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Report

Catalytic asymmetric synthesis, Palladium, Optically active aryl allenes, Optically active bis-allenes, Selectivities

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Highly Selective Nucleophilic 4-Aryl-2,3-allenylation of Malonates

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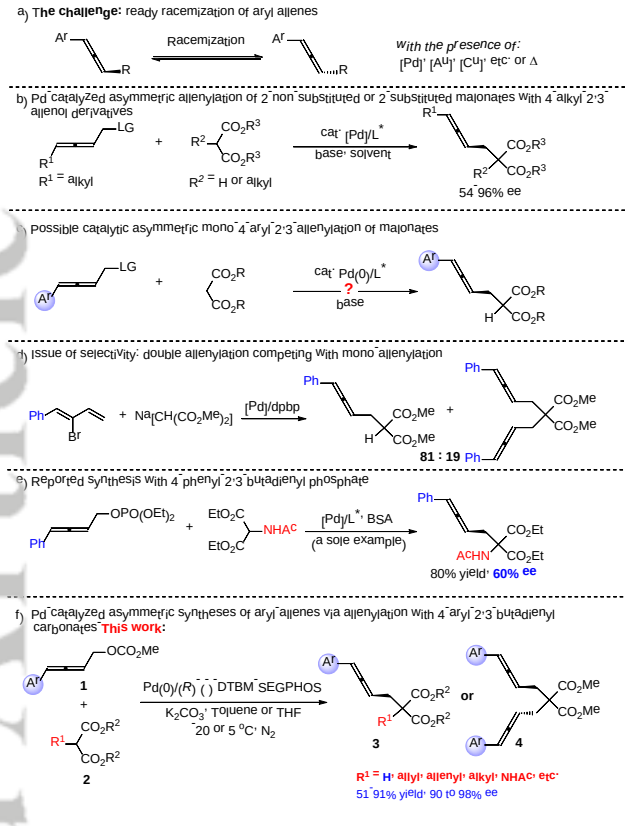
Summary of main observation and conclusion Allenes are a class of very important compounds and the development of straightforward, efficient, and highly enantioselective synthetic strategies for allenes have attracted extensive interests. Along this line, it is well known that aryl-substituted allenes may be readily racemized, thus, difficult to prepare in high ee. Herein, an efficient palladium-catalyzed nucleophilic allenylation of malonates with racemic 4-aryl-2,3-butadienyl carbonates has been developed. The selectivity issue of mono- vs. bis-allenylation with 2-non-substituted malonates has been addressed. By utilizing (*R*)-(-)-DTBM-SEGPHOS as the chiral ligand, various aryl-substituted allenes and bisallenes have been prepared with good to excellent yields with high chemoselectivity and enantioselectivity under mild reaction conditions. Au-catalyzed cycloisomerization and APK reaction affording optically active mono- and bicyclic products have been demonstrated.

Background and Originality Content

Allene units present widely in natural products and non-natural products with unique bioactivities.[1] Also, they have been demonstrated as versatile building blocks in organic syntheses,[2] providing novel methodologies to construct diverse and complex compounds, especially optically active chemicals via chirality transfer strategy.[3] Thus, design and development of new catalytic recipes to access functionalized chiral allenes are of high current interest.[4,5] However, it is well known that aryl-substituted allenes racemize easily in the presence of metal catalysts, which results mostly from the interaction of metal catalysts with the conjugate C=C in the allene parts (Scheme 1a)[6] and highly enantioselective syntheses of chiral aryl allenes are still challenging. Recently, catalytic asymmetric allenylation of malonates with 2,3-allenol derivatives[7] or 1,3-dien-2-yl derivatives[8] sharing the same intermediacy has been developed as an efficient approach for enantioselective syntheses of alkyl-substituted allenes (Scheme 1b). We wonder whether such a protocol may be applied to the syntheses of the thermo-sensitive aryl-allenes (Scheme 1c). The challenges are as follows: 1) such reactions with 4-aryl-2,3-allenol derivatives may be too reactive, resulting in the formation of a mixture of mono- and bis-allenylation products with non-substituted malonates (for such a report with 1,3-dien-2-yl derivatives, see: Scheme 1d);[9] 2) the reported enantioselectivity with 4-phenyl-2,3-allenyl derivatives is low even with the sterically bulky diethyl 2-acetamidomalonate (Scheme 1e);[7a,8] 3) a more active catalytic system, which will work at very mild reaction conditions to avoid the racemization of in situ generated sensitive aryl-substituted allenes, is required. Herein, we wish to report our recent realization of Pd-catalyzed highly chemoselective mono-allenylation of non-substituted malonates (Scheme 1f). The protocol also works well with allenylation of sterically bulkier 2-substituted malonates and bisallenylation of 2-non-substituted malonates under mild reaction conditions.

