DOI: 10.1002/anie.200504594

A General and Versatile Method for C–C Cross-Coupling Synthesis of Conjugated Enynes: One-Pot Sequence Starting from Carbonyl Compounds**

Ilya M. Lyapkalo and Michael A. K. Vogel*

In light of the pivotal role of the carbonyl group in organic synthesis,[1] new general transformations of the carbonyl compounds are always of particular importance. This is why the relatively recent discovery of transition-metal-catalyzed reactions of alkenyl triflates, readily available from enolizable carbonyl precursors, immediately found widespread application.[2] Following this line of research, alkenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonates (hereinafter referred to alkenyl nonaflates) were introduced and advantageously employed as a useful alternative to the triflates in Heck,[3] Negishi,[4] Stille,[5] and Sonogashira[6] coupling reactions.

Routinely, the coupling protocols consist of two steps that include O-sulfonylation of the starting carbonyl compounds, followed by Pd-catalyzed C–C cross-coupling of the isolated alkenyl perfluoroalkanesulfonate leading to the desired products. Alternatively, Reissig and co-workers established that isolation and purification of the alkenyl nonaflates is not necessary for the subsequent coupling reaction provided that the nonaflates are generated from trimethylsilyl enol ethers and the mild sulfonylating reagent nonafluorobutane-1-sulfonyl fluoride (NfF)[7] under catalysis by fluoride ion. This resulted in the development of a general, one-pot transformation of trimethylsilyl enol ethers into 1,3-dienes by in situ generation of alkenyl nonaflates followed by Heck reactions.[8] However, it requires an extra step to obtain the requisite trimethylsilyl enolates from the ultimate precursors, ketones or aldehydes. This requirement serves to highlight a major challenge in the development of general and straightforward coupling methods, namely, the conversion of carbon-

[*] Dr. I. M. Lyapkalo
Institute of Chemical & Engineering Sciences
1 Pesek Road, Jurong Island, Singapore 627833 (Singapore)
Fax: (+65) 6316-6184
E-mail: ilya_lyapkalo@ices.a-star.edu.sg
M. A. K. Vogel
Freie Universität Berlin
Institut für Chemie—Organische Chemie
Takustrasse 3, 14195 Berlin (Germany)

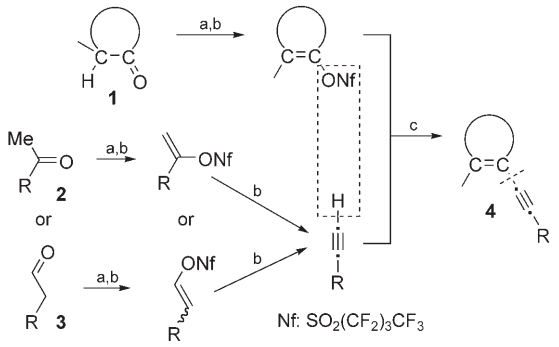
[**] We thank Prof. H.-U. Reissig (Freie Universität Berlin, Germany) and Prof. B. Cox (AstraZeneca, Macclesfield, UK) for useful discussions. Financial support by the Agency for Science Technology and Research (A*STAR Singapore) and by the Alexander von Humboldt Foundation is most gratefully acknowledged. We are indebted to Bayer AG for the generous donation of nonafluorobutane-1-sulfonyl fluoride.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

yl compounds to the alkenyl nonaflates, combined with the subsequent C–C cross-coupling step in a one-pot operation.

Here we report a novel general method for the synthesis of conjugated enynes based on the Sonogashira reaction, with both components originating from widely available carbonyl compounds, whereby the generated alkenyl nonaflate and alkyne intermediates interact smoothly under Pd^0 catalysis to give the anticipated cross-coupling products in an one-pot reaction sequence.

