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Studies Towards Asymmetric Catalyzed Metallo-ene Reactions

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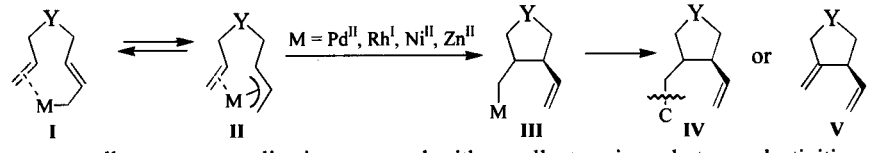
Abstract : The asymmetric catalyzed metallo-ene reaction was studied. Enantioselectivities up to 47% were observed using the Pd-ene reaction applied on the substrate **4**. © 1997 Elsevier Science Ltd.

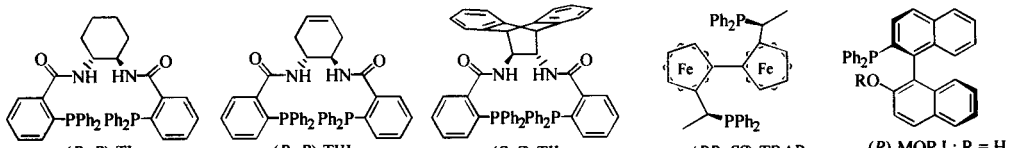
The metallo-ene reaction[1] is a powerful tool for organic chemists. Intramolecular Pd0[1b], Ni0[1b], RhI[1c], Zn0[1d-e] catalyzed alkene (or alkyne) allylations **II→III** coupled with β-eliminations **III→V**, carbonylations or C-C coupling **III→IV** efficiently provide various carbo or heterocycles in one synthetic operation, useful in the preparation of natural products[1f-j].



I **II** **III** **IV** **V**

Furthermore, metallo-ene type cyclizations proceed with excellent regio and stereoselectivities, allowing the preparation of enantiomerically pure intermediates or natural products[1l-m] through efficient chirality transfer from optically pure substrates. Howewer, the asymmetric version of the catalytic metallo-ene reaction, where enantiospecificity is induced by chiral ligands complexed on the metal moiety, remains to be elaborated. We now report our studies towards enantioselective catalyzed metallo-ene reaction.

One major difficulty in our work is that the mechanism of the metallo-ene reaction is still not totally elucidated although a major advance towards its understanding has recently been published[2]. It involves a π-allyl metal species, where the transition state of the reaction could have a high degree of freedom, certainly more important than in related reactions such as the Heck[3] and the Pd catalyzed Alder-ene[4] type cyclisations involving a C-Pd σ-bond in the transition state. Few examples of good asymmetric inductions were reported concerning the Heck[3] reaction and only one recent example of asymmetric Pd catalyzed Alder-ene type cyclisation[4a] has been published, with enantioselectivities up to 95%. The ligands of Scheme 1 were examined for their effects on yield and enantioselectivity on the model substrate **1** in the Rh, Pd, Ni catalyzed metallo-ene reaction. The ligands TI, TII[5a-d], TRAP[5e-f], MOPI, MOPII[5g-i], were synthesized as described in the literature. The ligand TIII[6] was prepared from enantiomerically pure[7a] cyclohexenediamine[7b] by coupling with 2-diphenylphosphinobenzoic acid using Trost's procedure. The results are shown in Table 1.



(*R, R*)-TI (*R, R*)-TIII (*S, S*)-TII (*RR, SS*)-TRAP (*R*)-MOP I : R = H
(*R*)-MOP II : R = Me

Scheme 1

† In memory of our post-doc supervisor, deceased 15-3-1996.

