86 (dd, J = 7.6, 1.9 Hz, 1H), 7.80-7.72 (m, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.48-7.32 (m, 2H), 6.74-6.67 (m, 2H), 6.33-6.22 (m, 2H), 5.71-5.60 (m, 2H), 4.32-4.21 (m, 1H), 1.40 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.23, 137.48, 133.39, 131.81, 130.78, 128.74, 127.59, 126.92, 124.56, 124.32, 124.01, 123.85, 42.10, 35.76, 32.20.

HRMS-APCI: calculated for $C_{21}H_{23}$ $[M+H]^+$: 275.1794; found: 275.1784.

M.p.: 105-106 °C.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropan-1-ol (SI2)



The title compound (white solid, 1.6 g, 98% yield) was prepared according to the general procedure (**C-step2**) from **5n** (2.7 g, 6.8 mmol), TBAF (1.0 M, 8.2

mL, 8.2 mmol).

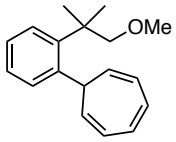
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.41 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.35 (td, *J* = 7.5, 1.4 Hz, 1H), 7.27-7.23 (m, 1H), 6.78-6.68 (m, 2H), 6.33-6.22 (m, 2H), 5.37-5.20 (m, 2H), 3.59 (s, 2H), 3.31-3.15 (m, 1H), 1.43 (s, 1H), 1.28 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.27, 143.51, 130.86, 130.42, 129.09, 127.76, 127.53, 126.59, 124.54, 72.02, 43.40, 41.23, 27.07, 26.92.

HRMS-APCI: calculated for $C_{17}H_{21}O$ $[M+H]^+$: 241.1587; found: 241.1592.

M.p.: 77-79 °C.

7-(2-(1-Methoxy-2-methylpropan-2-yl)phenyl)cyclohepta-1,3,5-triene (5k)



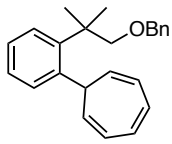
The title compound (colorless oil, 490 mg, 93% yield) was prepared according to the general procedure (**C-step3**) from **SI2** (500 mg, 2.1 mmol), MeI (0.23 mL, 3.7 mmol) and NaH (75mg, 3.1 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.31 (td, *J* = 7.5, 1.4 Hz, 1H), 7.27-7.19 (m, 1H), 6.78-6.71 (m, 2H), 6.33-6.22 (m, 2H), 5.39-5.30 (m, 2H), 3.35 (s, 2H), 3.32-3.24 (m, 4H), 1.25 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.87, 144.08, 130.77, 130.18, 129.60, 127.13, 127.04, 126.41, 124.29, 82.12, 59.32, 43.45, 40.05, 27.17.

HRMS-APCI: calculated for $C_{18}H_{23}O$ $[M+H]^+$: 255.1743; found: 255.1732.

7-(2-(1-(Benzyloxy)-2-methylpropan-2-yl)phenyl)cyclohepta-1,3,5-triene (5l)



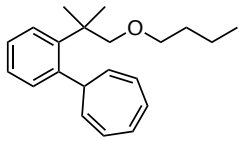
The title compound (colorless oil, 230 mg, 84% yield) was prepared according to the general procedure (**C-step3**) from **SI2** (200 mg, 0.83 mmol), BnBr (0.15 mL, 1.25 mmol) and NaH (40.0 mg, 1.66 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.44-7.28 (m, 7H), 6.85-6.74 (m, 2H), 6.41-6.26 (m, 2H), 5.46-5.34 (m, 2H), 4.53 (s, 2H), 3.53 (s, 2H), 3.42-3.29 (m, 1H), 1.38 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.91, 144.08, 138.83, 130.70, 130.13, 129.46, 128.33, 127.51, 127.41, 127.13, 127.09, 126.33, 124.26, 79.31, 73.33, 43.42, 40.15, 27.16.

HRMS-APCI: calculated for $C_{24}H_{27}O$ $[M+H]^+$: 331.2056; found: 331.2056.

7-(2-(1-Butoxy-2-methylpropan-2-yl)phenyl)cyclohepta-1,3,5-triene (5m)



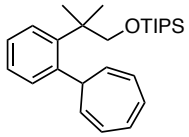
The title compound (colorless oil, 170 mg, 69% yield) was prepared according to the general procedure (**C-step3**) from **SI2** (200 mg, 0.83 mmol), BuI (0.17 mL, 1.5 mmol) and NaH (40.0 mg, 1.66 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.45 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.37 (td, *J* = 7.4, 1.5 Hz, 1H), 7.28 (ddd, *J* = 8.1, 7.2, 1.6 Hz, 1H), 6.88-6.68 (m, 2H), 6.39-6.25 (m, 2H), 5.46-5.35 (m, 2H), 3.47-3.32 (m, 5H), 1.61-1.47 (m, 2H), 1.44-1.28 (m, 8H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.23, 144.13, 130.73, 130.10, 129.65, 127.12, 127.02, 126.29, 124.26, 79.70, 71.26, 43.47, 40.15, 31.76, 27.02, 19.49, 14.05.

HRMS-APCI: calculated for $C_{21}H_{29}O$ $[M+H]^+$: 297.2213; found: 297.2212.

(2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-methylpropoxy)triisopropyl-silane (5n)



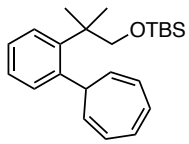
The title compound (colorless oil, 3.1 g, 75% yield) was prepared according to the general procedure (**C-step1**) from **SI1**(4.0 g, 10.4 mmol), *n*-BuLi (2.5 M, 4.2 mL, 10.4 mmol) and tropylium tetrafluoroborate (2.2 g, 12.5 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.51 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.34-7.22 (m, 1H), 6.88-6.67 (m, 2H), 6.42-6.14 (m, 2H), 5.45-5.28 (m, 2H), 3.68 (s, 2H), 3.44-3.29 (m, 1H), 1.35 (s, 6H), 1.14-1.01 (m, 21H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.11, 144.37, 130.76, 130.19, 129.62, 127.36, 127.07, 126.26, 124.33, 71.40, 43.60, 41.61, 26.36, 18.22, 12.09.

HRMS-APCI: calculated for $C_{26}H_{41}OSi$ $[M+H]^+$: 397.2921; found: 397.2915.

***tert*-Butyl(2-(2-(cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropoxy)-dimethylsilane (5o)**



The title compound (colorless oil, 250 mg, 85% yield) was prepared according to the general procedure (**C-step3**) from **SI2** (200 mg, 0.83 mmol), TBSCl (190 mg, 1.3 mmol) and imidazole (170 mg, 2.5 mmol).

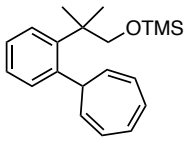
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.50 (dd, *J* = 8.1,

1.4 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.32-7.26 (m, 1H), 6.86-6.75 (m, 2H), 6.38-6.29 (m, 2H), 5.46-5.37 (m, 2H), 3.58 (s, 2H), 3.38-3.32 (m, 1H), 1.30 (s, 6H), 0.91 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.19, 144.26, 130.78, 130.11, 129.63, 127.37, 127.02, 126.23, 124.29, 71.20, 43.56, 41.11, 26.34, 26.02, 18.38, -5.30.

HRMS-APCI: calculated for $C_{23}H_{35}OSi$ $[M+H]^+$: 355.2452; found: 355.2434.

(2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2methylpropoxy)trimethylsilane (5p)



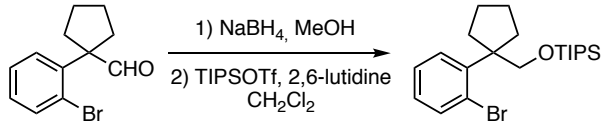
The title compound (colorless oil, 250 mg, 85% yield) was prepared according to the general procedure (**C-step 3**) from **SI2** (200 mg, 0.83 mmol), TMSCl (190 mg, 1.3 mmol) and imidazole (170 mg, 2.5 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.45 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.34 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29-7.20 (m, 1H), 6.85-6.63 (m, 2H), 6.38-6.19 (m, 2H), 5.45-5.23 (m, 2H), 3.52 (d, *J* = 1.1 Hz, 2H), 3.41-3.24 (m, 1H), 1.25 (d, *J* = 1.1 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.00, 144.18, 130.66, 130.03, 129.45, 127.18, 126.94, 126.15, 124.15, 70.65, 43.42, 40.74, 26.19, -0.47.

HRMS-APCI: calculated for $C_{20}H_{29}OSi$ $[M+H]^+$: 313.1909; found: 313.1919.

((1-(2-Bromophenyl)cyclopentyl)methoxy)triisopropylsilane (SI4)



SI3 **SI4**

Step 1: To a solution of **SI3**[107](1.9 g, 7.5 mmol) in anhydrous MeOH (0.1 M) at 0 °C was slowly added $NaBH_4$ (0.7 g, 18.8 mmol). The mixture was stirred 2 h at room temperature (23 ºC). It was quenched by addition of EtOAc at 0 °C, followed by water. It was extracted with EtOAc (x3), washed with brine and dried over $MgSO_4$. The crude was used in the next step without further purification.

Step 2: To a solution of the alcohol in anhydrous CH_2Cl_2 (0.1 M) at 0 °C was added 2,6-lutidine (1.7 mL, 15 mmol) dropwise followed by TIPSOTf (3.1 mL, 11.3 mmol). The mixture was stirred 6 h at room temperature (23 ºC). It was quenched by addition of EtOAc at 0 ºC, followed by water. It was extracted with EtOAc (x3), washed with brine and dried over $MgSO_4$. The crude reaction mixture was purified by column chromatography on silica gel with pentane as eluent giving **SI4** as a colorless oil (2.5 g, 81% yield in two steps).

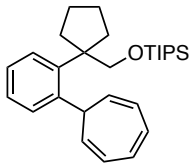
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.38 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.19 (ddd, *J* = 7.9, 7.2, 1.5 Hz, 1H), 7.00 (ddd, *J* = 7.9, 7.2, 1.8 Hz, 1H), 3.87 (s, 2H), 2.46-2.23 (m, 2H), 2.04-1.86 (m, 2H), 1.76-1.60 (m, 4H), 0.99-0.81 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.01, 134.60, 131.60, 127.30, 126.33, 122.79, 65.87, 54.56, 34.63, 24.38, 17.82, 11.88.

HRMS-APCI: calculated for $C_{21}H_{36}BrOSi$ $[M+H]^+$: 411.1713; found: 411.1695.

