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Palladium-Catalyzed Regio-, Diastereo-, and Enantioselective Allylic Alkylation of Acylsilanes with Monosubstituted Allyl Substrates

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Abstract: Acylsilanes as a new type of "hard" carbon prenucleophile reacted with monosubstituted allyl reagents under Pd-catalyzed asymmetric allylic alkylation reaction conditions to provide products with high regio-, diastereo-, and enantioselectivities. The usefulness of the protocol has been demonstrated by the ready conversion of the allylated products into the corresponding alcohols, esters, and ketones with retention of stereochemistry as well as by the enantioselective synthesis of *cis*-3-ethyl-4-phenylpiperidine and cinnamomumolide.

Palladium-catalyzed asymmetric allylic alkylation (AAA) is one of the most important methods for asymmetric formation of carbon−carbon bonds and has found widespread application in organic synthesis.[1] Recent achievements allow the use of "hard" carbanions derived from simple ketones[2] and aldehydes[3] as nucleophiles. Two adjacent chiral centers can also be installed in the products, although 1,3-disubstituted symmetric allyl reagents have been used in most cases.[4] Carboxylic acid derivatives, a powerful class of organic compounds with an easily transformable functional group, are also viable nucleophile precursors.[5] Only one chiral center can be formed usually,[5] although products with two vicinal chiral centers have been obtained using some special carboxylic acid derivatives with additional carbanion-stabilizing factors at the position α to the carboxylic acid group.[6] It remains a great challenge to establish two chiral centers by Pd-catalyzed AAA of "hard" carbanions with monosubstituted allyl substrates with high regio-, diastereo-, and enantioselectivities as well as with more readily transformable functional groups in the products.[7] To address this issue, several in situ-generated nucleophiles derived from aliphatic ketones and amide **1** were subjected to Pd-catalyzed AAA of cinnamyl methyl carbonate (**2a**) (eq 1). Though the diastereoselectivity was low in all cases, two indicative clues were found: (1) better diastereoselectivity was obtained with bulkier R groups and (2) ketones gave better regioselectivities than amide. To achieve high selectivities in the reaction, a new type of nucleophile had to be developed (Figure 1).

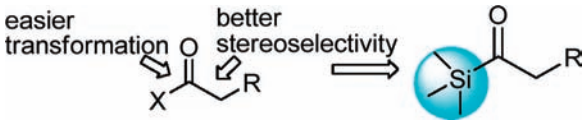
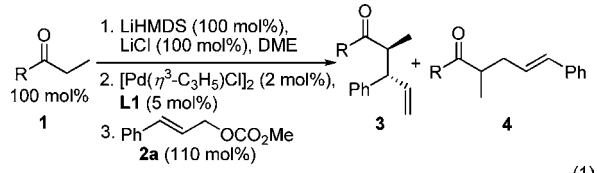


Figure 1. Demands on the New Type of "Hard" Carbon Nucleophile.

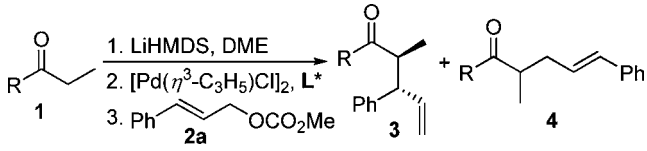


(1)

R	yield% 3 + 4	3/4	*anti*/*syn*	ee% (*anti*)
Et	29	92/8	2/1	99
i-Pr	44	92/8	4/1	99
c-C_6H_{11}	72	98/2	5/1	99 [ref 7a]
Ph_2N	90	84/16	5/1	98

Considering that acylsilanes bearing a bulky silyl group behave like typical ketones in reactions as well as like carboxylic acid derivatives in transformations,[8] we envisioned that they could serve as suitable nucleophile precursors in Pd-catalyzed AAA of monosubstituted allyl substrates to achieve high regio-, diastereo-, and enantioselectivities. The advantage of acylsilanes for further elaboration would enable the resulted products to be used as versatile starting materials in organic synthesis.[8] To test our idea, the reaction of 1-(trimethylsilyl)propan-1-one (**1a**) and cinnamyl methyl carbonate (**2a**) was carried out in the presence of [Pd(η^3-C_3H_5)Cl]$_2$ and (R_{phos},*R*)-SIOC-Phox (**L1**) as the catalyst with LiCl as an additive. Delightfully, allylated products were obtained in 44% yield with a **3a**/**4a** product ratio of 96/4, an *anti*/*syn* ratio of 11/1 for **3a**, and an ee of 96% for the *anti* isomer (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions for the Pd-Catalyzed Reaction of Acylsilanes **1** and Allyl **2a**[a]



entry	L	R	yield (%)[b]	3/4[c]	*anti*/*syn*[c]	*anti* ee (%)[d]
1[e,f]	**L1**	TMS	44	96/4	11/1	96
2[e]	**L1**	TMS	73	95/5	9/1	96
3	**L1**	TMS	93	96/4	10/1	96
4	**L2**	TMS	56	46/54	10/1	93
5	**L3**	TMS	86	92/8	10/1	94
6	**L1**	TBS	41	98/2	5/1	—[g]
7	**L1**	DMPS	20	97/3	13/1	—[g]

[a] **1**/**2a**/LiHMDS/[Pd(η^3-C_3H_5)Cl]$_2$/ligand molar ratio = 133/100/133/2/5. [b] Isolated yields of isomers **3** and **4**. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC. [e] With 133% LiCl added. [f] **1**/**2a** molar ratio = 100/110. [g] Not measured.

