doi:10.1246/cl.2013.40

β-Amination of Saturated Nitriles through Palladium-catalyzed Dehydrogenation, 1,4-Addition, and Re-dehydrogenation

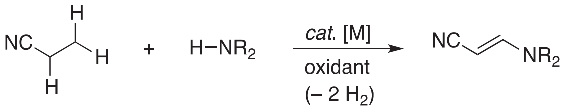
Satoshi Ueno,*[1] Ryohei Maeda,[1] Shohei Yasuoka,[1] and Ryoichi Kuwano*[1,2]
[1]*Department of Chemistry, Graduate School of Sciences, Kyushu University,*
6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581
[2]*International Research Center for Molecular Systems (IRCMS), Kyushu University,*
6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581

(Received October 8, 2012; CL-121033; E-mail: ueno@chem.kyushu-univ.jp, rkuwano@chem.kyushu-univ.jp)

Amination at the β-position of 2-arylpropionitriles through catalytic dehydrogenation occurred by using $[PdCl_2(PMe_3)_2]$ catalyst and bromobenzene. This is the first catalytic reaction involving the direct dehydrogenation of saturated nitriles.

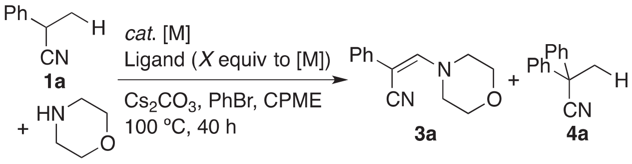
Developments of functionalizations on the alkane moiety of saturated nitriles would offer a new synthetic route to a variety of nitriles.[1] The saturated nitriles undergo deprotonation at their α-position with a base, and the generated (α-cyano)carbanion reacts with an electrophile to afford an α-substituted nitrile.[2] However, no report has been made on the functionalization of saturated nitriles at the β-position. The transition-metal-catalyzed β-functionalizations of saturated carbonyl derivatives through C–H activation using the carbonyl group as a directing group have been studied widely,[3] but the cyano group has never worked as the directing group for the sp^3-hybridized C–H activation because it does not strongly coordinate to the metal in a side-on manner. Therefore, it is important to develop a new method for a β-functionalization of saturated nitriles.

In 2009, we reported a catalytic method for a carbon–nitrogen bond formation of ethyl ketones at the β-position.[4] The ethyl ketones undergo dehydrogenation, 1,4-addition, and re-dehydrogenation to give β-amino-α,β-unsaturated ketones in the presence of chlorobenzene and a trimethylphosphine–nickel catalyst. Recently, Su,[5] Clot and Baudoin,[6] and Pihko[7] also independently reported β-functionalization of some saturated carbonyl and nitro compounds through dehydrogenation and addition sequences. Herein we report a β-amination of saturated nitriles through tandem catalytic dehydrogenation, conjugate addition, and re-dehydrogenation of saturated nitriles, which are transformed into β-aminated α,β-unsaturated nitriles (Scheme 1).



Scheme 1. β-Amination of saturated nitriles through a catalytic dehydrogenation.

Table 1. Catalytic β-amination of 2-phenylpropionitrile (**1a**) with morpholine (**2a**)[a]



1a

2a

3a

4a

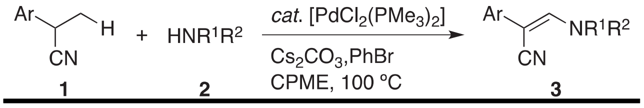
Entry	[M]	*X* Ligand	Yield of **3a**/%[b]	Yield of **4a**/%[c]	**3a**:**4a**
1[d]	$[Ni(cod)_2]$	3 PMe_3	0	0	—
2	$[\{Pd(\eta^3\text{-allyl})Cl\}_2]$	3 PMe_3	6	0	>99:1
3	$[\{Pd(\eta^3\text{-allyl})Cl\}_2]$	2 PMe_3	86	0	>99:1
4	$[\{Pd(\eta^3\text{-allyl})Cl\}_2]$	1 PMe_3	76	0	>99:1
5	$[\{Pd(\eta^3\text{-allyl})Cl\}_2]$	2 PBu_3	61	2	97:3
6	$[\{Pd(\eta^3\text{-allyl})Cl\}_2]$	2 P(2-furyl)$_3$	58	10	85:15
7	$[\{Pd(\eta^3\text{-allyl})Cl\}_2]$	2 PPh_3	71	22	76:24
8	$[\{Pd(\eta^3\text{-allyl})Cl\}_2]$	2 PCy_3	42	22	66:34
9	$[PdCl_2(PMe_3)_2]$	—	89	0	>99:1

[a]All reactions were conducted in CPME (1.0 mL). The ratio of **1a** (0.2 mmol)/**2a**/[M]/Cs_2CO_3/PhBr was 10:20:1:40:40. [b]The GC yield of **3a** is average of two runs. [c]The GC yield of **4a** is average of two runs. [d]Chlorobenzene was used in place of bromobenzene.

