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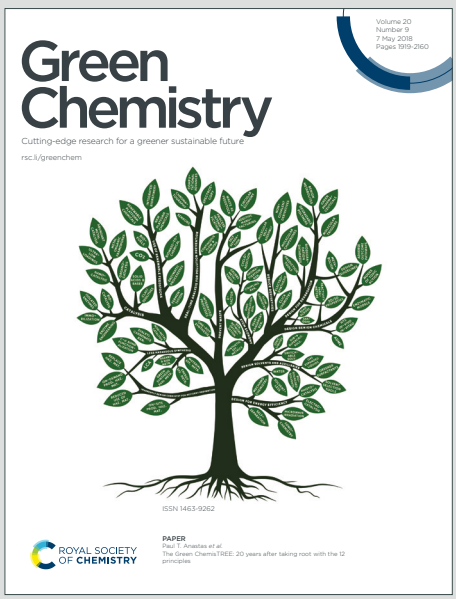

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ARTICLE

Chemoselective *O*-Formyl and *O*-Acyl Protection of Alkanolamines, Phenoxyethanols and Alcohols Catalyzed by Nickel-(II) and Copper-(II)-Catalysts

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Chemoselectivity is always crucial and challenging task for bi-functional compounds, as like alkanolamines, that have both amine and alcohol as reactive functional groups. Achieving 100% selectivity for *O*-formyl and *O*-acyl protection of alkanolamines is one of the examples of such reactions. To avoid protection and deprotection steps and overcome this problem, a novel chemoselective, efficient, and simple protocol of functional group protection as *O*-formylation and *O*-acylation of alkanolamines, phenoxyethanols and competitive *O*-selectivity between alcohols and amines, catalyzed by Ni-(II) and Cu-(II) complexes with 8-hydroxyquinoline at just catalyst loading of 5mol % in homogeneous medium has been presented here.Good to excellent yields are achieved in absence of solvent for *O*-formylation at room-temperature with formic acid as formyl source and *O*-acylation at 70 °C with acetic acid as acyl source. In addition, the minimal effluent and waste are generated during this reaction, as corresponding sodium salts of acids could be recovered during the process and can be reused. This chemistry readily tolerates variety of functional groups, demonstrated by 20 examples with 100% chemoselectivity for *O*-formylation and *O*-acylation of alkanolamines and 30 examples of *O*-formylation and *O*-acylation of phenoxyethanols and alcohols in presence of amines which have been synthesized successfully.

Introduction

O-formylation and *O*-acylation of alcohols are the most useful and versatile reactions in protective organic chemistry[1] that plays an important role in the synthesis of complex organic molecules such as natural products.[2] Moreover, many important drug molecules and natural flavoring food ingredients possess *O*-formyl and *O*-acyl moieties, to name a few like cefamandolenafate, ethynodioldiacetate, diltiazem, cefapirin, methacholine, citronellyl formate, geranyl formate, styralyl formate, geranyl acetate, vetiveryl acetate and benzyl acetate (Figure 1).

Many times it is observed that, in total synthesis, there is a need to protect one functional group and achieve the desired target molecule.[3] When two or more competitive reactive functional groups present in molecules like amino alcohols or alkanolamines, having both amine and alcohol groups; the chemoselective *O*-formylation and acylation in the presence of unprotected amines is still a challenging issue for academic and industrial researchers of organic chemistry. Moreover, significant examples of aromatic and aliphatic amino alcohols are not much studied in most of the known protocols. Hence, chemoselectivity in organic reactions is of enormous significance to synthetic organic chemists as it decreases excessive protection and deprotection steps and henceforth reduces the expense of the overall process.[2a]

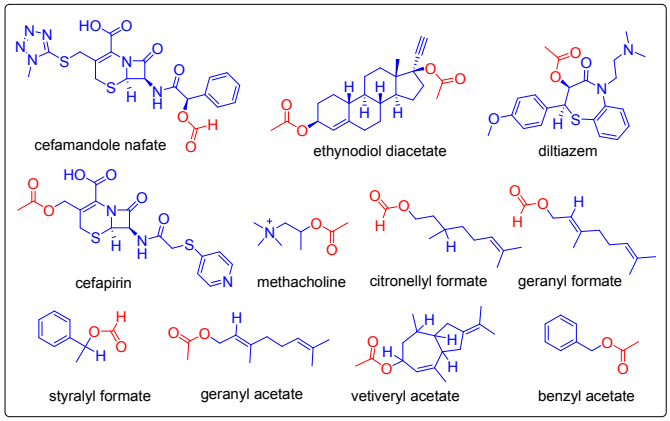

Figure 1. Drug molecules and natural flavoring food ingredients having *O*-formyl and *O*-acyl moieties.

As the nucleophilicity of the amino group is much more than that of the hydroxyl group, *N*-acylation takes place dominantly over *O*-acylation.[4] Moreover, formates show acid stability and easily can be removed under mildly basic conditions to which common esters are often stable.[5] In addition to permitting protection approaches, formates and acetates can be used as formyl and acyl sources in subsequent functional group interconversions.[6]

There are only few methodsavailable to protect –OH group chemoselectively[7] in the presence of $–NH_2$ group. The transesterification (*O*-acylation) of alcohols in presence of amines using various esters and μ-oxo-tetranuclear zinc cluster $Zn_4(OCOCF_3)_6O$[8] and μ-oxo-dinuclear iron(III) salen catalysts[9] have been reported. An esterification of hydrochloride salt of aminoalcohols using acid chloride has been studied.[10] Several

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acylating reagents are used for chemoselective *O*-acyaltion of aminoalcohols namely as 2,2'-bipyridyl-6-yl carboxylate with cesium fluoride,[11]2-acylpyridazin-3-ones,[12] 3-(trimethylacetyl)- 1,3-thiazolidine-2-thione,[13] carboxylic acid anhydrides,[14] acetic acid,[14a] acid chlorides,[14a] chloroacetyl chloride,[15] methyl benzoate,[16] vinyl enol esters[16,17]*ortho*-substituted*N,N*-diacetylaniline,[18]*N*-methoxydiacetamide,[19] 3-acylthiazolidine-2-thione,[20] andα-aryl-β-keto esters.[21]

Several catalysts have been used for chemoselective *O*-acyaltion of aminoalcohols such as $[\gamma\text{-}HGeW_{10}O_{36}]^{-7}$,[16] Cp*2Sm(thf)$_2$,[17]alkoxy-bridged dinuclear cobalt complex $[Co_4(OCOR)_6O]_2$ (R = CF_3, CH_3, tBu) with 2,2'-bipyridine ligand,[22] and microwave-promoted reactions catalyzed by dibutyltin oxide ($^nBu_2SnO$),[23] and $Y_5(OPr^i)_{13}O$[24] catalysts.

