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Intramolecular palladium-catalyzed alkene carboalkynylation

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ABSTRACT

Carbocycles are essential building blocks for the synthesis of natural and synthetic bioactive compounds. Herein, we report the first example of palladium-catalyzed intramolecular carboalkynylation of non-activated olefins. Using activated carbonyl compounds as nucleophiles and an alkynyl bromide as an electrophile, the reaction gives access to cyclopentanes in 44–93% yield and one example of cyclohexane in 31% yield with simultaneous formation of a SP^3–SP C–C bond. The reaction therefore combines ring formation with the introduction of a versatile triple bond for further functionalization.

1. Introduction

Carbocycles confer a well-defined tridimensional structure to organic molecules and therefore allow more selective interactions with biological targets (Fig. 1). This can already be achieved with a single five-membered ring, like in prostaglandin (**1**), or with more complex polycyclic frameworks, like the classical 6,6,6,5 ring system of the steroid cholesterol (**2**). Although five- and six-membered rings are most often encountered, other ring sizes can add further structural diversity, as exemplified by the diterpene ingenol (**3**) featuring three-, five- and seven-membered rings.[1] The importance of the exact cyclic structure of bioactive terpenes is also apparent from their biosynthesis via a cyclase and an oxidase phase, an approach, which has also inspired synthetic chemists.[2] The development of new cyclization or annulation reactions to construct saturated carbocycles has consequently been an intensively investigated field of organic chemistry.

In this context, the palladium-catalyzed cyclization of carbon-nucleophiles onto alkenes is a powerful method to construct efficiently five- and six-membered rings.[3] If ring-formation can be accompanied by a second C–C bond formation in a domino reaction, the efficiency of the process will be greatly increased.[4] Nevertheless, the selective formation of two different C–C bonds in a single reaction sequence is challenging, and has been realized only in few rare cases. Most impressive are the reports of Goré,

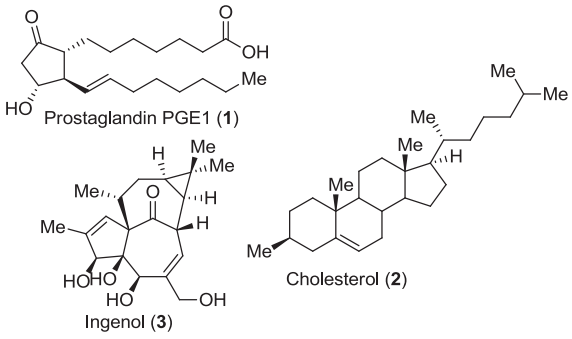

Fig. 1. Carbocycles in bioactive compounds.

Balme and co-workers on the cyclization of activated carbonyl compounds combined with arylation or vinylation (Scheme 1, **A**).[5] However, this method remains underdeveloped in comparison to the oxy- or amino-carbofunctionalization reactions, which have been intensively investigated in the last decade, in particular by Wolfe and co-workers (Scheme 1, **B**).[6]

Since 2010, our group has been particularly interested in the hetero-alkynylation of alkenes,[7] as alkynes are among the most useful functional groups in organic chemistry.[8] We have developed both a Pd^{II}-[7a–b] and a Pd^{0}-catalyzed[7c–d] intramolecular oxy/amino-alkynylation of olefins using EBX (Ethynylbenziodoxolone) hypervalent iodine reagents and alkynyl bromides respectively. Herein, we would like to report the first use of activated carbonyls as nucleophiles in a Pd^{0}-catalyzed carboalkynylation of olefins (Scheme

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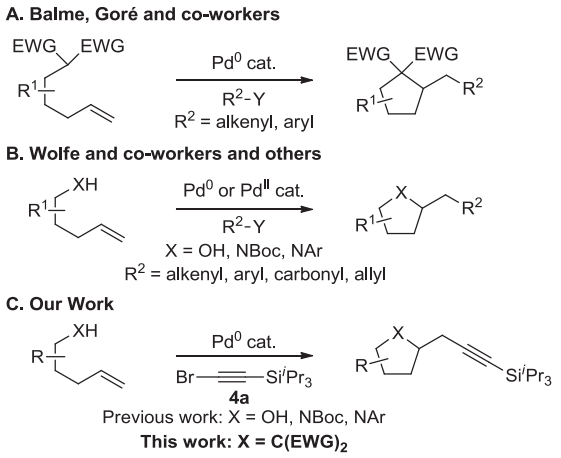
0040-4020/



Scheme 1. Pd-catalyzed intramolecular carbofunctionalization of olefins.

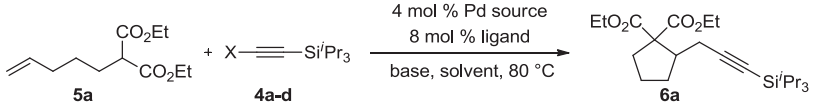
1, **C**). The method could be applied to the synthesis of five- and six-membered rings and was also successful in the case of 5,5-, 5,6- and 5,7-bicyclic ring systems.

