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Palladium Catalyzed Addition of Carbon Pronucleophiles to Conjugated Enynes

Vladimir Gevorgyan, Chie Kadowaki, Matthew M.Salter Isao Kadota†, Shinichi Saito, and Yoshinori Yamamoto*

Department of Chemistry, Graduate School of Science
and Research Center for Organic Resources and Materials Chemistry
Institute for Chemical Reaction Science, Tohoku University
Sendai 980-77, Japan

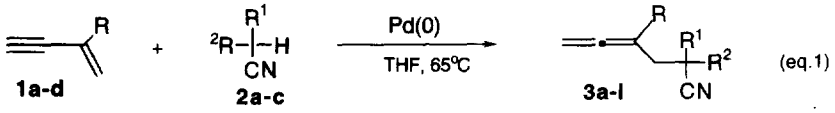
Abstract: Palladium catalyzed addition of certain carbon pronucleophiles **2** to conjugated enynes **1** afforded the corresponding allenes **3** in good to excellent yields. The most reactive methynes such as methylmalononitrile **2c** enabled to undergo double addition leading to alkenes **4**. Catalyst optimization supported $Pd_2(dba)_3 \bullet CHCl_3$ - dppf combination as the best system among all catalysts tested. The plausible mechanisms for these catalytic reactions were proposed. © 1997 Elsevier Science Ltd.

The addition of carbanionic organometallic compounds to activated alkenes, such as Michael acceptors, is a classical and standard procedure for the carbon-carbon bond formation. In modern organic synthesis, the use of transition metal catalysts enables the addition of carbanionic species to unactivated alkenes[1]. The additions of activated methylenes and methynes to activated alkenes in the presence of bases are commonly known as Michael reactions, which afford the C-C bond forming products. More recently, the transition metal catalyzed version of this type reaction has been developed.[2] We have recently demonstrated that palladium-catalyzed addition of carbon pronucleophiles to unactivated allenes proceeds smoothly, serving as a powerful tool in the synthesis of differently substituted olefins.[3] Shortly after we have communicated the palladium catalyzed addition of several cyano-based pronucleophiles **2** to conjugated enynes **1**, leading to the corresponding allenes **3**[4] in good to excellent yields. Now we report a detailed study on this reaction, as well as palladium catalyzed addition of cyano-based activated methylenes and Meldrum's acid derivative to **1**.

RESULTS

Optimization of catalyst system.

First we have briefly optimized a catalyst system for an addition of ethyl 2-cyanopropionate **2a** to enyne **1a** (eq. 1, Table 1). The starting point for optimization was our original neutral catalyst system that was found to be the best in the addition of pronucleophiles to allenes: $Pd_2(dba)_3 \bullet CHCl_3$ (5mol%) - Ligand (25mol%)[3a]. The initial



1 a R=Me
b R=Hex
c R=Bn
d R=TMS

2 a R^1=Me, R^2=CO_2Et
b R^1=Ph, R^2=CO_2Et
c R^1=Me, R^2=CN

3 a R=R^1=Me, R^2=CO2Et
b R=Me, R1=Ph, R2=CO_2Et
c R=R^1= Me, R^2=CN
d R=Hex, R^1=Me, R^2=CO_2Et
e R=Hex, R^1=Ph, R^2=CO_2Et
f R=Hex, R^1=Me, R^2=CN
g R=Bn, R^1=Me, R^2=CO_2Et
h R=Bn, R^1=Ph, R^2=CO_2Et
i R=Bn, R^1=Me, R^2=CN
j R=TMS, R^1=Me, R^2=CO_2Et
k R=TMS, R^1=Ph, R^2=CO_2Et
l R=TMS, R^1=Me, R^2=CN

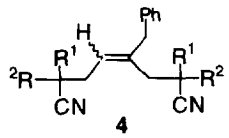


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Table 1. Optimization of Catalyst System in Addition of 2a to 1a[a]

entry	ligand	yield of 3a (%)[b]	recovery of 2a (%)[b]
1	none	no reaction	>95
2	PPh_3	no reaction	92
3	$AsPh_3$	no reaction	91
4	$SbPh_3$	no reaction	92
5	dppm[c]	traces	87
6	dppe[d]	no reaction	95
7	dppp[e]	12	71
8	dppb[f]	9	90
9	dppf	66	7
10	dppf	68[g]	-

