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CuCl-catalyzed stereoselective conjugate addition of Grignard reagents to 2,3-allenoates

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ABSTRACT

CuCl was found to be an efficient catalyst for the conjugate addition of 2,3-allenoates with Grignard reagents to synthesize poly-substituted β,γ-unsaturated alkenoates with high stereoselectivity in good to excellent yields. Primary, secondary, and tertiary alkyl, vinyl or phenyl Grignard reagents may all be used.

1. Introduction

Transition metal-catalyzed conjugate addition of carbon anions to α,β-unsaturated carbonyl compounds is a powerful strategy for carbon–carbon bond formation.[1] Of the various methods utilized, copper-based catalysts along with organometallic reagents have shown great potential in this field.[2] During the last decade, copper-catalyzed conjugate addition of Michael acceptors has been well studied in various aspects.[3] Although several examples on the copper-mediated addition of organometallic reagents to 2,3-allenoates have been reported,[4] stoichiometric or sub-stoichiometric organocuprate reagents were used in these reactions and no example on the catalytic reaction has been reported. Recently, we found that the iron-catalyzed conjugate addition of Grignard reagents to 2,3-allenoates has been proven to be an efficient method for the synthesis of β,γ-unsaturated alkenoates,[5,6] which are useful building blocks in organic synthesis. However, for the development of enantioselective version of this type of reaction, we showed strong interest in exploring the Cu-catalyzed such reactions. Herein, we wish to present our recent progress on the copper-catalyzed stereoselective conjugate addition of Grignard reagents to 2,3-allenoates.

2. Results and discussion

Due to the importance of methylmetalation in natural product syntheses, in our initial study, the reaction of ethyl 2-methyl-4-phenyl-2,3-butadienoate **1a** with CH_3MgCl was examined by using 5 mol % of CuI as the catalyst in the solution of toluene at −78 °C and we were pleased to find that ethyl 2,3-dimethyl-4-phenyl-3(*Z*)-butenoate *Z*-**2a** was afforded in 86% yield with a high stereoselectivity (*Z*/*E* >99:1) (entry 1, Table 1). Further screening of the solvents showed that toluene afforded the best results (compare entries 2–5 with entry 1, Table 1). It was found that when the reaction of **1a** with CH_3MgCl in the presence of CuI was conducted in diethyl ether, the reaction mixture would be heterogeneous. Thus the relative low solubility of the reaction intermediate in diethyl ether may account for the low reactivity (entry 5, Table 1). The reaction with 10 mol % or 2 mol % of CuI gave very similar results (entries 6 and 7, Table 1). However, when we reduced the loading of CuI to 0.5 mol %, the change resulted in a recovery of starting material **1a** in 3% yield (entry 8, Table 1). In the absence of CuI, the reaction in toluene and Et_2O was quite slow and no reaction occurred in THF (entries 9–11, Table 1). The use of 2.0 equiv of CH_3MgCl led to a lower yield of 71% (entry 12, Table 1). Reducing the amount of CH_3MgCl to 1.5 equiv resulted in an incomplete reaction with **1a** being recovered in 22% yield (entry 13, Table 1). CuCl (5 mol %) may also be used to complete the conversion (entry 14, Table 1). Other cuprous or cupric salts failed to afford better results (entries 15–17, Table 1). Thus, we defined 5 mol % of CuCl, 3 equiv of Grignard reagents in toluene at −78 °C as the optimized standard reaction conditions.

With the optimized reaction conditions in hand, we explored the substrate scope of the CuCl-catalyzed conjugate addition reaction of 2,3-allenoates with Grignard reagents and the results were summarized in Table 2. R^1 could be aryl or alkyl groups; R^2

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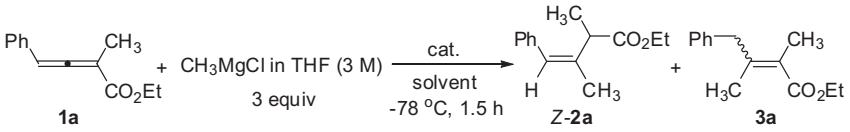
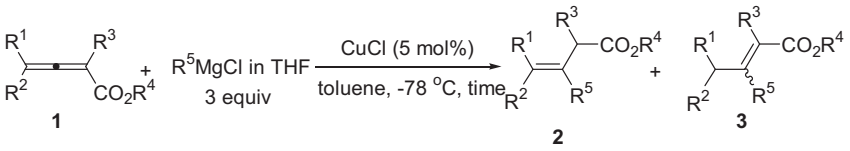
Table 1
Optimization of reaction conditions



Entry	Cat. (mol %)	Solvent	Yield of *Z*-**2a** (%) (*Z*/*E*)[a]	Recovery of **1a** (%)[a]	Yield of **3a** (%)[b]
1	CuI (5)	Toluene	88 (>99:1)	0	2.3
2	CuI (5)	THF	80 (98:2)	2.1	0.6
3	CuI (5)	CH_2Cl_2	82 (>99:1)	0	2.7
4	CuI (5)	*n*-Hexane	12 (>99:1)	64	0
5	CuI (5)	Et_2O	38 (>99:1)	44	1.1
6	CuI (10)	Toluene	83 (>99:1)	0	3.5
7	CuI (2)	Toluene	87 (>99:1)	0	2.7
8	CuI (0.5)	Toluene	77 (>99:1)	3	3.5
9[c]	—	Toluene	44 (>99:1)	40	4.5
10	—	THF	0	92	0
11	—	Et_2O	28 (>99:1)	57	1.4
12[d]	CuI (5)	Toluene	75 (>99:1)	0	4.5
13[e]	CuI (5)	Toluene	55 (>99:1)	22	2.9
14	CuCl (5)	Toluene	86 (>99:1)	0	1.9
15	CuBr (5)	Toluene	86 (>99:1)	0	2.3
16	CuCN (5)	Toluene	62 (>99:1)	23	2.8
17	$CuCl_2$ (5)	Toluene	78 (>99:1)	0	1.3
18[f]	CuCl (5)	Toluene	90 (96:4)	0	2.1

