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Nickel-mediated cyclization of enynes under an atmosphere of carbon dioxide

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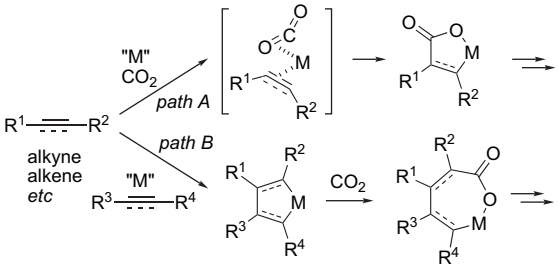
Dedicated to Professor Günther Wilke for his contribution to the field of organonickel chemistry

Abstract—Nickel-mediated carboxylation of α,ω-enyne was investigated. In the presence of a stoichiometric amount of zero-valent nickel complex, enynes having an electron-withdrawing group on alkene reacted with carbon dioxide via intramolecular cyclization to afford cyclic carboxylic acids in good yields. Various heterocyclic compounds were prepared by this carboxylative cyclization protocol. The reaction seems to proceed through oxidative cycloaddition of the α,ω-enyne moiety to a zero-valent nickel complex, regioselective insertion of carbon dioxide at the Csp^3-nickel bond, and hydrolysis of the resulting oxanickelacycle intermediate.

1. Introduction

Development of the carbon dioxide (CO_2) incorporation reaction into organic molecules is regarded as an important subject in synthetic organic chemistry. However, despite its abundant reserve and lower toxicity, the utility in synthetic organic chemistry has been limited because of its high thermodynamic stability and kinetic inertness. To overcome this disadvantage, various methods using transition metal complexes as promoters or catalysts have been explored.[1] The oxidative cycloaddition of CO_2 and unsaturated hydrocarbons to low-valent transition metal complexes is one of the most extensively studied CO_2 incorporation processes (Scheme 1, path A) and much interest has been shown in nickel-mediated processes.[2,3] Another potentially useful process is the insertion of CO_2 into metallacycle intermediates, which are readily prepared by oxidative cycloaddition of two unsaturated hydrocarbon components to low-valent transition metals (Scheme 1, path B). This process is also highly attractive because multiple carbon–carbon bond formations are accomplished during the process; however, synthetic reactions that utilize such a process have rarely been explored except for palladium- or nickel-catalyzed co-oligomerization of 1,3-dienes with CO_2, which proceeds through insertion of CO_2 into a bis-allylmetal intermediate.[4–9]



Scheme 1.

To fill this void in CO_2 incorporation chemistry, a nickel-mediated reaction using α,ω-enynes as metallacycle precursors have been explored. It was envisioned that α,ω-enyne **I** will readily react with a zero-valent nickel complex to form oxanickelacyclopentene **II** (Scheme 2).[10–13] There are two possible pathways by which CO_2 is inserted into **II**. If complex **II** undergoes insertion of CO_2 at the Csp^3-nickel bond (path a), oxanickelacycloheptene **III** would be formed, and this would be hydrolyzed to provide carboxylic acid **VI**. The other possible pathway, i.e., insertion of CO_2 into the Csp^2–nickel bond (path b), would provide α,β-unsaturated carboxylic acid **V** through the formation of oxanickelacycloheptene **IV**. Herein, we described the results of our investigation of a nickel-mediated cyclization–carboxylation cascade of α,ω-enynes.[14]

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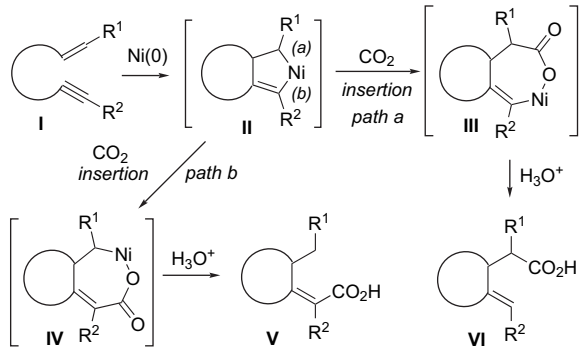
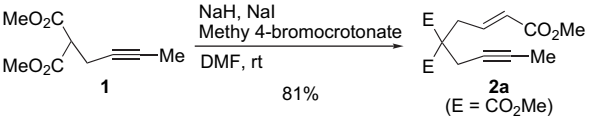


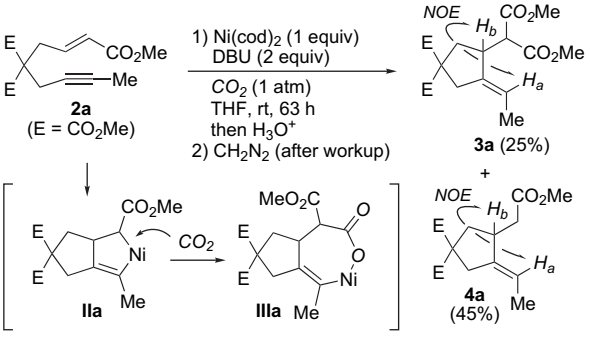
Scheme 2.

2. Results and discussion

To examine the feasibility of the above-described process, a reaction of 1,6-enyne **2a**, which was readily prepared from **1** (Scheme 3), was first carried out under conditions developed for carboxylation of unsaturated hydrocarbons.[2d,3] To a THF solution of $Ni(cod)_2$ (1 equiv) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 2 equiv to nickel) was slowly added a solution of enyne **2a** in THF at 0 °C under an atmosphere of CO_2, and the solution was stirred at room temperature for 63 h (Scheme 4). Hydrolysis of the resulting mixture followed by treatment with diazomethane afforded carboxylative cyclization product **3a** in 25% yield along with 45% of **4a**. The configurations of each double bond in **3a** and **4a** were determined to be (*E*) by the results of NOE experiments for **3a** and **4a**. The formation of **4a** was rationalized by protonolysis of nickelacycle **IIa**, and these results strongly suggested that the carboxylation proceeds through CO_2 insertion into the Csp^3–nickel bond of nickelacycle **IIa** giving oxanickelacycle **IIIa**.



Scheme 3.



Scheme 4.

To improve the yield of carboxylation product **3a**, enyne **2a** was submitted to various reaction conditions (Table 1). When the reaction was carried out in THF at 40 °C, the yield of **3a** was improved to 48% (entry 1). However, when the reaction was carried out under reflux conditions, only 9% of **3a** was obtained (entry 2). Formation of a significant amount of **4a** suggests the thermal instability of nickelacycle **IIa**. In addition, it seemed that the stability of **IIIa** was not so high at an elevated temperature because a shorter reaction period resulted in better yield of **3a** when the reactions were conducted at 40 °C (entry 3 vs entry 1). Although this carboxylative cyclization reaction could be carried out in toluene, the yield of **3a** slightly decreased (entry 4). Gratifyingly, the use of dioxane significantly improved the yield of the carboxylation product (entry 5). Interestingly, the yield of **3a** increased to 70% when the reaction was carried out in the presence of molecular sieves 4Å (entry 6).[15] The use of other ligands instead of DBU reduced the yields of **3a** (entries 7–9). The low combined yields of **3a** and **4a** in these reactions indicated that these ligands did not promote the formation of nickelacycle **IIa**. On the basis of these results, the reaction conditions employed in entry 6 were chosen as the standard reaction conditions for further investigations.

