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A Convenient and Efficient Route for the Allylation of Aromatic Amines and α-Aryl Aldehydes with Alkynes in the Presence of a Pd(0)/PhCOOH Combined Catalyst System

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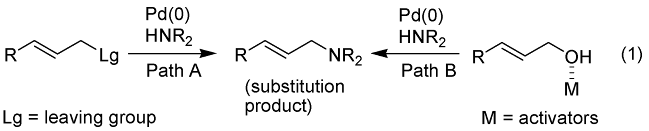
The allylation of aromatic amines with alkynes proceeded smoothly in the presence of catalytic amounts of $Pd(PPh_3)_4$ and benzoic acid. The allylation products were obtained in high yields in a regio- and stereoselective manner. The effect of various groups on the nitrogen atom of anilines was studied. Regardless of the substituent (electron withdrawing or electron donating) on the aromatic ring, the reaction proceeded well. Various functionalities, including $-CH_3$, $-OMe$, $-Cl$, $-CN$, $-COOMe$, $-NO_2$ and $-COCH_3$ were tolerated under the reaction conditions. Similarly, the allylation of α-aryl aldehydes proceeded well with the same level of regio- and stereoselectivity as the allylation of aromatic amines. This reaction provides the second example of the transition metal catalyzed direct α-allylation of aldehydes.

Introduction

Allylamines are an important class of compounds due to their utility as intermediates in organic synthesis,[1] biological properties,[2] and presence in several natural products.[3] In particular, considerable effort has been directed toward the development of new and efficient synthetic methodologies for the allylation of anilines. One of the reliable approaches for the synthesis of this class of compounds is the treatment of allyl alcohol derivatives, such as acetates, carbonates, halides, ..., etc., with amines in the presence of Pd(0) (eq 1, path A).[4,5] Recent progress



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shows that allyllic alcohols themselves can also be used as an allylating agent in the presence of activators which can coordinate with the hydroxyl group, thereby increasing the leaving group ability of the hydroxyl group (eq 1, path B).[6] Although a few reliable approaches are known in the literature for the allylation of anilines, the former procedure (path A) produces a stoichiometric amount of waste elements because the leaving group is liberated and the latter procedure (path B) needs a stoichiometric amount of activators to activate the hydroxyl group. Moreover, path B produces stoichiometric amount of M−OH.

The generation of quaternary carbon center through *catalytic* alkylation of ketone enolates has been the subject of investigation in recent years.[7] The palladium-catalyzed allylic alkylation of prochiral nucleophiles (the Tsuji−Trost reaction) represents one such strategy for the creation of quaternary chiral centers.[8] However, the generation of quaternary carbon center by α-allylic alkylation of nonstabilized ketones and aldehydes has not been thoroughly investigated.[9] The conventional method for *C*-allylation of these substrates involves the preactivation of the carbonyl compounds as their metal enolates,[10] silyl enol ethers,[11] enolstannanes,[12] or enamines.[13] However, in the case of aldehydes, the stoichiometric

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[1] (a) Walsh, C. *Tetrahedron* **1982**, *38*, 871−909. (b) Stutz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 320. (c) Prashad, M. *J. Med. Chem.* **1993**, *36*, 631−632. (d) Michalson, E. T.; Szmuszkovicz, J. *Prog. Drug. Res.* **1989**, *22*, 135.

[2] (a) Reina, M.; Mericli, A. H.; Cabrera, R.; Gonzales-Coloma, C. *Phytochemistry* **1995**, *38*, 355−358. (b) Bergdahl, M.; Hett, R.; Friebe, T. L.; Gangloff, A. R.; Iqbal, J.; Wu, Y.; Helquist, P. *Tetrahedron Lett.* **1993**, *34*, 7371−7374. (c) Genisson, Y.; Mehmandoust, M.; Marazano, C.; Das, B. C. *Heterocycles* **1994**, *39*, 811. (d) Jain, P.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **1995**, *58*, 100.

[3] Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685−700.

[4] For a review on allylic amination, see: Johannsen, M.; Jorgensen K. A. *Chem. Rev.* **1998**, *98*, 1689−1708.

[5] Moreno-Manas, M.; Morral, L.; Pleixats, R. *J. Org. Chem.* **1998**, *63*, 6160−6166 and references therein.

