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Synthesis of α,β-Unsaturated α′-Haloketones through the Chemoselective Addition of Halomethyllithiums to Weinreb Amides

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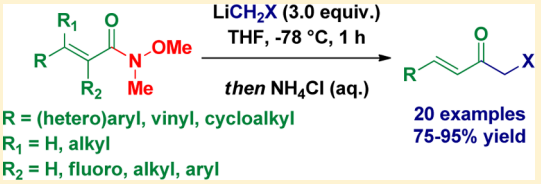
Supporting Information

ABSTRACT: A straightforward synthesis of variously functionalized α,β-unsaturated α′-haloketones has been achieved through the chemoselective addition of halomethyllithium carbenoids to Weinreb amides at −78 °C. A comparative study employing the corresponding esters under the same reaction conditions pointed out that the instability of the tetrahedral intermediate formed from the latter is responsible for the observed formation of carbinols instead of the desired haloketones.



α-Haloketones are invaluable versatile intermediates in organic synthesis as a consequence of the high reactivity displayed toward nucleophiles by both the electrophilic methylene and the carbonyl carbon atom.[1] The conjugation of the carbonyl group with a vinyl fragment introduces a third electrophilic site within this short carbon array; thus, the complex α,β-unsaturated α′-haloketone additionally becomes a Michael acceptor.[2] Indeed, in organic synthesis this motif has been employed in a plethora of transformations ranging from the synthesis of (bioactive) heterocycles[2,3] and natural products analogues (e.g., coruscanones)[4] to the preparation of silyloxy-1,3-dien-7-ynes.[5] Some known synthetic routes to α,β-unsaturated α′-haloketones are displayed in Scheme 1. A common route is the halogenation protocol (via *a*), where an α,β-unsaturated-α′-methylketone is transformed into a kinetically unstable (silyl)enol ether, which is subsequently trapped with a halonium source.[2a,3b] Alternatively, Wittig-type condensation between an aldehyde and a phosphorane derived from 1,3-dichloroacetone has been used (via *b*).[3a,6] Moreover, an approach employing a Cu(I)-mediated 1,2-H shift of copper chlorocarbenoids, generated from noneasily accessible trichloromethyl carbinols (via *c*) has been employed.[7] Unfortunately, these strategies suffer from a series of drawbacks ranging from chemo- and regioselective issues (i.e., overhalogenations, sensitivity of the conjugated C−C double bond to electrophilic haloniums) to low efficiency and lack of generality, for instance, in the case of Wittig-type reactions with EDG-substituted aldehydes or with Cu(I)-mediated processes.

Alternatively, the homologation of an α,β-unsaturated aldehyde to the corresponding halohydrin through the addition of a carbenoid followed by an oxidation step (Scheme 1, bottom, via *d*) has proven to be a moderately efficient two-pot procedure to access the target compounds.[8] In this sense, we argued that a homologation protocol of an adequate carboxylic acid derivative would satisfy the demand of an economic and direct access to the desired haloketones. To the best of our knowledge, the only example for the transformation of an α,β-unsaturated ester into an α,β-unsaturated α′-haloketone has been reported by Kowalski through a complex sequential bromomethylation reaction with $LiCHBr_2$ and *n*-BuLi at −90 °C (Scheme 1, bottom, via *e*).[9] Thus, we considered the use of simpler monohalomethyllithium carbenoids ($LiCH_2X$)[10] appropriate for the direct functionalization of a carboxylic surrogate.

Therefore, herein we present a chemoselective protocol to achieve α,β-unsaturated α′-haloketones via the lithium carbenoids homologation of suitable Weinreb amides (Scheme 1, bottom central). We also highlight why esters are not optimal substrates for such transformations at −78 °C because of double addition of the carbenoids, thus giving carbinols instead of the desired haloketones. To this end, we initially investigated the reaction of commercially available ethyl cinnamate (**1a**) with in situ formed chloromethyllithium (Table 1). By performing the reaction at −78 °C with an excess of $LiCH_2Cl$, only carbinol **2** resulting from double addition of the carbenoid to the ester could be isolated in 79% yield (entry 1). Analogously, also in the case of stoichiometric addition, carbinol **2** was the only reaction product (entry 2). On the other hand, when the reaction mixture was kept at −115 °C (Villieras conditions[11]) the desired chloroketone **3a** was the major reaction product (51%) along with 15% of the carbinol 2 (entry 3). An analogous outcome was observed when other cinnamate esters **1b−d** (methyl, benzyl, isopropyl) were used instead of **1a** (entries 4−9). These preliminary results indicated that esters are prone to undergo a double addition of the carbenoid at −78 °C, because of the instability of the tetrahedral intermediate at that temperature (vide infra). Thus, we turned our attention to the corresponding Weinreb amide **1e** because of the well-known stability of the tetrahedral intermediate formed upon addition of organometallic species to this carboxylic derivative.[12] Pleasingly, the addition of $LiCH_2Cl$ to such a substrate (**1e**) provided exclusively the desired chloroketone **3a** in excellent yield (88%, entry 10) without any trace of the corresponding carbinol. By lowering temperature to

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Scheme 1. Context of Presented Work

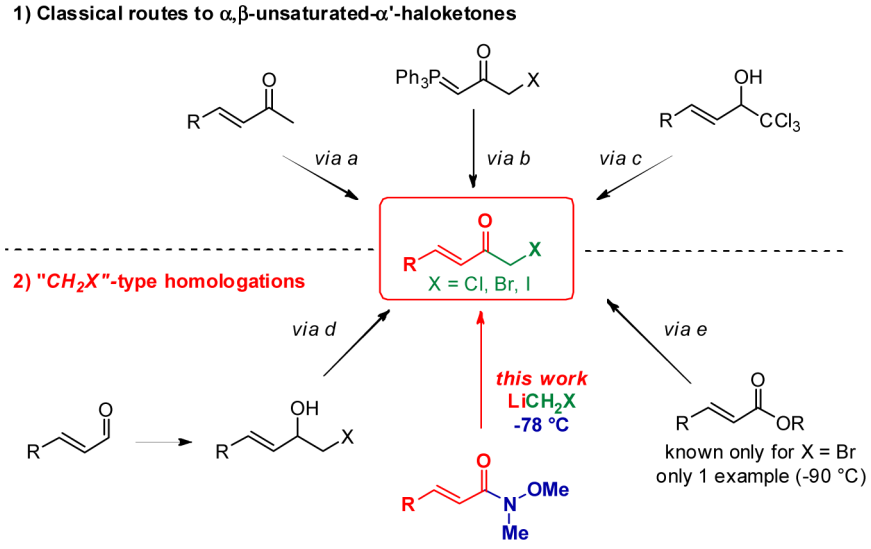
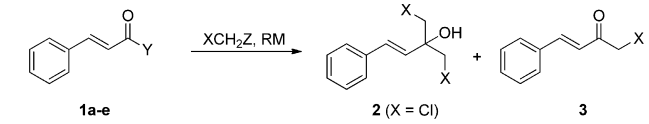


