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Accepted Article

Title: N-Heterocyclic Carbene/Cobalt Cooperative Catalysis for the chemo-and regioselective C–N Bond formation between aldehyde and amines/amides

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To be cited as: *ChemCatChem* 10.1002/cctc.202000156

Link to VoR: https://doi.org/10.1002/cctc.202000156

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10.1002/cctc.202000156

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N-Heterocyclic Carbene/Cobalt Cooperative Catalysis for the chemo-and regioselective C–N Bond formation between aldehyde and amines/amides

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Dedication ((optional))

Abstract: A novel methodology for the construction of various secondary (4 examples), tertiary amides (31 examples), and imides (16 examples) by a Cobalt(II) catalyzed oxidative amide coupling in aqueous media. The Co(III)-TMC was reacted with N-Heteroatom Carebene (NHC) to form active catalyst Co(II)NHC-TMC *in situ* which involves in the coordination with Breslow's intermediate and SET for the activation of aldehyde and amides. The mechanism for activation of amide and amine differs on the basis of SET based nucleophilic addition and ligand exchange respectively. The regeneration of the catalyst was achieved using Fe(III)(EDTA)-H_2O_2 as oxidant. The use of Co(II)TMC-O_2 was also found equally efficient in the process. The method is found regioselective for N-H activation in the presence of equally susceptible *ortho*-C–H bond activation. And amines were found more susceptible then the corresponding amide for the reaction.

Amide and imides are important functional groups present in various biomolecules, privileged pharmacophores and compounds of pharmaceutical importance. [1] In addition, Imide-functionalized π-conjugated polymer has received a great deal of interest owing to their unique physicochemical properties. The release of H_2O in conventional amide bond-forming procedures is the only byproduct [2] during the condensation of an amine with a carboxylic acid in the presence of a coupling reagent. However, the addition of an extra step for the activation of the carboxylic acid through the coupling reagents is not favored by the organic chemists as it leads to the formation of additional byproducts. Therefore, the development of newer alternative synthetic strategies to this ubiquitous functional group has attracted attention over the years. [3-13] Different reactions have been investigated including Schmidt reaction, Staudinger ligation, [4] Beckmann rearrangement of oximes, [5] aminocarbonylation of alkenes, haloarenes and alkynes, [6] oxidative amidation of aldehydes and alcohols [7] hydrative amide synthesis with alkynes, [8] and amidation of thioacids and ketones with azides/amines [9] including the recent high atom economic systems: transition-metal-catalyzed oxidative amidation of aldehyde with primary amines using Fe, Cu, Ru, Rh, Pd, lanthanide and Ag-based catalysts. [10] These synthetic methods require heated reaction conditions and prolonged time, and the substrate scope is limited.

Further, the above methods are mostly for the formation of amides but not for imides which need still higher activation of N-H bond present in the amide (-CONH). Additionally, Cobalt has shown a crucial role in hydroformylation reactions, Nicholas [11] and Pauson-Khand reaction, [12] cyclization reactions, homo and cross-coupling reaction of Grignard reagent, [13] radical dimerization, [14] radical cyclization, [15], Heck-type [16] and C-H activation reactions [17-18] as co-catalyst and as activator when coupled with SET reagents like NBS, NCS, NIS and AIBN/I_2 using peroxo-metal complexes as an oxidant in a stoichiometric amount in the presence various organic and inorganic bases in aqueous media (in the presence of ~10% of DMPU in DMF). Although transition-metals such as Pd, Pt, Ni, Cu, etc. can catalyze an oxidative amidation and esterification of aldehydes, the corresponding Co-catalyzed oxidative amidation and esterification have rarely reported, only very recently a Co-catalyzed oxidative esterification of aldehyde appeared.[19a] Among these oxidative derivatizations, the examples of the corresponding imidation between aldehydes and amides were rather fewer, and the Co-catalyzed such imidation has not been documented.[19b-d] Cobalt catalysis usually demonstrates high activity and efficiency in the *ortho* C-H activation of benzamides.[20] In the present amidation and imidation, the selectivity between N-H and *ortho* C-H of benzamides formed in the amidation of Ar-CHO or the substrates of imidation thus presents a big challenge.[20b, 21] The reported protocols usually proceeded under heated conditions and in anhydrous solvents, the present reactions could proceed in aqueous solution at room temperature.

