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C–H and C–C Bond Activation of Primary Amines through Dehydrogenation and Transimination

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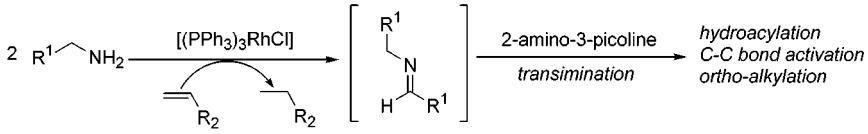
ABSTRACT



Dehydrogenation and subsequent transimination of primary amines offer a new pathway for C–H bond activation, *ortho*-alkylation, and C–C bond activation to afford a variety of ketones in the reaction of 1-alkene by a cocatalyt system of Rh(I) and 2-amino-3-picoline.

Activations of C−H and C−C bonds are current interests in organometallic chemistry.[1] These reactions have been developed in organic synthesis because they can be utilized in atom economical reactions.[2] Hydroacylation[3−5] and *ortho*-alkylation[6] are among the major applications of the C−H bond activation in organic synthesis. Recently, we have developed consecutive hydroacylation and *ortho*-alkylation using chelation-assistant tools, 2-amino-3-picoline and benzylamine.[7] Even in the C−C bond activation, 2-amino-3-picoline has been used as an important chelation-assistant tool.[8] In these reactions, formation of imine from amine and aldehyde or ketone is an important reaction step for transition metal catalyzed activation.[5,7,8]

During the course of our study of the activation of C−H and C−C bonds, we found that primary amines could also be used for the substrates since they were readily dehydrogenated by a transition metal catalyst to generate imines.[9] In this communication, we report a new synthetic method for the production of ketone from primary amines and 1-alkene through dehydrogenation and subsequent transimination.

(1) (a) Ryabov, D. *Chem. Rev.* **1990**, *90*, 403−424. (b). Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879−2932. (c) Dyker, G. *Angew. Chem.* **1999**, *111*, 1808−1822; *Angew. Chem., Int. Ed.* **1999**, *38*, 1698−1712.

(2) (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281 and references therein.

(3) (a) Sakai, K.; Ide, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett.* **1972**, *13*, 1287−1290. (b) Campbell, R. E.; Lochow, C. F.; Vora, K. P.; Miller, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5824−5830. (c) Mrader, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451−1453. (d) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286−1291. (e) Legens, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965−6979. (f) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667−674.

(4) (a) Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489. (b) Jun, C.-H.; Kang, J.-B.; Kim, J.-Y. *Tetrahedron Lett.* **1993,** *34*, 6431−6434. (c) Jun, C.-H.; Kang, J.-B.; Kim, J.-Y. *J. Organomet. Chem.* **1993**, *458*, 193−198. (d) Jun, C.-H.; Han, J.-S.; Kang, J.-B.; Kim, S.-I. *J. Organomet. Chem.* **1994**, *474*, 183−189.

(5) (a) Jun, C.-H.; Lee, H.; Hong, J.-B. *J. Org. Chem.* **1997**, *62*, 1200−1201. (b) Jun, C.-H.; Lee, D.-Y.; Hong, J.-B. *Tetrahedron Lett.* **1998**, *38*, 6673−6676. (c) Jun, C.-H.; Huh, C.-W.; Na, S.-J. *Angew. Chem.* **1998**, *110*, 150−152; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 145−147. (d) Jun, C.-H.; Hong, J.-B. *Org. Lett.* **1999**, *1*, 887−889. (e) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070−3072.

(6) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529−531. (b) Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 679−680. (c) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681−682. (d) Sonoda, M.; Kakiuchi, F.; Kamatani, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1996**, 109−110. (e) Murai, S.; Chatani, N.; Kakiuchi, F. *Pure Appl. Chem.* **1997**, *69*, 589−594 (f) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616−6623. (g) Kakiuchi, F.; Sekine, S.; Tanaka, T.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62−83 and references therein.

