# Efficient Assembly of Allenes, 1,3-Dienes, and 4*H*-Pyrans by Catalytic Regioselective Nucleophilic Addition to Electron-Deficient 1,3-Conjugated Enynes

Xiuzhao Yu, Hongjun Ren, Yuanjing Xiao, and Junliang Zhang*[a]

Catalytic nucleophilic addition[1] to electron-deficient olefins is an example of one of the cornerstones in modern synthetic organic chemistry, since the atom economy[2] of such addition reactions can be 100%. In this context, acroleins, acrylates, acrylonitriles, vinyl ketones, and α-nitroalkenes have been well studied as electrophiles for the 1,4-addition of nucleophiles in past years. Despite this, it is necessary to develop some readily available substrates as novel electrophiles for the modern synthetic community. Very recently, our group[4] and others[3] have found that 2-(1-alkynyl)-2-alken-1-ones can react with nucleophiles catalyzed by transition-metals or mediated by electrophiles to give polysubstituted furans. A cyclopropanation reaction of 2-(1-alkynyl)-2-alken-1-ones with dimethylsulfoxonium methylide for the synthesis of 1-alkynylcyclopropyl ketones, which can react with nucleophiles to afford highly substituted furans under gold-complex catalysis, was also developed.[5] We hypothesized that, in these transformations, 2-(1-alkynyl)-2-alken-1-ones might act as electrophiles in the reaction pathway. Thus, we became interested in the nucleophilic addition of various nucleophiles to electron-deficient 1,3-conjugated enynes. On comparison with simple electron-deficient olefins, there is an obvious new regioselectivity issue in this transformation of electron-deficient 1,3-enynes, that is, whether or not the reaction occurs by 1,4-addition, 4,5′-addition, or 4′,5′-addition leading to functionalized alkynes, 1,2-allenes, or 1,3-dienes, respectively (Scheme 1; EWG = electron-withdrawing group). Herein, we wish to report our recent results on the simple base-catalyzed highly regioselective nucleophilic addition to electron-deficient 1,3-conju-
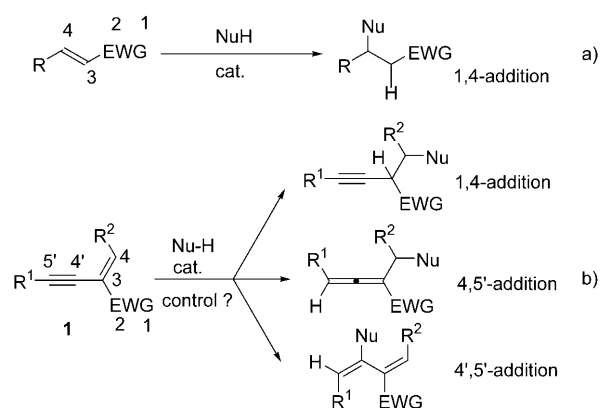
Scheme 1. a) Nucleophilic addition to simple electron-deficient alkenes. b) Regioselective nucleophilic addition to electron-deficient 1,3-conjugated enyne **1**.

gated enynes leading to highly functionalized 1,2-allenes,[6] 1,3-dienes,[7] and 4*H*-pyrans,[8] respectively. The regioselectivity is controllable by a subtle choice of nucleophile.[9]

Initially, we tested the reaction of 1,3-conjugated enyne (**1a**) with carbon-centered nucleophile dimethyl malonate (**2a**) in the presence of different catalysts (Table 1). After some attempts, we were pleased to find that the reaction of **1a** with **2a** (2.0 equiv) in THF at 0°C for 4 h in the presence of 10 mol% of KOH exclusively afforded 1,2-allene **3aa** as two diastereoisomers in 91% total isolated yield by a 4,5′-addition reaction. No transition metal or Lewis acid are needed in the reaction (Table 1, entry 5) and no alkyne or 1,3-diene were formed, as detected by ^{1}H NMR spectroscopic analysis of the crude product. Other bases, such as Na$_2$CO$_3$ and K$_2$CO$_3$, did not catalyze this transformation in THF at 0°C, but they worked well in DMF at RT (Table 1, entries 7–10). We also tested organic bases, such as Et$_3$N and DBU (Table 1, entries 1–2). The reaction proceeded smoothly in DMF when DBU was used as the catalyst (Table, entry 2). In contrast, no reaction occurred in the presence of Et$_3$N (Table 1, entry 1).