To achieve a clean conversion of the starting materials **1**–**3** to the mixture of a cyclic nonaflate and a terminal alkyne (Scheme 1), we needed to find a base that would not react



Scheme 1. One-pot synthesis of the enynes **4** starting from cyclic ketones **1** and methyl ketones **2** or aldehydes **3**. a) NfF; b) base; c) iPr_2NH (excess), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), CuI (10 mol%), LiCl, 24 h at 25 °C, or 17 h at 45–47 °C, or 5–6 h at 60 °C.

with NfF but be strong enough to provide α-deprotonation of the carbonyl substrates and effect E2 elimination of NfOH from the intermediate alkenyl nonaflates at ambient or subambient temperatures. Since lithium amide bases are known to react with NfF readily, even at low temperature,[9] we turned our attention to metal-free nitrogen bases. After extensive experimentation,[10] we found that (*tert*-butylimino)tris(1-pyrrolidinyl)phosphorane[11] (hereinafter referred to as P_1 base) and 1-(*tert*-butylimino)-1,1,3,3,3-pentakis(dimethylamino)-1λ^5,3λ^5-diphosphazene (P_2 base[12]), commercially available representatives of the family of phosphazene bases, were particularly successful (Figure 1).

When combined with NfF in dry aprotic solvent, the P bases effect clean and complete conversion of cyclic and acyclic ketones to the cyclic nonaflate and the respective alkyne intermediates which can be observed by ^{1}H NMR spectroscopy of the crude reaction mixtures. The one-pot reaction sequence culminates in Sonogashira coupling of these intermediates to give high yields of the desired products **4a**–**e** (Table 1, entries 1–5).

The metal-free noncoordinating P_1 base provided perfect regioselectivity control in favor of the deprotonation at the position most remote to the ring nitrogen[14] of **1c** leading exclusively to the product **4d** (Table 1, entry 4). However, the

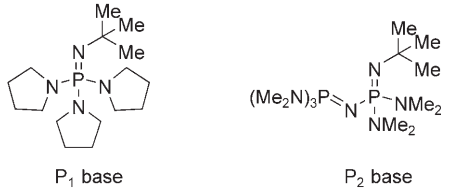
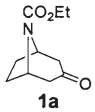
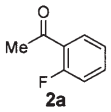
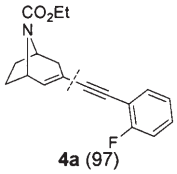
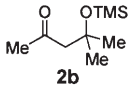
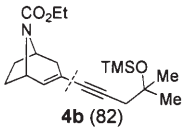
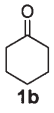
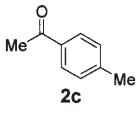
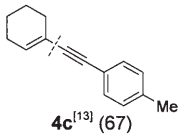
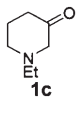
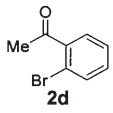
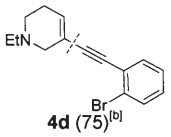
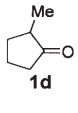
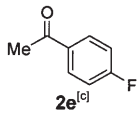
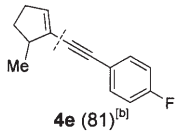
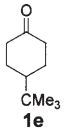
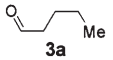
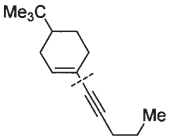
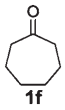
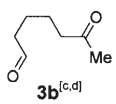
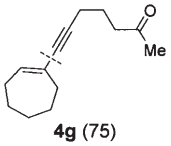
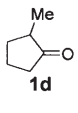
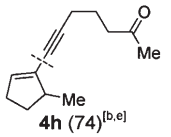


Figure 1. Phosphazene bases employed for generation of alkenyl nonaflates and terminal alkynes from the carbonyl compounds **1**–**3**.

Table 1: Reaction conditions and yields of the products **4** according to Scheme 1.