[a] Determined by NMR spectroscopy using mesitylene as the internal standard.
[b] Determined by NMR spectroscopy, if any.
[c] The reaction was carried out for 7 h.
[d] CH_3MgCl (2.0 equiv) was applied.
[e] CH_3MgCl (1.5 equiv) was applied.
[f] The reaction was quenched at 0 °C.

Table 2
CuCl-catalyzed conjugate addition of Grignard reagents to 2,3-allenoates[a]



Entry	R^1	R^2	R^3	R^4	R^5	Time (h)	Yield of **2** and **3** (%)[b]	Ratio of **2**/**3**[c]
1	Ph	H	Me	Et (**1a**)	Me	1.5	84 (*Z*-**2a**)	99:1
2	Ph	H	Allyl	Et (**1b**)	Me	1.5	90 (*Z*-**2b**)	96:4
3	*p*-FC_6H_4	H	Me	Et (**1c**)	Me	1.5	80 (*Z*-**2c**)	98:2
4	*p*-ClC_6H_4	H	Me	Et (**1d**)	Me	1.5	81 (*Z*-**2d**)	98:2
5	*p*-BrC_6H_4	H	Me	Et (**1e**)	Me	1.5	83(*Z*-**2e**)	96:4
6	*p*-BrC_6H_4	H	*n*-Pr	Et (**1f**)	Me	1.5	87 (*Z*-**2f**)	96:4
7	*p*-$MeOC_6H_4$	H	Me	Et (**1g**)	Me	2.5	86 (*Z*-**2g**)	>99:1
8	Me	Me	Ph	Me (**1h**)	Me	2	92 (**2h**)	>99:1
9	Ph	H	Me	Et (**1a**)	*i*-Pr	2	92 (*Z*-**2i**)	96:4
10	Ph	H	Me	Et (**1a**)	*c*-Hex	2	91 (*Z*-**2j**)	95:5
11	Ph	H	Me	Et (**1a**)	*t*-Bu	2	87 (*E*-**2k**)	>99:1
12	Ph	H	allyl	Et (**1b**)	Ph	1.5	93 (*E*-**2l**)	96:4
13	*p*-$MeOC_6H_4$	H	Me	Et (**1g**)	Ph	2.5	86 (*E*-**2m**)	>99:1
14	*n*-C_4H_9	H	Me	Et (**1i**)	Ph	1.5	92 (*E*-**2n**)	>99:1
15	*n*-C_7H_{15}	H	H	Et (**1j**)	Ph	1.5	85 (*E*-**2o**)	>99:1
16	*p*-ClC_6H_4	H	Me	Et (**1d**)	Vinyl[d]	2	87 (*Z*-**2p**)	>99:1
17	*n*-C_4H_9	H	Me	Et (**1i**)	Vinyl[d]	1.5	80 (*Z*-**2q**)	>99:1

[a] The reaction was conducted using 0.4 mmol of 2,3-allenoates, 3 equiv of Grignard reagents (solution in THF), and 5 mol % of CuCl in 5 mL of toluene at −78 °C.
[b] Isolated yields. Product **3** is inseparable from **2**.
[c] Ratio was determined by ^1H NMR analysis of the crude products.
[d] Vinyl magnesium bromide was used.

could be H or alkyl groups; R^3 could be alkyl, allyl or phenyl groups. Aryl groups with electron-withdrawing and electron-donating substituents are well tolerated (entries 3–7, Table 2). It should be mentioned that even the fully substituted allenoate **1h** may also be used to complete the reaction (entry 8, Table 2). In addition to primary alkyl Grignard reagents, secondary and tertiary Grignard reagents also afforded the corresponding β,γ-unsaturated alkenoates in good yields (entries 9–11, Table 2). Furthermore, phenyl

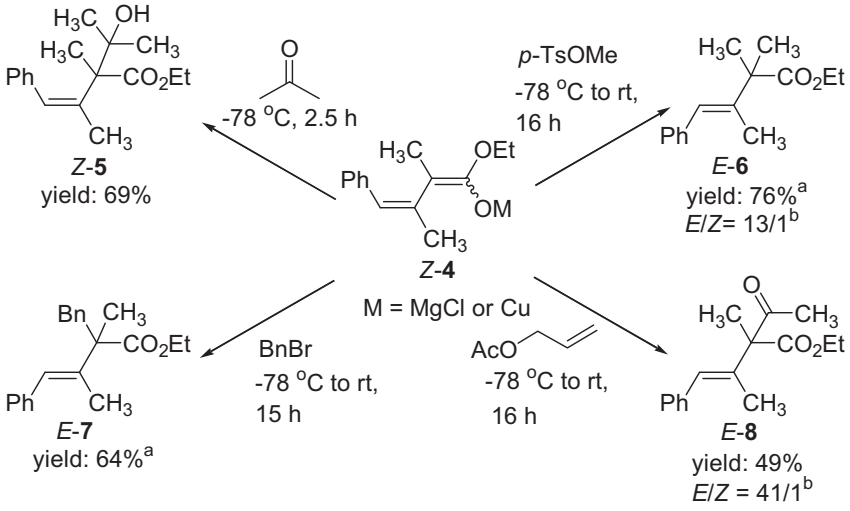
and vinyl magnesium chloride may also be applied to the conjugate addition of both 2 and/or 4-alkyl- and 4-aryl-substituted 2,3-allenoates (entries 12–17, Table 2). The yields of the CuCl-catalyzed conjugate addition are generally higher than those of the iron-catalyzed reactions using phenyl magnesium chloride as the nucleophile.[5]

