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Retention of Regiochemistry and Chirality in the Ruthenium Catalyzed Allylic Alkylation of Disubstituted Allylic Esters

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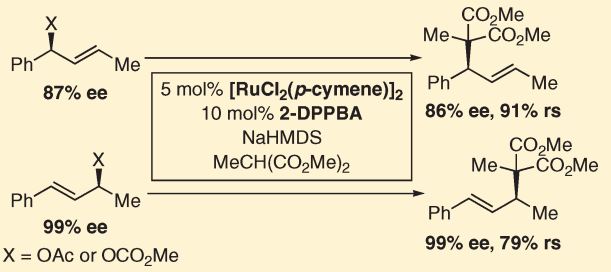
Supporting Information

ABSTRACT: The regiospecific nucleophilic substitution during the ruthenium catalyzed allylic alkylation of 1,3-unsymmetrical disubstituted allylic esters was demonstrated. The nucleophile was selectively introduced at the position originally substituted with leaving group in the 2-DPPBA or *ip*-pybox ligated $[RuCl_2(p\text{-cymene})]_2$ catalyzed allylic alkylation of 1,3-unsymmetrical disubstituted allylic esters. The chirality of the optically active allylic esters was also transferred to the alkylated products.



The transition metal-catalyzed allylic alkylation of allylic substrates is one of the most well-studied carbon−carbon bond formation reactions,[1] and the palladium-catalyzed allylic alkylation of allylic esters with malonate anions is a representative reaction system.[2] However, within recent years, several alternative transition metal catalysts containing metals such as iridium,[3] rhodium,[4] ruthenium,[5] tungsten,[6] iron,[7] and molybdenum[8] have also been reported. The reaction of two types of 1,3-unsymmetrical disubstituted allylic substrates potentially forms two types of regioisomers, and the regioselectivity depends on the type of the transition metal catalyst employed in the reaction. It has been observed that the reaction of either of the 1,3-unsymmetrical regioisomeric allylic substrates gives the same regioisomer in the transition metal-catalyzed allylic alkylations because the reaction generally proceeds via a π-allyl metal intermediate and the regiochemistry of the starting allylic substrate is lost during the reaction. However, several examples of an unusual regiochemical outcome, which is the selective substitution at the position originally substituted by the leaving group, were observed in the reactions when using the palladium,[9] rhodium,[4a,10] or iron[11] catalysts. We also observed the retention of the regiochemistry of the allylic esters during the $[RuCl_2(p\text{-cymene})]_2/PPh_3$ catalyzed allylic alkylation, but the allylic substrates were limited to the monosubstituted allylic acetates.[12,13] We now report the regiospecific nucleophilic substitution in the ruthenium-catalyzed allylic alkylation of 1,3-unsymmetrical disubstituted allylic esters.

We initially examined the allylic alkylation of the 1,3-unsymmetrical disubstituted allylic acetates **1** and **2** by $[RuCl_2(p\text{-cymene})]_2$ with a ligand. Typically, the reaction was carried out as follows: 5 mol % of $[RuCl_2(p\text{-cymene})]_2$, 10 mol % of phosphine ligand, and the allylic acetate **1** or **2** were allowed to react with the dimethyl methylmalonate anion, which was generated in situ from dimethyl methylmalonate and NaHMDS, in toluene. Substrates **1** and **2** were usually consumed (100% conversion) within 12 h. As shown in Table 1, the alkylation of **1a** in the presence of the ruthenium catalyst coordinated with PPh_3, which is our reported catalyst system,[12] took place and provided **3** in 65% yield with a 93% regioselectivity (Table 1, entry 1). The yield increased by changing the substrate from the allylic acetate **1a** to the allylic carbonate **1b**, and 2-(diphenylphophino)benzoic acid (2-DPPBA)[5f] gave a better result than PPh_3, although the regioselectivity was slightly decreased (entries 1−3). We next examined the reaction of **2**, which is a regioisomer of **1a**. When PPh_3 was used as the ligand, the reaction gave a complex mixture (entry 4), but the expected regiospecific allylic alkylation reaction proceeded using the 2-DPPBA ligated ruthenium catalyst and afforded the corresponding alkylated product **4** in excellent yield with over 89% regioselectivity (entries 5 and 6). These results clearly indicated that the nucleophile was selectively introduced at the position originally carried by the leaving group in the $[RuCl_2(p\text{-cymene})]_2$/2-DPPBA-catalyzed allylic alkylation of the 1,3-unsymmetrical disubstituted allylic esters.