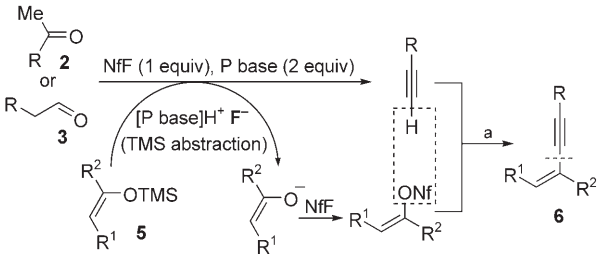
Entry	Cyclic ketone **1**	Ketone **2** or aldehyde **3**	Reaction conditions[a]	Product **4** (Yield [%])
1	 **1a**	 **2a**	A, 17 h	 **4a** (97)
2	**1a**	 **2b**	A, 24 h	 **4b** (82)
3	 **1b**	 **2c**	A, 24 h	 **4c**[13] (67)
4	 **1c**	 **2d**	A, 24 h	 **4d** (75)[b]
5	 **1d**	 **2e**[c]	1) B then 2) A, 17 h	 **4e** (81)[b]
6	 **1e**	 **3a**	A, 24 h	 **4f** (83)
7	 **1f**	 **3b**[c,d]	1) A, 36 h then 2) A, 17 h	 **4g** (75)
8	 **1d**	**3b**[c,d]	1) B then 2) A, 17 h	 **4h** (74)[b,e]

[a] Nonaflation/elimination conditions: A (P_1 base, NfF, DMF, 0 °C to 25 °C), B (P_2 base, NfF, THF, −78 °C to 25 °C, 4.5 h); for the Sonogashira coupling, see step c in Scheme 1. [b] >95:<5 selectivity in favor of the kinetically controlled double-bond regioisomer shown. [c] The component was added to the reaction mixture under the conditions 2 *after* the complete conversion of the cyclic ketone **1** to the nonaflate (^{1}H NMR control) under the conditions (1). [d] Added at −10 °C. [e] 1.2:1 mixture of the tri- (**4h**) and tetrasubstituted C–C double-bond regioisomers was obtained under the conditions specified in the entry 7.

P_1 base was not regioselective in the deprotonation of **1d** with regard to the α-methine and α-methylene positions (Table 1, footnote [e]). Fortunately, the regioselectivity was dramatically improved when the much stronger P_2 base was employed under the kinetically controlled conditions, resulting in the enynes **4e** and **4h** bearing the less substituted double bonds (Table 1, entries 5 and 8).

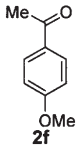
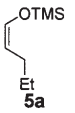
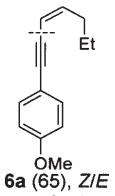
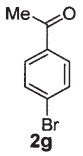
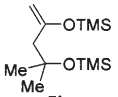
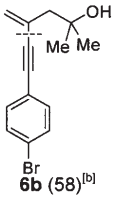
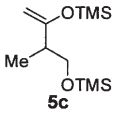
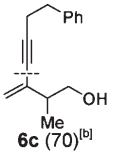
Aldehydes proved to be a promising source of terminal alkynes. In all cases, clean conversions were observed (entries 6–8 in Table 1, entry 3 in Table 2). Moreover, aldehydes are more acidic and react much faster than ketones, which enables the highly selective reaction of the aldehyde moiety in the presence of the unprotected keto group in the 6-oxo-heptanal **3b** (entries 7 and 8). To our knowledge, one-step formation of C–C triple bond by elimination of H_2O from aldehydes is unprecedented.[15,16]