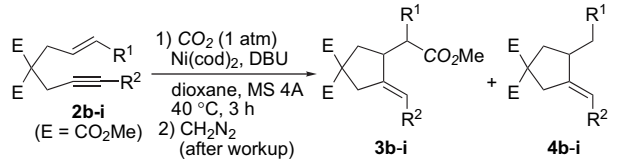
Table 1. Carboxylative cyclization of **2a** under various conditions[a]

Entry	Solvent	Ligand	Additive	Temp (°C)	Time (h)	Yields (%)	
						3a	**4a**
1	THF	DBU[b]	—	40	18	48	38
2	THF	DBU[b]	—	Reflux	13	9	77
3	THF	DBU[b]	—	40	3	55	30
4	Toluene	DBU[b]	—	40	18	41	15
5	Dioxane	DBU[b]	—	40	3	60	25
6	Dioxane	DBU[b]	MS 4Å	40	3	70	9
7	THF	PPh_3[b]	—	40	12	8	15
8	Dioxane	DPPE[c]	MS 4Å	40	4	0	0
9	Dioxane	TMEDA[c]	MS 4Å	40	3	22	0

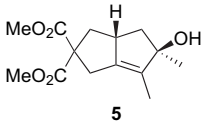
[a] All reactions were carried out using 1 equiv of $Ni(cod)_2$ under an atmosphere of CO_2 (1 atm). The obtained crude materials were treated with CH_2N_2 before isolation.
[b] 1 equiv.
[c] 2 equiv.

Carboxylative cyclizations of enynes having various substituents on the alkene or alkyne moiety were examined (Table 2). First, enynes **2b**–**2e**, whose alkene moieties were

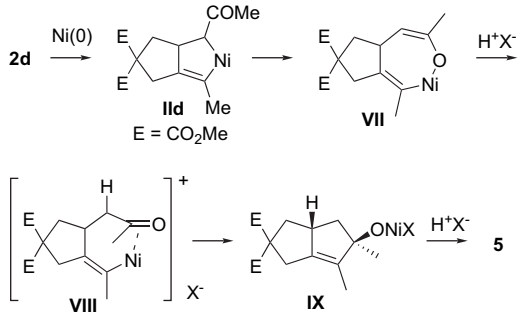
Table 2. Substituent effects of enynes



Entry	Enyne	R^1	R^2	Yields (%)		
				3	**4**	**3+4**
1	**2b**	H	Me	0	0	0
2	**2c**	Me	Me	0	0	0
3	**2d**	COMe	Me	0	54	54
4	**2e**	CN	Me	44	2	46
5	**2f**	CO_2Me	CH_2OMe	56	16	72
6	**2g**	CO_2Me	Ph	51	24	75
7	**2h**	CO_2Me	CO_2Me	27	61	88
8	**2i**	CO_2Me	$SiMe_3$	0	61	61



modified from enyne **2a**, were submitted to the carboxylation reaction. Reaction of enyne **2b**, which had no substituent at the terminus of alkyne, provided neither carboxylation product **3b** nor simply cyclized compound **4b** (entry 1). The reaction of **2c** having a methyl group on its alkene moiety also gave the same result. The fact that cyclized compounds **3** and **4** were not obtained in these two reactions indicated that oxidative cycloaddition of **2b** and **2c** did not proceed under these conditions. The reaction of enyne **2d** having an electron-withdrawing keto-carbonyl group on alkene afforded no carboxylation product (entry 3). However, in this reaction, cyclized product **4d** and bicyclic alcohol **5** were obtained in 54 and 39% yields, respectively. It was speculated that **5** was formed via the formal [3+2] cycloaddition pathway proposed by Montgomery.[12i,k,m] The reaction involves tautomerization of oxanickelacycle **IId** to nickel enolate **VII** and selective mono-protonation of **VII** followed by carbonyl insertion into the nickel–carbon bond of **VIII** to give **5** (Scheme 5). Thus, the formation **5** also indicated that oxidative cycloaddition of **2d** took place. In contrast to these results (entries 1–3), enyne **2e**, having a cyano group on alkene as an electron-withdrawing group, underwent carboxylative cyclization to give **3e** in 44% yield (entry 4).

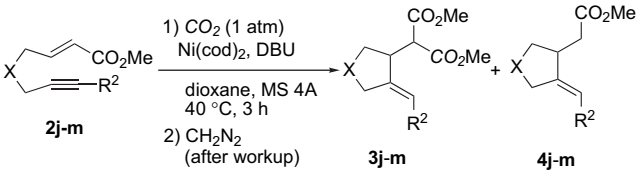


Scheme 5.

Next, the effects of substituents on the alkyne moiety were investigated using enynes **2f**–**2i**. Reaction of enynes **2f** or **2g** having an alkyl or aryl group on alkyne provided carboxylative cyclization product **3f** or **3g** in 56 or 51% yields, respectively (entries 5 and 6). In contrast to these results, the reaction of **2h** having a methoxycarbonyl group on alkyne gave **3h** in only 27% yield (entry 7) and that of **2i** afforded no carboxylation product. However, since the combined yields of **3** and **4** were relatively high in these reactions (entries 5–8), oxidative cycloaddition of enyne to Ni(0) might proceed. From the results shown in Table 2, the effects of substituents on alkene or alkyne are summarized as follows: (i) an electron-withdrawing substituent on alkene is necessary for oxidative cycloaddition of enynes to a Ni(0) complex and (ii) the carboxylation step, which would proceed through insertion of CO_2 into the nickelacyclopentenes, is greatly affected by substituents on both alkene and alkyne moieties (entries 3–8).

To explore the utility of this novel method for synthesis of cyclic compounds, reactions of enynes with various tethers were next examined (Table 3). In cyclization of enyne **2j** having no substituent on its tether, the desired carboxylation product **3j** was obtained in only 31% yield (Table 3, entry 1). In contrast to this result, carboxylative cyclizations of enynes **2k**, **2l**, and **2m**, which had a heteroatom in those tethers, proceeded smoothly to afforded desired heterocyclic products **3** in good yields (entries 2–4).

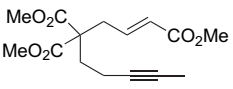
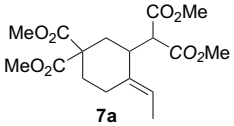
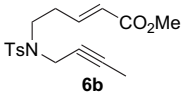
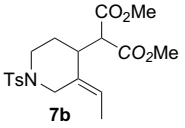
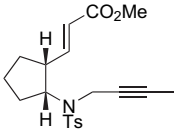
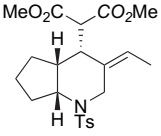
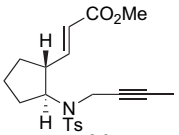
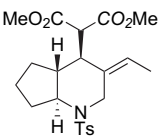
Table 3. Carboxylative cyclizations of various 1,6-enynes



Entry	Enyne	X	R^2	Yields (%)		Recovery of **2** (%)
				3	**4**	
1	**2j**	CH_2	Me	31	22	39
2	**2k**	TsN	Me	54	25	0
3	**2l**	TsN	CH_2OMe	55	34	0
4	**2m**	O	Me	68	12	0

Carboxylative cyclizations of 1,7-enynes **6** were then examined to apply this method for construction of a six-membered ring skeleton (Table 4). When reaction of **6a** was carried out under standard conditions for 8 h, the desired compound **7a** was obtained in 47% yield. Carboxylative cyclization of **6b**, which had a nitrogen atom in the tether chain, proceeded smoothly to afford compound **7b** with a piperidine skeleton in 80% yield. It was noteworthy that substrates **6c** and **6d**, in which a pre-existing five-membered ring was present in the tether chain, also underwent carboxylative cyclization to provide **7c** and **7d**, which have a bicyclic skeletal framework, in 55 and 75% yields, respectively, in a stereospecific manner.

