ORGANIC LETTERS
2011
Vol. 13, No. 13
3418–3421

β-Olefination of 2-Alkynoates Leading to Trisubstituted 1,3-Dienes

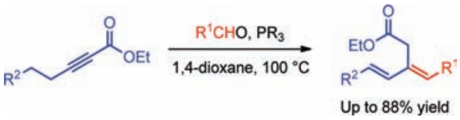
Mathias J. Jacobsen, Erik Daa Funder, Jacob R. Cramer, and Kurt V. Gothelf*

Danish National Research Foundation: Centre for DNA Nanotechnology (CDNA) and
Sino-Danish Centre for Molecular Assembly on Surfaces at Department of Chemistry
and iNANO, Aarhus University, Langelandsgade 140, DK-8000 Aarhus C, Denmark

kvg@chem.au.dk

Received May 2, 2011

ABSTRACT



A phosphine-mediated olefination of 2-alkynoates with aldehydes forming 1,3-dienes with high *E*-selectivity and up to 88% yield is described. Reaction conditions are optimized and reactions are demonstrated for various aryl, alkyl, and alkenyl aldehydes and for ethyl 2-alkynoates with different substituents in the δ-position. Proof of concept is shown for the generation of a β,γ-unsaturated lactone by intramolecular olefination, and furthermore the use of the generated 1,3-dienes in the Diels–Alder reaction has been demonstrated.

Conjugated dienes are abundant in a wide range of natural products,[1] and furthermore dienes constitute important scaffolds in the construction of complex organic molecules.[2] Preparation of 1,3-dienes can be facilitated e.g. by Wittig reactions,[3] the Julia olefination,[4] transition-metal-catalyzed cross-coupling reactions,[5] and the enyne metathesis reactions.[6] In 1992, Trost reported the isomerization of 2-alkynoates into $\alpha,\beta,\gamma,\delta$-dienes by a catalytic amount of triphenylphospine.[7] The proposed mechanism[8] for this transformation is initiated by a nucleophilic attack of phosphine on the β-carbon of the alkynoate. By a series of proton transfer reactions and phosphine elimination, the substrate is subsequently converted into a 1,3-diene with a phoshonium ylide as a key intermediate.

Phosphine-mediated reactions of 2-allenoates leading to e.g. γ-substituted α,β-unsaturated esters and 5-membered carbo- and heterocycles have been investigated extensively.[9]

Recently, Xu et al. and others have reported novel syntheses of 1,3-dienes by highly *E*-selective olefination of electron-deficient allenes with aldehydes in high yields.[10] However, allenes are relatively unstable and less readily available compounds.

Here we report on a new approach where ethyl 2-alkynoates are employed as reactants for olefination reactions instead of the corresponding allenes. Alkynes serve as versatile building blocks for a wide range of useful synthetic transformations.[11] In the past decades

---

(1) (a) DellaGreca, M.; Marino, C. D.; Zarrelli, A.; D'Abrosca, B. *J. Nat. Prod.* **2004**, *67*, 1492–1495. (b) Roth, G. N.; Chandra, A.; Nair, M. G. *J. Nat. Prod.* **1998**, *61*, 542–545. (c) Trisuwan, K.; Rukachaisirikul, V.; Sukpondma, Y.; Preedanon, S.; Phongpaichit, S.; Rungjindamai, N.; Sakayaroj, J. *J. Nat. Prod.* **2008**, *71*, 1323–1326.

(2) (a) Deagostino, A.; Prandi, C.; Zavattaro, C.; Venturello, P. *Eur. J. Org. Chem.* **2006**, 2463–2483. (b) Takeuchi, D.; Osakada, K. *Polymer* **2008**, *49*, 4911–4924.

(3) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.

(4) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

(5) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.

(6) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

(7) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933–7935. For a review on the phosphine-catalyzed isomerization, see: Kwong, C. K.-W.; Fu, M. Y.; Lam, C. S.-L.; Toy, P. H. *Synthesis* **2008**, 2307–2317.

