Nickel-Catalyzed Esterification of Amides Under Mild Conditions

Jun-Fei Li[1,2] · Yao-Fang Wang[1,2] · Yuan-Yuan Wu[1,2] · Wen-Jing Liu[1,2] · Jun-Wen Wang[1,2]

Abstract

The use of ligands to adjust the catalytic activity of the catalyst for esterification of amides is challenge in organic chemistry. In this paper, Nickel(II)-NHC-catalyzed the esterification reaction between N,N-di-Boc amide and alcohols at room temperature have been demonstrated. The imidazolium salt bearing a hydroxyl functionalized side arm showed high effective catalytic activity in the activation of the amide N–C bond in air atmosphere.

Graphic Abstract
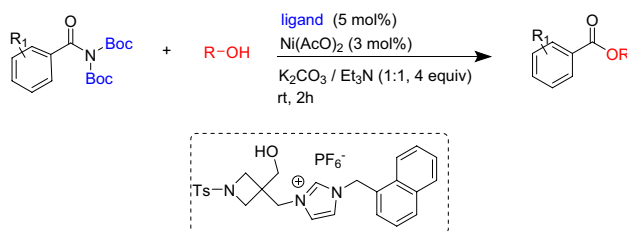
1 Introduction

Amides are a ubiquitous functional group in organic molecule, which are the important building blocks of proteins and were widely found in natural and synthetic compounds [1–4]. It's more difficult to break the C–N bond of amide in synthetic chemistry. Direct catalytic esterification of amides is one of the challenges in organic chemistry. The C–N bond of amide

Jun-Fei Li and Yao-Fang Wang have contributed equally to this work.

✉ Jun-Wen Wang
   wangjunwen2013@126.com

1 Key Laboratory of Magnetic Molecules & Magnetic
   Information Materials Ministry of Education, Shanxi Normal
   University, Linfen 041004, China

2 The School of Chemical and Material Science, Shanxi
   Normal University, No. 1, Gongyuan Street, Linfen 041004,
   China

undergoes activation by the principle of amide bond resonance destabilization, some examples of N-acyl-glutarimides, N-Boc-amides and N–Ts-amides have been documented the activation of C-bonds of amides. This approach allows for the breakdown of amides, and renders amides useful synthetic building blocks [5–7]. In 2015, Garg and co-workers first reported the esterification of amides using Ni-catalyzed activation of the amide bond, and used density functional theory (DFT) calculations to proved thermodynamically favoured (Fig. 1a) [8–11]. The catalytic system reported is the use of Ni(0) precatalyst (Ni(cod)$_2$, SIPr, PhMe, 60–110 °C). However, Ni(cod)$_2$ is not air-stable and requires handling in an inert atmosphere, which limits its widespread use in chemical synthesis. Later, Danoun provided the amide to ester interconversion using Co-catalyzed activation of the amide bond (Fig. 1b). This methodology presents a very practical process that does not require an inert atmosphere under mild reaction conditions (CoBr$_2$, Mn, bipyridine, DMF/pyridine, 60 °C) [12]. Soon afterwards, Takashi Ohshima and co-workers developed the direct catalytic alcoholysis of 8-aminoquinoline amides in presence of Ni(II) diketonate catalysts (Ni(tmhd)$_2$,

