Synthetic Methods

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Nickel-Catalyzed Formation of a Carbon–Nitrogen Bond at the β Position of Saturated Ketones**

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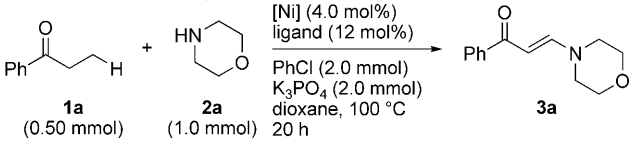
Ketone carbonyl groups can undergo a range of reactions at different sites. The positive carbonyl carbon center functions as an electrophile,[1] whereas the α position undergoes deprotonation in the presence of a base to act as a nucleophile.[2] However, bond formation on the β-carbon atom of saturated ketones still remains unexplored.[3–8] Herein, we describe a new catalytic formation of a carbon–nitrogen bond at the β position of alkyl ketones in the presence of a nickel complex.

Miura and co-workers reported that propiophenone couples with bromobenzene at its β position, as well as at its α position,[2b] in the presence of a base and a palladium complex.[3] The catalytic process involves the oxidation of the α-phenylated propiophenone by using a combination of the halobenzene and the palladium catalyst, to give the corresponding α,β-unsaturated ketone through a similar pathway to that of Saegusa–Ito oxidation.[7,8] The α,β-unsaturated ketone undergoes a Mizoroki–Heck reaction to form the carbon–carbon bond at the β position.[9] We envisioned that selective bond-formation on the β-carbon atom of ethyl ketones would be achieved if the oxidation with halobenzene proceeded without α arylation. This hypothesis inspired us to investigate the reaction of propiophenone (**1a**; see Table 1) with a nucleophile in the presence of a metal catalyst and a halobenzene.

A nickel catalyst was chosen as our candidate because nickel complexes are generally less active than palladium complexes in the catalytic α arylation of ketones.[2b] Various nickel precursors, monodentate ligands,[10] and bases were evaluated for the reaction of **1a** with morpholine (**2a**) in the presence of chlorobenzene at 100 °C (Table 1). We found that formation of a carbon–nitrogen bond occurred at the β position of **1a** when the reaction was conducted with a combination of $[Ni(cod)_2]$ (cod = cycloocta-1,5-diene), PMe_3, and K_3PO_4 (Table 1, entry 1). The reaction afforded β-enaminone **3a** in 86% yield (of isolated product) without significant formation of biphenyl, *N*-phenylmorpholine, or α-phenylated propiophenone (< 1%). The choice of a suitable phosphane ligand proved crucial for the formation of **3a**. The bulkiness of PBu_3 and PCy_3 (Cy = cyclohexyl) retarded the formation of the carbon–nitrogen bond (Table 1, entries 2 and 3). The use of a less electron-donating ligand exhibited no catalytic activity (Table 1, entries 4 and 5). To our surprise, no formation of **3a** was observed when other bases were used in place of K_3PO_4 (Table 1, entries 6–9). Most nickel(II) precursors did not exhibit catalytic activity for the reaction of **1a** and **2a** (Table 1, entries 10–12), although $[NiCl(Ph)(PMe_3)_2]$ exhibited catalytic activity comparable to that of $[Ni(cod)_2]$/PMe_3 (compare Table 1, entries 1 and 13). In the absence of chlorobenzene no enaminone **3a** was detected (Table 1, entry 14).

Table 1: Effects of catalyst and base.



