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Ni-catalyzed α-alkylation of unactivated amides and esters with alcohols *via* hydrogen auto-transfer strategy

Siba P. Midya,[1] Jagannath Rana,[1] Jayaraman Pitchaimani,[2]Avanashiappan Nandakumar,[1]Vedichi Madhu[2]* and Ekambaram Balaraman[1]*

Abstract: Transition-metal-catalyzed borrowing hydrogen/hydrogen auto-transfer (BH/HA) strategy allows to utilize feedstock alcohols as alkylating partner that avoids the formation of stoichiometric salt waste and enables a direct and benign approach for the construction of C-N and C-C bonds. Here,we reporta nickel-catalyzed α-alkylation of unactivated amides and ester (*tert*-butyl acetate) using primary alcohols under mild conditions. This C-C bond forming reaction catalyzed by a new, molecularly defined NNN-nickel(II) complex (0.1 - 1 mol%) and proceeds *via* HA strategy, thereby releasing water as the sole by-product. In addition, *N*-alkylation of cyclic amides under Ni-catalytic conditions is shown.

The development of new sustainable approaches that utilize the fundamental feedstocks in the key chemical transformation is extremely important in contemporary science. The α-alkylation of carbonyl derivatives using alcohols is one of the most important transformations and found manifold applications in natural product chemistry, and peptide modifications.[1-2] In general, the α-alkylation is achieved by electrophilic alkylation of an alkyl halide with an alkali-metal enolate of carbonyl derivative, which can generate the desired product along with a stoichiometric amount of metal salt.[3] Alternatively, transition-metal catalyzed hydrogen auto-transfer (HA) strategy has been explored for α-alkylation of the carbonyl compounds, wherein alcohol is used as an alkylating reagent. Moreover, HA strategy provides an excellent atom-economical as well as a step-economical process with the liberation of water as a sole by-product and thus, overcome the limitations of classical approaches.[4-7]

Notably, HA strategy has been widely investigated using the noble-metal catalysts for the C-alkylation (or α-alkylation) of carbonyl compounds, and amine derivatives.[5-7] However, C-alkylation of unactivated carbonyl compounds such as amides and esters remains extremely challenging, due to the least acidic nature of α-CH bond of amides and esters.[8] The catalytic α-alkylation of unactivated amides and esters by alcohols has significant advances in chemical synthesis. In this direction, noble-metal such as Ir, and Ru-catalyzed α-alkylation of amidesand esters (in particular *tert*-butyl acetate) have been reported in recent years.[9] The sustainability of such processes is highly challenging because of the use of less abundant and expensive noble-metal catalysts. Consequently, a numerous efforts have been devoted to replace the noble-metals with earth-abundant 3d transitionmetals for the similar or better reactivity.[10-11] Very recently, Kempe and co-workers reported earth-abundant and non-precious PN_3P-cobalt pincer complex for the C-alkylation of amides and esters, thereby enabling sustainable development for C-C bond forming reactions.[12]

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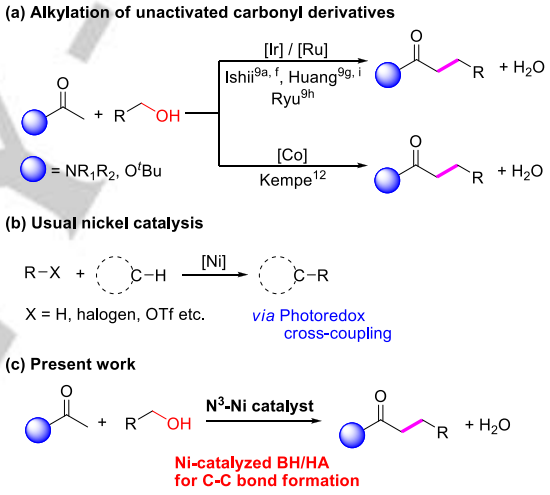
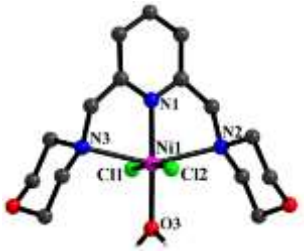
Nickel is one of the most naturally abundant and low-cost 3d transition metals and found manifold applications in various cross-coupling reactions,[13] and photo-redox catalysis[14] to activate the inert C-X (X = O, N, C or H) bonds.In recent times, intensive applications of nickel catalysis in chemical manufacturing and pharmaceutical industry are depicted as a conclusive sustainable alternative to the noble-metal catalysts. To date, the application of well-defined nickel catalyst for HA/BH reactions in homogeneous catalysis is highly demanding and remains elusive.[15] Herein, we reporta sustainable and phosphine ligand-free Ni-based catalytic system for α-alkylation of unactivated amides and ester (*tert*-butyl acetate) *via* C-C bond forming HA strategy (Scheme 1).



