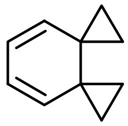
Armin de Meijere

Research Profile

Small rings encompass my scientific life. Having been exposed to physical-organic projects in the area of small-ring chemistry during my doctoral thesis and postdoctoral years, I was irresistably attracted by the fascinating world of small rings. Starting with very little synthesis and a lot of vibrational spectroscopy for my doctoral thesis,[1] switching to more synthetic involvement with my postdoctoral work on solvolysis kinetics of bicyclic cyclopropane derivatives,[2] I started to fully turn my attention to the de novo synthesis of theoretically interesting small ring molecules and eventually to synthetically useful small-ring building blocks. From there it was not very far to start developing synthetic methodology, first based on the particular reactivity of small ring compounds, yet later in the organometallic area. But even in this latest field of activities, we could not help but encountering a cyclopropyl group here and there.



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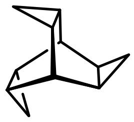

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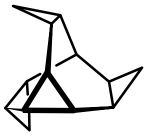

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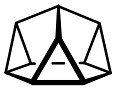

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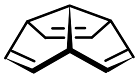

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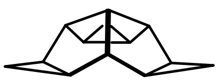

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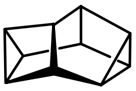

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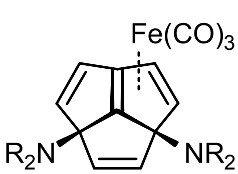

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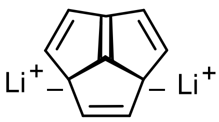

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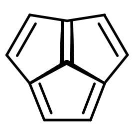

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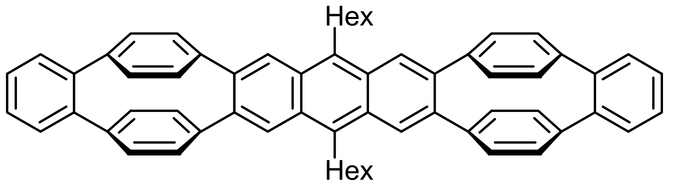
Starting with dispiro[2.0.2.4]deca-7,9-diene (**1**) as a model compound to study potential cyclic electron delocalization transmitted by cyclopropyl groups, trishomobarrelene **2** and trishomobullvalene **3** to quantify the effect of α-cyclopropyl groups on the stability of bridgehead cations, we slipped into studying some of the multiple rearrangements within the family of $(CH)_{10}$ hydrocarbons by our synthesis of diademane **4**. This led us to triquinacene **5**, trishomotriquinacene **6** and, among several other new polycyclic $(CH)_{10}$ isomers, the unique molecule barretane **7**. In one way or another, all these new hydrocarbons disclosed interesting physical and/or chemical properties.[3] E. g. chemical transformations led us to metal complexes of dehydrotriquinacene such as **8**, the aromatic acepentalenediide **9** and the short-lived antiaromatic $C_{10}H_6$ hydrocarbon acepentalene **10**.[4] Oligo- and polycyclic hydrocarbon skeletons including new derivatives of [2.2]paracyclophane such as **11**, **12**, **13**,[5] hexahydroxytricyclo[5.2.1.0^{4,10}]decane **14**, *p*-[3^2.5^6]octahedrane **15** the long-lived dication



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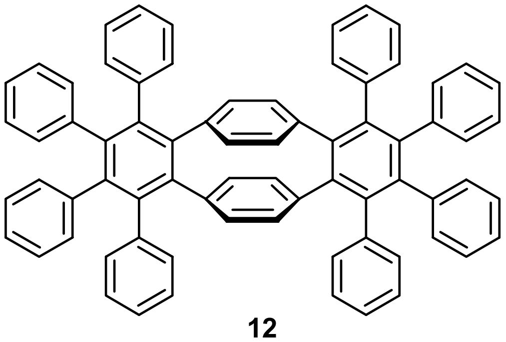

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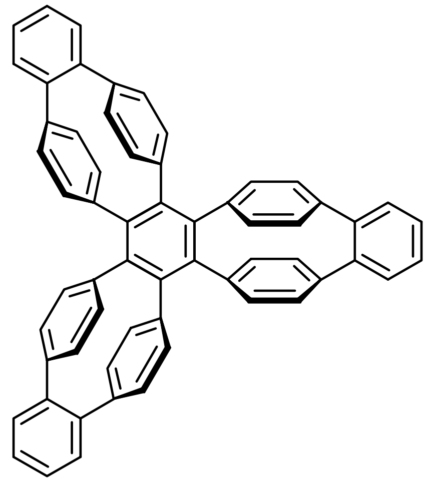