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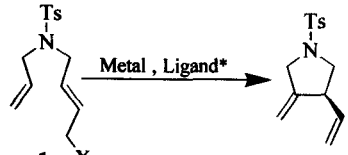


Rh : X = OCO_2Me; Pd, Ni : X = OAc

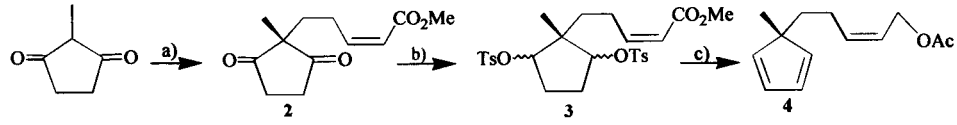
Entry	Ligand	Metal	Conditions	Yield (%)[a]	ee (%)[b]
1	10% (*S, S*)-DIOP	10% $Pd(dba)_2$[12]	MeOH, 75°C, 4.5 h	53	0
2	10% (*S, S*)-DIOP	10% $Ni(COD)_2$	THF, 60°C, 4 h	93	5
3	/	4% $HRh(DIOP)_2$[13]	AcOH, 80°C, 8 h	50	8
4	10% (*R*)-BINAP	10% $Pd(dba)_2$	MeOH, 75°C, 3.5 h	69	0
5	10% (*R*)- BINAP	10% $Ni(COD)_2$	THF, 60°C, 18 h	0	/
6	4% (*R*)-BINAP	2% $HRh(PPh_3)_4$[1c]	AcOH, 80°C, 7 h	25	0
7	32% (*R*) -MOPI	8% $Pd(dba)_2$	MeOH, 65°C, 18 h	53	8
8	20% (*R*)-MOP I	10% $Ni(COD)_2$	THF, 60°C, 20 h	0	/
9	8% (*R, R*)-TI	8% $Pd(dba)_2$	AcOH, 70°C, 3 h	50	4
10	10% (*R, R*)-TI	10% $Ni(COD)_2$	THF, RT, 24 h	24	12
11	10% (*R, R*)-TI	5% $HRh(PPh_3)_4$	AcOH, 80°C, 8 h	26	0
12	10% (*RR, SS*)-TRAP	10% $Pd(dba)_2$	AcOH, 80°C, 1 h	79	20

a) Isolated yield; b) HPLC analysis, chiral column Chiralcel OD

Table 1

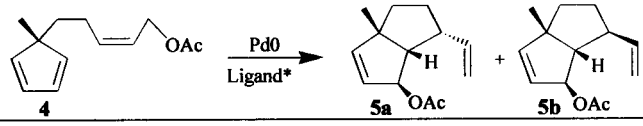
Standard ligands such as DIOP and BINAP, which are sometimes efficient for palladium-catalyzed allylic substitution[8a-b], were first examined. They gave an acceptable yield for the palladium-ene reaction but no asymmetric induction was observed (entries 1,4). Hayashi's monophosphines type ligands MOP[5g], which have a reactivity different from that of bidentate phosphines for palladium-catalyzed allylic reduction[5h] and substitution[5i] reactions, were then studied. A lower yield was obtained using MOP I and the enantioselection was still very low (entry 7). Based on the enhanced reactivity and selectivity observed in the nickel versus palladium-ene type cyclisation[1a-b], better enantioselectivities could have been expected using nickel as catalyst. Unfortunately, if a better yield was obtained with DIOP, the enantioselectivity was low (entry 2). Furthermore, no reaction was observed with the atropoisomeric ligands BINAP and MOP I (entries 5, 8). As the rhodium-ene reaction is known to give some major differences of selectivity in relation to Pd and Ni-ene reactions[1a,c], it was worth trying to improve enantioselectivity using rhodium, but the results were still disappointing (entries 3,6). We then turned to the idea advanced by Trost. In order to bring the stereocontroling centers on the phosphines as close to the reaction centers as possible, Trost described the ligands of type T which have a large bite angle[5a,b], suitable for inter[5c,d] and intramolecular[5a,b] palladium-catalyzed allylic substitutions. The ligand TI provided a slightly better enantioselectivity than the previous ones but only in the case of the Ni-ene reaction, at room temperature. However, the chemical yield was worse (entries 9-11). To increase the bite angle to its maximum, Ito's trans chelating ligand TRAP[5e-f] was used. TRAP ligand gave 20% ee, in 79% yield (entry 12) when the ene-reaction was performed with palladium.