Scheme 1.Ni-catalyzed C-C bond forming reactions.

The new N^3-nickel(II) pincer complexes **1**-**2** were synthesized and characterized using the state of the art analytical methods. Notably, the nitrogen-based tridentate ligand, 2,6-bis(morpholinomethyl)-pyridine (Py-N^3; **L**) can be synthesized by straightforward under open-air atmosphere, which has the practical advantages for the scaled-up process (gram-scale).[16] The reaction of Py-N^3 with $NiCl_2.6H_2O$, and $NiBr_2.6H_2O$ in MeOH at room temperature resulted the corresponding Ni-complexes **1**(85% yield) and **2** (81% yield), respectively (see ESI and Figure 1). Complexes **1**-**2** were characterized by elemental analysis, high-resolution mass spectrometry (HRMS), and infrared spectroscopy. Electron paramagnetic resonance (EPR) analysis showed the paramagnetic nature of Ni(II)-complexes. The X-ray crystal structure analysis of **1** indicated a unimolecular structure, which is made up of hexacoordinatedNi(II) ion. The neutral N^3 ligand is coordinated to the nickel center in a typical tridentate mode, with N1−Ni1−N2 and N1−Ni1−N3 bond angle of 77.19(5)° and 77.18(5)°, respectively. Selected bond distances and angles are given in the caption of Figure 1. Significantly, complexes **1** and **2** can be handled under ordinary atmosphere,since they are not sensitive towards oxygen and moisture over a considerable period (~ 1 month).



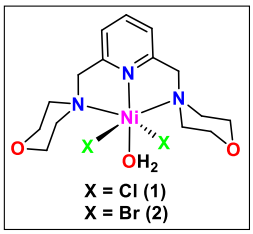
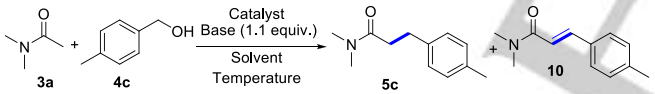


Figure 1.Single crystal X-ray structure of **1** (left). Hydrogen atoms (except H_2O) were omitted for clarity. Selected bond length [Å] and angle [°]: Ni1-N1 1.9945(14), Ni1-O3 2.0260(14), Ni1-N2 2.3520(14), Ni1-N3 2.3709(15), Ni1-Cl2 2.3979(5), Ni1-Cl1 2.4266(5) and N1-Ni1-O3 178.67(6), N1-Ni1-N2 77.19(5), O3-Ni1-N2 103.81(6), N2-Ni1-N3 154.37(5), N1-Ni1-Cl2 94.95(4), Cl2-Ni1-Cl1 172.23(17) [CCDC No: 1814945].

Remarkably, the present Ni-complexes have shown the finest activity in the α-alkylation of unactivated amides and esters using alcohols as alkylating agent. This reaction enables the direct synthesis of C-alkylated amides and esters with the liberation of water. The reaction of *N*,*N*-dimethyl acetamide (**3a**) with 4-methyl benzyl alcohol (**4c**) was taken as the model substrates (Table 1). Common reaction parameters including catalysts, solvents, reaction temperature, and base were investigated systematically using model substrates. Initially, the reaction of **3a** (0.25 mmol), and **4c** (0.125 mmol) in the presence of Ni-pincer complex **1** (2.5 mol%) and KO^{t}Bu (0.13 mmol) in THF at 100 °C resulted in 72% yield of dimethyl-3-*p*-tolylpropanamide (**5c**; Table 1, entry 1). Under similar conditions, Ni-pincer complex **2** gave 66% yield of **5c** (Table 1, entry 2), while the simple $NiBr_2.6H_2O$ afforded only 25% of the alkylated product (Table 1, entry 3).

