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Palladium-catalyzed asymmetric Diels–Alder reactions with novel chiral imino-phosphine ligands

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Abstract—Palladium-catalyzed asymmetric Diels–Alder reactions have been achieved with considerably high enantioselectivity by using chiral imino-phosphine ligands derived from (1*S*,4*R*)-(+)-fenchone, (1*R*,2*R*,5*R*)-(+)-2-hydroxy-3-pinanone derivatives, (1*S*,5*R*)-(−)-menthone, (1*R*,4*R*)-(+)-camphor, and (1*S*)-(+)-ketopinic acid. A mechanism for the asymmetric induction is proposed on the basis of the stereochemical outcome of the reactions.

The asymmetric Diels–Alder reaction has been widely used as a useful method for the enantio- and diastereoselective construction of six-membered ring compounds.[1] A number of asymmetric Diels–Alder reactions have been developed so far mostly with the use of Lewis acidic catalysts[2] such as aluminum,[3] silicon,[4] titanium,[5] boron,[6] zinc,[7,8] magnesium derivatives[8,9] and so on. Currently, much attention is being devoted to more efficient catalytic asymmetric Diels–Alder reactions with transition metal catalysts such as chromium,[10] iron,[11] cobalt,[12] copper,[13] ruthenium[14] and rhodium,[15] and lanthanide catalysts[16] and various chiral ligands suitable for the catalysis are being developed. However, few precedents of asymmetric Diels–Alder reactions with palladium catalysts[17] have appeared. We wish to communicate herein novel palladium-catalyzed asymmetric Diels–Alder reactions with new chiral imino-phosphine ligands.

Chiral imino-phosphine ligands **4**,[18] **7**, **8**, **9**[18] and **10** were derived from readily commercially available (+)-fenchone **2**, (+)-2-hydroxy-3-pinanone **5**, (−)-menthone, (+)-camphor, and (+)-ketopinic acid, respectively, as follows. Imine **3** was prepared in 68% yield by dehydration of 2-bromoaniline **1** and (+)-fenchone **2** in the presence of titanium tetrachloride (0.6 equiv.) in refluxing toluene over 12 h with Dean–Stark apparatus. Lithiation of the bromo compound **3** with *n*-butyllithium followed by phosphinylation with chlorodiphenylphosphine gave **4** in 57% yield.

Dehydration of **1** with (1*R*,2*R*,5*R*)-(+)-2-hydroxy-3-pinanone **5** was carried out in a similar way as described above by refluxing in benzene in the presence of boron trifluoride etherate (0.6 equiv.) and 4 Å molecular sieves, providing imine **6a**, which was alkylated with dimethyl sulfate or benzyl bromide using sodium hydride as a base to give **6b** and **6c** in good yields (80 and 70%, respectively). Phosphinylation of **6a**–**c** with chlorodiphenylphosphine was executed in the same way as mentioned above to give **7a**–**c**. Imines **8**, **9**, and **10** were obtained from (−)-menthone, (+)-camphor and (+)-ketopinic acid by similar procedures to those described for **4** (Scheme 1).

The geometry of the imino function in **7a** and **7b** thus obtained was clearly determined by the NOESY NMR spectral analysis: an NOE effect was observed between the hydrogen atoms at C(4) of the pinanone-derived part and the aromatic hydrogen atom adjacent to the imino group in **7a** and **7b**, which was determined by COSY in the NMR spectrum; however, no NOE effect was observed between the methyl substituent at C(2) and the aromatic hydrogen atom. Similarly, the imino group in **9** was determined to have (*E*)-geometry from the NOESY analysis, as shown in Fig. 1.

The chiral imino-phosphine ligands reported here did not catalyze asymmetric Diels–Alder reactions with Lewis acid catalysts such as $Mg(OTf)_2$ and $Cu(OTf)_2$, owing to their considerably high Lewis basicity. It should be noted, however, that the imino-phosphines were found to be useful as chiral ligands in palladium-catalyzed Diels–Alder reactions.

