Asymmetric Catalysis

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Catalytic Asymmetric Allenylation of Malonates with the Generation of Central Chirality**

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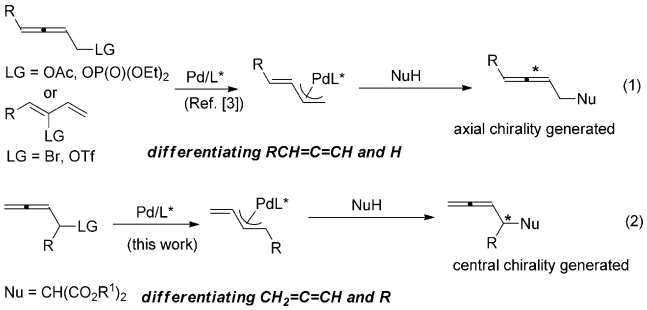
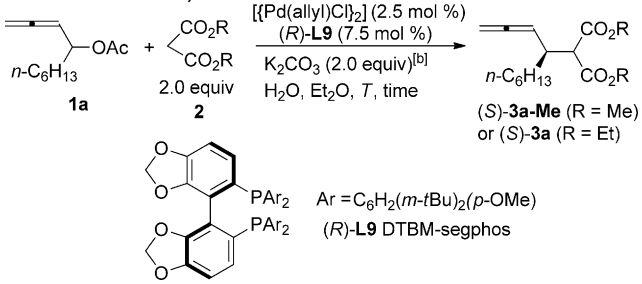
It is well-known that biomolecules exist mostly as single enantiomers. Since different enantiomers show different biological activities, asymmetric synthesis has always been of high interest. There is no universal approach to optically active compounds. Recent developments in the chemistry of allenes,[1] such as transition-metal-catalyzed reactions and radical, electrophilic, and nucleophilic addition reactions, may offer new efficient approaches, provided that optically active starting allene compounds are readily available. The malonate unit has been used as a tether for the synthesis of many complex molecules.[2] Thus, enantioselective approaches to 2-allenyl malonates are highly desirable. In pioneering studies on the palladium-catalyzed asymmetric construction of axially chiral allenyl malonates,[3] the remarkably different linear RCH=C=CH group and the hydrogen atom were differentiated [Scheme 1, Eq. (1)]. However, the synthesis of optically active 2-(2,3-alkadienyl)malonates with central chirality in the allene chain from racemic 2,3-alkadienyl precursors through differentiation of the relatively similar propadienyl and R groups is challenging [Scheme 1, Eq. (2)]. Herein, we describe the first example of such a reaction: a highly enantioselective synthesis of diethyl 2-(2,3-alkadienyl)malonates at room temperature.



Scheme 1. Transition-metal-catalyzed asymmetric allenylation. Tf = trifluoromethanesulfonyl.

In a comprehensive screening of ligands **L1**–**L9** (see Figure S1 in the Supporting Information) for the reaction of 2,3-allenyl acetate **1a** and dimethyl malonate (**2a**) in diethyl ether, the biphenyl ligand **L5** (Scheme 2) was promising (see Table S1 in the Supporting Information, entry 5 versus entries 1–4). Subsequent fine-tuning of the structure of the biphenyl ligand led to the identification of ligand (*R*)-**L9** as the most efficient (Table 1, entry 1). To our surprise, when commercial K_2CO_3 was baked in a Muffle furnace at 380 °C for 6 h and then used in the reaction, the yield determined by NMR spectroscopy dropped to 29%; **1a** was present at the end of the reaction in 42% yield (as determined by NMR spectroscopy; Table 1, entry 2). Thus, we explored the effect of the amount of water present on the yield (Table S2, entries 2–5) and found 1 equivalent of water to be optimal. At a lower reaction temperature, the enantioselectivity was

Table 1: Effect of water and fine-tuning of substrate **2** to improve the yield and enantioselectivity.[a]