Chemoselective synthesis of 4-aminocyclohexyl acetate hydrochloride from 1-aminocyclohexanol·HCl has been reported using amine hydrochloride salt strategy.[25] Also direct acylation of unprotected hydroxyamino acids with acyl halides or carboxylic anhydrides under appropriately acidic reaction conditions has been reported for chemoselective *O*-acylation.[14a] Chemoselectivity of the *N*, *O*-enzymatic acylation in organic media and in ionic liquids has also been reported.[26] NHC catalyzed oxidative chemoselective *O*-acylation using various aldehydes with alcohols in presence of amines has been reported for corresponding esters.[27] Also NHC catalyzed oxidative esterification has been studied using aldehydes and trans esterification of various esters with amino alcohols.[28] Wang et. al.[29] has studied base- and acid-catalyzed interconversions of *O*-acyl- and *N*-acyl-ethanolamines which could be helpful for lipid analyses.

Moreover, several methods are available using lipase enzyme catalyzed chemoselective *N*-acylation of aminoalcohols.[30] Various reagents and catalysts have been used for chemoselective *N*-acylation of amines such as 2-fluoro-*N*-acyl-*N*-mesylanilines,[31]*N*-acyl-*N*-(2,3,4,5,6-penta-uorophenyl)methanesulfonamides,[32]*N*-acyl-4,5-dihydro-4,4-dimethyl-*N*-methyl-2-thiazolamine,[33] acylmethanesulfonamides,[34b] enzoylisothiocyanates,[35] carboxylic acids[36] and acetic anhydride[37] as reagentsand 9-BBN,[38] $B(OH)_3$,[39] $Fe(NO_3)_3.9H_2O$,[40] I_2,[41] $Zn(OAc)_2$,[42] MgO,[43] $[RuCl_2(dppe)_2]$ [dppe = (1,2-bis(diphenylphosphino)ethane)] Ru/phosphine complex[44] and *N*-heterocyclic carbenes (NHC)[45] as catalysts.

Subsequently, chemoselective *O*-formylation and acylation are also reported, where selective formyl protection of primary hydroxyl groups were achieved by using 2,4,6-trichloro-1,3,5-triazine and *N,N*-dimethylformamide in presence of lithium fluoride.[46] Selective *O*-formylation of alcohols in presence of phenols using silica triflate as catalyst[47] and using chloral[48] have been studied. Selective *O*-acylation of diols achieved by using $YbCl_3$, $Yb(OTf)_3$, and $CeCl_3$ as a Lewis acid catalysts with carboxylic acid anhydrides,[49] and selective acetylation of primary in the presence of secondary hydroxyl groups using catalyst $Cu(NO_3)_2.3H_2O$ and acetic acid as acyl source[50] are studied.

There are several methods reported for *O*-formylation of alcohols using formyl sources such as formic acid,[51] paraformaldehyde,[52] methyl formate,[53] ethyl formate,[54] 2,2,2-trifluoroethyl formate,[55] and formyloxy-acetonitrile.[56] Also *O*-acylation of alcohols using acyl sources as carboxylic acids,[54c,57] carboxylic acid anhydrides,[51b-d,54g,i,58] acylchlorides,[59] ethyl acetate,[54a,f,h,j,60] isopropenyl acetate,[61] vinyl acetate,[62] formyloxyacetoxyphenylmethane,[6a] 1,1-diacylals,[6a]tert-butyl acetate,[6b] and tert-butyl benzoate[6b] are reported.Dehydrative condensation of carboxylic acids and alcohols in the presence of an acid catalyst, or with stoichiometric dehydrating reagents or activated carboxylic acid derivatives in the presence of a stoichiometric base[63] are studied.

Several catalysts are used for *O*-acylation of alcohols, *viz.* lithium bis(perfluoroalkylsulfonyl)imide,[58a] SBA-15-functionalized sulfonic acid confined acidic ionic liquid,[57a] $ZrOCl_2.8H_2O$,[59] $Fe(OTs)_3$,[58b] and choline chloride·$2CrCl_3·6H_2O$,[57b] DMAP,[58c] Cp_2TiCl, Mn,[60a]silphos [PCl_3_n(SiO_2)n][54h] silica-bonded *N*-propyl sulfamic acid (SBNPSA),[54i]sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl)ester,[54j] ceric ammonium nitrate (CAN),[57c] p-toluenesulfonyl chloride,[51b] tribromoisocyanuric acid (TBCA),[51c] $Zr(HSO_4)_4$,[51d] t-BuONa,[6b] Et_2Zn,[62a-b] $YbCl_3·6H_2O$ or $CeCl_3·7H_2O$,[58d] Au/TiO_2,[52] *N*-heterocyclic carbene (NHC),[53] $TiCl_3(OTf)$,[58e] $HfCl_4·(THF)_2$ and $ZrCl_4·(THF)_2$.[57d]

Oxidative esterification of aldehydes using $ZnBr_2$ and H_2O_2,[64]anddirect oxidative esterification of alcohols catalyzed by $PdCl_2(CH_3CN)_2$ with dioxygen as the environmentally benign oxidant[65] has been reported. While oxidative esterification of alcohols and aldehydes using supported iron oxide nanoparticle catalysts[66] and imidazoliumperrhenate catalysts[67] has also been studied.

Consequently, the development of simple, efficient and selective methods for such widely used organic transformation from readily available reagents is one of the major challenges in the organic synthesis. However, many of these methods require either special acylating reagents or costly metal catalysts, which prompted us to study the *O*-formylation and *O*-acylation of crucial bi-functional aminoalcohols or competitive *O*-selectivity between alcohols and amines as a general and simple protocol for the chemoselectivity.

In our previous studies, new synthetic methods were developed using transition metal catalyzed *N*-formylation and *N*-acylation of amines. And after successful use of Ni-(II) as $[Ni(quin)_2]$[68] and Cu-(II) as $[Cu(quin)_2]$[69] catalysts, the work was continued using nickel-(II) and copper-(II) catalysts for *O*-formylation and *O*-acylation of alkanolamines with formic acid and acetic acid as a formyl and acylating sources, and 8-hydroxyquinoline as bidentate ligand.

