HETEROCYCLES, Vol. 93, No. 2, 2016, pp. 512 - 528. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 25th August, 2015, Accepted, 30th September, 2015, Published online, 28th October, 2015
DOI: 10.3987/COM-15-S(T)22

PD(II)-CATALYZED LIGAND-CONTROLLED SYNTHESIS OF 2,3-DIHYDROISOXAZOLE-4-CARBOXYLATES AND BIS(2,3-DIHYDROISOXAZOL-4-YL)METHANONES

Tomohiro Ariyama, Taichi Kusakabe,* Keita Sato, Mifuyu Funatogawa, Dong Lee, Keisuke Takahashi, and Keisuke Kato*

Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan. E-mail: taichi.kusakabe@phar.toho-u.ac.jp, kkk@phar.toho-u.ac.jp

Dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday

Abstract – Pd(II)-catalyzed ligand-controlled switching between cyclization–carbonylation and cyclization–carbonylation–cyclization-coupling (CCC-coupling) reactions of propargylic *N*-hydroxylamines was investigated. The use of a [Pd(tfa)$_2$(box)] catalyst in MeOH afforded symmetric ketones bearing two 2,3-dihydroisoxazoles in good yields; replacing the catalyst and solvent with Pd(tfa)$_2$ and MeOH/DMSO led to the formation of methyl 2,3-dihydroisoxazole-4-carboxylates in good yields.

INTRODUCTION

2,3-Dihydroisoxazoles (Δ^4-isoxazolines) are versatile heterocycles known for their potent biological activities[1] as well as being useful building blocks for synthesis[2] (Figure 1). Diarylketones are also frequently present in natural products and pharmaceuticals,[3] *e.g.,* raloxifene (selective estrogen receptor modulator used for treatment of osteoporosis), benzbromarone (antipodagric), and amiodarone (antiarrhythmic). The importance of 2,3-dihydroisoxazoles in both chemistry and biology has led to various approaches[2] for their synthesis: (i) [3+2] cycloadditions between nitrones and alkynes,[2,4] (ii) oxaziridine ring opening,[5] (iii) addition of *N*-hydroxylamines to a 1,3-conjugated enyne[6] or an α,α-dicyanoolefin,[7] and (iv) a one-pot multicomponent approach by the reaction of an aldehyde with acetohydroxamic acid and malononitrile or methyl cyanoacetate.[8] A variety of heterocycles can be synthesized by transition-metal-catalyzed cyclization of unsaturated systems.[9] Propargylic

N-hydroxylamines are a good precursor for the synthesis of 2,3-dihydroisoxazoles,[10] but the cyclization–carbonylation reaction of propargylic *N*-hydroxylamines has not been investigated.

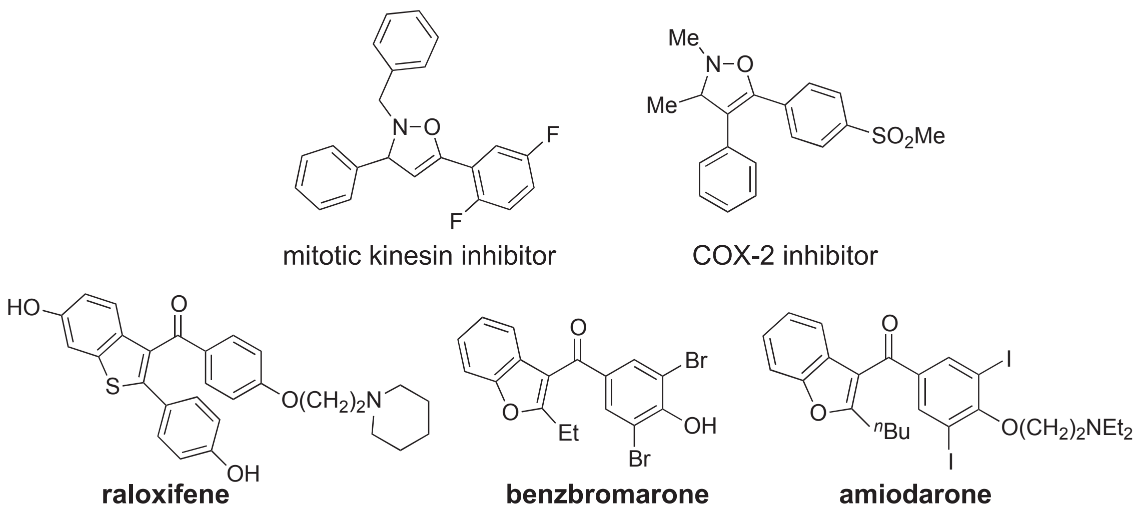
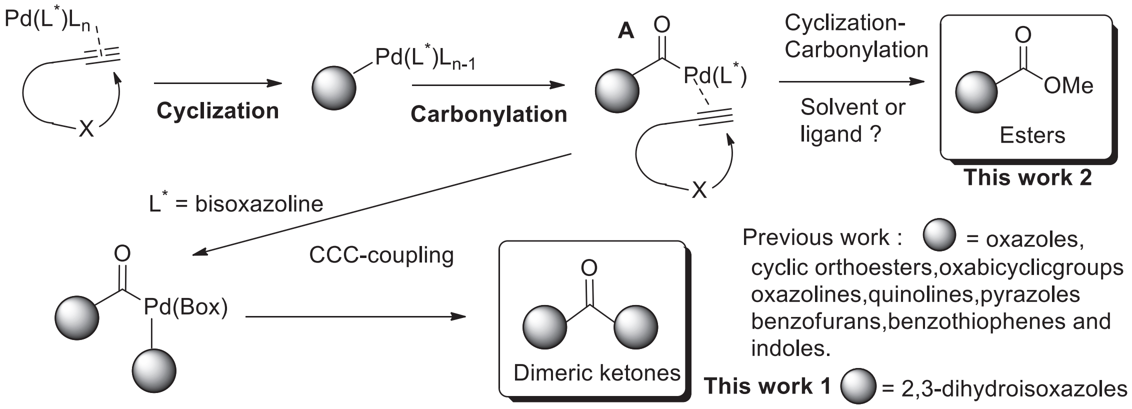


Figure 1. Structures of biologically active 2,3-dihydroisoxazoles and diarylketones

Recently, we reported a cyclization–carbonylation–cyclization-coupling reaction (CCC-coupling reaction) of propargyl acetates,[11a] amides,[11a] γ-propynyl-1,3-diketones,[11b] *N*-propargylanilines,[11c] *o*-alkynylphenols, [11c] and propargyl ureas[11d] catalyzed by palladium(II)-bisoxazoline (box) complexes.

We also very recently reported Pd(II)-catalyzed ligand-controlled switching between cyclization–carbonylation and CCC-coupling reactions of α,β-alkynic hydrazones,[11e,h] (*o*-alkynylphenyl) (methoxymethyl) sulfides,[11f,h] and 2-alkynylanilines[11g] (Scheme 1). In this transformation, the triple bond of the substrate coordinates to palladium(II) and undergoes nucleophilic attack by the intramolecular nucleophile X, followed by CO insertion to produce the acyl palladium intermediate **A**. Coordination of the triple bond of a second molecule induces the second cyclization,[12] then reductive elimination leads to the formation of a ketone bearing two heterocyclic groups. Methanolysis of the acyl palladium intermediate **A** gives the ester product as a result of cyclization–carbonylation. If the intramolecular cyclization reactions of propargylic *N*-hydroxylamine could be expanded to include carbonylative (coupling) reactions, the process would be a synthetically valuable method for direct preparation of ketones bearing two 2,3-dihydroisoxazole groups and 2,3-dihydroisoxazole-4-carboxylates. Herein, we investigated Pd(II)-catalyzed ligand-controlled switching between cyclization–carbonylation and CCC-coupling reactions of propargylic *N*-hydroxylamines.

