

# Palladium-Catalyzed Cross-Coupling of Styrenes with Aryl Methyl Ketones in Ionic Liquids: Direct Access to Cyclopropanes\*\*

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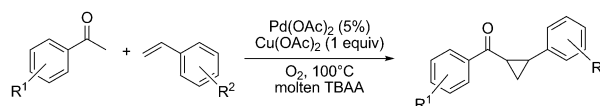
**Abstract:** The combined use of  $\text{Pd}(\text{OAc})_2$ ,  $\text{Cu}(\text{OAc})_2$ , and dioxygen in molten tetrabutylammonium acetate (TBAA) promotes an unusual cyclopropanation reaction between aryl methyl ketones and styrenes. The process is a dehydrogenative cyclizing coupling that involves a twofold C–H activation at the  $\alpha$ -position of the ketone. The substrate scope highlights the flexibility of the catalyst; a reaction mechanism is also proposed.

Cyclopropanes are important subunits of many natural products,<sup>[1]</sup> and a large number of synthetic compounds that carry a cyclopropane unit possess biological activities.<sup>[2]</sup> As a consequence, great efforts have been made to develop efficient methods for the synthesis of these small ring motifs and to incorporate them into pharmacologically active ingredients.<sup>[3]</sup>

The most important strategies for constructing three-membered rings start from olefins and involve the Simmons–Smith reaction,<sup>[4]</sup> the transition-metal-catalyzed decomposition of diazo compounds,<sup>[5]</sup> and the Michael-reaction-initiated ring closure (MIRC).<sup>[6]</sup> The first two strategies require special reagents, such as halomethyl–zinc carbenoids or highly reactive metal carbenes derived from copper, rhodium, ruthenium, or cobalt catalysts. The third method involves a sequence of a nucleophilic addition and a ring closure and requires the presence of both electron-withdrawing and leaving groups in the reaction partners. Nevertheless, the synthesis of three-membered rings remains a considerable challenge. In this context, the search for new methylene group sources that are easier to handle and more stable than currently used reagents, and the development of safer and greener methods are the major issues to be addressed.

In pursuing these objectives, we exploited our previous findings on palladium chemistry in ionic liquids (ILs),<sup>[7]</sup> in

trying to develop a green and simple catalytic cyclopropanation that circumvents the need for carbene (or carbenoid) reagents by using readily available starting materials. During our investigation of the Fujiwara–Moritani (oxidative Heck) coupling in ILs,<sup>[8,9]</sup> we found that the combined use of  $\text{Pd}(\text{OAc})_2$  and  $\text{Cu}(\text{OAc})_2$  in quaternary ammonium ILs can, under aerobic conditions, promote an unusual cyclopropanation reaction between aryl methyl ketones and styrenes (Scheme 1). This reaction can be regarded as a dehydrogenative cyclizing coupling involving a formal double C–H activation at the  $\alpha$ -position of the ketone, promoted by the  $\text{Pd}^{\text{II}}/\text{Cu}^{\text{II}}/\text{O}_2$  catalyst system with the assistance of the ionic liquid.



**Scheme 1.** Palladium-catalyzed cyclopropanation in ionic liquid.

Preliminary investigations showed a total inhibition of the catalysis in conventional solvents, while the reaction proceeded smoothly in molten tetrabutylammonium acetate (TBAA) as the solvent, thus confirming the beneficial effect that quaternary ammonium ILs often have on Pd coupling reactions (for details see the Supporting Information).<sup>[10]</sup> In addition, these earlier data demonstrated the need for basic conditions, with a particularly favorable effect of acetate ions, thus suggesting the involvement of a ketone enolate as the intermediate.

The conditions for the cyclizing coupling were optimized using acetophenone **1** and styrene **2** as model substrates (Table 1). First experiments showed that the dimerization of styrene is the main side reaction, and that the cyclopropanation took place as a major pathway to afford isolated product **3** in 95 % yield only when  $\text{Pd}(\text{OAc})_2$ ,  $\text{Cu}(\text{OAc})_2$ , and  $\text{O}_2$  were used together (Table 1, entries 1–3).