Entry	R	H_2O [equiv]	*T* [°C]/ *t* [h]	Yield [%][c]	*ee* [%][d]
1[e]	Me (**2a**)	0	35/16	93	89 (**3a-Me**)
2[f]	Me (**2a**)	0	35/16	29	87 (**3a-Me**)
3	Me (**2a**)	1	20/16	94	90 (**3a-Me**)
4	Et (**2c**)	1	20/24	80	94 (**3a**)
5[g–i]	Et (**2c**)	1	20/24	84	94 (**3a**)

[a] Reaction conditions: **1a** (0.4 or 0.5 mmol), **2** (2.0 equiv), [{Pd(allyl)Cl}$_2$] (2.5 mol%), (*R*)-**L9** (7.5 mol%), K_2CO_3 (2.0 equiv), Et_2O (4 or 5 mL). [b] Commercial K_2CO_3 was used after it had been baked in a Muffle furnace at 380 °C for 6 h. [c] The yield was determined by NMR spectroscopy. [d] The *ee* value was determined by HPLC analysis on a chiral phase. [e] Commercial K_2CO_3 was used as obtained. [f] The starting allene **1a** was present in 42% yield at the end of the reaction, as determined by NMR spectroscopy. [g] The K_2CO_3 used in this reaction was bought from Alfa Aesar and used after it had been baked in a Muffle furnace at 380 °C for 6 h. [h] [{Pd(π-cinnamyl)Cl}$_2$] was used instead of [{Pd(allyl)Cl}$_2$]. [i] (*R*)-**L9**: 6.0 mol%.

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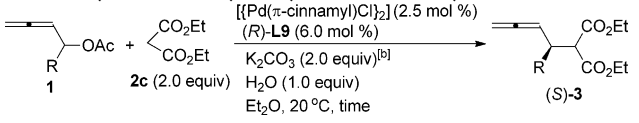
slightly higher (Table 1, entry 3). Interestingly, when dibenzyl malonate was used instead of dimethyl malonate, the *ee* value dropped to 82%. Further investigations showed that the reaction of diethyl malonate afforded **3a** with 94% *ee* (Table 1, entry 4; for details, see Tables S1 and S2 in the Supporting Information)! To establish a set of internationally reproducible standard reaction conditions, we used anhydrous K_2CO_3 bought from Alfa Aesar and dried in a Muffle furnace for 6 h for further study; this material afforded a very similar result. [{Pd(π-cinnamyl)Cl}$_2$] was then used instead of [{Pd(allyl)Cl}$_2$] as the metal catalyst for the sake of straightforward purification of the product through the removal of the catalyst-derived allylic malonate. Under these optimized conditions, 6.0 mol% of (*R*)-**L9** is enough for this transformation (Table 1, entry 5). The nature of the leaving group and the carbon nucleophile are also important for the enantioselectivity: the best results were observed with the allenyl acetate and diethyl malonate (Tables S3 and S4).

We studied the effects of solvents and bases in an attempt to improve the enantioselectivity and found Et_2O and K_2CO_3 to be the most suitable (Table S5, entries 1–9). The reaction at 10 °C gave the product with a higher *ee* value, but the reaction time was much longer (Table S5, entry 10). Thus, we defined the reaction conditions in entry 5 of Table 1 as optimal for further study.

We next explored the scope of the asymmetric allenylation of diethyl malonate with allenyl acetates under our optimized conditions (Table 2). The reaction is very general: when the length of the carbon chain of the R group was increased from ethyl to *n*-nonyl, the products were formed with very similar high *ee* values (93–95%; Table 2, entries 1–9). In particular, even an ethyl or propyl R group was recognized with remarkable enantioselectivity, although the size difference between the propadienyl group and the R group was so small. We also investigated the reaction of **1d** on a 1 g scale under the optimized conditions and isolated (*S*)-**3d** in 76% yield with 95% *ee* (Table 2, entry 4).

