**Abstract:** The synthesis of small rings by functionalization of C(sp³)–H bonds remains a great challenge. We report for the first time a copper-catalyzed [1+1+1] cyclotrimerization of acetophenone derivatives under mild reaction conditions. The reaction has a broad scope for the stereoselective synthesis of cyclopropanes by trimerization of acetophene. The developed transformation is based on an extraordinary copper-catalyzed cascade process that allows saturated carbocycles to be obtained for the first time by cyclotrimerization through functionalization of C(sp³)–H bonds. The cascade of sixfold C(sp³)–H bond functionalization allows the synthesis of cyclopropanes in a highly stereoselective approach.

Intermolecular cyclotrimerization reactions are among the most efficient methods for the synthesis of complex products in a single step from simple nonfunctionalized building blocks. The cyclotrimerization is expected to have outstanding potential because of its high atom economy, high product yields, and broad reaction scope. Efficient, selective, and practical procedures based on the [2+2+2] cyclotrimerization of alkenes were developed for the synthesis of polysubstituted benzenes (Figure 1a). Achievements in the regioselective formation of various benzenes resulted in the broad application of [2+2+2] cyclotrimerization for the synthesis of materials, drugs, and bioactive compounds. The [2+2+2] cyclotrimerization of acetophenones provides a regioselective approach to polysubstituted aromatic compounds. Those processes occur under mild reaction conditions and produce water as a by-product. However, known methods of cyclotrimerization only allow the synthesis of unsaturated carbocyclic compounds and the synthesis of fully saturated carbocycles has not been reported. The biggest problem for the synthesis of saturated carbocycles is associated with the possible formation of stereocenters, which would require a regio-, diastereo-, and stereoselective approach for the synthesis of target compounds. Here we demonstrate the first catalytic approach for the synthesis of small strained cyclopropanes by an unprecedented [1+1+1] cyclotrimerization of simple ketones. A notable feature of our approach is its high stereoselectivity and its extraordinary cascade of regioselective sixfold functionalization of reactive C(sp³)–H bonds. Our results reveal a new method for the synthesis of cyclopropanes and an unparalleled cascade reaction mechanism in which a single catalyst is used in several steps.

Having an interest in the development of novel oxidative coupling methods, we envisaged that a novel approach for the synthesis of cyclopropanones could be realized through the cyclotrimerization of acetophenone under radical reaction conditions (Figure 1c). A radical addition of acetophenone to unsaturated diketone A could provide the desired cyclopropane. Intermediate A could be obtained from 1,4-diketone B under oxidative reaction condition. Furthermore, diketone B can be obtained by the oxidative coupling of ketones. Therefore, we would need three molecules of ketones to create a small cycle.

To test our hypothesis, we began our study on the [1+1+1] cyclotrimerization of 4-fluoracetophenone (1a) using CuI (10 mol %) in the presence of 2,2′-bipyridine-based ligands (Table 1, entries 1–6, and see Table S1 in the Supporting Information). To our delight, we observed a ligand-induced
formation of the desired cyclopropane[10] 2a in the presence of di-tert-butyl peroxide (DTBP) as an oxidant in chlorobenzene at 100 °C under argon after 12 h. Pleasingly, we found that 4,4’-di-tert-butyl-2,2’-bipyridine (L5) was the best ligand for the copper-catalyzed cyclotrimerization of acetophenone 1a. It is notable that the product of the [1+1+1] cyclotrimerization (2a) was formed as a single stereoisomer. Unfortunately, other nitrogen-containing ligands did not give promising results for the synthesis of 2a (see Table S1). We then examined various oxidants. The yield of cyclopropane 2a was reduced when dicumyl peroxide or tert-butyl hydroperoxide were used (Table 1, entries 7 and 8, and see Table S2). Furthermore, cyclotrimerization occurred when benzoyl peroxide, hydrogen peroxide, K₂S₂O₈, or (diacetoxyiodo)benzene were used as oxidants (see Table S2). The formation of product 2a drastically decreased when air was used instead of argon. The highest yield of the desired product 2a (73 %) was obtained using DTBP (3 equiv). A reduction in the loading of CuI from 10 mol % to 5 mol % led to a decrease of 2a.

Various copper salts were examined to identify the best precatalyst (Table 1, entries 10–12 and Table S3). The yield of the cyclotrimerization product was reduced when various copper(I) salts were used. The application copper(II) salts as the precatalyst led to a further decrease in the product yield. Thus, subsequent cyclotrimerization reactions were performed in the presence of CuI. The effect of temperature was next examined. The yield of the desired product 2a was increased to 86 % on reduction of the reaction temperature from 100 °C to 90 °C (entry 13). However, a further decrease or increase in temperature led to a lower yield of 2a (see Table S4). No formation of the target product was observed when polar solvents such as H₂O, tert-AmOH, or DMSO were used (entries 14–17 and see Table S5). Only the formation of trace amounts of product was observed in nonpolar solvents such as toluene and p-xylene. Aromatic halogenated solvents were found to be suitable for the [1+1+1] cyclotrimerization of acetophenones, with chlorobenzene found to be the best solvent for the synthesis of cyclopropanes.