Table 4. Carboxylative cyclizations of various 1,7-enynes

Enyne	Product	Yield (%)
 **6a**	 **7a**	47
 **6b**	 **7b**	80
 **6c**	 **7c**	55
 **6d**	 **7d**	75

All reactions were carried out in dioxane at 40 °C for 8 h in the presence of MS 4Å under an atmosphere of CO_2 (1 atm). All products were isolated as methyl esters by treating crude products with diazomethane.

3. Conclusion

In summary, nickel-mediated carboxylative cyclization of enynes was investigated. The effects of substituents on alkene and alkyne were investigated, and it was revealed that an electron-withdrawing group on alkene is necessary for this process. The utility of this novel method was demonstrated by application to the synthesis of various carboxylic acid derivatives having five- to six-membered ring skeletons, involving bicyclic skeletal frameworks.

4. Experimental

4.1. General

All manipulations were performed under an argon atmosphere unless otherwise stated. $Ni(cod)_2$ was prepared according to the previously reported procedure.[16] DMF and DBU were distilled from CaH_2. THF (dehydrated, stabilizer-free) was purchased from Kanto Kagaku Co. and used as received. Toluene and dioxane were distilled from sodium benzophenone ketyl. CO_2 (UHP grade, >99.995%) was purchased from Sumitomo Seika Chemicals Co., Ltd and used without further purification. All other reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70–230 mesh or 230–400 mesh). Enyne **2b** was prepared by the procedure reported in the literature.[17] Methods for preparing enynes **2c**–**2m** and **6a**–**6d** are described in the electronic Supplementary data.

4.2. Preparation of enynes

4.2.1. Trimethyl (*E*)-Oct-1-en-6-yne-1,4,4,-tricarboxylate (2a). To a suspension of NaH (60% dispersion in oil, 240 mg, 6.0 mmol) in DMF (15 mL) was added **1**[18] (1.1 g, 6.6 mmol) in DMF (10 mL) at 0 °C, and then the mixture had been stirred at room temperature for 1 h. The resulting mixture was cooled to 0 °C, and then methyl 4-bromocrotonate (1.1 mL, 9.0 mmol) and NaI (90 mg, 0.6 mmol) were added. After the mixture had been stirred at room temperature for 3 h, saturated aqueous solution of NH_4Cl was added at 0 °C. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8/1) to afford **1a** (1.4 g, 81%) as a colorless crystal. Mp 53.0–55.0 °C; IR (neat) 2954, 1738, 1279 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (dt, J=8.0, 15.6 Hz, 1H), 5.93 (d, J=15.6 Hz, 1H), 3.75 (s, 6H), 3.72 (s, 3H), 2.93 (dd, J=1.5, 8.0 Hz, 2H), 2.75 (q, J=2.6 Hz, 1H), 1.76 (t, J=2.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.7, 166.1, 142.2, 124.9, 79.5, 72.7, 56.9, 52.9, 52.9, 51.5, 35.1, 23.5, 3.5; LRMS (EI, *m/z*) 281 (M^+−H), 251, 223, 191, 163; HRMS (EI, *m/z*) calcd for $C_{14}H_{18}O_6$: 282.1103. Found: 282.1107; Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.44; H, 6.38.

4.2.2. Dimethyl non-2-en-7-yne-5,5-dicarboxylate (2c). IR (neat) 2954, 1736, 1284 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63–5.53 (m, 1H), 5.26–5.19 (m, 1H), 3.72 (s, 3H), 2.81 (d, J=7.6 Hz, 0.5H), 2.73–2.69 (m, 3.5H), 1.75 (t, J=2.3 Hz, 3H), 1.65 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.4, 130.1, 124.1, 78.6, 73.3, 57.4, 52.5, 52.5, 35.3, 22.9, 18.0, 3.5; LRMS (EI, *m/z*) 239 (M^+), 207, 178, 147; HRMS (EI, *m/z*) calcd for $C_{12}H_{15}O_3$ (M^+−OMe): 207.1021. Found: 207.1027.

4.2.3. Dimethyl 2-(but-2-ynyl)-2-{(*E*)-4-oxopent-2-enyl}-malonate (2d). IR (neat) 2955, 1738, 1677, 1267 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.64 (dt, J=7.5, 14.5 Hz, 1H), 6.14 (d, J=14.5 Hz, 1H), 3.75 (s, 6H), 2.93 (d, J=7.5 Hz, 2H), 2.76 (q, J=2.5 Hz, 2H), 2.36 (s, 3H), 1.77 (t, J=2.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 170.6, 170.6, 141.9, 135.3, 80.1, 73.0, 57.3, 53.1, 53.1, 35.7, 27.0, 23.9, 3.5; LRMS (EI, *m/z*) 266 (M^+), 251, 235, 207, 175, 147; HRMS (EI, *m/z*) calcd for $C_{14}H_{17}O_5$ (M^+−H): 265.1076. Found: 265.1079.

4.2.4. Dimethyl 2-(but-2-ynyl)-2-(3-cyanoallyl)malonate (2e). IR (neat) 2956, 2225, 1733, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (dt, J=7.7, 15.4 Hz, 0.83H), 6.48 (dt, J=7.9, 10.9 Hz, 0.17H), 5.48 (d, J=15.4 Hz, 0.83H), 5.47 (d, J=10.9 Hz, 0.17H), 3.76 (s, 6H), 3.14 (d, J=7.9 Hz, 0.34H), 2.92 (d, J=7.7 Hz, 1.66H), 2.76–2.73 (m, 2H), 1.77 (t, J=2.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.4, 149.5, 148.4, 116.6, 115.1, 103.5, 102.7, 80.2, 80.0, 72.3, 72.2, 56.7, 56.7, 53.0, 53.0, 53.0, 53.0, 36.4, 34.8, 24.0, 23.9, 3.5, 3.4; LRMS (EI, *m/z*) 249 (M^+), 218, 189, 158; HRMS (EI, *m/z*) calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 240.1002.

4.2.5. Trimethyl (*E*)-8-methoxyoct-1-en-6-yne-1,4,4-tricarboxylate (2f). IR (neat) 2954, 1737, 1268 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (dt, J=7.6, 15.5 Hz, 1H), 5.93 (d, J=15.5 Hz, 1H), 4.06 (t, J=2.1 Hz, 2H), 3.75 (s, 6H), 3.72 (s, 3H), 3.34 (s, 3H), 2.94 (d, J=7.6 Hz, 2H), 2.86 (t, J=2.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.5, 166.0, 141.9, 125.2, 80.5, 79.7, 59.8, 57.4, 56.7, 53.0, 53.0, 51.6, 35.1, 23.5; LRMS (EI, *m/z*) 311 (M^+), 280, 253, 221, 193, 161; HRMS (EI, *m/z*) calcd for $C_{15}H_{20}O_7$: 311.1131. Found: 311.1128.