We next switched allylic substrates to other types of unsymmetrical disubstituted allylic esters **5** and **6** and investigated the alkylation reaction using the ruthenium catalyst and found that it was regiospecific. As shown in Table 2, the reaction of **5** smoothly proceeded by $[RuCl_2(p\text{-cymene})]_2$ with a ligand, and a better yield and improved regioselectivity were again obtained when the ligand was changed from PPh_3 to 2-DPPBA (entries 1 and 2). Especially, the reaction of **5** using the 2-DPPBA ligated ruthenium catalyst at 40 °C in THF exhibited a perfect regioselectivity and afforded **7** in 88% yield (entry 3). As expected, the reaction of **6a**, which is a regioisomer of **5**, produced a product **8** as a single regioisomer, but the yield was low (entries 4 and 5). Again, we examined several types of ligands, such as monophosphines,

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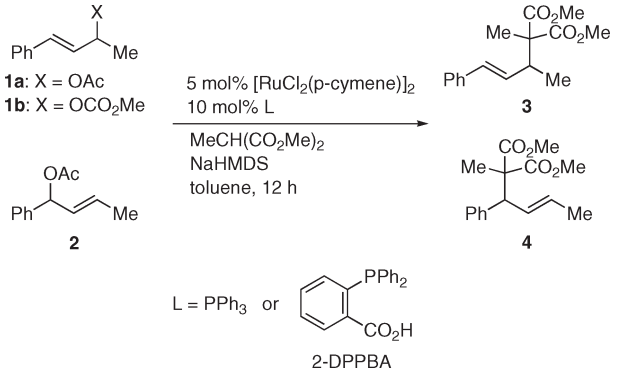
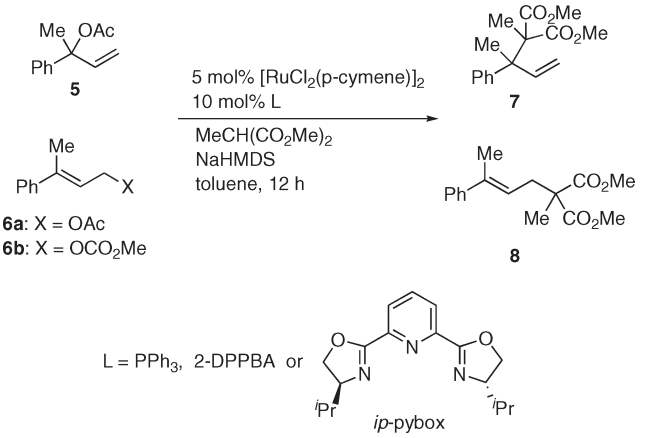
Table 1. Ruthenium-Catalyzed Allylic Alkylation of 1,3-Disubstituted Allylic Esters 1 and 2[a]



entry	substrate	L	temp. (°C)	yield (%)	3:4[b]
1	**1a**	PPh_3	100	65	93:7
2	**1a**	2-DPPBA	100	87	77:23
3	**1b**	2-DPPBA	100	89	80:20
4	**2**	PPh_3	60	<10	ND
5	**2**	2-DPPBA	60	96	11:89
6	**2**	2-DPPBA	40	99	9:91

[a] Reaction conditions: allylic esters (**1** or **2**) (0.28 mmol), $MeCH_2(CO_2Me)_2$ (0.42 mmol), NaHMDS (0.4 mmol, 1.0 M in THF), 5 mol % of $[RuCl_2(p\text{-cymene})]_2$, and 10 mol % L in toluene (0.4 mL). [b] Ratio was determined by ^1H NMR of the crude materials.

