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Enantioselective Allylic Substitution of Cinnamyl Esters Catalyzed by Iridium−Chiral Aryl Phosphite Complex: Conspicuous Change in the Mechanistic Spectrum by a Countercation and Solvent

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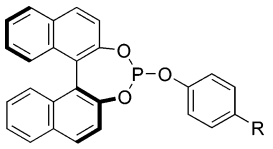
Iridium-catalyzed asymmetric allylic alkylation of monoaryl substrates **4**−**6** with chiral phosphites **1**−**3** has been investigated. Although branched isomers were formed with high regioselectivities, the enantioselectivities of these products were remarkably influenced by solvents, countercations, and additives ($ZnCl_2$ and LiCl).

Introduction

The plethora of recent papers, which include alkyne dimerization,[1] insertion of carbon monoxide,[2] the Heck-type raction,[3] allylic alkylations,[4] carbonylative [5 + 1] cycloaddition,[5] addition of nitriles to carbon−carbon triple bonds,[6] olefin arylation,[7] and cyclotrimerzation of alkynes,[8] reflects the importance of iridium-catalyzed carbon−carbon bond-forming reactions. Recently, an enantioselective Pauson−Khand-type reaction[9] and intramolecular [4 + 2] cycloaddition[10] catalyzed by iridium−chiral phosphine complex have been reported. Iridium-catalyzed allylic alkylations give the branched isomer as a major product,[4] which complements palladium-catalyzed allylations that give the linear isomer as a major product.[11] Helmchen et al.[12] reported the first asymmetric version of allylic alkylation catalyzed by iridium-chiral bidentate phosphinooxazoline. More recently, the asymmetric synthesis of amino acid derivatives by an iridium-catalyzed allylic substitution was reported.[13] We also reported enantioselective allylic alkylation catalyzed by iridium complex with (*S*)-1,1′-binaphthyl-2,2′-diyl phenyl phosphite (**1**) as a chiral ligand.[14] This paper describes in detail the enantioselective allylic alkylation of acyl cinnamates as well as their regioisomers with a chiral aryl phosphite **1** as a ligand, the remarkable effects of the countercation, and bias of the mechanism, which mainly depends on the solvent.



(*S*)-**1**: R = H
(*S*)-**2**: R = OMe
(*S*)-**3**: R = CF_3

Results and Discussion

Takeuchi and co-workers[4] reported that the electron-withdrawing phosphorus ligands in the iridium-catalyzed

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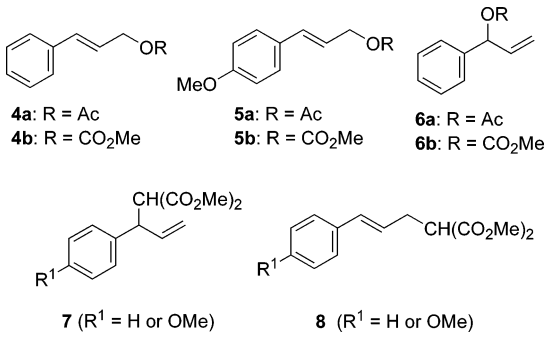
TABLE 1. Ir-Catalyzed Allylic Alkylation of 4 and 5 with Dimethyl Malonate Using $ZnEt_2$ as a Base[a]