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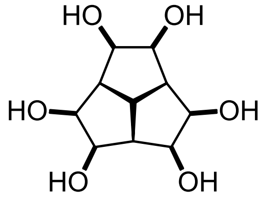

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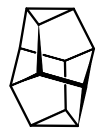

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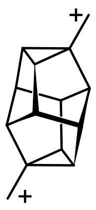

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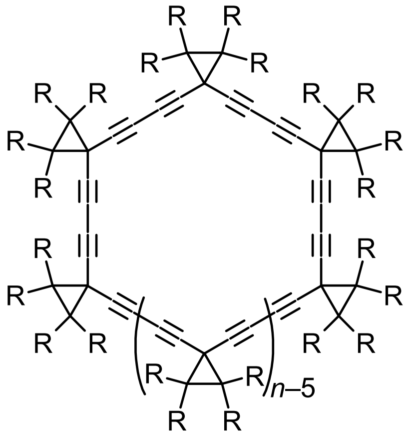
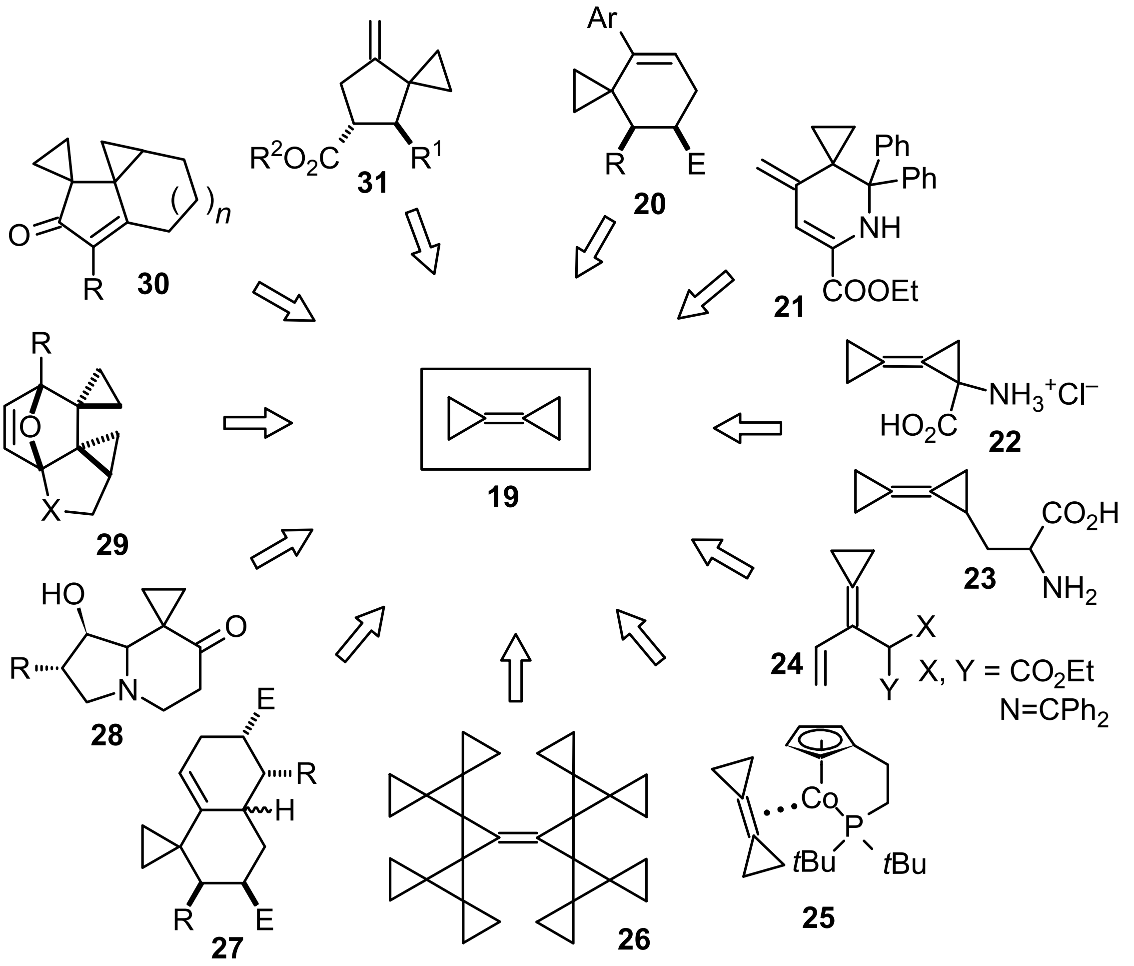


