Rapid 1,4-Alkynylation of Acyclic Enones Using K[$F_3BC{\equiv}CR$]

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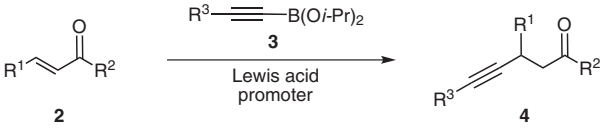
Abstract: Conjugate alkynylation of acyclic enones using sp-hybridised potassium organotrifluoroborates in the presence of $BF_3{\cdot}OEt_2$ is rapidly attained. The simplicity of the processes is suitable for the preparation of small compound libraries.

Key words: conjugated alkynylation, enones, potassium organotrifluoroborates

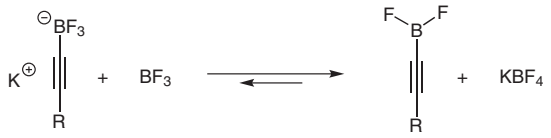
Since their introduction to organic chemistry, aryl boronic acids[1] [$ArB(OH)_2$] and more latterly vinyltrifluoroborates[2] [$F_3BCR{=}CR_2$]$^-$ have become mainstay sp^2-C nucleophiles. Their air-stability, long shelflife, functional group tolerance, and widespread commercial availability (over 2500 examples[3]) allow practical storage of C-nucleophile compound libraries. While good routes exist to sp-hybridised K[$F_3BC{\equiv}CR$] **1**[4] exist, fewer applications of these closely related air-stable, nonhygroscopic compounds have been reported.[4,5]

Recently, in connection with another project, we needed access to a library of compounds resulting from 1,4-alkynylation of enones.[6] While recent advances have been made in this demanding reaction, allowing direct use of alkynes alone, these are presently limited to the use of either specialist Michael acceptors[7] or specific alkynes.[8] For the main part, catalytic 1,4-additions of alkyne nucleophiles to enones **2** (whether asymmetric or not) have required in situ prepared derivatives of Cu,[9] Zn,[10] or Al.[11] We were attracted to the reports of Chong[12] and Suzuki[13] who used (1-alkynyl)diisopropoxyboranes **3** in Lewis acid promoted reactions (Scheme 1).



Scheme 1

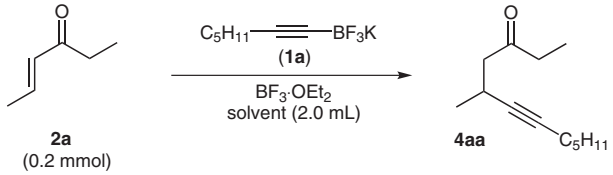
Despite the success of Scheme 1, use of **3** has a number of limitations: it is very sensitive to hydrolysis and its reactions can be very slow (up to 120 h). We speculated that increasing the Lewis acidity of the boron component would lead to a dramatic rate promotion in the 1,4-addition. One simple route to attaining this goal is fluoride abstraction from **1** by admixture of $BF_3{\cdot}OEt_2$, driven by the formation of stable KBF_4 (Equation 1).[14]



Equation 1

The reaction of alkynyltrifluoroborate **1a** with enone **2a** served as an optimization model (Table 1).

Table 1 Alkynylation of Enone **2a** with Potassium Organotrifluoroborate **1a** under Different Reaction Conditions



Entry	Solvent	Nucleophile (equiv)	$BF_3{\cdot}OEt_2$ (equiv)	Conditions	Yield (%)[a]
1[b]	THF	2.0	1.5	r.t., 18 h	23
2	toluene	2.0	1.5	70 °C, 45 min	13
3[c]	CH_2Cl_2	1.5	1.1	r.t., 50 min	47
4	CH_2Cl_2	2.0	1.5	0 °C, 40 min	56
5	CH_2Cl_2	2.0	1.5	r.t., 35 min	74
6	CH_2Cl_2	2.0	2.0	r.t., 5 min	70

[a] GC yields.
[b] Conversion: 58%.
[c] Conversion: 97%.

