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Catalytic cross deoxygenative and dehydrogenative coupling of aldehydes and alkenes: a redox-neutral process to produce skipped dienes†
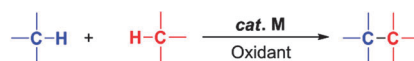
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A novel catalytic cross deoxygenative and dehydrogenative coupling reaction of aldehydes and alkenes was established *via* a cooperative catalysis approach. This transformation provided an efficient and atom-economic protocol for the synthesis of 1,4-skipped dienes from aldehydes and simple alkenes under oxidant-free reaction conditions.
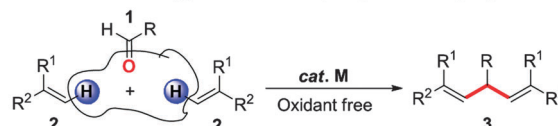
Transition-metal-catalyzed cross-dehydrogenative coupling (CDC) of R^1-H and R^2-H to construct a C–C bond, which avoids pre-functionalization of easily available chemicals while improving the atom economy and step economy, has received significant interest over the last ten years.[1] These protocols typically require the use of stoichiometric amounts of external oxidants to achieve the catalytic turnover, thus resulting in the generation of undesired waste, especially when metal salts are used as external oxidants. One of the most attractive strategies for overcoming this problem is developing a redox economy procedure, in which the external oxidant is not required and the redox process is furnished *via* exchange of oxidation states between reactants.[2] For the success of such a catalysis, a functional group contained in the reactants acting as an internal oxidant is a prerequisite. Consistent with this concept, some elegant external-oxidant-free CDC reactions have been explored,[3] but most of the reported reactions were established with the N–O bond as an oxidative functional group, which significantly limited the applications and the appeal of this strategy for establishing a powerful CDC reaction.[4] The C=O bond is another functional group with a high oxidation state and frequently exists in many organic molecules, which has proved to be a good oxidative moiety in various reactions such as Meerwein–Ponndorf–Verley reduction[5] and Oppenauer oxidation.[6] Inspired by these facts, we envisaged that the C=O bond could be utilized as an internal oxidative group for establishing an efficient redox-neutral CDC reaction.

Aldehydes are considered important carbon sources because of their general inexpensiveness, ready availability and stability, which have been widely used as coupling partners in synthetic organic chemistry for construction of the C–C bond. Among the various coupling reactions with aldehydes, the deoxygenation of aldehydes with organometallic reagents, such as the Wittig reagent,[7] Tebbe's reagent,[8] Grubbs' titanacycle,[9] the McMurry reagent,[10] organotitanium reagents and di-organolithium reagents developed by Xi,[11] are well known for forming the C=C and C–C bond. The importance of these reactions in organic synthesis has been illustrated by the industrial-scale synthesis of alkenes with Wittig reaction.[12] In spite of high efficiency, these methods suffer from high cost and moisture sensitivity of the required organo-metallic reagents as well as the generation of significant amounts of metal salts, which resulted from deoxygenation of aldehydes with the lower value metal. We envisioned that the stoichiometric metal salts could be avoided by using hydrocarbons as a coupling partner if the deoxygenation of aldehydes and dehydrogenation of hydrocarbons are compatible. Herein, we describe a new method for the catalytic cross deoxygenative and dehydrogenative coupling of aldehydes and alkenes that takes advantage of a cooperative catalysis approach, in which the C=O bond of aldehydes acts as a formal internal oxidant (Scheme 1). This study provides the first report on the direct coupling reaction of aldehydes and simple alkenes *via* C–H functionalization, leading to a new protocol for the synthesis of skipped dienes.[13]

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Scheme 1 New strategies for cross deoxygenative and dehydrogenative coupling reactions.
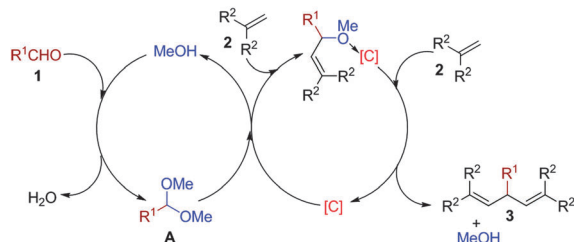
Scheme 2 Proposed cooperative catalytic system.