Air could be used in place of dioxygen, although the reaction became significantly slower (Table 1, entry 4). The true role played by  $\text{O}_2$  was carefully investigated by measuring the gas volume consumed during the reaction (gas burette). The requirement of a 2:1 stoichiometric ratio of acetophenone to  $\text{O}_2$  clearly indicated that molecular oxygen acts as the terminal oxidant, affording  $\text{H}_2\text{O}$  as by-product (Figure 1). Moreover, XPS analyses of the reaction mixture showed that at the end of the process negligible amounts of  $\text{Cu}^0$  and  $\text{Cu}^{\text{I}}$  were detected together with  $\text{Cu}^{\text{II}}$  (see the

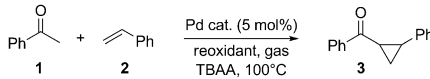
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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201408245>.

**Table 1:** Optimization of reaction conditions.<sup>[a]</sup>

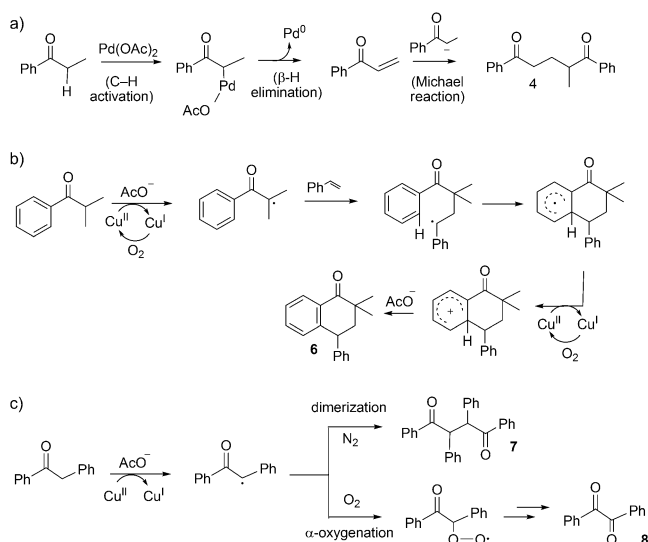
|  |                         |                                              |                |       |                          |                         |
|-----------------------------------------------------------------------------------|-------------------------|----------------------------------------------|----------------|-------|--------------------------|-------------------------|
| Entry                                                                             | Pd cat.                 | Reoxidant                                    | Gas            | t [h] | Conv. [%] <sup>[b]</sup> | Sel. [%] <sup>[c]</sup> |
| 1                                                                                 | —                       | Cu(OAc) <sub>2</sub>                         | O <sub>2</sub> | 2     | 0                        | 0 <sup>[d]</sup>        |
| 2                                                                                 | Pd(OAc) <sub>2</sub>    | —                                            | O <sub>2</sub> | 2     | 0                        | 0 <sup>[d]</sup>        |
| 3                                                                                 | Pd(OAc) <sub>2</sub>    | Cu(OAc) <sub>2</sub>                         | O <sub>2</sub> | 2     | > 99(95)                 | 100                     |
| 4                                                                                 | Pd(OAc) <sub>2</sub>    | Cu(OAc) <sub>2</sub>                         | air            | 6     | 98                       | 100                     |
| 5                                                                                 | Pd(OAc) <sub>2</sub>    | Cu(OAc) <sub>2</sub> <sup>[e]</sup>          | O <sub>2</sub> | 10    | 15                       | 100                     |
| 6                                                                                 | Pd(OAc) <sub>2</sub>    | Riboflavin                                   | air            | 2     | 0                        | —                       |
| 7                                                                                 | Pd(OAc) <sub>2</sub>    | benzoquinone                                 | air            | 6     | 0                        | —                       |
| 8                                                                                 | Pd(OAc) <sub>2</sub>    | K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> | air            | 6     | 0                        | —                       |
| 9                                                                                 | Pd(OAc) <sub>2</sub>    | FeCl <sub>3</sub>                            | O <sub>2</sub> | 2     | 0                        | —                       |
| 10                                                                                | Pd(OAc) <sub>2</sub>    | AgOAc                                        | O <sub>2</sub> | 2     | 0                        | —                       |
| 11                                                                                | Pd(OAc) <sub>2</sub>    | CuSO <sub>4</sub>                            | O <sub>2</sub> | 2     | 52                       | 100                     |
| 12                                                                                | Pd(OAc) <sub>2</sub>    | Cu(TfO) <sub>2</sub>                         | O <sub>2</sub> | 6     | 0                        | — <sup>[d]</sup>        |
| 13                                                                                | Pd(OAc) <sub>2</sub>    | CuOAc                                        | O <sub>2</sub> | 2     | 67                       | 100                     |
| 14                                                                                | PdCl <sub>2</sub>       | Cu(OAc) <sub>2</sub>                         | O <sub>2</sub> | 2     | > 99                     | 55 <sup>[f]</sup>       |
| 15                                                                                | Pd(dba) <sub>2</sub>    | Cu(OAc) <sub>2</sub>                         | O <sub>2</sub> | 2     | 0                        | —                       |
| 16                                                                                | Pd <sub>nanopart.</sub> | Cu(OAc) <sub>2</sub>                         | O <sub>2</sub> | 2     | 0                        | —                       |