Acyclic nonaflates are unsuccessful as cross-coupling components when generated directly from carbonyl compounds using phosphazene bases, because of their ease of elimination to give alkynes.[17] However, a modification of the protocol made it possible to obtain cross-coupling products from the combination of both acyclic carbonyl precursors. We realized that the highly reactive soluble fluoride sources phosphazenium fluorides [P base]H^+F^-, generated during the course of the alkyne formation from the compounds **2** and **3**, could be used to selectively produce the appropriate (acyclic) nonaflate[7b] (Scheme 2). Thus, the nonaflates required for the coupling products **6** were routinely generated in situ by simple addition of the trimethylsilyl enol ethers **5** to reaction mixtures containing the appropriate excess of NfF after the completion of the alkyne formation (Table 2), that is, when free phosphazene bases were no longer present. Remarkably, under these conditions the fluoride ion effects desilylation and nonaflation of the trimethylsilyl enol ether moiety in a highly selective manner, without appreciably affecting fragile trimethylsilyl alcohol protection[18] (Table 2, entries 2 and 3). The subsequent Sonogashira coupling resulted in good yields of the desired products **6a–c**. Noteworthy, the product **6a** is produced with almost complete retention of the *Z* configuration of the double bond originating from the parent enol ether **5a**.[19]



Scheme 2. One-pot synthesis of the acyclic enynes **6** employing trimethylsilyl enolates **5**. a) iPr_2NH (excess), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), CuI (10 mol%), LiCl, 17–24 h at 25 °C.

Table 2: Reaction conditions and yields of the products **6** according to Scheme 2.

Entry	Ketone **2** or aldehyde **3**	Reaction conditions[a]	TMS enolate **5**	Product **6** (Yield [%])
1	 **2f**	A, 17 h	 **5a**	 **6a** (65), *Z*/*E* >40 : 1
2	 **2g**	B	 **5b**	 **6b** (58)[b]
3	 **3c**	B	 **5c**	 **6c** (70)[b]

[a] For the conversions to the alkynes: A (P_1 base, NfF, DMF, 0 °C to 25 °C), B (P_2 base, NfF, THF, −78 °C to 25 °C, 4.5 h); for the Sonogashira coupling, see a) in Scheme 2. [b] Obtained and characterized as free alcohols after the TMS deprotection.

In conclusion, the method represents a straightforward, general, and versatile approach to highly diverse conjugated enynes, starting from readily available carbonyl precursors. Relatively low nucleophilicity, in combination with high basicity, makes phosphazene bases compatible with NfF, thereby permitting clean formation of alkenyl nonaflates under the "internal quench" conditions.[20] Furthermore, neither phosphazene bases nor their salts impede the bimetallic catalytic cycle of the subsequent Sonogashira reaction. The operational simplicity of our one-pot protocol and a wide selection of commercially available carbonyl compounds permit a flexible, convergent approach towards a variety of conjugated enynes. It should open up new and interesting opportunities for the synthesis of target products containing conjugated enyne[21] or enediyne fragments and exhibiting very promising antibiotic, antitumor, and other biological activities.[2d,22]

Experimental Section

Typical procedure for the one-pot synthesis of enynes: Synthesis of **4a** (entry 1, Table 1): Predried LiCl[23] (0.127 g, 3.00 mmol) was placed into a reaction flask equipped with a three-way tap and a magnetic stirrer coated with teflon, and was heated to ca. 250–300 °C with a heat gun under high vacuum for a few minutes. After the LiCl had cooled down under an atmosphere of dry argon, DMF (2 mL), *N*-ethoxycarbonyl tropinone (**1a**) (0.395 g, 2.00 mmol), 2-fluoroacetophenone (**2a**) (0.345 g, 2.50 mmol), and NfF (1.495 g, 4.95 mmol) were added successively. The reaction mixture was cooled down to 10 °C under vigorous stirring, and P_1 base (2.406 g, 7.70 mmol) was added dropwise within 2–3 min. After completion of the nonaflation and elimination steps (17 h at RT, ^{1}H NMR monitoring), iPr_2NH (3 mL) was added, followed by solid PPh_3 (0.052 g, 0.20 mmol), CuI