In view of above and in continuation of our recent endeavours in metal-based catalysis protocols [22] effective in the formation of the desired target molecules of importance in pharmaceutical, diagnostic (fluorescent probes) and material (OLED devices) sciences, the present investigation of exploring Co-based complexes as catalysts for N-H activation mediated amide bond formation was undertaken and results are reported in this paper.

In the first model reaction, the benzamide (**1a)** and benzaldehyde (**2a)** were used in direct cross-dehydrogenative coupling reaction conditions. Various single electron transfer

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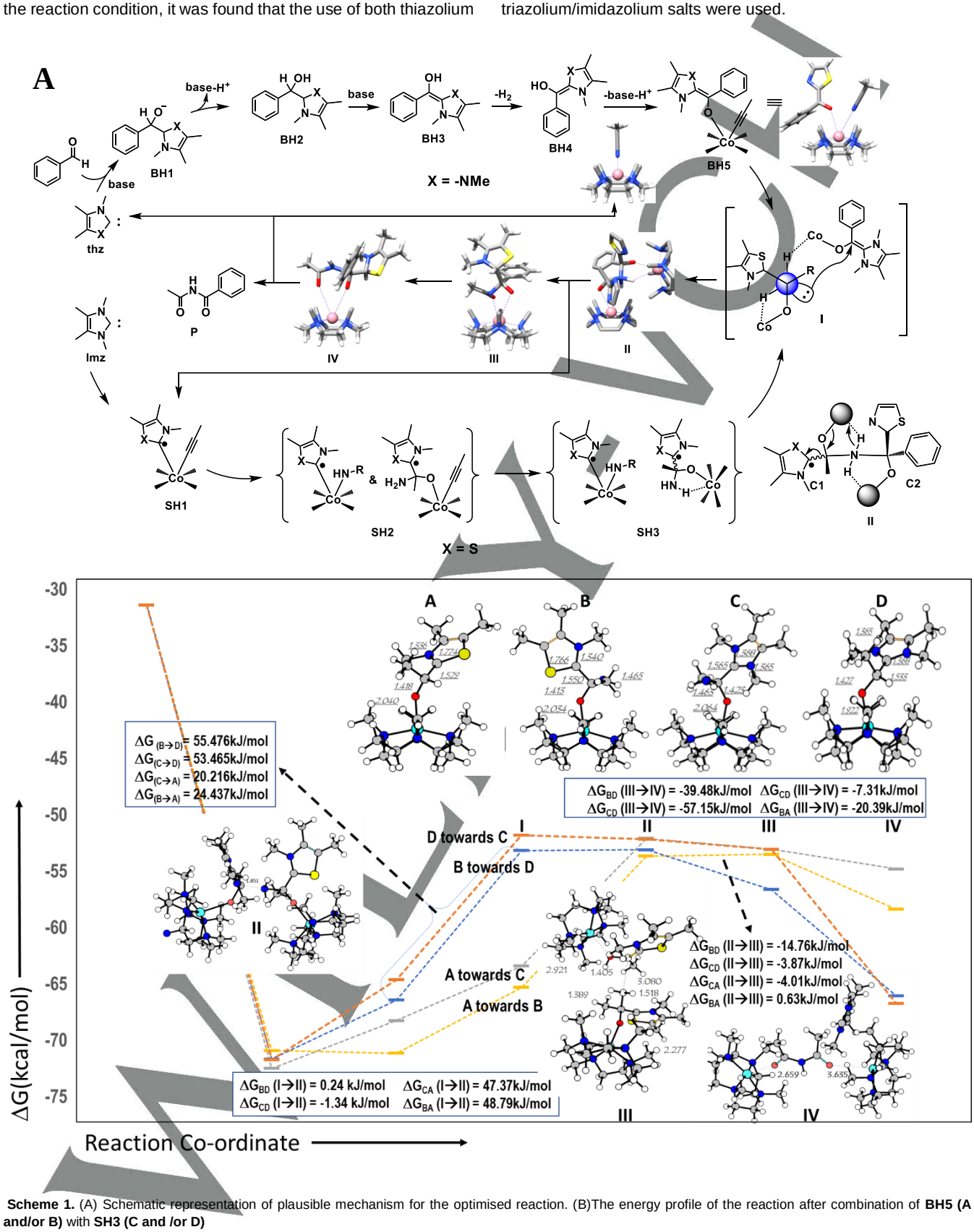
(SET) oxidants (11 examples) were screened with various transition metal complexes (16 examples) in combination with five N-heteroatom carbene (**Table 1**). During the standardization of the reaction condition, it was found that the use of both thiazolium and imidazolium precatalysts (in 20:20 mol% ratio) for the respective half of the reaction offered better reaction yield and rate than the cases where either thiazolium or triazolium/imidazolium salts were used.



