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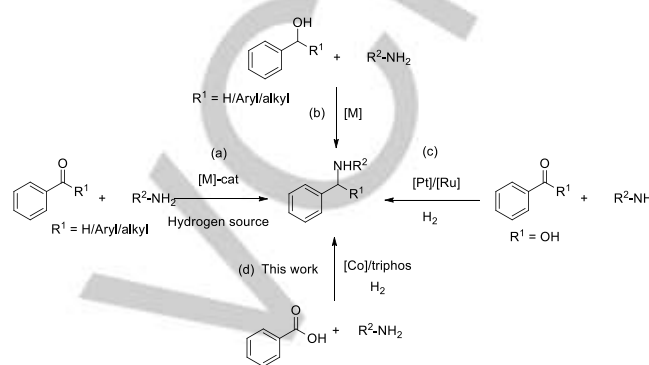
Cobalt-Catalyzed Reductive Alkylation of Amines with Carboxylic Acids

Balakumar Emayavaramban, Priyanka Chakraborty and Basker Sundararaju*

Dedication ((optional))

Abstract: We report a direct reductive alkylation of amines with carboxylic acid using inexpensive, air-stable cobalt/triphos catalytic system with molecular hydrogen. This efficient protocol proceed through reduction, condensation followed reduction of in-situ generated imine into amine via green catalytic process.

Amines are important building blocks in pharmaceutical drugs, agrochemicals, fine chemicals and organic materials.^[1] Alkylation of amines and reductive amination are the commonly practiced methods for the synthesis secondary and tertiary amines, while the former suffers from the selectivity issue and the latter requires carbonyl derivatives (Scheme 1a).^[2-4] In the recent times, hydrogen borrowing strategy was widely employed for alkylation of amines directly from alcohols through dehydrogenation-rehydrogenation pathway mediated by transition metals (Scheme 1b).^[5,6] Metal catalyzed direct reduction of imine or amide using various hydride sources including molecular hydrogen for the synthesis of secondary alkyl/aryl amine is well established but it necessitates additional step to prepare carbonyl derivatives.^[7] Conversely, reductive alkylation of amines directly from carboxylic acid is achieved using stoichiometric amount of organometallic borohydride as reducing agent.^[8] Direct reductive alkylation of amines starting from higher oxidized hydrocarbons such as carboxylic acid using molecular hydrogen is very attractive and it avoid the usage of toxic organometallic reagents.^{[9],[10]} To the best of our knowledge, only handful reports are known till date using molecular hydrogen as a clean source of reductant for the above-mentioned transformation. In this regard, Cole-Hamilton reported the first reductive alkylation of amines with carboxylic acids using Ru/triphos catalytic system and molecular hydrogen to access various alkylated amines albeit in low yield (Scheme 1c).^[11] Later, Beller and co-workers reported the first platinum catalyzed alkylation of amines starting from carboxylic acids using silane as reductant.^[12] Subsequently, the same group reported Ru-catalyzed functional group tolerant, high yield protocol for reductive alkylation of amine with carboxylic acids.^[13] However, the reported method required moisture sensitive triflamide as additive in order to obtain high yield.



Scheme 1. Overview of Alkylation of amine. ^a Reductive amination of aldehyde/ketone. ^b Alkylation of amine directly from alcohol via hydrogen borrowing methodology. ^c Pt/Ru-catalyzed reductive alkylation of amine with carboxylic acid. ^d Cobalt-catalyzed reductive alkylation of amine with carboxylic acids

Due to fast depletion and high-demand of expensive precious metal leave us with scarcity for its availability in future.^[14] Hence, it is necessary to find out an alternative metal that are earth-abundant, inexpensive and environmental friendly.^[15] In this regard, several metal complexes were reported in the recent times using earth abundant first-row transition metals (e.g. Fe, Co, Mn) for C-C and C-N bond formation via borrowing hydrogen methodology directly from alcohols.^[16] However, direct reductive functionalization of carboxylic acid to secondary alkylamine was never been reported using first-row transition metals.^[17] Recently, Bruin and co-workers reported the first efficient reduction of carboxylic acid to alcohol using Co(II)/triphos catalytic system and molecular hydrogen.^[18] Later, C-3 selective reductive alkylation indole was achieved by beller using the similar catalytic system.^[19] Inspired by these results and based on our continuous interest on base-metal catalysis,^[20] we envisage that the *in-situ* generated aldehyde *via* reduction of carboxylic acid, followed by condensation with amine to form imine, then the insitu formed imine reduced into amine using molecular hydrogen under Co/triphos catalytic system (Scheme 1d).