Table 1.Optimization of alkylation of *N*,*N*-dimethyl acetamide (**3a**) with 4-methyl benzyl alcohol (**4c**).[a]



Entry	Catalyst	Base	Solvent	Temperature (°C)	Yield (%) (**5c**/**10**)	TON/TOF (h^{-1})
1	**1**	KO^{t}Bu	THF	100	72/n.d	72/3
2	**2**	KO^{t}Bu	THF	100	66/n.d	66/2.8
3	$NiBr_2.6H_2O$	KO^{t}Bu	THF	100	25/n.d	25/1.1
4	**1**	KO^{t}Bu	n-Octane	100	87/7	87/3.6
5	**1**	KO^{t}Bu	m-Xylene	100	68/5	68/2.8
6	**1**	KO^{t}Bu	Dioxane	100	58/n.d	58/2.4
7	**1**	KOH	n-Octane	110	78/n.d	78/3.3
8	**1**	K^{i}OPr	n-Octane	110	71/n.d	71/3.0
9	**1**	Na^{t}OBu	n-Octane	110	47/n.d	47/2.0
10	-	KO^{t}Bu	n-Octane	110	0	-
11	**1**	-	n-Octane	110	trace	-
12	1	KO^{t}Bu	n-Octane	110	90[b]/3	90/3.8
13	**1**	KO^{t}Bu	n-Octane	110	77[b],[c],[d]/n.d	77/3.2
14	**1**	KO^{t}Bu	n-Octane	110	82[e]/3	820/34.2

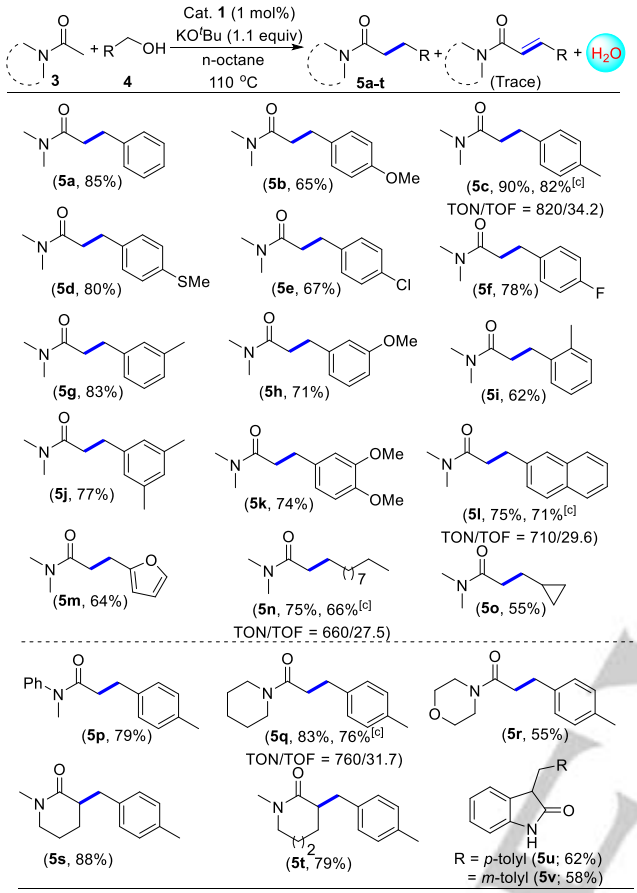
[a]Reaction conditions: 0.25 mmol of **3a**, 0.125 mmol of **4c**, catalyst **1** (2.5 mol%), KO^{t}Bu (1.1 equiv.), and 1 mL of solvent heated for 24 h. Yield determined by GC using 1,4-dibromo butane as an internal standard. [b] Isolated yield using 1 mol% of catalyst **1**. [c] 0.125 mmol of **3a** and 0.25 mmol of **4c**.[d] Formation of corresponding benzyl benzoate derivative (~3%). [e] Reaction performed using 0.1 mol% of cat.**1**. n.d = Not detected.

