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A convenient titanium-mediated intermolecular alkyne–carbonate coupling reaction

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Dedicated to the memory of Christian Marazano

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ABSTRACT

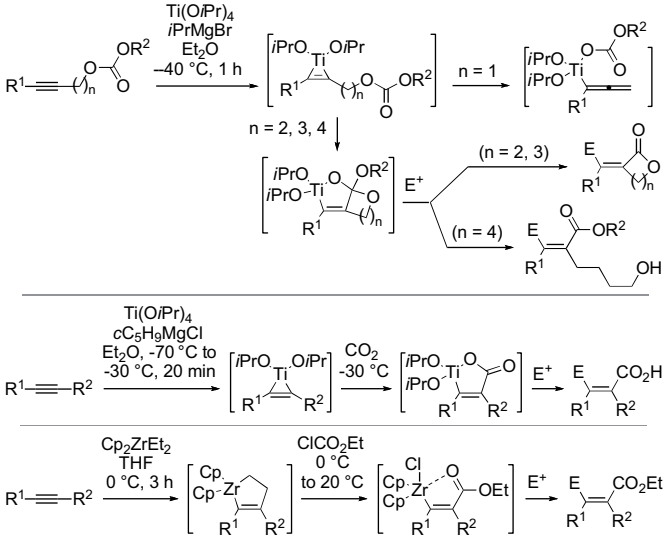
A direct diastereoselective titanium-mediated intermolecular coupling of internal alkynes with dialkyl carbonates under Kulinkovich-type reaction conditions is presented. The influence of the structures of the coupling partners on the yields and regioselectivities of this transformation is described.

1. Introduction

Since the initial report of Kulinkovich et al.,[1] the chemistry of dialkoxytitanacyclopropanes generated from Ti(O*i*-Pr)$_4$ (or ClTi(O*i*-Pr)$_3$) and Grignard reagents has been the subject of extensive development.[2] In particular, the group of Sato has shown that these species may undergo ligand exchange with alkynes to give alkyne–titanium complexes that can be viewed as dialkoxytitanacyclopropenes.[3] Their reactions with electrophiles or reactive unsaturated compounds allow functionalisation of both carbon atoms of the alkyne function with essentially complete diastereoselectivity.[3,4]

A particularly interesting process is the Intramolecular Nucleophilic Acyl Substitution (INAS) developed by Sato et al.: under Kulinkovich-type conditions, alkynes fitted with a carbonate function undergo regioselective intramolecular carboxylation at the proximal carbon atom of the alkyne moiety (Scheme 1, top).[5,6] However, this reaction can give two types of products depending on which of the σ_{C-O} bonds of the carbonate function is broken, and its scope is limited by the necessity for the alkyne substrates to contain a carbonate group at a suitable distance.

Related complementary processes have been reported, such as the carboxylation of alkynes with carbon dioxide, also involving dialkoxytitanacyclopropene intermediates (Scheme 1, middle),[7,8] the Cp$_2$Zr-mediated carboxylation of alkynes with chloroformates (Scheme 1, bottom)[9] and the Cp$_2$Zr-mediated carboxylation of alkynes with carbon dioxide.[10] These reactions are nonetheless not



Scheme 1. Titanium- or zirconium-mediated alkyne carboxylation reactions.

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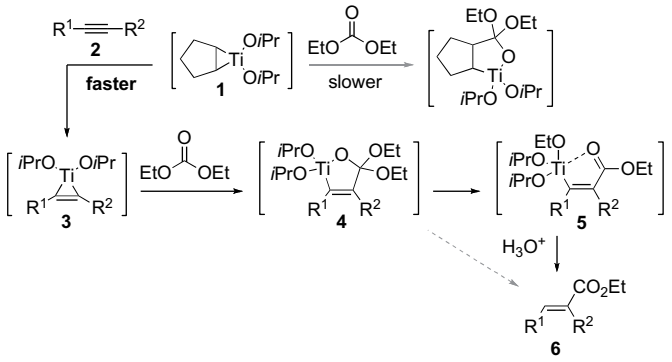
fully satisfactory, with stepwise practical procedures necessitating the intermediate formation of metallacycloalkene complexes, as well as low temperature (−30 °C) or long reaction times (typically several hours). In this context, nickel-mediated alkyne carboxylation processes with CO_2 are worth of mention too but they also suffer from the latter drawback.[11]

We have recently described the results of a study aimed at establishing a scale of reactivity of titanium complex **1**, generated from Ti(O*i*-Pr)$_4$ and *cyclo*-pentylmagnesium chloride, vis-à-vis several unsaturated compounds. Notably, it was found that this species is at least several hundred times more reactive towards alkynes than towards ethyl carbonate.[12] On the basis of this observation, it was anticipated that if complex **1** was generated in the presence of both diethyl carbonate and an internal alkyne **2**, it would first react selectively with the latter to give a titanacyclopropene species **3**. Since the 1,2-insertion of alkynes into titanacyclopropenes is essentially limited to the use of terminal alkynes, this complex would then react with the carbonate reagent rather than with a second molecule of **2**. The resulting complex **4** would then undergo rearrangement to a metallated α,β-unsaturated ester **5**, whose final hydrolysis would deliver the alkyne–carbonate coupling product **6** (Scheme 2).

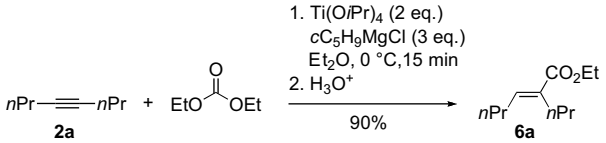


Scheme 2. Principle of the envisaged titanium-mediated coupling of alkynes with diethyl carbonate.

2. Results and discussion

2.1. Initial results

To probe our hypothesis, the coupling reaction of oct-4-yne **2a** with 1 equiv of diethyl carbonate was attempted. Pleasingly, under suitable conditions for the generation of 1 equiv of titanium intermediate complex **1**,[13] the transformation was complete within 15 min at 0 °C, delivering the expected (*E*)-α,β-unsaturated ester **6a** in 90% yield (Scheme 3). In this case, application of a lower temperature is not necessary because as soon as they are formed, the unstable species **1** and **3a** are quickly trapped with **2a** and diethyl carbonate, respectively.



Scheme 3. Ti-mediated carboxylation of oct-4-yne with diethyl carbonate.

For comparison purposes, the same transformation was performed under the conditions described by Sato et al. for the INAS reactions of alkynyl carbonates (TiO(*i*-Pr)$_4$, *i*-PrMgBr, Et$_2$O, −45 °C, 60 min),[6] giving product **6a** in 17% yield only.

Table 1
Alkyne carboxylation reactions with diethyl carbonate

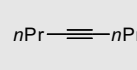
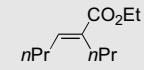
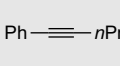
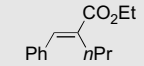
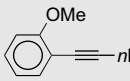
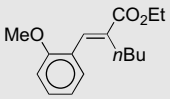
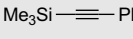
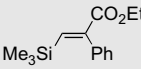
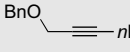
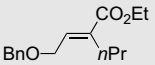
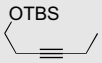
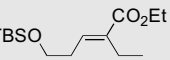
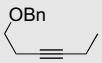
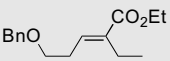
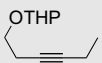
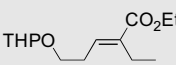
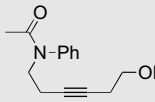
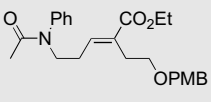
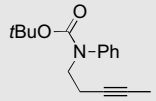
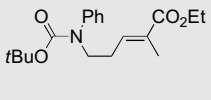
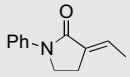
Entry	Alkyne **2**	Conditions[a]	Carboxylated product(s)[b] yield (regioselectivity)	**8** Yield
1	 **2a**	A	 **6a** 90%[c]	**8a** 0%[d]
2	 **2b**	A	 **6b** 66%[c] (79:21)[e]	**8b** 6%[d]
3	**2b**	B	**6b** 76%[c] (83:17)[e]	**8b** 5%[d]
4	 **2c**	A	 **6c** 62%[c] (78:22)[e]	**8c** 3%[d]
5	 **2d**	A	 **6d** 38%[c] (>95:5)[d,e] [starting **2d** 16%[c]]	**8d** 24%[d]
6	**2d**	C	**6d** 48%[c] (>95:5)[d,e] [starting **2d** 29%[c]]	**8d** 7%[d]
7	 **2e**	A	 **6e** 0%[d,e]	**8e** 77%[c]
8	 **2f**	A	 **6f** 28%[g] (55:45)[d] [starting **2f** 8%[e]]	**8f** 10%[d]
9	 **2g**	B	 **6g** 42%[c] (59:41)[d,f]	**8g** 16%[d]
10	**2g**	D	**6g** 68%[c] (58:42)[f]	**8g** 13%[f]
11	**2g**	E	**6g** 45%[c] (57:43)[f]	**8g** 24%[f]
12	 **2h**	B	 **6h** 62%[d] (62:38)[d]	**8h** 0%[d]
13	 **2i**	A	 **6i** 12%[c] (52:48)[h] [starting **2i** 58%[e]]	**8i** 20%[c]

Table 1 (*continued*)

Entry	Alkyne **2**	Conditions[a]	Carboxylated product(s)[b] yield (regioselectivity)	**8** Yield
14	 **2j**	A	 **6j** 46%[c] (75:25)[d]  **9** 26%[c]	**8j** 0%[d]

[a] Conditions A: Ti(O*i*-Pr)$_4$ (2 equiv), *c*-C_5H_9MgCl (3 equiv), Et_2O, 0 °C, 15 min. Conditions B: Ti(O*i*-Pr)$_4$ (2.5 equiv), *c*-C_5H_9MgCl (3.5 equiv), Et_2O, 0 °C, 15 min. Conditions C: Ti(O*i*-Pr)$_4$ (2 equiv), *c*-C_5H_9MgCl (3 equiv), Et_2O, 0 °C, 110 min. Conditions D: Ti(O*i*-Pr)$_4$ (2.5 equiv), *c*-C_5H_9MgCl (3.5 equiv), Et_2O, 0 °C, 60 min. Conditions E: Ti(O*i*-Pr)$_4$ (2.5 equiv), *c*-C_5H_9MgCl (3.5 equiv), Et_2O, −15 °C, 60 min.