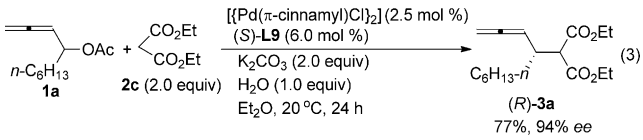
Table 2: Asymmetric allenylic alkylation of 2,3-allenyl acetates.[a]



Entry	R	*t* [h]	Yield [%][c]	*ee* [%][d]
1	Et (**1b**)	24	75	93 (**3b**)
2	*n*Pr (**1c**)	23	76	93 (**3c**)
3	*n*Bu (**1d**)	24	77	95 (**3d**)
4[e]	*n*Bu (**1d**)	24	76	95 (**3d**)
5	*n*-C_5H_{11} (**1e**)	24	78	95 (**3e**)
6	*n*-C_6H_{13} (**1a**)	24	81	94 (**3a**)
7	*n*-C_7H_{15} (**1f**)	26	78	93 (**3f**)
8	*n*-C_8H_{17} (**1g**)	27	75	93 (**3g**)
9	*n*-C_9H_{19} (**1h**)	26	75	93 (**3h**)

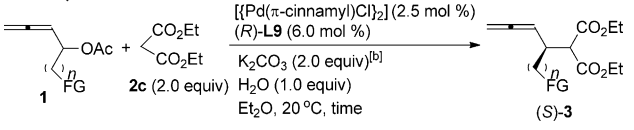
[a] Reaction conditions: **1** (0.5 mmol), **2c** (2.0 equiv), [{Pd(π-cinnamyl)Cl}$_2$] (2.5 mol%), (*R*)-**L9** (6.0 mol%), K_2CO_3 (2.0 equiv), H_2O (1.0 equiv), Et_2O (5 mL), 20 °C. [b] K_2CO_3 bought from Alfa Aesar was used after it had been baked in a Muffle furnace at 380 °C for 6 h. [c] Yield of the isolated product. [d] The *ee* value was determined by HPLC analysis on a chiral phase. [e] The reaction was conducted on a 1 g scale.

As expected, the reaction of **1a** with **2c** in the presence of (*S*)-**L9** as the ligand under the optimized conditions afforded the enantiomer (*R*)-**3a** in good yield with high enantioselectivity [Eq. (3)].



The reaction is sensitive to the steric bulkiness of the R group: reactions of substrates with a phenyl or isopropyl R group are extremely slow at room temperature. However, many synthetically useful functional groups, such as halide, −CN, −OH, −OAc, alkenyl, and alkynyl groups may be comfortably accommodated to afford the products with 92–96% *ee* (Table 3).

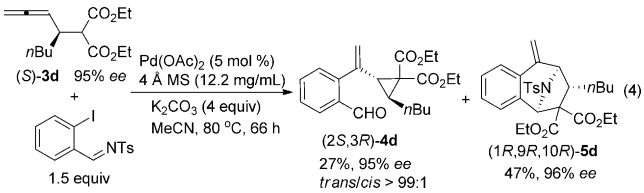
Table 3: Asymmetric allenylation with 2,3-allenyl acetates bearing synthetically useful functionalities.[a]



Entry	**1**	*n*	FG	*t* [h]	Yield [%][c]	*ee* [%][d]
1[e]	**1i**	5	Cl	26	72	94 (**3i**)
2	**1j**	8	vinyl	37	71	93 (**3j**)
3	**1k**	3	CN	36	83	95 (**3k**)
4	**1l**	5	OH	33	84	96 (**3l**)
5	**1m**	5	OAc	24	84	96 (**3m**)
6	**1n**	3	≡—TMS	47	72	92 (**3n**)