[a] X. Yu, Dr. H. Ren, Dr. Y. Xiao, Prof. Dr. J. Zhang
Shanghai Key Laboratory of Green Chemistry and
Chemical Processes Department of Chemistry
East China Normal University
3663 N. Zhangshan Road, Shanghai 200062 (P. R. China)
Fax: (+86)21-6223-5039
E-mail: jlzhang@chem.ecnu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801004.

Table 1. Screening reaction conditions for the addition of malonate **2a** to electron-deficient conjugated enyne **1a**.[a]
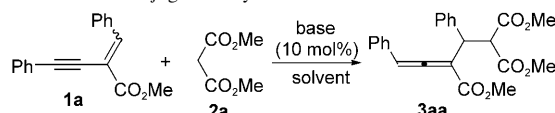
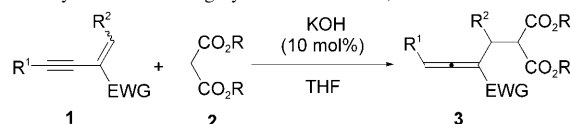| Entry	Base	Solvent	T [°C]	t [h]	d.r.[b]	Total yield [%]
1	Et₃N	DMF	RT	12	–	0
2	DBU[c]	DMF	RT	2	1.7:1.0	86
3	DBU	THF	RT	52	1.5:1.0	31
4	KOH	THF	RT	2	1.6:1.0	88
5[d]	KOH	THF	0	4	1.7:1.0	91
6	KOH	DMF	0	3	1.9:1.0	77
7	Na₂CO₃	THF	0	12	–	0
8	Na₂CO₃	DMF	RT	50	1.6:1.0	83
9	K₂CO₃	THF	0	12	–	0
10	K₂CO₃	DMF	RT	2	1.7:1.0	85

[a] The reaction was carried out by using **1a** (0.5 mmol) and **2a** (1.0 mmol) in solvent (2 mL). The yield is the isolated yield. [b] d.r. = diastereoisomer ratio. [c] DBU = 1,8-diazabicyclo[5.4.0]undecen-7-ene. [d] Even 1 mol % of KOH worked well on a 15 mmol scale.

Table 2. 4,5′-Addition of malonates to various electron-deficient 1,3-conjugated enynes **1** lead to highly functionalized 1,2-allenes **3**.[a]

Entry	Enyne **1** R¹/R²/EWG	Total yield of **3** ([%], d.r.)
1	Ph/4-MeOPh/CO₂Me (**1b**)	**3ba** (84, 1.1:1.0)
2	4-MeOph/Ph/CO₂Me (**1c**)	**3ca** (93, 1.4:1.0)
3	1-naphthyl/Ph/CO₂Me (**1d**)	**3da** (87, 1.8:1.0)
4[b]	Ph/Ph/COMe (**1e**)	**3ea** (96, 1.2:1.0)
5[b]	Ph/4-MeOPh/COMe (**1f**)	**3fa** (91, 1.3:1.0)
6[c]	n-C₄H₉/Ph/COMe (**1g**)	**3ga** (55, 1.1:1.0)
7	4-MeOPh/4-MeOPh/COMe (**1h**)	**3ha** (95, 15:1.0)
8[b]	1-naphthyl/Ph/COMe (**1i**)	**3ia** (83, 1.7:1.0)
9[d]	**1a**	**3ab** (93, 1.5:1.0)
10[e]	**1a**	**3ac** (92, 1.4:1.0)

[a] All reactions were carried out with enyne **1** (0.5 mmol), dimethyl malonate **2a** (1.0 mmol), and KOH (10 mol %) in THF at 0°C for 2–12 h, unless otherwise specified. [b] Two diastereoisomers can be separated easily by flash column chromatography. [c] 20 % of **1g** is recovered after 24 h. [d] Diethyl malonate **2b** (1.0 mmol) was used instead of **2a**. [e] Dibenzyl malonate **2c** (1.0 mmol) was used instead of **2a**. [f] The designation **3ba** for the product indicates that the reactants used were **1b** and **2a**, respectively.

