JOC The Journal of Organic Chemistry

Note

An Access to C(sp3)-C(sp2) and C(sp2)-C(sp2) Bond Formation via Sequential Intermolecular Carbopalladation of Multiple Carbon-Carbon Bonds

Yanmei Wen, Liangbin Huang, and Huanfeng Jiang

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo300662x • Publication Date (Web): 30 May 2012

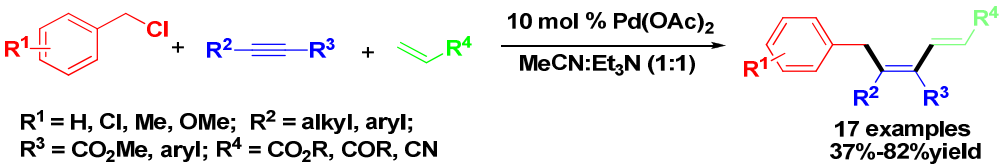
An Access to C(sp^3)-C(sp^2) and C(sp^2)-C(sp^2) Bond Formation via Sequential Intermolecular Carbopalladation of Multiple Carbon-Carbon Bonds

Yanmei Wen[a,b], Liangbin Huang[a], Huanfeng Jiang*[,a]

[a]School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China

jianghf@scut.edu.cn

[b]College of Science, Guangdong Ocean University, Zhanjiang 524088, China



Abstract: A synthetic strategy of 4-benzyl substituted 1,3-butadiene derivatives through Pd-catalyzed three-component coupling reaction of benzyl chlorides, alkynes, and monosubstituted alkenes is described. This tandem coupling reaction forms a C(sp^3)-C(sp^2) bond and a C(sp^2)-C(sp^2) bond sequentially in a single-step operation.

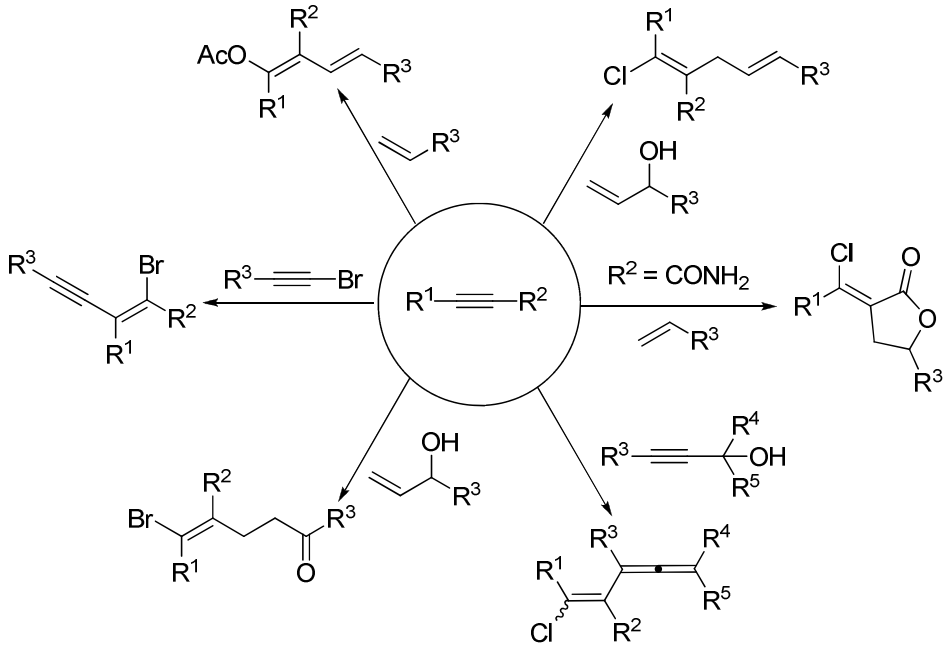
The transition-metal-catalyzed carbon-carbon bond-forming is regarded as in a sense the cornerstone of organic synthesis because of the possibility to frame complex structure from readily available components in diverse ways.[1] And nucleopalladation of carbon-carbon triple bonds followed by a cross-coupling with double bonds has been extensively researched.[2] Recently, the palladium-catalyzed sequential three

component coupling reaction was developed via carbopalladation of internal alkyne with corresponding halides or their synthetic equivalents followed by the addition of various terminators including organometallic reagents, alkenes, and terminal alkynes.[3] However, these synthetic developments were only demonstrated to provide $C(sp^2)$-$C(sp^2)$ and C(sp)-$C(sp^2)$ bonds, which have been extensively reported.[4] In contrast, researches in the field of $C(sp^3)$-$C(sp^2)$ bond forming reactions with sp^3-hybridized organic fragments are much less usual,[5] and remains one of the biggest challenges in organic synthesis. Obviously, the direct utilization of benzyl halides as coupling partners based upon two successive intermolecular carbopalladation reactions to form a $C(sp^3)$-$C(sp^2)$ and a $C(sp^2)$-$C(sp^2)$ in one batch would be an appealing approach.

