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Convenient synthesis of non-conjugated alkynyl ketones from keto aldehydes by a chemoselective one-pot nonaflation—base catalyzed elimination sequence

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This article is dedicated to the memory of Dr. Ilya Lyapkalo who passed away on September 10, 2010

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ABSTRACT

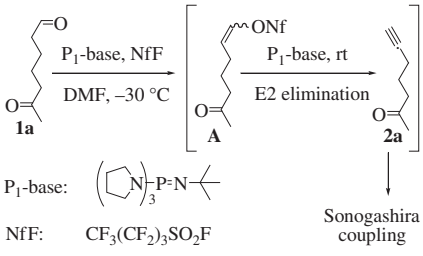
Keto aldehydes were selectively converted to non-conjugated alkynyl ketones possessing an unsubstituted alkyne terminus using one-pot nonaflation—base catalyzed elimination reaction sequences. Consecutive one-pot nonaflation of keto aldehydes with perfluorobutane-1-sulfonyl fluoride and elimination of the nonaflyl group using the P_1 phosphazene base resulted in the formation of a terminal C≡C triple bond with the keto group remaining intact. Careful optimization of the reaction conditions enabled a highly chemoselective conversion of the aldehyde function in the presence of unprotected keto groups exploiting a minor difference in acidity of their α-hydrogen atoms. Scope and limitations of the protocol as well as possible implementation of these substrates in Sonogashira coupling were explored.

1. Introduction

In line with our ongoing research devoted to the extension of Pd(0) catalyzed cross-coupling methodology to carbonyl group chemistry,[1a] we have recently described a general and straightforward synthesis of alkynes from aliphatic aldehydes and ketones,[1b] where carbonyl functionality underwent conversion into the enol nonaflate intermediate, followed by elimination of the nonaflyl group to give a C≡C triple bond in one synthetic operation. These one-pot transformations were uniformly induced by phosphazene bases combined with mildly electrophilic nonafluorobutane-1-sulfonyl fluoride.[2] On the other hand, it was noticed in an earlier study that conversion of aldehydes to enol nonaflates proceeded appreciably faster than that of ketones, apparently owing to the higher acidity of the α-hydrogen atoms of aldehydes compared to those of ketones.[3]

This difference in reactivity could allow the chemoselective transformation of a $CH_2CH{=}O$ functionality to a terminal C≡C triple bond in the presence of an unprotected keto group. From a synthetic viewpoint, this could result in a new protocol allowing the conversion of bifunctional substrates—keto aldehydes—having their carbonyl groups separated by a spacer to non-conjugated alkynyl ketones. These alkynyl ketones comprise functionalities with essentially orthogonal reactivities: the keto group represents an electrophile or an enolate nucleophile, whereas the acetylenic terminus can be subjected to Pd(0) catalyzed cross coupling (i.e. Sonogashira coupling reactions) or [3+2] cycloaddition reactions with nitrile oxides[4] or azides[5] (click chemistry).

We have shown the feasibility of this transformation previously for a single example, the conversion of 6-oxoheptanal **1a** to hept-6-yn-2-one **2a** (Scheme 1), which participated further in a Sonagashira coupling in situ.[1a] The formation and stereochemistry of an intermediate 6-oxoheptenyl nonaflate **A** (*E*/*Z* ratio 5:1) was described as well.[3]



Scheme 1.

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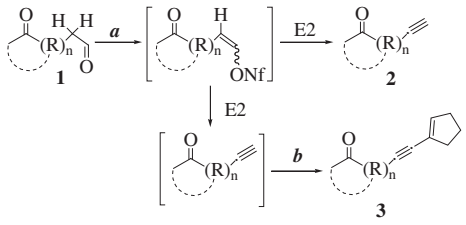
In this paper, we report a systematic study on the scope and limitations of the chemoselective one-step transformation of keto aldehydes **1** into non-conjugated alkynyl ketones **2**. This protocol will open up an easy approach to non-conjugated alkynyl ketones which, in turn, could serve as versatile cross-linking reagents connecting various pharmacologically relevant structural elements in the future.[5]

2. Results and discussion

To ensure the desired chemoselectivity of sulfonylation for the aldehyde group, the intermediate enol nonaflates were generated at −30 °C. Once the O-sulfonylation was complete, the reaction mixtures were allowed to gradually warm to rt to allow the required E2 elimination to occur (Scheme 2).



Scheme 2. Reagents and conditions: (a) *tert*-Butylimino-tris(1-pyrrolidinyl)phosphorane [hereinafter referred to as P_1-base] (≥2 equiv), NfF (1 equiv), DMF, −30 °C; E2: P_1-base, rt; (b) cyclopentenyl nonaflate, *i*-Pr_2NH (4 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), CuI (10 mol %), rt.

As evidenced by ^{1}H NMR analyses of the reaction mixtures upon completion, transformation of keto aldehydes **1** into alkynyl ketones **2** proceeded cleanly. Alkynyl ketones were isolated in good yields in most cases (Table 1, entries 1, 3–6, 9, 10). The isolated yields of products (**2**) were slightly lower than expected from the ^{1}H NMR data of the crude reaction mixtures. The observed losses were most likely due to the volatility of the products during workup and isolation on a small scale. Substrate **1b** was an exception, since it was impossible to isolate product **2b** despite high conversion according to the ^{1}H NMR spectrum of the crude reaction mixture due to its extremely high volatility (Table 1, entry 2).

To overcome these losses an additional series of experiments was carried out, in which products (**2**) were subjected in situ to a Sonogashira coupling reaction[1a] with cyclopentenyl nonaflate (Table 1, entries 11–17). Products (**3**) were isolated for all substrates in good to excellent yields, which exceeded those of their precursors (**2**) considerably, thus demonstrating the efficiency of the protocol.