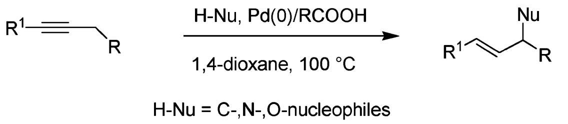
[6] The use of the following activators are known. For Et_3B as an activator see: (a) Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* **2003**, 234−235. For titanium(IV) isopropoxide as an activator, see: (b) Yang, S.-C.; Tsai, Y.-C. *Organometallics* **2001**, *20*, 763−770. (c) Yang, S.-C.; Tsai, Y.-C.; Shue, Y.-J. *Organometallics* **2001**, *20*, 5326−5330. (d) Yang, S.-C.; Chung, W.-H. *Tetrahedron Lett.* **1999**, *40*, 953−956. (e) Yang, S.-C.; Hung, C.-W. *Synthesis* **1999**, 1747−1752. (f) Yang, S.-C.; Hung, C.-W. *J. Org. Chem.* **1999**, *64*, 5000−5001. (g) Shue, Y.-J.; Yang, S.-C.; Lai, H.-C. *Tetrahedron Lett.* **2003**, *44*, 1481−1485. More recently, the use of (π-allyl)palladium complexes bearing DPCB ligand is also reported, see: (h) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H.; Yoshifuji, M *Organometallics* **2004**, *23*, 1698−1707. (i) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968−10969.

[7] (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (d) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

10.1021/jo0485684 CCC: $27.50

alkylation via their metal enolates has serious drawbacks, because of their tendency to undergo aldol, Cannizaro, and/or Tishchenko reactions.[14] To the best of our knowledge, there is only one report of the palladium-catalyzed direct α-allylation of aldehydes with allyl alcohols with stoichiometric amounts of Et_3B, Et_3N, and LiCl.[15]

Recently we reported an altogether new approach for the allylation of some pronucleophiles with alkynes in the presence of Pd(0)/carboxylic acid combined catalyst (eq 2).[16] Since the allylation products are obtained via formal addition of nucleophiles to alkynes,[17] no waste elements are produced in the process. In the course of our further investigation, we now report the Pd(0)/benzoic acid-catalyzed allylation of anilines[18] and α-aryl aldehydes[19] with alkynes (eq 3 and 4), thereby strengthening our previously reported methodology.



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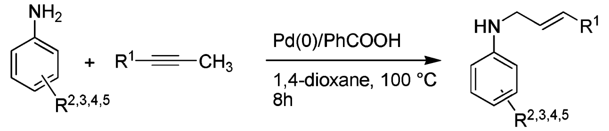

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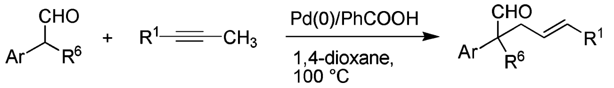

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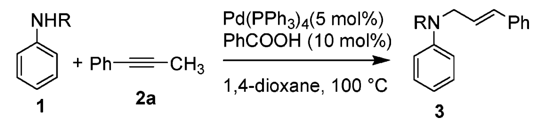
Results and Discussion

Allylation of Aromatic Amines. An equimolar mixture of *N*-methylaniline (**1a**) and 1-phenyl-1-propyne (**2a**) in the presence of $Pd(PPh_3)_4$ (5 mol %)/PhCOOH (10 mol %) was heated in 1,4-dioxane at 100 °C for 4 h. The starting materials completely disappeared giving the allylation product **3a** in 93% isolated yield as a single stereoisomer (Table 1, entry 1). In the absence of benzoic acid no reaction took place even after heating at 100 °C for 24 h as anticipated. Next, the allylation of anilines, bearing various groups on the nitrogen, with 1-phenyl-1-propyne (**2a**) was examined. The results are summarized in Table 1.

TABLE 1. Allylation of Aromatic Amines 1a–i with 1-Phenyl-1-propyne (2a)[a]



entry	R	time	product	yield (%)[b]
1	**1a**, R = Me	4h	**3a**	93
2	**1b**, R = Bn	4h	**3b**	94
3	**1c**, R = H	6h	**3c**	89[c]
4	**1d**, R = Ts	6h	**3d**	98
5	**1e**, R = Ms	6h	**3e**	91[d]
6	**1f**, R = Boc	24h	**3f**	trace[e]
7	**1g**, R = acetyl	24h	**3g**	0[e]
8	**1h**, R = Ph	8h	**3h**	81
9	**1i**, R = *β*-Np	24h	**3i**	52[f]

[a] 1-Phenyl-1-propyne (**2a**) (0.859 mmol) was added to a solution of anilines **1** (0.859 mmol) and $Pd(PPh_3)_4$ (0.043 mmol), PhCOOH (0.086 mmol) in 1,4-dioxane (2 mL) and the mixture was heated at 100 °C for the time specified in the table. [b] Isolated yields after column chromatography. [c] Combined yield of the monoallylated product **3c** and corresponding diallylated product **4**, $(PhCH{=}CH)_2NPh$. Ratio of **3c**:**4** was determined by comparing *N*-CH_2 protons in the ^1H NMR spectra of a crude mixture and found to be 83.17. [d] Yield after recrystallization. [e] The starting material was recovered in a quantitative yield. [f] The starting material **1i** was recovered in 30% yield.