Scheme 1 Ready racemization of chiral arylallenes and syntheses allenes via

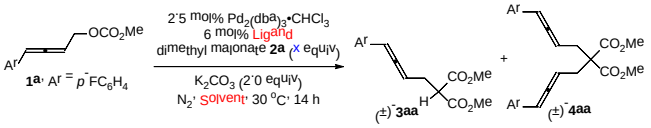
nucleophilic allenylation of different malonates



Results and Discussion

We commenced our study on the reaction of allenylic carbonate **1a** with the most challenging dimethyl malonate **2a** to address the selectivity issue of monoallenylation over bisallenylation. As expected, we found that treatment of **1a** with **2a** catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ with (±)-BINAP as ligand and K_2CO_3 as base in THF furnished (±)-**3aa** smoothly in 68% yield together with the bisallenylation product (±)-**4aa** (entry 1, Table 1) in a poor selectivity of 4:1.[9] Increasing the loading of **2a** would slightly increase the selectivity of monoallenylation product (±)-**3aa** over bisallenylation product (±)-**4aa** (entries 2 and 3, Table 1). The screening of ligands inferred that (±)-BINAP was still the best choice (entries 4-5, Table 1). Interestingly, a profound solvent effect was observed: By using dioxane as solvent the reaction afforded monoallenylation product (±)-**3aa** in 68% yield, exclusively (entry 6, Table 1). A much higher yield with an exclusive chemoselectivity was observed using toluene as solvent (entry 7, Table 1). In this solvent, reducing the amount of **2a** further increased the yield of (+)-**3aa** to 80%, with no formation of bisallenylation product (±)-**4aa**.

Table 1 Identifying the optimal reaction conditions for the reaction of **1a** with **2a**[a]

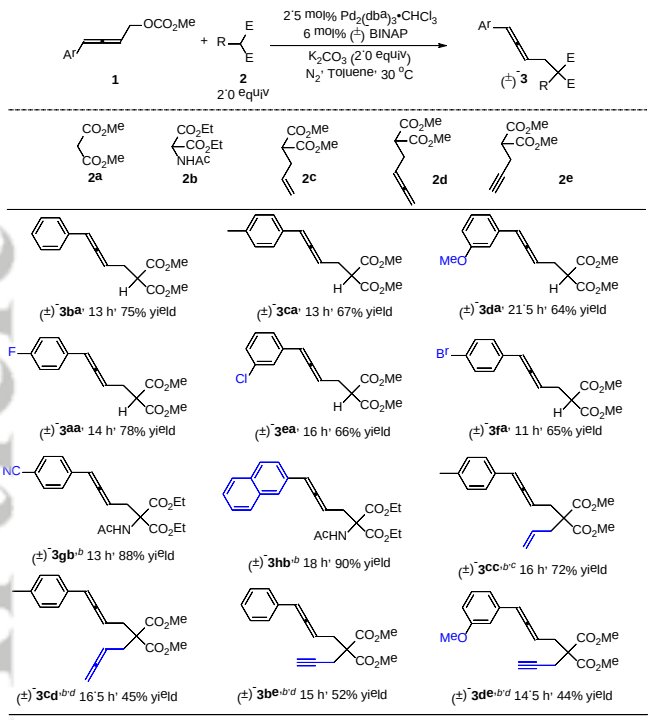


Entry	Ligand	x	Solvent	(±)-3aa (%)[b]	(±)-3aa:(±)-4aa[b]	Recovery of 1a[b]
1	(±)-BINAP	2.0	THF	68	81:19	-[c]
2	(±)-BINAP	3.0	THF	71	91:9	-[c]
3	(±)-BINAP	4.0	THF	63	93:7	-[c]
4	DPPE	4.0	THF	6	100:0	73
5	PPh_3[d]	4.0	THF	-[c]	-[c]	61
6	(±)-BINAP	4.0	Dioxane	68	100:0	-[c]
7	(±)-BINAP	4.0	Toluene	74	100:0	-[c]
8	**(±)-BINAP**	**2.0**	**Toluene**	**80 (78)[e]**	**100:0**	-[c]

[a]The reaction of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), ligand (0.012 mmol), K_2CO_3 (0.4 mmol), **2a** (x equiv)/solvent (1.0 mL), and **1a** (0.2 mmol) in solvent (1.0 mL) was stirred at 30 °C. [b]Data determined by NMR analysis of the crude reaction mixture. [c]Not detected. [d]12 mol% PPh_3 was used. [e]Isolated yield.