(7) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440−3442.

(8) (a) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880−881. (b) Jun, C.-H.; Lee, H.; Park, J.-B.; Lee, D.-Y. *Org. Lett.* **1999**, *1*, 2161−2164. (c) Jun, C.-H.; Lee, H.; Lim, S.-G. *J. Am. Chem. Soc.* **2000**, in press.

(9) (a) Yamazaki, S.; Yamazaki, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 301−303. (b) Khai, B.-T.; Concilio, C.; Porzi, G. *J. Organomet. Chem.* **1981**, *208*, 249−251. (c) Stock, L. M.; Tse, K. T.; Vorvick, L. J.; Walstrum, S. A. *J. Org. Chem.* **1981**, *46*, 1759−1760.

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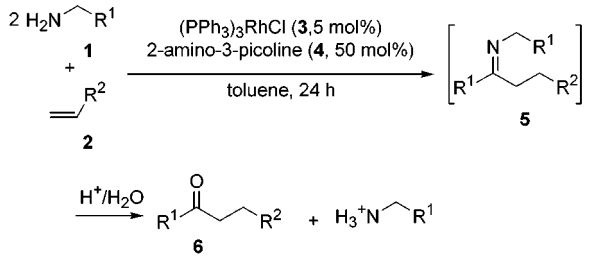
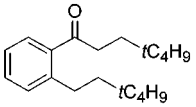
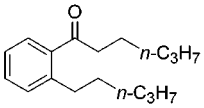
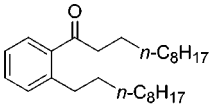
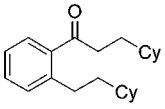
In our experiment, primary amine (**1**) reacts with 1-alkene (**2**) under a catalyst system of $(PPh_3)_3RhCl$ (**3**) and 2-amino-3-picoline (**4**) to give a hydroacylated product **6** after hydrolysis of the resulting ketimine **5** (Scheme 1). For

Scheme 1. Hydroacylation with Primary Amines through Dehydrogenation



example, when the reaction of phenethylamine (**1a**) and 3,3-dimethyl-1-butene (**2a**) was carried out at 170 °C for 24 h under the catalytic system of **3** (5 mol %) and **4** (50 mol %), 5,5-dimethyl-1-phenyl-hexan-2-one (**6a**) was isolated in 96% yield (Table 1, entry 1).

Table 1. Reaction of Various Olefins (**2**) with Primary Amines (**1**)[a]

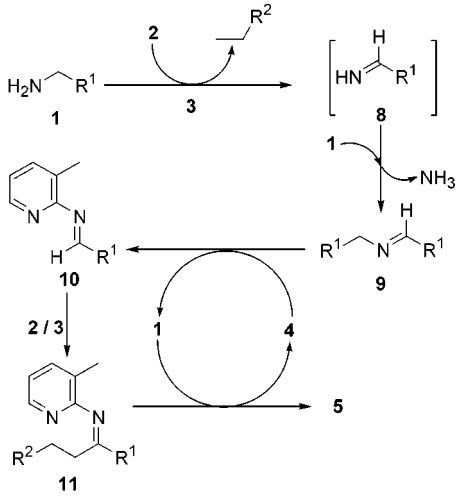
entry	**1** (R^1)	**2** (R^2)	Products (yield)[b]
1	**1a** ($PhCH_2$)	**2a** (t-C_4H_9)	**6a** (96 %)
2		**2b** (n-C_3H_7)	**6b** (70 %)
3		**2c** (n-C_8H_{17})	**6c** (78 %)
4		**2d** (Cy)	**6d** (84 %)
5[c]	**1b** (Ph)	**2a** (t-C_4H_9)	**6e** (6 %) **7e** (82 %) 
6[d]		**2b** (n-C_3H_7)	**6f** (12 %) **7f** (80 %) 
7[c]		**2c** (n-C_8H_{17})	**6g** (64 %) **7g** (14 %) 
8		**2d** (Cy)	**6h** (24 %) **7h** (40 %) 

[a] The reaction was carried out at 170 °C for 24 h under **3** (5 mol %) and **4** (50 mol %). [b] Yields of products were calculated presuming that one-half of **1** was used for the formation of imine **5**. [c] The reaction temperature is 170 °C. [d] 10 mol % of **4** was used.