1,3-Diene unit is often found in many natural products that have shown potential biological activities, such as cell-cycle regulating properties and apoptotic, antifungal, and antiviral activities.[6] Furthermore, 1,3-diene unit is also very useful synthon in organic synthesis.[7] Although there are numerous methods for the preparation of 1,3-butadiene, development of general and efficient routes to the regio- and stereoselective synthesis of benzylated 1,3-dienes is still challenging, and only an example was reported by Ma's group who developed 4-benzyl substituted 1,3-butadiene through Pd(0)-catalyzed coupling reactions of ethyl 2-benzylbuta-2,3-dienoate with 1-alkenylboronic acid.[8] Considering both the advantages of benzyl chlorides compared with those of the aryl iodides or iodoalkenes and a continuing interest in the coupling reactions on basis of internal alkynes

(Scheme 1),[9] we here report an efficient palladium-catalyzed sequential three-component coupling of benzyl chlorides, internal alkynes, and alkenes to selectively synthesize 4-benzyl substituted 1,3-butadienes. To the best of our knowledge, no example of intermolecular tandem benzylation/alkenylation of a simple alkyne has been reported. Herein, we describe our preliminary results for two sequential $C(sp^3)$-$C(sp^2)$ and $C(sp^2)$-$C(sp^2)$ bond-forming processes.

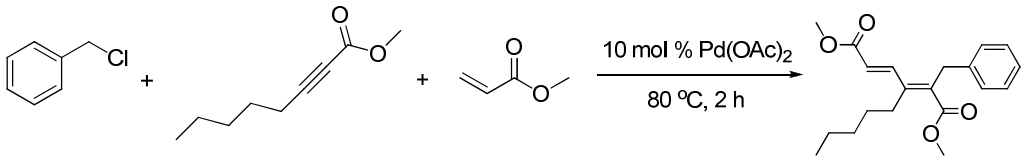
Scheme 1. Our group's works on difunctionalization of alkynes



Our initial work was aimed at developing a set of reaction conditions that would work well for a variety of substrates. The reaction of benzyl chloride (**1a**), methyl oct-2-ynoate (**2a**), and methyl acrylate (**3a**) was chosen as the model system for optimization of this process, and the results are summarized in Table 1. When the reaction of benzyl chloride, methyl oct-2-ynoate (1 equiv), and methyl acrylate (1

equiv) was conducted in the presence of $Pd(OAc)_2$ in CH_3CN/Et_3N (1:1) at 80 ^oC for 2 h, the 1:1:1 coupling proceeded to afford (2*E*,4*E*)-dimethyl 2-benzyl-3-pentylhexa-2,4-dienedioate (**4aaa**) in 18% yield, along with minor amounts of normal Mizoroki-Heck-type product was also detected by GC-MS. Fortunately, when 2 equiv of benzyl chloride, 1 equiv of methyl oct-2-ynoate, and 2 equiv of methyl acrylate were employed, the yield of 1:1:1 coupling products increased dramatically to 90%. Further experiments confirmed the ratio of benzyl chloride, methyl oct-2-ynoate and methyl acrylate played a significant role in forming product **4aaa** (Table 1, entries 1–3). Plus, the most suitable reaction temperature appears to be 80 ^oC and lower reaction temperature was not beneficial for the conversion (Table 1, entries 2, 4, 5). Efforts to further optimize the reaction conditions revealed that NEt_3 was the best base for this reaction (Table 1, entries 6–8). This reaction was subsequently repeated in the presence of 5 mol % $Pd(OAc)_2$ and the lower product yield of 16% was obtained (Table 1, entry 9). Unfortunately, when this reaction was conducted using benzyl bromide instead of benzyl chloride, only afforded a mixture of products (Table 1, entry 10). Moreover, when this reaction was conducted using aryl halide, the desired product wasn't obtained.

Table 1. Optimization Reaction Conditions of Benzyl Chloride (1a) with Methyl Oct-2-ynoate (2a) and Methyl Acrylate (3a) [a]



1a 2a 3a 4aaa

Entry	Ratio[b]	Solvent	T/ °C	Yield(%)[c]
1	1:1:1	CH_3CN/Et_3N	80	18
2	2:1:2	CH_3CN/Et_3N	80	90 (82)
3	3:1:3	CH_3CN/Et_3N	80	45
4	2:1:2	CH_3CN/Et_3N	60	n.r.
5	2:1:2	CH_3CN/Et_3N	40	n.r.
6[d]	2:1:2	CH_3CN	80	n.d.
7[e]	2:1:2	CH_3CN	80	n.d.
8[f]	2:1:2	CH_3CN	80	n.d.
9[g]	2:1:2	CH_3CN/Et_3N	80	16
10[h]	2:1:2	CH_3CN/Et_3N	80	n.d.

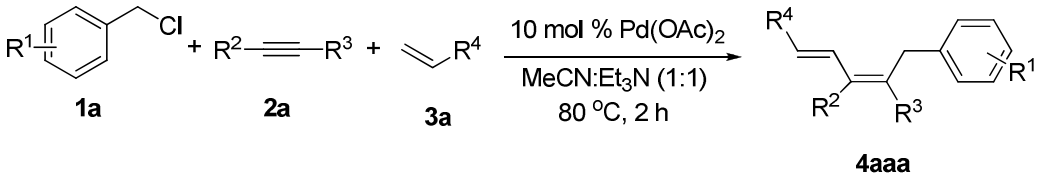
[a]All reactions were run on a 0.5-mmol scale (limiting reagent) employing $Pd(OAc)_2$ (10 mol %) as the catalyst in 2 mL of solvent for 2 h. [b]Ratio of benzyl chloride:alkynoate:alkene. [c]Determined by GC. Number in parentheses is isolated yield. [d]2.0 equiv K_2CO_3 instead of Et_3N. [e]2.0 equiv DBU instead of Et_3N. [f]2.0 equiv DABCO instead of Et_3N. [g]5 mol % $Pd(OAc)_2$. [h]Benzyl bromide instead of benzyl chloride. n.r. = no reaction, n.d. = no desired product.