Inspired by this promising result, we set out to optimize the reaction conditions (Table 1). Changing the **1**/**2a** substrate ratio

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from 1/1.1 to 1.3/1 increased the yield from 44 to 73%, and the selectivity remained high (entry 2 vs entry 1). In contrast to our early findings,[7] LiCl had little effect on the selectivity of the present reaction (entry 3 vs entry 2). The structure of the ferrocene ligand (Figure 2) was crucial for the control of the stereoselectivity. The regioselectivity was poor, notwithstanding the good diastereo- and enantioselectivities acquired when (S_{phos},*R*)-**L2** was used as the ligand (entry 4 vs entry 3). The regio- and enantioselectivities were slightly lower using **L3**, suggesting that the chiral center on the oxazoline ring was not beneficial in this reaction (entry 5 vs entry 3). The steric hindrance of the silyl group of the acylsilane indeed influenced the reaction. Changing the trimethylsilyl (TMS) group to a bulkier *tert*-butyldimethylsilyl (TBS) or dimethylphenylsilyl (DMPS) group made the reaction sluggish, although the regioselectivity was still fine (entries 6 and 7 vs entry 3) and even better diastereoselectivity was obtained (entry 7 vs entry 3). Further investigation of the impact of the reaction parameters revealed that the *tert*-butoxycarbonyl carbonate (OBoc) is the best leaving group for allyl substrates **2** and that 1,2-dimethoxyethane (DME) is the solvent of choice (see the Supporting Information).

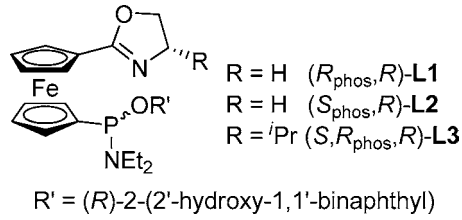
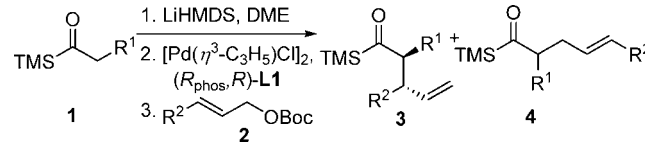
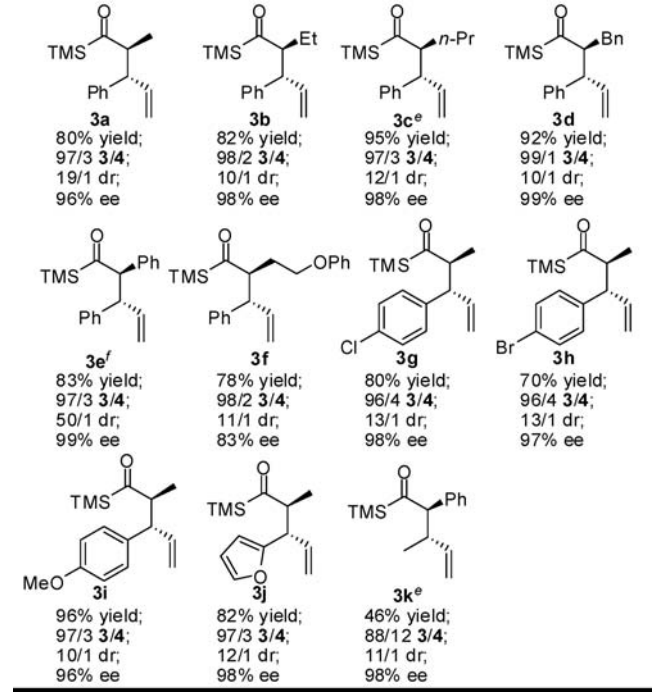


Figure 2. Ferrocene-based ligands **L1**−**L3**.

