Cyclotrimerization

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A Valuable Upgrade to the Portfolio of Cycloaddition Reactions

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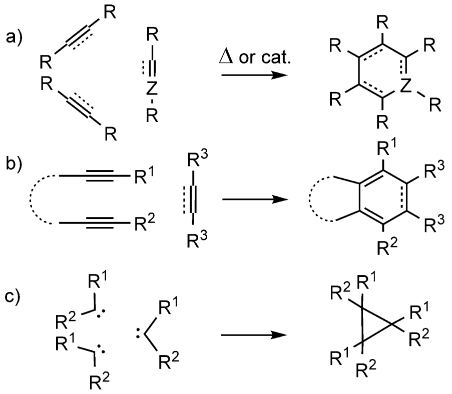
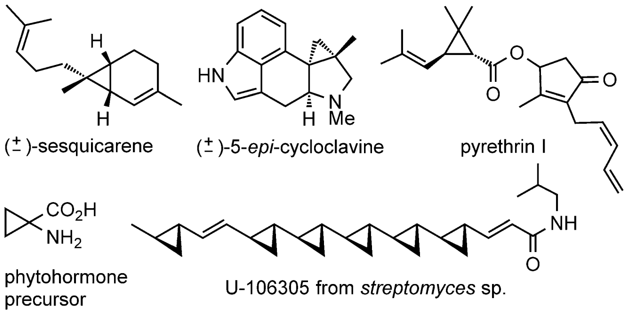
Cycloadditions maintain an aura of scientific glamour because of their almost magical organization of multiple components and because of the elegant orbital symmetry rules that underpin them. Cyclotrimerizations are a sub-group in this reaction portfolio, with [2+2+2] cycloadditions being the most familiar. The archetype of this group is the combination of three alkynes to produce benzenes (Scheme 1 a). Many related versions are known including those with other unsaturated moieties, those in which two of the unsaturated units are tethered together, thus lowering the entropy barrier (Scheme 1 b) and preparative versions permitting control of regio-, chemo- and stereo-selectivity.[1]



Scheme 1. Types of [2+2+2] and [1+1+1] cyclotrimerization reactions.

In principle, analogous [1+1+1] cyclotrimerizations can be imagined, involving either a singlet or triplet carbene, or carbene-like species for constructing cyclopropane (or aziridine, etc.) rings (Scheme 1 c). Not surprisingly, essentially no examples of concerted pericyclic reactions of this type can be found in the literature. Such processes would, however, be highly desirable for several reasons. First, cyclopropane rings are present in many natural products and biologically active compounds (see Scheme 2 for a small selection). Second, the reduced compound handling, reduced number of steps, reduced waste, and improved atom efficiency of cyclotrimerizations hold the prospect of more efficient syntheses of such materials. Third, the ring strain of a cyclopropane unit endows a molecule with a reservoir of about 110 kJ mol^{-1} of energy. Many and diverse methods of usefully deploying this energy to propel desired molecular transformations have been developed.[2] Accordingly, effective new means of constructing this versatile synthon are always of interest.



Scheme 2. Selected natural products and bioactive molecules containing cyclopropane rings.

Although concerted processes like that in Scheme 1 c are unknown, stepwise cascades also have the potential to diminish the entropic and thermodynamic barriers. When they are confined to one pot, many of the advantages delineated above can still be realized. A wide variety of precursors including carbenes, carbenoids, diazo compounds, and ylides participate in [2+1] cycloadditions to alkenes to produce cyclopropanes. Furthermore, enantioselective versions, often making use of metal catalysts with chiral ligands, are available.[3]

Aryl methyl ketones (**1**; for structure see Scheme 3) are stable and nontoxic, and therefore much more attractive reagents than the haloforms, diazo compounds, ylides etc. required in conventional cyclopropane syntheses. For that reason, the discovery in 2014 by Nacci, Monopoli, and coworkers of a way to use aryl methyl ketones as a C_1 source in [2+1] cycloadditions represented a noteworthy breakthrough.[4] They showed that $Pd(OAc)_2$ and $Cu(OAc)_2$ in aerated tetrabutylammonium acetate at 100 °C catalyzed the

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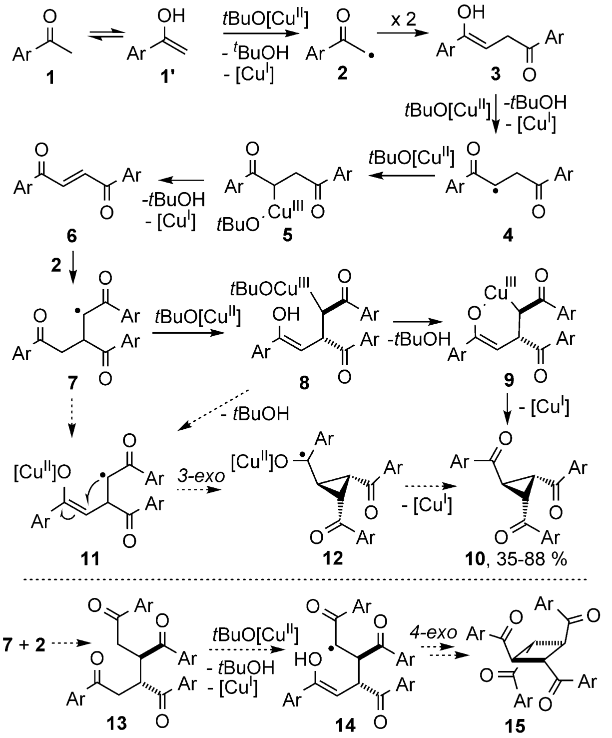