To determine the scope of this transformation, various electron-deficient 1,3-conjugated enynes **1** were studied and the results are summarized in Table 2. The reaction of 2-arylidene 3-alkynoates **1b–d** with dimethyl malonate **2a** afforded highly substituted functionalized 1,2-allenoates **3ba–3da** in high yields (Table 2, entries 1–3). Functionalized 1,2-allenyl ketones **3ea–3ia** could be produced in moderate to excellent yields (Table 2, entries 4–8). When R1 is alkyl group in the substrate, the reaction takes longer and could not complete after 24 h giving a 55 % yield of **3ga** and 20 % of recovered starting material (Table 2, entry 6). The reaction of enyne **1e** with dimethyl malonate **2a** provided further evidence for the structure and relative stereochemistry, since we established the structure and relative stereochemistry of **3ea** by single-crystal X-ray diffraction analysis of one of its stereoisomers (Figure 1a).[10] Dibenzyl and diethyl malonates can also be employed as nucleophiles to afford the corresponding functionalized 1,2-allenes in excellent yields with high regioselectivity (Table 2, entries 9–10). The reactions of dimethyl malonate **2a** with 1,3-enyne (Z)-**1j** and its stereoisomer (E)-**1j** gave the same product with the same diastereoselectivity; this indicates that they have the same reaction intermediary (Scheme 2).

Furthermore, it is surprising but also interesting to observe a totally different addition mode when 4-methylthiophenol **2d** was used as the nucleophile instead of dimethyl malonate **2a**. The reaction of 4-methylthio-

phenol **2d** with **1a** proceeds very well at RT in THF under similar conditions to afford a highly regioselective and stereospecific 4′,5′-addition product, 1,3-diene **4ad**, in 99 % yield. No 1,2-allene and alkyne-type products were formed, as detected by ¹H NMR spectroscopic analysis of the crude products [Eq. (1)]. The high stereoselectivity is quite surprising because **1a** contains two different stereoisomers based on the double bond; this indicates that the double bond of the enyne **1a** should be involved in the reaction pathway. Similar to the case of nucleophilic addition of dimethyl malonate **2a**, the reactions of (Z)-**1j** and its stereoisomer (E)-**1j** with **2d** give the same product, (3Z,4E)-**4jd**, which further
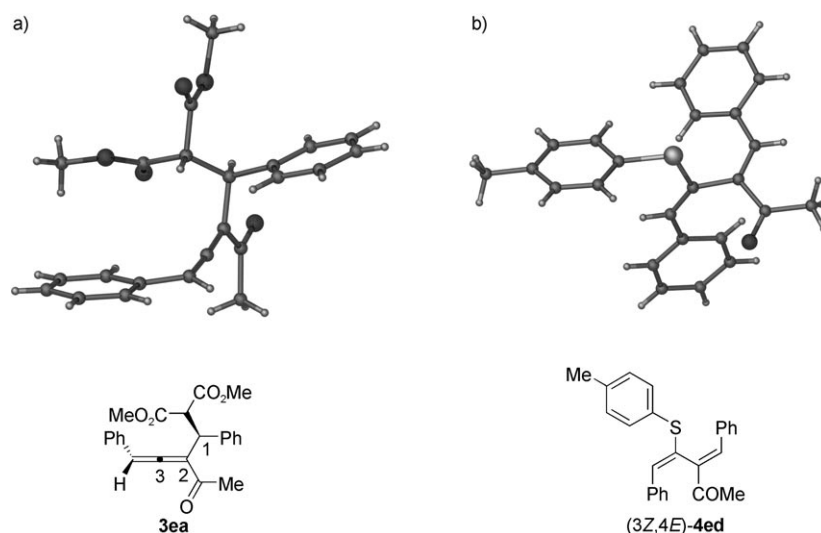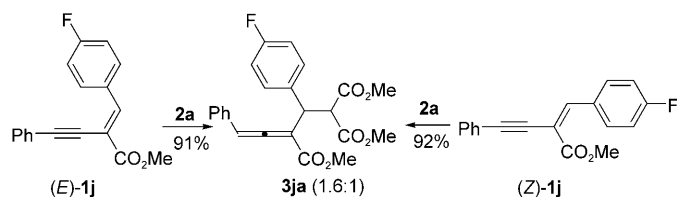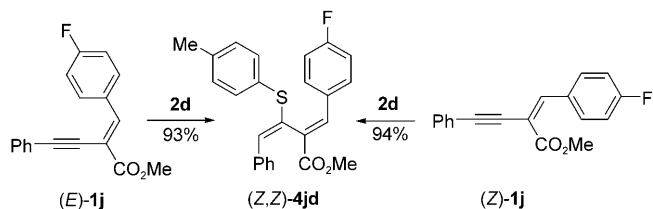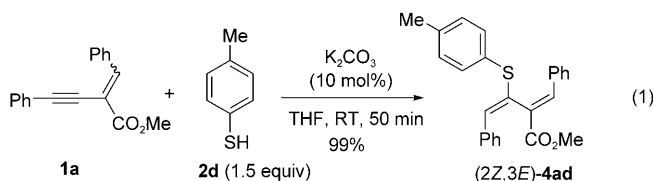