The reactivity of some substrates deserves further comment. The transformation of 6-oxo-6-phenylhexanal **1e** to the desired alkynyl ketone **2e** (Table 1, entry 5) was accompanied by an intramolecular aldol condensation, furnishing phenyl cyclopentenyl ketone as a side product. The ratio of **2e**/cyclopentenyl ketone amounted to 89/11 by ^{1}H NMR of the crude reaction mixture. This was a unique example among the substrates examined. This result can be rationalized by the somewhat higher acidity of alkyl aryl ketones in comparison with the dialkyl analogs (e.g., the pK_a values in DMSO for ethyl phenyl ketone and diethyl ketone are 24.4 and 27.1, respectively).[6] However, the existing difference in acidity of keto and aldehyde groups in **1e** is still sufficient for the reaction to proceed with a reasonable degree of chemoselectivity. A completely different situation was observed in the case of substrate **1h** possessing a cyclopentanone fragment (Table 1, entry 8). The reaction afforded only a small amount of desired **2h** accompanied by a complex mixture of unidentified products. The acidity difference of keto and aldehyde α-carbonyl hydrogen atoms in **1h** was probably not high enough to induce the desired chemoselectivity. Indeed, cyclopentanone (pK_a value in DMSO is 25.8)[7] is known to be

Table 1
Yields of alkynyl ketones **2** and Sonogashira coupling products **3** obtained from keto aldehydes **1** according Scheme 2

Entry	Substrate **1**	Product **2**	Yield %	Entry	Substrate **1**	Product **3**	Yield[a] %
1	**1a**	**2a**	76[a] (85)[b]			—	
2	**1b**	**2b**	(93)[b,c]	11	**1b**	**3b**	92
3	**1c**	**2c**	64[a] (90)[b]	12	**1c**	**3c**	88
4	**1d**	**2d**	86[a] (96)[b]	13	**1d**	**3d**	94
5	**1e**	**2e**	60[a,d] (89)[b]	14	**1e**	**3e**	86
6	**1f**	**2f**	60[a] (96)[b]	15	**1f**	**3f**	92
7[e]	**1g**	**2g**	18[a] (23)[b]			—	
8	**1h**	**2h**	(30)[b,f]			—	

(*continued on next page*)

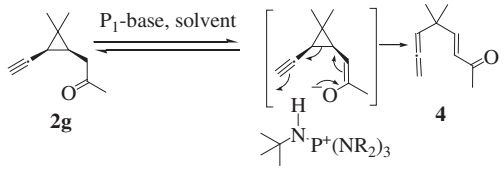
Table 1 (*continued*)

Entry	Substrate **1**	Product **2**	Yield %	Entry	Substrate **1**	Product **3**	Yield[a] %
9	**1i**	**2i**	60[a] (95)[b]	16	**1i**	**3i**	94
10	**1j**	**2j**	77[a] (92)[b]	17	**1j**	**3j**	89

[a] Isolated yield.
[b] Conversion determined by ^{1}H NMR of the crude reaction mixture.
[c] Product **2b** was not isolated due to its high volatility.
[d] Isolated product **2e** contained ca. 6 mol % (by ^{1}H NMR) of phenyl cyclopentenyl ketone as an admixture (the ratio of **2e**/cyclopentenyl ketone in the crude reaction mixture was 89/11 by ^{1}H NMR, see text).
[e] Reaction was carried out in THF, see text.
[f] Product **2h** was not isolated in a pure state due to the presence of a considerable amount of unidentified side products.

the most acidic of all cycloalkanones and the outcome of the reaction points out that the acidity of keto and aldehyde groups is comparable. An attempt to improve the yield for substrate **1h** by carrying out the reaction in less polar THF did not bring about a better result.

The conversion of keto aldehyde **1g** to alkynyl ketone **2g** under standard conditions in DMF was accompanied by the formation of an unexpected product, which was identified as (*E*)-5,5-dimethylocta-3,6,7-trien-2-one **4** (**2g**/**4** ratio=2.7:1). The latter is proposed to be formed by a P_1-base induced rearrangement of **2g**. The rate of this rearrangement proved to be remarkably solvent dependent (Scheme 3). A mixture of **2g** and **4** remained unchanged in the presence of P_1-base in C_6D_6 upon overnight storage at rt and only insignificant conversion (ca. 5%) to **4** was observed by heating at 50 °C overnight. However, **2g** was fully converted into allenic enone **4** upon overnight storage in DMSO-d_6 at rt.

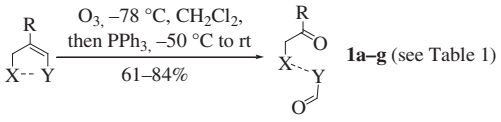


Scheme 3. Solvent dependent rearrangement of alkynyl ketone **2g** in the presence of P_1-base.

The ring opening—rearrangement process is proposed to occur via anionic enolate intermediate as depicted in Scheme 3. Since the enolate intermediate is more polar than starting **2g** and P_1-base, it should be better stabilized by a more polar solvent, hence the observed rate acceleration in DMSO or in DMF (to some extent). Only one example of a related transformation exists in the literature described by van Tamelen and co-workers for the rearrangement of car-3-ene-2-one to eucarvone.[8]

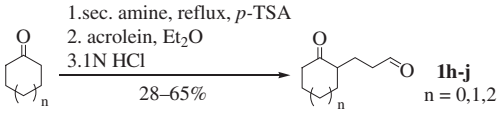
Based on this conclusion the transformation of **1g** to **2g** was repeated in less polar THF. Although the ring-opening product **4** was no longer detected in the ^{1}H NMR spectrum of the reaction mixture, the reaction was sluggish and led to incomplete conversion of the intermediate enol nonaflate and the formation of some unidentified side products. Therefore, a low overall yield of alkynyl ketone **2g** resulted (Table 1, entry 7).

The starting keto aldehydes **1a**–**g** were synthesized from readily available cyclic alkenes by ozonolysis as shown in Scheme 4.[9] Generally, PPh_3 afforded products **1** in higher yields and purities compared to Me_2S, which is due to a more efficient cleavage of the trioxolane intermediates by PPh_3.



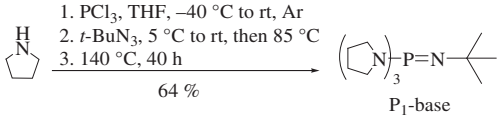
Scheme 4.

Alicyclic keto aldehydes **1h**–**j** were obtained by Michael addition of enamines derived from cycloalkanones to acrolein followed by acidic hydrolysis (Scheme 5).[10]



Scheme 5.

