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Highly Efficient Dehydrogenative Cross-Coupling of Aldehydes with Amines and Alcohols

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A common protocol for the synthesis of amides, esters and α-ketoesters via cross dehydrogenative coupling of aldehydes and amines/alcohols has been developed. The method is applicable to a wide variety of alcohols and amines as well as aliphatic and aromatic aldehydes. Also, the use of acetaldehyde for acetylation and ethyl glyoxalate to access 2-oxo-amino esters is presented for the first time.

Direct acyl C-H functionalization of aldehydes to access amides and esters represent an interesting and challenging strategy.[1] The C-H functionalization is also fascinating because of the fact that it circumvents the need of prefunctionalization and hence, has more step as well as atom economy.[2] However, the limiting factor behind their use is overcoming high bond energies of C-H bonds. In recent past this limitation has been addressed via employment of transition metal catalyst, which can facilitate the coupling of C-H of aldehydes with amines and alcohols.[3] Examples include CuI/$AgIO_3$ catalyzed oxidative amidation of aldehydes with primary amines,[4] utilization of $FeCl_3$/TBHP system[5] and $PdCl_2$/Xanthphos catalyzed synthesis of amides from amines and aldehydes.[6] The drawback of these protocols was the use of toxic and expensive metals, limited substrate scope and protection of amines as either amine hydrochloride or chloramines to prevent oxidation of amines. To deal with these impediments alternative strategies were explored, which avoided the use of metal catalysts. For example, Wan and co-workers developed a metal fee reaction of TBAI/TBHP catalyzed cross-coupling of aldehydes, however, it required use of preformed amides viz., *N,N*-disubstituted formamides and was limited to aromatic aldehydes/secondary amines.[7] Subsequently another method employing TBAI/TBHP as catalyst was developed using free amine, but, instead required the activation of aldehydes with N-hydroxy succinimde (NHS) and had broader substrate scope as it was applicable to primary amines as well as anilines.[8] Though all the methods presented some sort of improvements over the previous methods, but still a general method applicable to synthesis of amides as well as esters from aldehydes was lacking until recently, when a $Ni(cod)_2$/IPr catalyzed coupling of aldehdyes amines, anilines and alcohol for synthesis of esters and amides was reported.[9] The method nevertheless employed expensive nickel catalyst. Towards addressing this challenge and in continuation of our interests,[10] we made a conscious effort to develop a metal free catalytic system, which was not only applicable to amines and alcohols but also to aromatic/aliphatic aldehydes and 2-oxo aldehdyes to give amides, esters and α-keto esters.

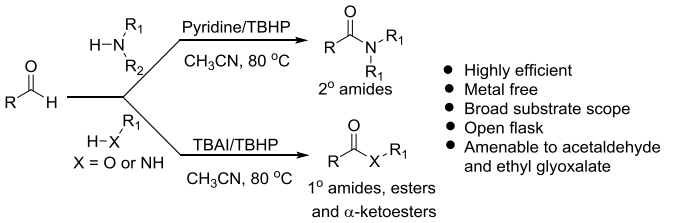
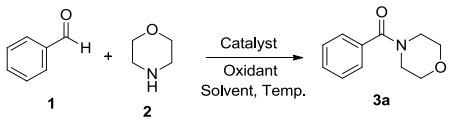


Figure 1. This work

To begin with we contemplated using pyridine in combination with *tert*-butyl hydroperoxide (TBHP), as it can facilitate its cleavage to generate a *tert*-butyloxy anion, which can further attack the C=N system to give corresponding amide.[11] The optimization studies were performed with benzaldehyde and morpholine as substrates. To our delight the reaction in presence of pyridine (1 equiv.) and TBHP (1.5 equiv) at 80 °C in ACN gave corresponding amide **3a** in 82% yields (table 1, entry 1). Lowering the temperature to rt resulted in drop of yields to 56% (table 1, entry 2). We also tried reaction with other bases, while triethyl amine (TEA) and K_2CO_3 gave **3a** in 42 and 51% yields, the use of KOH failed to give product (table 1, entry 3-5). Next, we screened other oxidants such as H_2O_2, *m*-CPBA and cumene hydroperoxide (CuHP), wherein in only CuHP gave **3a** in 71%

yields (table 1, entry 6-8). The reaction in other solvents gave product in comparatively lesser yields (table 1, entry 9-11).