Figure 1. X-ray crystal structures and line drawings of 1,2-allene **3ed** (a) and 1, 3-diene **4ed** (b).

COMMUNICATION

Scheme 2. Reactions of **2a** with (Z)-**1j** and its stereoisomer (E)-**1j** lead to the same product, **3ja**. Conditions: KOH (10 mol%), THF, 0 °C, 2 h.

confirms that the double bond of the enyne is involved in the reaction pathway (Scheme 3).

Scheme 3. Reactions of **2d** with (Z)-**1j** and its stereoisomer (E)-**1j** lead to the same product (2Z,3E)-**4jd**. Conditions: K$_2$CO$_3$ (10 mol%), THF, RT, 1 h.

Various 1,3-enynes **1** and heteroatom nucleophiles **2d–g** were then studied and typical results are listed in Table 3. Points to note: 1) not only arylenethiols, such as 4-methyl-thiophenol **2d** and 2-naphthalenethiol **2e**, but also benzyl mercaptan **2f** can act as S nucleophiles to give highly functionalized tetrasubstituted 1,3-dienes **4bd–af** with high regioselectivity and stereoselectivity in good to excellent yields (Table 3, entries 1–8); 2) initial results showed that pyrrolidine **2g** can act as a N nucleophile reacting with enyne **1a** to afford the corresponding substituted 3-pyrrolidinyl 1,3-diene **4ag** in 77% yield (Table 3, entry 11); and 3) the structure and relative stereochemistry of the products was established by single-crystal X-ray diffraction analysis of (3Z,4E)-**4ed** (Figure 1b).[11]

Some initial results showed that β-keto compounds can also react as nucleophiles with electron-deficient 1,3-conjugated enynes to give a very interesting heterocyclic compound, 4H-pyran, with potential bioactivity[8] by a formal [3+3] cycloaddition (cascade[12] intermolecular/intramolecular nucleophilic addition; Scheme 4). Although K$_2$CO$_3$ can catalyze this transformation in THF, DBU gives better results.

A plausible mechanism for this simple base-catalyzed highly regioselective nucleophilic addition to electron-defi-

Table 3. Regioselective and stereoselective synthesis of highly substituted functionalized 1,3-dienes.[a–c]

| Entry	Enyne **1** R^1/R^2/EWG	NuH **2**	Yield of **4** [%]
1	Ph/4-MeOPh/CO$_2$Me (**1b**)	**2d**	**4bd** (99)
2	4-MeOPh/Ph/CO$_2$Me (**1c**)	**2d**	**4cd** (82)
3	1-naphthyl/Ph/CO$_2$Me (**1d**)	**2d**	**4dd** (87)
4[b]	Ph/Ph/COMe (**1e**)	**2d**	**4ed** (94)
5[b]	Ph/4-MeOPh/COMe (**1f**)	**2d**	**4fd** (92)
6[c]	n-C$_4$H$_9$/Ph/COMe (**1g**)	**2d**	**4gd** (80)
7	4-MeOPh/4-MeOPh/COMe (**1h**)	**2d**	**4hd** (96)
8[b]	1-naphthyl/Ph/COMe (**1i**)	**2d**	**4id** (88)
9[d]	**1a**	**2e**	**4ae** (93)
10[e]	**1a**	**2f**	**4af** (84)
11	**1a**	**2g**	**4ag** (77)