The P_1-base was synthesized according to a synthetic protocol developed by our group as depicted in Scheme 6. This method includes phosphorylation of pyrrolidine with PCl_3 leading to the formation of tris(1-pyrrolidinyl)phosphine and a subsequent Staudinger reaction[11] with *tert*-butyl azide.



Scheme 6.

3. Conclusion

With the exception of very acidic ketones, the developed methodology represents a general and convenient approach to non-conjugated alkynyl ketones. Robustness, good reproducibility, easy up-scaling and availability of starting materials lend value to the synthesis. The combination of distinctly basic and mildly electrophilic reagents enabled a clear kinetic discrimination between aldehyde and non-activated aliphatic keto groups, allowing for structural elaborations to be achieved orthogonally. Last but not least, the phosphazene base can be easily recovered from its salts,[12] thus reducing the cost of the process.

4. Experimental

4.1. General

All reactions were carried out in pre-dried glassware equipped with PTFE-coated magnetic stirring bars in anhydrous solvents under an atmosphere of dry argon. Solvents were dried by standard procedures: hexane and dichloromethane were distilled over P_2O_5; THF was distilled over Na/K alloy with addition of Ph_2CO; DMF was distilled over CaH_2 in vacuo. Ozonolysis was carried out using an ozone generator OzoneLab™ OL80W (Yanco Industries LTD). ^{1}H NMR spectra of the reaction mixtures were routinely performed to ensure complete conversion of the starting materials. NMR spectra were recorded on a Bruker Avance I™ 400 (Bruker BioSpin GmbH) spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 162 MHz for ^{31}P) in C_6D_6 or $CDCl_3$. Chemical shifts were reported as δ scale in parts per million relative to $SiMe_4$ (δ=0) as an internal standard for ^{1}H NMR, to $CDCl_3$ (δ=77.16) or C_6D_6 (δ=128.06) for ^{13}C NMR and to $(MeO)_3PO$ (δ=3.7 ppm in C_6D_6)[13] as an internal standard for ^{31}P NMR. IR spectra were recorded on a Bruker Equinox 55 IR spectrometer (Bruker BioSpin GmbH) in films or in $CDCl_3$. High-resolution mass spectra were taken on GTC Premier spectrometer (WATERS) using EI ionization method or on LTQ Orbitrap XL spectrometer (Thermo Fisher Scientific) using ESI ionization method in methanol or acetonitrile. Melting points (mp, uncorrected) were determined using Wagner & Munz PolyTherm A apparatus. Preparative separations were performed by silica gel gravity column chromatography (Silica gel 60, Fluka, 12479). Column chromatography was monitored by TLC (Silica gel 60, Glass plates, Merck, 105631) and visualized using 5% phosphomolybdic acid solution in ethanol. All the obtained products were of more than 95% purity by NMR unless otherwise noted.

4.2. Synthesis of starting keto aldehydes 1

4.2.1. Synthesis of starting keto aldehydes by ozonolysis.[9] *Typical procedure*: A stream of ozone was passed through a solution of alkene (1 mol equiv) in dry CH_2Cl_2 (30 mL per 6 mmol of starting alkene) at −78 °C until the resulting solution became blue-violet. The excess of ozone was removed by passing a stream of oxygen followed by argon through the solution. The resulting mixture was allowed to reach −50 °C and carefully quenched by addition of Ph_3P (1.2 mol equiv) in dry CH_2Cl_2 (5 mL per 2 g of Ph_3P). After 24 h at rt the reaction mixture was concentrated and the residue was subjected to chromatography on SiO_2 (hexane/Et_2O) or distillation in vacuo to provide keto aldehydes **1a**–**g** as colorless liquids.

*4.2.1.1. 6-Oxoheptanal (**1a**).*[14] Yield 8.00 g (62%) starting from 1-methylcyclohex-1-ene (9.68 g, 101 mmol); ^{1}H NMR ($CDCl_3$) δ 9.77 (t, 1H, J=1.6 Hz, CHO), 2.50–2.43 (m, 4H), 2.15 (s, 3H, COMe), 1.66–1.58 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 208.5, 202.2, 43.7, 43.3, 29.9, 23.1, 21.5.

*4.2.1.2. 5-Oxohexanal (**1b**).*[9] Yield 1.16 g (84%) starting from 1-methylcyclopent-1-ene (1.00 g, 12.2 mmol); ^{1}H NMR ($CDCl_3$) δ 9.77 (t, 1H, J=1.4 Hz, CHO), 2.50–2.44 (m, 4H), 2.11 (s, 3H, COMe), 1.86 (quintet, 2H, J=7.1 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 207.8, 201.7, 42.8, 42.2, 29.8, 16.0.

*4.2.1.3. 7-Oxooctanal (**1c**).*[15] Yield 1.38 g (68%) starting from 1-methylcyclohept-1-ene (1.56 g, 14.2 mmol); ^{1}H NMR ($CDCl_3$) δ 9.77 (t, 1H, J=1.5 Hz, CHO), 2.48–2.42 (m, 4H), 2.14 (s, 3H, COMe), 1.68–1.56 (m, 4H), 1.37–1.29 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 208.6, 202.3, 43.6, 43.3, 29.8, 28.5, 23.3, 21.7.

*4.2.1.4. 7-Oxoundecanal (**1d**)* Yield 1.33 g (72%) starting from 1-*n*-butylcyclohept-1-ene (1.53 g, 10.0 mmol); bp 135–137 °C (0.7 mbar); ^{1}H NMR ($CDCl_3$) δ 9.75 (t, 1H, J=1.7 Hz, CHO), 2.45–2.36 (m, 6H), 1.67–1.50 (m, 6H), 1.35–1.25 (m, 4H), 0.89 (t, 3H, J=7.3 Hz, H-11); ^{13}C NMR ($CDCl_3$) δ 211.2, 202.5, 43.8, 42.7, 42.5, 28.9, 26.1, 23.6, 22.5, 22.0, 14.0; ESI-HRMS: m/z $[M+Na]^+$ calcd for $C_{11}H_{20}NaO_2$: 207.1361, found: 207.1356; IR (neat): 1714 (C=O) cm^{-1}.