N-Benzylaniline (**1b**) afforded **3b** in an excellent yield in 4 h under the established procedure (entry 2). The

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(8) For reviews of the palladium-catalyzed asymmetric allylic alkylation, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (b) Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975–1015. (c) Hayashi, T. In *Catalytic Asymmetric Synthesis*; I. Ojima, I., Ed.; VCH: New York, 1993. (d) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857–871. (e) Fiaud, J. C. In *Metal-Promoted Selectivity in Organic Synthesis*; Graziani, M., Hubert, A. J., Noels, A. F., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 1991. (f) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257–276.

(9) Palladium-catalyzed allylation of α-aryl ketones with allylic acetate is known, see: Trost, B. M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3492–3495.

(10) (a) Evans, P. A.; Lawler, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 8642–8643. (b) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, Z.-Z. *Org. Lett.* **2001**, *3*, 149–151. (c) Braun, M.; Laicher, F.; Meier, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 3494–3497. (d) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760. (e) Luo, F.-T.; Negishi, E. *Tetrahedron Lett.* **1985**, *26*, 2177–2180 and references therein.

(11) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1983**, 1325–1326. (b) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591–2594.

(12) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591–2594.

(13) (a) Hiroi, K.; Abe, J.; Suya, K.; Sato, S.; Koyama, T. *J. Org. Chem.* **1994**, *59*, 203-213 and references therein. (b) Huang, Y.; Lu, X. *Tetrahedron Lett.* **1988**, *29*, 5663–5664. (c) Murahashi, S.; Makabe, Y.; Kurita, K. *J. Org. Chem.* **1988**, *53*, 4489–4495.

(14) (a) Smith, M. B.; March, J. *Advanced Organic Chemistry*; Wiley: New York, 2001; Chapter 10-105. (b) Cane, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 3, Chapter 1.1.

(15) Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401–10402.

(16) (a) Kadota, I.; Shibuya, A.; Lutete, M. L.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570–4571. (b) Lutete, M. L.; Kadota, I.; Shibuya, A.; Yamamoto, Y. *Heterocycles* **2002**, *58*, 347–357. (c) Lutete, M. L.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622–1623. (d) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262–10263. (e) Patil, N. T.; Kadota, I.; Shibuya, A.; Gyoung Y. S.; Yamamoto, Y. *Adv. Synth. Catal.* **2004**, *346*, 800–804. (f) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *19*, 6478–6481. (g) Kadota, I.; Lutete, M. L.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207–6210.

(17) For a review on transition metal catalyzed addition of heteroatom-hydrogen bonds to alkynes, see: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004, *104*,** 3079–3159.

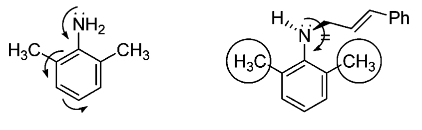
(18) The C–N bond formation in the case of aromatic amines is important because many alkaloids are known to have nitrogen functionality attached to the aromatic ring. For instance angustureine, galipinine, cuspareine, ..., etc.

(19) The palladium-catalyzed allylation of the carbonyl group of aldehydes with allylic substrates in the presence of the reductant is known, see: (a) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *2*, 847–849. (b) Ohno, H.; Hamaguchi, H.; Tanaka, T. *Org. Lett.* **2000**, *2*, 2161–2163. (c) Takemoto, Y.; Anzai, M.; Yanada, R.; Fujii, N.; Ohno, H.; Ibuka, T. *Tetrahedron Lett.* **2001**, *42*, 1725–1728. (d) Lee, W.; Kim, K.-H.; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 139–149. (e) Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6745–6751. (f) Hirashita, T.; Kambe, S.; Tsuji, H.; Omori, H.; Araki, S. *J. Org. Chem.* **2004**, *69*, 5054–5059. (g) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577–2586. (h) Kimura, M.; Kiyama, I.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1999**, *40*, 6795–6798. (i) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627–3629. (j) Kimura, M.; Shimizu, M.; Shibata, K.; Tazoe, M.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3392–3395. (k) Zanoni, G.; Gladiali, S.; Marchetti, A.; Piccinini, P.; Tredici, I.; Vidari, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 846–849.