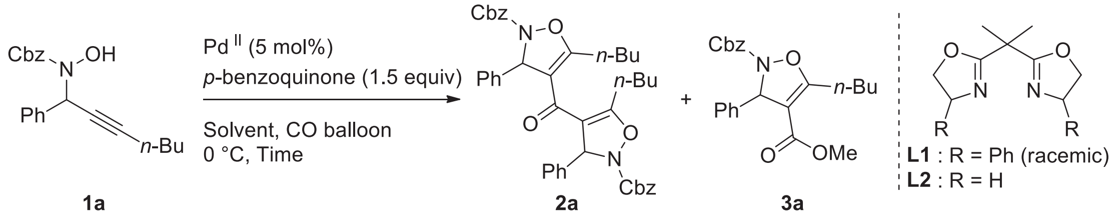


Scheme 1. Reaction courses of cyclization–carbonylation and cyclization–carbonylation–cyclization-coupling (CCC-coupling) in propargylic compounds

RESULTS AND DISCUSSION

Initially, we selected **1a** as a standard substrate to search for potential catalysts and solvents (Table 1). The reaction of **1a** with Pd(tfa)$_2$ (5 mol%) and *p*-benzoquinone (1.5 equiv.) in methanol under a carbon monoxide atmosphere (balloon) at 0 ºC afforded the 2,3-dihydroisoxazole-4-carboxylate derivative **3a** in 77% yield (Table 1, entry 1). The use of [PdCl$_2$(PPh$_3$)$_2$] was ineffective, affording **3a** in low yield along with recovery of substrate **1a** (74%) (Table 1, entry 2). The use of [PdCl$_2$(CH$_3$CN)$_2$] and [Pd(tfa)$_2$(bipy)] generated the dimeric ketone **2a** in 37-56% yield along with 5-38% yield of ester **3a** (Table 1, entries 3 and 4). Next, an attempt was made to use the box-Pd^{II} complexes according to our previous results[11] (Table 1, entries 5-7). Although the use of [Pd(tfa)$_2$(L1)] resulted in the formation of **2a** in 33% yield together with 54% yield of **3a**, [Pd(tfa)$_2$(L2)] accelerated the reaction, and the yield of dimeric ketone **2a** improved to 89%. It is conceivable that the steric hindrance of L1 inhibited the coordination of the second substrate to palladium, and thus the yield of **2a** was decreased. The nature of the counteranion of the palladium complexes somewhat influenced catalytic activity (Table 1, entry 8). Next, according to our previous findings,[11g,h] mixed solvent (MeOH/DMSO) was tested in the carbonylation reaction of **1a** (Table 1, entries 9-13). The best result was obtained using a 5/1 ratio of MeOH/DMSO, affording **3a** in 88% yield (Table 1, entry 11). PdCl$_2$ and Pd(OAc)$_2$ were found to be unsuitable catalysts for this reaction (Table 1, entries 12 and 13).

Table 1. Optimization of CCC-coupling and cyclization–carbonylation reactions of **1a**



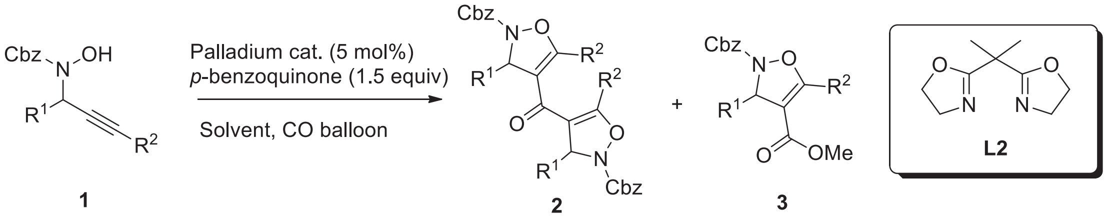
Entry	Pd $^{\mathrm{II}}$	Solvent	Time (h)	Yield of **2a** (%)	Yield of **3a** (%)	Recovery of **1a** (%)
1	Pd(tfa)$_2$	MeOH	52	-	77	-
2	[PdCl$_2$(PPh$_3$)$_2$]	MeOH	96	-	7	74
3	[PdCl$_2$(MeCN)$_2$]	MeOH	96	56	38	-
4	[Pd(tfa)$_2$(bipy)]	MeOH	48	37	5	29
5	[Pd(tfa)$_2$(L1)]	MeOH	96	33	54	-
6	[Pd(tfa)$_2$(L2)]	MeOH	24	87	13	-
7[1]	[Pd(tfa)$_2$(L2)]	MeOH	48	89	9	-
8	[PdCl$_2$(L2)]	MeOH	96	42	-	43
9	Pd(tfa)$_2$	MeOH / DMSO = 3 / 1	72	-	63	23
10	Pd(tfa)$_2$	MeOH / DMSO = 1 / 1	48	-	57	31
11	Pd(tfa)$_2$	MeOH / DMSO = 5 / 1	61	-	88	-
12	PdCl$_2$	MeOH / DMSO = 5 / 1	72	-	28	37
13	Pd(OAc)$_2$	MeOH / DMSO = 5 / 1	74	-	11	75

1) –20 ~ –10 ºC

Having elucidated the optimum conditions for both reactions, we then employed a variety of propargylic *N*-hydroxylamines **1** in the CCC-coupling reaction (Table 2, entries 1-10, condition A). The influence of aryl substituents at the propargylic position (R^1 = aryl) was investigated first (Table 2, entries 1-8). The substrate **1b** gave good results, similar to that of the parent substrate **1a** (Table 2, entry 2). The substrates **1c**–**1g**, bearing an electron-donating or halogen (F, Cl) group at the *para* or *ortho* position, afforded good to excellent yields of **2c**-**2g** (Table 2, entries 3-7). A good yield was obtained by using **1h**, containing an alkyl group instead of an aryl group at the propargylic position (Table 2, entry 8). The substrate **1i**, bearing an aryl substituent at the propargylic position and at the alkyne terminus, afforded a slightly lower yield (70%) of **2i** (Table 2, entry 9). However, terminal alkyne **1j** was ineffective under the optimized conditions (entry 10). The reaction pathways were switched by using condition B. Substrates bearing aryl substituents at the propargylic position were investigated; the substrate **1b** gave good results (Table 2, entry 12). Propargylic *N*-hydroxylamines **1c**-**1g**, containing an electron-donating or halogen (F, Cl) group at the *para* or *ortho* position, were transformed to the corresponding methyl

2,3-dihydroisoxazole-4-carboxylates **3c**-**3g** in good yield (Table 2, entries 11-17). The substrates **1h**-**1i**, bearing alkyl or aryl substituents at the propargylic position and alkyne terminus, afforded good yields of **3h**-**3i** (Table 2, entries 18 and 19). In contrast, terminal alkyne **1j** gave a complex mixture (Table 2, entry 20).

Table 2. Substrate scope of CCC-coupling (condition A) and cyclization–carbonylation reactions (condition B)

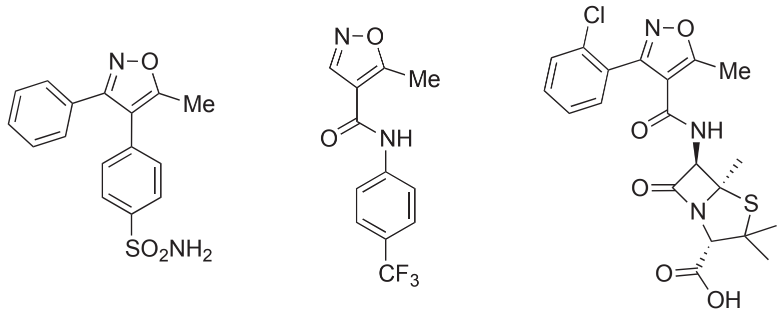


Condition A : [Pd(tfa)$_2$(**L2**)], MeOH (for entries 1-10, Table 2)
Condition B : Pd(tfa)$_2$, MeOH / DMSO = 5 / 1 (for entries 11-20, Table 2)

Entry	R^1	R^2	Temp (ºC)	Time (h)	Yield of **2**[3] (%)	Yield of **3** (%)
1	Ph	*n*-Bu	–20 ~ –10	48	**2a** : 89	**3a** : 9
2	Ph	cyclopropyl	0	24	**2b** : 89	**3b** : 4
3	4-MeOC$_6$H$_4$	*n*-Bu	–20 ~ –10	46	**2c** : 86	**3c** : 5
4	4-FC$_6$H$_4$	*n*-Bu	–20 ~ –10	76	**2d** : 82	**3d** : 9
5	4-ClC$_6$H$_4$	*n*-Bu	–20 ~ –10	72	**2e** : 81	**3e** : 10
6	2-FC$_6$H$_4$	*n*-Bu	–10 ~ 0	47	**2f** : 94	-
7	2-ClC$_6$H$_4$	Me	–10 ~ 0	44	**2g** : 85	**3g** : 8
8	C$_6$H$_5$-(CH$_2$)$_2$	*n*-Bu	–10	24	**2h** : 86	**3h** : 13
9[1]	Ph	4-MeC$_6$H$_4$	–5	69	**2i** : 70	**3i** : 17
10	Ph	H	–20	19	Recovery of **1j** : 44%	
11	Ph	*n*-Bu	0	61	-	**3a** : 88
12	Ph	cyclopropyl	0	35	-	**3b** :83
13[1]	4-MeOC$_6$H$_4$	*n*-Bu	0	72	-	**3c** : 81
14	4-FC$_6$H$_4$	*n*-Bu	0	65	-	**3d** : 85
15	4-ClC$_6$H$_4$	*n*-Bu	0	62	-	**3e** : 88
16	2-FC$_6$H$_4$	*n*-Bu	0	73	-	**3f** : 88
17[2]	2-ClC$_6$H$_4$	Me	10	72	-	**3g** : 89
18	C$_6$H$_5$-(CH$_2$)$_2$	*n*-Bu	0	38	-	**3h** : 88
19[1]	Ph	4-MeC$_6$H$_4$	5	71	-	**3i** : 86
20	Ph	H	0 ~ 10	43	complex mixture	

