HETEROCYCLES, Vol. 76, No. 1, 2008, pp. 197 - 202. © The Japan Institute of Heterocyclic Chemistry
Received, 15th March, 2008, Accepted, 14th April, 2008, Published online, 17th April, 2008. COM-08-S(N)39

PALLADIUM−CATALYZED ASYMMETRIC INTRAMOLECULAR METALLO-ENE REACTION USING MONODENTATE PHOSPHINES, 9-PBN AND 9-NapBN†

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Abstract – The palladium-catalyzed asymmetric intramolecular metallo-ene reaction of the type I substrate using 9-PBN and 9-NapBN smoothly takes place in the presence of $B(OAc)_3$ and/or $NaBF_4$ at room temperature to afford the products with up to 51%ee, the best value in this area.

Intramolecular metallo-ene reaction is one of synthetically powerful methods for construction of 5- or 6-memdered ring which contains in a variety of biologically active natural products. This reaction was well established by Oppolzer, who extensively studied on not only stoichiometric metallo-ene reactions but also catalytic processes.[1] As depicted in Figure 1, two types of this cyclization have been known, in which the enophile is linked by an appropriate bridge either to the olefinic terminal carbon (type I) or to the central carbon (type II) of the π-allyl intermediate. Although the asymmetric version of metallo-ene reaction using a stoichiometric reagent has been already reported,[2] the catalytic methods for the enantioselective reaction are limited to a few reports and their enantioselectivities are unsatisfactory in most cases.[3, 4] Therefore, catalytically enantioselective metallo-ene reaction still remains a formidable challenge. Herein we describe the preliminary results of palladium-catalyzed asymmetric type-I metallo-ene reaction using our chiral monodentate phosphines, 9-PBN and 9-NapBN, under mild reaction conditions.

† This manuscript is dedicated to Prof. Ryoji Noyori on the occasion of his 70th birthday.

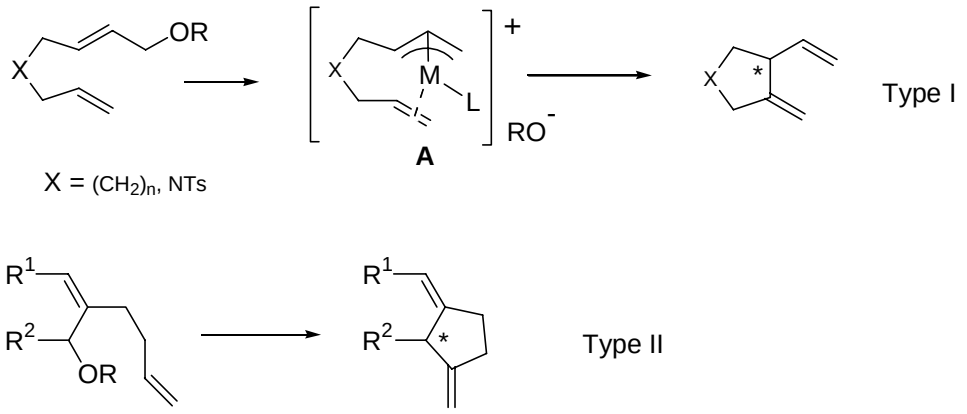
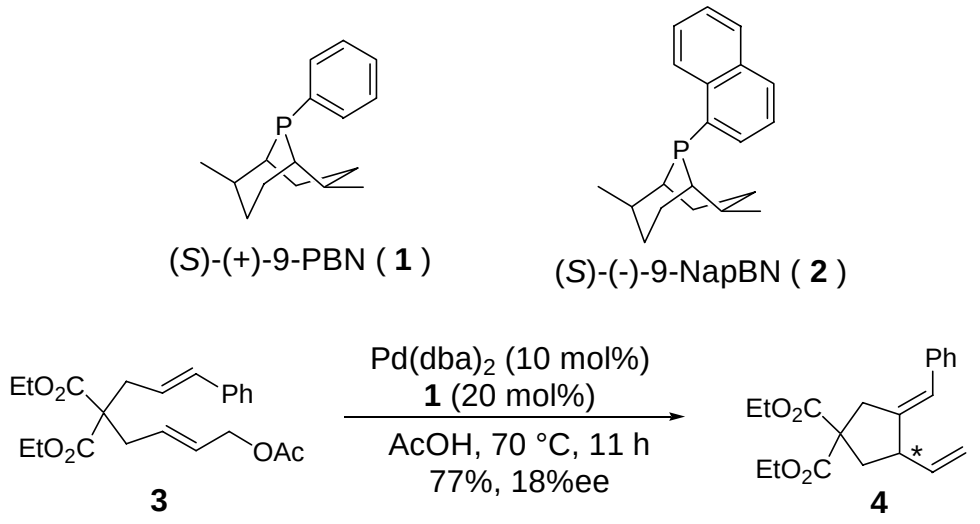