(8) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659–2660.

(9) For representative reviews, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535–544. (b) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520–530. (c) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140–1152. (d) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050.

(10) (a) Xu, S.; Zhou, L.; Zeng, S.; Ma, R.; Wang, Z.; He, Z. *Org. Lett.* **2009**, *11*, 3498–3501. (b) Xu, S.; Zou, W.; Wu, G.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 3556–3559. (c) Ma, R.; Xu, S.; Tang, X.; Wu, G.; He, Z. *Tetrahedron* **2011**, *67*, 1053–1061. (d) Khong, S. N.; Tran, Y. S.; Kwon, O. *Tetrahedron* **2010**, *66*, 4760–4768. (e) He, Z.; Tang, X.; He, Z. *Phosphorus Sulfur Silicon Relat. Elem.* **2008**, *183*, 1518–1525.

(11) For representative reviews, see: (a) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 843–871. (b) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302–1315. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346. (d) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420. (e) Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121–1150.

10.1021/ol2011677

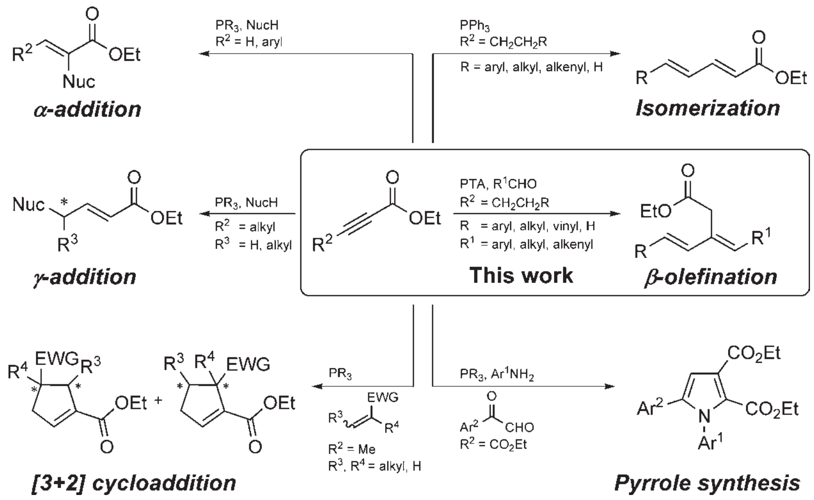


Figure 1. Examples of phosphine-mediated transformations utilizing electron-deficient 2-alkynoates.

phosphine-activated 2-alkynoates have been utilized in numerous reactions including Michael additions,[12] α-addition,[13] γ-addition,[14] pyrrole[15] and furan[16] synthesis, and [3 + 2] cycloaddition reactions[17] (Figure 1). Here it is demonstrated how *in situ* generated phosphonium ylides can be trapped with aldehydes in a Wittig olefination, transforming alkynoates into trisubstituted conjugated dienes and thereby expanding the scope of phosphine-mediated reactions of 2-alkynoates.

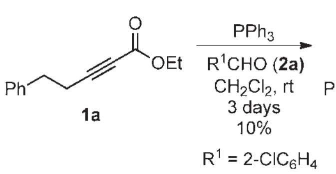
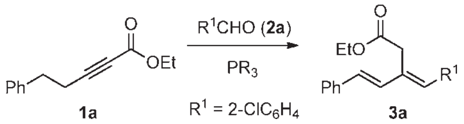


Figure 2. Reaction of **1a** with 2-chlorobenzaldehyde **2a**.

In our preliminary investigations we discovered that ethyl alkynoate **1a** underwent reaction with triphenylphosphine (1 equiv) and 2-chlorobenzaldehyde **2a** (0.8 equiv) in dichloromethane to afford the trisubstituted (*E*,*E*)-diene **3a** in 10% yield (Figure 2).