Under these optimized conditions (Table 1, entry 2), we examined the scope of

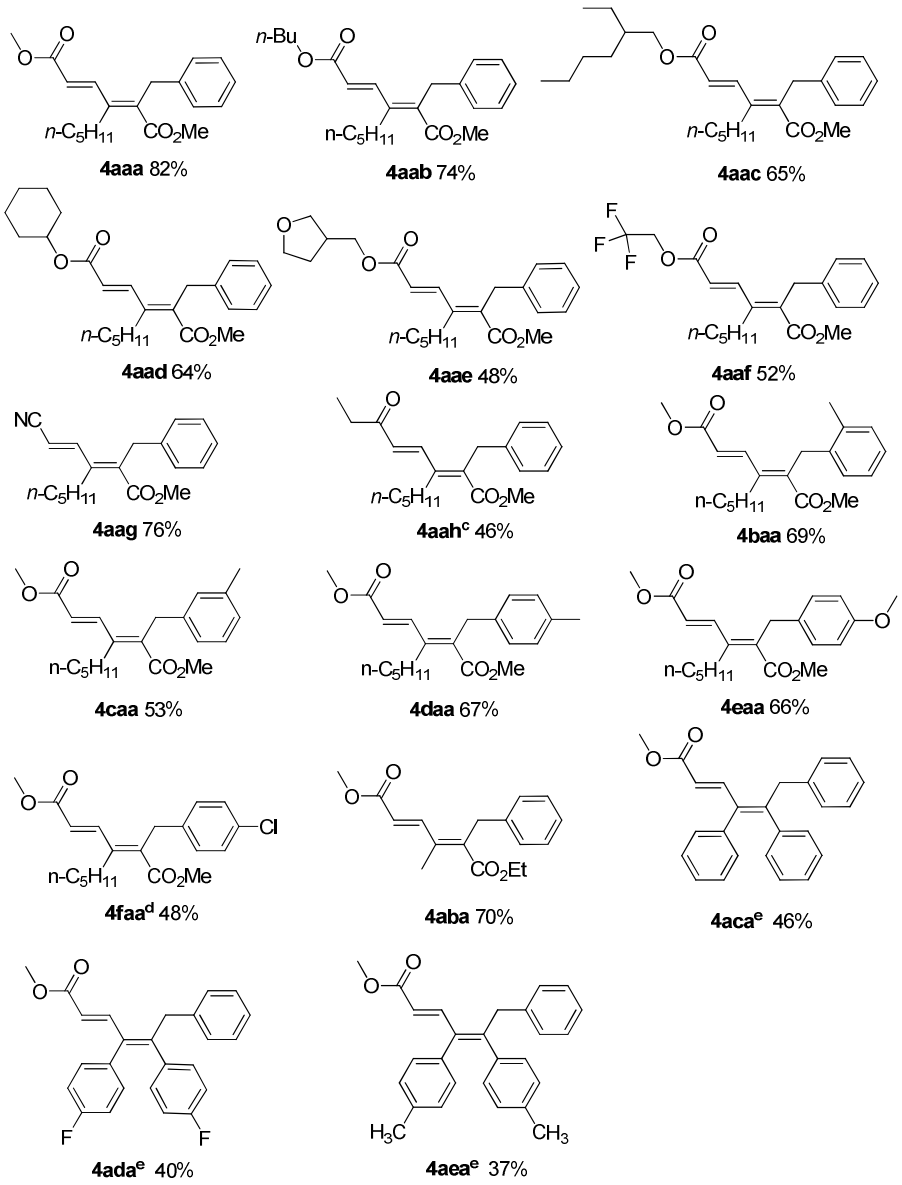
three-component coupling process with respect to a variety of benzyl chlorides, alkynes and alkenes(Scheme 2). As far as the scope of the substituted acrylates was concerned, acrylates in a common use within other acetoxypalladation systems provided the corresponding benzylated product with good activation (**4aaa**, **4aab,** **4aac**, **4aad**, **4aae**, **4aaf**). In addition, acrylonitrile and pent-1-en-3-one were also tolerated in this transformation to generate desired products (**4aag, 4aah**). Then, the scope of the palladium-catalyzed three-component coupling leading to 4-benzyl substituted 1,3-butadienes was further expanded to a range of substituted benzyl chlorides (**1a**). Both electron-rich and electron-deficient benzyl chlorides could be smoothly transformed into the desired products. Furthermore, substituents at different positions on the benzene ring (*para*, *meta*, and *ortho* positions) did not affect the reaction efficiency (**4baa**, **4caa**, **4daa, 4eaa**). It is noteworthy that halo-substituted benzyl chloride was tolerated well, thus leading to halo-substituted products, which could be used for further transformations (**4faa**). Inspired by these results, we became interested in further expanding the substrate scope of this methodology to alkynes. To our delight, aliphatic alkynoates afford good yields of the desired product (**4aaa**, **4aba**), but aromatic alkynes appears to require higher reaction temperature to achieve the comparable yields (**4aca**, **4ada**, **4aea**). The results show that alkynes bearing electron-donating substitutents gave lower yields than those bearing electron-withdrawing substitutents. One important reason for this fact is that benzyl chloride could react with methyl acrylate to give Mizoroki-Heck-type product very easily at higher temperature, thus suggesting a different reaction pathway leads to the

formation of our target product in a low yield. The stereochemistry of the double bond in **4aaa** was confirmed by ^{1}H NMR and NOESY spectra, which indicated the *cis*-carbopalladation involved in this reaction.