[a] All reactions were carried out with 0.75 mmol of **1** and 0.50 mmol of **2** in THF (0.25 - 0.5 M concentrations) at 65°C. The ratio of [P]:[Pd] or [heteroatom]:[Pd] was 5:1, as it was found to be the best in our previous study[3a]. [b] Determined by capillary GLC using tetradecane as an internal stndard. [c] dppm = Bis(diphenylphosphino)methane. [d] dppe = 1,2-Bis(diphenylphosphino)ethane. [e] dppp = 1,3-Bis(diphenylphosphino)propane. [f] dppb = 1,4-Bis(diphenylphosphino)butane. [g] One mol % of palladium catalyst was employed.

test experiments without ligand (Table 1, entry 1), as well as combination of palladium catalyst with monodentate ligands, indicated no reaction (entries 2-4). Combination of palladium catalyst with bidentate ligands such as dppm, dppe, dppp, and dppb gave disappointing results as well (Table 1, entries 5-8). In contrast, $Pd_2(dba)_3$•$CHCl_3$ - dppf combination appeared to be an effective catalyst system producing allene **3a** in 66% yield

(entry 9). Furthermore, the five fold decrease of amount of catalyst (from 5 to 1mol%) did not affect the reaction course, thus considerably increasing the turnover number of this catalyst system (Table 1, entry 10).

Palladium-catalyzed addition of cyano-containing methynes 2a-c to enynes 1a-d.

We next examined the addition of certain cyano-based pronucleophiles **2a-c** to conjugated enynes **1a-d** in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (1mol%) - dppf (5mol%) catalyst system (eq. 1, Table 2). The reaction of 2-methyl-1-buten-3-yne **1a** with ethyl 2-cynopropionate **2a** and methylmalononitrile **2c** gave the corresponding allenes **3a** and **3c** in good yields (Table 1, entries 1,3), while the addition of 2-phenyl-2-cynoacetate **2b** to **1a** was quantitative (entry 2). The reactions of **1b**, bearing a longer alkyl chain than **1a**, with pronucleophiles **2a-c** were quite sluggish giving lower yields of the allenes **3d-f** (entries 4-6). The reactions of **1c**, substituted by benzyl group at the C-2 position, proceeded smoothly when **2a** and **2b** were used as the pronucleophiles (entries 7,8). It was interesting to find that 1,4-bis adduct **4a** was formed as a major product (61%) along with 28% of allene **3i** when an 1.5 equiv. excess of the most reactive pronucleophile **2c** was utilized in the reaction with enyne **1c** (entry 9). The trimethylsilyl substituted enyne **1d** reacted with pronucleophiles **2a-c** easily, giving the allenic adducts **3j-l** in excellent to quantitative yields (Table 2, entries 10-12). In all cases the addition of pronucleophiles **2** to enynes **1** proceeded 1,4-regiospecifically: the nucleophilic portion adds to the terminal olefinic carbon, and hydrogen adds to the terminal alkyne moiety. However, it should be pointed out that the scope of this addition reaction is limited by the structure of enyne. Thus the addition of pronucleophiles to enynes, substituted at the alkyne moiety was very sluggish; furthermore the enynes, substituted at the terminal olefinic position, did not react with pronucleophiles under the tested conditions at all.

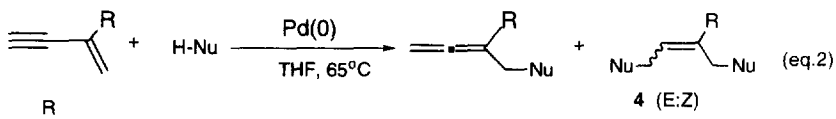
We propose two plausible mechanisms for the 1,4-addition of pronucleophiles **2** to enynes **1**. According with the first mechanism (Scheme 1) the oxidative insertion of Pd(0) into the C-H bond of pronucleophile **2** would produce the Pd(II) species **5**. Hydropalladation of **1** with **5** would afford the *exo*-methylene π-allylpalladium intermediate **6**. Reductive elimination would form the product **3** and regenerate the catalyst. Although the *exo*-methylene π-allylpalladium structure **6** is highly strained, a related intermediate has been proposed previously.[5] If the carbopalladation mechanism is involved in the palladium-catalyzed allene formation, the strained allenylpalladium intermediate **7** must be considered (Scheme 2).

