Nitrogen Heterocycles

DOI: 10.1002/ange.200500795

Direct Mannich and Nitro-Mannich Reactions with Non-Activated Imines: AgOTf-Catalyzed Addition of Pronucleophiles to *ortho*-Alkynylaryl Aldimines Leading to 1,2-Dihydroisoquinolines

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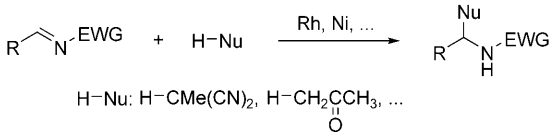
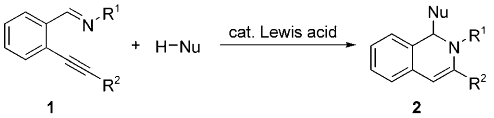
The Lewis acid and/or transition-metal-catalyzed addition of carbon nucleophiles to imines is one of the most important methods for the preparation of nitrogen-containing organic compounds.[1] In particular, the direct addition of carbon pronucleophiles to imines in the presence of catalysts is highly desirable as it represents an atom-economical approach. Previously, we reported the first example of the transition-metal-catalyzed direct addition of malononitrile derivatives and simple ketones, such as acetone, to activated imines [Eq. (1)].[2]



(1)

This transformation is useful for synthesizing amines and amino acid derivatives. However, activated imines that bear an electron-withdrawing group on the imine nitrogen atom have to be used as a substrate to induce the addition of pronucleophiles. Although direct Mannich-type reactions of activated ketones and malonates[3] and direct nitro-Mannich (aza-Henry) reactions catalyzed by metals and Brønsted acids were reported recently,[4] activated imines were also required in these cases. Herein, we report new direct Mannich and nitro-Mannich reactions of non-activated imines; AgOTf-catalyzed addition of carbon pronucleophiles to *ortho*-alkynylaryl aldimines **1** produces 1,2-dihydroisoquinoline derivatives **2** in good to high yields (Table 1).[5] Treatment of **1a** ($R^1 = R^2 = Ph$) with nitromethane (2 equiv) in the presence of AgOTf (3 mol%) in $(CH_2Cl)_2$ at 80°C for 1.5 h gave 1-nitromethyl-2,3-diphenyl-1,2-dihydro-isoquinoline (**2a**) in 85% yield (Table 1, entry 1). On the other hand, the reaction of benzylidene phenylamine, which bears no alkynyl group at the proximal position, under similar conditions did not give the corresponding addition product, and the starting material was recovered in 81% yield. This result clearly showed that the *ortho*-alkynyl group of **1a** is essential for the present direct addition of nitromethane to the imine moiety. Besides AgOTf, $Cu(OTf)_2$ was a suitable catalyst for the present reaction while the AuCl-catalyzed reaction gave **2a** in only 1% yield (Table 1, entries 2–3). Other starting materials **1b**–**e** were suitable for this reaction, and the corresponding

Table 1: Direct addition of pronucleophiles to **1**.[a]



Entry	1	R^1	R^2	Lewis acid	Nu-H	2	Yield [%][b]
1	**1a**	Ph	Ph	AgOTf	CH_3NO_2	**2a**	85
2	**1a**	Ph	Ph	$Cu(OTf)_2$	CH_3NO_2	**2a**	79
3	**1a**	Ph	Ph	AuCl	CH_3NO_2	**2a**	1
4[c]	**1b**	C_4H_9	Ph	AgOTf	CH_3NO_2	**2b**	56
5	**1c**	$PhCH_2$	Ph	AgOTf	CH_3NO_2	**2c**	58
6	**1d**	Ph	C_4H_9	AgOTf	CH_3NO_2	**2d**	72
7	**1e**	Ph	1-cC_6H_9	AgOTf	CH_3NO_2	**2e**	80
8	**1a**	Ph	Ph	AgOTf	$CH_3CH_2NO_2$	**2f**	72[d]
9	**1a**	Ph	Ph	AgOTf	acac	**2g**	77
10	**1a**	Ph	Ph	AgOTf	$CH_2(CO_2Me)_2$	**2h**	80
11	**1a**	Ph	Ph	AgOTf	$CH_2(CN)_2$	**2i**	84
12[e]	**1a**	Ph	Ph	AgOTf	acetone	**2j**	80
13[f]	**1a**	Ph	Ph	$[Rh(cod)(PPh_3)_2PF_6]$	CH_3CN	**2k**	61