Table 1. Halomethylation of Esters and Weinreb Amides



entry	substrate	MCH_2X (equiv)	temp (°C)	yield of **2**[b] (%)	yield of **3**[b] (%)
1	**1a**	$LiCH_2Cl$ (1.8)	−78	79	
2	**1a**	$LiCH_2Cl$ (1.0)	−78	48	
3	**1a**	$LiCH_2Cl$ (1.8)	−115	15	51
4	**1b**	$LiCH_2Cl$ (1.8)	−78	80	
5	**1c**	$LiCH_2Cl$ (1.8)	−78	73	
6	**1d**	$LiCH_2Cl$ (1.8)	−78	52	
7	**1d**	$LiCH_2Cl$ (1.8)	−115	11	33
8	**1e**	$LiCH_2Cl$ (1.8)	−115	18	47
9	**1a**	$LiCH_2Cl$ (1.8)	−115	21	56
10	**1e**	$LiCH_2Cl$ (1.8)	−78		88
11	**1e**	$LiCH_2Cl$ (1.8)	−90		96
12	**1e**	$LiCH_2Cl$ (3.0)[c]	−78		94
13	**1e**	$LiCH_2Cl$ (3.0)[c]	−60		63
14	**1e**	$Mg(CH_2Cl)_2$ (3.0)[c]	−78		
15	**1e**	$LiCH_2Br$ (3.0)[c]	−78		89[d]
16	**1e**	$LiCH_2I$ (3.0)[c]	−78		92[e]

[a]Unless otherwise indicated, MCH_2X were generated from ICH_2Cl and MeLi-LiBr in equimolar amounts. [b]Isolated yields. [c]Generated from 4.0 equiv of dihalomethane and 3.0 equiv of MeLi−LiBr or *i*-PrMgCl−LiCl (entry 14). [d]**3b**. [e]**3c**.

−90 °C, a further increase in the yield of **3a** was noticed (96%, entry 11), thus confirming the influence of this parameter on the stability of the carbenoid. A further improvement was the use of an excess of iodochloromethane (4.0 equiv) and MeLi−LiBr (3.0 equiv) which overcame this deleterious effect of temperature, and by running the reaction at −78 °C, chloroketone **3a** was obtained in an excellent 94% yield without needing to perform any chromatographic purification (entry 12). Attempts to increase the temperature up to −60 °C significantly decreased the yield (entry 13) and, remarkably, the use of a more stable but less nucleophilic magnesium carbenoid[13] did not provide any reaction product (entry 14). Analogously, the established reaction conditions allowed the efficient preparation of the corresponding α-bromo and α-iodoketones **3b** and **3c**, respectively, starting from CH_2Br_2 and CH_2I_2 as the carbenoid precursors (entries 15 and 16). Remarkably, under the reaction conditions applied the C−C double bond was not affected (i.e., cyclopropanation which is known to be accomplished by using Li carbenoids[14]), as reported for analogous substrates under Corey−Chaykovsky conditions.[15]

Once the optimal conditions had been established, we next examined the scope of the reaction. Various substituted cinnamoyl-type Weinreb amides afforded the corresponding α-haloketones of type **5** in high yields (Table 2). Some points merit mention: (a) a strong electron-releasing group (i.e., OMe) in activating position on the aromatic ring determines a considerable increase of the reaction time; however efficiency was not altered (to ensure non-degradation of the carbenoids, ICH_2Cl, and MeLi−LiBr were added portionwise); (b) substituents susceptible to reduction, such as halogens (**5e**, **5f**, **5h**) or even a nitro group (**5g**) are well tolerated; (c) an extended cinnamoyl system (**5k**), substituents across the olefinic double bond (**5o**−**p**), and also switching to the accordant alkyne system (**5i**), do not affect the reaction. Importantly, α-chloro-α′-fluoro ketone **5n** could be obtained in higher efficiency compared to previous procedures involving sulfur ylides.[16] Interestingly, the protocol is also applicable to naphtalenic (**5j**) and heteroaromatic substrates (**5l**, **m**): in the latter cases, no concomitant lithiations at the ortho positions to the heteroatoms are observed at all.

Remarkably, the procedure could also be applied to the synthesis of α,β-unsaturated ketones presenting cycloalkyl type substituents on the β-carbon such as a cyclohexyl (**5q**) or a cyclopropyl group (**5r**). However, in this latter case an inseparable mixture of *E*/*Z* isomers was obtained.

To rationalize the observed chemoselectivity, we considered the exceptional stability at −78 °C of the intermediate **II** furnished by the *N*-methoxy group of the Weinreb amide **I**, which evidently does not allow a second addition of $LiCH_2X$ (Scheme 2, path *a*). As a consequence of this high stability of **II**, the desired α-haloketone **III** is formed only after acidic

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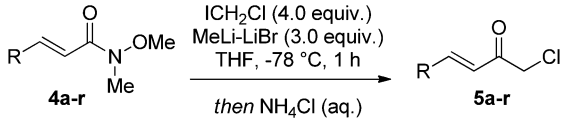
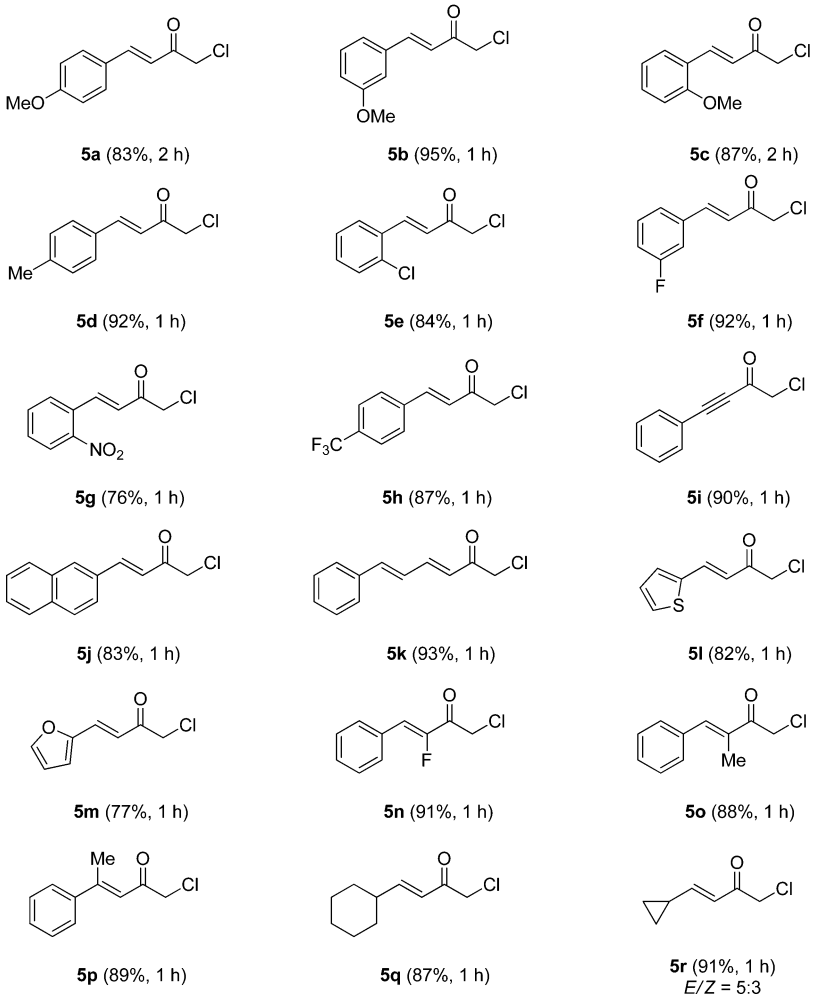
Table 2. Chloromethylation of Variously Functionalized α,β-Unsaturated Weinreb Amides[a]



