Palladium-catalysed asymmetric [4 + 2] cycloaddition of vinylallene with 1,3-diene

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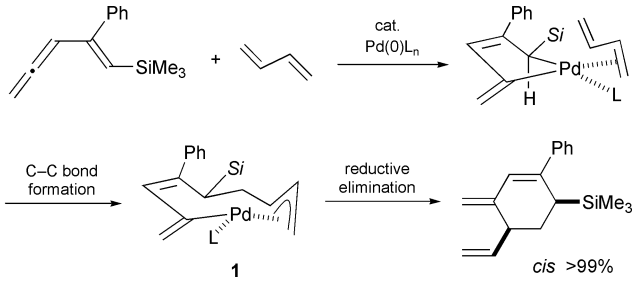
A catalytic asymmetric [4 + 2] cycloaddition reaction of a vinylallene with buta-1,3-diene was developed in which a palladium complex modified by a ferrocene-derived chiral monophosphine ligand acted as a template transferring chirality to the product.

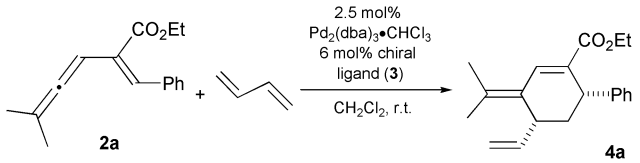
Cycloaddition reactions are among the most powerful methods for the rapid construction of carbocycles and heterocycles alike.[1] The [4 + 2] cycloaddition is most widely used to build six-membered ring carbon skeletons. However, strenuous reaction conditions are required for the combination of 1,3-dienes and dienophiles lacking electron-withdrawing or -donating substituents, which limits the range of the synthetic utility. The use of transition metal complexes as the promoter[2] provides considerably wider substrate scope. The transition metal acts as the template bringing the unsaturated substrates together in an array to promote the cycloaddition reaction. We have developed the palladium-catalysed directed intermolecular [4 + 2] cycloaddition between a vinylallene and an ordinary 1,3-diene.[3–5] The initially formed palladacyclopentene intermediate couples with a 1,3-diene before undergoing a ring-flipping isomerization, resulting in a highly stereospecific reaction [eqn. (1)]. We anticipated that a palladium complex modified by a chiral ligand would possibly differentiate the enantiofaces of vinylallene in its s-*cis* form and that this differentiation would be directly transferred to the product. This paper describes the catalytic asymmetric [4 + 2] cycloaddition of a vinylallene[6] with buta-1,3-diene which employs a palladium complex modified by a ferrocene-derived chiral monophosphine ligand as a template.

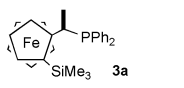
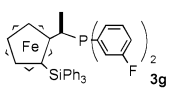
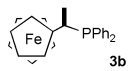
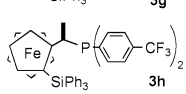
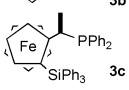
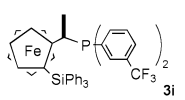
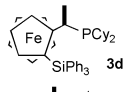
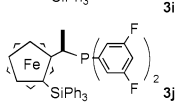
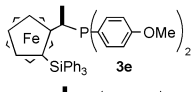
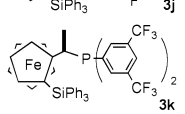
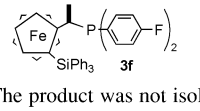


(1)

Initially, a variety of chiral phosphines were screened in the standard test cycloaddition reaction using vinylallene **2a** and buta-1,3-diene (excess). The catalyst complex was prepared by treatment of $[Pd_2(dba)_3{\cdot}CHCl_3]$ with a chiral phosphine ligand *in situ*. Highly reputed bidentate chiral diphosphine ligands like DuPHOS (1,2-bis[2,5-dimethylphospholanyl]benzene) and CHIRAPHOS (2,3-bis(diphenylphosphino)butane gave only low enantioselectivities. No reaction occurred with BINAP. Since our proposed mechanism involves a square planar palladium(II) intermediate **1** in which three of the four coordination sites are occupied by the cycloaddition partners, we supposed that monodentate ligands would be more effective transmitters of chirality. Whereas MOP (2-diphenylphosphino-1,1′-binaphthalene) afforded only 15% ee, a better result was

Table 1 Asymmetric induction in palladium-catalysed directed [4 + 2] cycloaddition of **2a** with buta-1,3-diene



Entry	Chiral ligand	Isolated yield (%) Enantioselectivity	Entry	Chiral ligand	Isolated yield (%) Enantioselectivity
1	 **3a**	90 47 % ee	7	 **3g**	85 47 % ee
2	 **3b**	62 6 % ee	8	 **3h**	77 52 % ee
3	 **3c**	82 51 % ee	9	 **3i**	87 64 % ee
4	 **3d**	80 [a] 18 % ee	10	 **3j**	74 71 % ee
5	 **3e**	30 [a] 40 % ee	11	 **3k**	85 83 % ee
6	 **3f**	90 63 % ee			

[a] Conversion of **2a**. The product was not isolated.