[b] The major regioisomer is displayed, except in the case of the major regioisomer of **6i**, for which the position of the ester group is uncertain.

[c] Isolated yield.

[d] Estimated by ^{1}H NMR of the crude product.

[e] Estimated by ^{13}C NMR of the crude product.

[f] Estimated by GC of the crude product.

[g] Isolated yield after deprotection of the TBS ether (AcOH, THF, H_2O).

[h] Estimated by ^{1}H NMR of the isolated product.

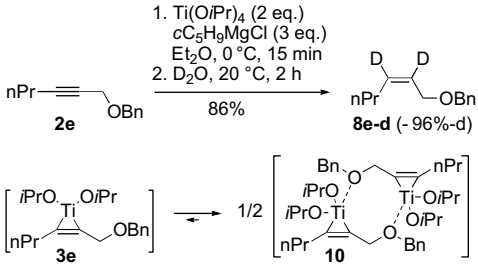
2.2. Influence of the alkyne reaction partner

The behaviours of other alkynes in the coupling reaction were next investigated. The results, collected in Table 1, show that yields are generally lower than with the simple substrate **2a**. For instance, under otherwise identical conditions, 1-phenyl-1-pentyne **2b** gave the corresponding coupling product **6b** in 66% yield only (entry 2). Performing the same transformation at 20 °C did not improve the conversion much. Moreover, its usefulness was then impaired by the production, along with the expected ethyl ester **6b**, of the corresponding *iso*-propyl ester **7b** (see Supplementary data), that proved difficult to separate from the former. This side-product stems from a documented transesterification process.[14–17]

The *ortho*-methoxyphenyl derivative **2c**[18] leads to a level of regioselectivity that is nearly identical to that of **2b** (entry 4 vs 2). Clearly, the so-called *ortho*-directing effect (ODE) that has been observed with other organometallic transformations does not operate here.[19] In contrast, trimethyl(phenylethynyl)silane **2d** undergoes carboxylation at the carbon atom bearing the aromatic substituent (entries 5 and 6), showing that the β-directing effect of the trimethylsilyl group is stronger than that of the phenyl group. This represents a striking difference with the reactions involving carbon dioxide,[8] and the pattern of regioselectivity observed here rather recalls that of reactions of titanacyclopropenes **3** with imines.[4a]

Alkyne **2e** exhibits a particular behaviour, giving no trace of the expected ester product. Instead, (*Z*)-alkene **8e** was isolated in 77% yield.[20] A deuteriolysis experiment revealed that the intermediate organometallic species involved, presumably titanacyclopropene **3e**, was stable at least up to 0 °C (Scheme 4). A possible explanation for the unusual low reactivity of intermediate **3e** could be the formation of a stable dimer **10**. Attempted carboxylation of **2e** with diethyl carbonate also proved unsuccessful in toluene at 0 °C and at 60 °C. In the latter case, the crude product contained mainly benzyl alcohol, which can be rationalised by β-elimination of benzyloxide from **3e** or **10**.

With alkynes **2f**–**h** bearing a protected 2-hydroxyethyl substituent, carboxylation occurred preferentially at the remote



Scheme 4. *epi*-Titanation of alkyne **2e** followed by deuteriolysis.

position with modest selectivity (entries 8–12). Besides, yields were generally moderate, with substantial amounts of (*Z*)-alkene by-products **8** being formed except in the case of the THP-protected substrate **2h** that gave the expected α,β-unsaturated ester **6h** exclusively (entry 12). With a view to try and improve the regioselectivity of the reaction, the transformation of **2g** was executed at −15 °C rather than 0 °C, but this only resulted in an erosion of the yield of the carboxylated product (entry 11 vs 10).

Alkynyl amide **2i** performed very poorly (entry 13), but the *N*-Boc substrate **2j** gave useful amounts of ethyl ester product, with carboxylation occurring predominantly at the distal position (entry 14). Interestingly, lactam **9** was formed as a by-product, whose production is likely to be caused by intramolecular nucleophilic attack of the titanacyclopropene moiety onto the carbonyl group of **3j**.[21] This is analogous to the INAS reactions of alkynyl carbonates described by Sato et al.[5,6] Finally, the reaction of phenylacetylene, a terminal alkyne, was attempted as well, but only gave a complex mixture of products containing trace amounts of 1,4-diphenylbuta-1,3-diene resulting from a known process.[22]

The regioselectivities of the reactions of compounds **2f**–**h** and **2j** are likely to be induced by the heteroatom-containing moiety. It may play the role of a Lewis base coordinating to the titanium centre of the titanacyclopropene intermediate **3**, thereby strengthening the proximal Csp^2–Ti bond at the expense of the distal one, making the latter more reactive.[23]

2.3. Influence of the carbonate reaction partner

A further set of experiments was performed in order to assess the influence of the carbonate educt on the reaction (Table 2).

In general, the amounts of reduced products **8** tended to be minimised with the smaller carbonate reagents, and the yields of carboxylated products tended to be higher. However, with the benzyloxy derivatives **2g** and **2l**, rather large amounts of the corresponding alkenes **8g** and **8l** were observed even using dimethyl carbonate (entries 6 and 15).

With the mixed carbonate reagent *O*-ethyl,*O*′-*iso*-propyl carbonate, mixtures of ethyl and *iso*-propyl ester products were generally obtained. The latter predominated with good to virtually complete selectivity (entries 3, 8 and 12), which can be rationalised by the better leaving group ability of the ethoxide ion relative to the *iso*-propoxide ion.

Regarding the regioselectivities of the carboxylation processes, two types of behaviours were observed. (i) With 1-phenyl-1-pentyne **2b** (entries 1–5), regioselectivity increased with the steric bulk of the carbonate reagent, as it would have been anticipated. Also in agreement with what one would have expected, the amounts of alkene by-product **8b** increased with the more hindered, less reactive carbonate reagents. (ii) With the functional alkynes **2g**–**h** and **2k**–**m**, rather surprisingly and perhaps against intuition, regioselectivity increased when the size of the carbonate reagent *decreased* (entries 6–9 and 10–13). As already mentioned, intramolecular coordination of the oxygen-based Lewis-basic group to the titanium atom is deemed responsible for the distal regioselectivity of the

Table 2
Alkyne carboxylation reactions with several carbonate reagents, performed under conditions B

Entry	Alkyne **2**	Carbonate	Coupling products [ratio] yield (regioselectivity)	Alkene **8**
1	Ph—≡—*n*Pr **2b**	MeO(C=O)OMe	Ph, CO_2Me, *n*Pr **11b** 39%[a] (82:18)[b]	**8b** 3%[b]
2	**2b**	EtO(C=O)OEt	Ph, CO_2Et, *n*Pr **6b** 76%[a] (83:17)[c]	**8b** 5%[b]
3	**2b**	EtO(C=O)O*i*Pr	**6b**+**7b** 34%[b] [13:87][b,c] **6b** (91:9)[c] **7b** (92:8)[c]	**8b** 6%[b]
4	**2b**	*i*PrO(C=O)O*i*Pr	Ph, CO_2iPr, *n*Pr **7b** 10%[b] (>90:10)[d] and a complex mixture of unidentified products	**8b** 8%[b]
5	**2b**	cyclic carbonate	Complex mixture containing starting **2b** (25%)[b]	**8b** 9%[b]
6	OBn **2g**	MeO(C=O)OMe	BnO, CO_2Me **11g** 41%[a] (70:30)[b]	**8g** 19%[b]
7	**2g**	EtO(C=O)OEt	BnO, CO_2Et **6g** 42%[a] (59:41)[b,c]	**8g** 16%[b]
8	**2g**	EtO(C=O)O*i*Pr	**6g** + BnO, CO_2iPr **7g** 38%[b] [24:76][b] **6g** (63:37)[b] **7g** (51:49)[b]	**8g** 20%[b]
9	**2g**	cyclic carbonate	Mixture of unidentified products	**8g** 39%[b]
10	OTHP **2h**	MeO(C=O)OMe	THPO, CO_2Me **11h** 43%[a] (74:26)[b]	**8h** 0%[b]
11	**2h**	EtO(C=O)OEt	THPO, CO_2Et **6h** 62%[b] (62:38)[b]	**8h** 0%[b]
12	**2h**	EtO(C=O)O*i*Pr	THPO, CO_2iPr **7h** 58%[b] (53:47)[b]	**8h** 14%[b]
13	**2h**	*i*PrO(C=O)O*i*Pr	THPO, CO_2iPr **7h** 33%[b] (53:47)[b]	**8h** 14%[b]
14	OMOM **2k**	MeO(C=O)OMe	MOMO, CO_2Me **11k** 48%[a] (72:28)[b]	**8k** 17%[b]
15	OBn **2l**	MeO(C=O)OMe	BnO, CO_2Me **11l** 45%[a] (71:29)[b]	**8l** 49%[a]
16	OTHP **2m**	MeO(C=O)OMe	THPO, CO_2Me **11m** 70%[e] (92:8)[f]	**8m** 0%[b]

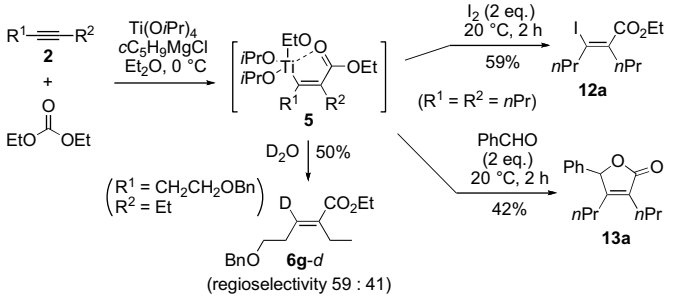
[a] Isolated yield.
[b] Estimated by ^{1}H NMR of the crude product.
[c] Estimated by GC of the crude product.
[d] Estimated by ^{13}C NMR of the crude product.
[e] Isolated yield after cleavage of the THP group (0.1 equiv *p*-TSA, MeOH, 20 °C).
[f] Estimated by ^{1}H NMR of the isolated deprotected product.

1,2-insertion of the carbonate reagent into the titanacyclopropene intermediate **3**. This elementary step must be preceded by preliminary coordination of the carbonate to the titanium atom. We thus tentatively propose that in the case of the larger carbonate molecules, this necessary intermolecular coordination induces steric constraints that destabilise the intramolecular coordination, thereby reducing regioselectivity. Conversely, with substrates containing an additional substituent between the alkyne and oxygen moieties, a Thorpe–Ingold effect favours intramolecular coordination, and regioselectivity increases (especially entry 16 vs 10).