entry	substrate	ligand	solvent	reaction time (h)	products **7**, **8** (R^1 =)	yield[b] (%)	ratio of **7**/**8** by GLC	ratio of **7**/**8** by ^{1}H NMR	% ee of (*S*)-**7**[c]
1	**4a**	(*S*)-**1**	CH_2Cl_2	42	H	68 (84)[d]	98:2		68
2	**4a**	(*R*)-**1**	CH_2Cl_2	43	H	73 (82)[d]	99:1		69[e]
3	**4a**	(*S*)-**1**	CH_2Cl_2[f]	10	H	50	87:13	88:12	62
4	**4a**	(*S*)-**2**	CH_2Cl_2	94	H	57	92:8	91:9	61
5	**4a**	(*S*)-**3**	CH_2Cl_2	47	H	62	94:6	96:4	32
6	**4a**	(*S*)-**1**	hexane/CH_2Cl_2[g]	24	H	69	87:13	90:10	84
7	**4a**	(*S*)-**1**	Et_2O/CH_2Cl_2[h]	48	H	64	94:6	87:13	68
8	**4a**	(*S*)-**1**	toluene	47	H	57 (58)[d]	82:18	81:19	67
9	**4a**	(*S*)-**1**	THF	91	H	40 (49)[d]	84:16	85:15	20
10	**4a**	(*S*)-**1**	CH_3CN	48	H	13 (29)[d]	86:14	81:19	54
11	**4b**	(*S*)-**1**	CH_2Cl_2	7	H	88	96:4	95:5	71
12	**4b**	none	CH_2Cl_2	2	H	83		95:5	0
13	**4b**	(*S*)-**1**	hexane/CH_2Cl_2[g]	7	H	84	95:5	92:8	77
14	**4b**	(*S*)-**1**	THF	68	H	39 (52)[d]		86:14	57
15	**4b**	(*S*)-**1**	THF[f]	2	H	78		89:11	67
16	**4b**	none	THF	24	H	74		95:5	0
17	**5a**	(*S*)-**1**	CH_2Cl_2	48	OMe	67		100:0	50
18	**5a**	(*S*)-**1**	hexane/CH_2Cl_2[g]	48	OMe	61 (67)[d]		100:0	61
19	**5b**	(*S*)-**1**	CH_2Cl_2	7	OMe	84		100:0	45
20	**5b**	(*S*)-**1**	hexane/CH_2Cl_2[g]	5	OMe	83		100:0	28
21	**5b**	(*R*)-BINAP	CH_2Cl_2	12	OMe	51		65:35	28
22	**5b**	PPh_3	CH_2Cl_2[f]	7	OMe	42		73:27	0

[a] All reactions were performed at room temperature, unless otherwise stated. [b] Isolated yields of the combined regioisomers. [c] Determined by HPLC on CHIRALCEL OJ-R (MeOH−H_2O = 75:25). [d] The number in parentheses indicates the yield based on the consumed starting material. [e] (*R*)-**7** was obtained. [f] At refluxing temperature. [g] Hexane/CH_2Cl_2 = 8/3. [h] Et_2O/CH_2Cl_2 = 5/1.

allylic alkylation give the branched isomer with high selectivity, while electron-donating ligands produce the linear isomer as the major product. Since triphenyl phosphite provides the highest ratio in favor of the branched isomer, chiral aryl phosphites **1**,[15] **2**,[16] and **3** were selected as chiral ligands. It is also noteworthy that Takeuchi et al. found that both esters **4** from linear allylic alcohols and branched ester **6** gave identical product distributions of the branched isomer **7** and the linear isomer **8**. Thus, our studies began by screening the reaction conditions using linear esters **4a**,[11a,b] **4b**,[17] **5a**,[11c] and **5b**[18] as substrates to avoid stereochemical ambiguities due to a chiral center.[11]



Diethylzinc was selected as the base since it gives a greater enantiomeric excess (ee) than other bases in the allylic alkylation catalyzed by palladium-(*R*)-BINAP[19] and in the Horner−Wadsworth−Emmons reaction.[20] [Ir(COD)Cl]$_2$ was the catalytic precursor, and a 1:2 ratio of iridium to a chiral ligand was constant for each reaction to observe the effects of other changes on the ratio of **7** to **8** and ee of **7**. Table 1 lists the results. Ligand **1** gave a high product ratio that favored the branched isomer **7** with moderate ee, but the absolute configuration depended upon the chiral ligand (entries 1 and 2). Electron-donating ligand **2** slightly decreased the ee (entry 4), but electron-withdrawing ligand **3** considerably decreased the ee (entry 5). Cinnamyl methyl carbonate (**4b**) was more reactive than the corresponding acetate **4a**, but the isomer ratio and the ee were unaffected (compare entry 1 with 11). Polar solvents such as THF decreased both the product ratio and the ee. The background reaction was quite rapid both in CH_2Cl_2 and THF (entries 12 and 16). An electron-donating substituent in the substrate increased the product ratio and gave solely branched isomer **7** (R^1 = OMe), but the ee decreased (entries 17−20). Increasing the reaction temperature had a negligible effect on the ee (entries 1, 3 and 14, 15). Phosphine derivatives were not ligands of choice for a high regioselectivity (entries 21 and 22).