Based on the initial result we have optimized the conditions for the reaction between alkynoate **1a** and aldehyde **2a**, and the results are given in Table 1. Various phosphines

Table 1. Optimization of Reaction Conditions for the Olefination of Alkynoate **1a** with 2-Chlorobenzaldehyde **2a**[a]



entry	PR$_3$	solvent	temp (°C)	time (h)	conversion (%)[e,f]
1[b]	PBu$_3$[d]	CH$_2$Cl$_2$	rt	18	–
2[b]	PTA	CH$_2$Cl$_2$	rt	18	15
3[b]	MePPh$_2$	CH$_2$Cl$_2$	rt	18	32
4[b]	P(2-furyl)$_3$	CH$_2$Cl$_2$	rt	18	–
5[b]	PMe$_3$[d]	CH$_2$Cl$_2$	rt	18	5
6[b]	PCy$_3$[d]	CH$_2$Cl$_2$	rt	18	–
7[b]	PCl$_3$	CH$_2$Cl$_2$	rt	18	–
8[b]	P(OEt)$_3$	CH$_2$Cl$_2$	rt	18	–
9[c]	PPh$_3$	CH$_2$Cl$_2$	100	72	9
10[c]	PPh$_3$	MeCN	100	72	14
11[c]	PPh$_3$	1,4-dioxane	100	72	31
12[c]	MePPh$_2$	CH$_2$Cl$_2$	100	72	60
13[c]	MePPh$_2$	MeCN	100	72	33
14[c]	PTA	CH$_2$Cl$_2$	100	72	<5
15[c]	PTA	MeCN	100	72	99 (62)
16[c]	PTA	MeCN	100	16	99 (75)
17[c]	PTA	1,4-dioxane	100	16	99 (86)

[a] Reaction conditions: **2a** (0.5 mmol), phosphine (0.6 mmol), and **1a** (0.6 mmol) were stirred in 1 mL of solvent in a sealed vial. [b] Reaction was performed under inert conditions. [c] Reaction was performed at ambient conditions. [d] The phosphine was used as its HBF$_4$-salt; 2 equiv of distilled Et$_3$N were added for activation of the phosphine. [e] Conversions were determined by ^{1}H NMR spectroscopy based on **2a**. [f] Isolated yields are reported in parentheses.

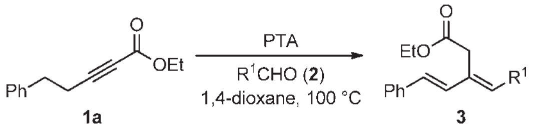
---

(12) (a) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, *22*, 241–244. (b) Yavari, I.; Ramazano, A. *Synth. Commun.* **1997**, *27*, 1449–1454. (c) Yavari, I.; Hekmat-Shoar, R.; Zonouzi, A. *Tetrahedron Lett.* **1998**, *39*, 2391–2392. (d) Trofimov, B. A.; Glotova, T. E.; Dvorko, M. Y.; Ushakov, I. A.; Schmidt, E. Y.; Mikhaleva, A. I. *Tetrahedron* **2010**, *66*, 7527–7532. (e) Kuroda, H.; Tomita, I.; Endo, T. *Polymer* **1997**, *38*, 3655–3662. (f) Kuroda, H.; Tomita, I.; Endo, T. *Macromolecules* **1995**, *28*, 433–436. (g) Kuroda, H.; Tomita, I.; Endo, T. *Macromolecules* **1995**, *28*, 6020–6025. (h) Grossman, R. B.; Pendharkar, D. S.; Patrick, B. O. *J. Org. Chem.* **1999**, *64*, 7178–7183. (i) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928–12929. (j) Yavari, I.; Souri, S.; Sirouspour, M.; Djahaniani, H. *Synthesis* **2006**, 3243–3249. (k) Tejedor, D.; Santos-Expósito, A.; Méndez-Abt, G.; Ruiz-Pérez, C.; García-Tellado, F. *Synlett* **2009**, 1223–1226. (l) Sriramurthy, V.; Kwon, O. *Org. Lett.* **2010**, *12*, 1084–1087.

were screened using dichloromethane as solvent at rt. In addition to PPh_3, application of 1,3,5-triaza-7-phospha-adamantane (PTA) and Ph_2PMe as reagents led to promising conversions in the olefination reaction.

