Regioselective Catalytic Allylic Alkylation Directed by Removable 2-PyMe$_2$Si Group

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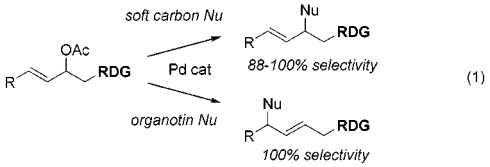
An intramolecular directing group provides a powerful strategy for enhancing the efficiency of an otherwise sluggish process and for steering the course of the reaction by taking advantage of attractive substrate−reagent interactions.[1] In most cases, such reactions are directed by the suitable heteroatoms on the substrate. However, the greatest flaw of the current directed reaction is the difficulty in removing or functionalizing such directing groups after the reaction.[2]

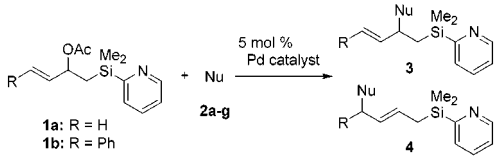
Recently, we discovered that a 2-pyridyldimethylsilyl (2-PyMe$_2$-Si) group functions as the removable directing group for various metal-catalyzed or -mediated processes.[3] In ongoing efforts to exploit this group for the metal-catalyzed reactions, we paid particular attention to the regioselectivity problem in the palladium-catalyzed allylic alkylation.[4] When unsymmetrically substituted allylic substrates are used, nucleophiles are preferentially introduced into the allylic terminus that is sterically less hindered. In this communication, we report on the palladium-catalyzed regioselective allylic alkylations[5] that are efficiently directed by the removable 2-PyMe$_2$Si group. Moreover, we observed the dramatic switch of the regioselectivity by the type of nucleophile (eq 1).



(1)

2-PyMe$_2$Si-substituted allylic acetates (**1a** and **1b**) were easily prepared by the reaction of 2-PyMe$_2$SiCH$_2$Li[3b] with α,β-unsaturated aldehydes followed by acetylation. Subjection of **1a** and NaCH(CO$_2$Me)$_2$ (**2a**) to the action of Pd/PPh$_3$ catalyst led to the predominant production of **3aa** as the result of a nucleophilic attack at the more substituted carbon of the allylic moiety (Table 1, entry 1). The catalyst/ligand combination of [allylPdCl]$_2$ and P(C$_6$F$_5$)$_3$ gave rise to higher yield and regioselectivity (entry 2). This unusual inner site-selective allylic alkylation was found to be a general phenomenon for the stabilized carbon nucleophiles (entries 3−8). Quite interestingly, the use of organotin compound as a nucleophile,[6] on the other hand, gave rise to the complete switch of the regioselectivity of the reaction, in which the nucleophilic attack occurred at the allylic terminus remote from the silyl group (entries 9 and 10). To the best of our knowledge, such a regioselectivity switch has never been observed in the (π-allyl)palladium chemistry.

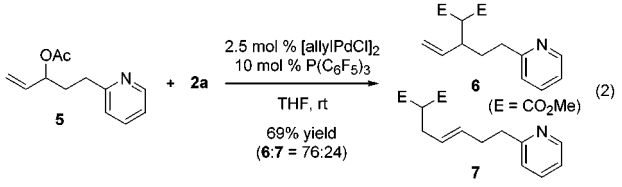
Table 1. Palladium-Catalyzed Directed Allylic Alkylation of **1** with Various Nucleophiles