Next, the substrate scope for the synthesis of racemic 1,3-disubstituted arylallenes was investigated (Table 2). The reaction of dimethyl malonate (**2a**) with allenylic carbonates **1a**-**1f** afforded the monoallenylation products (±)-**3aa** to (±)-**3fa** exclusively in 64-78% yields. As for nucleophilic reagents **2b**-**2e** equipped with useful functional groups, such as 2-acetamide, 2-allyl, 2-allenyl, and 2-propargyl, the reaction with different 4-aryl-2,3-allenylic carbonates **1** containing electron-withdrawing and electron-donating groups on the aryl ring could all deliver the desired products with moderate to excellent yields (44-90%), regardless of the location of the substituents.

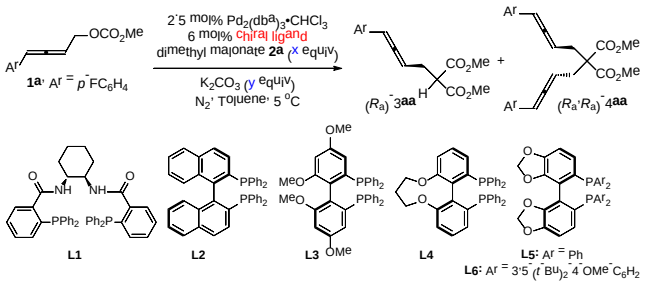
Table 2 The synthesis of racemic 1,3-disubstituted arylallenyl malonates[a]



[a]The mixture of $Pd_2(dba)_3$·$CHCl_3$ (0.005 mmol), (±)-BINAP (0.012 mmol), K_2CO_3 (0.4 mmol), **2** (0.4 mmol)/toluene (1.0 mL) and **1** (0.2 mmol)/toluene (1.0 mL) were added and the resulting mixture was stirred at 30 °C. The yields were gained after column chromatographic separation on silica gel. [b]THF was used instead of toluene. [c]DTBM-SEGPHOS was used instead of (±)-BINAP. [d]5 mol% Pd(dmdba)$_2$ was used instead of 2.5 mol% $Pd_2(dba)_3$·$CHCl_3$.

We went further to develop the asymmetric version of this transformation by using 4-aryl-2,3-allenylic carbonate **1a** and the much less sterically hindered dimethyl malonate (**2a**) as the model substrates. Under the catalysis of $Pd_2(dba)_3$·$CHCl_3$, different chiral ligands were tried (entries 1-6, Table 3) and (*R*)-(-)-DTBM-SEGPHOS was found to be the preferred ligand. The results in Table 3 showed that both the loadings of **2a** and base had an obvious effect on the enantioselectivity of (R_a)-**3aa** and the selectivity of monoallenylation product (R_a)-**3aa**/bisallenylation product (R_a,R_a)-**4aa** (entries 6-9, Table 3). With 2.0 equiv each of **2a** and K_2CO_3, the reaction afforded (R_a)-**3aa** in 77% yield with an ee of 93% and the ratio of (R_a)-**3aa**/(R_a,R_a)-**4aa** was improved to 92/8 in THF (entry 7, Table 3). Replacing THF with toluene, the reaction furnished monoallenylation product (R_a)-**3aa** overwhelmingly with an ee of 97% (entry 8, Table 3). Further optimization led to the establishment of the optimal reaction conditions for further scope study: with 2.5 equiv of **2a**, the reaction in toluene at -20 °C yielded (R_a)-**3aa** exclusively with an ee of 91% (entry 11, Table 3).