Fig. 1 a Conversion of amides to esters by the nickel-catalysed activation of amide C–N bonds. **b** Cobalt-catalyzed Esterification of Amides. **c** Transition-metal-free Esterification of Amides at rt (previous works). **d** Esterification of amides under the room temperature (this study)
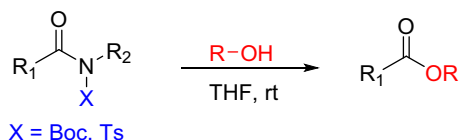
A Previous work: Conversion of amides to esters by the nickel-catalysed activation of amide C-N bonds
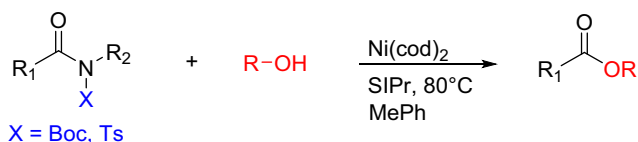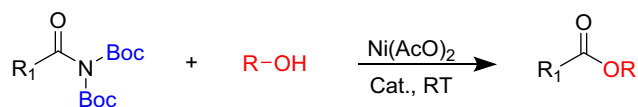
B Previous work : Cobalt-Catalyzed Esterification of Amides
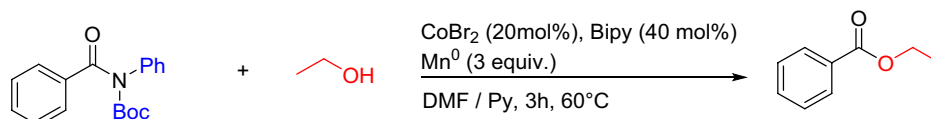
C Previous work : Transition-metal-free Esterification of Amides at rt

D This work: Esterification of amides under the room temperature

nickel(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate) at 80 °C for 12 h [13]. In 2018, Michal Szostak report a simple method for transition-metal-free esterification of amides under mild room temperature conditions (Fig. 1c) [14].

To our knowledge, N-heterocyclic carbene have been widely used to catalyze organic reactions, and various types of carbene catalysts with different structures have been synthesized [15–22]. Although the system of Ni(0) precatalyst and N-heterocyclic carbene (Ni(cod)$_2$, SIPr) has been successfully used in the esterification of amides, the esterification of amides reported in the literature was carried out at a high temperature (60–110 °C). It is necessary to explore a kind of catalyst that can catalyze the esterification of amides under mild conditions. Here in, we have prepared a novel the imidazolium salt precatalyst bearing a hydroxyl functionalized side arm, and designed a method for esterification of amide by using Ni(AcO)$_2$/NHC catalyst under mild conditions (Fig. 1c). It is worth nothing that this methodology is particularly effective for esterification of amide in air atmosphere relative to the Ni(0) precatalyst in an inert atmosphere.

2 Experimental Section

2.1 General Procedures

The compounds N,N-di-Boc amides were prepared according to literature methods. All reagents were obtained from commercial sources and used without further purification. The compound (**B**) were prepared according to the literature procedures [23–26], and 3-Bromo-2,2-bis(bromomethyl)propan-1-ol is commercially available which using as a flame retardant. NMR spectra were obtained on a Bruker Avance III HD 600 MHz spectrometer. The chemical shifts are expressed in ppm and are internally referenced. All products were characterized by their ^{1}H NMR and ^{13}C NMR that were identical to those in the literature. Melting point determination were measured by an WRS-2 melting point apparatus.

2.2 Synthesis of Imidazolium Salt Ligand (C)

3-(Bromomethyl)-1-(*p*-toluenesulfonyl) azetidin-3-yl)
methanol (**B**) (2 g, 5.99 mmol) and 1-(naphthalen-1-yl-
methyl) imidazole (1.25 g, 6.0 mmol) was dissolved in
the solvent of THF and the solution was stirred for 5
days at 60 °C. A white powder was obtained. The raw
imidazolium salt was purified by recrystallization with
DMF and water. NH_4PF_6 (1.23 g, 7.55 mmol) was added
to a CH_3OH (30 mL) solution of the obtained imidazo-
lium salt, and a white precipitate formed immediately.
The pure imidazolium salt was obtained by recrystal-
lization with CH_3CN and ethyl ether. Yield: 86%, M.P.
186.0–187.3 °C; ^{1}H NMR (d_6-DMSO, 600 MHz): δ = 9.37
(s, 1H), 8.13 (d, $J = 7.9$ Hz, 1H), 8.03 (t, $J = 6.3$ Hz, 2H),
7.76 (d, $J = 6.3$ Hz, 2H), 7.56–7.65 (m, 5H), 7.50 (d,
$J = 6.9$ Hz, 1H), 7.45 (d, $J = 7.9$ Hz, 2H), 5.94 (s, 2H),
5.17 (t, $J = 5.0$ Hz, 1H), 4.32 (s, 2H), 3.61 (d, $J = 8.8$ Hz,
2H), 3.45 (d, $J = 8.8$ Hz, 2H), 3.11 (d, $J = 5.0$ Hz,2H),
2.44 (s, 3H) ppm. ^{13}C NMR (d_6-DMSO, 125 MHz):
δ = 144.571, 137.862, 133.875, 131.233, 130.813,
130.548, 130.418, 130.072, 129.372, 128.596, 127.888,
127.662, 126.926, 126.163, 124.111, 123.336, 123.176,
63.195, 54.956, 51.403, 50.464, 38.910, 21.588 ppm.
Anal. calcd for $C_{26}H_{28}F_6N_3O_3PS$: C 51.40, H 4.65; found:
C 51.43, H 4.67.