With the optimized reaction conditions in hand, we next investigated the scope of the unprecedented copper-catalyzed [1+1+1] cyclotrimerization. We found that various acetophenones can be transformed into the corresponding products in moderate to good yields (Table 2). interestingly, a wide array of functional groups such as halogens, carbonyl, sulfonamide, nitryl, alkyloxy, and alkyl were tolerated under the optimized conditions (Table 2, entries 1–19). To our delight, various electron-withdrawing groups as well as electron-donating groups on the aryl moiety were tolerated. However, acetophenones with electron-withdrawing groups reacted faster than electron-rich derivatives. Furthermore, substitutions in the ortho-, meta-, and para- positions give comparable results under the developed reaction conditions. Polysubstituted acetophenones were also tested for the formation of the desired products. It is remarkable that heterocyclic derivatives such as 2-acetylthiophene were found to form the desired product in 52 % yield under the developed oxidative reaction conditions (Table 2, entry 20). It is interesting that although the bond dissociation energies (BDEs) of all the methyl groups in 3,4-dimethy lacetophenone are similar (BDE = 89–91 kcmol⁻¹), the reaction occurs by functionalization of the methyl group attached to the carbonyl group (Table 2, entry 15). Moreover, the reaction with allyl 4-acetylenzoate (Table 2, entry 6) gave the desired cyclopropane 2f in moderate yield, despite a methylene group with a dramatically lower BDE being present (BDE = 81 kcmol⁻¹). Therefore, the developed method allows the functionalization of a strong C(sp³)–H bond in the presence of a weak one. Finally, we scaled-up the experiment using 1c (6 mmol). Product 3c was formed smoothly in the scaled-up experiment in a yield of 66 %.

Following our synthetic studies, we performed a number of experiments to gain insight into the reaction mechanism of the copper-catalyzed [1+1+1] cyclotrimerization reaction. Based on the reaction design, we carried out control experiments using possible intermediates. Initially, we tested diketone 3, which can be formed by the oxidative dimerization of acetophenones (Figure 2a).[10] Under optimized reaction conditions, diketone 3 reacts with acetophenone 1d to afford cyclopropane 4 in good yield and regioselectivity. Moreover, under the same reaction conditions but in the

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**Table 1: Screening of reaction conditions[14]**

| Entry | Cu salt (mol %) | Ligand (mol %) | Solvent | Oxidant (equiv) | Yield [%] |
|-------|----------------|----------------|---------|----------------|----------|
| 1     | CuI (10)       | L1 (20)        | PhCl DTBP | traces         |          |
| 2     | CuI (10)       | L2 (20)        | PhCl DTBP | traces         |          |
| 3     | CuI (10)       | L3 (20)        | PhCl DTBP | traces         |          |
| 4     | CuI (10)       | L4 (20)        | PhCl DTBP | traces         |          |
| 5     | CuI (10)       | L5 (20)        | PhCl DTBP | traces         |          |
| 6     | CuI (10)       | L6 (20)        | PhCl DTBP | traces         |          |
| 7     | CuI (10)       | L7 (20)        | PhCl DCP  | traces         |          |
| 8     | CuI (10)       | L8 (20)        | PhCl TBHP | traces         |          |
| 9     | CuI (10)       | L9 (20)        | PhCl DTBP | traces         |          |
| 10    | CuBr (10)      | L10 (20)       | PhCl DTBP | traces         |          |
| 11    | CuCl (10)      | L11 (20)       | PhCl DTBP | traces         |          |
| 12    | Cu(OCOCl)₂ (10)| L12 (20)       | PhCl DTBP | traces         |          |

[a] Reaction conditions: 1a (0.5 mmol), oxidant (3 equiv), copper salt (10 mol %), ligand (20 mol %) in solvent (2.0 mL) at 100 °C for 8 h under argon.[b] Reaction carried out at 90 °C for 8 h. DTBP = di-tert-butyl peroxide, DCP = dicumyl peroxide, TBHP = tert-butyl hydrogen peroxide.
Table 2: Scope of the [1+1+1] cyclotrimerization.1