Table 3 Identifying the best ligand and optimization of reaction conditions[a]



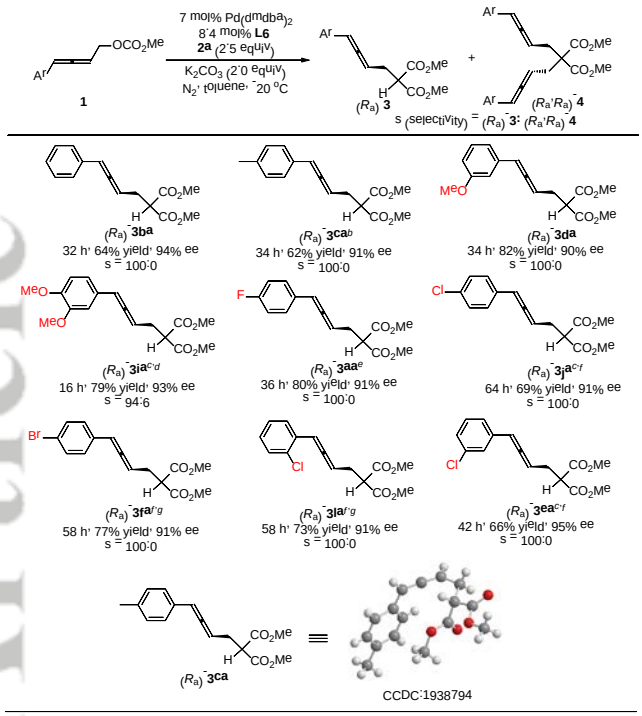
Entry	Ligand	x/y	t (h)	Yield of (R_a)-**3aa** (%)[b]	Ee of (R_a)-**3aa** (%)[c]	(R_a)-**3aa**:(R_a,R_a)-**4aa**[d]
1[e]	**L1**	2.0/2.2	10	-[f]	-[f]	-
2[e]	**L2**	2.0/2.2	10	77	40	89:11
3[e]	**L3**	2.0/2.2	11	74	75	84:16
4[e]	**L4**	2.0/2.2	13	73	84	82:18
5[e]	**L5**	2.0/2.2	11.5	74	77	89:11
6[e]	**L6**	2.0/2.2	18	69	84	85:15
7[e]	**L6**	2.0/2.0	12	77	93	92:8
8	**L6**	2.0/2.0	13	80	86	97:3
9[g]	**L6**	2.5/2.0	17	67	87	100:0
10[h,i]	**L6**	2.5/2.0	21	73	89	100:0
11[i,j]	**L6**	**2.5/2.0**	**36**	**80**	**91**	**100:0**

[a]A mixture of $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol%), chiral ligand (0.012 mmol), K_2CO_3 (y equiv), and dimethyl malonate **2a** (x equiv)/toluene (1.5 mL) was stirred at 25 °C for 30 min. The mixture was stirred at 5 °C for 10 min and then **1a** (0.2 mmol)/toluene (0.5 mL) was added. [b]Isolated yields. [c]The ees of (R_a)-**3aa** were determined by chiral HPLC analysis. [d]Data determined by NMR analysis of the crude product. [e]THF was used as solvent instead of toluene. [f](R_a)-**3aa** was not afforded and 89% of **1a** was recovered. [g]The reaction was conducted at -5 °C. [h]The reaction was conducted at -15 °C. [i]5 mol% Pd(dmdba)$_2$ was used instead of 2.5 mol% $Pd_2(dba)_3$·$CHCl_3$. [j]The reaction was conducted at -20 °C.

With the optimal reaction conditions in hand (entry 11, Table 3), the substrate scope of 2,3-allenylic carbonates with 2-non-substituted dimethyl malonate **2a** was studied (Table 4). Generally speaking, electronic and steric effects have a very limited impact on this reaction and the desired products were afforded in good yields (62-82%) with high ees (90-95%) and selectivity (s = 94:6 to 100:0). Substituents on phenyl rings in allene **1**, such as F, Cl, Br, and OMe, are all compatible. Importantly, the mono-substituted malonate-type products (R_a)-**3aa** to (R_a)-**3la** still possess a handle for further synthetic elaboration. The absolute configuration of major enantiomer of **3ca** was determined by X-ray single crystal diffraction study to be *R*.