2.3 Typical Procedure for the Esterification of the Amides

In a typical run, a mixture of $Ni(AcO)_2$ (3 mol%),
admides (0.195 mmol), base (4 equiv, 0.78 mmol), ligand
(5 mol%), alcohol (2 mL) was stirred at room tempera-
ture for 2 h. After the reaction time, the contents were
quenched with 10 mL water and extracted with dichlo-
romethane. The combined organic extract was washed
with brine (15 mL) and dried over anhydrous $MgSO_4$, fil-
tered, and concentrated under vacuum. The crude product
was purified by column chromatography to afford ester
compounds.

3 Results and Discussion

In this work, we prepared a NHC-precatalyst (**C**) fol-
lowing the synthetic methods shown in Scheme 1. The
6-(p-toluenesulfonyl)-2-oxa-6-azaspiro [3.3] heptane (**A**)
was synthesized from tribromopentaerythritol and p-tol-
uenesulfonamide by refluxing 96 h in ethanol with KOH
as base. Subsequently, the oxetane opening in a solution of
hydrobromic acid gave a (3-(Bromomethyl)-1-(p-toluene-
sulfonyl) azetidin-3-yl) methanol (**B**) [23–26]. The imida-
zole hexafluorophosphate ligand (**C**) was readily prepared
by refluxing the 3-(Bromomethyl)-1-(p-toluenesulfonyl)
azetidin-3-yl) methanol (**B**) and 1-(naphthalen-1-ylmethyl)
imidazole in THF, followed by ion-exchange with PF_6^- in
methanol.