reaction proceeded well in the case of aniline **1c**; however, the product obtained was a mixture of the monoallylated **3c** and diallylated product **4** in the ratio of 83:17 (entry 3). The sulfonyl protecting groups, such as −Ts and −Ms, were also found to be good substrates for this allylation reaction, giving **3d** and **3e** in 98% and 91% yields, respectively (entries 4 and 5). In the case of protecting groups such as −Boc and −Ac, however, the reaction did not proceed at all and the starting materials were recovered in a quantitative yield (entries 6 and 7). The allylation of less basic and nonnucleophilic anilines, such as diphenylaniline (**1h**) and naphthylphenylamine (**1i**), also proceeded smoothly to give the products **3h** and **3i** in 81% and 52% yield, respectively.

The scope of the allylation was explored by using a variety of anilines, containing either electron donating or electron withdrawing groups in the aromatic nucleus. The results are summarized in Table 2. Treatment of 2,4-dimethoxyaniline (**5a**) with 1-phenyl-1-propyne (**2a**) under the standard conditions gave the corresponding monoallylation product **6a** in 92% yield (entry 1). No formation of the diallylation product was observed in the ^{1}H NMR spectrum of the crude reaction mixture. Similarly, the reaction of alkynes **2b** and **2c** with **5a** also proceeded smoothly to afford the products **6b** and **6c** in 88% and 92% yields, respectively (entries 2 and 3). Unlike the hydrocarbonation reaction,[16e,f] the reaction of alkyne **2d** did not proceed and the starting materials were recovered (entry 4). Next, with use of 1-phenyl-1-propyne (**2a**) as a standard alkyne, several anilines were tested for this allylation reaction. In all cases, the corresponding allylation products were obtained in high yields (entries 5−10). The most striking observation was made when 4-nitroaniline (**5h**) was employed; a mixture of the monoallylation product **6k** and diallylation product **6k′** was obtained in the ratio of 80:20 (entry 11). At this stage it was not clear whether the diallylation product was obtained due to the presence of a strong electron withdrawing group or due to the absence of an ortho substituent, which minimizes the steric hindrance resulting in the formation of the diallylated product. To clarify this point, we next chose 4-methoxyaniline (**5i**) and 2-nitroaniline (**5j**) as substrates and the results of their allylations are shown in entries 12 and 13. These results indicate that the substituent at the ortho position created steric hindrance for the diallylation and therefore the reaction stopped at the monoallylation stage only. As expected, 3-acetylaniline (**5k**) also gave a mixture of **6n** and **6n′** as the ortho position was vacant (entry 14). However, in the case of 2,6-dimethylaniline, a mixture of the monoallylation product **6o** and diallylation product **6o′** was produced in a ratio of 45:55 (entry 15). This result unequivocally shows that the monoallylation product **6o** is more reactive and more nucleophilic than **5*l***. The stronger nucleophilicity of **6o**, as compared to **5*l***, can be explained as shown in Scheme 1. In the structure **5*l***, due to the electron donating resonance effect, the lone pair of $-NH_2$ is in conjugation with π-electrons of the aromatic ring, whereas in structure **6o**, due to the severe steric hindrance of methyl groups, the C−N bond goes out of plane therefore the lone pair becomes perpendicular to the plane of the ring, which would cease an electron donating resonance effect. In short, in structure **5*l***, the lone pair on nitrogen is involved in conjugation while in structure **6o**, the lone pair is not involved in conjugation hence **6o** is more nucleophilic than **5*l***.[20] In the case of 4-phenylaniline (**5m**), the monoallylation product **6p** was obtained in 91% yield (entry 16). α-Naphthylamine (**5n**) was found to be a good substrate for this allylation reaction giving **6q** in 88% yield (entry 17). Next, we studied the allylation of 2-aminopyridine, 2-aminothiazole, indole, and oxindole. However, the reaction was found to be sluggish and only trace amounts of products were detected by ^{1}H NMR spectra of the crude reaction mixture.