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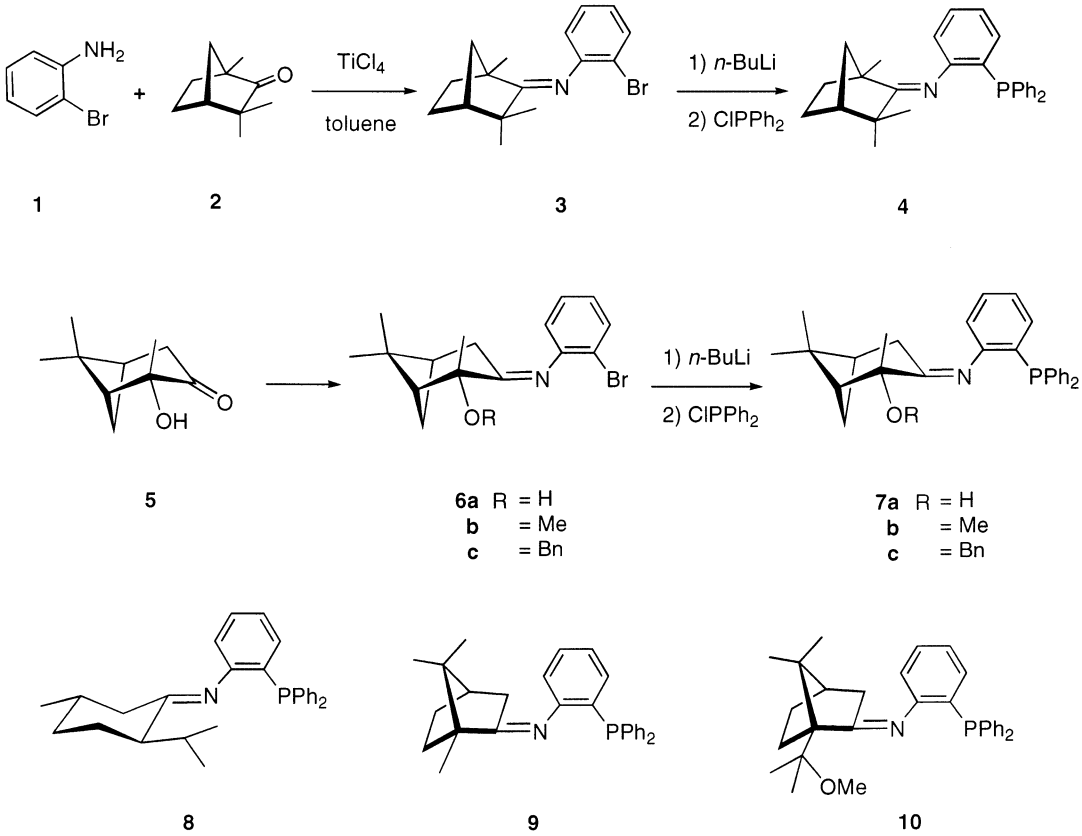


Scheme 1.

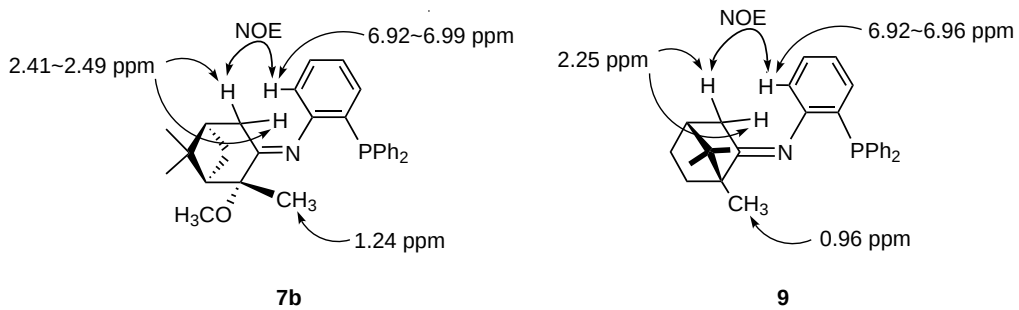


Figure 1.

Palladium complexes **11** and **12** were prepared by the reaction of the imino-phosphines **7** and **9** with $PdCl_2{\cdot}(CH_3CN)_2$ in methanol under reflux for 6 h (Fig. 2).

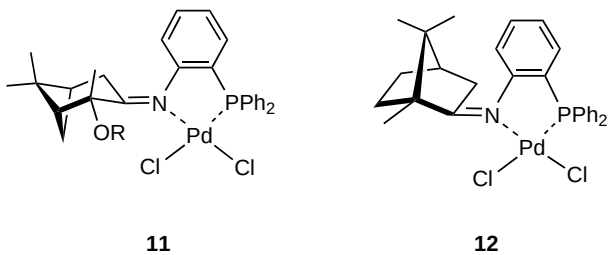


Figure 2.