The precedent of 1,4-double addition which was observed in the reaction between methylmalononitrile **2c** and benzyl-substituted enyne **1c** (Table 2, entry 9) prompted us to further study this reaction. Thus, we have examined the addition of pronucleophiles **2b,c** toward enynes **1b,c** (eq. 2). We found that use of two equivalents of the most reactive **2c** in the palladium-catalyzed addition to enynes **1b,c** led to the exclusive formation of the 1,4-double addition products **4a,b** in very good yields. In contrast, ethylphenylcyanoacetate **2b** reacted with **1b** in monoaddition manner, giving **3e** in 69% yield; and even under prolong reflux no trace of double addition product **4c** was detected by ^1H NMR analysis of crude reaction mixture (eq. 2). It is likely that the observed 1,4-double addition is a stepwise process. Initial formation of allenes **3f,i** *via* 1,4-addition of methylmalonitrile **2c** to enynes **1b,c**, followed by 3,4-addition of a second molecule of pronucleophile **2c** to **3f,i** will afford alkenes **4a,b** (eq. 2).[6]

Table 2. Palladium catalyzed addition of pronucleophiles **2** to enynes **1**[a]

entry	Enyne	Pronucleophile	Product	Time (h)	Yield of **3** (%)[b]
1	**1a**	**2a**	**3a**	65	60
2		**2b**	**3b**	63	100
3		**2c**	**3c**	63	75
4	**1b**	**2a**	**3d**	80	49
5		**2b**	**3e**	65	50
6		**2c**	**3f**	65	49
7	**1c**	**2a**	**3g**	36	65
8		**2b**	**3h**	72	95
9		**2c**[c]	**3i**	72	28[d]
10	**1d**	**2a**	**3j**	43	90
11		**2b**	**3k**	72	100
12		**2c**	**3l**	72	100

[a] All reactions were carried out with 0.75 mmol of **1** and 0.50 mmol of **2** in THF (0.5M) at 65°C in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ (1 mol%) - dppf (5 mol%), except where otherwise noted. [b] Isolated yield. [c] One and half equiv. of **2** was utilized. [d] 1,4-Bis adduct **4a** was isolated as a major product in 61% yield.



