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Solid-Phase Synthesis of Substituted Alkynes Using the Nicholas Reaction

Johan A. Cassel,† Stefanie Leue,‡
Natalie I. Gachkova, and Nina C. Kann*

Department of Organic Chemistry, Chalmers University of Technology, SE-412 96 Göteborg, Sweden

nina.kann@oc.chalmers.se

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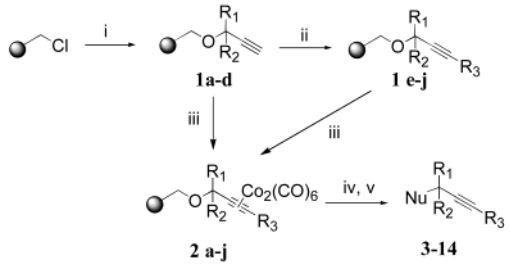
Abstract: The first example of a Nicholas reaction on solid phase is reported, involving the reaction of cobalt complexes of polymer-bound alkynols with different nucleophiles in the presence of a Lewis acid, to form carbon−oxygen or carbon−carbon bonds.

Combinatorial chemistry and solid-phase synthesis have evolved the last 10 years to become some of the most important techniques for decreasing the time involved in drug development.[1] To reach its full potential, however, solid-phase synthesis has to incorporate the many versatile organometallic reactions developed over recent decades. One example is the Nicholas reaction,[2] creating stable carbocations from propargylic alcohols or acetates via their cobalt−alkyne complexes and then exposing them to a variety of different nucleophiles, forming carbon−heteroatom or carbon−carbon bonds. Although several publications concerning solid-phase Pauson−Khand reactions have appeared in the literature,[3] the first as early as 1990, no examples of the Nicholas reaction on solid phase have yet been reported. One way of adapting this reaction to solid phase could be to attach propargylic alcohols to a Merrifield-type resin that could then be subjected to a number of different reactions. After cobalt complexation of the alkyne, the Nicholas reaction would then be used as a diversifying cleavage step, introducing different substituents at the propargylic position by using a variety of nucleophiles. A distinct advantage of running the reaction on solid phase, as compared to solution, is that unreacted substrate remains attached to the resin and does not contaminate the final product. In our case, we chose to combine the Nicholas reaction with a Sonogashira coupling[4] of the terminal alkyne with an aryl halide, to indicate the possibilities of preparing combinatorial libraries of derivatized alkynes using this strategy (Scheme 1).

SCHEME 1[a]



	R_1	R_2	R_3
a	Me	H	H
b	Et	H	H
c	n-pentyl	H	H
d	Me	Ph	H
e	Me	Me	1-naphtyl
f	Me	H	CH=CH-Ph
g	Me	H	p-$C_6H_4C(O)Me$
h	Et	H	Ph
i	Et	H	p-$C_6H_4CF_3$
j	n-pentyl	H	Ph

[a] Reagents and conditions: (a) alkynol, NaH, KI, DMF, rt, 18−48 h; (b) RI or RBr, $Pd(PPh_3)_4$, CuI, piperidine, rt, 18 h; (c) $Co_2(CO)_8$, CH_2Cl_2, rt, 3 h; (d) nucleophile, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 °C to rt, 18 h; (e) $(NH_4)_2Ce(NO_3)_6$, THF:H_2O 9:1, 0 °C, 10−25 min.

The alkynol was attached to Merrifield resin using standard conditions (NaH, DMF, rt, 18−48 h),[5,6] followed in some cases by a Sonogashira coupling to derivatize the terminal triple bond (RI or RBr, $Pd(PPh_3)_4$, CuI, piperidine, rt, 18 h).[7] The alkyne was subsequently complexed with $Co_2(CO)_8$ in CH_2Cl_2 at room temperature (3 h). IR was used to analyze each step in this sequence.[8] In the ensuing Nicholas reaction, a mixture of the

* To whom correspondence should be addressed. Phone: +46 31 772 8212. Fax: +46 31 772 3657.

† Present address: AstraZeneca R&D Mölndal, SE-431 83 Mölndal, Sweden.

