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Palladium-Catalyzed Formal Hydroacylation of Allenes Employing Acid Chlorides and Hydrosilanes

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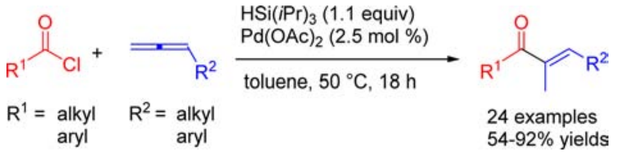
ABSTRACT



The palladium-catalyzed formal hydroacylation of allenes employing acid chlorides and hydrosilanes has been achieved. The reactions proceed with commercially available $Pd(OAc)_2$ as a catalyst and $HSi(\textit{i}Pr)_3$ as a reducing reagent, giving the corresponding α,β-unsaturated ketones regio- and stereoselectively.

The addition of aldehydes to carbon−carbon multiple bonds, namely hydroacylation, is a useful synthetic method to produce unsymmetrical ketones.[1] However, intermolecular additions of aldehydes to carbon−carbon multiple bonds such as alkenes or alkynes often suffer from low selectivity and low yields. To ensure high efficiency, (i) intramolecular addition,[2] (ii) carbon monoxide pressure,[3] (iii) substrates having proper directing groups,[1c,d,4] and (iv) oxidative or reductive formal hydroacylation employing alcohols[1b,5] or anhydrides[6] as acyl donors were often indispensable.

Meanwhile, oxidative addition of acid chlorides to a metal center is a more facile step than that of aldehydes.[7] Thus, acid chlorides were utilized as promising substrates

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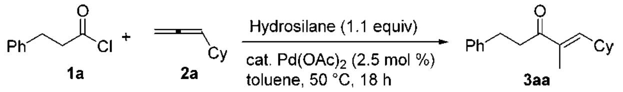
in various reactions. Cheng and co-workers reported the reactions of acid chlorides with allenes in the presence of a diboron, a disilane, or a distannane.[8] Recently, we found that the iridium-catalyzed addition of acid chlorides to terminal alkynes gives β-chloro-α,β-unsaturated ketones regio- and stereoselectively.[9] We also reported a palladium complex catalyzed reduction of acid chlorides with hydrosilanes to the corresponding aldehydes.[10]

Herein, we report palladium-catalyzed reactions of acid chlorides with hydrosilanes in the presence of allenes. The present reaction is regarded as a formal intermolecular hydroacylation of allenes. As for the hydroacylation of allenes using aldehydes,[11,12] there have been only two precedents to date, in which the aldehydes must bear hydroxyl[11a] or thioether[11b] functional groups as directing groups.[12] These reactions employing aldehydes as acyl sources afforded β,γ-unsaturated ketones while α,β-unsaturated ketones were obtained regio- and stereoselectively in the present reaction. Noteworthy is that no directing groups are necessary in the present reaction.

First, a reaction of 3-phenylpropionyl chloride (**1a**) with cyclohexylallene (**2a**) was carried out employing various hydrosilanes in the presence of a catalytic amount of $Pd(OAc)_2$ at 50 °C (Table 1). Employing $HSi(i\text{Pr})_3$ as a hydrosilane, a mixture of α,β-unsaturated ketones (**3aa**) was obtained in 96% total yield with high (*E*)-**3aa** selectivity ((*E*)-**3aa**/other isomers = 96/4, entry 1). Here, neither the reduction of **1a** to 3-phenylpropanal nor hydrosilylation of **2a** proceeded at all. Furthermore, there was no indication of styrene formation via decarbonylation of **1a** followed by the β-hydrogen elimination. By silica gel column chromatography, pure (*E*)-**3aa** was isolated in 92% yield (entry 1). Employing $HSiEt_3$, $HSiPh_3$, $HSi(OEt)_3$, or polymethylhydrosiloxane (PMHS) as the hydrosilane, the yield of **3aa** decreased considerably (entries 2–5). With H_2SiPh_2 or H_3SiPh_3 (entries 6 and 7), yields of **3aa** were low and the reduction of **1a** to 3-phenylpropanal occurred to some extent. Under the reaction conditions of entry 1, other Pd catalysts such as $PdCl_2(PhCN)_2$ and $Pd(dba)_2$ similarly afforded **3aa** in 96% yields. However, with the addition of PPh_3 or PCy_3 to the entry 1 conditions, the reaction ceased completely (entries 8 and 9). 1,4-Dioxane, 1,2-dichloroethane, and acetonitrile were as effective as toluene as a solvent, and **3aa** was afforded in 84%, 83%, and 93% yields, respectively, with high selectivity ((*E*)-**3aa**/isomers = 96/4). DMF as a solvent gave the products only in 28% yield with low selectivity ((*E*)-**3aa**/isomers = 70/30). When the corresponding *aldehyde*, 3-phenylpropanal, was used instead of a mixture of **1a** and $HSi(i\text{Pr})_3$, **3aa** was not obtained at all. Under otherwise the same conditions as those for entry 1, $HSnBu_3$ instead of $HSi(i\text{Pr})_3$ provided **3aa** in 13% yield. Other reducing reagents such as molecular hydrogen and pinacolborane in place of the hydrosilane did not afford **3aa** at all. Thus, the combination of acid chlorides and easy-to-handle hydrosilanes was most suitable to realize the intermolecular hydroacylation reaction of allenes.