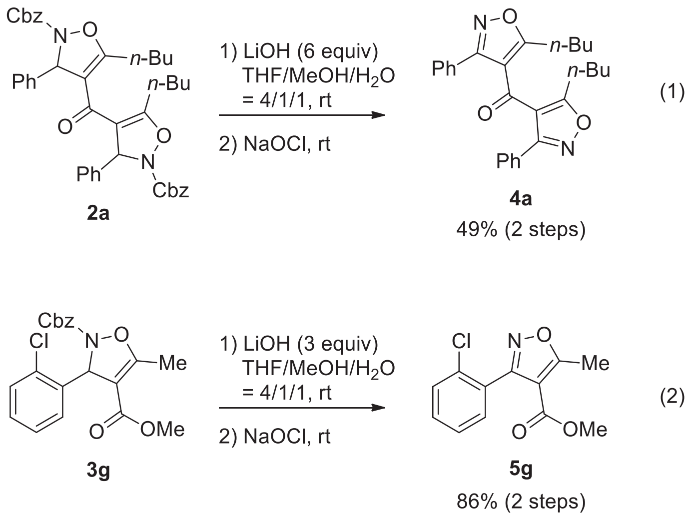
1) 1,4-Benzoquinone (2.5 equiv) was used. 2) 1,4-Benzoquinone (3.0 equiv) was used.
3) Mixture of diastereomers (ratio = 1:1~3:1)

Isoxazoles are a major class of five-membered heterocycles and are used for a variety of pharmaceutical and agrochemical products (Figure 2).[13] Accordingly, the synthetic utility of the obtained 2,3-dihydroisoxazoles was shown by conversion to isoxazoles (Scheme 2). Deprotection[14] of **2a** and **3g**, followed by oxidation, afforded the corresponding isoxazoles in 49-86% yield (2 steps).



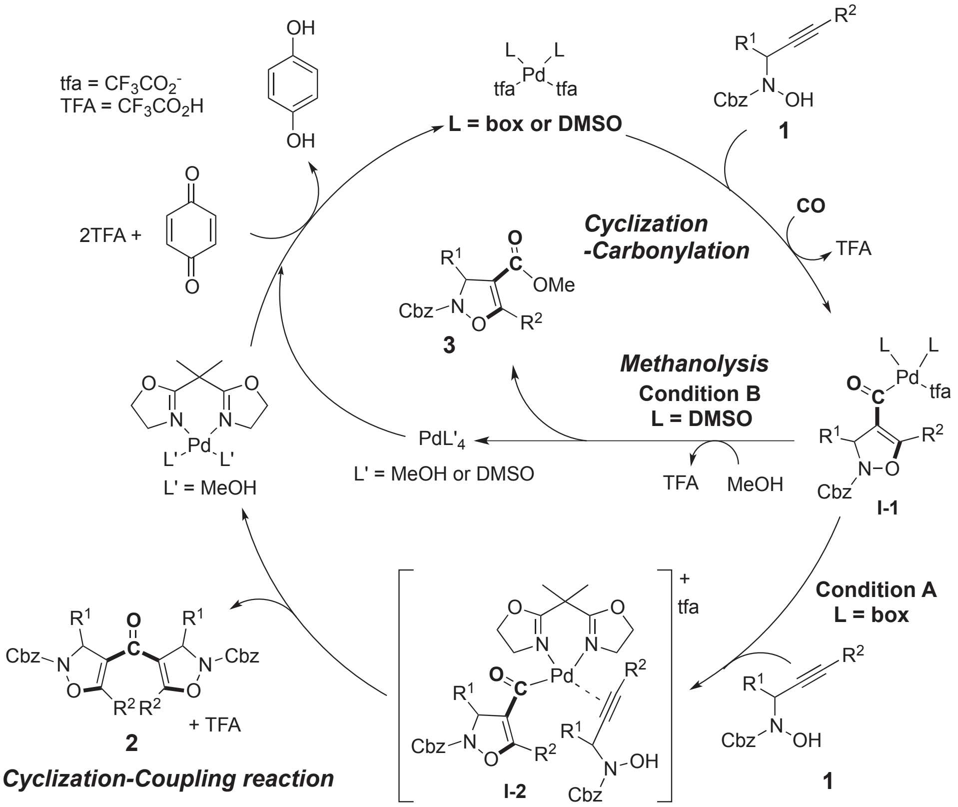
valdecoxib **leflunomide** **cloxacillin**

Figure 2. Structures of biologically active isoxazoles



Scheme 2. Synthesis of isoxazoles

A plausible mechanism for the CCC-coupling and cyclization–carbonylation reactions of **1** is shown in Scheme 3. Nucleophilic attack by the oxygen atom at the electrophilically activated triple bond is followed by CO insertion to produce the acyl palladium intermediate **I-1**. Under condition A (L = box), coordination of the triple bond of a second molecule (**I-2**) induces the second cyclization, and reductive elimination then leads to the formation of a ketone bearing two 2,3-dihydroisoxazole groups. We believe that the box ligand enhances the π-electrophilicity of palladium(II),[12] thus promoting coordination of the second triple bond to the acyl palladium intermediate **I-1** and leading to the dimerization reaction. Under condition B, DMSO acts as a neutral ligand instead of a box.[11g,h] Methanolysis of the acyl palladium intermediate **I-1** should be facilitated, giving 2,3-dihydroisoxazole-4-carboxylates **3** in good yields.



Scheme 3. Plausible mechanism for the CCC-coupling and cyclization–carbonylation reactions of **1**

In conclusion, we developed an efficient way of switching between CCC-coupling and cyclization–carbonylation reactions of propargylic *N*-hydroxylamines (**1**) catalyzed by Pd^{II}. The use of $[Pd(tfa)_2(box)]$ as a catalyst in MeOH afforded symmetric ketones bearing two 2,3-dihydroisoxazoles in good to excellent yields, whereas replacing the catalyst and solvent with $Pd(tfa)_2$ and MeOH/DMSO led to the formation of methyl 2,3-dihydroisoxazole-4-carboxylates in good yields. These reactions were general for a wide range of propargylic *N*-hydroxylamines. We have shown that these products can serve as precursors for the preparation of isoxazoles. We are currently investigating additional cascade reactions based on the reaction strategy of CCC-coupling and cyclization–carbonylation presented here for the synthesis of ketones containing two heterocyclic groups and heterocycles-carboxylates.

EXPERIMENTAL

The propargylic *N*-hydroxylamines **1** were prepared by $FeCl_3$-catalyzed nucleophilic substitution of corresponding propargylalcohol with Cbz-NHOH according to known literature procedures[15] except **1h**. The propargylic *N*-hydroxylamine **1a**, **1d**, **1e**, **1f**, **1i** were all known compounds.[16]

Benzyl (3-cyclopentyl-1-phenylprop-2-yn-1-yl)(hydroxy)carbamate (**1b**): colorless solid; mp 89-91 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.72-0.82 (4H, m), 1.29-1.36 (1H, m), 5.23 (2H, s), 5.86 (1H, br-s), 6.08 (1H, d, J = 2.0 Hz), 7.25-7.37 (8H, m), 7.49-7.50 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ -0.5, 8.4, 8.4, 55.7, 68.4, 69.8, 90.5, 127.9 (2C), 128.2 (2C), 128.2, 128.4 (3C), 128.7 (2C), 135.6, 136.2, 157.1; IR (KBr): 3375, 3017, 2241, 1665, 1597, 1413, 1348, 1290, 753, 691 cm^{-1}; HRMS-ESI: calcd for $C_{20}H_{19}NNaO_3$ [M+Na]$^+$: 344.1263; found: 344.1269.

Benzyl hydroxy(1-(4-methoxyphenyl)hept-2-yn-1-yl)carbamate (**1c**): brown oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.2 Hz), 1.38-1.56 (4H, m), 2.27 (2H, dt, J = 7.2, 2.0 Hz), 3.78 (3H, s), 5.23 (2H, s), 5.83 (1H, br-d), 6.06 (1H, t, J = 2.0 Hz), 6.84-6.87 (2H, m), 7.25-7.45 (7H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6, 18.5, 22.0, 30.7, 55.2, 55.3, 68.3, 74.9, 87.3, 113.7 (2C), 128.2 (2C), 128.4, 128.4, 128.6 (2C), 129.3 (2C), 135.7, 157.1, 159.5; IR (KBr): 3335, 2961, 2220, 1707, 1612, 1509, 1248, 1099, 746 cm^{-1}; HRMS-ESI: calcd for $C_{22}H_{25}NNaO_4$ [M+Na]$^+$: 390.1681; found: 390.1654.