Both polar and nonpolar solvents (entries 1 and 2) were ineffective for the reaction. Dichloromethane proved to be the optimal solvent (entries 3–6) presumably because the trifluoroborates of type **1** have marginal solubility in it while KBF_4 does not. The highest yields were attained in reactions where there were slight excesses of both the nucleophile **1** and the $BF_3{\cdot}OEt_2$ promoter in procedures carried out at ambient temperature (entries 5 and 6). Under these conditions enormous rate accelerations, compared to the chemistry of Suzuki[13] are attained. For example, the published equivalent of entry 6 carried out using the boron ester **3** takes 120 hours to complete, that is, over 1400 times slower. We propose that the rate enhancement in the

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present system is due to two factors: (i) increased boron Lewis acidity in transition state **A** (Figure 1); and (ii) an ability to operate at higher reaction mixture concentrations (0.1 M vs. 0.005 M).

To define the full scope of new reaction conditions synthesis of a small library of 1,4-alkynylation products was carried out (Table 2).

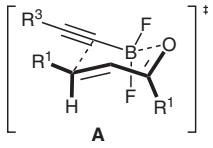


Figure 1

Table 2 Results of the Alkynylation of Acyclic Enones with Potassium Organotrifluoroborates in the Presence of $BF_3{\cdot}OEt_2$[a]

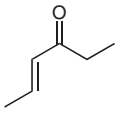
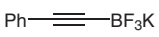
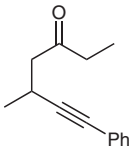
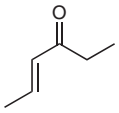
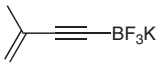
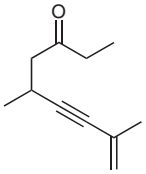
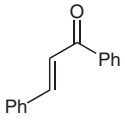
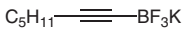
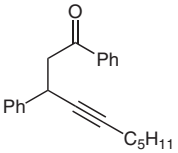
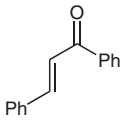
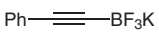
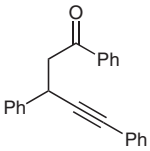
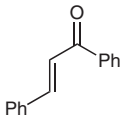
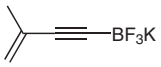
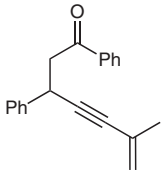
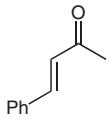
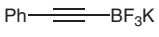
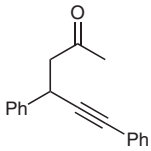
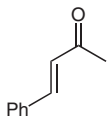
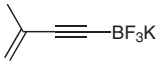
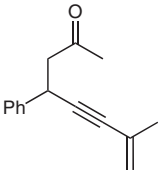
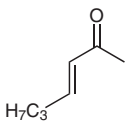
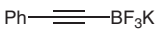
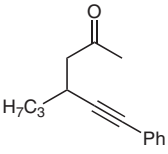
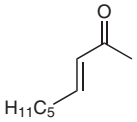
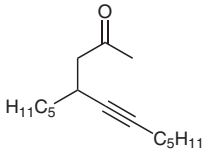
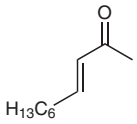
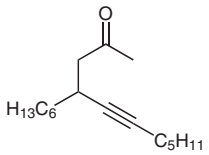
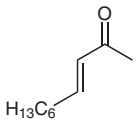
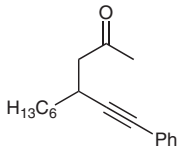
Entry		Enone	Potassium organotrifluoroborate		Time (min)	Product		Yield (%)[b]
1	**2a**		**1b**		30	**4ab**		70
2	**2a**		**1c**		40	**4ac**		57
3	**2b**		**1a**		30	**4ba**		75
4	**2b**		**1b**		25	**4bb**		87
5	**2b**		**1c**		40	**4bc**		77
6	**2c**		**1b**		25	**4cb**		65
7	**2c**		**1c**		30	**4cc**		54
8	**2d**		**1b**		30	**4db**		55

Table 2 Results of the Alkynylation of Acyclic Enones with Potassium Organotrifluoroborates in the Presence of $BF_3{\cdot}OEt_2$[a] (continued)

Entry		Enone	Potassium organotrifluoroborate	Time (min)	Product	Yield (%)[b]
9[c]	**2e**		**1a**	30	**4ea** 	40
10	**2f**		**1a**	150	**4fa** 	57
11	**2f**		**1b**	240	**4fb** 	48

[a] All reactions were performed in accordance with the general procedure (see experimental section).
[b] Isolated yields.
[c] Conversion = 75%.