We began our investigation using *p*-anisidine as a model substrate along with 2 equivalent of acetic acid as alkylating agent in the presence of 5 mol% of cobalt and 5-20 mol% of phosphine ligand in toluene at 140 °C for 24 h under 60 bar hydrogen pressure as depicted in table 1. Among the phosphine ligands we screened, triphos turned out to be the best ligand that provided the mono- and bis-alkylated product in the ratio of 82-88 / 12-15 with the maximum isolated yield of **3a** in 58% (entries 1-3). Neither additive nor change in the oxidation state of cobalt improves the isolated yield of **3a** (entries 4-5). Varying the solvent from toluene to ethereal solvent could improve the

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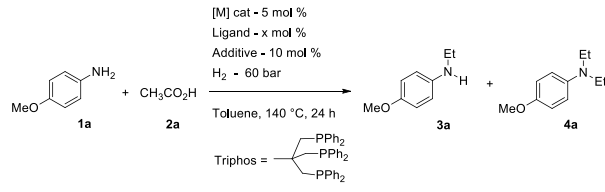
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yield to 70% with the **3a/4a** ratio of 98/2 (entries 6-7). Further, we have investigated selective double alkylation with excess of acetic acid.

Table 1. Reaction Optimization



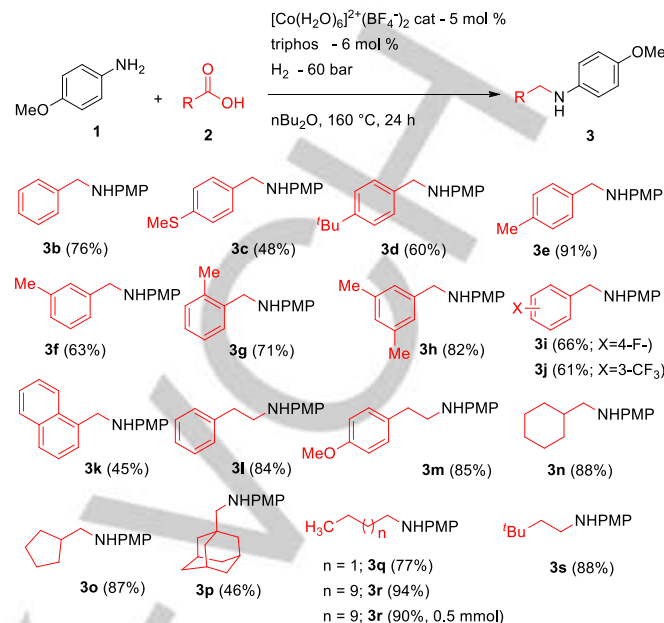
Entry	[M]	Ligand (mol %)	Yield	
			3a	4a
1	[Co(H ₂ O) ₆] ²⁺ (BF ₄) ₂	dppp (10)	88 (45)	15 (9)
2	[Co(H ₂ O) ₆] ²⁺ (BF ₄) ₂	PPh ₃ (20)	n.d.	n.d.
3	[Co(H ₂ O) ₆] ²⁺ (BF ₄) ₂	triphos (6)	88 (58)	12 (10)
4 ^d	Co(acac) ₂	triphos (6)	82 (46)	18 (9)
5 ^d	Co(acac) ₃	triphos (6)	n.d.	n.d.
6 ^e	[Co(H ₂ O) ₆] ²⁺ (BF ₄) ₂	triphos (6)	95 (56)	5 (3)
7 ^f	[Co(H ₂ O) ₆] ²⁺ (BF ₄) ₂	triphos (6)	98 (70)	2
8 ^g	[Co(H ₂ O) ₆] ²⁺ (BF ₄) ₂	triphos (6)	n.d.	>99 (50%)
9 ^h	[Co(H ₂ O) ₆] ²⁺ (BF ₄) ₂	triphos (6)	94 (57)	6 (2)
10	Ni(acac) ₂	triphos (6)	n.d.	n.d.
11	MnBr(CO) ₅	triphos (6)	n.d.	n.d.