‡ Present address: Chelona GMBH, Herrmannswerder Haus 15, D-144 73 Potsdam, Germany.

(1) For reviews on combinatorial chemistry and solid-phase synthesis, see: (a) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202. (b) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477−517. (c) *Combinatorial Chemistry: A Practical Approach*; Bannwarth, W., Felder, E., Eds.; Wiley-VCH: Weinheim, Germany, 2000. (d) Zaragoza Dörwald, F. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, Germany, 2000. (e) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091−2157. (f) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1581. (g) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385-15443. (h) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337.

(2) For reviews on the Nicholas reaction, see: (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214. (b) Caffyn, A.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science Ltd.: Oxford, UK, 1995; Vol. 12, Chapter 7.1, pp 685−702. (c) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809−826. (d) Müller, T. J. J. *Eur. J. Org. Chem.* **2001**, 2021−2033. (e) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133−4170.

(3) For Pauson−Khand approaches using polymer-bound substrates, see: (a) Schore, N. E.; Najdi, S. D. *J. Am. Chem. Soc.* **1990**, *112*, 441−442. (b) Bolton, G. L. *Tetrahedron Lett.* **1996**, *37*, 3433−3436. (c) Spitzer, J. L.; Kurth, M. J.; Schore, N. E.; Najdi, S. D. *Tetrahedron* **1997**, *53*, 6791−6808. For approaches using polymer-bound reagents see: (d) Kerr, W. J.; Lindsay, D. M.; Watson, S. P. *J. Chem. Soc., Chem. Commun.* **1999**, 2551−2552. (e) Comely, A. C.; Gibson, S. E.; Hales, N. J. *J. Chem. Soc., Chem. Commun.* **2000**, 305−306. (f) Brown, D. S.; Campbell, E.; Kerr, W. J.; Lindsay, D. M.; Morrison, A. J.; Pike, K. G.; Watson, S. P *Synlett* **2000**, 1573−1576. (g) Kerr, W. J.; Lindsay, D. M.; McLaughlin, M.; Pauson, P. L. *J. Chem. Soc., Chem. Commun.* **2000**, 1467−1468.

(4) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470. (b) Sonogashira, K. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, Chapter 2.4, pp 521−549.

(5) 18 h is generally sufficient for this step, only in the case of the quarternary alkynol 2-phenyl-3-butyn-2-ol was the loading increased if the reaction was left for 48 h.

(6) Nicolaou, K. C.; Pastor, J.; Winssinger, N.; Murphy, F. *J. Am. Chem. Soc.* **1998**, *120*, 5132−5133.

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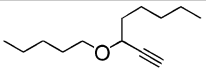
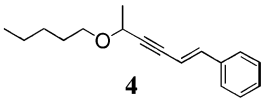
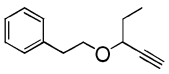
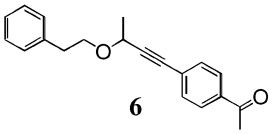
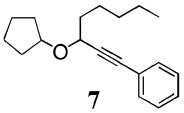
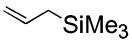
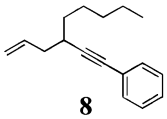
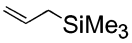
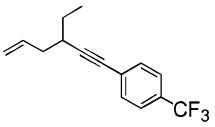
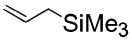
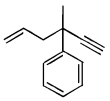
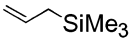
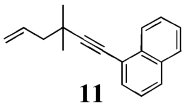
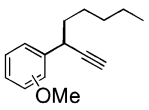
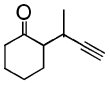
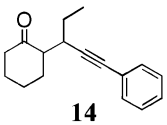
nucleophile and **2** in dichloromethane was cooled to −30 °C. $BF_3{\cdot}OEt_2$ was added and the reaction mixture was warmed to rt overnight. After quenching with triethylamine, the polymer was filtered off and washed with dichloromethane. The resulting dark red solution was concentrated and the alkyne liberated from the cobalt carbonyl by decomplexation with cerium ammonium nitrate[9] (THF:H_2O 9:1, 0 °C, 10−25 min). Extractive workup and chromatography yielded the desired Nicholas-type products.