((1-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)cyclopentyl)methoxy)triisopropylsilane (SI5)

107. Kesharwani, T.; Verma, A.; Emrich, D.; Ward, J.; Larock, R. *Org. Lett*. **2009**, *11*, 2591-2593.



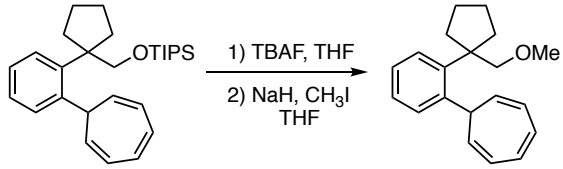
The title compound (colorless oil, 800 mg, 52% yield) was prepared according to the general procedure (**B**) from **SI4** (1.5 g, 3.7 mmol), *n*-BuLi (2.5 M, 1.5 mL, 3.7 mmol) and tropylium tetrafluoroborate (780 mg, 4.4 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.46 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (td, *J* = 7.4, 1.4 Hz, 1H), 7.27 (td, *J* = 7.6, 1.6 Hz, 1H), 6.80 (t, *J* = 3.2 Hz, 2H), 6.38-6.28 (m, 2H), 5.46-5.37 (m, 2H), 3.57 (s, 2H), 3.22-3.09 (m, 1H), 2.22-2.03 (m, 2H), 1.96-1.83 (m, 2H), 1.79-1.59 (m, 4H), 1.14-0.89 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.40, 143.79, 130.70, 129.51, 129.49, 128.88, 126.78, 125.69, 124.20, 69.86, 53.40, 43.33, 35.83, 25.36, 18.10, 12.02.

HRMS-APCI: calculated for $C_{28}H_{43}OSi$ $[M+H]^+$: 423.3005; found: 423.3004.

7-(2-(1-(Methoxymethyl)cyclopentyl)phenyl)cyclohepta-1,3,5-triene (5q)



Step 1: TBAF (1 M in THF, 1.2 ml, 1.2 mmol) was added dropwise to a solution of **SI4** (340 mg, 0.8 mmol) in dry THF (0.2 M) at 0 ºC under argon. The cooling bath was removed and the reaction was stirred at room temperature (23 ºC) for 6 h. The reaction was quenched by the addition of water. The aqueous phase was extracted with diethyl ether, the combined organic extracts were dried over $MgSO_4$, and the solvent was evaporated. The crude was used in the next step

without further purification.

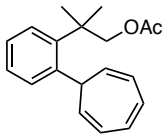
Step 2: To a solution of the alcohol in anhydrous THF (0.1 M) at 0 ºC was added NaH (48 mg, 2.0 mmol). After stirring for 30 min at the same temperature, MeI (0.14 mL, 2.3 mmol) was added. The reaction was stirred overnight at room temperature (23 ºC). The reaction was quenched with NH_4Cl (aq.), and extracted with diethyl ether (x3). After washing with brine and drying over $MgSO_4$, the product was purified on silica gel column chromatography pentane obtaining a colorless oil (160mg, 71% yield in two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.34 (m, 1H), 7.33-7.27 (m, 1H), 7.06-6.99 (m, 1H), 6.98-6.94 (m, 1H), 6.79-6.69 (m, 2H), 6.30-6.23 (m, 2H), 5.48-5.41 (m, 2H), 3.83 (d, J = 2.0 Hz, 3H), 3.19-3.12 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.36, 131.80, 130.78, 128.92, 127.79, 127.18, 124.14, 120.76, 110.93, 55.40, 40.49.

HRMS-APCI: calculated for $C_{20}H_{25}O$ $[M+H]^+$: 281.1900; found: 281.1896.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropyl acetate (5r)



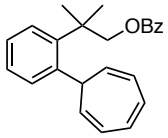
The title compound (colorless oil, 210 mg, 89% yield) was prepared according to the general procedure (**D**) from **SI2** (200 mg, 0.83 mmol), DMAP (10 mg, 0.08 mmol) and pyridine (0.2 mL, 2.5 mmol), AcCl (0.09 mL, 0.8 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.54 (m, 1H), 7.39-7.31 (m, 2H), 7.26-7.21 (m, 1H), 6.85-6.65 (m, 2H), 6.38-6.19 (m, 2H), 5.42-5.14 (m, 2H), 4.10 (s, 2H), 3.31-3.18 (m, 1H), 2.00 (s, 3H), 1.27 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.03, 144.08, 143.50, 130.67, 130.25, 128.94, 127.30, 126.63, 126.27, 124.36, 72.22, 43.25, 39.03, 26.72, 20.92.

HRMS-ESI: calculated for $C_{19}H_{22}NaO_2$ $[M+Na]^+$: 305.1512; found: 305.1510.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropyl benzoate (5s)



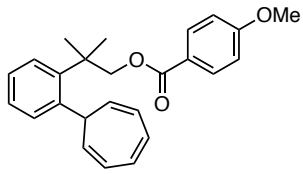
The title compound (colorless oil, 240 mg, 84% yield) was prepared according to the general procedure (**D**) from **SI2** (200 mg, 0.83 mmol), DMAP (10 mg, 0.08 mmol) and pyridine (0.2 mL, 2.5 mmol), benzoyl chloride (0.15 mL, 1.3 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.44-7.28 (m, 7H), 6.85-6.74 (m, 2H), 6.41-6.26 (m, 2H), 5.46-5.34 (m, 2H), 4.53 (s, 2H), 3.53 (s, 2H), 3.42-3.29 (m, 1H), 1.38 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.91, 144.08, 138.83, 130.70, 130.13, 129.46, 128.33, 127.51, 127.41, 127.13, 127.09, 126.33, 124.26, 79.31, 73.33, 43.42, 40.15, 27.16.

HRMS-ESI: calculated for $C_{24}H_{24}NaO_2$ $[M+Na]^+$: 367.1669; found: 367.1667.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropyl 4-methoxy-benzoate (5t)



The title compound (white solid, 240 mg, 77% yield) was prepared according to the general procedure (**D**) from **SI2** (200 mg, 0.83 mmol), DMAP (10 mg, 0.08 mmol) and pyridine (0.2 mL, 2.5 mmol), 4-methoxybenzoyl chloride (0.17 mL, 1.3 mmol).

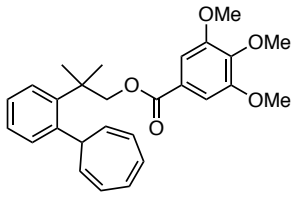
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.84 (m, 2H), 7.58 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.36 (td, *J* = 7.5, 1.4 Hz, 1H), 7.28-7.23 (m, 1H), 6.91-6.85 (m, 2H), 6.79-6.72 (m, 2H), 6.32-6.23 (m, 2H), 5.41-5.26 (m, 2H), 4.31 (s, 2H), 3.84 (s, 3H), 3.32-3.26 (m, 1H), 1.36 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.27, 163.45, 144.19, 143.86, 131.70, 130.86, 130.41, 129.08, 127.43, 126.81, 126.48, 124.54, 122.91, 113.72, 72.59, 55.55, 43.42, 39.46, 27.05.

HRMS-ESI: calculated for $C_{25}H_{26}NaO_3$ $[M+Na]^+$: 397.1774; found: 397.1787.

M.p.: 97-99 °C.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropyl 3,4,5-trimethoxybenzoate (5u)



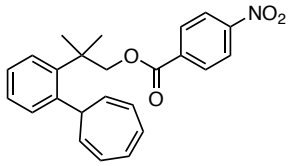
The title compound (colorless oil, 260 mg, 72% yield) was prepared according to the general procedure (**D**) from **SI2** (200 mg, 0.83 mmol), DMAP (10 mg, 0.08 mmol) and pyridine (0.2 mL, 2.5 mmol), 3,4,5-trimethoxybenzoyl chloride (290 mg, 1.3 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.39 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.29 (td, *J* = 7.5, 1.3 Hz, 1H), 7.23-7.15 (m, 1H), 7.03 (s, 2H), 6.75-6.66 (m, 2H), 6.23-6.15 (m, 2H), 5.30-5.18 (m, 2H), 4.24 (s, 2H), 3.82 (s, 3H), 3.74 (s, 6H), 3.27-3.15 (m, 1H), 1.33 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.86, 152.89, 144.09, 143.47, 142.12, 130.77, 130.23, 128.74, 127.35, 126.90, 126.22, 125.33, 124.50, 106.69, 72.90, 60.89, 56.16, 43.25, 39.41, 27.30.

HRMS-ESI: calculated for $C_{27}H_{30}NaO_5$ $[M+Na]^+$: 457.1985; found: 457.1986.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropyl 4-nitrobenzoate (5v)



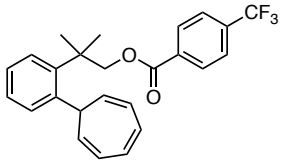
The title compound (colorless oil, 210 mg, 65% yield) was prepared according to the general procedure (**D**) from **SI2** (200 mg, 0.83 mmol), DMAP (10 mg, 0.08 mmol) and pyridine (0.2 mL, 2.5 mmol), 4-nitrobenzoyl chloride (0.15 mL, 1.3 mmol)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.20 (m, 2H), 8.08-8.02 (m, 2H), 7.60 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.44-7.35 (m, 2H), 7.30-7.24 (m, 1H), 6.85-6.69 (m, 2H), 6.34-6.22 (m, 2H), 5.40-5.26 (m, 2H), 4.37 (s, 2H), 3.29-3.22 (m, 1H), 1.39 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.56, 150.65, 144.14, 143.16, 135.79, 130.89, 130.76, 130.53, 128.84, 127.69, 126.74, 126.58, 124.64, 123.67, 73.70, 43.42, 39.46, 27.16.

HRMS-ESI: calculated for $C_{24}H_{23}NO_4$ $[M+Na]^+$: 412.1519; found: 412.1512.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropyl 4-(trifluoro-methyl)benzoate (5w)



The title compound (white solid, 320 mg, 93% yield) was prepared according to the general procedure (**D**) from **SI2** (200 mg, 0.83 mmol), DMAP (10 mg, 0.08 mmol) and TEA (0.7 mL, 5 mmol), 4-(trifluoromethyl)benzoyl chloride (0.19

mL, 1.3 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14-8.06 (m, 2H), 7.74-7.65 (m, 3H), 7.53 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.46 (td, *J* = 7.4, 1.4 Hz, 1H), 7.36 (td, *J* = 7.6, 1.6 Hz, 1H), 6.94-6.75 (m, 2H), 6.44-6.29 (m, 2H), 5.50-5.31 (m, 2H), 4.49 (s, 2H), 3.45-3.34 (m, 1H), 1.49 (s, 6H).

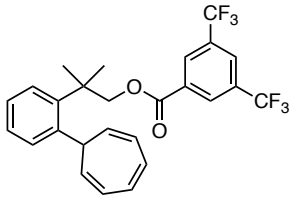
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.00, 144.09, 143.25, 134.32 (q, *J* = 32.6 Hz), 133.59, 130.77, 130.38, 129.96, 128.78, 127.55, 126.68, 126.48, 125.39 (q, *J* = 3.8 Hz), 124.53, 123.71 (q, *J* = 272.7 Hz), 73.19, 43.36, 39.36, 27.00.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.12 (s).

HRMS-ESI: calculated for $C_{25}H_{23}F_3NaO_2$ $[M+Na]^+$: 435.1542; found: 435.1532.