*4.2.1.5. 6-Oxo-6-phenylhexanal (**1e**).*[16] Yield 0.85 g (71%) starting from 1-phenylcyclohex-1-ene (1.00 g, 6.3 mmol); ^{1}H NMR ($CDCl_3$) δ 9.79 (t, 1H, J=1.6 Hz, CHO), 7.95–7.93 (m, 2H), 7.57–7.53 (m, 1H), 7.47–7.43 (m, 2H), 3.01 (t, 2H, J=6.8 Hz, H-5), 2.51 (td, 2H, J=1.6, 7.2 Hz, H-2), 1.82–1.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 202.1, 199.6, 136.9, 133.0, 128.6, 128.0, 38.1, 43.7, 23.6, 21.7.

*4.2.1.6. [(1R,3R)-3-Acetyl-2,2-dimethylcyclobutyl]acetaldehyde (**1f**).*[17] Yield 1.67 g (67%) starting from (−)-α-pinene (2.00 g, 14.7 mmol); ^{1}H NMR (C_6D_6) δ 9.22 (t, J=1.4 Hz, 1H, CHO), 2.33–2.28 (m, 1H), 2.00–1.87 (m, 2H), 1.83–1.68 (m, 2H), 1.67–1.62 (m, 1H), 1.60 (s, 3H, COMe), 0.99 (s, 3H, Me-2), 0.57 (s, 3H, Me-2); ^{13}C NMR (C_6D_6) δ 205.1, 199.8, 54.1, 45.1, 42.7, 35.9, 30.3, 29.7, 23.1, 17.6.

*4.2.1.7. [(1R,3S)-2,2-Dimethyl-3-(2-oxo-propyl)cyclopropyl]acetaldehyde (**1g**).*[18] Yield 1.13 g (61%) starting from (+)-3-carene (1.50 g, 11.0 mmol); ^{1}H NMR (C_6D_6) δ 9.39 (t, 1H, J=1.8 Hz, CHO), 1.81–1.78 (m, 2H), 1.76–1.72 (m, 2H), 1.70 (s, 3H, COMe), 0.96 (s, 3H, Me-2), 0.77–0.70 (m, 1H), 0.64–0.58 (m, 1H), 0.60 (s, 3H, Me-2); ^{13}C NMR (C_6D_6) δ 205.9, 200.2, 39.6, 39.1, 29.1, 28.5, 21.6, 19.7, 17.0, 15.1.

*4.2.2. Synthesis of starting keto aldehydes by Michael reaction. Keto aldehydes **1h**–**j** were prepared according to a literature procedure.*[10]

*4.2.2.1. 3-(2-Oxocyclopentyl)propanal (**1h**).*[10] Yield 1.2 g (28%); ^{1}H NMR (C_6D_6) δ 9.28 (t, 1H, J=1.4 Hz, CHO), 1.96–1.92 (m, 2H), 1.88–1.80 (m, 1H), 1.79–1.70 (m, 1H), 1.65–1.55 (m, 1H), 1.53–1.45 (m, 2H), 1.39–1.24 (m, 2H), 1.16–1.05 (m, 1H), 0.87–0.80 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 217.7, 200.3, 47.7, 41.6, 37.6, 29.6, 22.3, 20.6.

*4.2.2.2. 3-(2-Oxocyclohexyl)propanal (**1i**).*[10] Yield 3.6 g (65%); ^{1}H NMR (C_6D_6) δ 9.34 (t, 1H, J=1.4 Hz, CHO), 2.18–1.70 (m, 6H), 1.55–1.46 (m, 2H), 1.33–1.01 (m, 4H), 0.94–0.83 (m, 1H); ^{13}C NMR (C_6D_6) δ 210.2, 200.7, 49.6, 42.0, 41.8, 34.2, 27.9, 25.1, 22.5.

*4.2.2.3. 3-(2-Oxocycloheptyl)propanal (**1j**)*[10] Yield 4.2 g (60%); ^{1}H NMR (C_6D_6) δ 9.31 (t, 1H, J=1.4 Hz, CHO), 2.21–2.07 (m, 3H), 2.01–1.85 (m, 2H), 1.82–1.73 (m, 1H), 1.47–1.29 (m, 5H), 1.25–1.15 (m, 1H), 1.02–0.90 (m, 3H); ^{13}C NMR (C_6D_6) δ 213.0, 200.5, 51.0, 42.9, 41.8, 31.7, 29.5, 28.7, 24.8, 24.4.

4.3. Synthesis of P_1-base

4.3.1. tert-Butylimino-tris(1-pyrrolidinyl)phosphorane.[12] *Note*: All operations were performed using freshly distilled dry solvents under a positive atmosphere of dry argon. Freshly distilled pyrrolidine (85.20 g, 1.198 mol) and THF (300 mL) were placed into a 1 L three-neck round-bottom flask equipped with a PTFE-coated magnetic stirring bar, thermometer, dropping funnel, and argon inlet and cooled to −40 °C. Then solution of PCl_3 (20.05 g, 0.146 mol) in THF (200 mL) was added dropwise at −40 °C. After completion of the addition the reaction mixture was warmed slowly to rt and stirred at ambient temperature for 18 h. The solvent was removed from the reaction flask in vacuo (rt, 50 mbar) and the solid residue was washed twice with hexane (2×100 mL). The combined hexane fractions were concentrated in vacuo (rt, 50 mbar) to afford tris(1-pyrrolidinyl)phosphine (29.34 g, 0.122 mol) as colorless liquid. The obtained phosphine was placed

into a 250 mL three-necked round-bottom flask equipped with a PTFE-coated magnetic stirring bar, thermometer, dropping funnel, and argon inlet, cooled to 5 °C and *tert*-butyl azide[19] (14.5 g, 0.146 mol) was added dropwise. The reaction mixture was stirred overnight at rt, heated at 85 °C for 1 h and cooled to rt. Volatiles were removed at 50 mbar for 30 min. BaO (1.0 g) was added and the reaction mixture was heated at 140 °C for 40 h. Vacuum distillation over BaO afforded the P_1-base (29.1 g, 64%) as a viscous colorless oil; bp 112–114 °C (0.15 mbar) [lit.[12] bp 108 °C (0.05 Torr)]; ^{1}H NMR (C_6D_6) δ 3.08–3.12 (m, 12H, α-H-pyrrolidinyl), 1.60–1.50 (m, 12H, β-H-pyrrolidinyl), 1.56 (s, 9H, *t*-Bu); ^{31}P NMR (C_6D_6) δ 8.8.

