Oxidative Coupling

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Autoxidative Carbon–Carbon Bond Formation from Carbon–Hydrogen Bonds**

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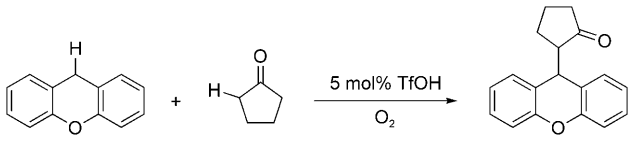
Cross-coupling reactions are of paramount importance in the synthesis of larger organic molecules. Many successful methods have been developed, but most of them rely on special activating or leaving groups which create unwanted waste and extra synthetic steps for their introduction. The principle of "green chemistry" raises awareness for more environmentally friendly reactions that should avoid unnecessary waste, cost, and energy.[1] In this context, the activation of carbon–hydrogen bonds for coupling reactions is a promising strategy, as C–H bonds are ubiquitous in organic molecules and thus the introduction of activating groups would no longer be necessary.[2] Under oxidative conditions, two C–H bonds can be coupled to form a new C–C bond; hydrogen acts as a "leaving group" and in the best case water as the only waste product.[3] These oxidative coupling reactions can be performed catalytically using only simple metal salts or organic redox-active molecules for the activation of C–H bonds. However, often synthetic oxidants, harsh conditions, and expensive reagents are required, thus diminishing the overall sustainability of the process. Here, we present an oxidative cross-coupling reaction for the formation of C–C bonds from two C–H bonds, requiring neither metal catalyst nor synthetic oxidant, only catalytic amounts of a simple acid and elemental oxygen.

During a study of metal-catalyzed aerobic oxidative coupling reactions under acidic conditions, we performed a control experiment without the metal catalyst, which unexpectedly resulted in similar yields of the desired product. With xanthene (**1**) as the electrophilic substrate and ketones like cyclopentanone (**2**), we could obtain high yields of the coupling product **3a** using only catalytic amounts of trifluoromethanesulfonic acid (TfOH) and elemental oxygen at elevated pressure (Scheme 1).

This reaction is remarkable, as it does not involve any redox-active catalyst or reagent commonly used for C–H bond activation and thus holds great potential for the design of sustainable syntheses with simple and cheap reagents and low levels of waste. To develop a general coupling method, we investigated this reaction in more detail (Table 1). The coupling could be performed under a high partial pressure of oxygen (up to 8 bar with a mixture of 10% O_2 and 90% N_2) but also at ambient pressure with only a slightly reduced reaction rate by simply using a balloon filled with pure oxygen or even air (Table 1, entries 1–3). Performing the reaction under an atmosphere of argon resulted in only traces of the desired product **3a** (see the Supporting Information for further details on the optimization study). To simplify the procedure, we choose pure oxygen at ambient pressure as the standard condition in further experiments. A catalytic amount of a strong acid is needed: sulfonic acids (Table 1, entries 2, 7, and 8) and mineral acids are effective, whereas a weaker acid



1 2 3a

Scheme 1. Metal-free, acid-catalyzed aerobic coupling of xanthene (**1**) and cyclopentanone (**2**).

Table 1: Optimization of reaction conditions for the synthesis of **3a** by the aerobic coupling of xanthene (**1**) and cyclopentanone (**2**).[a]

Entry	O_2 [bar]	Acid (mol%)	Solvent	Yield [%][b]
1	8[c]	TfOH (5)	–	76
2	1	TfOH (5)	–	64
3	0.2[d]	TfOH (5)	–	59
4	1	–	–	0
5	1	AcOH (5)	–	0
6	1	CF_3CO_2H (5)	–	20
7	1	CH_3SO_3H (5)	–	80
8	1	*p*TsOH (5)	–	76
9	1	CH_3SO_3H (5)	CH_2Cl_2	69
10	1	CH_3SO_3H (5)	hexane	63
11	1	CH_3SO_3H (5)	EtOAc	65
12	1	CH_3SO_3H (7)	–	85
13	1	CH_3SO_3H (10)	–	76
14	1	CH_3SO_3H (20)	–	70
15[e]	1	CH_3SO_3H (7)	–	94 (90)[f]