Other olefins were also applied for this reaction to give the corresponding ketones in good yields (Table 1, entries 2−4). By changing the substrate **1a** to benzylamine (**1b**), *ortho*-alkylated ketone as well as hydroacylated ketone was obtained. Benzylamine (**1b**) reacted with **2a** at 170 °C under the identical catalyst system to give a mixture of **6e** and **7e** in 6% and 82% yield after hydrolysis (Table 1, entry 5). Various 1-alkenes were also applied for the reaction of **1b** to afford a mixture of hydroacylated ketone and its *ortho*-alkylated ketone (entries 6−8). In the case of olefin, having a bulky alkyl chain such as *n*-octyl or cyclohexyl group, a small amount (14% and 40%) of orthoalkylated product was isolated (entries 7 and 8).

The reaction mechanism is explained in Scheme 2. Initially, primary amine **1** is dehydrogenated by catalyst **3**

Scheme 2 Reaction Mechanism of Dehydrogenaton/Hydroacylation

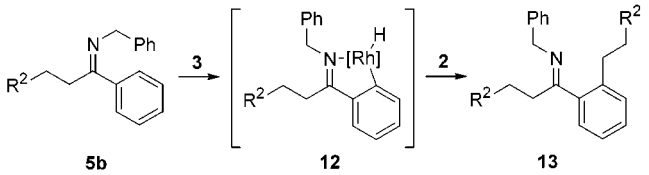


and **2** to give the imine **8**. The imine **8** is an unstable species that is transformed into the more stable imine **9** by transimination of the unreacted amine **1** with extrusion of NH_3.[10] This type of imine formation has been previously speculated in the synthesis of secondary amines from primary amines under transition metal catalysts.[9] In this reaction, 1-alkene acts as a hydrogen acceptor as well as a substrate for alkylation.[5c]

The generated imine **9** is hydroiminoacylated with **2** to afford **5** through transiminations of **9** to **10** and **11** to **5** in addition to hydroiminoacylation of **10** to **11**.[4] Hydrolysis of the resulting ketimine **5** produces the corresponding ketone **6** and **1**.

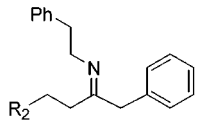
In the case of benzylamine (**1b**), further *ortho*-alkylation occurs at the generated ketimine **5b** to afford **13** (Scheme 3).[7]

Scheme 3 Reaction Pathway of *ortho*-Alkylation

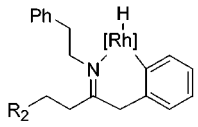


Then, the dialkylated product **7** was obtained after hydrolysis of **13**. It is interesting that *ortho*-alkylation as well as hydroacylation occurs in the reaction of **1b** with **2**, whereas exclusive hydroacylation occurs in the reaction of **1a** with **2**. This can be explained by the fact that the imine **5b** is able to form a stable metallacyclic five-membered ring intermediate **12** through the *ortho*-C−H bond activation.

However, the keimine **5a**, formed from **1a** and **2**, cannot cleave the *ortho*-C−H bond as a result of the formation of unstable six-membered ring intermediate complex **14**.