entry	1	2	catalyst	yield (%)	ratio (**3**/**4**)
1[a]	**1a**	NaCH(CO$_2$Me)$_2$	[allylPdCl]$_2$	48	90/10
		2a	PPh$_3$		(**3aa**/**4aa**)
2[a]	**1a**	**2a**	[allylPdCl]$_2$	67	94/6
			P(C$_6$F$_5$)$_3$		(**3aa**/**4aa**)
3[a]	**1a**	NaCH(CO$_2$Et)$_2$	[allylPdCl]$_2$	72	95/5
		2b	P(C$_6$F$_5$)$_3$		(**3ab**/**4ab**)
4[a]	**1a**	NaC(Me)(CO$_2$Et)$_2$	[allylPdCl]$_2$	82	88/12
		2c	P(C$_6$F$_5$)$_3$		(**3ac**/**4ac**)
5[a]	**1b**	**2b**	[allylPdCl]$_2$	99	100/0
			P(C$_6$F$_5$)$_3$		(**3bb**/**4bb**)
6[a]	**1b**	**2c**	[allylPdCl]$_2$	51	100/0
			P(C$_6$F$_5$)$_3$		(**3bc**/**4bc**)
7[a]	**1b**	NaCH(CN)(CO$_2$Et)	[allylPdCl]$_2$	62	100/0
		2d	P(C$_6$F$_5$)$_3$		(**3bd**/**4bd**)
8[a]	**1b**	NaCH(CN)$_2$	[allylPdCl]$_2$	56	100/0
		2e	P(C$_6$F$_5$)$_3$		(**3be**/**4be**)
9[b]	**1a**	(CH$_2$=CH)SnBu$_3$	Pd$_2$(dba)$_3$	48	0/100
		2f	LiCl (3 equiv)		(**3af**/**4af**)
10[b]	**1a**	PhSnMe$_3$	Pd$_2$(dba)$_3$	45	0/100
		2g	LiCl (3 equiv)		(**3ag**/**4ag**)

[a] Reactions were performed in THF at room temperature. [b] Reactions were performed in DMF at room temperature.

In general, the palladium-catalyzed allylic substitution occurs at the less substituted carbon of the allylic moiety.[4] Indeed, Szabó has established in the related allylic substitution of β-silyl allylic acetates that the nucleophilic attack selectively occurs at the allylic terminus remote from the silyl group because of the steric and electronic reasons.[7] The allylic acetate **5**, in which SiMe$_2$ is substituted by CH$_2$, underwent the alkylation with good regioselectivity (76/24) favoring the nucleophilic attack at the more hindered allylic carbon (eq 2). This result, together with the work of Szabó, clearly implies that the unusual regioselectivity observed for **1** (Table 1, entries 1−8) is primarily attributed to the effect of pyridyl group and that the effect of silyl group is at least additive with regard to the inner site regioselectivity.



(2)

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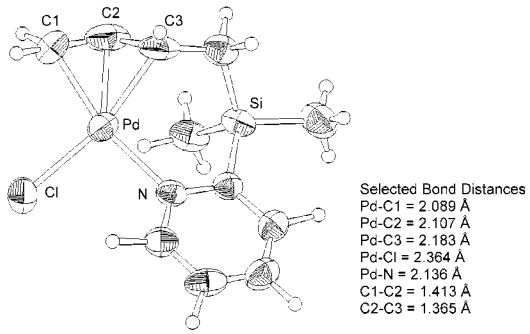
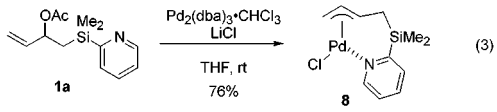


Figure 1. X-ray crystal structure of **8** (40% probability thermal ellipsoids).

To gain mechanistic insight into this unusual regioselectivity, we began by establishing the nature of (allyl)palladium complex generated from **1**. Thus, the stoichiometric reaction of **1a** and $Pd_2(dba)_3{\cdot}CHCl_3$ was conducted. However, the corresponding (allyl)palladium complex was decomposed during the isolation, presumably because of its instability. After several trials, we found that the addition of LiCl produces an air-stable (π-allyl)palladium complex **8** in 76% isolated yield (eq 3). Recrystallization from