4.4. Synthesis of alkynyl ketones 2

4.4.1. General procedure (GP1). Starting keto aldehyde **1** (1.00 mmol), NfF (0.305 g, 1.01 mmol) and DMF (1 mL) were placed in a round-bottom flask. The flask was cooled to −30 °C whereupon the P_1-base (0.628 g, 2.01 mmol) was added dropwise. The reaction mixture was allowed to warm up gradually to rt and stirred for 16–18 h (NMR monitoring). It was quenched with saturated aq NH_4Cl (15 mL) and extracted with Et_2O (3×15 mL). The combined organic layers were washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated. Products **2** were isolated by column chromatography on SiO_2.

*4.4.1.1. Hept-6-yn-2-one (**2a**).*[20] The reaction was carried out according to GP1 using **1a** (0.259 g, 2.02 mmol), NfF (0.715 g, 2.37 mmol), and P_1-base (1.455 g, 4.66 mmol). Column chromatography on SiO_2 (pentane/Et_2O, 5:1) afforded **2a** (0.169 g, 76%) as a colorless liquid; R_f 0.35; ^{1}H NMR ($CDCl_3$) δ 2.59 (t, 2H, J=7.2 Hz, H-3), 2.24 (dt, 2H, J=6.9, 2.6 Hz, H-5), 2.16 (s, 3H, COMe), 1.97 (t, 1H, J=2.6 Hz, ≡CH), 1.79 (quint, 2H, J=7.01 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 208.2, 83.5, 69.0, 42.0, 30.0, 22.2, 17.7.

*4.4.1.2. Oct-7-yn-2-one (**2c**).*[21] The reaction was carried out according to GP1 using **1c** (0.142 g, 1.00 mmol), NfF (0.305 g, 1.01 mmol), and P_1-base (0.628 g, 2.01 mmol). Column chromatography on SiO_2 (pentane/Et_2O, 10:1 to 5:1) afforded **2c** (0.079 g, 64%) as a colorless liquid; R_f 0.40; ^{1}H NMR ($CDCl_3$) δ 2.46–2.42 (m, 2H), 2.19 (td, 2H, J=7.0, 2.7 Hz, H-6), 2.13 (s, 3H, COMe), 1.93 (t, 1H, J=2.7 Hz, H-8), 1.72–1.64 (m, 2H), 1.55–1.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 208.6, 84.1, 68.7, 43.2, 29.9, 28.0, 23.0, 18.4.

*4.4.1.3. Undec-10-yn-5-one (**2d**).*[22] The reaction was carried out according to GP1 using **1d** (0.184 g, 1.00 mmol), NfF (0.305 g, 1.01 mmol), and P_1-base (0.628 g, 2.01 mmol). Column chromatography on SiO_2 (hexane/EtOAc, 20:1 to 10:1) afforded **2d** (0.143 g, 86%) as a colorless liquid; R_f 0.37; ^{1}H NMR ($CDCl_3$) δ 2.43–2.47 (m, 4H), 2.19 (td, 2H, J=7.0, 2.7 Hz, H-9), 1.93 (t, 1H, J=2.7 Hz, H-11), 1.72–1.64 (m, 2H), 1.58–1.47 (m, 4H), 1.34–1.24 (m, 2H), 0.89 (t, 3H, J=7.3 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 211.0, 84.2, 68.6, 42.7, 42.2, 28.1, 26.1, 23.0, 22.5, 18.4, 13.9.

*4.4.1.4. 1-Phenylhex-5-yn-1-one (**2e**).*[23] The reaction was carried out according to GP1 using **1e** (0.194 g, 1.02 mmol), NfF (0.311 g, 1.03 mmol), and P_1-base (0.640 g, 2.05 mmol). Column chromatography on SiO_2 (pentane to pentane/Et_2O, 20:1) afforded **2e** (0.104 g, 61%) as a yellow oil; R_f 0.33; ^{1}H NMR ($CDCl_3$) δ 7.99–7.97 (m, 2H), 7.59–7.55 (m, 1H), 7.49–7.45 (m, 2H), 3.14 (t, 2H, J=7.2 Hz, H-2), 2.34 (td, 2H, J=6.8, 2.7 Hz, H-4), 2.02–1.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 199.7, 137.1, 133.2, 128.7, 128.2, 83.9, 69.2, 37.2, 22.9, 18.1.

*4.4.1.5. 1-[(1R,3R)-3-Ethynyl-2,2-dimethylcyclobutyl]ethanone (**2f**).* The reaction was carried out according to GP1 using **1f** (0.231 g, 1.37 mmol), NfF (0.419 g, 1.39 mmol), and P_1-base (0.862 g, 2.76 mmol). Column chromatography on SiO_2 (hexane to hexane/EtOAc, 20:1) afforded **2f** (0.124 g, 60%) as a white solid; R_f 0.40; mp 44–45 °C; ^{1}H NMR ($CDCl_3$) δ 2.88 (dd, 1H, J=10.5, 7.6 Hz, H-1), 2.69 (ddd, 1H, J=10.7, 8.5, 2.4 Hz, H-3), 2.40–2.31 (m, 1H, H-4), 2.16 (d, 1H, J=2.4 Hz, ≡CH), 2.11–2.06 (m, 1H, H-4), 2.05 (s, 3H, COMe), 1.34 (s, 3H, Me-2), 1.04 (s, 3H, Me-2); ^{13}C NMR ($CDCl_3$) δ 206.8, 83.5, 71.6, 54.3, 44.2, 32.8, 30.1, 30.0, 24.3, 19.1; EI-HRMS: m/z $[M-H]^+$ calcd for $C_{10}H_{13}O$: 149.0966, found: 149.0967; IR ($CDCl_3$): 3305 (≡C–H), 1979 (C≡C), 1704 (C=O) cm^{-1}.