M.p.: 84-86 °C.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropyl 3,5-bis(trifluoro methyl)benzoate (5x)



The title compound (colorless oil, 360 mg, 90% yield) was prepared according to the general procedure (**D**) from **SI2** (200 mg, 0.83 mmol), DMAP (10 mg, 0.08 mmol) and TEA (0.7 mL, 5 mmol), 3,5-bis(trifluoromethyl)benzoyl chloride (0.23 mL, 1.3 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 1.6, 0.8 Hz, 2H), 8.09-8.04 (m, 1H), 7.64 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36-7.30 (m, 1H), 6.86-6.75 (m, 2H), 6.35-6.24 (m, 2H), 5.42-5.28 (m, 2H), 4.44 (s, 2H), 3.40-3.26 (m, 1H), 1.46 (s, 6H).

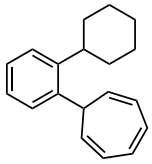
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.71, 144.07, 142.90, 132.65, 132.31 (q, *J* =

34.0 Hz), 130.90, 130.48, 129.74 (q, J = 3.8 Hz), 128.79, 127.80, 126.81, 126.61, 126.38 (q, J = 3.8 Hz), 124.65, 122.98 (q, J = 272.9 Hz), 73.85, 43.43, 39.51, 27.27.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.16 (s).

HRMS-ESI: calculated for $C_{26}H_{22}F_6NaO_2$ $[M+Na]^+$: 503.1416; found: 503.1410.

7-(2-Cyclohexylphenyl)cyclohepta-1,3,5-triene (5y)



The title compound (colorless oil, 1.0 g, 80% yield) was prepared according to the general procedure (**B**) from 1-bromo-2-cyclohexylbenzene (0.9 mL, 5.0 mmol), *n*-BuLi (2.5 M, 2.4 mL, 6 mmol) and tropylium tetrafluoroborate (1.2 g, 6.5 mmol).

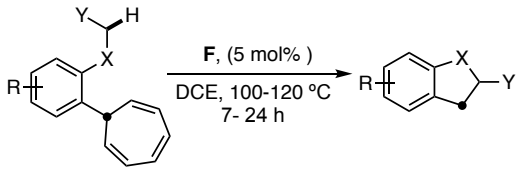
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.40 (m, 1H), 7.33-7.23 (m, 3H), 6.85-6.66 (m, 2H), 6.36-6.16 (m, 2H), 5.47-5.28 (m, 2H), 3.09-2.95 (m, 1H), 2.71-2.49 (m, 1H), 1.86-1.64 (m, 5H), 1.49-1.13 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.36, 131.80, 130.78, 128.92, 127.79, 127.18, 124.14, 120.76, 110.93, 55.40, 40.49.

^{19}F NMR (101 MHz, $CDCl_3$) δ 157.36, 131.80, 130.78, 128.92, 127.79, 127.18, 124.14, 120.76, 110.93, 55.40, 40.49.

HRMS-APCI: calculated for $C_{19}H_{23}$ $[M+H]^+$: 251.1794; found: 251.1792.

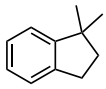
Gold-catalyzed C(sp^3)-H functionalization



General Procedure (E): A solution of the cycloheptatriene substrate (0.2 mmol) and gold complex **F** (9.3 mg, 5 mol%) in dry 1,2-dichloroethane (DCE, 8 mL) under argon was heated at 100-120 °C in a sealed tube until the starting material had been fully consumed (7-24 h). The reaction mixture had been allowed to cool to room temperature, the solvent was removed in vacuo, and the crude residue was purified by preparative TLC.

Compound Characterization

1,1-Dimethyl-2,3-dihydro-1*H*-indene (6a)



The title compound (colorless oil, 25.0 mg, 85% yield) was prepared according to the general procedure (**E**) from **5a** (50.0 mg, 0.2 mmol) at 100 °C after 7 h.

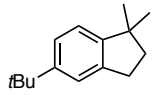
The spectroscopic data match with those reported in the literature.[108]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.10 (m, 4H), 2.90 (t, *J* = 7.2 Hz, 2H), 1.93 (t, *J* = 7.2 Hz, 2H), 1.27 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.69, 142.90, 126.44, 126.28, 124.60, 122.11, 44.08, 41.51, 30.20, 28.74.

5-(*tert*-Butyl)-1,1-dimethyl-2,3-dihydro-1*H*-indene (6b)

108. Bright , S. T.; Coxon , J. M.; Steel , P. J. *J. Org. Chem.* **1990**, *55*, 1338-1344.



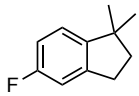
The title compound (colorless oil, 35.0 mg, 86% yield) was prepared according to the general procedure (**E**) from **5b** (56.0 mg, 0.2 mmol) at 100 °C after 7 h.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.21 (m, 2H), 7.11 (d, *J* = 7.9 Hz, 1H), 2.92 (t, *J* = 7.2 Hz, 2H), 1.96 (t, *J* = 7.2 Hz, 2H), 1.36 (s, 9H), 1.30 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.68, 149.27, 142.66, 123.49, 121.51, 121.47, 43.71, 41.78, 34.66, 31.80, 30.36, 28.84.

HRMS-APCI: calculated for $C_{14}H_{19}$ $[M\text{-}CH_3]^+$: 187.1481; found: 187.1483.

5-Fluoro-1,1-dimethyl-2,3-dihydro-1*H*-indene (6c)



The title compound (colorless oil, 29.4 mg, 90% yield) was prepared according to the general procedure (**E**) from **5c** (48.5 mg, 0.2 mmol) at 100 °C after 7 h.

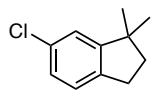
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 8.0, 5.2 Hz, 1H), 6.91-6.72 (m, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 1.94 (t, *J* = 7.2 Hz, 2H), 1.24 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.07 (d, *J* = 242.3 Hz), 148.15, 144.96 (d, *J* = 8.0 Hz), 122.93 (d, *J* = 8.9 Hz), 113.17 (d, *J* = 22.3 Hz), 111.46 (d, *J* = 21.5 Hz), 43.52, 41.82, 30.13 (d, *J* = 2.2 Hz), 28.87.

^{19}F NMR (376 MHz, $CDCl_3$) δ -118.25 (dt, *J* = 9.2, 5.3 Hz).

HRMS-APCI: calculated for $C_{11}H_{13}F$ $[M+H]^+$: 165.1102; found: 165.1104.

6-Chloro-1,1-dimethyl-2,3-dihydro-1*H*-indene (6d)



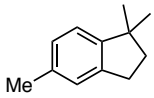
The title compound (colorless oil, 30.0 mg, 83% yield) was prepared according to the general procedure (**E**) from **5d** (51.8 mg, 0.2 mmol) at 100 °C after 7 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (s, 3H), 2.85 (t, *J* = 7.2 Hz, 2H), 1.94 (t, *J* = 7.2 Hz, 2H), 1.25 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.80, 141.28, 132.11, 126.39, 125.71, 122.58, 44.39, 41.70, 29.72, 28.55.

HRMS-APCI: calculated for $C_{10}H_{10}Cl$ $[M\text{-}CH_3]^+$: 165.0466; found: 165.0466.

1,1,5-Trimethyl-2,3-dihydro-1*H*-indene (6e)



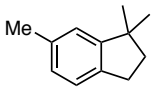
The title compound (colorless oil, 29.0 mg, 90% yield) was prepared according to the general procedure (**E**) from **5e** (47.7 mg, 0.2 mmol) at 100 °C after 7 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-6.91 (m, 3H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.94 (t, *J* = 7.2 Hz, 2H), 1.28 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.84, 143.12, 135.90, 127.23, 125.35, 121.87, 43.70, 41.71, 30.09, 28.82, 21.37.

HRMS-APCI: calculated for $C_{12}H_{15}$ $[M\text{-}H]^+$: 159.1168; found: 159.1168.

1,1,6-Trimethyl-2,3-dihydro-1*H*-indene (6f)



The title compound (colorless oil, 27.0 mg, 84% yield) was prepared according to the general procedure (**E**) from **5f** (47.7 mg, 0.2 mmol) at 100 °C after 7 h.

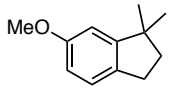
The spectroscopic data match with those reported in the literature[108].

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.08 (m, 1H), 7.02-6.95 (m, 2H), 2.88 (t, *J*

= 7.2 Hz, 2H), 2.37 (s, 3H), 1.94 (t, *J* = 7.2 Hz, 2H), 1.28 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.82, 139.87, 135.96, 127.13, 124.34, 122.83, 43.95, 41.80, 29.77, 28.72, 21.53.

6-Methoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene (6g)



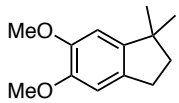
The title compound (colorless oil, 31.0 mg, 88% yield) was prepared according to the general procedure (**E**) from **5g** (51.0 mg, 0.2 mmol) at 100 °C after 7 h.

The spectroscopic data match with those reported in the literature.[109]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.04 (m, 1H), 6.75-6.65 (m, 2H), 3.80 (s, 3H), 2.82 (t, *J* = 7.1 Hz, 2H), 1.92 (t, *J* = 7.2 Hz, 2H), 1.25 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.97, 154.34, 134.91, 125.05, 111.77, 108.03, 55.58, 44.26, 42.07, 29.35, 28.60.

5,6-Dimethoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene (6h)



The title compound (colorless oil, 31.0 mg, 75% yield) was prepared according to the general procedure (**E**) from **5h** (57.0 mg, 0.2 mmol) at 100 °C after 7 h.

The spectroscopic data match with those reported in the literature[108].

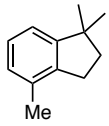
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.67 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.83 (t, *J* = 7.1 Hz, 2H), 1.93 (t, *J* = 7.2 Hz, 2H), 1.24 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.26, 148.05, 144.45, 134.23, 107.94, 105.70,

109. Wang, J.; Zhou, P.; Wang, Y. *Eur. J. Org. Chem.* **2011**, 264-270.

56.28, 56.15, 44.21, 41.94, 30.03, 28.88.

1,1,4-Trimethyl-2,3-dihydro-1*H*-indene (6i)



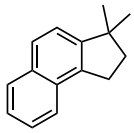
The title compound (colorless oil, 24.6 mg, 77% yield) was prepared according to the general procedure (**E**) from **5i** (47.7 mg, 0.2 mmol) at 120 °C after 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (t, *J* = 7.4 Hz, 1H), 7.05-6.94 (m, 2H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.27 (s, 3H), 1.94 (t, *J* = 7.2 Hz, 2H), 1.27 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.47, 141.66, 133.91, 127.22, 126.73, 119.46, 44.28, 41.08, 28.94, 28.71, 19.17.

HRMS-APCI: calculated for $C_{12}H_{15}$ $[M-H]^+$: 159.1168; found: 199.1167.