Herein, a novel, chemoselective, efficient, and simple protocol of *O*-formyl and *O*-acyl protection of alkanolamines, phenoxyethanols, and competitive *O*-selectivity between alcohols and amines present together, catalyzed by $[Ni(quin)_2]$ catalyst (**C1**) and $[Cu(quin)_2]$ catalyst (**C2**) (Figure 2), the complexes with 8-hydroxyquinoline in homogeneous medium is reported (Schemes 1-5). Good to excellent yields are achieved in absence of solvent for *O*-formylation at room-temperature with formic acid as formyl source and *O*-acylation at 70 °C with acetic acid as acyl source. The reagents used are cheaper and do not require an inert atmosphere during the reaction. The corresponding protected *O*-formyl and *O*-acyl alkanolamines products are isolated with high selectivity (100%) and good to excellent yields (83-98%). Similarly, protection of phenoxyethanols and alcohols in presence of amines are synthesized with good to excellent yields (93–99%). This chemistry readily tolerates variety of functional groups with 100% chemoselectivity for *O*-formylation and *O*-acylation of various alkanolamines, phenoxyethanols, and few other alcohols.

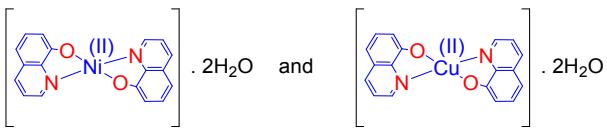


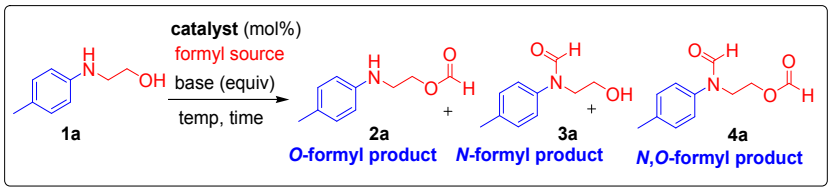
Figure 2.$[Ni(quin)_2]$ Catalyst (**C1**) and $[Cu(quin)_2]$ Catalyst (**C2**)

Results and discussion

Synthesis of [Ni(quin)$_2$] catalyst (C1) and [Cu(quin)$_2$] catalyst (C2): Catalysts (C1)[68] and (C2)[69] were synthesized and characterized by reported methods(Figure2) and used as such for this study.

Synthesis of alkanolamines (1) and phenoxyethanols (8): The starting materials alkanolamines and phenoxyethanols were synthesized and characterized by reported method and used as such for reactions.[70]

Table 1. Selected Observations during Reaction Optimization[a]



sr. no.	cat. (mol%)	formyl source (volume)	base (equiv)	temp (°C)	time (h)	conversion[b] (%)	**2a** yield[b] (%)	**3a** yield[b] (%)	**4a** yield[b] (%)
1	(**C1**) (5)	DMF (5)	triethylamine (2)	150	24	Nd	Nd	nd	nd
2	(**C1**) (5)	DMF (5)	DIPEA (2)	150	24	Nd	Nd	nd	nd
3	(**C1**) (5)	DMF (5)	2,6-lutidine (2)	150	24	Nd	Nd	nd	nd
4	(**C1**) (5)	DMF (5)	imidazole (3)	150	24	65	Nd	65	nd
5	(**C1**) (5)	DMF (5)	1,2,4-triazole (3)	150	24	62	Nd	62	nd
6	(**C1**) (5)	DMF (5)	$NaOCOCH_3$ (3)	150	24	Trace	Nd	trace	nd
7	(**C1**) (5)	DMF 5)	Na_2CO_3 (3)	150	24	15	Nd	15	nd
8	(**C1**) (5)	DMF (5)	$CsCO_3$ (3)	150	24	24	Nd	24	nd
9	(**C1**) (5)	DMF (5)	K_2CO_3 (3)	150	24	25	Nd	25	nd
10	(**C1**) (5)	DMF (5)	K_3PO_4 (3)	150	24	27	Nd	27	nd
11	(**C1**) (5)	98% FA (5)	--	70	6	85	24	nd	61
12	**(C1) (5)**	**98% FA(5)**	**--**	**Rt**	**6**	**95**	**95**	**nd**	**nd**
13	--	98% FA (5)	--	Rt	24	15	15	nd	nd
14	(**C1**) (2.5)	98% FA (5)	--	Rt	24	72	72	nd	nd
15	(**C1**) (1)	98% FA (5)	--	Rt	24	33	33	nd	nd
16	**(C2) (5)**	**98% FA (5)**	**--**	**Rt**	**6**	**95**	**95**	**nd**	**nd**
17	(**C3**)(5)	98% FA (5)	--	Rt	24	27	27	nd	nd
18	(**C4**)(5)	98% FA (5)	--	Rt	24	25	25	nd	nd
19[c]	(**C3**) (5)	98% FA (5)	--	Rt	24	92	92	nd	nd
20[c]	(**C4**) (5)	98% FA (5)	--	Rt	24	91	91	nd	nd
21[d]	(**C1**) (5)	98% FA (5)	--	Rt	24	Trace	Trace	nd	nd
22[e]	(**C1**) (5)	98% FA (5)	--	Rt	24	5	5	nd	nd
23[f]	(**C1**) (5)	98% FA (5)	--	Rt	24	7	7	nd	nd
24[g]	(**C1**) (5)	98% FA (5)	--	Rt	24	12	12	nd	nd
25[h]	(**C1**) (5)	98% FA (5)	--	Rt	24	5	5	nd	nd
26[i]	(**C1**) (5)	98% FA (5)	--	Rt	24	29	29	nd	nd
27[j]	(**C1**) (5)	98% FA (5)	--	Rt	24	25	25	nd	nd
28	(**C1**) (5)	50% FA (5)	--	Rt	24	7	7	nd	nd
29	(**C1**) (5)	98% FA (2.5)	--	Rt	24	75	75	nd	nd
30	(**C1**) (5)	98% FA (1)	--	Rt	24	52	52	nd	nd

[a]All reactions were carried out on a 0.2 g scale using (**1a**) (1.32mmol, 1 equiv), formyl source (5 volume), catalyst (**C1**) [Ni(quin)$_2$] or (**C2**) [Cu(quin)$_2$] or (**C3**) $NiCl_2.6H_2O$ or (**C4**) $CuCl_2.2H_2O$ (1 - 5 mol%) at temperature (rt to 150 °C) for 6-24 h. All reagent and substrate additions were done at room temperature (25 °C). [b]Isolated yields. [c]With 8-hydroxyquinoline as ligand (10 mol%). [d]Methanol (5 volume). [e]Dichloromethane (5 volume). [f]Acetonitrile (5 volume). [g]1,4-dioxane (5 volume). [h]Toluene (5 volume). [i]DMF (5 volume). [j]DMSO (5 volume).