Interestingly, increasing the temperature and changing the solvent from dichloromethane to acetonitrile or 1,4-dioxane led to a significant increase in conversion, especially when using PTA as the phosphine reagent. Furthermore, when increasing the reaction time beyond 20 h the isolated yield decreased due to degradation of the product or other side reactions over time at elevated temperatures. It was noted that application of acetonitrile as the solvent led to a lower isolated yield than use of 1,4-dioxane; hence 1,4-dioxane was used as the solvent in later reactions. To investigate whether traces of water influenced the yield of **3a**, a series of reactions were performed in 1,4-dioxane with varying water content. For reactions performed in 1,4-dioxane with a water content varying from 0.1 to 3.2 mg/mL, high conversions ($>95\%$) to the olefination product were observed.

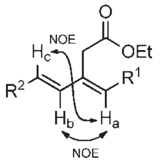
Table 2. Synthesis of 1,3-Dienes **3** from Aldehydes **2** and Alkynoate **1a**[a]



entry	R^1	time (h)	yield (%)[b]	E/Z[c]
1	$2\text{-}ClC_6H_4$ (**2a**)	19	86 (**3a**)	*E* only
2	$3\text{-}ClC_6H_4$ (**2b**)	16	57 (**3b**)	*E* only
3	$4\text{-}ClC_6H_4$ (**2c**)	16	81 (**3c**)	*E* only
4	$4\text{-}FC_6H_4$ (**2d**)	19	77 (**3d**)	*E* only
5	$2\text{-}(NO_2)C_6H_4$ (**2e**)	19	–	–
6	$3\text{-}(NO_2)C_6H_4$ (**2f**)	15	19 (**3f**)	*E* only
7	C_6H_5 (**2g**)	16	68 (**3g**)	*E* only
8	$2\text{-}(CH_3)C_6H_4$ (**2h**)	19	83 (**3h**)	*E* only
9	$4\text{-}(CH_3)C_6H_4$ (**2i**)	16	73 (**3i**)	*E* only
10	$4\text{-}(CH_3O)C_6H_4$ (**2j**)	16	–	–
11	$3\text{-}(CH_3O)C_6H_4$ (**2k**)	16	–	–
12	3-pyridyl (**2l**)	15	88 (**3l**)	*E* only
13	2-furyl (**2m**)	15	70 (**3m**)	7:2
14	$CH{=}CH_2$ (**2n**)	15	–	–
15	(*E*)-$CH{=}CHPh$ (**2o**)	15	–	–
16	(*E*)-$CH{=}CHCH_3$ (**2p**)	16	42 (**3p**)	*E* only
17	*n*-C_4H_9 (**2q**)	15	53 (**3q**)	5:1

[a] Reaction conditions: **2** (0.5 mmol), PTA (2 mmol), and **1a** (1 mmol) were stirred in 1,4-dioxane (1 mL) at 100 °C in a sealed vial. [b] Isolated yields. [c] Geometry of trisubstituted alkene, determined by ^1H NMR spectroscopy and 1D NOESY experiments.

Having established satisfactory conditions for the olefination of **1a** with **2a** the reactions of a variety of different aldehydes were investigated (Table 2). Moderately electron-deficient aldehydes (**2a**–**2d**) provided fair to good yields, whereas strongly electron-deficient nitrobenzaldehydes (**2e** and **2f**) led to unsatisfactory yields. Neutral or slightly electron-rich benzaldehydes gave rise to good yields while very electron-rich aldehydes, such as **2j** and **2k**, gave none of the desired product. The reaction of heteroaromatic aldehydes as well as aliphatic aldehydes afforded good to moderate yields. Furthermore, it was demonstrated how the (*E,E,E*)-triene **3p** can be formed by employing α,*β*-unsaturated aldehyde **2p**.

