A New N,P-Ligand with Achiral *gem*-Dimethyloxazoline for Palladium(II)-Catalyzed Cyclization of 1,6-Enynes: Transition State Probe for the *N*/*C trans* Mode in Mizoroki−Heck-Type C−C Bond Formation

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A highly effective C_1-symmetric *gem*-dimethyl N,P-ligand has been developed for enantioselective palladium(II)-catalyzed carbocyclization of 1,6-enynes, in which the *N*/*C trans* mode is established for the first time in the "Mizoroki–Heck-type" transition state by virtue of the C_1-symmetric N,P-ligand.

Introduction

Transition metal-catalyzed ene-type carbocyclizations of 1,6-enynes[1−9] are useful methods, particularly for five-membered rings. However, previous examples of enantioselective catalysis with chiral metal complexes are limited,[10−17] despite its synthetic potential to afford not only carbocycles but also heterocycles. Here we report efficient catalysis by chiral palladium(II) complexes of a new N,P-ligand bearing an achiral oxazoline with sterically demanding *gem*-dialkyl groups. The C_1-symmetric N,P-ligand with the achiral oxazoline provides deep insight into the key transition states for C−C bond formation.

Results and Discussion

Because of the limitations of P,P-ligands such as BINAP and SEGPHOS with ene substrates (vide infra),[6] we investigated bidentate C_1-symmetric N,P-ligands for a variety of substrates under polar conditions ([$(MeCN)_4Pd$]$(BF_4)_2$/HCOOH/DMSO). In order to achieve high enantioselectivity, NP-ligands[18−33] **7a** and **7b**, containing chiral *t*Bu oxazoline units, were first prepared (Table 1). N,P-ligands **7a** and **7b** gave enantioselectivities (81−93% *ee*, Entries 4, 5, 7, 8) higher than those obtained with the C_2-symmetric P,P-ligand Xyl-SEGPHOS (**9**)[17,34] (6−61% *ee*: vide supra) (Entries 10, 11). Interestingly enough, the same (*S*)-(+)-products were obtained from all substrates (**1**, **3**, and **5**) on use of these two epimeric N,P-ligands **7a** and **7b**. In contrast, N,P-ligand **8**, with no alkyl substituent in the oxazoline unit, showed poor enantiomeric excesses (35−50% *ee*, Entries 3, 6, 9). These results imply that the center of chirality (*R* or *S*) at the 4-position of the oxazolines is *not* important and that the presence of a sterically demanding substituent is necessary.

Encouraged by these interesting results, we examined X-ray analyses of dichloropalladium(II) complexes **10a**, **10b** with N,P-ligands of **7a** and **7b**.[35,36] The ORTEP drawings are shown in Figure 1 (top and bottom).[37]

A general representation of a Pd^{II} complex, according to the X-ray analyses of these diastereomeric Pd^{II} complexes **10a** and **10b**, is shown in Figure 2, divided into four quadrants (from I to IV). In sharp contrast to Pd^{II} complexes with P,P-ligands, such as BINAP,[38] there is essentially no steric difference in axial and equatorial phenyl groups located in quadrants II and III, respectively, due to: (1) a small difference in the N−Pd−P−Ph torsion angle, and (2) similar direction of phenyl ring such as face and edge rotating on the C−P bond (Figure 1, top and bottom). Furthermore, the substituents R or R′ are located in quadrant IV. This is caused by a *strong twist* of the oxazoline from Pd square planar. The P−Pd−N−C(−O) torsion angles in **10a** and **10b** are 72° and 79°, respectively.

