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Synthesis of 1,2-dihydroisoquinolines via palladium(0)-catalyzed addition–cyclization of chloroform to *ortho*-alkynylaldimines

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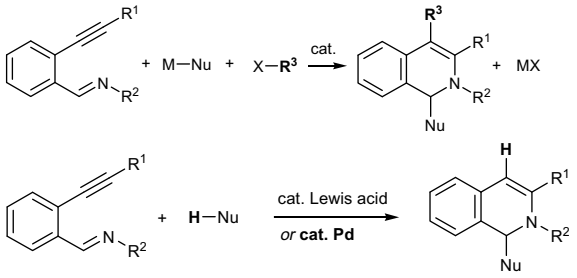
Abstract

Addition–cyclization of chloroform to *ortho*-alkynylaldimines proceeded in the presence of $PdCl_2(PPh_3)_2$/dppe or $Pd_2dba_3{\cdot}CHCl_3$/dppe at 100 °C to afford the corresponding 1-(trichloromethyl)-1,2-dihydroisoquinolines in good to high yields.

The Lewis acid and transition metal-catalyzed C–H bond activation of carbon pronucleophiles is one of the important requirements in regard to 'atom economy' for a C–C bond forming reaction in organic synthesis.[1] Especially, addition reactions of the activated pronucleophiles to imines have been developed for the synthesis of various organoic amines in recent years.[2,3] Although 1,2-dihydroisoquinolines have been synthesized by tandem addition–cycloadditions of organometallic compounds (M–Nu) to alkynylaldimines under transition-metal catalyzed condition and the resulting organometallic species were able to be trapped by electrophiles (X–R^3), metal salts were often generated as side products in the transformations (Scheme 1).[4] The tandem addition–cyclization of carbon pronucleophiles to *ortho*-alkynylaldimines catalyzed by AgOTf was first developed by Asao, Yamamoto, and their co-workers. In this transformation, AgOTf as a Lewis acid would activate the C–C triple bond, which undergoes the intramolecular attack of the imine nitrogen to generate highly electrophilic iminium cations as a reactive species. This is highly potent from environmental and atom-economical points of view, because various carbon pronucleophiles (H–Nu), such as nitroalkanes, acetylacetone, malononitrile, and dimethylmalonate, can be introduced into an 1,2-dihydroisoquinoline framework without generating any waste metal salts (Scheme 1).



Scheme 1. Synthesis of 1,2-dihydroisoquinolines via tandem addition–cyclizations of M–Nu and H–Nu to *ortho*-alkynylaldimines.

Furthermore, three-component coupling reaction with *ortho*-alkynylbenzaldehydes, primary amines, and pronucleophiles was also investigated in the presence of molecular sieves.[6] We found that pronucleophiles, such as chloroform, nitromethane, and acetonitrile, react with *ortho*-alkynylaldimines **1** in the presence of palladium catalysts under essentially neutral conditions to give the corresponding 1,2-dihydroisoquinolines in good to high yields. This is a first example of the C–H activation of chloroform by palladium catalysts.

We first examined the addition–cyclization with the *ortho*-alkynylaldimine **1a** in chloroform under various

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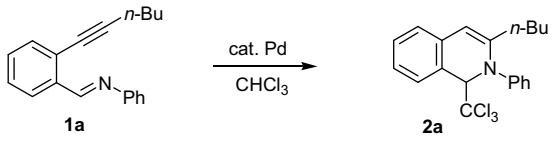
Table 1
Addition–cyclization of chloroform to *ortho*-alkynylaldimine **1a**[a]



1a **2a**

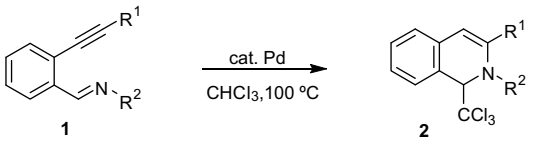
Entry	Pd cat. (mol %)	Ligand (mol %)	Yield[b] (%)
1	$PdCl_2(PPh_3)_2$ (10)	None	73
2	$PdCl_2(PPh_3)_2$ (10)	dppe (10)	97
3	$PdCl_2(PPh_3)_2$ (5)	dppe (5)	96
4	$PdCl_2(PPh_3)_2$ (3)	dppe (3)	92
5	$PdCl_2(PPh_3)_2$ (5)	PPh_3 (5)	86
6	$Pd(PPh_3)_4$ (10)	None	70
7	$Pd(PPh_3)_4$ (10)	dppe (10)	>99

[a] All reactions were carried out in chloroform at 100 °C for 8 h using a vial tube.
[b] Isolated yield based on **1a**.