Scheme 2. Reaction of Benzyl Chlorides with Alkynoates and Alkenes[a,b]



1a **2a** **3a** **4aaa**

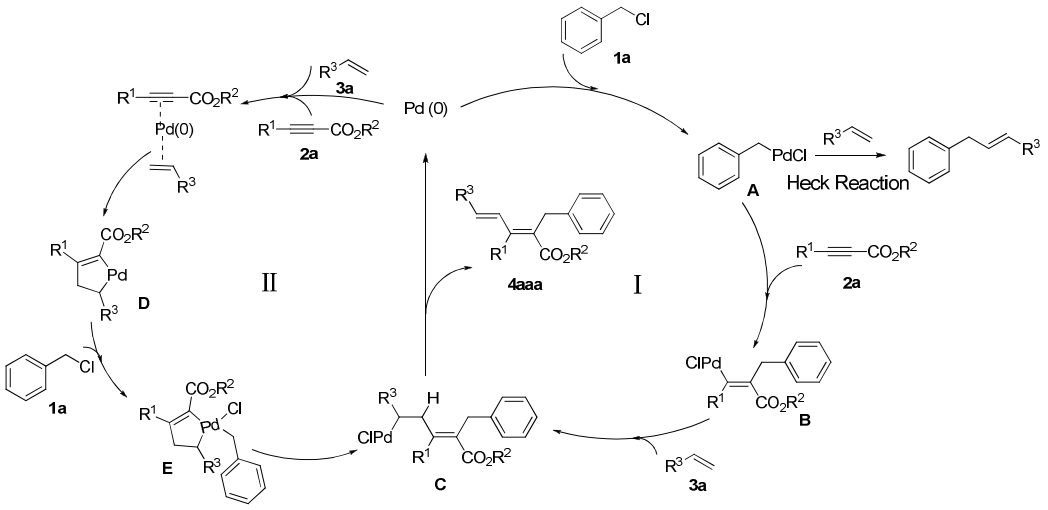


[a] Reactions were carried out using benzyl chloride (1 mmol), alkynoate (0.5 mmol), alkene (1 mmol), $Pd(OAc)_2$ (10 mol %), acetonitrile (1.0 mL), triethylamine (1.0 mL), 80 °C, 2 h. [b] Isolated yields. [c] Ratio of benzyl chloride alkynoate and alkene: 2:1:4. [d] Ratio of benzyl chloride, alkynoate and alkene: 3:1:3. [e] 110 °C for 2 h.

We suggest two possible mechanisms (cycles **I** and **II**) to account for the present processes (Scheme 3). The main difference between these two mechanisms is the first Pd(0) oxidative addition step. In cycle **I**, the Pd(0) complex initially undergoes

oxidative addition with the benzyl chloride **1a** to generate benzylpalladium species **A** in which the metal atom is bonded to a sp^3-hybridized carbon. Subsequent reaction with the alkyne **2a** affords vinylpalladium intermediate **B**, which undergoes cross-coupling with alkene **3a** to give alkylpalladium species **C**. Subsequent *β*-H elimination yields the observed product **4aaa** with simultaneous regeneration of the Pd(0) catalyst. Cycle **II** involves initial oxidative cyclization of alkyne (**2a**) and alkene (**3a**) to Pd(0) to generate palladacyclopentene intermediate **D**, which then reacts with the benzyl chloride **(1a)** to afford intermediate **E**. Subsequent reductive elimination yields intermediate **C** which regenerates the Pd(0) catalyst with the release of the target product. The regiochemical course of the reaction seems to favor the process described in cycle **II**, and other mechanistic possibilities are also under consideration. While the majority of the reactions reported here are quite clean, in reactions affording much lower yields of 1,3-dienes, side products consistent with this mechanism are observed. The potential side reactions are immediate cross-coupling of intermediate **A** with the alkene to give simple Heck products.

Scheme 3. Mechanistic Hypothesis for the Palladium-Catalyzed Domino Process for Synthesis of 4-Benzyl Substituted 1,3-Butadienes



In conclusion, we have developed a novel three-component coupling reaction for the synthesis of 1,3-butadiene derivatives, which allows the rapid, efficient, and selective construction of a $C(sp^3)$-$C(sp^2)$ bond and a $C(sp^2)$-$C(sp^2)$ bond in a single reaction. This is the first example of palladium-catalyzed one-pot reaction forming butadienes bearing benzyl groups in a chemo-, regio-, and stereoselective manner from simple, readily available starting materials. Further studies for construction of other benzylated alkene systems using this method are underway.

Experimental Section

General method. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. HRMS was carried out on a MAT 95XP (Thermo). All reagents were purchased as reagent grade and used without further purification.

Typical procedure for the synthesis of 4-benzyl substituted 1,3-butadienes. $Pd(OAc)_2$ (11 mg, 0.05 mmol) was mixed with CH_3CN (1.0 mL)/Et_3N (1.0 mL) in a test tube (10 mL) equipped with a magnetic stirring bar. Then, alkyne (0.5 mmol), benzyl chloride (1.0 mmol) and alkene (1.0 mmol) were added. The mixture was stirred at 80 ^oC for 2 h. The reaction mixture was taken up by in ether (10 mL) and washed with brine (10 mL). The organic layer was dried ($MgSO_4$),

concentrated in vacuo and purified by flash silica gel chromatography using petroleum ether/ethyl acetate 50:1 to give the desired products. The stereochemistry of **4aaa** was further confirmed by NOESY methods.

