

Published in final edited form as:

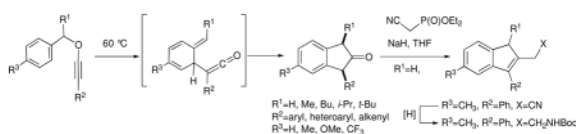
J Org Chem. 2011 May 6; 76(9): 3576–3581. doi:10.1021/jo200271s.

[3,3]-Sigmatropic Rearrangement/5-Exo-Dig Cyclization Reactions of Benzyl Alkynyl Ethers: Synthesis of Substituted 2-Indanones and Indenes

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Abstract



Substituted benzyl alkynyl ethers, prepared from the corresponding α -alkoxy ketones in a two-step sequence involving enol triflate formation and KO^tBu -induced E2 elimination, undergo [3,3]-sigmatropic rearrangement/intramolecular 5-exo-dig cyclization at 60 °C to form substituted 2-indanones in good overall yields. 1,3-*cis*-disubstituted-2-indanones are formed preferentially when the benzylic substituent R^1 is bulky. Substituted indenenes may be prepared from 2-indanones in high yields by Horner-Wadsworth-Emmons reaction.

Ynol ethers are functional groups that possess significant potential in organic chemistry for the formation of carbon-carbon bonds.^{1–3} Due to their linear geometry, alkynyl ethers are relatively unhindered to approach by functional groups present in the same or different molecules; furthermore, alkynyl ethers can prospectively form up to three new bonds in a single reaction.⁴

We have recently uncovered a straightforward methodology for the preparation of alkynyl ethers (Scheme 1)² involving the coupling of alcohols **2** with diazoketones **1** in the presence of indium triflate as a catalyst; the α -alkoxy ketone product **3** is readily transformed into the enol triflate or phosphate at low temperatures, which then undergoes base-induced elimination.³ Allyl-1-alkynyl ethers **7** are thermally unstable and undergo a rapid [3,3] sigmatropic rearrangement⁵ upon generation at –78 °C to form allyl ketene intermediate **8**, which is subsequently trapped by an alcohol or amine to form γ,δ -unsaturated carboxylic acid derivatives **9** in high yields.⁴

Guided by the pioneering studies of Arens⁶ and Schmidt,⁷ we have also shown that benzyl-1-alkynyl ether **12**, which is stable at ambient temperatures, undergoes sigmatropic rearrangement and intramolecular cyclization at 60 °C to form 1-phenyl-2-indanone **13** in 98% yield. Due to the efficiency of this process, we decided to further explore its scope and utility, and in this Note we report our findings on the diastereoselectivity of the benzyl

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 Supporting Information Available: Experimental details, characterization data, ¹H, ¹³C spectra of all products, and ¹H NMR kinetic data at 330K. This material is available free of charge via the Internet at <http://pubs.acs.org>.

alkynyl ether sigmatropic rearrangement/intramolecular cyclization reaction and its applicability to the preparation of substituted 2-indanones and indenenes.

The α -alkoxy ketones **3** (Scheme 2 and Table 1) necessary for the synthesis of benzyl alkynyl ethers **12** were prepared either by coupling of the appropriate diazoketones **1⁸** with benzyl alcohol **2** in the presence of 10 mol% In(OTf)₃ (path **A**, Scheme 2; Table 1, entries 1, 2, and 5),⁹ or by reaction of aryloxyacetic acid¹⁰-derived Weinreb amide¹¹ **10** with the appropriate organolithium or Grignard reagent (path **B**, Scheme 2; Table 1, entries 3–4 and 6–10). Pathway **B** proved to be more general for the synthesis of α -alkoxy ketones; indeed, attempted synthesis of electron-rich substrates **3g** and **3i** by diazoketone-alcohol coupling led to extensive decomposition and minimal yields of the desired products.

Treatment of α -alkoxy ketones **3** with LHMDs at -78 °C, followed by addition of NPhTf₂ in THF/DMPU, led to enol triflates **11a–j**, which were sensitive to trace amounts of acid and heat. After rapid filtration of the crude reaction mixture through silica gel, the enol triflates were immediately treated with potassium *tert*-butoxide (1M in THF) at -78 °C to effect elimination of triflate ion, affording benzyl alkynyl ethers **12a–i**. The crude benzyl alkynyl ethers were also sensitive to heat and silica gel chromatography, so they were directly warmed to 60 °C in toluene to effect [3,3]-sigmatropic rearrangement/5-exo-dig cyclization to provide the substituted indanones **13a–i** in good overall yields. This process was successfully employed for alkynyl ether substrates derived from electron-rich (Table 1, entries 2 and 3) and electron-deficient (entry 4) benzylic alcohols and electron-rich (entries 6 and 7) and electron deficient (entry 8) aryl ketones.

Alkynyl ethers derived from α,β -unsaturated ketones (entry 5) and heteroaryl ketones (entry 9) also smoothly underwent the rearrangement/cyclization process, furnishing indanones **13e** and **13i** in 95 and 62% yields, respectively. However, attempted elimination and thermolysis of alkyne-substituted enol triflate **11j** (entry 10) led to a complex mixture of products, likely arising from the intermediacy of various allenic species³ under the basic conditions employed for elimination.