Scheme 1. (A) Schematic representation of plausible mechanism for the optimised reaction. (B)The energy profile of the reaction after combination of **BH5 (A and/or B)** with **SH3 (C and /or D)**

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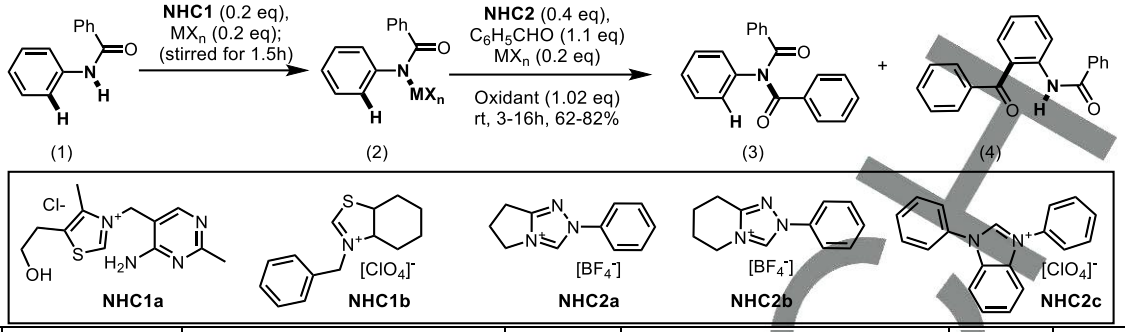
Table 1. Standardization of the reaction condition for the synthesis of imides and *ortho*-substituted amides.



Entry [a]	NHC1	M(X)n [b]	NHC2	Oxidant	Time [c]	Yield [d, e]
1	NHC1a, NHC1b	$CoCl_2.2H_2O$	NHC2c NHC2c NHC2c	UHP Fe(III)-EDTA-H_2O_2 Co(EDTA)-H_2O_2	15h	54, 35 28, 15 26, 21
2	NHC1a	CoBr	NHC2c NHC2c NHC2c NHC2c NHC2c NHC2c NHC2c	NCS+Ag_2O BzOOH H_2O_2 TBHP UHP Fe(III)-EDTA-H_2O_2 Co(EDTA)-H_2O_2	12h	15 14 31 42 32 48 35
3	NHC1a	$PdCl_2$ + EDTA	NHC2b, NHC2c	Fe(EDTA)-H_2O_2	12h	32, 42
4	NHC1a	$Pd(OAc)_2$ + EDTA	NHC2b, NHC2c	Fe(EDTA)-H_2O_2	24h	41, 56
5	NHC1a	$FeBr_2$	NHC2c	UHP Fe(EDTA)-H_2O_2	32h	28 22
6	NHC1a	$Co(acac)_3$	NHC2c	Co(II)-EDTA-H_2O_2 Fe(III)-EDTA-H_2O_2	22h	42 64
7	NHC1a	$Co(bpym)Cl_2$	NHC2c	Co(II)-EDTA-H_2O_2 Fe(III)-EDTA-H_2O_2	12h	62 68
8	NHC1a	Co(bibim-2)	NHC2c	Co(II)-EDTA-H_2O_2 Fe(III)-EDTA-H_2O_2	12h	71 76
9	NHC1a	Co(bibim-3)	NHC2c	Co(II)-EDTA-H_2O_2 Fe(III)-EDTA-H_2O_2	12h	60 69
10	NHC1a	(*i*PrPDI)$CoCl_2$[18e]	NHC2c	Co(II)-EDTA-H_2O_2 Fe(III)-EDTA-H_2O_2	12h	71 85
11	NHC1a	$Co(trop_2DAD)Br_2$	NHC2c	Co(II)-EDTA-H_2O_2 Fe(III)-EDTA-H_2O_2	12h	74 89
12	NHC1a	$(PPh_3)_3CoCl$	NHC2c	Co(II)-EDTA-H_2O_2 Fe(III)-EDTA-H_2O_2	24h	45 54
13	NHC1a	$[Co(12\text{-}TMC)(ACN)](ClO_4)_2$	NHC2c	$[Co(12\text{-}TMC)(O_2)](ClO_4)$ [18f] Fe(III)-EDTA-H2O2	12h	86 96
14	NHC1a	$[Co(13\text{-}TMC)(ACN)](ClO_4)_2$	NHC2c	$[Co(12\text{-}TMC)(O_2)](ClO_4)$ [18f] Fe(III)-EDTA-H_2O_2	12h	88 96
15	NHC1a	$[Co(12\text{-}TMC)(ACN)](ClO_4)_2$	NHC1a	Fe(III)-EDTA-H_2O_2	12h	<5
16	NHC2c	$[Co(12\text{-}TMC)(ACN)](ClO_4)_2$	NHC2c	Fe(III)-EDTA-H_2O_2	12h	32