17 R = H; *n* = 5, 6, 8, 10, 12
18 R = Me; *n* = 6

16[6] derived from **15**, and the perspirocyclopropanated exploding [*n*]rotanes **17**[7] as well as one of their permethylated analogues **18**[8] kept us busy for various reasons, and this interest extends into the present days. Originating from the idea for a rather tedious and inefficient preparation of bicyclopropylidene (**19**) back in 1971,[9] we were able to make this unique tetrasubstituted alkene available in multiples of 100 g quantities[10] and develop it into a valuable oligofunctional C_6-building block (Scheme 1).[11] A vast array of new structures is accessable from **19**, frequently in only one or two steps. Particularly noteworthy is the newly developed three-component reaction cascade consisting of a palladium-catalyzed cross coupling with rearrangement and [4+2] cycloaddition(s) between **19**, an aryl (or alkenyl) halide and a dienophile which furnishes compounds of type **20** (or **28**) in a single operational step in up to quantitative yield. This reaction has been used to prepare libraries of small molecules on a synthesizing robot.

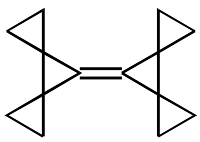
Small rings galore, one may say by looking at the third-generation bicyclopropylidene **26** which was also prepared from bicyclopropylidene (**19**). En route to the record-setting molecule **26** were the perspirocyclopropanated bicyclopropylidene **32** and the perspirocyclopropanated [3]rotane **34**. The whole series **19**, **26**, **32** and the perspirocyclopropanated bicyclobutylidene **33** display interesting physical and chemical features. Especially the

Scheme 1.



D_{3h}-symmetric hydrocarbon **34**, which consists of spiro-linked cyclopropane rings only, shows unique bonding properties. The current world record – as far as the number of spiroannelated cyclopropane rings is concerned, is held by the [15]triangulane **35**, which could be prepared from the third-generation bicyclopropylidene **26**.[12]

Another kind of world record was set by the chiral [4]- **36** and [5]triangulane **37**. When enantiomerically pure, **36** and **37** display specific rotations of ±192 and ±373 degrees, respectively, because they possess rigidly held helical arrangements of σ-bonds. In fact, these molecules are the first real σ-analogues of the aromatic helicenes and thus have been termed σ-helicenes by us.[13] And even these records were recently surpassed by the specific rotation $[\alpha]_D^{20} = -890$ degrees for (*M*)-[9]triangulane (*M*)-**39** which was prepared along a completely new convergent route to enantiomerically pure higher [*n*–2]triangulanedimethanols and [*n*]triangulanes with $n \geq 7$. The triangulanedimethanol, when crystallized from tetrahydrofuran, turned out to organize itself as a supramolecular double helix in the crystal.[14]



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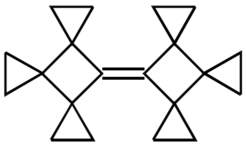

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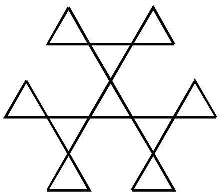

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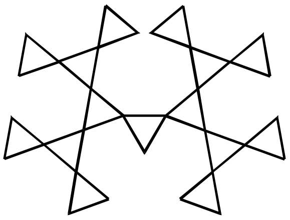

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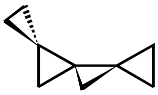
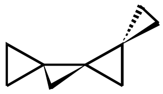
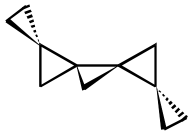