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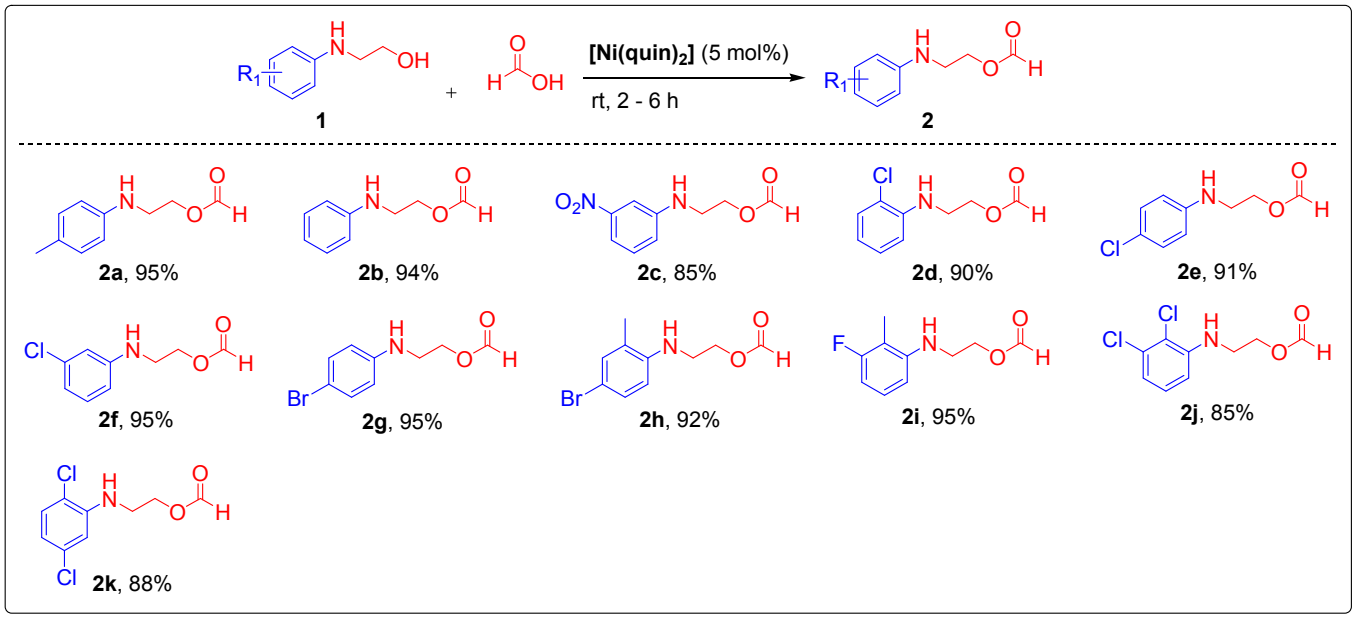
***O*-formylation and *O*-acylation of alkanolamines:** In preliminary reactions, 2-(p-tolylamino)ethanol (**1a**) was treated with 1 mL of *N,N*-dimethyl formamide (DMF) in the presence of 5 mol% of catalyst (**C1**) and 2 equiv of weak organic bases like triethylamine, DIPEA, and 2,6-lutidine at 150 °C for 24 h, however, no any conversion of chemoselective *O*-formylated product (**2a**) were observed by TLC (Table 1, entries 1–3). While, when 3 equiv of bases like imidazole and 1,2,4-triazole were used, dramatically only *N*-formamide product (**3a**) was observed instead of *O*-formyl product (**2a**) with moderate yields up to 62–65% (Table 1, entries 4–5). Subsequently, with inorganic bases like CH_3COONa, Na_2CO_3, $CsCO_3$, K_2CO_3,and K_3PO_4,*N*-formamide product (**3a**) was observed with lower yields up to 15–27% (Table 1, entries 6–10). After these trials, it was decided to use formic acid as formyl source instead of DMF for the reaction. Hence, a reaction was carried out with 2-(p-tolylamino)ethanol (**1a**) using 1 mL of 98% formic acid (FA) in the presence of 5 mol% of catalyst (**C1**) without any base and solvent at 70 °C; where *N, O*-formyl product (**4a**) was observed predominantly with 61% yield, while *O*-formyl product (**2a**) formed with only 24% yield and *N*-formyl product (**3a**) did not observed (Table 1, entry 11). To avoid di-formylation product and to know the effect of temperature, reaction was carried at room temperature, and to our surprise, chemoselective formation of *O*-formyl product (**2a**) was observed with excellent yield up to 95% (Table 1, entry 12). To know the effect of catalyst on reaction, a control experiment was performed without addition of catalyst (**C1**); decrease in yield of product (**2a**) was observed with 15% (Table 1, entry 13). This proves that catalyst (**C1**) is responsible for this conversion and plays important role. Hence, two more experiments were performed with limiting the concentration of catalyst (**C1**) at 2.5 mol% and 1 mol% instead of 5 mol% and remarkable decrease in the yields of product (**2a**) were observed respectively as 72% and 33% (Table 1, entries 14-15). These control experiments support the fact that the catalyst **C1** catalyses the reaction and plays vital role in presence of formic acid as formyl source. After successful trials on $[Ni(quin)_2]$ catalyst (**C1**), reaction was performed with 5 mol% of $[Cu(quin)_2]$ catalyst (**C2**) to explore the catalyst activity, where exciting result was observed similar to the catalyst (**C1**) giving desired chemoselective *O*-formyl product (**2a**) with 95% yield (Table 1, entry 16). When reactions were carried out using metal salts like $NiCl_2.6H_2O$ and $CuCl_2.2H_2O$ as catalyst (**C3**) and (**C4**) respectively, without addition of ligand 8-hydroxyquinoline, lower yields of product (**2a**) were observed respectively as 27% and 25% (Table 1, entries 17-18).

Scheme 1. Scope of *O*-formylation of alkanolamines catalyzed by $[Ni(quin)_2]$ catalyst[a]



[a]All reactions were carried out on a 0.2 g scale using (**1**) (1 equiv), formic acid (1mL, 5 volume), catalyst (**C1**) $[Ni(quin)_2]$ (5 mol%) at room temperature for 2-6 h. All reagent and substrate additions were done at room temperature (25 °C). [b]Isolated yields.