palladium catalysts. The results are summarized in Table 1. The *ortho*-alkynylaldimine **1a** underwent the addition–cyclization in the presence of $PdCl_2(PPh_3)_2$ (10 mol %) at 100 °C to give the corresponding 1,2-dihydroisoquinoline **2a** in 73% yield (entry 1). The addition of bisdiphenylphosphinoethane (dppe) as a ligand to the reaction was effective and the yield of **2a** increased to 97% (entry 2). Less amounts of catalysts or the addition of triphenylphosphine instead of dppe gave lower yields of the product (entries 3–5). Although $Pd(PPh_3)_4$ (10 mol %) was not effective and **2a** was obtained in 70% yield (entry 6), the combination of $Pd(PPh_3)_4$ (10 mol %) and dppe (10 mol %) dramatically increased the yield, and **2a** was obtained quantitatively (entry 7).

We next examined the addition–cyclization of chloroform to various *ortho*-alkynylaldimines **1**. The results are summarized in Table 2. The *ortho*-alkynylaldimines, which were prepared from 2-(hex-1-ynyl)benzaldehyde (R^1 = *n*-Bu) with aniline (**1a**), 2-aminoanisole (**1b**), 4-aminoanisole (**1c**), 3-chloroaniline (**1d**), and *n*-propylamine (**1f**), underwent the addition–cyclization in the presence of $PdCl_2(PPh_3)_2$ (5 mol %) and dppe (5 mol %) at 100 °C (condition A) to give the corresponding 1-(trichloromethyl)-1,2-dihydroisoquinolines **2a–e** in good to high yields (entries 1–5). The *ortho*-alkynylaldimine (**1f**) derived from 2-(hex-1-ynyl)benzaldehyde and 2-pyridylamine gave **2f**, quantitatively (entry 6). In this case, a combination of $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol %) and dppe (5 mol %) was effective (condition B). The reaction of *ortho*-alkynylaldimines **1g–j**, which were prepared from 2-(phenylethynyl)benzaldehyde (R^1 = Ph) with aniline and aminoanisoles, gave **2g–j** in 87–97% yields (entries 7–10). We also examined the *ortho*-alkynylaldimines, **1k** and **1l**, which have a *N*,*N*-dicyclohexylaminomethyl group at R^1. In these cases, $[(C_6F_5)_2PCH_2-]_2$ was employed as a ligand (condition C) and the corresponding 1-(trichloromethyl)-1,2-dihydroisoquinolines (**2k** and **2l**) were obtained in 32% and 40% yields, respectively (entries 11 and 12). The structure of **2k** was confirmed by X-ray crystallographic analysis and

Table 2
Synthesis of various 1,2-dihydroisoquinolines **2**



1 **2**

Entry	R^1	R^2	Condition[a]	Yield (%)	
1	*n*-Bu	Ph	A	**2a**	96
2	*n*-Bu	2-$MeOC_6H_4$	A	**2b**	70
3	*n*-Bu	4-$MeOC_6H_4$	A	**2c**	65
4	*n*-Bu	3-ClC_6H_4	A	**2d**	53
5	*n*-Bu	*n*-Pr	A	**2e**	45
6	*n*-Bu	3-Pyridyl	B	**2f**	>99
7	Ph	Ph	B	**2g**	95
8	Ph	2-$MeOC_6H_4$	A	**2h**	95
9	Ph	3-$MeOC_6H_4$	A	**2i**	97
10	Ph	4-$MeOC_6H_4$	A	**2j**	87
11	Cy_2NCH_2	2-$MeOC_6H_4CH_2$	C	**2k**	32
12	Cy_2NCH_2	Bn	C	**2l**	40

[a] The reaction was carried out in the presence of $PdCl_2(PPh_3)_2$/dppe (5 mol %) (condition A), $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol)/dppe (5 mol %) (condition B), or $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol)/$[(C_6F_5)_2PCH_2-]_2$ (5 mol %) (condition C) in $CHCl_3$ at 100 °C for 6–8 h in a vial tube.

the ORTEP diagram in Figure 1 confirms the disubstituted 1,2-dihydroisoquinoline framework.[7]

Typical procedure for the synthesis of 1,2-dihydroisoquinoline **2a** via the palladium-catalyzed addition–cyclization of chloroform to *ortho*-alkynylaldimine **1a** (condition A) is as follows: A mixture of **1a** (128 mg, 0.49 mmol), $PdCl_2(PPh_3)_2$ (17 mg, 0.025 mmol), and dppe (10 mg, 0.0025 mmol) was dissolved in $CHCl_3$ (1 mL) under Ar and stirred at 100 °C until **1a** was consumed (~6 h) in a vial tube. The reaction progress was monitored by TLC and GC. When **1a** was consumed, the solvent was removed under the reduced pressure, and the residue was purified by silica gel column chromatography with hexane/ethyl