[a] The reaction was carried out using **1** (1 equiv) and pronucleophiles (2 equiv) in the presence of Lewis acid (3 mol%) in $(CH_2Cl)_2$ at 80°C within 6 h unless otherwise noted. [b] Yields of isolated products. [c] The reaction was carried out at 60°C. [d] d.r. 84:16. [e] The reaction was carried out in acetone as a solvent at 70°C. [f] The reaction was conducted with $[Rh(cod)(PPh_3)_2PF_6]$ catalyst (2 mol%) using CH_3CN as a solvent. 1-cC_6H_9 = 1-cyclohexenyl; Tf = trifluoromethanesulfonyl; cod = 1,5-cyclooctadiene.

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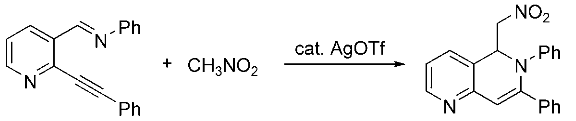
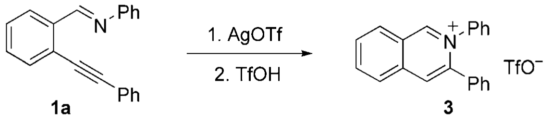
products **2b–e** were obtained in moderate to high yields (Table 1, entries 4–7). The reaction of **1a** with nitroethane gave **2f** as a mixture of diastereomers (d.r. 84:16, stereochemistry not determined; Table 1, entry 8). The reaction of **1a** with other pronucleophiles that bear activated methylene groups proceeded smoothly, and the corresponding dihydroisoquinoline derivatives **2g–i** were obtained in moderate to high yields (Table 1, entries 9–11). The reaction of **1a** with acetone (2 equiv) gave **2j** in a low yield. However, when acetone was used as the solvent, the direct addition proceeded smoothly, and **2j** was obtained in 80% yield (Table 1, entry 12). The reaction with CH_3CN proceeded in a low yield, even when the reaction was carried out in CH_3CN; however, when $[Rh(cod)(PPh_3)_2PF_6]$ was used as catalyst instead of AgOTf, the corresponding product **2k** was obtained in 61% yield (Table 1, entry 13).

Interestingly, the direct pronucleophile addition could also be applied to the pyridine derivative **1f**; treatment with nitromethane gave the naphthyridine derivative **2l** in 75% yield [Eq. (2)].



1f **2l** (2)

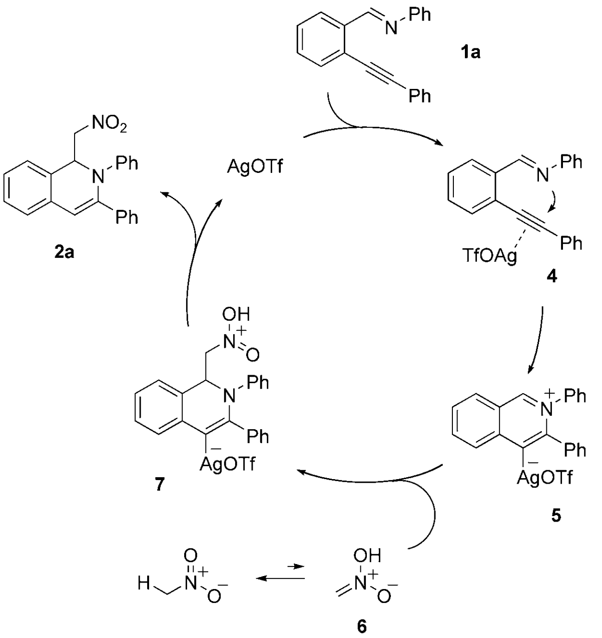
To clarify the mechanism of the process, we examined the reaction of **1a** with AgOTf in the absence of any pronucleophiles. Treatment of **1a** with AgOTf (1 equiv) in CH_2Cl_2, followed by addition of TfOH gave a crude material, which was recrystallized from a mixture of hexane and EtOH to give isoquinolinium salt **3** in 86% yield [Eq. (3)].[6]