3,3-Dimethyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene (6j)



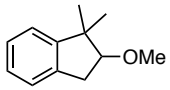
The title compound (colorless oil, 29.0 mg, 74% yield) was prepared according to the general procedure (**E**) from **5j** (55.0 mg, 0.2 mmol) at 120 °C after 12 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2H), 7.78-7.72 (m, 1H), 7.53-7.47 (m, 1H), 7.47-7.41 (m, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 3.25 (t, *J* = 7.2 Hz, 2H), 2.13 (t, *J* = 7.2 Hz, 2H), 1.36 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.27, 137.88, 132.88, 130.63, 128.52, 127.27, 125.95, 124.92, 124.48, 121.16, 45.03, 41.15, 29.02, 28.43.

HRMS-APCI: calculated for $C_{15}H_{15}$ $[M-H]^+$: 195.1168; found: 195.1163.

2-Methoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene (6k)



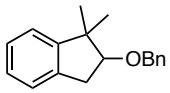
The title compound (colorless oil, 28.5 mg, 81% yield) was prepared according to the general procedure (**E**) from **5k** (51.0 mg, 0.2 mmol) at 100 °C after 7 h.

The spectroscopic data match with those reported in the literature.[110]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.11 (m, 4H), 3.75 (dd, *J* = 7.6, 6.7 Hz, 1H), 3.48 (s, 3H), 3.17 (dd, *J* = 15.4, 6.7 Hz, 1H), 2.84 (dd, *J* = 15.4, 7.6 Hz, 1H), 1.35 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 150.72, 138.44, 127.06, 126.74, 124.99, 122.34, 90.41, 58.18, 46.43, 35.46, 26.90, 22.31.

2-(Benzyloxy)-1,1-dimethyl-2,3-dihydro-1*H*-indene (6l)



The title compound (colorless oil, 43.7 mg, 87% yield) was prepared according to the general procedure (**E**) from **5l** (61.1 mg, 0.2 mmol) at 100 °C after 7 h.

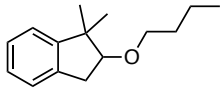
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.36 (m, 4H), 7.35-7.28 (m, 1H), 7.25-7.14 (m, 4H), 4.75 (d, *J* = 12.1 Hz, 1H), 4.65 (d, *J* = 12.1 Hz, 1H), 3.97 (dd, *J* = 7.8, 6.7 Hz, 1H), 3.16 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.94 (dd, *J* = 15.4, 7.8 Hz, 1H), 1.37 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.71, 139.11, 138.53, 128.44, 127.57, 127.56, 127.03, 126.70, 124.95, 122.31, 88.00, 72.11, 46.59, 35.92, 26.77, 22.61.

HRMS-ESI: calculated for $C_{18}H_{20}NaO$ $[M+Na]^+$: 275.1406; found: 275.1409.

110. Scholl, B.; Jolidon, S.; Hansen, H. *Helv. Chim. Acta* **1986**, *69*, 184-194.

2-Butoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene (6m)



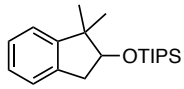
The title compound (colorless oil, 31.5 mg, 72% yield) was prepared according to the general procedure (**E**) from **5m** (59.3 mg, 0.2 mmol) at 100 °C after 7 h.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.11 (m, 4H), 3.82 (dd, *J* = 7.8, 6.8 Hz, 1H), 3.62 (dt, *J* = 9.3, 6.4 Hz, 1H), 3.52 (dt, *J* = 9.3, 6.6 Hz, 1H), 3.14 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.84 (ddd, *J* = 15.5, 7.8, 1.1 Hz, 1H), 1.67-1.54 (m, 2H), 1.50-1.38 (m, 2H), 1.35 (s, 3H), 1.16 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.91, 138.75, 126.94, 126.63, 124.94, 122.32, 88.69, 70.34, 46.48, 36.12, 32.35, 26.88, 22.43, 19.57, 14.10.

HRMS-ESI: calculated for $C_{15}H_{22}NaO$ $[M+Na]^+$: 241.1563; found: 241.1557.

((1,1-Dimethyl-2,3-dihydro-1*H*-inden-2-yl)oxy)triisopropylsilane (6n)



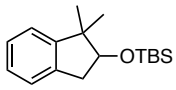
The title compound (colorless oil, 28.0 mg, 44% yield, 66% brsm) was prepared according to the general procedure (**E**) from **5n** (79.0 mg, 0.2 mmol) at 120 °C after 24 h and 26.0 mg of **5n** was recovered.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.12 (m, 4H), 4.31 (dd, *J* = 8.8, 7.1 Hz, 1H), 3.08 (dd, *J* = 15.0, 7.1 Hz, 1H), 2.88 (dd, *J* = 15.1, 8.8 Hz, 1H), 1.35 (s, 3H), 1.20-1.07 (m, 24H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.74, 138.68, 126.93, 126.59, 124.77, 122.53, 81.82, 47.09, 39.39, 25.91, 22.31, 18.34, 18.28, 12.71.

HRMS-ESI: calculated for $C_{20}H_{34}NaOSi$ $[M+Na]^+$: 341.2271; found: 341.2288.

***tert*-Butyl((1,1-dimethyl-2,3-dihydro-1*H*-inden-2-yl)oxy)dimethylsilane (6o)**



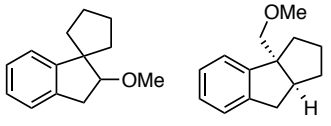
The title compound (colorless oil, 28.0 mg, 51% yield, 69% brsm) was prepared according to the general procedure (**E**) from **5o** (71.0 mg, 0.2 mmol) at 120 °C after 24 h and 14.0 mg of **5o** was recovered.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.10 (m, 4H), 4.12 (dd, *J* = 8.4, 7.0 Hz, 1H), 3.01 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.81 (dd, *J* = 15.2, 8.4 Hz, 1H), 1.27 (s, 3H), 1.08 (s, 3H), 0.94 (s, 9H), 0.11 (d, *J* = 1.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.70, 138.84, 126.90, 126.58, 124.80, 122.56, 81.56, 46.73, 39.12, 26.01, 25.87, 22.24, 18.29, -4.26, -4.74.

HRMS-ESI: calculated for $C_{17}H_{28}NaOSi$ $[M+Na]^+$: 299.1802; found: 299.1795.

2'-Methoxy-2',3'-dihydrospiro[cyclopentane-1,1'-indene] and *cis*-3a-(methoxymethyl)-1,2,3,3a,8,8a-hexahydrocyclopenta[a]indene (6q/6q´)



1.4 : 1

The title compounds (colorless oil, 31.0 mg, 77% overall yield) was prepared according to the general procedure (**E**) from **5q** (56.1 mg, 0.2 mmol) at 100 °C after 12 h as a 1.4:1 mixture of isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.10 (m, major4H + minor4H), 3.77 (t, *J* = 5.6 Hz, major1H), 3.51-3.39 (m, major 3H + minor 2H), 3.31 (s, minor3H), 3.23 (dd, *J* = 16.9, 9.4 Hz, minor1H), 3.12 (dd, *J* = 15.5, 5.8 Hz, major1H), 2.86 (dd, *J* = 15.5, 5.5 Hz, major1H), 2.70-2.60 (m, minor2H), 2.33-2.20 (m, major1H)

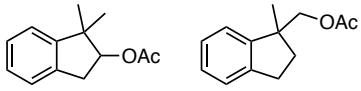
1.95-1.39 (m, major7H + minor6H).

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 150.82, 148.78, 143.84, 139.29, 127.01, 126.89, 126.61, 126.50, 124.79, 124.66, 124.20, 122.45, 89.53, 80.09, 61.49, 59.51, 58.42, 57.69, 45.79, 38.80, 38.68, 37.39, 35.91, 35.39, 32.32, 26.12, 25.90, 25.84.

HRMS-APCI: calculated for $C_{13}H_{15}$ $[M\text{-}OMe]^+$: 171.1168; found: 171.1166.

Note: The relative configuration of minor was assigned based on simple structure modelling and geometry considerations, as the *cis*-configuration is much more favorable in octahydropentalene than the *trans*-configuration.

1,1-Dimethyl-2,3-dihydro-1*H*-inden-2-yl acetate and (1-methyl-2,3-dihydro -1*H*-inden-1-yl)methyl acetate (6r/6r´)



1 : 1.5

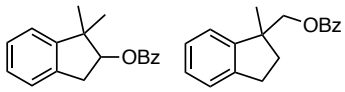
The title compounds (colorless oil, 35.3 mg, 86% overall yield) was prepared according to the general procedure (**E**) from **5r** (56.5 mg, 0.2 mmol) at 100 °C after 12 h as a 1:1.5 mixture of isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.15 (m, major4H + minor4H), 5.21 (dd, *J* = 6.4, 4.8 Hz, minor1H), 4.12-3.97 (m, major2H), 3.35 (dd, *J* = 16.4, 6.4 Hz, minor1H), 3.95-3.84 (m, major2H + minor1H), 3.18-3.11 (m, major1H), 2.07 (s, minor3H), 2.05 (s, major3H), 1.91-1.84 (m, major1H), 1.33 (s, major3H), 1.27 (s, minor3H), 1.25 (s, minor3H),

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 171.34, 171.18, 149.85, 147.73, 143.73, 138.54, 127.24, 127.22, 127.04, 126.49, 124.85, 124.80, 123.31, 122.27, 82.46, 70.87, 47.67, 46.84, 36.77, 36.64, 30.23, 27.22, 23.96, 22.15, 21.29, 21.06.

HRMS-ESI: calculated for $C_{13}H_{16}NaO_2$ $[M+Na]^+$: 227.1043; found: 227.1048.

1,1-Dimethyl-2,3-dihydro-1*H*-inden-2-yl benzoate and (1-methyl-2,3-dihydro-1*H*-inden-1-yl)methyl benzoate (6s/6s´)



1 : 1.2

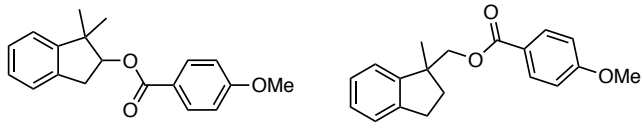
The title compounds (colorless oil, 45.4 mg, 85% overall yield) was prepared according to the general procedure (**E**) from **5s** (68.9 mg, 0.2 mmol) at 100 °C after 12 h as a 1:1.2 mixture of isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.04 (m, major2H + minor2H), 7.63-7.56 (m, major1H + minor1H), 7.51-7.43 (m, major2H + minor2H), 7.33-7.20 (m, major4H + minor4H), 5.48 (ddd, *J* = 6.1, 5.4, 0.7 Hz, minor1H), 4.34 (d, *J* = 0.7 Hz, major2H), 3.51 (dd, *J* = 16.4, 6.6 Hz, minor1H), 3.10-2.94 (m, major2H + minor1H), 2.34-2.24 (m, major1H), 2.05-1.95 (m, major1H), 1.47 (s, major3H), 1.40 (d, *J* = 1.6 Hz, minor6H).