Next, the effect of solvents on α-alkylation reaction was examined. The n-octane found to be the optimal solvent and gave 87% of **5c** (Table 1, entry 4), whereas other solvents such as *m*-xylene or 1,4-dioxane provided unsatisfactory yields under standard conditions (Tabl1 1, entries 5-6). Screening of various bases such as KOH, KO^{i}Pr, and NaO^{t}Bu under similar catalytic conditions gave also unsatisfactory results (Table 1, entries 7-9). In absence of the catalyst or the base, no formation of product was observed (Table 1, entries 10-11). After careful investigations, the best result was obtained by employing amide (2 equiv) and alcohol (1 equiv) in the presence of Ni-pincer complex **1** (1 mol%) and KO^{t}Bu (1.1 equiv) in n-octane at 110 °C (93% GC yield). Indeed, changing the ratio of *N*,*N*-dimethyl acetamide (**3a**):4-methyl benzyl alcohol (**4c**) to 1:2, lowered the yield of the desired C-alkylated amide to 77% (Table 1, entry 13). Gratifyingly, using a low catalytic amount of (0.1 mol% of **1**) the C-alkylation reaction worked efficiently, and the product **5c** was isolated in 82% yield with TON of 820 (Table 1, entry 14). It is noteworthy to mention that the present N^3-nickel(II) pincer complex **1** showed the superior reactivity with a low catalytic loading (0.1 - 1 mol%), when compared to previously reported PN_3P-cobalt pincer complex (2.5 mol%).[12]

With this excellent progress on optimization condition, we studied the substrate scope of the Ni-catalyzed α-alkylation process by varying alcohols and amides (Table 2). The reaction of *N*,*N*-dimethyl acetamide (**3a**) with benzyl alcohol proceeded well to afford the alkylated amide **5a** in 85% isolated yield. Benzyl alcohol derivatives containing electron-donating substituents at the *para* position (methoxy, methyl, and thiomethyl) also led to the desired products **5b**-**5d** in good to excellent yields (up to 90% yields; Table 2). Electron-withdrawing substituents (chloro and fluoro) at the *para* position of benzyl alcohol provided the corresponding α-alkylated products**5e** and **5f** with good yields under optimal conditions (products **5e** in 67%, and **5f** in 78% yields). Methyl and methoxy substituents at the *meta* and the *ortho* position of the benzyl alcohol furnished the expected C-alkylated amides in very good yields (Table 2, **5g**-**i**). Furthermore, benzyl alcohol containing dimethyl and dimethoxy substituents provided the corresponding products **5j** (77%), and **5k** (74%) in excellent yields and 2-naphthyl methanol readily converted into α-alkylated amide **5l** in 75% yield. The reaction of furfuryl alcohol with **3a** offered the expected C-alkylated amide **5m**in 64% isolated yield.It is noteworthy that aliphatic alcohols (**4n** and **4o**) smoothly reacted with **3a** under our nickel-catalyzed conditions and offered the cross-dehydrogenative coupling products **5n** and **5o** in 75% and 55% isolated yields, respectively. Gratifyingly, using a low catalytic amount of (0.1 mol% of **1**) the C-alkylation reaction worked efficiently, and the product **5n** was isolated in 66% yield. Under similar conditions (0.1 mol% of cat.**1**), the C-alkylated products **5c**, **5l**, and **5q** were obtained in 82%, 71%, 76% yields, respectively with excellent TONs (products **5c** in 820, **5l** in 710, and **5q** in 760). Next, we have investigated the scope of amide substrates under the optimal reaction conditions. Thus, *N*-methyl-*N*-phenylacetamide (**3p**), 1-(piperidin-1-yl)ethan-1-one (**3q**), and 1-morpholinoethan-1-one (**3r**) smoothly reacted with **4c** under nickel-catalyzed conditions and led to the corresponding C-alkylated amides (Table 2, products **5p**-**5r**) in moderate to good yields (55% - 83% yields). Gratifyingly, *N*-methylated cyclic amides (**3s** and **3t**) underwent C-alkylation and gave the corresponding α-branched amides **5s** (88% yield) and **5t** (79% yield) under standard reaction conditions. Interestingly, 2-oxindole efficiently reacted with various alcohols (aryl alcohols) under optimized reaction conditions and led to the corresponding C-alkylated derivatives (products **5u**-**5v**) in good yields (up to 62% yield)Thus, the present N^3-nickel(II) pincer

complex catalyzed C-alkylation amides using alcohols showed broad substrate scope and operates under mild conditions.