Since the ee was unsatisfactory from the preparative point of view, our attention then shifted to the effects of countercations using **4b** as a substrate in THF. Table 2 summarizes the results. An interesting finding was that (*R*)-**7** was the major enantiomer with phosphazene base P_4-*t*-Bu (entry 1) since P_4-*t*-Bu generated a naked anion.[21] The proportion of (*R*)-**7** to (*S*)-**7** decreased as the ionic character of the malonate anion decreased (entries 1−3).

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TABLE 2. Effect of a Counter Cation on the Allylic Alkylation of the Carbonate 4b Catalyzed by [Ir(COD)Cl]$_2$-(*S*)-1 in THF at Room Temperature

entry	base	reaction time (h)	combined yield (%) of products (R^1 = H), **7** and **8**	ratio of **7/8**[a]	% ee of **7**[b]	config
1	*t*-BuP$_4$-base	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)[c]	46:54	22	*S*
5	LDA	30	85 (88)[c]	94:6	17	*S*
6	*n*-BuLi	30	71 (97)[c]	92:8	24	*S*
7	*n*-BuLi/ZnCl$_2$[d]	3	99	93:7	96	*S*
8[e]	*n*-BuLi/ZnCl$_2$[d]	38	81	96:4	94	*S*
9	*n*-BuLi/LiCl[f]	68	33 (60)[c]	85:15	77	*S*
10	*n*-BuLi/LiCl[g]	68	55 (77)	86:14	84	*S*
11	ZnEt$_2$/LiCl[f]	20	65	96:4	17	*S*
12	ZnEt$_2$/LiCl[h]	20	67	96:4	34	*S*

[a] Determined by ^{1}H NMR. [b] Determined by HPLC on CHIRALCEL OJ-R (MeOH/H$_2$O = 75:25). [c] The number in parentheses indicates the yield based on the consumed starting material. [d] ZnCl$_2$ was added to the anion solution. [e] The result with acetate **4a**. [f] LiCl was added to the anion solution. [g] *n*-BuLi was added to the solution of dimethyl malonate and LiCl to generate the anion solution. [h] ZnEt$_2$ was added to the solution of dimethyl malonate and LiCl to generate the anion solution.