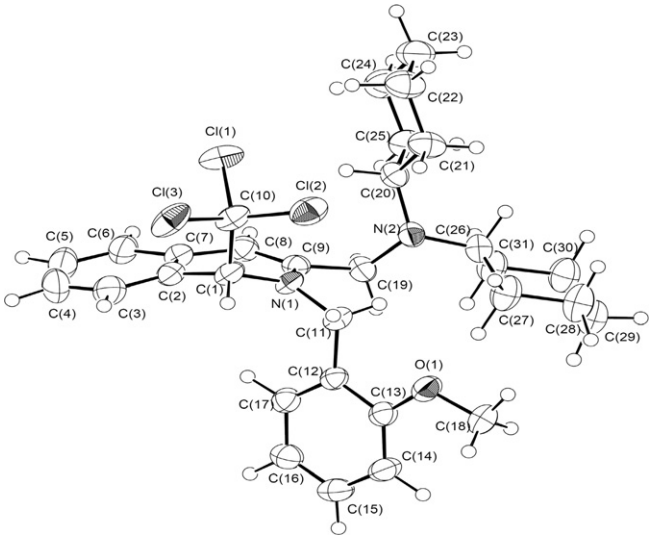
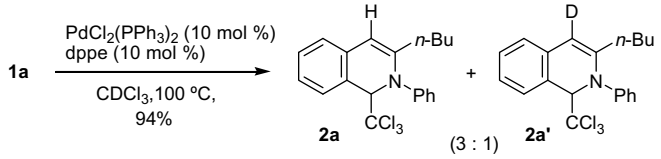
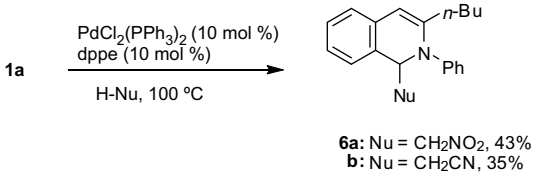


Fig. 1. The X-ray crystallographic structure of **2k**.



Scheme 2. Deuterium labeling study.

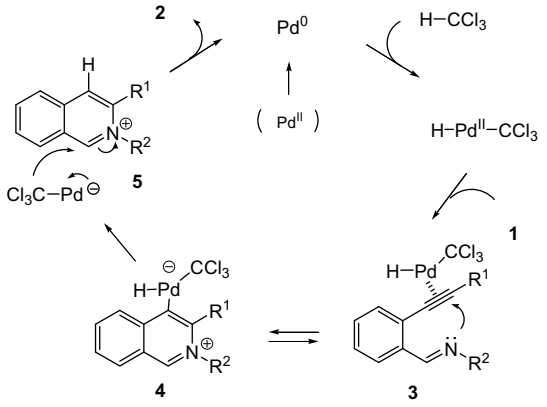


Scheme 4. Addition–cyclization of nitromethane and acetonitrile to *ortho*-alkynylaldimine **1a**.

acetate (30:1) to give 3-butyl-2-phenyl-1-(trichloromethyl)-1,2-dihydroisoquinoline **2a** (179 mg, 0.47 mmol, 96% yield) as a white solid.

In order to clarify the mechanism of the current 1,2-dihydroisoquinoline formation reaction, a deuterium labeling study was performed as shown in Scheme 2. The reaction of **1a** was carried out in $CDCl_3$ to give a 3:1 mixture of 1-(trichloromethyl)-1,2-dihydroisoquinoline **2a** and 4-deuterio-1-(trichloromethyl)-1,2-dihydroisoquinoline **2a′**. Based on the result of the deuterium labeling study, the proposed mechanism is shown in Scheme 3. The oxidative insertion of palladium(0) to C–H bond of chloroform followed by π-coordination with **1** at a carbon–carbon triple bond would form complex **3**, and the intramolecular nucleophilic attack of the imine nitrogen to alkyne would generate the palladium anion species **4**. There would be equilibrium between **3** and **4**. The migration of the hydride on a palladium to the isoquinoline ring followed by the nucleophilic attack of a trichloromethyl anion to the iminium ion of **5** would give **2** and the palladium(0) is regenerated.

In the previous report by Asao et al.,[6] chloroform underwent hydrogen absorption by the zwitterionic isoquinoline species directly in the reaction course, which resulted in higher D content of the product in their deuterium labeling study. In the current reaction, the hydrogen on the trichloromethylpalladium hydride complex generated by the C–H insertion of palladium to chloroform would be readily be exchanged from other hydrogen sources in the reaction mixture. Therefore, the D content of the product in Scheme 2 became low.



Scheme 3. Proposed mechanism.