Table 1. Optimization of the reaction conditions[a]

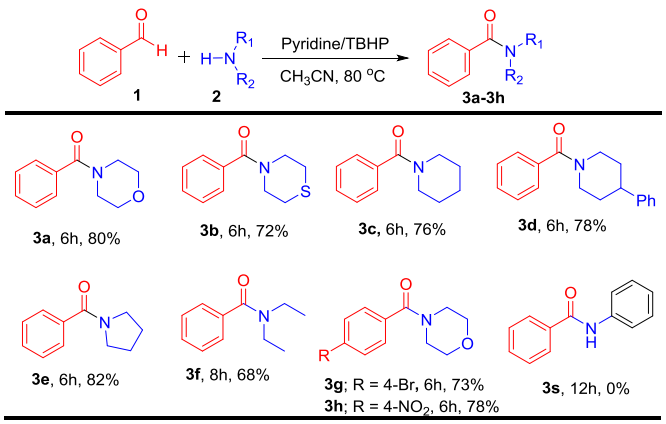


1 2 3a

entry	solvent	base	oxidant	temp (°C)	yield [%]
1	CH_3CN	pyridine	TBHP	80	82
2	CH_3CN	pyridine	TBHP	rt	56
3	CH_3CN	TEA	TBHP	80	42
4	CH_3CN	K_2CO_3	TBHP	80	51
5	CH_3CN	KOH	TBHP	80	-
6	CH_3CN	pyridine	H_2O_2	80	-
7	CH_3CN	pyridine	*m*-CPBA	80	-
8	CH_3CN	pyridine	CuHP	80	71
9	Toluene	pyridine	TBHP	80	45
10	THF	pyridine	TBHP	80	58
11	DCE	pyridine	TBHP	80	54

[a] Reactants: **1** (1 mmol); **2** (1 mmol); base (1 equiv); oxidant (1.5 equiv)

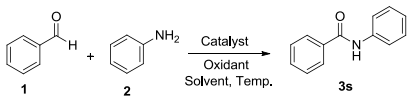
Having conditions optimized, we explored the scope of different aldehydes with amines (Scheme 1). The reaction proceeds readily with a range of amines secondary amines to give corresponding products. The reaction of benzaldehyde with different secondary amines including heterocyclic amines such as thiomorpholine, piperidine, 4-phenyl piperidine, pyrrolidine, diethyl amines gave corresponding amides (**3b-3f**) in excellent yields (scheme-1). Furthermore, the reaction of 4-bromo and 4-nitro benzaldehyde with morpholine also gave amides **3g** and **3h** in 73% and 78% yields respectively. However, the reaction failed to give desired product when aniline was used as a coupling partner.



Scheme 1. Generality of the reaction in terms of aldehydes and 2° amines

Thus, further optimization studies were performed to expand its scope to primary amines and anilines. We reasoned that it's probably iminium ion formation with secondary amine that is facilitating the oxidation of C=N system, hence, we envisaged finding alternate catalytic system, which circumvents the need of iminium ion formation and instead proceeds through a radical mechanism. Thus, we used I_2, which is known to generate *tert*-butoxyl and *tert*-butylperoxyl radicals instead of tert-butoxyl anion.[12] The reaction of benzaldehyde with aniline in presence of I_2/TBHP was chosen as model reaction. The reaction lead to the formation of desired product **3s** in 65% yields (table 2 entry 5). We deliberated the screening of other iodine sources such as NIS, KI, TBAI and $PhI(OAc)_2$. While there was no product formation with $PhI(OAc)_2$, the yields with NIS and KI were comparable to that of I_2 (table 2 entry 2-4). However, to our surprise the TBAI was found to be catalyst of choice giving corresponding amide **3s** in 74% yields (table 2 entry 5). The reaction in other solvents though gave product, but in comparatively lesser yields (table 2, entry 6-9).

