

Asymmetric construction of quaternary carbon stereocenter by Pd-hemilabile ligand-catalyzed allylic substitution

Yoshimasa Fukuda, Kazuhiro Kondo* and Toyohiko Aoyama*

Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

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Dedicated to the memory of Professor Yoshihiko Ho, deceased on 23 December 2006

Abstract—The catalyst comprised $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)_2]$ and a simple chiral hemilabile ferrocene ligand, 1',2-bis(diphenylphosphinoethyl)ferrocenyl alcohol, provides synthetically acceptable results for an enantioselective Pd-catalyzed allylic alkylation of cyclohexanone derivatives bearing an electron-withdrawing group at the α -position to form the quaternary carbon with up to 90% enantioselectivity under mild reaction conditions.

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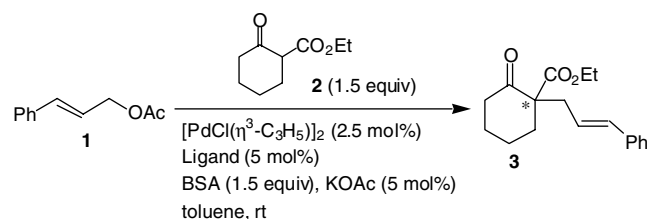
Creating quaternary carbon centers in which the absolute stereochemistry can be controlled by allylic alkylation represents a major challenge in organic synthesis.¹ We have quite recently constructed quaternary carbon stereocenters with up to 65% enantioselectivity in Pd-catalyzed enantioselective intramolecular α -arylation of *N*-(2-bromophenyl)-*N*-methyl-2-arylpropanamides;² the enantioselectivity obtained is of the good level reported in the literature.³ And we have developed hemilabile ligands⁴ with both soft and hard coordinated centers within one molecule.⁵ As part of our research program in relation to the above described methodology, we planned to construct chiral quaternary carbon centers by enantioselective Pd-catalyzed allylic alkylation with a hemilabile ligand. Since, in general, enantioselective Pd-catalyzed allylic alkylations involving prochiral nucleophiles are a formidable challenge,⁶ we became interested in these reactions with prochiral nucleophiles, cyclohexanone derivatives bearing an electron-withdrawing group at the α -position. We herein would like to describe that a chiral hemilabile ligand, 1',2-bis(diphenylphosphinoethyl)ferrocenyl alcohol,⁷ was found to serve as a good ligand for a Pd-catalyzed enantioselective allylic alkylation of cyclohexanone derivatives bearing an electron-withdrawing group at the α -position.

Keywords: Asymmetric quaternary carbon; Chiral hemilabile ligand; Enantioselective Pd-catalyzed allylic substitution.

* Corresponding authors. Fax: +81 52 836 3439 (K.K.); e-mail addresses: kazuk@phar.nagoya-cu.ac.jp; aoyama@phar.nagoya-cu.ac.jp

At first, the Pd-catalyzed enantioselective allylic alkylation of 2-carboethoxycyclohexanone (**2**) with cinnamyl acetate (**1**) using a variety of chiral hemilabile ligands was examined: nonhemilabile-type BINAP, Segphos, DIOP, Binaphane, and *i*-Pr-Duphos were not good ligands. The selected results are shown in Table 1.⁸ As can be seen, among the hemilabile ligands screened, only ligand **10** bearing an OH group exhibited good asymmetric induction (**3**: 85% ee, entry 7).

Encouraged by the good results with ligand **10**, the reaction of several cinnamyl acetates with the cyclohexanone derivatives bearing various α -electron-withdrawing groups was examined (Table 2). As can be seen in all entries, the reactions were completed within 30 min at rt, affording the corresponding products in 99% yield. In terms of enantioselectivity, the electronic effect in the cinnamyl acetates was not observed (entry 1 vs entry 2, entry 5 vs entry 6). The acetate bearing a 1-naphthyl group in place of a phenyl group gave good enantioselectivity (entries 3, 7, and 12). Among the pronucleophiles examined, cyclohexanone derivative **12** bearing an α -tosyl group led to the best enantioselectivity (up to 90% ee, entries 4–7). To the best of our knowledge, this is the first example of Pd-catalyzed enantioselective allylic alkylations using cyclohexanone derivative bearing an α -tosyl group as a pronucleophile. And the enantioselectivity obtained by α -nitroketone and α -diketone as pronucleophiles is of the good level reported in the literature.⁹ A reaction that the simple chiral hemilabile ferrocene **10** serves as a good ligand exhibiting good enantioselectivity is a rare case,^{10,11} although many

