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Construction of Chiral Quaternary Carbon Centers by Pd-Catalyzed Asymmetric Allylic Substitution with *P*,*N*-1,1′-Ferrocene Ligands

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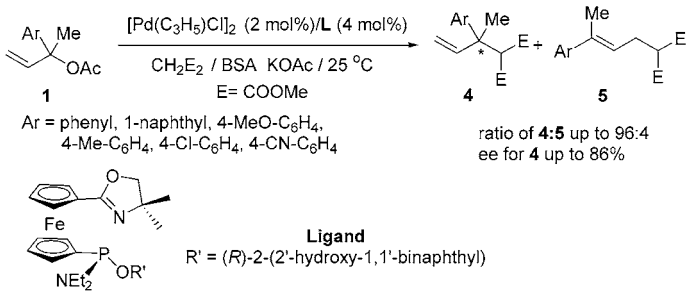
ABSTRACT



A chiral quaternary carbon center on allyl substrates was constructed by Pd-catalyzed allylic alkylation reaction in good to high regio- and enantioselectivities for a wide range of substrates for the first time.

Construction of a chiral quaternary carbon center by catalytic asymmetric reactions represents a demanding and challenging area in organic synthesis because of its great importance for the synthesis of enantiomerically pure natural products and pharmaceuticals.[1] Several protocols to construct an all-carbon-substituted chiral quaternary carbon center such as Diels−Alder reaction,[1c] Heck reaction,[1d] Michael addition,[1e] and metal-catalyzed allylic alkylation[2] have been well documented. Although palladium-catalyzed allylic alkylation reaction is a powerful tool for carbon−carbon bond formation, one of its major limitations was that the reaction of monosubstituted allylic substrates would lead to achiral linear products.[3] Only recently, some significant progress has been made by Hayashi, Pfaltz, and us,[4,5,6h] and for some substrates excellent regio- and enantioselectivities were obtained. However, to the best of our knowledge, there has been no report on the construction of an all-carbon-substituted chiral quaternary carbon center on an allyl substrate using Pd-catalyzed allylic alkylation. Obviously, this is a more challenging issue. Recently, some encouraging results have been obtained by us using novel ferrocene ligands.[6] It was found that high regio- and enantioselectivities were realized

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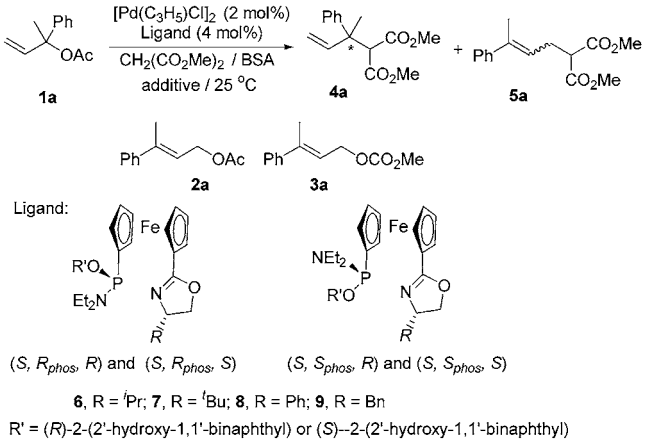
in Pd-catalyzed allylic substitution reactions using newly designed chiral *P*,*N*-1,1′-ferrocene ligands.[6h] Now we show that these ligands are also useful in construction of a chiral quaternary carbon center with high regio- and enantioselectivities by palladium-catalyzed allylic alkylation after some modification.

The branched and linear acetates and carbonate **1a**−**3a** were investigated using *P*,*N*-1,1′-ferrocene ligands **7**, which have been successfully applied to Pd-catalyzed regio- and enantioselective allylic substitution reactions of monosubstituted substrates (Scheme 1).[6h] Among four diastereomers,

Scheme 1. Pd-Catalyzed Allylic Substitution Reaction of **1a**−**3a**



ligand (S,S_{phos},R)-**7** gave the best regio- and enantioselectivity using **1a** as a substrate (products **4a** and **5a** in a ratio of 90:10 with 49% ee for **4a**) because of a match of different chiralities. Branched acetate **1a** reacted faster than linear substrates **2a** and **3a** using ligand (S,S_{phos},R)-**7**. Reaction of acetate **1a** was completed within 6 h, while that of branched acetate **2a** was incomplete after 72 h and the ratio of **4a** and **5a** was 38:62 with 52% ee for **4a**. Similar regioselectivity was given by linear carbonate **3a** (ratio of **4a** and **5a** was 35:65 with 54% ee for **4a**). These results differed from those of monosubstituted substrates.[6h] Moreover, the stereochemistry of the starting allylic esters **2a** and **3a** was retained to a certain extent in the alkylation products due to the "memory effect".[7]