(0.038 g, 0.20 mmol), and $Pd(OAc)_2$ (0.022 g, 0.10 mmol) (all together in one lot), and the reaction mixture was stirred at 60 °C for 5.5 h. It was then subjected to aqueous workup (benzene/water; in other cases usually *t*BuOMe/water or hexane/water), the two-phase mixture was filtrated carefully through a pad of celite and the aqueous phase re-extracted with benzene. The combined organic layers were dried (Na_2SO_4), the solvent was then removed under vacuum, and the residue was subjected to column chromatography (silica gel, gradient elution (1. hexane, 2. benzene/hexane 1:4, 3. benzene/hexane 1:1, 4. benzene) to give pure **4a** (0.579 g, 97% yield) as a yellow oil. ^{1}H NMR (C_6D_6, 500 MHz, 75 °C): $\delta = 1.05$ (t, $J = 7.1$ Hz, 3H, Me), 1.29–1.36 (br m, 1H), 1.55 (ddd, $J = 11.8$, 9.0, 2.8 Hz, 1H), 1.64 (m_c, 1H), 1.77 (ddddd, $J = 12.5$, 12.5, 8.0, 2.8, 1.7 Hz, 1H), 1.83 (br d, $J =$ 17 Hz, 1H), 2.99 (br d, $J = 17$ Hz, 1H) (all CH_2), 4.06 (dq, $J = 10.8$, 7.1 Hz, 1H), 4.09 (dq, $J = 10.8$, 7.1 Hz, 1H) (both OCH_2), 4.29 (br s, 1H, CHN), 4.37 (br s, 1H, CHN), 6.29 (ddd, $J = 5.3$, 1.9, 1.8 Hz, 1H, CH=C), 6.68 (td, $J = 7.6$, 1.3 Hz, 1H), 6.74 (ddd, $J = 9.5$, 8.3, 1.3 Hz, 1H), 6.78–6.73 (m, 1H), 7.25 ppm (td, $J = 7.4$, 1.8 Hz, 1H) (all CH_{Ar}); ^{13}C (C_6D_6, 125.8 MHz, 75 °C): $\delta = 14.8$ (q, Me), 29.9, 34.5, 38.2 (all br t, CH_2), 52.4, 53.7 (both d, CHN), 61.0 (t, OCH_2), 82.8 (s, C=C), 95.0 (d, $^3J_{^{13}C,^{19}F} = 3.2$ Hz, C=C), 112.8 (d, $^2J_{^{13}C,^{19}F} = 15.7$ Hz, C_{Ar}), 115.7 (dd, $^2J_{^{13}C,^{19}F} = 21.0$ Hz), 124.1 (dd, $^3J_{^{13}C,^{19}F} = 3.8$ Hz), 129.9 (dd, $^3J_{^{13}C,^{19}F} =$ 7.9 Hz), 133.6 (dd, $^4J_{^{13}C,^{19}F} = 1.3$ Hz) (all CH_{Ar}), 118.6 (br s, *C*=CH), 139.7 (br d, C=*CH*), 154.4 (s, C=O), 163.2 ppm (d, $^1J_{^{13}C,^{19}F} = 251.6$ Hz, C-F); IR (film): $\tilde{\nu} = 3060$–3035 cm^{-1} (=C-H), 2980–2835 (C-H), 2210 (C=C), 1700 (C=O), 1620–1490 (C=C); MS (EI, 80 eV): m/z (%) = 300 (M^++1, 21), 299 (M^+, 100), 271 ([$M^+ - C_2H_4$], 37), 270 ([$M^+ - C_2H_5$], 91), 242 ([$M^+ - C_2H_5 - CO$], 45), 226 ([$M^+ - C_2H_5 - CO_2$], 28), 198 ([$M^+ - CO_2Et - C_2H_4$], 85), 183 ([$M^+ - CO_2Et - C_2H_4 - NH$], 10), 29 ($C_2H_5^+$, 44); C,H,N analysis (%): calcd for $C_{18}H_{18}FNO_2$ (299.4): C 72.22, H 6.06, N 4.68; found C 71.91, H 5.95, N 4.64.