Initially, a mixture of 2-phenylpropionitrile (**1a**), morpholine (**2a**), cesium carbonate, and chlorobenzene was heated in the presence of a catalytic amount of trimethylphosphine and $[Ni(cod)_2]$ in cyclopentyl methyl ether (CPME) at 100 °C (Table 1, Entry 1). Unfortunately, **1a** remained intact at 40 h. Next, palladium was used in place of the nickel catalyst since the palladium complexes have been used as efficient catalysts for the dehydrogenation of carbonyl compounds.[8,9] In the presence of $[\{Pd(\eta^3\text{-allyl})Cl\}_2]$ and three equivalents of trimethylphosphine, the reaction was conducted by using bromobenzene in place of chlorobenzene,[10] the formation of a small amount of β-enaminonitrile **3a** was detected by GC analysis at 40 h (Entry 2). When the amount of trimethylphosphine was decreased to two equivalents to palladium, **1a** completely disappeared at 40 h and the yield of **3a** was dramatically increased to 86% (Entry 3). Use of equimolar trimethylphosphine to palladium caused a slight decrease in the yield of **3a**, while the 1:1 complex showed higher catalytic activity (Entry 4).[11] In the course of the optimization with trimethylphosphine, neither α-phenylation of **1a** (**4a**)[12] nor *N*-phenylation of **2a**[13] was observed by GC analysis.

Next, we investigated the effect of the monodentate phosphine ligand. When tributylphosphine was used in place of trimethylphosphine, **3a** was produced in 61% yield with the formation of α-phenylated nitrile **4a** in 2% yield (Entry 5).[12] We used some phosphines to elucidate the correlation between the cone angle of the ligands and the product ratio of **3a**/**4a** (Entries 6–8). In these reactions, the ratio of **3a**/**4a** decreased with the increasing cone angle of the phosphine ligand.[14,15] Moreover, $[PdCl_2(PMe_3)_2]$ was the most effective catalyst, producing **3a** in 89% yield (Entry 9).

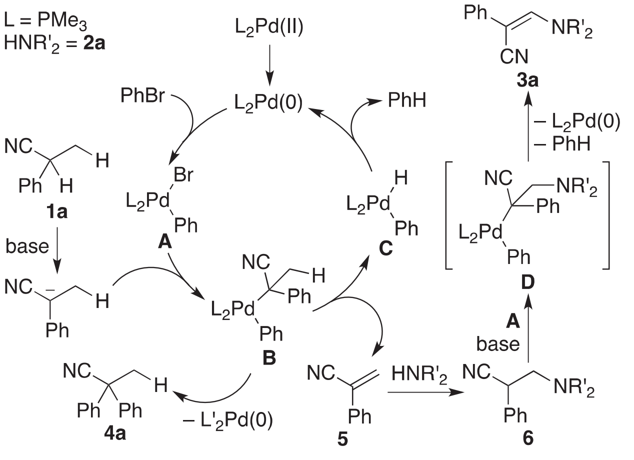
Table 2. Scope of palladium-catalyzed β-amination of nitriles **1** with amines **2**[a]



