ORGANIC LETTERS

2005
Vol. 7, No. 23
5151−5154

Highly Regio- and Enantioselective Palladium-Catalyzed Allylic Alkylation and Amination of Dienyl Esters with 1,1′-*P*,*N*-Ferrocene Ligands

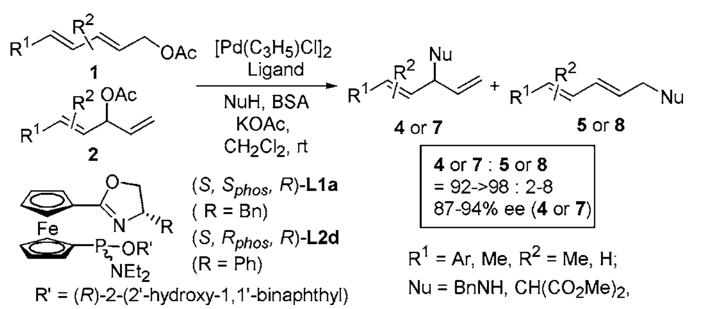
Wen-Hua Zheng,† Na Sun,‡ and Xue-Long Hou*,†,‡

State Key Laboratory of Organometallic Chemistry and Shanghai−Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

xlhou@mail.sioc.ac.cn

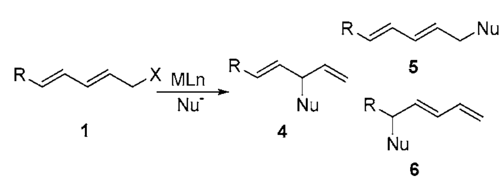
Received August 5, 2005

ABSTRACT



Pd-catalyzed asymmetric allylic alkylation of dienyl acetates 1 and amination of allyl acetates 2 provides the corresponding chiral products in high regio- and enantioselectivities using 1,1′-*P*,*N*-ferrocenes L1a and L2d as ligands, respectively.

The past decades have witnessed great success in Pd-catalyzed asymmetric allylic substitution reactions using a variety of substrates and reagents to form diversified types of bonds with excellent enantioselectivity. Today, this reaction is one of the most important carbon−carbon bond-forming processes in asymmetric catalysis and a powerful tool in organic synthesis.[1] Although significant progress has been made recent years in obtaining good regio- and enantioselectivity of Pd-catalyzed allylic substitution reactions of monosubstituted allyl substrates,[2,3] reaction of polyenyl esters, a special variant of monosubstituted allylic esters, mainly provided linear products.[4] Many efforts have been made to address the issue of regioselectivity as well as enantioselectivity of allylic substitution reactions of polyenyl esters employing other metal complexes. The first example was provided by Trost.[5] When a chiral Mo complex was used, high regio- and enantioselectivities were achieved; the ratio of branched and linear products **4** and **5** was (6−49):1 with 86−99% ee for **4** (eq 1).[5] Takeuchi realized perfect



(eq. 1)

regioselectivity in the same reaction using $[Ir(COD)Cl]_2$ and $P(OPh)_3$ as catalyst; in most cases, the reaction afforded branched product **4** only.[6] Recently, Helmchen reported an

† State Key Laboratory of Organometallic Chemistry.
‡ Shanghai−Hong Kong Joint Laboratory in Chemical Synthesis.
(1) For some reviews: (a) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, Chapter 24. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

10.1021/ol051882f CCC: $30.25 © 2005 American Chemical Society
Published on Web 10/19/2005

asymmetric version of Ir-catalyzed alkylation and amination reaction.[7] Excellent regioselectivity in favor of branched products **4** with 96% ee in the alkylation reaction and up to 99:1 for the ratio of **4** and **5** with 97% ee for **4** in the amination reaction was obtained. To the best of our knowledge, there is no report on the asymmetric allylic alkylation and amination reactions of polyenyl esters using chiral Pd complex as catalyst.

Recently, we developed several ferrocene-based chiral ligands and used them successfully in asymmetric catalysis.[3,8] High regio- and enantioselectivity were realized in Pd-catalyzed allylic alkylation and amination reactions of monosubstituted allyl substrates when 1,1′-*P*.*N*-ligands were used.[3] Further studies showed that they are also good ligands in Pd-catalyzed allylic substitution reactions of polyenyl esters. Herein, we report our preliminary results for these Pd-catalyzed highly regio- and enantioselective allylic alkylation and amination reactions using polyenyl esters as substrates.