On the basis of these X-ray analyses, a more effective N,P-ligand **11**, *doubly* substituted with methyl groups, was developed (Figure 3). The advantage of the C_1-symmetric Pd^{II} complex with the (a*S*)-N,P-ligand **11** could be predicted in view of steric and electronic features. Two possible (*N*/*C trans* and *cis*) modes in the *four*-coordinate transition states[39,40] (**TS1** and **TS2**) would afford the (*S*)-(+)-products. In the *N*/*C trans* mode (**TS1**), high enantioselectivities should be achieved by use of N,P-ligand **11** because of significant steric repulsion between the terminal Me groups of the substrate (**1**, **3**, and **5**) and the dimethyl substituents of

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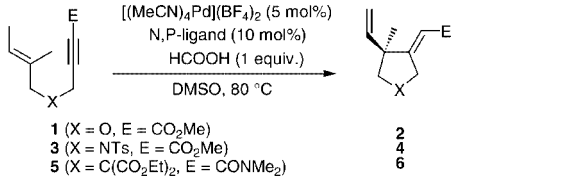
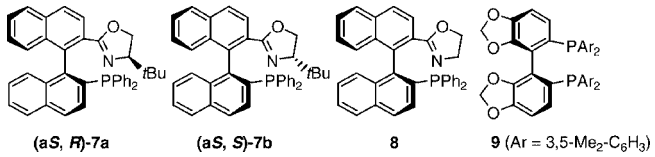
Table 1. Enantioselective carbocyclization of 1,6-enynes catalyzed by Pd^{II} complexes with (a*S*)-P,P- and N,P-ligands





(a*S*, *R*)-7a (a*S*, *S*)-7b 8 9 (Ar = 3,5-Me_2-C_6H_3)

Entry[a]	Substrate	N,P-ligand	Reaction time (h)	Yield (%)	*ee* (%) (config.[b])
1[c]	**1**	7a	12	>99	78 (*S*)-(+)
2[c]	1	7b	24	92	87 (*S*)-(+)
3[c]	1	8	18	89	41 (*S*)-(+)
4	3	7a	3	>99	93 (*S*)-(+)
5	3	7b	3	>99	92 (*S*)-(+)
6	3	8	3	>99	35 (*S*)-(+)
7	5	7a	24	42	81 (*S*)-(+)
8	5	7b	9	>99	86 (*S*)-(+)
9[d]	5	8	24	9	50 (*S*)-(+)
10	3	9	3	>99	61 (*R*)-(−)
11	5	9	3	>99	6 (*R*)-(−)

[a] Reactions were carried out in thoroughly degassed solvents at 80 °C with 5 mol % of $[(MeCN)_4Pd](BF_4)_2$, 10 mol % of chiral ligand and 1 equiv. of HCOOH unless otherwise noted. [b] For **4** and **6**, by analogy. [c] 0.2 equiv. of HCOOH were used. [d] Temperature was 100 °C.

the oxazoline unit in quadrant IV.[41−43] In contrast, lower enantioselectivity should be observed in the *N*/*C cis* mode (**TS2**), since the terminal alkenyl Me group should not be able to differentiate fully between the two Ph groups in quadrants II and III. The (*S*)-(+)-enantiomers would be obtained highly enantioselectively through Mizoroki−Heck-type C−C bond formation[44−47] and β-H elimination via **TS1**, by effective differentiation with the dimethyloxazoline (quadrant I vs. IV).

The preference for the *N*/*C trans* mode is clearly illustrated by ONIOM calculations.[48−51] Steric factors dominate the enantioselectivity of N,P-ligand **11**, while electronic factors produce the *N*/*C trans* mode. Details of the 3D geometries of **CP1** and **CP2** (X = O, an aldehyde group was used instead of an ester group as the models of **TS1** and **TS2**) were optimized by use of the ONIOM (B3LYP/631SDD: HF/321LAN) approach (Figure 3).[52] The *N*/*C trans* mode of **CP1** is 6.3 kcal/mol lower in energy than the *N*/*C cis* mode of **CP2**. This indicates that the C−C bond formation proceeds through the *N*/*C trans* mode transition state (**TS1**). The relative energy difference between **CP1** and **CP2** is due to the *trans* influence of the electronically asymmetric N,P-ligand, which affects the Pd−C1 and Pd−C2 (and Pd−C3) lengths. Since the P-coordinating unit acts as an electron acceptor and the N-coordinating unit as a donor,[41] π-coordination of the olefinic carbons C2−C3 *trans* to the phosphane in **CP1** is electronically favored. The Pd−C1 bond in **CP1** (2.02 Å) is stronger than that in **CP2** (2.08 Å) because of the *trans* influence of the *N*-coordinating unit. In contrast, the π-coordination of C2−C3 *trans* to the *N*-coordinating unit as a donor in **CP2** is electronically mismatched, and so the coordination structure around the Pd center in **CP2** is distorted in comparison with the square planar structure in **CP1**. The electronic influence can be combined with the steric differentiation in the oxazoline to form **TS1** in the *N*/*C trans* mode, which can achieve the high enantioselectivity.