Monitoring the rates of rearrangement/cyclization¹² for alkynyl ether substrates **12a–d** by ¹H NMR spectroscopy revealed interesting trends (Table 2). Whereas unsubstituted parent compound **12a** underwent first-order decay to **13a** at 57 °C in CDCl₃ with a half-life of 4.8 minutes, alkynyl ether **12b** under the same conditions displayed a half-life of only 0.8 minutes, and methoxy-substituted substrate **12c** could not be isolated at room temperature, having completely rearranged to indanone **13c** upon warming the KO^tBu elimination reaction of **11c** from -78 °C to ambient. In contrast, CF₃-substituted alkynyl ether **12d** displayed a half-life of 13.3 minutes at 57 °C. Assuming that the rate-determining step of the transformation **12**→**13** is the [3,3] sigmatropic rearrangement, the rate acceleration observed for substrates bearing electron-donating substituents (**Y**) on the benzyl moiety suggests the development of charge deficiency (either a radical or cationic intermediate)¹³ at the benzylic carbon atom during the transition state for sigmatropic rearrangement.

A similar analysis of the rates of rearrangement of **12f–h** compared to **12a** revealed again that electron-donating substituents accelerated the rearrangement/cyclization process: whereas **12f** displayed a half life of 3.6 minutes at 57 °C, substrate **12g** had completely rearranged to **13g** upon reaching room temperature after generation at -78 °C. Intriguingly, however, it was found that CF₃-substituted alkynyl ether **12h** underwent first-order decay slightly *faster* than **12a**, displaying a half-life of 4.6 minutes at 57 °C. These observations are consistent with a change in mechanism¹⁴ upon proceeding from electron-donating to electron-withdrawing substituents on the aromatic moiety **X**, with a radical mechanism

(pathway **A**, figure 1) likely operative for the former and a polar mechanism (pathway **B**, figure 1) for the latter.

Next, we sought to examine the stereoselectivity of the rearrangement/cyclization reaction when α -substituted benzyl ethers are employed. Ketones **14a–e** were prepared by protocol **A** (Scheme 2) and subjected to enol triflate formation, *tert*-butoxide induced triflate elimination, and thermal rearrangement/cyclization to furnish 1,3-disubstituted-2-indanones **15** (Table 3). Only in the case of the phenyl-substituted ketone **14e** did the reaction sequence fail to afford the desired indanone product; enol triflate formation from **14e** led to complicated mixtures due to the heightened acidity of the benzylic proton and the basic conditions involved.

Low to moderate diastereoselectivity was observed for methyl-, butyl-, and isopropyl-substituted indanones **15a–c**; however, excellent diastereoselectivity (>95:5) was obtained for 1-*tert*-butyl-3-phenyl-indanone **15d**. The presence of crosspeaks between the C.1 and C.3 protons (H_b and H_a , respectively) observed in the NOESY spectrum of **15d** (as well as correlations between H_a and H_c , H_c and H_d , and H_d and H_b) confirmed the *cis* stereochemistry (Scheme 3). Mechanistically, we propose that the large *tert*-butyl substituent prefers to be oriented *trans* to the ketene in the nonaromatic intermediate **16a**;¹⁵ 5-exo dig cyclization, followed by a *syn*-1,2-proton migration to the enolate carbon atom, would give rise to the product with the observed stereochemistry.

Finally, we sought to transform our 2-indanone products **13** into synthetically useful substituted indenenes. Indenes are building blocks in the synthesis of biologically active pharmaceutical agents¹⁶ and are often used as ligands in olefin polymerization catalysts.¹⁷ Addition of indanone **13b** to a solution of diethyl(cyanomethyl)phosphonoacetate and NaH in THF and stirring for 4 hours at room temperature resulted in clean transformation to indene **18b** (91% isolated yield), arising from carbonyl olefination and base-mediated isomerization (Scheme 4). Reduction of the nitrile functional group and *in situ* primary amine protection as a *tert*-butyl carbamate was accomplished in a single step by employing Caddick's protocol¹⁸ (cat. $NiCl_2 \cdot H_2O$, $NaBH_4$, Boc_2O , MeOH) to afford indene **19b** in 60% yield.

In conclusion, we have shown that the [3,3]-sigmatropic rearrangement of benzyl alkynyl ethers may be successfully employed for a variety of substrates bearing electron-deficient and electron-rich aromatic and heteroaromatic ring systems, and the rates of rearrangement vary depending upon the electronic nature of the aromatic substituents. Furthermore, 1,3-*cis*-disubstituted-2-indanones are formed in excess when α -substituted benzyl alkynyl ethers are employed as substrates. The 2-indanones obtained by this method may be easily transformed into useful substituted indene products.

Experimental Section

Representative procedure for the synthesis of ketones **3a**, **3b**, **3e**, **14a–e**. 2-(Benzyloxy)-1-phenylethanone **3a**

A mixture of the diazoacetophenone (136 mg, 1 mmol) and benzyl alcohol (162 mg, 1.5 mmol) were dissolved in dry toluene (4 mL) under argon and stirred at room temperature for 2 minutes. Indium (III) trifluoromethanesulfonate (56.2 mg, 0.1 mmol, 10 mol%) was added and a rapid evolution of nitrogen gas was observed. The reaction was monitored by TLC, and when complete consumption of the starting material was observed, saturated $NaHCO_3$ (10 mL) was added and the reaction mixture was diluted with ether (20 mL). The phases were separated and the aqueous phase was back-extracted with ether (1 \times 20 mL). The

combined organic extracts were then dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO_2) afforded α -alkoxyketone **3a**.