Although we were primarily interested in the formation of carbon−carbon bonds on solid phase, we initially used alcohols as nucleophiles. As polymers cross-linked with 2% DVB have been found to give higher yields in the solid phase Pauson−Khand reaction as compared to the more commonly used 1% DVB resins,[3c] we tested both 1% and 2% DVB Merrifield resin in most cases. Yields are calculated from the initial loading of the commercial Merrifield resin.

1-Octyn-3-ol as the substrate in a Nicholas reaction with pentanol gave a 48% yield of **3** (see Table 1) with 2% DVB Merrifield resin for the four-step sequence (36% if 1% DVB Merrifield resin was used). Including a Sonogashira coupling with *β*-bromostyrene in the sequence gave 30% of the conjugated enyne (**4**). A similar substrate, 1-pentyn-3-ol, was treated with 2-phenylethanol under Nicholas conditions, also with satisfactory results, although in this case 1% DVB Merrifield resin was found to give the better yield (50% of **5**, as compared to 26% with 2% DVB resin). Including a Sonogashira coupling with 4-iodoacetophenone in the sequence worked well. Disappearance of the terminal alkyne signal in IR indicated a complete reaction, and the five-step sequence gave the desired product **6** in 44% yield. The use of a secondary alcohol gave, not suprisingly, a rather low yield of 26% (compound **7**), accompanied by a substantial amount of elimination product.

Carbon nucleophiles worked equally well in most cases. Trimethylallylsilane as the nucleophile in a sequence comprising 1-octyn-3-ol and a Sonogashira coupling with iodobenzene gave an encouraging yield of 56% (compound **8**). Somewhat surprisingly, a similar substrate with a *p*-trifluoromethyl-substitued phenyl group gave none of the desired product **9** when treated with trimethylallylsilane and Lewis acid. The polymer remained dark red and the solution colorless, indicating that no cation was formed. It may be that the electron-withdrawing effect of the trifluromethyl group disfavors the formation of the propargylic cation. The use of a quarternary substrate, 2-phenyl-3-butyn-2-ol, gave a rather modest yield (34%) with trimethylallylsilane as the nucleophile (**10**). The problem in this case lies partly in the attachment of the alkynol to the solid phase. IR indicated a rather low loading, even with prolonged reaction times. Another

TABLE 1. Overall Yields for the Substituted Alkynes after Decomplexation

Nucleophile	2	Product	Yield
1-Pentanol	**2c**	 **3**	48%[a]
1-Pentanol	**2f**	 **4**	30%[a]
2-Phenylethanol	**2b**	 **5**	50%[b]
2-Phenylethanol	**2g**	 **6**	44%[a]
Cyclopentanol	**2j**	 **7**	26%[a]
	**2j**	 **8**	56%[b]
	**2i**	 **9**	0%[a,c]
	**2d**	 **10**	34%[a]
	**2e**	 **11**	0%[a,d]
Anisole	**2c**	 **12**	44%[a,e]
	**2a**	 **13**	43%[a]
	**2h**	 **14**	25%[a]

[a] 2% DVB Merrifield resin. [b] 1% DVB Merrifield resin. [c] No product was cleaved from the resin in the Nicholas reaction in this case (the polymer remained dark red). [d] Only elimination product was formed in this case. [e] Ortho 11%, para 33% (separated).

(7) Piperidine has been found to be more efficient than other amines in the Sonogashira coupling of aliphatic alkynes and aryl iodides, see: (a) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403−6406. (b) Kilså, K.; Kajanus, J.; Mårtensson, J.; Albinsson, B. *J. Phys. Chem. B* **1999**, *103*, 7329−7339.

(8) A signal for the terminal alkyne is seen at ∼3290 cm^{-1}, which subsequently disappears upon Sonogashira derivatization. After formation of the cobalt carbonyl complex a broad CO signal is seen at ∼2000 cm^{-1}.

