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# Asymmetric allylic substitution reactions of 2-substituted 2-cycloalkenyl carbonates using 9-PBN coordinated palladium

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**Abstract**—2-Substituted 2-cycloalkenyl carbonates are suitable substrates for asymmetric allylic substitution reaction using 9-PBN coordinated palladium, producing the allylic substituted products with high enantiomeric excess. 

Palladium-catalyzed asymmetric allylic substitution reactions have been shown to be an expedient procedure for carbon–carbon and carbon–nitrogen bond formations, and both chiral phosphine and chiral nitrogen ligands in combination with palladium have provided very high enantioselectivity with a variety of allylic substrates.[1] Recently our efforts have demonstrated that the new monodentate chiral phosphines, (*1R*, 2*S*, 5*R*, 6*S*)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]-nonane and its enantiomer ((*R*)-(−)- and (*S*)-(+)-9-PBNs),[2,3] are valuable ligands with lack of chelating ability and these phosphines in combination with palladium are efficient catalysts for formation of carbon–carbon, carbon–nitrogen, and carbon–oxygen bonds through asymmetric allylic substitution reaction.[4,5] In the course of our studies on asymmetric synthesis using 9-PBNs we have focussed on 2-cycloalkenyl esters as substrates for the asymmetric allylic substitution reaction.[6,7] The substituted products obtained from the 2-cycloalkenyl esters are useful as chiral building blocks for a variety of natural products, and the 2-aryl-2-cyclohexenyl methyl carbonates have been efficiently utilized in total synthesis of some alkaloids through asymmetric allylic substitution reaction.[8] Disappointingly, however, 2-cyclohexenyl pivalate and 2-cyclopentenyl pivalate under the conditions using 9-PBN yielded the allylic substituted products with poor enantiomeric excess, 12% ee and 26% ee, respectively, in both quantitative yields. Mechanistic considerations concerning the low efficiency revealed that the 2-substituted 2-cycloalkenyl ester might be effective for the asymmetric synthesis using 9-PBN and palladium as shown in the Fig. 1. Thus, we envisioned that the effect of the interaction of the 2-substituent with the bicyclic carbon skeleton of the 9-PBN should be more serious in **B** than **A**, and the bulkiness of the 2-substituent should influence the enantiomeric excess of the substituted product. We describe here the 2-substituted 2-cycloalkenyl esters to be suitable substrates for the asymmetric synthesis using 9-PBN and palladium.

First, we investigated the methyl 2-methyl-2-cyclohexenyl carbonate **1a** for the asymmetric allylic substitution reaction. The reaction of **1a** with dimethyl malonate using (−)-9-PBN (4 mol%) and bis(benzylidene)palladium (2 mol%) in the presence of bis(trimethylsilyl)acetamide (BSA, 3 equiv.) and lithium acetate (1 equiv.) in 1,2-dichloroethane proceeded smoothly after 3 h at room temperature to give the corresponding product **2a** in 95% yield with 51% ee. Indeed, the 2-substituent doubled the value of enantiomeric excess compared with the cyclohexenyl pivalate. With this encouraging result in hand, we expected this asymmetric synthesis could be extended and various 2-substituted 2-cycloalkenyl esters could be investigated (Table 1). The methyl 2-phenyl-2-cyclohex-

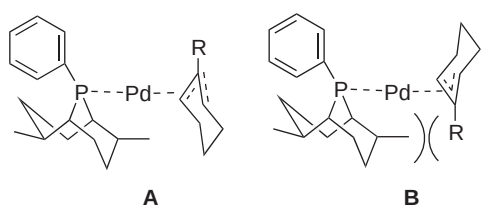


**Figure 1.**

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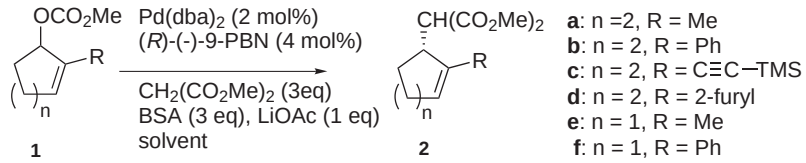
**Table 1.** Asymmetric allylic substitution reaction using 9-PBN and palladium




| Run | n | R | Time | Solvent | Yield | % ee |
|---|---|---|---|---|---|---|
| 1 | 2 | Me | 12 h | $ClCH_2CH_2Cl$ | 95% | 51[a] |
| 2 | 2 | Ph | 2 h | $ClCH_2CH_2Cl$ | 97% | 95[b] |
| 3 | 2 | Ph | 2 h | THF | 96% | 91 |
| 4 | 2 | Ph | 2 h | $PhCF_3$ | 96% | 90 |
| 5 | 2 | C≡C-TMS | 3 h | $ClCH_2CH_2Cl$ | 97% | 90[a] |
| 6 | 2 | 2-furyl | 4 h | $ClCH_2CH_2Cl$ | 96% | 54[c] |
| 7 | 1 | Me | 12 h | THF | 97% | 50[a,d] |
| 8 | 1 | Ph | 4 h | $ClCH_2CH_2Cl$ | 96% | 83[b,d] |

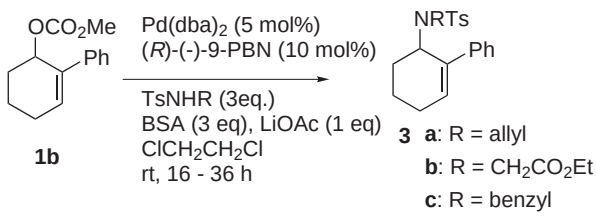
[a] Determined by NMR analysis using $Eu(hfc)_3$.
[b] Determined by HPLC analysis using Daicel Chiralcel OD-H after conversion to the anilide of the corresponding monocarboxylic acid.
[c] Determined by HPLC analysis using Daicel Chiralcel OD-H.
[d] The absolute configuration was not determined.