3a³ (87%): ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, $J=7.6$ Hz, 2H), 7.57 (t, $J=7.6$ Hz, 1H), 7.46 (t, $J=8.0$ Hz, 2H), 7.40–7.27 (m, 5H), 4.82 (s, 2H), 4.70 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.2, 136.9, 134.6, 133.9, 129.4, 128.8, 128.6, 128.2, 127.9, 127.1, 123.6, 73.4, 72.4; HRMS (ESI) calculated for $\text{C}_{15}\text{H}_{14}\text{NaO}_2$ 249.0892, found 249.0854 ($\text{M}+\text{Na}$)⁺. **3b** (82%): ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, $J=7.6$ Hz, 2H), 7.51 (t, $J=7.6$ Hz, 1H), 7.46–7.27 (m, 6H), 4.72 (s, 2H), 4.65 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.3, 137.6, 135.0, 134.4, 133.5, 129.2, 128.7, 128.2, 128.0, 73.2, 72.5, 21.2; HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{16}\text{NaO}_2$ 263.1048, found 263.1107 ($\text{M}+\text{Na}$)⁺.

3e (61%): ^1H NMR (400 MHz, CDCl_3) δ 7.83 (dd, $J=8.4, 1.2$ Hz, 2H), 7.45–7.25 (m, 5H), 6.83 (d, $J=8.8$ Hz, 2H), 4.62 (s, 2H), 4.54 (s, 2H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.3, 159.4, 134.9, 133.4, 129.7, 129.4, 128.6, 128.3, 127.8, 113.8, 72.9, 72.2, 55.1; HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{16}\text{NaO}_3$ 279.0997, found 279.1098 ($\text{M}+\text{Na}$)⁺.

14a (75%): ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, $J=7.6$ Hz, 2H), 7.46 (t, $J=7.6$ Hz, 1H), 7.36–7.25 (m, 7H), 4.65 (d, $J=16.8$ Hz, 1H), 4.54 (q, $J=6.4$ Hz, 1H), 4.52 (d, $J=16.8$ Hz, 1H), 1.54 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 195.9, 142.9, 135.0, 131.1, 128.6, 128.5, 128.2, 127.8, 127.7, 126.3, 78.3, 77.9, 71.2, 24.0, 23.9; HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{16}\text{NaO}_2$ 263.1048 found 263.1632 ($\text{M}+\text{Na}$)⁺.

14b (78%): ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, $J=8.4$ Hz, 2H), 7.50 (t, $J=7.6$ Hz, 1H), 7.40–7.25 (m, 7H), 4.63 (d, $J=16.8$ Hz, 1H), 4.49 (d, $J=16.8$ Hz, 1H), 4.40 (t, $J=6.8$ Hz, 1H), 1.97 (m, 1H), 1.72 (m, 1H), 1.43 (m, 1H), 1.30 (m, 1H), 0.86 (t, $J=7.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.4, 141.7, 135.1, 133.3, 128.6, 128.5, 128.3, 127.9, 127.0, 83.1, 71.3, 37.9, 28.0, 22.6, 14.0; HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{22}\text{NaO}_2$ 305.1517, found 305.1343 ($\text{M}+\text{Na}$)⁺.

14c (73%): ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, $J=8.0$ Hz, 2H), 7.43 (t, $J=7.8$ Hz, 1H), 7.33–7.21 (m, 7H), 4.52 (d, $J=16.0$ Hz, 1H); 4.35 (d, $J=16.0$ Hz, 1H); 3.97 (d, $J=8.0$ Hz, 1H); 1.96 (m, $J=8.0$ Hz, 1H); 0.98 (d, $J=8.0$ Hz, 3H); 0.65 (d, $J=8.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.6, 140.3, 135.2, 133.3, 128.6, 128.5, 128.2, 128.0, 127.8, 127.7, 88.6, 71.6, 34.8, 19.2, 19.0; HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{20}\text{NaO}_2$ 291.1361, found 291.1440 ($\text{M}+\text{Na}$)⁺.

14d (66%): ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J=8.0$ Hz, 2H), 7.49 (t, $J=7.8$ Hz, 1H); 7.37 (t, $J=7.8$ Hz, 2H). 7.32–7.25 (m, 5H), 4.62 (d, $J=16.0$ Hz, 1H), 4.41 (d, $J=16.0$ Hz, 1H), 4.15 (s, 1H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.5, 138.8, 135.3, 133.3, 128.6, 128.5, 128.0, 127.7, 127.6, 90.6, 71.9, 35.8; 26.4; HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{22}\text{NaO}_2$ 305.1517, found 305.1962 ($\text{M}+\text{Na}$)⁺.

14e (71%): ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, $J=7.6$ Hz, 2H), 7.55 (t, $J=7.4$ Hz, 1H), 7.46–7.41 (m, 6H), 7.35 (t, $J=7.6$ Hz, 4H), 7.28 (t, $J=7.8$ Hz, 2H), 5.64 (s, 1H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.3, 141.3, 135.1, 133.5, 128.7, 128.5, 128.0, 127.8, 127.4, 83.8, 77.4, 77.1, 76.8, 71.4; HRMS (ESI) calculated for $\text{C}_{21}\text{H}_{18}\text{NaO}_2$ 325.1204, found 325.1541 ($\text{M}+\text{Na}$)⁺.

Representative procedure for the synthesis of ketones **3c**, **3d**, **3f–j**

To a solution of the aryloxy acetic acid¹⁰ (1 g, 6 mmol) in 11 mL dichloromethane at 0 °C was added 1,1'-carbonyl diimidazole (1.26 g, 7.82 mmol) at 0 °C. The solution bubbled and upon completion it was warmed to room temperature for 30 minutes. The solution was

cooled to 0 °C and triethylamine (1.1 mL, 8.4 mmol) was added, followed by the Weinreb amine hydrochloride salt (0.82 g, 8.4 mmol). The solution was allowed to warm to room temperature and was stirred overnight. The mixture was diluted with 1M HCl (10 mL) and EtOAc (20 mL). The phases were separated and the aqueous phase was back-extracted with EtOAc (1 × 20 mL). The combined organic extracts were then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Crude amide **10** was taken directly to the next step without further purification.