1a **3** (3)

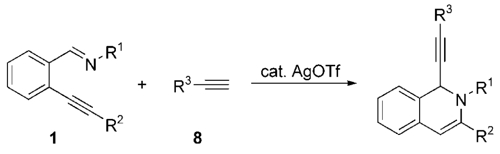
This result clearly indicates that at the beginning of the cyclization the triple bond coordinates to the Lewis acid, as shown in **4** (Scheme 1). Subsequent attack of the nitrogen atom at the electron-deficient triple bond leads to the isoquinolinium intermediate **5**. The addition of aci-nitromethane **6**, which is derived from nitromethane, gives the product **2** via **7**. As shown in Table 1, the AuCl-catalyzed reaction gave **2a** in a very low yield. Indeed, when **1a** was treated with AuCl (1 equiv) under similar reaction conditions as shown in Equation (3), the isoquinolinium salt **3** was obtained in 10% yield, which indicates that the formation of the isoquinolinium intermediate **5** is a key step in the present reaction.

Because the 1,2-dihydroisoquinoline derivatives **2** were produced unexpectedly easily from **1**, we were interested in whether the terminal alkynes **8** could be used as a pronucleophile. The results are summarized in Table 2. The reaction of **1a** with phenylacetylene **8a** under the similar reaction conditions as those given in Table 1 afforded 1-phenylethynyl-1,2-dihydroisoquinoline derivative **9a** in 93% yield. Analogously, the reaction proceeded smoothly with aliphatic alkynes, such as hexyne (**8b**), and even with ethyl propanoate (**8c**), and the products **9b** and **9c**, respectively, were obtained in high yields (Table 2, entries 2 and 3). Not only **1a** but also the other substrates **1b**,**c**, and **f**, which have alkyl groups on the nitrogen atom of the imine moiety, were suitable for the present reaction (Table 2, entries 4–6). The reaction of **1d**, which has a butyl group at the end of the alkynyl group, with **8a** also gave **9g** in 58% yield (Table 2, entry 7). Interestingly, the reaction of **1g** with phenylacetylene (**8a**) gave the 3,4,5,6-tetrahydrobenzo[*f*]isoquinoline derivative **9h** in 62% yield [Eq. (4)]. Several methods for direct addition of terminal alkynes to imine compounds have been reported.[7–8] However, the direct addition of alkynes to benzylidene phenylamine, which bears no alkynyl group at the proximal position, did not proceed at all under the present reaction conditions.



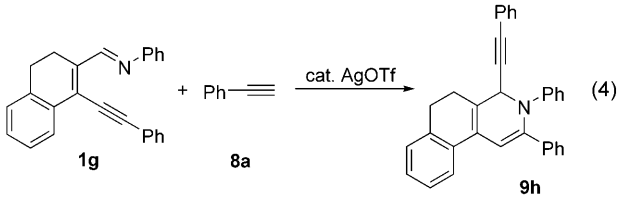
Scheme 1. Proposed mechanism for the AgOTf-catalyzed direct addition of nitromethane to **1a**.