[a] Reaction conditions: **1** (0.5 mmol), **2** (2.5 mmol), and acid were stirred under an atmosphere of oxygen at room temperature for 1 day. [b] Yields were determined by GC analysis of the crude reaction mixture unless indicated otherwise. [c] 80 bar of 10% O_2 in N_2. [d] Air rather than oxygen. [e] 18 h, 40°C. [f] Yield of isolated product. pTsOH = *p*-toluene sulfonic acid.

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like trifluoroacetic acid gave much lower reaction rates and acetic acid gave no reaction at all (Table 1, entries 5 and 6). Without acid, no reaction took place (Table 1, entry 4). Among the sulfonic acids, methanesulfonic acid and *p*-toluene sulfonic acid worked best and gave comparable results (Table 1, entries 7 and 8). Trifluoromethanesulfonic acid is considerably more expensive than the other sulfonic acids and in a few cases gave irreproducible results. We also tested the polymeric sulfonic acid Nafion as a catalyst; it gave high conversion but a significantly reduced reaction rate. We chose the liquid methanesulfonic acid for further studies because it is easy to handle and gave the highest yields.

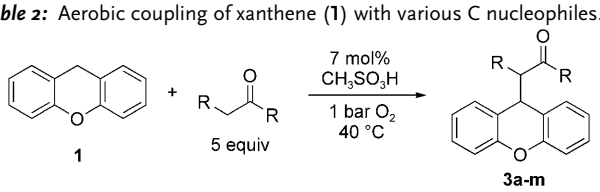
The coupling reaction can be performed in solvents: the best results were obtained with dichloromethane, ethyl acetate, and hexane (Table 1, entries 9–11). However, the highest yields were obtained when the reaction was performed without any solvent, provided the reaction mixture was homogeneous (Table 1, entry 7). To ensure that xanthene was completely in solution, we generally used five equivalents of liquid ketone, but lower amounts could also be used. A slightly higher acid loading (7 mol%) proved to be optimal, while higher loadings resulted in decreased yields (Table 1, entries 12–14). The reaction proceeds well at ambient temperature, but a slightly elevated temperature of 40 °C improves the rate and gives optimal results (Table 1, entry 15). At higher temperatures the yields dropped again and the increased formation of aldol condensation products from cyclopentanone was observed.

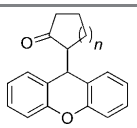
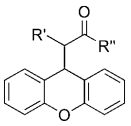
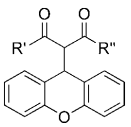
Using these optimized conditions, we tested a variety of other carbon nucleophiles in the reaction with xanthene (Table 2). In many cases, full conversion and high yields of isolated products were achieved after reaction times of up to two days. Xanthene (**1**) could be coupled with cyclic as well as open-chain ketones, giving yields of up to 95% (Table 2, entries 1–9). In some cases the reaction stopped before full conversion was reached, but most of the leftover xanthene could be recovered. (Table 2, entries 5 and 7). Further additions of acid or different amounts of acetone did not "restart" the reaction or change the yield.

In a few cases it was beneficial to run the reaction at an elevated partial pressure of oxygen to increase the yield. For example, the coupling product with cyclooctanone, **3d**, was formed in 71% yield at 6 bar (Table 2, entry 4) compared with 50% yield at ambient pressure. Similar trends were observed for reactions with β-keto esters and 1,3-diesters as nucleophiles; usually high yields were achieved only at higher pressure (Table 2, entries 10–13). In a few cases, the use of triflic acid was beneficial (Table 2, entries 12 and 13). Also, in these cases, a small amount of solvent was added to achieve a homogeneous solution.