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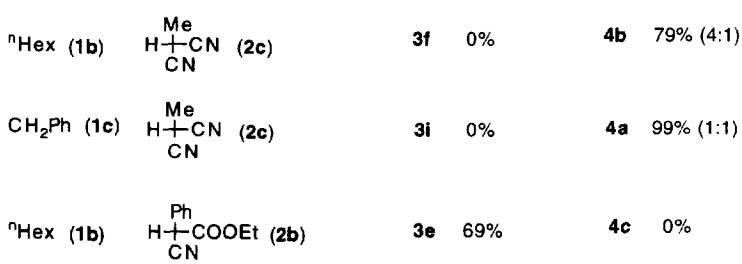
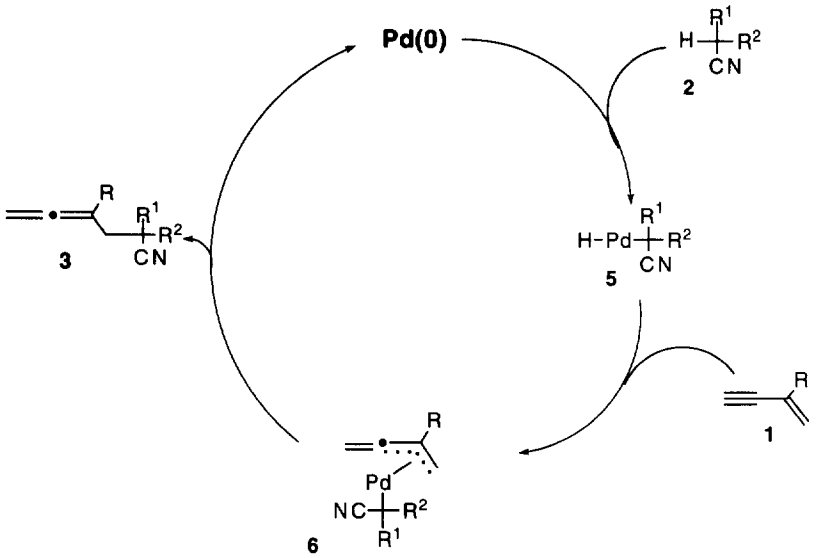
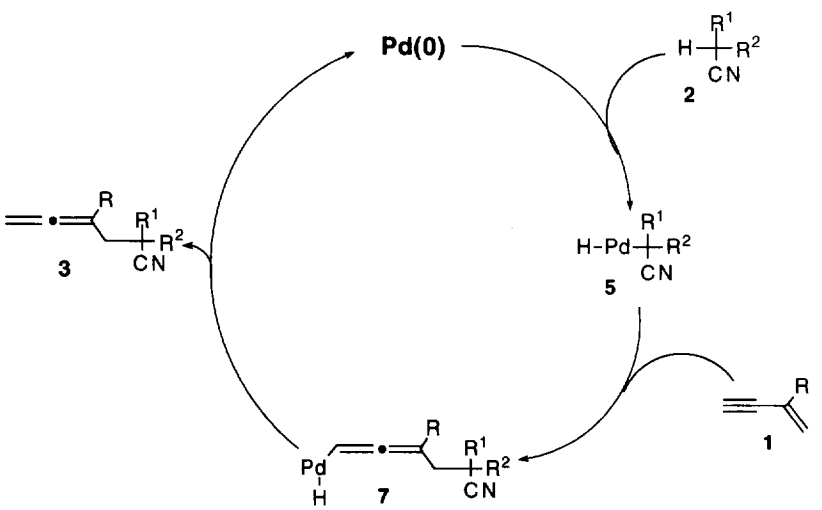


Palladium-catalyzed double alkylation of enynes 1a-c with cyano-containing methylenes 2d,e

Further, we have examined the palladium-catalyzed addition of methylenes **2d,e** to the conjugated enynes **1a-c**. Since the molecule of pronucleophiles **2d,e** contains two active hydrogen atoms, it was expected that one equivalent of **2** could react with two equivalents of **1**. Indeed, experiments exhibited that in the presence of palladium catalyst the activated methylenes **2d,e** in two fold excess *vs* enynes **1** could undergo this kind of

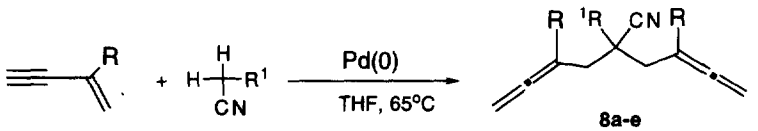


Scheme 1. Hydropalladation Mechanism.



Scheme 2. Carbopalladation Mechanism.

double addition (eq.3). Although the reactions of **1a-c** with **2d,e** were rather sluggish (one day reflux in THF) and the yields of double-addition products **8a-e** were low to reasonable (15-61%), the present procedure could be used as a simple and regiospecific pathway for preparation of differently substituted 1,3-diallenyl alkanes **8**.

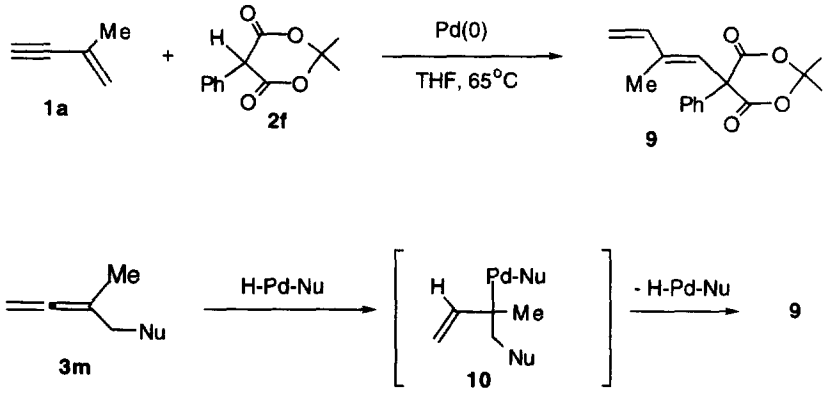


1a-c **2d,e**

R	R^1		
Me	CN	**8a**	34%
Me	CO_2Me	**8b**	15%
^nHex	CN	**8c**	61%
^nHex	CO_2Me	**8d**	42%
CH_2Ph	CN	**8e**	35%