2. Results and discussion

We started our investigations by examining the cyclization-alkynylation of diester **5a** with triisopropylsilylethynyl bromide (**4a**)[9] using the conditions developed previously for oxyalkynylation ($Pd_2(dba)_3$ with DPE-Phos as ligand, Table 1). Gratifyingly, the desired carboalkynylation product was obtained in 44% yield (entry 1). We then decided to systematically vary the palladium source, the phosphine ligand, the solvent, the base and the alkynylation reagent **4** in order to improve the yield. The palladium source used had a strong influence on the yield (entries 1–6).

Low yields were obtained with $Pd(dba)_2$, $Pd(PPh_3)_4$ or $Pd(OAc)_2$ (entries 2–4). With $PdCl_2(PPh_3)_2$, the yield could be improved to 72% (entry 5). Finally, the best result (86% yield) was obtained with $[Pd(allyl)(cod)]BF_4$[10] as precursor (entry 6). When other bisphosphine ligands were tested (entries 7–12), only dppf, which has a bite angle similar to DPE-Phos (99 vs 102°) gave a substantial yield of **6a** (40%, entry 9). With the bulky monophosphine Ru-Phos, the carboalkynylation product **6a** could be obtained in 37% yield (entry 13). Up to now, no ligand superior to DPE-Phos could be found. Examination of the base confirmed that sodium *tert*-butoxide was the best (entries 14–19). Lithium *tert*-butoxide gave a similar yield (83%, entry 14), whereas **6a** was obtained in 64% yield with potassium *tert*-butoxide (entry 15). Stronger (entries 16 and 17) and weaker (entries 18 and 19) bases gave lower yields. Interestingly, product **6a** could still be obtained in 74% yield using DBU as a base (entry 18). The solvent effect was then examined (entries 20–26). A comparable yield was obtained in dioxane (83%, entry 20). Moderate yields were still observed in trifluorotoluene and toluene (entries 21 and 22), but no desired product could be obtained in dichloroethane, acetonitrile, NMP and DMSO (entries 23–26). It is interesting to note that highly polar solvents such as NMP and DMSO, which gave the best results for the related carboarylation reaction,[5a] did not work in this case. To conclude our optimization studies, we turned to variation of the alkynylation reagent (entries

Table 1
Optimization of the carboalkynylation reaction



Entry	Pd source	Ligand/bite angle	Base	Solvent	X	Yield[a]
1	$Pd_2(dba)_3$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	44%
2	$Pd(dba)_2$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	14%
3	$Pd(PPh_3)_4$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	3%
4	$Pd(OAc)_2$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	25%
5	$PdCl_2(PPh_3)_2$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	72%
6	**[Pd(allyl)(cod)]BF$_4$**	**DPE-Phos/102°**	**NaO^{t}Bu**	**THF**	**Br**	**86%**
7	[Pd(allyl)(cod)]BF$_4$	dppe/76°	NaO^{t}Bu	THF	Br	5%
8	[Pd(allyl)(cod)]BF$_4$	dppp/86°	NaO^{t}Bu	THF	Br	<1%
9	[Pd(allyl)(cod)]BF$_4$	dppf/99°	NaO^{t}Bu	THF	Br	40%
10	[Pd(allyl)(cod)]BF$_4$	XANT-Phos/111°	NaO^{t}Bu	THF	Br	9%
11	[Pd(allyl)(cod)]BF$_4$	SEG-Phos/67°	NaO^{t}Bu	THF	Br	<1%
12	[Pd(allyl)(cod)]BF$_4$	BINAP/93°	NaO^{t}Bu	THF	Br	14%
13	[Pd(allyl)(cod)]BF$_4$	Ru-Phos	NaO^{t}Bu	THF	Br	37%
14	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	LiO^{t}Bu	THF	Br	83%
15	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	KO^{t}Bu	THF	Br	64%
16	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaHMDS	THF	Br	27%
17	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaH	THF	Br	19%
18	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	DBU	THF	Br	74%
19	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	Cs_2CO_3	THF	Br	0%
20	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	Dioxane	Br	83%
21	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	Trifluorotoluene	Br	57%
22	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	Toluene	Br	22%
23	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	Dichloroethane	Br	3%
24	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	Acetonitrile	Br	1%
25	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	DMSO	Br	<1%
26	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	NMP	Br	<1%
27	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	THF	Cl	67%
28	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	THF	I	43%
29	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	THF	BX	<1%

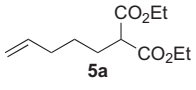
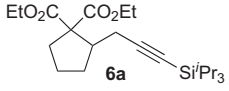
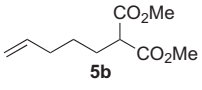
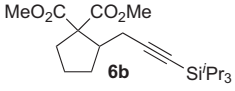
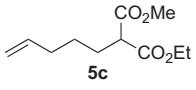
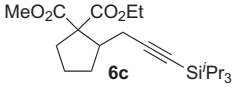
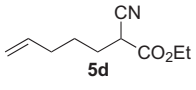
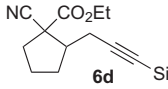
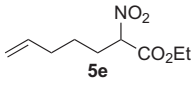
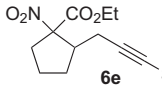
The best conditions are indicated in bold.
[a] Reaction conditions: 0.10 mmol **5a**, 0.15 mmol **4**, 4 mol% Pd source, 8 mol% ligand, 0.15 mmol base, 0.5 mL solvent, 80 °C. Yield determined by GC–MS. BX=Benziodoxolone.