Therefore, our axially chiral N,P-ligand **11**, without any center of chirality in the oxazoline moiety, was prepared by a modified method involving the use of a catalytic amount of sodium with the corresponding methoxycarbonyl and 2-amino-2-methyl-1-propanol (see the supporting information, for supporting information see also the footnote on the first page of this article). The synthesis of the achiral *gem*-dimethyloxazoline (**11**) was otherwise unsuccessful, giving quite low yields. Our *gem*-dimethyl N,P-ligand **11** prepared in this way gave the carbocyclization products (**2**, **4**, and **6**) with high enantiomeric excesses and in almost quantitative yields (up to 95% *ee*, 99% yield) (Table 2, Entries 1−3). The key to the success achieved in increasing the enantioselectivity in carbocyclization of amide **5** in particular, from 6% *ee* by Xyl-SEGPHOS **9** to 95% *ee* by **11**, is the employment of the sterically demanding *gem*-dimethyl achiral oxazoline.

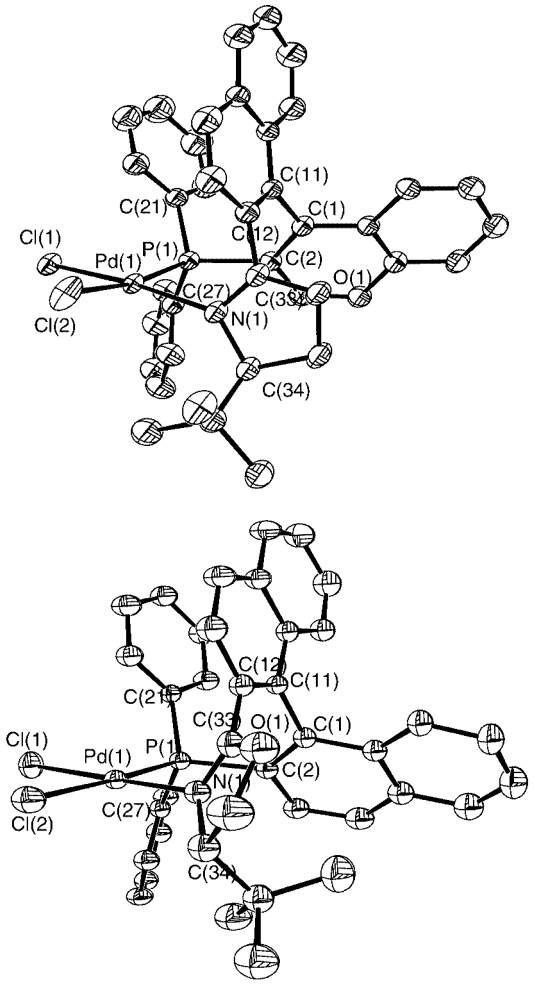


Figure 1. ORTEP drawings of chiral dichloropalladium(II) complexes with N,P-ligands; (top) [(a*S*,*R*)-**7a**]$PdCl_2$ complex **10a**; (bottom) [(a*S*,*S*)-**7b**]$PdCl_2$ complex **10b**

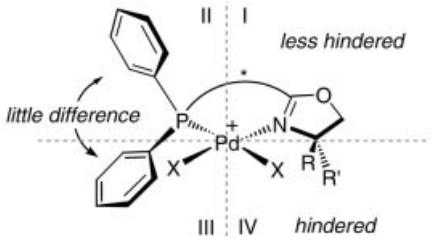


Figure 2. Drawing of Pd^{II} complexes with (a*S*)-N,P-ligands

Conclusion

In summary, we have developed the highly effective *gem*-dimethyl N,P-ligand for enantioselective palladium(II)-catalyzed ene-type carbocyclization of 1,6-enynes to produce not only carbocycles but also heterocycles. The *N*/*C trans* mode has thus been established for the asymmetric catalytic Mizoroki−Heck-type C−C bond formation by virtue of the C_1-symmetric N,P-ligand.