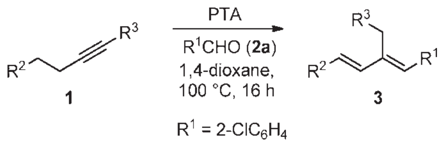


3

Figure 3. General structure of (*E,E*)-**3**.

Except for **3m** and **3q** the dienes **3** are formed exclusively with (*E,E*)-configuration. The *E*-configuration of the disubstituted alkene was confirmed by a coupling constant of 16 Hz whereas the configurations of the trisubstituted alkenes in dienes **3** have been determined by 1D NOESY experiments (see Supporting Information) showing an NOE effect from H_a to H_b/H_c (Figure 3).

Table 3. Olefination of Alkynes **1** with 2-Chlorobenzaldehyde **2a**[a]



entry	R^2	R^3	yield (%)[b,c]
1	$CH{=}CH_2$	CO_2Et (**1b**)	17 (**3r**)
2	H	CO_2Et (**1c**)	8 (**3s**)
3	*n*-C_3H_7	CO_2Et (**1d**)	52 (**3t**)
4	*n*-C_6H_{13}	CO_2Et (**1e**)	55 (**3u**)
5	Ph	CN (**1f**)	0

[a] Reaction conditions: aldehyde **2a** (0.5 mmol), PTA (2 mmol), and alkyne **1** (1 mmol) were stirred in 1,4-dioxane (1 mL) at 100 °C in a sealed vial. [b] Isolated yields. [c] The products have (*E,E*)-geometry exclusively.

---

(13) (a) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595–7596. (b) Meng, L.-G.; Tang, K.; Liu, H.-F.; Xiao, J.; Xue, S. *Synlett* **2010**, 1833–1836. (c) Xue, S.; Zhou, Q.-F.; Zheng, X.-Q. *Synth. Commun.* **2005**, *35*, 3027–3035.

(14) (a) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167–3168. (b) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819–10820. (c) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670–5671. (d) Alvarez-Ibarra, C.; Csáky, A. G.; Gómez de la Oliva, C. *Tetrahedron Lett.* **1999**, *40*, 8465–8467. (e) Alvarez-Ibarra, C.; Csáky, A. G.; Gómez de la Oliva, C. *J. Org. Chem.* **2000**, *65*, 3544–3547. (f) Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2225–2227.

(15) Anary-Abbesinejad, M.; Charkhati, K.; Anaraki-Ardakani, H. *Synlett* **2009**, 1115–1117.

(16) (a) Jung, D.-K.; Wang, J.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118–4119. (b) McDougal, N. T.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3117–3119.

(17) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906–2908.

The diversity of substrates applicable for the olefination reaction was further investigated by the reaction of different alkynes **1** with aldehyde **2a** (Table 3). Interestingly, changing the phenyl substituent in **1a** with an alkyl chain (**1d** and **1e**) gave rise to fair yields of 1,3-dienes **3t** and **3u** while **1b** afforded 1,3,5-triene **3r**. Exchanging the ethyl ester with electron-poor aryls, a methyl ketone, or a nitrile (entry 5) showed no product, thereby indicating the crucial role of an activating ester moiety adjacent to the alkyne.

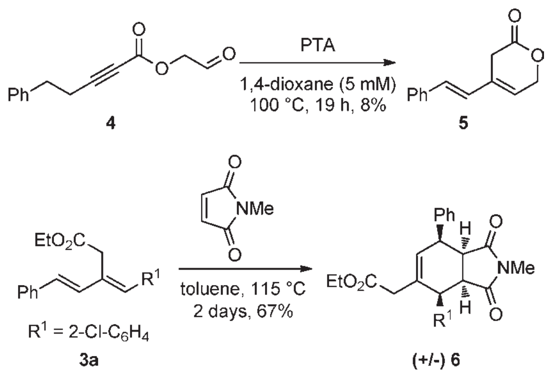


Figure 4. Annulation of **4** by an intramolecular Wittig olefination and Diels–Alder reaction of 1,3-diene **3a** with *N*-methylmaleimide.