4.2.6. Trimethyl (*E*)-7-phenylhept-1-en-6-yne-1,4,4-tricarboxylate (2g). IR (neat) 2954, 1737, 1278 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.36 (m, 2H), 7.31–7.29 (m, 3H), 6.83 (dt, J=7.8, 15.5 Hz, 1H), 5.97 (d, J=15.5 Hz, 1H), 3.78 (s, 6H), 3.72 (s, 3H), 3.03 (s, 2H), 3.01 (d, J=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.4, 165.9, 141.9, 131.4, 131.4, 128.0, 128.0, 127.9, 125.0, 122.7, 84.0, 83.4, 56.8, 53.4, 52.9, 51.4, 35.2, 24.0; LRMS (EI, *m/z*) 344 (M^+), 329, 312, 285, 253, 225; HRMS (EI, *m/z*) calcd for $C_{19}H_{20}O_6$: 344.1260. Found: 344.1259.

4.2.7. Tetramethyl (*E*)-hept-1-en-6-yne-1,4,4,7-tetracarboxylate (2h). IR (neat) 2955, 1723, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (dt, J=7.6, 15.2 Hz, 1H), 5.97 (d, J=15.2 Hz, 1H), 3.78 (s, 6H), 3.76 (s, 3H), 3.73 (s, 3H), 2.96 (s, 2H), 2.95 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.7, 166.6, 154.0, 141.7, 126.2, 83.0, 76.1, 56.4, 53.3, 53.3, 52.9, 51.8, 35.3, 23.4; LRMS (EI, *m/z*) 326 (M^+), 311, 295, 267, 235; HRMS (EI, *m/z*) calcd for $C_{15}H_{18}O_8$: 326.1001. Found: 326.1005.

4.2.8. Trimethyl (*E*)-7-(trimethylsilyl)hept-1-en-6-yne-1,4,4-tricarboxylate (2i). IR (neat) 2956, 1736, 1279 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (dt, J=7.9, 15.5 Hz, 1H), 5.93 (d, J=15.5 Hz, 1H), 3.74 (s, 6H), 3.72 (s, 3H), 2.93 (dd, J=0.8, 8.0 Hz, 2H), 2.81 (s, 2H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.5, 166.0, 142.0, 125.2, 100.5, 89.0, 56.8, 53.0, 53.0, 51.6, 35.1, 24.6, 0.0, 0.0, 0.0; LRMS (EI, *m/z*) 340 (M^+), 325, 309, 281; HRMS (EI, *m/z*) calcd for $C_{16}H_{24}O_6Si$: 340.1342. Found: 340.1345.

4.2.9. Methyl (*E*)-non-2-en-7-ynoate (2j). IR (neat) 2950, 1724, 1268 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (dt, J=7.0, 14.0 Hz, 1H), 5.86 (d, J=14.0 Hz, 1H), 3.73 (s, 3H), 2.31 (dt, J=8.5, 8.5 Hz, 2H), 2.19–2.15 (m, 2H), 1.78 (t, J=2.5 Hz, 3H), 1.64 (tt, J=7.1, 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 148.6, 121.3, 78.1, 76.3, 51.4, 31.2, 27.3, 18.2, 3.5; LRMS (EI, *m/z*) 165 (M^+−H), 151, 134, 107; HRMS (EI, *m/z*) calcd for $C_{10}H_{13}O_2$ (M^+−H): 165.0915. Found: 165.0915.

4.2.10. Methyl (*E*)-4-{*N*-(but-2-ynyl)-*N*-tosylamino}but-2-enoate (2k). IR (neat) 3055, 1724, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=8.3 Hz, 2H), 7.31 (d, J=8.3 Hz, 2H), 6.82 (dt, J=5.8, 15.7 Hz, 1H), 6.03 (d, J=15.7 Hz, 1H), 4.02 (q, J=2.3 Hz, 2H), 3.96 (d, J=5.8 Hz, 2H), 3.74 (s, 3H), 2.43 (s, 3H), 1.55 (t, J=2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 143.5, 141.9, 135.5, 129.2, 129.2, 127.6, 127.6, 123.6, 82.2, 71.0, 51.6, 47.0, 37.2, 21.4, 3.2; LRMS (EI, *m/z*) 321 (M^+), 290, 262, 166; HRMS (EI, *m/z*) calcd for $C_{16}H_{19}NO_4S$: 321.1035. Found: 321.1039.

4.2.11. Methyl (*E*)-4-{*N*-(4-methoxybut-2-ynyl)-*N*-tosylamino}but-2-enoate (2l). IR (neat) 2951, 2255, 1725, 1279 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.72 (m, 2H), 7.32–7.30 (m, 2H), 6.82 (dt, J=5.6, 15.6 Hz, 1H), 6.04 (d, J=15.6 Hz, 1H), 4.13 (s, 2H), 3.98 (d, J=5.6 Hz, 2H), 3.85 (s, 2H), 3.74 (s, 3H), 3.20 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 144.4, 142.2, 136.2, 130.0, 130.0, 128.1, 128.1, 124.4, 82.3, 78.8, 59.6, 57.5, 51.8, 47.4, 37.1, 21.5; LRMS (EI, *m/z*) 351 (M^+), 335, 196, 155; HRMS (EI, *m/z*) calcd for $C_{17}H_{21}NO_5S$: 351.1140. Found: 351.1128.

4.2.12. Methyl (*E*)-4-(but-2-ynyloxy)but-2-enoate (2m). IR (neat) 2952, 1724, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (dt, J=4.0, 15.6 Hz, 1H), 6.09 (d, J=15.6 Hz, 1H), 4.21 (dd, J=2.4, 4.0 Hz, 2H), 4.15 (q, J=2.4 Hz, 2H), 3.74 (s, 3H), 1.86 (t, J=2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 143.9, 121.1, 83.1, 74.5, 67.9, 58.5, 51.6, 3.6; LRMS (EI, *m/z*) 167 (M^+−H), 153, 138, 109; HRMS (EI, *m/z*) calcd for $C_9H_{11}O_3$ (M^+−H): 167.0708. Found: 167.0706.

4.2.13. Trimethyl (*E*)-non-1-en-7-yne-1,4,4-tricarboxylate (6a). IR (neat) 3054, 1734, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (dt, J=7.8, 15.5 Hz, 1H), 5.89 (d, J=15.5 Hz, 1H), 3.74 (s, 6H), 3.72 (s, 3H), 2.81 (d, J=7.8 Hz, 2H), 2.12 (s, 4H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.8, 166.3, 142.7, 125.2, 77.6, 76.8, 57.1, 52.9, 52.9, 51.7, 35.8, 32.4, 14.4, 3.6; LRMS (EI, *m/z*) 295 (M^+−H), 281, 264, 230, 198; HRMS (EI, *m/z*) calcd for $C_{15}H_{20}O_6$: 296.1260. Found: 296.1256.

4.2.14. Methyl (*E*)-5-{*N*-(but-2-ynyl)-*N*-tosylamino}pent-2-enoate (6b). IR (neat) 2951, 1722, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73–7.71 (m, 2H), 7.30–7.29 (m, 2H), 6.90 (dt, J=6.9, 15.5 Hz, 1H), 5.89 (d, J=15.5 Hz, 1H), 4.05 (q, J=1.9 Hz, 2H), 3.73 (s, 3H), 3.29 (t, J=7.4 Hz, 2H), 2.50 (dt, J=6.9, 7.4 Hz, 2H), 2.42 (s, 3H), 1.58 (t, J=1.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 144.6, 143.2, 135.3, 129.1, 129.0, 127.5, 127.4, 122.7, 81.7, 71.3, 51.3, 44.8, 37.1, 30.7, 21.4, 3.1; LRMS (EI, *m/z*) 335 (M^+), 304, 236, 184, 155, 91; HRMS (EI, *m/z*) calcd for $C_{17}H_{21}O_4NS$: 335.1191. Found: 335.196.