Table 2. Ruthenium-Catalyzed Allylic Alkylation of Disubstituted Allylic Esters 5 and 6[a]



entry	substrate	L	temp. (°C)	yield (%)	7:8[b]
1	**5**	PPh_3	60	66	96:4
2	**5**	2-DPPBA	60	86	97:3
3[c]	**5**	2-DPPBA	40	88	>98:2
4	**6a**	PPh_3	100	39	2:>98
5	**6a**	2-DPPBA	100	45	2:>98
6	**6b**	PPh_3	100	70	8:92
7	**6b**	2-DPPBA	100	45	2:>98
8	**6b**	*ip*-pybox	100	81	2:>98

[a] Reaction conditions: allylic esters (**5** or **6**) (0.28 mmol), $MeCH_2(CO_2Me)_2$ (0.42 mmol), NaHMDS (0.4 mmol, 1.0 M in THF), 5 mol % of $[RuCl_2(p\text{-cymene})]_2$, and 10 mol % **L** in toluene (0.4 mL). [b] Ratio was determined by ^1H NMR of the crude materials. [c] THF was used as the solvent.

bisphophines, bisoxazolines, bisimines, and pybox type ligands etc., for the allylic alkylation of **6b**, then determined that the reaction of the allylic carbonate **6b** by $[RuCl_2(p\text{-cymene})]_2$ with *ip*-pybox gave **8** in 81% yield with complete regioselectivity (entry 8). We thus confirmed that the regiospecific nucleophilic substitution had also occurred in the reactions of the regioisomeric allylic esters **5** and **6**.

We also examined the reaction of the enantiomerically enriched allylic esters (Scheme 1).[5c,14] The reaction of the enantiomerically enriched monosubstituted allylic acetate (*S*)-**9** (95% ee) using our previously reported catalyst[12] ($[RuCl_2(p\text{-cymene})]_2/2PPh_3$) gave a branch-type product (*S*)-**10** with a high regioselectivity (96% rs), but the enantiomeric excess of (*S*)-**10** decreased to 84% ee (Scheme 1, eq 1). Changing the ligand from PPh_3 to 2-DPPBA effectively retained the chirality of the substrate, and we succeeded in obtaining (*S*)-**10** with a 94% ee. We further attempted the reactions of the enantiomerically enriched 1,3-disubstituted allylic substrates, such as (*S*)-**1b** and (*S*)-**2**, by $RuCl_2(p\text{-cymene})$/2-DPPBA catalyst (eq 2 and 3). In both reactions, we observed an almost perfect chirality transfer from the allylic substrates (*S*)-**1b** (99% ee) and (*S*)-**2** (87% ee) to the alkylated products (*S*)-(*E*)-**3** (99% ee) and (*S*)-(*E*)-**4** (86% ee), respectively. Furthermore, we confirmed that the reaction of the enantiomerically enriched (*R*)-**5** (95% ee) gives a 95% ee of (*R*)-**7**, which has a enantiomerically enriched quaternary carbon center, in 83% yield with a perfect regioselectivity (>98% rs) at room temperature (eq 4). It is obvious that in all the reactions, the chirality of the allylic substrates was transferred to the products in a regiospecific manner, and there are no epimerization steps. Generally, the π-allylruthenium,[5e,14,15] σ-allylruthenium, or σ-enylruthenium[14a] complexes are possible reaction intermediates in the ruthenium-catalyzed allylic alkylation. Although the details of the reaction mechanism involved in the retention of the regiochemistry in the 2-DPPBA ligated $[RuCl_2(p\text{-cymene})]_2$-catalyzed allylic alkyaltion are still not clear, our present results may also support the fact that the reaction proceeds with double inversion mechanism through the σ-allyl or σ-enyl complexes like the rhodium-catalyzed reaction.[4a,13] Further investigations about the mechanistic details and the reactions of other types of substrates, such as (*Z*)-substrates, will be the subject of a future study.