enyl carbonate **1b** was found to be the best substrate for this reaction and afforded the product **2b** with 95% ee in 97% yield under the same conditions.[9] It was again observed that the bulkiness of the 2-substituent affects the enantioselection. The enantiomeric excess of **2b** was determined by HPLC analysis after anilide formation through decarboxylation of the malonic function followed by coupling with aniline.[10] Several solvents for this reaction were tested, and both tetrahydrofuran and trifluorotoluene as well as 1,2-dichloroethane were found to afford highly enantioselective reaction. The 2-methyl- and 2-phenyl-2-cyclopentyl methyl carbonates **1e** and **1f** showed similar propensity with the corresponding cyclohexyl ones, affording the corresponding products **2e** and **2f** in moderate to high enantioselection. An interesting example was 2-trimethylsilylacetylenylcyclohexyl carbonate **1c** which smoothly produced the 2-substituted product **2c** with 90% ee in 96% yield. The 2-furyl substrate **1d** similar to **1b**, however, resulted in moderate enantioselection.

Next, we investigated the asymmetric reaction with nitrogen nucleophiles. Reaction of **1b** with benzylamine, however, unexpectedly yielded only the urethane side product of **1b**. The corresponding acetate ester in place of the methyl carbonate **1b** gave the product in moderate enantioselection but the yield was poor. Finally, sulfonamides were found to be suitable nitrogen nucleophiles for the asymmetric allylic substitution reaction as shown in Table 2. Reactions of *N*-allyl, *N*-ethoxycarbonylmethyl, and *N*-benzyl sulfonamides afforded the corresponding products with high enantiomeric excess, 99% ee, 97% ee, and 99% ee, respectively. For determination of absolute configuration of the products, X-ray crystallographic analysis of **3b**[11] was carried out and unambiguously disclosed it to bear (*S*)-configuration.

In summary, we have demonstrated that the 2-substituted 2-cycloalkenyl esters are suitable substrates for the asymmetric allylic substitution reaction using 9-PBNs and palladium(0) and the observed enantiomeric excess depends upon the bulkiness of the 2-substituents, although the exact mechanism is unclear and remains to be disclosed. Further investigation for the asymmetric synthesis using 9-PBNs coordinated transition metals and application of the above reaction to the synthesis of biologically interesting natural products are in progress in our laboratories.

**Table 2.** Asymmetric allylic substitution reaction with nitrogen nucleophiles




| Run | R | Yield | % ee[a] |
|---|---|---|---|
| 1[b] | –[c] | 8% | 75 |
| 2 | Allyl | 84%[d] | 99 |
| 3 | $CH_2CO_2Et$ | 77%[e] | 97 |
| 4 | Benzyl | 71%[f] | 99 |

[a] Determined by HPLC analysis using Daicel Chiralcel OJ.
[b] The corresponding acetate was used instead of the methyl carbonate **1b**.
[c] Benzylamine was used instead of the sulfonamide.
[d] **1b** was recovered in 8.5% yield.
[e] **1b** was recovered in 18% yield.
[f] **1b** was recovered in 22% yield.

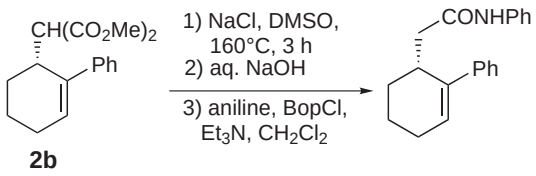



**Figure 2.**

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9. Typical procedure for the asymmetric allylic substitution reaction: to a stirred mixture of $Pd(dba)_2$ (41 mg, 0.071 mmol) and lithium acetate (236 mg, 3.57 mmol) in dichloroethane (12 ml) under an argon atmosphere at 0°C was added a 0.1 M solution of (–)-9-PBN and the mixture was stirred at 0°C for 30 min. then the mixture was cooled to −15°C and dimethyl malonate (1.23 ml, 10.7 mmol), the methylcarbonate (830 mg, 3.57 mmol), BSA (2.6 ml, 10.7 mmol), and dichloroethane (12 ml) were added. The mixture was allowed to warm to 23°C and stirred at 23°C for 4 h. After removal of the volatiles, the mixture was diluted with ethyl acetate/hexane (1:5, 180 ml), washed with 1 M $KHSO_4$, water, and brine, dried over $MgSO_4$, and concentrated in vacuo to leave a yellow oil. The residue was chromatographed on silica gel using hexane/ethyl acetate (8:1) to give the product (915 mg, 97%) as a colorless oil: IR $\nu_{max}^{neat}$ 3022, 1735, 1637 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.59–1.94 (5H, m), 2.18–2.23 (2H, m), 3.22 (3H, s), 3.56 (1H, s), 3.65 (3H, s), 5.92 (1H, m) 7.18–7.37 (5H, m).
10. The alkylated product **2b** was transformed to the anilide in 3 steps as shown in Fig. 2 and analyzed by HPLC.
11. **3b**: mp 104–106°C (ether-*n*-hexane); $[\alpha]_D^{25}$+84.2 (*c* 1.59, MeOH). Crystal data for **3b**: $C_{23}H_{27}NO_4S$, F.W. 413.5, orthorhombic, space group $P2_12_12_1$, $a=8.753$ (1) Å, $b=10.373$ (1) Å, $c=24.528$ (1) Å, $V=2227.0$ (2) $Å^3$, $Z=8$, Nonius Kappa CCD, Mo K$\alpha$, $R=0.0508$, $Rw=0.0536$.