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CHEMISTRY

Regiospecific and Stereoselective Alkylation of Allylic Substrates on Pd, Ir, and Rh Complexes with Chiral Phosphite Ligands

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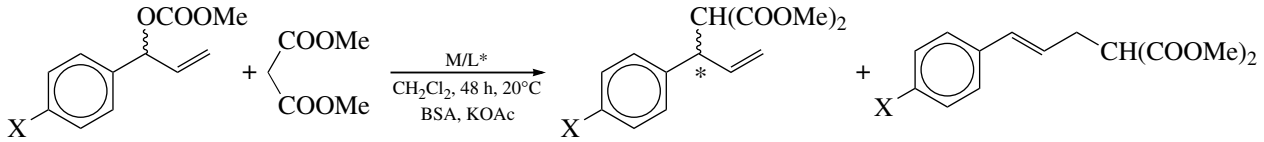
Substitution reactions in allylic systems by different nucleophiles catalyzed by transition metal complexes have been widely used in recent years in organic synthesis, including asymmetric synthesis [1]. Asymmetrically substituted allylic systems are the most general and important in synthetic practice. The substitution in allylic substrates containing, along with a leaving group, only one substituent at one of the terminal carbon atoms of the allylic system may be accompanied by allylic rearrangement to give, in the general case, a mixture of two products: linear and branched. The branched product contains an asymmetric center and, therefore, can exist as two enantiomers. When complexes with chiral ligands are used as catalysts, the regio- and stereoisomeric composition of the reaction products depends on the nature of both the chiral ligand and the transition metal. In recent years, in addition to palladium catalysis, catalysis by Rh, Ir, and other metals has been often used in allylation reactions [2–4]. The search for new types of chiral ligands, especially phosphite ones, is taking place in parallel. Therefore, it is an important problem to reveal factors affecting the regio- and stereoselectivity of allylation reactions.

In this work, we carried out, for the first time, the comparative study of dimethyl malonate allylation reactions on Pd, Ir, and Rh complexes with chiral ligands of phosphite and amidophosphite types and established the decisive effect of the metal nature on the regioselectivity of the process: the use of Ir and Rh catalysis favors the formation of a branched product, while Pd catalysis assists the production of a linear substitution product. In combination with a particular type of ligand, Pd- and Ir-catalyzed reactions were shown to ensure the regiospecific formation of the linear or branched product, respectively. The main structural features of chiral ligands facilitating the enhancement of the stereoselectivity of formation of the branched product were also revealed.

As model reactions, we used the allylation of dimethyl malonate with methyl 3-phenylallyl carbonate (**1**) and its *p*-chloro-substituted analogue **2** (Scheme 1) to form compounds **3** and **5** or **4** and **6**, respectively.



1 (X = H)
2 (X = Cl)

3 (X = H)
4 (X = Cl)

5 (X = H)
6 (X = Cl)

Scheme 1.

In this work, we used chiral ligands of the following types:

(1) phosphite ligands **7**–**10** based on the chiral fragment of 1,1'-bis-2-naphthol (BINOL): both bidentate P,N-ligands containing a cymantrenylimino (**7**, **8**) (cymantrenyl = η^5-$(C_5H_4)Mn(CO)_3$) or oxazoline fragment (**10**, complexes **11**, **12**) and monodentate phosphite ligand **9**;

(2) monodentate P*-diamidophosphites (**13**, complexes **14**–**16**);