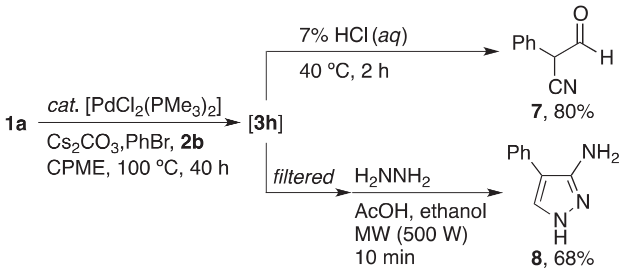
Entry	Ar (**1**)	HNR^1R^2 (**2**)	**3**	Time /h	Yield /%[b]
1	Ph (**1a**)	morpholine (**2a**)	**3a**	40	82
2	*p*-$CF_3C_6H_4$ (**1b**)	**2a**	**3b**	40	80
3	*p*-FC_6H_4 (**1c**)	**2a**	**3c**	40	70
4	*p*-$MeO_2CC_6H_4$ (**1d**)	**2a**	**3d**	20	76
5	*p*-ClC_6H_4 (**1e**)	**2a**	**3e**	40	83
6	*p*-$MeOC_6H_4$ (**1f**)	**2a**	**3f**	72	41
7	**1f**	piperidine (**2b**)	**3g**	40	78
8	**1a**	**2b**	**3h**	40	92
9	**1a**	**2c**[c]	**3i**	60	60
10	**1a**	pyrrolidine (**2d**)	**3j**	72	50
11	**1d**	$HNBu_2$ (**2e**)	**3k**	40	68
12[d]	**1a**	*n*-OctylNH_2 (**2f**)	**3l**	72	63

[a]All reactions were conducted in CPME (2.0 mL). The ratio of **1** (0.4 mmol)/**2**/[$PdCl_2(PMe_3)_2$]/Cs_2CO_3/PhBr was 10:20:1:40:40. [b]Yields of the isolated product **3**. [c]Compound **2c** is *N*-Boc-piperazine. [d]The reaction was conducted at 120 °C.

With [$PdCl_2(PMe_3)_2$] catalyst, we explored the scope of the β-amination of saturated nitriles. The results are summarized in Table 2. The reaction of various *para*-substituted 2-arylpropionitriles **1** was conducted (Entries 2–6). Electron-withdrawing groups scarcely affect the yield of **3** (Entries 2–5). The chlorinated substrate **1e** was converted into **3e** without losing the carbon–chlorine bonds, although most trialkylphosphine–palladium complexes are known to cleave the carbon–halogen bond (Entry 5).[16] Electron-donating methoxy groups on the aromatic ring cause a decrease in the yield of **3f** (Entry 6). When the reaction of propionitrile and α-alkylated propionitriles was conducted, no reaction was observed.[17] The nitriles **1** reacted with some secondary amines **2** to be converted to β-enaminonitriles **3** (Entries 7–11). Piperidine (**2b**) smoothly reacted with **1f** and **1a**, affording **3g** and **3h** in 78% and 92% yields (Entries 7 and 8). *N*-Boc-piperazine (**2c**), pyrrolidine (**2d**), and acyclic secondary amine **2e** could be employed as substrates to afford the corresponding β-aminated acrylonitriles **3i**–**3k** (Entries 9–11). It is noteworthy that a primary amine **2f** participated in the palladium-catalyzed β-amination of **1a**, although the primary amine did not work as a nucleophile for the related nickel-catalyzed reaction of ketones in our previous reports[4] (Entry 12).



Scheme 2. A plausible pathway for the reaction of **1a** with **2a**.



Scheme 3. Transformation of β-enaminonitrile **3h**.

A possible reaction pathway for the formation of **3a** is shown in Scheme 2. The phenylpalladium bromide **A**, generated by the oxidative addition of bromobenzene to palladium(0), reacts with the deprotonated **1a** to give the (α-cyanoalkyl)(phenyl)palladium complex **B**. β-Hydrogen elimination from **B** occurs to produce α,β-unsaturated nitrile **5** and the palladium(II) hydride complex **C**.[18] 1,4-Addition of amine to **5** leads to the formation of the carbon–nitrogen bond at the β-position.[19] The final product **3a** is formed by the reoxidation of the β-aminonitrile **6** with a base and **A** through the β-hydrogen elimination from the (2-amino-1-cyanoalkyl)palladium **D**. The forementioned intermediate **C** undergoes reductive elimination to regenerate the palladium(0) species and produce benzene.[20] On the other hand, reductive elimination from the intermediate **B** gives α-phenylated product **4a**. The reductive elimination from **B** would be accelerated by using the bulkier monophosphine ligand.[21] Therefore, the formation of the α-phenylated product **4a** was observed when the bulkier ligand with the larger cone angle was used in place of trimethylphosphine (Table 1, Entries 5–8).