Table 2: Direct addition of terminal alkynes **8** to **1**.[a]



Entry	1	R^1	R^2	8	R^3	9	Yield [%][b]
1	**1a**	Ph	Ph	**8a**	Ph	**9a**	93
2	**1a**	Ph	Ph	**8b**	C_4H_9	**9b**	90
3	**1a**	Ph	Ph	**8c**	CO_2Et	**9c**	86
4	**1b**	C_4H_9	Ph	**8a**	Ph	**9d**	42
5	**1c**	$PhCH_2$	Ph	**8a**	Ph	**9e**	70
6	**1f**	Allyl	Ph	**8a**	Ph	**9f**	70
7	**1d**	Ph	C_4H_9	**8a**	Ph	**9g**	58

[a] The reaction was carried out with **1** (1 equiv) and terminal alkynes **8** (1.2 equiv) in the presence of AgOTf (3 mol%) in $(CH_2Cl)_2$ at 80 °C within 6 h. [b] Yields of isolated products.



(4)

This result again indicates that the presence of an *ortho*-alkynyl group is essential for the imine addition, and the formation of the isoquinolinium intermediate **5** is a key step.

We are now in a position to synthesize functionalized 1,2-dihydroisoquinoline skeletons through the direct addition of various carbon pronucleophiles to *ortho*-alkynylaryl aldimines. Even without the use of the usual activated imines that bear an electron-withdrawing group, the addition to imines proceeded well, probably due to the formation of the reactive isoquinolinium intermediates **5** in situ. In general, the 1,2-dihydroisoquinoline framework can be constructed by nucleophilic addition to isoquinolinium salts, which are derived from the corresponding isoquinolines by acylation or alkylation.[9] Evidently, the present reaction proceeded without such activation, and the current transformation provides an alternative method for the construction of 1,2-dihydroisoquinolines.[10] Further studies to elucidate the precise mechanism of this reaction and to extend the scope of its synthetic utility are in progress in our laboratory.[11]

Received: March 4, 2005
Revised: May 31, 2005

Keywords: imines · Mannich reaction · nitrogen heterocycles · pronucleophiles · synthetic methods

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[1] For reviews on catalytic asymmetric Mannich-type reactions, see: a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094; b) A. E. Taggi, A. M. Hafez, T. Lectka, *Acc. Chem. Res.* **2003**, *36*, 10–19.

[2] a) Y. Yamamoto, Y. Kubota, Y. Honda, H. Fukui, N. Asao, H. Nemoto, *J. Am. Chem. Soc.* **1994**, *116*, 3161–3162; b) N. Shida, Y. Kubota, H. Fukui, N. Asao, I. Kadota, Y. Yamamoto, *Tetrahedron Lett.* **1995**, *36*, 5023–5026.

[3] For recent direct Mannich reactions, see: a) N. Kumagai, S. Matsunaga, M. Shibasaki *J. Am. Chem. Soc.* **2004**, *126*, 13632–13633; b) L.-W. Xu, C.-G. Xia, L. Li *J. Org. Chem.* **2004**, *69*, 8482–8484; c) T. Ooi, M. Kameda, J. Fujii, K. Maruoka, *Org. Lett.* **2004**, *6*, 2397–2399; d) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357; e) S. Matsunaga, N. Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713; f) M. Marigo, A. Kjrsgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359–2367; g) B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339; h) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083–3085; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997; i) H. Nemoto, R. Ma, H. Moriguchi, I. Suzuki, M. Shibuya, *J. Organomet. Chem.* **2000**, *611*, 445–448.

[4] For recent direct nitro-Mannich (aza-Henry) reactions, see: a) B. M. Nugent, R. A. Yoder, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419; b) N. Tsuritani, K. Yamada, N. Yoshikawa, M. Shibasaki, *Chem. Lett.* **2002**, 276–277; c) N. Nishiwaki, K. R. Knudsen, K. V. Gothelf, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3080–3083; *Angew. Chem. Int. Ed.* **2001**, *40*, 2992–2995; d) C. Qian, F. Gao, R. Chen, *Tetrahedron Lett.* **2001**, *42*, 4673–4675; e) K. Yamada, S. J. Harwood, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 3713–3715; *Angew. Chem. Int. Ed.* **1999**, *38*, 3504–3506.