To a solution of Weinreb amide **10** (5 mmol) in THF (5 mL) at -78 °C under argon was added a solution of aryllithium reagent (generated from the corresponding aryl bromide 1M in THF by the addition of 0.95 equiv *n*-BuLi) dropwise. Upon completion of the addition, TLC indicated complete conversion to the aryl ketone. The mixture was allowed to warm to -20 °C and was quenched with saturated NH₄Cl solution (10 mL). The mixture was diluted with ether (3 mL) and was allowed to stir at room temperature for one hour. The phases were separated and the aqueous phase was back-extracted with EtOAc (1 × 20 mL). The combined organic extracts were then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO₂) afforded α -alkoxyketones **3**.

3c (71%): ¹H NMR (400 MHz, CDCl₃) δ 7.83 (dd, *J*=8.4, 1.2 Hz, 2H), 7.45–7.25 (m, 5H), 6.83 (d, *J*=8.8 Hz, 2H), 4.62 (s, 2H), 4.54 (s, 2H), 3.67 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 196.3, 159.4, 134.9, 133.4, 129.7, 129.4, 128.6, 128.3, 127.8, 113.8, 72.9, 72.2, 55.1; HRMS (ESI) calculated for C₁₆H₁₆NaO₃ 279.0997, found 279.1098 (M+Na)⁺.

3d (68%): ¹H NMR (400 MHz, CDCl₃) δ 7.91 (dd, *J*=9.6 Hz, 2H), 7.61–7.42 (m, 7H), 4.81 (s, 2H), 4.72 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 196.0, 141.6, 134.7, 133.7, 129.5, 128.8, 127.9, 127.8, 125.4, 125.3, 115.4, 72.8, 72.5; HRMS (ESI) calculated for C₁₆H₁₃F₃NaO₂ 317.0765, found 317.0852 (M+Na)⁺.

3f (69%): ¹H NMR (400 MHz, CDCl₃) δ 7.83–7.80 (d, *J*=8.4 Hz, 2H), 7.41–7.23 (m, 7H), 4.73 (s, 2H), 4.68 (s, 2H), 2.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 195.9, 144.4, 137.4, 132.4, 129.3, 128.5, 128.1, 128.0, 73.3, 72.5, 21.7; HRMS (ESI) calculated for C₁₆H₁₆NaO₂ 263.1048, found 263.1055 (M+Na)⁺.

3g (82%): ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J*=8.8 Hz, 2H), 7.40–7.32 (m, 5H), 6.88 (d, *J*=8.8 Hz, 2H), 4.69 (s, 2H), 4.66 (s, 2H), 3.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 194.9, 163.8, 150.6, 137.5, 130.3, 128.5, 128.0, 127.9, 116.2, 114.7, 113.9, 73.3, 72.5, 55.4; HRMS (ESI) calculated for C₁₆H₁₆NaO₃ 279.0997, found 279.0780 (M+Na)⁺.

3h (73%): ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J*=8.0 Hz, 2H), 7.74 (d, *J*=8.4 Hz, 2H), 7.39–7.33 (m, 5H), 4.76 (s, 2H), 4.70 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 195.6, 137.5, 136.9, 134.8, 128.6, 128.4, 128.2, 128.1, 125.7, 73.5, 72.8; HRMS (ESI) calculated for C₁₆H₁₃F₃NaO₂ 317.0765, found 317.0923 (M+Na)⁺.

3i (85%): ¹H NMR (400 MHz, CDCl₃) δ 7.53 (s, 1H), 7.52–7.24 (m, 6H), 6.47 (m, 1H), 4.63 (s, 2H), 4.54 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 185.5, 150.9, 146.7, 137.3, 128.5, 128.3, 128.0, 127.9, 118.2, 112.3, 73.4, 72.2; HRMS (ESI) calculated for C₁₃H₁₂NaO₃ 239.0684, found 239.0717 (M+Na)⁺.

3j (92%): ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.25 (m, 5H), 4.62 (s, 2H), 4.19 (s, 2H), 2.37 (t, *J*=6.8 Hz, 2H), 1.56 (m, *J*=7.2 Hz, 2H), 1.38–1.26 (m, 5H), 0.89 (t, *J*=6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 185.0, 137.1, 128.4, 127.9, 97.5, 82.7, 75.8, 73.3, 31.2, 28.5, 27.5, 22.5, 22.4, 19.0, 14.0; HRMS (ESI) calculated for C₁₇H₂₂NaO₂ 281.1517, found 281.1582 (M+Na)⁺.

Representative procedure for enol triflate (11a–i) formation

Hexamethyldisilazane (0.29 mL, 2.5 mmol) dissolved in dry THF (1 mL) under argon was cooled to 0 °C in an ice bath and *n*-BuLi (0.75 mL), 2M in cyclohexane, 1.5 mmol) was added dropwise. After 10 minutes, the mixture was cooled to –78 °C and a solution of α -alkoxyketone (1 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred for one hour at –78 °C and then a solution of *N*-phenyl triflimide (1.5 mmol) in 1:1 THF : DMPU (1 mL) was added rapidly (1 s). The mixture was allowed to warm to room temperature and then was stirred for one hour, at which time TLC indicated >90% consumption of starting material. The phases were separated and the aqueous phase was back-extracted with ether (1 \times 20 mL). The combined organic extracts were then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude enol triflate was filtered over silica gel employing 1% Et₃N in the eluant (95:5 hexanes:ether), and the material obtained was used directly in the next reaction.