27–29). The use of chloro- or iodo-alkynes **4b** and **4c** gave lower yields (entries 27 and 28). Finally, the use of the hypervalent iodine reagent TIPS-EBX (**4d**) was not successful (entry 29).

On preparative scale, cyclopentane **6a** was obtained in 85% yield (Table 2, entry 1). We then investigated, which types of activated carbonyl compounds could be used in the cyclization reaction.[11] Dimethylmalonate derivative **5b** gave the desired product **6b** in 62% yield (entry 2). The reaction was also successful in the case of mixed malonate **5c** and cyano ester **5d**, although in this case mixtures of diastereoisomers were obtained (entries 3 and 4). No product was observed when using nitro ester **5e** (entry 5).

We then turned to further modification of the diethyl malonate

Table 2
Scope of activated carbonyl compounds

Entry	Starting material	Product	Yield[a]
1	 **5a**	 **6a**	85%
2	 **5b**	 **6b**	62%
3	 **5c**	 **6c**	53%[b]
4	 **5d**	 **6d**	82%[b]
5	 **5e**	 **6e**	—

[a] Reaction conditions: 0.40 mmol **5**, 0.60 mmol **4a**, 0.015 mmol [Pd(allyl)(cod)]BF_4, 0.03 mmol DPE-Phos, 0.60 mmol NaO^tBu, 2 mL THF, 80 °C. Isolated yields after column chromatography are given.

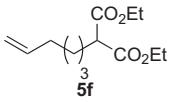
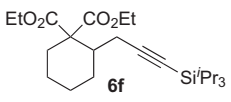
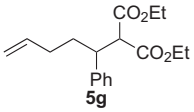
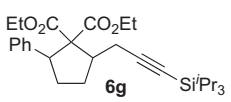
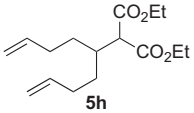
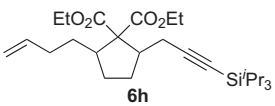
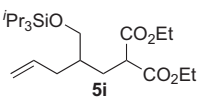
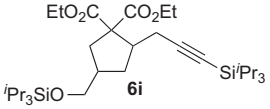
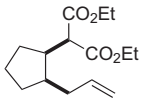
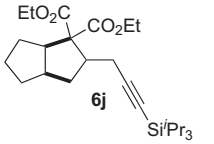
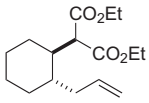
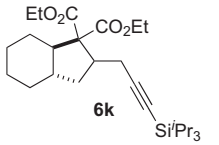
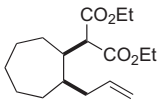
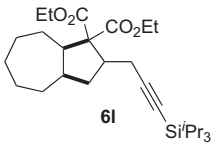
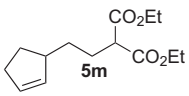
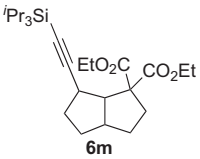
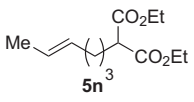
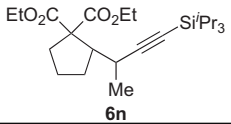
[b] Obtained as a mixture of diastereoisomer (<2:1 dr), the diastereoselectivity could not be determined exactly due to peaks overlap.

substrates (Table 3). Cyclohexane **6f** could be obtained in 31% yield, demonstrating that the synthesis of six-membered rings was also possible, albeit in lower yield (entry 1).

Substituents in β or γ positions of the malonates were well tolerated (entries 2–4). However, a low diastereoselectivity (<2:1) was observed. Substituted five-, six-, and seven-membered rings were then examined in order to access important bicyclic systems (entries 5–7). The reaction proceeded in 60–93% yield and gave a mixture of diastereoisomers at the newly formed stereocenter. Currently, the method is limited to terminal alkenes, as no product was observed when using cyclic or acyclic internal alkenes (entries 8 and 9). In addition, a complex mixture of compounds was obtained when aliphatic or aryl alkynyl bromides were used under these conditions.