Palladium-catalyzed addition of phenyl Meldrum's acid 2f to 1a

As a final remark of our investigation we would like to disclose our initial experiments on palladium-catalyzed addition of non cyano-based pronucleophile **2f** to the conjugated enyne **1a**. Surprisingly we found no expected allene **3m** was produced, instead the isomeric 1,3-diene **9** was formed in 28% yield as a single product of this reaction (Scheme 3). As a working hypothesis of the formation of **9** we could propose the following: the simple 1,4-addition of **2f** to **1a** would produce the allene **3m**, which then would undergo the further hydropalladation with the H-Pd-Nu leading to intermediate **10**. The elimination of hydride palladium species from **10** would produce more stable 1,3-diene **9** instead of **3m**.



Scheme 3. Palladium-catalyzed addition of phenyl Meldrum's acid to 1a.

Conclusion

This type of the transformation *via* catalytic process has not been known previously, and thus the present development provides a further example of transition metal-catalyzed addition of carbon pronucleophiles to unsaturated C-C bonds. Although further investigation is needed to clarify whether the hydropalladation or carbopalladation mechanism is involved, the present reaction provides a new and efficient route to the synthesis of differently substituted allenes.

EXPERIMENTAL SECTION

General Information ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-GSX-270 (270 MHz) and JEOL JMN - A500 (500 MHz) instruments. IR spectra were recorded on a Shimadzu FTIR-8200A spectrometer. High-resolution mass spectra were recorded on a Hitachi M-2500S spectrometer. Capillary GLC analysis was performed on SHIMADZU GC-14A (CPB20-M25-025 column). Column chromatography was carried out employing Merck silica gel (Kieselgel 70-230 mesh), and analytical thin layer chromatography (TLC) was performed on 0.2 mm precoated silica gel plates (Kieselgel 60 F_{254}). All manipulations were conducted under an argon atmosphere using standard Schlenk techniques and Wheaton mini reactors equipped with mininert valves. Anhydrous solvents were purchased from Kanto Chemicals. The enynes **1b**[7], **1c**[8], **1d**[9], and methylmalononitrile **1e**[10] were prepared according with known procedures. All other compounds used were commercially available and purchased from Aldrich and TCI.

Palladium-catalyzed addition of pronucleophiles to conjugated enynes (General Method) The pronucleophile (500 μmol) was added at room temperature to the stirring mixture of $Pd_2(dba)_3$•$CHCl_3$ (5 μmol) and dppf (25 μmol) in THF (1.0 mL) followed by the addition of enyne (750 μmol). Reaction temperature was kept at 65°C and reaction course was monitored by capillary GLC and TLC analyses. After completion of the reaction the mixture was filterred through the short column (silica gel) and concentrated. The product was purified by column chromatography (silica gel).

3a: ^1H NMR (270 MHz, $CDCl_3$) δ 4.80-4.64 (m, 2H), 4.23 (q, 2H, J=7Hz), 2.64 (ddd, 1H, J=14.0, 3.2, and 3.0 Hz), 2.35 (ddd, 1H, J=14.0, 3.2, and 3.0 Hz), 1.76 (t, 3H, J=3.3 Hz), 1.62 (s, 3H), 1.31 (t, 3H, J=7Hz); IR (neat) 2985, 2909, 2877, 1961, 1743, 1452, 1426, 1380, 1367, 1244, 1218, 1183, 1155, 1055, 994, 858 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO_2$ 193.2456, found 193.1102.

3b: ^1H NMR (270 MHz, $CDCl_3$) δ 7.61-7.55 (m, 2H), 7.43-7.35 (m, 3H), 4.81-4.13 (m, 2H), 4.31-4.13 (m, 2H), 3.14 (dt, 1H, J=15.0 and 3.0 Hz), 2.62 (dt, 1H, J=15.0 and 3.0 Hz), 1.71 (t, 3H, J=3.3 Hz), 1.25 (t, 3H, J=7.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 206.7, 167.2, 134.7, 129.0, 128.8, 126.1, 118.3, 93.7, 77.4, 63.0, 53.1, 41.6, 19.4, 13.7; IR (neat) 2983, 1960, 1744, 1494, 1463, 1230, 857 cm^{-1}; HRMS calcd for $C_{16}H_{17}NO_2$ 255.1245, found 255.1254.

