Enantioselective allylic substitution catalyzed by an iridium complex: remarkable effects of the counter cation

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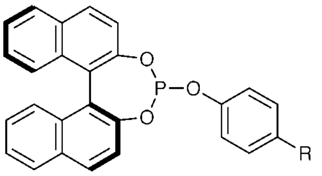
Allylic substitution of a methyl carbonate of cinnamyl alcohol with the anion of dimethyl malonate gave the branched olefin with high enantioselectivity in the presence of (*S*)-1,1′-binaphthyl-2,2′-diyl phenyl phosphite when a combination of lithium and zinc was used as counter cation.

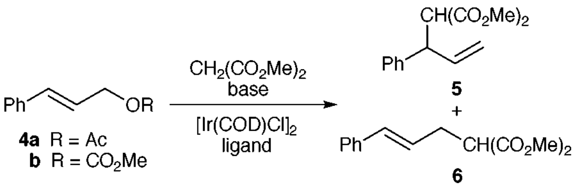
Unlike palladium-catalyzed allylic alkylations, iridium-catalyzed alkylations take place at the more substituted allylic terminus.[1] Recently, asymmetric versions of this reaction have been reported, where chiral phosphinooxazolines[2] or phosphorous amidites[3] were used as ligands. We report here enantioselective allylic substitutions catalyzed by an iridium complex of chiral aryl phosphite (*S*)-**1**.



1 R = H
2 R = OMe
3 R = CF_3

We chose **4a** as a standard substrate to avoid ambiguities arising from a chiral centre (Scheme 1), although the ester of an isomeric secondary alcohol, 1-phenylprop-2-en-1-ol, can also be a substrate for the same reaction. It has been reported that the iridium-catalyzed allylic substitution of acetates of secondary alcohols proceeds with 70–80% retention of configuration.[3] Aryl phosphites are known to be efficient ligands for allylic alkylation with soft carbon nucleophiles catalyzed by an iridium complex.[1] Chiral phosphites **1**,[4] **2**[5] and **3**[6] have been used as ligands. Diethylzinc was used as a base because it is known to give a greater ee than other bases in allylic alkylations catalyzed by a palladium–(*R*)-BINAP complex.[7] The results are shown in Table 1. Both electron-releasing and -withdrawing groups on the phenyl rings of the ligands gave lower ees (entries 2 and 3) than the parent phosphite (*S*)-**1** (entry 1). CH_2Cl_2 is the solvent of choice (compare entry 1 with entries 4–6). Allylic methyl carbonate **4b** gave a better yield than the corresponding acetate **4a** in a shorter reaction time (entries 1 and 7).

The effect of the counter cation was investigated using **4b**, and the results are shown in Table 2. A conspicuous feature of these results is that the proportion of (*R*)-**5** to (*S*)-**5** increases as the ionic character of the malonate anion increases (entries 1–3). Thus, (*R*)-**5** was obtained in 36% ee by using Bu^tP_4 base, which is known to generate naked anions.[8,9] Metals, such as lithium and zinc, that strongly coordinate with anion gave (*S*)-**5** as the major enantiomer. The intermediacy of a π-allyl–iridium complex has been suggested for iridium complex-catalyzed allylic alkylation with triphenyl phosphite as ligand.[1] On the other hand, the involvement of a σ-allyl–iridium complex is indicated for the alkylation of secondary allylic acetates.[3] Although there is an apparent divergence of mechanistic considerations, the π-allyl–iridium complex is more likely than the σ-complex when aryl phosphites are used as ligands. The predominant formation of (*S*)-**5** with lithium and/or zinc as the



Scheme 1

Table 1 Ir-catalysed allylic alkylation of **4a** and **4b** with dimethyl malonate using $ZnEt_2$ as base[ab]