Representative procedure for alkynyl ether (12a–i) formation and sigmatropic rearrangement/cyclization to indanones 13a–i and 15a–d

The enol triflate obtained from the above procedure (~1 mmol) was dissolved in THF (1 mL) under argon and cooled to –78 °C. A solution of potassium *tert*-butoxide (1M in THF, 3.0 mL, 3.0 mmol) was added dropwise, and the reaction mixture darkened in color. After 20 minutes, a solution of saturated NaHCO₃ (10 mL) was added and the mixture was allowed to warm to room temperature with stirring. Ether (10 mL) was added, and the phases were separated. The aqueous layer was back-extracted with ether (1 \times 20 mL), and the combined organic extracts were then dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude alkynyl ether was then dissolved in toluene (2 mL) and heated on an oil bath under argon for one hour, at which time TLC indicated complete conversion to the indanone product. Concentration *in vacuo* and purification of the residue by flash chromatography (SiO₂) afforded indanones **13a–i** and **15a–d**.

13a³ (98%): ¹H NMR (400 MHz, CDCl₃) δ 7.43–7.22 (m, 7H), 7.17 (d, *J*=7.6 Hz, 2H), 4.71 (s, 1H), 3.68 (s, 2H); ¹³C NMR (100 MHz, C₆D₆) δ 213.8, 141.4, 138.2, 137.3, 128.8, 128.5, 128.0, 127.9, 127.3, 126.0, 124.9, 59.8, 43.0; HRMS (ESI) calculated for C₁₅H₁₂NaO 231.0786, found 231.0777 (M+Na)⁺.

13b (93%): ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.24 (m, 3H), 7.17–7.10 (m, 3H), 7.01 (s, 1H), 4.63 (s, 1H), 3.62 (s, 2H), 2.33 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 216.8, 143.3, 140.0, 137.7, 128.8, 128.5, 128.0, 127.9, 126.7, 124.3, 123.1, 60.2, 47.1, 23.5; HRMS (ESI) calculated for C₁₆H₁₄NaO 245.0942, found 245.1399 (M+Na)⁺.

13c (65%): ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.27 (m, 4H), 7.15 (d, *J*=7.6 Hz, 2H), 6.93 (m, 1H), 6.74 (m, 1H), 4.66 (s, 1H), 3.78 (s, 3H), 3.62 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 214.2, 159.5, 142.4, 138.0, 129.1, 128.8, 128.4, 127.3, 125.7, 114.7, 110.7, 60.2, 55.4, 42.3; HRMS (ESI) calculated for C₁₆H₁₄NaO₂ 261.0891, found 261.0922 (M+Na)⁺.

13d (72%): ¹H NMR (400 MHz, CDCl₃) δ 7.63–7.26 (m, 7H), 7.11 (dd, *J*=9.2 Hz, 1H), 4.75 (m, 1H), 3.72 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 212.3, 142.2, 137.2, 130.5, 130.2, 129.0, 128.4, 128.1, 127.2, 126.4, 125.0, 123.0, 122.9, 122.7, 59.6, 42.8; HRMS (ESI) calculated for C₁₆H₁₁F₃NaO 299.0660, found 299.0598 (M+Na)⁺.

13e (95%): ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.24 (m, 4H), 5.54 (s, 1H), 3.98 (s, 1H), 3.53 (s, 2H), 1.67–1.49 (m, 8H); ¹³C NMR (100 MHz, CDCl₃) δ 215.8; 141.3; 137.3; 134.7; 127.6; 127.5; 127.0; 125.3; 124.7; 62.3; 43.4; 26.1; 25.4; 22.7; 22.1; HRMS (ESI) calculated for C₁₅H₁₆NaO 235.1099, found 235.1174 (M+Na)⁺.

13f (90%): ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.30 (m, 3H), 7.21 (d, $J=7.2$ Hz, 1H), 7.14 (d, $J=7.6$ Hz, 2H), 7.02 (d, $J=8.0$ Hz, 2H), 4.63 (s, 1H), 3.65 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 214.2, 141.5, 137.2, 137.0, 135.2, 129.5, 128.5, 128.3, 127.9, 127.8, 126.0, 124.8, 59.4, 42.9, 21.1; HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{14}\text{NaO}$ 245.0942, found 245.0921 ($\text{M}+\text{Na}$) $^+$.

13g (88%): ^1H NMR (400 MHz, CDCl_3) δ 7.38–7.20 (m, 5H), 7.05 (d, $J=6.4$ Hz, 2H), 6.87 (d, $J=6.4$ Hz, 2H), 4.63 (s, 1H), 3.78 (s, 3H), 3.66 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 214.4, 158.9, 141.6, 137.2, 130.3, 129.5, 128.3, 127.9, 127.8, 126.0, 124.8, 114.2, 58.9, 55.2, 42.8; HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{14}\text{NaO}_2$ 261.0891, found 261.0664 ($\text{M}+\text{Na}$) $^+$.