^[a]All reagents were added under argon atmosphere unless otherwise stated using **1a/2a**/[Co]/L/additive in 0.3/0.6/0.015/0.018-0.06/0.03 mmol in a closed reactor under hydrogen pressure (60 bar) in toluene (1.5 mL) at 140 °C for 24 h. ^[b]ratio of **3a/4a** was determined by Gas Chromatography ^[c]Number in parenthesis are isolated yield. ^[d]10 mol% of HBF₄ was used as additive. ^[e]nBu₂O was used as solvent. ^[f]CPME was used as solvent. ^[g]4 equiv. of AcOH was used. ^[h]1.7 equiv. of AcOH was used.

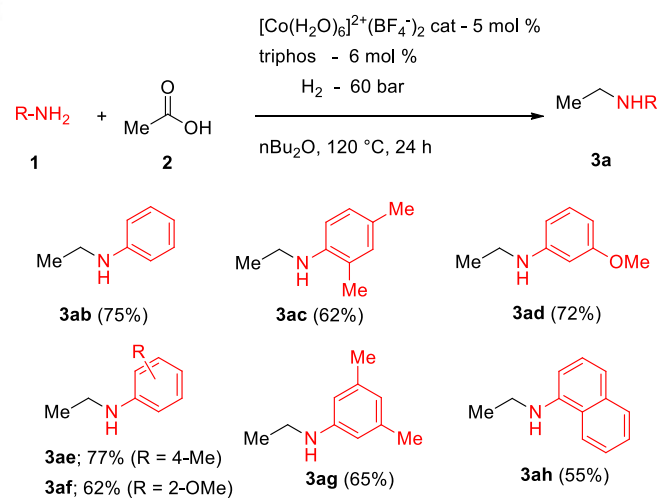
To our delight, double alkylation was achieved with 4-equivalent of acetic acid under standard conditions, and the ratio is in complete favour of **4a** with the isolated yield of 50% (entry 8). The lower yield of **4a** is partly due to the volatility of the compound after isolated from the column chromatography. We further optimize the amount of acetic acid from 2 to 1.7 equivalents that resulted in similar isolated yield as that of earlier (entry 9). Other metal precursors such as Ni(II) or Mn(I) did not be effective for the reductive alkylation under optimized conditions.

With the best conditions in hand, we next investigated the scope of the acids as depicted in scheme 2. Benzoic acids containing various substituents such as -OMe, -SMe, ^tBu, Me, F and CF₃ were amenable under standard alkylation conditions using **1a** with the isolated yields of mono alkylated products (**3b-3j**) ranges from 48-91%. To our delight, 1-naphthoic acid, phenylacetic acid and *p*-methoxyphenyl acetic acid gave the expected secondary amines (**3k-3m**) in 84-85% isolated yield. Cyclic carboxylic acids such as cyclohexyl, cyclopentyl and adamantly works equally well with good yields (**3n-3p**). Alicyclic carboxylic acids such as propanoic acid, dodecanoic acid and

3,3-dimethylbutyric acid provided the corresponding alkylation products (**3q-3s**) in good-to-excellent yields.



Next, we examined the scope of amine using acetic acids as alkylating partner as shown in scheme 3. Aniline provided the expected N-ethyl aniline (**3ab**) in 75% yield. Various substituents such as Me-, OMe- at various position of arenes were tolerated (**3ac-3ag**). Even, naphthyl amine was amenable under our reaction conditions and provides the expected mono-alkylated product (**3ah**) in good yield. Under the optimized reaction conditions, aliphatic amines did not provide the expected alkylation products in satisfactory yields.