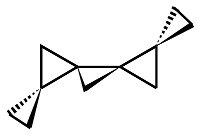
(*M*)-**36**



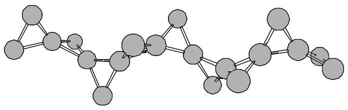
(*P*)-**36**



(*M*)-**37**



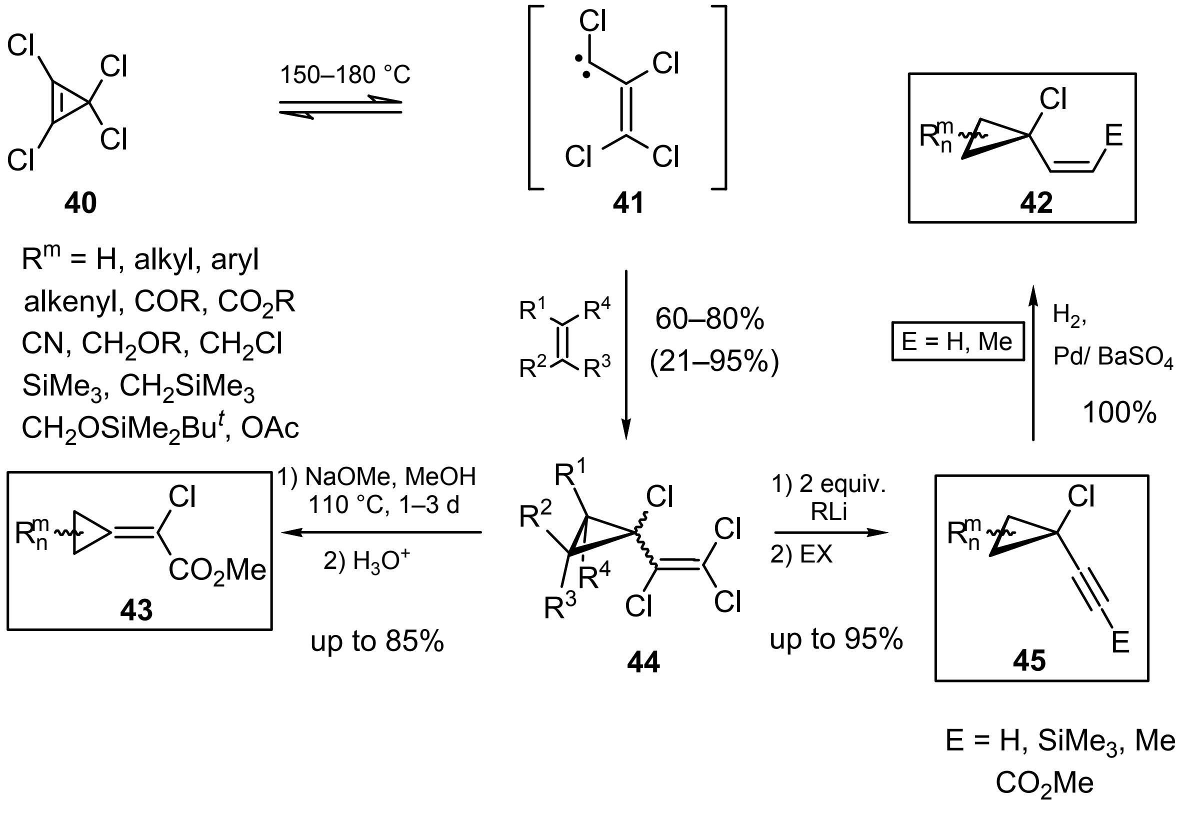
(*P*)-**38**



(*M*)-**39**

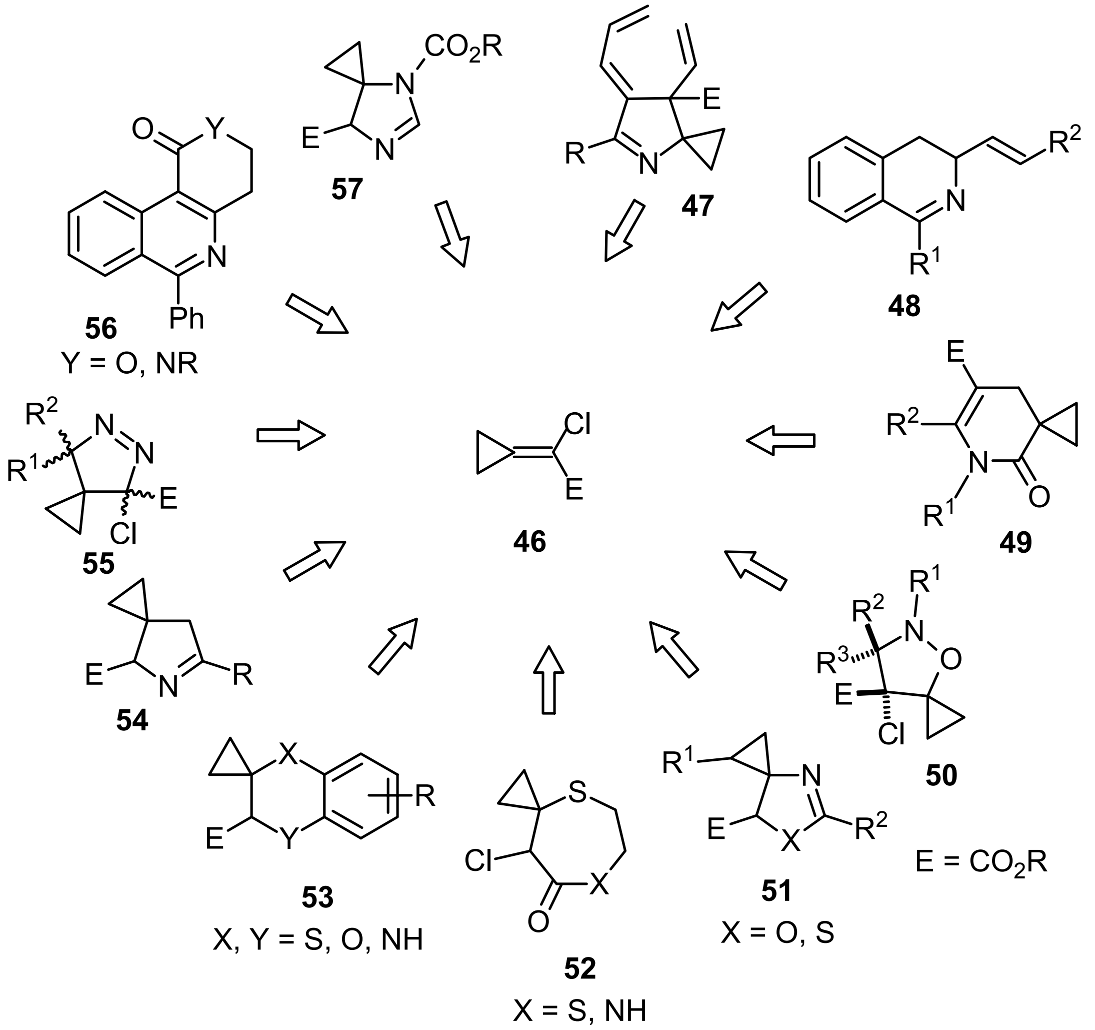
Not only was bicyclopropylidene (**19**) elaborated as a starting material and functional building block for a multitude of complex organic molecules, it also inspired the development of yet another multifunctional building block in our laboratories. When we were testing the idea to perform a [2+2] cycloaddition of tetrachlorocyclopropene (**40**) with bicyclopropylidene (**19**) in particular[15] and with alkenes in general,[16] we discovered the facile ring opening of tetrachlorocyclopropene (**40**) to perchloroethenylcarbene (**41**) and its efficient trapping to yield 1-chloro-1-ethenylcyclopropanes **44** on a broad scope (Scheme 2). The latter can be converted to highly substituted cyclopropylacetylenes **45** which in turn can be hydrogenated to alkenylcyclopropanes **42**.[17] The most interesting transformation of compounds **44**, however, is that by treatment with sodium methoxide in methanol and subsequent acidic work-up to yield methyl 2-chloro-2-cyclopropylideneacetates **43** of a wide range. The parent