13h (91%): ^1H NMR: (400 MHz, CDCl_3) δ 8.06 (d, $J=8.0$ Hz, 1H), 7.75 (d, $J=8.4$ Hz, 2H), 7.61 (d, $J=8.0$ Hz, 2H), 7.45–7.18 (m, 5H), 4.71 (s, 1H), 3.73 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 212.9, 140.2, 136.7, 129.8, 129.4, 128.9, 128.5, 128.2, 126.9, 125.9, 125.7, 125.6, 125.4, 59.4, 42.8; HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{NaO}$ 299.0659, found 299.0721 ($\text{M}+\text{Na}$) $^+$.

13i (62%): ^1H NMR (400 MHz, CDCl_3) δ 7.39–7.27 (m, 5H), 6.35 (m, 1H), 6.16 (m, 1H), 4.82 (s, 1H), 3.72 (d, $J=8.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 211.4, 150.5, 142.7, 136.9, 128.3, 127.8, 125.6, 124.9, 110.4, 107.8, 53.3, 42.9; HRMS (ESI) calculated for $\text{C}_{13}\text{H}_{10}\text{NaO}_2$ 221.0578, found 221.0842 ($\text{M}+\text{Na}$) $^+$.

15a (61%; dr=1:1): ^1H NMR (400 MHz, CDCl_3) δ 7.41–7.26 (m, 6H); 7.18–7.10 (m, 3H); 4.70 (s, 1H); 3.61 (q, $J=4.2$ Hz, 1H); 1.48 (d, $J=5.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 216.4, 143.2, 140.1, 138.3, 128.9, 128.6, 128.0, 127.6, 126.0, 124.2, 59.0, 46.7, 15.8; HRMS (ESI) calculated for $\text{C}_{16}\text{H}_{14}\text{NaO}$ 245.0942, found 245.4017 ($\text{M}+\text{Na}$) $^+$.

15b (53%; dr=4:1): ^1H NMR (400 MHz, CDCl_3) δ 7.33–7.21 (m, 9H), 4.42 (s, 1H), 3.34 (t, $J=5.4$ Hz, 1H), 1.86 (m, 2H), 1.41–1.19 (m, 4H), 0.80 (t, $J=6.0$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 214.2, 142.3, 141.0, 128.9, 128.5, 128.0, 127.7, 127.5, 58.9, 52.0, 31.2, 28.8, 22.7, 19.6; HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{20}\text{NaO}$ 287.1412, found 287.1361 ($\text{M}+\text{Na}$) $^+$.

15c (48%; dr=2:1): ^1H NMR (400 MHz, CDCl_3) δ 7.24–7.01 (m, 9H), 4.38 (s, 1H), 3.25 (d, $J=3.6$ Hz, 1H), 2.29 (m, $J=4.0$ Hz, 1H), 1.01 (d, $J=6.4$ Hz, 3H), 0.89 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 213.8, 141.3, 140.9, 138.0, 128.9, 128.4, 128.0, 127.7, 127.5, 126.9, 126.1, 124.7, 58.9, 58.0, 31.2, 19.9, 19.6; HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{18}\text{NaO}$ 273.1255, found 273.1271 ($\text{M}+\text{Na}$) $^+$.

15d (69%): ^1H NMR (400 MHz, CDCl_3) δ 7.42 (d, $J=10.0$ Hz, 2H); 7.31 (m, 1H); 7.20–7.09 (m, 6H); 4.40 (s, 1H), 3.09 (s, 1H), 0.99 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 213.3, 141.3, 140.7, 138.6, 128.5, 128.0, 127.9, 127.6, 127.3, 126.6, 62.3, 58.6, 35.0; 30.5, 28.6; HRMS (ESI) calculated for $\text{C}_{19}\text{H}_{20}\text{NaO}$ 287.1412, found 287.1438 ($\text{M}+\text{Na}$) $^+$.

Synthesis of 2-(5-methyl-3-phenyl-1H-inden-2-yl)ethanenitrile **18b**

To a solution of diethyl(cyanomethyl)phosphonate (531 mg, 3.0 mmol) in THF (1 mL) was added NaH (100 mg, 2.5 mmol) at 0 °C and the solution was allowed to stir for 30 minutes. Then a solution of 2-indanone **13b** (100 mg, 0.45 mmol) in THF (1 mL) was added and the mixture was allowed to stir for 4 hours at room temperature. The mixture was diluted with saturated NaHCO_3 (10 mL). Ether (20 mL) was added, and the phases were separated. The aqueous later was back-extracted with ether (1 \times 20 mL), and the combined organic extracts were then dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO_2) afforded indene **18b**. **18b** (91%): ^1H NMR (400 MHz, CDCl_3) δ 7.53–7.35 (m, 6H), 7.09–7.05 (m, 2H), 3.63 (s, 2H), 3.55 (s, 2H), 2.35 (s, 3H); ^{13}C

NMR: (100 MHz, CDCl_3) δ 144.8, 139.1, 136.4, 133.6, 130.5, 128.9, 128.8, 128.1, 126.5, 123.6, 121.2, 40.2, 21.5, 17.9; HRMS (ESI) calculated for $\text{C}_{18}\text{H}_{15}\text{NNa}$ 268.1102, found 268.1099 ($\text{M}+\text{Na}$)⁺.

Synthesis of tert-butyl 2-(5-methyl-3-phenyl-1H-inden-2-yl)ethylcarbamate 19b

To a solution of nitrile **18b** (35.0 mg, 0.142 mmol) in methanol (1.2 mL) at 0 °C were added Boc_2O (69.0 mg, 0.32 mmol) and $\text{NiCl}_2\cdot 6\text{H}_2\text{O}$ (3.8 mg, 0.016 mmol). Then NaBH_4 (42.4 mg, 1.12 mmol) was added in small portions over 30 minutes. After warming to room temperature and stirring for 2 hours, the mixture was diluted with saturated NaHCO_3 (10 mL) and concentrated *in vacuo* to remove methanol. Ethyl acetate (10 mL) was added and the phases were separated. The aqueous layer was back-extracted with ethyl acetate (1 × 10 mL), and the combined organic extracts were then dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (SiO_2) afforded indene **19b**.