In previous studies of oxidative coupling reactions xanthene had been employed. In these studies an Fe^{III} catalyst together with *tert*-butyl peroxide,[4] stoichiometric amounts of the quinone DDQ,[5] or equimolar amounts of a Mn^{III} compound at high temperature were used to synthesize products like **3e** and **3j**–**m**.[6] Substituted xanthenes like **3e** and **3g** have recently been synthesized via arynes.[7] The present method offers an alternative with fewer steps, cheaper reagents, and less waste.

Table 2: Aerobic coupling of xanthene (**1**) with various C nucleophiles.[a]



Entry	Product	*t* [h]	Yield [%][b]
			
1	**3a** $n=1$	18	90
2	**3b** $n=2$	36	94
3	**3c** $n=3$	64	81[c]
4	**3d** $n=4$	64	71[c]
			
5	**3e** R′ = H, R″ = Me	15	34
6	**3f** R′ = Me, R″ = Et	15	68
7	**3g** R′ = H, R″ = Ph	24	49
8	**3h** R′ = Ph, R″ = Me	5	95
9	**3i** R′ = Ph, R″ = nBu	8	93
			
10	**3j** R′ = Me, R″ = OEt	64	85[c]
11	**3k** R′ = Ph, R″ = OEt	96	80[d]
12	**3l** R′, R″ = OMe	128	42[c,e]
13	**3m** R′, R″ = OEt	128	39[c,e]

[a] Reactions were conducted at ambient pressure and 40 °C, unless stated otherwise. [b] Yields of isolated products. [c] Reaction at 6 bar partial pressure of O_2 and room temperature. [d] 2.5 equiv nucleophile. [e] CH_2Cl_2 as solvent and 7 mol% TfOH.

Diphenylmethanes did not react under these conditions, but acridanes **4** could be coupled with ketones (Figure 1). As seen for products **3e** and **3g**, the reactions did not go to completion but did not otherwise lead to side products. The products were isolated with yields around 40% when oxygen was used at ambient pressure (**6b**,**d**), while higher yields up to 77% were achieved at elevated oxygen pressure (**6a**,**c**,**e**). Only tertiary N-substituted acridanes could be employed as substrates; however, acridanes **6b** and **6e** should be deprotected easily to the secondary amines. *N*-phenyltetrahydroisoquinoline (**5**) could also be used successfully in the coupling with ketones, provided elevated oxygen pressure was used.[8] The products **7** and **8** were prepared in moderate yields, but leftover starting material could be recovered.

Product **6c** had been synthesized before from an acridinium salt and a preformed enamine.[9] Product **7** had been synthesized previously by oxidative copper catalysis using the corresponding silyl enolate as the ketone equivalent,[10] product **8** by metal catalysis at elevated temperature[11] or with an amino acid co-catalyst and a peroxide oxidant.[12] The

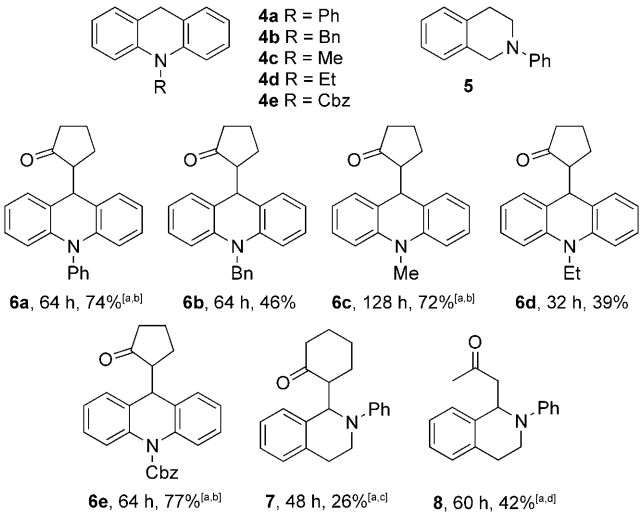
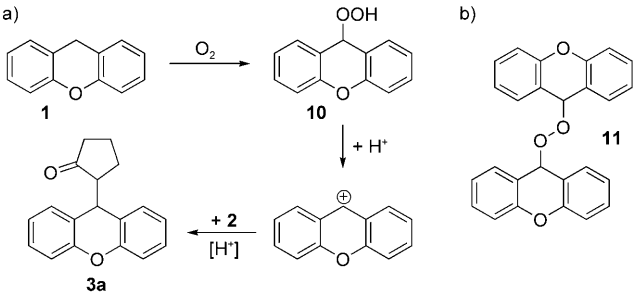