At this early stage of research, only a very speculative proposal for the reaction mechanism can be made based on previous works in the field (Scheme 2).[5–7] Under the reaction conditions, a Pd^0-phosphine complex **I** is probably first generated. Oxidative addition on alkynyl bromide **4a** then gives Pd^{II} intermediate **II**. At this point, two mechanisms can be envisaged for carbopalladation: *anti* palladation via transition state **III** to give alkyl palladium complex **V**, or first ligand exchange resulting in formation of intermediate **IV**, followed by *syn* palladation to give **V**. The strong dependence on base strength indicates that deprotonation of malonate **5a** is required for the reaction to proceed. In our previous work on oxyalkynylation, we could

Table 3
Scope of substituents on the diethylmalonate substrates

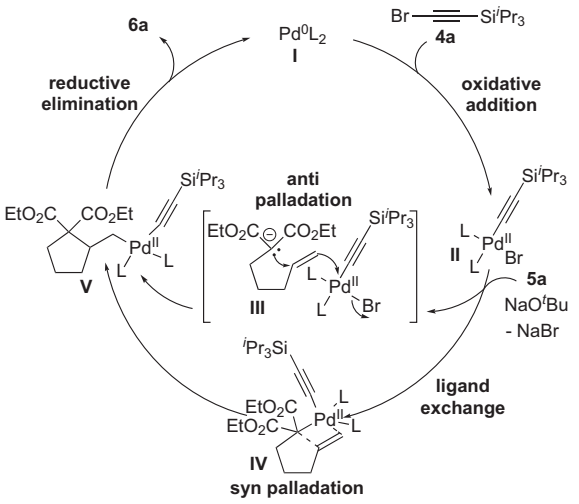
Entry	Starting material	Product	Yield[a]
1	 **5f**	 **6f**	31%
2	 **5g**	 **6g**	60%[b,c]
3	 **5h**	 **6h**	44%[b,c]
4	 **5i**	 **6i**	78%[b]
5	 **5j**	 **6j**	60%[b,c]
6	 **5k**	 **6k**	86%[b]
7	 **5l**	 **6l**	93%[b]
8	 **5m**	 **6m**	—
9	 **5n**	 **6n**	—

[a] Reaction conditions: 0.40 mmol **5**, 0.60 mmol **4a**, 0.015 mmol [Pd(allyl)(cod)]BF_4, 0.03 mmol DPE-Phos, 0.60 mmol NaO^tBu, 2 mL THF, 80 °C. Isolated yields after column chromatography are given.

[b] Obtained as a mixture of diastereoisomer (<2:1 dr), the diastereoselectivity could not be determined exactly due to peaks overlap.

[c] Compound obtained in about 90% purity as determined by ^1H NMR.

demonstrate through the use of internal alkenes as substrates that the reaction proceeded via *syn* palladation.[7c–d] On the other hand, Balme, Goré and co-workers reported strong evidence for an *anti* palladation mechanism for the related carboarylation reaction.[5a] As the reaction did not work for internal olefins under our conditions, the stereochemistry of the carbopalladation step unfortunately cannot yet be established.[12] Nevertheless, the low diastereoselectivity observed would be more in agreement with an *anti* palladation process. Finally, reductive elimination with formation of the C(SP)–C(SP^3) bond gives product **6a** and regenerates the active Pd^0 complex **I**.



Scheme 2. Speculative mechanism for the carboalkynylation reaction.

In conclusion, we have described the first example of intramolecular carboalkynylation of alkenes using activated carbonyl compounds as nucleophiles and triisopropylsilylalkynyl bromide (**4a**). The reaction proceeded in good yields for the formation of five-membered rings and tolerated a broad range of substitution patterns on the alkyl chain between the olefin and the carbonyl compound. The formation of a six-membered ring was also possible, albeit only in moderate yields. Future investigations will focus on increasing the diastereoselectivity of the process, extending the scope to internal alkenes and other types of alkynylation reagents, as well as on in-depth understanding of the reaction mechanism.

3. Experimental section

3.1. General methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma–Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content <10 ppm, Karl-Fischer titration). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40–63, 60 Å, using the solvents indicated as eluent with 0.1–0.5 bar reduced pressure. TLC was performed on Merck silica gel 60 F254 TLC glass plates or aluminium plates and visualized with UV light, permanganate stain or anisaldehyde stain. ^{1}H NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d and all signals are reported in ppm with the internal chloroform signal at 7.26 ppm The data is being reported as (s=singlet, d=doublet, t=triplet, q=quadruplet, qi=quintet, m=multiplet or unresolved, br=broad signal, app=apparent, coupling constant(s) in Hz, integration, interpretation). ^{13}C NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm. Infrared spectra were recorded on a JASCO FTIR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prism and are reported as cm^{-1} (w=weak, m=medium, s=strong, br=broad). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. All starting materials were synthesized using adapted reported procedures.[11]

3.2. General procedure for carboalkynylation

The starting material **5** (0.40 mmol) was introduced into a sealed tube containing [Pd(allyl)(cod)]BF_4 (5.2 mg, 0.015 mmol, 0.04 equiv), DPE-Phos (17 mg, 0.030 mmol, 0.08 equiv), NaO^{t}Bu (57 mg, 0.60 mmol, 1.5 equiv), dry THF (2.0 mL) and TIPS acetylene bromide (**4a**) (0.17 g, 0.60 mmol, 1.5 equiv). The vial was heated to 80 °C and the reaction stirred until complete conversion of the starting material (analysis by TLC). The mixture was then allowed to cool to room temperature, silica gel was added and the solvent was removed under reduced pressure. The crude product adsorbed on silica gel was directly put on column chromatography for purification, eluting with PET:Et_2O, 15:1.