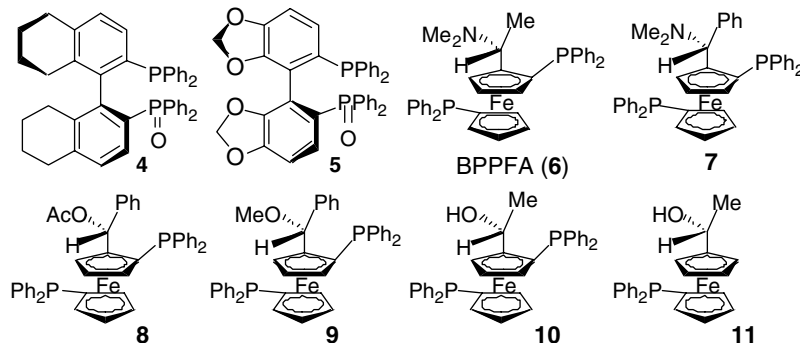
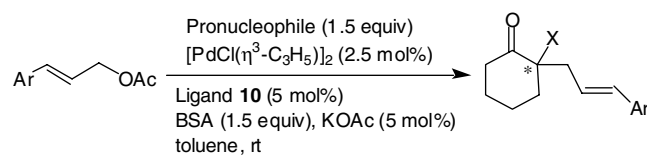
Table 1. Effects of hemilabile ligands^a

| Entry | Ligand | Time | Yield (%) | ee ^b (%) |
|-------|--------------------|--------|-----------------|---------------------|
| 1 | 4 | 12 h | 99 | 22 (<i>S</i>) |
| 2 | 5 | 12 h | 99 | 30 (<i>S</i>) |
| 3 | BPPFA (6) | <5 min | 99 | 8 (<i>S</i>) |
| 4 | 7 | <5 min | 99 | 53 (<i>S</i>) |
| 5 | 8 | <5 min | 99 | 23 (<i>S</i>) |
| 6 | 9 | <5 min | 99 | 29 (<i>S</i>) |
| 7 | 10 | <5 min | 99 | 85 (<i>R</i>) |
| 8 | 11 | 12 h | 51 ^c | 11 (<i>S</i>) |

^a K_2CO_3 , Cs_2CO_3 , and *i*-Pr₂NEt in place of BSA as a base, $\text{Zn}(\text{OAc})_2$, and $\text{Co}(\text{OAc})_2$ as an additive, and other solvents such as THF, CH_2Cl_2 , and DMF gave less satisfactory results.

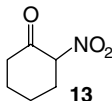
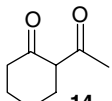
^b Determined by HPLC analysis.

^c Remainder of mass balance was the starting cinnamyl acetate.

**Table 2.** Generality of substrate and pronucleophile

| Entry | Ar Ar= | Pronucleophile | Time (min) | Yield (%) | ee ^a (%) |
|-------|---------------------------------------|----------------|------------|-----------|---------------------|
| 1 | 4-Cl-C ₆ H ₄ - | 2 | <5 | 99 | 83 |
| 2 | 4-MeO-C ₆ H ₄ - | 2 | <5 | 99 | 81 |
| 3 | 1-Naphthyl | 2 | <5 | 99 | 79 |
| 4 | Ph | 12 | 30 | 99 | 86 |
| 5 | 4-Cl-C ₆ H ₄ - | 12 | 20 | 99 | 85 |
| 6 | 4-MeO-C ₆ H ₄ - | 12 | 20 | 99 | 85 |
| 7 | 1-Naphthyl | 12 | 30 | 99 | 90 |

Table 2 (continued)

| Entry | Ar Ar= | Pronucleophile | Time (min) | Yield (%) | ee ^a (%) |
|-------|---------------------------------------|---|------------|-----------|---------------------|
| 8 | Ph |  | <5 | 99 | 77 |
| 9 | 4-MeO-C ₆ H ₄ - | 13 | <5 | 99 | 73 |
| 10 | Ph |  | <5 | 99 | 74 |
| 11 | 4-Cl-C ₆ H ₄ - | 14 | <5 | 99 | 71 |
| 12 | 1-Naphthyl | 14 | <5 | 99 | 83 |

^a Determined by HPLC analysis.

examples using highly tuned and functionalized ferrocene ligands have been reported.⁹

In summary, we have shown that a simple chiral hemilabile ferrocene ligand is efficient in forming a chiral quaternary carbon center¹² by an enantioselective Pd-catalyzed allylic alkylation of cyclohexanone derivatives bearing an α -electron-withdrawing group. Development and research of hemilabile ligands are now in progress for constructing chiral quaternary carbon centers.

Acknowledgments

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