Benzyl hydroxy(1-(2-chlorophenyl)but-2-yn-1-yl)carbamate (**1g**): colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.90 (3H, d, J = 2.4 Hz), 5.25 (2H, s), 5.86 (1H, br-d), 6.40 (1H, q, J = 2.4 Hz), 7.26-7.40 (8H, m), 7.86-7.89 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 3.7, 53.2, 68.4, 73.6, 83.1, 126.6, 128.1 (2C), 128.3, 128.5 (2C), 129.5, 129.8, 131.5, 133.6, 133.7, 135.7, 157.0; IR (KBr): 3299, 2234, 1704, 1582, 1407, 1286, 1101, 749 cm^{-1}; HRMS-ESI: calcd for $C_{18}H_{16}NNaO_3$ [M+Na]$^+$: 352.0716; found: 352.0696.

Benzyl hydroxy(1-phenylnon-4-yn-3-yl)carbamate (**1h**)

To a solution of 1-phenyl-4-nonyn-3-ol[17] (0.50 g, 2.31 mmol) and Ph_3P (1.21 g, 4.62 mmol) in MeCN (15 mL) was added CBr_4 (1.53 g, 4.62 mmol) at 0 ºC. The solution was stirred at 0 ºC for 1.5 h, then filtered, rinsed with AcOEt (20 mL), and dried over $MgSO_4$. Concentration by rotary evaporation furnished a crude mixture that was purified by silica gel chromatography (hexane) to afford 3-bromo-4-nonyn-1-yl-benzene (90%). Yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.6 Hz), 1.39-1.55 (4H, m), 2.25-2.30 (4H, m), 2.83-2.87 (2H, m), 4.48-4.52 (1H, m), 7.19-7.30 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6, 18.6, 21.9, 30.5, 33.5, 37.8, 41.7, 79.0, 88.8, 126.2, 128.5 (2C), 128.6 (2C), 140.3; IR (KBr): 2958, 2933, 2233, 1724, 1709, 1603, 1453, 748, 699 cm^{-1}; HRMS-EI: calcd for $C_{15}H_{19}Br$ [M+]: 278.0670; found: 278.0668.

To a solution of 3-bromo-4-nonyn-1-yl-benzene (0.50 g, 1.79 mmol) in 1-methyl-2-pyrrolidone (6 mL) was added NH_2OH (50% in water, 2 mL), and the mixture was stirred at rt for 18 h. The mixture was diluted with AcOEt (40 mL), washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was dissolved in dioxane (8 mL) and sat. a.q. $NaHCO_3$ (8 mL). Benzyl chloroformate (611 mg, 3.58 mmol) was added dropwise to the mixture at rt and stirred for 1 h. The mixture was diluted with AcOEt (20 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography. The fraction eluted with hexane/AcOEt (6 /1) afforded **1h** (66%, 2 steps). Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.2 Hz), 1.35-1.50 (4H, m), 2.04-2.20 (4H, m), 2.71 (2H, t, *J* = 7.6 Hz), 4.74-4.78 (1H, m), 5.17 (1H, d, *J* = 12.4 Hz), 5.20 (1H, d, *J* = 12.4 Hz), 6.21 (1H, br-d), 7.15-7.37 (10H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6, 18.3, 21.9, 30.7, 32.2, 34.5, 51.8, 68.2, 76.2, 85.6, 126.0, 128.1 (2C), 128.3, 128.4 (2C), 128.5 (2C), 128.5 (2C), 135.7, 141.0, 157.6; IR (KBr): 3276, 2952, 2235, 1704, 1596, 1102, 747, 698 cm^{-1}; HRMS-ESI: calcd for $C_{23}H_{27}NNaO_3$ $[M+Na]^+$: 388.1889; found: 388.1886.

Benzyl hydroxy(1-phenylprop-2-yn-1-yl)carbamate (**1j**): yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.56 (1H, d, *J* = 2.4 Hz), 5.24 (2H, s), 5.94 (1H, br-s), 6.14 (1H, d, *J* = 2.4 Hz), 7.34-7.55 (10H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 55.3, 68.6, 74.8, 78.6, 128.0 (2C), 128.3 (2C), 128.5, 128.6 (3C), 128.6 (2C), 135.1, 135.4, 157.1; IR (KBr): 3288, 2118, 1705, 1286, 1100, 752, 722, 697 cm^{-1}; HRMS-ESI: calcd for $C_{17}H_{15}NNaO_3$ $[M+Na]^+$: 304.0950; found: 304.0936.

Typical procedure for the CCC-coupling reaction of benzyl hydroxy(1-phenylhept-2-yn-1-yl)carbamate (**1a**): **condition A**

A 30 mL two-necked round-bottom flask containing a magnetic stir bar, benzyl hydroxy(1-phenylhept-2-yn-1-yl)carbamate (**1a**) (135 mg, 0.40 mmol), *p*-benzoquinone (64.9 mg, 0.60 mmol), and MeOH (5 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling via the three-way stopcock. A MeOH (1 mL) suspension of $[Pd(tfa)_2(L2)]$ (10.3 mg, 0.02 mmol) was added to the stirred solution using a syringe at −20 ºC. The remaining $[Pd(tfa)_2(L2)]$ was washed in MeOH (1 mL) twice and stirred for 48 h at −20 to −10 ºC. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with 5% a.q. NaOH (40 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane–ethyl acetate (40/1) afforded dimeric ketone **2a** as a diasteromixture (ratio 1.5:1) (monomeric ester **3a**, hexane–AcOEt = 50/1).

Compound 2a: inseparable mixture of diastereomers (ratio = 1.5:1); yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.76 (12/5H, t, *J* = 7.2 Hz), 0.84 (18/5H, t, *J* = 7.2 Hz), 1.02-1.57 (8H, m), 2.23-2.50 (4H, m), 5.14-5.22 (4H, m), 5.89 (6/5H, s), 6.25 (4/5H, s), 7.13-7.35 (20H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6 (4/5C), 13.6 (6/5C), 22.3 (4/5C), 22.4 (6/5C), 25.3 (4/5C), 25.6 (6/5C), 28.9 (4/5C), 29.0 (6/5C), 68.5 (4/5C), 68.5 (4/5C), 68.6 (6/5C), 69.2 (6/5C), 113.9 (6/5C), 114.7 (4/5C), 126.6 (8/5C), 126.7 (12/5C), 128.1 (8/5C), 128.2 (12/5C), 128.2 (4/5C), 128.3 (6/5C), 128.4 (4/5C), 128.5 (6/5C), 128.5 (8/5C), 128.6 (12/5C), 128.6 (12/5C), 128.7 (8/5C), 135.1 (2C), 139.4 (4/5C), 139.5 (6/5C), 156.3 (6/5C), 156.4 (4/5C), 162.1 (4/5C), 162.5 (6/5C), 182.3 (2/5C), 182.7 (3/5); IR (KBr): 2961, 1729, 1606, 1390, 1308, 1221, 1103, 745, 696 cm^{-1}; HRMS-EI: calcd for $C_{43}H_{44}N_2O_7$ [M$^+$]: 700.3149; found: 700.3151.

Compound 2b: inseparable mixture of diastereomers (ratio = 1.2:1); yellow oil; ^{1}H-NMR (400 MHz, CD_2Cl_2) δ 0.84-1.24 (8H, m), 2.06-2.20 (2H, m), 5.14-5.20 (4H, m), 6.08 (12/11H, s), 6.23 (10/11H, s), 7.18-7.37 (20H, m); ^{13}C-NMR (100 MHz, CD_2Cl_2) δ 8.1 (12/11C), 8.2 (10/11C), 8.4 (10/11C), 8.6 (12/11C), 8.7 (10/11C), 9.2 (12/11C), 68.8 (10/11C), 68.9 (12/11C), 70.1 (10/11C), 70.3 (12/11C), 114.2 (12/11C), 115.5 (10/11C), 127.1 (24/11C), 127.2 (20/11C), 128.3 (20/11C), 128.4 (24/11C), 128.5 (10/11C), 128.5 (12/11C), 128.7 (10/11C), 128.8 (12/11C), 128.9 (4C), 128.9 (20/11C), 128.9 (24/11C), 135.7 (2C), 140.1 (12/11C), 140.1 (10/11C), 157.2 (10/11C), 157.4 (12/11C), 162.7 (10/11C), 164.3 (12/11C), 181.9 (5/11C), 182.6 (6/11C); IR (KBr): 3033, 1732, 1624, 1596, 1456, 1392, 1306, 904, 750, 697 cm^{-1}; HRMS-EI: calcd for $C_{41}H_{36}N_2O_7$ [M$^+$]: 668.2523; found: 668.2523.