While, when reactions were performed using metal salts as catalysts (**C3**) and (**C4**), with addition of 10 mol% ligand 8-hydroxyquinoline to generate in-situ catalyst (**C1**) and (**C2**), competitive yields of product (**2a**), were observed, vis-à-vis with ready complexes as catalyst (**C1**) and (**C2**) (Table 1, entries 19-20). These experiments prove that ligand 8-hydroxyquinoline plays an important role in catalysis and also helps to make catalysts soluble in acidic medium as a homogeneous catalyst. To know the effect of solvent on reaction, various solvents were tested such as methanol, dichloromethane, acetonitrile, 1,4-dioxane, toluene, DMF and DMSO, but little conversion with lower yields of product (**2a**) were obtained in all cases (Table 1, entries 21-27). Also one experiment was performed using 50% formic acid in water instead of 98%, which also showed negligible conversion and lower yield of product (**2a**) like other solvents (Table 1, entry 28). This is may be due to decreased solubility of the catalyst in solvents used for reaction. To know the effect of limiting the volume of formyl source, reactions were performed using 2.5 and 1 volume of formyl source where lower yields of product (**2a**) were observed (Table 1, entries 29-30). Thus, these experiments suggest that reaction is suitable without any solvent using 5 volume of formic acid as formyl source.

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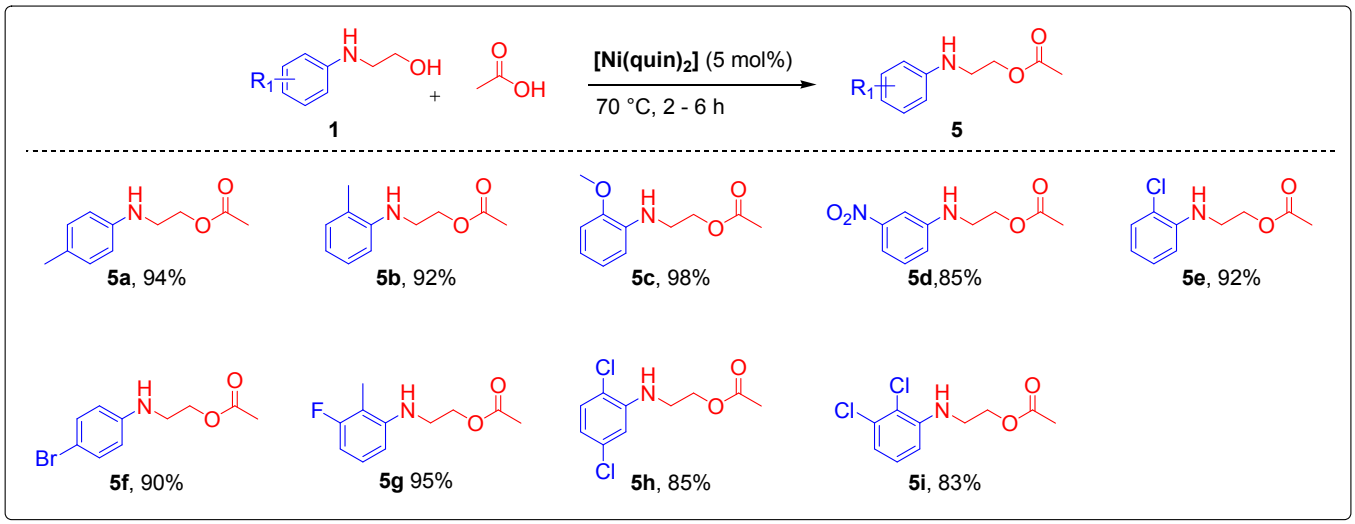
While exploring a method for *O*-acylation, a separate experiment was performed on 2-(p-tolylamino)ethanol (**1a**) using acetic acid instead of formic acid and without any other solvent, at optimized conditions; but no *O*-acylated product (**5a**) was observed at room temperature. Hence, it was decided to increase the temperature from ambient temperature to 70 °C where excellent conversion and yield of chemoselective *O*-acylated product (**5a**) up to 94% was obtained within 6 h.

Once optimized, chemoselective *O*-formylation and *O*-acylation using formic acid and acetic acid were successfully carried out for differently substituted alkanolamines, phenoxyethanols, and alcohols (Schemes 1-5). It was observed that different functionalities on alkanolamines such as alkyl, nitro and halides (F, Cl, Br) were unaltered (Schemes 1-2). Aromatic alkanolamines containing electron-donating group like –Me underwent the conversion smoothly to give excellent yield along with excellent chemoselectivity of *O*-formyl products **2a**, **2h** and electron-withdrawing group like $–NO_2$ at meta position gave high selectivity with good yield **2c**. For halide substituted alkanolamines, better conversions as well as yields were seen at all ortho, meta and para positions **2d-2k**. Similarly, *O*-acylation of various different functionalities on alkanolamines using acetic acid as acyl source also experienced similar effects on conversion with substituents having electron donating / withdrawing groups on ortho, meta and para positions that gave good to excellent yields (Scheme 2, **5a-5i**).

Scheme 2. Scope of *O*-acylation of alkanolamines catalyzed by [Ni(quin)$_2$] catalyst[a]



[a]All reactions were carried out on a 0.2 g scale using (**1**) (1 equiv), acetic acid (1mL, 5 volume), catalyst (**C1**) [Ni(quin)$_2$] (5 mol%) at 70 °C for 2-6 h. All reagent and substrate additions were done at room temperature (25 °C). [b]Isolated yields.

At the end of this study, a two gram-scale reaction of **1a** was performed for *O*-formylation and *O*-acylation respectively and similar reactivity was observed with excellent yields up to 95% for **2a** and 94% for **5a**. Also, formic acid and acetic acid were recovered from the reaction as their corresponding sodium salts as sodium formate and sodium acetate respectively. The recovery of both acids was found to be satisfactory with 96.7% for sodium formate and 96.5% for sodium acetate. The assay of both recovered salts was determined by titration method using 0.1N HCl solution and phenolphthalein as an indicator and assay found 99.6% for sodium formate and 99.5% for sodium acetate.

The strategy was further extrapolated for *O*-formylation and *O*-acylation of various different functionalities on phenoxyethanol (Schemes 3-4); which gave similar results as that for earlier strategy (Schemes 3-4, **9a-9l**, **10a-10h**). It also tolerated panel of broad functional groups as alkyl, halides, alkyl halide, methoxy, nitro, and esters.