TABLE 3. Results of the Ir-Catalyzed Allylic Alkylation of 6 with the ligand 1

				products (R^1 = H), **7** and **8**		
entry	substrate	absolute config of ligand	reaction conditions[a]	combined yield[b] (%)[c]	ratio[d] of **7/8**	% ee of **7**[e]
1	(*S*)-**6a**[f]	*S*	ZnEt$_2$, CH$_2$Cl$_2$, 25 h	76	98:2	63 (*S*)
2	(*R*)-**6a**[f]	*S*	ZnEt$_2$, CH$_2$Cl$_2$, 49 h	68	98:2	57 (*S*)
3	*dl*-**6a**	*S*	ZnEt$_2$, CH$_2$Cl$_2$, 22 h	76	99:1	58 (*S*)
4	(*S*)-**6a**[f]	racemic	ZnEt$_2$, CH$_2$Cl$_2$, 24 h	78	98:2	0
5	(*S*)-**6a**[f]	*S*	NaH, THF, 19 h	73	>99:1	4 (*S*)
6	(*S*)-**6a**[f]	*S*	*n*-BuLi, THF, 20 h	89	>99:1[g]	97 (*R*)
7	(*R*)-**6a**[f]	*S*	*n*-BuLi, THF, 20 h	73	90:10[g]	89 (*S*)
8	*dl*-**6a**	*S*	*n*-BuLi, THF, 20 h	81	93:7[g]	18 (*R*)
9	(*S*)-**6a**[f]	*R*	*n*-BuLi/ZnCl$_2$, THF, 47 h	71	>99:1	97 (*R*)
10	(*R*)-**6a**[f]	*R*	*n*-BuLi/ZnCl$_2$, THF, 48 h	67	>99:1	90 (*S*)
11	*dl*-**6a**	*R*	*n*-BuLi/ZnCl$_2$, THF, 48 h	66	98:2	11 (*R*)
12	(*S*)-**6a**[f]	*S*	ZnEt$_2$, THF, 48 h	72	99:1[g]	83 (*R*)
13	(*R*)-**6a**[f]	*S*	ZnEt$_2$, THF, 48 h	76	99:1[g]	86 (*S*)
14	*dl*-**6a**	*S*	ZnEt$_2$, THF, 48 h	69	99:1[g]	0
15	(*S*)-**6b**[f]	*S*	*n*-BuLi, THF, 3 h	80	>99:1[g]	92 (*R*)
16	(*R*)-**6b**[f]	*S*	*n*-BuLi, THF, 3 h	73	97:3[g]	90 (*S*)
17	*dl*-**6b**[f]	*S*	*n*-BuLi, THF, 3 h	73	98:2[g]	7 (*R*)

[a] 10 mol % [Ir(cod)Cl]$_2$, Ir/L = 1:2. [b] Isolated yields of the combined regioisomers. [c] The number in parentheses indicates the yield based on the consumed starting material. [d] Determined by GLC unless otherwise stated. [e] Determined by HPLC. [f] Enantiopure compounds (ee >99%). [g] Determined by ^{1}H NMR.

The absolute configuration of product **7** switched from *R* to *S* when lithium or zinc was the countercation since the stronger coordination makes the anion softer. The ee of (*S*)-**7** and the reaction rate were remarkably increased with a zinc enolate, which was generated by the metal exchange of lithium enolate (entries 7 and 8), but the ee was not great when lithium or zinc alone was the countercation (entry 6 in Table 2 and entry 14 in Table 1). This type of "mixed-metal cation effect" was observed in the asymmetric nitroolefination.[22] The reactions were conducted in the presence of additional LiCl to determine if LiCl, which was formed in situ under the reaction conditions, played an important role.[23] Adding LiCl considerably increased the ee when *n*-BuLi was used as the base (entries 9 and 10), but not as much as entry 7, which indicates that ligand exchange to the chloride is partially responsible for the increase in ee, but other factor should be considered. Adding LiCl before or after anion formation when ZnEt$_2$ was the base gave a lower ee than without LiCl (compare entries 11 and 12 in Table 2 with entry 14 in Table 1). The structural changes in the malonate anion including the aggregation stage may be responsible for the dramatic increase in ee in entry 7.

To shed light on the mechanistic picture of the current asymmetric allylic alkylation with **1**, branched isomers **6a**[11b,c] and **6b**[17] were allylated under various conditions. Table 3 lists the results. Branched isomer **6a** gave divergent results that depended upon the reaction conditions. When ZnEt$_2$ was the base in CH$_2$Cl$_2$, the chiral ligand (*S*)-**1** was powerful enough to override the stereochemistry of substrate **6a** to yield (*S*)-**7** in a moderate ee regardless the absolute sense of the starting material (entries 1−4). A dynamic kinetic resolution[24,25] occurred

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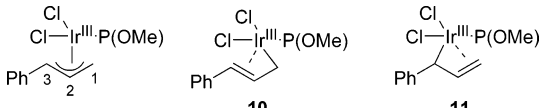
with racemic **6a** (entry 3). These results are consistent with a mechanism proposed by Takeuchi et al., which involves a π-allyl iridium complex as a crucial intermediate.[4]