In conclusion, we examined the retention of the regiochemistry and chirality during the ruthenium-catalyzed allylic alkylation of the 1,3-unsymmetrical disubstituted allylic esters. The regioselective introduction of a nucleophile at the position originally substituted with leaving group of the allylic esters and chirality transfer occurred using the 2-DPPBA or *ip*-pybox ligated $[RuCl_2(p\text{-cymene})]_2$ catalysts.

EXPERIMENTAL SECTION

General and Materials. All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. NMR spectra were recorded on a 500 MHz (for ^1H) and 125 MHz (for ^{13}C) instrument. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^1H NMR. Residual chloroform (δ 77.0 for ^{13}C) was used as internal reference for ^{13}C NMR. $[RuCl_2(p\text{-cymene})]_2$, 2-DPPBA, *ip*-pybox and other reagents, including solvents, were purchased from common commercial sources and used without further

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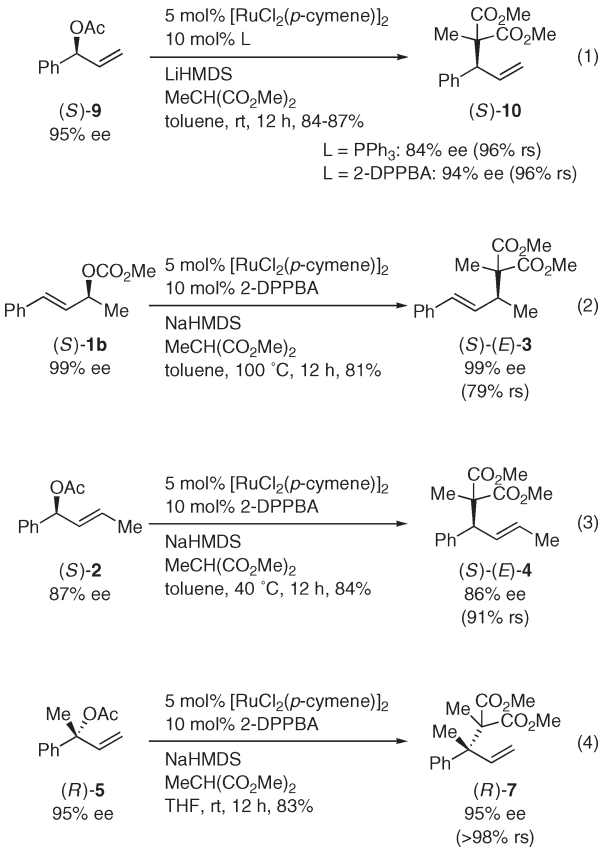
Scheme 1. Ruthenium-Catalyzed Allylic Alkylation of Chiral Allylic Esters



purification. Allylic esters (**1a**−**b**,[16] **2**,[17] **5**,[18] and **6a**−**b**[18]) and optically active allylic esters [(*S*)-**1b**,[16] (*S*)-**2**, (*R*)-**5**, and (*S*)-**9**[19]] were prepared according to the literature.

General Procedure for the Ruthenium-Catalyzed Allylic Alkylation of 1, 2, 5, and 6. A typical procedure is given for the reaction of **1b** (Table 1, entry 3). To a solution of $[RuCl_2(p\text{-cymene})]_2$ (8.6 mg, 0.014 mmol) and 2-DPPBA (8.6 mg, 0.028 mmol) in anhydrous toluene (0.4 mL) were added **1b** (58 mg, 0.28 mmol) and dimethyl methylmalonate (61 mg, 0.42 mmol). NaHMDS (0.4 mmol, 0.4 mL of 1.0 M in THF) was slowly added at 0 °C, and the reaction mixture stirred at 100 °C for 12 h. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers dried over $MgSO_4$ and evaporated. The ratio of **3** to **4** was determined to be 80:20 by ^{1}H NMR of the crude materials. The residue was chromatographed on silica gel (hexane/ethyl acetate = 99/1) to give 69 mg (89%) of **3** and **4**.