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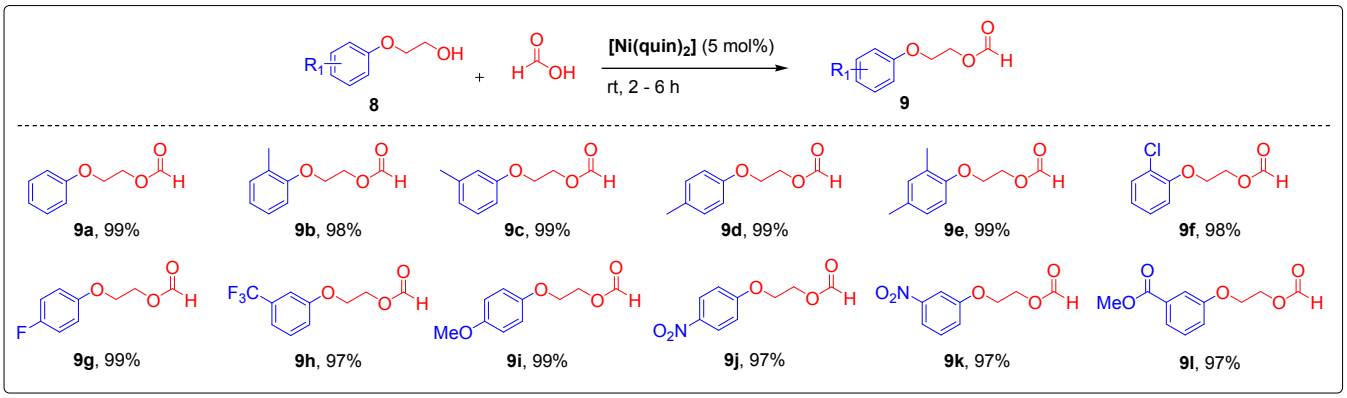
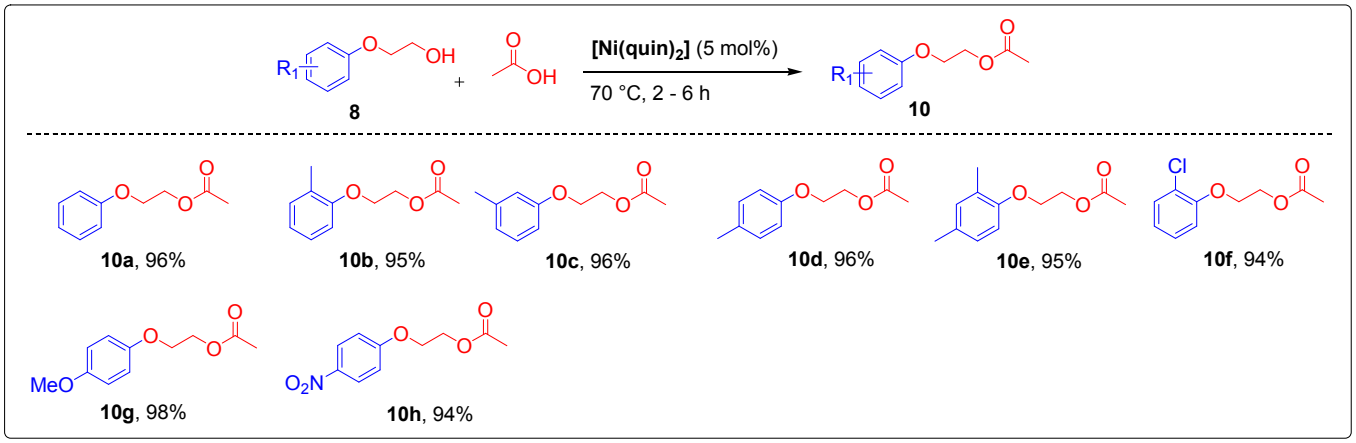
Scheme 3. Scope of *O*-formylation of phenoxyethanols catalyzed by [Ni(quin)$_2$] catalyst[a]



[a]All reactions were carried out on a 0.2 g scale using (**8**) (1 equiv), formic acid (1mL, 5 volume), catalyst (**C1**) [Ni(quin)$_2$] (5 mol%) at room temperature for 2-6 h. All reagent and substrate additions were done at room temperature (25 °C). [b]Isolated yields.

Scheme 4. Scope of *O*-acylation of phenoxyethanols and alcohols catalyzed by [Ni(quin)$_2$] catalyst[a]



[a]All reactions were carried out on a 0.2 g scale using (**8**) (1 equiv), acetic acid (1mL, 5 volume), catalyst (**C1**) [Ni(quin)$_2$] (5 mol%) at 70 °C for 2-6 h. All reagent and substrate additions were done at room temperature (25 °C). [b]Isolated yields.

After successful chemoselective *O*-formylation and *O*-acylation of alkanolamines and phenoxyethanols, this developed protocol was extended for various alcohols in presence of amines to show competitive *O*-formylation and *O*-acylation; and was found to give excellent yields (Scheme 5, **13a-13c**, **2b, 9a, and 15a-15c)**.In this study aromatic amines did not show any conversion of *N*-formyl product (**14a**)and *N*-acyl product (**16a**) when reacted with formic acid and acetic acid as acyl sources in presence of alcohols. While aliphatic amines reacted sluggishly and formed negligible yields of *N*-formyl and *N*-acyl products respectively. Also, reaction of alkanolamine (**1b**) in presence of phenoxyethanol (**8a**) (Scheme 5) showed similar reactivity, and the competitive *O*-formyl products **2b** and **9a** were obtained with 94% and 99% yields respectively with excellent chemoselectivity and did not show any formation of *N*-formyl product (**3b**) and *N,O*-formyl product (**4b**).