4.2.15. Methyl (*E*)-3-[(1*R,2*R**)-2-{*N*-(but-2-ynyl)-*N*-tosylamino}cyclopentyl]acrylate (6c).** IR (neat) 2954, 1720, 1653, 1261 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79–7.77 (m, 2H), 7.28–7.26 (m, 2H), 6.97 (dd, J=8.3, 15.6 Hz, 1H), 5.77 (d, J=15.6 Hz, 1H), 4.19 (dq, J=2.1, 18.4 Hz, 1H), 4.11 (dt, J=8.5, 8.5 Hz, 1H), 3.75 (dq, J=2.3, 18.4 Hz, 1H), 3.72 (s, 3H), 2.99–2.92 (m, 1H), 2.42 (s, 3H), 1.93–1.81 (m, 4H), 1.65–1.48 (m, 2H), 1.64 (t, J=2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 148.0, 143.0, 137.2, 129.1, 129.1, 127.6, 127.7, 121.8, 80.8, 74.6, 61.5, 51.5, 45.4, 36.2, 29.0, 27.7, 21.7, 21.5, 3.4; LRMS (EI, *m/z*) 375 (M^+), 344, 290, 220; HRMS (EI, *m/z*) calcd for $C_{20}H_{25}O_4NS$: 375.1504. Found: 375.1503.

4.2.16. Methyl (*E*)-3-[(1*R,2*S**)-2-{*N*-(but-2-ynyl)-*N*-tosylamino}cyclopentyl]acrylate (6d).** IR (neat) 2952, 1722, 1656, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74–7.73 (m, 2H), 7.24–7.22 (m, 2H), 6.64 (dd, J=8.5, 16.0 Hz, 1H), 5.71 (d, J=16.0 Hz, 1H), 4.15 (dq, J=1.9, 18.1 Hz, 1 H), 4.02 (dt, J=8.1, 8.1 Hz, 1H), 3.93 (dq, J=2.5, 18.1 Hz, 1H), 3.70 (s, 3H), 2.84 (ddt, J=8.7, 8.7, 8.7 Hz, 1H), 2.40 (s, 3H), 1.90–1.83 (m, 2H), 1.77–1.65 (m, 3H), 1.71 (t, J=2.5 Hz, 3H), 1.48–1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.3, 143.0, 137.5, 129.0, 129.0, 127.4, 127.4, 121.5, 80.6, 75.1, 63.8, 51.3, 44.9, 33.1, 30.1, 28.7, 22.0, 21.5, 3.4; LRMS (EI, *m/z*) 375 (M^+), 344, 316, 220; HRMS (EI, *m/z*) calcd for $C_{20}H_{25}O_4NS$: 375.1504. Found: 375.1504.

4.3. Typical procedure for nickel-mediated carboxylative cyclization (Table 1, entry 4)

A flame-dried round bottom flask was charged with $Ni(cod)_2$ (49 mg, 0.18 mmol), MS 4Å (500 mg), and degassed dioxane (1.5 mL). To this was added DBU (0.055 mL, 0.35 mmol), and the flask was immersed in a liquid nitrogen bath. After the mixture had been frozen, the flask was evacuated to 0.05 mmHg. The flask was backfilled with CO_2 in a plastic balloon and the frozen mixture was slowly thawed at ambient temperature. To this suspension was slowly added **2a** (50 mg, 0.18 mmol) in degassed dioxane (2 mL) over a period of 1 h. The resulting mixture was stirred at 40 °C for 3 h and then quenched with 10% aqueous HCl at 0 °C. The mixture was extracted with AcOEt and the combined organic layers were extracted with saturated aqueous $NaHCO_3$ (base extraction). The basic aqueous layers were acidified with 10% HCl and then extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was treated with diazomethane according to the standard procedure. The obtained crude material was purified by silica gel

column chromatography (hexane/AcOEt = 5/1) to afford **3a** (42.4 mg, 70%) as a colorless oil. From the residual organic layer of the base extraction, **4a** (4.5 mg, 9%) was obtained as a colorless oil after standard workup and purification by a silica gel column chromatography (hexane/AcOEt = 5/1).

4.3.1. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-ethylidenecyclopentane-1,1-dicarboxylate (3a). IR (neat) 2955, 1736, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.27–5.21 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.58 (d, J=8.0 Hz, 1H), 3.32–3.25 (m, 1H), 3.02 (d, J=16.8 Hz, 1H), 2.84 (d, J=16.8 Hz, 1H), 2.57 (dd, J=7.6, 13.1 Hz, 1H), 2.27 (dd, J=9.5, 13.1 Hz, 1H), 1.59 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.8, 168.7, 168.3, 139.3, 118.0, 58.3, 54.9, 52.9, 52.8, 52.5, 52.4, 41.9, 36.9, 36.8, 14.8; LRMS (EI, *m*/*z*) 342 (M^+), 311, 282, 250, 222, 191; HRMS (EI, *m*/*z*) calcd for $C_{16}H_{22}O_8$: 342.1315. Found: 342.1308.

4.3.2. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-ethylidenecyclopentane-1,1-dicarboxylate (4a). IR (neat) 2954, 1736, 1258 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.26–5.20 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.02 (d, J=17.4 Hz, 1H), 2.94–2.92 (m, 1H), 2.84 (d, J=17.4 Hz, 1H), 2.63 (dd, J=7.4, 13.0 Hz, 1H), 2.59 (dd, J=5.4, 15.5 Hz, 1H), 2.28 (dd, J=8.7, 15.5 Hz, 1H), 1.89 (dd, J=10.6, 13.0 Hz, 1H), 1.60 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 172.9, 172.8, 141.9, 117.0, 58.5, 53.1, 53.0, 51.8, 40.2, 38.9, 38.7, 37.2, 14.7; LRMS (EI, *m*/*z*) 284 (M^+), 253, 224, 192; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}O_6$: 284.1260. Found: 284.1267.

4.3.3. Dimethyl (*E*)-3-ethylidene-4-(2-oxopropyl)cyclopentane-1,1-dicarboxylate (4d). IR (neat) 2955, 1733, 1267 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.20–5.15 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.01 (d, J=17.0 Hz, 1H), 2.99–2.93 (m, 1H), 2.82 (d, J=17.0 Hz, 1H), 2.70 (dd, J=5.3, 17.0 Hz, 1H), 2.62 (dd, J=7.4, 12.6 Hz, 1H), 2.45 (dd, J=8.3, 17.0 Hz, 1H), 2.15 (s, 3H), 1.78 (dd, J=10.5, 12.9 Hz, 1H), 1.59 (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 172.2, 172.0, 141.7, 116.1, 58.3, 52.8, 52.8, 48.3, 40.1, 37.8, 37.0, 30.3, 14.6; LRMS (EI, *m*/*z*) 268 (M^+), 237, 208, 176, 151; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}O_5$: 268.1310. Found: 268.1313.