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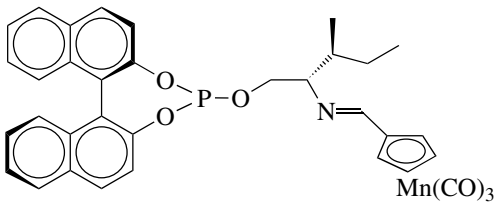
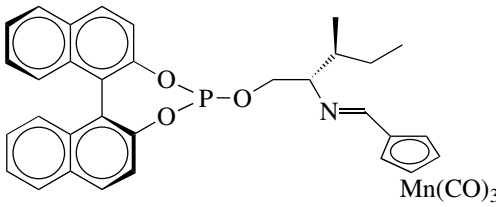
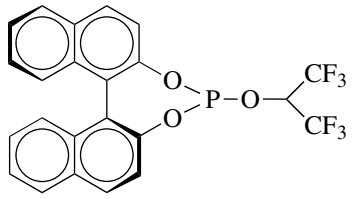
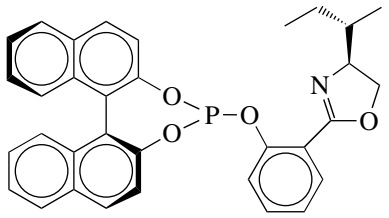
Table 1. Allylation of dimethyl malonate with carbonate **1** in the presence of complexes with BINOL-derived ligands

Ligand	Precatalyst	M/L	Yield of **3** + **5**, %	**3/5**	*ee* **3**, %
7. 	$[Pd(allyl)Cl]_2$	1/1	82	29/71	5(*S*)
		1/2	28	15/85	25(*R*)
	$[Ir(COD)Cl]_2$	1/1	83	99/1	0
		1/2	69	80/20	15(*R*)
	$[Rh(COD)Cl]_2$	1/1	32	86/14	9(*R*)
		1/2	92	90/10	0
8. 	$[Pd(allyl)Cl]_2$	1/1	47	33/67	10(*R*)
		1/2	98	19/81	20(*R*)
	$[Ir(COD)Cl]_2$	1/1	37	96/4	4(*S*)
		1/2	28	99/1	1(*S*)
	$[Rh(COD)Cl]_2$	1/1	32	82/18	7(*R*)
		1/2	75	90/10	17(*R*)
9. 	$[Ir(COD)Cl]_2$	1/1	79	99/1	6(*S*)
		1/2	20	93/7	36(*S*)
	$[Rh(COD)Cl]_2$	1/1	99	95/5	8(*S*)
		1/2	13	91/9	23(*S*)
10. 	$[Pd(allyl)Cl]_2$	1/1	60	46/54	61(*S*)
		1/2	84	34/66	17(*S*)
	$[Ir(COD)Cl]_2$	1/1	95	99/1	64(*S*)
		1/2	70	99/1	45(*S*)
	$[Rh(COD)Cl]_2$	1/1	14	96/4	0
		1/2	12	96/4	0
11. $[Pd(allyl)L]^+BF_4^-$ (L = **10**)			97	63/37	59(*S*)
12. $[Rh(COD)L]^+BF_4^-$ (L = **10**)			36	96/4	0

(3) a bidentate P,N-ligand of the diamidophosphite type with the N donor center in the ferrocenylimino fragment (complexes **17**, **18**);

(4) bidentate P,N-ligands of the phosphite type based on phenols with the N donor center in the ferrocenylimino fragment (**19**, complexes **20**, **21**) or the oxazoline fragment (complex **22**).

A chiral catalyst was used as an individual complex or was preliminarily obtained by the reaction of a chiral ligand with a precatalyst, a complex of the corresponding transition metal with an achiral ligand. All reactions were carried out in an inert atmosphere (argon) for 48 h. The analysis of reaction mixture compositions by TLC and ^1H NMR showed only the presence of compounds **3**–**6** and the unreacted initial compounds. No marked amounts of by-products were detected. Thus, the yield of allylation products **3**–**6** under these conditions indicated the extent of conversion of the initial allylic substrates (**1** or **2**) and, in the case of incomplete conversion, allowed us to semiquantitatively estimate reaction rates. The corresponding results are given in Tables 1 and 2.