Scheme 2.



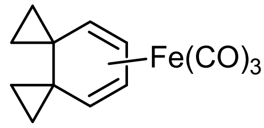
compound **46** in this series, which can be prepared in multiple 100 g quantities from tetrachlorocyclopropene (**40**) and ethylene, is a particularly reactive dienophile and Michael acceptor. As such it turned out to be an extremely versatile building block for all sorts of carbo- and heterocyclic structures like **47**–**57** and many more (Scheme 3).[16]

Scheme 3.



In view of its most recent application towards the construction of various bi- and tricyclic conformationally rigidified peptidomimetics with potentially interesting biological activities, a more convenient, easily scalable access to **46** from inexpensive starting materials has been developed.[18]

Our experience and broad interest in small ring chemistry also led us to get involved in organometallics, and these engagements have become a major part of our research in the last 15 years. With first attempts in coordination chemistry made with the tricarbonyliron complex **58** of dispiro[2.0.2.4]decadiene (**1**),[19] we soon engaged ourselves in Pauson-Khand reactions with e. g. **59**,[20,21] chromiumcarbene chemistry with **60** and **61**[22] and eventually palladium-catalyzed transformations with **62**.[23]



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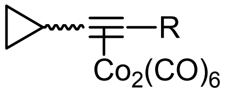

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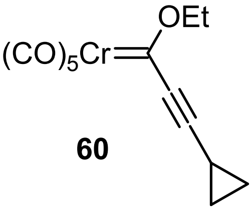

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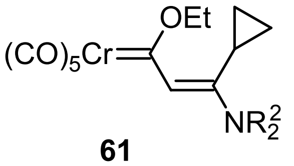

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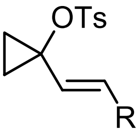

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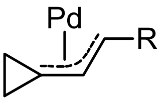

