One-pot approach for the synthesis of *trans*-cyclopropyl compounds from aldehydes. Application to the synthesis of GPR40 receptor agonists†

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A novel multicatalytic one-pot process providing *trans*-cyclopropyl compounds from corresponding aldehydes has been developed and applied to the synthesis of GPR40 small molecule agonists.

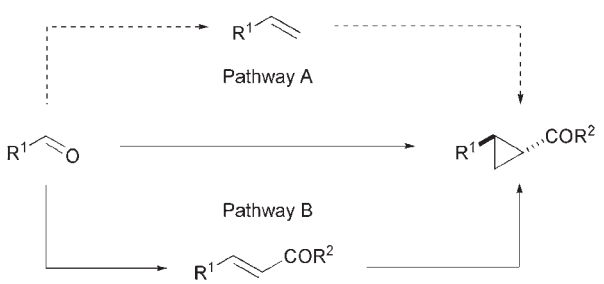
In the past few years, transition-metal-catalyzed one-pot strategies have emerged as a powerful tool in organic synthesis.[1] These environmentally friendly processes save cost and time by avoiding the purification of potentially sensitive intermediates and by minimizing the amount of solvent and reagent used.

A few years ago, we reported the rhodium-catalyzed methylenation of aldehydes and ketones using trimethylsilyldiazomethane, 2-propanol and triphenylphosphine.[2] Terminal alkenes were produced from carbonyl compounds in high yields and chemoselectivity. This method was successfully used in several one-pot strategies.[3] More recently, inexpensive copper(I) complexes showed an improved catalytic activity in the olefination of aldehydes with various diazo reagents.[4,5] Overall, copper(I)-catalyzed olefination reactions displayed a good functional group tolerance, as shown in its application in total synthesis.[4b,6] Moreover, the efficiency of a few multicatalytic processes involving palladium-catalyzed cross-coupling reactions was improved while using copper(I) complexes instead of rhodium complexes.[3d]

Recently, Taylor *et al*. have developed a tandem oxidation process that allows access to polysubstituted cyclopropanes from alcohols or α-hydroxyketones using stoichiometric phosphorus- and sulfur-ylides as reactants.[7] However, to the best of our knowledge, there is no report of a catalytic one-pot process providing cyclopropyl compounds from aldehydes *via* the cyclopropanation of an alkene. In this communication, we now report a novel one-pot process to synthesize cyclopropyl esters from the corresponding aldehydes (Scheme 1).

In theory it should be possible to use a copper complex as a catalyst to perform both the methylenation and the cyclopropanation reactions (pathway A). However, the excess of the alkene required in the cyclopropanation step precludes the efficient development of such a one-pot process. Alternatively, a multicatalytic approach was envisioned involving the formation of the α,β-unsaturated carbonyl compound in good *E*/*Z* diastereoselectivity followed by a stereospecific palladium-catalyzed cyclopropanation using diazomethane (pathway B).[8] More precisely, the copper-catalyzed decomposition of a diazocarbonyl reagent in the presence of triphenylphosphine will lead to the formation of the corresponding phosphorane which, upon reaction with an aldehyde, will provide access to the α,β-unsaturated carbonyl compound (Scheme 2). The latter will then enter the second catalytic cycle to undergo the palladium-catalyzed cyclopropanation reaction and yield the desired product.

We first studied the synthesis of ethyl 2-phenylcyclopropanecarboxylate (**1**) from benzaldehyde (Table 1). When benzaldehyde was treated under the standard copper-catalyzed olefination conditions[4b] in dichloromethane, followed by the addition of diazomethane in the presence of 1 mol% of $Pd(OAc)_2$ at 0 °C, only 15% conversion for the desired cyclopropane was observed. Conversely, the use of 1 mol% of $Pd_2(dba)_3$ at −78 °C in the cyclopropanation step led to 85% of **1** (entry 1). It is noteworthy that triphenylphosphine oxide, produced in the olefination step, does not inhibit the palladium-catalyzed cyclopropanation reaction. However, it is required to use exactly 1 equiv. of triphenylphosphine, as inhibition of the cyclopropanation reaction was observed even in the presence of a slight excess of this reagent. The reaction is more effective at −78 °C than at 0 °C, probably due to competitive copper-catalyzed decomposition of diazomethane at the latter temperature.[9] Ethyl 2-phenylcyclopropanecarboxylate (**1**) could also be obtained in good yields, using $Pd(OAc)_2$ in toluene or $Pd_2(dba)_3$ in dichloroethane at −78 °C (entries 2–3). At that temperature, the palladium-catalyzed cyclopropanation step is clearly not affected by the presence of the copper salt used in the olefination reaction. $Pd_2(dba)_3$ was then chosen over $Pd(OAc)_2$ as the latter palladium source needs to be reduced from Pd(II) to Pd(0) prior to entering the catalytic cycle. The scope of this new one-pot process was studied and a variety of aromatic aldehydes



Scheme 1 Strategy for one-pot processes toward the synthesis of cyclopropyl esters.