1a (0.50 mmol) + **2a** (1.0 mmol) → **3a**

Entry	[Ni]	Ligand	Base	Yield [%][a]
1	$[Ni(cod)_2]$	PMe_3	K_3PO_4	62 (91)[b]
2	$[Ni(cod)_2]$	PBu_3	K_3PO_4	29
3	$[Ni(cod)_2]$	PCy_3	K_3PO_4	16
4	$[Ni(cod)_2]$	PPh_3	K_3PO_4	< 1
5	$[Ni(cod)_2]$	$P(OEt)_3$	K_3PO_4	0
6	$[Ni(cod)_2]$	PMe_3	KOAc	0
7	$[Ni(cod)_2]$	PMe_3	K_2CO_3	0
8	$[Ni(cod)_2]$	PMe_3	KO*t*Bu	0
9	$[Ni(cod)_2]$	PMe_3	Cs_2CO_3	1
10	$NiCl_2$	PMe_3	K_3PO_4	6
11	$[Ni(acac)_2]$	PMe_3	K_3PO_4	2
12	$[NiCl_2(PMe_3)_2]$	–	K_3PO_4	5
13	$[NiCl(Ph)(PMe_3)_2]$	–	K_3PO_4	68
14[c]	$[Ni(cod)_2]$	PMe_3	K_3PO_4	0

[a] Yield based on GC analysis of **3a** (average of two runs). [b] Yield based on GC analysis at 40 hours. [c] The reaction was conducted in the absence of chlorobenzene. acac = acetylacetonate.

The nickel/PMe_3 catalyst system was effective for the transformation of various ethyl ketones into the corresponding enaminones (Table 2). The β-enaminones **3b**–**3f**, which have a substituent at the *para* position, were obtained from ethyl ketones **1b**–**1f** in the presence of the nickel catalyst in high yields (Table 2, entries 1–5). Electron-withdrawing groups brought about an enhancement of the reaction rate,[11] even though the yields of **3e** and **3f** were relatively low. Although unsymmetrical aliphatic ketones **1h** and **1i** contain two reactive sites around their carbonyl groups, the reaction occurred on the ethyl group to afford the corresponding enaminone as the sole product (Table 2, entries 7 and 8).[12] Secondary aliphatic amines **2b**–**2e** proved to be

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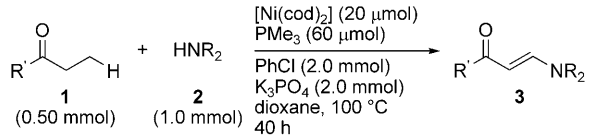
Table 2: Scope of the nickel-catalyzed formation of a carbon–nitrogen bond.

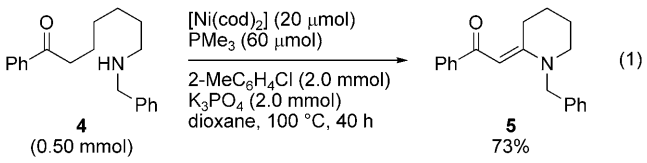


Entry	R′ (**1**)	HNR_2 (**2**)	**3**	Yield [%][a]
1[b,c]	4-$Me_2NC_6H_4$ (**1b**)	morpholine (**2a**)	**3b**	80
2[b]	4-$MeOC_6H_4$ (**1c**)	**2a**	**3c**	93
3	4-MeC_6H_4 (**1d**)	**2a**	**3d**	98
4[b]	4-FC_6H_4 (**1e**)	**2a**	**3e**	78
5	4-$CF_3C_6H_4$ (**1f**)	**2a**	**3f**	70
6[b]	1-Np (**1g**)	**2a**	**3g**	84
7[b]	Cy (**1h**)	**2a**	**3h**	53
8[d,e]	*i*Bu (**1i**)	**2a**	**3i**	54
9	Ph (**1a**)	piperidine (**2b**)	**3j**	85
10	**1a**	$HNBu_2$ (**2c**)	**3k**	77
11[b]	**1a**	$HNEt_2$ (**2d**)	**3l**	58
12	**1a**	$HNBn_2$ (**2e**)	**3m**	75

[a] Yields of the isolated products **3**. [b] The reaction was conducted for 60 hours. [c] The reaction was conducted with 0.3 mmol of **1b**. [d] *N*,*N*-dimethylformamide was used in place of dioxane. [e] The reaction was conducted with 0.3 mmol of **1i**. Np = naphthyl.

successful as the amine substrate in the nickel-catalyzed reaction (Table 2, entries 9–12). However, benzylamine and *N*-methylaniline could not be used in the present reaction.