[a] Reaction conditions: TBA (0.2 g), **1** (0.25 mmol), **2** (0.25 mmol), Pd(OAc)<sub>2</sub> (5 mol%), and reoxidant (1 equiv) heated at 100°C under O<sub>2</sub> (or air) atmosphere (1 atm). In all cases, **3** was obtained in a *trans/cis* ratio higher than 99:1. [b] With regard to **1**, evaluated by GC-MS (in brackets isolated yields of **3**). [c] Based on the ratio of GLC peak areas of **3** to by-products. [d] Only styrene dimerization products were observed. [e] With 0.2 equiv of Cu(OAc)<sub>2</sub>. [f] Oxidative dimerization of styrene was observed (1,4-diphenyl-1,3-butadiene obtained in 45% yield).

Supporting Information), thus suggesting that Cu(OAc)<sub>2</sub> is simply involved as an electron-transfer mediator in the reoxidation of Pd<sup>0</sup> by the terminal oxidizing agent O<sub>2</sub>.<sup>[11]</sup> Concerning the role of copper, it is important to point out that direct reoxidation with O<sub>2</sub> is feasible, but this reaction was found to be very slow in the ionic medium in the absence of Cu<sup>II</sup>.<sup>[12]</sup> This could explain the requirement for equimolar amounts of Cu(OAc)<sub>2</sub> for a complete conversion into cyclopropane (Table 1, entry 5).<sup>[13]</sup> However, the total inefficacy of other oxidants commonly used in Pd-catalyzed oxidative couplings (Table 1, entries 6–10) suggested another role of Cu<sup>II</sup> in the catalytic cycle. In the absence of more direct evidence, one could speculate that Cu<sup>2+</sup> might also assist in the nucleopalladation of styrene by the Pd<sup>II</sup> enolate intermediate **A** through a preliminary  $\pi$ -coordination of the double bond (see Figure 1). Other copper(II) sources, such as CuSO<sub>4</sub> and Cu(OTf)<sub>2</sub>, were also tested, but with disappointing results. This confirms the beneficial effect of the acetate anion (Table 1, entries 11 and 12). As expected, Cu<sup>I</sup>OAc exhibited fairly good activity, but required an induction period because of the necessary preliminary oxidation of Cu<sup>I</sup> to the active species Cu<sup>II</sup> (Table 1, entry 13). The preliminary screening was completed by the investigation of some other Pd sources. PdCl<sub>2</sub> provided unsatisfactory results in terms of selectivity (Table 1, entry 14), while Pd<sup>0</sup> catalysts, such as [Pd(dba)<sub>2</sub>] and reformed Pd<sup>0</sup> nanoparticles, were completely inefficient, thus indicating that Pd<sup>II</sup> is the catalytically active species (Table 1, entries 15 and 16).