Table 1. Effect of Hydrosilanes on the Palladium-Catalyzed Formal Hydroacylation of Cyclohexylallene (**1a**) Employing 3-Phenylpropionyl Chloride (**2a**)[a]



entry	hydrosilanes	total yield of **3aa** (%)[b]	(*E*)-**3aa**/ isomers[c]
1	$HSi(i\text{Pr})_3$	96 (92)[d]	96/4
2	$HSiEt_3$	76	94/6
3	$HSiPh_3$	69	94/6
4	$HSi(OEt)_3$	68	94/6
5	PMHS[e]	46	90/10
6	H_2SiPh_2	28	93/7
7	H_3SiPh	12	74/26
8[f]	$HSi(i\text{Pr})_3$	0	–
9[g]	$HSi(i\text{Pr})_3$	0	–

[a] Reaction conditions: 3-phenypropionyl chloride (**1a**, 0.20 mmol), cyclohexylallene (**2a**, 0.22 mmol), hydrosilane (0.22 mmol), $Pd(OAc)_2$ (0.0050 mmol, 2.5 mol %), in toluene (0.40 mL), at 50 °C, for 18 h. [b] Yield by the GC internal standard method. [c] Selectivity of (*E*)-**3aa**. The isomers consist of (*Z*)-**3aa** and another isomeric product (GCMS and NMR). [d] Isolated yield of (*E*)-**3aa** with 0.40 mmol of **1a** scale. [e] Polymethylhydrosiloxane. [f] A mixture of $Pd(OAc)_2$ (0.0050 mmol) and PPh_3 (0.010 mmol) was used as the catalyst. [g] A mixture of $Pd(OAc)_2$ (0.0050 mmol) and PCy_3 (0.010 mmol) was used as the catalyst.

Under the optimum conditions of entry 1 in Table 1, various acid chlorides (**1b–m**) afforded the corresponding (*E*)-α,β-unsaturated ketones ((*E*)-**3ba–ma**) in good to high isolated yields (Table 2). The regio- and stereochemistry of all the isolated products were unambiguously determined utilizing 2D NMR. The structure of **3la** was also confirmed by a single-crystal X-ray diffraction study (see Supporting Information for details). Aliphatic acid chlorides (**1b–f**) gave the corresponding products (**3ba–fa**) in good to high yields. Ester functional groups were tolerated in the reaction (entry 3). With pivaroyl chloride (**1e**) as a substrate, an *E*/*Z* mixture of **3ea** was obtained in 82% crude yield with a ratio of *E*/*Z* = 81/19. From the mixture, (*E*)-**3ea** was isolated in 54% yield (entry 4). Phenylacetyl chloride (**1f**) afforded the corresponding adduct in 84% yield (entry 5). Various benzoyl chloride derivatives (**1g–k**) having electron-donating (**1h**) and electron-withdrawing substituents (**1i–k**) afforded **3ga–ka** in good to high yields (entries 6–10). Under the reaction conditions, bromo as well as chloro functional groups on phenyl rings remained intact (entries 9 and 10). 2-Naphthoyl chloride (**1l**) and 2-thienoyl chloride

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(9) (a) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2012**, *134*, 1268–1274. (b) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6668–6669.

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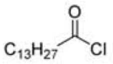
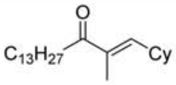
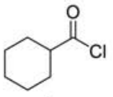
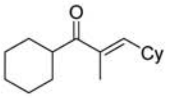
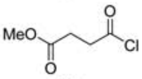
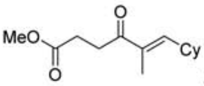
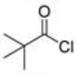
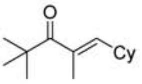
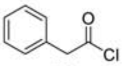
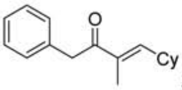
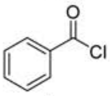
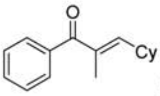
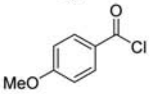
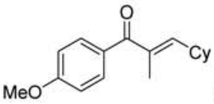
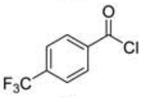
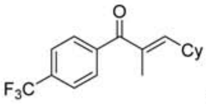
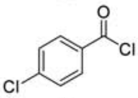
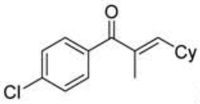
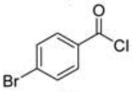
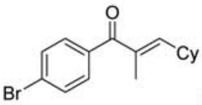
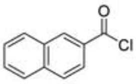
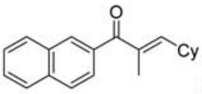
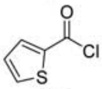
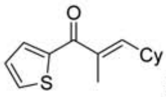
(11) (a) Kokubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303–311. (b) Osborne, J. D.; Randell-Sly, H. E.; Currie, G. S.; Cowley, A. R.; Willis, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 17232–17233.