4a-r **5a-r**



5a (83%, 2 h) **5b** (95%, 1 h) **5c** (87%, 2 h)

5d (92%, 1 h) **5e** (84%, 1 h) **5f** (92%, 1 h)

5g (76%, 1 h) **5h** (87%, 1 h) **5i** (90%, 1 h)

5j (83%, 1 h) **5k** (93%, 1 h) **5l** (82%, 1 h)

5m (77%, 1 h) **5n** (91%, 1 h) **5o** (88%, 1 h)

5p (89%, 1 h) **5q** (87%, 1 h) **5r** (91%, 1 h) *E*/*Z* = 5:3

[a]Yields are referred to isolated products; otherwise indicated *E*/*Z* > 99:1 (^{1}H NMR).

hydrolysis of the tetrahedral intermediate **II**. By contrast, the addition of the carbenoid to an ester **IV** results in the formation of a tetrahedral intermediate **V** (not stable at −78 °C), which is in equilibrium with the transient α-haloketone **III**, the latter more susceptible to a second attack of the carbenoid (compared to the starting ester), and thus furnishing the carbinol **VI** (Scheme 2, path *b*). This explanation is in agreement with the finding that by running the halomethylation of esters at −115 °C the major product is the α-haloketone. Thus, it is conceivable that the tetrahedral intermediate **V** formed through monoaddition to an ester, is only stable (thus, hindering the second addition) at that very low temperature but not at −78 °C.

To conclude, we have disclosed a direct and straightforward access to synthetically useful α,β-unsaturated α′-haloketones through the addition of halomethyllithium carbenoids to Weinreb amides. Remarkably, the use of these starting materials allows the chemoselective addition of only one equivalent of the carbenoids without any trace of side products such as carbinol or 1,4-addition products neither cyclopropanes generated through Simmons−Smith-type processes. Interestingly, the observed experimental results fit with the theoretical explanation based on the temperature-dependent stability of the tetrahedral intermediate formed upon addition of the carbenoids to esters, which at −78 °C undergo double addition to provide carbinols instead of the desired α-haloketones.

EXPERIMENTAL SECTION

General Experimental Methods. All ^{1}H NMR and ^{13}C NMR spectra were recorded on spectrometers operating at 200, 300, 400, or 500 MHz and at 50, 75, 100, or 125 MHz. The ^{15}N and ^{19}F NMR experiments were conducted on a 400 MHz spectrometer (40 and 377 MHz, respectively). The ^{15}N NMR spectra were referenced against external nitromethane; for the ^{19}F NMR spectra absolute referencing via the Ξ ratio was used. All melting points are uncorrected. Column chromatography purifications were conducted on silica gel 60 (40−63 μm). TLC was carried out on aluminum sheets precoated with silica gel 60F254; the spots were visualized under UV light (λ = 254 nm) and/or $KMnO_4$ (aq) was used as revealing system. All nonaqueous reactions were run under an inert atmosphere (argon) with flame-dried glassware using standard techniques. THF was distilled over Na using benzophenone as an indicator. Cynamic esters, chloroiodo-

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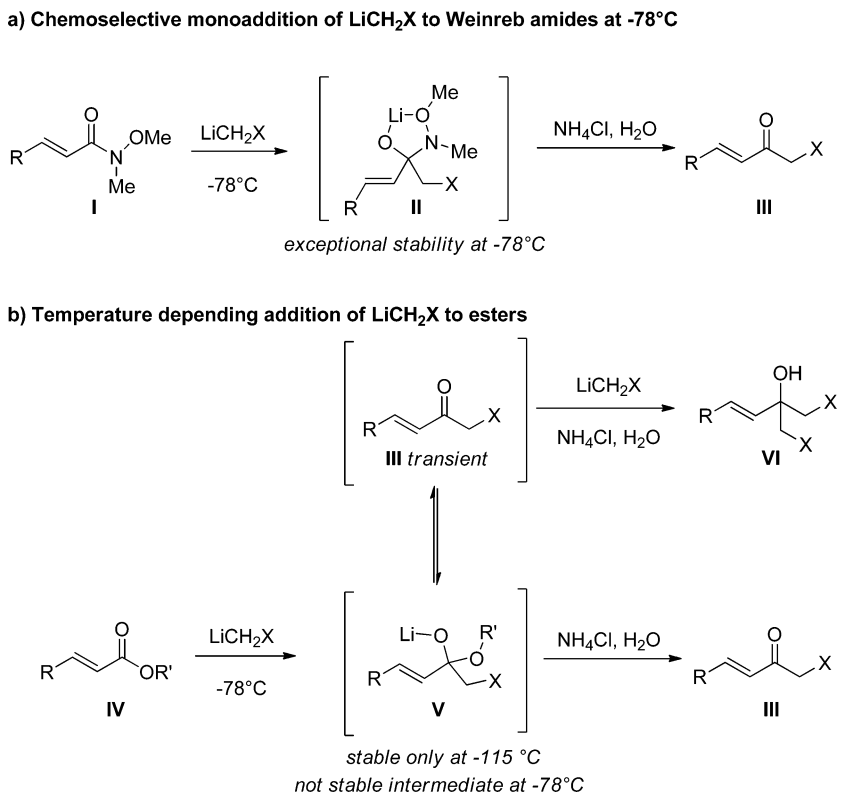
Scheme 2. Temperature-Based Mechanistic Explanation of the Different Behavior toward Halomethylithium Reagents of Weinreb Amides (Path a) and Esters (Path b)



methane, dibromomethane, diiodomethane, and MeLi–LiBr complex (1.5 M in diethyl ether) are commercially available. Weinreb amides **1e**,[17] **4a**,[17] **4b**,[18] **4c**,[19] **4d**,[20] **4e**,[21] **4f**,[18] **4g**,[17] **4h**,[22] **4i**,[23] **4j**,[24] **4k**,[17] **4l**,[21] **4m**,[25] **4n**,[26] **4o**,[27] **4p**,[27] and **4r**[28] are known compounds prepared as previously reported. However, copies of ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information.