The best result is obtained with the carboxylation of substrate **2m** with dimethyl carbonate, proceeding in 70% isolated yield with 92:8 regioselectivity (entry 16). No alkene **8m** is observed, and this example confirms the remarkably positive role of the THP protecting group, for which we have no explanation at present. It is noteworthy that the related methoxymethyl group performs much more poorly, giving similar results to those of the benzyl group (entries 6 and 14).

2.4. Use of the residual Csp^2–Ti bond

In order to ascertain the possibility of functionalising both sp carbon atoms of the alkyne starting materials, carboxylation reactions of **2a** and **2g** were executed with the final addition of either deuterium oxide, iodine or benzaldehyde. The results confirmed

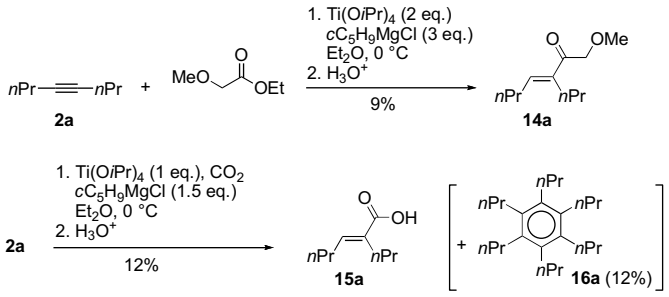


Scheme 5. Ti-mediated alkyne–carbonate couplings with functionalisation of both sp atoms of the alkyne substrates.

that the method can be applied to the preparation of deuteriated products like **6g**-*d*, as well as fully substituted iodoalkenes or butenolides such as **12a** or **13a** (Scheme 5).

2.5. Additional results

We wondered whether the presently described experimental protocol could be extended to reagents other than dialkyl carbonates. The reactions of alkyne **2a** with ethyl methoxyacetate and carbon dioxide[24] were thus attempted, but proved poorly efficient (Scheme 6). Surprisingly, in the latter case a small but significant amount of hexa-*n*-propylbenzene **16a** was isolated. This compound



Scheme 6. Attempted alkyne carbonylation reactions with an ester or with carbon dioxide.

was also formed in the absence of carbon dioxide or in the case of the reaction leading to **14a**, albeit in trace amounts. Alkyne cyclotrimerisation processes mediated by titanium complexes have been reported previously.[25–29]

3. Conclusion

Our results show that α,β-unsaturated carboxylic esters can be prepared by an intermolecular coupling reaction of alkynes and carbonates mediated by Ti(O*i*-Pr)$_4$ and *cyclo*-pentylmagnesium chloride. The experimental procedure is very simple, and does not necessitate the application of low temperatures, nor the preliminary preparation of organometallic intermediates. None of the coupling partners needs to be used in excess amounts, and the reaction times do not usually exceed 60 min.

The products are formed diastereospecifically, usually in moderate to good yields, and good regioselectivities can be achieved depending on the starting alkyne and carbonate structures.

Substrates bearing a THP-protected hydroxyl group at the β position relative to the alkyne moiety perform especially well, with essentially no by-product being formed. Their carboxylations occur at the distal sp carbon atom. Importantly, this pattern of regioselectivity is complementary to the Intramolecular Nucleophilic Acyl Substitution (INAS) reactions of the corresponding carbonates as described by Sato et al.,[5,6] which highlights the value of the present method.

4. Experimental

4.1. General

NMR spectra were recorded with AM 300, AVANCE 300 (^{1}H at 300 MHz, ^{13}C at 75.5 MHz) and AVANCE 500 (^{1}H at 500 MHz, ^{13}C at 125.8 MHz) Bruker spectrometers. Chemical shifts are given in parts per million, referenced to the peak of tetramethylsilane, defined at δ=0.00 (^{1}H NMR), or the solvent peak of $CDCl_3$, defined at δ=77.0 (^{13}C NMR). Infrared spectra were recorded with a Perkin-Elmer BX FT-IR spectrometer. Melting points were determined using a Büchi BS540 apparatus and were not corrected. Flash column chromatography was performed on SDS Chromagel silica gel 60 (35–70 μm). All reactions were carried out under argon. The temperatures mentioned are the temperatures of the cold baths or the oil baths used. Analytical grade toluene was purchased from SDS and used as such. THF and diethyl ether were purified using a PureSolv solvent purification system (Innovative Technology Inc.). Chloroform was passed through a column containing a 10 cm high amount of silica gel of the type specified above. Carbon dioxide gas was obtained by sublimation of dry ice placed in a separate flask with $MgSO_4$, and was passed through calcium chloride before being bubbled through the reaction mixture. Titanium(IV) *iso*-propoxide (VERTEC® TIPT) was purchased from Alfa Aesar, distilled under reduced pressure and stored under argon for several months. *cyclo*-Pentylmagnesium chloride 2 M solution in diethyl ether was purchased from Sigma–Aldrich or Fluka and titrated once a month according to a previously reported method.[7b] Alkynes **2a** and **2b** were purchased from Alfa Aesar, alkyne **2d** from Sigma–Aldrich, and they were used as such. Alkynes **2e** and **2i** were prepared as we reported earlier.[7b,17] Dimethyl carbonate and diethyl carbonate were purchased from Sigma–Aldrich and distilled before use.

4.2. Ti-mediated carboxylation of alkynes, general experimental procedure

Titanium(IV) *iso*-propyloxide (*m* equiv, *m* mmol) is added to a solution of alkyne (1.0 equiv, 1.0 mmol) and carbonate (1.0 equiv, 1.0 mmol) in Et_2O (5.0 mL) at *T* °C. *cyclo*-Pentylmagnesium chloride (2.0 M in Et_2O, *n* equiv, *n* mmol) is then added dropwise at *T* °C. After *t* min of stirring at *T* °C, 1 N HCl aq solution (20 mL) and Et_2O (15 mL) are added. The organic layer is separated, and the aqueous layer extracted with Et_2O (2×20 mL). The combined organic phases are then dried over $MgSO_4$, filtered and concentrated to afford the crude product. The pure carboxylated products are obtained by flash column chromatography.

Conditions A: *m*=2.0; *n*=3.0; *T*=0; *t*=15. *Conditions B*: *m*=2.5; *n*=3.5; *T*=0; *t*=15. *Conditions C*: *m*=2.0; *n*=3.0; *T*=0; *t*=110. *Conditions D*: *m*=2.5; *n*=3.5; *T*=0; *t*=60. *Conditions E*: *m*=2.5; *n*=3.5; *T*=−15; *t*=60.

*4.2.1. Carboxylation of oct-4-yne **2a** with diethyl carbonate (Scheme 3 and Table 1, entry 1)*

Conditions A were applied, and flash column chromatography of the crude product (AcOEt/heptane, gradient from 0% to 2%) afforded **6a** (90% yield).

This carboxylation process was also performed under the conditions described by Sato et al. for INAS reactions:[6] *iso*-propylmagnesium bromide (1.05 M in Et_2O, 2.6 equiv, 7.8 mmol, 7.4 mL) was added dropwise at −50 °C to a solution of Ti(O*i*-Pr)$_4$ (1.3 equiv, 3.9 mmol, 1.2 mL), 4-octyne (1.0 equiv, 3.0 mmol, 0.44 mL) and diethyl carbonate (1.0 equiv, 3.0 mmol, 0.36 mL) in Et_2O (45 mL). The resulting black-green solution was stirred for 1 h at −45 °C to −40 °C. HCl aq solution (1 N, 30 mL) was then added at −40 °C. The mixture was warmed to room temperature and stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with Et_2O (60 mL). The combined organic layers were washed with satd $NaHCO_3$ aq solution (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford a yellow oil (0.27 g). Analysis of the crude product by ^{1}H and ^{13}C NMR spectroscopies revealed the presence of ester **6a** and extensive amounts of the starting alkyne and carbonate reactants. Purification by flash column chromatography on silica gel (AcOEt/petroleum ether, gradient from 0% to 2%) afforded pure **6a** (96 mg, 0.52 mmol, 17%).

*4.2.1.1. (E)-Ethyl 2-propylhex-2-enoate (**6a**)*[9]. Colourless oil. IR (neat): 2958, 2932, 2871, 1708, 1463, 1278, 1214, 1144, 1107 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, *J*=7.5 Hz, 3H), 0.95 (t, *J*=7.5 Hz,

3H), 1.29 (t, J=7.0 Hz, 3H), 1.42 (sext, J=7.5 Hz, 2H), 1.47 (sext, J=7.5 Hz, 2H), 2.16 (q, J=7.5 Hz, 2H), 2.28 (t, J=7.5 Hz, 2H), 4.18 (q, J=7.0 Hz, 2H), 6.75 (t, J=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.9, 13.9, 14.2, 22.1, 22.5, 28.7, 30.5, 60.2, 132.5, 142.3, 168.1.

*4.2.2. Carboxylation of pent-1-ynylbenzene **2b** with diethyl carbonate (Table 1, entry 3 and Table 2, entry 2)*

Using conditions B, flash column chromatography of the crude product (AcOEt/heptane, gradient from 0% to 10%) afforded **6b** (76% yield) as an 83:17 mixture of regioisomers.

*4.2.2.1. α,β-Unsaturated ester (**6b**).* Mixture of regioisomers (83:17). Colourless oil. IR (neat): 2959, 2932, 2871, 1706, 1257, 1222, 1200, 1127, 765, 699 cm^{-1}. MS (ES$^+$) m/z 173, 219 (MH$^+$), *241* (MNa$^+$). HRMS (ES$^+$) m/z calcd for $C_{14}H_{18}NaO_2$ (MNa$^+$) 241.1204, found 241.1216.

*4.2.2.2. (E)-Ethyl 2-benzylidenepentanoate (**6b**, major regioisomer)[30].* ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, J=7.5 Hz, 3H), 1.34 (t, J=7.0 Hz, 3H), 1.57 (m, 2H), 2.50 (t, J=8.0 Hz, 2H), 4.26 (q, J=7.0 Hz, 2H), 7.10–7.49 (m, 5H), 7.66 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 14.3, 22.6, 29.5, 60.7, 128.2, 128.4, 129.1, 133.8, 135.9, 138.5, 168.5.