Figure 1. Intramolecular metallo-ene reactions.

In the light of the proposed mechanism in the palladium-catalyzed metallo-ene reaction, monodentate phosphine ligands are preferable because the key intermediate of this reaction is cationic complex **A** in which the palladium can be coordinated with the only monodentate phosphine ligand (L in **A**).[5] We have already demonstrated that (*1R*,2*S*,5*R*,6*S*)-2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane ((*S*)-(+)-9-PBN, **1**) and the *P*-naphthyl counterpart, (*S*)-(-)-9-NapBN (**2**), are valuable monodentate ligands and these phosphines in combination with palladium are efficient catalysts for asymmetric allylic alkylation reactions.[6,7] Therefore, we focused on the palladium-catalyzed metallo-ene reactions as shown in Scheme 1.

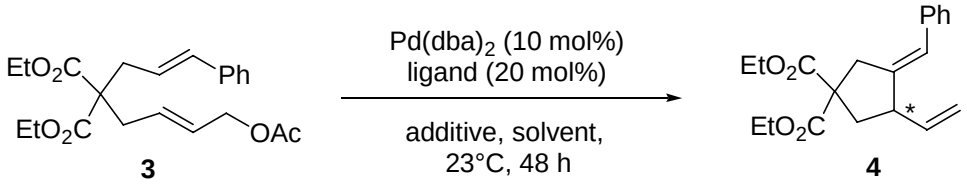


Scheme 1. Palladium-catalyzed metallo-ene reaction

Generally, the catalytic metallo-ene reaction has been carried out with Pd or Rh complex in combination with phosphine ligands in acetic acid or MeOH at 70–120°C. We first tried the reaction under the standard conditions using the ene-allyl ester (**3**), which was easily prepared by the known method. The model substrate (**3**) was treated with bis(dibenzylideneacetone)palladium ($Pd(dba)_2$, 10 mol%) and

(*S*)-(+)-9-PBN (20 mol%) in acetic acid at 70°C for 11 h to give the desired compound (**4**) as a single isomer in 77% yield, which stereochemistry was determined to bear the *E* geometry by the NOE experiment. Disappointingly, the enantiomeric excess was only 18%ee by chiral HPLC analysis. We next started examining the reaction at room temperature for the improvement of enantiomeric excess as shown in Table 1.

Table 1. Palladium-catalyzed metallo-ene reaction



3 **4**

Entry	Ligand	Additive	Solvent	Yield[a] (%)	ee (%)[b]
1	(*S*)-9-PBN	----	$(CH_2Cl)_2$-AcOH[c]	12 (83)	18
2	(*S*)-9-PBN•BH_3	----	$(CH_2Cl)_2$-AcOH[c]	73	21
3	(*S*)-9-PBN	$NaBF_4$	AcOH	41 (50)	16
4	(*S*)-9-PBN	$NaBF_4$	$(CH_2Cl)_2$-AcOH[c]	14 (76)	19
5	(*S*)-9-PBN	$B(OAc)_3$	$(CH_2Cl)_2$-AcOH[c]	30 (54)	21
6	(*S*)-9-PBN	$B(OCOCF_3)_3$	$(CH_2Cl)_2$-AcOH[c]	14 (65)	21
7	(*R*)-9-PBN	$NaBF_4$, $B(OAc)_3$	$(CH_2Cl)_2$-AcOH[c]	73	21
8	(*R*)-9-PBN	$NaBF_4$, $B(OAc)_3$	$(CH_2Cl)_2$	38	21
9	(*S*)-9-NapBN	$NaBF_4$, $B(OAc)_3$	$(CH_2Cl)_2$-AcOH[c]	89	47
10[d]	(*S*)-9-NapBN	$B(OAc)_3$	$(CH_2Cl)_2$-AcOH[c]	82	51

[a] The value in the parentheses is the recovery yield of starting material.