Preparation of (2*E*)-3-Cyclohexyl-*N*-methoxy-*N*-methylacrylamide (4q). To a dry THF (9 mL) solution of (*E*)-methyl 3-cyclohexylacrylate[29] (575 mg, 3.42 mmol, 1 equiv) cooled at −10 °C was added *N*,*O*-dimethylhydroxylamine hydrochloride (500 mg, 5,13 mmol, 1.5 equiv), and after 2 min, *i*-PrMgCl (2 M THF solution) (1.06 g, 5.13 mL, 10.26 mmol, 3.0 equiv) was added dropwise during 5 min. The solution was allowed to reach rt during 3 h and then was quenched with satd NH_4Cl. The organic phase was extracted with Et_2O (3 × 15 mL), dried, and filtered. After removal of the solvent in vacuo, Weinreb amide **4q** was obtained in 94% yield (634 mg) as a light yellow oil. ^{1}H NMR (300 MHz $CDCl_3$,) δ: 6.93 (dd, J = 15.6, J = 7.0 Hz, 1H), 6.34 (dd, J = 15.6, J = 1.4 Hz, 1H), 3.70 (s, 3H), 3.23 (s, 3H), 2.22–2.09 (m, 1H), 1.79–1.65 (m, 5H), 1.29–1.14 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.1, 152.6, 115.9, 61.3, 40.4, 32.1, 31.7, 31.3, 25.6, 25.4, 25.4. IR (NaCl, ν_{max}, cm^{-1}): 2964, 1685, 1620, 1419, 1390, 1297, 1171, 1012, 706. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.09; H, 9.59; N, 7.23.

General Procedure for the Halomethylation of Weinreb Amides with Li Carbenoids. To a solution of Weinreb amide (1.0 equiv) in THF cooled at −78 °C was added the dihalomethane (4.0 equiv), and subsequently, MeLi–LiBr complex (1.5 M solution in diethyl ether, 3.0 equiv) was added dropwise during 5 min. The resulting solution was stirred at that temperature for 1–2 h (see text), and then NH_4Cl saturated aqueous solution was added at −78 °C. After removal of the cooling bath, the mixture was allowed to reach rt and washed with Et_2O and brine. The two resulting phases were separated, and the organic phase was dried over anhydrous $MgSO_4$, filtered, and removed in vacuo to give the desired haloketones in a pure form without needing to perform further purifications.

(3*E*)-1-Chloro-4-phenyl-3-buten-2-one (3a).[7] Following the general procedure, starting from (2*E*)-*N*-methoxy-*N*-methyl-3-phenylacrylamide (**1e**) (0.27 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **3a** was obtained in 95% yield (0.23 g) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, J = 16.1 Hz, 1H, PhC*H*═), 7.59 (m, 2H, Ph H-2, H-6), 7.43 (m, 1H, Ph H-4), 7.42 (m, 2H, Ph H), 6.98 (d, 1H, J = 16.1 Hz), 4.30 (s, 2H, CH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.1 (C═O), 145.2 (Ph-CH═), 133.9 (Ph C-1), 131.1 (Ph C-4), 129.0 (Ph C-3), 129.0 (Ph C-5), 128.6 (Ph C-2), 128.6 (Ph C-6), 121.6 (═CHCO), 47.4 (CH_2Cl). IR (NaCl, ν_{max}, cm^{-1}): 3080, 1682, 1594, 1511, 1255, 904. Mp: 56 °C (lit.[7] mp 55 °C). Anal. Calcd for $C_{10}H_9ClO$: C, 66.49; H, 5.02. Found: C, 66.35; H, 4.89.

(3*E*)-1-Bromo-4-phenyl-3-buten-2-one (3b).[30] Following the general procedure, starting from (2*E*)-*N*-methoxy-*N*-methyl-3-phenylacrylamide (**1e**) (0.27 g, 1.43 mmol), CH_2Br_2 (990 mg, 0.40 mL, 5.7 mmol), and MeLi-LiBr (2.85 mL, 4.28 mmol) in THF, α-bromoketone **3b** was obtained in 89% yield (0.29 g) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, J = 16.1 Hz, 1H, ArC*H*═), 7.59 (m, 2H Ph H-2, 6), 7.42 (m, 1H; Ph H-4), 7.41 (m, 2H, Ph H-3, Ph), 6.95 (d, J = 16.1 Hz, ═CHCO), 4.09 (s, 2H, CH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.0 (C═O), 145.4 (ArCH═), 133.9 (Ph C-1), 131.1 (Ph C-4), 129.0 (Ph C-3), 129.0 (Ph C-5), 128.6 (Ph C-4), 128.6 (Ph C-6), 122.2 (═CHCO), 33.1 (CH_2Cl). IR (NaCl, ν_{max}, cm^{-1}): 1693, 1611, 1498, 1450, 1390, 1069, 990, 890, 749. Mp: 45 °C (lit.[30] mp 44–45 °C). Anal. Calcd for $C_{10}H_9BrO$: C, 53.36; H, 4.03. Found: C, 53.48; H, 4.17.

(3*E*)-1-Iodo-4-phenyl-3-buten-2-one (3c):[31] Following the general procedure, starting from (2*E*)-*N*-methoxy-*N*-methyl-3-phenylacrylamide (**1e**) (0.27 g, 1.43 mmol), CH_2I_2 (1.53 g, 0.46 mL, 5.7 mmol), and MeLi-LiBr (2.85 mL, 4.28 mmol) in THF, α-iodoketone **3c** was obtained in 92% yield (0.36 g) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 16.4 Hz, 1H), 7.59–7.57 (m, 2H), 7.43–7.41 (m, 3H), 6.89 (d, J = 16.4 Hz, 1H), 4.02 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.1, 144.8, 133.8, 130.9, 128.9, 128.4, 122.2,

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5.0. IR (NaCl, ν_{max}, cm^{-1}): 1640, 1573, 1438, 1270, 1072, 990, 874, 803, 764, 704. Mp: 57 °C (lit.[31] mp 56.5−58.5 °C). Anal. Calcd for $C_{10}H_9IO$: C, 44.14; H, 3.33. Found: C, 44.32; H, 3.50.

(3*E*)-1-Chloro-2-(chloromethyl)-4-phenyl-3-buten-2-ol (2).[32] To a solution of ethyl cinnamate (176 mg, 1.0 mmol) in THF (3 mL) cooled at −78 °C was added chloroiodomethane (317 mg, 1.8 mmol, 0.13 mL) and, after 2 min, MeLi−LiBr ethereal solution (1.5 M, 1.8 mmol, 1.20 mL). The resulting solution was stirred at that temperature for 1 h, and then NH_4Cl saturated aqueous solution was added at −78 °C. After removal of the cooling bath the mixture was allowed to reach rt and washed with Et_2O and brine. The two resulting phases were separated, and the organic phase was dried over anhydrous $MgSO_4$, filtered, and removed in vacuo to give **2** after flash chromatography on silica gel (hexanes−AcOEt, 9:1) as a light yellow oil (182 mg, 79% yield). ^1H NMR (500 MHz, $CDCl_3$) δ: 7.35−7.17 (m, 5H), 6.83 (d, J = 15.9 Hz, 1H), 6.24 (d, J = 15.9 Hz, 1H), 3.71 (d, J = 9.9 Hz, 1H), 3.24 (d, J = 9.9 Hz, 1H), 2.59 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.8, 132.5, 128.6, 128.2, 127.1, 126.7, 74.2, 49.3 (×2). IR (NaCl, ν_{max}, cm^{-1}): 3502, 2993, 712, 961, 903. Anal. Calcd for $C_{11}H_{12}Cl_2O$: C, 57.16; H, 5.23. Found: C, 57.33; H, 5.38.