*4.2.2.3. (E)-Ethyl 2-phenylhex-2-enoate (**6b**, minor regioisomer).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, J=7.5 Hz, 3H), 1.25 (t, J=7.0 Hz, 3H), 1.44 (sext, J=7.5 Hz, 2H), 2.06 (q, J=7.5 Hz, 2H), 4.20 (q, J=7.0 Hz, 2H), 7.06 (t, J=7.5 Hz, 1H), 7.16 (br d, J=7.5 Hz, 2H), 7.28–7.41 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 13.8, 22.1, 31.4, 127.2, 127.8, 129.7, 144.9, 168.9.

*4.2.2.4. (Z)-Pent-1-enylbenzene (**8b**)[12,31].* ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, J=7.5 Hz, 3H), 1.45 (sext, J=7.5 Hz, 2H), 2.29 (qd, J=7.5, 2.0 Hz, 2H), 5.64 (dt, J=11.5, 7.5 Hz, 1H), 6.40 (dt, J=11.5, 2.0 Hz, 1H), 7.15–7.40 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 23.1, 30.7, 126.4, 128.0, 128.7, 128.8, 132.9, 137.5.

*4.2.3. Carboxylation of 1-(hex-1-ynyl)-2-methoxybenzene **2c** with diethyl carbonate (Table 1, entry 4)*

Conditions A were applied, and flash column chromatography of the crude product (AcOEt/heptane, gradient from 0% to 5%) allowed the separation of the two regioisomers of **6c** (53% and 9% yield).

*4.2.3.1. (E)-Ethyl 2-(2-methoxybenzylidene)hexanoate (**6c**, major regioisomer).* Colourless oil. IR (neat): 2954, 2928, 2869, 1704, 1486, 1462, 1241, 1208, 1195, 1130, 1109, 1026, 750 cm^{-1}. MS (ES$^+$) m/z 217, 285 (MNa$^+$), *431*. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.25, H, 8.66. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J=7.5 Hz, 3H), 1.34 (t, J=7.0 Hz, 3H), 1.46–1.58 (m, 4H), 2.45 (t, J=8.0 Hz, 2H), 3.83 (s, 3H), 4.26 (q, J=7.0 Hz, 2H), 6.89 (d, J=8.5 Hz, 1H), 6.95 (t, J=7.5 Hz, 1H), 7.26 (d, J=7.5 Hz, 1H), 7.30 (dd, J=8.5, 7.5 Hz, 1H), 7.78 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 14.3, 22.8, 27.5, 31.5, 55.4, 60.5, 110.4, 120.1, 125.0, 129.5, 129.6, 133.8, 134.5, 157.5, 168.4.

*4.2.3.2. (E)-Ethyl 2-(2-methoxyphenyl)hept-2-enoate (**6c**, minor regioisomer).* Colourless oil. IR (neat): 2954, 2930, 2869, 1711, 1491, 1462, 1241, 1209, 1176, 1109, 1048, 1027, 750 cm^{-1}. MS (ES$^+$) m/z *285* (MNa$^+$), 383, 431. HRMS (ES$^+$) m/z calcd for $C_{16}H_{22}NaO_3$ (MNa$^+$) 285.1467, found 285.1471. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J=7.0 Hz, 3H), 1.22 (t, J=7.0 Hz, 3H), 1.11–1.47 (m, 4H), 2.04 (q, J=7.5 Hz, 2H), 3.77 (s, 3H), 4.18 (q, J=7.0 Hz, 2H), 6.90 (d, J=8.5 Hz, 1H), 6.95 (t, J=7.5 Hz, 1H), 7.02 (t, J=7.5 Hz, 1H), 7.06 (dd, J=7.5, 1.5 Hz, 1H), 7.30 (ddd, J=8.5, 7.5, 1.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 14.2, 22.3, 29.2, 30.8, 55.4, 60.5, 110.7, 120.1, 124.8, 129.0, 131.0, 134.2, 144.9, 157.2, 167.5.

*4.2.3.3. (Z)-1-(Hex-1-enyl)-2-methoxybenzene (**8c**).* ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 2.25 (qd, J=7.5, 2.0 Hz, 2H), 5.72 (dt, J=11.5, 7.5 Hz, 1H), 6.51 (dt, J=11.5, 2.0 Hz, 1H).

*4.2.4. Carboxylation of trimethyl(phenylethynyl)silane **2d** with diethyl carbonate (Table 1, entry 6)*

Using conditions C, flash column chromatography of the crude product (AcOEt/heptane, gradient from 0% to 10%) afforded (*Z*)-alkene **8d** (7% yield), starting alkyne **2d** (29% yield) and **6d** as the single major regioisomer (48% yield). The minor regioisomer could not be detected by NMR analysis of the crude product.

*4.2.4.1. (E)-Ethyl 2-phenyl-3-(trimethylsilyl)acrylate (**6d**, major regioisomer)[32].* Colourless oil. IR (neat): 2952, 2868, 1712, 1247, 1215, 836, 760, 699 cm^{-1}. MS (ES$^+$) m/z 249 (MH$^+$), 271 (MNa$^+$). HRMS (ES$^+$) m/z calcd for $C_{14}H_{20}NaO_2Si$ (MNa$^+$) 271.1130, found 271.1123. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.15 (s, 9H), 1.22 (t, J=7.0 Hz, 3H), 4.17 (q, J=7.0 Hz, 2H), 7.14–7.19 (m, 2H), 7.18 (s, 1H), 7.26–7.32 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −0.8, 14.1, 61.1, 127.6, 127.6, 129.3, 138.3, 144.9, 147.9, 166.7.

*4.2.4.2. (Z)-Trimethyl(styryl)silane (**8d**).* This compound has already been described elsewhere.[7b]

*4.2.5. Attempted carboxylation of ((hex-2-ynyloxy)methyl)benzene **2e** with diethyl carbonate (Table 1, entry 7)*

Conditions A were applied, and the α,β-unsaturated ester **6e** was not detected by ^{1}H and ^{13}C NMR analysis of the crude product. Purification by flash column chromatography (AcOEt/heptane, gradient from 0% to 5%) gave (*Z*)-alkene **8e** (77% yield). This compound has already been described elsewhere.[7b]

*4.2.6. Carboxylation of tert-butyl(hex-3-ynyloxy)dimethylsilane **2f** with diethyl carbonate (Table 1, entry 8)*

Conditions A were applied, and flash column chromatography of the crude product (AcOEt/heptane, gradient from 0% to 10%) gave a 54:46 mixture of regioisomers of **6f** containing some impurities that was then subjected to cleavage of the TBS group.

*4.2.6.1. (E)-Ethyl 5-(tert-butyldimethylsilyloxy)-2-ethylpent-2-enoate (**6f**, major regioisomer).* ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 0.06 (s, 6H), 0.90 (s, 9H), 1.29 (t, J=7.0 Hz, 3H), 2.41 (dt, J=7.5, 6.5 Hz, 2H), 3.71 (t, J=6.5 Hz, 2H), 4.19 (q, J=7.0 Hz, 2H), 6.73 (t, J=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 20.1, 138.1.

*4.2.6.2. (E)-Ethyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)pent-2-enoate (**6f**, minor regioisomer).* ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 0.07 (s, 6H), 0.90 (s, 9H), 1.29 (t, J=7.0 Hz, 3H), 2.55 (t, J=7.0 Hz, 2H), 3.64 (t, J=7.0 Hz, 2H), 4.19 (q, J=7.0 Hz, 2H), 6.84 (t, J=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 22.0, 146.2.

*4.2.6.3. (Z)-tert-Butyl(hex-3-enyloxy)dimethylsilane (**8f**).* ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 2.05 (quint, J=7.5 Hz, 2H), 3.60 (t, J=7.0 Hz, 2H), 5.27–5.51 (m, 2H).

The above-mentioned mixture containing **6f** (221 mg obtained from 1.00 mmol of alkyne **2f**) was dissolved in THF (1.0 mL). Water (1.0 mL) and AcOH (3.0 mL) were then added, and the mixture was stirred at 20 °C for 2 h. The volatile components were removed under vacuum to afford a colourless oil (95.4 mg). Purification by flash column chromatography (AcOEt/heptane, gradient from 5% to 30%) afforded the corresponding hydroxyester as a 52:48 mixture of two regioisomers (48.8 mg, 283 μmol, 28% over the two steps).

4.2.6.3.1. Mixture of two regioisomers (52:48). Colourless oil. IR (neat): 3416, 2967, 2935, 2875, 1704, 1288, 1239, 1133, 1094, 1043,

758 cm^{-1}. MS (ES^+) *m/z 195* (MNa^+), 208. HRMS (ES^+) *m/z* calcd for $C_9H_{16}NaO_3$ (MNa^+) 195.0997, found 195.0980.

4.2.6.3.2. (E)-Ethyl 2-ethyl-5-hydroxypent-2-enoate (major regioisomer). ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (t, *J*=7.5 Hz, 3H), 1.30 (t, *J*=7.0 Hz, 3H), 2.12 (br s, 1H, OH), 2.34 (q, *J*=7.5 Hz, 2H), 2.47 (dt, *J*=7.5, 6.5 Hz, 2H), 3.74 (t, *J*=6.5 Hz, 2H), 4.20 (q, *J*=7.0 Hz, 2H), 6.73 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 14.1, 20.1, 31.7, 60.4, 61.4, 136.2, 137.5, 167.7.

4.2.6.3.3. (E)-Ethyl 2-(2-hydroxyethyl)pent-2-enoate (minor regioisomer). ^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (t, *J*=7.5 Hz, 3H), 1.30 (t, *J*=7.0 Hz, 3H), 2.12 (br s, 1H, OH), 2.25 (quint, *J*=7.5 Hz, 2H), 2.59 (t, *J*=6.5 Hz, 2H), 3.67 (t, *J*=6.5 Hz, 2H), 4.20 (q, *J*=7.0 Hz, 2H), 6.87 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.2, 14.1, 21.9, 30.1, 60.7, 62.0, 128.3, 146.5, 168.4.

4.2.7. Carboxylation of ((hex-3-ynyloxy)methyl)benzene ***2g*** *with diethyl carbonate (Table 1, entry 10)*

Using conditions D, flash column chromatography of the crude product (AcOEt/heptane, 10%) afforded **6g** as a 59:41 mixture of the two regioisomers (68% yield).

*4.2.7.1. α,β-Unsaturated ester (**6g**).* Mixture of regioisomers (59:41). Colourless oil. IR (neat): 2970, 1714, 1453, 1273, 1246, 1096, 1025, 713, 698 cm^{-1}. MS (ES^+) *m/z* 269, *285* (MNa^+), 286. HRMS (ES^+) *m/z* calcd for $C_{16}H_{22}NaO_3$ (MNa^+) 285.1467, found 285.1466.