3.3. Characterization data for cyclization products

*3.3.1. Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (**6a**).* The product was isolated as a yellow oil (0.138 g, 3.84 mmol, 85%) Rf: 0.5 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25–4.08 (m, 4H, $CO_2CH_2CH_3$), 2.80–2.72 (m, 1H, ring proton), 2.57 (dd, J=16.5, 3.9 Hz, 1H, propargylic H), 2.46–2.38 (m, 1H, ring proton), 2.17–2.01 (m, 2H, ring protons), 2.11 (dd, J=16.5, 11.2 Hz, 1H, propargylic H), 1.89–1.78 (m, 1H, ring proton), 1.70–1.56 (m, 2H, ring protons), 1.25 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.24 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.07–1.03 (m, 21H, TIPS protons). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 170.8, 107.3, 81.1, 62.8, 61.2, 61.1, 45.1, 34.4, 30.7, 22.5, 22.1, 18.6, 14.1, 14.0, 11.3. IR (neat), 2946(m), 2868(m), 2173 (w), 1731 (s), 1462 (m), 1372 (w), 1259 (s), 1200 (m), 1068 (m), 1027 (m), 881 (w). HRMS (ESI) calcd for $C_{23}H_{42}O_4Si^+$ $[M+H]^+$ 409.27741; found 409.2778.

*3.3.2. Dimethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (**6b**).* The product was isolated as a yellow oil (93.4 mg, 0.246 mmol, 62%) Rf: 0.42 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H, CO_2Me), 3.70 (s, 3H, CO_2Me), 2.81–2.73 (m, 1H, ring proton), 2.55 (dd, J=16.5 Hz, 4.0 Hz, 1H, propargylic H), 2.47–2.39 (m, 1H, ring proton), 2.16–2.03 (m, 3H, ring protons and propargylic H), 1.88–1.80 (m, 1H, ring protons), 1.71–1.58 (m, 2H, ring protons), 1.09–1.00 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 171.2, 107.0, 81.3, 62.8, 52.6, 52.3, 45.2, 34.4, 30.6, 22.5, 22.1, 18.6, 11.3. IR (neat), 2943 (m), 2865 (m). 2173 (m), 1732 (s), 1464 (m), 1463 (m), 1260 (s), 1205 (m), 1155 (m), 883 (s). HRMS (ESI) calcd for $C_{21}H_{36}NaO_4Si^+$ $[M+Na]^+$ 403.2275; found 403.2274.

*3.3.3. 1-Ethyl 1-methyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (**6c**).* The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr <2:1, 83.6 mg, 0.212 mmol, 53%). Rf: 0.48 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz $CDCl_3$) δ 4.23–4.08 (m, 4H, $CO_2CH_2CH_3$), 3.71 (s, 3H, CO_2CH_3), 3.69 (s, 3H, CO_2CH_3), 2.81–2.72 (m, 2H, ring protons), 2.59–2.51 (m, 2H, propargylic H), 2.46–2.39 (m, 2H, ring protons), 2.14–2.01 (m, 6H, ring protons and propargylic H), 1.88–1.79 (m, 2H, ring protons), 1.71–1.55 (m, 4H, ring protons), 1.26–1.21 (m, 6H, $CO_2CH_2CH_3$), 1.09–1.02 (m, 42H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 171.9, 171.3, 170.7, 107.2, 107.1, 81.1, 62.9, 62.8, 61.3, 61.2, 52.5, 52.2, 45.2, 45.0, 34.3, 30.7, 30.6, 22.5, 22.2, 22.1 18.6, 14.2, 14.1, 11.3. Not all signals for each diastereoisomer could be resolved. IR (neat), 2941 (m), 2865 (m), 2173 (m), 1731 (s), 1464 (m), 1367 (w), 1258 (s), 1202 (m), 1153 (m), 1075 (m), 1029 (m), 996 (m), 883 (m).

HRMS (ESI) calcd for $C_{22}H_{38}NaO_4Si^+$ $[M+Na]^+$ 417.2432; found 417.2413.