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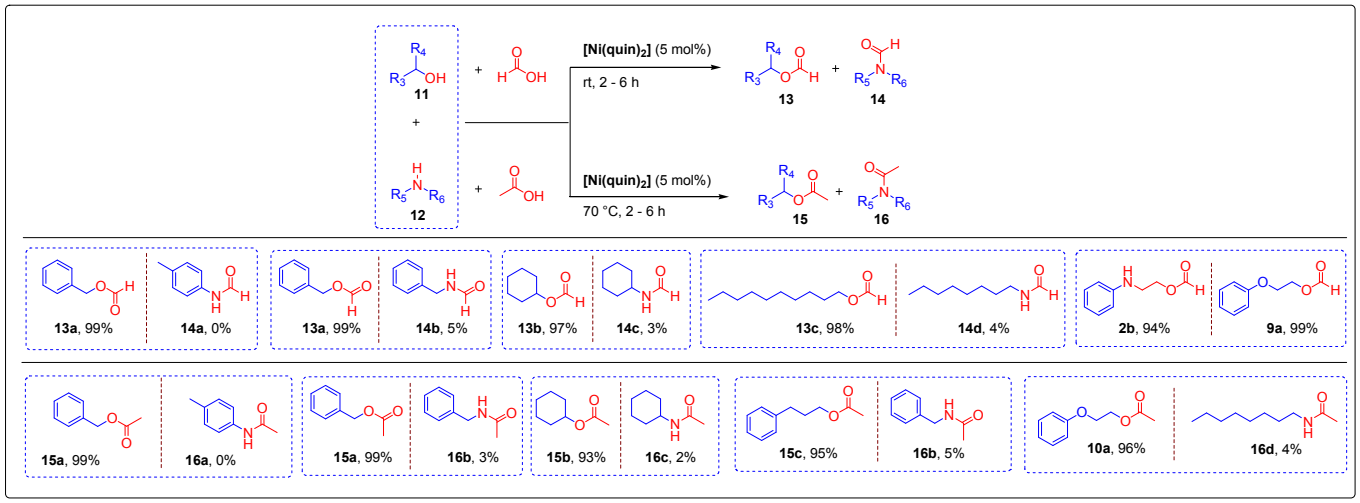
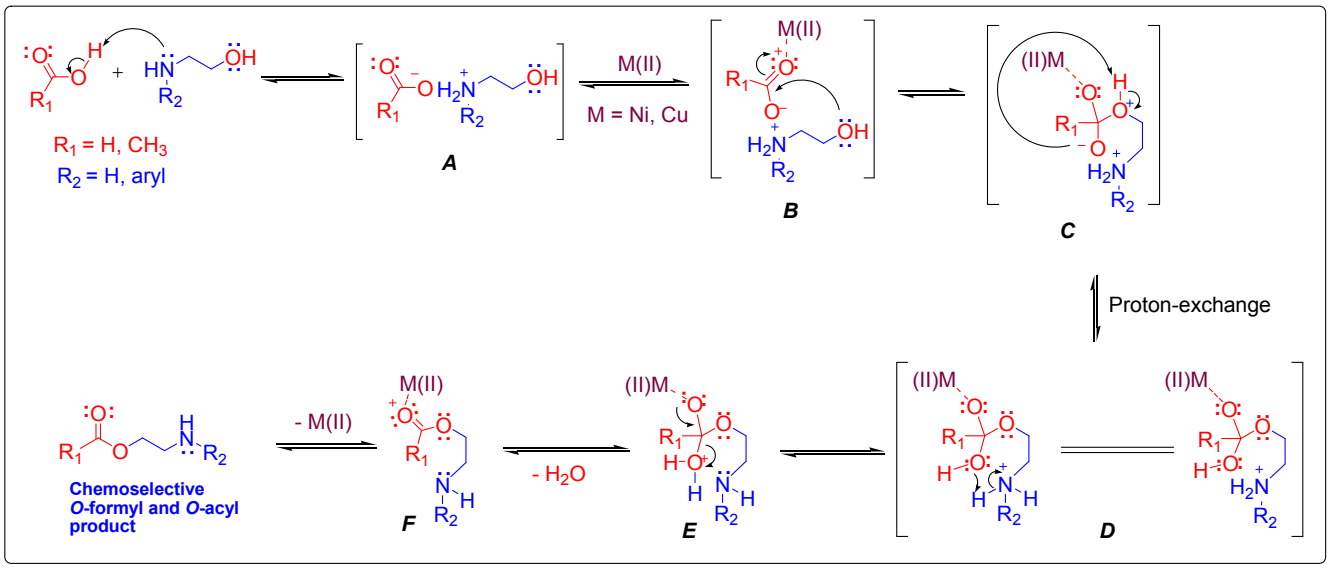
Scheme 5. Competitive chemoselective *O*-formylation and *O*-acylation of alcohols in presence of amines[a,b]



[a]All reactions were carried out on a 0.2 g scale using alcohol (**11**) (1 equiv), amine (**12**) (1 equiv), formic acid (1mL, 5 volume), catalyst (**C1**) $[Ni(quin)_2]$ (5 mol%) at room temperature for 2-6 h.
[b]All reactions were carried out on a 0.2 g scale using alcohol (**11**) (1 equiv), amine (**12**) (1 equiv), acetic acid (1mL, 5 volume), catalyst (**C1**) $[Ni(quin)_2]$ (5 mol%) at 70 °C for 2-6 h. All reagent and substrate additions were done at room temperature (25 °C). [c]Isolated yield given.

Plausible Mechanism of Chemoselective *O*-formylation and *O*-acylation of Alkanolamines: A plausible mechanism for the chemoselective *O*-formylation and *O*-acylation of alkanolamines, in accordance with the experimental results, is represented in (Scheme 6). Initially, amine of amino alcohol reacts with acidic hydrogen of carboxylic acid to form quaternary ammonium salt of amino alcohol (intermediate-***A***), then subsequently formic or acetic acid moiety gets activated via coordination with Ni-(II) or Cu-(II) catalysts (intermediate-***B***). Intermediate-***B***then gets cyclized to give intermediate-***C*** by attack of more nucleophilic oxygen, followed by proton exchange by shifting of acidic proton from one oxygen to another to give intermediate-***D.*** Then theacidic hydrogen from ammonium salt goes to more susceptible hydroxy group to give intermediate-***E***. Finally, intermediate-***E*** furnishes 100% chemoselective *O*-formyl and *O*-acyl product (intermediate-***F***) by eliminating water molecule followed by loss of Ni-(II) or Cu-(II) catalysts for next catalytic cycle.

Scheme 6. Plausible mechanism of *O*-formylation and *O*-acylation of alkanolamines catalyzed by Ni-(II) and Cu-(II) catalysts