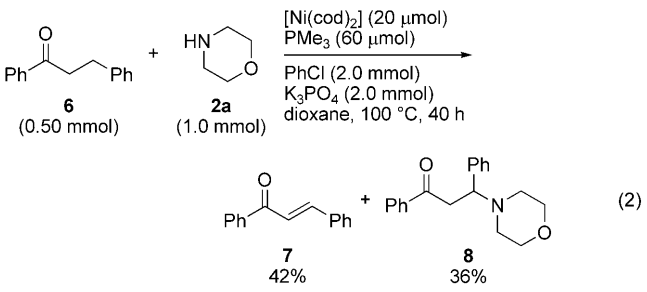
The exclusive regioselectivity in the reaction of **1h** and **1i** implies that the present catalysis is ineffective for the reaction of α- and/or β-substituted propiophenones. Butyrophenone, isobutyrophenone, and α-tetralone remained intact after the nickel-catalyzed reaction was carried out for 40 hours. However, the intramolecular formation of the carbon–nitrogen bond of **4** proceeded in the presence of the nickel catalyst, and afforded the piperidine **5** in good yield [Eq. (1)]. The



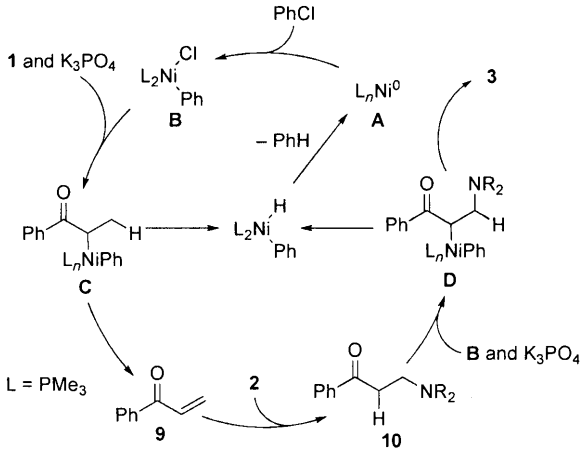
(1)

successful cyclization of **4** indicates that the nickel catalysis is adaptable to the transformation of ketones into α,β-unsaturated ketones by the dehydrogenation of an alkyl chain that is longer than an ethyl group.[7]

1,3-Diphenylpropan-1-one (**6**) also failed to be converted into the β-enaminone (< 3 %), but the reaction afforded a 1:1 mixture of α,β-unsaturated ketone **7** and β-aminoketone **8** [Eq. (2)]. This observation suggests that the catalytic transformation of ethyl ketones **1** into β-enaminones **3** may proceed through the oxidation of **1** to an α,β-unsaturated ketone and the subsequent 1,4-addition of amine, as speculated in our working hypothesis. A possible pathway of the catalytic reaction of **1** is shown in Scheme 1. The nickel(0) species **A** generated from $[Ni(cod)_2]$ and PMe_3 undergoes an



(2)

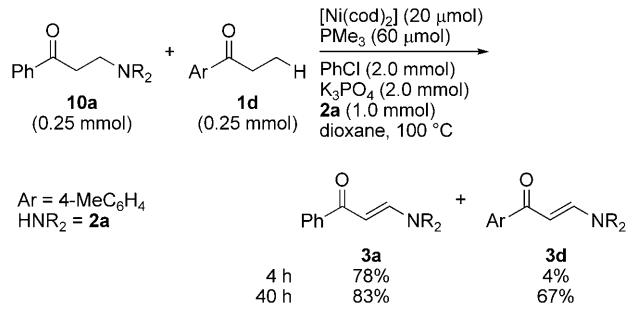


Scheme 1. A possible pathway for the nickel-catalyzed oxidative amination of **1** with **2**.