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 166.76, 166.58, 149.82, 147.73, 143.76, 138.47, 133.07, 133.02, 130.60, 130.52, 129.76, 129.67, 128.52, 128.49, 127.30, 127.28, 127.09, 126.58, 124.92, 124.86, 123.36, 122.31, 82.93, 71.40, 47.97, 47.10, 36.84, 36.80, 30.30, 27.22, 24.08, 22.61.

HRMS-ESI: calculated for $C_{18}H_{18}NaO_2$ $[M+Na]^+$: 289.1199; found: 289.1197.

1,1-Dimethyl-2,3-dihydro-1*H*-inden-2-yl 4-methoxybenzoate and (1-methyl-2,3-dihydro-1*H*-inden-1-yl)methyl 4-methoxybenzoate (6t/6t´)



1.7 : 1

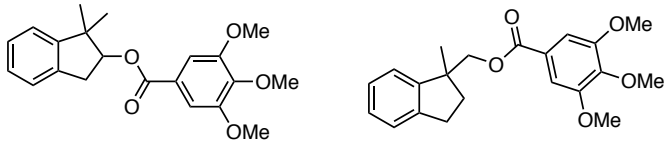
The title compounds (colorless oil, 49.0 mg, 83% overall yield) was prepared according to the general procedure (**E**) from **5t** (75.0 mg, 0.2 mmol) at 100 °C after 12 h as a 1.7:1 mixture of isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-7.98 (m, major2H + minor2H), 7.32-7.20 (m, major4H + minor4H), 6.98-6.91 (m, major2H + minor2H), 5.45 (dd, *J* = 6.7, 5.4 Hz, major1H), 4.31 (s, minor2H), 3.92-3.86 (m, major3H + minor3H), 3.49 (ddd, *J* = 16.4, 6.6, 1.0 Hz, major1H), 3.09-2.97 (m, major1H + minor2H), 2.28 (ddd, *J* = 12.9, 8.0, 4.9 Hz, minor1H), 1.98 (ddd, *J* = 12.9, 8.7, 7.8 Hz, minor1H), 1.46 (s, minor3H), 1.38 (s, major6H).

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 166.50, 166.31, 163.50, 163.46, 149.90, 147.83, 143.75, 138.56, 131.77, 131.66, 127.23, 127.22, 127.03, 126.54, 124.90, 124.82, 123.35, 123.01, 122.92, 122.29, 113.77, 113.72, 82.56, 71.09, 55.53, 55.53, 47.98, 47.06, 36.82, 30.30, 27.21, 24.07, 22.59.

HRMS-ESI: calculated for $C_{19}H_{20}NaO_3$ $[M+Na]^+$: 319.1305; found:319.1308.

1,1-Dimethyl-2,3-dihydro-1*H*-inden-2-yl 3,4,5-trimethoxybenzoate and (1-methyl-2,3-dihydro-1*H*-inden-1-yl)methyl 3,4,5-trimethoxybenzoate (6u/6u´)



1 : 1

The title compounds (colorless oil, 58.0 mg, 81% overall yield) was prepared according to the general procedure (**E**) from **5u** (87.0 mg, 0.2 mmol) at 100 °C after 12 h as a 1:1 mixture of isomers.

Some proton signals arising of the two isomers could be differentiated (labeled as *isomer a* and *isomer b*); however, these could not be assigned definitively to **6u** or **6u´**.

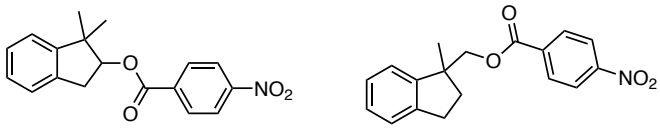
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 2H), 7.31-7.18 (m, 10H), 5.43 (dd, *J* = 6.8, 5.6 Hz, *isomer a* 1H), 4.32 (s, *isomer b* 2H), 3.94-3.88 (m, *isomer a* 9H + *isomer b* 9H), 3.54-3.45 (m, *isomer a* 1H), 3.09-2.94 (m, *isomer a* 1H + *isomer*

b 2H), 2.26 (ddd, *J* = 12.8, 8.1, 4.6 Hz, *isomer b* 1H), 2.00 (ddd, *J* = 13.0, 8.8, 8.0 Hz, *isomer b* 1H), 1.45 (s, *isomer b* 3H), 1.38 (d, *J* = 4.9 Hz, *isomer a* 6H).

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 159.08, 158.01, 147.85, 146.70, 145.09, 144.25, 138.54, 136.21, 136.00, 135.34, 128.68, 128.65, 127.57, 127.09, 126.46, 126.06, 125.63, 125.32, 124.06, 121.29, 112.19, 110.82, 110.38, 106.50, 55.58, 55.51, 39.07, 38.26.

HRMS-ESI: calculated for $C_{21}H_{24}NaO_5$ $[M+Na]^+$: 379.1516; found: 379.1512.

1,1-Dimethyl-2,3-dihydro-1*H*-inden-2-yl 4-nitrobenzoate and (1-methyl-2,3-dihydr-1*H*-inden-1-yl)methyl 4-nitrobenzoate (6v/6v´)



1 : 5

The title compounds (yellow oil, 48.3 mg, 78% overall yield) was prepared according to the general procedure (**E**) from **5v** (78.0 mg, 0.2 mmol) at 100 °C after 12 h as a 1:5 mixture of isomers.

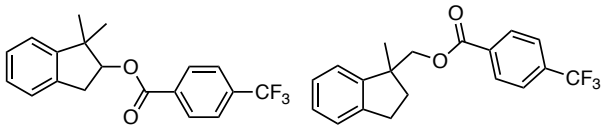
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35-8.26 (m, major2H+minor2H), 8.24-8.13 (m, major2H+minor2H), 7.33-7.21 (m, major4H+minor4H), 5.50 (dd, *J* = 6.5, 5.0 Hz, minor1H), 4.38 (s, major2H), 3.69-3.34 (m, minor1H), 3.11-2.97 (m, major2H+ minor1H), 2.28 (ddd, *J* = 12.9, 7.5, 5.3 Hz, major1H), 2.08-1.97 (m, major1H), 1.47 (s, major3H), 1.39 (d, *J* = 2.2 Hz, minor6H).

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 164.82, 164.68, 150.66, 149.44, 147.23, 143.70, 138.08, 135.90, 135.83, 130.85, 130.73, 127.48, 127.27, 126.66, 124.97, 124.93, 123.72, 123.67, 123.21, 122.34, 84.08, 72.24, 47.91, 47.21, 36.83, 36.79, 30.29, 27.29, 24.02, 22.48.

HRMS-ESI: calculated for $C_{18}H_{17}NNaO_4$ $[M+Na]^+$: 334.1050; found: 334.1056.

1,1-Dimethyl-2,3-dihydro-1*H*-inden-2-yl 4-(trifluoromethyl)benzoate and

(1-methyl-2,3-dihydro-1*H*-inden-1-yl)methyl 4-(trifluoromethyl)benzoate (6w/6w´)



1 : 3

The title compounds (yellow oil, 50 mg, 75% overall yield) was prepared according to the general procedure (**E**) from **5w** (82.0 mg, 0.2 mmol) at 100 °C after 12 h as a 1:3 mixture of isomers.

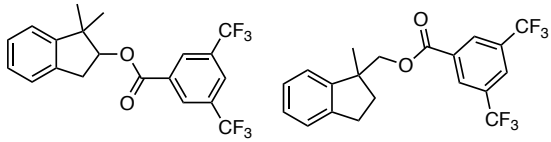
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.16 (m, minor2H), 8.16-8.09 (m, major2H), 7.79-7.70 (m, major2H + minor2H), 7.33-7.21 (m, major4H + minor4H), 5.51 (dd, *J* = 6.6, 5.1 Hz, minor1H), 4.38 (s, major2H), 3.53 (ddd, *J* = 16.5, 6.6, 1.1 Hz, minor1H), 3.11-2.94 (m, major2H + mifnor1H), 2.32-2.23 (m, major1H), 2.08-1.95 (m, major1H), 1.48 (s, major3H), 1.40 (s, minor6H).

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 165.51, 165.36, 149.60, 147.43, 143.73, 138.23, 134.60 (q, *J* = 32.7 Hz, minor), 134.56 (q, *J* = 32.6 Hz, major), 133.93-133.70 (m, minor), 133.76-133.65 (m, major), 130.16, 130.05, 127.42, 127.21, 126.64, 125.59 (q, *J* = 3.9 Hz), 125.55 (q, *J* = 3.9 Hz), 124.93, 123.78 (q, *J* = 272.8 Hz, major), 123.27, 122.34, 83.62(minor), 71.91(major), 47.95 (major), 47.18(minor), 36.84(major), 36.80(minor), 30.30(major), 27.26 (minor), 24.03(major), 22.52(minor).

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.21 (s).

HRMS-APCI: calculated for $C_{19}H_{17}F_3NaO_2$ $[M+Na]^+$: 357.1073; found: 357.1077.

1,1-Dimethyl-2,3-dihydro-1*H*-inden-2-yl 4-(trifluoromethyl)benzoate and (1-methyl-2,3-dihydro-1*H*-inden-1-yl)methyl 4-(trifluoromethyl)benzoate (6x/6x´)



1 : 7

The title compounds (yellow oil, 66 mg, 82% overall yield) was prepared according to the general procedure (**E**) from **5x** (96.0 mg, 0.2 mmol) at 100 °C after 12 h as a 1:7 mixture of isomers.

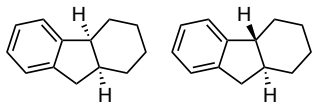
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, minor2H), 8.44 (s, major2H), 8.15-8.05 (m, major1H + minor1H), 7.35-7.21 (m, major4H + minor4H), 5.53 (dd, *J* = 6.7, 5.3 Hz, minor1H), 4.47-4.37 (m, major2H), 3.55 (dd, *J* = 16.5, 6.7 Hz, minor1H), 3.13-2.95 (m, major2H + minor1H), 2.34-2.23 (m, major1H), 2.11-1.98 (m, major1H), 1.50 (s, major3H), 1.41 (d, *J* = 3.4 Hz, minor6H).

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 164.04, 149.36(minor), 147.08 (major), 143.75(minor), 137.90(major), 132.78(minor), 132.68(major), 132.38 (q, *J* = 34.0 Hz), 129.98-129.66 (m), 127.59(major), 127.56(minor), 127.35 (minor), 126.59-126.33 (m), 125.01(major), 124.96(minor), 123.23(major), 123.01 (q, *J* = 272.9 Hz), 122.40(minor), 84.40(minor), 72.62(major), 47.96 (major), 47.17(minor), 36.96(major), 36.71(minor), 30.37(major), 27.31(minor), 23.93(major), 22.55(minor).

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.10 (s), -63.17 (s).

HRMS-APCI: calculated for $C_{20}H_{16}F_6NaO_2$ $[M+Na]^+$: 425.1057; found: 425.1055.