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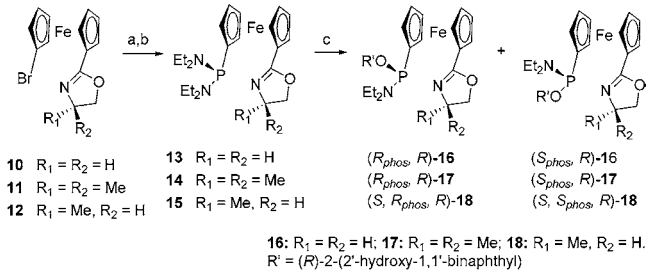
Table 1. Pd-Catalyzed Regio- and Enantioselective Allylic Alkylation of **1a** with Various Ligands[a]

entry	ligand	time (h)	yield (%)[b]	**4a**/(*E*)-**5a**/(*Z*)-**5a**[c]	**4a** ee (%)[d]
1	(S,S_{phos},R)-**6**	6	89	90/5/5	49
2	(S,S_{phos},R)-**7**	72	76	92/8/0	39
3	(S,S_{phos},R)-**8**	20	96	74/22/4	38[e]
4	(S,S_{phos}, R)-**9**	2.5	96	79/5/16	35
5	(S_{phos},R)-**16**	1	92	59/16/25	24
6	(S_{phos},R)-**17**	19	66	96/4/0	73
7	(R_{phos},R)-**17**	19	56	96/4/0	49[e]
8	(S,S_{phos},R)-**18**	16	77	90/10/0	63

[a] Reactions of entries 1−7 were performed in CH_2Cl_2 at 12 °C, while that of entry 8 proceeded in ethyl ether at 25 °C, all with a molar ratio of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/KOAc/substrate/$CH_2(CO_2Me)_2$/BSA = 2/4/6/100/300/300. [b] Isolated yield based on substrate. [c] Determined by 300 MHz ^{1}H NMR of the crude product after preparative TLC. [d] Determined by chiral HPLC. [e] Sign of optical rotation is opposite.

On the basis of the above results, ligands (S,S_{phos},R)-**7**−**9** were screened further using substrate **1a** and the results are showed in Table 1. The most profound feature is that the steric effect of the substituent on the oxazoline ring has great impact on the regio- and enantioselectivities of the reaction. When the substituent on the oxazoline ring was changed from *iso*-propyl to *tert*-butyl, the ee value of the product decreased from 49 to 39%, although the regioselectivity was slightly different (entry 1 vs entry 2). The reaction gave lower regio- and enantioselectivities when the substituent was phenyl and benzyl (entries 3 and 4). It is interesting that the product gave the opposite sign of optical rotation when the ligand (S,S_{phos},R)-**8** with a phenyl group as a substituent on the oxazoline was used (entry 3). It seemed that the decrease in the steric hindrance of the substituent would improve the regio- and enantioselectivities of the reaction. Thus, ligands **16**−**18** with structural modification were synthesized from 1-bromo-1′-oxazolidinylferrocenes **10**−**12** using known procedures in 44, 20, and 39% total yields, respectively (Scheme 2).[6h] The absolute configuration of chiral center on the phosphorus atom of (R_{phos},R)-**16** was determined by X-ray diffraction analysis.[8]

Scheme 2. Synthesis of Ligands **16**−**18**[a]



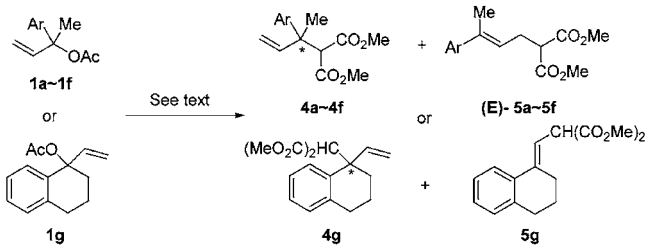
[a] Conditions: (a) BuLi; (b) $(Et_2N)_2PCl$; (c) (*R*)-binol.