It is seen from these data that the use of Pd catalysis leads, depending on the ligand, mainly or exclusively to the formation of the linear products. In contrast, the use of Rh and Ir catalysis allows one to obtain the branched regioisomers (Table 1). Both metals ensure high regioselectivity. Iridium is slightly more efficient than rhodium and, in the case of certain ligands (**7**–**10**, **13**), leads to the regiospecific formation of only the branched isomer. In this respect, diamidophosphite ligand **13** is the most striking example: depending on the metal, it permits the regiospecific preparation of the linear isomer on the palladium catalyst or the branched isomer on the iridium catalyst. This feature is observed for both unsubstituted allyl carbonate **1** and its *n*-chloro-substituted analogue **2** (Table 2).

The use of individual palladium complexes **14**–**18** with diamidophosphite ligands results in the regiospecific preparation of linear products **5** and **6**. The size

Table 2. Allylation of dimethyl malonate with carbonates **1** and **2**

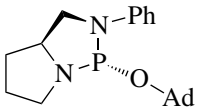
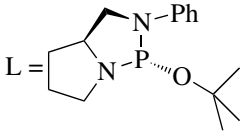
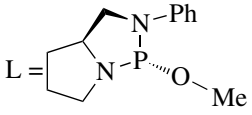
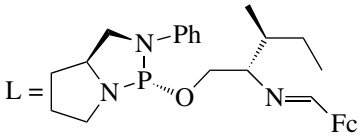
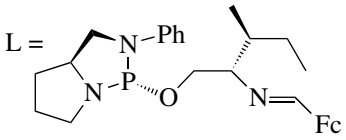
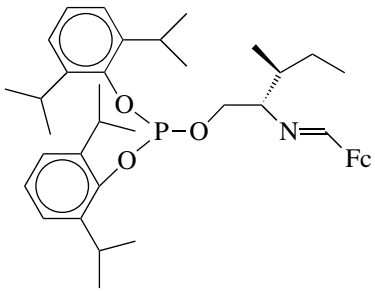
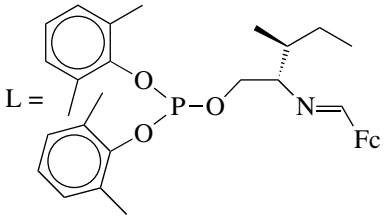
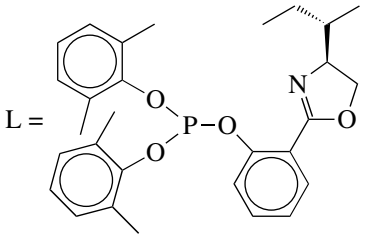
Complex, ligand	Precatalyst	M/L	Yield of **3** + **5**, %	**3/5**	*ee* **3**, %	Yield of **4** + **6**, %	**4/6**	*ee* **4**, %
13.  (Ad = adamantyl)	$[Pd(allyl)Cl]_2$	1/1	81	10/90	30(*S*)	84	–/100	
		1/2	85	–/100		85	–/100	
	$[Ir(COD)Cl]_2$	1/1	97	>99/1	0	72	99/1	2(*S*)
		1/2	79	98/2	4(*R*)	65	99/1	0
	$[Rh(COD)Cl]_2$	1/1	79	78/22	0	52	72/28	11(*R*)
		1/2	59	92/8	18(*R*)	62	89/11	11(*R*)
14. $[Pd(allyl)L_2]^+BF_4^-$ (L = **13**)			50	–/100		60	–/100	
15. $[Pd(allyl)L_2]^+BF_4^-$ 			62	–/100		68	–/100	
16. $[Pd(allyl)L_2]^+BF_4^-$ 			69	–/100		71	–/100	
17. $[Pd(allyl)L]^+BF_4^-$  (Fc = ferrocenyl)	–		95	–/100		90	–/100	
18. $[Pd(allyl)L_2]^+BF_4^-$ 			84	–/100		71	–/100	
19. 	$[Pd(allyl)Cl]_2$	1/1	94	38/62	50(*R*)	69	41/59	80(*R*)
		1/2	81	39/61	48(*R*)	78	41/59	75(*R*)
20. $[Pd(allyl)L]^+BF_4^-$ (L = **19**)			87	50/50	39(*R*)	62	54/46	56(*R*)

Table 2. (Contd.)