[a] All reactions were carried out with enyne **1** (0.5 mmol), **2d/2e/2f/2g** (0.75 mmol), and K$_2$CO$_3$ (10 mol%) in THF at RT for 0.5–2 h. [b] Yields are isolated yields. [c] The stereoselectivity is more than 95% if the stereoselectivity issue exists.
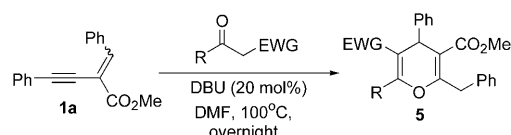
5a: R = Me, EWG = COMe (91%)
5b: R = Me, EWG = CO$_2$Et (88%)
5c: R = Ph, EWG = CO$_2$Me (80%)

Scheme 4. DBU-catalyzed formal [3+3] cycloaddition of β-keto compounds with **1a**.

cient 1,3-enynes is proposed in Scheme 5. The addition of a nucleophilic anion, generated by the deprotonation of the nucleophile in the presence of base, to electron-deficient enyne **1** afforded intermediate 1,2-allenic/propargylic anion
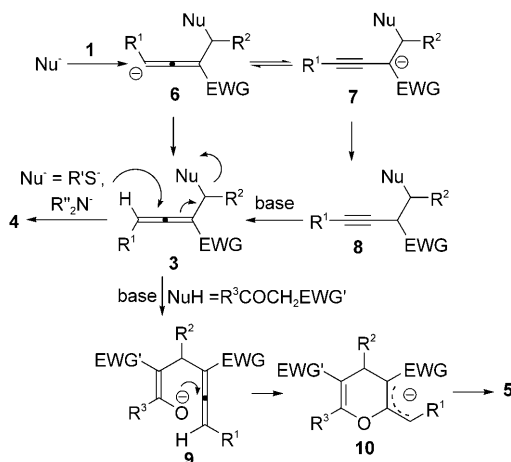
Scheme 5. Plausible mechanism for the simple base-catalyzed highly regioselective nucleophilic addition to electron-deficient 1,3-enynes.

6/7, which can then undergo subsequent protonation (proton from the nucleophile) to give 1,2-allene **3** or alkyne **8**. The alkyne **8**, if formed, can then undergo a quick rearrangement to give 1,2-allene **3** under the basic conditions.[13] 1,3-Diene **4** was produced by a tandem stereospecific nucleophilic addition to electron-deficient 1,2-allene[14] from the less bulky side and subsequent β-heteroatom elimination when heteroatom nucleophiles, such as thiols and amines, were used, since these heteroatom groups are also good leaving groups. 4*H*-Pyrans were afforded by a cascade intermolecular/intramolecular nucleophilic addition under base catalysis.

In summary, we have demonstrated that electron-deficient 1,3-conjugated enynes can serve as novel and readily available[15] electrophiles for the nucleophilic addition. The addition patterns depend on the nucleophiles. 4,5′-Addition leading to functionalized 1,2-allenes was realized when carbon-centered nucleophiles, such as malonates, were used, whereas functionalized 1,3-dienes were formed by a 4′,5′-addition mode if heteroatom nucleophiles were applied and 4*H*-pyrans were afforded by a formal [3+3] cycloaddition. This methodology provides an efficient, atom-economic, and mild route to synthesize highly functionalized 1,2-allenes, 1,3-dienes, and 4*H*-pyrans, which are useful building blocks in organic synthesis. Investigations by our group into the synthetic applications, scope, and asymmetric catalysis of these reactions are actively underway.