Table 2. Optimization of the reaction conditions[a]



1 2 3s

entry	solvent	catalyst	oxidant	temp (°C)	yield [%]
1	CH_3CN	I_2	TBHP	80	65
2	CH_3CN	NIS	TBHP	80	61
3	CH_3CN	KI	TBHP	80	59
4	CH_3CN	$PhI(OAc)_2$	TBHP	80	-
5	CH_3CN	TBAI	TBHP	80	74
6	Toluene	TBAI	TBHP	80	45
7	THF	TBAI	TBHP	80	58
8	DCE	TBAI	TBHP	80	54
9	DMSO	TBAI	TBHP	80	52

[a] Reactants: 1 (20 mmol); 2 (1 mmol); catalyst (30 mol%); oxidant (3 equiv)

Next, we investigated the scope of reaction with different aldehydes and amines (scheme 2). To begin with, we tested the catalytic system with acetaldehyde as the coupling partner, which would probably be the simplest way for acetylation and has no precedence in literature. The reaction of acetaldehyde under optimized conditions proceeded smoothly with different amines i.e., aniline, 4-methyl, 4-bromo and 4-(trifluoromethoxy) anilines to give corresponding products **3i-3l** in good yields. Interestingly, the reaction of acetaldehyde with *p*-hydroxy and *p*-ethoxy aniline as coupling partners accomplishes possibly the simplest synthesis of paracetamol (**3m**, 60%) and phenacetin (**6n**, 65%) respectively. Notably, previously the use of acetaldehyde has proven difficult as a result of its tendency to polymerise, low-boiling point and the formation of side-products.[13] Intriguingly, with present catalytic system, there was no side product formation observed as well as reaction could be carried out in open flask. Since, the reaction was amenable to aliphatic aldehydes we thought of using ethyl glyoxalate, as it would give access to 2-oxo-amino esters, which are also hitherto unreported. The advantage of having a vicinal ester group is that it can be used as a handle for further diversification. The reaction of ethylglyoxalate as expected with aniline, 4-bromo, 4-methyl, 4-(trifluoromethyl) anilines gave corresponding 2-oxo-amino esters **3o-3r** in excellent yields. The scope of the reaction with respect