In all cases high or complete conversions were attained rapidly to afford single-component reaction mixtures from which the products of type **4** were easily isolated. Aryl-substituted enones[15] afforded the highest yields. In the cases of dialkyl-substituted enones (e.g., entry 9) the mass balance was accounted for by noneluting oligomeric byproducts which were easily separated by filtration through silica.[16] Attempts to suppress oligomerisation in the case of entry 9 by changing the reaction concentration in the range 0.2–0.06 M did not change the isolated yield of addition product.

In summary we have found improved experimental conditions for in situ generation of $F_2BC{\equiv}CR$ and its addition to enones. The reaction is technically simple and uses an indefinitely stable acetylene anion equivalent in the form of $K[F_3BC{\equiv}CR]$.

Acknowledgment

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References and Notes

(1) For a recent review, see: Hall, D. G. In *Boronic Acids - Preparation, Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, **2005**, 1–99.
(2) (a) Darses, S.; Michaud, G.; Genet, J.-P. *Tetrahedron Lett.* **1998**, *39*, 5045. (b) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107.
(3) Based on a survey of the SciFinder Scholar (ACS), CAPLUS and MEDLINE databases, September 2008.
(4) (a) Darses, S.; Michaud, G.; Genet, J.-P. *Eur. J. Org. Chem.* **1999**, 1875. (b) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416; while presently relatively few $K[F_3BCCR]$ are commercially available, this situation is changing rapidly.
(5) (a) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729. (b) Ochiai, M.; Miyamoto, K.; Yokota, Y.; Suefuji, T.; Shiro, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 75. (c) Vieira, A. S.; Ferreira, F. P.; Fiorante, F. P.; Guadagnin, F. C.; Stefani, H. A. *Tetrahedron* **2008**, *64*, 3306.
(6) For a recent review on 1,4-alkynylations of enones, see: Shinji, F.; Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Boyall, D.; Carreira, E. M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635.
(7) (a) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054. (b) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682. (c) Chang, S.; Na, Y.; Choi, E.; Kim, S. *Org. Lett.* **2001**, *3*, 2089.
(8) Nishimura, T.; Guo, X. X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576.
(9) Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182.
(10) Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627.
(11) Kwak, Y. S.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385.
(12) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244.
(13) Fujishima, H.; Takada, E.; Hara, S.; Suzuki, A. *Chem. Lett.* **1992**, 658.
(14) The nucleophile described in Equation 1 has been recently used by Tehrani and co-workers for the alkynylation of two imines. However, the corresponding products were obtained only in poor yields (17–31%). See: Stas, S.; Tehrani, K. A.; Laus, G. *Tetrahedron* **2008**, *64*, 3457.
(15) α,β-Unsaturated esters were unreactive under the present conditions.
(16) **Typical Procedure for the Conjugated Alkynylation of Acyclic Enones (Entry 4, Table 2)**
Under an argon atmosphere, $BF_3{\cdot}OEt_2$ (0.45 mmol, 63.9 mg), was added at r.t. to a stirred suspension of potassium organotrifluoroborate **1b** (0.6 mmol, 124.8 mg) in CH_2Cl_2 (3.0 mL). To the resulting mixture was added a solution of enone **2b** (0.3 mmol, 62.6 mg), and the reaction was allowed to react for 25 min at r.t. The reaction was then quenched with brine (2.0 mL) and then diluted with CH_2Cl_2 (6 mL).

Evaporation of the dried ($MgSO_4$) organic solution afforded a crude reaction mixture which was purified by silica gel column chromatography eluting with light petroleum–Et_2O (9:1) to give pure 1,3,5-triphenylpent-4-yn-1-one (**4bb**; 87%) as a white solid, mp 89–90 °C. IR ($CHCl_3$): ν = 3009, 1687, 1601, 1491, 1449, 1351, 1239 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.47 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 6.0 Hz), 3.71 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 8.0 Hz), 4.66–4.73 (m, 1 H), 7.28–7.32 (m, 4 H), 7.38–7.43 (m, 4 H), 7.48–7.52 (m, 2 H), 7.57–7.61 (m, 3 H), 7.98–8.04 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.8, 47.3, 83.4, 90.8, 123.4, 127.1, 127.6, 127.9, 128.2, 128.7, 128.8, 131.7, 133.3, 136.9, 141.3, 197.15. ESI-MS (+): *m/z* = 333.12 $[M + Na]^+$.