Compound 2c: inseparable mixture of diastereomers (ratio = 1:1); yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, t, J = 7.2 Hz), 0.85 (3H, t, J = 7.2 Hz), 1.01-1.60 (8H, m), 2.33-2.57 (4H, m), 3.75 (3H, s), 3.76 (3H, s), 5.14-5.22 (4H, m), 5.84 (1H, s), 6.18 (1H, s), 6.72-6.74 (2H, m), 6.77-6.79 (2H, m), 7.07-7.09 (2H, m), 7.12-7.14 (2H, m), 7.26-7.36 (10H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6 (1C), 13.7 (1C), 22.3 (1C), 22.4 (1C), 25.5 (1C), 25.7 (1C), 29.0 (1C), 29.1 (1C), 55.2 (1C), 55.2 (1C), 68.1 (1C), 68.5 (1C), 68.5 (1C), 68.7 (1C), 113.8 (1C), 114.0 (2C), 114.0 (2C), 114.4 (1C), 128.1 (4C), 128.1(2C), 128.4 (2C), 128.5 (2C), 128.5 (2C), 128.6 (2C), 131.4 (1C), 131.6 (1C), 135.2 (2C), 156.3 (1C), 156.4 (1C), 159.5 (1C), 159.5 (1C), 162.5 (1C), 162.6 (1C), 182.6 (1/2C), 183.0 (1/2C); IR (KBr): 2961, 1726, 1606, 1509, 1311, 1176, 1004, 1030, 741 cm^{-1}; HRMS-EI: calcd for $C_{45}H_{48}N_2O_9$ [M$^+$]: 760.3360; found: 760.3360.

Compound 2d: diastereomeric ratio = 1.5:1

major diastereomer: yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (6H, t, J = 7.2 Hz), 1.19-1.28 (4H, m), 1.39-1.60 (4H, m), 2.44-2.48 (4H, m), 5.17 (2H, d, J = 12.0 Hz), 5.21 (2H, d, J = 12.0 Hz), 5.90 (2H, s), 6.91-6.97 (4H, m), 7.10-7.15 (4H, m), 7.26-7.36 (10H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6 (2C), 22.4 (2C), 25.7 (2C), 29.0 (2C), 68.5 (2C), 68.7 (2C), 113.6 (2C), 115.6 (4C, d, $^2J_{C\text{-}F}$ = 20.9 Hz), 128.2 (4C), 128.5 (4C, d, $^3J_{C\text{-}F}$ = 8.6 Hz), 128.6 (6C), 135.0 (2C), 135.4 (2C, d, $^4J_{C\text{-}F}$ = 2.8 Hz), 156.3 (2C), 162.6 (2C, d, $^1J_{C\text{-}F}$ = 246.0 Hz), 162.9 (2C), 182.6 (1C); IR (KBr): 2965, 1728, 1608, 1507, 1386, 1306, 1224, 1100, 744 cm^{-1}; HRMS-EI: calcd for $C_{43}H_{42}N_2O_7F_2$ [M+]: 736.2960; found: 736.2964.

minor diastereomer: colorless solid, mp 111-112 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.79 (6H, t, J = 7.2 Hz), 0.84-1.48 (8H, m), 2.30-2.38 (2H, m), 2.46-2.54 (2H, m), 5.16 (2H, d, J = 12.0 Hz), 5.21 (2H, d, J = 12.0 Hz), 6.20 (2H, s), 6.85-6.91 (4H, m), 7.16-7.29 (4H, m), 7.25-7.36 (10H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6 (2C), 22.3 (2C), 25.4 (2C), 28.9 (2C), 67.9 (2C), 68.7 (2C), 114.3 (2C), 115.6 (4C, d, $^2J_{C\text{-}F}$ = 21.0 Hz), 128.2 (4C), 128.4 (4C, d, $^3J_{C\text{-}F}$ = 8.6 Hz), 128.6 (6C), 135.0 (2C), 135.2 (2C, d, $^4J_{C\text{-}F}$ = 2.9 Hz), 156.4 (2C), 162.4 (2C), 162.6 (2C, d, $^1J_{C\text{-}F}$ = 246.0 Hz), 182.2 (1C); IR (KBr): 2957, 1727, 1644, 1605, 1509, 1391, 1225, 733 cm^{-1}; HRMS-EI: calcd for $C_{43}H_{42}N_2O_7F_2$ [M$^+$]: 736.2960; found: 736.2959.

Compound 2e: diastereomeric ratio = 1.3:1

major diastereomer: colorless solid; mp 50-52 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.79 (6H, t, *J* = 7.2 Hz), 0.87-1.47 (8H, m), 2.28-2.35 (2H, m), 2.43-2.50 (2H, m), 5.16 (2H, d, *J* = 12.0 Hz), 5.21 (2H, d, *J* = 12.0 Hz), 6.19 (2H, s), 7.12-7.34 (18H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6 (2C), 22.3 (2C), 25.4 (2C), 29.0 (2C), 68.0 (2C), 68.7 (2C), 114.3 (2C), 127.9 (4C), 128.2 (4C), 128.6 (6C), 128.9 (4C), 134.2 (2C), 134.9 (2C), 137.9 (2C), 156.3 (2C), 162.3 (2C), 182.0 (1C); IR (KBr): 2960, 1726, 1594, 1492, 1305, 1390, 1217, 1090, 755 cm^{-1}; HRMS-EI: calcd for $C_{43}H_{42}N_2O_7Cl_2$ [M$^+$]: 768.2369; found: 768.2366.

minor diastereomer: yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (6H, t, *J* = 7.2 Hz), 1.18-1.26 (4H, m), 1.36-1.57 (4H, m), 2.42-2.46 (4H, m), 5.17 (2H, d, *J* = 12.0 Hz), 5.22 (2H, d, *J* = 12.0 Hz), 5.91 (2H, s), 7.07-7.11 (4H, m), 7.22-7.36 (14H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6 (2C), 22.4 (2C), 25.7 (2C), 29.1 (2C), 68.5 (2C), 68.8 (2C), 113.5 (2C), 128.1 (4C), 128.2 (4C), 128.6 (4C), 128.6 (2C), 128.8 (4C), 134.2 (2C), 134.9 (2C), 138.0 (2C), 156.2 (2C), 163.0 (2C), 182.3 (1C); IR (KBr): 2959, 1727, 1605, 1493, 1386, 1092, 752, 697 cm^{-1}; HRMS-EI: calcd for $C_{43}H_{42}N_2O_7Cl_2$ [M$^+$]: 768.2369; found: 768.2363.

Compound 2f: inseparable mixture of diastereomers (ratio = 2:1); colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.80 (2H, t, *J* = 7.2 Hz), 0.85 (4H, t, *J* = 7.2 Hz), 1.10-1.63 (8H, m), 2.35-2.64 (4H, m), 5.14-5.23 (4H, m), 6.13 (4/3H, s), 6.51 (2/3H, s), 6.90-7.07 (4H, m), 7.15-7.35 (14H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6 (4/3C), 13.7 (2/3C), 22.3 (2/3C), 22.4 (4/3C), 25.3 (2/3C), 25.6 (4/3C), 28.9 (4/3C), 28.9 (2/3), 63.7 (4/3C, d, $^3J_{C\text{-}F}$ = 2.9 Hz), 63.7(2/3C, d, $^3J_{C\text{-}F}$ = 2.9 Hz), 68.6 (2/3C), 68.6 (4/3C), 112.7 (4/3C), 113.4 (2/3C), 115.7 (4/3C, d, $^2J_{C\text{-}F}$ = 21.0 Hz), 115.8 (2/3C, d, $^2J_{C\text{-}F}$ = 21.0 Hz), 124.4 (2C, d, $^4J_{C\text{-}F}$ = 2.9 Hz), 126.3 (2/3C, d, $^2J_{C\text{-}F}$ = 12.4 Hz), 126.6 (4/3C, d, $^2J_{C\text{-}F}$ = 12.4 Hz), 128.1 (4/3C), 128.2 (8/3C), 128.4 (2/3C), 128.5 (4/3C), 128.6 (4C), 128.8 (4/3, d, $^3J_{C\text{-}F}$ = 3.8 Hz), 129.4 (2/3C, d, $^3J_{C\text{-}F}$ = 3.8 Hz), 130.1 (2/3C, d, $^3J_{C\text{-}F}$ = 8.6 Hz), 130.1 (4/3C, d, $^3J_{C\text{-}F}$ = 8.6 Hz), 135.0 (2C), 156.1 (2/3C), 156.2 (4/3C), 160.1 (4/3C, d, $^1J_{C\text{-}F}$ = 247.9 Hz), 160.3 (2/3C, d, $^1J_{C\text{-}F}$ = 247.9 Hz), 162.9 (2/3C), 163.0 (4/3C), 181.5 (1/3C), 182.1 (2/3C); IR (KBr): 2964, 1730, 1607, 1387, 1307, 1223, 1102, 897, 754 cm^{-1}; HRMS-EI: calcd for $C_{43}H_{42}N_2O_7F_2$ [M$^+$]: 736.2960; found: 736.2960.