The β-enaminonitrile **3** could be transformed into various organic molecules with an operationally simple method (Scheme 3). After the β-amination of **1a** with **2b**, the resulting mixture was heated in the presence of aqueous hydrochloric acid at 40 °C for 2 h.[22] The enamine moiety in **3h** was hydrolyzed to form α-cyanophenylacetaldehyde (**7**) in 80% yield. The one-pot transformation is equivalent to an oxidation of the terminal β-carbon of propionitriles. After the reaction of **1a** with **2b**, the resulting suspension was filtered and concentrated, and then the unpurified product **3h** was treated with hydrazine under microwave irradiation.[23] As a result of the sequential manipulation, 3-aminopyrazole **8** was obtained in only two steps from **1a**.

In conclusion, we successfully developed the catalytic β-amination of saturated nitriles. To the best of our knowledge, this is the first catalytic reaction that involves the direct dehydrogenation of saturated nitriles. In addition, the small monophosphine, trimethylphosphine, was found to be an effective ligand for avoiding the reductive elimination leading to the formation of the undesired by-product. Further studies on the bond formation through catalytic dehydrogenation by using the combination of the transition-metal catalyst and halobenzene are currently underway in our group.

This work was supported by Grant-in-Aids for Scientific Research on Innovation Areas "Molecular Activation Directed toward Straightforward Synthesis" (No. 23105534), and Young Scientists (B) (No. 23750043), from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We acknowledge Prof. Tsutomu Katsuki for GCMS analysis.

References and Notes

1 For a review, see: V. Y. Kukushkin, A. J. L. Pombeiro, *Chem. Rev.* **2002**, *102*, 1771.

2 For a review, see: S. Arseniyadis, K. S. Kyler, D. S. Watt, in *Organic Reactions*, John Wiley & Sons, Inc., **1984**, Vol. 31, pp. 1–364. doi:10.1002/0471264180.or031.01.

3 The transition–metal-catalyzed β-C–H functionalizations of saturated carbonyl compounds have been reported by using a directing group. For carboxylic acids: a) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510. For amides: b) L. D. Tran, O. Daugulis, *Angew. Chem., Int. Ed.* **2012**, *51*, 5188. c) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984. d) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 8070. e) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965. f) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680. g) Y. Feng, Y. Wang, B. Landgraf, S. Liu, G. Chen, *Org. Lett.* **2010**, *12*, 3414. h) M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886. i) D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190. For oxazolines: j) R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. k) R. Giri, J. Liang, J.-G. Lei, J.-J. Li, D.-H. Wang, X. Chen, I. C. Naggar, C. Guo, B. M. Foxman, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. For oxime ethers: l) S. R. Neufeldt, M. S. Sanford, *Org. Lett.* **2010**, *12*, 532. m) H.-Y. Thu, W.-Y. Yu, C.-M. Che, *J. Am. Chem. Soc.* **2006**, *128*, 9048. n) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542.

4 a) S. Ueno, R. Shimizu, R. Kuwano, *Angew. Chem., Int. Ed.* **2009**, *48*, 4543. b) S. Ueno, K. Usui, R. Kuwano, *Synlett* **2011**, 1303. c) S. Ueno, R. Shimizu, R. Maeda, R. Kuwano, *Synlett* **2012**, *23*, 1639.

5 Su et al. reported palladium-catalyzed decarboxylative β-arylation of nitroethane and ethyl ketones with through dehydrogenation/1,4-addition. For nitroethane: a) M. Zhang, J. Zhou, J. Kan, M. Wang, W. Su, M. Hong, *Chem. Commun.* **2010**, *46*, 5455. For ethyl ketones: b) J. Zhou, G. Wu, M. Zhang, X. Jie, W. Su, *Chem.—Eur. J.* **2012**, *18*, 8032.

6 Clot, Baudoin, et al. reported palladium-catalyzed β-arylation of esters through dehydrogenation/hydroarylation: a) A. Renaudat, L. Jean-Dérard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem., Int. Ed.* **2010**, *49*, 7261. b) P. Larini, C. E. Kefalidis, R. Jazzar, A. Renaudat, E. Clot, O. Baudoin, *Chem.—Eur. J.* **2012**, *18*, 1932.

7 Pihko et al. reported palladium-catalyzed β'-functionalization of β-ketoesters with indoles through dehydrogenation/1,4-addition: M. V. Leskinen, K.-T. Yip, A. Valkonen, P. M. Pihko, *J. Am. Chem. Soc.* **2012**, *134*, 5750.