a) All the reaction were carried out using DMPU:H_2O as solvent system and K_2CO_3 + $KHCO_3$ as base (0.6:0.6 mol)
b) These complexes were prepared using the method reported in the literature. The catalyst was used in 20 mol%.
c) in hrs;
d) Isolated yield in percentage (%).
e) In entry 1 the conversion of reactant was quantitative therefore the crude yield (**3 and 4**) was found to be in approximately 100-Yield%.

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Catalytic effects of various transition metal salts on the cross-coupling of benzamide (**1a)** with benzaldehyde (**2a**) were firstly evaluated in the presence of Fe(III)-EDTA-H_2O_2[23] as oxidant. The best result was obtained in DMPU using slightly excess stoichiometry of oxidant in both Fe and Co-based catalysis (**Entry 2-4, Table 1**). The oxidants having the same central atoms though the stability of these peroxo-metal complexes limits further exploration of [Co(12-TMC)(O_2)](ClO_4) and [Co(13-TMC)(O_2)] (ClO_4) as oxidant through their high propensity worth noting for future consideration.

The possible mechanism of the reaction is depicted in **scheme 1**, which closely very related NHC-catalyzed oxidative coupling with TEMPO various exogenous alcohols, water, and benzyl mercaptan reacted with aldehydes to afford esters, cinnamic acid, and thioesters.[20] The anticipated reactivity difference between the thiazolium and imidazolium salt with aldehyde separated the path into respective two halves where the imidazolium (**BH1**) goes for Breslow's intermediate formation with the aldehyde and thiazolium catalyst (**SH1**) proceeds for the SET based activation of amide or amine in cooperativity of Co-cat. The DFT calculations using Qchem5.2 [24] were carried out at B3LYP/6-31g(d) level and LanL2Dz level for C, H, O, N and S and Co respectively to rationalize that thiazoline based catalyst are upright for activating amide whereas aldehyde is activated through imidazolium-based catalyst. As the energy change during the aldehyde to Breslow intermediate was found to be -35.9kJ/mol for thiazolium based catalyst (**NHC1**) and imidazolium (**NHC2**) afforded -25.9kJ/mol. The conversion of **BH2** to **BH4** accomplished with ΔG of 0.76 and -5.59kJ/mol for thiazolium and imidazolium catalyst. The activation of amide before the formation of intermediate **II** via **I** afforded at an expense of -24.7kJ/mol and -25.3kJ/mol for imidazolium and thiazolium mediated Breslow and SET halves respectively which justifies the observed better yield in entry **16** than entry **15** (table 1) since a larger proportion of the thiazolium would get engage formation of Breslow's intermediates. Thus, after carrying out both possibilities, it is found that the amide forms **SH1, SH2 and SH3** intermediate with ΔΔG values of -2.4, -17.7 and -6.9 kJ/mol *via* coordination through NH and CO thus are more stable than the amine. Also, we can clearly say the formation of **BH5** as endoergic with 5.3 and 14.9kJ/mol for **NHC1** and **NHC2** respectively.