Experimental Section

Synthesis of 1,2-allene 3aa (Table 1, entry 5): Solid KOH (0.05 mmol, 3 mg) was added in one portion to a solution of dimethyl malonate (**2a**; 1.0 mmol, 132 mg) and methyl 2-benzylidene-4-phenylbut-3-ynoate (**1a**; 0.5 mmol, 131 mg) in THF (2 mL) at 0°C. The reaction mixture was then stirred until the enyne **1a** had been consumed, as determined by TLC analysis. H_2O (5 mL) was added to quench the reaction and the mixture was extracted by diethyl ether (3×10 mL). The combined organic layer was dried over $MgSO_4$. After filtration and concentration, the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate 2:1) to give **3aa** (d.r.=1.7:1.0) in 91% yield.

First fraction: Solid; ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.39–7.30 (m, 10H), 6.83 (d, J=1.0 Hz, 1H), 4.74 (dd, J=12.0, 1.0 Hz, 1H), 3.97 (d, J=12.0, 1H), 3.71 (s, 3H), 3.40 (s, 3H), 3.39 ppm (s, 3H); ^{13}C NMR (125.8 MHz, CDCl$_3$): δ=165.50, 210.67, 167.70, 167.68, 138.70, 131.37, 128.80, 128.46, 128.38, 128.28, 127.70, 127.52, 106.78, 101.68, 55.60, 53.41, 52.36, 52.32, 44.29 ppm; MS (70 eV): m/z (%): 394 (1.98) [M^+], 105 (100) [C_6H_5CO]$^+$; HRMS: m/z: calcd for $C_{23}H_{22}O_6$: 394.1416; found: 394.1416.

Second fraction: Colorless oil; ^{1}H NMR (500 MHz, CDCl$_3$): δ=6.78 (d, J=2.0 Hz, 1H), 7.25–7.38 (m, 10H); 4.74 (dd, J=12.0, 2.0 Hz, 1H), 4.04 (d, J=12.0 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.43 ppm (s, 3H); ^{13}C NMR (125.8 MHz, CDCl$_3$): δ=210.81, 167.82, 167.46, 165.43, 138.77, 131.39, 128.82, 128.36, 128.28, 127.50, 127.39, 106.66, 101.51, 55.66, 52.68, 52.31, 52.24, 44.23 ppm; MS (70 eV): m/z (%): 394 (2.09) [M^+], 105 (100) [C_6H_5CO]$^+$; HRMS m/z: calcd for $C_{23}H_{22}O_6$: 394.1416; found: 394.1416.

Synthesis of 1,3-diene (2Z,3E)-4ad [Eq. (1)]: Solid K_2CO_3 (0.05 mmol, 6.9 mg) was added to a solution of 4-methylthiophenol **2d** (0.75 mmol, 93.1 mg) and **1a** (0.5 mmol, 131.0 mg) in THF (2 mL) at RT. The reaction mixture was then stirred until the enyne **1a** had been consumed, as determined by TLC analysis. After the routine workup, the crude product was purified by column chromatography on silica gel to give (2Z,3E)-**4ad**

(190.5 mg) in 99% yield. ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.79 (s, 1H), 7.71–7.69 (m, 2H); 7.39–7.37 (m, 5H), 7.31 (d, J=7.5 Hz, 2H), 7.24 (t, J=7.5 Hz, 2H), 7.18 (d, J=7.5 Hz, 1H), 7.12 (d, J=7.5 Hz, 2H), 6.69 (s, 1H), 3.72 (s, 3H), 2.37 ppm (s, 3H); ^{13}C NMR (125.8 MHz, CDCl$_3$): δ=166.81, 142.51, 139.09, 136.55, 135.45, 134.29, 133.92, 130.48, 129.94, 129.74, 129.26, 128.43, 128.38, 128.31, 127.79, 127.72, 127.16, 52.37, 21.27 ppm; MS (70 eV): m/z (%): 386 (100) [M^+]; HRMS: m/z: calcd for $C_{25}H_{22}O_2S$: 386.1341; found: 386.1343.