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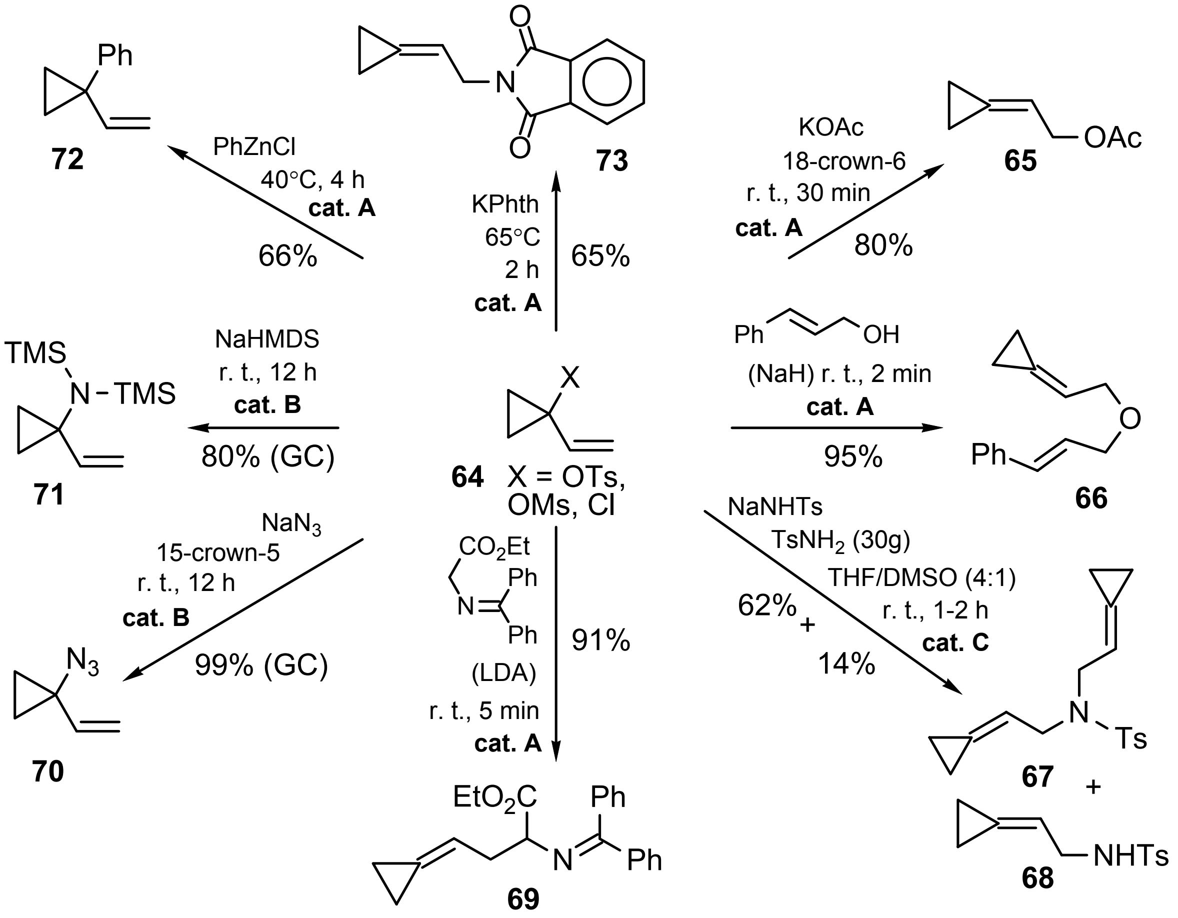
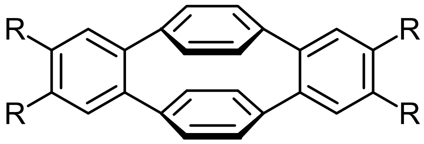
At the same time as we were developing the π-allyl-substitution reactions of **63** generated from 1-alkenylcyclopropyl tosylates **62** and analogous esters **64** including halides, leading to an interesting spectrum of functionalized methylenecyclopropane derivatives such as **65**–**73** (Scheme 4), we became interested in palladium-catalyzed cross-coupling reactions.

Scheme 4.

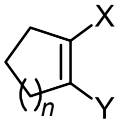


Catalyst: **A**: 2 mol% pd(dba)$_2$/dppe (1:1). – **B**: 2mol% Pd(dba)$_2$/PPh$_3$ (1:2). –
C: 2 mol% Pd(PPh$_3$)$_4$

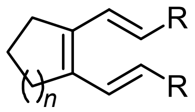
These were first employed to solve a specific problem, namely to get access to bridge-annelated [2.2]paracyclophanediene derivatives such as **74**,[24] but we soon recognized that our twofold Heck coupling of vicinal dihalocycloalkenes and 2-halocycloalkenylperfluoroalkanesulfonates **75** with subsequent 6π-electrocyclization of the resulting 1,3,5-hexatrienes could be developed into a general new {2+2+2} assembly of 6-membered carbocycles from three two-carbon building blocks.[25] This methodology can be applied inter-inter-, inter-intra- and all-intramolecularly to provide easy accesses to bi-, tri- and higher oligocyclic systems of types **77**, **78**, **79** and many more.[25] It must have been the *genus loci* that for certain cases of the attempted all-intramolecular cascade twofold cross-coupling-6π-electrocyclization diverted the reaction mode to lead to tetracyclic systems of type **80** with a bridging cyclopropane ring. Utilizing our more recently developed sequential Stille-Heck cross coupling and 6π-electrocyclization, steroid analogues, e. g. **81** could be assembled in just a few steps.[26]



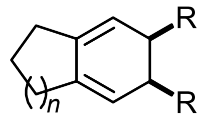
74 R = H, Ph etc.