8 For a review, see: J. Muzart, *Eur. J. Org. Chem.* **2010**, 3779.

9 a) W. Gao, Z. He, Y. Qian, J. Zhao, Y. Huang, *Chem. Sci.* **2012**, *3*, 883. b) T. Diao, T. J. Wadzinski, S. S. Stahl, *Chem. Sci.* **2012**, *3*, 887. c) T. Imahori, T. Tokuda, T. Taguchi, H. Takahata, *Org. Lett.* **2012**, *14*, 1172. d) T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566. e) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209. f) J. Zhu, J. Liu, R. Ma, H. Xie, J. Li, H. Jiang, W. Wang, *Adv. Synth. Catal.* **2009**, *351*, 1229. g) M. Tokunaga, S. Harada, T. Iwasawa, Y. Obora, Y. Tsuji, *Tetrahedron Lett.* **2007**, *48*, 6860. h) Y. Shvo, A. H. I. Arisha, *J. Org. Chem.* **1998**, *63*, 5640. i) R. J. Theissen, *J. Org. Chem.* **1971**, *36*, 752.

10 When the reaction was conducted with chlorobenzene in the presence of the palladium catalyst, no reaction was observed.

11 For further information on the effects of palladium precursor and ligand, see the Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

12 a) L. Wu, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 15824. b) J. You, J. G. Verkade, *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. c) J. You, J. G. Verkade, *J. Org. Chem.* **2003**, *68*, 8003. d) D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 9330. e) N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 541. f) S. R. Stauffer, N. A. Beare, J. P. Stambuli, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 4641. g) T. Satoh, J.-i. Inoh, Y. Kawamura, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239.

13 For reviews on palladium-catalyzed *N*-arylation of amines with haloarenes, see: a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534. b) D. S. Surry, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

14 A cone angle = 118° for PMe$_3$, 132° for PBu$_3$, 133° for P(2-furyl)$_3$, 145° for PPh$_3$, 170° for PCy$_3$: a) N. G. Andersen, B. A. Keay, *Chem. Rev.* **2001**, *101*, 997. b) C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313.

15 The formation of *N*-phenylmorpholine (0.138 mmol, 29% yield based on **2a**) was observed when PCy$_3$ was used (Table 1, Entry 8). For reviews on the palladium-catalyzed *N*-arylation, see ref. 13.

16 A. Littke, G. C. Fu, *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

17 Some nitriles having electron-withdrawing group at the α-position, such as α-cyanoester, malononitrile, and α-halopropionitriles, were used, but these reactions all failed to produce the β-enaminonitriles. In these cases, the generated electron-deficient α,β-unsaturated nitriles seem to be unstable under the reaction condition, so that the oligomerization of them occurred.

18 For reports on β-hydrogen elimination from a transition-metal enolate, see: a) E. J. Alexanian, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 15627. b) R. C. Larock, T. R. Hightower, G. A. Kraus, P. Hahn, D. Zheng, *Tetrahedron Lett.* **1995**, *36*, 2423. c) I. Shimizu, I. Minami, J. Tsuji, *Tetrahedron Lett.* **1983**, *24*, 1797. d) Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011.

19 The *aza*-Wacker type pathway would be ruled out because the formation of **5** was observed in the palladium-catalyzed β-amination of **1a** in the absence of amine by GCMS analysis, and furthermore 1,4-addition of **2a** to **5** proceeded quantitatively at room temperature without any assistance of the palladium.

20 The mechanism in Scheme 2 was supported by the formation of naphthalene in the following experiment by using 2-bromonaphthalene in place of bromobenzene. When a mixture of **1a** (0.22 mmol), **2a**, and the palladium catalyst was treated with 2-bromonaphthalene (0.80 mmol) at 100 °C for 40 h, naphthalene (0.38 mmol) and **3a** (0.14 mmol, 63%) were obtained from the resulting mixture.

21 For the competition between reductive elimination and β-hydrogen elimination by using different monodentate phosphines, see: J. E. Ney, J. P. Wolfe, *J. Am. Chem. Soc.* **2005**, *127*, 8644.

22 R. L. Cobb, V. C. Vives, J. E. Mahan, *J. Org. Chem.* **1978**, *43*, 926.

23 A. M. Salaheldin, M. K. Alphy, *J. Heterocycl. Chem.* **2008**, *45*, 307.