No cycloaddition reaction occurred with these chloropalladium complexes. Therefore, exchange of the counter ion (Cl^-) with other anions was required to achieve a high level of the catalytic cycle in chemical yield and enantioselectivity. The counter ion (Cl^-) of the palladium complexes was exchanged with hexafluoroantimonate, perchlorate and trifluoromethanesulfonate ion by treating **11** and **12** with $AgSbF_6$, $AgClO_4$ and AgOTf in dichloromethane at room temperature for 1 h. The Diels–Alder reactions of **13** with cyclopentadiene **14** were carried out at −78 to −20°C in the presence of the palladium complexes (20 mol%) obtained above to afford optically active Diels–Alder adducts. The results obtained under various reaction conditions are summarized in Table 1.

Table 1. Studies on the palladium-catalyzed asymmetric Diels–Alder reactions with chiral imino-phosphine ligands[a]

Entry	Ligand	Counter ion	Solvent	Temp. (°C)	Time (h)	Yield (%)	*endo*/*exo* **15a**/**15b**	E.e. (%) of **15a**
1	**4** (20)	SbF_6	CH_2Cl_2	−20	6	92	89/11	54 (*S*)
2	**4** (20)	SbF_6	CH_2Cl_2	−78	8	89	95/5	72 (*S*)
3	**4** (20)	ClO_4	CH_2Cl_2	−78	14	75	95/5	55 (*S*)
4	**4** (20)	OTf	CH_2Cl_2	−78	36	68	94/6	43 (*S*)
5	**7a** (20)	SbF_6	CH_2Cl_2	−78	111	6	94/6	4 (*R*)
6	**7b** (20)	SbF_6	CH_2Cl_2	−78	16	74	85/15	44 (*R*)
7	**7b** (20)	ClO_4	CH_2Cl_2	−78	24	71	85/15	37 (*R*)
8	**7c** (20)	SbF_6	CH_2Cl_2	−78	8	77	88/12	39 (*R*)
9	**7c** (20)	ClO_4	CH_2Cl_2	−78	24	83	89/11	46 (*R*)
10	**8** (20)	SbF_6	CH_2Cl_2	−78	8	94	87/13	48 (*S*)
11	**8** (20)	ClO_4	CH_2Cl_2	−78	12	91	85/15	41 (*S*)
12	**8** (20)	OTf	CH_2Cl_2	−78	28	73	88/12	37 (*S*)
13	**9** (20)	SbF_6	CH_2Cl_2	−20	6	98	91/9	66 (*S*)
14	**9** (10)	SbF_6	CH_2Cl_2	−78	24	68	92/8	53 (*S*)
15	**9** (20)	SbF_6	CH_2Cl_2	−78	8	99	93/7	84 (*S*)
16	**9** (30)	SbF_6	CH_2Cl_2	−78	8	96	91/9	79 (*S*)
17	**9** (20)	ClO_4	CH_2Cl_2	−78	18	95	94/6	58 (*S*)
18	**9** (20)	OTf	CH_2Cl_2	−78	24	75	93/7	37 (*S*)
19	**9** (20)	SbF_6	Toluene	−78	36	71	83/17	32 (*S*)
20	**9** (20)	SbF_6	THF	−78	36	45	83/17	9 (*S*)
21	**9** (20)	SbF_6	Et_2O	−78	36	46	80/20	71 (*S*)
22	**9** (20)	SbF_6	$C_2H_5NO_2$	−78	36	80	94/6	83 (*S*)
23	**10** (20)	SbF_6	CH_2Cl_2	−78	36	81	83/17	75 (*S*)
24	**10** (20)	OTf	CH_2Cl_2	−78	36	78	87/13	77 (*S*)

[a] The reactions of **13** with **14** (5.0 equiv.) were carried out in CH_2Cl_2 in the presence of palladium complexes PdX_2 (X = SbF_6, ClO_4, OTf), which were prepared by reacting ligands **4** and **7**–**10** with $PdCl_2(CH_3CN)_2$ under reflux in MeOH for 6 h in the presence of AgX.

As listed in Table 1, the *endo* adduct **15a** was preferentially formed with high diastereoselectivity in every case (Scheme 2).