(3*E*)-1-Chloro-4-(4-methoxyphenyl)-3-buten-2-one[3a] **(5a).** Following the general procedure, starting from (*E*)-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methylacrylamide (**4a**) (0.32 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi-LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5a** was obtained in 83% yield (0.25 g) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, J = 15.9 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 16.0 Hz, 1H), 4.28 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.4, 162.3, 145.2, 130.7, 130.7, 126.8, 119.4, 114.7, 144.7, 55.6, 47.6. IR (NaCl, ν_{max}, cm^{-1}): 1681, 1594, 1571, 1511, 1302, 1255, 1172, 905, 727. Mp: 98 °C (lit.[3a] mp 98 °C). Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.61; H, 5.15.

(3*E*)-1-Chloro-4-(3-methoxyphenyl)-3-buten-2-one (5b). Following the general procedure, starting from (*E*)-*N*-methoxy-3-(3-methoxyphenyl)-*N*-methylacrylamide (**4b**) (0.32 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi-LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5b** was obtained in 95% yield (0.29 g) as a thick oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.67 (d, J = 16.0 Hz, 1H), 7.33 (m, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 6.95 (d, J = 16.0 Hz, 1H), 4.36 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 191.2, 158.8, 145.1, 135.2, 130.0, 121.9, 121.3, 116.9, 113.4, 55.3, 47.4. IR (NaCl, ν_{max}, cm^{-1}): 1684, 1608, 1579, 1246, 905, 727. Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.85; H, 4.99.

(3*E*)-1-Chloro-4-(2-methoxyphenyl)-3-buten-2-one (5c). Following the general procedure, starting from (*E*)-*N*-methoxy-3-(2-methoxyphenyl)-*N*-methylacrylamide (**4c**) (0.32 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi-LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5c** was obtained in 87% yield (0.26 g) as a light yellow thick oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, J = 16.3 Hz, 1H, ArC*H*═), 7.56 (m, 1H, Ph H-6), 7.39 (m, 1H, Ph H-4), 7.02 (d, J = 16.3 Hz, ═CHCO), 6.98 (m, 1H, Ph H-5), 6.93 (m, 1H, Ph H-3), 4.33 (s, 2H, CH_2Cl), 3.90 (s, 3H, $ArOCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.6 (C═O), 158.8 (Ph C-2), 140.4 (ArCH═), 132.4 (Ph C-4), 129.1 (Ph C-6), 122.8 (Ph C-6), 122.4 (═*C*HCO), 120.8 (Ph C-5), 111.2 (Ph C-3), 55.5 ($ArOCH_3$), 47.3 (CH_2Cl). IR (NaCl, ν_{max}, cm^{-1}): 3075, 1682, 1613, 1583, 1242, 902, 708. Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.72; H, 5.26. Found: C, 62.64; H, 5.13.

(3*E*)-1-Chloro-4-(4-methylphenyl)-3-buten-2-one[6b] **(5d).** Following the general procedure, starting from (2*E*)-*N*-methoxy-*N*-methyl-3-(4-methylphenyl)acrylamide (**4d**) (0.29 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5d** was obtained in 92% yield (0.26 g) as a yellowish solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J = 16.1 Hz, 1H, ArC*H*═), 7.48 (m, 2H, Ph H-2,6), 7.22 (m, 2H, Ph H-3,5), 6.93 (d, J = 16.1 Hz, 1H, ═CHCO), 4.29 (s, 2H, CH_2Cl), 2.39 (s, 3H, $ArCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.3 (C═O), 145.3 (ArCH═), 141.8 (Ph C-4), 131.2 (Ph C-1), 129.8 (Ph C-3), 129.8 (Ph C-5), 128.7 (Ph C-2), 128.7 (Ph C-6), 120.6 (═CHCO), 47.4 (CH_2Cl), 21.6 ($ArCH_3$). IR (NaCl, ν_{max}, cm^{-1}): 1690, 1662, 1618, 1601, 801, 782. Mp: 100 °C (lit.[6b] mp 99−101 °C). Anal. Calcd for $C_{11}H_{11}ClO$: C, 67.87; H, 5.70. Found: C, 67.74; H, 5.84.

(3*E*)-1-Chloro-4-(2-chlorophenyl)-3-buten-2-one (5e). Following the general procedure, starting from (2*E*)-3-(2-chlorophenyl-*N*-methoxy-*N*-methylacrylamide (**4e**) (0.32 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5e** was obtained in 84% yield (0.26 g) as an orange, thick oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, J = 16.1 Hz, 1H, ArC*H*═), 7.68 (1H, dd, J = 7.6 Hz, 1.9 Hz, Ph H-6), 7.44 (m, 1H, Ph H-3), 7.35 (m, 1H, Ph H-4), 7.30 (m, 1H, Ph H-5), 6.95 (d, J = 16.1 Hz, ═CHCO), 4.33 (s, 2H, CH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.1 (C═O), 140.9 (ArCH═), 135.7 (Ph C-2), 132.2 (Ph C-1), 131.8 (Ph C-4), 130.4 (Ph C-3), 127.7 (Ph C-6), 127.2 (Ph C-5), 124.2 (═*C*HCO), 47.2 ($^1J(CH_2)$ = 148.5 Hz, $^3J(CH_2$, ═CH) = 1.2 Hz, CH_2Cl). IR (NaCl, ν_{max}, cm^{-1}): 1684, 1605, 1594, 1362, 805. Anal. Calcd for $C_{10}H_8Cl_2O$: C, 55.84; H, 3.75. Found: C, 55.91; H, 3.61.

(3*E*)-1-Chloro-4-(3-fluorophenyl)-3-buten-2-one (5f). Following the general procedure, starting from (2*E*)-3-(3-fluorophenyl)-*N*-methoxy-*N*-methylmethylacrylamide (**4f**) (0.30 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi-LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5f** was obtained in 92% yield (0.26 g) as a yellow thick oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, J = 16.1 Hz, 1H, Ph−C*H*═), 7.38 (m, 1H, Ph H-5), 7.36 (m, 1H, Ph H-6), 7.28 (m, 1H, Ph H-2), 7.13 (m, 1H, Ph H-4), 6.97 (d, J = 16.1 Hz, 1H, ═CHCO), 4.29 (s, 2H, CH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.1 (C═O), 163.0 (d, ^1J(C,F) = 247.4 Hz, Ph C-3), 143.7 (d, ^4J(C,F) = 2.8 Hz, Ph-*C*H═), 136.2 (d, ^3J(C,F) = 7.7 Hz, Ph C-1), 130.6 (d, ^3J(C,F) = 8.3 Hz, Ph C-5), 124.7 (d, ^4J(C,F) = 2.9 Hz, Ph C-6), 122.7 (═*C*HCO), 118.0 (d, ^2J = 21.5 Hz, Ph C-4), 114.7 (d, ^2J = 22.0 Hz, Ph C-2), 47.4 (CH_2Cl). ^{19}F NMR (377 MHz, $CDCl_3$) δ: −112.1. IR (NaCl, ν_{max}, cm^{-1}): 1681, 1602, 1591, 1362, 1297, 1078, 905, 727. Anal. Calcd for $C_{10}H_8ClFO$: C, 60.47; H, 4.06. Found: C, 60.34; H, 4.19.