Table 4 The substrate scope of allenylic carbonates with dimethyl

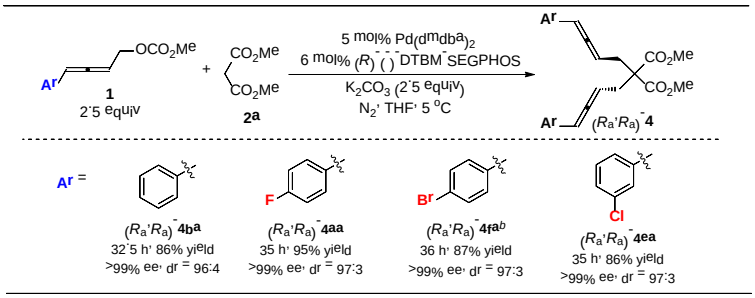
malonate[a]



[a]The mixture of 7 mol% Pd(dmdba)$_2$, 8.4 mol% **L6**, K_2CO_3 (0.4 mmol), and **2a** (2.5 mmol)/solvent (1.5 mL) were stirred at 25 °C for 30 min. The mixture was stirred at -20 °C for 10 min and then **1** (0.2 mmol)/solvent (0.5 mL) was added. The s values were calculated by NMR yields of (R_a)-**3** and (R_a,R_a)-**4** as determined by NMR analysis of the crude product. [b]5 mol% PPh_3 and 9.8 mol% **L6** were used as ligands. [c]2.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 6 mol% **L6** were used. [d]The reaction using 2.0 equiv **2a** with THF as solvent was conducted at 5 °C. [e]5 mol% Pd(dmdba)$_2$ and 6 mol% **L6** were used. [f]The mixed solvent (Toluene:THF = 30:1) was used. [g]3.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ was used.

Moreover, bis(arylallenylation) of dimethyl malonate **2a** was also realized in good to excellent yields (86-95%) and excellent enantio- and diastereoselectivities (>99% ee, 96:4 to 97:3 dr) upon the molar ratio of **1**:**2a** being adjusted to 2.5:1 (Table 5).

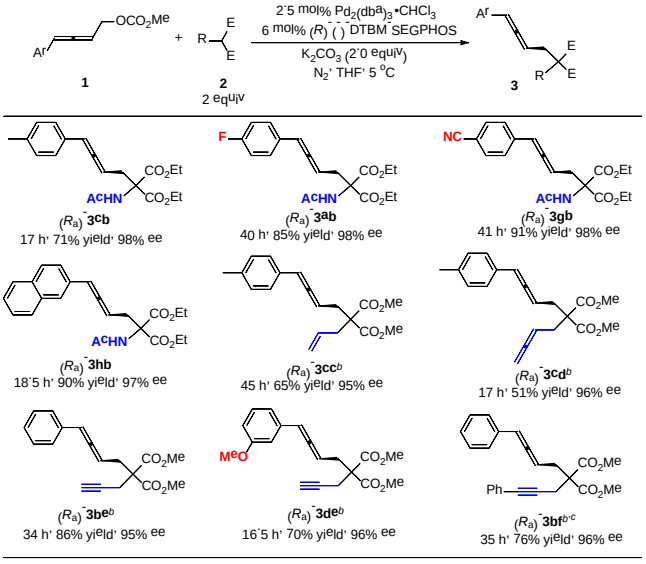
Table 5 Highly enantio- and diastereoselective bis(arylallenylation)[a]



[a]The mixture of Pd(dmdba)$_2$ (0.01 mmol), (*R*)-(-)-DTBM-SEGPHOS (0.012 mmol), K_2CO_3 (0.5 mmol), and **2a** (0.2 mmol)/THF (1.5 mL) were stirred at 25 °C for 30 min. The mixture was stirred at 5 °C for 10 min and then **1** (0.5 mmol)/THF (0.5 mL) was added. The ee values and drs were determined by chiral HPLC analysis. [b]3.0 equiv **1f** was used.

Then the scope of 2-substituted malonates for this enantioselecctive transformation was evaluated (Table 6). Compared to **2a**, 2-substituted malonates (**2b**-**2f**) could afford the arylallenes with relatively higher ees as expected. When diethyl 2-acetamidomalonate (**2b**) was exploited as nucleophile, allenylic carbonates with the aryl group substituted with 4-Me, 4-F, 4-CN, and 2-naphthyl gave the products with 97-98% ee.[7a,8] In addition, 2-allyl, 2-allenyl, 2-propargyl, and 2-(3-phenylpropargyl)-substituted malonates all worked smoothly. These synthetically useful groups combined with the chiral allene unit could afford other chiral cyclic molecules via different types of [4+2][3f,3g], [2+2+1][3h] or [2+2][10] cycloaddition reactions.

