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Lewis- and Brønsted-acid cooperative catalytic radical coupling of aldehydes and azodicarboxylate†

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An efficient radical coupling reaction of aldehydes and azodicarboxylate was developed by using the strategy of merging Lewis- and Brønsted- acid catalysis.

The formation of the C–N bond is one of the most important transformations in organic synthesis that has wide applications for the synthesis of numerous natural and unnatural biologically active molecules.[1] As a result, tremendous efforts have been made to develop various C–N bond forming methods over the last few decades. One subclass of these efficient reactions using azodicarboxylates as electrophiles has generated a considerable amount of interest.[2–6] Although many types of reactions using azodicarboxylates have been extensively studied, the hydroacylation reaction with aldehydes has far less been investigated.[7–10] Some limitations still exist and need to be further addressed despite a few elegant reports of this kind of hydroacylation. Especially, the reactivity and scope of substrates need to be significantly improved. For examples, the reactions with aromatic aldehydes are very slow and generally complete in several days with low yields. Therefore, it is highly desired to develop an efficient and straightforward method with broad scope of the substrates and high yields for such reactions.[7–11] Cooperative catalysis has emerged as one of the most stimulating, dynamic and synthetically powerful areas in contemporary organic synthesis,[12] while Lewis acid catalysis and Brønsted acid catalysis represent two fundamental activation modes in organic synthesis. We envisaged that the merging of these two modes could provide new insights into designing and developing new reactions.

Modern transition-metal-catalysed reactions have been shown to be of indispensable value for organic synthesis.[8,9] Cobalt, as one of the "life" elements existing in many metalloenzymes, has received considerable attention from synthetic community. The development of cobalt-mediated radical reactions such as cyclization and polymerization *etc.* has attracted great interests.[13–21]

Inspired by these elegant cobalt-mediated radical works, we further reasoned that with the use of both an appropriate cobalt catalyst and Brønsted acid catalyst, an efficient radical coupling of aldehydes and azodicarboxylate with broad substrates scope might be realized. Here, we report that the merging of cobalt Lewis acid catalysis and Brønsted acid catalysis can efficiently promote the radical coupling of aldehydes and azodicarboxylates.

However, due to its low reactivity, 4-methoxybenzaldehyde has a limited application on this kind of reaction.[7–10] Therefore, we reasoned that this relative inert substrate could serve as a good starting point to test the feasibility of our hypothesis. To our delight, very simple and cheap catalysts can promote the reaction efficiently. The desired product can be obtained with 91% yield in the presence of 20 mol% of $CoCO_3$ and 5 mol% TFA (trifluoroacetic acid) (Table 1, entry 1). In sharp contrast, in the absence of either $CoCO_3$ or TFA, only very low conversion was observed. These results indicated that $CoCO_3$ and TFA worked cooperatively to generate the product (Table 1, entries 2 and 3). In the presence of TFA, two different cobalt catalysts were tested, as shown in Table 1, the desired hydroacylation product **2a** was obtained in 74% and 56% yield, respectively (Table 1, entries 2 and 3). However, poor yield was obtained when $Co(acac)_2$ was used as catalyst (Table 1, entry 4).

Next, we investigated the solvent effect. As shown in Table 1, when toluene or CH_3CN was used as the solvent, the desired product was obtained with 85% and 88% yield, respectively (Table 1, entries 5 and 6). However, complex mixture was observed when Et_2O or THF was used as the solvent (Table 1, entries 7 and 8). Poor yield was also obtained when methanol was used as the solvent (Table 1, entry 9).

We further optimized the catalyst loading. When we reduced the loading of $CoCO_3$ from 20 mol% to 10 mol%, there is no

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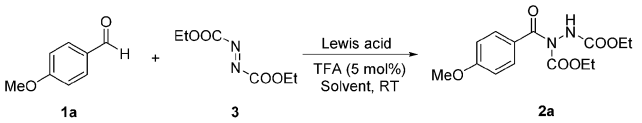
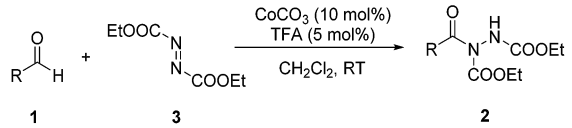
Table 1 Screening the reaction conditions[a]