Our initial attempt was to optimize reaction conditions
using N,N-di-Boc activated amide and methanol with
different bases at room temperature (Table 1). Initially,
among the different types of bases examined in the esterifi-
cation reaction, yields of **2a** vary by 10–90%. We observed
about 10–20% yield of products using strong bases KO^tBu
and KOH in the esterification of amide at room tempera-
ture for 2 h (Table 1, entries 3 and 4). To our delight, and
then we tried to use some weak bases, such as K_2CO_3,
Et_3N, K_3PO_4, KOAc and Na_3PO_4, and the yields went up.
The product **2a** was obtained in 62% and 70% yields using
K_2CO_3 and Et_3N as bases in the esterification of amides
under mild condition, respectively (Table 1, entries 1 and
2). Interestingly, when the mixed bases K_2CO_3 and Et_3N
(1:1, 4 equiv) were accidentally used as bases, the yield
(90%) was dramatically improved in methanol at 25 °C
(Table 1, entry 6). Recently, Michal Szostak report the
general, mild, and highly chemoselective method for
transamidation of unactivated tertiary amides by a direct
acyl N–C bond cleavage with non-nucleophilic amines
[27–29]. So we tried to reduce the amount of nickel ace-
tate, and found that nickel acetate facilitated the reaction
under optimal conditions (entry 13 and 14). These show
that the nickel plays a vital role in the metal-catalysed
activation of C–N bonds of amides under mild condition
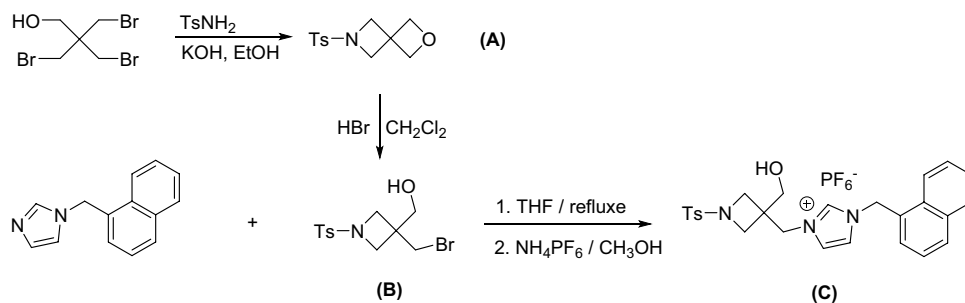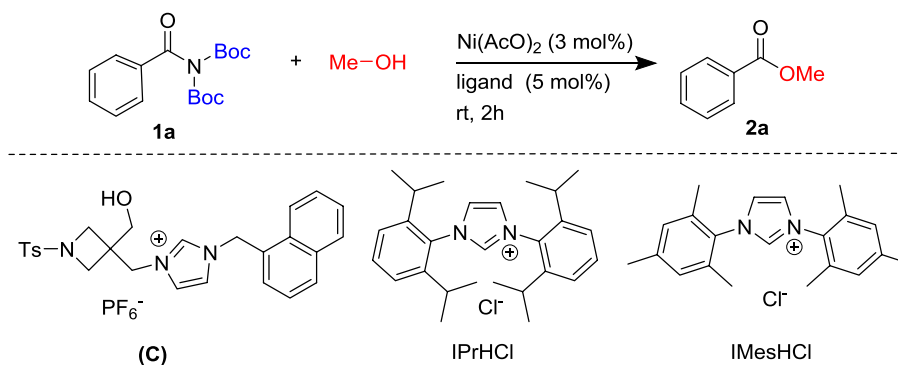with alcohols as reactants and solvents.

Scheme 1 Synthesis of the ligand (**C**)

Table 1 Optimization of reaction conditions

Entry	Base	Ligand	Time	Yield (%)[a]
1	K_2CO_3	**C**	2	62
2	Et_3N	**C**	2	70
3	KO^tBu	**C**	2	21
4	KOH	**C**	2	12
5	K_3PO_4	**C**	2	35
6	$K_2CO_3 + Et_3N$	**C**	2	90
7	$K_2CO_3 + Et_3N$	IPrHCl	2	78
8	$K_2CO_3 + Et_3N$	IMesHCl	2	81
9	Na_2CO_3	**C**	2	31
10	KOAc	**C**	2	41
11	Na_3PO_4	**C**	2	37
12	$K_2CO_3 + Et_3N$	**No**	2	36
13	$K_2CO_3 + Et_3N$	**C**	2	58[b]
14	$K_2CO_3 + Et_3N$	**C**	2	38[c]