Figure 1. Products from the aerobic coupling of acridanes **4** and tetrahydroisoquinoline **5** with ketones. The reactions were performed as described in Table 2. [a] Reaction at 6 bar partial pressure of O_2 and room temperature. [b] Solvent: CH_2Cl_2. [c] Solvent: MeOH. [d] 7 mol% triflic acid. Cbz = benzyloxycarbonyl.

current method is clearly an improvement as the ketones can be used directly without a metal catalyst.

Initially, we could not rule out that impurities of transition-metal salts catalyze the reaction. Analysis of the reaction mixture leading to the successful synthesis of **3a** by atomic adsorption spectroscopy did not reveal any common redox-active transition metals like V, Mn, Fe, Cu, Ru, or Pd above the detection limit of 0.5 ppm. Also, performing the reaction in the presence of small amounts (1 mol%) of various metal salts resulted at best in unchanged rates and product yields, whereas Cu^{II} and Fe^{II} salts, likely impurities and known redox catalysts, actually inhibited the reaction (see the Supporting Information). Accordingly, we believe the reaction to proceed without the involvement of metal catalysts.

A potential mechanistic rationale involves autoxidative formation of a xanthene hydroperoxide **10**, which would react in an acid-catalyzed S_N1 type reaction with nucleophiles like ketone **2** to form product **3a** and hydrogen peroxide (Scheme 2a). The oxidation of **1** to the hydroperoxide **10** could proceed by a radical pathway without the involvement of a metal catalyst. Such autoxidation reactions are well known for many organic compounds in the presence of oxygen,[13] also, for example, for compound **5**.[14] Hydroperoxides are not commonly used as electrophiles; instead they are known to undergo acid-catalyzed rearrangement reactions as in the synthesis of phenol from cumene hydroperoxide.[15] However, peroxides like **10** and **11** (Scheme 2b) are known to react by acid-catalyzed C–O bond cleavage with carbon nucleophiles.[16] We could successfully convert hydroperoxide **10** and cyclopentanone to **3a** under our reaction conditions without added oxygen. Similarly, other peroxides have been employed as alkylating agents mediated by Lewis acids.[17]

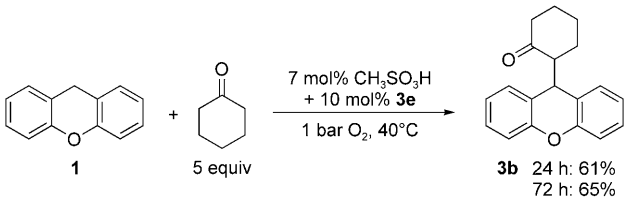


Scheme 2. a) Potential mechanism for the autoxidative coupling of xanthene (**1**) and cyclopentanone (**2**) via hydroperoxide **10**. b) Structure of the isolated side product **11**.

In agreement with this mechanistic proposal, the addition of catalytic amounts of a radical inhibitor (5 mol% 2,4,6-tris-*tert*-butylphenol) completely blocked the reaction. We found evidence for the formation of hydrogen peroxide in some cases: addition of MnO_2 at the end of a reaction resulted in gas evolution, indicating catalytic decomposition. Since MnO_2 was shown not to inhibit the reaction, its catalytic ability offers an interesting improvement: it could be used to continuously decompose any hydrogen peroxide formed to oxygen, which can again enter the reaction, and water, which then constitutes the final, truly environmentally benign waste product.