Dimethyl 2-Methyl-2-((*E*)-4-phenylbut-3-en-2-yl)malonate (3[20]). Yield: 89% (Table 1, entry 3). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (d, J = 5.6 Hz, 3H), 1.39, (s, 3H), 3.15 (dq, J = 5.6, 8.6 Hz, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 6.14 (dd, J = 8.6, 16.1 Hz, 1H), 6.43 (d, J = 16.1 Hz, 1H), 7.19−7.22 (m, 1H), 7.27−7.34 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.1, 17.0, 42.1, 52.4, 57.8, 126.3, 127.3, 128.5, 130.5, 131.5, 137.3, 171.8. IR (neat) 2998, 2952, 1732, 1494, 1449, 1262, 1106, 971, 747 cm^{-1}.

(*S*)-(*E*)-**3**: HRMS (ESI): m/z: calcd for $C_{16}H_{21}O_4^+$ $[M + H]^+$ 277.1440, found 277.1433. $[\alpha]_D^{27}$ −28.8 (c 0.4, $CHCl_3$) (99% ee). Enantiomer ratio was determined by HPLC using a Daicel CHIRALCEL OJ-H (hexane/2-propanol = 99/1, flow: 1.0 mL/min, 254 nm, 35 °C, t_R 15.5 min (major); t_R 20.9 min (minor)). The absolute configuration was determined to be *S* by comparison with the sign of optical rotation of (*S*)-**3** ($[\alpha]_D^{25}$ −35.2 (c 1.0, $CHCl_3$) (99% ee)), which was obtained by the methylation of dimethyl 2-((*S*,*E*)-4-phenylbut-3-en-2-yl)malonate[21] (99% ee) with NaH, MeI in THF.

Dimethyl 2-Methyl-2-((*E*)-1-phenylbut-2-enyl)malonate 4[20]. Yield: 99% (91:9 ratio) (Table 1, entry 6). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.66 (d, J = 6.9 Hz, 3H), 3.60 (s, 3H), 3.70 (s, 3H), 4.11 (d, J = 9.1 Hz, 1H), 5.50 (dq, J = 6.9, 15.9 Hz, 1H), 5.93 (dd, J = 9.1, 15.9 Hz, 1H), 7.19−7.28 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.1, 18.2, 52.3, 52.3, 53.6, 59.1, 126.9, 128.1, 128.8, 129.2, 129.4, 139.8, 171.4, 171.6.

(*S*)-(*E*)-**4**: HRMS (ESI): m/z: calcd for $C_{16}H_{21}O_4^+$ $[M + H]^+$ 277.1440, found 277.1429. IR (neat) 2952, 1732, 1452, 1434, 1242, 1111, 971 cm^{-1}. $[\alpha]_D^{25}$ 5.6 (c 0.5, $CHCl_3$) (86% ee). Enantiomer ratio was determined by HPLC using a Daicel CHIRALCEL OJ-H (hexane/2-propanol = 99/1, flow: 0.4 mL/min, 254 nm, 35 °C, t_R 18.7 min (minor); t_R 21.5 min (major)). The absolute configuration was determined to be *S* by comparison with the sign of optical rotation of (*S*)-**4** ($[\alpha]_D^{24}$ +8.6 (c 2.1, $CHCl_3$) (99% ee)), which was obtained by the methylation of dimethyl 2-((*S*)-1-phenylbut-2-enyl)malonate[21] (89% ee) with NaH, MeI in THF.