Encouraged by this latter result, we decided to change our model substrate. Since there is no possibility of controling the olefin facial selectivity of the molecule **1**, we synthesized the prochiral substrate **4** with a cyclopentadiene[3a] moiety suitable for metallo-ene cyclisation and olefin facial selectivity control. The synthesis is outlined as follows :



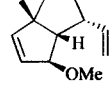
a) i) Acroleine, AcOH, H_2O, 98% ii) $(CF_3CH_2O)_2POCH_2CO_2Me$, KHMDS, 18-crown-6, THF, 80% b) i) $NaBH_4$, MeOH, 88% ii) TsCl, C_5H_5N, DMAP, 85% c) i) DibalH, CH_2Cl_2, 80% ii) DBU, PhH, 54% iii) AcCl, C_5H_5N, THF, 92%

Michael addition of 2-methyl-1,3-cyclopenanedione on acroleine[9], followed by Wittig reaction under Still's conditions[10] gave the cis methyl acrylate **2**. The diketone moiety was then reduced and tosylated giving **3** as a mixture of diastereomers. Reduction of the ester, elimination of the tosylates then acetylation of the allylic alcool furnished the desired substrate **4** in 23% overall yield. The Ni and Rh catalysts were ineffective on this substrate. However, the Pd-ene reaction led to a mixture of two diastereomers **5a**[11] (major) and **5b** (minor). The results of the Pd-ene reaction are outlined in Table 2.



Entry	$Pd_2(dba)_3$ [12]	Ligand	Conditions c = 0.1M	Conversion (%)[a]	ratio **5a** / **5b**[a]	ee **5a**	ee **5b**(%)[f]
1	3%	6% (*S, S*)-DIOP	AcOH, 80°C, 5h	30	69 / 31	14	/
2[c]	3%	6.5% (*R*)-BINAP	AcOH, 80°C, 12h	100	74 / 26	23	22
3[e]	4%	20% (*R*)-MOP II	MeOH, 70°C, 2h	100	62 / 38	0	0
4[e]	4%	20% (*R*)-MOP I	MeOH, 70°C, 2h	100	67 / 33	32	27
5[e]	4%	32% (*R*)- MOP I	MeOH, 45°C, 12h	100	61 / 39	42	32
6[b]	5%	10% (*RR,SS*)-TRAP	AcOH, 70°C, 7h	92	82 / 18	5	8
7	4%	8.5 % (*S, S*)-TII	AcOH, 86°C, 3h30	100	81 / 19	0	0
8	3%	6.5% (*R, R*)-TI	AcOH, 75°C, 7h	100	89 / 11	32	26
9	4%	10% (*S, S*) -TI	MeOH, 70 °C, 8h30	100	88 / 12	34	19
10[d]	4%	18% (*R, R*)-TI	MeOH, 40 °C, 36h	100	93 / 7	45	10
11	4%	12 % (*R, R*)-TIII	MeOH, 72 °C, 24h	100	88 / 12	40	/
12	4%	15% (*R, R*)-TIII	MeOH, 45°C, 36h	97	87 / 13	47	15

a) GC Analysis, capillary column HP1(OV1) b) PhH as cosolvent c) DMSO as cosolvent d) 20%mol AcOH

e) 20 -30% of the byproduct : 

f) GC Analysis, chiral capillary column Lipodex E.