*4.2.7.2. (E)-Ethyl 5-(benzyloxy)-2-ethylpent-2-enoate (**6g**, major regioisomer)*[33]. ^1H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, *J*=7.5 Hz, 3H), 1.22 (t, *J*=7.0 Hz, 3H), 2.25 (q, *J*=7.5 Hz, 2H), 2.43 (dt, *J*=7.5, 6.5 Hz, 2H), 3.48 (t, *J*=6.5 Hz, 2H), 4.12 (q, *J*=7.0 Hz, 2H), 4.45 (s, 2H), 6.67 (t, *J*=7.5 Hz, 1H), 7.11–7.36 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 14.2, 20.2, 29.0, 60.3, 68.8, 73.0, 127.4, 127.6, 128.3, 135.7, 137.7, 138.2, 167.6.

*4.2.7.3. (E)-Ethyl 2-(2-(benzyloxy)ethyl)pent-2-enoate (**6g**, minor regioisomer).* ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, *J*=7.5 Hz, 3H), 1.19 (t, *J*=7.0 Hz, 3H), 2.16 (quint, *J*=7.5 Hz, 2H), 2.58 (t, *J*=7.0 Hz, 2H), 3.44 (t, *J*=7.0 Hz, 2H), 4.09 (q, *J*=7.0 Hz, 2H), 4.43 (s, 2H), 6.77 (t, *J*=7.5 Hz, 1H), 7.11–7.36 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.3, 14.2, 22.0, 27.3, 60.4, 69.2, 72.7, 127.4, 127.6, 128.2, 128.2, 138.5, 146.1, 167.7.

*4.2.7.4. (Z)-((Hex-3-enyloxy)methyl)benzene (**8g**).* Compound **8g** is a known compound.[34,35]

4.2.8. Carboxylation of 2-(hex-3-ynyloxy)tetrahydro-2H-pyran ***2h*** *with diethyl carbonate (Table 1, entry 12 and Table 2, entry 11)*

Conditions B were applied, and analysis of the crude product by ^1H NMR spectroscopy revealed the presence of ester **6h**, whose yield was estimated at 62% by measuring half of the integral of the signals of the $CO_2CH_2CH_3$ protons at 4.12 ppm relative to the total integral of the O–*CH*–O protons of the THP groups of all the compounds present (4.42–4.60 ppm). The regioisomeric ratio was estimated at 62:38 by measuring the relative integrals of the signals of the olefinic protons of both regioisomers (6.67 and 6.77 ppm). (*Z*)-Alkene **8h** was not detected.

*4.2.8.1. α,β-Unsaturated ester (**6h**).* Mixture of regioisomers (62:38). HRMS (ES^+) *m/z* calcd for $C_{14}H_{24}NaO_4$ (MNa^+) 279.1572, found 279.1566.

*4.2.8.2. (E)-Ethyl 2-ethyl-5-(tetrahydro-2H-pyran-2-yloxy)pent-2-enoate (**6h**, major regioisomer).* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 0.95 (t, *J*=7.5 Hz, 3H), 1.22 (t, *J*=7.0 Hz, 3H), 2.27 (q, *J*=7.5 Hz, 2H), 2.43 (dt, *J*=7.5, 6.5 Hz, 2H), 4.12 (q, *J*=7.0 Hz, 2H), 6.67 (t, *J*=7.5 Hz, 1H).

*4.2.8.3. (E)-Ethyl 2-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)pent-2-enoate (**6h**, minor regioisomer).* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 0.99 (t, *J*=7.5 Hz, 3H), 1.22 (t, *J*=7.0 Hz, 3H), 2.18 (quint, *J*=7.5 Hz, 2H), 2.56 (t, *J*=7.0 Hz, 2H), 4.12 (q, *J*=7.0 Hz, 2H), 6.77 (t, *J*=7.5 Hz, 1H).

4.2.9. Carboxylation of N-(6-(4-methoxybenzyloxy)hex-3-ynyl)-N-phenylacetamide ***2i*** *with diethyl carbonate (Table 1, entry 13)*

Using conditions A, flash column chromatography of the crude product (AcOEt/heptane, gradient from 0% to 40%) afforded a 27:73 mixture of (*Z*)-alkene **8i** and starting alkyne **2i** (20% and 58% yields, respectively), and **6i** as 52:48 mixture of regioisomers (12% yield). Because of the low yield of **6i**, the regioselectivity of the carboxylation could not be determined by analysis of the crude product. Moreover, the structures of the regioisomers could not be assigned with certainty due to the similarities of their NMR data.

*4.2.9.1. α,β-Unsaturated ester (**6i**).* Mixture of regioisomers (52:48). Colourless oil. IR (neat): 2934, 1703, 1656, 1651, 1511, 1495, 1299, 1245, 1198, 1093, 1032, 701 cm^{-1}. MS (ES^+) *m/z 448* (MNa^+), 449. HRMS (ES^+) *m/z* calcd for $C_{25}H_{31}NNaO_5$ (MNa^+) 448.2100, found 448.2091. ^1H NMR (300 MHz, $CDCl_3$): δ 1.83 (s, 3H), 2.48 (q, *J*=7.5 Hz, 1H), 2.53–2.69 (m, 3H), 3.80 (s, 1.5H), 3.80 (s, 1.5H), 6.86 (dd, *J*=8.5, 7.5 Hz, 2H), 7.08–7.46 (m, 7H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.7, 22.7, 25.7, 27.4, 27.5, 29.2, 48.1, 48.9, 55.3, 55.3, 60.4, 60.5, 127.7, 127.8, 128.0, 128.0, 128.2, 129.1, 129.2, 129.6, 129.7, 159.2, 167.3, 170.3.

*4.2.9.2. Compound **6i**, major regioisomer.* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 1.25 (t, *J*=7.0 Hz, 3H), 3.44 (t, *J*=7.0 Hz, 2H), 3.71 (m, 2H), 4.08 (q, *J*=7.0 Hz, 2H), 4.45 (s, 2H), 6.90 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 14.1, 68.6, 72.5, 113.8, 141.8.

*4.2.9.3. Compound **6i**, minor regioisomer.* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 1.17 (t, *J*=7.0 Hz, 3H), 3.55 (t, *J*=6.5 Hz, 2H), 3.79 (m, 2H), 4.15 (q, *J*=7.0 Hz, 2H), 4.36 (s, 2H), 6.76 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 14.2, 68.4, 72.4, 113.7, 140.4.

*4.2.9.4. (Z)-N-(6-(4-Methoxybenzyloxy)hex-3-enyl)-N-phenylacetamide (**8i**).* This compound has already been described elsewhere.[17]

4.2.10. Carboxylation of tert-butyl pent-3-ynyl(phenyl)carbamate ***2j*** *with diethyl carbonate (Table 1, entry 14)*

Conditions A were applied, and flash column chromatography of the crude product (AcOEt/heptane, gradient from 10% to 30%) afforded a 78:22 mixture of regioisomers of **6j** (46% yield) and lactam **9** (26% yield). Compound **8j** was obtained independently in pure form (see note 21), which allowed us to obtain detailed analytical data for this compound.

*4.2.10.1. α,β-Unsaturated ester (**6j**).* Mixture of regioisomers (78:22). Colourless oil. IR (neat): 2975, 2931, 1702, 1697, 1693, 1389, 1364, 1275, 1255, 1164, 1144, 755, 696 cm^{-1}. MS (ES^+) *m/z* 256, *300*, 356 (MNa^+). HRMS (ES^+) *m/z* calcd for $C_{19}H_{27}NNaO_4$ (MNa^+) 356.1838, found 356.1838.

*4.2.10.2. (E)-Ethyl 5-(tert-butoxycarbonyl(phenyl)amino)-2-methylpent-2-enoate (**6j**, major regioisomer).* ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J*=7.0 Hz, 3H), 1.44 (s, 9H), 1.80 (d, *J*=1.0 Hz, 3H), 2.43 (q, *J*=7.5 Hz, 2H), 3.75 (t, *J*=7.5 Hz, 2H), 4.17 (q, *J*=7.0 Hz, 2H), 6.71 (tq, *J*=7.5, 1.0 Hz, 1H), 7.10–7.40 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.4, 14.2, 28.0, 28.2, 48.6, 60.3, 80.2, 126.1, 127.1, 128.7, 129.6, 138.0, 142.1, 154.5, 167.7.

*4.2.10.3. (E)-Ethyl 2-(2-(tert-butoxycarbonyl(phenyl)amino)ethyl)-but-2-enoate (**6j**, minor regioisomer).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J=7.0 Hz, 3H), 1.45 (s, 9H), 1.83 (d, J=7.0 Hz, 3H), 2.66 (dd, J=9.0, 6.5 Hz, 2H), 3.68 (dd, J=9.0, 6.5 Hz, 2H), 4.10 (q, J=7.0 Hz, 2H), 6.93 (q, J=7.0 Hz, 1H), 7.10–7.40 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 14.1, 14.3, 30.3, 49.1, 60.2, 80.1, 139.4, 154.3.

*4.2.10.4. (Z)-tert-Butyl pent-3-enyl(phenyl)carbamate (**8j**).* Pale yellow oil. IR (neat): 2974, 2930, 1693, 1494, 1385, 1364, 1296, 1166, 1143 cm^{-1}. MS (ES$^+$) *m/z 284* (MNa^+), 316, 545 (M_2Na^+). HRMS (ES$^+$) *m/z* calcd for $C_{16}H_{23}NNaO_2$ (MNa^+) 284.1626, found 284.1633. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.57 (dd, J=6.5, 1.5 Hz, 3H), 2.30 (tdd, J=7.5, 7.0, 1.5 Hz, 2H), 3.64 (t, J=7.5 Hz, 2H), 5.42 (AB part of an ABX_2Y_3 system, δ_A=5.34, δ_B=5.51, J_{AB}=10.5 Hz, J_{AX}=7.0 Hz, J_{AY}=1.5 Hz, J_{BX}=1.5 Hz, J_{BY}=6.5 Hz, 2H), 7.09–7.41 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.7, 26.1, 28.2, 49.4, 79.7, 125.8, 125.9, 126.5, 127.0, 128.5, 142.4, 154.5.