The investigation of the substrate scope revealed a profound influence of the ketone skeleton on the reaction outcome. Indeed, the simultaneous presence of two potentially active metals opened the way to a plethora of processes with either Pd or Cu (or both) behaving as active catalysts. Table 2 summarizes the major processes promoted in the ionic medium, thus indicating the true operating catalyst.

It is noteworthy that aryl ketones were the most reactive substrates, and among them acetophenone **1** was unique in affording the cyclopropanation product **3**, requiring the simultaneous presence of Pd<sup>II</sup>, Cu<sup>II</sup>, and O<sub>2</sub> (Table 2, entries 1 and 2). Other aryl ketones underwent different reactions, depending on both the reaction conditions and the degree of substitution at the  $\alpha$ -position of the carbonyl group. For example, propiophenone (Table 1, entries 3 and 4) was predominantly converted into the self-condensed diketone **4**, most likely through three Pd<sup>II</sup>-mediated consecutive steps involving C–H activation/ $\beta$ -hydride elimination/Michael addition (Scheme 2a).<sup>[14]</sup> This might represent a useful mechanistic suggestion, as the preliminary C–H activation step can



**Scheme 2.** Plausible pathways for reactions of aryl ketones.

be assumed to also occur for acetophenone, whose enolate, which is not compatible with a  $\beta$ -H elimination, would evolve in a different way, giving oxa- $\pi$ -allylpalladium **A** and then resulting in the cyclopropanation process (Figure 1). In contrast, the presence of a tertiary carbon atom at the  $\alpha$ -position of isobutyrophenone opened the way to known  $\alpha$ -alkylation reactions (promoted exclusively by Cu<sup>II</sup>), the outcome of which was dependent on the presence of O<sub>2</sub> (Table 2, entries 5 and 6). Indeed, under inert atmosphere, the simple addition of the ketone enolate to styrene was observed with the formation of adduct **5**.<sup>[15]</sup> On the contrary, under oxygen atmosphere, a radical pathway was initiated by a single-electron oxidation of the same enolate moiety followed by a cyclizing step that led to the dihydronaphthalen-1-one **6**<sup>[16]</sup> (Scheme 2b and Table 2, entry 6). Different results were obtained with 1,2-diphenylethanone, which bears