Entry	Substrate	Ligand	Solvent	Reaction time/h	Combined yield of **5** and **6** (%)	Ratio of **5** : **6** GLC[c]	 ^1H NMR	Ee of (*S*)-**5**[d](%)
1	**4a**	**1**	CH_2Cl_2	35	58 (64)[e]	92 : 8	—	76
2	**4a**	**2**	CH_2Cl_2	94	57	92 : 8	91 : 9	61
3	**4a**	**3**	CH_2Cl_2	47	62	94 : 6	96 : 4	32
4	**4a**	**1**	toluene	47	57 (58)[e]	82 : 18	81 : 19	67
5	**4a**	**1**	THF	91	40 (49)[e]	84 : 16	85 : 15	20
6	**4a**	**1**	MeCN	48	13 (29)[e]	86 : 14	81 : 19	54
7	**4b**	**1**	CH_2Cl_2	7	88	96 : 4	95 : 5	71
8	**4b**	**1**	THF	68	44 (65)[e]	—	85 : 15	55

[a] General procedure (entry 1): A solution of (*S*)-**1** (81.7 mg, 0.2 mmol), $[Ir(COD)Cl]_2$ (33.6 mg, 0.05 mmol) and cinnamyl acetate (83.1 μl, 0.5 mmol) in dry CH_2Cl_2 (1 ml) was stirred for 45 min under argon. To this solution was added a solution prepared by stirring dimethyl malonate (133 mg, 1.0 mmol) and Et_2Zn (1.0 M in hexane, 1.0 ml) in CH_2Cl_2 (3 ml) under argon for 1 h at room temperature. After stirring for the indicated time, usual extractive work-up with EtOAc followed by preparative TLC (EtOAc–hexane 1:6) gave 58 mg of a mixture of **5** and **6**. [b] All reactions were performed at room temperature. [c] Determined by GLC on a Chirasil-DEX CB column at 150 °C. [d] Determined by HPLC on CHIRALCEL OJ-R (MeOH–H_2O = 75:25). [e] The number in parenthesis indicates the yield based on the consumed starting material.

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counter cation may be explained by the transition state, shown in Fig. 1. The bulky phosphite ligand should be located *trans* to the more-substituted allylic terminus to avoid steric repulsion. Nucleophilic attack *anti* to the phosphite ligand gives (*S*)-**5**. As the anion becomes harder, it favours initial attack at iridium metal, which is harder than the allylic carbon. Intramolecular migration of malonate from iridium to the allylic carbon proceeds to give (*R*)-**5**.

Table 2 Effect of the counter cation on the allylic alkylation of the carbonate **4b** catalyzed by $[\mathrm{Ir(COD)Cl}]_2$–(*S*)-**1** in THF at room temperature[a]

Entry	Base	Reaction time/h	Combined yield of **5**:**6**	Ratio of **5** and **6**[b]	Ee of **5**[c] (%)	Config.
1	$\mathrm{Bu^tP_4}$	24	87	93:7	36	*R*
2	KH	7	90	90:10	18	*R*
3	NaH	24	96	95:5	6	*R*
4	LiH	92	14 (74)[d]	46:54	22	*S*
5	LDA	30	85 (88)[d]	94:6	17	*S*
6	BuLi	30	71 (97)[d]	92:8	24	*S*
7	BuLi/$\mathrm{ZnCl_2}$	3	99	93:7	96	*S*

[a] Two equivalents of dimethyl malonate and base were used. [b] Determined by ^{1}H NMR. [c] Determined by HPLC on a CHIRALCEL OJ-R (MeOH–H_2O = 75:25). [d] The number in parenthesis indicates the yield based on the consumed starting material.

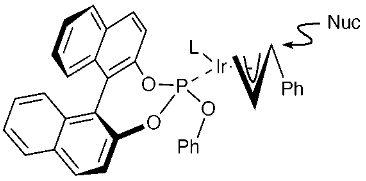

Fig. 1 Transition state structure.

Another feature is that the ee of (*S*)-**5** is remarkably increased to 96% when lithium and zinc are present in the reaction medium (entry 7). It is premature to give a detailed rationalization for this extraordinary increase in ee. However, it is possible that lithium chloride formed *in situ* may play a role.[3] Work is currently underway along these lines.

Notes and references

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