SCHEME 1. Plausible Explanation for the Higher Nucleophilicity of 6o as Compared to 5*l*

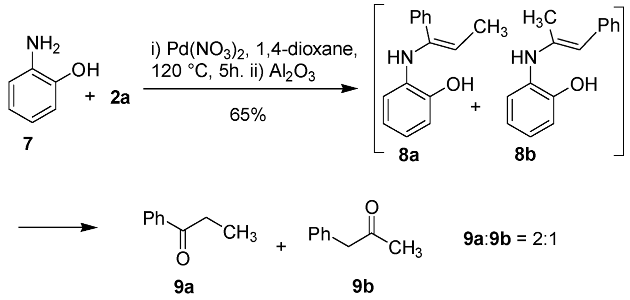


5l
Resonance
(less nucleophilic)

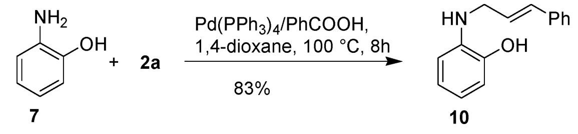
6o
Inhibition of Resonance
(more nucleophilic)

Recently, we reported the reaction of the internal alkyne **2a** with *o*-aminophenol (**7**) to afford a mixture of the regioisomeric ketones **9a** and **9b** (Scheme 2) under $Pd(NO_3)_2$ catalysis.[21] The reaction proceeds via the intermolecular hydroamination process between **2a** and **7**, which gives the intermediates **8a** and **8b**. The products **9a** and **9b** are obtained after tautomerization followed by hydrolysis. However, under the present reaction conditions, no formation of either **9a** or **9b** was detected; the corresponding allylated product **10** was obtained in 83% yield (Scheme 3). Thus, just by switching the palladium catalysts we are now in a position to synthesize *N*-allylanilines instead of the corresponding hydroamination products. Regardless of the substituent's nature and position, the reaction proceeded well in the case of all anilines. This observation is in contrast to the previously reported cases[6b,c] wherein the transition metal-catalyzed allylation of anilines with allyl alcohols proceeded well with *anilines containing electron-donating*

SCHEME 2



SCHEME 3



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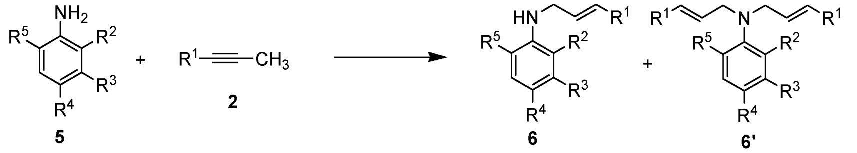
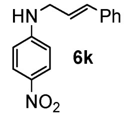
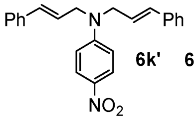
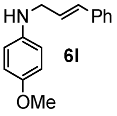
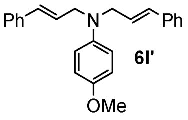
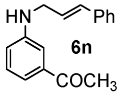
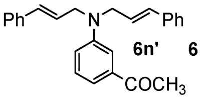
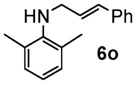
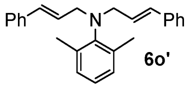
[20] In the literature it is well-known that 2,6-dialkylaniline is less nucleophilic than its *N*-monoalkylated derivatives.

[21] Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12670−12671.

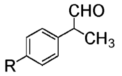
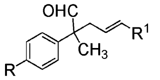
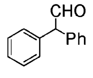
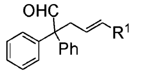
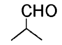
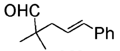
TABLE 2. Allylation of Substituded Anilines with Alkynes[a]