(9) Seyferth, D.; Wehman, A. T. *J. Am. Chem. Soc.* **1970**, *92*, 5520−5522.

quarternary substrate, 2-methyl-3-butyn-2-ol, was also tried. The Sonogashira coupling with 1-iodonaphthalene was quantitative according to IR, while attempted cleavage under Nicholas conditions with trimethylallysilane yielded only the corresponding elimination product instead of the desired compound **11**. Apparently the steric hindrance in this case slows down the nucleophilic attack, making elimination the favored pathway.

Electron-rich aromatics can also be used in the Nicholas reaction,[10] and anisole gave a 1:3 ortho:para mixture[11] of **12** in a total yield of 44%. Silyl enol ethers, versatile intermediates in organic synthesis, are also suitable nucleophiles as they are deprotected in situ under the reaction conditions. 1-Trimethylsilyloxycyclohexene[12] yielded **13** as a mixture of diastereomers in a 43% yield. Including a Sonogashira coupling with iodobenzene lowered the yield somewhat, compound **14** being formed in 25% (also as a mixture of diastereomers).

Although we chose to purify the final products by flash chromatography, in many cases a simple plug of silica gel was sufficient, making the sequence well adapted for the preparation of combinatorial libraries. The Sonogashira coupling and the cobalt complexation were close to quantitative according to IR. Incomplete attachment of the starting alkynol to the resin may lower the yield, but does not cause any contamination of the final product. Likewise, incomplete conversion in the Nicholas reaction does not give rise to any byproducts as unreacted material remains attached to the resin, causing the main contaminant in the final product to be excess nucleophile, which in many cases is easily removed due to the differences in polarity of the nucleophile used and the product.

We have shown that the Nicholas reaction is well suited as a way of introducing diversity while cleaving substitued alkynes from solid phase, creating new carbon−oxygen or carbon−carbon bonds. Current efforts in our research group are concentrated toward developing an alternative version of this reaction, where the alkyne is tethered to the solid phase via polymer-bound ligands complexed to cobalt, as well as applying the methodology in the preparation of compounds of pharmacological interest. These results will be presented in due course.

Experimental Section

All procedures, with the exception of the oxidative decomplexations, were carried out under an atmosphere of argon or nitrogen. 1% and 2% DVB Merrifield resin was purchased from Novabiochem or Aldrich. 2% DVB Merrifield resin was used unless stated otherwise. Aryl iodides were used for the Sonogashira coupling reaction except for the formation of polymer **2f**, where β-bromostyrene was used. $Pd(PPh_3)_4$ was purchased from Lancaster or Fluka.

General Procedure for Attaching Alkynols to Merrifield Resin, Exemplified by Compound 1c. To a suspension of Merrifield resin (1 or 2% DVB, 500 mg, 0.60 mmol) in dry DMF (10 mL) in a fritted reaction vessel for solid-phase synthesis were added NaH (60% in mineral oil, 120 mg, 3 mmol) and KI (20 mg, 0.12 mmol). The alkynol (3.0 mmol) was added dropwise and the resulting slurry was shaken for 2 days. The reaction was quenched with 0.5 mL of water. The polymer was filtered and washed (DMF:H_2O 1:1, THF, MeOH, DCM), then used directly in the next step (Sonogashira coupling or cobalt carbonyl complexation). A small sample was taken out, dried, and analyzed by IR (KBr pellet): 3294 cm^{-1}.

General Procedure for the Sonogashira Coupling Reaction, Exemplified by Compound 1j. To a mixture of polymer **1c** (0.60 mmol), $Pd(PPh_3)_4$ (0.03 mmol, 35 mg), and CuI (0.06 mmol, 11 mg) in a fritted reaction vessel for solid-phase synthesis was added piperidine (10 mL) followed by the dropwise addition of iodobenzene (1.8 mmol, 202 μL). The resulting slurry was shaken for 1−2 days, then washed with DMF (degassed), THF:H_2O 1:1, THF, MeOH, and CH_2Cl_2. A small sample was dried and analyzed by IR (KBr pellet), showing that the terminal alkyne peak at 3294 cm^{-1} had disappeared. The rest of **1j** was used directly in the next step (cobalt carbonyl complexation).