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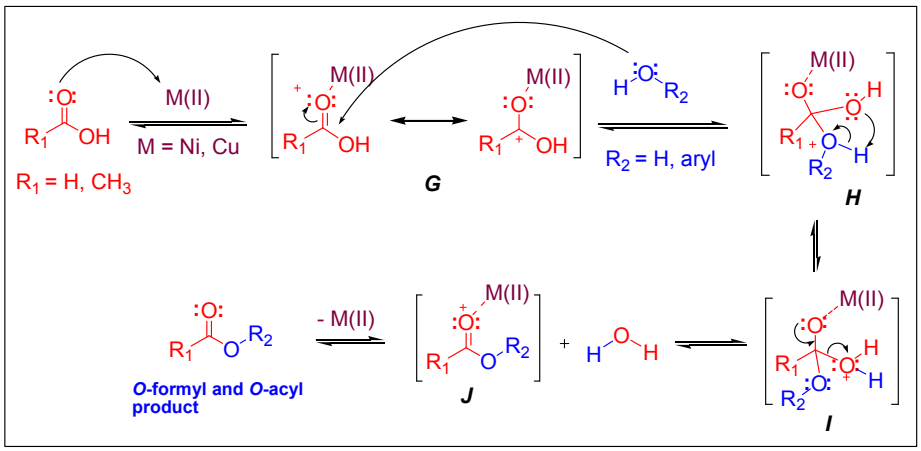
Plausible Mechanism of *O*-formylation and *O*-acylation of Phenoxyethanols and Alcohols: A similar mechanism can be predicted for the *O*-formylation and *O*-acylation of phenoxyethanols and alcohols, as represented in (Scheme 7). Initially, formic or acetic acid gets activated via coordination with Ni-(II) or Cu-(II) catalysts (intermediate-***G***). Then alcoholic –OH of phenoxyethanols or alcohols attack on carbonyl carbon of activated intermediate-***G*** and forms tetrahedral intermediate-***H***; which then undergoes proton exchange by shifting of acidic proton to give intermediate-***I***. This is followed by the elimination of water molecule giving intermediate-***J***. Finally, intermediate-***J*** furnishes *O*-formyl and *O*-acyl product leaving behind the Ni-(II) or Cu-(II) catalysts for next cycle. All the control experiments data, afford several revelations regarding the identity of this plausible mechanism. Pleasantly, all the *O*-formylation and *O*-acylation reactions proceeded efficiently to furnish respective substituted phenoxyethanols and alcohols with moderate to excellent yields.

Scheme 7. Plausible mechanism of *O*-acylation of phenoxyethanols and alcohols catalyzed by Ni-(II) and Cu-(II) catalysts



Conclusions

In conclusion, a novel, chemoselective, and simple method to attain the *O*-formyl and *O*-acyl protection of alkanolamines, phenoxyethanols, and competitive *O*-selectivity between alcohols and amines present together, catalyzed by Ni-(II) and Cu-(II) complexes with 8-hydroxyquinoline in homogeneous medium has been developed. *O*-formylation at room-temperature using formic acid as formyl source and *O*-acylation at 70 °C using acetic acid as acyl source, with good to excellent yields in absence of solvent could be achieved. The effluent and waste are generated during this reaction are minimal and corresponding sodium salts of acids could be recovered and reused. The milder conditions allow the broad functional group tolerance for alkanolamines and phenoxyethanols. No need of inert atmosphere, easy operational and workup procedures are useful for many future syntheses.

Conflicts of interest

There are no conflicts to declare.

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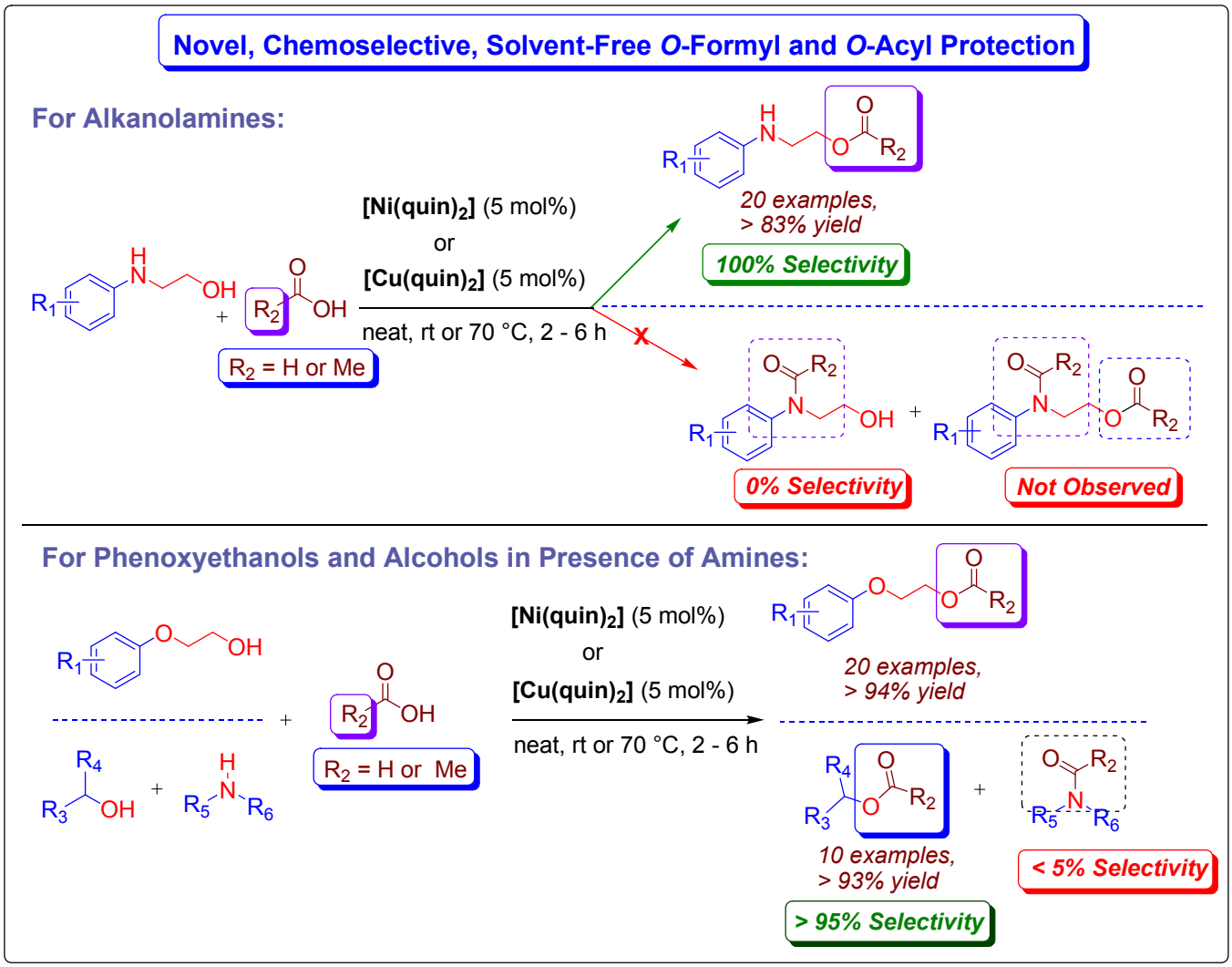

A crucial chemoselective *O*-formyl and *O*-acyl protection of alkanolamines and phenoxyethanols, and alcohols in presence of amines catalyzed by Ni-(II) and Cu-(II) complexes with 8-hydroxyquinoline in homogeneous medium is achieved.