The solvent effects in the Diels–Alder reactions were studied. Among the solvent examined (CH_2Cl_2, toluene, THF, Et_2O and $C_2H_5NO_2$), CH_2Cl_2 and $C_2H_5NO_2$ were the most effective for achieving high enantioselectivity. The use of CH_2Cl_2 as solvent provided the highest chemical yield, as shown in Table 1.

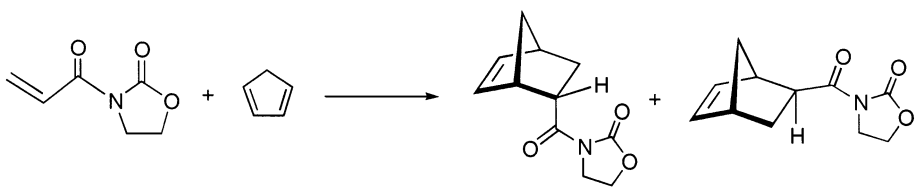
The unambiguous effects of the counter ion in the palladium complex are demonstrated in Table 1. The use of perchlorate or trifluoromethanesulfonate as a counter ion resulted in lower enantioselectivity. On the use of **7a** and **7c** as ligands, no cycloaddition reaction proceeded with trifluoromethanesulfonate. It should be noted that the hexafluoroantimonate ion was the most effective for achieving high enantioselectivity.

Very high enantioselectivity was obtained by using **4**, **9** or **10** as a ligand with hexafluoroantimonate: the highest enantioselectivity (84%) of (*S*)-**15a** was achieved with **9**.

The use of **10** derived from (1*S*)-(+)-ketopinic acid as a chiral ligand provided a slightly lower enantioselectivity (75 and 77%), compared to that induced by the camphor-derived ligand **9**.

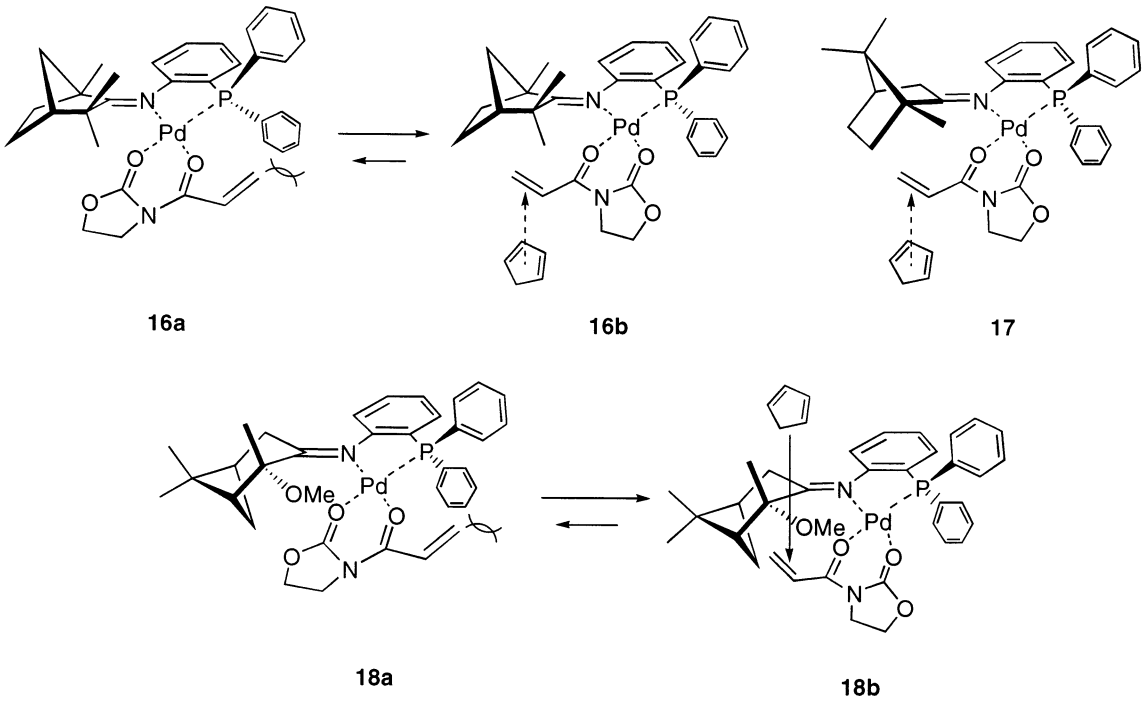
In the case of (+)-pinanone derivatives, the presence of a hydroxy function in the ligand dramatically decreased the reactivity.