Complex, ligand	Precatalyst	M/L	Yield of **3** + **5**, %	**3/5**	*ee* **3**, %	Yield of **4** + **6**, %	**4/6**	*ee* **4**, %
21. $[Pd(allyl)L]^+BF_4^-$ 			97	37/63	33(*R*)	86	45/55	62(*R*)
22. $[Pd(allyl)L]^+BF_4^-$ 			93	54/46	59(*S*)			

and nature of the exocyclic substituent in the ligand has no effect on the regioselectivity. Thus, the variation of metal and ligand makes it possible to achieve the regiospecific formation of any regioisomer.

When a catalytic species results from ligand exchange by the reaction of a chiral ligand with a precatalyst, the use of two equivalents of the ligand per equivalent of the metal (M/L = 1/2) usually improves the stereoselectivity as compared with the ratio M/L = 1/1. However, this is often accompanied by a decrease in the reaction rate. The variation of the M/L ratio for the same ligand can accelerate or retard the reaction depending on M (Table 1, ligands **7**, **8**, **10**; Table 2, ligand **13**).

The optical yields of the branched products are low irrespective of the metal and ligand nature and their ratio. Exceptions are ligand **10** and complex **22**, as well as ligand **19** and complexes **20** and **21**, containing oxazoline and ferrocenylimino fragments, respectively, which allowed us to obtain the branched allylation products with satisfactory optical purity (*ee* 56–80%). This is observed only for Pd and Ir. Rh catalysis usually leads to a very low, if any, enantioselectivity of the process. Obviously, it is the oxazoline and ferrocenylimino fragments in the bidentate ligands used that are responsible for the enantioselectivity of the allylation reaction. It should be noted that this does not refer to the cymantrenylimino fragment (compare the data for ligands **7**, **8**, and **19**). This is likely due to the difference in the electronic properties of the ferrocenyl and cymantrenyl groups (which are close in size) as substituents in the imine fragment and, therefore, to the differences in the *n*-donor properties of the imine nitrogen atom in these ligands.

The addition of LiCl to iridium catalysts is known to increase both regio- and stereoselectivity [4]. We used this method for the first time for palladium catalysis for alkylation of substrate **1** in the presence of Pd complex **22**: 1 equiv of LiCl was added, which changed the ratio of regioisomers **3** : **5** toward the formation of chiral product **3** (from 54/46 to 63/37), the optical purity of **3** increasing from 59 to 75%.

Thus, the comparative study of the allylation reactions of dimethyl malonate with asymmetrically substituted allyl carbonates on Pd, Ir, and Rh complexes with chiral phosphites and amidophosphites revealed the decisive factors (metal nature, ligand type) that provide for the regiospecific formation of one of the possible isomers when allylic substrates allowing the reaction to proceed with nondegenerate allylic rearrangement are used. We also found the major structural features of the chiral ligands that improve the enantioselectivity of formation of the product with an asymmetric center.

EXPERIMENTAL

All reactions were carried out in a dry argon atmosphere in anhydrous solvents. Ligands **9** [5], **13** [6], and **19** [7]; complexes $[Pd(allyl)Cl]_2$ [8], $[Ir(COD)Cl]_2$ [8], $[Rh(COD)Cl]_2$ [9], **14**–**16** [6], **17** and **18** [10], **20** and **21** [7]; and **22** [11]; and (S_{ax})- and (R_{ax})-2-chlorodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin [12] and substrates **1** and **2** [13] were obtained by published procedures. *N*,*O*-Bis(trimethylsilyl)acetamide (BSA) and dimethyl malonate (Acros Organics) were used without additional purification.