**Table 2:** Substrate scope.<sup>[a]</sup>

|       |        | $\text{R}-\text{C}(=\text{O})-\text{R}^1 + \text{Ph}-\text{CH}=\text{CH}_2 \xrightarrow[\text{TBAA / gas, 100}^\circ\text{C, 2 h}]{\text{Pd}(\text{OAc})_2 (5 \text{ mol}\%), \text{Cu}(\text{OAc})_2 (1 \text{ equiv})}$ |                           |                          |                                    |                                   |
|-------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|--------------------------|------------------------------------|-----------------------------------|
| Entry | Ketone | Gas                                                                                                                                                                                                                       | Major product             | Conv. [%] <sup>[b]</sup> | Operating catalyst <sup>[c]</sup>  | Promoted process                  |
| 1     |        | N <sub>2</sub>                                                                                                                                                                                                            |                           | < 5                      | —                                  | cyclopropanation                  |
| 2     |        | O <sub>2</sub>                                                                                                                                                                                                            |                           | > 99                     | Pd <sup>II</sup> /Cu <sup>II</sup> | cyclopropanation                  |
| 3     |        | O <sub>2</sub>                                                                                                                                                                                                            |                           | 90                       | Pd <sup>II</sup>                   | dehydrogenation/ Michael reaction |
| 4     |        | N <sub>2</sub>                                                                                                                                                                                                            |                           | 85                       | Pd <sup>II</sup>                   | dehydrogenation/ Michael reaction |
| 5     |        | N <sub>2</sub>                                                                                                                                                                                                            |                           | 88                       | Cu <sup>II[d]</sup>                | —                                 |
| 6     |        | O <sub>2</sub>                                                                                                                                                                                                            |                           | 96                       | Cu <sup>II[d]</sup>                | α-alkylation                      |
| 7     |        | N <sub>2</sub>                                                                                                                                                                                                            |                           | 20                       | Cu <sup>II[d]</sup>                | α-oxidative homocoupling          |
| 8     |        | O <sub>2</sub>                                                                                                                                                                                                            |                           | 95                       | Cu <sup>II[d]</sup>                | α-oxygenation                     |
| 9     |        | N <sub>2</sub>                                                                                                                                                                                                            | —                         | 0                        | —                                  | —                                 |
| 10    |        | O <sub>2</sub>                                                                                                                                                                                                            | —                         | 0                        | —                                  | —                                 |
| 11    |        | N <sub>2</sub>                                                                                                                                                                                                            |                           | 100                      | Pd <sup>II</sup>                   | dehydrogenation                   |
| 12    |        | O <sub>2</sub>                                                                                                                                                                                                            |                           | 100                      | Pd <sup>II</sup>                   | dehydrogenation                   |
| 13    |        | N <sub>2</sub>                                                                                                                                                                                                            |                           | 0                        | —                                  | dehydrogenation                   |
| 14    |        | O <sub>2</sub>                                                                                                                                                                                                            |                           | 50                       | Pd <sup>II</sup>                   | dehydrogenation                   |
| 15    |        | N <sub>2</sub>                                                                                                                                                                                                            | mixture of octene isomers | 0                        | Pd <sup>II</sup>                   | isomerization                     |
| 16    |        | O <sub>2</sub>                                                                                                                                                                                                            | mixture of octene isomers | 0                        | Pd <sup>II</sup>                   | isomerization                     |

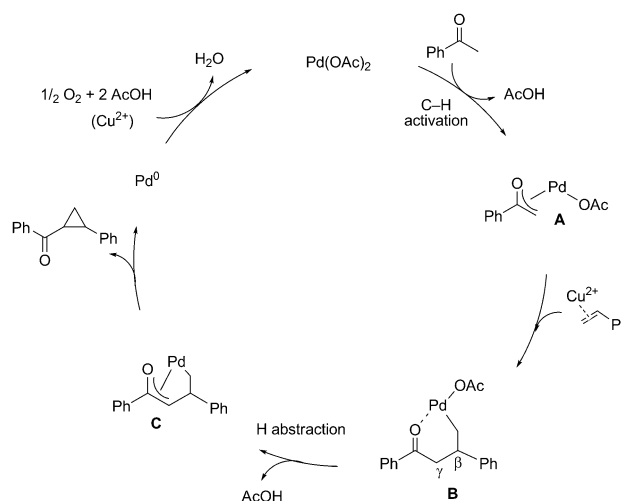
[a] Reaction conditions: TBAA (0.2 g), ketone (0.25 mmol), styrene (0.25 mmol), Pd(OAc)<sub>2</sub> (5 mol %), Cu(OAc)<sub>2</sub> (0.25 mmol) heated at 100°C under O<sub>2</sub> (or N<sub>2</sub>) atmosphere (1 atm). [b] With regard to the starting ketone, evaluated by GLC. [c] As deduced from appropriate catalytic tests carried out by using the two metals separately. [d] Reaction proceeds also with 20 mol % of Cu(OAc)<sub>2</sub> alone.

a benzylic carbon atom at the α-position to the carbonyl group (Table 2, entries 7 and 8). In this case, the formation of a stable α-carbonylbenzyl radical promoted by copper accounts for the observed transformations: the oxidative homo-coupling to 1,4-dione **7**<sup>[17]</sup> under inert atmosphere, or the α-oxygenation reaction to benzil **8**<sup>[18]</sup> (Scheme 2c and Table 2, entries 7 and 8).