75 X, Y = I, Br, OTf, ONf



76 R = Ph, CO_2R' $SiMe_3$ etc.



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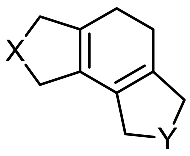
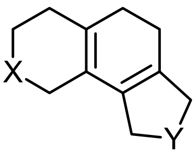


78 X,Y = CMe_2, $C(CO_2R)_2$, O, NTs



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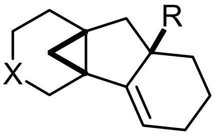

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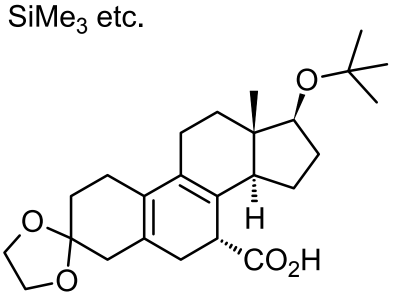

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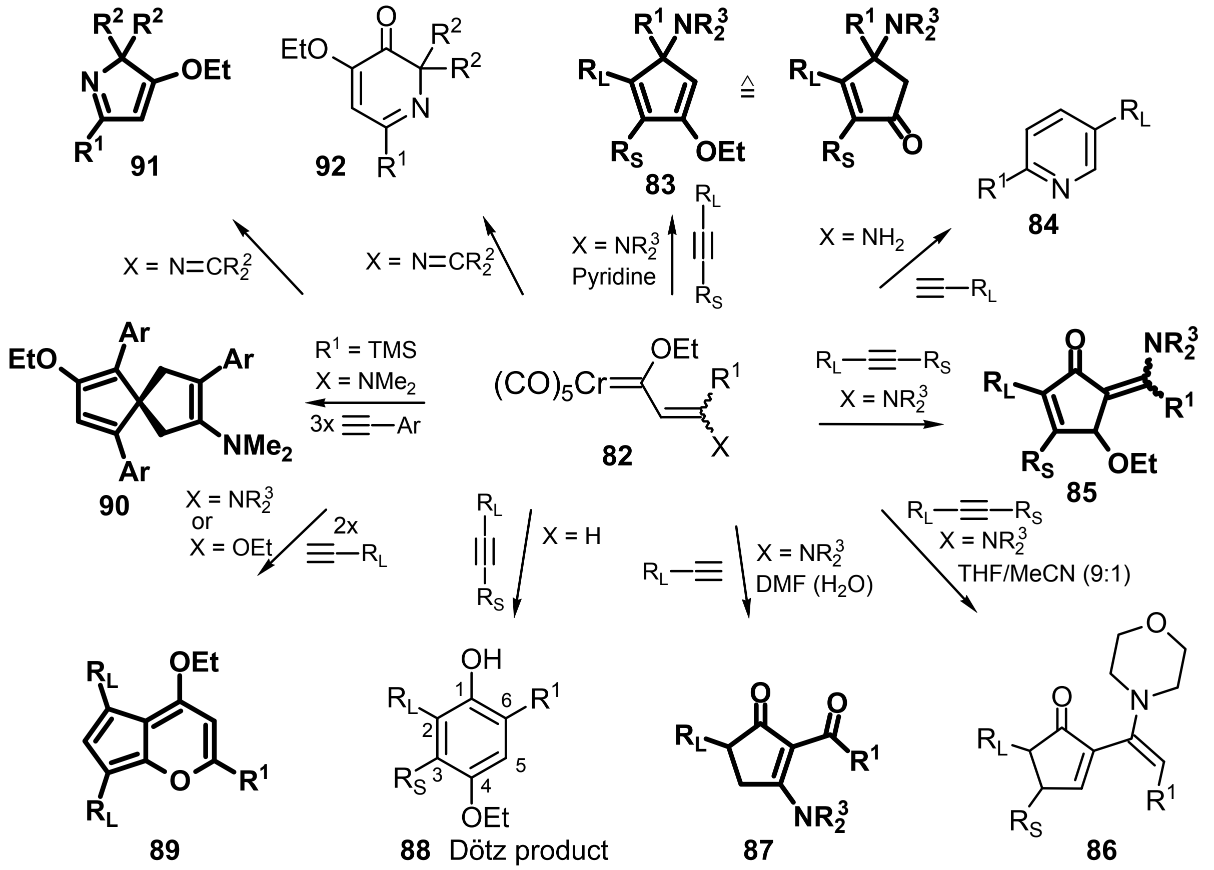
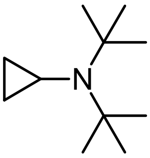
With the idea in mind to activate cyclopropyl groups for nucleophilic attack by the strongly electron-withdrawing effect of e. g. a pentacarbonylchromiumcarbene substituent, we prepared Fischer carbene complexes of types **60** as well as **61**, and soon discovered a whole range of new transformations that turned out to be useful in the toolbox for organic synthesis.[27,28] The new accesses to highly substituted, protected and unprotected, cyclopentenones such as **83**, **85**–**87** are certainly the most versatile reactions, yet in view of the incredible range of products **83**–**93** (Scheme 5) from such β-donor-substituted α,β-unsaturated Fischer carbenes, the latter truly deserve to be called "chemical multitalents".[27,28]