[a]Isolated yield based on an N,N-Boc$_2$-amide. Reaction condition: 0.195 mmol of admides, 0.78 mmol base, 5 mol% of ligand, 3 mol% of Ni(AcO)$_2$, rt, 2 h
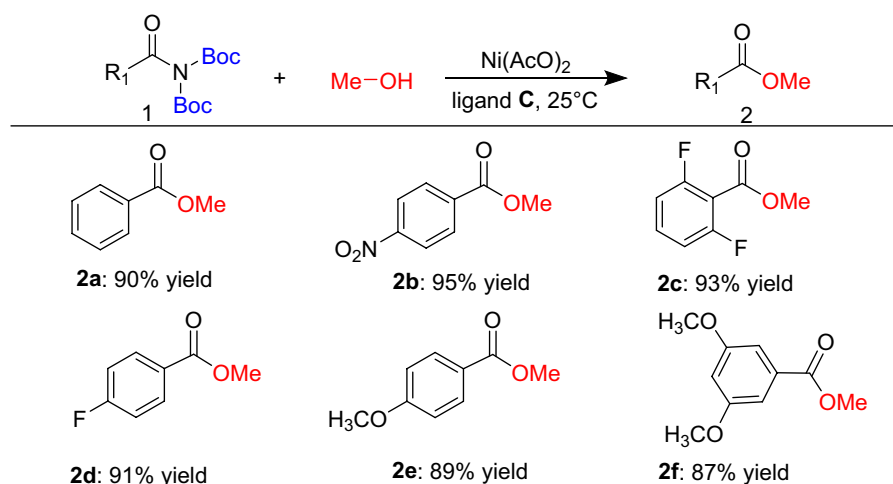
[b]1.0 mol% of Ni(AcO)$_2$

[c]Without Ni(OAc)$_2$

After extensive optimization, we were delighted to find that the reaction of N,N-di-Boc activated amide and methanol achieved a yield of 90% at room temperature using K_2CO_3 and Et_3N (1:1, 4 equiv) as mixed base and Ni(OAc)$_2$/ligand (**C**) as catalyst (Table 1, entry 6). We then focused on testing the catalytic efficiency of different catalysts. On comparing the results with those catalysts, a considerably higher activity of ligand (**C**) can be observed than the analogous IPrHCl and IMesHCl in methanol under optimized condition of the esterification reaction (entries 6–8). We further evaluated the ligands in the reaction of N,N-di-Boc activated amides and methanol at room temperature, and found that the reaction could be complete within 2 h using the system of Ni(OAc)$_2$/ligand

(**C**) as catalyst, while other catalysts took 5 h. We identified the ligand (**C**) as a promising Ni(II)-NHC precatalyst for the esterification of amides.

The good catalytic activity of ligand (**C**) may be attributed to hydroxyl functional groups in ligand molecules structure. In recent years, some N-heterocyclic carbene containing functional groups (N, O) has been reported successively [30]. With the assistance of these functional arms, the N-heterocyclic carbene complexes formed are more stable and have better catalytic activity. For example, in 2014, Hameury studied the influence of hydroxyl functional group in the arm of the N-heterocyclic carbene Pd (II) and Ni (II) complexes, the results show that hydroxyl side arm raised the Ni (II) complex catalytic activity in

Scheme 2 Substrate Scope for the esterification of amides. Isolated yield based on an N,N-Boc₂-amide. Reaction condition: 0.195 mmol of admides, 0.78 mmol of K₂CO₃ and Et₃N (1:1, 4 equiv), 5 mol% of ligand **C**, 3 mol% of Ni(AcO)₂, rt, 2 h

[a] Isolated yield based on an N,N-Boc₂-amide. Reaction condition: 0.195 mmol of admides, 0.78 mmol of K₂CO₃ and Et₃N (1:1, 4 equiv), 5 mol% of ligand **C**, 3 mol% of Ni(AcO)₂, rt, 2 h.

ethylene oligomerization [31]. In 2016, Ohmiya also reported that the chiral N-heterocyclic carbene ligand modified by naphthol hydroxyl was used as the precatalyst to catalyze allylic alkylation of azoles, and the selectivity of this reaction was as high as 93% [32]. According to the methods reported in the literature, the value of the one-bond CH J-coupling constant of ligand C is 223.2 Hz, which is slightly smaller than that in the literature ($^1J_{CH}$(IPr) = 223.7 and $^1J_{CH}$ IMes = 225.2 Hz) [33]. This suggests that salt c has a slightly stronger σ-donor ability than IPr and IMes as a nucleophilic carbene.