The reaction with both amine and amide as the starting material resulted in the formation of imine in larger excess than the corresponding amide which supports the proposed mechanism, due to the more stability of the Co(12TMC)-amide complex **SH3** than the complex with the amine. The combination of **SH3** and **BH5** resulted in the formation of **I** which found to be twice endoergic for **B-D** and **C-D** (when **NHC2** as aldehyde activating) than **B-A** and **C-A** (**NHC1** as aldehyde activating). Followed by conversion of **I** to **II** *via* Nucleophilic addition of activated amide on the Breslow half (**I**, **Figure 1A**). The $\Delta G_{BD\ (I\rightarrow II)}$, $\Delta G_{BD\ (I\rightarrow II)}$, showing that the **I** to **II** conversion is free energy favored step than their respective counterparts. The conversion of **II** to **III** due to N to O hydrogen transfer to form Co-chelated aminal complex followed by conversion of **III** to **IV** *via* deprotonation mediated oxidation of aminal to imide is a highly exoergic process for **B-D** combination (approximately ~3 time of **C-D**, **C-A** and ~30 time of **B-A** combination reaction pathway for the former step and 39.5kJ/mol for the latter step which is lower than the **C-D** combination reaction pathway but favorable than **C-A** and **B-A**) the favoring the reaction towards the formation of our desired product.

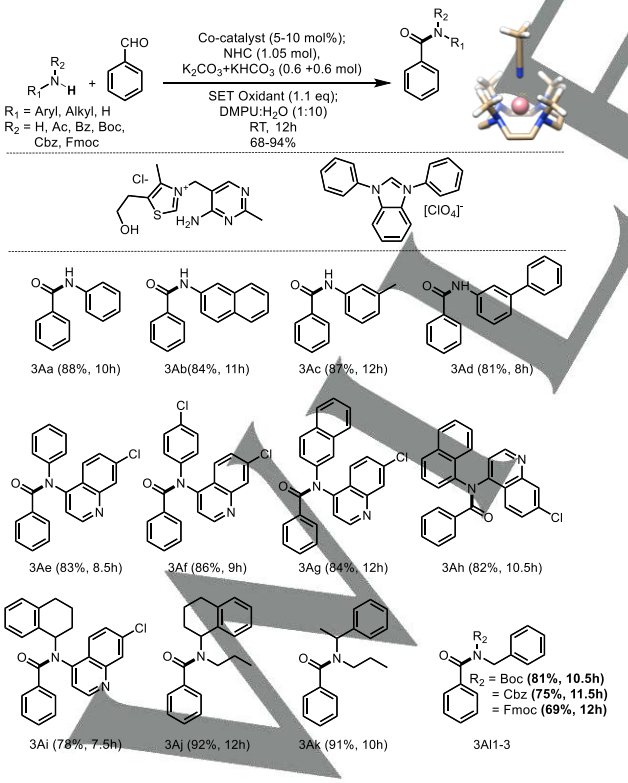

Figure 1. Substrate scope for N-Aroylation of amine to amide

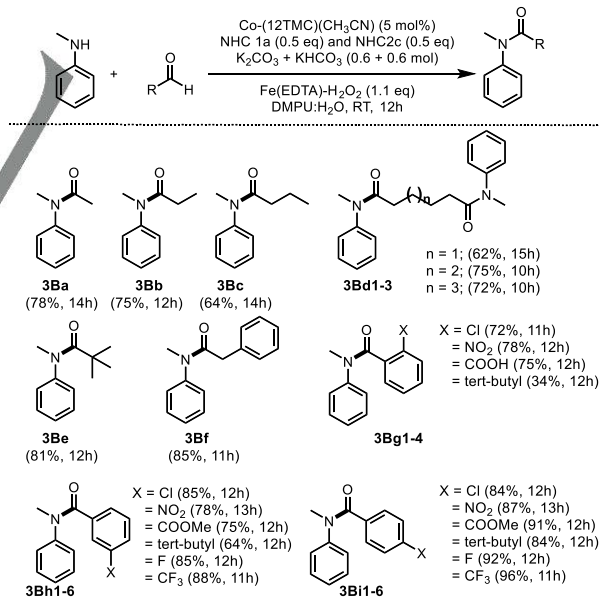

Figure 2. Substrate scope for N-Alkoxylation and Aroylation of secondary amines

All the common metal complexes were prepared through reported protocols and screened, where Co-based paramagnetic complexes were found more effective (84%) than their commonly available precursors like $Co(acac)_2$ (59%), $CoCl_2{\cdot}6H_2O$ (48%) and CoBr (62%). Other transition metal catalysts such as $Pd(OAc)_2$, $FeBr_2$ and $NiCl_2{\cdot}6H_2O$ (**Table 1**) showed significant