The dienolate intermediate *Z*-**4** derived from the reaction of CuCl-catalyzed conjugate addition of **1a** and CH_3MgCl may react with acetone to form the addition product *Z*-**5**. What should be mentioned is that its reaction with methyl *p*-toluenesulfonate, benzyl bromide, or allyl acetate afforded the methylation product *E*-**6**, 2-benzyl unsaturated alkenoate *E*-**7** or β-ketoester derivative *E*-**8** with high reversed *E*-stereoselectivity (Scheme 1), which is in accordance with our previous report.[6] The configurations of the carbon–carbon double bonds were determined by NOE analysis (Fig. 1).

temperature. It should also be noted that all the reactions occurred at the α-position of the ester group.

3. Conclusions

In summary, we have developed an efficient CuCl-catalyzed conjugate addition of 2,3-alleonates with Grignard reagents to synthesize poly-substituted β,γ-unsaturated *Z*-alkenoates with high regio- and stereoselectivity. Primary, secondary, and tertiary alkyl, vinyl, or phenyl groups may be introduced from the readily available Grignard reagents to the 3-position of 2,3-allenonates. Good to excellent yields were achieved with a catalytic loading of CuCl (5 mol %). The in situ formed magnesium dienolate may also react with different electrophiles to obtain a series of compounds containing an allylic quaternary carbon at the α-position of the ester group. Compared to iron catalyst, the regioselectivity of the



[a] Contaminated with *E*-**2a**.

[b] Ratio was determined by ^{1}H NMR analysis of the crude products.

Scheme 1. Reactions of in situ generated dienolate intermediate **4** with different electrophiles.

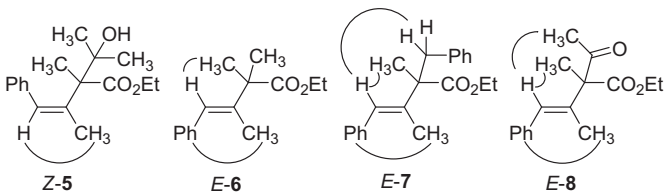


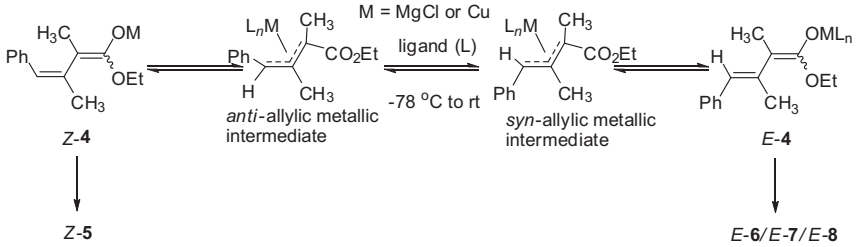
Fig. 1. NOE study on β,γ-unsaturated alkenoate derivatives.

When methyl *p*-toluenesulfonate, benzyl bromide, or allylic acetate was added as the electrophile, the carbon–carbon unsaturated bond and/or the carbonyl oxygen may coordinate with the metal to increase the steric hindrance between the coordinated metal and the phenyl group. This type of interaction led to the complete conversion of 1,3-(*Z*)-dienoate *Z*-**4** to 1,3-(*E*)-dienoate *E*-**4** when the reaction system gradually warmed up to rt (Scheme 2).[7] The subsequent reaction with methyl *p*-toluenesulfonate, benzyl bromide, or allyl acetate resulted in the formation of *E*-**6**, *E*-**7**, or *E*-**8**. On the contrary, the reaction with acetone should be very fast, occurring before the isomerization from *Z* to *E* at relatively low reaction with CuCl was slightly lower. However, due to the difference between copper and iron, the reaction may show a distinct approach to other tandem transformations, especially the enantioselective form, considering the wide application of copper catalyst in asymmetric synthesis. Further studies in this area including enantioselective transformations with copper catalyst are being conducted in our laboratory.

4. Experimental

4.1. General information

Toluene was distilled with Na wire in the presence of benzophenone. Methyl magnesium chloride (3.0 M solution in THF), *iso*-propyl magnesium chloride (2.0 M solution in THF), and *tert*-butyl magnesium chloride (1.0 M solution in THF) used in this study were purchased from Aldrich. *cyclo*-Hexyl magnesium chloride (1.3 M solution in THF), phenyl magnesium chloride (1.6 M or 1.8 M solution in THF), and vinyl magnesium bromide (0.7 M solution in THF) used in this study were purchased from Acros Organics. The other commercially available chemicals were purchased and used without additional purification unless noted otherwise. All ^{1}H NMR



Scheme 2. Plausible mechanism in the stereoselective reactions.

experiments were measured relative to the signal of tetramethylsilane (0 ppm).