***cis*-2,3,4,4a,9,9a-Hexahydro-1*H*-fluorene and *trans*-2,3,4,4a,9,9a-hexahydro -1*H*-fluorene (6y/6y´)**



2 : 1

The title compounds (colorless oil, 29 mg, 84% overall yield) was prepared according to the general procedure (**E**) from **5y** (51.0 mg, 0.2 mmol) at 100 °C after 12 h as a 2:1 mixture of isomers.

The spectroscopic data of *cis*-product match with those reported in the literature.[111]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.61 (m, major2H + minor2H), 7.44-7.31 (m, major4H + minor4H), 7.20 (s, major1H + minor1H), 7.10 (d, J = 0.7 Hz, minor1H), 6.99 (d, J = 2.4 Hz, major1H), 6.87 (dd, J = 8.2, 2.4 Hz, minor1H), 6.78 (dd, J = 8.1, 2.4 Hz, major1H), 3.87 (s, major3H + minor3H), 3.79 (s, minor2H), 3.77 (s, major2H).

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 159.08, 158.01, 147.85, 146.70, 145.09, 144.25, 138.54, 136.21, 136.00, 135.34, 128.68, 128.65, 127.57, 127.09, 126.46, 126.06, 125.63, 125.32, 124.06, 121.29, 112.19, 110.82, 110.38, 106.50, 55.58, 55.51, 39.07, 38.26.

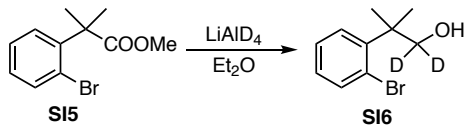
HRMS-APCI: calculated for $C_{13}H_{17}$ $[M+H]^+$: 173.1255; found: 173.1257.

Mechanistic study

Synthesis of deuterated starting materials

2-(2-Bromophenyl)-2-methylpropan-1,1-d_2-1-ol (SI6)

111. Flinker, M.; Yin, H.; Juhl, R. W.; Eikeland, E. Z.; Overgaard, J.; Nielsen, D. U.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2017**, *56*, 15910-15915.



SI5 **SI6**

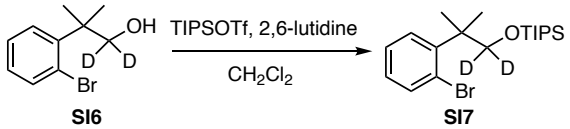
To a solution of the methyl **SI5**[112] (2.2 g, 8.6 mmol) in anhydrous diethyl ether (0.15 M) at -20 °C, $LiAlD_4$ (800 mg, 18.4 mmol) was added slowly. After stirring 1 h at the same temperature, the reaction quenched with aqueous HCl (0.5M, 20 mL), and extracted with diethyl ether (x3). After washing with brine and drying over $MgSO_4$, the crude reaction mixture was purified by column chromatography on silica gel with cyclohexane/EtOAc as eluent giving **SI6** as a colorless oil (1.7 g, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.46 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.27 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 7.06 (td, *J* = 7.6, 1.7 Hz, 1H), 1.66 (s, 1H), 1.50 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$, mixed signals) δ 143.82, 135.82, 130.14, 128.03, 127.40, 122.34, 68.67 (p, *J* = 21.8 Hz), 42.03, 25.10.

HRMS-ESI: calculated for $C_{10}H_{11}BrD_2NaO$ $[M+Na]^+$: 253.0168; found: 253.0160.

(2-(2-Bromophenyl)-2-methylpropoxy-1,1-*d*$_2$)triisopropylsilane (SI7)



SI6 **SI7**

To a solution of **SI6** (1.5g, 6.5 mmol) in anhydrous CH_2Cl_2 (0.1 M) at 0 °C was added 2,6-lutidine (2.3 mL, 19.5 mmol) dropwise followed by TIPSOTf (3.5 mL, 13.0 mmol). The mixture was stirred 6 h at room temperature (23 ºC). It was quenched by addition of EtOAc at 0 °C, followed by water. It was extracted with

112. Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566-3570.

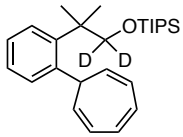
EtOAc (x3), washed with brine and dried over $MgSO_4$. The crude reaction mixture was purified by column chromatography on silica gel with pentane as eluent giving **SI7** as a colorless oil (1.9 g, 76% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.34-7.22 (m, 1H), 7.12-7.01 (m, 1H), 1.58 (s, 6H), 1.19-1.02 (m, 21H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.06, 135.71, 130.17, 127.71, 127.12, 122.65, 70.16-68.14 (m), 42.47, 25.03, 18.13, 12.18.

HRMS-ESI: calculated for $C_{19}H_{31}BrD_2NaOSi$ $[M+Na]^+$: 409.1502 ; found: 409.1506.

(2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropoxy-1,1-*d*$_2$)triiso-propylsilane (5n-*d*$_2$)



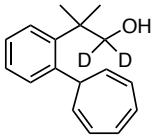
The title compound (colorless oil, 750 mg, 91% yield) was prepared according to the general procedure (**B**) from **SI7** (800 mg, 2.1 mmol), *n*-BuLi (2.5 M, 0.83 mL, 2.1 mmol) and tropylium tetrafluoroborate (440 mg, 2.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 6.82 (dd, *J* = 3.7, 2.7 Hz, 2H), 6.41-6.31 (m, 2H), 5.50-5.39 (m, 2H), 3.46-3.36 (m, 1H), 1.41 (s, 6H), 1.22-1.04 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.04, 144.34, 130.72, 130.14, 129.58, 127.30, 127.05, 126.25, 124.31, 71.49-69.71 (m), 43.56, 41.39, 26.28, 18.19, 12.07.

HRMS-ESI: calculated for $C_{26}H_{38}D_2NaOSi$ $[M+Na]^+$: 421.2866; found: 421.2869.

2-(2-(Cyclohepta-2,4,6-trien-1-yl)phenyl)-2-methylpropan-1,1-*d*$_2$-1-ol (SI2-*d*$_2$)



The title compound (white solid, 270 mg, 99% yield) was prepared according to the general procedure (**C-step2**) from **5n-*d*$_2$** (450 mg, 1.1 mmol), TBAF (1.0 M, 1.4 mL, 1.4 mmol).

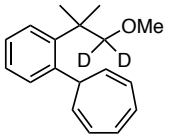
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.41 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35-7.28 (m, 1H), 6.86-6.77 (m, 2H), 6.40-6.29 (m, 2H), 5.46-5.35 (m, 2H), 3.37-3.26 (m, 1H), 1.88 (s, 1H), 1.34 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.09, 143.64, 130.66, 130.18, 128.98, 127.54, 127.27, 126.38, 124.35, 71.24-70.40 (m), 43.22, 40.78, 26.64.

HRMS-ESI: calculated for $C_{17}H_{18}D_2NaO$ $[M+Na]^+$: 265.1532; found: 265.1529.

M.p: 78-79 ºC.

7-(2-(1-Methoxy-2-methylpropan-2-yl-1,1-*d*$_2$)phenyl)cyclohepta-1,3,5-triene (5k-*d*$_2$)



The title compound (colorless oil, 240 mg, 88% yield) was prepared according to the general procedure (**C-step3**) from **SI2-*d*$_2$** (260 mg, 1.1 mmol), MeI (0.12 mL, 1.9 mmol) and NaH (38mg, 1.6 mmol).

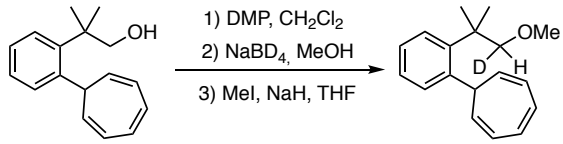
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.48 (dd, *J* = 8.0,

1.4 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 6.88-6.81 (m, 2H), 6.41-6.33 (m, 2H), 5.48-5.42 (m, 2H), 3.42-3.38 (m, 1H), 3.37 (s, 3H), 1.37 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.78, 143.99, 130.68, 130.07, 129.49, 127.06, 126.95, 126.36, 124.24, 81.52, 81.52-80.85 (m), 59.15, 43.36, 39.80, 27.06.

HRMS-ESI: calculated for $C_{18}H_{20}D_2NaO$ $[M+Na]^+$: 279.1688; found: 279.1682.

7-(2-(1-Methoxy-2-methylpropan-2-yl-1-*d*)phenyl)cyclohepta-1,3,5-triene (5k-d_1)



SI2 **5k-d_1**

Step 1: To a solution of **SI2** (0.8 g, 3.3 mmol) in CH_2Cl_2 (30 mL) was added DMP (2.1 g, 5.0 mmol) at 0 ºC. The reaction mixture stirred for 2 h and was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) at 0 ºC. The layers were separated and aqueous layer was extracted with CH_2Cl_2 (3×25 mL), the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated, the crude was used in the next step without further purification.

Step 2: Over a 0 ºC solution of the crude aldehyde in anhydrous MeOH (30 mL), was added $NaBD_4$ (350 mg, 8.3 mmol) portionwise. The reaction was stirred overnight at room temperature (23 ºC). When completed, EtOAc was added followed by NH_4Cl (aq.). The reaction was extracted with EtOAc (x3), washed with brine, dried over $MgSO_4$ and concentrated. The crude was used in the next step without further purification.

Step 3: To a solution of the alcohol in anhydrous THF (30 mL) at 0 ºC was added NaH (240 mg, 10 mmol). After stirring for 30 min at the same temperature, MeI (0.8 mL, 13.3 mmol) was added. The reaction was stirred overnight at RT. The

reaction was quenched with NH_4Cl (aq.) and extracted with diethyl ether (x3). After washing with brine and drying over $MgSO_4$, the product was purified on silica gel column chromatography pentane obtaining a colorless oil (510 mg, 60% yield in three steps).

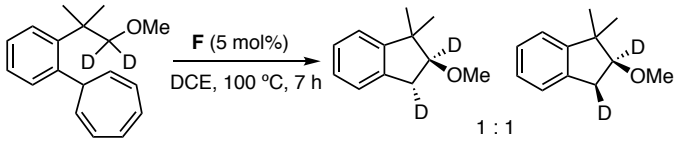
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.44 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.38 (td, *J* = 7.4, 1.4 Hz, 1H), 7.29 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 6.84-6.76 (m, 2H), 6.37-6.28 (m, 2H), 5.45-5.36 (m, 2H), 3.40 (s, 1H), 3.38-3.34 (m, 1H), 3.33 (s, 3H), 1.33 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.78, 144.00, 130.70, 130.09, 129.51, 127.08, 126.97, 126.36, 124.25, 81.79-81.45 (m), 59.20, 43.38, 39.89, 27.09.

HRMS-ESI: calculated for $C_{18}H_{21}D_1NaO$ $[M+Na]^+$: 278.1789; found: 278.1772.