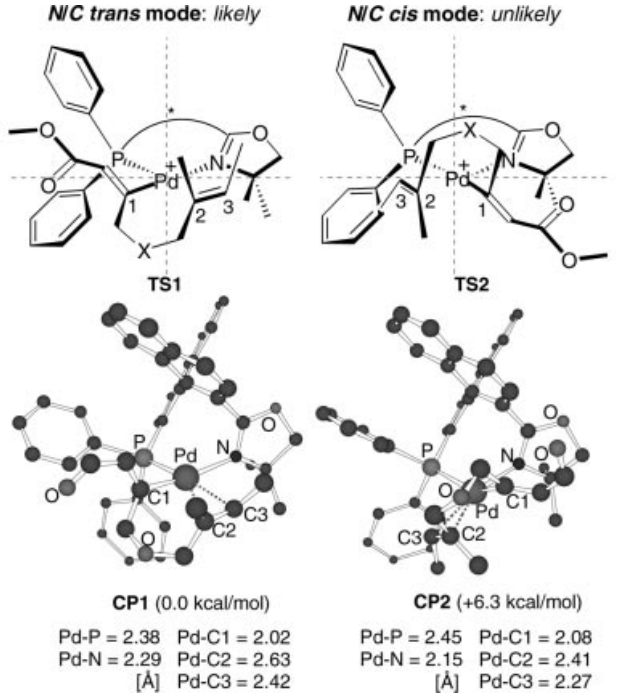
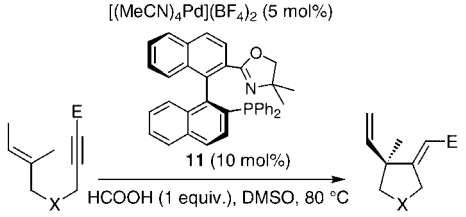


Figure 3. Transition states for C−C bond formation, producing (*S*)-(+)-products, in the presence of (a*S*)-N,P-ligand **11**; three-dimensional structures of CP1 and CP2 optimized by use of ONIOM (B3LYP/631SDD:HF/321LAN)

Table 2. Asymmetric carbocyclization of 1,6-enynes catalyzed by Pd^{II} complexes with *gem*-dimethyl N,P-ligand **11**



Entry[a]	Substrate	Reaction time (h)	Yield (%)	*ee* (%) (config.)
1[b]	1	24	87	88 (*S*)-(+)
2	3	3	>99	93 (*S*)-(+)
3	5	3	>99	95 (*S*)-(+)

[a] Reactions were carried out at 80 °C with 10 mol % of N,P-ligand **11**, 5 mol % of $[(MeCN)_4Pd](BF_4)_2$ and 1 equiv. of HCOOH unless otherwise noted. [b] 0.2 equiv. of HCOOH were used.

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[36] Crystal data for **10b** (dichloro[(*S*,a*S*)-2-[4-(*tert*-butyl)oxazol-2-yl]-2′-diphenylphosphanyl-1,1′-binaphthyl]palladium) in X-ray analysis: formula $C_{39}H_{34}Cl_2NOPPd{\cdot}CH_2Cl_2$, orthorhombic, space group $P2_12_12_1$ (#19), a = 14.973(3) Å, b = 19.989(4) Å, c = 12.208(3) Å, V = 3653.8(14) Å^3, Z = 4, and D = 1.347 g cm^{-3}. R = 0.0255 and Rw = 0.0676. CCDC-179395 contains the supplementary crystallographic data for this paper.
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