*3.3.4. Ethyl 1-cyano-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentanecarboxylate (**6d**).* The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr: <2:1, 0.123 g, 0.339 mmol, 82%). Rf: 0.40 (PET:Et_2O/15:1). ^1H NMR (400 MHz $CDCl_3$) δ 4.24 (q, J=7.0 Hz, 2H, $CO_2CH_2CH_3$), 2.74–2.44 (m, 3H, ring protons and propargylic H), 2.36–2.14 (m, 3H, ring protons and propargylic H), 2.04–1.65 (m, 3H, ring protons), 1.37–1.31 (m, 3H, $CO_2CH_2CH_3$) 1.08–0.97 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 167.8, 120.7, 118.1, 105.3, 104.9, 82.6, 82.0, 62.8, 62.6, 52.6, 50.5, 50.2, 47.9, 37.9, 36.7, 30.7, 30.6, 23.2, 22.6, 22.4, 21.4, 18.5, 18.4, 14.1, 14.0, 11.3, 11.2. IR (neat), 2943 (s), 2866 (s), 2243(w), 2176 (m), 2121 (m), 2062 (w), 1742 (s), 1464 (s), 1384 (w), 1369 (m), 1257 (s), 1222 (s), 1020 (s), 921 (m), 883 (s). HRMS (ESI) calcd $C_{21}H_{36}NO_2Si^+$ $[M+H]^+$ 362.2515; found 362.2516.

*3.3.5. Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclohexane-1,1-dicarboxylate (**6f**).* The product was isolated as a yellow oil (52.2 mg, 0.124 mmol, 31%). Rf: 0.49 (PET:Et_2O/15:1). ^1H NMR (400 MHz, $CDCl_3$), δ 4.21–4.15 (m, 4H, $CO_2CH_2CH_3$), 2.54–2.49 (m, 1H, propargylic H), 2.31–2.24 (m, 2H, ring protons and propargylic H), 2.17–2.10 (m, 1H, ring proton), 2.07–2.00 (m, 1H, ring proton), 1.88–1.81 (m, 1H, ring proton), 1.63–1.58 (m, 1H, ring proton), 1.52–1.30 (m, 4H, ring protons), 1.26–1.23 (m, 6H, $CO_2CH_2CH_3$), 1.07–1.02 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.5, 108.9, 81.1, 61.2, 60.9, 58.4, 41.0, 31.2, 26.4, 23.4, 22.6, 22.1, 18.6, 14.1, 11.3 (2C). IR (neat), 2942 (m), 2865 (m), 2172 (m), 1730 (s), 1261 (m), 1368 (m), 1245 (s), 1197 (m), 1142 (m), 1022 (m), 883 (m). HRMS (ESI) calcd for $C_{24}H_{43}O_4Si^+$ $[M+H]^+$ 423.2925; found 423.2938.

*3.3.6. Diethyl 2-phenyl-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (**6g**).* The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr: 2:1, 0.116 g, 0.250 mmol, 60%, >90% pure). The dr was calculated by integrating the peaks at 3.92 and 3.76 ppm in the ^1H NMR. Rf: 0.44 (PET:Et_2O/15:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.32 (m, 1H, Ar–H, both diastereoisomers), 7.23–7.17 (m, 6.5H, Ar–H, both diastereoisomer), 4.30–4.07 (m, 4H, $CO_2CH_2CH_3$ both diastereoisomer and benzylic CH major diastereoisomer), 3.98–3.87 (m, 1H, benzylic H, minor diastereoisomer and 1H, $CO_2CH_2CH_3$, minor diastereoisomer), 3.76 (dq, J=10.7, 7.1, Hz, 1H, $CO_2CH_2CH_3$, major diastereoisomer), 3.65 (dq, J=10.7, 7.2 Hz, 0.5H, $CO_2CH_2CH_3$, minor diastereoisomer), 3.36 (dq, J=10.7, 7.2 Hz, 1H, $CO_2CH_2CH_3$, major diastereoisomer), 3.16–3.08 (m, 1H, ring proton), 2.77 (dd, J=15.6, 2.5 Hz, 0.5H, propargyl CH_2, minor diastereoisomer), 2.67–2.50 (m, 2H, propargyl CH_2, major diastereoisomer and ring proton), 2.38–2.52 (m, 3H, ring protons), 2.18–2.05 (m, 1H, ring proton), 2.10 (dd, J=16.5, 10.3 Hz, 1H, propargyl CH_2, major diastereoisomer), 2.02–1.91 (m, 1H, ring proton), 1.75–1.62 (m, 1H, ring proton), 1.24 (t, J=7.1 Hz, 3H, OCH_2CH_3, major diastereoisomer), 1.21 (t, J=7.1 Hz, 1.5H, OCH_2CH_3, minor diastereoisomer), 1.09–1.05 (m, 31.5H, TIPS), 0.88 (t, J=7.2 Hz, 1.5H, OCH_2CH_3, minor diastereoisomer), 0.77 (t, J=7.2 Hz, 3H, OCH_2CH_3, major diastereoisomer). ^{13}C NMR (101 MHz, $CDCl_3$), δ 170.6, 170.1, 142.0, 139.8, 128.9, 128.7, 127.9, 127.7, 127.0, 126.8, 106.9, 81.3, 68.0, 67.6, 61.2, 61.1, 60.7, 60.5, 52.3, 51.7, 48.5, 45.1, 31.6, 30.4, 29.6, 29.0, 22.6, 21.8, 18.6, 14.1, 14.0, 13.6, 13.3, 11.4, 11.3. Not all peaks of the minor diastereoisomer could be resolved for the alkyne and the TIPS. IR (neat), 2961 (broad, s), 2172 (w), 1724 (s), 1462 (m), 1377 (m), 1252 (s), 1057 (s), 881 (m). HRMS (ESI) calcd for $C_{29}H_{45}O_4Si$ $[M+H]^+$ 485.3082; found 485.3062.

