Strikingly Simple Direct α-Allylation of Aldehydes with Allyl Alcohols: Remarkable Advance in the Tsuji−Trost Reaction

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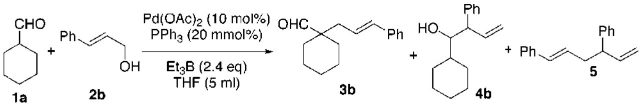
Palladium-catalyzed allylic alkylation of active methylene compounds such as β-ketoesters and malonates (the Tsuji−Trost reaction) is a reliable and widely used method for C−C bond formation.[1] However, the α-allylic alkylation of nonstabilized ketones and aldehydes remains to be developed. The alkylation reported so far requires both reaction partners to be preactivated: allyl alcohols as their esters and halides and ketones and aldehydes as their metal enolates,[2] enol silyl ethers,[3] or enamines.[4] In this context, for the alkylation of ketones, a traditional stoichiometric alkylation via their metal enolates might still be regarded as an alternative to be compared favorably.[5,6] On the other hand, the stoichiometric alkylation of aldehydes via their metal enolates has numerous drawbacks, because of their tendency to undergo aldol condensation and the Cannizaro and Tishchenko reactions.[7]

Here we disclose that the α-alkylation of aldehydes can be readily achieved by direct use of aldehydes and allyl alcohols[8] under catalytic conditions with respect to palladium. In most cases, the reaction is complete within 1 day at room temperature to ∼50 °C and provides the α-allyl aldehydes derived from a variety of alkyl aldehydes and allyl alcohols in good to excellent yields.

Scheme 1. Pd-Catalyzed Amphiphilic Allylation of a Secondary Aldehyde with an Allyl Alcohol: Effects of Additives (**1a** = 1.1 mmol, **2b** = 1.0 mmol)



run	additive (eq)	temp/time (h)	% isolated yield **3b**	**4b**	**5**
1	none	rt/4	30	39	20
2	Et_3N (1.2)	rt/18	70	23	0
3	K_2CO_3 (1.2)	rt/19	60	36	0
4	LiCl (1.0)	rt/24, 50 °C/36	0	0	0
5	Et_3N (1.2) + LiCl (1.0)	rt/40	92	4	0

As is shown in run 1 in Scheme 1, under the reaction conditions developed recently for the α-allylation of active methylene compounds[9] and *o*-hydroxyacetophenones,[10] **1a** and **2b** reacted to provide a mixture of the expected product **3b** along with a nucleophilic allylation product **4b** and a biallyl **5** in comparable amounts. To improve the yield in favor of **3b**, the bases (runs 2 and 3) and chloride ion sources (run 4)[11] were examined as additives, the former to increase the enol content of aldehyde and the latter to suppress nucleophilic allylation.[12b] As was expected, the bases turned out to be very effective at increasing the yield of **3b** and completely suppressed the formation of **5**, but **4b** was formed still in considerable amounts (runs 2 and 3). Surprisingly, however, LiCl[11,13] completely inhibited the reaction, and no **3b**, **4b**, and **5** was produced at all (run 4). In sharp contrast to these results, to our pleasant surprise, a combination of Et_3N and LiCl turned out to be most satisfactory and furnished **3b** selectively in excellent yield (run 5).

Under the conditions thus established, the α-allylation of a variety of combinations of secondary aldehydes and allyl alcohols was examined (runs 1−8, Table 1). As is evident from these results, the reaction shows quite high generality and provides a wide structural variety of **3**. Only in a limited number of cases (run 5, Scheme 1 and runs 1 and 2, Table 1) was the reaction accompanied with nucleophilic allylation, providing **4a**−**c** as minor products.[12] Usually, 10 mol % of $Pd(OAc)_2$ and 20 mol % of PPh_3 were employed (conditions A); however, the results shown in runs 5−7 indicate that 5 mol % of $Pd(OAc)_2$−10 mol % of PPh_3 might be sufficient to complete the reaction within a reasonable reaction time at 50 °C (conditions B).[14]

The reaction feature of primary aldehydes turned out to be quite different from that of secondary aldehydes and selectively provided α-allylation products **7** of the self-aldols (runs 9 and 10, Table 1).[15] The quantitative conversion of 1-cyclohexenecarboxaldehyde (**1e**) into its α-alkylated products, **7c** and **7d**, further supports the above-mentioned sequence (runs 11 and 12).

It may be pertinent to look at the present unique direct α-allylic alkylation of aliphatic aldehydes with allyl alcohols, especially focusing on the dramatic effects of the chloride ion and Et_3N additives (Schemes 1 and 2). Mechanistic studies have clarified that $Pd(OAc)_2$ is reduced to Pd(0) by trialkyl- and triarylphosphines, where 1 equiv of phosphine is oxidized to the corre-

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[1] (a) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: Chichester, 2000. (b) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 8E.

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

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

[4] (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.