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catalytic activities for the formation of the product (**3**) but along with the undesired *ortho* C-H activated acylation product (**4**) in considerable amount. This led to the insight towards the regioselectivity in the Metal catalyzed methodology for the construction of the N-H activation mediated functionalization and C-H activation mediated functionalization having unequal propensity of formation under conditions either differing in terms of catalysts or base used in the reaction. In order, to decide regioselectivity of [Co(13-TMC)(ACN)](ClO_4) screening of different base was performed and found that the use of $CsCO_3$ resulted in the formation of C-H activation based substitution product (*ortho*-arylation, **4**) in major amounts which are beyond the scope of this work, whereas K_2CO_3/ $KHCO_3$ was found to give N-H activation mediated desired product in major amount (**3, Table 1**), the reaction afforded quantitative conversion thus the obtained two product was in the cases where both aldehyde and N-partners are aromatic whereas the cases where aromatic amides or amines coupled with alkyl aldehyde the *ortho*-alkylation product was not obtained but traceable respective carboxylic acid were obtained (**Figure 2** and **3**). The reaction showed no indication of product formation when only Co-catalyst and NHC were used even after 48hrs at room temperature conditions thus we recovered our starting materials with some trace of the respective carboxylic acid of aldehyde due to Arial oxidation under the optimized reactions conditions.

After screening a series of peroxides and other oxidants, [25] the Fe(III)-EDTA-H_2O_2 was found to offer the best results (**Table 1, entries 2 and 14–19**). The use of the [Co(13-TMC)(O_2)](ClO_4) as oxidant offered an almost similar result. The other oxidants like UHP, TBHP, H_2O_2, Ag_2O offered lesser yields while CoBr was used as catalyst (**Entry 1**, **Table 1**). The higher temperature was not beneficial for this reaction (**Table S2†, entry 23**), meanwhile, yields were slowly decreasing with the lowering of the reaction temperature (**Table S1†**). It was worth noting that the cross-coupling reaction also took place at room temperature giving the coupling product in a moderate yield (**Table S1†**). Although a high coupling yield could be obtained in just 6-7 hours (**68% Table S1†**), but for assuring quantitative yields all the reactions were executed for 12h to assure higher yields.

With a highly efficient cobalt catalyst in hand, we tested its versatility in the direct N-aroylation of various aromatic amines (**Figure 1**). Thus, both electron-rich amines and electron-deficient aldehydes (**Figure 1** and **2**) and vice-versa were successfully employed for the formation of the amides. Even the case where electron-rich and electron-deficient amines and aldehyde were also employed to obtain the amides in moderate to good yields. However, in the cases where the *steric bulk* was high (like **3Bg4** and **3Bh4** where X = *tert* butyl) the yields were lower may be due to the destabilized Breslow's intermediate formation. (**Figure 2**). After the achievement of the N-H bond activation mediated coupling based amide/imide formation using *in-situ* generated benzaldehyde derived Breslow intermediates as aroylating agent with various amines and amides, the scope of various aldehydes as the N-acylating and aroylating agents using amides as starting materials were further explored. (**Figure 3**) The good to excellent yields were obtained in almost all the cases and the steric effect seemed to play a predominant role in lowering the yields in cases where bulkier substituents were present proximal to the carbonyl group resulting destabilization of the Breslow intermediates (**Scheme 1, BH2**). In addition, we also have screened our optimized reaction condition in the synthesis of cyclic imides. (**Figure 4**)

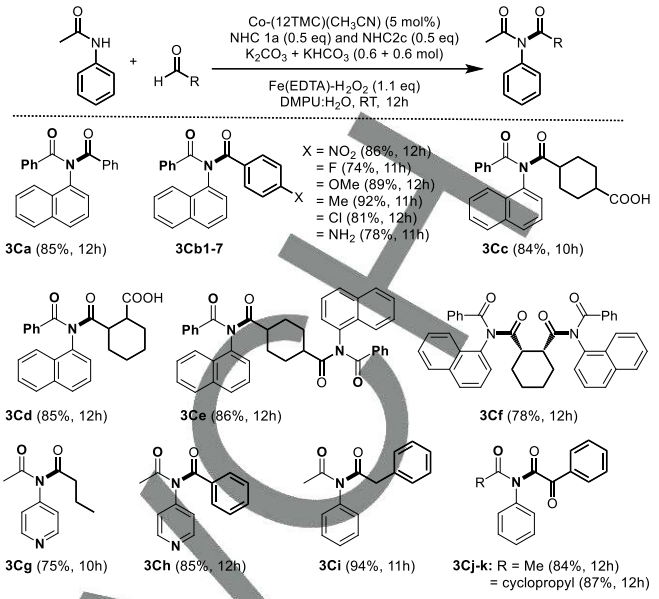

Figure 3. Substrate scope for the formation of imides.

