Transformation of α-Substituted Propanols into γ-Amino Alcohols through Nickel-Catalyzed Amination on the Terminal γ-Carbon of Propanols

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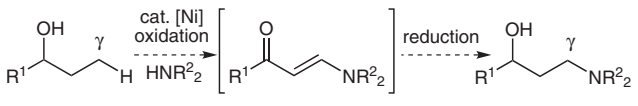
Abstract: A nickel–phosphine complex was found to be effective as the catalyst for the transformation of alcohols into β-enaminones, which was successively converted into γ-amino alcohols by a conventional reductant. The sequential transformation is equivalent to the carbon–nitrogen bond formation at the γ-position of saturated alcohols.

Key words: nickel, alcohols, amination, amino alcohols, oxidation

γ-Amino alcohols are regarded as important structural motifs in organic chemistry.[1] Although many reports have been made on the synthesis of γ-amino alcohols,[2] only one example is known as the synthetic strategy of γ-amino alcohols by the carbon–nitrogen bond formation at the γ-position of saturated alcohols.[3] In 2001, Du Bois and coworkers reported a transformation of alcohols into γ-amino alcohols through intramolecular C–H amination of sulfamate esters with rhodium catalyst. However, the rhodium catalyst is applicable to the amination of only secondary or tertiary carbon atom,[4] and synthesis of γ-amino alcohols through the amination on the alkyl terminus has been unexplored. Herein we present a new strategy for the γ-amination of α-substituted propanols.

Recently, we developed a method for the transformation of ethyl ketones into β-enaminones by using a nickel catalyst.[5] We suppose that the reaction proceeds as follows. An ethyl ketone is oxidized to α,β-unsaturated ketone by chlorobenzene in the presence of the nickel complex.[6–8] The conjugated enone successively undergoes the 1,4-addition of an amine and the re-oxidation of the resulting β-aminoketone to give the β-enaminone. We envisioned that a transformation of α-substituted propanols into γ-amino alcohols might be achieved if the nickel catalysis would work for conversion of alcohols into ketones[9] as well as that of ketones into β-enaminones, which is reduced by a hydride source (Scheme 1).[10]



Scheme 1 Our strategy for transformation of α-substituted propanols into γ-amino alcohols

First, we attempted to prepare β-enaminones from α-substituted propanols and amines. A mixture of 1-phenyl-1-propanol (**1a**), morpholine (**2a**), chlorobenzene (4.0 equiv), and potassium phosphate (4.0 equiv) was heated in 1,5-dioxane at 100 °C in the presence of the nickel catalyst, which was generated in situ from $Ni(cod)_2$ (cod = cycloocta-1,4-diene) and trimethylphosphine for 40 hours. The β-enaminone **3a** was obtained in 77% isolated yield. The yield of **3a** was increased to 86% by using six equivalents of chlorobenzene and potassium phosphate (Table 1, entry 1).[11] We conducted the catalytic transformation using a variety of 1-aryl-1-propanols (entries 2–7). Both electron-withdrawing and electron-donating *para* substituents scarcely affected the yields of β-enaminones **3** (entries 2 and 3), although the methoxy group of **1c** caused a slight decrease in the reaction rate. The chloro group in **1d** was incompatible with the above reaction conditions using chlorobenzene: the dechlorinated product **3a** was obtained in 75% yield. The undesirable dechlorination was restrained by using a bromobenzene in place of chlorobenzene, and the desired β-enaminone **3d** was obtained in 84% yield (entry 4).[12] Higher reaction temperature was required for the formation of **3e** from **1e** (entry 5). The *ortho* substituent of **1e** obstructed the nickel-catalyzed reaction. Propanols **1f** and **1g** bearing a naphthyl group at the α-position were converted into **3f** and **3g** in high yields, respectively (entries 6 and 7). The nickel catalyst system is also applicable to the transformation of α-alkyl-substituted substrates **1h**–**1j** (entries 8–10). The reaction of **1h** with **2a** afforded **3h** in moderate yield (entry 8). Other aliphatic alcohols **1i** and **1j** as well as **1a** were applicable to the nickel-catalyzed synthesis of β-enaminones **3i**–**3k** with piperidine (**2b**; entries 9–11). A variety of secondary aliphatic amines reacted with α-substituted propanols to give the corresponding β-enaminones (Table 1, entries 12–15). However, a primary amine, **2g**, did not work as the amine substrate in the nickel-catalyzed reaction (entry 16).[13]