Compound 2g: inseparable mixture of diastereomers (ratio = 2:1); colorless solid; mp 43-45 ºC; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.15 (6H, s), 5.11-5.25 (4H, m), 6.22 (4/3H, s), 6.66 (2/3H, s), 7.05-7.34 (18H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.8 (2/3C), 11.8 (4/3C), 66.1 (4/3C), 66.5 (2/3C), 68.8 (2/3C), 68.9 (4/3C), 114.0 (4/3C), 114.6 (2/3C), 127.4 (2/3C), 127.6 (4/3C), 128.5 (4/3C), 128.6 (10/3C), 128.7 (8/3C), 128.7 (4/3C), 128.7 (4/3C), 129.2 (4/3C), 129.7 (2/3C), 129.8 (4/3C), 129.9 (4/3C), 129.9 (2/3C), 130.2 (2/3C), 132.8 (4/3C), 133.1 (2/3C), 135.1 (2/3C), 135.1 (4/3C), 136.2 (2/3C), 136.8 (4/3C), 155.6 (2/3C), 155.8 (4/3C), 159.1 (2/3C), 159.1 (4/3C), 181.4 (1/3C), 182.2 (2/3C); IR (KBr): 1741, 1603, 1390, 1317, 1218, 1099, 896, 751 cm^{-1}; HRMS-EI: calcd for $C_{37}H_{30}N_2O_7Cl_2$ [M$^+$]: 684.1430; found: 684.1434.

Compound 2h: inseparable mixture of diastereomers (ratio = 1.5:1); yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.80 (12/5H, t, J = 7.2 Hz), 0.81 (18/5H, t, J = 7.2 Hz), 1.19-1.29 (4H, m), 1.42-1.58 (4H, m), 1.78-2.18 (4H, m), 2.37-2.74 (8H, m), 5.17-5.33 (6H, m), 7.07-7.37 (20H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.6 (4/5C), 13.6 (6/5C), 22.3 (4/5C), 22.4 (6/5C), 25.7 (6/5C), 25.7 (4/5C), 29.0 (2C), 31.4 (2C), 36.8 (4/5C), 37.2 (6/5C), 65.9 (6/5C), 66.9 (4/5C), 68.7 (2C), 113.5 (4/5C), 113.6 (6/5C), 125.9 (6/5C), 125.9 (4/5C), 128.3 (8/5C), 128.3 (6C), 128.3 (8/5C), 128.4 (16/5C), 128.6 (8/5C), 128,7 (4C), 135.1 (2C), 141.1 (6/5C), 141.3 (4/5C), 157.9 (4/5C), 158.0 (6/5C), 163.9 (6/5C), 164.2 (4/5C), 182.7 (3/5C), 183.4 (2/5C); IR (KBr): 2958, 1722, 1600, 1385, 1308, 1105, 1036, 744, 697 cm^{-1}; HRMS-EI: calcd for $C_{47}H_{52}N_2O_7$ [M$^+$]: 756.3775; found: 756.3772.

Compound 2i: inseparable mixture of diastereomers (ratio = 3:1); yellow amorphous; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.34 (9/2H, s), 2.36 (3/2H, s), 5.06-5.22 (4H, m), 6.08 (3/2, s), 6.22 (1/2H, s), 6.95-7.04 (8H, m), 7.23-7.35(20H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.6 (2C), 68.3 (1/2C), 68.4 (3/2C), 70.3 (3/2C), 70.4 (1/2C), 112.2 (3/2C), 112.5 (1/2C), 122.6 (3/2C), 122.7 (1/2C), 127.0 (3C), 127.3 (1C), 127.9 (3C), 128.2 (1/2C), 128.3 (3/2C), 128.4 (1/2C), 128.5 (5/2C), 128.5 (1C), 128.6 (4C), 128.6 (3C), 128.8 (1C), 128.9 (3C), 129.1 (3C), 129.1 (1C), 135.1 (1/2C), 135.2 (3/2C), 138.9 (1/2C), 139.2 (3/2C), 141.8 (1/2C), 142.0 (3/2C), 155.9 (1/2C), 156.2 (3/2C), 158.8 (1/2C), 159.1 (3/2C), 182.0 (1/4C), 182.4 (3/4C); IR (KBr): 3033, 1724, 1607, 1508, 1386, 1307, 1104, 744, 697 cm^{-1}; HRMS-ESI: $C_{49}H_{41}N_2O_7$ [M+H]$^+$: 769.2914; found: 769.2883.

Typical procedure for the cyclization–carbonylation reaction of benzyl hydroxy(1-phenylhept-2-yn-1-yl)carbamate (1a): condition B

A 30 mL two-necked round-bottom flask containing a magnetic stir bar, benzyl hydroxy(1-phenylhept-2-yn-1-yl)carbamate (**1a**) (100 mg, 0.40 mmol), *p*-benzoquinone (64.9 mg, 0.60 mmol), and MeOH/DMSO = 5/1 (5 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling via the three-way stopcock. A MeOH/DMSO = 5/1 (1 mL) solution of $Pd(tfa)_2$ (6.6 mg, 0.02 mmol) was added to the stirred solution using a syringe at 0 °C. The remaining $Pd(tfa)_2$ was washed in MeOH/DMSO = 5/1 (1 mL) twice and stirred for 72 h at 0 °C. The mixture was diluted with CH_2Cl_2 (40 mL) and washed with 5% a.q. NaOH (40 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane–AcOEt (50/1) afforded monomeric ester **3a**.

Compound 3a: colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.2 Hz), 1.38-1.47 (2H, m), 1.64-1.69 (2H, m), 2.79-2.83 (2H, m), 3.60 (3H, s), 5.21 (2H, s), 6.08 (1H, s), 7.26-7.36 (10H, m);

^{13}C-NMR (100 MHz, CDCl$_3$) δ 13.7, 22.4, 25.4, 29.1, 51.2, 68.0, 68.5, 104.3, 127.2 (2C), 128.2 (2C), 128.2, 128.5, 128.5 (2C), 128.6 (2C), 135.2, 139.9, 156.4, 163.4, 167.0; IR (KBr): 2957, 1714, 1658, 1223, 1113, 1031, 695 cm^{-1}; HRMS-EI: calcd for $C_{23}H_{25}NO_5$ [M$^+$]: 395.1733; found: 395.1732.

Compound 3b: colorless solid; mp 120-122 ºC; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 1.03-1.31 (4H, m), 2.71-2.76 (1H, m), 3.63 (3H, s), 5.19 (2H, s), 6.09 (1H, s), 7.30-7.36 (10H, m); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 7.8, 7.9, 9.0, 51.2, 68.6, 68.6, 104.2, 127.1 (2C), 128.1, 128.2 (2C), 128.5 (2C), 128.5 (2C), 128.6, 135.2, 139.9, 156.9, 164.1, 167.6; IR (KBr): 1712, 1643, 1335, 1122, 1055, 700 cm^{-1}; HRMS-EI: calcd for $C_{22}H_{21}NO_5$ [M$^+$]: 379.1420; found: 379.1422.

Compound 3c: colorless oil; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.94 (3H, t, J = 7.6 Hz), 1.38-1.47 (2H, m), 1.61-1.71 (2H, m), 2.78-2.82 (2H, m), 3.60 (3H, s), 3.79 (3H, s), 5.21 (2H, s), 6.04 (1H, s), 6.84-6.86 (2H, m), 7.24-7.33 (7H, m); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 13.7, 22.4, 25.4, 29.1, 51.2, 55.3, 67.6, 68.5, 104.3, 113.9 (2C), 128.2 (2C), 128.4 (2C), 128.4, 128.5 (2C), 132.1, 135.2, 156.4, 159.5, 163.5, 166.8; IR (KBr): 2956, 1714, 1658, 1512, 1248, 1227, 1113, 1033, 697 cm^{-1}; HRMS-EI: calcd for $C_{24}H_{27}NO_6$ [M$^+$]: 425.1838; found: 425.1838.

Compound 3d: colorless oil; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.94 (3H, t, J = 7.6 Hz), 1.37-1.46 (2H, m), 1.63-1.71 (2H, m), 2.78-2.82 (2H, m), 3.60 (3H, s), 5.21 (2H, s), 6.06 (1H, s), 6.98-7.02 (2H, m), 7.31-7.34 (7H, m); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 13.7, 22.4, 25.4, 29.1, 51.3, 67.4, 68.6, 104.1, 115.4 (2C, d, $^2J_{C\text{-}F}$ = 21.0 Hz), 128.3 (2C), 128.6 (2C, d, $^3J_{C\text{-}F}$ = 5.7 Hz), 128.9, 129.0 (2C), 135.1, 135.8 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 156.3, 162.6 (d, $^1J_{C\text{-}F}$ = 245.0 Hz), 163.3, 167.0; IR (KBr): 2958, 1717, 1655, 1510, 1227, 1114, 674 cm^{-1}; HRMS-EI: calcd for $C_{23}H_{24}NO_5F$ [M$^+$]: 413.1638; found: 413.1638.