*3.3.7. Diethyl 2-(but-3-en-1-yl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (**6h**).* The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr <2:1, 81.2 mg, 0.180 mmol, 44%, >90% purity by ^1H NMR). Rf: 0.50 (PET:Et_2O/15:1). ^1H NMR (400 MHz, $CDCl_3$) δ 5.84–5.72 (m, 1H, $CH_2CH{=}CH_2$), 5.03–4.93 (m, 2H, $CH_2CH{=}CH_2$), 4.28–4.08 (m, 4H, $CO_2CH_2CH_3$), 2.92–2.76 (m, 1H), 2.71–1.80 (m, 7H), 1.72–1.60 (m, 1H), 1.38–1.24 (m, 9H), 1.11–1.00 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 171.0, 170.9, 170.4, 138.5 (2C), 114.6. 114.5, 106.9, 81.2, 66.6, 66.5, 61.0, 60.9, 47.2, 44.6, 44.0, 32.5, 32.3, 31.3, 30.8, 29.2, 29.0, 28.9, 28.2, 23.2, 18.6, 18.0, 14.2, 14.1, 11.3. Not all peaks of the minor diastereoisomer could be resolved. IR (neat), 2969 (br, s), 2173 (w), 1726 (s), 1464 (m), 1394 (m), 1252 (m), 1190 (m), 1067 (s), 883(m). HRMS (ESI) calcd for $C_{27}H_{47}O_4Si^+$ $[M+H]^+$ 463.3238; found 463.3243.

*3.3.8. Diethyl 4-(((triisopropylsilyl)oxy)methyl)-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (**6i**).* The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr <2:1, 0.186 g, 0.313 mmol, 78%). Rf: 0.51 (PET:Et_2O/15:1). ^1H NMR (400 MHz, $CDCl_3$) δ 4.23–4.09 (m, 4H, $CO_2CH_2CH_3$), 3.71–3.54 (m, 2H, OCH_2), 2.90–2.72 (m, 1H), 2.63 (dd, J=16.5, 3.8 Hz, 0.4H, propargylic H, *minor diastereoisomer*), 2.56–2.52 (m, 1.6H), 2.30–1.96 (m, 4H), 1.87–1.78 (m, 1H), 1.46–1.36 (m, 1H), 1.26–1.22 (m, 6H, $CO_2CH_2CH_3$), 1.08–1.02 (m, 42H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 171.8, 170.9, 170.8, 107.3, 107.2, 81.2, 81.0, 66.8, 66.6, 63.0, 62.5, 61.4, 61.3, 61.1, 44.6, 44.5, 39.9, 38.4, 37.1, 36.9, 34.6, 33.3, 22.5, 21.9, 18.7, 18.1, 14.1, 14.0, 12.0, 11.3. Not all signals for each diastereoisomer could be resolved. IR (neat), 1942 (m), 2892 (m), 2865 (s), 2173 (w), 1731 (s), 1464 (m), 1367 (m), 1254 (m), 1195 (m), 1098 (m), 1015 (m), 883 (s). HRMS (ESI) calcd for $C_{33}H_{63}O_5Si_2^+$ $[M+H]^+$ 595.4209; found 595.4217.

*3.3.9. Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)hexahydropentalene-1,1(2H)-dicarboxylate (**6j**).* The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr <2:1, 0.106 g, 0.237 mmol, 60%, >90% purity). Rf: 0.53 (PET:Et_2O/15:1). ^1H NMR (400 MHz, $CDCl_3$) δ 4.22–4.07 (m, 4H, $CO_2CH_2CH_3$), 3.19–3.12 (m, 0.5H), 3.04–2.95 (m, 0.3H), 2.91–2.75 (m, 1H), 2.71–2.20 (m, 3.2H), 2.17–1.87 (m, 1H), 1.85–1.40 (m, 6H), 1.26–1.22 (m, 7H, ring proton and $CO_2CH_2CH_3$), 1.06–1.02 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 170.7, 170.0, 108.1, 107.7, 80.9, 80.3, 66.1, 65.4, 61.1, 61.0, 60.7, 60.5, 51.9, 50.3, 50.2, 42.4, 42.3, 40.4, 37.9, 36.5, 35.5, 32.6, 30.7, 29.3, 28.1, 27.4, 21.8, 21.3,18.6, 14.2, 14.0, 11.3. Not all signals for each diastereoisomer could be resolved. IR (neat), 2943 (m), 2865 (m), 2173 (w), 1728 (s), 1464 (m), 1368 (m), 1252 (s), 1203 (m), 1098 (m), 1021 (m), 884 (m). HRMS (ESI) calcd for $C_{22}H_{44}NaO_4Si^+$ $[M+Na]^+$ 423.2901; found 423.2922.