In connection with our interest in cooperative catalysis,[14] we envisioned that a cooperative catalysis consisting of alcohol, Lewis acid and Brønsted acid may accomplish this type of coupling reaction. Our cooperative catalysis protocol is shown in Scheme 2, which arose from the fact that dimethyl acetal **A** could be formed when aldehydes **1** are exposed to a catalytic amount of methanol in the presence of Lewis acids or Brønsted acids,[15] and a Prins-type reaction[16] of **A** and alkene **2** might occur and enable the generation of allylic ether in the catalysis of Lewis acids or Brønsted acids. Finally, the allylic ether could be further reacted with alkene **2** to produce skipped diene **3** under the same reaction conditions. To test this hypothesis, we began our study on synthesis of skipped diene by examining the reaction of benzaldehyde **1a** with 1,1-diphenylethylene **2a** in the presence of a catalytic amount of methanol, Brønsted acid or Lewis acid. To our delight, the application of TsOH·H$_2$O as the Brønsted acid at 80 °C in the presence of 25 mol% of methanol resulted in the formation of the desire product **3aa** in 67% yield (Table 1, entry 1). It is worth noting that **3aa** was the only isomer detected, indicating a highly stereoselective reaction. The transformation efficiency was dramatically improved and product **3aa** was obtained in 88% yield (Table 1, entry 2) when a catalytic amount of Fe(OTs)$_3$ was introduced to the catalytic system. An extensive Lewis acid screening showed that other typical Lewis acids such as AlCl$_3$, ZnCl$_2$ and Cu(OAc)$_2$ could

also catalyze the reaction, but none of these catalysts improved the yield (Table 1, entries 3–7). Subsequently, solvent screening was conducted.

Both non-polar solvents such as toluene, xylene, and mesitylene and polar solvents such as dichloromethane and 1,2-dichloroethane could result in moderate to excellent yields (Table 1, entries 2 and 8–11). However, the product **3aa** was not detected when DMF and DMSO served as solvents (see ESI†). Trace amount of product **3aa** was detected when the reaction was conducted in the absence of a Brønsted acid or methanol, demonstrating the importance of these two catalysts. Furthermore, the control reactions demonstrated that the diene **3aa** was not formed in the absence of a Brønsted acid or Lewis acid. These results declared that methanol and Brønsted acid were essential for promoting the reactivity of the transformation.

Encouraged by the optimization results, we started to investigate the scope of this protocol (Table 2). The optimized reaction conditions were compatible to a broad range of aromatic aldehydes. Both electron-withdrawing (Table 2, entries 2–10) and electron-donating (Table 2, entries 11 and 12) groups on the aromatic rings were compatible under the reaction conditions. Many valuable functional groups such as chloro, bromo, nitro and methoxy were well tolerated to give the corresponding dienes in good to excellent yields. These functional groups provided a good opportunity for further transformations to obtain the additional functionalization compounds. The structure of the skipped diene was confirmed by X-ray crystallographic analysis of the derivative **3da**.[17] In addition to the substituted phenyl aldehydes, cinnamyl aldehyde was also subjected to the present reaction successfully and the product **3ma** was obtained in 45% yield (Table 2, entry 13). In addition to the aryl aldehydes, alkyl aldehydes also participated in this reaction. For example, although the reaction of 3-phenylpropanal gave the corresponding product **3na** in lower yield,[18] the reaction with paraformaldehyde proceeded smoothly to give the corresponding skipped diene **3oa** in good yield (Table 2, entries 14 and 15).