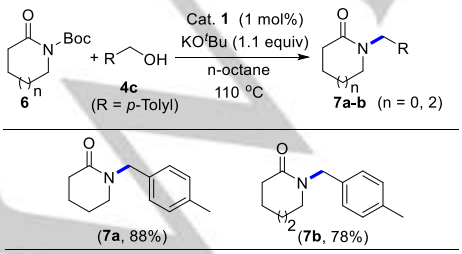
Table 2.Ni-catalyzed α-alkylation of amides: Scope of alcohols and amides.[a],[b]



[a] Reaction conditions: 0.4 mmol of **3**, 0.2 mmol of **4**, 1 mol% of catalyst **1**, KO^{t}Bu (0.22 mmol), and 1 mL of n-octane heated at 110 °C under argon atmosphere for 24 h. [b] Isolated yields. [c] 0.1 mol% of [Ni] and yields based on GC.

Interestingly, *N*-Boc protected cyclic amides (**6a** and **6b**) underwent *N*-alkylation of cyclic amides to afford **7a** (88%), and **7b** (78%) in excellent yields under standard reaction conditions (Table 3).Indeed, we didn't observe the formation of C-alkylated product. The reaction proceeds through a base-mediated Boc-deprotection[17] followed by Ni-catalyzed *N*-alkylation of liberated *sec*.cyclic amides (see ESI).

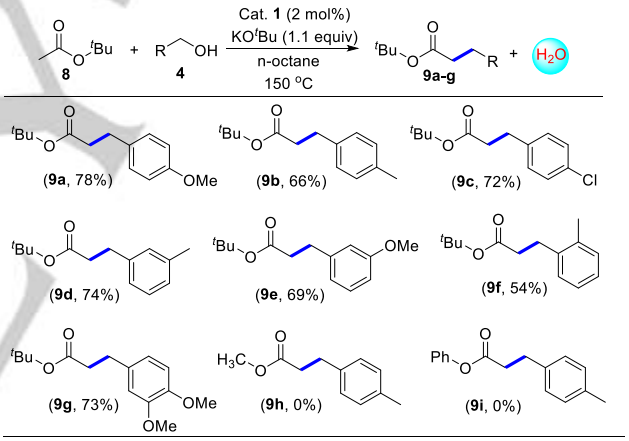
Table 3.Tandem *N*-deprotection-*N*-alkylation of amides.[a],[b]



[a] Reaction conditions: 0.4 mmol of **6**, 0.2 mmol of **4c**, 1 mol% of catalyst **1**, KO^{t}Bu (0.22 mmol), and 1 mL of n-octane heated at 110 °C under argon atmosphere for 24 h. [b] All reported isolated yields are the average of two independent experiments.

In light of the high activity of the Ni-catalytic system, we began to explore the use of *tert*-butyl acetate as coupling partner to access α-alkylated ester derivatives. In the initial study, the reaction between *tert*-butyl acetate (**8**) and 4-methoxy benzyl alcohol (**4b**) in the presence of 1 mol% of catalyst **1** at 110 °C to form a corresponding *C*-alkylated ester **9a** in 27% yield (see SI for details). However, the changing of other solvents, such as toluene, *m*-xylene, and 1,4-dioxane did not improve the product yield. The highest yield (80%) of the product **9a** was obtained at the elevated temperature (150 °C; see ESI). With this optimized condition in hand, various benzyl alcohols have been regio-selectively introduced and thus, giving rises to the C-alkylated *tert*-butyl acetate. All the C-alkylated acetate derivatives (**9a–g**) were isolated in moderate to good yields (54-78%; Table 4). Thus, the present Py-N^3-Ni(II) complex displayed a general method for direct synthesis of α-alkylated *tert*-butyl acetates. However, under standard conditions other acetate derivatives (ethyl acetate and benzyl acetate) failed to yield the expected C-alkylated products. This is due to the competing base-mediated transesterification reaction.