3c: ^1H NMR (270 MHz, $CDCl_3$) δ 4.93 (m, 2H), 2.56 (m, 2H), 1.86 (s, 6H); IR (neat) 2987, 2947, 2925, 2862, 2250, 1961, 1726, 1450, 1425, 1384, 1278, 1250, 1178, 1146, 995, 916, 862 cm^{-1}; HRMS calcd for $C_9H_{10}N_2$ 146.1919, found 146.0846.

3d: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.89-4.73 (m, 2H), 4.24 (q, 2H, J=7.0 Hz), 2.65 (dt, 1H, J=15.0 and 3.0 Hz), 2.35 (dt, 1H, J=15.0 and 3.0 Hz), 2.03-1.94 (m, 2H), 1.64 (s, 3H), 1.33 (t, 3H, J=7.0 Hz), 1.32-1.24 (m, 8H), 0.88 (m, 3H); IR (neat) 2957, 2928, 2956, 2019, 1958, 1856, 1744, 858 cm^{-1}; HRMS calcd for $C_{16}H_{25}NO_2$ 263.3800, found 263.1892.

3e: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.62-7.55 (m, 2H), 7.43-7.32 (m, 3H), 4.89-4.70 (m, 2H), 4.30-4.12 (m, 2H), 3.14 (dt, 1 H, J=15.0, 3.0 Hz), 2.56 (dt, 1 H, J=15.0, 3.0 Hz), 1.93 (m, 2H), 1.40-1.20 (m, 8H), 0.87 (m, 3H); IR (neat) 3064, 2957, 2929, 2871, 2253, 1954, 1746, 1450, 1230, 1055, 911, 857, cm^{-1}; LRMS 325 (M^+, 6), 168 (100); HRMS calcd for $C_{21}H_{27}NO_2$ 325.2042, found 325.2036.

3f: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.00 (m, 2H), 2.54 (dd, 3H, J=2.5 and 2.5 Hz), 2.07 (m, 2H), 1.85 (s, 3H), 1.50-1.20 (m, 8H), 0.89 (t, 3H, J=7.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 206.4, 116.1, 97.1, 80.2, 40.7, 32.2, 31.5, 30.8, 28.6, 27.2, 25.3, 22.5, 14.0; IR (neat) 2997, 2956, 2929, 2871, 2858, 1957, 1458, 1430, 1380, 1277, 1165, 1143, 989, 921, 857 cm^{-1}; HRMS calcd for $C_{14}H_{20}N_2$ 216.1626, found 216.1616.

3g: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27-7.18 (m, 5H), 4.93-4.75 (m, 2H), 4.24 (m, 2H), 3.39 (m, 2H), 2.59 (dt, 1H, J=15.0 and 3.0 Hz), 2.28 (dt, 1H, J=15.0 and 3.0 Hz), 1.60 (s, 3H), 1.32 (t, 3H, J= 7.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 207.0, 168.9, 138.2, 128.7, 128.3, 126.4, 119.8, 97.6, 78.3, 62.5, 43.0, 39.6, 38.4, 24.3, 13.8; IR (neat) 3061, 3028, 2986, 2245, 1960, 1744, 1603, 1495, 1454, 1381, 1244, 1018, 858, 739, 702, 665 cm^{-1}; HRMS calcd for $C_{17}H_{18}NO_2$ 268.1338, found 268.1337.

3h: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.55-7.20 (m, 10H), 4.91-4.71 (m, 2H), 4.27-4.15 (m, 2H), 3.32 (m, 2H), 3.06 (ddd, 1H, J= 15.5, 3.0, and 3.0 Hz), 2.52 (ddd, 1H, J= 15.5, 3.0, and 3.0 Hz), 1.24 (t, 3H, J=7.0 Hz); IR (neat) 3063, 3028, 2980, 2936, 2907, 2870, 2247, 1960, 1744, 1601, 1495, 1450, 1231, 858, 762, 729, 698 cm^{-1}. HRMS calcd for $C_{22}H_{21}NO_2$ 331.4143, found 331.1569.