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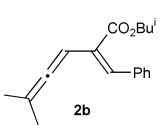
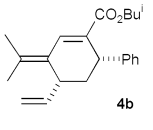
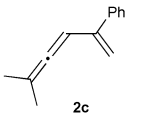
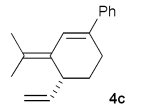
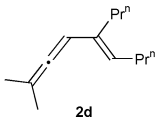
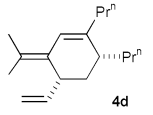
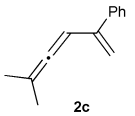
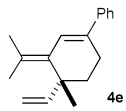
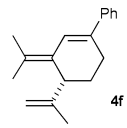
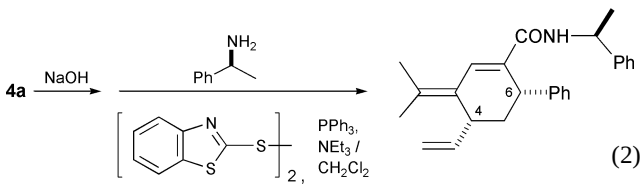
Table 2 Palladium-catalysed asymmetric [4 + 2] cycloaddition of vinylallenes (**2**) with 1,3-dienes[a]

Entry	Vinylallene (**2**)	1,3-Diene	Product (**4**)[b]	Isolated yield (%) Enantioselectivity
1	 **2b**		 **4b**	63 82 % ee
2	 **2c**		 **4c**	89 77 % ee
3	 **2d**		 **4d**	76 52 % ee
4	 **2c**		 **4e**  **4f**	89 (**4e**:**4f** = 81:19)[c] **4e** 63 % ee **4f** 65 % ee

[a] The reaction was carried out using 5 mol% of palladium(0) and 6 mol% of **3k** in CH_2Cl_2 at rt. [b] The absolute configuration was not determined. [c] The ratio was determined by HPLC.

obtained with PPFA (2-(1-dimethylaminoethyl)-1-diphenylphosphinoferrocene 27% ee). Among ferrocene-derived ligands, the monodentate phosphine ligand **3a** gave a moderate selectivity (Table 1, entry 1). This result directed our detailed investigation to ligands of analogous structures. The ligands **3b**–**k** listed in Table 1 were prepared‡ and applied to the test reaction. Ligand **3b** lacking a silyl group at the *ortho* position gave a low selectivity (entry 2). The triphenylsilyl-substituted ligand **3c** gave slightly better selectivity than the trimethylsilyl-substituted ligand **3a** (entry 3). Diphenylphosphine-substituted ligands were significantly more effective than dicyclohexylphosphine derivatives (entry 4). The effect of the electronic nature of the diarylphosphinyl group was examined in detail (entries 5–11). Ligands having an electron-withdrawing group gave comparable or better selectivities than **3c**. In particular, the phosphine possessing two 3,5-bis(trifluoromethyl)phenyl groups (**3k**) afforded the highest enantioselectivity of 83% ee.§¶ Although solvents other than DCM were also screened, little effect was observed in terms of the enantioselectivity. The absolute stereochemistry of the major enantiomer was determined to be (4*R*,6*S*) by an X-ray crystallographic study of the amide derived from **4a** and (*S*)-1-phenylethylamine [eqn. (2)].



(2)

Thus, **3k** proved to be the ligand of choice, and was applied to the reactions of other vinylallenes with buta-1,3-dienes.‖ The [4 + 2] cycloadducts were produced with moderate to good enantioselectivities in good yields (Table 2). Note that a useful level of asymmetric induction was obtained in the case of **2c** lacking any coordinating heteroatom functionalities (entry 2). For the unsymmetrical 1,3-diene (2-methylbuta-1,3-diene), incorporation of the more substituted C–C double bond was favoured to afford **4e** as the predominant product (entry 4).

A number of highly successful asymmetric [4 + 2] cycloadditions have been reported in which the carbonyl group of an electron-deficient dienophile coordinates to a chiral Lewis acid to induce an excellent enantioselection.[1] On the other hand, it is difficult to gain stereocontrol over a substrate lacking coordinating heteroatom functionalities. The asymmetric [4 + 2] cycloaddition documented herein presents a promising new example which may be applied to such unactivated substrates. The full potential of this new process remains to be elucidated.