The nickel-catalyzed reaction of **1g** with **2a** was conducted in the presence of 1-chloronaphthalene as the oxidant (Scheme 2). After two hours, **1g** was converted into the corresponding ketone **4g** in >99% yield (0.51 mmol) along with the formation of equimolar naphthalene (0.47 mmol). When the resulting solution was further heated for 48 hours, the formation of β-enaminone **3g** (0.49 mmol) and three equivalents of naphthalene (1.43 mmol) were observed.

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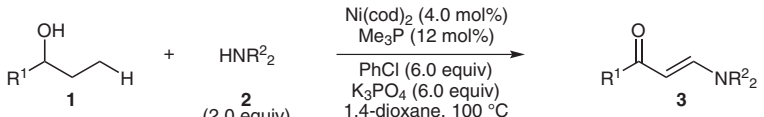
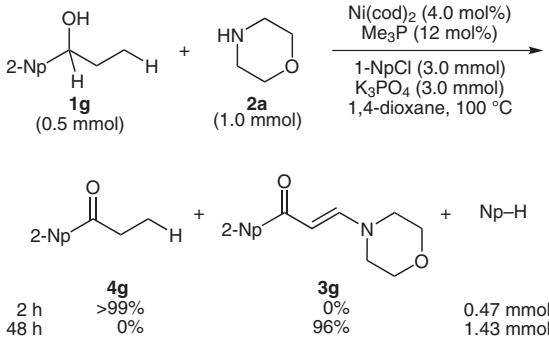
Table 1 Catalytic Formation of β-Enaminones **3** from α-Substituted Propanols **1** and Amines **2**



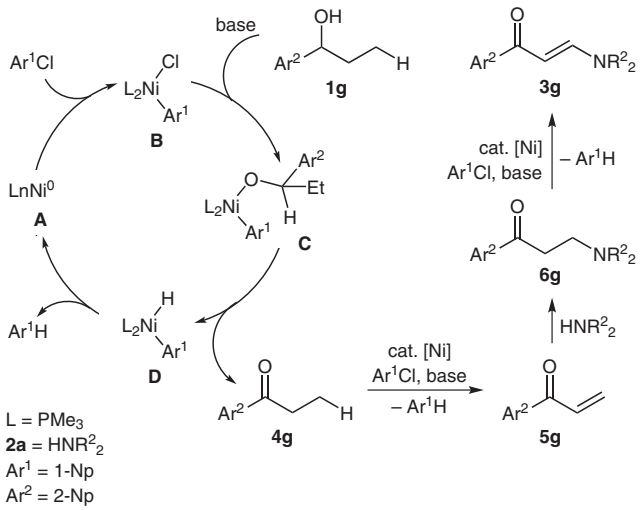
Entry	1	R^1	2	HNR^2_2	3	Yield (%)[a]
1	**1a**	Ph	**2a**	morpholine	**3a**	86
2	**1b**	4-$F_3CC_6H_4$	**2a**	morpholine	**3b**	82
3[b]	**1c**	4-$MeOC_6H_4$	**2a**	morpholine	**3c**	77
4[c]	**1d**	4-ClC_6H_4	**2a**	morpholine	**3d**	84
5[b,d]	**1e**	2-MeC_6H_4	**2a**	morpholine	**3e**	59
6[b]	**1f**	1-Np[e]	**2a**	morpholine	**3f**	93
7[b]	**1g**	2-Np[e]	**2a**	morpholine	**3g**	96
8[b]	**1h**	Cy	**2a**	morpholine	**3h**	51
9[b,d]	**1i**	*i*-Bu	**2b**	piperidine	**3i**	44
10[b,d]	**1j**	Et	**2b**	piperidine	**3j**	53
11	**1a**	Ph	**2b**	piperidine	**3k**	87
12[b]	**1a**	Ph	**2c**	1,2,3,4-tetrahydroisoquinoline	**3l**	75
13	**1a**	Ph	**2d**	*N*-Boc-piperazine	**3m**	56
14[b]	**1a**	Ph	**2e**	$HNBu_2$	**3n**	81
15[b]	**1a**	Ph	**2f**	$HNBn_2$	**3o**	91
16	**1a**	Ph	**2g**	H_2NBn	**3p**	0