Under the optimized conditions, we evaluated the preparative substrate scope of the reaction of the esterification of N,N-di-Boc amides and methanol at room temperature (Scheme 2). We were pleased to find that the formation of methyl ester (**2a**–**f**) occurred in 87–95% of yields for the substituted aromatic amides, which tolerates electron-rich (**2e**,**f**) and electron-withdraw (**2b**–**d**) substituents on the aromatic rings. The electron-withdrawing groups substituted on the benzene ring (**2b**–**d**) were lightly favored for the reaction, and the reaction could be finished in 2 h at room temperature. Meanwhile, the position of the substituents such as ortho-position (**2c**), meta-position (**2f**), and para-position (**2b**, **2d**,**e**) have little effect under the optimized reaction conditions. 2,6-difluoro-substituted N,N-di-Boc amide afforded **2c** in 93% yield, 3,5-dimethoxyl-substituted amide also gave the corresponding ester (**2f**) in 87% isolated yields, respectively.

The scope of alcohols is focus on the alkyl alcohols (**3a**–**r**), and tolerates a range of primary alcohols (**3a**–**f**, **3m**–**r**), secondary alcohols (**3g**–**l**), and tertiary alcohols (**3s**,**t**). Notable, the reaction can be carried out under mild conditions with alcohols as reactants and solvents, and afford the desired products in modest to good yields (Scheme 3). Importantly, the sterically hindered alcohols such as tertiary alcohols (**3s**,**t**) react relatively slowly under the optimized conditions. Tertiary alcohols can be smoothly transformed, affording the desired products (**3s**,**t**) in 12 h.

The hypothesis of the reaction mechanism has been described in reference (Scheme 4) [8, 10, 11]. The catalytic mechanism of the nickel-catalyzed esterification of amides is thought to proceed via oxidative addition, ligand exchange, and reductive elimination.