Initially, the reaction of pentadienyl acetate **1a** with dimethyl malonate was carried out using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and (*S*, S_{phos}, *R*)-ligands **L1**[3a,9,10] as catalyst because our previous work demonstrated that 1,1′-*P*,*N*-ferrocene ligands with such a combination of three chiral elements gave better regio- and enantioselectivity in the allylic alkylation of monosubstituted substrates (Scheme 1).[3] The branched allyl substrate **2a** and pentadienyl carbonate **3a** were also investigated. The results are given in Table 1.

Scheme 1

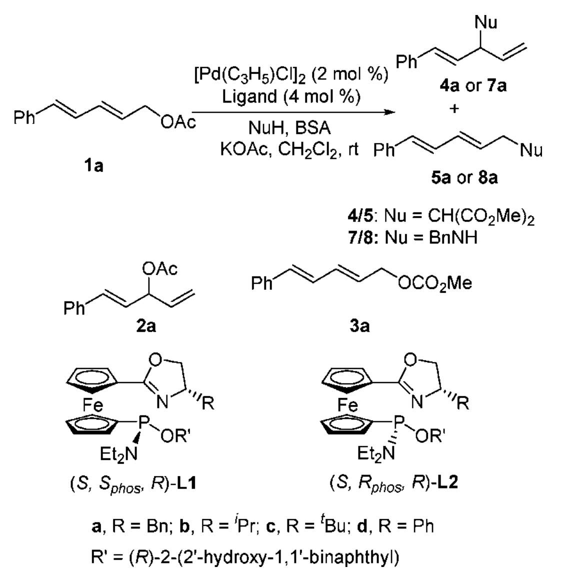


Table 1. Pd-Catalyzed Regio- and Enantioselective Allylic Substitution Reaction of **1a** with Various Ligands **L1** and **L2**[a]

entry	S[b]	L[b]	time (h)	yield (%) of **4+5** or **7+8**[c]	**4a/5a** or **7a/8a**[d]	ee (%)[e]
1	**1a**	**L1a**	0.5	80	98/2	**4a**: 92
2	**1a**	**L1b**	72	77	96/4	**4a**: 79
3	**1a**	**L1c**	72	41	94/6	**4a**: 37
4	**1a**	**L1d**	10	92	98/2	**4a**: 89
5	**2a**	**L1a**	0.5	81	96/4	**4a**: 60
6	**3a**	**L1a**	0.5	77	95/5	**4a**: 92
7	**1a**	**L2a**	0.5	87	60/40	**4a**: 16
8	**2a**	**L2d**	3	85	>98/2	**7a**: 90
9	**2a**	**L2a**	3	88	73/27	**7a**: 90
10	**2a**	**L1b**	3	83	0/100	**7a**: –
11	**1a**	**L2d**	36	NR[f]		**7a**: –

[a] Molar ratio of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/KOAc/substrate/NuH/BSA = 2/4/6/100/300/300. [b] S = substrate, L = ligand. [c] Isolated yield base on substrate. [d] Determined by 300 MHz ^{1}H NMR of the crude product after preparative TLC. [e] Determined by chiral HPLC. [f] No reaction.

All reactions with substrates **1a**–**3a** afforded branched and linear products **4a** and **5a** with high regioselectivity in favor of branched **4a** (entries 1–7, Table 1). As a result of the

(2) (a) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun.* **1997**, 561. (b) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681. (c) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (d) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814. (e) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61. (f) Trost, B M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907. (g) Faller, J. W.; Wilt, J. C.; Parr, J. *Org. Lett.* **2004**, *6*, 1301. (h) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646. (i) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641.

(3) (a) You, S. L.; Zhu, X. Z.; Luo, Y. M.; Hou, X. L.; Dai, L. X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (b) Hou, X. L.; Na, S. *Org. Lett.* **2004**, *6*, 4399 (Corrections: *Org. Lett.* **2005**, *7*, 1435).