Next, the substrate scope of the reaction was examined (Table 2).The reaction proceeded well in all cases, affording alkylation products in high yields with excellent regio-, diastereo-, and enantioselectivities, with **3**/**4** ratios of 88−99/12−1, *anti*/*syn* ratios of 10−50/1 for **3**, and ee values of 96−99% for *anti*-**3**; the only exception was **3f** bearing a phenoxy group at the γ-position (see below). The length of the alkyl chain of the acylsilane did not affect the regio- and enantioselectivities of the reaction, though the diastereoselectivity decreased from 19/1 to 10/1 or 12/1 when the alkyl chain was lengthened (**3a** vs **3b** or **3c**, respectively). A substrate with a heteroatom at the γ-position was also tolerated, providing the corresponding product in high regio- and diastereoselectivity but a little bit lower enantioselectivity (**3f**). Interestingly, when the R^1 group was phenyl ring, the *anti*/*syn* ratio of products reached 50/1 (**3e**). The reaction is tolerant of functional groups on the phenyl group of allyl **2** (**3g**−**i**), although the diastereoselectivity decreased slightly for allyl **2** with an electron-donating group (**3i**). Remarkably, allyl **2** with a furanyl substituent was suitable for the reaction, affording the allyl products in high yield with excellent selectivity (**3j**). The reaction also worked well for the methyl-substituted allyl substrate, affording allyl product **3k** with high diastereo- and enantioselectivity, though the yield was moderate and the regioselectivity was slightly lower. It is worthwhile to note that the diastereoselectivity of the current reaction is much better than that using acyclic ketones.[7a] The reaction proceeded smoothly even on a gram scale. Treatment of 0.82 g of 1-(trimethylsilyl)butan-1-one with 1.02 g of cinnamyl *tert*-butoxycarbonyl carbonate under the given conditions still furnished an 86% yield of products **3b** and **4b** with the same regio-, diastereo-, and enantioselectivity as shown in Table 2. In addition, when the catalyst loading was decreased to 0.5 mol % [Pd(η^3-C_3H_5)Cl]$_2$ and 1.1 mol % (R_{phos},*R*)-**L1**, the products **3b** and **4b** were obtained in 87% yield with a

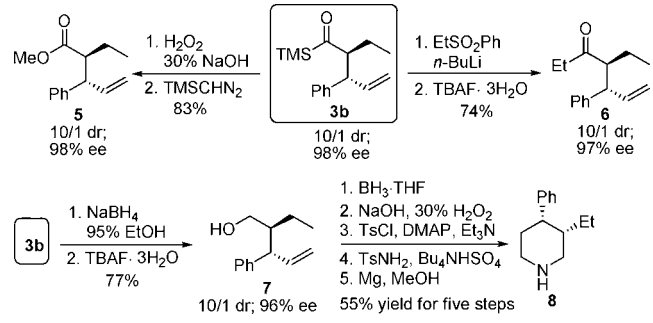
Table 2. Reaction Scope for Pd-Catalyzed AAA of Acylsilanes **1** with Allyls **2**[a−d]





[a] **1**/**2**/LiHMDS/[Pd(η^3-C_3H_5)Cl]$_2$/**L1** molar ratio = 133/100/133/2/5. [b] Isolated yields of isomers **3** and **4**. [c] Regio- and diastereoselectivities were determined by ^{1}H NMR spectroscopy. [d] Enantioselectivities were determined by chiral HPLC. [e] The enantioselectivity was determined by chiral HPLC after conversion of the −COSiMe$_3$ group of **3c** into the corresponding −CH$_2$OH group. [f] Run at 5 °C.

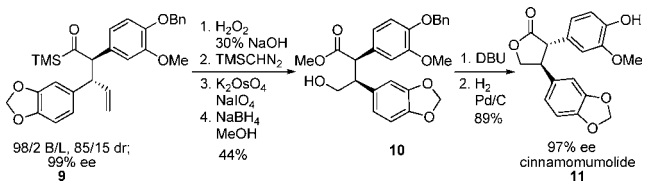
Scheme 1. Transformation of the Allylated Product **3b** to Other Functionalized Compounds



3b/**4b** ratio of 95/5, an *anti*/*syn* ratio of 8/1 for product **3b**, and an ee of 98% for the *anti* isomer.

The synthetic utility of the alkylated acylsilanes was illustrated by the versatile conversion of the allyl product **3b** bearing two chiral centers into other functionalized compounds, such as ester **5**, ketone **6**, and alcohol **7**, without changes in the diastereo- and enantioselectivities (Scheme 1). It is worth noting that chiral ketone **6** is usually difficult to obtain because of the difficulty in controlling the regioselectivity of unsymmetric ketones. The usefulness of our methodology was also demonstrated by the synthesis of chiral piperidine **8** possessing dopaminergic activity[9] from **3b** in seven

Scheme 2. Enantioselective Synthesis of Cinnamomumolide



steps with 42% overall yield (Scheme 1). Strategic application of our protocol facilitated the first concise enantioselective synthesis of cinnamomumolide (**11**), a compound isolated from the dried tender stems of *Cinnamomum cassia*, a traditional Chinese medicine,[10] in 39% overall isolated yield with 97% enantioselectivity by using **9** obtained from Pd-catalyzed AAA as a key intermediate (Scheme 2).

In conclusion, we have successfully developed a new "hard" carbon nucleophile for the Pd-catalyzed AAA reaction, and two chiral centers have been installed in products with high regio-, diastereo-, and enantioselectivities. The advantages of the acylsilane functional group have been revealed by the transformation of the products, and the usefulness of the protocol has also been demonstrated by the enantioselective synthesis of biologically active *cis*-3-ethyl-4-phenylpiperidine and the natural product cinnamomumolide. The further utility of the methodology in organic synthesis and the exploration of other kinds of "hard" carbon nucleophiles in Pd-catalyzed AAA reactions are in progress.

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Supporting Information Available: Experimental procedures, spectral data for compounds **3**−**11**, and determination of the absolution configuration of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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