(3*E*)-1-Chloro-4-(2-nitrophenyl)-3-buten-2-one (5g). Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-(2-nitrophenyl)acrylamide (**4g**) (0.34 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5g** was obtained in 76% yield (0.24 g) as a yellow thick oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 8.14 (d, J = 16.0 Hz, 1H), 7.72−7.58 (m, 4H), 6.87 (d, J = 16.0 Hz, 1H), 4.38 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 190.8, 148.5, 133.7, 131.9, 130.9, 130.4, 129.2, 126.6, 125.2, 46.9. IR (NaCl, ν_{max}, cm^{-1}): 1684, 1605, 1592, 1360, 1273, 1128, 904, 807. Anal. Calcd for $C_{10}H_8ClNO_3$: C, 53.23; H, 3.57; N, 6.21. Found: C, 53.35; H, 3.44; N, 6.08.

(3*E*)-1-Chloro-4-[4-(trifluoromethyl)phenyl]-3-buten-2-one (5h). Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-(4-(trifluoromethyl)phenyl)acrylamide (**4h**) (0.37 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5h** was obtained in 87% yield (0.31 g) as a yellow thick oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.72 (d, J = 16.0 Hz, 1H, COCH═C*H*), 7.65−7.70 (m, 4H, Ph-H), 7.06 (d, J = 16.0 Hz, 1H, COC*H*), 4.31 (s, 2H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 191.0 (C═O), 143.2 (COCH═*C*H), 137.3 (Ph C-1), 132.4 (q, J = 32.8 Hz, Ph C-4), 128.7 (Ph C-2,6), 126.0 (q, J = 3.9 Hz, Ph C-3,5), 123.7 (q, J = 272.5 Hz, CF_3), 123.6 (COCH═), 47.5 (CH_2). ^{19}F NMR (471 MHz, $CDCl_3$) δ: −62.93. IR (NaCl, ν_{max}, cm^{-1}): 1684, 1604, 1593, 1362, 1173, 1077, 905, 728. Anal. Calcd for $C_{11}H_8ClF_3O$: C, 53.14; H, 3.24. Found: C, 53.00; H, 3.36.

1-Chloro-4-phenyl-3-butyn-2-one[33] **(5i).** Following the general procedure, starting from *N*-methoxy-*N*-methyl-3-phenylpropiolamide (**4i**) (0.27 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5i** was obtained in 90% yield (0.23 g) as a yellow thick oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.64−7.54 (m, 2H), 7.51−7.37 (m, 3H), 4.33 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 179.0, 133.5, 131.6, 128.9, 128.9, 119.3, 95.5, 85.7, 49.6. IR (NaCl, ν_{max}, cm^{-1}): 2201, 1671, 758, 689. Anal. Calcd for $C_{10}H_7ClO$: C, 67.24; H, 3.95. Found: C, 67.09; H, 4.06.

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(3*E*)-1-Chloro-4-(2-naphthyl)-3-buten-2-one (5j). Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-(naphthalen-2-yl)acrylamide (**4j**) (0.35 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5j** was obtained in 83% yield (0.27 g) as a pale yellow thick oil. ^{1}H NMR (500 MHz $CDCl_3$) δ 8.02−7.97 (m, 1H), 7.87 (ddd, *J* = 14.9, 10.2, 4.7 Hz, 4H), 7.71 (dt, *J* = 8.7, 2.1 Hz, 1H), 7.60−7.50 (m, 2H), 7.04 (dd, *J* = 47.7, 15.9 Hz, 1H), 4.34 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 191.6, 145.7, 135.0, 133.6, 131.8, 131.7, 129.3, 129.1, 128.2, 128.1, 127.3, 123.8, 122.6, 122.0, 47.9. IR (NaCl, ν_{max}, cm^{-1}): 3083, 1683, 1591, 901. Anal. Calcd for $C_{14}H_{11}ClO$: C, 72.89; H, 4.81. Found: C, 73.01; H, 4.71.

(3*E*,5*E*)-1-Chloro-6-phenyl-3,5-hexadien-2-one (5k). Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-(naphthalen-2-yl)acrylamide (**4k**) (0.31 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5k** was obtained in 93% yield (0.27 g) as a brown thick oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (m, *J* = 15.3 Hz, 10.7 Hz, 1H, *CH*=CHCO), 7.48 (m, 2H, Ph H-2, H-6), 7.38 (m, 2H, Ph H-3, H-5), 7.35 (m, 1H, Ph H-4), 7.02 (d, *J* = 15.5 Hz, 1H, ArC*H*=), 6.92 (dd, *J* = 15.5 Hz, 10.7 Hz, 0.6 Hz, 1H, ArCH=C*H*), 6.52 (d, *J* = 15.3 Hz, 1H, CH=C*H*CO), 4.23 (s, 2H, CH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.1 (C=O), 145.2 (*C*H=CHCO), 143.2 (ArCH=), 135.7 (Ph C-1), 129.6 (Ph C-6), 128.9 (Ph C-3), 128.9 (Ph C-5), 127.4 (Ph C-2), 127.4 (Ph C-6), 126.2 (ArCH=*C*H), 124.8 (CH=*C*HCO), 47.2 (CH_2Cl). IR (NaCl, ν_{max}, cm^{-1}): 3081, 1685, 1590, 1275, 905, 788. Anal. Calcd for $C_{12}H_{11}ClO$: C, 69.74; H, 5.36. Found: C, 69.91; H, 5.21.

(3*E*)-1-Chloro-4-(2-thienyl)-3-buten-2-one (5l). Following the general procedure, starting from (2*E*)-*N*-methoxy-*N*-methyl-3-(2-thienyl)acrylamide(**4l**) (0.28 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5l** was obtained in 82% yield (0.22 g) as a brown thick oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, *J* = 15.6, 1H ArCH=), 7.45 (dd, ^3J = 5.1, 1H, Th H-5), 7.36 (d, ^3J = 3.6 Hz, 1H, Th H-3), 7.09 (dd, ^3J = 5.1 Hz, ^3J = 3.6 Hz, 1H, Th H-4), 6.76 (d, *J* = 15.6 Hz, 1H; =CHCO), 4.24 (s, 2H, CH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.9 (C=O), 139.4 (Th C-2), 137.5 (^1J = 158.1 Hz, ArCH=), 132.8 (^1J (ThC3,H3) = 167.5 Hz, Th C-3), 129.8 (^1J (ThC5,H5) = 186.8 Hz, ^2J (ThC5,H4) = 7.3 Hz, ^3J (ThC5,H3) = 10.9 Hz, Th C-5), 128.5 (^1J (ThC4,H4) = 169.5 Hz, ^2J (ThC4,H3) = 5.2 Hz, ^3J (ThC4,H5) = 4.0 Hz, Th C-4), 120.1 (^1J = 159.3 Hz, ^3J = 2.8 Hz, =CHCO), 47.4 ($^1J(CH_2)$ = 149.4 Hz, $^3J(CH_2$, =CH) = 2.8 Hz, CH_2Cl). IR (NaCl, ν_{max}, cm^{-1}): 3078, 1681, 1587, 1279. Anal. Calcd for C_8H_7ClOS: C, 51.48; H, 3.78; S, 17.18. Found: C, 51.48; H, 3.63; S, 17.32.