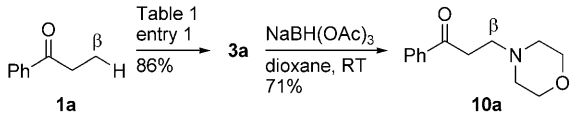
oxidative addition with chlorobenzene. The resulting $[NiCl(Ph)(PMe_3)_2]$ (**B**) reacts with deprotonated **1** to form the carbon-bound nickel enolate **C**,[13] which affords enone **9** through β-hydride elimination.[7] The 1,4-addition of **2** to **9** occurs to form the carbon–nitrogen bond at the β position. The β-aminoketone **10** is converted into β-enaminone **3** through the formation of the nickel enolate **D** and the subsequent β-hydride elimination, which regenerates the nickel(0) species **A** and produces benzene.[14]

In contrast to the findings illustrated by Equation (2), phenyl vinyl ketone **9** and β-aminoketone **10a** were rarely observed during the course of the conversion of **1a** into **3a**. This result indicates that the dehydrogenation of **10a** to form **3a** is much faster than that of **1a** to form **9**. Indeed, preferential consumption of aminoketone **10a** was observed in the reaction of the 1:1 mixture of **1d** and **10a** with the present catalyst system (Scheme 2). Coordination of the β-nitrogen atom in **10a** to the nickel species may accelerate the formation of the nickel enolate **D**, thus leading to the high substrate selectivity.[15] In the case of Equation (2), the dehydrogenation of **8** might be disturbed by the steric hindrance of the β-phenyl group.

The β-enaminones **3** prepared here are known to be selectively transformed into β-aminoketones, which are compounds of pharmaceutical interest (Scheme 3).[16] The selective hydrogenation of the olefin moiety in **3a** was achieved using $NaBH(OAc)_3$,[17] which gave β-aminoketone **10a** in 71 % yield. The nickel-catalyzed transformation of ethyl ketones into enaminones and the subsequent selective hydro-



Scheme 2. A competitive reaction between **10a** and **1d**.



Scheme 3. Formal amination at the β position of **1a** through nickel-catalyzed oxidative amination.

genation will offer a new protocol for the β amination of ethyl ketones.

In conclusion, we have developed a method involving the nickel-catalyzed formation of a carbon–nitrogen bond at the β position of alkyl ketones. To the best of our knowledge, this is the first example of a one-step catalytic bond-formation at the β-carbon atom of saturated ketones.

Experimental Section

General procedure for the nickel-catalyzed formation of a carbon–nitrogen bond: In a nitrogen-filled drybox, a 4 mL screw-capped vial was charged with $[Ni(cod)_2]$ (5.5 mg, 0.020 mmol), K_3PO_4 (424.5 mg, 2.0 mmol), dioxane (0.2 mL). After a magnetic stir bar was added, the vial was fitted with a septum cap, and removed from the drybox. A THF solution of PMe_3 (60 μL, 1M THF solution, 0.060 mmol), chlorobenzene (0.2 mL, $d = 1.106\ g\,mL^{-1}$, 2.0 mmol), amine (1.0 mmol), and ethyl ketone (0.50 mmol) were added to the vial. The resulting reaction mixture was heated at 100 °C. The progress of the reaction was monitored by GC analysis. After complete consumption of the starting material, the mixture was diluted with water (1 mL) and extracted with EtOAc (3 × 1 mL). The organic layer was concentrated, and the crude product was purified by column chromatography on silica gel (eluent: *n*-hexane/EtOAc 1:1).

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[14] Consistent with the mechanism in Scheme 1 was the formation of naphthalene in the following experiment by using 1-chloronaphthalene in place of chlorobenzene. When a mixture of **1a** (0.51 mmol), **2a**, and the nickel catalyst was treated with 1-chloronaphthalene (2.0 mmol) at 100 °C for 40 hours, naphthalene (0.84 mmol) and **3a** (0.42 mmol) were obtained from the resulting mixture.

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