Table 1 Optimization of the reaction conditions[a]

| Entry	Lewis acid	Brønsted acid	Solvent	Yield[b] (%)
1	—	TsOH·H$_2$O	PhCH$_3$	72(67)
2	Fe(OTs)$_3$	TsOH·H$_2$O	PhCH$_3$	91(88)
3	FeCl$_3$	TsOH·H$_2$O	PhCH$_3$	37
4	ZnCl$_2$	TsOH·H$_2$O	PhCH$_3$	46
5	AlCl$_3$	TsOH·H$_2$O	PhCH$_3$	4
6	Ni(OAc)$_2$	TsOH·H$_2$O	PhCH$_3$	28
7	Cu(OAc)$_2$	TsOH·H$_2$O	PhCH$_3$	21
8	Fe(OTs)$_3$	TsOH·H$_2$O	DCM	48
9	Fe(OTs)$_3$	TsOH·H$_2$O	Xylene	62
10	Fe(OTs)$_3$	TsOH·H$_2$O	Mesitylene	48
11	Fe(OTs)$_3$	TsOH·H$_2$O	DCE	59
12	Fe(OTs)$_3$	—	PhCH$_3$	11
13	Fe(OTs)$_3$	TsOH·H$_2$O	PhCH$_3$	17[c]
14	—	—	PhCH$_3$	NR

[a] Reaction conditions: benzaldehyde **1a** (0.4 mmol, 1.0 equiv.), 1,1-diphenylethylene **2a** (1.2 mmol, 3.0 equiv.), Lewis acid (0.02 mmol, 5 mol%), Brønsted acid (0.08 mmol, 20 mol%), MeOH (0.1 mmol, 25 mol%), solvent (2.0 mL), 80 °C, 12 h, under an argon atmosphere. [b] Yield determined by GC analysis using *n*-tetradecane as an internal standard (isolated yield in parentheses). [c] Without MeOH.

Table 2 Substrate scope of aldehydes[a]

Entry	R	Yield[b] (%)
1	C$_6$H$_5$	**3aa**, 88
2	4-FC$_6$H$_4$	**3ba**, 89
3	4-ClC$_6$H$_4$	**3ca**, 87
4	3-ClC$_6$H$_4$	**3da**, 95
5	2-ClC$_6$H$_4$	**3ea**, 97
6	4-BrC$_6$H$_4$	**3fa**, 84
7	2-BrC$_6$H$_4$	**3ga**, 73
8	4-NO$_2$C$_6$H$_4$	**3ha**, 98
9	2,3-Cl$_2$C$_6$H$_3$	**3ia**, 93
10	2,6-Cl$_2$C$_6$H$_3$	**3ja**, 73
11	4-MeC$_6$H$_4$	**3ka**, 70
12	3-MeOC$_6$H$_4$	**3la**, 91
13	(*E*)-PhCH=CH	**3ma**, 45
14	PhCH$_2$CH$_2$	**3na**, 19
15	H	**3oa**, 64[c]

[a] Reaction conditions: aldehydes **1** (0.4 mmol, 1.0 equiv.), 1,1-diphenylethylene **2a** (1.2 mmol, 3.0 equiv.), Fe(OTs)$_3$ (0.02 mmol, 5 mol%), TsOH·H$_2$O (0.08 mmol, 20 mol%), MeOH (0.1 mmol, 25 mol%), PhCH$_3$ (2.0 mL), 80 °C, 12 h, under an argon atmosphere. [b] Isolated yield. [c] Paraformaldehyde **1o** (12.0 mg, 0.4 mmol).