[5] Although the organocatalytic direct Mannich reaction proceeded well with non-activated imines to afford β-aminocarbonyl compounds, pronucleophiles were limited to aldehydes and ketones; see: a) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987–1997; b) W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, C. F. Barbas III, *J. Org. Chem.* **2003**, *68*, 9624–9634; c) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805–3808; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677–3680; d) A. Córdova, S.-i. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867; e) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843; f) A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 7749–7752; g) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833; h) W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199–201; i) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.

[6] A Pd-catalyzed isoquinoline synthesis from *ortho*-alkynylaryl aldimines was reported; see: Q. Huang, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 980–988, and references therein.

[7] For reviews, see: a) C. M. Wei, Z. G. Li, C. J. Li, *Synlett* **2004**, 1472–1483; b) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2004**, 4095–4105.

[8] For recent examples, see: a) M. Benaglia, D. Negri, G. Dell'Anna, *Tetrahedron Lett.* **2004**, *45*, 8705–8708; b) B. M. Choudary, C. Sridhar, M. L. Kantam, B. Sreedhar, *Tetrahedron Lett.* **2004**, *45*, 7319–7321; c) C. Wei, J. T. Mague, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5749–5754; d) C. Fischer, E. M. Carreira, *Synthesis* **2004**, 1497–1503; e) S. Sakaguchi, T. Mizuta, M. Furuwan, T. Kubo, Y. Ishii, *Chem. Commun.* **2004**, 1638–1639; f) L. Shi, Y.-Q. Tu, M. Wang, F.-M. Zhang, C.-A. Fan, *Org. Lett.* **2004**, *6*, 1001–1003; g) J. N. Rosa, A. G. Santos, C. A. M. Afonso, *J. Mol. Catal. A* **2004**, *214*, 161–165; h) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585; i) C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473–4475; j) B. Jiang, Y.-G. Si, *Tetrahedron Lett.* **2003**, *44*, 6767–6768; k) C. Koradin, N. Gommermann, K. Polborn, P. Knochel, *Chem. Eur. J.* **2003**, *9*, 2797–2811; l) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639; m) C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268–269; n) C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2002**, *114*, 2651–2654; *Angew. Chem. Int. Ed.* **2002**, *41*, 2535–2538; o) H. Z. S. Huma, R. Halder, S. S. Kalra, J. Das, J. Iqbal, *Tetrahedron Lett.* **2002**, *43*, 6485–6488; p) C. Fischer, E. M. Carreira, *Org. Lett.* **2001**, *3*, 4319–4321.

[9] For recent examples, see: a) F. Diaba, C. L. Houerou, M. Grignon-Dubois, B. Rezzonico, P. Gerval, *Eur. J. Org. Chem.* **2000**, 2915–2921; b) F. Diaba, I. Lewis, M. Grignon-Dubois, S. Navarre, *J. Org. Chem.* **1996**, *61*, 4830–4832.

[10] Recently, we developed a synthetic method for 1,2-dihydroisoquinoline derivatives in the presence of a bis-π-allylpalladium catalyst: M. Ohtaka, H. Nakamura, Y. Yamamoto, *Tetrahedron Lett.* **2004**, *45*, 7339–7341.

[11] The asymmetric version of the present reaction was investigated briefly. The reaction of **1** with nitromethane was carried out in the following catalytic systems; $Cu(OTf_2)$–(*R*)-(+)-2,2′-isopropylidenebis-(4-phenyl-2-oxazoline), $Cu(OTf_2)$–2,2′-isopropylidenebis[(4S)-4-*tert*-butyl-2-oxazoline], $Cu(OTf_2)$–2,6-bis[(4*S*)-(−)-isopropyl-2-oxazolin-2-yl]pyridine, and AgOTf–(*R*)-(+)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene. The reaction gave **2** in good yields, but the enantioselectivities were very low (≈1% *ee*).