5-Methyl-7-phenylhept-6-yn-3-one (4ab, Entry 1, Table 2)

Yield 70%. Yellow liquid. IR ($CHCl_3$): ν = 3011, 2979, 2937, 1713, 1599, 1489, 1459, 1410, 1359, 1239, 1116 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, 3 H, *J* = 7.2 Hz), 1.30 (d, 3 H, *J* = 7.2 Hz), 2.48–2.55 (m, 2 H), 2.58 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 7.2 Hz), 2.76 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 6.8 Hz), 3.19–3.26 (m, 1 H), 7.27–7.32 (m, 3 H), 7.37–7.41 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.7, 21.0, 22.4, 36.7, 49.1, 80.9, 93.2, 123.6, 127.4, 128.2, 131.6, 209.4. ESI-MS (+): *m/z* = 223.11 $[M + Na]^+$.

5,8-Dimethylnon-8-en-6-yn-3-one (4ac, Entry 2, Table 2)

Yield 57%; pale yellow liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, 3 H, *J* = 7.2 Hz), 1.22 (d, 3 H, *J* = 6.8 Hz), 1.89 (s, 3 H), 2.41–2.53 (m, 3 H), 2.69 (dd, 1 H, J_1 = 16.0 Hz, J_2 = 7.2 Hz), 3.08–3.14 (m, 1 H), 5.15–5.20 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.7, 20.9, 22.3, 23.8, 36.6, 49.1, 82.1, 92.2, 120.8, 127.0, 209.4.

1,3-Diphenyldec-4-yn-1-one (4ba, Entry 3, Table 2)

Yield 75%; colorless oil. IR ($CHCl_3$): ν = 3008, 2933, 2861, 1686, 1600, 1494, 1449, 1351, 1255, 1181, 1024, 977 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 6.0 Hz), 1.22–1.39 (m, 4 H), 1.41–1.50 (m, 2 H), 2.19 (dt, 2 H, J_1 = 7.2 Hz, J_2 = 2.4 Hz), 3.30 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 7.2 Hz), 3.57 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 8.0 Hz), 4.40–4.46 (m, 1 H), 7.23–7.30 (m, 1 H), 7.32–7.38 (m, 2 H), 7.43–7.51 (m, 4 H), 7.54–7.61 (m, 1 H), 7.95–8.00 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 18.8, 22.2, 28.6, 31.1, 33.4, 47.7, 81.0, 83.7, 126.9, 127.5, 128.2, 128.3, 128.6, 133.1, 137.0, 142.0, 197.6. ESI-MS (+): *m/z* = 327.17 $[M + Na]^+$.

6-Methyl-1,3-diphenylhept-6-en-4-yn-1-one (4bc, Entry 5, Table 2)

Yield 77%; solid; mp 44–46 °C. IR ($CHCl_3$): ν = 3009, 1687, 1600, 1494, 1450, 1351, 1255, 1023, 976, 900 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.86 (m, 3 H), 3.38 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 6.4 Hz), 3.61 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 7.6 Hz), 4.57 (dd, 1 H, J_1 = 7.6 Hz, J_2 = 6.4 Hz), 5.17–5.23 (m, 2 H), 7.24–7.30 (m, 1 H), 7.33–7.39 (m, 2 H), 7.44–7.51 (m, 4 H), 7.57–7.62 (m, 1 H), 7.94–8.01 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 33.6, 47.3, 84.6, 89.7, 121.2, 126.9, 127.1, 127.6, 128.2, 128.6, 128.7, 133.2, 136.9, 141.3, 197.2. ESI-MS (+): *m/z* = 297.12 $[M + Na]^+$.

4,6-Diphenylhex-5-yn-2-one (4cb, Entry 6, Table 2)

Yield 65%; pale yellow liquid. IR ($CHCl_3$): ν = 3011, 1717, 1601, 1491, 1453, 1405, 1360, 1240, 1160, 1070, 1027 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3 H), 2.93 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 6.0 Hz), 3.11 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 8.0 Hz), 4.44–4.48 (m, 1 H), 7.22–7.50 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7, 33.6, 51.9, 83.3, 90.4, 123.3, 127.2, 127.5, 128.0, 128.3, 128.8, 131.7, 141.0, 205.8. ESI-MS (+): *m/z* = 271.10 $[M + Na]^+$.