Table 3 Substrate scope of alkenes[a]
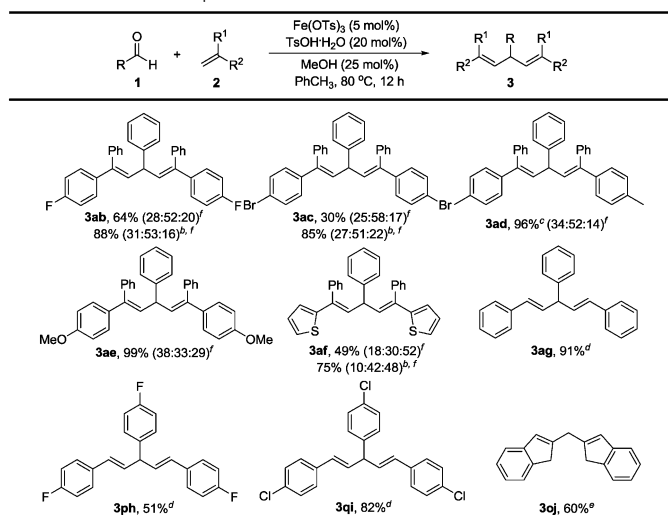
[a] Reaction conditions: aldehydes **1** (0.4 mmol, 1.0 equiv.), alkenes **2** (1.0 mmol, 2.5 equiv.), Fe(OTs)$_3$ (0.02 mmol, 5 mol%), TsOH·H$_2$O (0.08 mmol, 20 mol%), MeOH (0.1 mmol, 25 mol%), PhCH$_3$ (2.0 mL), 80 °C, 12 h, under an argon atmosphere, isolated yield. [b] Benzaldehyde dimethyl acetal (0.4 mmol, 1.0 equiv.), alkenes **2** (1.2 mmol, 3.0 equiv.), NH$_2$SO$_3$H (0.08 mmol, 20 mol%), 100 °C. [c] 1-Methyl-4-(1-phenylvinyl)-benzene **2d** (1.2 mmol, 3.0 equiv.). [d] Alkenes **2** (2.4 mmol, 6.0 equiv.), MeOH (1.0 mmol, 2.5 equiv.), 120 °C. [e] Without MeOH, 70 °C. [f] The ratio of E/E : E/Z : Z/Z determined by GC analysis or ^{1}H NMR.

After investigation of the scope of substitution of the aldehydes, we next explored the scope for the alkene partners (Table 3). Both electron-donating and electron-withdrawing substituent 1,1-diaryl alkenes were shown to couple with benzaldehyde to give corresponding products **3ab–3ae** in moderate to excellent yields (30–99% yield). The heteroaryl substituent alkene **2f** also provided adduct **3af** in 49% yield.

When benzaldehyde dimethyl acetal **A** was used as a coupling partner instead of benzaldehyde, Fe(OTs)$_3$ as a catalyst and NH$_2$SO$_3$H as an additive at 100 °C for 12 h, the yields of 1,4-dienes **3ab**, **3ac** and **3af** could be dramatically increased from 64%, 30% and 49% to 88%, 85% and 75%, respectively. These results suggested that acetal is most likely involved in the present reaction. In addition to 1,1-diphenylethylene, styrene could react with benzaldehyde to afford the desired product **3ag** in 91% yield in the presence of slightly modified reaction conditions. Furthermore, different substituted styrenes with arylaldehydes, such as 4-fluoro and 4-chloro, gave the corresponding dienes in 51% and 82% yields (**3ph** and **3qi**).[19] We were delighted to find that 1H-indene could also react with paraformaldehyde successfully and 60% yield of skipped diene **3oj** was attained.[17]

In summary, we have successfully developed a novel catalytic cross deoxygenative and dehydrogenative coupling of aldehydes and simple alkenes using a simple cooperative catalytic system consisting of methanol, TsOH·H$_2$O and Fe(OTs)$_3$. This protocol represents a user-friendly and atom-economic reaction for preparing 1,4-skipped dienes from commercial and simple substrates under redox-neutral reaction conditions. This oxidant-free cross-coupling reaction together with the novel cooperative

catalytic system developed here holds significant promise for synthetic endeavours, which should pave the way for establishing some new and efficient oxidant-free CDC reactions. Development of other efficient and selective C–C bond forming reactions established using the present strategy is in progress.

Notes and references

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17 CCDC 946280 (**3da**) and 946281 (**3oj**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/data_request/cif.
18 Penta-1,3-diene-1,1,5-triyltribenzene was obtained in 57% yield, see the ESI† for details.
19 The unsymmetric 1,4-skipped diene was obtained with a lower yield in the crossover reaction with ethene-1,1-diyldibenzene and 1-methoxy-4-(1-phenylvinyl)benzene as alkenes. See the ESI† for details.