General procedure for the synthesis of ligands based on BINOL. Triethylamine (0.2 mL, 1.4 mmol)

and 1.4 mmol of the appropriate iminoalcohol or oxazoline were added to a solution of 0.491 g (1.4 mmol) of (S_{ax})- or (R_{ax})-2-chlorodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin in 15 mL of toluene with stirring and cooling (ice–water). The reaction mixture was heated to 110°C and cooled to ambient temperature, the $Et_3N{\cdot}HCl$ precipitate was filtered off, and the solvent was removed in vacuum (40 Torr). Twenty-five milliliters of heptane was added to the residue, the mixture was heated to 98°C, the resulting solution was separated from the insoluble residue by decantation, and the solvent was removed in vacuum (40 Torr). The products were dried in vacuum (1 Torr) for 1.5 h.

(R_{ax},2''*S*,3''*S*)-2-[3''-Methyl-2''-{(cymantrenylidene)amino}pentyloxy]dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin (7). Pale yellow powder, yield 69%. Mp 78–80°C. ^{31}P NMR ($CDCl_3$, δ_P, ppm): 142.4 (s). ^{13}C NMR ($CDCl_3$, δ_C, ppm, $J_{C,P}$, Hz): 223.8 (s, CO), 155.1 (s, C=N), 148.4 (d, $^2J_{C,P}$ = 6.1), 147.3, 132.3, 131.2, 130.7, 130.1, 129.7, 128.1, 128.0, 126.7, 126.6, 125.9, 124.8, 124.6, 123.8, 122.4, 121.6, 121.3, 120.6 (C_{Ar}), 94.9 (s, C_{Cp} *ipso*), 85.6, 83.6, 82.8, 81.8 (s, C_{Cp}), 75.5 (s, NCH), 66.1 (d, $^2J_{C,P}$ = 5.3, OCH_2), 36.2 (s, CH), 24.9 (CH_2), 15.4 (s, CH_3), 10.8 (s, CH_3). IR ($CHCl_3$, ν, cm^{-1}): 2026 and 1947 (CO). MS (electrospray, *m*/*z* (*I*, %)): 646 (46, $[M]^+$), 547 (4), 314 (100).

For $C_{35}H_{29}MnNO_6P$ anal. calcd. (wt %): C, 65.12; H, 4.53; N, 2.17.

Found (wt %): C, 65.42; H, 4.39; N, 2.39.

(S_{ax},2''*S*,3''*S*)-2-[3''-Methyl-2''-{(cymantrenylidene)amino}pentyloxy]dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin (8). Pale yellow powder, yield 72%. Mp 71–73°C. ^{31}P NMR ($CDCl_3$, δ_P, ppm): 144.6 (s). ^{13}C NMR ($CDCl_3$, δ_C, ppm, $J_{C,P}$, Hz): 223.8 (s, CO), 155.2 (s, C=N), 148.3 (d, $^2J_{C,P}$ = 6.0), 147.4, 132.6, 132.4, 131.3, 130.8, 129.7, 128.3, 128.0, 126.7, 126.6, 125.9, 124.8, 124.6, 123.8, 122.5, 121.7, 121.4, 120.8 (C_{Ar}), 95.1 (s, C_{Cp} *ipso*), 85.7, 83.5, 82.9, 81.8 (s, C_{Cp}), 75.7 (s, NCH), 66.4 (d, $^2J_{C,P}$ = 5.1, OCH_2), 36.8 (s, CH), 25.0 (CH_2), 15.3 (s, CH_3), 10.2 (s, CH_3). IR ($CHCl_3$, ν, cm^{-1}): 2028 and 1950 (CO). MS (electrospray, *m*/*z* (*I*, %)): 646 (39, $[M]^+$), 547 (9), 314 (100).

For $C_{35}H_{29}MnNO_6P$ anal. calcd. (wt %): C, 65.12; H, 4.53; N, 2.17.

Found (wt %): C, 65.28; H, 4.59; N, 2.02.