[a] Yields of the isolated product **3**.
[b] The reactions were conducted for 60 h.
[c] Bromobenzene was used in place of chlorobenzene.
[d] The reaction was conducted at 120 °C.
[e] Np = naphthyl.



Scheme 2 A monitoring on nickel-catalyzed reaction by using 1-chloronaphthalene

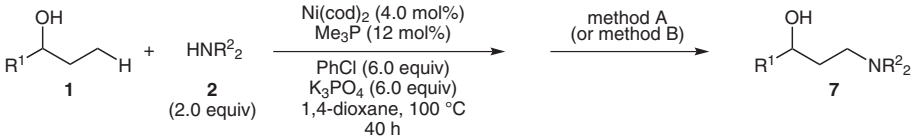
The formation of naphthalene implies that 1-chloronaphthalene in the presence of the nickel catalyst works as the oxidant for conversion of **1g** into **4g** as well as of **4g** into **3g**. We show a possible reaction pathway of the oxidation of **1g** with 1-chloronaphthalene in Scheme 3.[9] [NiCl(1-naphthyl)(PMe_3)$_2$] (**B**), generated from 1-chloronaphthalene and trimethylphosphine–nickel(0) species **A**, reacts with deprotonated **1g** to form nickel alkoxide **C**. Subsequent β-hydrogen elimination affords **4g** and the nickel hydride intermediate **D**, which undergoes reductive elimination to regenerate **A** and to produce naphthalene. We suggest that the transformation from **4g** into **3g** proceeds through the reaction pathway similar to our previous report (Scheme 3).[5] The resulting ketone **4g** was converted into α,β-unsaturated ketone **5g** with the nickel catalysis. The 1,4-addition of **2a** occurs to form the carbon–nitrogen bond on the terminal carbon. The resulting β-aminoketone **6g** is oxidized into β-enaminone **3g** with the nickel catalysis. Enone **5g** and β-aminoketone **6g** were not detected in the course of the catalytic reaction. The finding means that the dehydrogenation of **6g** would be faster than that of ethyl ketone **4g**.[14] The proposed reaction pathway was supported by the formation of three equivalents of naphthalene.