General Procedure for Cobalt Carbonyl Complexation, Exemplified by Compound 2j. To a suspension of **1j** (0.60 mmol) in CH_2Cl_2 (10 mL) was added $Co_2(CO)_8$ (0.90 mmol, 308 mg) in portions (Caution! CO evolution). The dark red slurry was shaken for 3 h, then washed with CH_2Cl_2 and ether. The polymer was transferred to a 25-mL round-bottom flask and dried under vacuum. No IR data are available for this compound, but IR spectra of cobalt complexes **2a** and **2c**, **2d** and **2g** all show a strong CO band at ∼2000 cm^{-1} (KBr pellet).

General Procedure for the Nicholas Reaction and Oxidative Decomplexation, Exemplified by Compound 8. Polymer **2j** (0.60 mmol) was suspended in CH_2Cl_2 (10 mL) in a 25-mL round-bottom flask and the nucleophile (trimethylallylsilane in this case, 1.8 mmol, 286 μL) was added. The reaction mixture was cooled to −30 °C, whereupon boron trifluoride etherate (0.9 mmol, 147 μL) was added dropwise. The reaction was shaken gently overnight, then quenched by adding triethylamine (0.90 mmol, 126 μL). The polymer was filtered off and washed with 3 × 10 mL of CH_2Cl_2. The resulting dark red solution was concentrated by rotary evaporation, then dissolved in a small amount of pentane and eluted through a plug of silica to remove amine salts (pentane or pentane/EtOAc 95/5 as eluent). After concentration the crude product was dissolved in 5 mL of THF/H_2O (9/1) and cooled to 0 °C. A solution of cerium ammonium nitrate (1.8 mmol, 987 mg) in 10 mL of THF/H_2O (9/1) was added dropwise until the dark red solution turned orange-yellow (the amount of CAN solution used corresponded to approximately 2.5 equiv). The reaction mixture was poured into a mixture of brine (10 mL) and diethyl ether (25 mL) in a separatory funnel. The phases were separated and the aqueous phase extracted with 2 × 25 mL of diethyl ether. The combined organic phases were dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (pentane) yielding 77 mg (56% overall yield) of **8** as a pale yellow oil.

3-Pentoxy-oct-1-yne (3). 3 was prepared from **2c** according to the general procedure for the Nicholas reaction, using pentanol as the nucleophile, yielding 48% of **3** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (td, J = 6.8, 1.6 Hz, 1H), 3.72 (dt, J = 8.8, 6.8 Hz, 1H) and 3.35 (dt, J = 8.8, 6.8 Hz, 1H), 2.39 (d, J = 1.6 Hz, 1H), 1.80−1.63 (m, 2H), 1.62−1.53 (m, 2H), 1.52−1.39 (m, 2H), 1.39−1.24 (m, 8H), 0.96−0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.54, 73.05, 69.41, 69.04, 35.65, 31.47, 29.30, 28.32, 24.91, 22.54, 22.50, 14.03, 14.01; IR (KBr) 3309, 2100 cm^{-1}; MS (EI) 125 (28), 71 (100). Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.38; H, 12.40.

5-Pentoxy-1-phenyl-1-hexen-3-yne (4): 4 was prepared from **2f** according to the general procedure for the Nicholas reaction, using 1-pentanol as the nucleophile, yielding 30% of **4** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5 H), 6.94 (d, J = 16.4 Hz, 1 H), 6.18 (dd, J = 16.2, 1.8 Hz, 1 H), 4.32 (qd, J = 6.7, 1.8 Hz, 1 H), 3.74 (dt, J = 9.0, 6.8 Hz, 1 H), 3.40 (dt, J = 9.0, 6.8 Hz, 1 H), 1.66−1.58 (m, 2 H), 1 48 (d, J = 6.6 Hz, 3 H), 1.39−1.31 (m, 4 H), 0.91 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.34, 136.13, 128.64, 128.54, 126.17, 107.67, 91.82, 83.73, 68.99, 65.73, 29.41, 28.34, 22.53, 22.21,

(10) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, 4163−4166.