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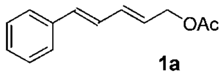
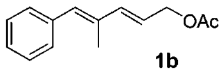
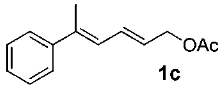
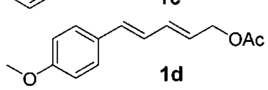
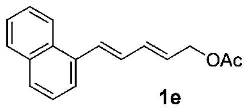
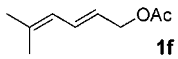
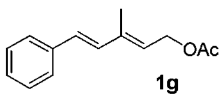
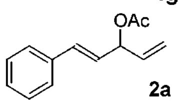
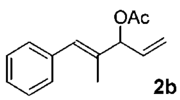
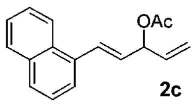
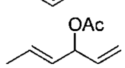
(6) Takeuchi, R.; Tanabe, K. *Angew. Chem., Int. Ed*. **2000**, *39*, 1975.

(7) (a) Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 116. (b) Lipowski, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595.

(8) (a) Dai, L. X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659. (b) Deng, W. P.; Hou, X. L.; Dai, L. X.; Dong, X. W. *Chem. Commun.* **2000**, 1483. (c) You, S. L.; Hou, X. L.; Dai, L. X.; Cao, B. X.; Sun, J. *Chem. Commun.* **2000**, 1933. (d) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. *Org. Lett.* **2001**, *3*, 149. (e) Tu, T.; Deng, W. P.; Hou, X. L.; Dai, L. X.; Dong, X. C. *Chem. Eur. J.* **2003**, *9*, 3073. (f) Tu, T.; Hou, X. L.; Dai, L. X. *Org. Lett.* **2003**, *5*, 3651.

(9) **Procedures for the synthesis of ligand L1a and L2a.**[10] **(a) Synthesis of 1-Diethylaminophosphino-1′[(*S*)-4-benzyl-2,5-oxazolinyl]ferrocene.** 1-Bromo-1′-[(*S*)-4-benzyl-2,5-oxazolinyl]ferrocene (2.54 g, 6 mmol)[11] was dissolved in freshly distilled THF (40 mL) under argon and cooled to −78 °C. At this tempreture, *n*-BuLi (4.2 mL, 6.6 mmol, 1.6 M in *n*-hexane) was added, and the resulting deep red solution was stirred for 20 min. Then, chlorodiethylaminophosphine (1.7 mL, 8 mmol) was added, and the resulting mixture was continually stirred and warmed to room temperature over 30 min. The reaction mixture was diluted with ether (20 mL), washed with distilled water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography on silica gel with ethyl acetate/petroleum/Et_3N (1:10:1) as eluent to give 2.02 g of 1-diethylaminophosphino-1′-[(*S*)-4-benzyl-2,5-oxazolinyl]ferrocene (65%) as a deep red oil: $[\alpha]^{20}_D = +2.9$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, $J = 7.0$ Hz, 12H), 2.68 (dd, $J = 9.2$, 13.8 Hz, 1H), 2.96–3.11 (m, 8H), 3.23 (dd, $J = 4.6$, 13.7 Hz, 1H), 4.04 (dd, $J = 7.5$, 8.0 Hz, 1H), 4.21–4.25 (m, 5H), 4.34 (m, 2H), 4.38–4.45 (m, 1H), 4.73 (m, 2H), 7.22–7.33 (m, 5H); ^{31}P NMR (161.92 MHz, $CDCl_3$) δ 89.32; MS (EI) *m/z* (rel) 519 (M^+, 12), 447 (100), 374 (43), 313 (28), 242 (28), 91 (10); IR (KBr) 2966 (m), 2930 (w), 1653 (s), 1481 (m), 1375 (m), 1187 (m), 1022 (s). Anal. Calcd for $C_{28}H_{38}N_3OPFe$: C, 64.74; H, 7.37; N, 8.09. Found: C, 65.18; H, 7.44; N, 8.43. **(b) Synthesis of (*S*)-1-Diethylamino[(*R*)-binaphthol]phosphite-1′-[(*S*)-4-benzyl-2,5-oxazolinyl]ferrocene L1a and (*R*)-1-Diethylamino[(*R*)-binaphthol]phosphite-1′-[(*S*)-4-benzyl-2,5-oxazolinyl]ferrocene L2a.** 1-Diethylaminophosphino-1′-[(*S*)-4-benzyl-2,5-oxazolinyl]ferrocene (519 mg, 1 mmol) and (*R*)-binaphthol (286 mg, 1 mmol) were dissolved in freshly distilled THF (40 mL) under argon. The reaction was completed after being refluxed for 12 h. The reaction mixture was condensed in vacuo, and the crude product was purified by flash chromatography on silica gel with ethyl acetate/petroleum/Et_3N (1:10:1) as an eluent to give (*S*, R_{phos}, *R*)-**L2a** (329