[5] Ruthenium-catalyzed direct α-propargylation of ketones with propargyl alcohols: Nishibayashi, Y.; Wakiji, I.; Ishii, Y.; Uemura, S.; Hidai, M. *J. Am. Chem. Soc.* **2001**, *123*, 3393−3394.

[6] Palladium-catalyzed α-*arylation* (not *allylation*) of ketones and aldehydes has been developed rapidly in recent years: (a) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370 and references therein. (b) Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1999**, *40*, 5345−5348. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478. (d) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1998**, *39*, 6203−6206. (e) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7577−7580; 7581−7582.

[7] (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, 1991; Vol. 3, Chapter 1.1.

[8] Allyl alcohols as π-allylpalladium precursors: (a) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *2*, 847−849. (b) Yang, S.-H.; Hung, C.-W. *J. Org. Chem.* **1999**, *64*, 5000−5001. (c) Xiao, W.-J.; Alper, H. *J. Org. Chem.* **1998**, *63*, 7939−7944. Also see references cited in refs 9, 10, and 12b.

[9] Tamaru, Y.; Horino, Y.; Araki, M.; Tanaka, S.; Kimura, M. *Tetrahedron Lett.* **2000**, *41*, 5705−5709.

[10] Horino, Y.; Naito, M.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2001**, *42*, 3113−3116.

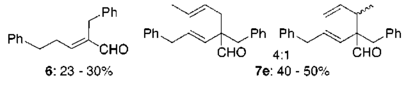
[11] Tetrabutylammonium chloride (1.0 mmol, completely soluble in the reaction mixture) showed almost the same reaction behavior as LiCl.

[12] (a) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627−3629. (b) Kimura, M.; Kiyama, I.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1999**, *40*, 6795−6798. For a discussion of umpolung of π-allylpalladium, see: (c) Tamaru, Y. *J. Organomet. Chem.* **1999**, *576*, 215−231.

[13] A large portion of LiCl remains undissolved in the reaction mixture.

[14] Interestingly, under the same conditions as run 1 in Table 1, both allyl chloride and acetate were unreactive and provided **3a** in much lower isolated yield (ca. 35%) after 80 h at room temperature.

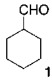
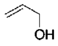
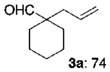
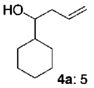
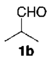
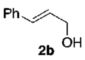
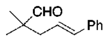
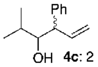
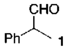
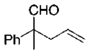
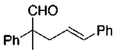
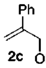
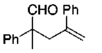
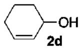
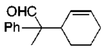
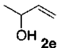
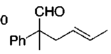
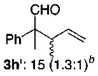
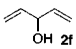
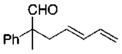
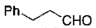
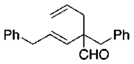
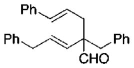
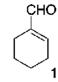
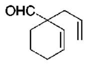
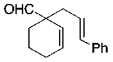
[15] For the reaction with relatively unreactive allyl alcohols (e.g., α- and γ-methylallyl alcohols), a mixture of a self-aldol condensation product **6** and its α-allylation product **7e** was obtained in comparable amounts.



6: 23 - 30% **7e**: 40 - 50%

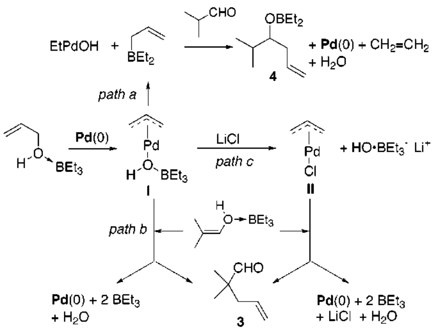
10.1021/ja011656a CCC: $20.00

Table 1. Pd-Catalyzed α-Allylation of Aldehydes with Allyl Alcohols

run	aldehyde	alcohol	temp/time (conditions)[a]	product, % isolated yield
1	 **1a**	 **2a**	rt/48 (A)	 **3a**: 74  **4a**: 5
2	 **1b**	 **2b**	rt/36 (A)	 **3c**: 89  **4c**: 2
3	 **1c**	**2a**	50 °C/12 (A)	 **3d**: 87
4	**1c**	**2b**	50 °C/12 (A)	 **3e**: 83
5	**1c**	 **2c**	50 °C/12 (B)	 **3f**: 85
6	**1c**	 **2d**	50 °C/45 (B)	 **3g**: 63
7	**1c**	 **2e**	50 °C/20 (B)	 **3h**: 79  **3h'**: 15 (1.3:1)[b]
8	**1c**	 **2f**	rt/18 (A)	 **3i**: 69
9	 **1d**	**2a**	50 °C/22 (C)	 **7a**: 70
10	**1d**	**2b**	rt/36 (C)	 **7b**: 74
11	 **1e**	**2a**	rt/24 (A)	 **7c**: 90
12	**1e**	**2b**	rt/24 (A)	 **7d**: 82

[a] Conditions A: **1** (1.1 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.1 mmol), PPh_3 (0.2 mmol), Et_3B (2.4 mmol, 1 M hexane), Et_3N (1.2 mmol), LiCl (1.0 mmol) in dry THF (5 mL) under N_2. Conditions B: **1** (1.1 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.10 mmol), Et_3B (2.4 mmol, 1 M hexane), Et_3N (1.2 mmol), LiCl (1.0 mmol) in dry THF (5 mL) under N_2. Conditions C: **1** (2.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (0.1 mmol), PPh_3 (0.2 mmol), Et_3B (2.4 mmol, 1 M hexane), Et_3N (1.2 mmol), LiCl (1.0 mmol) in dry THF (5 mL) under N_2. [b] Diastereomer ratio.