*4.4.1.6. Mixture of 1-[(1S,3S)-3-ethynyl-2,2-dimethylcyclopropyl] propan-2-one (**2g**) and (E)-5,5-dimethylocta-3,6,7-trien-2-one (**4**).* The reaction was carried out according to GP1 using **1g** (0.219 g, 1.30 mmol), NfF (0.397 g, 1.32 mmol), and P_1-base (0.818 g, 2.62 mmol). Column chromatography on SiO_2 (hexane to hexane/EtOAc, 30:1 to 20:1 to 10:1) afforded a mixture of **2g** and **4** (0.05 g, 26%, ratio **2g**/**4**=2.7/1 by ^{1}H NMR) as a pale yellow oil; R_f 0.41; ^{1}H NMR ($CDCl_3$) for compound **2g** (from the mixture with **4**) δ 2.58 (dd, 1H, J=18.1, 7.5 Hz, H-1), 2.42 (dd, 1H, J=18.1, 6.3 Hz, H-1), 2.17 (s, 3H, COMe), 1.91 (d, 1H, J=2.2 Hz, ≡CH), 1.29 (dd, 1H, J=8.6, 2.2 Hz, H-3′), 1.15–1.10 (m, 1H, H-1′), 1.10 (s, 3H, Me-2′), 1.03 (s, 3H, Me-2′); ^{1}H NMR ($CDCl_3$) for compound **4** (from the mixture with **2g**) δ 6.74 (d, 1H, J=16.2 Hz, H-3), 6.02 (d, 1H, J=16.2 Hz, H-4), 5.09 (t, 1H, J=6.6 Hz, H-6), 4.79 (d, 2H, J=6.6 Hz, H-8), 2.24 (s, 3H, COMe), 1.18 (s, 6H, 2Me-5); ^{13}C NMR ($CDCl_3$) for the mixture of **2g** and **4** δ 208.0, 206.9, 199.0, 155.4, 127.4, 98.4, 82.6, 77.7, 68.7, 40.2, 37.0, 30.0, 27.23, 27.20, 27.19, 24.2, 21.4, 17.4, 16.2.

*4.4.1.7. 1-[(1S,3S)-3-Ethynyl-2,2-dimethylcyclopropyl]propan-2-one (**2g**).* The reaction was carried out according to GP1 using **1g** (0.185 g, 1.10 mmol), NfF (0.336 g, 1.11 mmol), and P_1-base (0.691 g, 2.21 mmol) in THF as the reaction medium. Column chromatography on SiO_2 (hexane/EtOAc, 30:1 to 20:1 to 10:1) afforded **2g** (0.03 g, 18%) as a pale yellow oil; R_f 0.35; ^{1}H NMR (C_6D_6) δ 2.34 (dd, 1H, J=18.0, 7.3 Hz, H-1), 2.17 (dd, 1H, J=18.0, 6.5 Hz, H-1), 1.73 (s, 3H, COMe), 1.72 (d, 1H, J=2.2 Hz, ≡CH), 1.10 (dd, 1H, J=8.6, 2.2 Hz, H-3′), 0.98 (s, 3H, Me-2′), 0.98–0.93 (m, 1H, H-1′), 0.82 (s, 3H, Me-2′); ^{13}C NMR (C_6D_6) δ 205.4, 82.7, 69.0, 40.0, 29.4, 27.0, 24.6, 21.3, 17.6, 16.3; EI-HRMS: m/z $[M-H]^+$ calcd for $C_{10}H_{13}O$: 149.0966, found: 149.0971; IR (neat): 3294 (C–H), 2110 (C≡C), 1715 (C=O) cm^{-1}.

*4.4.1.8. 2-(Prop-2-ynyl)cyclohexanone (**2i**).*[24] The reaction was carried out according to GP1 using **1i** (0.154 g, 1.00 mmol), NfF (0.305 g, 1.01 mmol), and P_1-base (0.628 g, 2.01 mmol). Column chromatography on SiO_2 (hexane/EtOAc, 10:1 to 5:1) afforded **2i** (0.082 g, 60%) as a pale yellow oil; R_f 0.32; ^{1}H NMR ($CDCl_3$) δ 2.62–2.55 (m, 1H), 2.52–2.25 (m, 4H), 2.20–2.13 (m, 1H), 2.10–2.05 (m, 1H), 1.94 (t, 1H, J=2.6 Hz, ≡CH), 1.94–1.87 (m, 1H), 1.74–1.57 (m, 2H), 1.44–1.34 (m, 1H); ^{13}C NMR (C_6D_6) δ 210.8, 82.7, 69.5, 49.6, 42.0, 33.3, 27.9, 25.2, 18.9.

*4.4.1.9. 2-(Prop-2-ynyl)cycloheptanone (**2j**).*[25] The reaction was carried out according to GP1 using **1j** (0.168 g, 1.00 mmol), NfF (0.305 g, 1.01 mmol), and P_1-base (0.628 g, 2.01 mmol). Column chromatography on SiO_2 (hexane/EtOAc, 5:1 to 2:1) afforded **2j** (0.115 g, 77%) as a pale yellow liquid; R_f 0.37; ^{1}H NMR ($CDCl_3$) δ 2.77–2.70 (m, 1H), 2.59–2.42 (m, 3H), 2.24 (ddd, 1H, J=17.0, 4.4, 2.7 Hz, H-1), 2.03–1.99 (m, 1H), 1.94 (t, 1H, J=2.7 Hz, ≡CH), 1.94–1.81 (m, 3H), 1.70–1.60 (m, 1H), 1.53–1.31 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 213.9, 82.8, 69.4, 50.9, 43.5, 30.5, 29.5, 29.0, 24.0, 21.0.