[b] Determined by HPLC analysis using Daicel Chiralcel OJ.

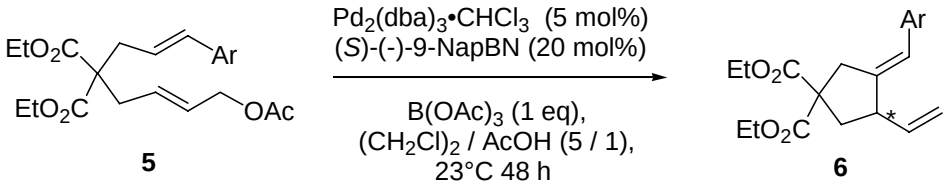
[c] Ratio of $(CH_2Cl)_2$ - AcOH = 5:1.

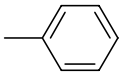
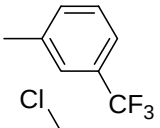
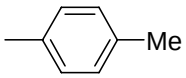
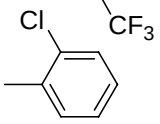
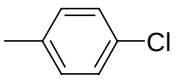
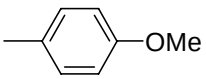
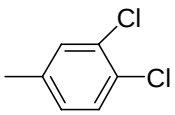
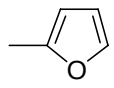
[d] $Pd_2(dba)_3$•$CHCl_3$(5mol%) in the place of $Pd(dba)_2$ was used.

Incidentally, the reaction in the presence of 9-PBN•BH_3 complex, the intermediate for preparation of 9-PBN, as the chiral ligand was found to smoothly proceed at 23°C and give the desired product (**4**) in 73% yield (entries 1 and 2). This result suggested that the side product generated from the 9-PBN•BH_3 and acetic acid might accelerate the catalytic reaction. Then, we investigated additive effects for the reaction. After some trials and errors, sodium tetrafluoroborate ($NaBF_4$, 1 equiv) and triacetoxyborane ($B(OAc)_3$, 1 equiv) were disclosed to activate the reaction at 23°C (entries 3 and 5). The combination of $NaBF_4$ (1 equiv) and $B(OAc)_3$ (1 equiv) as the additives proved to reproduce the result of the entry 2 and maximize the chemical yield (entry 7) but the enantiomeric excess remained to be improved. Due to the

solution of the problem, we next investigated the effect of phosphine ligands. In this metallo-ene reaction, (*S*)-9-NapBN (**2**) also effectively worked as the chiral phosphine. The use of (*S*)-9-NapBN in the place of (*S*)-9-PBN improved the enantioselectivity to give the corresponding product (**4**) in 89% with 47%ee (entry 9). Surprisingly, in the case of (*S*)-9-NapBN as the chiral ligand, tris(dibenzylideneacetone)dipalladium chloroform complex ($Pd_2(dba)_3$•$CHCl_3$) as the palladium catalyst could be used without $NaBF_4$ for this metallo-ene reaction to afford the highest enantiomeric excess, 51%ee ($[\alpha]_D$ -25.6 (*c*, 1.0, $CHCl_3$))(entry 10).[8] Although the precise role of $NaBF_4$ and $B(OAc)_3$ is not clear at present, we have speculated that the $NaBF_4$ and $B(OAc)_3$ as the additives might accelerate the reaction by the contribution to easy generation and stability of the cationic complex **A** in the catalytic cycle.

Table 2. Palladium-catalyzed metallo-ene reaction using NapBN.



Entry	Ar	Yield[a] (%)	ee (%)	Entry	Ar	Yield[a] (%)	ee (%)
1		82	51[b]	5		65(11)	26[c]
2		61 (30)	35[b]	6		82	30[d]
3		88	20[c]	7		17 (57)	39[d]
4		59 (27)	44[d]	8		16 (45)	40[d]

[a] The value in the parentheses is the recovery yield of starting material.