Table 2. Pd-Catalyzed Allylic Substitution Reactions of **1** and **2**[a]

entry	substrate	yield (%) 4+5 or 7+8[b]	4/5 or 7/8[c]	ee (%)[d]
1[e]	 **1a**	80	98/2	**4a**: 92
2[e]	 **1b**	89	94/6	**4b**: 93
3[e]	 **1c**	81	93/7	**4c**: 88
4[e]	 **1d**	79	98/2	**4d**: 87
5[e]	 **1e**	86	97/3	**4e**: 87
6[e]	 **1f**	82	96/4	**4f**: 91
7[e]	 **1g**	83	92/8	**4g**: 56
8[f]	 **2a**	85	>98/2	**7a**: 90
9[f]	 **2b**	80	>98/2	**7b**: 93
10[f]	 **2c**	79	94/6	**7c**: 94
11[f]	 **2d**	76	>98/2	**7d**: 88

[a] Molar ratio of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/KOAc/substrate/NuH/BSA = 2/4/6/100/300/300. [b] Isolated yield based on substrate. [c] Determined by 300 MHz ^{1}H NMR of the crude product after preparative TLC. [d] Determined by chiral HPLC. [e] **L1a** was used. [f] **L2d** was used.

reactions of monosubstituted allyl substrates,[3a] linear acetate **1a** and carbonate **3a** gave better regio- and enantioselectivities (entries 1 and 6, Table 1), while branched acetate **2a** afforded the product with only 60% ee although the regioselectivity remains good (entry 5, Table 1). Ligand (*S*, R_{phos}, *R*)-**L2a**[3a] was also tested. It can be seen from Table 1 that both regio- and enantioselectivity of the reactions using ligands (*S*, S_{phos}, *R*)-**L1a−d** are better than that using ligand (*S*, R_{phos}, *R*)-**L2a** (entries 1−4 vs entry 7, Table 1). Among the ligands tested, ligand **L1a** with benzyl as the substituent on the oxazoline ring provided better results for both the regio- and enantioselectivity (entries 1, Table 1). It should be pointed out that the reaction using **L1a** proceeded faster than that using ligands **L1b−d** (entry 1 vs entries 2−4). The study of the effect of additives showed that the reaction using LiCl[7] and Bu_4NF as additive gave almost the same regioselectivity but lower enantioselctivity (**4a**/**5a** = 96:4, 88% ee for **4a** using LiCl as additive, **4a**/**5a** = 94:6, 68% ee for **4a** using TBAF).

The amination reaction of pentadienyl acetate **1a** and branched allyl acetate **2a** with benzylamine was also carried out. As in the amination reaction of monosubstituted allyl substrates,[3a] better regio- and enantioselectivities were

mg, 45% yield) and (*S*, S_{phos}, *R*)-**L1a** (263 mg, 36% yield) by turn. (*S*, S_{phos}, *R*)-**L1a** as an orange solid: mp 154−155 °C; $[\alpha]^{20}_D = -357$ (*c*, 0.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (t, *J* = 7.0 Hz, 6H), 2.67 (dd, *J* = 9.1, 13.7 Hz, 1H), 2.86 (m, 4H), 3.18 (dd, *J* = 4.7, 13.7 Hz, 1H), 3.39 (m, 1H), 3.73 (m, 1H), 3.88 (m, 1H), 3.94 (m, 1H), 4.01 (t, *J* = 7.8 Hz, 1H), 4.05−4.13 (m, 2H), 4.18 (t, *J* = 8.6 Hz, 1H), 4.34−4.42 (m, 2H), 4.52 (m, 1H), 5.24 (br, 1H), 7.21−7.39 (m, 12H), 7.82−8.05 (m, 5H); ^{31}P NMR (161.92 MHz, $CDCl_3$) δ 127.86; MS (EI) *m/z* (rel) 732 (M^+, 2), 659 (42), 541 (100), 447 (20), 315 (27), 286 (74); IR (KBr) 3055 (w), 2966 (w), 1641 (s), 1588 (m), 1504 (m), 1458 (m), 1226 (s), 1023 (s). Anal. Calcd for $C_{44}H_{41}N_2O_3PFe$: C, 72.13; H, 5.64; N, 3.82. Found: C, 71.73; H, 5.94; N, 3.69. (*S*, R_{phos}, *R*)-**L2a** as an orange solid: mp 68−70 °C; $[\alpha]^{20}_D$ = 403 (*c*, 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, *J* = 7.0 Hz, 6H), 2.41−2.62 (m, 4H), 2.67 (dd, *J* = 8.9, 13.8 Hz, 1H), 3.17 (dd, *J* = 5.0, 13.7 Hz, 1H), 3.74 (m, 1H), 3.92 (m, 1H), 4.07 (dd, *J* = 7.2, 8.1 Hz, 1H), 4.29−4.33 (m, 3H), 4.41 (m, 1H), 4.57 (t, *J* = 1.2 Hz, 1H), 4.59−4.64 (m, 1H), 5.09 (t, *J* = 1.2 Hz, 1H), 7.11−7.41 (m, 12H), 7.79−8.03 (m, 5H), 9.25 (br, 1H); ^{31}P NMR (161.92 MHz, $CDCl_3$) δ 119.50; MS (EI) *m/z* (rel) 732 (M^+, 1), 659 (9), 541 (19), 447 (11), 315 (5), 286 (100); IR (KBr) 3055 (w), 2967 (w), 1639 (s), 1589 (m), 1504 (m), 1461 (m), 1232 (s), 1023 (s). Anal. Calcd for $C_{44}H_{41}N_2O_3PFe$: C, 72.13; H, 5.64; N, 3.82. Found: C, 72.00; H, 5.66; N, 3.85.