(2*E*,4*E*)-dimethyl 2-benzyl-3-pentylhexa-2,4-dienedioate (4aaa, 135 mg, 82%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 16.0 Hz, 1H), 7.30–7.26 (m, 2H), 7.21–7.14 (m, 3H), 6.18 (d, *J* = 15.6 Hz, 1H), 3.89 (s, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 2.49–2.45 (m, 2H), 1.55–1.47 (m, 2H), 1.36–1.30 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.2, 141.2, 141.0, 138.3, 136.0, 128.6, 128.3, 126.5, 122.2, 51.8, 51.7, 35.5, 32.1, 30.7, 29.3, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2951, 1720, 1620, 1441, 1300, 1227, 1174, 1090; HRMS EI (m/z): calcd for $C_{20}H_{26}O_4$, 330.1831; found, 330.1825.

(2*E*,4*E*)-6-butyl 1-methyl 2-benzyl-3-pentylhexa-2,4-dienedioate (4aab, 138 mg, 74%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 15.6 Hz, 1H), 7.26 (t, *J* = 7.2 Hz, 2H), 7.20–7.13 (m, 3H), 6.15 (d, *J* = 15.6 Hz, 1H), 4.17 (t, *J* = 6.8 Hz, 2H), 3.88 (s, 2H), 3.66 (s, 3H), 2.46 (t, *J* = 8.0 Hz, 2H), 1.69–1.62 (m, 2H), 1.52–1.47 (m, 2H), 1.45–1.37 (m, 2H), 1.33–1.29 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.9, 141.2, 141.0, 138.4, 135.8, 128.5, 128.3, 126.4, 122.6, 64.6, 51.7, 35.5, 32.1, 30.7, 29.3, 22.4, 19.2, 14.0, 13.7 ppm; ν_{max}(KBr)/cm^{-1} 2957, 1718, 1617, 1459, 1229, 1171; HRMS EI (m/z): calcd for $C_{23}H_{32}O_4$, 372.2301; found, 372.2296.

(2*E*,4*E*)-6-(2-ethylhexyl) 1-methyl 2-benzyl-3-pentylhexa-2,4-dienedioate (4aac, 139 mg, 65%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 15.6 Hz, 1H), 7.24 (d, *J* = 6.8 Hz, 2H), 7.19–7.12 (m, 3H), 6.14 (d, *J* = 16.0 Hz, 1H), 4.09–4.05 (m, 2H), 3.86 (s, 2H), 3.66 (s, 3H), 2.48–2.42 (m, 2H), 1.63–1.58 (m, 1H), 1.53–1.46 (m, 2H), 1.36–1.28 (m, 12H), 0.90–0.87 (m, 9H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 169.4, 166.9, 141.3, 140.9, 138.4, 135.7, 128.5, 128.3, 126.4, 122.6, 67.2, 51.7, 38.8, 35.5, 32.1, 30.6, 30.5, 29.3, 28.9, 23.9, 22.9, 22.4, 14.0, 11.0 ppm; ν_{max}(KBr)/cm^{-1} 2930, 1719, 1459, 1227, 1170; HRMS EI (m/z): calcd for $C_{27}H_{40}O_4$, 428.2927; found, 428.2922.

(2*E*,4*E*)-6-cyclohexyl 1-methyl 2-benzyl-3-pentylhexa-2,4-dienedioate (4aad, 127 mg, 64%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 16.0 Hz, 1H), 7.29–7.25 (m, 2H), 7.22–7.14 (m, 3H), 6.14 (d, *J* = 16.0 Hz, 1H), 4.88–4.82 (m, 1H), 3.88 (s, 2H), 3.67 (s, 3H), 2.48–2.44 (m, 2H), 1.91–1.87 (m, 2H), 1.75–1.72 (m, 2H), 1.56–1.43 (m, 6H), 1.40–1.29 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.2, 141.4, 140.7, 138.5, 135.6, 128.5, 128.3, 126.4, 123.1, 73.0, 51.7, 35.5, 32.1, 31.7, 30.7, 29.3, 25.4, 23.8, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2938, 1716, 1455, 1228, 1175; HRMS EI (m/z): calcd for $C_{25}H_{34}O_4$, 398.2457; found, 398.2453.

(2*E*,4*E*)-6-(tetrahydrofuran-3-yl)methyl 1-methyl 2-benzyl-3-pentylhexa-2,4-dienedioate (4aae, 96 mg, 48%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 15.6 Hz, 1H), 7.31–7.27 (m, 2H), 7.22–7.15 (m, 3H), 6.25 (d, *J* = 16.0 Hz, 1H), 4.31–4.27 (m, 1H), 4.14–4.09 (m, 1H), 3.93–3.80 (m, 4H), 3.68 (s, 3H), 2.50–2.46 (m, 2H), 2.08–2.00 (m, 1H), 1.97–1.90 (m, 2H), 1.68–1.45 (m, 4H), 1.37–1.31 (m, 4H), 0.92 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 166.8, 141.5, 141.0, 138.3, 136.1, 128.5, 128.3, 126.4, 122.1, 76.5, 68.5, 66.8, 51.7, 35.5, 32.1, 30.7, 29.3, 28.0, 25.7, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2953, 1719, 1226, 1169; HRMS EI (m/z): calcd for $C_{24}H_{32}O_5$, 400.2250; found, 400.2245.