The mechanism of the asymmetric induction with chiral imino-phosphine ligands is rationalized on the basis of the stereochemical outcome. In view of the conformation of the imino palladium complex derived from (+)-fenchone and the substrate **13**, the product **16b** would be favored over **16a** because of the existence of steric compression between the vinyl group in the substrate and the diphenyl substituents on the phosphine function in **16a**. Cyclopentadiene attacks the acryloyl olefin from the *Re*-face in **16b** preferentially in an *endo*



13 **14** (*S*)-*endo*-**15a** (*S*)-*exo*-**15b**

Scheme 2.



Scheme 3.

fashion, providing (*S*)-*endo*-**15a** as the main product with high diastereo- and enantioselectivity. In the case of the (+)-camphor-derived imino-phosphine ligand **9**, a similar reaction path via **17** provides mainly (*S*)-*endo*-**15a** with high enantioselectivity. With the chiral ligands **7a**–**c** derived from (+)-2-hydroxy-3-pinanone, the palladium complex **18b** would be preferred to **18a** due to the steric interference, as mentioned above, between the vinyl and diphenyl groups in **18a**. Thus, cyclopentadiene attacks the electrophilic olefin in **18b** from the sterically less crowded *Si*-face side in an *endo* fashion to give (*R*)-*endo*-**15a** as the main product (Scheme 3).

The readily available imino-phosphine ligands developed by us here were clearly demonstrated to serve as good chiral ligands in palladium-catalyzed asymmetric Diels–Alder reactions, which have been scarcely investigated so far, providing a highly efficient and useful methodology for the construction of six-membered carbocycles.

References

1. (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876–889; (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, Heidelberg, 1986; Vol. 4, pp. 261–306; (c) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741–761.
2. *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH; Weinheim, 2000; Vols 1 and 2.
3. (a) Rebiere, F.; Riant, O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1990**, *1*, 199–214 and references cited therein; (b) Naraku, G.; Hori, K.; Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **1977**, *38*, 8231–8232.
4. Mathieu, B.; Fays, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 9561–9564.
5. (a) Manickam, G.; Sundararajan, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2913–2925 and references cited therein; (b) Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1263–1265; (c) Sundarajan, G.; Prabagaran, N.; Varaghese, B. *Org. Lett.* **2001**, *3*, 1973–1976.
6. (a) Starmans, W. A. J.; Walgers, R. W. A.; Thijs, L.; Gelder, R.; de Smits, J. M. M.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 4991–5004 and references cited therein; (b) Ishihara, K.; Inanaga, K.; Kondo, S.; Funahashi, M.; Yamamoto, H. *Synlett* **1998**, 1053–1056.
7. Crosigani, S.; Desimoni, G.; Faita, G.; Filippone, S.; Mortoni, A.; Righetti, P. P.; Zema, M. *Tetrahedron Lett.* **1999**, *40*, 7007–7010.
8. Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron* **1998**, *54*, 15721–15730 and references cited therein.
9. Honda, Y.; Date, T.; Hiramatsu, H.; Yamauchi, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1411–1412.
10. Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, *51*, 845–851 and references cited therein.
11. Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728–729.
12. Li, L.-S.; Wu, Y.; Hu, Y.-J.; Xia, L.-J.; Wu, Y.-L. *Tetrahedron: Asymmetry* **1998**, *9*, 2271–2277.
13. Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335 and references cited therein.
14. (a) Faller, J. W.; Smart, C. J. *Tetrahedron Lett.* **1989**, 1189–1192; (b) Mihara, J.; Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1999**, 1160–1162.
15. Gilebertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075–2078 and references cited therein.

16. (a) Hamamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 79–80; (b) Saito, T.; Kawamura, M.; Nishimura, J. *Tetrahedron Lett*. **1997**, *38*, 3231–3234; (c) Nishida, A.; Yamanaka, M.; Nakagawa, M. *Tetrahedron Lett*. **1999**, *40*, 1555–1558.
17. (a) Oi, S.; Kashiwagi, K.; Inoue, Y. *Tetrahedron Lett*. **1998**, *39*, 6253–6256; (b) Ghosh, A. K.; Matsuda, H. *Org*. *Lett*. **1999**, *1*, 2157–2159.
18. Suzuki, Y.; Ogata, Y.; Hiroi, K. *Tetrahedron: Asymmetry* **1999**, *10*, 1219–1222.