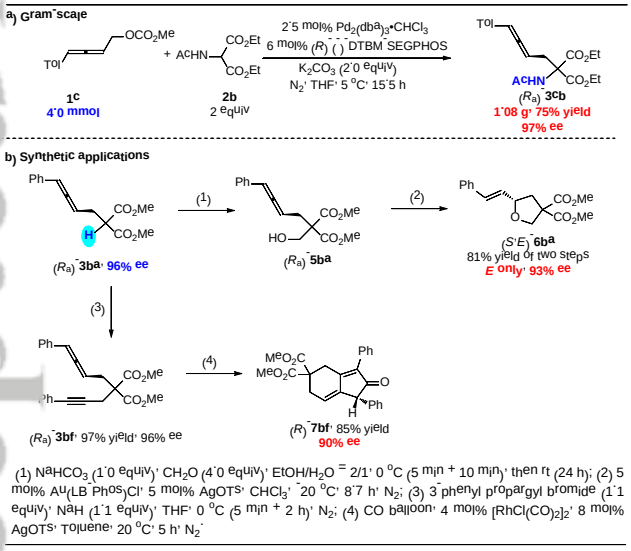
Table 6 The substrate scope of allenylic carbonates with substituted malonates[a]



[a]The mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol), (*R*)-(-)-DTBM-SEGPHOS (0.03 mmol), K_2CO_3 (1.0 mmol), and **2** (1.0 mmol)/THF (4.0 mL) was stirred at 25 °C for 30 min. The mixture was stirred at 5 °C for 10 min and then **1** (0.5 mmol)/THF (1.0 mL) was added. [b]5 mol% $Pd(dmdba)_2$ was used instead of 2.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$. [c]**2f** was dimethyl 2-(3-phenylprop-2-ynyl) malonate.

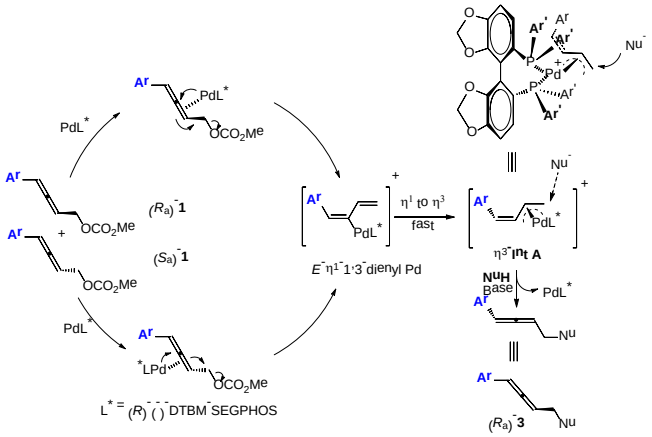
This transformation could be easily conducted on a gram-scale: The reaction of allenylic carbonate **1c** (4.00 mmol) with diethyl 2-acetamidomalonate (**2b**) gave (R_a)-**3cb** (1.08 g) in 75% yield and 97% ee. Synthetic applications have been demonstrated to highlight the potential values of this methodology. Treatment of (R_a)-**3ba** with HCHO (37%, aq.) in the presence of $NaHCO_3$ gave γ-allenol (R_a)-**5ba**, which subsequently produced optically active tetrahydrofuran derivative (*S*,*E*)-**6ba** with an exclusive *E*-C=C bond through gold-catalyzed cycloisomerization.[3e] Reaction of (R_a)-**3ba** with 3-phenylpropargyl bromide gave (R_a)-**3bf** and its subsequent APK reaction of (R_a)-**3bf** in the presence of CO co-catalyzed by $[Rh(CO)_2Cl]_2$/AgOTs afforded the optically active bicyclopentenone compound (*R*)-**7bf** with a highly sensitive chiral center via chirality transfer strategy.[3h]

Scheme 2 Scheme captionGram-scale reaction and synthetic applications



Finally, a rationale was proposed (Scheme 3): S_N2'-type oxidation addition of PdL* with (R_a)-**1** or (S_a)-**1** from the back side of the C-OCO_2Me bond would generate the same intermediate *E*-η^1-1,3-dienyl Pd,[11] which would immediately undergo delocalization to yield intermediate η^3-**Int A**. Subsequently, the nucleophile would attack from the back side of the terminal carbon atom to generate the chiral allene **3** in *R* configuration as shown in the model on the up right corner.