Scheme 3 A proposed reaction pathway from **1g** to **3g**

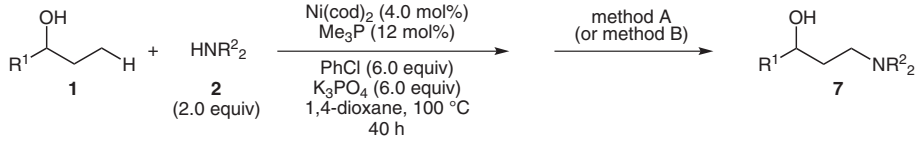
Next, we attempted the sequential transformation of α-substituted propanols into γ-amino alcohols. After the reaction of **1a** (0.5 mmol) with **2a** was conducted under the condition as mentioned above, the resulting mixture was diluted with methanol (4.0 mL). Sodium borohydride (2.0 mmol) was added to the solution at 0 °C, and the mixture was heated at 60 °C for 1.5 hours.[10b] As **3a** was not completely consumed, sodium borohydride (2.0 mmol) was again added at 0 °C, and then the resulting solution was heated at 60 °C. When the manipulation, which is an addition of sodium borohydride at 0 °C and stirring at 60 °C, was additionally repeated twice, **3a** was completely consumed. The desired γ-amino alcohol **7a** was obtained in 73% isolated yield. Next, to improve the yield of **7a**, the reaction mixture of **1a** and **2a** was filtered to remove the insoluble inorganic salt before the resulting solution was diluted with methanol (4.0 mL). The filtrate was treated with sodium borohydride (2.0 mmol) at 0 °C and stirred for 10 minutes, and the mixture was heated at 60 °C for 1.5 hours. When the manipulation, which is an addition of sodium borohydride at 0 °C and stirring at 60 °C, was repeated three times, **3a** was completely converted into **7a** in 84% yield (Table 2, entry 1). The hydride reduction enabled γ-amino alcohols to be prepared from a variety of propanols and cyclic amines. The electronic and steric properties of the α-substituent in propanols **1** did not affect the reaction efficiency of the reduction of β-enaminones **3b–h** (entries 2–8). It is noteworthy that no dechlorination of **3d** occurred (entry 4), while a nickel boride, which is generated from nickel(II) salt and sodium borohydride in methanol solution, is known to work for dehalogenation of aryl chloride to form the corresponding hydrogenated products.[15] The reduction of β-enaminones derived from cyclic amine proceeded smoothly (entries 9–13). However, the hydride reduction of the β-enaminone, which is prepared in situ from **1a** and acyclic amine **2e** or **2f**, failed to afford γ-amino alcohols **7n** or **7o** (entries 14 and 16). The reduction of **3n** and **3o** was improved by a treatment with sodium borohydride in acetic acid in place of methanol at room temperature to afford **7n** and **7o** in 84% and 72% yields, respectively (entries 15 and 17).[10c,e]

Table 2 Transformation of Alcohols **1** into δ-Amino Alcohols **7**



Entry	**1**	R^1	**2**	HNR^2_2	**7**	Method[a]	Yield (%)[b]
1	**1a**	Ph	**2a**	morpholine	**7a**	A	84
2	**1b**	4-$F_3CC_6H_4$	**2a**	morpholine	**7b**	A	76
3[c]	**1c**	4-$MeOC_6H_4$	**2a**	morpholine	**7c**	A	73
4[d]	**1d**	4-ClC_6H_4	**2a**	morpholine	**7d**	A	70
5[c,e]	**1e**	2-MeC_6H_4	**2a**	morpholine	**7e**	A	51
6[c]	**1f**	1-Np	**2a**	morpholine	**7f**	A	85
7[c]	**1g**	2-Np	**2a**	morpholine	**7g**	A	84
8[c]	**1h**	Cy	**2a**	morpholine	**7h**	A	49
9[c,e]	**1i**	*i*-Bu	**2b**	piperidine	**7i**	A	21 (40)[f]
10[c,e]	**1j**	Et	**2b**	piperidine	**7j**	A	45
11	**1a**	Ph	**2b**	piperidine	**7k**	A	86
12[c]	**1a**	Ph	**2c**	1,2,3,4-tetrahydroisoquinoline	**7l**	A	81

Table 2 Transformation of Alcohols **1** into δ-Amino Alcohols **7** (continued)



Entry	**1**	R^1	**2**	HNR^2_2	**7**	Method[a]	Yield (%)[b]
13	**1a**	Ph	**2d**	*N*-Boc-piperazine	**7m**	A	62
14[c]	**1a**	Ph	**2e**	$HNBu_2$	**7n**	A	21
15[c]	**1a**	Ph	**2e**	$HNBu_2$	**7n**	B	84
16[c]	**1a**	Ph	**2f**	$HNBn_2$	**7o**	A	0
17[c]	**1a**	Ph	**2f**	$HNBn_2$	**7o**	B	72

[a] Method A: the reduction with sodium borohydride was conducted in methanol at 60 °C. Method B: the reduction with sodium borohydride was conducted in acetic acid at r.t.
[b] Yields of the isolated product **7**.
[c] The reactions were conducted for 60 h.
[d] Bromobenzene was used in place of chlorobenzene.
[e] The reaction was conducted at 120 °C.
[f] Yield based on ^{1}H NMR analysis in parenthesis.