(12) Recently, Murakami and co-workers reported the rhodium-catalyzed 1:2 coupling of aldehydes and allenes: Toyoshima, T.; Miura, T.; Murakami, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10436–10439.

Table 2. Palladium-Catalyzed Formal Hydroacylation of **2a** Employing Various Acid Chlorides (**1**) and HSi(*i*Pr)$_3$^{a}

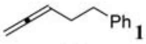
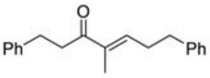
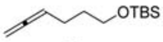
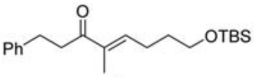
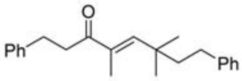
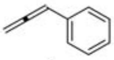
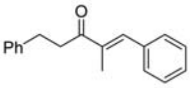
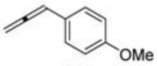
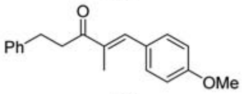
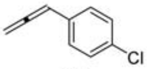
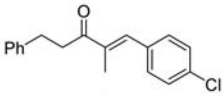
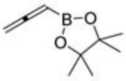
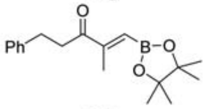
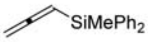
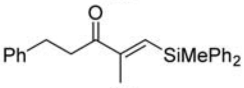
entry	acid chloride **1**	product (*E*)-**3**	yield (%)^b
1	 **1b**	 **3ba**	90
2	 **1c**	 **3ca**	81
3	 **1d**	 **3da**	65
4	 **1e**	 **3ea**	54
5	 **1f**	 **3fa**	84
6	 **1g**	 **3ga**	74
7	 **1h**	 **3ha**	56
8	 **1i**	 **3ia**	86
9	 **1j**	 **3ja**	78
10	 **1k**	 **3ka**	81
11	 **1l**	 **3la**	75
12	 **1m**	 **3ma**	59

[a] Reaction conditions: acid chloride (**1**, 0.50 mmol), **2a** (0.55 mmol), HSi(*i*Pr)$_3$ (0.55 mmol), Pd(OAc)$_2$ (0.0125 mmol, 2.5 mol %), toluene (1.0 mL) at 50 °C for 18 h. [b] Isolated yield of (*E*)-**3ba**−**ma**.

(**1m**) gave the corresponding products (**3la** and **3ma**) in good yields (entries 11 and 12).

Various monosubstituted allenes (**2b**−**i**) were smoothly converted to the corresponding α,*β*-unsaturated ketones (**3ab**−**3ai**) in good to high yields with high (*E*)-selectivity (entries 1−8, Table 3). An allene bearing a tertiary alkyl moiety (**2d**) gave the product smoothly (entry 3). Phenylallene derivatives (**2e**−**g**) also gave the adducts efficiently (entries 4−6). Boryl- and silyl-substituted allenes (**2h** and **2i**) afforded the corresponding α,*β*-unsaturated ketones (**3ah** and **3ai**) in good isolated yields (entries 7 and 8).

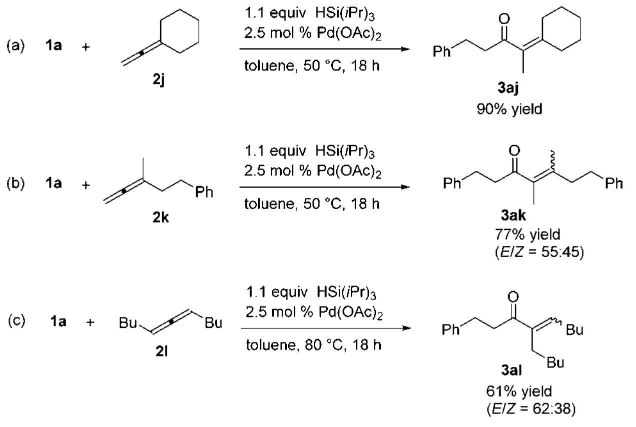
Table 3. Palladium-Catalyzed Formal Hydroacylation of Various Allenes (**2**) Employing **1a** and HSi(*i*Pr)$_3$^{a}

entry	allene **2**	product (*E*)-**3**	yield (%)^b
1	 **2b**	 **3ab**	79
2	 **2c**	 **3ac**	92
3	 **2d**	 **3ad**	77
4	 **2e**	 **3ae**	68
5	 **2f**	 **3af**	79
6	 **2g**	 **3ag**	64
7	 **2h**	 **3ah**	67
8^c	 **2i**	 **3ai**	81