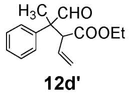
entry	anilines (**5**)	alkynes (**2**)	product (**6** and **7**)[b]	yield (%)[c]
1	**5a** $R^2 = R^4 = OMe$, $R^3 = R^5 = H$	**2a** $R^1 = C_6H_5$	**6a** $R^1 = C_6H_5$, $R^2 = R^4 = OCH_3$, $R^3 = R^5 = H$	92
2	**5a**	**2b** $R^1 = C_6H_4$-*p*Cl	**6b** $R^1 = C_6H_4$-*p*Cl, $R^2 = R^4 = OCH_3$, $R^3 = R^5 = H$	88
3	**5a**	**2c** $R^1 = C_6H_4$-*pOMe*	**6c** $R^1 = C_6H_4$-*pOMe,* $R^2 = R^4 = OCH_3$, $R^3 = R^5 = H$	92
4	**5a**	**2d** R^1 = COOEt	**6d** R^1 = COOEt, $R^2 = R^4 = OCH_3$, $R^3 = R^5 = H$	0[c]
5	**5b** $R^2 = R^4 = CH_3$, $R^3 = R^5 = H$	**2a**	**6e** $R^1 = C_6H_5$, $R^2 = R^4 = CH_3$, $R^3 = R^5 = H$	91
6	**5c** $R^2 = R^3 = CH_3$, $R^4 = R^5 = H$	**2a**	**6f** $R^1 = C_6H_5$, $R^2 = R^3 = CH_3$, $R^4 = R^5 = H$	82
7	**5d** $R^2 = CH_3$, $R^4 = Cl$, $R_3 = R_5 = H$	**2a**	**6g** $R^1 = C_6H_5$, $R^2 = CH_3$, $R^4 = Cl$, $R^3 = R^5 = H$	96
8	**5e** $R^2 = CN$, $R^3 = R^4 = R^5 = H$	**2a**	**6h** $R^1 = C_6H_5$, $R^2 = CN$, $R^3 = R^4 = R^5 = H$	93
9	**5f** $R^2 = OCH_3$, $R^4 = NO_2$, $R^3 = R^5 = H$	**2a**	**6i** $R^1 = C_6H_5$, $R^2 = OCH_3$, $R^4 = NO_2$, $R^3 = R^5 = H$	91
10	**5g** R^2 = COOMe, $R^3 = R^4 = R^5 = H$	**2a**	**6j** $R^1 = C_6H_5$, R^2 = COOMe, $R^3 = R^4 = R^5 = H$	98
11	**5h** $R^4 = NO_2$, $R^2 = R^3 = R^5 = H$	**2a**	 **6k**  **6k'** **6k**:**6k'** = 80:20[d]	82%[e]
12	**5i** R^4 = OMe, $R^2 = R^3 = R^5 = H$	**2a**	 **6l**  **6l'** **6l**:**6l'** = 87:13[d]	89%[e]
13	**5j** $R^2 = NO_2$, $R^3 = R^4 = R^5 = H$	**2a**	**6m** $R^1 = C_6H_5$, $R^2 = NO_2$, $R^3 = R^4 = R^5 = H$	92
14	**5k** $R^3 = COCH_3$, $R^2 = R^4 = R^5 = H$	**2a**	 **6n**  **6n'** **6n**:**6n'** = 84:16[d]	88%[e]
15	**5l** $R^2 = R^5 = CH_3$, $R^3 = R^5 = H$	**2a**	 **6o**  **6o'** **6o**:**6o'** = 45:55[d]	93%[e]
16	**5m** R^4 = Ph, $R^2 = R^3 = R^5 = H$	**2a**	**6p** R^1 = Ph, R^4 = Ph, $R^2 = R^3 = R^5 = H$	91
17	**5n** R^2, R^3 = -CH=CH-CH=CH- $R^4 = R^5 = H$	**2a**	**6q** R^1 = Ph, R^2 and R^3 = -CH=CH-CH=CH-, R^4 = R^5 = H	88

[a] All reactions were carried out as per the general procedure described in the Experimental Section. [b] Isolated yields. [c] The starting materials were recovered in a quantative yield. [d] The ratio was determined by comparing *N*-CH_2 protons in the ^1H NMR spectra of a crude mixture. [e] Combined yield of the mono- and diallylated products based on alkyne.

TABLE 3. Pd(0)/PhCOOH Catalyzed Direct Allylation of Aldehydes with Alkynes[a]

entry	aldehyde (**11**)	alkyne (**2**)	product (**12**)	yield (%)[b]
		$H_3C—\equiv—R^1$		
1	**11a** R = H	**2a**	**12a** R^1 = C_6H_5, R = H	96
2	**11a** R = H	**2b**	**12b** R^1 = C_6H_4-*p*Cl, R = H	87
3	**11a** R = H	**2c**	**12c** R^1 = C_6H_4-*p*OMe, R = H	99
4	**11a** R = H	R^1 = COOEt **2d**	**12d** R^1 = COOEt, R = H	79[c]
5	**11a** R = H	R^1 = *p*-CF_3-C_6H_4 **2e**	**12e** R^1 = C_6H_4-*p*CF_3, R = H	99
6	**11b** R = CH_3	**2a**	**12f** R^1 = C_6H_5, R = CH_3	86
7	**11c** = OCH_3	**2a**	**12g** R^1 = C_6H_5, R = OCH_3	90
8	**11d** R = Cl	**2a**	**12h** R^1 = C_6H_5, R = Cl	95
9	 **11e**	**2a**	 **12i** R^1 = Ph	93
10	**11e**	**2b**	**12j** R^1 = C_6H_4-*p*Cl	97
11	 **11f**	**2a**	 **12k**	26[d]

[a] All reactions were carried out with 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of benzoic acid in 1,4-dioxane at 100 °C for 15 h. [b] Isolated yield. [c] The yield corresponds to the combined yield of regioisomers **12d** and **12d′**. [d] Reaction mixture was heated at 100 °C for 48 h.