Scheme 3. [1+1+1] Cyclotrimerization of aryl methyl ketones with a tentative mechanism.

formation of cyclopropanes from aryl methyl ketones and styrenes. The aryl (or heteroaryl) rings were shown to be essential structural features because aliphatic and other ketone types were unreactive or yielded alternative products. These authors proposed that the ketones formed oxa-π-allylpalladium complexes, which coupled with styrene to provide six-membered ring oxa-π-allylpalladium complexes (analogous to **9** in Scheme 3). Reductive elimination of Pd^0 then generated the three-membered rings.

Stimulated by this, Antonchick and Manna discovered a simpler system comprising CuI, bipy, and di-*tert*-butylperoxide (DTBP) in chlorobenzene, and it catalyzed cyclopropanations of maleimides by the same aryl methyl ketones.[5] They then conceived the insightful idea that if an alkene component could be generated in situ, and from the same ketone, then with an appropriate experimental protocol a unique one-pot [1+1+1] cyclotrimerization might be realized.[6] Remarkably they achieved this unique cascade in practice when the acetophenones **1** were treated with CuI, 4,4′-di-*tert*-butyl-2,2′-bipyridine ligands, and DTBP, as the oxidant, in chlorobenzene solvent. The copper catalyst transformed each of 20 ketones, irrespective of either electron-releasing or electron-withdrawing substituents in their aryl rings, into triaroyl-cyclopropanes (**10**) in yields of 35–88 % (Scheme 3). Furthermore, these extraordinary [1+1+1] cyclotrimerizations took place stereoselectively.

Evidence of a radical mechanism was provided, with 1,4-diketones (shown as enol tautomers **3** in Scheme 3) being obtained from dimerization of the aroylmethyl radicals **2**. Oxidation and β-hydride elimination delivered the *trans* unsaturated 1,4-diketones **6** needed for the [2+1] cycloaddition step. Capture of more **2** by **6** generated the tri-aroyl alkyl radical **7**. It was proposed that **7** coupled with Cu^{II} to give the organocuprate **8** and hence metallacycle **9**, which reductively eliminated Cu^I with ring closure to stereospecifically afford the cyclopropanes **10**. This plausible sequence accounts for most features of the process. It seems to imply, however, that aliphatic ketones could also take part in such cycloadditions, whereas no examples were reported. As a possible alternative, the Cu^{II}/enolate radical **11** might form from either **7** or **8**. The 3-*exo* ring closures of **11** would be very favorable because of the large benzylic-type stabilization in the ring-closed radicals **12**.[2a,7] Elimination of Cu^I would then complete the cyclotrimerization. The intermediacy of **12** would suitably explain the exclusivity for aryl ketone precursors.

Could the cascade succeed with other ketone types? The $C(=O)CH_3$ unit is probably essential because enolization ability is needed and because of steric constraints on coupling and addition steps. The driving force for formation of the strained three-membered rings is the large benzylic resonance stabilization of the ring-closed species **12**. If closure actually occurs on reductive elimination from **9** it is probable that the transition state develops stabilization akin to that shown in **12**. Cyclotrimerizations of ketones $Z-C(=O)CH_3$, where Z strongly stabilizes an adjacent radical, might therefore succeed and Z = heteroarene, RCH=CH-, and RC≡C- are possible candidates.

Numerous preparative sequences based around the cyclotrimerization products can be expected. The cyclopropanes **10** contain three electron-withdrawing Bz substituents so ring cleavage by nucleophiles should be facile.[8] The resulting enolates, $BzCH(Nu)CH(Bz)CH{=}C(Ar)O^-$, are promising for alkylations of many electron-deficient substrates. A large variety of other reagent types are expected to afford ring-opened propene, halo-propane, and other derivatives.

The system involves multiple intermediates and so other protocols might direct it down alternative pathways. For example, cross-coupling of **7** and **2** would produce the tetrabenzoylbutane **13** (Scheme 3). The Cu reagent could generate the radical **14** from an enol of **13** and then a [1+1+1+1] cyclotetramerization yielding the cyclobutane **15** might take place either via a metallacycle or a copper enolate analogous to **11** (homodimerization of radicals **4** could provide an alternative entry to cyclotetramerizations). Note however that formation of tertiary radicals from **13** might compete and that appropriate control of the concentrations of **7** and **2** would be difficult to arrange.

Antonchick and Manna's intriguing discovery extends the portfolio of cycloaddition processes in a mechanistically fascinating and totally unexpected direction. It marshals three simple components and assembles them efficiently into energy-rich structures ready for exploitation in a multitude of different ways. It is sure to stimulate the discovery of new variants and varieties as well as useful applications.

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