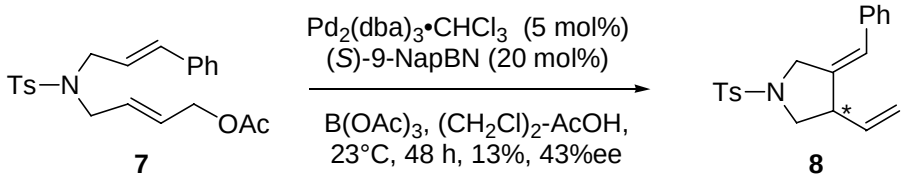
[b] Determined by HPLC analysis using Daicel Chiralcel OJ.

[c] Determined by HPLC analysis using Daicel Chiralcel OD-H.

[d] Determined by HPLC analysis using Daicel Chiralcel AD.

Using the optimized mild conditions, we carried out the asymmetric metallo-ene reaction of several substrates as shown in Table 2. The reaction of **5** proceeded using $Pd_2(dba)_3$•$CHCl_3$ (5 mol%) and (*S*)-9-NapBN (20 mol%) in the presence of $B(OAc)_3$ (1 equiv) in 1,2-dichloroethylene/acetic acid (5/1) at 23°C for 48 h to furnish the cyclized product (**6**). As might see from the results in Table 2, the chemical

yield strongly depended upon the substituent on aromatic nucleus. The methyl, Cl, and CF_3 derivatives gave similar results as well as **3** on their chemical yield but the enantiomeric excesses varied (entry 2-6). On the other hand, the furan and MeO derivatives, electron-rich aromatic compounds, were sluggishly cyclized under our developed conditions. Finally, we briefly examined the different type-I substrate (**7**) with the sulfonamide tether. Cyclization of **7**, however, gave the pyrrolidine (**8**) in the unsatisfactory yield and enantioselectivity (13 %, 43%ee) as shown in Scheme 2. Nevertheless, it should be noted that the asymmetric metallo-ene reaction described above not only takes place under the exceedingly mild conditions but also affords the highest enantiomeric excess in this area.



Scheme 2. Synthesis of the pyrrolidine derivative using metallo-ene reaction.

In conclusion, we developed the palladium-catalyzed asymmetric type-I metallo-ene reactions using our phosphines, 9-PBN and 9-NapBN, in the presence of $B(OAc)_3$. The reaction using 9-NapBN takes place at room temperature and affords the highest enantiomeric excess in this area. Further investigation of asymmetric metallo-ene reaction for the type-II substrates is underway.

ACKNOWLEDGEMENTS

This work was financially supported in part by a Grant-in-Aid for Scientific Research (B) (to YH) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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8. Typical procedure of the metallo-ene reaction using NapBN: A 0.1 M solution of triacetoxyborane in $ClCH_2CH_2Cl$ was prepared by mixing 1 M $BH_3 \cdot THF$ (0.4 mL) and acetic acid (2 mL) at 23°C for 2 h, drying the mixture, and dissolving the residue in $ClCH_2CH_2Cl$ (4 mL). The solution of triacetoxyborane (0.1 M, 1.5 mL) was added to a solution of the substrate (**3**) (61 mg, 0.157 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (8.3 mg, 0.008 mmol), (*S*)-(-)-9-NapBN (9.2 mg, 0.031 mmol) in acetic acid (0.3 mL) under nitrogen atmosphere. The reaction mixture was stirred at 23°C for 48 h and then diluted with AcOEt (100 mL). The mixture was washed with saturated aqueous sodium hydrogen sulfate and brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel using *n*-hexane/AcOEt (15/1) to give the cyclized product (**4**) (42 mg, 82%, 51% ee) as colorless solids: $[\alpha]_D$ -25.6 (*c*, 1.0, $CHCl_3$); IR (neat) 2987, 1732, 1263, 1146, 758, 694 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.22-1.27 (6H, m), 2.00 (1H, dd, *J* = 12.9 Hz, 11.2 Hz), 2.62 (1H, ddd, *J* = 13.1 Hz, 7.3 Hz, 1.2 Hz), 3.20 (1H, dt, *J* = 17.6 Hz, 2.9 Hz), 3.32-3.42 (2H, br), 4.14-4.26 (4H, m), 5.14 (1H, s), 5.17 (1H, d, *J* = 2.7 Hz), 5.66-5.75 (1H, m), 6.20 (1H, d, *J* = 2.5 Hz), 7.17-7.34 (5H, m); LR FABMS: 329 (M + H). Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.13; H, 7.37.