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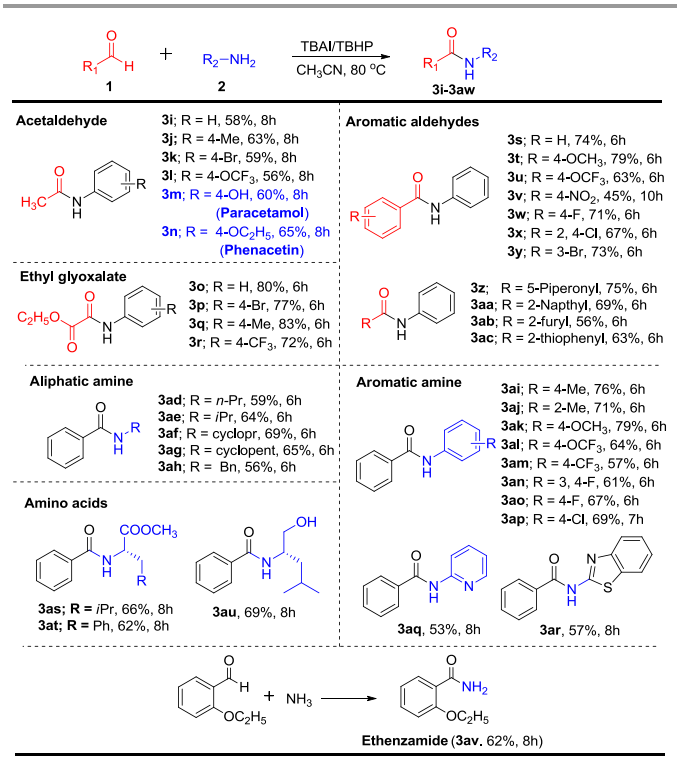
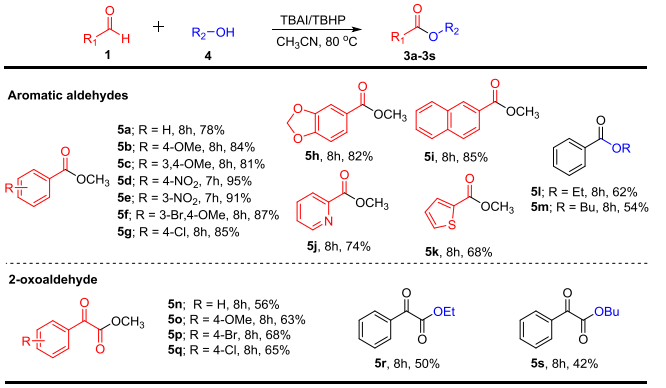
to different aromatic aldehydes having electron withdrawing and releasing function was also investigated. The reaction with different aromatic aldehydes such as benzaldehyde, 4-methoxy, 4-(trifluoromethoxy), 3,4-methylenedioxy, 4-nitro benzaldehyde and 2-napthaldehyde gave the corresponding products (**3s-3v** and **3z-3aa**) in good yields. Furthermore, the reaction with halogenated aldehydes such as 4-fluoro, 2,4-dichloro and 3-bromo benzaldehyde to give (**3w-3y**) in excellent yields and providing possibility for further functionalization. The method also proceeds efficiently with heterocyclic aldehydes like 2-furyl and 2-thiophenyl carboxaldehyde to give corresponding products **3ab** and **3ac** in 56 and 63% yields respectively.



Scheme 2. Synthesis of various amides

Next, we expanded the scope to various primary amines aliphatic as well aromatic (scheme 2). Aliphatic amines such as *n*-propyl, *iso*-propyl, cyclopropyl, cyclopentyl and benzyl amines reacted efficiently with benzaldehyde to give corresponding products (**3ad-3ah**) in good yields. Also, the reaction with different aromatic amines viz., 4-methyl, 2-methyl 4-methoxy, 4-OCF_3 and 4-CF_3 aniline proceeded gave amides (**3ai-3am**) in excellent yields. In addition the reaction of halogenated amines such as 3,4-difluoro, 4-fluoro and 4-chloro anilines also gave the corresponding products (**3an-3ap**) in good yields respectively, which not to mention provide the possibility of further functionalization. Furthermore, heterocyclic amines like 2-amino pyridine and 2-amino benzothiazole were also found suitable for this transformation to give **3aq** and **3ar** in 53 and 57% yields. We also extended the reaction to different aminoacids, which have very few literature reports. To our delight the reaction of amino acid methyl esters such as leucine and phenylalanine as well as amino alcohol, leucinol gave corresponding products (**3as-3au**) in 66, 62 and 69% yields. Importantly, there was no side product formation with alcohol of leucinol possibly due to more nucleophilicity of amine and its stoichiometric use. The use of 2-ethoxybenzaldehyde and ammonia as coupling partners leads to the synthesis of ethenzamide (**3av**) in 62% yields. It would be pertinent to mention here that the reaction with secondary amines failed to proceed with TBAI/TBHP catalytic system.