4.5. Synthesis of cyclopentenyl nonaflate

4.5.1. Cyclopentenyl nonaflate.[26] Cyclopentanone (1.00 g, 11.9 mmol) and NfF (4.13 g, 13.7 mmol) were mixed in dry DMF (12 mL), and the resulting solution was cooled to 0 °C, followed by dropwise addition of P_1-base (4.28 g, 13.7 mmol). The reaction

mixture was stirred at rt for 18 h, quenched with saturated NH_4Cl solution (20 mL) and extracted with hexane (3×25 mL). The combined organic layers were washed with water (25 mL), brine (25 mL), dried over Na_2SO_4, and concentrated. Flash chromatography on SiO_2 (hexane/EtOAc, 20:1) afforded cyclopent-1-enyl nonaflate (3.98 g, 91%) as a colorless oil; ^1H NMR ($CDCl_3$) δ 5.65–5.63 (m, 1H, H-2), 2.60–2.55 (m, 2H), 2.45–2.39 (m, 2H), 2.07–2.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 149.9, 117.9, 31.1, 28.1, 21.0.

4.6. One-pot palladium catalyzed Sonogashira coupling

*4.6.1. General procedure for Sonogashira coupling (GP2) exemplified by the synthesis of 6-cyclopentenylhex-5-yn-2-one (**3b**).* Keto aldehyde **1b** (0.220 g, 1.93 mmol), NfF (0.588 g, 1.95 mmol), and DMF (2 mL) were placed in a round-bottom flask. The flask was cooled to −30 °C whereupon the P_1-base (1.210 g, 3.87 mmol) was added dropwise. The reaction mixture was allowed to warm gradually to rt and stirred for 16–18 h (NMR monitoring). It was purged with argon. Subsequently PPh_3 (0.032 g, 0.12 mmol), a mixture of $PdCl_2$ (0.011 g, 0.06 mmol) and CuI (0.023 g, 0.12 mmol), cyclopentenyl nonaflate (0.441 g, 1.20 mmol) and *i*-Pr_2NH (0.487 g, 4.82 mmol) were added. The reaction mixture was stirred overnight, quenched with saturated aq NH_4Cl (15 mL) and extracted with Et_2O (4×15 mL). The combined ethereal extracts were washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated.

*4.6.1.1. 6-Cyclopentenylhex-5-yn-2-one (**3b**).* Column chromatography on SiO_2 (hexane to hexane/EtOAc, 20:1 to 10:1) afforded **3b** (0.180 g, 92%) as a colorless oil; R_f 0.40; ^1H NMR ($CDCl_3$) δ 5.95–5.93 (m, 1H, =CH), 2.71–2.68 (m, 2H), 2.60–2.56 (m, 2H), 2.42–2.37 (m, 4H), 2.18 (s, 3H, COMe), 1.91–1.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 206.7, 136.7, 124.8, 89.7, 78.4, 42.8, 36.7, 33.2, 30.0, 23.4, 14.3; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{11}H_{14}O$: 162.1045, found: 162.1047; IR (neat): 1716 (C=O), 1612 (C=C) cm^{-1}.

*4.6.1.2. 8-Cyclopentenyloct-7-yn-2-one (**3c**).* The reaction was carried out according to GP2 using **1c** (0.142 g, 1.00 mmol), NfF (0.305 g, 1.01 mmol), P_1-base (0.628 g, 2.01 mmol), PPh_3 (0.018 g, 0.067 mmol), $PdCl_2$ (0.006 g, 0.034 mmol), CuI (0.013 g, 0.067 mmol), cyclopent-1-enyl nonaflate (0.244 g, 0.67 mmol), and *i*-Pr_2NH (0.271 g, 2.68 mmol). Column chromatography on SiO_2 (hexane/EtOAc, 10:1 to 5:1) afforded **3c** (0.113 g, 88%) as a yellow oil; R_f 0.37; ^1H NMR ($CDCl_3$) δ 5.93–5.92 (m, 1H, =CH), 2.45 (t, 2H, *J*=7.3 Hz), 2.42–2.36 (m, 4H), 2.33 (t, 2H, *J*=7.1 Hz), 2.13 (s, 3H, COMe), 1.90–1.83 (m, 2H), 1.73–1.63 (m, 2H), 1.57–1.49 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 208.8, 136.3, 125.0, 90.8, 78.3, 43.3, 36.8, 33.2, 30.0, 28.4, 23.4, 23.2, 19.4; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{13}H_{18}O$: 190.1358, found: 190.1356; IR (neat): 1713 (C=O) cm^{-1}.

*4.6.1.3. 11-Cyclopentenylundec-10-yn-5-one (**3d**).* The reaction was carried out according to GP2 using **1d** (0.184 g, 1.00 mmol), NfF (0.305 g, 1.01 mmol), P_1-base (0.628 g, 2.01 mmol), PPh_3 (0.024 g, 0.09 mmol), $PdCl_2$ (0.008 g, 0.045 mmol), CuI (0.017 g, 0.09 mmol), cyclopent-1-enyl nonaflate (0.330 g, 0.90 mmol), and *i*-Pr_2NH (0.364 g, 3.60 mmol). Column chromatography on SiO_2 (pentane/Et_2O, 30:1 to 20:1) afforded **3d** (0.196 g, 94%) as a pale yellow oil; R_f 0.40; ^1H NMR ($CDCl_3$) δ 5.94–5.92 (m, 1H, =CH), 2.44–2.31 (m, 10H), 1.91–1.83 (m, 2H), 1.72–1.65 (m, 2H), 1.58–1.49 (m, 4H), 1.35–1.26 (m, 2H), 0.90 (t, 3H, *J*=7.3 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 211.2, 136.3, 125.0, 90.9, 78.3, 42.7, 42.4, 36.8, 33.2, 28.5, 26.2, 23.4, 23.2, 22.5, 19.5, 14.0; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{16}H_{24}O$: 232.1827, found: 232.1833; IR (neat): 1712 (C=O), 1612 (C=C) cm^{-1}.