Entirely different results, which displayed a memory effect,[26] were obtained with a zinc enolate generated by $ZnEt_2$ in THF as a solvent (entries 12−14). An intensive memory effect also occurred with the zinc enolate generated by a metal exchange with lithium enolate (entries 9 and 10) and for the lithium enolate (entries 6, 7, 15, and 16). Although the chiral ligand slightly influenced the absolute sense of chirality of the product (entries 8, 11, and 17), the absolute sense of the product mainly depended upon the absolute stereochemistry of the starting material. These results are in accord with Helmchen's observation, which favored a σ-allyl iridium complex as an intermediate. When NaH was the base, the effects of the ligand and the substrate counterbalance each other, leading to nearly racemic **7** from (*S*)-**6a** with (*S*)-**1** as a ligand (entry 5). It was obvious that the mechanistic spectrum of the current iridium-catalyzed reaction strongly depended upon the reaction conditions.

The interconversion of iridium(III) allyl complexes is believed to involve a $\pi-\sigma-\pi$ rearrangement. Reported X-ray structures of iridium(III) η^3-allyl complexes indicate that the bond lengths of the two carbon−carbon bonds in an allylic system are unequal when the allylic system has a substituent, which means that one bond has a single bond character and the other has a double-bond character.[27] This type of complex is called a $\sigma-\pi^2$ complex,[28] or an enyl ($\sigma + \pi$) complex.[28,29] Evans et al. indicated an intermediate enyl ($\sigma + \pi$) complex in the rhodium-catalyzed allylic alkylation.[30] Herein a η^3-allyl complex is employed in our mechanistic consideration since model calculations with the iridium(III) allyl complexes **9**, **10**, and **11** revealed that the η^3-complex **9** is more stable than the discrete enyl ($\sigma + \pi$) complexes **10** and **11** by 5.0 and 7.7 kcal/mol, respectively (the protocol for the calculations is clarified in the Experimental Section). In η^3-complex **9**, electrons are unsymmetrically distributed between the terminal carbons in the allylic system (Figure 1). The Ir−C(3) bond (2.256 Å) is longer than that of Ir−C(1) (2.176 Å), which leads to the preferential attack of a nucleophile at C(3), which causes back-bonding to the electron-deficient iridium(III) atom.[31]



Meanwhile, the ^{1}H NMR spectrum of a 1:2 mixture of dimethyl malonate and $ZnEt_2$ reveals that ethylzinc enolate is completely formed in THF-d_8 within 30 min.

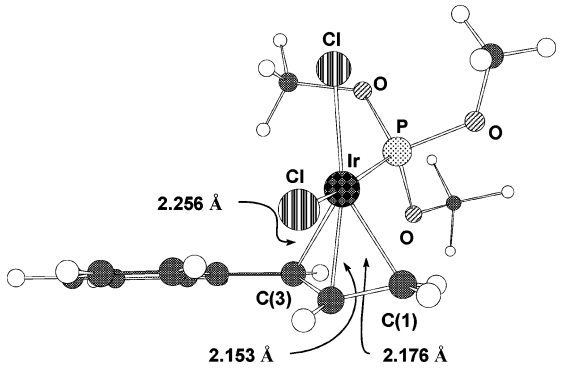


FIGURE 1. Optimized structure of **9**.

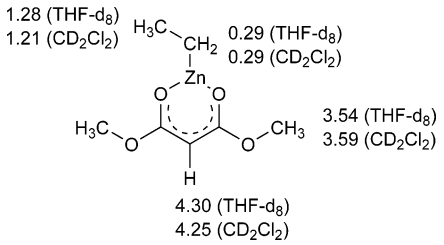


FIGURE 2. Chemical shifts of ethylzinc enolate of dimethyl malonate.