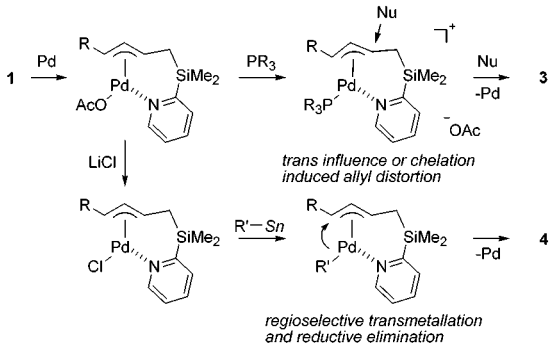
EtOAc/hexane generated orange crystals. The molecular structure, characterized by X-ray crystallographic analysis, depicts *syn*-η^3-coordination at the allylic moiety (Figure 1). Additionally, the intramolecular pyridyl group occupies one coordination site *trans* to the terminal allylic C1 atom with a pseudo square planar geometry. More importantly, the distortion of allylic moiety was observed. The Pd−C bond *trans* to chlorine (Pd−C3 = 2.183 Å) is substantially longer than the Pd−C bond *trans* to nitrogen (Pd−C1 = 2.089 Å). The allylic C−C bond *trans* to chlorine (C2−C3 = 1.365 Å) is substantially shorter than the allylic C−C bond *trans* to nitrogen (C1−C2 = 1.413 Å). The stoichiometric reaction of **8** and **2b** afforded **3ab** with 90% regioselectivity, which is close to that observed in the catalytic reaction (Table 1, entry 3).

One explanation for this allylic distortion may be the result of the difference of *trans* influence.[8] The stronger *trans* influence of chlorine compared to the pyridyl group might elongate the Pd−C3 bond. In the catalytic reactions, difference of the *trans* influence in (π-allyl)palladium intermediate should be greater than that in **8**, since the *trans* influence of phosphine ligand is known to be stronger than that of chlorine.[8] Another plausible explanation may be the structural reason. Allylpyridyl chelate might be responsible for the allylic distortion.

Thus, the observed inner site-selective allylic alkylation for the stabilized carbon nucleophiles is most likely attributed to the *trans* influence or chelation-induced distortion of allylic moiety, in which the soft carbon nucleophile preferentially attacks the longer and, accordingly, more reactive Pd−C bond (Scheme 1).[9]

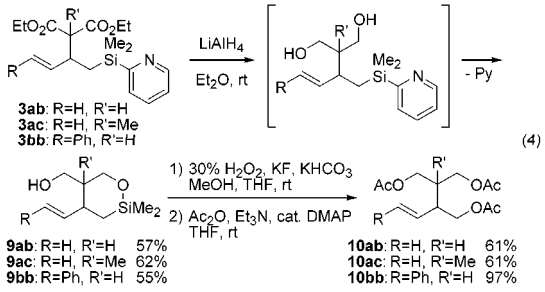
The explanation for the regioselectivity observed with the organotin nucleophiles should be mechanistically different.

Scheme 1



Whereas soft carbon nucleophiles add to (π-allyl)palladium intermediate directly on the allyl ligand, nucleophilic attack of organotin compounds occurs to the metal (transmetalation), and the subsequent reductive elimination process produces the products.[10] In the (π-allyl)palladium complex **8**, the chlorine atom sits on palladium *cis* to the allylic C1 atom. On the other hand, the coordination site *cis* to the allylic C3 atom is occupied by the intramolecular pyridyl group. We assume that this regioselective transmetalation and reductive elimination might be responsible for the complete regioselectivity switch.

Finally, the removal of 2-$PyMe_2Si$ group was demonstrated as shown in eq 4. The $LiAlH_4$ reduction of **3** afforded cyclic silyl ether **9** in good yield with in situ removal of the pyridyl group. Cyclic ether **9** was then subjected to H_2O_2 oxidation[11] to give the corresponding triol, which was converted into the corresponding triacetate **10** in good overall yield.



In summary, we have established that the palladium-catalyzed allylic alkylation was effectively directed by the removable 2-$PyMe_2Si$ group and that the regioselectivity can be completely switched by the type of nucleophile. The structural analysis of the (π-allyl)palladium complex revealed the distortion of allyl ligand on palladium, which might be the reason for unusual inner site-selective nucleophilic attack of soft carbon nucleophiles. We believe that this study should provide the strategic basis for controlling the regioselectivity in the palladium-catalyzed allylic alkylation.

Supporting Information Available: Experimental procedures and analytical and spectroscopic data; tables of crystallographic data for **8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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