To the best of our knowledge there is only a single method known, capable of transforming aldehydes into esters and amides using alcohols and amines.[9] Thus, using our optimized conditions we carried out the reaction of benzaldehyde with methanol to delightfully get methyl benzoate **5a** in 78% yields (scheme 3). Furthermore, the methanol could easily be coupled with different aromatic aldehydes such as 4-methoxy, 3,4-di-methoxy, 4-nitro, 3-nitro, 3-bromo-4-methoxy, 4-chloro, 3,4-methylenedioxy benzaldehyde and 2-napthaldehyde to get the corresponding esters (**5b-5i**) in excellent yields. Importantly, heterocyclic aldehydes such as 2-pyridine and 2-thiophene carboxaldehdye could also be easily transformed into esters **5j** and **5k** in 74 and 68% yields respectively. Also, ethanol and butanol could be utilized as coupling partners with benzadehyde to get corresponding esters **5l** and **5m** in 62 and 54% yields. We also explored the substrate scope of 2-oxoaldehydes for synthesis of corresponding α-ketoesters, which find pervasive presence in a large number of bioactive compounds and have lead to the development of copious methods for their synthesis in recent years.[14] Likewise, the reaction of 2-oxo-phenyl acetaldehyde and methanol under optimized condition gave corresponding α-ketoester **5n** in 56% yield. Similarly, other substituted 2-oxoaldehydes such as 4-OMe, 4-Br and 4-Cl gave corresponding α-ketoesters (**5o-5q**) in good yields. The reaction of 2-oxo-phenyl acetaldehyde with ethanol and butanol also gave corresponding products **5r** and **5s** in 50 and 42% yields respectively.



Scheme 3. Synthesis of esters and α-keto-esters

The reaction possibly proceeds via two different routes for secondary amines and primary amines with pyridine and TBAI as catalyst. For route A; benzaldehyde possibly reacts with secondary amine to form iminium ion intermediate (**I**). Subsequently, *tert*-butylperoxy anion generated by abstraction of a proton from TBHP by pyridine,[11] attacks the iminium ion (**I**) to

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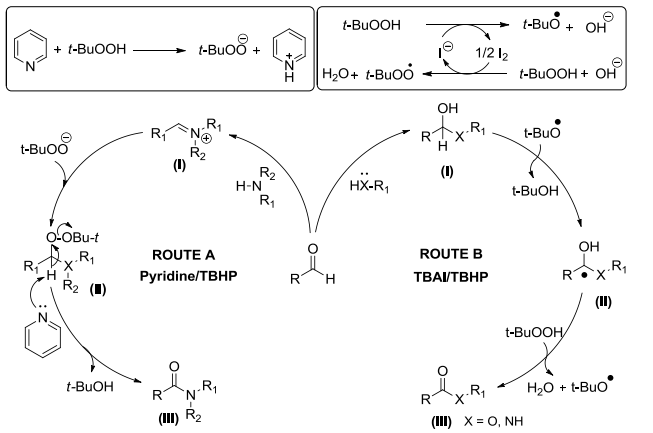
give intermediate (**II**). The pyridine also further abstracts a proton from intermediate (**II**) to eliminate *tert*-butanol and give the desired product (**III**). For route B; on the basis of previous publications,[7,8,12] we assume the TBAI catalyses the formation of *tert*-butoxyl and *tert*-butylperoxyl radicals from TBHP. The acetal or aminal species (**I**) formed by nucleophilic addition with aldehyde, undergoes hydrogen atom abstraction by these radicals to give corresponding radical species (**II**). The species (**II**) consequently oxidizes to the corresponding amide or ester. Also, the addition of TEMPO (2,2,6,6-tetramethylpiperidinooxy) inhibits the reaction and instead couples with acyl radical to give corresponding product (**6**, supporting info).



Scheme 5. Plausible Mechanism

In summary, we have developed an efficient cross-coupling strategy for the synthesis of amides, esters and α-ketoesters from aldehydes. The method also presents a first use of acetaldehyde for acetylation and ethyl glyoxalate for 2-oxo-amino esters respectively. The method employs a simple experimental procedure, broad substrate scope and sustainable to wide range of functionalities.

Notes and references

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[†]Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectras. See DOI: 10.1039/c000000x/

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