Scheme 2. Plausible Mechanism for Pd-Catalyzed Amphiphilic Allylation of Aldehyde



sponding phosphine oxide.[16] To perform the reduction of $PdCl_2$ to Pd(0), on the other hand, requires water and an amine base in addition to a phosphorus ligand.[17] The contrasting phenomena observed in runs 4 and 5 (Scheme 1) might be rationalized by taking the contrasting reactivity of $Pd(OAc)_2$ and $PdCl_2$ into consideration. In the absence of Et_3N, no reaction takes place, because $PdCl_2$ is tough under the conditions and remains intact (run 4);[18] however, in the presence of Et_3N, $PdCl_2$ might be reduced to a Pd(0) species and the reaction recovers (run 5). In run 5, an allyl alcohol might take the place of water to produce a Pd(0) species from $PdCl_2$ and Ph_3P. However, note that 1 equiv of water forms in every one catalytic cycle of all the pathways a−c (Scheme 2).[19]

Oxidative addition of an allyl alcohol activated by the coordination with BEt_3 to the Pd(0) species leads to an intermediate **I**, which would enjoy three different pathways: path a, an allyl−ethyl exchange to form allyldiethylborane and EtPdOH,[12] path b, nucleophilic attack by an aldehyde enol, and path c, a counterion exchange to form a π-allylpalladium chloride species **II**, which further reacts with the aldehyde enol to form the final product **3**.[20]

In the absence of LiCl (runs 1−3, Scheme 1), either pathway a predominates over pathway b and provides a mixture of **4** and **5** as the major products (run 1),[12b,c] or pathway b predominates over pathway a in the presence of a base, since the base might increase an enol content (runs 2 and 3). On the other hand, in the presence of LiCl and Et_3N, all the pathways a−c vie with one another; consequently, the contribution of pathway a might become smaller and negligible, resulting in the selective formation of **3** (run 5).

Although in the mechanism outlined in Scheme 2 the roles of Et_3B were explicitly referred to as a Lewis acid to activate both an alcohol and an aldehyde and also as an ethyl group source to generate EtPdOH and allylborane (path a), we believe that Et_3B might play some presently unknown, decisively important role to promote the present catalytic reaction effectively. It should be noted also that Et_3N apparently reduces its ability as a base, not only because it forms a Lewis acid−base complex with Et_3B that is present in excess in the reaction mixture,[21] but also because it quenches HCl and HOAc generated upon the reduction of $PdCl_2$ and $Pd(OAc)_2$, respectively; nevertheless, Et_3N is absolutely indispensable to promote the selective α-alkylation of aldehydes (run 5, Scheme 1).

In conclusion, we have disclosed for the first time the direct α-allylic alkylation of aldehydes with allyl alcohols, which proceeds catalytically with respect to palladium (5−10 mol %) in the presence of stoichiometric amounts of Et_3B, Et_3N, and LiCl at room temperature to ∼50 °C. The mildness of the reaction conditions, wide applicability to a variety of combinations of aldehydes and allyl alcohols, the ease with which the reaction can be performed, and, most importantly, the fact that there is no need for preactivation of both reaction partners (atom economy)[22] all combine to contribute to greatly advance the Tsuji−Trost reaction.

Acknowledgment. We thank Mr. Y. Ohhama, NMR Facility, for his outstanding technical assistance. Financial support by the Ministry of Education, Culture, Sports, Science, and Technology, Japanese Government, is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for **3a**−**i**, **4a**−**c**, **6**, and **7a**−**e** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513−2516. (b) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009−3013. (c) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177−2180.

(17) (a) Meier, M.; Basolo, F. *Inorg. Synth.* **1972**, *13*, 113−115. (b) Mason, M. R.; Verkade, J. G. *Organometallics* **1992**, *11*, 2212−2220.

(18) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375−8384.

(19) See Supporting Information for further discussion.

(20) Another pathway is conceivable that involves Pd-catalyzed Claisen rearrangement of vinyl allyl ethers that might be formed in situ via Et_3B-catalyzed condensation of allyl alcohols and aldehydes; however, the fact that cinnamyl alcohol provides selectively α-cinnamyl aldehydes (e.g., **3b**,**c**) clearly excludes the possibility.

(21) Brown, H. C. *J. Am. Chem. Soc.* **1945**, *67*, 374−378.

(22) For a general discussion of atom economy in organic synthesis, see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. (b) Trost, B. M. *Science* **1991**, *254*, 1471−1477.