Notes and references

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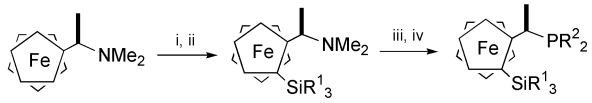
‡ The chiral ferrocenyl phosphines **3** were prepared as follows [eqn. (3)]:



(3)

i, BuLi; ii, Cl-SiR^1_3; iii, Ac_2O; iv, R^2_2P-H /AcOH

ortho-lithiation of (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine (**5**) with butyllithium followed by treatment with chlorosilane afforded (*S*)-1-silyl-2-[(*R*)-1-(dimethylamino)ethyl]ferrocene **6**. A diarylphosphinyl group was then introduced by successive treatment of **6** with excess acetic anhydride, and then with diarylphosphine in acetic acid to furnish (*S*)-1-silyl-2-[(*R*)-1-(diarylphosphino)ethyl]ferrocene **3**.

§ The experimental procedure for the formation of **4a** is as follows: to a mixture of $[Pd_2(dba)_3{\cdot}CHCl_3]$ (3.4 mg, 3.3 μmol) and the ligand **3k** (7.4 mg, 7.9 μmol) in CH_2Cl_2 (3 mL) under N_2 at rt were successively added buta-1,3-diene (4.4 M in CH_2Cl_2, 0.3 mL, 1.32 mmol) and the vinylallene **2a** (32.0 mg, 0.132 mmol). The reaction was complete within 10 min. The mixture was evaporated under vacuum, and the residue was subjected to preparative TLC (silica gel, ether–hexane = 1:10) to afford **4a** (33.2 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ + 12.3 (*c* 1.0, $CHCl_3$). The enantioselectivity was determined to be 83% ee by chiral HPLC analysis [SUMICHIRAL OA-2500-I (4.0 × 250 mm), 1.0 mL min^{-1}, hexane–$ClCH_2CH_2Cl$–EtOH = 2000:20:1, (4*S*,6*R*) t_1 = 17 min, (4*R*,6*S*) t_2 = 19 min].

¶ Platinum was also tested as a metal using $Pt(cod)_2$ and provided 77% ee. However, platinum suffered from low conversion.

‖ Cyclohexa-1,3-diene failed to undergo the cycloaddition, suggesting that 1,3-diene reacts in its s-*cis* form as shown in eqn. (1).

1 For reviews, see: (*a*) W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Oxford, 1990; (*b*) *Advances in Cycloaddition*, ed. D. P. Curran, Vol. 1–3, JAI Press, Connecticut, 1994.

2 For a review of transition metal-mediated cycloaddition reactions, see: M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49.

3 M. Murakami, K. Itami and Y. Ito, *J. Am. Chem. Soc.*, 1997, **119**, 7163.

4 For thermal Diels-Alder reactions of vinylallenes, see: J. Spino, C. Thibault and S. Gingras, *J. Org. Chem.*, 1998, **63**, 5283; U. Koop, G. Handke and N. Krause, *Liebigs Ann.*, 1996, 1487 and refs. therein.

5 For other examples of transition metal-catalysed cycloaddition reactions of vinylallenes, see: (*a*) H. Siegel, H. Hopf, A. Germer and P. Binger, *Chem. Ber.*, 1978, **111**, 3112; (*b*) T. Mandai, S. Suzuki, A. Ikawa, T. Murakami, M. Kawada and J. Tsuji, *Tetrahedron Lett.*, 1991, **32**, 7687; (*c*) M. S. Sigman and B. E. Eaton, *J. Am. Chem. Soc.*, 1996, **118**, 11 783; (*d*) T. Mandai, J. Tsuji and Y. Tsujiguchi, *J. Am. Chem. Soc.*, 1993, **115**, 5865; (*e*) C. Darcel, C. Bruneau and P. H. Dixneuf, *Synlett*, 1996, 218; (*f*) M. Murakami, K. Itami and Y. Ito, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2691; (*g*) M. Murakami, K. Itami and Y. Ito, *J. Am. Chem. Soc.*, 1997, **119**, 2950; (*h*) M. Murakami, M. Ubukata, K. Itami and Y. Ito, *Angew. Chem., Int. Ed.*, 1998, **37**, 2248; (*i*) M. Murakami, K. Itami and Y. Ito, *Organometallics*, 1999, **18**, 1326; (*j*) M. Murakami, K. Itami and Y. Ito, *J. Am. Chem. Soc.*, 1999, **121**, 4340; (*k*) M. Murakami, K. Itami and Y. Ito, *Angew. Chem., Int. Ed.*, 1998, **37**, 3418; (*l*) M. Murakami, K. Itami and Y. Ito, *Synlett*, 1999, 951.

6 For allene-participating [4 + 2] cycloaddition reactions which involve chirality transfer, see: (*a*) I. Ikeda, K. Honda, E. Osawa, M. Shiro, M. Aso and K. Kanematsu, *J. Org. Chem.*, 1996, **61**, 2031; (*b*) P. A. Wender, T. E. Jenkins and S. Suzuki, *J. Am. Chem. Soc.*, 1995, **117**, 1843; (*c*) X. Wang, J. Donovalova, A. Hollis, D. Johnson, A. Rodriguez, G. D. Kennedy, G. Krishnan and H. Banks, *J. Heterocycl. Chem.*, 1994, **31**, 871.