*4.2.10.5. (E)-3-Ethylidene-1-phenylpyrrolidin-2-one (**9**).* Colourless solid. Mp 98–99 °C. IR (neat): 2923, 2897, 1686, 1664, 1595, 1482, 1400, 1284, 1238 cm^{-1}. MS (ES$^+$) *m/z* 188 (MH^+), 189, *210* (MNa^+), 211. HRMS (ES$^+$) *m/z* calcd for $C_{12}H_{13}NNaO$ (MNa^+) 210.0892, found 210.0899. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84 (dt, J=7.0, 2.0 Hz, 3H), 2.80 (tdq, J=7.0, 3.0, 2.0 Hz, 2H), 3.88 (t, J=7.0 Hz, 2H), 6.67 (qt, J=7.0, 3.0 Hz, 1H), 7.15 (t, J=7.5 Hz, 1H), 7.38 (dd, J=8.0, 7.5 Hz, 2H), 7.73 (d, J=8.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.7, 21.3, 45.3, 119.6, 124.4, 128.8, 129.5, 132.8, 139.9, 167.5.

*4.2.11. Carboxylation of pent-1-ynylbenzene **2b** with dimethyl carbonate (Table 2, entry 1)*

Conditions B were applied, and flash column chromatography of the crude product (AcOEt/heptane, gradient from 0% to 10%) allowed the separation of the two regioisomers of **11b** (30% and 9% yields).

*4.2.11.1. (E)-Methyl 2-benzylidenepentanoate (**11b**, major regioisomer)[36].* Colourless oil. IR (neat): 2957, 2871, 1709, 1434, 1260, 1223, 1200, 1127, 1058, 765, 699 cm^{-1}. MS (EI) *m/z* 91, 115, 143, *144*, 145, 172, 173, 204 ($M^{+\bullet}$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, J=7.5 Hz, 3H), 1.57 (tq, J=8.0, 7.5 Hz, 2H), 2.49 (t, J=8.0 Hz, 2H), 3.81 (s, 3H), 7.29–7.43 (m, 5H), 7.66 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 22.6, 29.5, 51.9, 128.1, 128.4, 129.2, 133.5, 135.8, 138.9, 169.0.

*4.2.11.2. (E)-Methyl 2-phenylhex-2-enoate (**11b**, minor regioisomer)[37].* Colourless oil. IR (neat): 2957, 2870, 1714, 1494, 1453, 1247, 750, 699 cm^{-1}. MS (EI) *m/z 69*, 77, 91, 105, 115, 145. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, J=7.5 Hz, 3H), 1.45 (sext, J=7.5 Hz, 2H), 2.05 (q, J=7.5 Hz, 2H), 3.73 (s, 3H), 7.08 (t, J=7.5 Hz, 1H), 7.16 (br d, J=7.5 Hz, 2H), 7.28–7.41 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 13.8, 22.1, 31.4, 52.0, 127.3, 128.0, 129.7, 133.8, 145.4.

*4.2.12. Carboxylation of pent-1-ynylbenzene **2b** with O-ethyl,O′-iso-propyl carbonate (Table 2, entry 3)*

Conditions B were applied, and analysis of the crude product by ^{1}H NMR spectroscopy revealed the presence of (*Z*)-alkene **8b**, whose yield was estimated at 6% by measuring the integrals of the signals of the olefinic protons relative to the total integral of the aromatic protons of all the compounds present (7.00–7.40 ppm). The yields of **6b** and **7b** were estimated at 4% and 30%, respectively, by measuring the integrals of the $CO_2CH_2CH_3$ and CO_2CHMe_2 signals, respectively, again relative to the total integral of the aromatic protons. Regioisomeric ratios were assessed by GC.

*4.2.12.1. α,β-Unsaturated ester (**7b**).* Mixture of regioisomers (92:8). HRMS (ES$^+$) *m/z* calcd for $C_{15}H_{20}NaO_2$ (MNa^+) 255.1361, found 255.1360.

*4.2.12.2. (E)-iso-Propyl 2-benzylidenepentanoate (**7b**, major regioisomer).* ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, J=7.5 Hz, 3H), 1.25 (d, J=6.5 Hz, 6H), 1.50 (tq, J=8.0, 7.5 Hz, 2H), 2.41 (t, J=8.0 Hz, 2H), 5.07 (hept, J=6.5 Hz, 1H), 7.10–7.41 (m, 5H), 7.55 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 21.8, 22.5, 29.4, 68.0, 128.1, 128.3, 129.1, 134.2, 135.9, 138.3, 168.0.

*4.2.12.3. (E)-iso-Propyl 2-phenylhex-2-enoate (**7b**, minor regioisomer).* ^{1}H NMR (500 MHz, $CDCl_3$), characteristic signals: δ 1.99 (q, J=7.5 Hz, 2H), 5.00 (hept, J=6.5 Hz, 1H).

*4.2.13. Carboxylation of ((hex-3-ynyloxy)methyl)benzene **2g** with dimethyl carbonate (Table 2, entry 6)*

Using conditions B, flash column chromatography of the crude product (AcOEt/heptane, gradient from 5% to 10%) afforded **11g** as a 70:30 mixture of the two regioisomers (41% yield).

*4.2.13.1. α,β-Unsaturated ester (**11g**).* Mixture of regioisomers (70:30). Colourless oil. IR (neat): 2950, 2869, 1711, 1454, 1434, 1239, 1208, 1140, 1093, 734, 696 cm^{-1}. MS (ES$^+$) *m/z 271* (MNa^+), 272. HRMS (ES$^+$) *m/z* calcd for $C_{15}H_{20}NaO_3$ (MNa^+) 271.1310, found 271.1309.

*4.2.13.2. (E)-Methyl 5-(benzyloxy)-2-ethylpent-2-enoate (**11g**, major regioisomer).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (t, J=7.5 Hz, 3H), 2.33 (q, J=7.5 Hz, 2H), 2.51 (dt, J=7.5, 6.5 Hz, 2H), 3.56 (t, J=6.5 Hz, 2H), 3.74 (s, 3H), 4.53 (s, 2H), 6.75 (t, J=7.5 Hz, 1H), 7.21–7.42 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7, 20.2, 29.0, 51.5, 68.8, 73.0, 127.4, 127.6, 128.3, 135.4, 138.1, 138.5, 168.0.

*4.2.13.3. (E)-Methyl 2-(2-(benzyloxy)ethyl)pent-2-enoate (**11g**, minor regioisomer).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (t, J=7.5 Hz, 3H), 2.23 (quint, J=7.5 Hz, 2H), 2.66 (t, J=7.0 Hz, 2H), 3.52 (t, J=7.0 Hz, 2H), 3.72 (s, 3H), 4.50 (s, 2H), 6.85 (t, J=7.5 Hz, 1H), 7.21–7.42 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.2, 22.0, 27.3, 51.6, 69.1, 72.7, 127.4, 127.6, 127.9, 128.2, 138.6, 146.5, 168.1.

*4.2.14. Carboxylation of ((hex-3-ynyloxy)methyl)benzene **2g** with O-ethyl,O′-iso-propyl carbonate (Table 2, entry 8)*

Conditions B were applied, and analysis of the crude product by ^{1}H NMR spectroscopy revealed the presence of (*Z*)-alkene **8g**, whose yield was estimated at 20% by measuring the integrals of the signals of the olefinic protons relative to the total integral of the aromatic protons of all the compounds present (7.23–7.44 ppm). Similarly, the total yield of carboxylated compounds **6g** and **7g** was estimated at 38% by measuring the integral of the signals corresponding to their vinylic protons (6.70–6.90 ppm), again relative to the total integral of aromatic protons. Regioisomeric ratios were assessed by measuring the relative integrals of the vinylic protons of each regioisomer of **6g** and **7g**.

*4.2.14.1. (E)-iso-Propyl 5-(benzyloxy)-2-ethylpent-2-enoate (**7g**, major regioisomer).* ^{1}H NMR (500 MHz, $CDCl_3$), characteristic signals: δ 0.93 (t, J=7.5 Hz, 3H), 1.20 (d, J=6.5 Hz, 6H), 2.25 (q, J=7.5 Hz, 2H), 2.43 (dt, J=7.5, 6.5 Hz, 2H), 3.49 (t, J=6.5 Hz, 2H), 4.46 (s, 2H), 4.98 (hept, J=6.5 Hz, 1H), 6.64 (t, J=7.5 Hz, 1H).

*4.2.14.2. (E)-iso-Propyl 2-(2-(benzyloxy)ethyl)pent-2-enoate (**7g**, minor regioisomer).* ^{1}H NMR (500 MHz, $CDCl_3$), characteristic signals: δ 0.96 (t, J=7.5 Hz, 3H), 1.17 (d, J=6.5 Hz, 6H), 2.15 (quint, J=7.5 Hz, 2H), 2.58 (t, J=7.0 Hz, 2H), 3.44 (t, J=7.0 Hz, 2H), 4.44 (s, 2H), 4.98 (hept, J=6.5 Hz, 1H), 6.74 (t, J=7.5 Hz, 1H).

*4.2.15. Carboxylation of 2-(hex-3-ynyloxy)tetrahydro-2H-pyran **2h** with dimethyl carbonate (Table 2, entry 10)*

Conditions B were applied, and flash column chromatography of the crude product (AcOEt/heptane, 10%) afforded **11h** as a 78:22

mixture of the two regioisomers (43% yield). (*Z*)-Alkene **8h** was not detected in the crude product.

*4.2.15.1. α,β-Unsaturated ester (**11h**).* Mixture of regioisomers (78:22). Colourless oil. IR (neat): 2942, 2872, 1712, 1435, 1239, 1134, 1119, 1070, 1031, 983 cm^{-1}. MS (ES^+) *m/z 265* (MNa^+), 266. HRMS (ES^+) *m/z* calcd for $C_{13}H_{22}NaO_4$ (MNa^+) 265.1416, found 265.1412.

*4.2.15.2. (E)-Methyl 2-ethyl-5-(tetrahydro-2H-pyran-2-yloxy)pent-2-enoate (**11h**, major regioisomer).* ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (t, *J*=7.5 Hz, 3H), 1.42–1.93 (m, 6H), 2.34 (q, *J*=7.5 Hz, 2H), 2.50 (dt, *J*=7.5, 6.5 Hz, 2H), 3.38–3.56 (m, 2H), 3.74 (s, 3H), 3.76–3.92 (m, 2H), 4.61 (dd, *J*=4.0, 3.0 Hz, 1H), 6.75 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 19.4, 20.2, 25.4, 29.0, 30.6, 51.6, 62.2, 66.0, 98.8, 135.4, 138.3, 168.1.