Although benzylamine (**2g**) failed to directly react with **1a** (Table 1, entry 16), we found that the treatment of β-enaminone **3a** with **2g** in methanol successfully gave (*Z*)-*N*-benzyl-β-enaminone **3p**.[16] Therefore, the resulting mixture from the reaction of **1a** with **2a** was treated with **2g** in methanol at 60 °C for 14 hours, and then the solution was filtered and concentrated (Scheme 4). As the result of the sequential manipulation, **3p** was obtained in 75% isolated yield. Hydrogenation of the isolated **3p** was conducted under a hydrogen atmosphere (5 atm) in the presence of 10% Pd/C in methanol at room temperature, affording **7p** in 57% yield.[10d]

In conclusion, we have successfully developed a novel transformation from α-substituted propanols into the γ-amino alcohols. The strategy involves nickel-catalyzed formation of β-enaminone and then the conventional reduction with sodium borohydride. We strongly believe that the present oxidation–1,4-addition–re-oxidation–reduction process will be a powerful method for the bond formation at the γ-position of alcohols.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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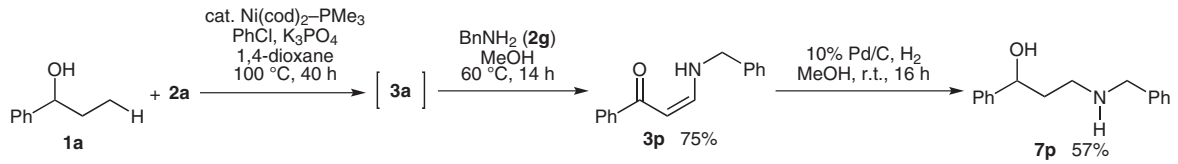

Scheme 4 Carbon–nitrogen bond formation with a primary amine at the γ-position via transamination

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(11) **Typical Procedure for the Transformation of 1a into 3a**: In a nitrogen-filled drybox, a 4-mL screw-capped vial was charged with $Ni(cod)_2$ (5.5 mg, 0.02 mmol), K_3PO_4 (636.8 mg, 3.0 mmol), and dioxane (0.3 mL). After a magnetic stir bar was added, the vial was fitted with a septum cap, and removed from the drybox. A solution of trimethylphosphine (60 μL, 1 M THF solution, 0.06 mmol), chlorobenzene (0.3 mL, *d* 1.106 g/mL, 2.95 mmol), morpholine (**2a**), and 1-phenyl-1-propanol (**1a**) was added. The resulting mixture was heated at 100 °C. The progress of the reaction was confirmed by GC analysis. After complete consumption of the starting material, the reaction mixture was quenched with H_2O (1 mL) and extracted with EtOAc (3 × 1 mL). The organic layer was concentrated, and purified by silica gel column chromatography (hexane–EtOAc = 3:1 → 1:8), which gave the β-enaminone **3a** (92.9 mg, 86%) as a pale yellow solid. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.27–3.53 (m, 4 H), 3.63–3.93 (m, 4 H), 5.88 (d, *J* = 12.6 Hz, 1 H), 7.33–7.56 (m, 3 H), 7.74 (d, *J* = 12.6 Hz, 1 H), 7.83–8.00 (m, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 48.3 (br s), 66.2, 92.4, 127.4, 128.1, 131.1, 140.1, 152.7, 189.1.

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