| Entry | R          | Product | t [h] | Yield [%] |
|-------|------------|---------|-------|-----------|
| 1     | F          | 2a      | 8     | 86        |
| 2     | Cl         | 2b      | 8     | 66        |
| 3     | Br         | 2c      | 8     | 73        |
| 4     | MeO2C      | 2d      | 8     | 88        |
| 5     | EtO2C      | 2e      | 8     | 65        |
| 6     |           | 2f      | 6     | 43        |
| 7     | F3C        | 2g      | 5     | 79        |
| 8     | NC         | 2h      | 6     | 62        |
| 9     | N3         | 2i      | 8     | 35        |
| 10    | Me         | 2j      | 8     | 43        |
| 11   | Me         | 2k      | 12    | 69        |
| 12    | F3C        | 2l      | 8     | 46        |
| 13    | NC         | 2m      | 7     | 68        |
| 14    | Me         | 2n      | 8     | 77        |
| 15    | Me         | 2o      | 18    | 53        |
| 16    | Me         | 2p      | 18    | 43        |
| 17    | F          | 2q      | 8     | 65        |
| 18    | MeO2C      | 2r      | 12    | 46        |
| 19    | F          | 2s      | 8     | 41        |
| 20    |            | 2t      | 8     | 52        |

[a] Reaction conditions: 2 (0.5 mmol), DTBP (3 equiv), Cul (10 mol %), LS (20 mol %) in PhCl (2.0 mL) at 90 °C for 5–8 h under argon. Yields are given for isolated products. All products were formed with d.r. > 20:1.
[b] Cul (20 mol %), LS (30 mol %) were used at 75 °C for 12 h under argon.
[c] Reaction was carried out in 1 mL DMF for 18 h.

absence of acetophenone 1d, the unsaturated diketone 5 was formed in excellent yield from diketone 3. The reaction of diketone 5 with acetophenone 1d provided product 4 in high yield. Based on those experiments, we concluded that the [1+1+1] cyclotrimerization proceeds through the following reaction sequence: 1) dimerization of ketones to 1,4-diketones, 2) oxidation of 1,4-diketones to but-2-ene-1,4-dione, and 3) annulation of but-2-ene-1,4-dione with a third equivalent of acetophenone. The formation of cyclopropanes was suppressed in the presence of radical scavengers such as TEMPO under the optimized reaction conditions. Therefore, cyclotrimerization involves the formation of radical intermediates. However, the kinetic isotopic effect was the same at

Figure 2. Studies on reaction mechanism and plausible reaction mechanism. a) Control experiments. b) Reaction mechanism.
1.4 (see the Supporting Information for details). Hence, the abstraction of any of the six hydrogen atoms is not the rate-limiting step. The use of trideuterated acetophenone ([D$_2$]-1k) in the cyclotrimerization resulted in the trideuterated product ([D$_3$]-2k), with a deuterium incorporation of $>95\%$. Therefore, the observed diastereoselectivity of the reaction is not a result of epimerization after formation of the cyclopropane.

On the basis of the above preliminary results, a plausible mechanism is shown in Figure 2b. Initially, the Cu$^{II}$ complex is generated by oxidation of CuI in the presence of DTBP. In the next step, acetophenone 1 is oxidized in its enol form 1' by a Cu$^{II}$ species to afford radical 6. Subsequent dimerization of 6 leads to the formation of diketone 7. Diketone 7 subsequently undergoes the next step of oxidation through its enol form 7' to form radical 8, which is trapped by the Cu$^{II}$ species to form organocuprate 9. Intermediate 9 then undergoes a β-hydride elimination to yield unsaturated diketone 10 with complete trans selectivity. Subsequent addition of radical 6 to 10 leads to the formation of radical 11, which is trapped by the Cu$^{II}$ species to form intermediate 12. In a next step, 12 is converted into the key metallallocycle 13 through ligand exchange of the enol form 12'. Reductive elimination of the Cu$^{II}$ species from intermediate 13 results in the stereoselective formation of cyclopropane 2.

In conclusion, we have discovered an extraordinary [1+1+1] cyclotrimerization for the synthesis of cyclopropane rings. For the first time, cyclotrimerization was applied to the stereoselective synthesis of small saturated carbocycles from nonfunctionalized acetoephene derivatives. The discovery is based on an unprecedented copper-catalyzed cascade process. The cyclotrimerization showed broad scope. Mechanistic studies revealed the reaction had a novel radical pathway. This general catalytic [1+1+1] cyclotrimerization reaction allows direct access to the stereoselective synthesis of cyclopropanes and provides an inspiration for the development of novel methods for the synthesis of saturated carbocycles by cyclotrimerization.

**Acknowledgements**

We gratefully acknowledge Prof. Dr. H. Waldmann (Max-Planck-Institut für molekulare Physiologie) for his generous support. This work was supported by the Max-Planck-Gesellschaft.

**Keywords:** copper · cyclopropanes · cyclotrimerization · oxidative coupling · radicals

**How to cite:** Angew. Chem. Int. Ed. 2016, 55, 5290–5293

**Angew. Chem. 2016, 128, 5376–5379**

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