12d'

groups; on the other hand, anilines having electron-withdrawing groups gave the allylation products in lower yields. Substrates bearing −Br and −I substituents were not tolerated under the present reaction conditions presumably due to the oxidative insertion of Pd(0) to the aryl-bromide/iodide bond.

Allylation of α-Aryl Aldehydes. The treatment of the aldehyde **11a** with 1 equiv of 1-phenyl-1-propyne (**2a**) in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of benzoic acid in 1,4-dioxane at 100 °C gave the α-allylated aldehyde **12a** as the sole product in 96% yield (Table 3, entry 1). We then investigated the scope and limitations of the reaction using a variety of aldehydes and alkynes. The reaction of the aldehyde **11a** with the alkynes **2b** and **2c** afforded the desired allylation products **12b** and **12c**, respectively, in excellent yields and with perfect regiocontrol on the allylic unit (entries 2 and 3). When the alkyne **2d** was employed, however, a mixture of the regioisomer **12d** and **12d′** was formed in the ratio of 5:1 as shown by the ^1H NMR spectrum of the crude reaction mixture (entry 4). When the alkyne **2e** was used, the corresponsing allylated product **12e** was obtained in 99% yield (entry 5). Substituents such as $-CH_3$, $-OCH_3$, and −Cl in the aromatic aldehydes at the para position do not affect the efficiency of the reaction. Thus, when **11b**, **11c**, and **11d** were treated with 1-phenyl-1-propyne (**2a**), the corresponding allylation products **12f**, **12g**, and **12h** were obtained in 86%, 90%, and 95% yield, respectively (entries 6−8). In the case of the sterically bulky aldehyde **11e**, the reaction also proceeded with the alkyne **2a** cleanly giving rise the product **12i** in 93% yield (entry 9). When the aldehyde **11e** was treated with alkyne **2b**, the corresponding allylated product **12j** was obtained in excellent yield (entry 10). Aliphatic aldehydes were found to be poor substrates for this reaction. As shown in entry 11, 2-methylpropionaldehyde (**11f**) when treated with **2a** gave the product **12k** in only 26% yield even after heating for 48 h. It should be noted that in the present catalytic system there is no need for preactivation of the substrates and there is no need for use of any additives. In the absence of any additives, the reaction proceeded smoothly giving the corresponding α-allylated aldehydes in high yields. It is noteworthy that under the reaction conditions the α-hydrogen of aldehydes is easily substituted by allylic groups, without damaging labile aldehyde functionality. The reaction can also be carried out under neat conditions (without solvent). For instance, the treatment of the aldehyde **11a** with 1 equiv of 1-phenyl-1-propyne (**2a**) in the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of benzoic acid under neat conditions at 100 °C gave the product **12a** in 88% yield within 4 h. The alkynes such as 3-hexyne and 1-phenyl-1-butyne did not react with any of the nucleophiles (aromatic amines and α-aryl aldehydes) mentioned above under these reaction conditions.

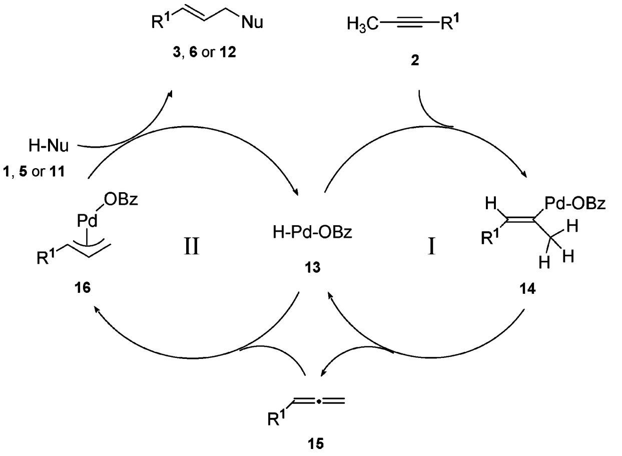


FIGURE 1. A mechanism for the allylation of anilines and α-aryl aldehydes with alkynes.