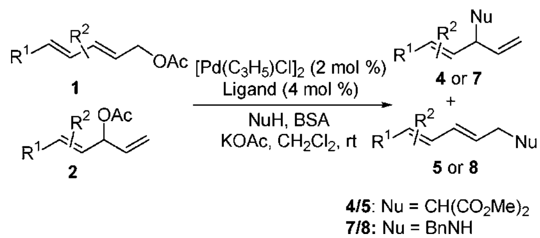
(10) For the synthesis of other ligands, see the Supporting Information of ref 3a.

(11) Chesney, A.; Bryce, M. R.; Chubb, R. W. J.; Batsanov, A. S.; Howard, J. A. K. *Synthesis* **1998**, 413.

provided when branched allyl acetate **2a** was used as substrate (entry 8 vs entry 11, Table 1). Among the ligands tested, ligand (*S*, R_{phos}, *R*) **L2d**[3a] is best (entry 8 vs entries 9 and 10, Table 1), while **L2a** was better than **L1b** (entry 9 vs entry 10, Table 1).

On the basis of the above results, alkylation reactions using (*S*, S_{phos}, *R*) **L1a** and amination reaction using (*S*, R_{phos}, *R*) **L2d** with a wide range of substrates **1** and **2** were carried out (Scheme 2, Table 2). All substrates, not only with aromatic substituents but also with alkyl substituents at the terminal position gave branched products in high regio- and enantioselectivities in both alkylation and amination reactions. The regioselectivity is between 92/8 and >98/2 in favor of branched products **4** and **7** with an ee value of 87−94% for **4** and **7** (Table 2). The only except is substrate **1g**, which gave product **4g** containing chiral quaternary carbon center and **5g** in the ratio of 92:8 with 56% ee for **4g** (entry 7, Table 2).[3b] The substituent on the distal double bond has no effect on the regio- and enantioselectivities of the reactions (entries 2, 3, and 9, Table 2). When the reaction of **1a** proceeded at 0 °C, the ee value of **4a** increased from 92% to 94%, and it increased further to 97% if the reaction was run at −20 °C. However, the reaction of all other substrates proceeded very slow at 0 °C.

Scheme 2



In summary, high regio- and enantioselctivities were realized in palladium-catalyzed allylic alkylation and amination reactions of dienyl acetate using 1,1′-*P*,*N*-ferrocene derivatives as ligands. These results demonstrated the usefulness of the ligands in further control of regio- and enantioselectivities of allylic substitution reactions.[3,8] Investigations on that why the alkylation and amination need different ligands and on the applications of these ligands in asymmetric catalysis are in progress.

Acknowledgment. This research was financially supported by the Major Basic Research Development Program (Grant No. G 200077506), National Natural Science Foundation of China, Chinese Academy of Sciences, and Shanghai Committee of Science and Technology. N.S. gratefully acknowledges the Hong Kong Croucher Foundation for a Studentship.

Supporting Information Available: General procedure for allylic alkylation and amination and spectral data for **4a**−**g** and **7a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051882F