Received: December 27, 2005
Published online: May 9, 2006

Keywords: C–C coupling · cross-coupling · enynes · homogeneous catalysis · phosphazene bases

[1] *"The chemistry of carbonyl compounds is virtually the backbone of synthetic organic chemistry"*: J. D. Roberts, M. C. Caserio, *Basic Principles of Organic Chemistry*, Benjamin, New York, **1965**, p. 426.

[2] a) W. J. Scott, J. E. McMurry, *Acc. Chem. Res.* **1988**, *21*, 47–54; b) K. Ritter, *Synthesis* **1993**, 735–762; c) S. Cacchi, *Pure Appl. Chem.* **1996**, *68*, 45–52; d) R. Brückner, J. Suffert, *Synlett* **1999**, 657–679.

[3] a) K. Voigt, P. von Zezschwitz, K. Rosauer, A. Lansky, A. Adams, O. Reiser, A. de Meijere, *Eur. J. Org. Chem.* **1998**, 1521–1534; b) S. Bräse, *Synlett* **1999**, 1654–1656.

[4] F. Bellina, D. Ciucci, R. Rossi, P. Vergamini, *Tetrahedron* **1999**, *55*, 2103–2112.

[5] A. Wada, Y. Ieki, M. Ito, *Synlett* **2002**, 1061–1064.

[6] a) J. Suffert, A. Eggers, S. W. Scheuplein, R. Brueckner, *Tetrahedron Lett.* **1993**, *34*, 4177–4180; b) T. Okauchi, T. Yano, T. Fukamachi, J. Ichikawa, T. Minami, *Tetrahedron Lett.* **1999**, *40*, 5337–5340.

[7] a) R. Zimmer, M. Webel, H.-U. Reissig, *J. Prakt. Chem.* **1998**, *340*, 274–277, and references therein; b) I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Eur. J. Org. Chem.* **2002**, 1015–1025.

[8] a) M. Webel, H.-U. Reissig, *Synlett* **1997**, 1141–1142; b) I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Eur. J. Org. Chem.* **2002**, 3646–3658; c) I. M. Lyapkalo, J. Hogermeier, H.-U. Reissig, *Tetrahedron* **2004**, *60*, 7721–7729.

[9] The reaction results in the anticipated nonafluorobutane-1-sulfonamides: I. M. Lyapkalo, H.-U. Reissig, A. Schaefer, A. Wagner, *Helv. Chim. Acta* **2002**, *85*, 4206–4215.

[10] Trialkylamines are not basic enough to promote the nonaflation, whereas DBU gives low conversions as a result of the side reaction with NfF. The results will be reported in a subsequent full account.

[11] R. Schwesinger, J. Willaredt, H. Schlemper, M. Keller, D. Schmitt, H. Fritz, *Chem. Ber.* **1994**, *127*, 2435–2454. It has the highest basicity ($pK_a = 28.35$ in MeCN) of the commercially available P_1 bases.

[12] a) Commercially available as a 2 M solution in THF ($pK_a = 33.49$ in MeCN); b) According to the primary classification given by Schwesinger, the subscript designates the number of P atoms in the molecule. For the synthesis and properties of P_2 or higher order phosphazene bases, see: R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. W. Rotter, F. G. Bordwell, A. V. Satish, G. Z. Ji, E. M. Peters, K. Peters, H. G. von Schnering, L. Walz, *Liebigs Ann.* **1996**, 1055–1082 and references therein.

[13] S. Chang, S. H. Yang, P. H. Lee, *Tetrahedron Lett.* **2001**, *42*, 4833–4836.

[14] T. Imahori, Y. Kondo, *J. Am. Chem. Soc.* **2003**, *125*, 8082–8083.

[15] For the relevant multistep methods known to date, see a) M. Shibasaki, Y. Torisawa, S. Ikegami, *Tetrahedron Lett.* **1982**, *23*, 4607–4610; b) L. A. Paquette, S. Hormuth, C. J. Lovely, *J. Org. Chem.* **1995**, *60*, 4813–4821; c) T. Matsuura, S. Yamamura, Y. Terada, *Tetrahedron Lett.* **2000**, *41*, 2189–2192.