Compound 3e: colorless oil; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.93 (3H, t, J = 7.2 Hz), 1.37-1.46 (2H, m), 1.62-1.70 (2H, m), 2.77-2.83 (2H, m), 3.61 (3H, s), 5.21 (2H, s), 6.04 (1H, s), 7.26-7.36 (9H, m); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 13.7, 22.4, 25.4, 29.1, 51.3, 67.4, 68.7, 104.0, 128.3 (2C), 128.5 (2C), 128.6 (3C), 128.7 (2C), 134.0, 135.0, 138.5, 156.2, 163.2, 167.1; IR (KBr): 2957, 1717, 1658, 1345, 1222, 1113, 1032, 697 cm^{-1}; HRMS-EI: calcd for $C_{23}H_{24}NO_5Cl$ [M$^+$]: 429.1343; found:429.1345.

Compound 3f: colorless oil; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.94 (3H, t, J = 7.2 Hz), 1.38-1.48 (2H, m), 1.62-1.72 (2H, m), 2.79-2.84 (2H, m), 3.59 (3H, s), 5.21 (2H, s), 6.39 (1H, s), 7.00-7.13 (2H, m), 7.26-7.33 (7H, m); ^{13}C-NMR (100 MHz, CDCl$_3$) δ 13.7, 22.4, 25.4, 29.0, 51.3, 62.3 (d, $^{3'}J_{C\text{-}F}$ = 3.9 Hz), 68.5, 103.3, 115.7 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 124.3 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 127.0 (d, $^2J_{C\text{-}F}$ = 12.4 Hz), 128.2 (2C), 128.4, 128.5 (2C), 129.1 (d, $^4J_{C\text{-}F}$ = 3.8 Hz), 130.0 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 135.2, 156.0, 160.5, 163.2, 167.4; IR (KBr): 2957, 1715, 1659, 1222, 1114, 1035, 757 cm^{-1}; HRMS-EI: calcd for $C_{23}H_{24}NO_5F$ [M$^+$]: 413.1638; found: 413.1640.

Compound 3g: colorless solid; mp 163-164 ºC; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 2.39 (3H, d, J = 1.2 Hz), 3.59 (3H, s), 5.15 (1H, d, J = 12.0 Hz), 5.22 (1H, d, J = 12.0 Hz), 6.59 (1H, d, J = 1.2 Hz), 7.20-7.33 (9H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.6, 51.3, 64.8, 68.6, 104.8, 127.2, 128.4 (2C), 128.5, 128.5 (2C), 129.3, 129.4, 129.7, 133.4, 135.0, 137.2, 155.4, 163.1, 163.2; IR (KBr): 2952, 1719, 1655, 1405, 1337, 1230, 1119, 750, 701 cm^{-1}; HRMS-EI: calcd for $C_{20}H_{18}NO_5Cl$ [M$^+$]: 387.0873; found: 387.0874.

Compound 3h: yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.6 Hz), 1.32-1.41 (2H, m), 1.54-1.61 (2H, m), 1.88-1.97 (1H, m), 2.11-2.18 (1H, m), 2.67-2.80 (4H, m), 3.71(3H, s), 5.20-5.30 (3H, m), 7.16-7.39 (10H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.7, 22.3, 25.4, 29.0, 31.1, 35.9, 51.3, 65.4, 68.6, 103.3, 125.8, 128.3 (4C), 128.4 (2C), 128.5, 128.6 (2C), 135.2, 141.6, 158.0, 163.7, 168.0; IR (KBr): 2955, 1716, 1658, 1373, 1310, 1215, 1111, 1034, 698 cm^{-1}; HRMS-EI: calcd for $C_{25}H_{29}NO_5$ [M$^+$]: 423.2046; found: 423.2048.

Compound 3i : colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.41 (3H, s), 3.59 (3H, s), 5.27 (2H, s), 6.30 (1H, s), 7.24-7.26 (2H, m), 7.31-7.37 (8H, m), 7.44-7.46 (2H, m), 7.80-7.82 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.7, 51.4, 68.7, 69.3, 103.8, 122.6, 127.2 (2C), 128.2 (2C), 128.3, 128.5 (2C), 128.6 (3C), 128.8 (2C), 130.0 (2C), 135.2, 139.9, 142.4, 157.1, 162.1, 163.0; IR (KBr): 3033, 1718, 1640, 1232, 1084, 821, 753, 698 cm^{-1}; HRMS-EI: calcd for $C_{26}H_{23}NO_5$ [M$^+$]: 429.1576; found: 429.1576.

Preparation of bis(5-butyl-3-phenylisoxazol-4-yl)methanone (4a)

To a solution of **2a** (91.7 mg, 0.131 mmol) in THF/MeOH/H_2O = 4/1/1 (3 mL) was added LiOH·H_2O (33.0 mg, 0.786 mmol), and the mixture was stirred at rt. After 20 min, the mixture was neutralized with 5% a.q. citric acid. Sodium hypochlorite solution (0.5 mL) was then added to the mixture at rt, and stirred for 20 min. The mixture was diluted with CH_2Cl_2 (20 mL) and 10% a.q. $Na_2S_2O_3$ (20 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (20 mL) twice, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography. The fraction eluted with hexane/AcOEt (20/1-4/1) afforded **4a** (22.7 mg, 49%, 2 steps). Yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.97 (6H, t, J =7.6 Hz), 1.38-1.47 (4H, m), 1.71-1.79 (4H, m), 2.89-2.93 (4H, m), 7.15-7.17 (4H, m), 7.26-7.30 (4H, m), 7.36-7.40 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.7 (2C), 22.5 (2C), 26.6 (2C), 29.3 (2C), 116.6 (2C), 127.2 (2C), 128.2 (4C), 128.8 (4C), 130.1 (2C), 160.9 (2C), 177.8 (2C), 183.2; IR (KBr): 2960, 1652, 1590, 1570, 1410, 886, 768, 697 cm^{-1}; HRMS-EI: calcd for $C_{27}H_{28}N_2O_3$ [M$^+$]: 428.2100; found: 428.2102.

Preparation of methyl 3-(2-chlorophenyl)-5-methylisoxazole-4-carboxylate (5g)

To a solution of **3g** (115.9 mg, 0.299 mmol) in THF/MeOH/H_2O = 4/1/1 (9 mL) was added LiOH·H_2O (37.6 mg, 0.897 mmol), and the mixture was stirred at rt. After 20 min, the mixture was neutralized with 5% a.q. citric acid. Sodium hypochlorite solution (0.5 mL) was then added to the mixture at rt, and stirred for 20 min. The mixture was diluted with CH_2Cl_2 (20 mL) and 10% a.q. $Na_2S_2O_3$ (20 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (20 mL) twice, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography. The fraction eluted with hexane/AcOEt (20/1-4/1) afforded **5g** (64.4 mg, 86%, 2 steps). Colorless solid; mp 58-59 ºC. (lit.[18] mp 58-59 ºC); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.76 (3H, s), 3.70 (3H, s), 7.35-7.47 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 13.3, 51.7, 109.7, 126.6, 128.4, 129.4, 130.9, 130.9, 134.0, 160.8, 162.1, 175.2; IR (KBr):1728, 1607, 1450, 1318, 1107, 762 cm^{-1}; HRMS-APCI: calcd for $C_{12}H_{11}ClNO_3$ $[M+H]^+$: 252.0428; found: 252.0437.

ACKNOWLEDGEMENTS

This work was supported by a JSPS KAKENHI grant (No.15K078771).