Gold(I)-catalyzed cyclization of deuterated substrates

(2*R,3*R**)-2-Methoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene-2,3-d_2 and (2*R**,3*S**)-2-methoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene-2,3-d_2 (6k-d_2a/ 6k-d_2b)**



5k-d_2 (100% *d*) → **6k-d_2a + 6k-d_2b** (90%, 1:1 *dr,* 100% *d*)

The title compounds (yellow oil, 32 mg, 90% overall yield) was prepared according to the general procedure (**E**) from **5k-d_2** (51.3 mg, 0.2 mmol) at 100 °C after 7h as a 1:1 mixture of isomers.

Some proton signals arising of the two isomers could be differentiated (labeled as *isomer a* and *isomer b*); however, these could not be assigned definitively to **6k-d_2a** or **6k-d_2b**.

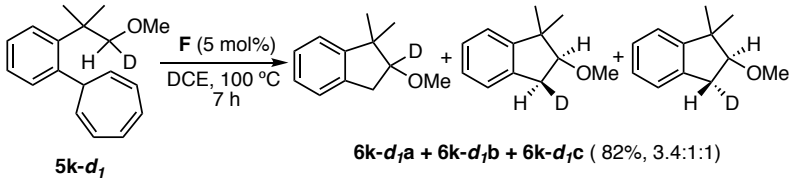
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.13 (m, *isomer a* 4H + *isomer b* 4H), 3.48

(s, *isomer a* 3H + *isomer b* 3H), 3.15 (s, *isomer a* 1H), 2.83 (s, *isomer b* 1H), 1.36 (d, *J* = 1.1 Hz, *isomer a* 3H + *isomer b* 3H), 1.16 (s, *isomer a* 3H + *isomer b* 3H).

^{13}C NMR (101 MHz, $CDCl_3$, mixed signals) δ 150.75, 138.39, 127.06, 126.73, 125.01, 124.99, 122.33, 90.07-89.64 (m), 58.15, 46.35, 46.31, 35.23-34.82 (m), 26.86, 26.84, 22.32.

HRMS-APCI: calculated for $C_{11}H_{11}D_2$ $[M\text{-}OMe]^+$: 147.1137; found: 147.1138.

(*R)-2-methoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene-2-*d* and (2*R**,3*S**)-2-methoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene-3-*d*, (2*R**,3*R**)-2-methoxy-1,1-dimethyl-2,3-dihydro-1*H*-indene-3-*d* (6k-d_1a, 6k-d_1b, 6k-d_1c)**



5k-d_1 **6k-d_1a + 6k-d_1b + 6k-d_1c** (82%, 3.4:1:1)

The title compounds (yellow oil, 29 mg, 82% overall yield) was prepared according to the general procedure (**E**) from **5k-d_1** (51.1 mg, 0.2 mmol) at 100 °C after 7h as a 3.4:1:1 mixture of isomers.

Some proton signals arising of the three isomers could be differentiated (labeled as *isomer a*, *isomer b* and *isomer c*); however, these could not be assigned definitively to **6k-d_1a**, **6k-d_1b**, **6k-d_1c**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.13 (m, *isomer a* 4H + *isomer b* 4H + *isomer c* 4H), 3.77-3.73 (m, *isomer b* 1H + *isomer c* 1H), 3.48 (s, *isomer a* 3H + *isomer b* 3H + *isomer c* 3H), 3.19-3.12 (m, *isomer a* 1H + *isomer b* 1H), 2.87-2.80 (m, *isomer a* 1H + *isomer c* 1H), 1.35 (s, *isomer a* 3H + *isomer b* 3H + *isomer c* 3H), 1.16 (s, *isomer a* 3H + *isomer b* 3H + *isomer c* 3H).

^{13}C NMR (101 MHz, CDCl3, mixed signals) δ 150.76, 150.74, 150.73, 138.44,

138.39, 138.38, 127.06, 127.05, 126.73, 125.01, 124.98, 122.33, 90.37, 90.35, 90.10-89.76 (m), 58.17, 58.15, 46.45, 46.42, 46.34, 35.36, 35.28-34.97 (m), 26.91, 26.89, 26.85, 22.32, 22.30.

HRMS-APCI: calculated for $C_{11}H_{12}D_1$ $[M\text{-}OMe]^+$: 146.1157; found: 146.1158.

Theoretical DFT Computations

Computational Methods

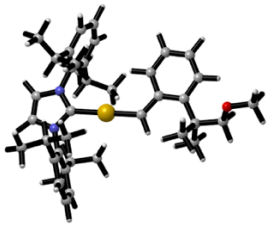
Calculations were performed by means of the Gaussian 09 suite of programs.[113] DFT was applied using M06.[114] The SDD basis set was used to describe Au.[115] The 6-31G(d) basis set[116] was used for all remaining atoms (C, H, O, Si and P). Full geometry optimizations were carried out in dichloromethane, through an implicit solvent SMD.[117] The stationary points were characterized by vibrational analysis. Transition states were identified by the presence of one imaginary frequency while minima by a full set of real frequencies. The connectivity of the transition states was confirmed by relaxing each transition state towards both the reactant and the product. The energy for the optimized geometry of some specific non-critical structures, that could not be located, was estimated through constrained optimizations with distances or angles frozen at reasonable values. Reported energies are potential energies (E) and free energies

113. Gaussian 09, Revision B.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, Jr. J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R.L.; Morokuma, K.;, Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT **2009**.
114. (a) Truhlar, D. G. *J. Am. Chem. Soc.* **2008** *130*, 16824-16827. (b) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2009**, *5*, 324-333.
115. Andrae, D.; Haussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Theor. Chim. Acta* **1990**, *77*, 123-141.
116. Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257-2261.
117. Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B.* **2009**, *113*, 6378–6396.

(G) in solution, computed at 298 K and 1 atm.