(2*E*,4*E*)-6-(2,2,2-trifluoroethyl) 1-methyl 2-benzyl-3-pentylhexa-2,4-dienedioate (4aaf, 103 mg, 52%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 16.0 Hz, 1H), 7.20–7.17 (m, 2H),

7.12–7.04 (m, 3H), 6.10 (d, *J* = 16.0 Hz, 1H), 4.46 (q, *J* = 8.4 Hz, 2H), 3.79 (s, 2H), 3.59 (s, 3H), 2.38–2.34 (m, 2H), 1.45–1.37 (m, 2H), 1.25–1.21 (m, 4H), 0.81 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 165.0, 143.4, 140.4, 138.1, 137.5, 128.6, 128.3, 126.6, 120.1, 77.0, 60.7, 60.3, 51.8, 35.59, 32.1, 30.6, 29.2, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2956, 1728, 1279, 1228, 1157; HRMS EI (m/z): calcd for $C_{21}H_{25}F_3O_4$, 398.1705; found, 398.1697.

(2*E*)-methyl 2-benzyl-3-((*E*)-2-cyanovinyl)oct-2-enoate (4aag, 113 mg, 76%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 16.4 Hz, 1H), 7.32–7.28 (m, 2H), 7.24–7.21 (m, 1H), 7.14–7.10 (m, 2H), 5.64 (d, *J* = 16.4 Hz, 1H), 3.84 (s, 2H), 3.68 (s, 3H), 2.44–2.40 (m, 2H), 1.53–1.44 (m, 2H), 1.34–1.30 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 147.0, 140.0, 137.5, 136.9, 128.7, 128.1, 126.8, 117.9, 100.8, 51.9, 35.4, 32.0, 29.8, 29.1, 22.3, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2954, 1722, 1458, 1300, 1230, 1197; HRMS EI (m/z): calcd for $C_{19}H_{23}NO_2$, 297.1729; found, 297.1722.

(2*E*,4*E*)-methyl 2-benzyl-6-oxo-3-pentylocta-2,4-dienoate (4aah, 75 mg, 46%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 16.0 Hz, 1H), 7.31–7.27 (m, 2H), 7.22–7.15 (m, 3H), 6.44 (d, *J* = 16.0 Hz, 1H), 3.90 (s, 2H), 3.69 (s, 3H), 2.63–2.58 (m, 2H), 2.51–2.47 (m, 2H), 1.55–1.47 (m, 2H), 1.35–1.33 (m, 4H), 1.12 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 169.4, 141.7, 138.5, 136.2, 130.9, 129.7, 128.6, 128.3, 126.5, 51.8, 35.5, 34.3, 32.1, 30.6, 29.4, 22.4, 14.0, 8.1 ppm; ν_{max}(KBr)/cm^{-1} 2956, 1725, 1595, 1280, 1192; HRMS EI (m/z): calcd for $C_{21}H_{28}O_3$, 328.2038; found, 328.2036.

(2*E*,4*E)*-dimethyl 2-(2-methylbenzyl)-3-pentylhexa-2,4-dienedioate (4baa, 119 mg, 69%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 15.6 Hz, 1H), 7.15–7.08 (m, 3H), 7.04–7.02 (m, 1H), 6.17 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 2H), 3.76 (s, 3H), 3.60 (s, 3H), 2.48–2.44 (m,

2H), 2.31 (s, 3H), 1.57–1.50 (m, 2H), 1.35–1.23 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.2, 141.0, 140.3, 136.4, 136.2, 135.9, 130.2, 128.3, 126.6, 126.1, 122.0, 51.8, 51.6, 33.1, 32.1, 30.8, 29.3, 22.4, 19.6, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2952, 1722, 1437, 1226, 1170; HRMS EI (m/z): calcd for $C_{21}H_{28}O_4$, 344.1988; found, 344.1985.

(2*E*,4*E*)-dimethyl 2-(3-methylbenzyl)-3-pentylhexa-2,4-dienedioate (4caa, 91 mg, 53%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 15.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.04–6.95 (m, 3H), 6.19 (d, J = 16.0 Hz, 1H), 3.87 (s, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 2.51–2.47 (m, 2H), 2.33 (s, 3H), 1.56–1.49 (m, 2H), 1.36–1.31 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 167.2, 141.3, 140.8, 138.1, 136.1, 129.2, 128.4, 127.2, 125.3, 122.1, 51.8, 51.7, 35.4, 32.1, 30.7, 29.3, 22.4, 21.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2952, 1722, 1224, 1169; HRMS EI (m/z): calcd for $C_{21}H_{28}O_4$, 344.1988; found, 344.1982.

(2*E*,4*E*)-dimethyl 2-(4-methylbenzyl)-3-pentylhexa-2,4-dienedioate (4daa, 115 mg, 67%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 15.8 Hz, 1H), 7.11–7.04 (m, 4H), 6.19 (d, J = 16.0 Hz, 1H), 3.86 (s, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 2.49–2.45 (m, 2H), 2.32 (s, 3H), 1.54–1.48 (m, 2H), 1.37–1.34 (m, 4H), 0.94–0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 167.2, 146.4, 141.3, 140.6, 136.3, 135.1, 129.3, 128.2, 124.4, 122.6, 122.0, 51.8, 51.7, 35.1, 32.1, 30.7, 29.3, 22.40, 21.0, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2953, 1722, 1226, 1170; HRMS EI (m/z): calcd for $C_{21}H_{28}O_4$, 344.1988; found, 344.1985.