(3*E*)-1-Chloro-4-(2-furyl)-3-buten-2-one[6a] (5m). Following the general procedure, starting from (*E*)-3-(furan-2-yl)-*N*-methoxy-*N*-methylacrylamide (**4m**) (0.26 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5m** was obtained in 77% yield (0.19 g) as a colorless thick oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (d, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 15.6 Hz, 1H), 6.86 (d, *J* = 15.6 Hz, 1H), 6.74 (d, *J* = 3.5 Hz, 1H), 6.51 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.24 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.6, 151.3, 146.2, 131.5, 119.3, 117.9, 113.4, 48.2. IR (NaCl, ν_{max}, cm^{-1}): 3087, 1691, 1606, 1590, 1232, 908, 809. Anal. Calcd for $C_8H_7ClO_2$: C, 56.32; H, 4.14. Found: C, 56.44; H, 4.26.

(3*Z*)-1-Chloro-3-fluoro-4-phenyl-3-buten-2-one[16] (5n). Following the general procedure, starting from (2*Z*)-2-fluoro-*N*-methoxy-*N*-methyl-3-phenylacrylamide (**4n**) (0.29 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5n** was obtained in 91% yield (0.26 g) as a light yellow thick oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (m, 2H; Ph H-2,6), 7.43 (m, 3H, Ph H-3,4,5), 6.95 (d, *J* = 37.2 Hz, 1H ArCH=), 4.51 (d, *J* = 2.3 Hz, CH_2Cl). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.8 (d, ^2J = 34.6 Hz, C=O), 152.4 (d, ^1J = 270.4, ^1J (CF, =CH) =6.0 Hz, =CF), 131.0 (d, ^4J = 8.2, Ph C-2), 131.0 (d, ^4J = 8.2, Ph C-6) 130.5 (d, ^6J = 2.8 Hz, Ph C-4), 130.4 (Ph C-1), 129.0 (Ph C-3), 129.0 (Ph C-5), 117.3 (d, ^2J = 4.2 Hz, ArCH=), 45.6 (^1J (CH_2) = 150.0 Hz, CH_2Cl). ^{19}F NMR (377 MHz, CDCl3) δ: −127.6 (d, *J* = 37.2 Hz, t, *J* = 2.2 Hz). IR (NaCl, ν_{max}, cm^{-1}): 1685, 1605, 1594, 1362, 1174, 907, 724. Anal. Calcd for $C_{10}H_8ClFO$: C, 60.47; H, 4.06. Found: C, 60.34; H, 3.93.

(3*E*)-1-Chloro-3-methyl-4-phenyl-3-buten-2-one (5o). Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-2-dimethyl-3-phenylacrylamide (**4o**) (0.29 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5o** was obtained in 88% yield (0.24 g) as a brown thick oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 1.5 Hz, 1H), 7.46−7.37 (m, 5H), 4.59 (s, 2H), 2.13 (d, *J* = 1.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 193.3, 140.8, 135.3, 135.1, 130.0, 130.0, 129.3, 128.7, 128.7, 45.4, 13.6. IR (NaCl, ν_{max}, cm^{-1}): 1677, 1598, 1574, 1378, 1093, 904, 728. Anal. Calcd for $C_{11}H_{11}ClO$: C, 67.87; H, 5.70. Found: C, 67.72; H, 5.83.

(3*E*)-1-Chloro-4-phenyl-3-penten-2-one[34] (5p). Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-phenylbut-2-enamide (**4p**) (0.29 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5p** was obtained in 89% yield (0.25 g) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.52 (m, 2H), 7.44−7.42 (m, 3H), 6.71 (d, *J* = 1.2 Hz, 1H), 4.20 (s, 2H), 2.61 (d, *J* = 1.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.9, 158.5, 142.1, 129.8, 128.8, 128.8, 126.7, 126.7, 120.1, 49.6, 19.0. IR (NaCl, ν_{max}, cm^{-1}): 1677, 1597, 1446, 1378, 1093, 905. Mp: 71 °C (lit.[34] mp 71−71.5 °C). Anal. Calcd for $C_{11}H_{11}ClO$: C, 67.87; H, 5.70. Found: C, 67.99; H, 5.59.

(3*E*)-1-Chloro-4-cyclohexyl-3-buten-2-one (5q). Following the general procedure, starting from (*E*)-3-cyclohexyl-*N*-methoxy-*N*-methylacrylamide (**4q**) (0.28 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5q** was obtained in 87% yield (0.23 g) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 16.0, 6.8 Hz, 1H), 6.24 (dd, *J* = 16.0, 1.4 Hz, 1H), 4.21 (s, 2H), 2.22−2.11 (m, 1H), 1.80−1.71 (m, 5H), 1.32−1.09 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 155.5, 123.8, 47.2, 40.9, 32.1, 31.7, 25.9, 25.9, 25.7. IR (NaCl, ν_{max}, cm^{-1}): 1684, 1615, 1380, 1280, 1051, 901. Anal. Calcd for $C_{10}H_{15}ClO$: C, 64.34; H, 8.10. Found: C, 64.47; H, 8.22.

(3*E*/*Z*)-1-Chloro-4-cyclopropyl-3-buten-2-one (5r). Following the general procedure, starting from (*E*)-3-cyclopropyl-*N*-methoxy-*N*-methylacrylamide (**4r**) (0.22 g, 1.43 mmol), ICH_2Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi−LiBr (2.85 mL, 4.28 mmol) in THF, α-chloroketone **5r** was obtained in 91% yield (0.19 g) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.48−6.38 (m, 3.4H, major + minor), 4.16 (s, 2H, major), 3.86 (s, 1.1H, minor), 1.65−1.59 (m, 2H, major + minor), 1.05−1.02 (m, 3.5H major + minor), 0.75−0.69 (m, 3.5H, major + minor). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 191,4, 190.3, 156.0, 155.8, 123.0, 122.7, 47.0, 15.2, 15.0, 9.5, 9.4, 4.6. IR (NaCl, ν_{max}, cm^{-1}): 1686, 1681, 1597, 1381, 903. Anal. Calcd for C_7H_9ClO: C, 58.14; H, 6.27. Found: C, 58.28; H, 6.42.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR for all compounds (Weinreb amides and α-haloketones). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) De Kimpe, N.; Verhé, R. The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines. In *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines*; Patai, S., Ed.; Wiley: Chichester, 1988; pp 1−119.

(2) (a) Barbee, T. R.; Albizati, K. F. *J. Org. Chem.* **1991**, *56*, 6764−6773. (b) Barbee, T. R.; Guy, H.; Heeg, M. J.; Albizati, K. F. *J. Org. Chem.* **1991**, *56*, 6773−6781. (c) Babu, K. S.; Li, X.-C.; Jacob, M. R.; Zhang, Q.; Khan, S. I.; Ferreira, D.; Clark, A. M. *J. Med. Chem.* **2006**, *49*, 7877−7886.