*4.2.15.3. (E)-Methyl 2-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)pent-2-enoate (**11h**, minor regioisomer).* ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, *J*=7.5 Hz, 3H), 1.42–1.93 (m, 6H), 2.26 (quint, *J*=7.5 Hz, 2H), 2.63 (t, *J*=7.0 Hz, 2H), 3.38–3.56 (m, 2H), 3.73 (s, 3H), 3.76–3.92 (m, 2H), 4.58 (dd, *J*=4.0, 3.0 Hz, 1H), 6.85 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 13.2, 19.4, 22.0, 25.4, 27.3, 30.6, 51.6, 62.1, 66.2, 98.6, 146.5.

*4.2.16. Carboxylation of 2-(hex-3-ynyloxy)tetrahydro-2H-pyran **2h** with O-ethyl,O′-iso-propyl carbonate (Table 2, entry 12) and with di-iso-propyl carbonate (Table 2, entry 13)*

Using conditions B and with *O*-ethyl,*O*′-*iso*-propyl carbonate, analysis of the crude product by ^1H NMR spectroscopy revealed the presence of (*Z*)-Alkene **8h**, whose yield was estimated at 14% by measuring half of the integral of the signals of the olefinic protons relative to the total integral of the O–*CH*–O protons of the THP groups of all the compounds present (4.38–4.64 ppm). Only traces of ethyl esters **6h** were observed. The yield of **7h** was estimated at 58% by measuring the integral of the CO_2CHMe_2 signals, again relative to the total integral of the O–*CH*–O THP protons. The regioisomeric ratio was estimated at 53:47 by measuring the relative integrals of the signals of the olefinic protons of both regioisomers (6.64 and 6.75 ppm).

*4.2.16.1. (E)-iso-Propyl 2-ethyl-5-(tetrahydro-2H-pyran-2-yloxy)-pent-2-enoate (**7h**, major regioisomer).* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 0.94 (t, *J*=7.5 Hz, 3H), 1.19 (d, *J*=6.5 Hz, 6H), 2.26 (q, *J*=7.5 Hz, 2H), 2.42 (dt, *J*=7.5, 6.5 Hz, 2H), 4.98 (hept, *J*=6.5 Hz, 1H), 6.64 (t, *J*=7.5 Hz, 1H).

*4.2.16.2. (E)-iso-Propyl 2-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-pent-2-enoate (**7h**, minor regioisomer).* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 0.99 (t, *J*=7.5 Hz, 3H), 1.19 (d, *J*=6.5 Hz, 6H), 2.18 (quint, *J*=7.5 Hz, 2H), 2.55 (t, *J*=7.0 Hz, 2H), 4.98 (hept, *J*=6.5 Hz, 1H), 6.75 (t, *J*=7.5 Hz, 1H).

*4.2.16.3. (Z)-2-(Hex-3-enyloxy)tetrahydro-2H-pyran (**8h**).* ^1H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 0.90 (t, *J*=7.5 Hz, 3H), 2.33 (dt, *J*=7.5, 7.0 Hz, 2H), 5.21–5.46 (m, 2H).

*4.2.17. Carboxylation of 1-(methoxymethoxy)hex-3-yne **2k** with dimethyl carbonate (Table 2, entry 14)*

Conditions B were applied, and analysis of the crude product by ^1H NMR spectroscopy revealed the presence of (*Z*)-alkene **8k**, whose yield was estimated at 17% by measuring the integrals of the signals of the olefinic protons relative to the total integral of the O–CH_2–O protons of the MOM groups of all the compounds present (4.54–4.68 ppm). The regioisomeric ratio of **11k** was estimated at 72:28 by measuring the relative integrals of the signals of the olefinic protons of both regioisomers (6.75 and 6.86 ppm). Purification by flash column chromatography (AcOEt/heptane, gradient from 1% to 10%) afforded **11k** as a 76:24 mixture of the two regioisomers (48% yield).

*4.2.17.1. α,β-Unsaturated ester (**11k**).* Mixture of regioisomers (76:24). Colourless oil. IR (neat): 2950, 2878, 1713, 1436, 1241, 1149, 1108, 1030, 918 cm^{-1}. MS (ES^+) *m/z 225* (MNa^+). HRMS (ES^+) *m/z* calcd for $C_{10}H_{18}NaO_4$ (MNa^+) 225.1103, found 225.1105.

*4.2.17.2. (E)-Methyl 2-ethyl-5-(methoxymethoxy)pent-2-enoate (**11k**, major regioisomer).* ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (t, *J*=7.5 Hz, 3H), 2.34 (q, *J*=7.5 Hz, 2H), 2.49 (dt, *J*=7.5, 6.5 Hz, 2H), 3.37 (s, 3H), 3.63 (t, *J*=6.5 Hz, 2H), 3.74 (s, 3H), 4.63 (s, 2H), 6.75 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7, 20.2, 28.9, 51.6, 55.2, 66.3, 96.4, 135.5, 138.2, 168.0.

*4.2.17.3. (E)-Methyl 2-(2-(methoxymethoxy)ethyl)pent-2-enoate (**11k**, minor regioisomer).* ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, *J*=7.5 Hz, 3H), 2.25 (quint, *J*=7.5 Hz, 2H), 2.62 (t, *J*=7.0 Hz, 2H), 3.34 (s, 3H), 3.56 (t, *J*=7.0 Hz, 2H), 3.74 (s, 3H), 4.60 (s, 2H), 6.86 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.2, 22.0, 27.3, 51.7, 55.1, 66.4, 96.2, 127.8, 146.6, 168.2.

*4.2.17.4. (Z)-1-(Methoxymethoxy)hex-3-ene (**8k**).* ^1H NMR (500 MHz, $CDCl_3$), characteristic signals: δ 0.98 (t, *J*=7.5 Hz, 3H), 2.07 (quint, *J*=7.5 Hz, 2H), 3.54 (t, *J*=7.0 Hz, 2H), 5.29–5.54 (m, 2H).

*4.2.18. Carboxylation of ((oct-4-yn-2-yloxy)methyl)benzene **2l** with dimethyl carbonate (Table 2, entry 15)*

Conditions B were applied, and flash column chromatography of the crude product (AcOEt/heptane, 5%) afforded **8l** and **11l** (49% and 45% yields, respectively), the latter being obtained as a 76:24 mixture of the two regioisomers.

*4.2.18.1. α,β-Unsaturated ester (**11l**).* Mixture of regioisomers (76:24). Colourless oil. IR (neat): 2959, 2931, 2870, 1711, 1454, 1434, 1281, 1215, 1129, 1089, 1027, 733, 696 cm^{-1}. MS (ES^+) *m/z 299* (MNa^+), 300. HRMS (ES^+) *m/z* calcd for $C_{17}H_{24}NaO_3$ (MNa^+) 299.1623, found 299.1623.

*4.2.18.2. (E)-Methyl 5-(benzyloxy)-2-propylhex-2-enoate (**11l**, major regioisomer).* ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, *J*=7.5 Hz, 3H), 1.23 (d, *J*=6.0 Hz, 3H), 1.41 (sext, *J*=7.5 Hz, 2H), 2.28 (t, *J*=7.5 Hz, 2H), 2.43 (AB part of an ABXY system, δ_A=2.37, δ_B=2.49, J_{AB}=15.0 Hz, J_{AX}=7.5 Hz, J_{AY}=6.0 Hz, J_{BX}=7.5 Hz, J_{BY}=6.0 Hz, 2H), 3.64 (sext, *J*=6.0 Hz, 1H), 3.73 (s, 3H), 4.54 (AB system, δ_A=4.50, δ_B=4.58, J_{AB}=12.0 Hz, 2H), 6.80 (t, *J*=7.5 Hz, 1H), 7.21–7.40 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.9, 19.7, 22.3, 28.9, 35.6, 51.5, 70.5, 73.9, 127.4, 127.5, 128.3, 133.7, 138.5, 138.6, 168.2.

*4.2.18.3. (E)-Methyl 2-(2-(benzyloxy)propyl)hex-2-enoate (**11l**, minor regioisomer).* ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, *J*=7.5 Hz, 3H), 1.17 (d, *J*=6.5 Hz, 3H), 1.44 (sext, *J*=7.5 Hz, 2H), 2.19 (q, *J*=7.5 Hz, 2H), 2.54 (AB part of an ABX system, δ_A=2.39, δ_B=2.69, J_{AB}=13.5 Hz, J_{AX}=6.5 Hz, J_{BX}=7.0 Hz, 2H), 3.48 (dquint, *J*=7.0, 6.5 Hz, 1H), 3.70 (s, 3H), 4.52 (AB system, δ_A=4.48, δ_B=4.56, J_{AB}=12.0 Hz, 2H), 6.85 (t, *J*=7.5 Hz, 1H), 7.21–7.40 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 19.6, 21.9, 30.9, 34.0, 51.5, 70.6, 74.3, 127.2, 127.4, 128.1, 129.0, 138.9, 144.8, 168.4.

*4.2.18.4. (Z)-((Oct-4-en-2-yloxy)methyl)benzene (**8l**).* Colourless oil. IR (neat): 2958, 2928, 2867, 1454, 1373, 1339, 1126, 1091, 1070, 1028, 732, 695 cm^{-1}. MS (ES^+) *m/z 241* (MNa^+). HRMS (ES^+) *m/z* calcd for $C_{15}H_{22}NaO$ (MNa^+) 241.1568, found 241.1568. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, *J*=7.5 Hz, 3H), 1.19 (d, *J*=6.5 Hz, 3H), 1.37 (qt, *J*=7.5, 7.0 Hz, 2H), 2.02 (td, *J*=7.0, 6.5 Hz, 2H), 2.30 (AB part of an ABXY

system, δ_A=2.23, δ_B=2.38, J_{AB}=14.0 Hz, J_{AX}=6.5 Hz, J_{AY}=6.5 Hz, J_{BX}=6.0 Hz, J_{BY}=5.5 Hz, 2H), 3.55 (quintd, J=6.5, 5.5 Hz, 1H), 4.54 (AB system, δ_A=4.52, δ_B=4.56, J_{AB}=12.0 Hz, 2H), 5.45 (AB part of an ABX_2Y_2 system, δ_A=5.41, δ_B=5.48, J_{AB}=11.5 Hz, J_{AX}=6.0 Hz, J_{AY}=0 Hz, J_{BX}=0 Hz, J_{BY}=6.5 Hz, 2H), 7.15–7.48 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8, 19.6, 22.7, 29.5, 34.1, 70.3, 74.9, 125.6, 127.3, 127.5, 128.3, 131.7, 139.0.