3i: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36-7.20 (m, 5H), 5.07 (m, 2H), 3.46 (m, 2H), 2.45 (m, 2H), 1.82 (s, 3H); IR (neat) 3028, 2926, 2855, 2249, 1960, 1736, 1601, 1495, 1454, 1115, 1074, 1030, 862, 802, 741, 700 cm^{-1}. HRMS calcd for $C_{15}H_{14}N_2$ 222.2896, found 222.1155.

3j: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.60-4.43 (m, 2H), 4.30-4.18 (m, 2H), 2.65 (ddd, 1H, J= 16.0, 3.0, and 3.0 Hz), 2.31 (ddd, 1H, J= 16.0, 3.0, and 3.0 Hz), 1.65 (s, 3H), 1.32 (t, 3H, J=7.0 Hz), 0.13 (s, 9H); IR (neat) 2986, 2859, 2905, 2245, 1929, 1743, 1456, 1379, 1250, 1124, 1020, 842, 756 cm^{-1}. HRMS calcd for $C_{13}H_{21}NO_2Si$ 251.4008, found 251.1334.

3k: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.62-7.57 (m, 2H), 7.44-7.35 (m, 3H), 4.60-4.42 (m, 2H), 4.30-4.15 (m, 2H), 3.13 (ddd, 1H, J= 16.0, 3.0, and 3.0 Hz), 2.50 (ddd, 1H, J= 16.0, 3.0, and 3.0 Hz), 1.26 (t, 3H, J=7.0 Hz), 0.12 (s, 9 H); IR (neat) 3063, 2959, 2247, 1931, 1746, 1599, 1495, 1450, 1250, 1231, 1020, 842, 756 cm^{-1}. HRMS calcd for $C_{18}H_{23}NO_2Si$ 313.4717, found 313.1502.

3l: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.75 (t, 2H, J=3.5 Hz), 2.53 (t, 2H, J=3.5 Hz), 1.88 (s, 3H), 0.16 (s, 9H); IR (neat) 2959, 2899, 2249, 1942, 1927, 1292, 1252, 1146, 1013, 839, 756 cm^{-1}. HRMS calcd for $C_{11}H_{16}N_2Si$ 204.3470, found 204.1086.

E-4a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 3H), 7.28-7.22 (m, 2H), 5.90 (t, 1H, J=7.0 Hz), 3.76 (s, 2H), 2.94 (d, 2H, J=7.0 Hz), 2.61 (s, 2H), 1.88 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 138.80, 136.54, 129.10, 128.63, 127.20, 125.09, 116.06, 115.74, 44.35, 37.39, 36.30, 31.48, 25.37, 24.07; IR (neat) 3584, 2359, 2341, 1726, 1497, 1454, 1271, 1138, 1076, 1030, 914, 665 cm^{-1}; HRMS calcd for $C_{19}H_{18}N_4$ 302.1531, found 302.1542.

Z-4a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 3H), 7.28-7.22 (m, 2H), 5.88 (t, 1H, J=8.0 Hz), 3.77 (s, 2H), 2.86 (d, 2H, J=8.0 Hz), 2.65 (s, 2H), 1.86 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 139.30, 137.05, 129.13, 128.95, 127.15, 125.49, 116.17, 115.68, 43.81, 37.79, 37.70, 31.84, 30.97, 26.12, 24.31; IR (neat) 3086, 3063, 3030, 3001, 2928, 2251, 1958, 1815, 1722, 1665, 1603, 1495, 1454, 914, 745 cm^{-1}; HRMS calcd for $C_{19}H_{18}N_4$ 302.1531, found 302.1522.

E-4b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (t, 1H, J=7.6 Hz), 2.80 (t, 2H, J=7.3 Hz), 2.71 (s, 2H), 2.32 (t, 2H, J=7.6 Hz), 1.45 (m, 2H), 1.31 (m, 6H), 0.90 (t, 3H, J=7.0 Hz); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 140.68, 123.28, 115.98, 115.78, 44.99, 37.04, 31.55, 30.71, 29.14, 28.49, 25.25, 23.94, 22.25, 13.99; IR (neat) 2955, 2932, 2858, 2251, 1650, 1456, 1383, 1271, 1144, 890, 704, 665 cm^{-1}; HRMS calcd for $C_{18}H_{24}N_4$ 296.2001, found 296.2003.