4 Conclusion

In conclusion, a convenient and direct esterifications of N,N-di-Boc amides using the Ni-NHC catalyst has been developed at room temperature. The imidazolium salt with a hydroxyl functionalized side arm showed high effective catalytic activity in the esterification of N,N-di-Boc amide. The reactions could be successfully carried out by using Ni(AcO)₂/NHC catalyst in the alkyl alcohols solvents with the mixed bases of K₂CO₃ and Et₃N (1:1) as base at room temperature. Notable, this methodology is particularly effective for esterification of amide in air atmosphere relative to the Ni(0) precatalyst in an inert atmosphere.
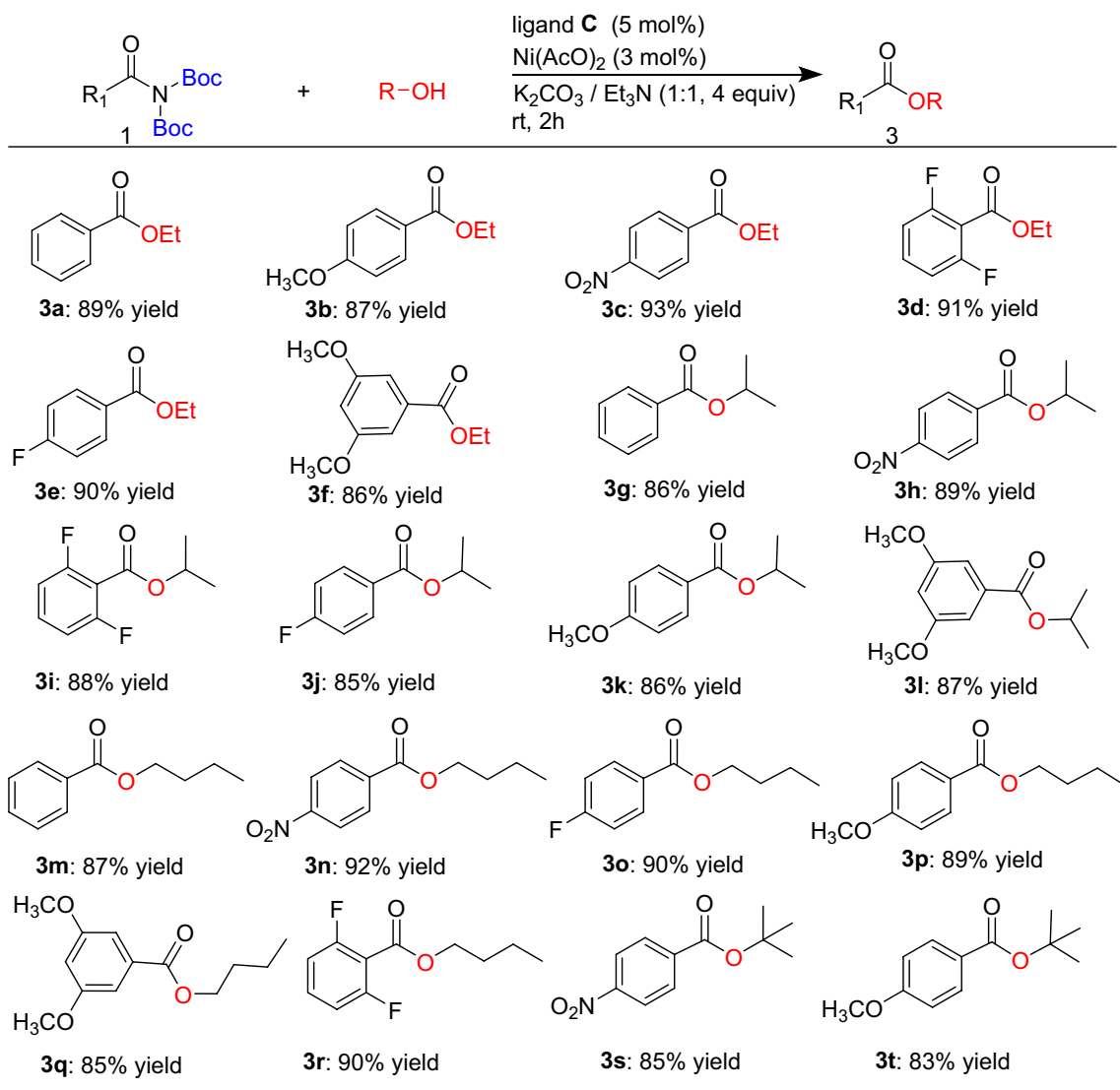
^{a} Isolated yield based on an N,N-Boc$_2$-amide. Reaction condition: 0.195 mmol of admides, 0.78 mmol of K$_2$CO$_3$ and Et$_3$N (1:1, 4 equiv), 5 mol% of ligand **C**, 3 mol% of Ni(AcO)$_2$, rt, 2 h.

Scheme 3 Nickel-NHC-Catalyzed Esterification of N,N-di-Boc Amides. Isolated yield based on an N,N-Boc$_2$-amide. Reaction condition: 0.195 mmol of admides, 0.78 mmol of K$_2$CO$_3$ and Et$_3$N (1:1, 4 equiv), 5 mol% of ligand **C**, 3 mol% of Ni(AcO)$_2$, rt, 2 h
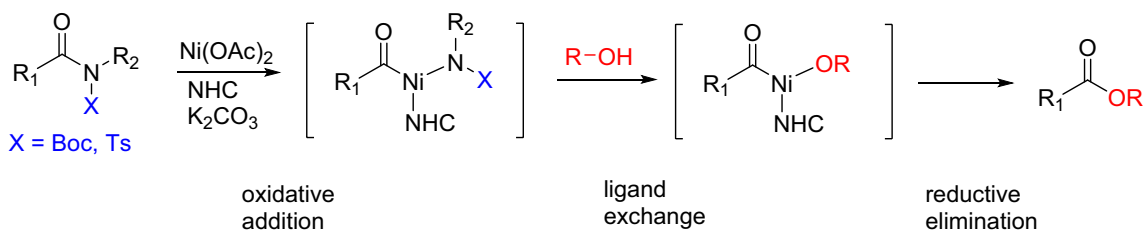
Scheme 4 Proposed mechanism of the reaction nickel-catalyzed esterification of amides

5 Supplementary Material

Supplementary data associated with this article can be found in the online version.