REFERENCES

1. (a) A. G. Habeeb, P. N. Rao, and E. E. Knaus, *J. Med. Chem.*, 2001, **44**, 2921; (b) R. D. Cramer, R. J. Jilek, S. Guessregen, S. J. Clark, B. Wendt, and R. D. Clark, *J. Med. Chem.*, 2004, **47**, 6777; (c) M. E. Fraley, R. M. Garbaccio, and G. D. Hartmann, Patent WO 2006023440, 2006.
2. (a) J. P. Freeman, *Chem. Rev.*, 1983, **83**, 241; (b) T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.*, 2010, 3363.
3. (a) M. Ehrlich and T. Carell, *Eur. J. Org. Chem.*, 2013, 77; (b) K. Grossmann and T. Ehrhardt, *Pest Manage. Sci.*, 2007, **63**, 429; (c) H. Neumann, A. Brennführer, and M. Beller, *Chem. Eur. J.*, 2008, **14**, 3645; (d) F. Jafarpour, P. Rashidi- Ranjbar, and A. O. Kashani, *Eur. J. Org. Chem*., 2011, 2128; (e) M. J. Lo Fiego, G. F. Silbestri, A. B. Chopa, and M. T. Lockhart, *J. Org. Chem*., 2011, **76**, 1707; (f) Y.-S. Wu, M. S. Coumar, J.-Y. Chang, H.-Y. Sun, F.-M. Kuo, C.-C. Kuo, Y.-J. Chen, C.-Y. Chang, C.-L. Hsiao, J.-P. Liou, C.-P. Chen, H.-T. Yao, Y.-K. Chiang, U.-K. Tan, C.-T. Chen, C.-Y. Chu, S.-Y. Wu, T.-K. Yeh, C.-Y. Lin, and H.-P. Hsieh, *J. Med. Chem*., 2009, **52**, 4941; (g) K. Kobayashi, Y. Nishimura, F. Gao, K. Gotoh, Y. Nishihara, and K. Takagi, *J. Org. Chem*., 2011, **76**, 1949, and references cited therein.
4. For selected recent examples, see: (a) S. M. M. Lopes, C. M. Nunes, and T. M. V. D. Pinho e Melo, *Tetrahedron*, 2010, **6**, 6078; (b) H. Valizadeh and L. Dinparast, *Synth. Commun.*, 2011, **41**, 291; (c) X. Cai, C. Wang, and J. Suna, *Adv. Synth. Catal.,* 2012, **354**, 359; (d) M. P. Sibi, K. L. Dunkle, and D. Rane, *Heterocycles,* 2014, **88**, 1639; For the reaction of nitrones with vinyldiazoacetates, see: (e) C. Qin and H. M. L. Davies, *J. Am. Chem. Soc.,* 2013, **135**, 14516.
5. M. Fabio, L. Ronzini, and L. Troisi, *Tetrahedron*, 2008, **64**, 4979.
6. X. Yu, B. Du, K. Wang, and J. Zhang, *Org. Lett*., 2010, **12**, 1876.
7. P. Li, B.-T. Teng, F.-G. Jin, X.-S. Li, W.-D. Zhu, and J.-W. Xie, *Org. Biomol. Chem.*, 2012, **10**, 244.

8. S. Madabhushi, K. R.y Godala, R. Jillella, K. K. R. Mallu, and N. Chinthala, *Tetrahedron Lett*., 2014, **55,** 514.

9. For recent reviews, see: (a) X.-F. Wu, H. Neumann, and M. Beller, *Chem. Rev*., 2013, **113**, 1; (b) H. Clavier and H. H. Pellissier, *Adv. Synth. Catal*., 2012, **354**, 3347; (c) T. Vlaar, E. Ruijter, and R. V. A. Orru, *Adv. Synth. Catal*., 2011, **353**, 809; For the palladium catalyzed carbonylative coupling reactions, see: (d) A. Brennführer, A. H. Neumann, and M. Beller, *ChemCatChem*, 2009, **1**, 28; (e) C. Torborg and M. Beller, *Adv. Synth. Catal*., 2009, **351**, 3027; (f) C. F. J. Barnard, *Organometallics*, 2008, **27**, 5402; (g) X.-F. Wu, H. Neumann, and M. Beller, *Angew. Chem*., 2009, **121**, 4176 (*Angew. Chem. Int. Ed*., 2009, **48**, 4114); (h) X.-F. Wu, H. Neumann, and M. Beller, *Angew. Chem*., 2010, **122**, 5412 (*Angew. Chem. Int. Ed*., 2010, **49**, 5284); (i) R. Grigg and S. P. Mutton, *Tetrahedron*, 2010, **66**, 5515; (j) X.-F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao, and M. Beller, *J. Am. Chem. Soc*., 2010, **132**, 14596. For the tandem dimerization and cyclization of acetylenic compounds, see: (k) A. Jeevanandam, K. Narkunan, and Y.-C. Ling, *J. Org. Chem*., 2001, **66**, 6014; (l) H. A. Wegner, S. Ahles, and M. Neuburger, *Chem. Eur. J.*, 2008, **14**, 11310; (m) M. G. Auzias, M. Neuburger, and H. A. Wegner, *Synlett*, 2010, 2443. For oxidative carbonylation reactions, see: (n) S. T. Gadge and B. M. Bhanage, *RSC Adv*., 2014, **4**, 10367; (o) X.-F. Wu, H. Neumann, and M. Beller, *ChemSusChem*, 2013, **6**, 229; (p) B. Gabriele, R. Mancuso, and G. Salerno, *Eur. J. Org. Chem*., 2012, 6825.

10. (a) E. J. Stoner, B. A. Roden, and S. Chemburkar, *Tetrahedron Lett*., 1997, **38**, 4981; (b) P. Aschwanden, D. E. Frantz, and E. M. Carreira, *Org. Lett*., 2000, **2**, 2331; (c) O. Debleds, C. D. Zotto, E. Vrancken, J.-M. Campagne, and P. Retailleau, *Adv. Synth. Catal*. 2009, **351**, 1991; (d) E. Gayon, O. Quinonero, S. Lemouzy, E. Vrancken, and J.-M. Campagne, *Org. Lett*., 2011, **13**, 6418.

11. (a) S. Yasuhara, M. Sasa, T. Kusakabe, H. Takayama, M. Kimura, T. Mochida, and K. Kato, *Angew. Chem*., 2011, **123**, 3998 (*Angew. Chem. Int. Ed*., 2011, **50**, 3912); (b) T. Kusakabe, Y. Kawai, R. Shen, T. Mochida, and K. Kato, *Org. Biomol. Chem*., 2012, **10**, 3192; (c) T. Kusakabe, E. Sekiyama, S. Motodate, S. Kato, T. Mochida, and K. Kato, *Synthesis*, 2012, 1825; (d) T. Kusakabe, K. Kawaguchi, M. Kawamura, N. Niimura, R. Shen, H. Takayama, and K. Kato, *Molecules,* 2012, **17**, 9220; (e) T. Kusakabe, H. Sagae, and K. Kato, *Org. Biomol. Chem*., 2013, **11**, 4943; (f) Y. Jiang, T. Kusakabe, K. Takahashi, and K. Kato, *Org. Biomol. Chem*., 2014, **12**, 3380; (g) R. Shen, T. Kusakabe, K. Takahashi, and K. Kato, *Org. Biomol. Chem*., 2014, **12**, 4533; (h) Y. D. Dhage, H. Daimon, C. Peng, T. Kusakabe, K. Takahashi, Y. Kanno, Y. Inouye, and K. Kato, *Org. Biomol. Chem*., 2014, **12**, 8619.

12. (a) K. Kato, S. Motodate, T. Mochida, T. Kobayashi, and H. Akita, *Angew. Chem*., 2009, **121**, 3376 (*Angew. Chem. Int. Ed*., 2009, **48**, 3326); (b) S. Motodate, T. Kobayashi, M. Fujii, T. Mochida, T. Kusakabe, S. Katoh, H. Akita, and K. Kato, *Chem. Asian J*., 2010, **5**, 2221; (c) K. Kato, R. Teraguchi, S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin, and O. V. Gusev, *Synlett*, 2007,

638; (d) K. Kato, R. Teraguchi, S. Motodate, A. Uchida, T. Mochida, T. A. Peganova, N. V. Vologdin, and H. Akita, *Chem. Commun.*, 2008, 3687; (e) T. Kusakabe, T. Takahashi, R. Shen, A. Ikeda, A. Y. D. Dhage, Y. Kanno, Y. Inouye, H. Sasai, T. Mochida, and K. Kato, *Angew. Chem.*, 2013, **125**, 7999 (*Angew. Chem. Int. Ed.*, 2013, **52**, 7845).

13. D. Giomi, F. M. Cordero, and F. Machetti, 'In Comprehensive Heterocyclic Chemistry III, Vol. 4, ed. by A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, and R. J. K. Taylor, Elsevier, Oxford, 2008, pp. 365-485.
14. F. Benfatti, G. Cardillo, S. Contaldi, L. Gentilucci, E. Mosconi, A. Tolomelli, E. Juaristi, and G. R-Rangel, *Tetrahedron*, 2009, **65**, 2478.
15. Z.-P. Zhan, J.-L. Yu, H.-J. Liu, Y.-Y. Cui, R.-F. Yang, W.-Z. Yang, and J.-P. Li, *J. Org. Chem.*, 2006, **71**, 8298.
16. E. Gayon, M. Szymczyk, H. Gérard,, E. Vrancken, and J.-M. Campagne, *J. Org. Chem.*, 2012, **77**, 9205.
17. T. Harada and E. Kutsuwa, *J. Org. Chem.,* 2003, **68**, 6716.
18. L. C. Cheney and L. B. Crast Jr., Patent FR 1535810, 1968.