Dimethyl 2-Methyl-2-(2-phenylbut-3-en-2-yl)malonate 7. Yield: 88% (>98:2 ratio) (Table 2, entry 3). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (s, 3H), 1.71 (s, 3H), 3.59 (s, 3H), 3.61 (s, 3H), 5.02 (dd, J = 1.1, 17.8 Hz, 1H), 5.21 (dd, J = 1.1, 10.8 Hz, 1H), 6.88 (dd, J = 10.8, 17.8 Hz, 1H), 7.17−7.21 (m, 1H), 7.23−7.27 (m, 2H), 7.38−7.41 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.5, 22.9, 49.0, 52.0, 52.0, 61.3, 114.3, 126.5, 127.3, 128.6, 143.8, 144.1, 171.6, 171.6. IR (neat) 2999, 2952, 1732, 1433, 1259, 1111, 921, 755, 703 cm^{-1}.

(*R*)-**7**: HRMS (ESI): m/z: calcd for $C_{16}H_{21}O_4^+$ $[M+H]^+$ 277.1440, found 277.1431. $[\alpha]_D^{22}$ −103 (c 0.5, $CHCl_3$) (95% ee). Enantiomer ratio was determined by HPLC using a Daicel CHIRALCEL OJ-H (hexane/2-propanol = 199/1, flow: 1.0 mL/min, 215 nm, 35 °C, t_R 18.7 min (minor); t_R 21.5 min (major)). The absolute configuration was determined to be *R* by comparison with the sign of optical rotation of (*R*)-**7** ($[\alpha]_D^{24}$ −16.2 (c 0.6, $CHCl_3$) (66% ee)), which was obtained by the methylation of dimethyl 2-((*S*)-2-phenylbut-3-en-2-yl)malonate[22] (65% ee) with NaH, MeI in THF.

Alkylated Product 8[23]. Yield: 81% (2:>98 ratio) (Table 2, entry 8). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 3H), 1.97 (d, J = 1.8 Hz, 3H) 2.72 (d, J = 7.5 Hz, 2H), 3.65 (s, 6H), 5.53 (dt, J = 1.8, 7.5 Hz, 1H), 7.13−7.17 (m, 1H), 7.20−7.26 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.1, 20.0, 34.8, 52.5, 53.9, 121.7, 125.8, 126.9, 128.2, 138.7, 143.7, 172.5.

Dimethyl 2-Methyl-2-((*S*)-1-phenylallyl)malonate (*S*)-10[9c]. Yield: 85% (4:96 ratio) (Scheme 1). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 3H), 3.62 (s, 3H), 3.71 (s, 3H), 4.15 (d, J = 8.7 Hz, 1H), 5.11 (d, J = 17.2 Hz, 1H), 5.14 (d, J = 10.3 Hz, 1H), 6.32 (ddd, J = 8.7, 10.3, 17.2 Hz, 1H), 7.22−7.28 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.4, 52.4, 52.4, 54.5, 58.8, 117.8, 127.1, 128.2, 129.5, 136.8, 139.0, 171.3, 171.5. $[\alpha]_D^{22}$ 22.1 (c 1.0, $CHCl_3$) (94% ee) {lit.[9c] $[\alpha]_D^{20}$ 46.4 (c 1.8, $CHCl_3$) (86% ee)}. Enantiomer ratio was determined by HPLC using a Daicel CHIRALCEL OJ-H (hexane/2-propanol = 99/1, flow: 1.0 mL/min, 254 nm, 35 °C, t_R 9.1 min (major); t_R 10.5 min (minor)). The absolute configuration was determined to be *S* by comparison with the sign of optical rotation of (*S*)-**10** ($[\alpha]_D^{24}$ 23.8 (c 2.2, $CHCl_3$) (94% ee)), which was obtained by the methylation of dimethyl 2-((*S*)-1-phenylallyl)malonate[24] (95% ee) with NaH, MeI in THF.