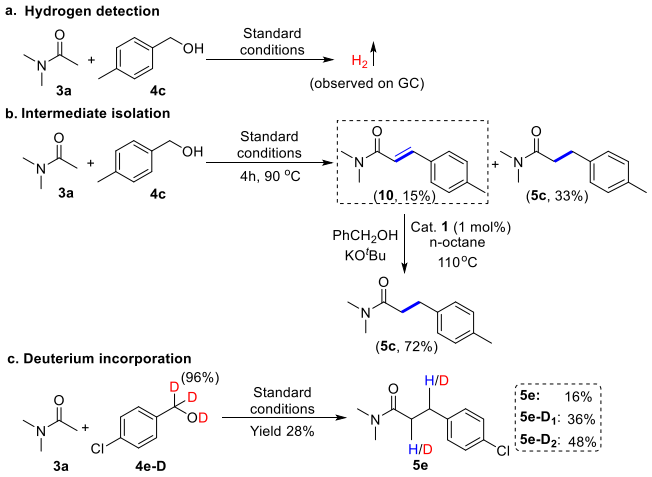
Table 4. The scope of alcohols for the α-alkylation of ester.[a],[b]



[a] Reaction conditions: 0.8 mmol of **8**, 0.2 mmol of **4**, 2 mol% of catalyst **1**, KO^{t}Bu (0.22 mmol), and 1 mL of n-octane heated at 150 °C under argon atm for 24 h. [b] Isolated yields.

To understand the mechanistic insights, the benchmark substrate *N*,*N*-dimethyl acetamide**3a** with 4-methyl benzyl alcohol **4c** was investigated under standard catalytic conditions (Scheme 2). The formation of hydrogen gas was qualitatively analyzed using gas chromatography (GC). This result suggests that the present Ni-catalysis proceeds *via*dehydrogenative pathway (Scheme 2a). Importantly, the reaction of *N*,*N*-dimethyl acetamide (**3a**) with 4-methyl benzyl alcohol (**4c**) under standard reaction conditions (at 90 °C) in 4 hr gave the mixture of intermediate **10** (15%) and **5c** (33%).Further, the treatment of intermediate (*E*)-*N*,*N*-dimethyl-3-*p*-tolylacrylamide (**10**) in presence of benzyl alcohol under catalytic conditions smoothly converted into hydrogenated product **5c** (Scheme 2b). This result revealed that the formation of **10** is the critical intermediate in the catalytic cycle and upon catalytic hydrogenation (either by hydrogen molecule generated in the initial dehydrogenation step or transfer of Ni-H to the C=C unsaturated bond) lead to the C-C bond forming alkylation process. The deuterium labeling experiment was carried out with amide **3a** and 4-chloro benzyl alcohol **4e-D** under standard

reaction conditions (Scheme 2c). The formation of amide **5e** is in agreement with the microreversibility of initial alcohol dehydrogenation process. The resulted product ratio of mono and bis-deuterated amides (**5e-D1** and **5e-D2**) revealed that one of the benzylic C-H/D bonds has to be cleaved to initiate the α-alkylation process.



Scheme 2.Mechanistic investigations of Ni-catalyzed α-alkylation of amide.

The addition of 200 equiv. of mercury to the catalytic reaction slightly reduced the reaction yield (78%), though it could not quench the reaction completely. Time-dependent kinetic study on *α*-alkylation of amide **3a**with alcohol **4c**was carried out under our Ni-catalyzed conditions (Fig. 2a). With different time interval, continuous sampling was undertaken, and the yield of C-alkylated amide **5c** was determined. These experimental findings showed that the present Ni-catalysis is homogeneous in nature and stable during the catalysis. The reusability of the present homogeneous Ni-catalyzed C-alkylation of amide was demonstrated (Fig. 2b). Thus, the reaction of **3a** with **4c** under standard reaction conditions was carried out by externally adding starting materials into the reaction mixture (without additional catalyst) after every 24 h and monitored the catalytic efficiency of the nickel catalyst. Interestingly, the desired product **5c** was obtained in moderate yield after 3rd cycle.[18]