(S_{ax})-2-[2''-((4'''*S*)-4'''-sec-Butyl-2'''-oxazolin-2'''-yl)phenoxy]dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin (10). White powder, yield 74%. Mp 65–67°C. ^{31}P NMR ($CDCl_3$, δ_P, ppm): 142.7 (s). ^{13}C NMR ($CDCl_3$, δ_C, ppm, $J_{C,P}$, Hz): 160.1 (s, C=N), 149.9 (d, $^2J_{C,P}$ = 6.4), 146.7 (d, $^2J_{C,P}$ = 3.3), 133.5, 133.0, 132.8, 132.1, 131.3, 130.8, 130.5, 130.4, 128.8, 128.3, 128.0, 127.8, 127.2, 126.9, 126.7, 126.5, 125.2, 124.3, 123.5, 122.8, 121.7, 120.6, 119.8, 118.3 (C_{Ar}), 71.4 (s, NCH), 69.1 (s, OCH_2), 39.0 (s, CH), 25.3 (CH_2), 14.4 (s, CH_3), 11.4 (s, CH_3). MS (EI, *m*/*z* (*I*, %)): 534 (2, $[M]^+$), 408 (15), 332 (63), 268 (51), 219 (47), 162 (100).

For $C_{33}H_{28}NO_4P$ anal. calcd. (wt %): C, 74.29; H, 5.29; N, 2.63.

Found (wt %): C, 74.54; H, 5.20; N, 2.89.

((S_{ax})-2-[2''-((4'''*S*)-4'''-sec-Butyl-2'''-oxazolin-2'''-yl)phenoxy]dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-*P*,*N*)(π-allyl)palladium(II) tetrafluoroborate (11). Yellow powder. Mp 123–125°C (decomp.). ^{31}P NMR ($CDCl_3$, δ_P, ppm): 148.9 (s), 44% and 147.9 (s), 56%. MS (electrospray, *m*/*z* (*I*, %)): 681 (100, $[M–BF_4]^+$), 640 (1, $[M–allyl–BF_4]^+$).

For $C_{36}H_{33}BF_4NO_4PPd$ anal. calcd. (wt %): C, 56.31; H, 4.33.

Found (wt %): C, 56.64; H, 4.44.

((S_{ax})-2-[2''-((4'''*S*)-4'''-sec-Butyl-2'''-oxazolin-2'''-yl)phenoxy]dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-*P*,*N*)([1,2:5,6-η-(1,5-cyclooctadiene)]rhodium(I) tetrafluoroborate (12). Dark yellow powder. Mp 146–148°C (decomp.). ^{31}P NMR ($CDCl_3$, δ_P, ppm, $^1J_{P,Rh}$, Hz): 149.2 (d, 291.6). MS (electrospray, *m*/*z* (*I*, %)): 745 (100, $[M–BF_4]^+$).

For $C_{41}H_{40}BF_4NO_4PRh$ anal. calcd. (wt %): C, 59.23; H, 4.85.

Found (wt %): C, 59.43; H, 4.72.

Catalytic allylation of dimethyl malonate with carbonates 1 and 2 (general procedure). A solution of a precatalyst (0.01 mmol) and a corresponding ligand (0.02–0.04 mmol) in 5 mL of CH_2Cl_2 was stirred for 40 min (or 0.02 mmol of individual complexes were dissolved in 5 mL of CH_2Cl_2). Allylic substrate **1** or **2** (0.5 mmol) was added, and the mixture was stirred for 20 min; then dimethyl malonate (0.75 mmol), BSA (0.75 mmol), and KOAc (2 mg) were added. The reaction mixture was stirred for 48 h at 20°C. The solvent was evaporated and the products were isolated by chromatography on a SiO_2 column (200 × 17 mm, hexane–EtOAc (9 : 1) as eluent). The solvent was removed and the fraction composed of a mixture of regioisomers **3** and **5** (or **4** and **6**) was analyzed by ^1H NMR ($CDCl_3$, 300 MHz) to determine the isomer ratio. The optical yield of compounds **3** and **4** was determined by HPLC (Diacel Chiracel OJ-H chiral column for **3** and Diacel Chiracel OD-H for **4**).

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