Synthesis of 4H-pyran 5a: A solution of acetylactone (60 mg, 0.60 mmol), methyl 2-benzylidene-4-phenylbut-3-ynoate **1a** (131.0 mg, 0.50 mmol), and DBU (7.6 mg, 0.05 mmol) in DMF (2 mL) was stirred at 100°C. After stirring for 12 h, the reaction was complete, as determined by TLC analysis. After cooling down to RT, H_2O (10 mL) was added and the mixture was extracted by diethyl ether (3×15 mL). The combined organic layers were washed with saturated brine solution and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by column chromatography on silica gel (hexanes/ethyl ether 3:1) to afford 164.3 mg (91%) of **5a**. ^{1}H NMR (500 MHz, CDCl$_3$): δ=7.30–7.18 (m, 10H), 4.83 (s, 1H), 4.19 (d, J=14.0 Hz, 1H), 4.01 (d, J=14.0 Hz, 1H), 3.72 (s, 3H), 2.27 (s, 3H), 2.15 ppm (s, 3H); ^{13}C NMR (125.8 MHz, CDCl$_3$): δ=198.52, 166.71, 159.18, 157.19, 144.39, 136.95, 128.65, 128.45, 128.42, 128.38, 128.13, 126.93, 126.58, 115.82, 109.26, 51.52, 39.09, 37.15, 29.84, 18.90 ppm; MS (EI): m/z (%): 362 (89.76) [M^+], 285 (100); HRMS: m/z: calcd for $C_{23}H_{22}O_4$: 362.1518; found: 362.1518.

[1] *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, Oxford, **1991**, Chapters 1.1–1.6, pp. 1–268.

[2] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.

[3] a) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164; b) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 7679; c) Y. H. Liu, S. Zhou, *Org. Lett.* **2005**, *7*, 4609; d) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531.

[4] Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929; *Angew. Chem. Int. Ed.* **2008**, *47*, 1903.

[5] J. Zhang, H. G. Schmalz, *Angew. Chem.* **2006**, *118*, 6856; *Angew. Chem. Int. Ed.* **2006**, *45*, 6704.

[6] 1,2-Allenes are useful building blocks in organic synthesis, see: a) *Modern Allene Chemistry, Vols. 1–2* (Eds.: N. Krause, A. S. K. Hashmi),Wiley-VCH, Weinheim, **2004**; b) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; c) S. Ma, *Aldrichimica Acta* **2007**, *40*, 91; for a very recent review on the synthesis of allenes, see: d) K. M. Brummond, J. E. DeForrest, *Synthesis* **2007**, 795.

[7] 1,3-Dienes are useful building blocks for cycloaddition reactions, especially Diels–Alder reactions, see: a) F. Fringuelli, A. Taticchi, *Dienes in the Diels–Alder Reaction*; Wiley: New York, **1990**; b) W. Oppolzer in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M Trost, I. Fleming), Pergamon Press, Oxford, UK, **1991**, Chapter 4.1, pp. 315–400; c) W. R. Roush in *Comprehensive Organic Synthesis* (Eds.: B. M Trost, I. Fleming), Pergamon Press, Oxford, UK, **1991**, Vol. 5, Chapter 4.4, pp. 513–550.

[8] 4*H*-Pyrans are bioactive compounds, see: K. Urbahns, E. Horváth, J.-P. Stasch, F. Mauler, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2637, and references therein.

[9] Regioselectivity control is an important issue in organic synthesis, for recent reviews, see: a) J.-J. Brunet, R. Poli, *Chemtracts* **2004**, *17*, 381; b) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368; c) M. Schlosser, F. Mongin, *Chem. Rev. Soc.* **2007**, *36*, 1161; d) M. T. Reetz, *Angew. Chem.* **2008**, *120*, 2592; *Angew. Chem. Int. Ed.* **2008**, *47*, 2556; e) for selected recent examples, see: Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962; f) K. M. Miller, T. F. Jamison, *J. Am. Chem. Soc.* **2004**, *126*, 15342; g) S. Ma, L. Lu, J. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 9645; h) S. Kamijo, C. Kanazawa, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 9260; i) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem.* **2005**, *117*, 3185; *Angew. Chem. Int. Ed.* **2005**, *44*, 3125; j) V. I. Timokhin, S. S. Stahl, *J. Am. Chem. Soc.* **2005**, *127*, 17888; k) S. Chaudhury, W. A. Donaldson, *J. Am. Chem. Soc.* **2006**, *128*, 5984; l) E. M. Beck, N. P. Grimster, R. Hatley, M. J. Gaunt, *J. Am. Chem. Soc.* **2006**, *128*, 2528; m) R. Shintani, W.-L. Duan, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 5268; n) S. Brandau, E. Maerten, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986; o) L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3276; p) for a review on the regioselective addition of organocopper reagents to 1,3-conjugated enynes with an acceptor group at the 1-position, see: N. Krause, Andreas Gerold, *Angew. Chem.* **1997**, *109*, 194; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186.