4.2. General procedure for CuCl-catalyzed conjugate addition of alkyl/vinyl/aryl magnesium chlorides/bromides to 2,3-allenoates

CuCl (5 mol %, 0.02 mmol), **1** (0.4 mmol), and toluene (5 mL) were added sequentially to a dry Schlenk tube under nitrogen atmosphere at rt. A solution of Grignard reagent in THF (3 equiv, 1.2 mmol) was then added by a syringe to the reaction mixture within 6 min at −78 °C. After the reaction was over as monitored by TLC, the reaction mixture was quenched slowly with a saturated aqueous solution of NH_4Cl (2 mL) at −78 °C, which was followed by warming up to rt naturally. After extraction with diethyl ether (15–20 mL×3), the organic layer was washed with diluted HCl (5%, aqueous), a saturated aqueous solution of $NaHCO_3$, brine sequentially and dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=100:1) afforded **2**.

*4.2.1. Ethyl 2,3-dimethyl-4-phenyl-3(Z)-butenoate (Z-**2a**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1a** (80.2 mg, 0.4 mmol), toluene (5 mL), and a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) afforded *Z*-**2a**[5a] (73.1 mg, 84%, 99% in purity): liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H, Ar–H), 6.42 (s, 1H, =CH), 4.23–4.08 (m, 2H, OCH_2), 3.82 (q, *J*=7.1 Hz, 1H, CH), 1.84 (d, *J*=1.5 Hz, 3H, CH_3), 1.28–1.22 (m, 3H, 2×CH_3).

*4.2.2. Ethyl 2-allyl-3-methyl-4-phenyl-3(Z)-butenoate (Z-**2b**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1b** (90.9 mg, 0.4 mmol), toluene (5 mL), and a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) afforded *Z*-**2b** (87.9 mg, 90%, *Z*-**2b**/**3b**=96:4): liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H, Ar–H), 6.49 (s, 1H, =CH), 5.65–5.52 (m, 1H, =CH), 5.04–4.92 (m, 2H, 2×=CH), 4.25–4.10 (m, 2H, OCH_2), 3.79 (t, *J*=7.7 Hz, 1H, CH), 2.66–2.55 (m, 1H, one proton of CH_2), 2.36–2.25 (m, 1H, one proton of CH_2), 1.85 (d, *J*=1.5 Hz, 3H, CH_3), 1.27 (t, *J*=7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 137.4, 135.2, 134.6, 129.4, 128.7, 128.1, 126.4, 116.3, 60.6, 46.3, 33.9, 19.7, 14.2; MS (EI) *m*/*z* (%) 245 (M^++1, 1.31), 244 (M^+, 7.13), 129 (100); IR (neat, cm^{-1}) 3079, 3023, 2979, 1732, 1642, 1492, 1443, 1368, 1336, 1272, 1231, 1180, 1112, 1031. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.78; H, 8.24.

*4.2.3. Ethyl 4-(p-fluorophenyl)-2,3-dimethyl-3(Z)-butenoate (Z-**2c**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1c** (87.4 mg, 0.4 mmol), toluene (5 mL), and a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) afforded *Z*-**2c** (74.9 mg, 80%, *Z*-**2c**/**3c**=98:2): liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.20 (m, 2H, Ar–H), 7.05–6.95 (m, 2H, Ar–H), 6.37 (s, 1H, =CH), 4.23–4.09 (m, 2H, OCH_2), 3.75 (q, *J*=7.1 Hz, 1H, CH), 1.83 (d, *J*=1.5 Hz, 3H, CH_3), 1.29–1.21 (m, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 161.5 (d, J_{FC}=244.1 Hz), 137.1, 133.6 (d, J_{FC}=3.5 Hz), 130.2 (d, J_{FC}=7.4 Hz), 126.8, 115.0 (d, J_{FC}=20.8 Hz), 60.6, 40.8, 19.4, 15.2, 14.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.0; MS (EI) *m*/*z* (%) 237 (M^++1, 4.37), 236 (M^+, 27.66), 163 (100); IR (neat, cm^{-1}) 2980, 2940, 1733, 1651, 1602, 1507, 1450, 1377, 1323, 1225, 1186, 1160, 1093, 1075, 1033; HRMS calcd for $C_{14}H_{17}O_2F$ (M^+): 236.1213; found: 236.1212.

*4.2.4. Ethyl 4-(p-chlorophenyl)-2,3-dimethyl-3(Z)-butenoate (Z-**2d**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1d** (93.8 mg, 0.4 mmol), toluene (5 mL), and a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) afforded *Z*-**2d** (81.1 mg, 81%, *Z*-**2d**/**3d**=98:2): liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H, Ar–H), 7.21–7.19 (m, 2H, Ar–H), 6.36 (s, 1H, =CH), 4.21–4.11 (m, 2H, OCH_2), 3.74 (q, *J*=7.1 Hz, 1H, CH), 1.83 (d, *J*=1.5 Hz, 3H, CH_3), 1.29–1.21 (m, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 137.7, 136.0, 132.2, 129.9, 128.3, 126.7, 60.6, 40.9, 19.4, 15.2, 14.2; MS (EI) *m*/*z* (%) 255 ($M^+(^{37}Cl)$+1, 1.30), 254 ($M^+(^{37}Cl)$, 9.25), 253 ($M^+(^{35}Cl)$+1, 4.20), 252 ($M^+(^{35}Cl)$, 28.23), 179 (100); IR (neat, cm^{-1}) 2980, 2939, 1733, 1650, 1593, 1489, 1450, 1377, 1323, 1241, 1185, 1092, 1032, 1015; HRMS calcd for $C_{14}H_{17}O_2^{35}Cl$ (M^+): 252.0917; found: 252.0917.