Entry	Solvent	Lewis acid	Yield[b] (%)
1	CH_2Cl_2	$CoCO_3$	91
2	CH_2Cl_2	$Co(OAc)_2$	74
3	CH_2Cl_2	$CoCl_2$	56
4	CH_2Cl_2	$Co(acac)_2$	26
5	Toluene	$CoCO_3$	85
6	CH_3CN	$CoCO_3$	88
7	Et_2O	$CoCO_3$	Complex
8	THF	$CoCO_3$	Complex
9	MeOH	$CoCO_3$	<5
10[c]	CH_2Cl_2	$CoCO_3$	93
11[d]	CH_2Cl_2	$CoCO_3$	64
12[e]	CH_2Cl_2	$CoCO_3$	<10
13[f]	CH_2Cl_2	$CoCO_3$	<10
14[g]	CH_2Cl_2	$CoCO_3$	<10

[a] Unless otherwise noted, the reactions were carried out with **1a** (0.24 mmol, 32.6 mg), diethyl azodicarboxylate (34.8 mg, 0.2 mmol), Lewis acid (0.04 mmol, 20 mol%) and TFA (0.01 mmol, 5 mol%) in the indicated solvent (0.2 mL) for 12 h. [b] Isolated yield. [c] 10 mol% $CoCO_3$ was used. [d] 5 mol% $CoCO_3$ was used. [e] In the absence of $CoCO_3$. [f] 1 mol% TFA was used. [g] Without TFA.

Table 2 Substrates scope[a]



Entry	Aldehyde	R	Product	Yield[b] (%)
1	**1a**	4-$MeOC_6H_4$	**2a**	92
2	**1b**	4-FC_6H_4	**2b**	94
3	**1c**	3-$CH_3C_6H_4$	**2c**	92
4	**1d**	3-BrC_6H_4	**2d**	93
5	**1e**	2-$CH_3C_6H_4$	**2e**	80
6	**1f**	2-ClC_6H_4	**2f**	77
7	**1g**	C_6H_5	**2g**	94
8	**1h**	2-Methyl propyl	**2h**	96
9	**1i**	Isopropyl	**2i**	95
10	**1j**	Propyl	**2j**	96
11	**1k**	*tert*-Butyl	**2k**	94
12	**1l**	Cyclohexyl	**2l**	94
13	**1m**	$C_6H_5(CH_2)_2$	**2m**	96
14	**1n**	Propenyl	**2n**	95
15	**1o**	$C_6H_5CH(CH_3)$	**2o**	51
16	**1p**	$C_6H_5(CH)_2$	**2p**	52
17	**1q**	2-thienyl	**2q**	77

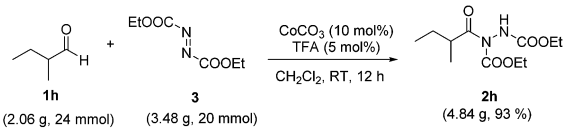
[a] Unless otherwise noted, the reactions were carried out with **1** (0.24 mmol), diethyl azodicarboxylate (34.8 mg, 0.2 mmol), $CoCO_3$ (2.4 mg, 0.02 mmol, 10 mol%) and TFA (0.01 mmol, 5 mol%) in CH_2Cl_2 (0.2 mL) for 12 h. [b] Isolated yield.

effect on the reaction (Table 1, entries 1 and 10). However, when the catalyst loading was further reduced, the yield of **2a** decreased dramatically. (Table 1, entry 11). Further optimization of the reaction conditions showed that DCM was the solvent of choice and $CoCO_3$ and TFA were the optimal catalysts. This new cooperative catalysis system showed powerful reactivity since the desired product was obtained with excellent yield only in 12 h while this compound was obtained only in low yield even after 96 h with all the previously reported procedures.[7–10]

Encouraged by these results, we next probed the scope of this hydroacylation reaction with a variety of aldehydes (Table 2). All reactions were carried out simply by mixing the reactants in a single operation at room temperature to afford the corresponding products **2a–q**. To our delight, various aliphatic and aromatic aldehydes could be well tolerated in our optimised reaction system. Different type of aliphatic aldehydes, regardless of steric effect, either linear or branched, gave the desired products in excellent yields (Table 2, entries 8 and 15). Cyclohexanecarbaldehyde is also an excellent partner for this reaction and the desired product was obtained in 94% yield (Table 2, entry 12). The aromatic aldehydes, bearing either electron withdrawing or donating groups in *para*-, *meta*-, and *ortho*-positions, were tolerated as well. Heteroaromatic aldehydes such as thienyl aldehyde could also be successfully employed to afford amide with excellent yield (Table 2, entries 1–7 and 17). The steric effect was observed when aldehydes **1e** and **1f** were used as substrates which resulted in lower yields (Table 2, entries 5 and 6). The application of cinnamaldehyde as a substrate in the title reaction was also successful albeit with lower yield (Table 2, entry 16).