(11) The ortho and para isomers can be separated before the CAN-decomplexation step.

(12) Trimethylsilyloxycyclohexene was prepared according to: Varghese, V.; Saha, M.; Nicholas, K. M. *Org. Synth.* **1988**, *67*, 141−148.

14.06; IR (KBr) 1104, 953 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.16, H, 9.22.

3-(2-Phenylethoxy)pent-1-yne (5). 5 was prepared from **2b** according to the general procedure for the Nicholas reaction, using 2-phenylethanol as the nucleophile. 1% DVB Merrifield resin was found to be more favorable in this case, yielding 50% of **5** as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.19 (m, 5H), 4.02−3.92 (m, 2 H), 3.60 (dt, J = 9.6, 8.0 Hz, 1 H), 2.93 (t, J = 7.2 Hz, 2 H), 2.42 (s, 1 H), 1.82−1.69 (m, 2 H), 1.00 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.81, 128.90, 128.26, 126.13, 82.89, 73.49, 70.76, 69.76, 36.16, 28.76, 9.56; IR (KBr) 3299, 1104, 1079 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.99, H, 8.63.

1-(4-Acetylphenyl)-3-phenylethoxybut-1-yne (6). 6 was prepared from **2g** according to the general procedure for the Nicholas reaction, using 2-phenylethanol as the nucleophile, yielding 44% of **6** as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2 H), 7.49 (d, J = 8 Hz, 2 H), 7.33−7.19 (m, 5 H), 4.42 (q, J = 6.7 Hz, 1 H), 4.01 (app q, J = 8.0 Hz, 1 H), 3.68 (app q, J = 8.0 Hz, 1 H), 2.96 (t, J = 7.2 Hz, 2 H), 2.60 (s, 3 H), 1.53 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.79, 138.96, 136.45, 132.08, 129.16, 128.61, 128.44, 127.92, 126.51, 92.93, 84.38, 70.17, 66.13, 36.52, 26.88, 22.28; IR (KBr) 1684, 1100 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 82.22; H, 6.82.

3-Cyclopentoxy-1-phenyloct-1-yne (7). 7 was prepared from **2j** according to the general procedure for the Nicholas reaction, using cyclopentanol as the nucleophile, yielding 26% of **7** as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.40 (m, 2H), 7.32−7.27 (m, 3 H), 4.33−4.27 (m, 1 H), 4.23 (t, J = 6.8 Hz, 1 H), 1.9−1.2 (m, 16 H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.67, 128.18, 128.04, 123.10, 89.61, 84.68, 79.50, 67.99, 36.26, 33.16, 31.61, 31.53, 25.22, 23.54, 23.48, 22.59, 14.06. IR (KBr) 1073, 750, 691 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.46; H, 9.61.

3-Allyl-1-phenyloct-1-yne (8). 8 was prepared from **2j** according to the general procedure for the Nicholas reaction, using trimethylallylsilane as the nucleophile. 1% DVB Merrifield resin gave a better yield in this case, affording 56% of **8** as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.36 and 7.32−7.24 (m, 5 H), 6.03−5.87 (m, 1 H), 5.17−5.04 (m, 2 H), 2.67−2.55 (m, 1 H), 2.31 (t, J = 6.8 Hz, 2 H), 1.63−1.23 (m, 8 H), 0.91 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.20, 131.58, 128.12, 127.44, 124.06, 116.42, 93.08, 82.01, 39.47, 34.48, 32.22, 31.68, 27.02, 22.60, 14.06; IR (KBr) 913, 755, 691 cm^{-1}. Anal. Calcd for $C_{17}H_{22}$: C, 90.20; H, 9.80. Found: C, 90.08; H, 9.75.