Aliphatic ketones were almost unreactive or underwent unproductive side reactions, thus indicating that the presence of an aromatic ring linked to the carbonyl group is essential for the coupling with styrene. Indeed, pinacolone was completely inert under the various conditions (Table 2, entries 9 and 10), while 2-heptanone underwent a Pd<sup>II</sup>-promoted β-H elimination,<sup>[10b,14]</sup> affording a complex mixture of polyunsaturated heptanones (Table 2, entries 11 and 12). In a similar manner, cyclohexanone was partially dehydrogenated to phenol in the presence of dioxygen<sup>[14b]</sup> (Table 2, entries 13 and 14). Finally, terminal aliphatic alkenes proved to be useless reactants that were converted to a complex mixture of alkenes with isomerized double bonds under the conditions (Table 2, entries 15 and 16), while internal alkenes were completely unreactive.

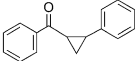
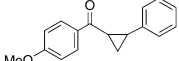
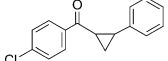
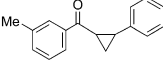
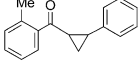
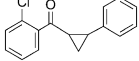
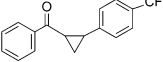
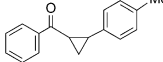
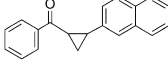
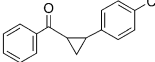
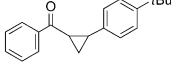
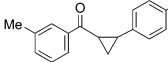
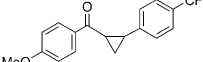
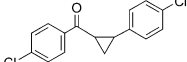
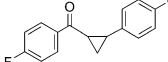
Based on these findings, we proposed the reaction mechanism depicted in Figure 1 for the cyclopropanation. The cycle is initiated by Pd<sup>II</sup> which gives rise to the C–H activation at the α-position of acetophenone, leading to the

oxa-π-allylpalladium complex **A**. With regard to reports suggesting the possible formation of oxa-π-allylpalladium intermediates,<sup>[19]</sup> we gained direct evidence of the formation of **A** by monitoring the reaction mixture by ESI-HRMS (Figure S3). The addition to styrene (Markovnikov's rule) should afford the intermediate **B**, in which the proton abstraction from the γ-position leads to the formation of a new oxa-π-allylpalladium complex **C** (releasing acetic acid). Reductive elimination from **C** provides the cyclopropane ring and Pd<sup>0</sup>, which is then reoxidized to the Pd<sup>II</sup> catalyst by molecular O<sub>2</sub> (with the assistance of Cu<sup>2+</sup>). The γ-selectivity governing the hydrogen abstraction on intermediate **B** represents the key feature of the whole process. The reason for such a selectivity could be found not only in the higher acidity of protons in that position, but also in the chelating structure of **B** that should impede palladium to reach the syn co-planarity with the β-hydrogen to result in β-H elimination. In addition, the γ-deprotonation could occur intramolecularly by coordination of the


**Figure 1.** The plausible cyclopropanation mechanism.

acetate anion to Pd, which could explain the need for the presence of AcO<sup>−</sup> as a counterion of both the Pd<sup>II</sup> source and ionic liquid medium. Any alternative radical mechanism could be ruled out by appropriate experiments involving the addition of TEMPO or BHT, which did not noticeably affect the reaction.

**Table 3:** Synthesis of aryl(2-arylcyclopropyl)methanones.<sup>[a]</sup>

| $\text{Ar}^1\text{C(=O)Me} + \text{Ar}^2\text{CH=CH}_2 \xrightarrow[\text{molten TBAA, 100}^\circ\text{C, 6-8 h}]{\text{Pd(OAc)}_2 \text{ (5 mol\%)}, \text{Cu(OAc)}_2, \text{O}_2} \text{Ar}^1\text{C(=O)-Cyclopropyl-Ar}^2$ |                                                                                                       |                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <br><b>3</b> , 95 %                                                                                                                          | <br><b>9</b> , 70 %  | <br><b>10</b> , 72 % |
| <br><b>11</b> , 75 %                                                                                                                         | <br><b>12</b> , 93 % | <br><b>13</b> , 92 % |
| <br><b>14</b> , 92 %                                                                                                                         | <br><b>15</b> , 87 % | <br><b>16</b> , 50 % |
| <br><b>17</b> , 94 %                                                                                                                         | <br><b>18</b> , 89 % | <br><b>19</b> , 83 % |
| <br><b>20</b> , 77 %                                                                                                                         | <br><b>21</b> , 87 % | <br><b>22</b> , 85 % |