19b (60%): ^1H NMR (400 MHz, CDCl_3) δ 7.49–7.35 (m, 6H), 7.00 (m, 2H), 3.47 (s, 2H), 3.35 (m, 2H), 2.71 (t, $J=6.8$ Hz, 2H) 2.34 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.7, 146.3, 141.1, 138.0, 135.2, 129.1, 128.5, 128.3, 127.3, 125.3, 123.3, 120.4, 100.0, 79.2, 40.2, 40.0, 29.4, 28.3, 21.5; HRMS (ESI) calculated for $\text{C}_{23}\text{H}_{27}\text{NNaO}_2$ 372.1939, found 372.1763 ($\text{M}+\text{Na}$)⁺.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (SC2 GM081064-01) and the Henry Dreyfus Teacher-Scholar Award for their generous support of our research program.

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13. A Hammett plot of $\ln(k/k_0)$ vs. σ for the data for substrates 12a, b, and d shows a break in slope at the data point for 12a, with a strongly negative slope ($\rho = -10.5$) to 12b and a moderately negative slope ($\rho = -1.9$) to 12d. The break in slope is suggestive of a change in mechanism upon proceeding from substrates bearing electron-donating substituents (12b) to substrates bearing electron-withdrawing substituents (12d). See: Ritchie CD, Sager WF. *Prog Phys Org Chem.* 1964; 2:323. See supporting information for data graphs.
14. A Hammett plot of $\ln(k/k_0)$ vs. σ for the data for substrates 12a, f, and h shows a break in slope at the data point for 12a, with a negative slope ($\rho = -1.62$) to 12f and a slightly positive slope ($\rho = +0.05$) to 12h. Again, the break in slope is suggestive of a change in mechanism upon proceeding from substrates bearing electron-donating substituents (12f) to substrates bearing electron-withdrawing substituents (12h). See supporting information for data graphs.
15. (a) We thank a reviewer for mentioning the allylic strain apparent in the *anti* disposition of the *tert*-butyl group in structure 16^a. We believe that steric interactions between the *tert*-butyl group and the phenyl-substituted ketene in the corresponding *syn* form (16^s, see Supporting Information) hinder alignment of the ketene carbonyl carbon with the benzylic carbon atom (which is necessary for 5-exo-dig cyclization to occur) by favoring rotamers in which the ketene is directed away from the benzylic carbon atom. Thus, despite the allylic strain present in 16^a, it appears that the reaction proceeds preferentially through 16^a to 15d. (b) To assess if the product ratios obtained for 15a-c represent an equilibrium mixture arising from a reversible process, we have attempted to obtain pure major or minor isomer from these reactions and resubject them individually to the reaction conditions. Chromatographic separation of the *cis* and *trans* indanone products has proven quite difficult since the diastereomers co-elute in most solvents. Thus, a mixture enriched in the major isomer of indanone 15c (dr ~ 5:1) was heated to 57°C in an NMR tube (CDCl₃ as solvent) for 30 minutes, and essentially no change in the isomer ratio was observed. This suggests that the 5-exo-dig cyclization is irreversible under these reaction conditions and that the isomer distributions are under kinetic control.
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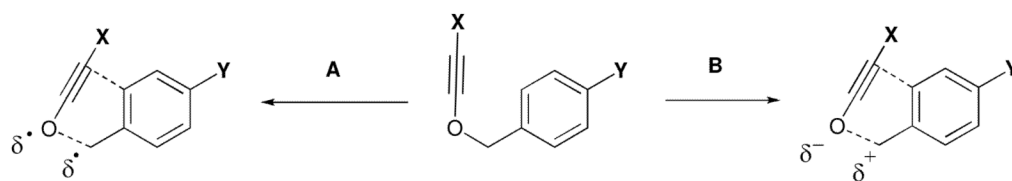
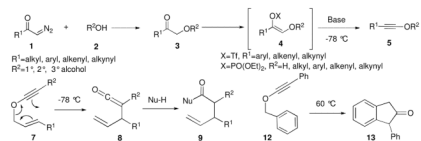


FIGURE 1.
Possible TS charge development for benzyl alkynyl ether sigmatropy



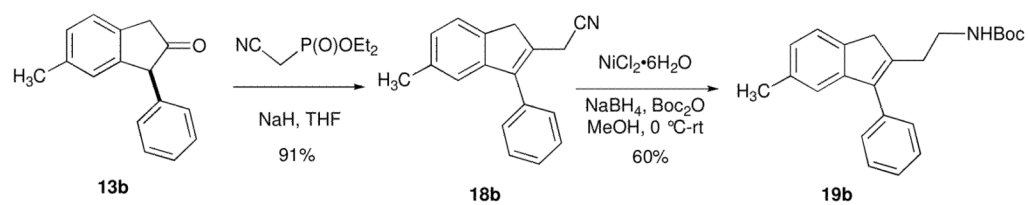
SCHEME 1.
1-alkynyl ether synthesis and [3,3]-sigmatropy



SCHEME 2.
Two methods for the synthesis of ketones 3



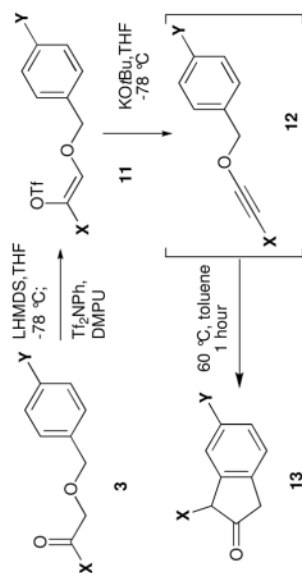
SCHEME 3.
Mechanistic proposal for the formation of indanone 15d.