Preparation of Optically Active Allylic Acetate (*S*)-2. Allylic acetate (*S*)-**2** was obtained by treatment of the corresponding chiral alcohol[25] with acetic anhydride and pyridine. Experimental procedure: To a solution of chiral alcohol (577 mg, 3.9 mmol), pyridine (0.5 mL, 5.8 mmol) and catalytic amount of 4-dimethylaminopyridine in CH_2Cl_2 (8 mL) was added acetic anhydride (0.45 mL, 4.7 mmol). The mixture was stirred at room temperature for 12 h, quenched with saturated $CuSO_4$ solution, and extracted with ether. The organic phase was

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washed with water and brine, dried over $MgSO_4$, and evaporated. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 95/5) to give 580 mg (78%) of chiral (*S*)-**2** as colorless oil. $[\alpha]_D^{27}$ 5.2 (*c* 1.8, $CHCl_3$) (87% ee). Enantiomer ratio was determined by HPLC using a Daicel CHIRALCEL OJ-H (hexane/2-propanol = 99/1, flow: 1.0 mL/min, 254 nm, 35 °C, t_R 6.7 min (minor); t_R 7.2 min (major)).

(*S*)-1-Phenylbut-2-enyl Acetate ((*S*)-2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.72 (d, *J* = 5.7 Hz, 3H), 2.09 (s, 3H), 5.67 (ddq, *J* = 1.4, 6.8, 15.1 Hz, 1H), 5.76 (dqd, *J* = 0.7, 5.7, 15.1 Hz, 1H), 6.22 (d, *J* = 6.8 Hz, 1H), 7.27−7.36 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17,7, 21.3, 76.3, 126.8, 127.9, 128.4, 129.5, 129.6, 139.7, 170.0. IR (neat) 3033, 2918, 1735, 1452, 1370, 1237, 1017, 962 755, 697 cm^{-1}. HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{15}O_2^+$ ($M + H^+$) 191.1072, found 191.1066.

Preparation of Optically Active Allylic Acetate (*R*)-5. Allylic acetate (*R*)-**5** was obtained by treatment of the corresponding chiral alcohol[26] with acetyl chloride and *n*-butyllithium. Experimental procedure: To a solution of chiral allyl alcohol (413 mg, 2.79 mmol) and catalytic amount of 1,10-phenanthroline in THF was added 2.6 M *n*-butyllithium in hexane (1.3 mL, 2.6 mmol) at −78 °C and stirred for 30 min. To this reaction mixture was added acetyl chloride (0.24 mL, 2.62 mmol) at −78 °C and stirred for 10 min. The mixture was allowed to warm to room temperature and stirred for 90 min. The reaction was quenched with saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with saturated sodium bicarbonate solution and brine, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 99/1) to give 147 mg (28%) of chiral (*R*)-**5** as colorless oil. $[\alpha]_D^{20}$ 1.2 (*c* 0.6, $CHCl_3$) (95% ee). Enantiomer ratio was determined by HPLC using a Daicel CHIRALCEL OJ-H (hexane/2-propanol = 49/1, flow: 1.0 mL/min, 215 nm, 35 °C, t_R 11.8 min (major); t_R 15.1 min (minor)).

(*R*)-2-Phenylbut-3-en-2-yl Acetate ((*R*)-5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.88 (s, 3H), 2.08 (s, 3H), 5.24 (dd, *J* = 0.8, 10.8 Hz, 1H), 5.27 (dd, *J* = 0.8, 17.5 Hz, 1H), 6.27 (dd, *J* = 10.8, 17.5 Hz, 1H), 7.23−7.27 (m, 1H), 7.32−7.38 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 25.4, 83.1, 114.4, 125.1, 127.2, 128.2, 141.5, 143.7, 169.4. IR (neat) 2988, 1743, 1447, 1244, 1016, 944, 765, 700 cm^{-1}. HRMS (ESI): *m*/*z*: calcd for $C_{12}H_{15}O_2^+$ ($M + H^+$) 191.1072, found 191.1066.

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR Spectra and HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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