Notably, this coupling reaction is also amenable to scale-up. When the reaction was carried out on a 24 mmol scale, the desired product was obtained in 93% yield. Therefore, this method is fast, easy to handle, and adaptable to large scale synthesis (Scheme 1).

Finally, the mechanism of this transformation was studied preliminarily. Under the optimal conditions, no desired product was obtained with using either catalytic amount (0.02 mmol, 10 mol%) but also stoichiometric amount (0.30 mmol, 1.5 equiv.) of TEMPO, which indicated that this transformation was likely to involve a radical intermediate (Scheme 2).[22] As shown in Fig. 1, electron paramagnetic resonance (EPR) experiments were then performed in the presence of a mixture of $CoCO_3$, **1h**, DEAD and TFA. A strong signal was clearly detected which revealed a free radical of nitrogen was formed. However, In the absence of either $CoCO_3$ or TFA, no signal was detected.[23–26]



Scheme 1 Example of scalable synthesis.

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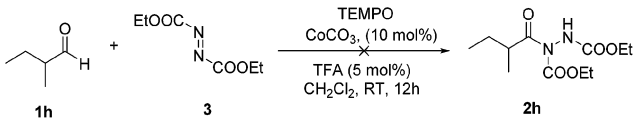


Scheme 2 Mechanism study.

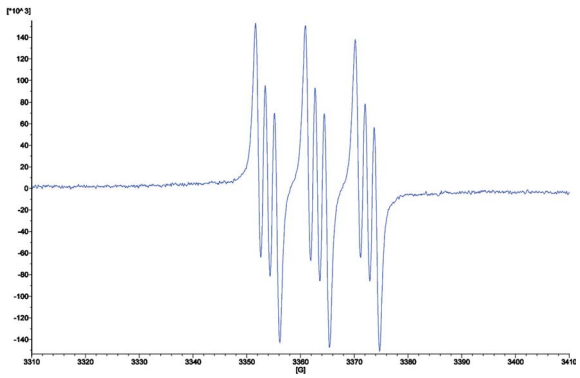
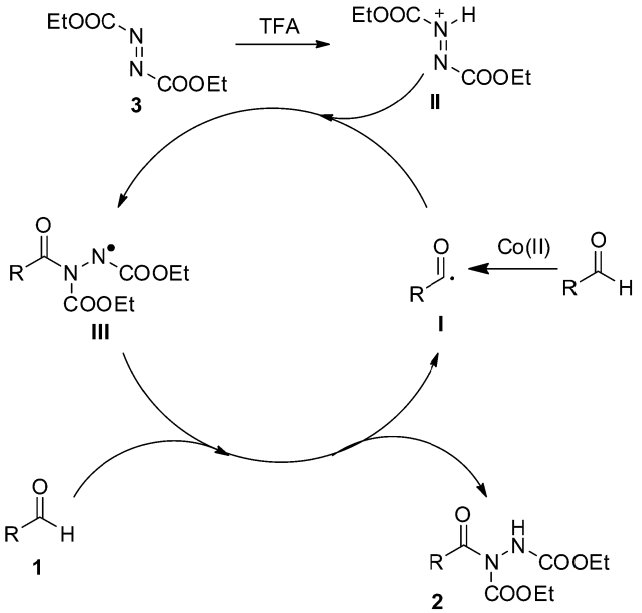


Fig. 1 EPR experiment in the presence of **1h**, diethyl azodicarboxylate, $CoCO_3$ and TFA in CH_2Cl_2 at room temperature.



Scheme 3 Proposed mechanism.

Based on these experimental results, we proposed a possible mechanism for the reaction. Initially, an acyl radical **I** is generated by cobalt catalyst, which then reacts with the Brønsted acid activated intermediate **II** to form radical **III**. Finally, intermediate **III** is trapped by aldehyde to give product **2** and regenerates acyl radical. In this transformation, radical **III** can be identified by EPR (Scheme 3).[27–29]

Conclusions

In conclusion, we have developed a new and efficient radical coupling reaction of aldehydes and azodicarboxylates employing the strategy of merging Lewis- and Brønsted- acid catalysis. This powerful reaction system afforded the desired products with broader substrates scope, in shorter reaction time, more efficiently.

Acknowledgements

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