3-Allyl-3-phenylbut-1-yne (10). 10 was prepared from **2d** according to the general procedure for the Nicholas reaction, using trimethylallylsilane as the nucleophile, yielding 34% of **10** as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.5 Hz, 2 H), 7.34 (t, J = 7.5 Hz, 2 H), 7.28−7.21 (m, 1 H), 5.84−5.71 (m, 1 H), 5.06 (app s, 1 H), 5.03 (app br d, J = 3.5 Hz, 1 H), 2.64−2.48 (m, 2 H), 2.43 (s, 1 H), 1.60 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.50, 134.39, 128.20, 126.55, 126.03, 117.83, 89.04, 71.60, 48.31, 39.98, 29.02; IR (KBr) 3304, 2110, 900 cm^{-1}. Anal. Calcd for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.60; H, 8.36.

3-(*o*/*p*-Methoxyphenyl)oct-1-yne (12). 12 was prepared from **2c** according to the general procedure for the Nicholas reaction, using anisole as the nucleophile, yielding 44% (ortho 11%, para 33%) of **12** as yellow oils (the isomers were separated before the decomplexation step). Ortho isomer: ^1H NMR δ (400 MHz, $CDCl_3$) 7.52 (d, J = 7.2 Hz, 1 H), 7.21 (t, J = 7.6 Hz, 1 H), 6.95 (t, J = 7.6 Hz, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 4.12−4.07 (m, 1H), 3.82 (s, 3H), 2.18 (d, J = 2.4 Hz, 1 H), 1.76−1.58 (m, 2 H), 1.56−1.38 (m, 2 H), 1.36−1.20 (m, 4 H), 0.88 (t, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.05, 130.08, 128.26, 127.72, 120.61, 110.35, 86.68, 69.79, 55.38, 36.41, 31.44, 30.58, 27.00, 22.53, 14.07; IR (KBr) 3302, 1487, 1241, 749 cm^{-1}; MS (EI) 216 (21), 145 (100). Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.12; H, 9.48. Para isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.0 Hz, 2 H), 6.86 (d, J = 8.4 Hz, 2 H), 3.80 (s, 3 H), 3.60−3.54 (m, 1 H), 2.24 (d, J = 2.8 Hz, 1 H), 1.80−1.63 (m, 2 H), 1.50−1.32 (m, 2 H), 1.32−1.22 (m, 4 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.32, 133.84, 128.28, 113.81, 86.53, 70.50, 55.26, 38.34, 36.70, 31.45, 26.87, 22.51, 14.03; IR (KBr) 3292, 1508, 1246, 825 cm^{-1}; MS (EI) 216 (10), 145 (100). Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.44; H, 9.26.

2-(But-1-yn-3-yl)cyclohexanone (13). 13 was prepared from **2a** according to the general procedure for the Nicholas reaction, using 1-trimethylsilyloxycyclohexene[12] as the nucleophile, yielding 43% of **13** as a mixture of diastereomers (pale yellow oil). ^1H NMR and IR data are in accordance with published data for this compound.[13]

2-(1-Phenylpent-1-yn-3-yl)cyclohexanone (14). 14 was prepared from **2h** according to the general procedure for the Nicholas reaction, using 1-trimethylsilyloxycyclohexene[12] as the nucleophile, yielding 25% of **14** as a mixture of diastereomers (pale yellow oil). Spectral data for the mixture of diastereomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.37 and 7.30−7.24 (m, 5 H), 3.11−3.05 (m) and 3.01 (dt, J = 10.8, 3.6 Hz, in a 1:1 ratio, 1 H in total), 2.64−2.56 (m), 2.52−2.16 (m), 2.10−1.86 (m) and 1.80−1.40 (m, 11 H), 1.09 (app q, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.36, 210.55, 131.56, 131.53, 128.08, 127.48, 123.86, 92.15, 91.02, 83.32, 81.89, 54.26, 53.87, 42.24, 42.08, 33.27, 33.22, 31.35, 29.28, 27.92, 27.40, 26.62, 24.89, 24.84, 24.06, 12.62, 12.16; IR (KBr) 1711, 757, 692 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 85.08; H, 8.35.

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