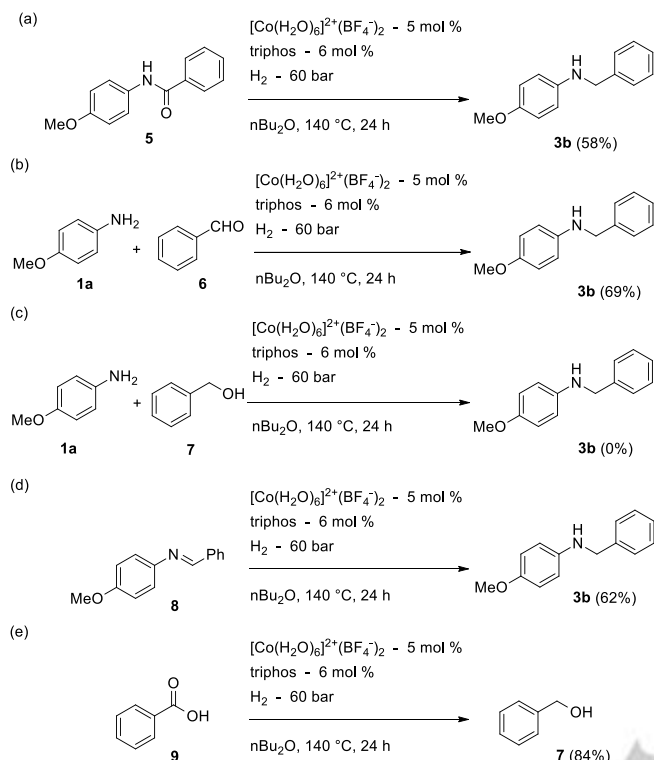
Scheme 3. Scope of Amines

To probe the reaction mechanism several control experiments, were carried out as depicted in scheme 4. Reduction of amide **5** into N-benzylamine (**3b**) under standard conditions was achieved in 58% isolated yield. Although reduction of amide was

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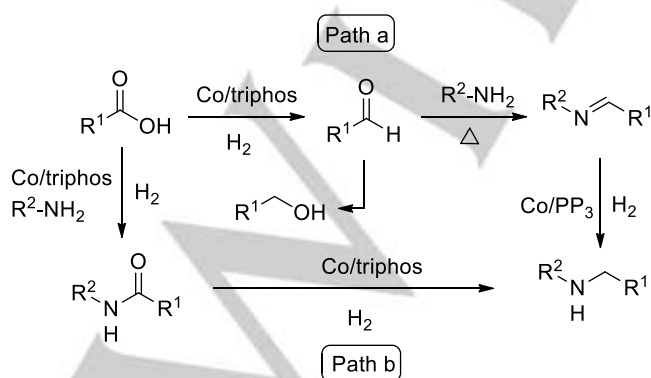
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possible under standard conditions, we have not observed any amide formation even at low hydrogen pressure (20-40 bar).



Scheme 4. Control experiments

Next, we have carried out the reaction with amine **1a** and benzaldehyde **6** that provided the expected product (**3b**) in 69% yield after isolation along with small amount of benzyl alcohol. Also, we have performed the reaction with benzyl alcohol **7** as a coupling partner instead of benzaldehyde that did not provide the corresponding benzylated amine, which suggests that the reaction did not proceed through oxidation-reduction (borrowing hydrogen) pathway. We have also employed the isolated imine **8** under established reaction conditions provided the expected amine in 62% yield along with small amount of benzyl alcohol. Last, benzoic acid **9** alone was tested without amine that resulted the expected benzyl alcohol **7** in 84% yield.



Scheme 5. Proposed mechanism

Based on these above results, the following mechanism was drawn as shown in Scheme 5. Carboxylic acid **2** reduced into

aldehyde followed by condensation with amine to form the corresponding imine. This in-situ formed imine will further reduced into amine catalyzed Co/triphos using molecular hydrogen. In absence of amine, the in-situ formed aldehyde will reduce into alcohol. Alternatively, carboxylic acid reacts with amine to provide the amide, which then subsequently reduced into amine. Based on our results, it appears that the former presumably the major pathway and the latter likely to be considered as minor pathway.

In summary, we have developed an efficient, economical and green alternate protocol for reductive alkylation of amine with carboxylic acid using molecular hydrogen as source of reductant. Selective monoalkylation was achieved in good yield with various carboxylic acids including aliphatic and aromatic acids. Our preliminary mechanistic investigation revealed that the reduction of carboxylic acid followed by condensation, reduction is a major pathway. Further application and mechanistic investigation is currently under progress in our laboratory.

Acknowledgements

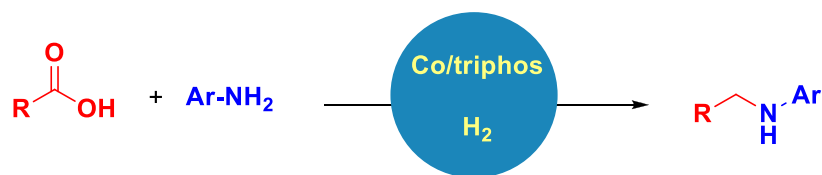
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An efficient cobalt-catalyzed reductive alkylation of amine was achieved using carboxylic acid as alkylating agent and molecular hydrogen as reductant under additive free conditions.

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