Z-4b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (t, 1H, J=7.8 Hz), 2.81 (d, 2H, J=7.8 Hz), 2.78 (s, 2H), 2.38 (t, 2H, J=7.6 Hz), 1.88 (s, 3H), 1.83 (s, 3H), 1.52 (m, 2H), 1.31 (m, 6H), 0.89 (t, 3H, J=7.1 Hz); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 140.25, 122.89, 116.01, 115.66, 114.88, 38.48, 37.50, 37.16, 31.87, 31.48, 30.92, 28.58, 28.26, 25.86, 24.20, 22.50, 13.96; IR (neat) 2999, 2930, 2850, 2251, 1726, 1650, 1456, 1385, 1273, 1207, 1161, 1146, 916, 665 cm^{-1}; HRMS calcd for $C_{18}H_{24}N_4$ 296.2001, found 296.2010.

8a: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.92 (m, 4H), 2.63 (t, 4H, J=2.6 Hz), 1.86 (t, 6H, J=2.9 Hz); IR (neat) 2986, 2953, 2920, 2856, 2249, 1960, 1495, 1445, 856 cm^{-1}; HRMS calcd for $C_{13}H_{14}N_2$ 198.1157, found 198.1123.

8b: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.73 (m, 4H), 3.78 (s, 3H), 2.55 (dt, 4H, J=14.7 and 2.6 Hz), 1.78 (t, 6H, J=3.3 Hz); IR (neat) 2984, 2953, 2924, 2858, 2245, 1960, 1747, 1437, 1234, 1171, 854, 665 cm^{-1}; HRMS calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1261.

8c: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.99 (qnt, 4H, J=2.9 Hz), 2.61 (t, 4H, J=2.9 Hz), 2.07 (m, 4H), 1.45 (m, 4H), 1.29 (m, 12 H), 0.88 (t, 6H, J=6.6 Hz); IR (neat) 2957, 2928, 2858, 1950, 1440, 850, 665 cm^{-1}; HRMS calcd for $C_{23}H_{34}N_2$ 338.2722, found 338.2725.

8d: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.79 (m, 4H), 3.76 (s, 3H), 2.64 (dt, 2H, J=15.0 and 2.5 Hz), 2.44 (dt, 2H, J=15.0 and 2.5 Hz), 2.00 (m, 4H), 1.41 (m, 4H), 1.28 (m, 12H), 0,88 (t, 6H, J=6.6 Hz); IR (neat) 2955, 2928, 2856, 2245, 1956, 1749, 1437, 1234, 851, 665 cm^{-1}; HRMS calcd for $C_{24}H_{37}NO_2$ 371.2824, found 371.2826.

8e: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.31-7.19 (m, 10H), 4.98 (m, 4H), 3.44 (t, 4H, J=2.2 Hz), 2.49 (t, 4H, J=2.9 Hz); IR (neat) 3084, 3063, 3028, 2986, 2914, 2841, 2249, 1958, 1601, 1495, 1454, 1431, 1060, 1010, 860, 738, 665 cm^{-1}; HRMS calcd for $C_{25}H_{22}N_2$ 350.1783, found 350.1775.

9: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.38 (m, 5H), 6.34 (dd, J=17.3 and 11.5 Hz, 1H), 5.69 (s, 1H), 5.29 (d, J=17.3 Hz, 1H), 5.13 (d, J=10.7 Hz, 1H), 1.80 (s, 3H), 1.67 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 166.57, 139.61, 139.42, 136.36, 131.78, 129.58, 128.92, 127.20, 114.84, 105.86, 59.85, 29.37, 27.93, 13.96; IR (neat) 3063, 2976, 2928, 2868, 1778, 1744, 1697, 1603, 1497, 1448, 1394, 1279, 1219, 1074, 1030, 930, 698, 665 cm^{-1}; HRMS calcd for $C_{17}H_{18}O_4$ 286.1205, found 286.1212.

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