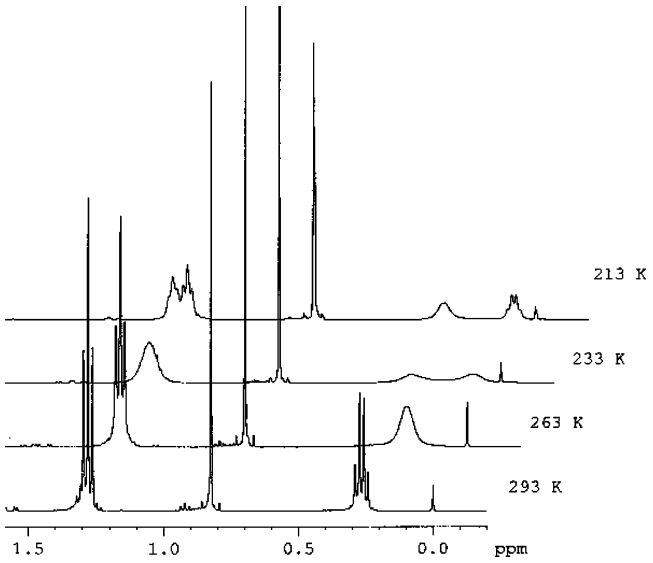


FIGURE 3. Portion of the temperature-dependent ^{1}H NMR spectra of a 1:2 mixture of dimethyl malonate and Et_2Zn in THF-d_8.

As shown in Figure 2, the chemical shifts of the enolate in THF-d_8 are nearly identical to those in CD_2Cl_2, indicating that the structures of enolate including the aggregation state are similar. Thus, in the cases of entries 1, 2, 12, and 13 in Table 3, chirality of the product is mainly controlled by the electrophile. The signals of the ethyl group in the enolate and $ZnEt_2$ are not separated due to the rapid exchange on the NMR time scale (Figure 3). A clear quartet of the methylene group at 20 °C becomes two distinct signals at −60 °C via a coalescence temperature at about −30 °C. A similar type of exchange between an ethylzinc α-amino ester enolate and $ZnEt_2$ is reported.[32]

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Conclusion

We have shown that in CH_2Cl_2 the chiral ligand was powerful enough to override the stereochemistry of substrate to give the product with nearly the same ee regardless absolute sense of the starting material, but a memory effect is observed in THF. These results indicate that the choice of the solvent is very important for improving the yield and ee in the transition metal-catalyzed reactions.

Another interesting finding is that the chlorozinc enolate displayed a marked reactivity toward the iridium complex to give an extremely high ee. Although the origin remains to be clarified, using a chlorozinc enolate, which is easily prepared in situ by adding $ZnCl_2$ to the lithium enolate, may be the method of choice for increasing the ee of the transition metal-catalyzed reactions. We are currently investigating these possibilities.

Experimental Section

(*S*)-1,1′-Binaphthyl-2,2′-diyl 4-Trifluoromethylphenyl Phosphite (3). A solution of PCl_3 (1.05 mL, 12 mmol) in CH_2Cl_2 (10 mL) was gradually added to a suspension of imidazole (5.72 g, 84 mmol) in CH_2Cl_2 (40 mL) under argon at room temperature. After being stirred for 1 h, (*S*)-1,1′-bi-2-naphthol (2.29 g, 8 mmol) was added and the mixture was stirred for an additional 2 h. Then 4-trifluoromethylphenol (1.30 g, 8 mmol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred for 37 h, filtered, and evaporated to give a residue which was partitioned between water and Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a powder (2.5 g). Column chromatography over silica gel (AcOEt/hexane = 3/97) afforded crystalline (*S*)-**3** (1.38 g, 36%). An analytical sample was obtained by washing with hexane. Mp: 134−136 °C, ee > 99%, determined by HPLC (CHIRALPAK AD, 2-propanol/hexane = 1/99, flow rate 1.0 mL/min, t_R 10 min for (*S*)-**3**, 19 min for (*R*)-**3**). ^{1}H NMR ($CDCl_3$): δ 7.25−7.48 (m, 9H), 7.58 (t, J = 8.8 Hz, 3H), 7.89−7.96 (m, 3H), 8.02 (d, J = 8.8 Hz, 1H). ^{31}P NMR ($CDCl_3$, 85% H_3PO_4): δ 143.7 (s). $[\alpha]^{25}_D$: +225.2 (*c* 1.0, THF). IR (KBr): 1613, 1511, 1325, 1217, 824 cm^{-1}. MS *m/z*: 476 (M^+, base peak), 315, 268, 252, 239. HRMS *m/z*: calcd for $C_{27}H_{16}F_3O_3P$ (M^+) 476.0789, found 476.0781. Anal. Calcd for $C_{27}H_{16}F_3O_3P$: C, 68.07; H, 3.39. Found: C, 67.69; H, 3.29.