*3.3.10. Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)octahydro-1H-indene-1,1-dicarboxylate (**6k**).* Reaction done using 0.0810 g (0.290 mmol) of the starting malonate. The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr <2:1, 0.111 g, 0.240 mmol, 86%). Rf: 0.53 (PET:Et_2O/15:1). ^1H NMR (400 MHz, $CDCl_3$) δ 4.27–4.06 (m, 4H, $CO_2CH_2CH_3$), 3.08–3.01 (m, 0.6H), 2.60–2.50 (m, 1H), 2.42 (dd, J=16.4, 4.3 Hz, 0.6H, propargylic H, major diastereoisomer), 2.17 (dd, J=16.3, 9.8 Hz, 0.6H, propargylic H, major diastereoisomer), 2.25–2.12 (m, 0.6H), 2.08–1.60 (m, 6H), 1.35–1.20 (m, 9H, ring protons and $CO_2CH_2CH_3$), 1.07–1.02 (m, 23H, TIPS and ring protons), 0.87–0.77 (m, 0.6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 171.4, 170.2, 169.2, 108.5, 106.5, 81.6, 80.1, 65.3, 65.0, 61.0, 60.9, 60.8, 60.5, 53.3, 51.1, 45.1, 41.4, 41.2, 41.1, 37.8, 35.6, 32.7, 32.2, 28.9, 28.1, 26.3, 26.2, 26.1, 25.8, 23.5, 22.5, 18.6, 14.2, 14.1, 14.1, 14.0, 11.3, 11.3. The methyl peaks at 18.6 ppm for the TIPS groups of both isomers were overlapping. IR (neat), 2928 (m), 2864 (m), 2173 (w), 1726 (s), 1464 (m), 1367 (w), 1250 (s), 1193 (s), 1088

(w), 1017 (m), 883 (m). HRMS (ESI) calcd for $C_{27}H_{47}O_4Si^+$ $[M+H]^+$ 463.3238; found 463.3239.

*3.3.11. Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)octahydroazulene-1,1(2H)-dicarboxylate (**6l**).* The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr <2:1, 0.176 g, 0.370 mmol, 93%). Rf: 0.54 (PET:Et_2O/15:1). ^1H NMR (400 MHz, $CDCl_3$), δ 4.28–4.07 (m, 4H, CO_2CH_2), 2.94–2.86 (m, 0.4H), 2.82 (dd, J=16.4, 3.3 Hz, 0.6H, propargylic H, major diastereoisomer), 2.76–2.68 (m, 0.4H), 2.68–2.60 (m, 0.6H), 2.54–2.44 (m, 1H), 2.41 (dd, J=16.7, 3.9 Hz, 0.4H, propargylic H, minor diastereoisomer), 2.36–2.20 (m, 1.4H), 2.09 (dd, J=16.4, 5.2 Hz, 0.6H, propargylic H, major diastereoisomer), 2.20–1.74 (m, 4.6H), 1.66–1.45 (m, 3H), 1.29–1.13 (m, 10H, ring protons and $CO_2CH_2CH_3$), 1.07–1.02 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.0, 170.6, 169.6, 107.8, 107.3, 81.2, 80.5, 68.4, 66.5, 61.0, 60.9, 60.6, 60.5, 51.7, 48.5, 46.5, 43.8, 41.7, 40.8, 39.0, 38.1, 33.4, 32.0, 31.4, 31.2, 30.6, 29.7, 29.6, 29.2, 28.0, 27.8, 22.1, 21.5, 18.6, 14.2, 14.1, 13.9, 11.3. The signals for the TIPS and for one methyl group on the esters for each diastereoisomer could not be resolved. IR (neat), 2921 (m), 2865 (m), 2173 (m), 1726 (s), 1464 (m), 1367 (m), 1252 (s), 1204 (m), 1182 (s), 1101 (m), 1076 (m), 1019 (s), 883 (s). HRMS (ESI) calcd for $C_{28}H_{49}O_4Si^+$ $[M+H]^+$ 477.3395; found 477.3411.

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Supplementary data

Supplementary data (Detailed synthesis procedures, characterization data for starting materials and copies of NMR and IR spectra for new compounds.) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.06.030.

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12. Future work will focus on the use of deuterated alkenes to investigate the stereochemistry of the carbopalladation step.