Scheme 3 A rationale for the formation of product (R_a)-**3**



Conclusions

In summary, we have developed a Pd(0)-catalyzed synthesis of the easily racemizable aryl-substituted allenes via highly selective nucleophilic allenylation of 2-non-substituted and 2-substituted malonates with allenylic carbonates. The highly enantioselective version of this transformation has been successfully realized with (*R*)-(-)-DTBM-SEGPHOS as the chiral ligand. This method features high efficiency, high selectivity, good substrate scope, and very mild reaction conditions avoiding racemization. Synthetic applications have also been demonstrated. We are actively pursuing other targets in this area.

Experimental

The asymmetric synthesis of (R_a)-**3aa** (Ssh-07-128): To a dry Schlenk tube were added K_2CO_3 (55.4 mg, 0.4 mmol), (*R*)-(-)-DTBM-SEGPHOS (14.2 mg, 0.012 mmol) inside a glove box. Then $Pd(dmdba)_2$ (8.3 mg, 0.01 mmol), and **2a** (65.7 mg, 0.5 mmol)/toluene (1.5 mL) were added into this Schlenk tube under nitrogen atmosphere outside the glove box. After being stirred at 25 °C for 30 min, the resulting mixture was stirred at -20 °C for 10 min. Then **1a** (43.3 mg, 0.2 mmol)/toluene (0.5 mL) was added with stirring. After being stirred for 36 h at -20 °C, the reaction was complete as monitored by TLC. Filtration through a short column of silica gel (eluent: ethyl acetate (10 mL × 3)) and evaporation afforded crude product (R_a)-**3aa** exclusively ((R_a)-**3aa** : (R_a,R_a)-**4aa** = 100 : 0, which was calculated by NMR yields of (R_a)-**3aa** and (R_a,R_a)-**4aa** as determined by ^{1}H NMR analysis of the crude product). Column chromatography on silica gel afforded (R_a)-**3aa** (44.8 mg, 80%) (eluent: petroleum ether (60-90 °C)/ethyl acetate/DCM = 20/1/1) as a liquid: 91% ee (HPLC conditions; Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 90/10, 0.3 mL/min, λ = 214 nm, t_R(major) = 22.7 min, t_R(minor) = 23.7 min); $[\alpha]_D^{20}$ = -197.1 (c = 0.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.17 (m, 2 H, ArH), 7.03-6.93 (m, 2 H, ArH), 6.22-6.12 (m, 1 H, =CH), 5.62 (q, *J* = 6.0 Hz, 1 H, =CH), 3.73 (s, 3 H, OCH_3), 3.64-3.52 (m, 4 H, CH + OCH_3), 2.85-2.62 (m, 2 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9 (d, *J* = 2.0 Hz), 169.2, 169.0, 162.0 (d, *J* = 244.9 Hz), 130.0 (d, *J* = 3.1 Hz), 128.2 (d, *J* = 7.4

Hz), 115.5 (d, J = 21.3 Hz), 95.5, 92.0, 52.6, 52.5, 50.9, 27.8; ^{19}F NMR (282 MHz, $CDCl_3$) -115.6 (s, 1 F); IR (neat, cm^{-1}) 3002, 2955, 2847, 1951, 1753, 1737, 1602, 1508, 1436, 1342, 1226, 1157, 1094, 1039; MS (EI, 70 eV) m/z (%) 279 (M^+ + 1, 5.38), 278 (M^+, 31.41), 146 (100); HRMS calcd. for $C_{15}H_{15}O_4F$ [M^+]: 278.0954, found: 278.0952.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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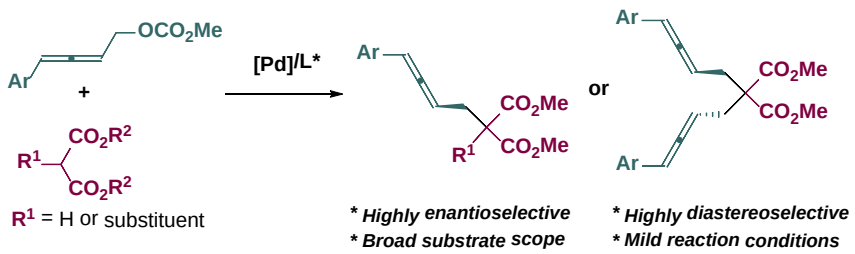
Highly Selective Nucleophilic 4-Aryl-2,3-allenylation of Malonates



A Pd(0)-catalyzed synthesis of the easily racemizable aryl-substituted allenes via highly selective nucleophilic allenylation of 2-non-substituted and 2-substituted malonates with allenylic carbonates has been developed.

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