*4.2.5. Ethyl 4-(p-bromophenyl)-2,3-dimethyl-3(Z)-butenoate (Z-**2e**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1e** (113.0 mg, 0.4 mmol), toluene (5 mL), and a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) afforded *Z*-**2e**[5a] (98.6 mg, 83%, *Z*-**2e**/**3e**=96:4): liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J*=8.4 Hz, 2H, Ar–H), 7.15 (d, *J*=8.4 Hz, 2H, Ar–H), 6.33 (s, 1H, =CH), 4.22–4.11 (m, 2H, OCH_2), 3.74 (q, *J*=7.0 Hz, 1H, CH), 1.83 (d, *J*=1.5 Hz, 3H, CH_3), 1.29–1.21 (m, 6H, 2×CH_3).

*4.2.6. Ethyl 4-(p-bromophenyl)-3-methyl-2-propyl-3(Z)-butenoate (Z-**2f**).* The reaction of CuCl (2.1 mg, 0.021 mmol, 5.3 mol %), **1f** (124.6 mg, 0.4 mmol), toluene (5 mL), and a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) afforded *Z*-**2f**[5a] (113.3 mg, 87%, *Z*-**2f**/**3f**=96:4): liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47–7.40 (m, 2H, Ar–H), 7.18–7.14 (m, 2H, Ar–H), 6.40 (s, 1H, =CH), 4.17 (q, *J*=7.1 Hz, 2H, OCH_2), 3.61 (dd, J_1=8.3 Hz, J_2=6.8 Hz, 1H, CH), 1.82 (d, *J*=1.5 Hz, 3H, CH_3), 1.80–1.71 (m, 1H, one proton of CH_2), 1.60–1.47 (m, 1H, one proton of CH_2), 1.28 (t, *J*=7.1 Hz, 3H, CH_3), 1.21–1.01 (m , 2H, CH_2), 0.77 (t, *J*=7.2 Hz, 3H, CH_3).

*4.2.7. Ethyl 2,3-dimethyl-4-(p-methoxyphenyl)-3(Z)-butenoate (Z-**2g**).* The reaction of CuCl (2.2 mg, 0.022 mmol, 5.5 mol %), **1g** (92.0 mg, 0.4 mmol), toluene (5 mL), and a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) afforded *Z*-**2g**[5b] (84.7 mg, 86%): liquid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.19 (m, 2H, Ar–H), 6.90–6.83 (m, 2H, Ar–H), 6.36 (s, 1H, =CH), 4.23–4.09 (m, 2H, OCH_2), 3.86–3.78 (m, 4H, CH+CH_3), 1.82 (d, *J*=1.2 Hz, 3H, CH_3), 1.29–1.22 (m, 6H, 2×CH_3).

*4.2.8. Methyl 3,4-dimethyl-2-phenyl-3-pentenoate (**2h**).* The reaction of CuCl (2.2 mg, 0.022 mmol, 5.5 mol %), **1h** (80.5 mg, 0.4 mmol), toluene (5 mL), and a solution of CH_3MgCl in THF

(0.4 mL, 3 M, 1.2 mmol, 3 equiv) afforded **2h** (79.6 mg, 92%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5H, Ar–H), 4.96 (s, 1H, CH), 3.72 (s, 3H, OCH_3), 1.81 (d, J=1.5 Hz, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.63 (d, J=1.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 138.2, 129.3, 128.23, 128.21, 126.6, 124.7, 53.4, 51.8, 21.1, 20.6, 15.6; MS (EI) m/z (%) 218 (M^+, 0.03), 145 (100); IR (neat, cm^{-1}) 3062, 3027, 2994, 2950, 2922, 2862, 1740, 1602, 1496, 1451, 1434, 1376, 1308, 1232, 1196, 1161, 1122, 1011. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.03; H, 8.53.

*4.2.9. Ethyl 2-methyl-3-(iso-propyl)-4-phenyl-3(Z)-butenoate (Z-**2i**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1a** (79.6 mg, 0.4 mmol), toluene (5 mL), and a solution of *i*-PrMgCl in THF (0.6 mL, 2 M, 1.2 mmol, 3 equiv) afforded *Z*-**2i** (89.1 mg, 92%, *Z*-**2i**/**3i**=96:4): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H, Ar–H), 6.50 (s, 1H, =CH), 4.17–4.09 (m, 2H, OCH_2), 3.85 (q, J=6.9 Hz, 1H, CHH), 2.41 (hept, J=6.9 Hz, 1H, CH), 1.28–1.23 (m, 6H, 2×CH_3), 1.17 (d, J=6.9 Hz, 3H, CH_3), 1.11 (d, J=7.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 148.1, 138.0, 128.7, 128.1, 126.3, 125.2, 60.5, 41.3, 29.7, 24.9, 24.2, 15.7, 14.2; MS (EI) m/z (%) 247 (M^++1, 3.59), 246 (M^+, 18.47), 145 (100); IR (neat, cm^{-1}) 3059, 3024, 2963, 2935, 2872, 1732, 1643, 1599, 1494, 1462, 1444, 1377, 1323, 1236, 1186, 1092, 1057, 1028; HRMS calcd for $C_{16}H_{22}O_2$ (M^+): 246.1620; found: 246.1623.