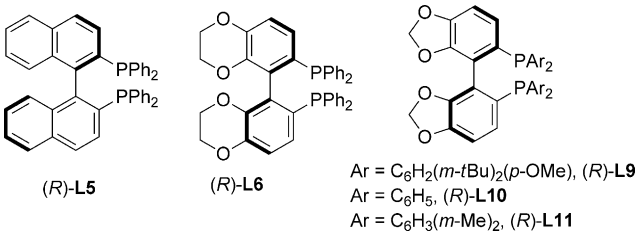
[a] Reaction conditions: **1** (0.5 mmol), **2c** (2.0 equiv), [{Pd(π-cinnamyl)Cl}$_2$] (2.5 mol%), (*R*)-**L9** (6.0 mol%), K_2CO_3 (2.0 equiv), H_2O (1.0 equiv), Et_2O (5 mL), 20 °C. [b] K_2CO_3 bought from Alfa Aesar was used after it had been baked in a Muffle furnace at 380 °C for 6 h. [c] Yield of the isolated product. [d] The *ee* value was determined by HPLC analysis on a chiral phase. [e] The reaction was conducted with [{Pd(allyl)Cl}$_2$] as the metal catalyst instead of [{Pd(π-cinnamyl)Cl}$_2$]. TMS = trimethylsilyl.

The absolute configurations of the products were assigned tentatively on the basis of an X-ray single-crystal diffraction study of (1*R*,9*R*,10*R*)-**5d**[4] (Figure S2), which was formed from (*S*)-**3d** according to our previously reported procedure[5] [Eq. (4); MS = molecular sieves, Ts = *p*-toluenesulfonyl].



To gain an understanding of the factors dictating the enantioselectivity observed with ligand **L9**, we carried out

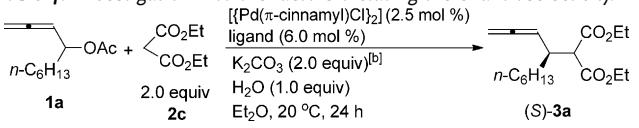
a number of control experiments with commercially available ligands (Scheme 2, Table 4).



Scheme 2. Ligands used in control experiments to unveil the role of each unit in ligand **L9**.

The enantioselectivities and catalytic activities observed with the Ph_2P-substituted ligands **L5** and **L6** were very similar; the reaction proceeded (albeit at a very slow rate) with higher enantioselectivity with another Ph_2P-substituted ligand, **L10**, most probably because of the presence of the two five-membered rings. As expected, the more electron-rich nature of the phosphorus atoms in **L11** as a result of the electron-donating Ar group greatly improved the activity of the oxidative addition to cleave the C–O bond in the allene **1a** (Table 4, entry 4). Thus, we conclude that in **L9**, the 4,4′-bibenzo[*d*][1,3]dioxole unit together with the bulky $C_6H_2(m\text{-}t\text{Bu})_2(p\text{-OMe})$ group are responsible for the high enantioselectivity, and the electron-rich nature of the phosphorus atoms leads to the high catalytic activity.

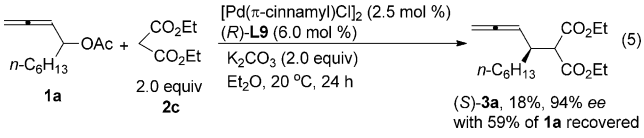
Table 4: Investigation into the factors dictating the enantioselectivity.[a]



Entry	Ligand	Recovery of **1a** [%][c]	Yield [%][d]	*ee* [%][e]
1	(*R*)-**L5**	22	51	48
2	(*R*)-**L6**	20	59	54
3	(*R*)-**L10**	66	9	67
4	(*R*)-**L11**	0	83	67
5	(*R*)-**L9**	0	81	94

[a] Reaction conditions: **1a** (0.5 mmol), **2c** (2.0 equiv), [{Pd(π-cinnamyl)Cl}$_2$] (2.5 mol %), chiral ligand (6.0 mol %), K_2CO_3 (2.0 equiv), H_2O (1.0 equiv), Et_2O (5 mL), 20 °C, 24 h. [b] K_2CO_3 bought from Alfa Aesar was used after it had been baked in a Muffle furnace at 380 °C for 6 h. [c] The quantity of **1a** was determined by NMR spectroscopy by analysis of the crude product with mesitylene as an internal standard. [d] Yield of the isolated product. [e] The *ee* value was determined by HPLC analysis on a chiral phase.