*4.6.1.4. 6-Cyclopentenyl-1-phenylhex-5-yn-1-one (**3e**).* The reaction was carried out according to GP2 using **1e** (0.184 g, 0.965 mmol), NfF (0.295 g, 0.98 mmol), P_1-base (0.606 g, 1.94 mmol), PPh_3 (0.016 g, 0.06 mmol), $PdCl_2$ (0.005 g, 0.03 mmol), CuI (0.012 g, 0.06 mmol), cyclopent-1-enyl nonaflate (0.220 g, 0.60 mmol), and *i*-Pr_2NH (0.244 g, 2.41 mmol). Column chromatography on SiO_2 (hexane/EtOAc, 30:1) and further purification by preparative TLC (hexane/EtOAc=10:1) afforded **3e** (0.128 g, 86%) as a beige solid; R_f 0.45; mp 33–34 °C; ^1H NMR ($CDCl_3$) δ 8.00–7.97 (m, 2H, *o*-Ph), 7.58–7.54 (m, 1H, *p*-Ph), 7.48–7.45 (m, 2H, *m*-Ph), 5.95–5.93 (m, 1H, =CH), 3.13 (t, 2H, *J*=7.3 Hz), 2.47 (t, 2H, *J*=6.8 Hz), 2.43–2.39 (m, 4H), 2.02–1.95 (m, 2H), 1.92–1.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 199.9, 137.2, 136.5, 133.1, 129.0, 128.7, 128.3, 128.2, 125.0, 90.5, 78.9, 37.5, 36.8, 33.2, 23.45, 23.43, 19.2; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{17}H_{18}O$: 238.1358, found: 238.1362; IR ($CDCl_3$): 1684 (C=O), 1645 (C=C) cm^{-1}.

*4.6.1.5. 1-[(1R,3S)-3-(Cyclopentenylethynyl)-2,2-dimethylcyclobutyl]ethanone (**3f**).* The reaction was carried out according to GP2 using **1f** (0.239 g, 1.42 mmol), NfF (0.433 g, 1.44 mmol), P_1-base (0.892 g, 2.86 mmol), PPh_3 (0.023 g, 0.09 mmol), $PdCl_2$ (0.008 g, 0.04 mmol), CuI (0.017 g, 0.09 mmol), cyclopent-1-enyl nonaflate (0.325 g, 0.89 mmol), and *i*-Pr_2NH (0.359 g, 3.55 mmol). Column chromatography on SiO_2 (hexane/EtOAc, 30:1 to 20:1) afforded **3f** (0.176 g, 92%) as a tan solid; R_f 0.35; mp 32–33 °C; ^1H NMR ($CDCl_3$) δ 5.95–5.94 (m, 1H, =CH), 2.87 (dd, 1H, *J*=10.6, 7.6 Hz), 2.80 (dd, 1H, *J*=10.6, 8.6 Hz), 2.42–2.31 (m, 5H), 2.13–2.08 (m, 1H), 2.05 (s, 3H, COMe), 1.91–1.84 (m, 2H), 1.33 (s, 3H, Me-2), 1.02 (s, 3H, Me-2); ^{13}C NMR ($CDCl_3$) δ 207.1, 136.7, 124.9, 90.2, 81.3, 54.4, 44.9, 36.8, 33.3, 30.11, 30.06, 23.4, 19.2; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{20}O$: 216.1514, found: 216.1519; IR ($CDCl_3$): 1706 (C=O), 1612 (C=C) cm^{-1}.

*4.6.1.6. 2-(3-Cyclopentenylprop-2-ynyl)cyclohexanone (**3i**).* The reaction was carried out according to GP2 using **1i** (0.154 g, 1.00 mmol), NfF (0.305 g, 1.01 mmol), P_1-base (0.628 g, 2.01 mmol), PPh_3 (0.016 g, 0.063 mmol), $PdCl_2$ (0.006 g, 0.031 mmol), CuI (0.012 g, 0.063 mmol), cyclopent-1-enyl nonaflate (0.229 g, 0.625 mmol), and *i*-Pr_2NH (0.253 g, 2.50 mmol). Column chromatography on SiO_2 (hexane/EtOAc, 10:1) afforded **3i** (0.118 g, 94%) as a pale yellow solid; R_f 0.33; mp 29–30 °C; ^1H NMR ($CDCl_3$) δ 5.93–5.92 (m, 1H, =CH), 2.75 (dd, 1H, *J*=17.2, 4.2 Hz), 2.53–2.25 (m, 9H), 2.10–2.05 (m, 1H), 1.92–1.82 (m, 3H), 1.73–1.59 (m, 3H), 1.43–1.33 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 211.1, 136.4, 125.0, 89.3, 79.1, 50.0, 42.1, 36.7, 33.5, 33.2, 28.0, 25.2, 23.4, 19.9; ESI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{14}H_{19}O$: 203.1436 $[M^+ + H]$, found: 203.1430; IR ($CDCl_3$): 1708 (C=O) cm^{-1}.

*4.6.1.7. 2-(3-Cyclopentenylprop-2-ynyl)cycloheptanone (**3j**).* The reaction was carried out according to GP2 using **1j** (0.168 g, 1.00 mmol), NfF (0.305 g, 1.01 mmol), P_1-base (0.628 g, 2.01 mmol), PPh_3 (0.022 g, 0.083 mmol), $PdCl_2$ (0.007 g, 0.042 mmol), CuI (0.016 g, 0.083 mmol), cyclopent-1-enyl nonaflate (0.305 g, 0.830 mmol), and *i*-Pr_2NH (0.336 g, 3.32 mmol). Column chromatography on SiO_2 (hexane/EtOAc, 10:1 to 5:1) afforded **3j** (0.160 g, 89%) as a beige solid; R_f 0.37; mp 39–41 °C; ^1H NMR ($CDCl_3$) δ 5.93–5.92 (m, 1H, =CH), 2.75–2.66 (m, 1H), 2.65–2.61 (m, 1H), 2.57–2.36 (m, 7H), 2.04–2.00 (m, 1H), 1.90–1.82 (m, 5H), 1.69–1.59 (m, 1H), 1.51–1.31 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 214.3, 136.5, 124.9, 89.3, 79.0, 51.3, 43.5, 36.7, 33.2, 30.5, 29.6, 29.0, 24.2, 23.4, 22.1; EI-HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{20}O$: 216.1514, found: 216.1511; IR ($CDCl_3$): 1699 (C=O), 1613 (C=C) cm^{-1}.

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Supplementary data

Supplementary data contain ^{1}H and ^{13}C NMR spectra of **1d**, **2f**, mixture **2g**+**4**, **2g**, **3b**–**f**, **3i**, **3j**. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.05.095.

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