Scheme 5.



Several of these selectively addressable products have been used as starting materials for natural products or analogues as well as interesting complex structures.[28]

Having become acquainted with the so-called Kulinkovich reaction, the transformation of esters to cyclopropanols,[29] we conceived and exented the transformation of *N,N*-dialkylcarboxamides to cyclopropylamines,[29,30] recently termed "de Meijere reaction" by other colleagues.[31] In view of the fact that more than 190 pharmacologically relevant compounds contain cyclopropylamine moieties, this is an important development. A vast spectrum of differently substituted cyclopropylamines including precursors to various cyclopropyl-group containing amino acids, di-*tert*-butylcyclopropylamine **93** – the most highly sterically congested tertiary amine known to date – bicyclic derivatives **94**, **95** and even tri- and tetracyclic **96**, **97** systems can easily be prepared by intramolecular versions of this transformation.[32]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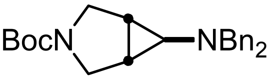
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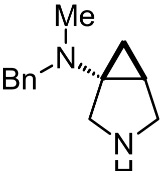
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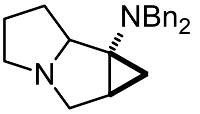
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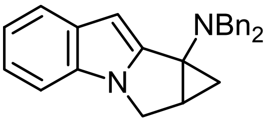
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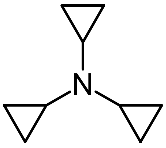
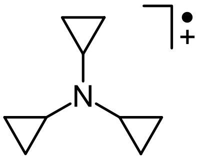
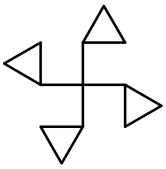
This methodology also provided an easy access to tricyclopropylamine **98**, a molecule which took me back to my roots as a physical organic chemist with a strong interest in unusual new molecules. This molecule not only led us to investigate its molecular shape and that of its radical cation **99**,[33] but also inspired us to synthezise and investigate structural features and conformational dynamics of tetracyclopropylmethane (**100**), tetraisopropylmethane (**101**),[34] as well as tetracyclopropyladamantane (**102**) and tetraisopropyladamantane (**103**).[35] This certainly is not the end of our efforts of putting cyclopropyl groups around known skeletons to modify their properties. Our most recent achievement is the proof of principle that cyclopropyl groups can significantly influence the properties of a cyclopentadienyl ligand on a metal as accessable from the newly synthesized pentacyclopropylcyclopentadiene (**104**),[36] as well as stabilize even an antiaromatic cation as in **105**.[37]


98


99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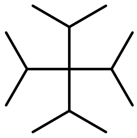
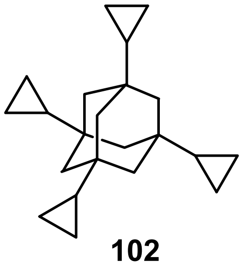
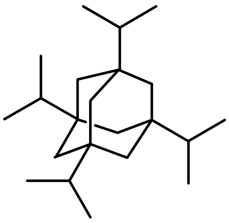

101


102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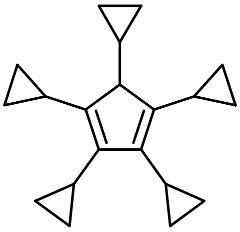
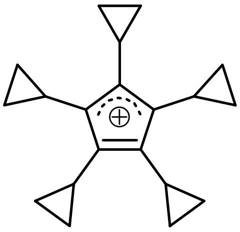

104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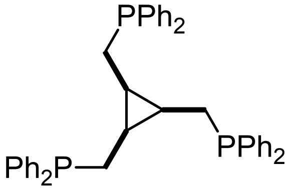
106

Cyclopropanes are beautiful is our credo. In a situation as in the newly born new ligand **106**, it may go beyond beauty, actually.[38]

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