To explain the effect of water, we reasoned that the solubility of K_2CO_3 in water makes the two-phase reaction a three-phase reaction and increases the efficiency of deprotonation to generate the malonate anion, since it was noted that the enantioselectivity is almost the same in the absence of water: the difference lies in the yield [Eq. (5)]. In fact, it was observed by SEM studies (Hitachi SU 1510) that



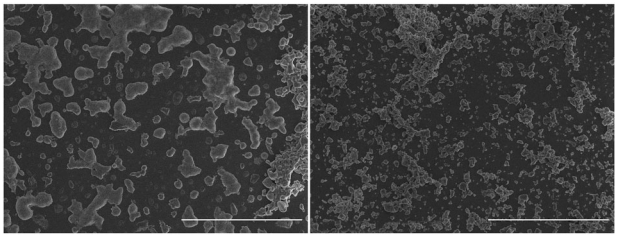


Figure 1. SEM of the ground anhydrous K_2CO_3 suspended in Et_2O in the absence (left) and presence of H_2O (1 equiv; right). Scale bar: 200 μm.

the particle size of K_2CO_3 in Et_2O upon the addition of water (1 equiv) with stirring (Figure 1, right) is much smaller than that of anhydrous K_2CO_3 (Figure 1, left; for detailed information, see the Supporting Information).

In conclusion, we have developed a highly enantioselective protocol for the asymmetric allenylation of diethyl malonate with racemic 2,3-allenyl acetates. Owing to the excellent generality of the reaction, its functional-group tolerance, the mild reaction conditions, the ready availability of all starting chemicals,[6] and the synthetic potential of the chiral products, this reaction will be of high interest for organic, materials, and medicinal chemists. We are pursuing further studies in this area, in particular the construction of both axial and central chirality in allenyl malonates.

Experimental Section

Typical procedure: [{Pd(π-cinnamyl)Cl}$_2$] (6.4 mg, 0.0125 mmol), (*R*)-DTBM-segphos (**L9**; 35.5 mg, 0.03 mmol), **1b** (70.5 mg, 0.5 mmol), and Et_2O (2.5 mL) were added sequentially to a Schlenk tube containing ground anhydrous K_2CO_3 (138.1 mg, 1.0 mmol) under nitrogen. Then **2c** (160.0 mg, 1.0 mmol), Et_2O (2.5 mL), and H_2O (9 μL, 0.5 mmol) were added sequentially with stirring, and the Schlenk tube was equipped with a reflux condenser to avoid loss of the solvent. The reaction was complete after the mixture had been stirred at 20 °C for 24 h, as monitored by TLC (eluent: petroleum ether/ethyl acetate (20:1)). After filtration through a short pad of silica gel with Et_2O (50 mL) and the evaporation of volatile components of the mixture, purification by chromatography on silica gel afforded (*S*)-**3b** (90.2 mg, 75 %, 93 % *ee*, eluent: *n*-hexane/ethyl acetate (50:1)) as a liquid. HPLC conditions: Chiralpak PA-2 column, eluent: *n*-hexane/*i*PrOH (97:3), rate: 0.5 mL min^{-1}; $\lambda =$ 220 nm; $t_R = 14.6$ min (major), 15.7 min (minor). $[\alpha]_D^{20} = +18.1$ ($c =$ 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.17$–5.01 (m, 1H, =CH), 4.75–4.61 (m, 2H, $=CH_2$), 4.25–4.07 (m, 4H, $2 \times CH_2$), 3.35 (d, $J = 8.7$ Hz, 1H, CH), 2.79–2.63 (m, 1H, CH), 1.60–1.15 (m, 8H, CH_2 and $2 \times CH_3$), 0.90 ppm (t, $J = 7.4$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 208.4$, 168.3, 168.1, 90.3, 75.6, 61.2, 61.1, 56.6, 40.3, 25.5, 14.0, 11.4 ppm; IR (neat): $\tilde{\nu} = 2979$, 2937, 2872, 1958, 1751, 1732, 1464, 1369, 1258, 1177, 1097, 1035 cm^{-1}; MS (EI): *m*/*z* (%): 240 (M^+, 36.71), 79 (100); HRMS calcd for $C_{13}H_{20}O_4$ (M^+): 240.1362; found: 240.1369.

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