4.3.4. (3a*R,5*R**)-Dimethyl 2-(methyl)bicyclo[3,3,0]oct-1-en-3-ol-7,7-dicarboxylate (5).** IR (neat) 3507, 2952, 1732, 1262 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.69 (s, 3H), 2.67 (dd, J=1.7, 13.1 Hz, 1H), 2.65 (dd, J=1.7, 13.2 Hz, 1H), 2.51 (d, J=14.0 Hz, 1H), 2.44 (br s, 1H), 2.43–2.37 (m, 1H), 2.25 (d, J=14.0 Hz, 1H), 1.89 (d, J=13.1 Hz, 1H), 1.86 (dd, J=9.0, 13.2 Hz, 1H), 1.62 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 171.3, 134.0, 133.2, 96.4, 60.9, 53.0, 52.6, 47.8, 45.4, 42.1, 42.0, 14.3, 9.3; LRMS (EI, *m*/*z*) 268 (M^+), 250, 237, 190, 131; HRMS (EI, *m*/*z*) calcd for $C_{14}H_{20}O_5$: 268.1310. Found: 268.1313.

4.3.5. Dimethyl (*E*)-3-{(methoxycarbonyl)(cyano)methyl}-4-ethylidenecyclopentane-1,1-dicarboxylate (3e). IR (neat) 3520, 2954, 1731, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.50–5.43 (m, 0.33H), 5.41–5.34 (m, 0.67H), 3.83 (s, 3H), 3.80 (d, J=4.8 Hz, 0.67H), 3.76 (s, 3H), 3.74 (s, 3H), 3.63 (d, J=6.0 Hz, 0.33H), 3.30–3.25 (m, 1H), 3.05 (d, J=17.2 Hz, 1H), 2.90 (d, J=17.2 Hz, 1H), 2.65 (dd, J=3.6, 11.2 Hz, 0.33H), 2.61 (dd, J=6.8, 11.6 Hz, 0.66H), 2.17 (dd, J=11.6, 13.2 Hz, 0.66H), 2.14 (dd, J=3.6, 9.6 Hz, 0.33H), 1.68 (d, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.1, 148.1, 145.2, 132.7, 127.9, 127.9, 126.4, 125.5, 125.5, 93.9, 63.3, 53.0, 52.9, 49.8, 46.6, 40.0, 32.1, 10.4; LRMS (EI, *m*/*z*) 330 (M^+), 312, 299, 280, 253; HRMS (EI, *m*/*z*) calcd for $C_{19}H_{22}O_5$: 330.1467. Found: 330.1470.

4.3.6. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-(2-methoxyethylidene)cyclopentane-1,1-dicarboxylate (3f). IR (neat) 2955, 1735, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.36–5.33 (m, 1H), 3.91 (dq, J=6.6, 13.1 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.65 (d, J=7.5 Hz, 1H), 3.36–3.30 (m, 1H), 3.28 (t, J=11.5 Hz, 3H), 3.07 (d, J=16.9 Hz, 1H), 2.92 (d, J=16.9 Hz, 1H), 2.59 (dd, J=8.2, 13.1 Hz, 1H), 2.32 (dd, J=9.9, 13.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 171.5, 168.5, 168.1, 143.0, 120.3, 69.6, 58.4, 57.7, 54.4, 53.0, 52.9, 52.6, 52.4, 42.1, 37.1, 36.3; LRMS (EI, *m*/*z*) 341 (M^+−OMe), 309, 280, 249, 240, 221, 180; HRMS (EI, *m*/*z*) calcd for $C_{16}H_{21}O_8$ (M^+−OMe): 341.1236. Found: 341.1234.

4.3.7. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-(2-methoxyethylidene)cyclopentane-1,1-dicarboxylate (4f). IR (neat) 2953, 1734, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37–5.33 (m, 1H), 3.93 (d, J=6.3 Hz, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.31(s, 3H), 3.08 (d, J=17.3 Hz, 1H), 3.02–2.95 (m, 1H), 2.92 (d, J=17.3 Hz, 1H), 2.68–2.62 (m, 2H), 2.34 (dd, J=8.7, 15.7 Hz, 1H), 1.92 (dd, J=10.7, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.7, 171.7, 145.0, 118.7, 69.8, 58.4, 57.9, 53.0, 52.9, 51.7, 39.5, 39.1, 38.2, 37.1; LRMS (EI, *m*/*z*) 314 (M^+), 282, 250, 222, 191; HRMS (EI, *m*/*z*) calcd for $C_{15}H_{22}O_7$: 314.1365. Found: 314.1361.

4.3.8. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-benzylidenecyclopentane-1,1-dicarboxylate (3g). IR (neat) 2955, 1732, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5H), 6.29 (s, 0.77H), 3.82–3.68 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.56–3.51 (m, 1H), 3.29 (d, J=17.5 Hz, 1H), 3.25 (d, J=17.5 Hz, 1H), 2.65 (dd, J=8.0, 13.0 Hz, 1H), 2.37 (dd, J=9.5, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 172.5, 169.5, 169.1, 142.1, 142.0, 137.9, 137.8, 129.1, 128.9, 127.3, 124.8, 59.5, 55.3, 53.2, 53.2, 52.9, 52.8, 44.0, 38.9, 36.1; LRMS (EI, *m*/*z*) 404 (M^+), 373, 344, 312, 284, 253, 225; HRMS (EI, *m*/*z*) calcd for $C_{21}H_{24}O_8$: 404.1471. Found: 404.1477.

4.3.9. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-benzylidenecyclopentane-1,1-dicarboxylate (4g). IR (neat) 2954, 1732, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.19 (m, 5H), 6.25 (s, 0.86H), 3.73 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.36 (d, J=17.5 Hz, 1H), 3.23–3.19 (m, 1H), 3.21 (d, J=17.5 Hz, 1H), 2.75 (dd, J=5.3, 15.6 Hz, 1H), 2.71 (dd, J=8.5, 13.0 Hz, 1H), 2.45 (dd, J=9.0, 15.6 Hz, 0.76H), 1.98 (dd, J=10.5, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.8, 171.7, 143.3, 143.2, 137.2, 131.6, 128.3, 128.2, 126.5, 122.7, 59.1, 52.9, 52.9, 51.7, 40.6, 40.5, 39.1, 39.0; LRMS (EI, *m*/*z*) 346

(M^+), 315, 286, 256, 226; HRMS (EI, *m/z*) calcd for $C_{19}H_{22}O_6$: 345.1416. Found: 346.1417.

4.3.10. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-{(methoxycarbonyl)methylene}cyclopentane-1,1-dicarboxylate (3h). IR (neat) 2955, 1735, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68–5.66 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.74–3.66 (m, 2H), 3.73 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.48–3.42 (m, 1H), 3.34 (d, *J*=19.2 Hz, 1H), 2.59 (dd, *J*=8.4, 13.2 Hz, 1H), 2.40 (dd, *J*=10.8, 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.0, 168.0, 167.5, 166.2, 162.4, 113.4, 58.4, 53.3, 52.9, 52.9, 52.8, 52.6, 51.2, 43.5, 40.3, 35.6; LRMS (EI, *m/z*) 386 (M^+), 354, 322, 294, 262, 235, 207; HRMS (EI, *m/z*) calcd for $C_{17}H_{22}O_{10}$: 386.1212. Found: 386.1203.

4.3.11. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-{(methoxycarbonyl)methylene}cyclopentane-1,1-dicarboxylate (4h). IR (neat) 2954, 1735, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (br s, 1H), 3.74 (s, 6H), 3.71 (s, 3H), 3.70 (s, 3H), 3.72–3.67 (m, 1H), 3.36 (d, *J*=19.6 Hz, 1H), 3.19–3.11 (m, 1H), 2.70–2.65 (m, 1H), 2.65 (dd, *J*=5.2, 16.4 Hz, 1H), 2.41 (dd, *J*=8.4, 16.4 Hz, 1H), 2.00 (dd, *J*=11.2, 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.5, 171.3, 166.5, 164.5, 112.7, 58.4, 53.0, 52.9, 51.8, 51.2, 40.8, 40.4, 38.8, 37.5; LRMS (EI, *m/z*) 328 (M^+), 296, 268, 236, 209; HRMS (EI, *m/z*) calcd for $C_{15}H_{20}O_8$: 328.1158. Found: 328.1165.