*4.2.10. Ethyl 3-(cyclo-hexyl)-2-methyl-4-phenyl-3(Z)-butenoate (Z-**2j**).* The reaction of CuCl (2.2 mg, 0.022 mmol, 5.5 mol %), **1a** (81.8 mg, 0.4 mmol), toluene (5 mL), and a solution of *c*-HexMgCl in THF (0.9 mL, 1.3 M, 1.2 mmol, 3 equiv) afforded *Z*-**2j**[5a] (105.9 mg, 91%, *Z*-**2j**/**3j**=95:5): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.19 (m, 5H, Ar–H), 6.46 (s, 1H, =CH), 4.21–4.07 (m, 2H, OCH_2), 3.84 (q, J=7.0 Hz, 1H, CH), 2.05–1.92 (m, 1H, CH), 1.79–1.62 (m, 5H, five protons of *cyclo*-hexyl), 1.36–1.18 (m, 11H, five protons of *cyclo*-hexyl+2×CH_3).

*4.2.11. Ethyl 3-(tert-butyl)-2-methyl-4-phenyl-3(E)-butenoate (E-**2k**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1a** (81.4 mg, 0.4 mmol), toluene (5 mL), and a solution of *t*-BuMgCl in THF (1.2 mL, 1 M, 1.2 mmol, 3 equiv) afforded *E*-**2k**[5b] (90.7 mg, 87%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.25 (m, 2H, Ar–H), 7.21–7.16 (m, 1H, Ar–H), 7.14–7.11 (m, 2H, Ar–H), 6.56 (s, 1H, =CH), 4.10–3.87 (m, 2H, OCH_2), 3.44 (q, J=7.3 Hz, 1H, CH), 1.24–1.15 (m, 15H, 5×CH_3).

*4.2.12. Ethyl 2-allyl-3,4-diphenyl-3(E)-butenoate (E-**2l**).* The reaction of CuCl (1.9 mg, 0.019 mmol, 4.8 mol %), **1b** (91.1 mg, 0.4 mmol), toluene (5 mL), and a solution of phenyl magnesium chloride in THF (0.76 mL, 1.6 M, 1.2 mmol, 3 equiv) afforded *E*-**2l** (114.1 mg, 93%, *E*-**2l**/**3l**=96:4): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.24 (m, 10H, Ar–H), 6.85 (s, 1H, =CH), 5.65–5.52 (m, 1H, =CH), 4.92–4.82 (m, 2H, 2×=CH), 4.20 (q, J=7.2 Hz, 2H, OCH_2), 4.03 (dd, J_1=8.7 Hz, J_2=6.3 Hz, 1H, CH), 2.68–2.59 (m, 1H, one proton of CH_2), 2.30–2.19 (m, 1H, one proton of CH_2), 1.25 (t, J=7.1 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 140.8, 139.6, 137.3, 135.4, 132.9, 128.8, 128.3, 128.1, 127.8, 127.3, 127.0, 116.4, 60.9, 45.9, 33.9, 14.1; MS (EI) m/z (%) 307 (M^++1, 3.43), 306 (M^+, 14.06), 191 (100); IR (neat, cm^{-1}) 3057, 2980, 1729, 1641, 1600, 1495, 1445, 1367, 1254, 1187, 1116, 1074, 1030. Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.52; H, 7.28.

*4.2.13. Ethyl 4-(p-methoxyphenyl)-2-methyl-3-phenyl-3(E)-butenoate (E-**2m**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1g** (92.6 mg, 0.4 mmol), toluene (5 mL), and a solution of phenyl magnesium chloride in THF (0.67 mL, 1.8 M, 1.2 mmol, 3 equiv) afforded *E*-**2m**[5b] (105.8 mg, 86%) (eluent: petroleum ether/ethyl acetate=60:1): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.23 (m, 7H, Ar–H), 6.92 (d, J=8.7 Hz, 2H, Ar–H), 6.74 (s, 1H, =CH), 4.19–4.07 (m, 3H, CH+OCH_2), 3.82 (s, 3H, OCH_3), 1.25 (d, J=6.9 Hz, 3H, CH_3), 1.20 (t, J=7.1 Hz, 3H, CH_3).

*4.2.14. Ethyl 2-methyl-3-phenyl-3(E)-octenoate (E-**2n**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1i** (73.0 mg, 0.4 mmol), toluene (5 mL), and a solution of phenyl magnesium chloride in THF (0.67 mL, 1.8 M, 1.2 mmol, 3 equiv) afforded *E*-**2n**[5b] (96.3 mg, 92%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18 (m, 5H, Ar–H), 5.64 (t, J=7.4 Hz, 1H, =CH), 4.16–4.06 (m, 2H, OCH_2), 3.80 (q, J=7.2 Hz, 1H, CH), 2.32–2.13 (m, 2H, CH_2), 1.52–1.34 (m, 4H, 2×CH_2), 1.29 (d, J=7.2 Hz, 3H, CH_3), 1.15 (t, J=7.1 Hz, 3H, CH_3), 0.93 (t, J=7.1 Hz, 3H, CH_3).