5a



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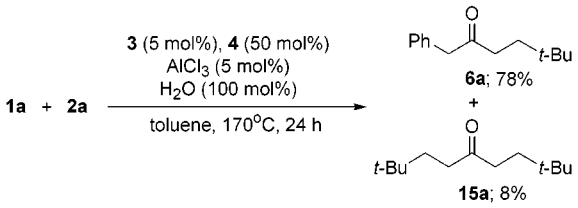
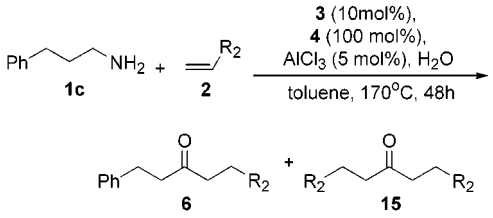
In these reactions, only half of amine **1** is consumed in the formation of ketone **6** since the ketimine **5** consists of two starting amine moieties. Therefore, if the starting amine **1** is liberated from the ketimine **5** during the reaction process, the regenerated amine **1** can also be transformed into the ketone **6**. For this purpose, the reaction of phenethylamine (**1a**) and **2a** was carried out in H_2O and $AlCl_3$ ambient under **3** and **4**, and 78% yield of hydroacylated ketone **6a** was isolated along with 8% yield of C−C bond cleavage product **15a** (Scheme 4).[11] In this reaction, ketimine **5a** was hydrolyzed with H_2O to produce ketone **6a** with generation of **1a**, which was reused for the starting material of the dehydrogenative hydroacylation until all of **1a** was consumed.[12]

Scheme 4. Hydroacylation of Phenethylamine with H_2O



When the reaction of 3-phenyl propylamine (**1c**) and **2a** was performed in H_2O and $AlCl_3$ ambient under catalyst system of **3** (10 mol %) and **4** (100 mol %) at 170 °C for 48 h, the C−C bond cleaved ketone **15a** and the hydroacylated ketone **6i** were isolated in 97% yield in a 50:50 ratio (**6i** and **15a**) (Scheme 5). Successive hydroacylation and C−C bond cleavage reaction of **1c** with **2** give the symmetric dialkyl ketone **15** in a fairly good yield. This type of C−C bond cleavage was previously reported with ketone bearing β-hydrogen through the chelation-assistance of 2-amino-3-picoline (**4**).[8]

Scheme 5. C−C Bond Activation of 3-Phenylpropylamine with H_2O



R_2 (**2**)	ratio of **6** / **15**	total yield (%)
t-C_4H_9 (**2a**)	50 (**6i**) / 50 (**15a**)	97
n-C_3H_7 (**2b**)	59 (**6j**) / 41 (**15b**)	88
n-C_6H_{13} (**2c**)	40 (**6k**) / 60 (**15c**)	81
n-C_8H_{17} (**2d**)	36 (**6l**) / 64 (**15d**)	77
Cy (**2e**)	48 (**6m**) / 52 (**15e**)	73

In conclusion, hydroacylation, *ortho*-alkylation, and C−C bond activation of primary amines have been successfully achieved through dehydrogenation and transimination of the resulting imine with a chelation-assistant amine such as 2-amino-3-picoline and benzylamine. Depending on the primary amine substrate, a variety of products was isolated on this catalytic reaction. With phenethylamine as a substrate, an exclusive hydrocylation product was obtained. An *ortho*-alkylated product was formed with benzylamine, and a C−C bond cleaved product was isolated with 2-phenylpropylamine in addition to the hydroacylated product.

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Supporting Information Available: General experimental procedures and the characterization of compounds **6j**, **7f**, and **7g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Khai, B.-T.; Concilio, C.; Porzi, G. *J. Organomet. Chem.* **1981**, *208*, 249−251.

(11) The C−C bond activation by the cocatalytic system of **3**/**4** occurred only in the ketone containing a β-hydrogen to carbonyl. However, in this case the Rh-hydrides, generated from dehydrogenation of amine, probably allows reaction with **6a** through C−C bond activation to give toluene and **15a**.

(12) The role of $AlCl_3$ is not clear, but addition of $AlCl_3$ improves the yield of products, and it was reported that a mixture of $AlCl_3$ and H_2O acts as a Lewis acid catalyst for polymerization of aromatic compounds. Kovacic, P.; Oziomex, J. *J. Org. Chem.* **1964**, *29*, 100−104.