[10] X-ray data for one stereoisomer of compound **3ea**: $C_{23}H_{21}O_5$; $M_w = 377.40$; monoclinic; space group $= P2(1)$; $Mo_{K\alpha}$; final R indices [$I > 2\sigma(I)$], $R1 = 0.0509$, $wR2 = 0.1144$; $a = 13.0956(16)$, $b = 8.0263(10)$, $c = 19.516 (2)$ Å; $\alpha = 90$, $\beta = 95.751(2)$, $\gamma = 90°$; $V = 2040.9(4)$ Å^3; $T = 293(2)$ K; $Z = 4$; reflections collected/unique $= 9959/3958$ ($R_{int} = 0.0907$); number of observations [$I > 2\sigma(I)$] $= 2081$; parameters $= 265$.

[11] X-ray data for compound (3*Z*,4*E*)-**4ed**: $C_{25}H_{22}OS$, $M_w = 370.49$; monoclinic; space group $= Cc$; $Mo_{K\alpha}$; final R indices [$I > 2\sigma(I)$], $R1 =$ 0.0289, $wR2 = 0.0789$; $a = 14.66600(10)$, $b = 15.82580(10)$, $c = 11.1284(2)$ Å; $\alpha = 90$, $\beta = 95.751(2)$, $\gamma = 90°$; $V = 2037.11(4)$ Å^3; $T = 296(2)$ K; $Z = 4$; reflections collected/unique $= 21969/3345$ ($R_{int} = 0.0199$); number of observations [$I > 2\sigma(I)$] $= 3248$; parameters $= 244$. CCDC 664022 (**3ea**) and 684235 (3*Z*,4*E*)-**4ed**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge form The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] For representative reviews on cascade or domino reaction see: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) L. F. Tietze, M. E. Lieb, *Curr. Opin. Chem. Biol.* **1998**, *2*, 363; c) J. Rodriguez, *Synlett* **1999**, 505; d) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; e) Multicomponent reactions often involve domino process, see: *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**; f) for a very recent nice example in this journal, see: Y. Coquerel, M.-H. Filippini, D. Bensa, J. Rodriguez, *Chem. Eur. J.* **2008**, *14*, 3078, and references therein.

[13] B. B. Snider, D. K. Spindell, *J. Org. Chem.* **1980**, *45*, 5017.

[14] For examples of the nucleophilic addition of heteroatom nucleophiles to electron-deficient 1,2-allenes, see: a) R. W. Spencer, T. F. Tam, E. Thomas, V. J. Robinson, A. Krantz, *J. Am. Chem. Soc.* **1986**, *108*, 5589; b) T. Sugita, M. Eida, H. Ito, N. Komatsu, K. Abe, M. Suama, *J. Org. Chem.* **1987**, *52*, 3789.

[15] Electron-deficient 1,3-enynes are easily prepared by the cross-coupling reaction of α-bromo(iodo)-α,β-unsaturated esters or ketones with terminal alkynes, see: a) R. Rossi, F. Bellina, C. Bechini, L. Mannina, P. Verganmini, *Tetrahedron* **1998**, *54*, 135; b) W.-M. Dai, J. Wu, K. C. Fong, M. Y. H. Lee, C. W. Lau, *J. Org. Chem.* **1999**, *64*, 5062; c) Y. Wang, D. J. Burton, *Org. Lett.* **2006**, *8*, 5295; d) references [3–5]; for a recent review, see: e) H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850; *Angew. Chem. Int. Ed.* **2007**, *46*, 834.