*4.2.15. Ethyl 3-phenyl-3(E)-undecenoate (E-**2o**).* The reaction of CuCl (1.0 mg, 0.01 mmol, 5 mol %), **1j** (43.5 mg, 0.2 mmol), toluene (2.5 mL), and a solution of phenyl magnesium chloride in THF (0.38 mL, 1.6 M, 0.6 mmol, 3 equiv) afforded *E*-**2o**[5a] (49.2 mg, 85%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.35 (m, 2H, Ar–H), 7.32–7.25 (m, 2H, Ar–H), 7.23–7.18 (m, 1H, Ar–H), 5.94 (t, J=7.4 Hz, 1H, =CH), 4.09 (q, J=7.1 Hz, 2H, CO_2CH_2), 3.50 (s, 2H, CH_2CO), 2.21 (q, J=7.4 Hz, 2H, CH_2), 1.52–1.42 (m, 2H, CH_2), 1.39–1.23 (m, 8H, 4×CH_2), 1.18 (t, J=7.2 Hz, 3H, CH_3), 0.89 (t, J=6.8 Hz, 3H, CH_3).

*4.2.16. Ethyl 4-(p-chlorophenyl)-2-methyl-3-vinyl-3(Z)-butenoate (Z-**2p**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1d** (95.0 mg, 0.4 mmol), toluene (5 mL), and a solution of vinyl magnesium bromide in THF (1.8 mL, 0.7 M, 1.2 mmol, 3 equiv) afforded *Z*-**2p**[5b] (92.4 mg, 87%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.31 (m, 2H, Ar–H), 7.27–7.24 (m, 2H, Ar–H), 6.64 (s, 1H, =CH), 6.31 (dd, J_1=17.7 Hz, J_2=11.2 Hz, 1H, =CH), 5.34 (d, J=17.7 Hz, 1H, =CH), 5.14 (d, J=11.2 Hz, 1H, =CH), 4.19–4.10 (m, 2H, OCH_2), 3.86 (q, J=7.2 Hz, 1H, CH), 1.36 (d, J=7.2 Hz, 3H, CH_3), 1.23 (t, J=7.2 Hz, 3H, CH_3).

*4.2.17. Ethyl 2-methyl-3-vinyl-3(Z)-octenoate (Z-**2q**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1i** (71.0 mg, 0.4 mmol), toluene (5 mL), and a solution of vinyl magnesium bromide in THF (1.8 mL, 0.7 M, 1.2 mmol, 3 equiv) afforded *Z*-**2q**[5b] (65.7 mg, 80%) (eluent: petroleum ether (bp=30–60 °C)/diethyl ether=50:1): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (dd, J_1=17.7 Hz, J_2=11.1 Hz, 1H, =CH), 5.60 (t, J=7.4 Hz, 1H, =CH), 5.11 (d, J=17.7 Hz, 1H, =CH), 4.92 (d, J=11.1 Hz, 1H, =CH), 4.13 (q, J=7.2 Hz, 2H, OCH_2), 3.62 (q, J=7.2 Hz, 1H, CH), 2.20–2.03 (m, 2H, CH_2), 1.45–1.30 (m, 7H, 2×CH_2+CH_3), 1.22 (t, J=7.1 Hz, 3H, CH_3), 0.91 (t, J=7.1 Hz, 3H, CH_3).

4.3. Stereocontrollable reactions of the dienolate intermediate *Z*-4 with different electrophiles

*4.3.1. Addition reaction of acetone with the organometallic intermediate Z-**4**. 4.3.1.1. Synthesis of ethyl 2-(1′-hydroxyl-1′-methyl-ethyl)-2,3-dimethyl-4-phenyl-3(Z)-butenoate (Z-**5**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1a** (0.0810 g, 0.4 mmol), and toluene (5 mL) with a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) formed the solution at −78 °C after 1.5 h. To this solution was slowly added acetone (0.15 mL, d=0.79 g/mL, 0.1185 g, 2 mmol, 5 equiv) at −78 °C. After 2.5 h as monitored by TLC, the reaction mixture was quenched slowly with a saturated aqueous solution of NH_4Cl (2 mL) at −78 °C followed by warming up to rt naturally. After extraction with diethyl ether (3×15 mL), the organic layer was washed subsequently with diluted HCl (5%, aqueous), a saturated aqueous solution of $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: hexane/ethyl acetate=30:1) afforded *Z*-**5** (76.0 mg, 69%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.15 (m, 5H, Ar–H), 6.65 (s, 1H, =CH), 4.07 (br, 1H, OH), 3.94–3.74 (m, 2H,

CH_2), 2.04 (d, J=1.8 Hz, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.20 (t, J=7.2 Hz, 3H, CH_3), 1.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 139.3, 136.8, 130.3, 128.9, 127.3, 126.1, 74.9, 60.6, 58.54, 27.8, 26.5, 26.1, 22.5, 13.8; MS (EI) m/z (%) 277 ((M^++H), 2.10), 259 (M^++H−18, 15.97), 185 (M^+−91, 100); IR (neat, cm^{-1}) 3523, 2983, 2928, 1709, 1462, 1388, 1249, 1173, 1101, 1023. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.96; H, 8.93.