Table 2

As expected, the Pd-ene reaction applied to the substrate **4** gave better enantioselectivities than the substrate **1** using standard ligands such as DIOP and BINAP (entries 1,2). BINAP gave more then 20% ee in an average diastereomeric ratio. The monodentate phosphine MOP II was very effective in catalyzing the reaction, but no asymmetric induction was observed (entry 3). By contrast, 32% ee was obtained using the ligand MOP I in the same conditions (entry 4). This difference of behaviour could be due to the free naphthol group of MOP I, suitable for Pd chelation, which could confer on this ligand a bidentate nature. Lowering the temperature to 45°C improved the ee to 42%, but increased the reaction time, and the diastereomeric ratio was still low (entry 5). Ligands having a large bite angle and the trans chelating ligand TRAP were then studied. Surprisingly, the ligand TII which has the largest bite angle of the ligands of type T, and the TRAP ligand, were effective to catalyze the reaction in an acceptable diastereomeric ratio, but no asymmetric induction was obtained (entries 6, 7). By contrast, TI increased the ee to the value observed for MOP I, in a much better diastereomeric ratio (entries 8, 9). The reaction was best performed at 45°C, in MeOH, with 2 to 3 equivalents

of ligand per Pd (entry10). Under these conditions, the diastereomeric ratio was excellent and the ee reached 45%. A slightly increase of the ee was even observed with the more rigid ligand TIII under the same conditions (entry 12).

In conclusion, we have opened the way to new methodologies toward enantioselective catalyzed metalloene reaction. We have shown that ligands with closely related structures can have totally different behaviours. The best inductions were obtained using the Pd-ene reaction applied to the substrate **4** derived from cyclopentadiene. The bidentate ligands TII and TIII were shown to be the most effective for this substrate. Thus, new improvements can be expected in the field of asymmetric catalysis.

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6. Data for ligand TIII : $[\alpha]_D^{25}$ = +59 (c = 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) : 1.8-1.9 (m, 2 H), 2.25-2.35 (m, 2 H); 4.05-4.2 (m, 2 H), 5.5 (m, 2 H); 6.32 (d, J = 8 Hz, 2 H); 6.9-6.95 (m, 2 H); 7.15-7.26 (m, 24 H); 7.52-7.58 (m, 2 H). ^{31}P NMR (80 MHz, $CDCl_3$) : -9.17.
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11. Data for **5a** : IR : 3038, 2952, 2865, 1724, 1639, 1453, 1371, 1256, 1017, 935, 913, 788. ^1H NMR (400 MHz, $CDCl_3$) : 1.27 (s, 3 H); 1.28-1.43 (m, 2 H); 1.63-1.69 (m, 2 H); 2.01 (s, 3 H); 2.18 (dd, J = 8.1 Hz, 1.8 Hz, 1 H); 2.65-2.75 (m, 1 H); 5.03 (dt, J = 17.2 Hz, 1.5 Hz, 1 H); 5.075 (dt, J = 10.2 Hz, 1.5 Hz, 1 H); 5.48 (t, J = 1.8 Hz, 1 H); 5.67 (dd, J = 5.5 Hz, 1.8 Hz, 1 H), 5.73 (d, J = 5.5 Hz, 1 H); 5.9-6.05 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): 170.7 (s), 145.43 (d), 138.74 (d), 127.67 (d), 115.24 (t), 82.02 (d), 57.85 (d), 56.3 (s) 45.98 (d), 37.92 (t), 29.57 (t), 27.63 (q), 21.4 (q). MS : 206 (0.91), 164 (38), 146 (13), 131 (28), 118 (16), 109 (33), 96 (100), 91 (48), 77 (34), 67 (28). HR-MS : 164.1182 ($[C_{13}H_{18}O_2$-$CH_2CO]^{+\cdot}$) calc. 164.1201. Compound **5b** was not isolated. Its structure was assigned following references 1 and 3a.
12. Palladiumdibenzylideneacetone was prepared according to Rettig M.F., Maitlis P.M., *Inorg. Synth.*, **1990**, *28*, 110-111, but the exact structure of this complex ($Pd(dba)_2$ or $Pd_2(dba)_3$) seems to depend on the experimental conditions used for its synthesis, see Moreno-Manas M., Pajuelo F., Pleixats R., *J. Org. Chem.*, **1995**, *60*, 2396-2397.
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