(3) For a selection of recent examples, see: (a) Alajarín, M.; Cabrera, J.; Pastor, A.; Sánchez-Andrada, P.; Bautista, D. *J. Org. Chem.* **2007**, *72*, 2097−2105. (b) Onizawa, Y.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 802−803. (c) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924−6927. (d) Gao, K.; Yu, C.-B.; Wang, D.-S.; Zhou, Y.-G. *Adv. Synth. Catal.* **2012**, *354*, 483−488. For a recent synthesis of monofluoroalkyl α,β-unsaturated ketones, see: (e) Jin, Z.; Hidinger, R. S.; Xu, B.; Hammond, G. B. *J. Org. Chem.* **2012**, *77*, 7725−7729.

(4) Li, X.-C.; Ferreira, D.; Jacob, M. R.; Zhang, Q.; Khan, S. I.; ElSohly, H. N.; Nagle, D. G.; Smillie, T. J.; Khan, I. A.; Walker, L. A.; Clark, A. M. *J. Am. Chem. Soc.* **2004**, *126*, 6872−6873.

(5) Brazeau, J.-F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, *134*, 2742−2749.

(6) (a) Hudson, R. F.; Chopard, P. A. *J. Org. Chem.* **1963**, *28*, 2446−2447. (b) Alajarín, M.; Cabrera, J.; Pastor, A.; Sánchez-Andrada, P.; Bautista, D. *J. Org. Chem.* **2006**, *71*, 5328−5339. (c) Byrne, P. A.; Higham, L. J.; McGovern, P.; Gilheany, D. G. *Tetrahedron Lett.* **2012**, *53*, 6701−6704.

(7) Ram, R. N.; Manoj, T. P. *J. Org. Chem.* **2008**, *73*, 5633−5635.

(8) Hampel, T.; Neubauer, T.; van Leeuwen, T.; Bach, T. *Chem.—Eur. J.* **2012**, *18*, 10382−10392.

(9) Kowalski, C. J.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 7194−7208.

(10) For selected reviews on lithium carbenoids, see: (a) Capriati, V.; Florio, S. *Chem.—Eur. J.* **2010**, *16*, 4152−4162. (b) Braun, M. Lithium Carbenoids. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley-VCH: Chichester, 2004; Vol. 2, pp 829−899. (c) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697−756. For a recent example of using $LiCH_2Cl$ to prepare α-arylamino-α′-chloroacetones from our group, see: (d) Pace, V.; Holzer, W.; Verniest, G.; Alcántara, A. R.; De Kimpe, N. *Adv. Synth. Catal.* **2013**, *355*, 919−926. For selected examples from the recent literature, see: (e) Kapeller, D. C.; Hammerschmidt, F. *J. Am. Chem. Soc.* **2008**, *130*, 2329−2335. (f) Concellón, J. M.; Rodríguez-Solla, H.; Bernad, P. L.; Simal, C. *J. Org. Chem.* **2009**, *74*, 2452−2459. (g) Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3068−3069. (h) Savoia, D.; Alvaro, G.; Di Fabio, R.; Gualandi, A.; Fiorelli, C. *J. Org. Chem.* **2006**, *71*, 9373−9381.

(11) Pioneering studies by Villieras revealed that Li carbenoids are not stable at temperatures above −115 °C; see: (a) Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835−838. Also, previous work by Köbrich pointed out this instability at higher temperatures: (b) Köbrich, G.; Akhtar, A.; Ansari, F.; Breckoff, W. E.; Büttner, H.; Drischel, W.; Fischer, R. H.; Flory, K.; Fröhlich, H.; Goyert, W.; Heinemann, H.; Hornke, I.; Merkle, H. R.; Trapp, H.; Zündorf, W. *Angew. Chem., Int. Ed.* **1967**, *6*, 41−52.

(12) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

(13) For an excellent review, see: Satoh, T. *Chem. Soc. Rev.* **2007**, *36*, 1561−1572.

(14) Ke, Z.; Zhou, Y.; Gao, H.; Zhao, C.; Phillips, D. L. *Chem.—Eur. J.* **2007**, *13*, 6724−6731.

(15) De Simone, F.; Andrès, J.; Torosantucci, R.; Waser, J. *Org. Lett.* **2009**, *11*, 1023−1026.

(16) Elkik, E.; Imbeaux-Oudotte, M. *Bull. Soc. Chim. Fr.* **1987**, 861.

(17) Pace, V.; Castoldi, L.; Alcantara, A. R.; Holzer, W. *RSC Adv.* **2013**, *3*, 10158−10162.

(18) Newcomb, M.; Choi, S.-Y.; Toy, P. H. *Can. J. Chem.* **1999**, *77*, 1123−1135.

(19) Chen, G.; Cho, S. J.; Huang, X.-P.; Jensen, N. H.; Svennebring, A.; Sassano, M. F.; Roth, B. L.; Kozikowski, A. P. *ACS Med. Chem. Lett.* **2011**, *2*, 929−932.

(20) Davi, M.; Lebel, H. *Org. Lett.* **2008**, *11*, 41−44.

(21) Alonso, D. A.; Fuensanta, M.; Gómez-Bengoa, E.; Nájera, C. *Eur. J. Org. Chem.* **2008**, 2915−2922.

(22) Toy, P. H.; Dhanabalasingam, B.; Newcomb, M.; Hanna, I. H.; Hollenberg, P. F. *J. Org. Chem.* **1997**, *62*, 9114−9122.

(23) Brummond, K. M.; Chen, D. *Org. Lett.* **2005**, *7*, 3473−3475.

(24) Lee, T.; Jones, J. B. *J. Am. Chem. Soc.* **1997**, *119*, 10260−10268.

(25) Rudzinski, D. M.; Kelly, C. B.; Leadbeater, N. E. *Chem. Commun.* **2012**, *48*, 9610−9612.

(26) Alonso, D. A.; Fuensanta, M.; Gómez-Bengoa, E.; Nájera, C. *Adv. Synth. Catal.* **2008**, *350*, 1823−1829.

(27) Shang, J.; Han, Z.; Li, Y.; Wang, Z.; Ding, K. *Chem. Commun.* **2012**, *48*, 5172−5174.

(28) Arai, S.; Koike, Y.; Hada, H.; Nishida, A. *J. Org. Chem.* **2010**, *75*, 7573−7579.

(29) Tosatti, P.; Horn, J.; Campbell, A. J.; House, D.; Nelson, A.; Marsden, S. P. *Adv. Synth. Catal.* **2010**, *352*, 3153−3157.

(30) Kuse, M.; Isobe, M. *Tetrahedron* **2000**, *56*, 2629−2639.

(31) Southwick, P. L.; Pursglove, L. A.; Numerof, P. *J. Am. Chem. Soc.* **1950**, *72*, 1604−1607.

(32) Tanyeli, C.; Demir, A. S.; Akhmedov, I. M.; Özgül, E.; Kandemir, C. G. *Synth. Commun.* **1996**, *26*, 2967−2980.

(33) Raghavan, S.; Mustafa, S.; Sridhar, B. *J. Org. Chem.* **2009**, *74*, 4499−4507.

(34) Moore, J. A. *J. Org. Chem.* **1955**, *20*, 1607−1612.