*4.3.2. Coupling reaction of methyl p-toluenesulfonate with the organometallic intermediate Z-**4**. 4.3.2.1. Synthesis of ethyl 2,2,3-trimethyl-4-phenyl-3(E)-butenoate (E-**6**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1a** (0.0802 g, 0.4 mmol), and toluene (5 mL) with a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) formed the solution at −78 °C after 1.8 h. To this solution was added methyl *p*-toluenesulfonate (0.3726 g, 2 mmol, 5 equiv) at −78 °C followed by warming up to rt naturally after 1 h. After 16 h as monitored by TLC, the reaction mixture was sequentially quenched with a saturated aqueous solution of NH_4Cl (2 mL) at 0 °C. After extraction with diethyl ether (3×15 mL), the organic layer was washed as usual and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=100:1) afforded *E*-**6** ((61.4 mg (pure) and 10.7 mg (mixture of *E*-**6** and *E*-**2a**, molar ratio by NMR: 82:18, content of *E*-**6**: 83% by weight), combined yield: 76%: liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.30 (m, 2H, Ar−H), 7.25−7.17 (m, 3H, Ar−H), 6.43 (s, 1H, =CH), 4.15 (q, J=7.1 Hz, 2H, OCH_2), 1.81 (d, J=1.2 Hz, 3H, CH_3), 1.41 (s, 6H, 2×CH_3), 1.24 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 140.8, 138.2, 129.0, 127.9, 126.1, 124.0, 60.6, 48.9, 24.6, 15.5, 14.1; MS (EI) m/z (%) 233 (M^++1, 4.83), 232 (M^+, 28.85), 159 (100); IR (neat, cm^{-1}) 2980, 1730, 1645, 1600, 1446, 1382, 1253, 1144, 1107, 1028; HRMS calcd for $C_{15}H_{20}O_2$ (M^+): 232.1463; found: 232.1470.

*4.3.3. Coupling reaction of benzyl bromide with the organometallic intermediate Z-**4**. 4.3.3.1. Synthesis of ethyl 2-benzyl-2,3-dimethyl-4-phenyl-3(E)-butenoate (E-**7**).* The reaction of CuCl (2.1 mg, 0.021 mmol, 5.2 mol %), **1a** (0.0820 g, 0.4 mmol), and toluene (5 mL) with a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) formed the solution at −78 °C after 1.5 h. To this solution was added benzyl bromide (0.24 mL, d=1.44 g/mL, 0.3456 g, 2 mmol, 5 equiv) at −78 °C followed by warming up to rt naturally after 0.5 h. After 15 h as monitored by TLC, the reaction mixture was sequentially quenched with a saturated aqueous solution of NH_4Cl (2 mL). After extraction with diethyl ether (3×15 mL), the organic layer was washed subsequently with diluted HCl (5%, aqueous), a saturated aqueous solution of $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=100:1) afforded *E*-**7** (83.8 mg (mixture of *E*-**7** and *E*-**2a**, molar ratio by NMR: 94:6), 64%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.29 (m, 2H, Ar−H), 7.27−7.16 (m, 6H, Ar−H), 7.12−7.09 (m, 2H, Ar−H), 6.20 (s, 1H, =CH), 4.18 (q, J=7.1 Hz, 2H, OCH_2), 3.21 (d, 1H, J=13.2 Hz, one proton of CH_2), 3.10 (d, 1H, J=13.2 Hz, one proton of CH_2), 1.86 (s, 3H, CH_3), 1.30−1.24 (m, 6H, 2×CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 138.7, 138.1, 137.6, 130.6, 128.9, 128.0, 127.7, 126.3, 126.2, 126.1, 60.7, 53.4, 41.8, 21.3, 16.0, 14.1; MS (ESI) m/z (%) 309 (($M+H)^+$, 100); IR (neat, cm^{-1}) 3059, 3027, 2980, 2936, 1728, 1601, 1494, 1453, 1375, 1232, 1100, 1025; HRMS calcd for $C_{21}H_{24}O_2Na^+$ ($M+Na^+$): 331.1669; found: 331.1664.

*4.3.4. Coupling reaction of allyl acetate with the organometallic intermediate Z-**4**. 4.3.4.1. Synthesis of ethyl 2,3-dimethyl-2-methylcarbonyl-4-phenyl-3(E)-butenoate (E-**8**).* The reaction of CuCl (2.0 mg, 0.02 mmol, 5 mol %), **1a** (0.0798 g, 0.4 mmol), and toluene (5 mL) with a solution of CH_3MgCl in THF (0.4 mL, 3 M, 1.2 mmol, 3 equiv) formed the solution at −78 °C after 1.5 h. To this solution was added allyl acetate (0.22 mL, d=0.93 g/mL, 0.2046 g, 2 mmol, 5 equiv) at −78 °C. After 16 h as monitored by TLC, the reaction mixture was sequentially quenched with a saturated aqueous solution of NH_4Cl (2 mL) at 0 °C. After extraction with diethyl ether (3×15 mL), the organic layer was washed subsequently with diluted HCl (5%, aqueous), a saturated aqueous solution of $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=100:1 to 30:1) afforded *E*-**8**[6] (50.6 mg, 49%): liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.32 (m, 2H, Ar−H), 7.27−7.22 (m, 3H, Ar−H), 6.40 (s, 1H, =CH), 4.26 (q, J=7.0 Hz, 2H, OCH_2), 2.29 (s, 3H, CH_3), 1.87 (d, J=1.2 Hz, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.31 (t, J=7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.6, 171.9, 137.2, 136.1, 129.0, 128.6, 128.1, 126.8, 67.1, 61.4, 27.2, 19.7, 16.4, 14.0.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.01.027.

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7. When the reaction of **1a** with CH_3MgCl under standard conditions was quenched at 0 °C instead of −78 °C, the *Z*/*E* ratio dropped to 96:4 (entry 18, Table 1), which clearly supports the hypothesis of isomerization from 1,3-(*Z*)-dienoate *Z*-**4** to 1,3-(*E*)-dienoate *E*-**4** at higher temperature. See also Ref. 6.