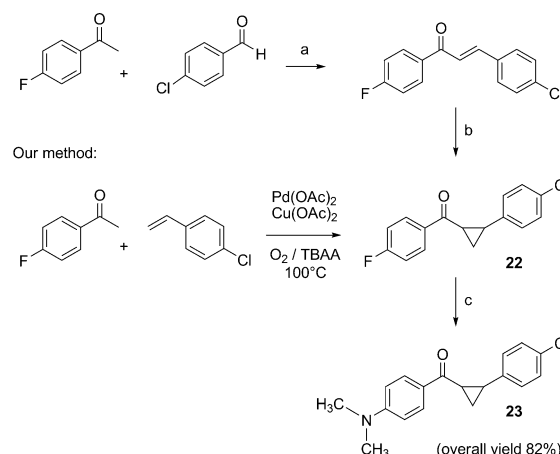
[a] Reaction conditions: TBAA (0.2 g), aryl ketone (0.25 mmol), olefin (0.25 mmol), Pd(OAc)<sub>2</sub> (5 mol%), and Cu(OAc)<sub>2</sub> (0.25 mmol), heated at 100 °C for 2–8 h under O<sub>2</sub>. All reported yields are of isolated products. Cyclopropanes were always obtained in a *trans/cis* ratio higher than 98:2.

With these results in hand, we extended the substrate scope to an array of substituted aryl methyl ketones and styrenes. The results in Table 3 show that the catalyst system exhibits good activity on these substrates, affording aryl(2-arylcyclopropyl)methanones **3** and **9–22** in moderate to excellent yields. It is noteworthy that only a little influence of the nature of substituents on the catalyst activity was observed, with an expected beneficial effect exerted by electron-withdrawing groups.

To highlight the synthetic value of our method, we attempted its application to a synthesis of practical importance in medicinal chemistry. We thus prepared cyclopropane **23** (which belongs to the alkylaminophenyl(2-arylcyclopropyl)methanones, a class of antitubercular and antimalarial agents) in good yield (82 %) in only two steps, thus improving a reported protocol (Scheme 3).<sup>[20]</sup>

In conclusion, we have discovered a Pd<sup>II</sup>-catalyzed dehydrogenative cyclizing coupling between acetophenones and styrenes proceeding through a double C–H activation at the α-position of a ketone. The practical advantages of this protocol include the use of readily available starting materials (ketones and styrenes), and the avoidance of any preliminary functionalization or the need for special carbene (or carbenoid) species. Furthermore, it requires very simple experimental procedures and occurs with relatively high yields. In addition, the method can be considered eco-friendly by virtue of the use of a green solvent (TBAA, an ionic liquid), ligand-free conditions, relatively mild temperatures (100 °C), molecular oxygen as the oxidant, and gives water as the sole by-product. A limitation of this method resides in the structures of the substrates, which may not include ketones and alkenes

Ref. [20]:



**Scheme 3.** Synthesis of the antimalarial compound **23**. a) KOH, EtOH, RT; b) TMSOI, TBAB, NaOH, 80 °C; c) Me<sub>2</sub>NH, K<sub>2</sub>CO<sub>3</sub>, DMF, 120 °C. DMF = *N,N*-dimethylformamide. TBAB = tetrabutylammonium bromide, TMSOI = trimethylsulphoxonium iodide.

with long aliphatic chains because of reactions that lead to dehydrogenated by-products. Studies are in progress to further confirm the mechanism and ascertain the exact role of copper and the ionic liquid.

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