[16] Preliminary investigations show that the nonaflation/elimination protocol is applicable to a wide range of carbonyl compounds, leading to terminal or internal alkynes or allenes, depending on the stereoelectronic effects of the substituents in the carbonyl substrate. The results will be reported in due course.

[17] In our attempts to generate the nonaflates from isopropyl methyl ketone or benzyl methyl ketone using P_2 base (1 equiv) and NfF under the kinetic conditions, we could detect only mixtures of the alkyne and the starting material, which clearly indicates that nonaflation is the rate-determining step.

[18] ^{1}H NMR analyses of the reaction mixtures towards the end of the final coupling step indicated that the Me_3SiO group at sp^3-hybridized carbon centers of the coupling products remained intact, which should warrant the stability of the most frequently used alcohol silyl protecting groups, such as *t*BuMe$_2$Si, *t*BuPh$_2$Si, or Et$_3$Si, under our reaction conditions.

[19] Trimethylsilyl enolate **5a** was obtained as an 8:92 *E*/*Z* mixture by silylation of the freshly distilled pentanal with Me_3SiCl/NaI/*i*Pr$_2$NEt in MeCN at −45 °C to 5 °C. The pure *Z* isomer was then isolated by preparative HPLC (68% yield).

[20] E. J. Corey, A. W. Gross, *Tetrahedron Lett.* **1984**, *25*, 495–498.

[21] The antimycotic agent terbinafine (Lamisil) manufactured by Novartis Pharmaceuticals is perhaps most prominent example of a widely applied drug bearing an eneyne structural motif; for other interesting bioactive compounds, see: a) L. Garlaschelli, E. Magistrali, G. Vidari, O. Zuffardi, *Tetrahedron Lett.* **1995**, *36*, 5633–5636; b) H.-J. Zhang, K. Sydara, G. T. Tan, C. Ma, B. Southavong, D. D. Soejarto, J. M. Pezzuto, H. H. S. Fong, *J. Nat. Prod.* **2004**, *67*, 194–200.

[22] J. W. Grissom, G. U. Gunawardena, D. Klingberg, D. Huang, *Tetrahedron* **1996**, *52*, 6453–6518, and references therein.

[23] Since $Pd(OAc)_2$ was used as a uniform source of catalytic Pd in our method, LiCl was considered as an additive for in situ generation of $[Pd(PPh_3)_2Cl_2]$ from $Pd(OAc)_2$ and PPh_3 at the outset of the cross-coupling step. $[Pd(PPh_3)_2Cl_2]$ is one of the most frequently used precatalysts for the Sonogashira reaction of alkenyl sulfonates: a) S. W. Scheuplein, K. Harms, R. Brueckner, J. Suffert, *Chem. Ber.* **1992**, *125*, 271–278; b) L.

Castedo, A. Mourino, L. A. Sarandeses, *Tetrahedron Lett.* **1986**, *27*, 1523 – 1526; c) L. Castedo, J. L. Mascarenas, A. Mourino, L. A. Sarandeses, *Tetrahedron Lett.* **1988**, *29*, 1203 – 1206; d) M. Moniatte, M. Eckhardt, K. Birckmann, R. Brueckner, J. Suffert, *Tetrahedron Lett.* **1994**, *35*, 1965 – 1968; e) J. Suffert, E. Abraham, S. Raeppel, R. Brueckner, *Liebigs Ann.* **1996**, 447 – 456; f) A. L. Braga, D. J. Emmerich, C. C. Silveira, T. L. C. Martins, O. E. D. Rodrigues, *Synlett* **2001**, 369 – 370; g) P. E. Tessier, N. Nguyen, M. D. Clay, A. G. Fallis, *Org. Lett.* **2005**, *7*, 767 – 770.
However, we did not carry out a specific study on the LiCl effect.