Structures and Energies

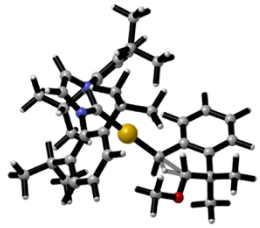
I



E = -1836.507973 Hartrees

G = -1835.760270 Hartrees

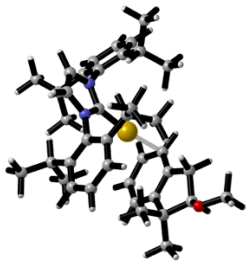
TS_{I-II}



E = -1836.506029 Hartrees

G = -1835.758411 Hartree

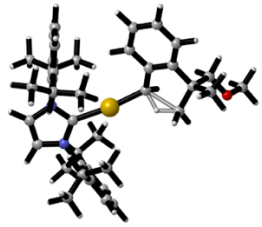
II



E = -1836.589345 Hartrees

G = -1835.840335 Hartrees

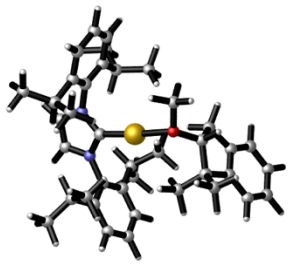
TS_{I-III}



E = -1836.487628 Hartrees

G = -1835.745316 Hartrees

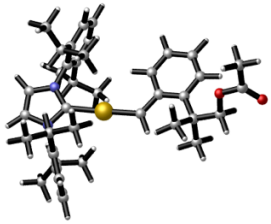
II-*O*



E = -1836.586966 Hartrees

G = -1835.835759 Hartrees

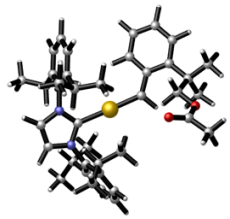
IV_{Me}



E = -1949.816938 Hartrees

G = -1949.065625 Hartrees

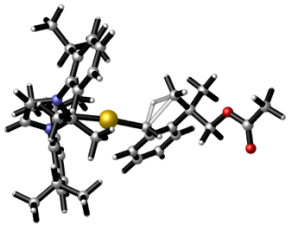
V_{Me}



E = -1949.817219 Hartrees

G = -1949.060226 Hartrees

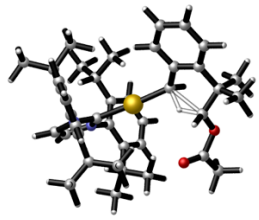
$TS_{IV_{Me}\text{-}VI_{Me}}$



E = -1949.797243 Hartrees

G = -1949.048697 Hartrees

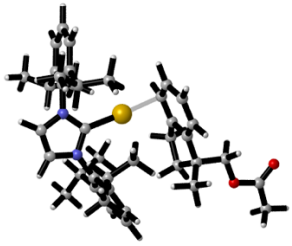
$TS_{V_{Me}\text{-}VII_{Me}}$



E = -1949.800560 Hartrees

G = -1949.047573 Hartrees

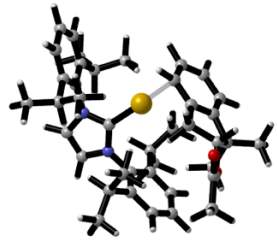
VI_{Me}



E = -1949.897769 Hartrees

G = -1949.140017 Hartrees

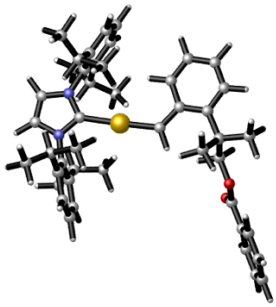
VII_{Me}



E = -1949.900116 Hartrees

G = -1949.142593 Hartrees

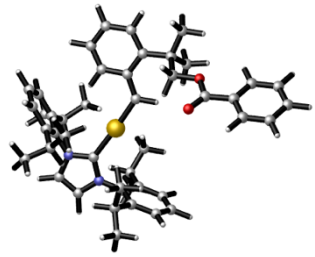
IV_{Ph}



E = -2141.408273 Hartrees

G = -2140.607866 Hartrees

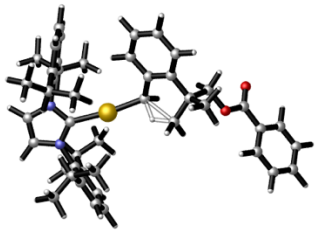
V_{Ph}



E = -2141.408506 Hartrees

G = -2140.605001 Hartrees

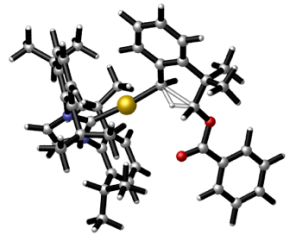
$TS_{IVPh\text{-}VIPh}$



E = -2141.388745 Hartrees

G = -2140.591023 Hartrees

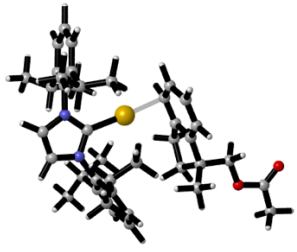
$TS_{VPh\text{-}VIIPh}$



E = -2141.393442 Hartrees

G = -2140.591339 Hartrees

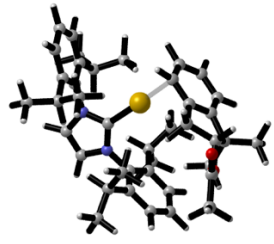
VI_{Ph}



E = -2141.489301 Hartrees

G = -2140.681771 Hartrees

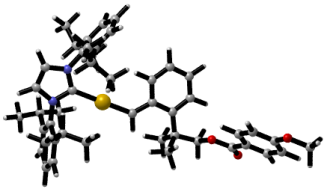
VII_{Ph}



E = -2141.493267 Hartrees

G = -2140.686015 Hartrees

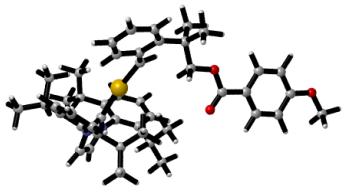
IV*p*MeOPh



E = -2255.873696 Hartrees

G = -2255.043862 Hartrees

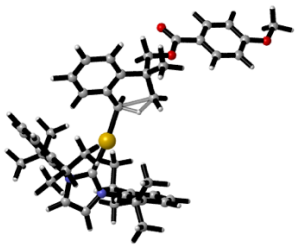
V*p*MeOPh



E = -2255.873468 Hartrees

G = -2255.038153 Hartrees

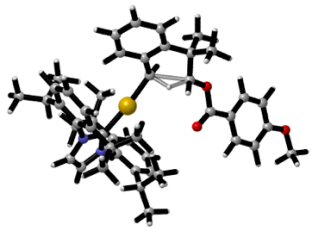
TSIV*p*MeOPh-VI*p*MeOPh



E = -2255.853410 Hartrees

G = -2255.026408 Hartrees

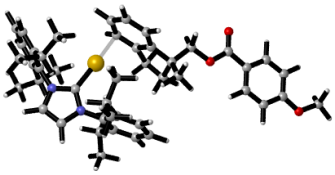
TSV*p*MeOPh-VII*p*MeOPh



E = -2255.859220 Hartrees

G = -2255.028168 Hartrees

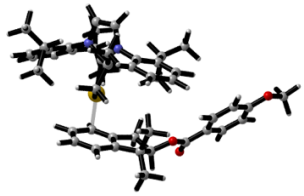
VI*p*MeOPh



E = -2255.954016 Hartrees

G = -2255.117823 Hartrees

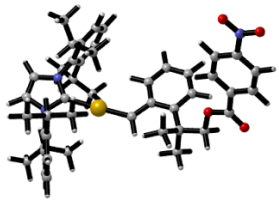
VII*p*MeOPh



E = -2255.958180 Hartrees

G = -2255.119666 Hartrees

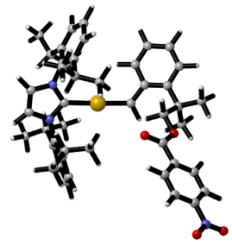
IV$_{p\mathrm{NO_2Ph}}$



E = -2345.820114 Hartrees

G = -2345.019892 Hartrees

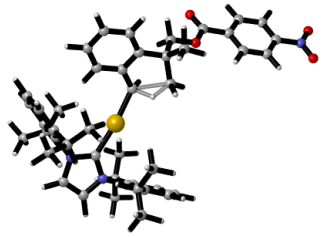
V$_{p\mathrm{NO_2Ph}}$



E = -2345.819960 Hartrees

G = -2345.015995 Hartrees

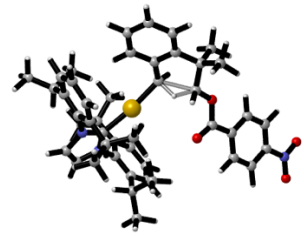
TS$_{\mathrm{IV}p\mathrm{NO_2Ph}\text{-}\mathrm{VI}p\mathrm{NO_2Ph}}$



E = -2345.799988 Hartrees

G = -2345.003290 Hartrees

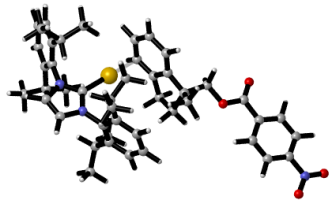
TS$_{\mathrm{V}p\mathrm{NO_2Ph}\text{-}\mathrm{VII}p\mathrm{NO_2Ph}}$



E = -2345.802412 Hartrees

G = -2345.001997 Hartrees

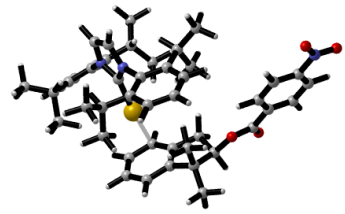
VI $_{p\mathrm{NO_2Ph}}$



E = -2345.900849 Hartrees

G = -2345.095337 Hartrees

VII $_{p\mathrm{NO_2Ph}}$

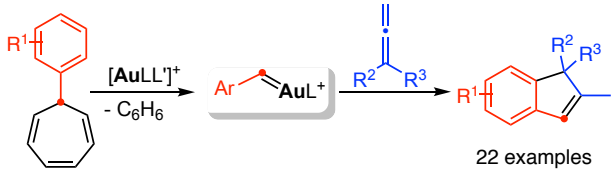


E = -2345.904429 Hartrees

G = -2345.098486 Hartrees

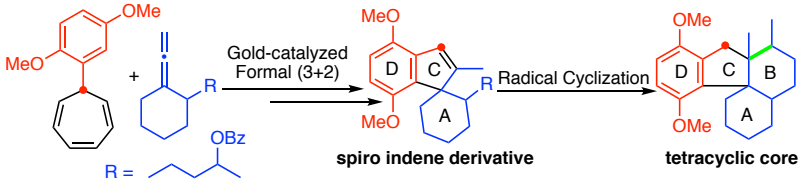
General Conclusions

- A new gold(I)-catalyzed formal (3 + 2) cycloaddition reaction was developed by reaction of allenes with aryl gold(I) carbenes generated by retro-Buchner reaction of 7-substituted cycloheptatrienes, leading to a various of highly substituted indenes (Scheme GC-1).



Scheme GC-1. Formal (3 + 2) cycloaddition reaction of gold carbenes with allenes.

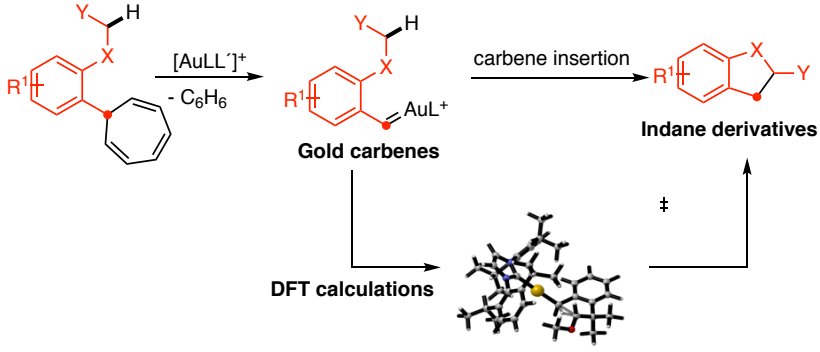
- The synthesis of tetracyclic core of cycloaurenone A-C and disherbol A-C was achieved *via* two key reactions, the cyclization of gold(I) carbene generated from 7-substituted-cycloheptatriene with a terminal allene followed by an AIBN-promoted radical cyclization (Scheme GC-2).



Scheme GC-2. Synthesis of tetracyclic core of cycloaurenone A-C and disherbol A-C.

- A novel synthesis of indanes based on the intramolecular insertion of gold(I) carbenes generated by retro-Buchner into C(sp^3)-H bonds was developed. Deuterium-labeling experiments support the hypothesis that the C(sp3)-H functionalization process takes place through an intramolecular carbon-hydrogen bond transfer to the gold(I) carbene intermediate, while our

measured kinetic isotope effect and DFT calculations were consistent with the three-centered concerted mechanism proposed for these C-H insertions.



Scheme GC-3. Synthesis of indanes by the reaction of gold(I) carbenes insertion into C(sp3)-H bonds.

Appendix

Publication and Patent list:

1. **Xiang Yin,** Mauro Mato, and Antonio M. Echavarren*. "Gold(I)-Catalyzed Synthesis of Indenes and Cyclopentadienes: Access to (±)-Laurokamurene B and the Skeletons of the Cycloaurenones and Dysiherbols". *Angew. Chem. Int. Ed.* **2017**, *56*, 14591- 14595.
2. **Xiang Yin,** Yi Zheng, Xin Feng, Kun Jiang, Xue-Zhen Wei, Ning Gao,* and Ying-Chun Chen*. "Chiral primary amines-catalyzed: Asymmetric [5 + 3] Cycloadditions With Cyclic Enones via Cascade Dienamine-Dienamine Catalysis". *Angew. Chem. Int. Ed.* **2014**, *53*, 6245-6248.
3. **Yin-Xiang,** Zhou-Qingqing, Dong-Lin, Chen-Yingchun* "Asymmetric Sequential Aza-Diels-Alder and O-Michael Addition:Efficient Construction of Chiral Hydropyrano[2,3-b]pyridines". *Chin. J. Chem.* **2012**, *30*, 2669-2675.
4. Wei Xiao, **Xiang Yin,** Zhi Zhou, Wei Du, Ying-Chun Chen* "Asymmetric α,γ-Regioselective [3 + 3] Formal Cycloadditions of α,β-Unsaturated Aldehydes via Cascade Dienamine−Dienamine Catalysis". *Org. Lett.* **2016**, *18*, 116-119.
5. Zhi Zhou, Xin Feng, **Xiang Yin,** Ying-Chun Chen* "Direct Remote Asymmetric Bisvinylogous 1,4-Additions of Cyclic 2,5-Dienones to Nitroalkenes". *Org. Lett.* **2014**, *16*, 2370-2373.
6. Xin Feng, Zhi Zhou, Chao Ma, **Xiang Yin**, Rui Li, Lin Dong, and Ying-Chun Chen* "Induced Trienamines with Interrupted Cyclic 2,5-Dienones: Remote δ,ε-C=C Bond Activation for Asymmetric Inverse-Electron-Demand Aza-Diels–Alder Reaction and Cascade". *Angew. Chem. Int. Ed.* **2013**, *125*, 14423-14426.
7. Zhi-Jun Jia, Hao Jiang, Jun-Long Li, Björn Gschwend, Qing-Zhu Li, **Xiang Yin,** Julie Grouleff, Ying-Chun Chen*, and Karl Anker Jørgensen* "Trienamines in Asymmetric Organocatalysis: Diels−Alder and Tandem Reactions". *J. Am. Chem. Soc.* **2011**, *133*, 5053-5061.
8. Kun Jiang, Zhi-Jun Jia, **Xiang Yin,** Li Wu and Ying-Chun Chen* "Asymmetric Quadruple Aminocatalytic Domino Reactions to Fused Carbocycles Incorporating a Spirooxindole Motif". *Org. Lett.* **2010**, *12*, 2766-2769.

Patent: cn 201410036421.x

UNIVERSITAT ROVIRA I VIRGILI
SYNTHESIS OF INDENES AND INDANES BY GOLD(I)-CATALYZED DECARBENATION
Xiang Yin

UNIVERSITAT
ROVIRA i VIRGILI