The mechanism of this reaction is shown in Figure 1. The initial step is the hydropalladation of alkynes **2** with the hydridopalladium species **13** generated from Pd(0) and benzoic acid[22] (catalytic cycle I).[23] The resulting vinyl palladium species **14** would produce phenyl allene **15** and the active catalyst **13** via *β*-elimination.[24] Hydropallada-

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[22] Acetic acid can also be used as a cocatalyst; however, we preferred benzoic acid because of the simplicity for weighing.

[23] Trost, B. M.; Rise, F. *J. Am. Chem. Soc.* **1987**, *109*, 3161−3163.

[24] Palladium-catalyzed isomerization of alkynes to allenes, see: (a) Sheng, H.; Lin, S.; Huang, Y. *Tetrahedron Lett.* **1986**, *27*, 4893−4894. (b) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301−2303. (c) Lu, X.; Ji, J.; Ma, D.; Shen, W. *J. Org. Chem.* **1991**, *56*, 5774−5778.

tion of **15** with **13** presumably gives the π-allylpalladium species **16**, which reacts with anilines and α-aryl aldehydes to give the allylation products along with the hydridopalladium species **13** (cycle II).

In conclusion, the palladium-catalyzed allylation of aromatic amines and α-aryl aldehydes with alkynes provides a new efficient route to *N*-allylanilines and α-allylated aldehydes, respectively. The cleanliness of the process, high atom economy,[25] and minimization of the waste elements greatly enhance the usefulness of the present reaction. The α-allylated aldehydes are important substances for various transformations in synthetic organic chemistry. The present study has provided a useful method for the synthesis of α-allylated aldehydes having a quaternary carbon center. The methodology reported herein complements the known method for the transition metal catalyzed allylation of some pronucleophiles. Moreover, to the best of our knowledge, the present reaction represents the first example for the coupling of aldehydes with internal alkynes to form α-allylated aldehydes.[26] Unfortunately, at this stage, the allylation of α-alkyl-alkyl substituted aldehydes (instead of α-aryl-alkyl or aryl-aryl substituded aldehydes) is inefficient. Further investigation on the allylation of α-alkyl-alkyl substituded aldehydes employing a different catalyst system is now in progress in our laboratory. Applications of this strategy for the synthesis of natural products are currently underway in our laboratories.

Experimental Section

General Procedure for the Allylation of α-Aryl Aldehydes. The reaction of *N*-methylaniline (**1a**) with 1-phenyl-1-propyne (**2a**) is representative. To a mixture of *N*-methylaniline (**1a)** (0.092 g, 0.859 mmol), 1-phenyl-1-propyne (**2a**) (0.100 g, 0.859 mmol), and tetrakis(triphenylphosphine)-palladium (0.050 g, 0.043 mmol) in dry 1,4-dioxane (2 mL) was added benzoic acid (0.010 g, 0.086 mmol), and the mixture was stirred at 100 °C for 8 h. The reaction mixture was then filtered through a short silica gel column, using ether as an eluent, and the filtrate was concentrated. The residue was purified by a silica gel column chromatography (hexane/AcOEt, 9:1) to give the allylated product **3a** (0.194 g, 93%) as an oil.

General Procedure for the Allylation of α-Aryl Aldehydes. The reaction of the aldehyde **11a** with 1-phenyl-1-propyne (**2a**) is representative. To a mixture of **11a** (0.100 g, 0.745 mmol), 1-phenyl-1-propyne (**2a**) (0.087 g, 0.745 mmol), and Pd(PPh$_3$)$_4$ (0.043 g, 0.037 mmol) in dry 1,4-dioxane (2 mL) was added benzoic acid (0.009 g, 0.075 mmol), and the mixture was stirred at 100 °C for 15 h. The reaction mixture was filtered through a short silica gel column with ether as an eluent, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane/AcOEt, 9:1) to give **12a** (0.179 g, 96%).

Acknowledgment. N.T.P. thanks the Japan Society for the Promotion of Science (JSPS) for a postdoctoral research fellowship.

Supporting Information Available: Experimental details, characterization data of compounds **6a**, **6b**, **6c**, **6f**, **6h**, **6i**, **6n**, **6p**, **10**, and **12a**−**j**, and ^{1}H NMR of spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0485684

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[25] (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 259−281.

[26] Nickel-catalyzed reductive coupling of aldehydes with internal alkynes is known, see: (a) Huang, W.-S.; Chan J.; Jamison, T. F. *Org. Lett*. **2000**, *2*, 4221−4223. (b) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442−3443.