Since the AgOTf-catalyzed addition–cyclization of pronucleophiles, such as nitromethane, malononitrile, acetylacetone, and dimethylmalonate, to *ortho*-alkynylaldimines has been reported,[3] we employed nitromethane and acetonitrile as pronucleophiles for the current reaction. However, these were not suitable pronucleophiles under palladium-catalyzed conditions and the corresponding adducts **6a** and **6b** were obtained in 43% and 35% yields, respectively (Scheme 4).

In conclusion, we found that the palladium-catalyzed addition–cyclization of pronucleophiles to *ortho*-alkynylaldimines to affords the functionalized 1,2-dihydroisoquinolines. Chloroform underwent the C–H insertion by palladium in this transformation. Since various transformations from a trichloromethyl group have been reported, such as the C–Cl addition of olefins,[8] ester formation,[9] and alkene and alkyne formations,[10] we believe that the current finding enables us to conduct new atom-economical strategy for carbon–carbon bond formation in organic synthesis.

Acknowledgments

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References and notes

1. (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595; (b) List, B. *Tetrahedron* **2002**, *58*, 5573.
2. (a) Yamamoto, Y.; Kubota, Y.; Honda, Y.; Fukui, H.; Asao, N.; Nemoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 3161; (b) Shida, N.; Kubota, Y.; Fukui, H.; Asao, N.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 5023.
3. (a) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632; (b) Xu, L.-W.; Xia, C.-G.; Li, L. *J. Org. Chem.* **2004**, *69*, 8482; (c) Ooi, T.; Kameda, M.; Fujii, J.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397; (d) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356; (e) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712; (f) Marigo, M.; Kjrsgaard, A.; Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Eur. J.* **2003**, *9*, 2359; (g) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338; (h) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995; (i) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418; (j) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992; (k) Qian, C.; Gao, F.; Chen, R. *Tetrahedron Lett.*

2001, *42*, 4673; (l) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504.

4. Recent papers for the synthesis of 1,2-dihydroisoquinolines from *ortho*-alkynylaldimines: (a) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339; (b) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980; (c) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920; (d) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437; (e) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042; (f) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553; (g) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822.
5. Asao, N.; Yudha, S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526.
6. Three-component reaction with *ortho*-alkynylaldehydes, amines, and chloroform in the presence of MS4A was recently reported: Asao, N.; Iso, K.; Yudha, S. *Org. Lett.* **2006**, *8*, 4149.
7. *Spectral data of compound* **2k**: White solid: mp 120–121 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, $J = 7.6$ Hz, 2H), 7.09–7.14 (m, 3H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.65 (t, $J = 7.6$ Hz, 1H), 6.47 (d, $J = 7.2$ Hz, 1H), 5.78 (br s, 2H), 5.10 (s, 1H), 4.53 (d, $J = 18.8$ Hz, 2H), 3.71 (s, 1H), 3.25–3.38 (m, 1H), 2.78 (br s, 2H), 1.53–1.80 (m, 10H), 0.95–1.34 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 135.5, 129.7, 128.6, 127.8, 127.5, 126.1, 124.1, 123.2, 122.0, 120.5, 109.7, 106.5, 103.8, 78.2, 56.5, 54.9, 53.1, 49.1, 32.6, 29.9, 26.5, 26.3, 26.2; IR (KBr) 2926, 2851, 1624, 1601, 1564, 1450, 1421, 1254, 1231, 1151, 1103, 893, 824 cm^{-1}; MS (EI) m/z 561 (M^+); Anal. Calcd for $C_{31}H_{39}Cl_3N_2O$: C, 66.25; H, 6.99; N, 4.98. Found: C, 66.45; H, 7.08; N, 4.92. Crystal data: $C_{31}H_{39}Cl_3N_2O$, $M = 561.99$, Crystal system, space group, monoclinic, $C2/c$, $a = 17.4590(17)$, $b = 14.1930(14)$, $c = 24.4150(12)$ Å, $V = 5955.8(9)$ Å^3, $Z = 8$, $D_c = 1.254$ g/cm^3, μ(Mo-Kα) = 0.71073 Å, $l = 0.334$ mm^{-1}, $F(000) = 2384$, $T = 200$ K. The sample ($0.25 \times 0.25 \times 0.20$ mm) was studied on a Oxford Diffraction Xcalibur Saphir 3 diffractometer with graphite monochromatized Mo-Kα radiation. Reflections were collected ($2.65° < h < 26.79°$), of which 5957 had $I > 2.0\sigma(I)$. Final results: $R_1 = 0.0506$, $wR_2 = 0.1507$, goodness of fit 1.146, 335 parameters, Largest diff. peak and hole: 0.251 and −0.335 e Å^{-3}, extinction coefficient: 0.0011(3).
8. Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329.
9. Habay, S. A.; Schafmeister, C. E. *Org. Chem.* **2004**, *6*, 3369.
10. Aggarwal, V. K.; Mereu, A. *J. Org. Chem.* **2000**, *65*, 7211.