4.2.19. Carboxylation of 2-(oct-4-yn-2-yloxy)tetrahydro-2H-pyran ***2m*** *with dimethyl carbonate (Table 2, entry 16)*

Conditions B were applied, and each regioisomer of *α,β-unsaturated ester* ***11m*** was obtained as a mixture of two diastereoisomers with, possibly, several stable conformations at room temperature. Nonetheless, two main isomers/conformers were detected by ^{1}H NMR spectroscopy of the crude product, with signals at 6.77 (t, J=7.5 Hz, 1H) and 6.85 (tt, J=7.5, 2.5 Hz, 1H) ppm, respectively, but detailed analysis of the crude product proved complicated and we decided to carry out the cleavage of the THP group as follows.

The crude product of the carboxylation step (320 mg obtained from 1.00 mmol of alkyne **2m**) was dissolved in methanol (5.0 mL). *para*-Toluenesulfonic acid (0.100 equiv, 100 μmol, 19.0 mg) was then added, and the mixture was stirred at 20 °C for 30 min. The solvent was removed under vacuum, and the residue redissolved in diethyl ether (25 mL). The solution was washed with satd Na_2CO_3 aq solution (5.0 mL) and water (20 mL), then dried over $MgSO_4$, filtered and concentrated to afford 206 mg of crude product. Purification by flash column chromatography afforded the corresponding hydroxyester as a 92:8 mixture of two regioisomers (130 mg, 69.8 μmol, 70% over the two steps).

4.2.19.1. Mixture of two regioisomers (92:8). Colourless oil. IR (neat): 3420, 2960, 2872, 1712, 1697, 1643, 1456, 1435, 1285, 1221, 1140, 1104, 1059, 944, 742 cm^{-1}. MS (ES$^+$) *m/z* 193, *209* (MNa^+), 210. HRMS (ES$^+$) *m/z* calcd for $C_{10}H_{18}NaO_3$ (MNa^+) 209.1154, found 209.1153.

4.2.19.2. (E)-Methyl 5-hydroxy-2-propylhex-2-enoate (major regioisomer). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, J=7.5 Hz, 3H), 1.25 (d, J=6.0 Hz, 3H), 1.43 (sext, J=7.5 Hz, 2H), 1.80 (br s, 1H, OH), 2.24–2.43 (m, 4H), 3.74 (s, 3H), 3.96 (tq, J=6.5, 6.0 Hz, 1H), 6.80 (t, J=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.0, 22.4, 23.3, 28.9, 38.2, 51.7, 67.3, 134.4, 138.2, 168.3.

4.2.19.3. (E)-Methyl 2-(2-hydroxypropyl)hex-2-enoate (minor regioisomer). ^{1}H NMR (300 MHz, $CDCl_3$), characteristic signals: δ 1.20 (d, J=6.5 Hz, 3H), 1.48 (sext, J=7.5 Hz, 2H), 2.21 (q, J=7.5 Hz, 2H), 3.73 (s, 3H), 6.91 (t, J=7.5 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$), characteristic signals: δ 22.0, 22.7, 31.9, 36.4, 51.9, 67.6, 145.5, 168.8.

4.3. Ti-mediated deuteriation of ((hex-2-ynyloxy)methyl)benzene 2e (Scheme 4)

Titanium(IV) *iso*-propyloxide (2.00 equiv, 2.00 mmol, 590 μL) was added to a solution of **2e** (1.00 equiv, 1.00 mmol, 188 mg) in Et_2O (5.0 mL) at 0 °C, followed by *cyclo*-pentylmagnesium chloride (1.94 M in Et_2O, 3.00 equiv, 3.00 mmol, 1.55 mL), dropwise at 0 °C. After 15 min of stirring at 0 °C, deuterium oxide (0.5 mL) was added, and the mixture was stirred for 2 h at 20 °C. HCl aq solution (1 N, 20 mL) and Et_2O (15 mL) were then added. The organic layer was separated, and the aqueous layer extracted with Et_2O (2×20 mL). The combined organic phases are then dried over $MgSO_4$, filtered and concentrated to afford a colourless oil (186 mg). Purification by flash column chromatography (AcOEt/heptane, gradient from 0% to 5%) afforded pure deuteriated (*Z*)-alkene ***8e-d*** (165 mg, 85.8 μmol, 86%), with ≈96% of deuterium incorporation at both vinylic carbon atoms as measured by ^{1}H NMR spectroscopy.

*4.3.1. (Z)-1-Benzyloxyhex-2-ene-2,3-^{2}H (**8e**-d)*

Colourless oil. IR (neat): 2955, 2924, 2868, 2360, 2340, 1456, 1090, 1071, 697 cm^{-1}. MS (EI) *m/z 90*, 91, 104, 107, 148. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J=7.5 Hz, 3H), 1.37 (sext, J=7.5 Hz, 2H), 2.01 (t, J=7.5 Hz, 2H), 4.06 (s, 2H), 4.49 (s, 2H), 7.22–7.42 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.6, 22.6, 29.4, 65.5, 71.9, 125.6 (t, J=24.0 Hz), 127.4, 127.6, 128.2, 133.1 (t, J=24.0 Hz), 138.4.

4.4. β-Iodo α,β-unsaturated ester 12a (Scheme 5)

Conditions A were applied starting from alkyne **2a** and diethyl carbonate, but before carrying out the hydrolysis, iodine (2.00 equiv, 2.00 mmol, 508 mg) was added at 0 °C and the mixture was stirred at 20 °C for 2 h. HCl aq solution (1 N, 20 mL), sodium metabisulfite $Na_2S_2O_5$ (≈500 mg) and Et_2O (15 mL) were then added. The organic layer was separated, and the aqueous layer extracted with Et_2O (2×20 mL). The combined organic phases were then dried over $MgSO_4$, filtered and concentrated to afford a yellow oil (305 mg). Purification by flash column chromatography (AcOEt/heptane, gradient from 0% to 5%) afforded **12a** (182 mg, 587 μmol, 59%).

*4.4.1. (Z)-Ethyl 3-iodo-2-propylhex-2-enoate (**12a**)*[9]

Colourless oil. IR (neat): 2958, 2931, 2870, 1725, 1463, 1271, 1217, 1134, 1101, 1025 cm^{-1}. MS (ES$^+$) *m/z* 319, *333* (MNa^+), 341, 399. HRMS (ES$^+$) *m/z* calcd for $C_{11}H_{19}INaO_2$ (MNa^+) 333.0328, found 333.0338. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, J=7.5 Hz, 3H), 0.95 (t, J=7.5 Hz, 3H), 1.34 (t, J=7.0 Hz, 3H), 1.46 (sext, J=7.5 Hz, 2H), 1.59 (sext, J=7.5 Hz, 2H), 2.34 (t, J=7.5 Hz, 2H), 2.53 (t, J=7.5 Hz, 2H), 4.26 (q, J=7.0 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.9, 13.6, 14.0, 21.7, 22.5, 33.5, 42.4, 61.0, 104.7, 141.6, 169.6.

4.5. Butenolide 13a (Scheme 5)

Conditions A were applied starting from alkyne **2a** and diethyl carbonate, but before carrying out the hydrolysis, benzaldehyde (2.00 equiv, 2.00 mmol, 203 μL) was added at 0 °C and the mixture was stirred at 20 °C for 2 h. HCl aq solution (1 N, 20 mL) and Et_2O (15 mL) were then added. The organic layer was separated, and the aqueous layer extracted with Et_2O (2×20 mL). The combined organic phases were then dried over $MgSO_4$, filtered and concentrated to afford a yellow oil (459 mg). Purification by flash column chromatography (AcOEt/heptane, gradient from 0% to 30%) afforded **13a** (101 mg, 415 μmol, 42%).

*4.5.1. 5-Phenyl-3,4-dipropylfuran-2(5H)-one (**13a**)*

This compound has already been described.[7b,38]

4.6. α,β-Unsaturated ketone 14a (Scheme 6)

Conditions A were applied starting from alkyne **2a**, but ethyl methoxyacetate was used instead of the carbonate reagent. The crude product was obtained as a yellow-orange oil (201 mg). Purification by flash column chromatography (AcOEt/heptane, gradient from 0% to 20%) afforded **14a** (16.6 mg, 90.0 μmol, 9%).

*4.6.1. (E)-1-Methoxy-3-propylhept-3-en-2-one (**14a**)*

Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J=7.0 Hz, 3H), 0.97 (t, J=7.5 Hz, 3H), 1.36 (m, 2H), 1.50 (sext, J=7.5 Hz, 2H), 2.24 (q, J=7.5 Hz, 2H), 2.28 (m, 2H), 3.43 (s, 3H), 4.40 (s, 2H), 6.53 (t, J=7.5 Hz, 1H).

4.7. α,β-Unsaturated acid 15a and hexa-*n*-propylbenzene 16a (Scheme 6)

Titanium(IV) *iso*-propyloxide (1.00 equiv, 4.00 mmol, 1.18 mL) was added to a solution of alkyne **2a** (1.00 equiv, 4.00 mmol,

586 μL) in Et_2O (10 mL) at 20 °C. *cyclo*-Pentylmagnesium chloride (1.91 M in Et_2O, 1.50 equiv, 6.00 mmol, 3.14 mL) was then added dropwise at 0 °C while carbon dioxide was bubbled into the solution. After 15 min of stirring at 0 °C, 1 N HCl aq solution (40 mL) and Et_2O (30 mL) were added. The organic layer was separated, and the aqueous layer extracted with Et_2O (2×40 mL). The combined organic phases were then dried over $MgSO_4$, filtered and concentrated to afford a brown-orange oil (476 mg) that was purified by flash column chromatography (AcOEt/heptane, gradient from 0% to 2%) afforded compound **16a** contaminated with grease (111 mg), pure **15a** (70.3 mg, 450 μmol, 11%), and an 85:15 mixture of cyclopentanecarboxylic acid and **15a** (43.5 mg, 307 and 54.1 μmol, respectively). The yield of **16a** was estimated at 12% by comparing the integrals of the signals of the $ArCH_2$ protons (2.47 ppm) with that of the vinylic CH proton of **15a**.

4.7.1. (*E*)-2-Propylhex-2-enoic acid (***15a***)

This compound has already been described.[7b,39]

4.7.2. 1,2,3,4,5,6-Hexapropylbenzene (***16a***)

This compound has already been described.[40]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.07.015.

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