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Highly enantioselective alkaloid synthesis *via* ene-type cyclizations catalyzed by cationic chiral palladium(II) complexes of PN-ligands with an *achiral* oxazoline unit †

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A highly efficient asymmetric alkaloid synthesis *via* ene-type cyclizations catalyzed by cationic chiral palladium(II) complexes of PN-ligands with an achiral *gem*-dimethyl oxazoline unit is shown to give 5-membered products with a quaternary carbon center, including a spiro-amide, almost quantitatively with extremely high enantiomeric excesses.

Catalytic asymmetric alkaloid synthesis remains as a challenge,[1] in spite of the pharmaceutical importance of kainic acid[2] *etc*. Chiral transition metal complexes are the catalysts[3] of choice for the cyclization of enynes,[4,5] dienes[6] or diynes.[7] Recently, a highly enantioselective Rh-catalyzed cycloisomerization[8] of enynes and a Pd-catalyzed ene-type cyclization,[9] particularly using cationic chiral Pd(II) catalysts with PP-ligands such as BINAPs,[10] have been developed. Herein, we report a highly enantioselective alkaloid synthesis *via* an ene-type cyclization with axially chiral PN-ligands having an *achiral gem*-dimethyl oxazoline unit, to afford alkaloids including spiro derivatives.

Initially, the combined use of 5 mol% of a cationic Pd(II) catalyst ($[(MeCN)_4Pd](BF_4)_2$) and 10 mol% of our PN-ligand[11] bearing an achiral *gem*-dimethyl oxazoline unit in DMSO was employed in the cyclization of **1a** and **1b** leading eventually to kainic acid derivatives (eqn. (1)). For **1a**, PN-ligand (a*S*)-**3** was effective to afford **2a** with 93% ee quantitatively, but (*R*)-BINAP as a PP-ligand resulted in only 78% ee. A more apparent difference was seen in the cyclization of **1b**. Reaction with (*R*)-BINAP proceeded smoothly to provide the corresponding product **2b** in moderate (72%) yield with quite low enantiomeric excess (34% ee). However, our PN-ligand (a*S*)-**3** showed an advantage over the PP-ligand not only in chemical yield but also in enantioselectivity (90%, 66% ee).

Interestingly, *double* substitution of Me-groups in the 4-position of oxazoline is critical to achieve higher enantioselectivities. Mono-methyl substituted PN-ligands (a*S*,*R*)-**4** and (a*S*,*S*)-**5** were less effective even with a new chiral center in the 4-position of the oxazoline moiety in addition to axial chirality, to afford **2a** in 89% ee and 52% ee, respectively (Fig. 1). Moreover, the enantioselectivity seriously dropped to 35% ee in the case of non-substituted PN-ligand (a*S*)-**6**.

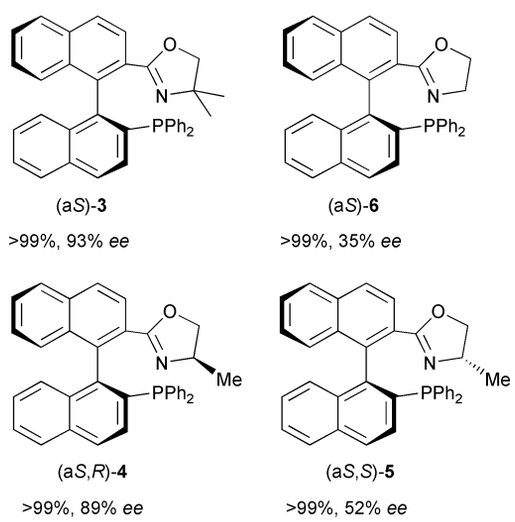
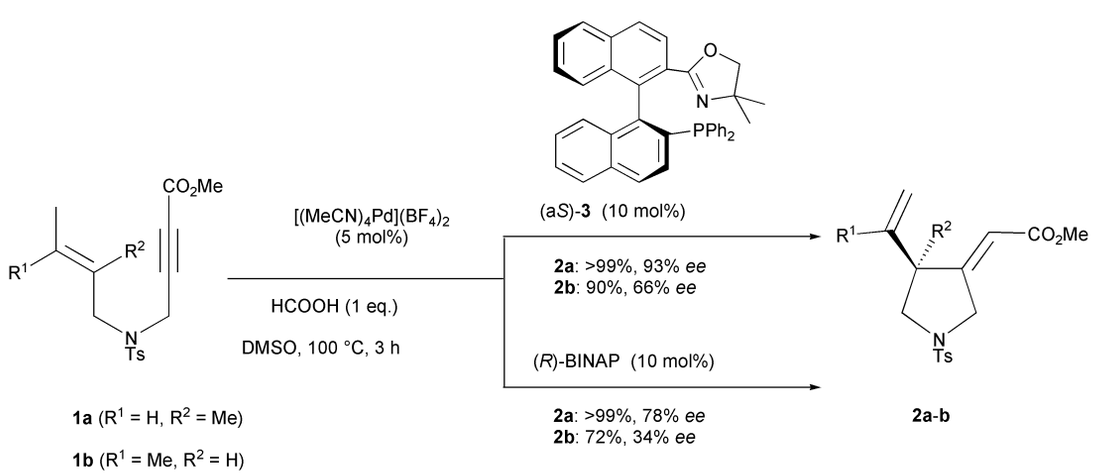