Then, the role of ligands **16**−**18** was also investigated using substrate **1a** (Table 1). When the substituent on the

oxazoline ring was changed from *iso*-propyl to methyl, the ee value of the reaction were enhanced from 49 to 63% (entry 1 vs entry 8). Alhough the ligand (S_{phos},*R*)-**16** with no substituent on the oxazoline ring gave lower selectivity (entry 5), the ligand (S_{phos},*R*)-**17** with two methyl groups on the oxazoline ring provided a much better result. The reaction gave a regioselectivity of 96/4 in favor of **4a** with 73% ee (entry 6). These results also showed that the chirality on the oxazoline ring might not be necessary. In addition, when the ligand (R_{phos},*R*)-**17** with a different configuration on the phosphorus atom was used, the configuration of the product was reversed (entry 6 vs entry7). This result gave us a hint that the chirality of the phosphine might determine the configuration of the product to some extent.

Optimization of the reaction parameters (solvent, temperature, and additive) showed that the reaction carried out at 25 °C gave the best result and the ethyl ether was the best solvent among those tested (CH_2Cl_2, THF, CH_3CN, toluene, Et_2O), while KOAc is the best additive among LiOAc, NaOAc, Bu_4NOAc, KF, K_2CO_3 $^tBuCO_2K$, and $PrCO_2K$. Under the optimized conditions using ligand (S_{phos},*R*)-**17**, a wide range of substrates were tested (Scheme 3, Table 2).

Scheme 3. Pd-Catalyzed Allylic Substitution Reaction of Various Substrates **1a**−**g**



All substrates including **1g** derived from α-tetralone (entries 1,2, 5−7 and 8, Table 2) provided chiral quaternary carbon center-containing products with high regioselectivity and good enantioselectivity, except **1c** with a strong electron-donating group MeO as a substituent at the para position of phenyl, which gave a low regioselectivity but still good enantioselectivity (entry 4, Table 2). The reaction of substrate **1b** gave good selectivity (**4b/(*E*)-5b** 86/14, 91% ee, entry 2, Table 2) but could not be completed at room temperature, perhaps due to steric reasons. If the reaction was carried out at 35 °C, substrate **1b** was consumed after 24 h but regio- and enantioselectivities were decreased (entry 3, Table 2). In addition, the low yield was caused by incremental elimination byproduct. The electronic property of the substituent had superior effects on this reaction. An electron-withdrawing group may accelerate the reaction (entries 6 and 7, Table 2).

(8) See Supporting Information.

Table 2. Pd-Catalyzed Regio- and Enantioselective Allylic Alkylation with Ligand (S_{phos},*R*)-**17**[a]

entry	substrate Ar	temp/time (h)	yield (%)[b]	**4/(*E*)-5**[c]	**4** ee (%)[d]
1	**1a** phenyl	25 °C/19	66	96/4	73
2	**1b** 1-naphthyl	25 °C/96[e]	13	86/14	91
3	**1b** 1-naphthy	35 °C/24	46	76/24	78
4	**1c** 4-MeO−C_6H_4	25 °C/72[e]	31	43/57	79
5	**1d** 4-Me- C_6H_4	25 °C/16	90	95/5	78
6	**1e** 4-Cl− C_6H_4	25 °C/5	90	95/5	69
7	**1f** 4-CN− C_6H_4	25 °C/2	86	89/11	78
8	**1g**	25 °C/6	92	84/16	86

[a] $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/($S_{phos}$,*R*)-**17**/KOAc/substrate/$CH_2(CO_2Me)_2$/BSA = 2/4/6/100/300/300. Ethyl ether was the solvent. [b] Isolated yield based on substrate. [c] Determined by 300 MHz ^1H NMR of the crude product after preparative TLC. [d] Determined by chiral HPLC. [e] Reaction was not complete.

The absolute configuration of the product **4a** was determined as *R* through converting it into substituted succinic acid by oxidation using $NaIO_4/KMnO_4$ followed by treatment of product with NaOH/MeOH then HCl[9,10] and through comparing the sign of optical rotation of the product with that of the authentic sample.[11]

In summary, good to high regio- and enantioselectivities were realized in palladium-catalyzed allylic alkylation to construct chiral quaternary carbon centers for a wide range of substrates for the first time. Investigations on the reaction mechanism and reactions using different kinds of nucleophiles are in progress.

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Supporting Information Available: Synthetic procedure and spectral data for ligands **16**−**18**; X-ray structural information on compound (R_{phos},*R*)-**16** as well as its X-ray crystallographic file (CIF); general procedure for allylic alkylation; and spectral data for **1b**−**f**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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