Cyclization reactions are of great value in the syntheses of complex structures.[18] Strategic incorporation of an aldehyde in an alkynoate could be used in the syntheses of cyclic structures, and as an example a novel synthesis of **5** was performed (Figure 4). Subjecting **4** to olefination conditions resulted in annulation to **5**. In spite of the low yield the example provides proof of concept for the generation of β,γ-unsaturated lactones by taking advantage of an intramolecular Wittig olefination.

An important synthetic application of dienes leading to a variety of complex products is the Diels–Alder reaction.[19] Hence, the diene **3a** was tested in a [4 + 2] cycloaddition with *N*-methylmaleimide affording 67% yield of the *endo*-isomer **6** (Figure 4).

In Figure 5 we have proposed a mechanism for the novel olefination reaction. The mechanism is derived from earlier studies on related internal redox reactions of alkynoates.[8]

The reaction is initiated by a nucleophilic attack of the phosphine on the β-position of alkynoate **1** followed by a range of proton shifts leading to phosphonium ylide **8**. In the absence of an aldehyde, alkynoate **1** is known to isomerize into diene **10**. Nevertheless, if an aldehyde is present the proposed ylide **8** reacts in a Wittig reaction forming the trisubstituted 1,3-diene **3**. Trace amounts of water present in the solvent might support the isomerization of **7** to **8** since rapid proton shifts are favored in the presence of a proton donor/acceptor as described in earlier studies of phosphine-mediated reactions of allenes.[20]

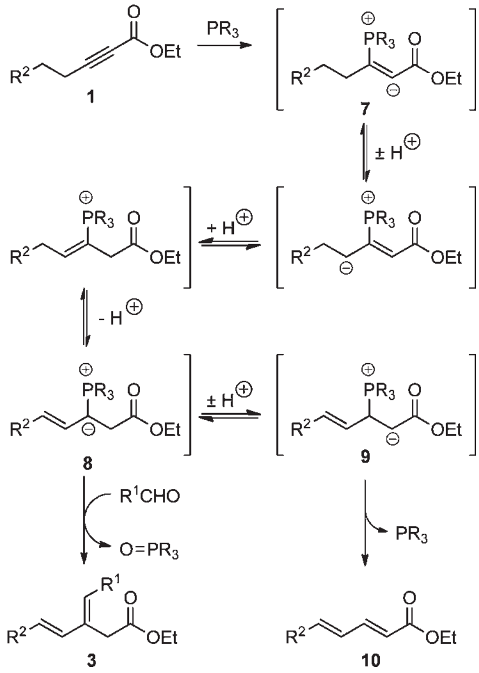


Figure 5. Proposed mechanism for the formation of **3** and **10**.

In summary, a highly stereoselective olefination of ethyl alkynoates yielding a variety of conjugated trisubstituted dienes in good yields has been demonstrated. The key step in this reaction is the trapping of *in situ* generated phosphonium ylides with aldehydes expanding the wide range of applications of alkynes. Furthermore, it has been shown how this olefination can be used in a cyclization reaction yielding a β,γ-unsaturated lactone while the generated 1,3-dienes show good reactivity in the Diels–Alder reaction. Further investigation on utilizing *in situ* generated ylides in synthetic transformations will be considered.

Acknowledgment. The Danish National Research Foundation through Centre for DNA Nanotechnology, Sino-Danish Centre for Molecular Self-assembly on Surfaces, Centre of Functionally Integrative Neuroscience, and OChem graduate school are greatly acknowledged for financial support.

Supporting Information Available. Experimental procedures, characterization, and ^{1}H NMR, ^{13}C NMR, and 1D NOESY spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(18) For representative reviews, see: (a) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125–4149. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963.

(19) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.

(20) (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470–3471. (b) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. *Chem.—Eur. J.* **2008**, *14*, 4361–4373.