Fig. 1 Asymmetric cyclization of **1a** to **2a** with PN-ligands.

Encouraged by the observation of the enantioselectivities arising from sensitive recognition of Me-substitution, we examined X-ray analyses of η^3-allyl Pd(II) complexes easily prepared from $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$–$AgSbF_6$ and PN-ligands



(1)

† Electronic supplementary information (ESI) available: spectral data of substrates, cyclized products and PN-ligands and crystallographic data of Pd complexes. See http://www.rsc.org/suppdata/ob/b3/b305865b/

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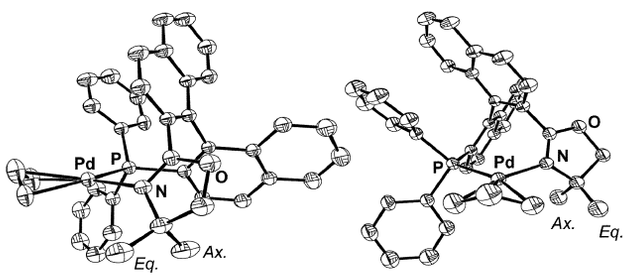
3, **4**, **5**, and **6**, respectively. The ORTEP drawings of η^3-allyl palladium complex **7**[12] derived from **3** are shown in Fig. 2 (hydrogens and anionic moiety of SbF_6^- are omitted for clarity). In Pd(II) complex **7** with PN-ligand (a*S*)-**3**, for instance, the bond distance of Pd–P is 2.304 Å and that of Pd–N is 2.096 Å. The bite angle of P–Pd–N is 96.74°. The other corresponding four η^3-allyl Pd(II) complexes with PN-ligands show no significant difference in the backbone structure of the binaphthyl moiety and phosphine part (see the ESI). Therefore, we focused our attention only on the oxazoline parts of these complexes. PN-ligands **3** and **4** have the ability to induce high enantioselectivity by virtue of the Me-group on the upper-side of the oxazoline. This *equatorial* methyl moiety directs toward the coordination site of substrates (*i.e.* the allyl moiety in this complex). On the other hand, the lower-side Me group as seen in PN-ligand **5** is less effective in order to obtain high enantioselectivity, because the direction of the *axial* Me-group is to the opposite side of the substrate coordination. Obviously, PN-ligand **6** with no methyl-substitution is not effective at all in view of the enantiofacial selectivity.



a) side view b) front view

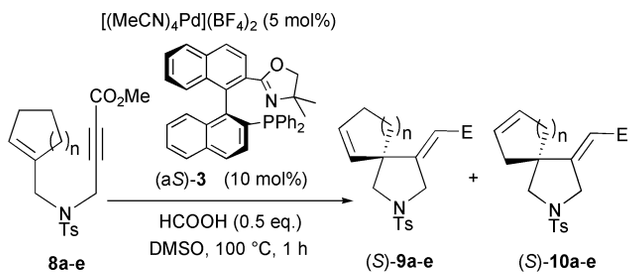
Fig. 2 ORTEP drawings of η^3-allyl Pd(II) complex **7** with PN-ligand **3**.