^{1}H and ^{13}C NMR Spectra of Products.

References

1. Pattabiraman VR, Bode JW (2011) Nature 480:471
2. Tani K, Stoltz BM (2006) Nature 441:731
3. Takise R, Muto K, Yamaguchi J (2017) Chem Soc Rev 46:5864
4. Walsh CT, O'Brien RV, Khosla C (2013) Angew Chem Int Ed 52:7098
5. Shi S, Nolan SP, Szostak M (2018) Acc Chem Res 51:2589–2599
6. Buchspies J, Szostak M (2019) Catalysts 9:53
7. Meng G, Szostak M (2018) Eur J Org Chem 20–21:2352
8. Hie L, Nathel NF, Shah T, Baker EL, Hong X, Yang Y-F, Liu P, Houk KN, Garg NK (2015) Nature 524:79
9. Dander JE, Weires NA, Garg NK (2016) Org Lett 18:3934
10. Dander JE, Garg NK (2017) ACS Catal 7:1413
11. Weires NA, Caspi DD, Garg NK (2017) ACS Catal 7:4381
12. Bourne-Branchu Y, Gosmini C, Danoun G (2017) Chem Eur J 23:10043
13. Deguchi T, Xin H-L, Morimoto H, Ohshima T (2017) ACS Catal 7:3157
14. Li G, Lei P, Szostak M (2018) Org Lett 20:5622
15. She Z, Wang Y, Wang D, Zhao Y, Wang T, Zheng X, Yu Z-X, Gao G, You J (2018) J Am Chem Soc 140:12566
16. Cheng J, Sun J, Yan J, Yang S, Zheng P, Jin Z, Chi YR (2017) J Org Chem 82:13342
17. Guo C, Janssen-Müller D, Fleige M, Lerchen A, Daniliuc CG, Glorius F (2017) J Am Chem Soc 139:4443
18. Pucino M, Inoue M, Gordon CP, Schowner R, Stöhr L, Sen S, Hegedüs C, Robé E, Tóth F, Buchmeiser MR, Copéret C (2018) Angew Chem Int Ed 57:14566
19. Halima TB, Zhang W, Yalaoui I, Hong X, Yang Y-F, Houk KN, Newman SG (2017) J Am Chem Soc 139:1311
20. Wang D, Astruc D (2017) Chem Soc Rev 46:816
21. Begum T, Mondal M, Borpuzari MP, Kar R, Kalita G, Gogoi PK, Bora U (2017) Dalton Trans 46:539
22. Ohtsuki A, Yanagisawa K, Furukawa T, Tobisuand M, Chatani N (2016) J Org Chem 81:9409
23. Burkhard JA, Wagner B, Fischer H, Schuler F, Müller K, Carreira EM (2010) Angew Chem Int Ed 49:3524
24. Burkhard JA, Guérot C, Knust H, Rogers-Evans M, Carreira EM (2010) Org Lett 12:1944
25. Burkhard J, Carreira EM (2008) Org Lett 10:3525
26. Wuitschik G, Rogers-Evans M, Buckl A, Bernasconi M, Märki M, Godel T, Schneider J, Alker A, Schweizer WB, Müller K, Carreira EM (2008) Angew Chem Int Ed 47:4512
27. Meng G, Szostak I (2018) ACS Catal 7:7251
28. Meng G, Shi S, Lalancette R, Szostak R, Szostak M (2018) J Am Chem Soc 140:727
29. Meng G, Shi S, Szostak M (2016) ACS Catal 6:7335
30. Zhang D, Zi G (2015) Chem Soc Rev 44:1898
31. Hameury S, de Frémont P, Breuil PAR, Olivier-Bourbigou H, Braunstein P (2014) Inorg Chem 53:5189
32. Ohmiya H, Zhang H, Shibata S, Harada A, Sawamura M (2016) Angew Chem Int Ed 55:4777
33. Meng G, Kakalis L, Nolan SP, Szostak M (2019) Tetrahedron Lett 60:378