4.3.12. Dimethyl (*E*)-3-{(methoxycarbonyl)methyl}-4-{(trimethylsilyl)methylene}cyclopentane-1,1-dicarboxylate (4i). IR (neat) 2985, 1741, 1243 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.31 (s, 0.16H), 3.74 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 3.08 (d, *J*=16.5 Hz, 1H), 2.94–2.89 (m, 1H), 2.91 (d, *J*=16.5 Hz, 1H), 2.68–2.61 (m, 2H), 2.29 (dd, *J*=9.2, 15.9 Hz, 0.34H), 1.92 (dd, *J*=10.4, 13.2 Hz, 1H), 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.3, 172.2, 159.0, 120.9, 59.0, 53.3, 53.2, 52.0, 41.6, 40.8, 39.4, 39.1, 0.0, 0.0, 0.0; LRMS (EI, *m/z*) 342 (M^+), 327, 311, 283, 251; HRMS (EI, *m/z*) calcd for $C_{16}H_{26}O_6Si$: 342.1498. Found: 342.1496.

4.3.13. Dimethyl 2-{(*E*)-2-ethylidenecyclopentyl}malonate (3j). IR (neat) 2962, 1735, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.23–5.21 (m, 1H), 3.72 (s, 3H), 3.72 (s, 3H), 3.45 (d, *J*=9.0 Hz, 1H), 3.12–3.09 (m, 1H), 2.35–2.16 (m, 2H), 1.84–1.71 (m, 2H), 1.65–1.54 (m, 2H), 1.56 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.8, 143.2, 116.3, 55.3, 52.2, 44.0, 30.5, 28.3, 23.4, 14.8, 1.0; LRMS (EI, *m/z*) 226 (M^+), 195, 166; HRMS (EI, *m/z*) calcd for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1204.

4.3.14. Methyl 2-{(*E*)-2-ethylidenecyclopentyl}acetate (4j). IR (neat) 2954, 1733, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24–5.18 (m, 1H), 3.67 (s, 3H), 2.79–2.69 (m, 1H), 2.52 (dd, *J*=5.2, 14.8 Hz, 1H), 2.31–2.12 (m, 3H), 2.22 (dd, *J*=8.8, 14.8 Hz, 1H), 1.91 (dt, *J*=7.2, 19.2 Hz, 1H), 1.79–1.70 (m, 1H), 1.61–1.54 (m, 1H), 1.58 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 145.6, 114.4, 51.3, 40.6, 39.2, 33.1, 28.7, 23.8, 14.6; LRMS (EI, *m/z*) 168 (M^+), 108, 95, 79; HRMS (EI, *m/z*) calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1156.

4.3.15. Dimethyl 2-{(*Z*)-4-ethylidene-1-tosylpyrrolidin-3-yl}malonate (3k). IR (neat) 2953, 1737, 1347, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75–7.70 (m, 2H), 7.38–7.32 (m, 2H), 7.35–7.31 (m, 1H), 3.88 (d, *J*=15.2 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.61 (d, *J*=15.2 Hz, 1H), 3.52 (d, *J*=9.0 Hz, 1H), 3.42 (dd, *J*=2.7, 9.7 Hz, 1H), 3.29–3.24 (m, 1H), 3.18 (dd, *J*=6.5, 9.7 Hz, 1H), 2.44 (s, 3H), 1.51 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 168.0, 143.7, 135.3, 132.0, 129.6, 129.6, 127.8, 127.8, 120.2, 54.5, 52.7, 52.5, 51.7, 49.0, 42.7, 21.6, 14.7; LRMS (EI, *m/z*) 381 (M^+), 350, 250, 226; HRMS (EI, *m/z*) calcd for $C_{18}H_{23}NO_6S$: 381.1246. Found: 381.1266.

4.3.16. Methyl 2-{(*Z*)-4-ethylidene-1-tosylpyrrolidin-3-yl}acetate (4k). IR (neat) 2953, 1736, 1346, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75–7.70 (m, 2H), 7.38–7.32 (m, 2H), 5.31–5.26 (m, 1H), 3.81 (d, *J*=14.2 Hz, 1H), 3.74 (d, *J*=14.2 Hz, 1H), 3.67 (s, 3H), 3.47–3.43 (m, 1H), 2.98 (d, *J*=6.0 Hz, 2H), 2.49 (dd, *J*=9.3, 16.1 Hz, 1H), 2.44 (s, 3H), 2.32 (dd, *J*=8.7, 16.1 Hz, 1H), 1.61 (d, *J*=5.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 143.6, 137.8, 132.3, 129.6, 129.6, 127.8, 127.8, 117.8, 53.3, 51.8, 49.4, 39.0, 37.6, 21.6, 14.6; LRMS (EI, *m/z*) 323 (M^+), 292, 250, 168; HRMS (EI, *m/z*) calcd for $C_{16}H_{21}NO_4S$: 323.1191. Found: 323.1188.

4.3.17. Dimethyl 2-{(*Z*)-4-(2-methoxyethylidene)-1-tosylpyrrolidin-3-yl}malonate (3l). IR (neat) 2953, 1736, 1347, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.69 (m, 2H), 7.35–7.34 (m, 2H), 5.44–5.42 (m, 1H), 3.93 (d, *J*=14.3 Hz, 1H), 3.80–3.77 (m, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 3.68 (d, *J*=14.3 Hz, 1H), 3.56 (d, *J*=8.8 Hz, 1H), 3.43 (dd, *J*=3.2, 9.9 Hz, 1H), 3.33–3.29 (m, 1H), 3.26 (s, 3H), 3.21 (dd, *J*=6.4, 9.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 167.6, 143.7, 138.0, 131.8, 129.6, 129.6, 127.6, 121.8, 121.8, 69.3, 58.2, 54.3, 52.9, 52.7, 51.2, 49.0, 43.0, 21.7; LRMS (EI, *m/z*) 411 (M^+), 379, 366, 348; HRMS (EI, *m/z*) calcd for $C_{19}H_{25}NO_7S$: 411.1352. Found: 411.1345.

4.3.18. Methyl 2-{(*Z*)-4-(2-methoxyethylidene)-1-tosylpyrrolidin-3-yl}acetate (4l). IR (neat) 2927, 1735, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–7.70 (m, 2H), 7.35–7.33 (m, 2H), 5.40–5.39 (m, 1H), 3.86 (d, *J*=15.0 Hz, 1H), 3.81 (d, *J*=7.1 Hz, 2H), 3.67 (s, 3H), 3.48 (dd, *J*=7.1, 9.3 Hz, 1H), 3.33 (d, *J*=15.0 Hz, 1H), 3.28 (s, 3H), 3.07–3.05 (m, 1H), 2.98 (dd, *J*=6.2, 9.3 Hz, 1H), 2.53 (dd, *J*=5.2, 16.3 Hz, 1H), 2.44 (s, 3H), 2.38 (dd, *J*=8.7, 16.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 143.8, 141.0, 132.4, 129.7, 129.7, 127.8, 127.8, 119.6, 69.5, 58.2, 52.8, 51.8, 49.4, 39.4, 37.3, 21.6; LRMS (EI, *m/z*) 353 (M^+), 321, 308, 248, 198, 155; HRMS (EI, *m/z*) calcd for $C_{17}H_{23}NO_5S$: 353.1297. Found: 353.1291.