7-Methyl-4-phenyloct-7-en-5-yn-2-one (4cc, Entry 7, Table 2)

Yield 54%; pale yellow liquid. IR ($CHCl_3$): ν = 3011, 1715, 1602, 1494, 1453, 1359, 1240, 1160, 900 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.91 (s, 3 H), 2.18 (s, 3 H), 2.85 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 6.4 Hz), 3.01 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 8.0 Hz), 4.33 (dd, 1 H, J_1 = 8.0 Hz, J_2 = 6.4 Hz), 5.21–5.28 (m, 2 H), 7.25–7.43 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 30.7, 33.5, 52.0, 84.5, 89.3, 121.3, 126.8, 127.1, 127.4, 128.7, 141.0, 205.8. ESI-MS (+): *m/z* = 235.11 $[M + Na]^+$.

4-(Phenylethynyl)heptan-2-one (4db, Entry 8, Table 2)

Yield 55%; light yellow liquid.IR ($CHCl_3$): ν = 3010, 2961, 2933, 2874, 1713, 1600, 1490, 1442, 1362, 1239, 1163, 909 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, 3 H, *J* = 6.0 Hz), 1.45–1.62 (m, 4 H), 2.25 (s, 3 H), 2.62 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 6.4 Hz), 2.78 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 7.6 Hz), 3.09–3.15 (m, 1 H), 7.28–7.31 (m, 3 H), 7.39–7.42 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 20.5, 27.6, 30.6, 37.0, 49.0, 81.9, 92.0, 123.6, 127.7, 128.2, 131.6, 207.0. ESI-MS (+): *m/z* = 237.12 $[M + Na]^+$.

4-Pentylundec-5-yn-2-one (4ea, Entry 9, Table 2)

Yield 40% (conversion 75%); colorless liquid. IR ($CHCl_3$): ν = 3007, 2958, 2932, 2860, 1713, 1602, 1466, 1361, 1239, 1163 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.82–0.93 (m, 6 H), 1.18–1.55 (m, 14 H), 2.15 (dt, 2 H, J_1 = 6.8 Hz, J_2 = 2.4 Hz), 2.20 (s, 3 H), 2.48 (dd, 1 H, J_1 = 16.0 Hz, J_2 = 6.0 Hz), 2.61 (dd, 1 H, J_1 = 16.0 Hz, J_2 = 8.0 Hz), 2.78–2.90 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (2 C), 18.7, 22.2, 22.6, 26.9, 27.5, 28.7, 30.6, 31.0, 31.5, 35.2, 49.5, 81.9, 82.1, 207.4.

4-Hexylundec-5-yn-2-one (4fa, Entry 10, Table 2)

Yield 57%; pale yellow liquid. IR ($CHCl_3$): ν = 3010, 2958, 2931, 2859, 1713, 1602, 1466, 1361, 1239, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.81–0.92 (m, 6 H), 1.21–1.52 (m, 16 H), 2.15 (dt, 2 H, J_1 = 7.2 Hz, J_2 = 2.0 Hz), 2.20 (s, 3 H), 2.48 (dd, 1 H, J_1 = 15.6 Hz, J_2 = 6.4 Hz), 2.61 (dd, 1 H, J_1 = 15.6 Hz, J_2 = 8.0 Hz), 2.78–2.87 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.1, 18.7, 22.2, 22.6, 27.2, 27.5, 28.8, 29.0, 30.6, 31.0, 31.8, 35.2, 49.5, 81.9, 82.1, 207.5. ESI-MS (+): *m/z* = 273.21 $[M + Na]^+$.

4-(Phenylethynyl)decan-2-one (4fb, Entry 11, Table 2)

Yield 48%; light yellow liquid. IR ($CHCl_3$): 3011, 2930, 2858, 1714, 1601, 1490, 1466, 1362, 1161, 913 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.94 (m, 3 H), 1.25–1.41 (m, 6 H), 1.43–1.62 (m, 4 H), 2.20 (s, 3 H), 2.62 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 6.4 Hz), 2.78 (dd, 1 H, J_1 = 16.4 Hz, J_2 = 7.6 Hz), 3.06–3.13 (m, 1 H), 7.28–7.33 (m, 3 H), 7.39–7.43 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 27.3, 27.9, 29.0, 30.6, 31.8, 34.9, 49.0, 81.9, 92.1, 123.7, 127.7, 128.2, 131.6, 206.9. ESI-MS (+): *m/z* = 279.17 $[M + Na]^+$.