(2*E*,4*E*)-dimethyl 2-(4-methoxybenzyl)-3-pentylhexa-2,4-dienedioate (4eaa, 119 mg, 66%)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 16.0 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.17 (d, J = 15.6 Hz, 1H), 3.85–3.82 (m, 3H), 3.78 (d, J = 2.0 Hz, 6H), 3.66 (s, 2H), 2.46–2.42 (m, 2H), 1.56–1.46 (m, 2H), 1.34–1.29 (m, 4H), 0.90 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 169.4, 167.3, 158.2, 141.2, 140.3, 136.6, 130.2, 129.4, 122.0, 114.0, 55.2, 51.7, 34.6, 32.1, 30.7, 29.7, 29.3, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2953, 1728, 1226, 1170; HRMS EI (m/z): calcd for $C_{21}H_{28}O_5$, 360.1937; found, 360.1933.

(2*E*,4*E*)-dimethyl 2-(4-chlorobenzyl)-3-pentylhexa-2,4-dienedioate (4faa, 87 mg, 48%)

White solid, m. p.: 69-71 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 15.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.18 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 2H), 3.77 (s, 3H), 3.66 (s, 3H), 2.49–2.45 (m, 2H), 1.52–1.47(m, 2H), 1.31–1.26 (m, 4H), 0.90 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 167.1, 141.6, 140.9, 136.8, 135.3, 132.3, 129.7, 128.7, 122.5, 51.8, 51.7, 34.8, 32.0, 30.7, 29.3, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2950, 1719, 1383, 1168; HRMS EI (m/z): calcd for $C_{20}H_{25}ClO_4$, 364.1441; found, 364.1435.

(2*E*,4*E*)-1-ethyl 6-methyl 2-benzyl-3-methylhexa-2,4-dienedioate (4aba, 101 mg, 70%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 15.6 Hz, 1H), 7.25–7.23 (m, 2H), 7.19–7.13 (m, 3H), 6.16 (d, *J* = 15.6 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.90 (s, 2H), 3.76 (s, 3H), 2.06 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 167.2, 142.0, 138.2, 137.1, 135.3, 128.5, 126.5, 122.3, 60.8, 51.8, 35.5, 16.5, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2950, 1718, 1301, 1225, 1176; HRMS EI (m/z): calcd for $C_{17}H_{20}O_4$, 288.1362; found, 288.1358.

(2*E*,4*Z*)-methyl 4,5,6-triphenylhexa-2,4-dienoate (4aca, 81 mg, 46%)

White solid, m. p.: 108-110 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 15.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.38–7.25 (m, 6H), 7.17–7.07 (m, 5H), 6.85 (d, *J* = 7.6 Hz, 2H), 5.33 (d, *J* = 15.2 Hz, 1H), 3.67 (s, 2H), 3.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 148.9, 145.6, 139.8, 138.6, 138.4, 137.3, 129.8, 129.4, 128.9, 128.7, 128.2, 128.1, 127.7, 127.5, 126.0, 121.1, 51.4, 42.3 ppm; ν_{max}(KBr)/cm^{-1} 3028, 1712, 1608, 1507, 1227; HRMS EI (m/z): calcd for $C_{25}H_{22}O_2$, 354.1620; found,

354.1617.

(2*E*,4*Z*)-methyl 4,5-bis(4-fluorophenyl)-6-phenylhexa-2,4-dienoate (4ada, 78 mg, 40%)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 15.6 Hz, 1H), 7.24–7.20 (m, 2H), 7.16–7.10 (m, 7H), 7.03–7.01 (m, 2H), 6.84–6.82 (m, 2H), 5.32 (d, *J* = 15.6 Hz, 1H), 3.64 (s, 2H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 163.5 (d, 10 Hz), 161.1 (d, 9 Hz), 148.2, 145.1, 138.2, 136.7, 135.6 (d, 3 Hz), 134.0 (d, 4 Hz), 131.4 (d, 8 Hz), 131.0 (d, 8 Hz), 128.7, 128.3, 126.2, 121.5, 115.6 (d, 67 Hz), 115.5 (d, 24 Hz), 51.5, 42.3 ppm; ν_{max}(KBr)/cm^{-1} 3031, 1716, 1606, 1507, 1227, 1166; HRMS EI (m/z): calcd for $C_{25}H_{20}F_2O_2$, 390.1431; found, 390.1427.

(2*E*,4*Z*)-methyl 6-phenyl-4,5-dip-tolylhexa-2,4-dienoate (4aea, 71 mg, 37%)

Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 15.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.13–7.03 (m, 9H), 6.88 (d, *J* = 7.2 Hz, 2H), 5.34 (d, *J* = 15.6 Hz, 1H), 3.67 (s, 2H), 3.62 (s, 3H), 2.39 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 148.8, 146.1, 138.9, 137.4, 137.2, 137.0, 136.9, 135.5, 129.6, 129.3, 128.9, 128.0, 125.9, 120.7, 51.3, 42.2, 21.2 ppm; ν_{max}(KBr)/cm^{-1} 2921, 1711, 1268, 1166; HRMS EI (m/z): calcd for $C_{27}H_{26}O_2$, 382.1933; found, 382.1926.

Acknowledgements

The authors are grateful to the National Natural Science Foundation of China (20932002, 21172076), National Basic Research Program of China (973 Program) (2011CB808600), Guangdong Natural Science Foundation (10351064101000000), and the Fundamental Research Funds for the Central Universities (2010ZP0003) for financial support.

Supporting Information

Spectral data for all new compounds; NOE studies on stereochemistry of **4aaa**. This material is

available free of charge via the Internet at http://pubs. acs. org.

References

[1] (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644−4680. (b) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453−3516. (c) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318−5365. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**, *100*, 3009−3066. (e) Negishi, E.; Anastasia L. *Chem. Rev*. **2003**, *103*, 1979−2018. (f) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457−2483. (g) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469. (h) Chinchilla, R.; Nájera, C. *Chem. Rev*. **2007**, *107*, 874−922. (i) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2964.