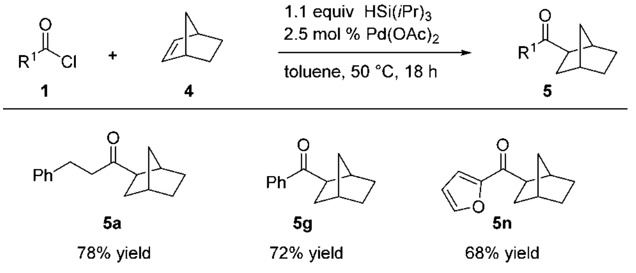
[a] Reaction conditions: **1a** (0.50 mmol), allene (**2**, 0.55 mmol), HSi(*i*Pr)$_3$ (0.55 mmol), Pd(OAc)$_2$ (0.0125 mmol, 2.5 mol %), toluene (1.0 mL) at 50 °C for 18 h. [b] Isolated yield of (*E*)-**3ab**−**ai**. [c] At 60 °C.

Besides monosubstituted allenes, disubstituted allenes afforded the corresponding α,*β*-unsaturated ketones (Scheme 1). The reaction employing a symmetrical 1,1-disubstituted allene (**2j**) afforded the corresponding adduct (**3aj**) in high isolated yield (Scheme 1a). An unsymmetrical 1,1-disubstituted allene (**2k**) gave an *E*/*Z* mixture of the adducts in 77% total yield (Scheme 1b). A 1,3-disubstituted allene (**2l**) reacted with **1a** at 80 °C and gave the products in moderate yield with poor stereoselectivity (63:38) (Scheme 1c). Gratifyingly, norbornene (**4**) could be employed in the reaction (Scheme 2). With **1a**, **1g**, and **1n**, the reaction afforded **5a**, **5g**, and **5n** in 78%, 72%, and 68% yields in a highly *exo*-selective manner.

Scheme 1. Reactions of **1a** with 1,1- or 1,3-Disubstituted Allenes

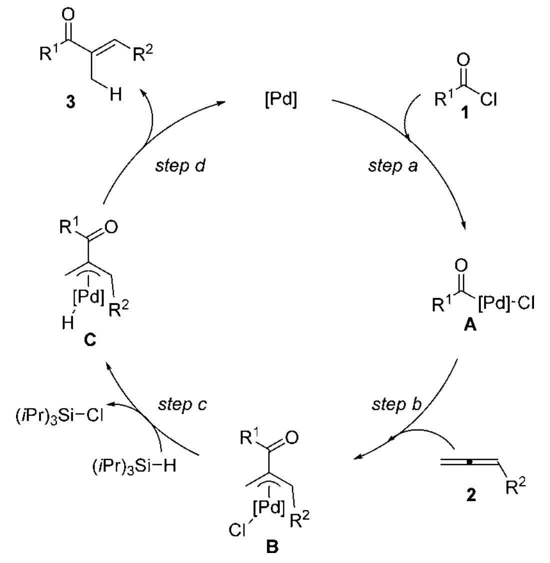


Scheme 2. Reactions with Norbornene (**4**)



A possible catalytic cycle is shown in Scheme 3. First, the oxidative addition of acid chlorides (**1**) to an active palladium(0) species affords an acylpalladium species **A** (step a). Successful insertion of an allene (**2**) before the decarbonylation gives a π-allylpalladium intermediate **B** (step b). Then, reaction of **B** with a hydrosilane gives a hydridopalladium intermediate (**C**) (step c). Finally, reductive elimination provides an α,β-unsaturated ketone (**3**) and the palladium(0) species regenerates (step d). Consistent with the mechanism, the reaction of **1a** with **2e** in the presence of DSi(iPr)$_3$[13] afforded the adduct (E)-**3ae**-d in 61% isolated yield with 99% D incorporation at the methyl position (eq 1).

Scheme 3. A Plausible Catalytic Cycle



(1)

In conclusion, we have developed the palladium-catalyzed formal hydroacylation of allenes employing acid chlorides and hydrosilanes. The reactions afforded α,β-unsaturated ketones regio- and stereoselectively without any directing group on the acid chlorides. Further studies on applications and the reaction mechanism are now in progress.

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Supporting Information Available. Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

[13] Ogata, K.; Atsuumi, Y.; Fukuzawa, S. *Org. Lett.* **2010**, *12*, 4536–4539.