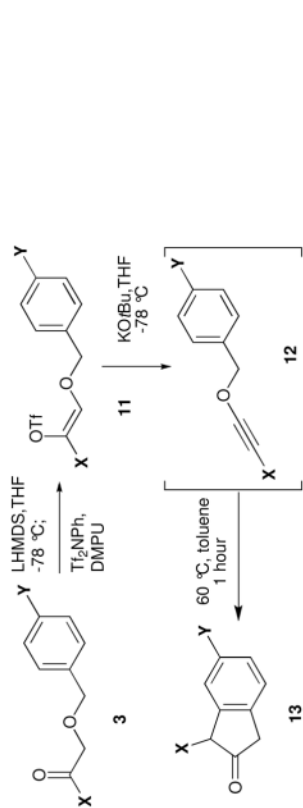
SCHEME 4.
Transformation of 2-indanones into substituted indenes

TABLE 1

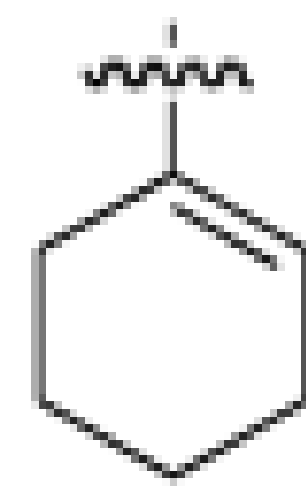
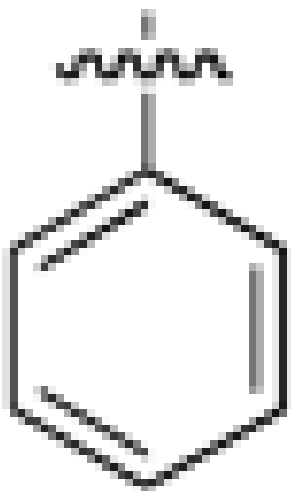
Scope of benzyl alkynyl ether [3,3]sigmatropy/5-exo-dig cyclization



entry	X	Y	3	% yield 11 ^d	% yield 13 ^e
1		H	a ^d	75	98
2		CH ₃	b ^d	73	93



entry	X	Y	3	% yield 11 ^d	% yield 13 ^e
3	X	OCH ₃	<i>c</i> , <i>b</i>	68	65
4	X	CF ₃	<i>d</i> , <i>b</i>	81	72

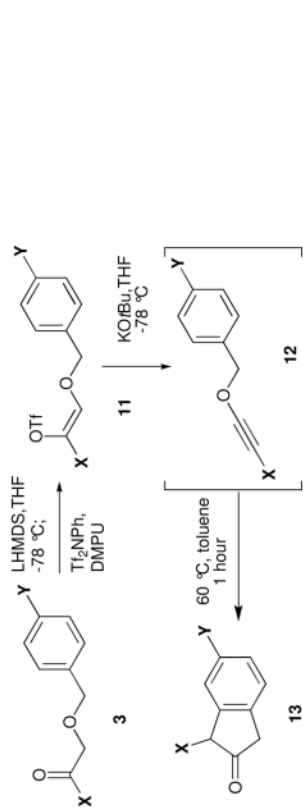


5

H

85

95



entry	X	Y	3	11 ^d	% yield 13 ^e
6		H	<i>i</i> ^b		90
7		H	<i>i</i> ^b		88
8		H	<i>i</i> ^b		91
9		H	<i>i</i> ^b		62
10		H	<i>i</i> ^b		82

^a α -Alkoxy ketone **3** prepared by method **A** (Scheme 2).

^b α -Alkoxy ketone **3** prepared by method **B** (Scheme 2).

^c A complex mixture of products was formed.

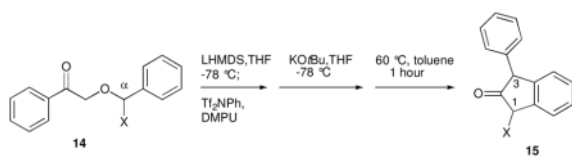
^d Yield (from **3**) based on weight obtained after rapid filtration of the crude triflation reaction mixture through silica gel (see text).

^e Isolated yield (from **11**) after silica gel chromatography.

TABLE 2Kinetic data for the first-order decay of 12 to 13 at 57 °C in CDCl₃

Substrate	$t_{1/2}(min)$	$k (min^{-1})$
12a	4.8	0.145
12b	0.8	0.905
12d	13.3	0.052
12f	3.6	0.191
12h	4.6	0.149

Table 3

Rearrangement/cyclization of α -substituted benzyl alkynyl ethers^a

entry	X	14	% yield 15 (from 14) ^b	d.r.
1	CH ₃	a	61	1:1
2	CH ₃ (CH ₂) ₃	b	53	4:1
3	(CH ₃) ₂ CH	c	48	2:1
4	(CH ₃) ₃ C	d	69	>95:5
5		e	—	—

^a Ketones **14** prepared by method A (Scheme 2).^b Isolated yields.