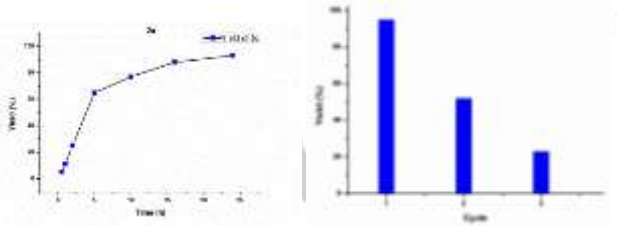
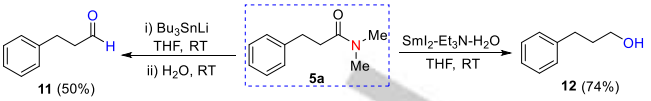


Figure 2a.Kinetic profile for the C-alkylation of **3a**. ***Figure 2b.*** Recyclability test of Ni-catalyzedC-alkylation of **3a**.

The direct transformation of amides to other value-added chemicals is an emerging area, and many practical methods have been developed.[19]The direct transformation of *α*-alkylated amide (**5a**) is shown in Scheme 3. The compound **5a** was reacted with Bu_3SnLi to afford the aldehyde **11** with 50% isolated yield.[20a] The amide **5a** was converted into alcohol **12** in 74% yield by using samarium(II) iodide-water-amine reagent.[20b] As shown in Scheme 3, the resulted α-alkylated amide was efficiently converted into the corresponding aldehyde and alcohol derivatives, and thus, these methods can be used for the extension the alcohol substrate by two carbon atoms.



Scheme 3.The direct transformation of α-alkylated amide.

In summary, we developed an efficient Ni-catalyzed α-alkylation of unactivated amides and ester (*tert*-butyl acetate)*via* hydrogen auto-transfer strategy. The present C-C bond forming reaction of amide and ester is catalyzed by a new, air-stable molecularly defined N^3-nickel (II) complex under mild conditions with a low-catalytic loading (0.1 - 1 mol%). The practical late-stage transformation was successfully demonstrated to extend the scope of α-alkylated amides.

Acknowledgements

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Keywords: Nickel catalysis• Amides• Hydrogen auto-transfer• C-Alkylation• Homogeneous catalysis

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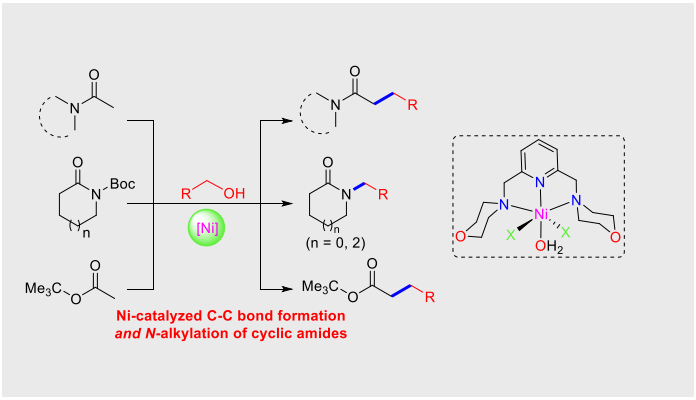
Table of Contents:

Herein,most efficient 3d transition metal, nickel-catalyzed α-alkylation of unactivated amides and esters using primary alcohols is presented. This C-C bond forming reaction catalyzed by a new, molecularly defined NNN-nickel(II) complex(0.1 - 1 mol%) and proceeds *via* borrowing hydrogen/hydrogen auto-transfer (BH/HA) strategy, thereby releasing water as the sole by-product. The scope of this methodology was applied for the synthesis of corresponding alcohol and aldehyde, which showed the extension of carbon backbone of alkylating alcohol by two units. In addition, *N*-alkylation of cyclic amides (transamidation reaction) under Ni-catalytic conditions is shown.



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Ni-catalyzed α-alkylation of unactivated amides and esters with alcohols *via* hydrogen auto-transfer strategy