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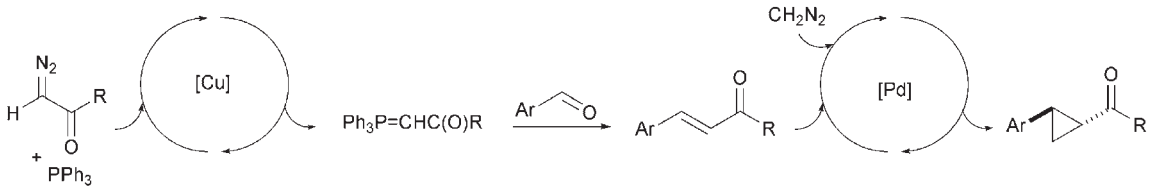
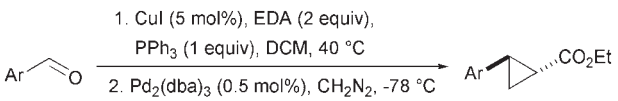
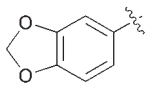


Scheme 2 Mechanistic scheme of the one-pot olefination–cyclopropnation process.

Table 1 Multicatalytic one-pot olefination–cyclopropanation process of aromatic aldehydes



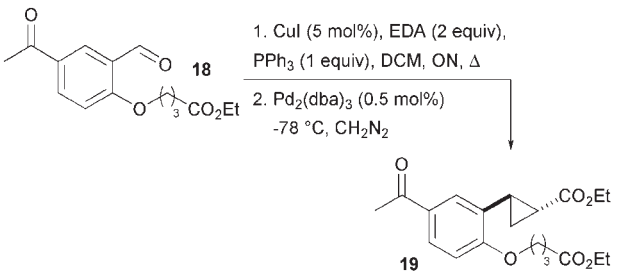
Entry	Aryl group (Ar)	Product	Yield (%)[a]
1	C_6H_5	**1**	85
2[b]	C_6H_5	**1**	69
3[c]	C_6H_5	**1**	77
4	2-$CO_2MeC_6H_4$	**2**	89
5	2-ClC_6H_4	**3**	70
6	2-BrC_6H_4	**4**	67
7	3-$MeOC_6H_4$	**5**	92
8	4-Tolyl	**6**	80
9	4-ClC_6H_4	**7**	75
10	4-BrC_6H_4	**8**	72
11	4-$(MeO)C_6H_4$	**9**	76
12	4-$(Me_2N)C_6H_4$	**10**	63
13	4-$(NO_2)C_6H_4$	**11**	59
14		**12**	73
15	3-Furfuryl	**13**	71
16	2-Thiophenyl	**14**	77
17	2-*N*-(Tosyl)pyrrolyl	**15**	82
18[d]	3-*N*-Boc-Indolyl	**16**	69
19	2-Pyridyl	**17**	61

[a] Isolated yield after column chromatography. [b] Reaction was performed in toluene at 80 °C for the first step and with 1 mol% of $Pd(OAc)_2$ as catalyst for the second step. [c] Reaction was performed in DCE at 80 °C for the first step and with 0.5 mol% $Pd_2(dba)_3$ as catalyst for the second step. [d] After an oxidative work-up.

showed good reactivity. 2-Substituted benzaldehydes were converted to the corresponding cyclopropyl ester in good to excellent yields (entries 4–6). The reaction conditions were shown to be compatible with ester, chloride and bromide groups (entries 4–6, 9–10). The latter gave access to a cyclopropane product that is easy to functionalize further using transition-metal-catalyzed cross-coupling reactions. Benzaldehydes containing strong electron-donating groups, such as 3- and 4-anisaldehyde, 4-dimethylaminobenzaldehyde and piperonal, also led to the desired cyclopropane product in good to excellent yields (entries 7, 11–12, 14).

A nitro group was also well tolerated in this one-pot process (entry 13). Furthermore, cyclopropanes derived from 3-furaldehyde and 2-thiophenecarboxaldehyde were obtained in 71% and 77% yields respectively (entries 15–16). *N*-Protected pyrrole and indole aldehydes also proceeded efficiently (entries 17 and 18). Finally, even a strongly coordinating substrate such as 2-pyridylcarboxaldehyde was converted in 61% yield (entry 19).