Dimethyl (1-Phenylprop-2-en-1-yl)malonate (7, R^1 = H) and Dimethyl [(2*E*)-3-Phenylprop-2-en-1-yl]malonate (8, R^1 = H).[11c,12d,17] **General Procedure.** A mixture of the phosphite ligand (0.2 mmol, 40 mol %) and $[Ir(cod)Cl]_2$ (34 mg, 0.05 mmol, 10 mol %) in the solvent (1 mL) indicated in Tables 1−3 was stirred under ice-cooling in the argon atmosphere. After 10 min, acyl cinnamate **4**, **5**, or isocinnamate **6** (0.5 mmol) in THF (0.5 mL) was added to the solution to give orange color, which was stirred for 1 h at room temperature resulting in the catalyst solution. To the anion, prepared from dimethyl malonate under the conditions described in Tables 1−3, was added the catalyst solution cooled at 0 °C through a Teflon tube, and the mixture was stirred for the time shown in Tables 1−3. After the addition of 1 N HCl, the reaction mixture was extracted with AcOEt. The organic layer was successively washed with aq $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated to dryness. Preparative thin-layer chromatography (PTLC) on silica gel (AcOEt/hexane = 1/7) of the residue gave a mixture of dimethyl (1-phenylprop-2-en-1yl)malonate **7** (R^1 = H) and dimethyl [(2*E*)-3-phenylprop-2-en-1-yl]malonate **8** (R^1 = H). $[\alpha]^{22}_D$: −29.2 (*c* 1.1, $CHCl_3$)[11a,33,34] for the product **7** (R^1 = H, 96% ee) in the entry 7 in Table 2. The ratio of **7** (R^1 = H) to **8** (R^1 = H) was determined by ^{1}H NMR and/or GLC (Chirasil-DEX CB column, 0.25 mm × 25 m, injection temp 150 °C, oven temp 180 °C, t_R 4.3 min for **7** (R^1 = H) and 7.2 min for **8** (R^1 = H). The ee of **7** (R^1 = H) was determined by HPLC (CHIRALCEL OJ-R, MeOH/H_2O = 75/25, flow rate 0.5 mL/min, t_R 30 min for the (*S*)-isomer and 34 min for the (*R*)-isomer.

Dimethyl (1-(4-Methoxyphenyl)prop-2-en-1-yl)malonate (7, R^1 = OMe) and Dimethyl [(2*E*)-3-(4-Methoxyphenyl)-prop-2-en-1-yl]malonate (8, R^1 = OMe).[11a,c] The ratio of these two products was determined by ^{1}H NMR, and the ee of the former was determined by (CHIRALCEL OD, 2-propanol/hexane = 2/98, flow rate 0.5 mL/min, t_R 29 min for the (*R*)-isomer and 34 min for the (*S*)-isomer. The absolute configuration of the branched product **7** (R^1 = OMe) was determined by the optical rotation ($[\alpha]_D^{25}$: −13.3 (*c* 1.0, $CHCl_3$)[11a] for the product in entry 17 in Table 1).

Density Functional Theory (DFT) Calculations of Ir(III)−Allyl Complexes. The DFT calculations were performed with a Gaussian 98 package,[35] employing the B3LYP hybrid functional[36] and a basis set consisting of the LANL2DZ basis set including a double-ζ valence basis set with the Hay and Wadt effective core potential (ECP) for Ir[37] and the 6-31G(d) for the rest.[38] After thorough examination of various coordination geometries of a simple model complex $Ir^{III}(PH_3)(allyl)Cl_2$, three favorable geometries of more realistic model (**9**−**11**) were obtained.

Supporting Information Available: Table of coordinates for minimized structure **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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