4.3.19. Dimethyl 2-{(*Z*)-4-ethylidene-tetrahydrofuran-3-yl}malonate (3m). IR (neat) 2954, 1737, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.41–5.38 (m, 1H), 4.36 (d, *J*=13.5 Hz, 1H), 4.28 (d, *J*=13.5 Hz, 1H), 3.90 (dd, *J*=5.6, 9.3 Hz, 1H), 3.85 (dd, *J*=3.0, 9.3 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.55 (dd, *J*=9.6 Hz, 1H), 3.32–3.29 (m, 1H), 1.56 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 168.4, 139.1, 117.3, 71.8, 68.7, 54.5, 52.6, 52.3, 43.7, 14.8; LRMS (EI, *m/z*) 228 (M^+), 197, 132,

97; HRMS (EI, *m/z*) calcd for $C_{11}H_{16}O_5$: 228.0998. Found: 228.0997.

4.3.20. Methyl 2-{(*Z*)-4-ethylidene-tetrahydrofuran-3-yl}acetate (4m). IR (neat) 2952, 1735, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35–5.32 (m, 1H), 4.35 (d, *J*=15.8 Hz, 1H), 4.32 (d, *J*=15.8 Hz, 1H), 4.05 (dd, *J*=6.6, 8.6 Hz, 1H), 3.69 (s, 3H), 3.56 (dd, *J*=5.9, 8.6 Hz, 1H), 3.06–2.99 (m, 1H), 2.54 (dd, *J*=5.6, 16.1 Hz, 1H), 2.39 (dd, *J*=9.2, 16.1 Hz, 1H), 1.57 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 141.7, 114.9, 73.7, 69.1, 51.6, 40.0, 37.5, 14.7; LRMS (EI, *m/z*) 170 (M^+), 139, 110, 97; HRMS (EI, *m/z*) calcd for $C_9H_{14}O_3$: 170.0943. Found: 170.0939.

4.3.21. Dimethyl (*E*)-3-{di(methoxycarbonyl)methyl}-4-ethylidenecyclohexane-1,1-dicarboxylate (7a). IR (neat) 2955, 1734, 1240 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.07 (q, *J*=6.7 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H), 3.56 (d, *J*=10.8 Hz, 1H), 2.97–2.93 (m, 1H), 2.45–2.40 (m, 1H), 2.28 (dd, *J*=4.6, 13.6 Hz, 1H), 2.17–1.98 (m, 4H), 1.57 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.3, 168.4, 168.3, 136.9, 116.8, 54.5, 54.3, 52.7, 52.7, 52.5, 52.4, 41.3, 35.0, 32.0, 23.6, 12.9; LRMS (EI, *m/z*) 356 (M^+), 325, 264, 237, 205; HRMS (EI, *m/z*) calcd for $C_{17}H_{24}O_8$: 356.1471. Found: 356.1475.

4.3.22. Dimethyl 2-{(*Z*)-3-ethylidene-1-tosylpiperidin-4-yl}malonate (7b). IR (neat) 2954, 1736, 1268 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67–7.66 (m, 2H), 7.34–7.33 (m, 2H), 5.38 (q, *J*=6.8 Hz, 1H), 3.88 (d, *J*=13.0 Hz, 1H), 3.71 (s, 3H), 3.63 (s, 3H), 3.55 (d, *J*=11.2 Hz, 1H), 3.39 (d, *J*=13.0 Hz, 1H), 3.31–3.27 (m, 1H), 3.00–2.91 (m, 2H), 2.45 (s, 3H), 1.88–1.81 (m, 1H), 1.66 (d, *J*=6.8 Hz, 3H), 1.64–1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.8, 143.4, 133.1, 130.7, 129.5, 129.5, 127.5, 127.4, 122.8, 52.9, 52.7, 52.5, 43.9, 43.3, 41.4, 28.8, 21.7, 13.2; LRMS (EI, *m/z*) 395 (M^+), 364, 304, 264, 240; HRMS (EI, *m/z*) calcd for $C_{19}H_{25}O_6NS$: 395.1395. Found: 395.1399.

4.3.23. Dimethyl 2-{(*Z*,4*R,4a*R**,7a*S**)-3-ethylidene-octahydro-1-tosyl-1*H*-cyclopenta[*b*]pyridin-4-yl}malonate (7c).** IR (neat) 2953, 1736, 1263 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75–7.74 (m, 2H), 7.32–7.31 (m, 2H), 5.42–5.40 (m, 1H), 4.31 (dd, *J*=8.1, 18.7 Hz, 1H), 4.21 (d, *J*=15.6 Hz, 1H), 3.82 (d, *J*=11.8 Hz, 1H), 3.72 (s, 3H), 3.66 (d, *J*=15.6 Hz, 1H), 3.60 (s, 3H), 2.76 (d, *J*=11.8 Hz, 1H), 2.44 (s, 3H), 2.30–2.25 (m, 1H), 1.84–1.80 (m, 1H), 1.60–1.52 (m, 3H), 1.53 (t, *J*=6.9 Hz, 3H), 1.27–1.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.7, 143.2, 136.2, 129.6, 129.6, 129.4, 129.4, 127.3, 124.4, 55.2, 54.7, 52.5, 52.1, 46.3, 40.7, 39.1, 31.6, 28.0, 24.2, 21.6, 12.9; LRMS (EI, *m/z*) 435 (M^+), 404, 304, 280; HRMS (EI, *m/z*) calcd for $C_{22}H_{29}O_6NS$: 435.1715. Found: 435.1707.

4.3.24. Dimethyl 2-{(*Z*,4*S,4a*R**,7a*S**)-3-ethylidene-octahydro-1-tosyl-1*H*-cyclopenta[*b*]pyridine-4-yl}malonate (7d).** IR (neat) 2953, 1736, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.24–7.22 (m, 2H), 5.28 (q, *J*=7.0 Hz, 1H), 4.13 (d, *J*=13.5 Hz, 1H), 3.64 (s, 3H), 3.60 (s, 3H), 3.57 (d, *J*=13.5 Hz, 1H), 3.56 (d, *J*=6.9 Hz, 1H), 2.66 (dd, *J*=6.9, 10.9 Hz, 1H), 2.48 (ddd, *J*=6.9, 10.9, 10.9 Hz, 1H), 2.43 (s, 3H), 2.30–2.25 (m, 1H), 2.02–1.99 (m, 1H), 1.85–1.62 (m, 4H), 1.60 (d, *J*=7.0 Hz, 3H), 1.16–1.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.6, 143.3, 134.3, 132.5, 129.5, 129.4, 127.6, 127.6, 122.6, 62.8, 54.7, 52.5, 47.2, 46.7, 46.1, 31.1, 26.5, 21.5, 20.8, 13.9, 13.9; LRMS (EI, *m/z*) 435 (M^+), 404, 304, 280; HRMS (EI, *m/z*) calcd for $C_{22}H_{29}O_6NS$: 435.1715. Found: 435.1707.

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Supplementary data

Information on procedures for preparation of enynes **2c**–**2n** and **6a**–**6d**, spectral data for all synthetic intermediates of those enynes, and determination of the stereochemistry of **7c** and **7d** are described. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.03.121.

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