We could also isolate xanthene peroxide **11** (Scheme 2b) as a side product of a reaction with trifluoroacetic acid as the catalyst (Table 1, entry 6). This is strong support for the occurrence of a hydroperoxide, as **11** likely forms from reaction of hydroperoxide **10** by acid catalysis.[16] Strangely, the addition of a radical initiator did not accelerate the reaction. More detailed studies are needed to better understand the mechanism of this reaction.

In preliminary experiments we have observed that tertiary C–H bonds in 9-methyl-substituted xanthenes are very unreactive under our reaction conditions. Also, the addition of substoichiometric amounts of product **3e** to a reaction of xanthene and cyclohexanone considerably slowed down the reaction (Scheme 3).



Scheme 3. The rate of the formation of **3b** is suppressed by the addition of **3e**.

These results could indicate why 1) the reaction products bearing tertiary C–H groups are stable under the reaction conditions and do not undergo a second coupling step or other oxidative degradations and 2) why **3e** is only formed in low yields. The C–H bond cleavage in the products might be hindered for steric reasons, as has been observed for 9-

phenylxanthene.[18] Product **3e** might suppress the reaction rate because it acts as an antioxidant by formation of highly stabilized radicals, slowing down and finally stopping the autoxidation.[19]

The proposed reaction mechanism presents a possibility for the further development of "green" oxidative coupling reactions using oxygen, drawing on the rich experience in radical chemistry and peroxide formation.[13b] Substrates not as easily autoxidizable as xanthene could be employed at higher temperatures, under irradiation with light or by using radical initiators or singlet oxygen, for example. Thereby, a wide range of organic compounds bearing C–H bonds would be accessible to autoxidative coupling reactions using only oxygen, an acid catalyst, and maybe an initiator. One possible difficulty may be the issue of acid-catalyzed O–O versus C–O bond cleavage of the hydroperoxides, but the appropriate choice of acid can steer the reaction course towards the desired product.[17]

In summary, we have developed an aerobic oxidative coupling method for activated benzylic CH_2 groups like that in xanthene with ketones and 1,3-dicarbonyl compounds; the reaction proceeds smoothly under mild conditions without a metal reagent and requires simply cheap methane sulfonic acid and oxygen. The reaction fulfills several criteria of "green" chemistry:[1] 1) It does not require intensive heating, a solvent, or extractive workup, 2) it is catalytic and uses a cheap acid, 3) it is very atom-economic as two hydrogen atoms serve as "leaving groups", and 4) it produces only hydrogen peroxide as the waste product, which can be decomposed to water in situ. Xanthene and acridane derivatives are pharmaceutically active compounds and are used as dyes and fluorescent materials and chiroptical molecular switches; they also occur in natural products.[7,20] Accordingly, we anticipate further elaborations of this autoxidative coupling principle and applications towards the synthesis of complex products.

Experimental Section

Representative procedure: Xanthene (**1**) (91 mg, 0.5 mmol), cyclopentanone (**2**) (0.22 mL; 2.5 mmol) and methanesulfonic acid (2.3 μL, 7 mol%) were mixed in a glass vial or round-bottom flask equipped with a magnetic stirring bar. The vial was flushed with oxygen and then connected to a balloon filled with oxygen. After rapid stirring at 40 °C for 10–18 h, the reaction mixture was purified directly by column chromatography (silica gel, toluene) without further workup, giving the product **3a** as colorless solid (119 mg, 90% yield). Reactions at high pressure were performed with 10% oxygen in nitrogen for reasons of safety, as most flammable organic compounds have a limiting oxygen concentration around 10%.

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