We next turned our attention to the syntheses of spiro-alkaloid analogues with PN-ligand (a*S*)-**3** having *double* methyl groups, because 5-membered ring formation of **2** with a quaternary carbon center[13] proceeds with extremely high enantioselectivity almost quantitatively. For 5-membered ring substrate **8a**, PN-ligand (a*S*)-**3** provided the corresponding spiro-product **9a** with high enantiomeric excess and in excellent yield (96% ee, 90%) for 1 h at 100 °C (Table 1, entry 1). Even for other common rings, spiro-cyclization proceeded smoothly, although accompanied with olefin-migration[14] products (**10a**–**c**). For **8b**, however, enantio-enriched **9b** was the major product (84% ee, 71%) with minor isomer **10b** (entry 2). Surprisingly enough, serious olefin-migration occurred in the case of **8c** leading to isomeric product **9c** with 95% ee in 93% yield (entry 3). Medium ring substrate **8d** also cyclized successfully, to afford **10d** (91% ee) as the major product and **9d** (92% ee) as the minor one (entry 4). For the large ring system, spiro-cyclization of 15-membered ring **8e** proceeded successfully without olefin-migration, to afford the sole product **9e** in 84% ee almost quantitatively (entry 5).

Further spiro-cyclization was executed on pyran substrate **11**, showing the special advantage of no olefin-migration. The cyclization of **11** with PN-ligand (a*S*)-**3** proceeded smoothly, to give the corresponding spiro-pyran **12** in 93% ee and almost quantitative yield (eqn. (2)). The structure of **12** was also confirmed by X-ray analysis. Spiro-pyran **12** is rich in functional groups such as conjugated ester, vinyl ether (pyran) and sulfonylamide. This result reflects the high potential of the cationic Pd(II) complexes with PN-ligand (a*S*)-**3** in the syntheses of heterocycles including alkaloids.

In conclusion, we have established a highly efficient alkaloid synthesis from 1,6-enynes catalyzed by a cationic chiral palladium(II) complex of the PN-ligand with an *achiral gem*-dimethyl oxazoline unit. A wide variety of spiro compounds, from common to large membered rings, were synthesized with high to excellent enantioselectivities in high yields.

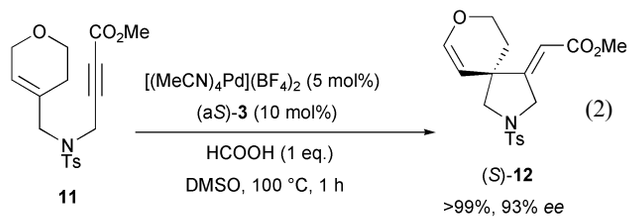
Table 1 Spiro-alkaloid synthesis by ene-type cyclization



8a-e (*S*)-**9a-e** (*S*)-**10a-e**

5-15 memb.

Entry	Substrate	Yields[%] (% ee) **9**	**10**
1	**8a**	90(96)	9(−)
2	**8b**	71(84)	29(35)
3	**8c**	6(95)	93(95)
4	**8d**	25(92)	70(91)
5	**8e**	>95(84)	0(−)



11 (*S*)-**12**

>99%, 93% *ee*

Experimental

General procedure of ene-type spiro-cyclization catalyzed by cationic Pd(II) complex with PN-ligand: Thoroughly degassed dimethyl sulfoxide (DMSO) (3.0 mL) was injected under argon into a Pyrex Schlenk tube containing $[(MeCN)_4Pd](BF_4)_2$ (11.1 mg, 0.025 mmol) and PN-ligand (a*S*)-**3** (26.7 mg, 0.050 mmol), and this solution was stirred at room temperature for 5 min. Then **11** (181.5 mg, 0.50 mmol) and formic acid (18.8 μL, 0.50 mmol) were added and the tube was sealed with a screw cap. The mixture was stirred at 100 °C for 1 h. The reaction mixture was washed with brine, and the ether-extracted organic layer was evaporated *in vacuo* and the residue was purified by short column chromatography (neutral silica-gel, pentane–ether = 10 : 1) to afford (*S*)-**12** in 93% ee quantitatively. $[\alpha]^{29}$(Na 589 nm) = +76.008 (c = 0.850 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (m, 1H), 2.05 (m, 1H), 2.43 (s, 3H), 2.69 (d, J = 9.6 Hz, 1H), 3.46 (d, J = 9.6 Hz, 1H), 3.68 (s, 3H), 3.85–4.10 (2H), 3.98 (dd, J = 18.3, 2.4 Hz, 1H), 4.23

(d, J = 6.3 Hz, 1H), 4.59 (dd, J = 18.3, 2.4 Hz, 1H), 5.73 (t, J = 3.0 Hz, 1H), 6.57 (d, J = 6.3 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H). HPLC analysis (DAICEL CHIRALCEL AD-H, eluent, hexane–2-propanol = 85 : 15, flow rate 1.0 mL min^{-1}, 28 °C, detection 254 nm light) t_R: 16.0 min ((*S*)-isomer) and 23.5 min ((*R*)-isomer).

Notes and references

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