[2] (a) Yin, G.; Liu, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 5442 –5445. (b) Ye, S.; Gao, K.; Zhou, H.; Yang, X.; Wu, J. *Chem. Comm.* **2009**, 5406–5408. (c) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604–7605. (d) Zhang, Q.; Xu, W.; Lu, X. *J. Org. Chem.* **2005**, *70*, 1505–1507. (e) Zhao, L.; Lu, X.; Wu, W. *J. Org. Chem.* **2005**, *70*, 4059–4063. (f) Wu, W.; Kong, A.; Lu, X. *J. Org. Chem.* **2006**, *71*, 3854–3858. (g) Tello-Aburto, R.; Harned, A. M. *Org. Lett.* **2009**, *11*, 3998–4000. (h) Ye, S.; Gao, K.; Zhou, H.; Yang, X.; Wu, J. *Chem. Comm.* **2009**, 5406–5408. (i) Chen, X.; Kong, W.; Cai, H.; Kong, L.; Zhu, G. *Chem. Commun.* **2011**, *47*, 2164–2166.

[3] (a) Satoh, T.; Ogino, S.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5063−5065. (b) Kantam, M. L.; Srinivas, P.; Kumar, K. B. S.; Trivedi, R. *Catal. Commun.* **2007**, *8*, 991−996. (c) Zhang, X.; Larock, R. C. *Org. Lett.* **2003**, *5*, 2993−2996. (d) Zhang, X.; Larock, R. C. *Tetrahedron* **2010**, *66*, 4265−4277. (e) Zhou, P.; Huang, L. B.; Jiang, H. F.; Wang, A. Z.; Li, X. W. *J. Org. Chem.* **2010**, *75*, 8279–8282. (f) Shibata, K., Satoh, T., Miura, M. *Org. Lett*., **2005**, *7*, 1781−1783. (g) Horiguchi, H., Hirano, K., Satoh, T.; Miura, M. *Adv. Synth. Catal.* **2009**, *351*,

1431−1436. (h) Shibata K., Satoh, T.; Miura, M. *Adv. Synth. Catal*. **2007**, *349*, 2317−2325.

[4] (a) Zhou, C.; Larock, R. C.; *Org. Lett*. **2003**, *5*, 1579−1582. (b) Zhou, C.; Larock, R. C. *J. Org. Chem.*, **2005**, 70, 3765−3777. (c) Sakai, N.; Komatsu, R.; Uchida, N.; Ikeda, R.; Konakahara, T. *Org. Lett*. **2010**, *12*, 1300−1303. (d) Cheng, Y. N.; Duan, Z.; Yu, L. J.; Li, Z. X.; Zhu, Y.; Wu, Y. J. *Org. Lett*. **2008**, *10*, 901−904. (e) Chen, X. Y.; Kong, W.; Cai, H. T.; Kong, L. C.; Zhu, G. G. *Chem. Comm*. **2011**, *47*, 2164−2166. (f) Zhao, L. G.; Lu, X. Y. *Org. Lett*. **2002**, *4*, 3903−3906. (g) Chen, X. Y.; Kong, W.; Cai, H. T.; Kong, L. C.; Zhu, G. G. *Chem. Comm*., **2011**, *47*, 2164−2166.

[5] (a) Liu, C.; Tang, S.; Liu, D.; Yuan, J. W.; Zheng, L. W.; Meng, L. K.; Lei, A. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 1−5. (b) Liu, Q.; Duan, H.; Luo, X. C.; Tang, Y.; Li, G.; Huang, R.; Lei, A. W. *Adv. Synth. Catal.* **2008**, *350*, 1349−1354. (c) Jin, L. Q.; Zhao, Y. S.; Zhu, L. Z.; Zhang, H.; Lei, A. W. *Adv. Synth. Catal.* **2009**, *351*, 630−634. (d) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc*. **2005**, *127*, 510−511. (e) Kirchoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am.Chem. Soc.* **2002**, *124*, 13662−13663. (f) Murakami, K.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J*. **2010**, *16*, 7688−7691.

[6] (a) Amans, D.; Bellosta, V.; Cossy, J. *Chem. Eur. J.* **2009**, *15*, 3457−3473. (b) Ramamoorthy, G.; Acevedo, C. M.; Alvira, E.; Lipton, M. A. *Tetrahedron: Asymmetry* **2008**, *19*, 2546−2554. (c) Boldi, A. M. *Curr.Opin. Chem. Biol*. **2004**, *8,* 281−286.

[7] Xi, Z. F.; Zhang, W. X. *Synlett* **2008**, *17*, 2557−2570.

[8] Ma, S. M.; Jiao, N.; Ye, L. W. *Chem. Eur. J*. **2003**, *9*, 6049−6056.

[9] (a) Li, Y. B.; Liu, X. H.; Jiang, H. F.; Feng, Z. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 3338−3341. (b) Jiang, H. F.; Liu, X. H.; Zhou, L. *Chem. Eur. J.* **2008**, *14*, 11305−11309. (c) Zhou, P.; Huang, L. B.; Jiang, H. F.; Li, X. W. *Chem. Commun.* **2011**, *47*, 1003−1005. (d) Huang, J. M.; Zhou, L.;

Jiang, H. F. *Angew. Chem. Int. Ed.* **2006**, *45*, 1945−1949. (e) Wen, Y. M.; Huang, L. B.; Jiang, H. F.; Chen, H. J. *J. Org. Chem*. **2012**, *77*, 2029−2034.