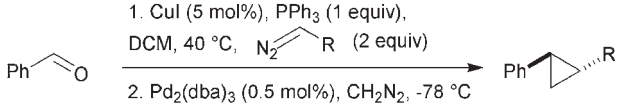
As both the olefination and the cyclopropanation steps are highly chemoselective, cyclopropane **19** was produced from aldehyde **18** in 52% yield without reaction to either the ketone or to the ester moiety [eqn (1)].



(1)

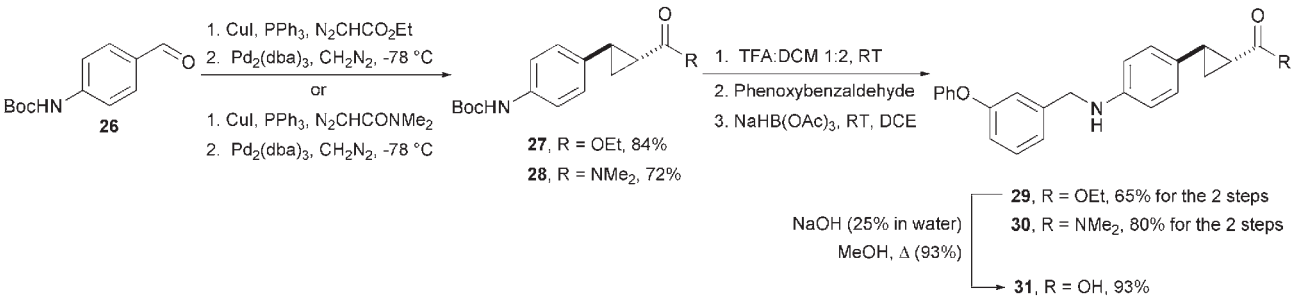
The copper-catalyzed olefination reaction is equally effective with other diazo reagents.[4b] A variety of *trans*-cyclopropyl products are indeed accessible from benzaldehyde using the one-pot olefination–cyclopropanation process (Table 2). Both methyl and *tert*-butyl diazoacetate were used to produce the corresponding cyclopropyl ester in good yields (entries 1–2). Less reactive diazo derivatives, including diazoacetophenone (entry 3), diazoacetamides (entries 4–5) and dimethyl (diazomethyl)phosphonate (entry 6) were also efficient olefination reagents and were used in the one-pot process to produce the corresponding cyclopropane derivative in good yields. The use of such functionalized diazo reagents (compared to ethyl diazoacetate) allowed more straightforward syntheses while limiting the number of functional group manipulations.

Table 2 Multicatalytic one-pot olefination-cyclopropanation process



Entry	R	Product	Yield (%)[a]
1	CO_2Me	**20**	81
2[b]	$CO_2{}^tBu$	**21**	74
3[b]	COPh	**22**	73
4[b]	$CONMe_2$	**23**	82
5[c]	CON(OMe)Me	**24**	88
6[b]	$PO(OMe)_2$	**25**	69

[a] Isolated yield after column chromatography. [b] Reaction was performed in toluene at 80 °C for the first step and with 1 mol% of $Pd(OAc)_2$ as catalyst for the second step. [c] Reaction was performed in DCE at 80 °C for the first step and with 0.5 mol% $Pd_2(dba)_3$ as catalyst for the second step.



Scheme 3 Synthesis of the GPR40 receptor agonists.

Indeed such an approach was used in the total synthesis of cyclopropyl alkanoic derivatives **30** and **31** developed as human GPR40 receptor agonists (active at low nanomolar concentrations).[10] Cyclopropyl ester **27** was produced from 4-(*tert*-butoxycarbonylamino)benzaldehyde **26** in 84% yield using our novel one-pot process (Scheme 3). Cleavage of the Boc group, followed by reductive amination and saponification under standard reaction conditions, provided the GPR40 receptor agonist **31** in 51% overall yield. It is also possible to prepare the unprotected cyclopropyl ester **27** from the (4-nitrophenyl)cyclopropyl ester **11** (Table 1, entry 13), by reduction of the nitro group under pressure of hydrogen in presence of PtO_2 (49% for two steps). Finally cyclopropyl amide **30** was also synthesized, as carboxamide derivatives were found to be equally active as GPR40 agonists. The same synthetic strategy was used and cyclopropyl amide **30** was produced in 58% overall yield from aldehyde **26** in 3 steps.

In conclusion, we have developed the first multicatalytic approach for the synthesis of *trans*-cyclopropyl compounds from aldehydes. The copper-catalyzed olefination reaction was directly followed by the palladium-catalyzed cyclopropanation reaction, which was clearly not affected by the olefination residual by-products and catalyst still present in the reaction mixture. The one-pot process produced a variety of cyclopropyl derivatives in good to excellent yields, while the isolation of the alkene intermediate was not required. The one-pot methodology allows the formation of three new C–C bonds and was applied to the synthesis of GPR40 small molecule agonists.

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