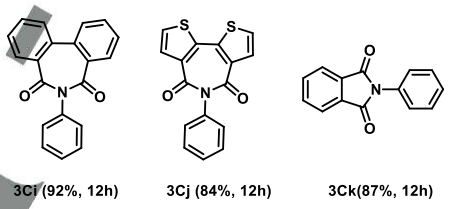

Figure 4. Substrate scope for the formation of cyclic imides.

In conclusion, a novel methodology for the regioselective construction of amide and imides using a Co-catalysed N-H activation based functionalization methodology has been developed which is capable of amide formation in a highly effective manner with appreciable temperature-controlled kinetics

Experimental Section

General Procedure: To a solution of [Co(13-TMC)(ACN)](ClO_4)$_2$ (65.6 mg, 0.2 mmol) was added NHC2c (55.5 mg, 0.15 mmol) in DMPU (0.5 mL) and stirred the reaction for 1.5 h at r.t. the colour change from brown to dirty green was observed which considered as an indicator of the formation of Co(NHC)L after such, Fe(III)-EDTA-H_2O_2 complex (~382 mg, 1.0 mmol, 1.0 equiv.) and [Co(13-TMC)(NHC)](ClO_4)$_2$ (49.2 mg, 0.15 mmol) were added to a stirred solution of specified aldehyde (1 mmol) in DMPU (1.5 mL) then NHC1c (60 mg, 0.2 mmol) and amine/amide (1.1 mmol) was added to the solution and diluted the reaction mixture with TDW (8 mL) followed by the addition of $KHCO_3$:K_2CO_3 (0.6: 0.6 mmol) to the resulting reaction mixture, the completion of amide formation was (6 to 14 h) was checked by TLC or GC/MS. After a few hours (2-10 h), the mixture was quenched carefully with aq. NH_4Cl (10 mol %, 10 mL) and extracted with Et_2O or EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The purification was carried out by running the resulting mixture through Celite:SiO_2 bed column.

Acknowledgements

We thankfully acknowledge the technical and analytical support by Mrs Anjum Baig, DIF-Jamia Hamdard, and CIF-Jamia Hamdard. One of us (I.A.K.) is thankful to UGC, New Delhi, for the award of Startup grant and Department of Chemistry, Jamia Hamdard for providing facility, space, and infrastructure for concluding part of the project. One of us (AK) is thankful to Hamdard foundation for the award of Hamdard National fellowship.

Keywords: Breslow's Intermediate, SET oxidant, N-heteroatom carbene.

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25. For details of preparation of the used oxidant see: S. Sharma, I. A. Khan, A. K. Saxena, *Adv. Syn. Cat.* **2013**, *355*, 673.

10.1002/cctc.202000156

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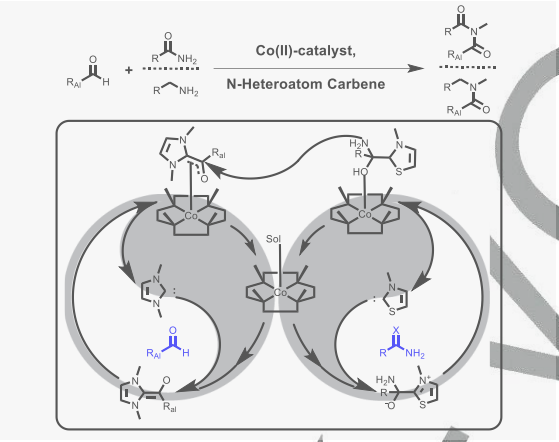
Layout 1:

COMMUNICATION

A novel methodology for the construction of various secondary (4 examples), tertiary amides (31 examples) and imides (16 examples) by a metal catalyzed oxidative amide coupling in aqueous media, has been devised using *insitu* generated Co(II)(L)(NHC) based catalytic system and Fe(III)(EDTA)-H_2O_2 as oxidizing agent. The method is regioselective for N-H activation in presence of equally susceptible *ortho*-C–H bond activation.



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N-Heterocyclic Carbene/Cobalt Cooperative Catalysis for the chemo-and regioselective C–N Bond formation between aldehyde and amines/amides