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Sourav Ghorai, Daesung Lee

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Graphical Abstract

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Aryne Formation via the Hexadehydro Diels-Alder Reaction and Their Ritter-type Transformations Catalyzed by a Cationic Silver Complex

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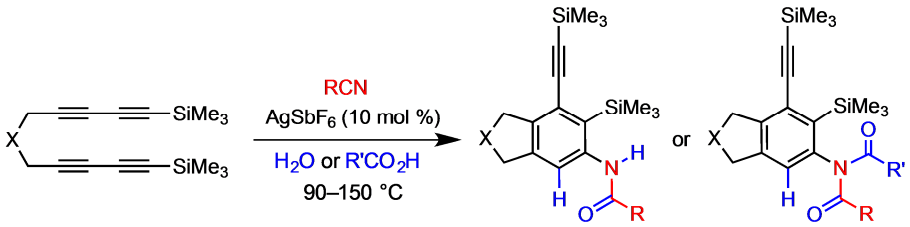
Sourav Ghorai and Daesung Lee*
Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, IL 60607, USA



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Aryne Formation via the Hexadehydro Diels-Alder Reaction and Their Ritter-type Transformations Catalyzed by a Cationic Silver Complex

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ABSTRACT

Despite their electrophilic nature, arynes are not known to react with nitriles under typical conditions for their formation. We demonstrated, however, that structurally diverse arynes could be generated via the hexadehydro Diels-Alder reaction and trapped with nitriles to induce the Ritter-type reaction when catalyzed by a cationic silver species. Presumably, under these conditions, the transiently formed aryne-silver complexes react with nitriles initially to form nitrilium ion intermediates, which then subsequently react with either water or carboxylic acid to yield the observed arylamides or arylimides.

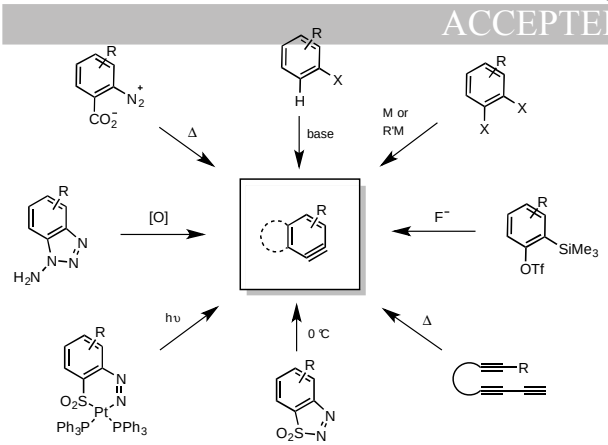
1. Introduction

Arynes, as a form of transient electrophilic intermediate, have been employed in a large number of natural product synthesis and the development of various synthetic methodologies.[1] Despite the versatility, the effective formation of arynes still renders a significant challenge and barrier for further expansion of their utility in synthetic organic chemistry.

Traditionally, the 1,2-elimination of suitably functionalized aromatic precursors has been employed for the formation of arynes,[2] many of which are pericyclic reactions in nature (Scheme 1). Among these pericyclic processes, only one protocol involves the *de novo* construction of the aromatic framework of arynes starting from non-aromatic precursors. Although, this particular form of pericyclic reaction was discovered more than a century ago,[3] the reactions of the corresponding intramolecular variants pioneered by Johnson and Ueda were reported since 1997.[4] Recently, the formation of arynes by this pericyclic reaction has been rejuvenated, and Hoye introduced a term hexadehydro Diels-Alder reaction (HDDAR) for the process.[5]

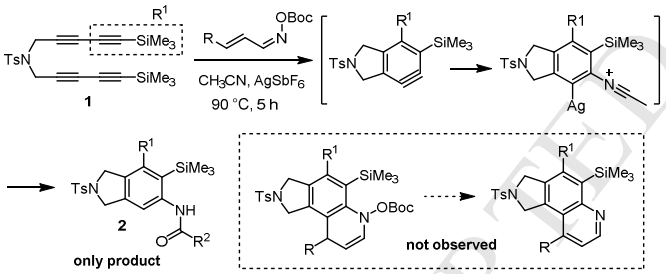
Despite the synthetic versatility of HDDAR and its uniqueness of forming aryne frameworks from non-aromatic precursors, the development of this protocol still is in its infancy compared to the silyltriflate-based protocol of Kobayashi.[6] Compared to the rapid development of new aryne chemistry based on silyltriflates and related aryne precursors, the corresponding HDDAR-based approaches starting from non-aromatic precursors are significantly underdeveloped.[7] Thus, it is necessary to garner information about the general reactivity profiles of the aryne species generated via HDDAR, and expand the suitable substrate classes.

Scheme 1. Aryne formation via various protocols



In light of developing a *de novo* synthesis of structurally complex pyridine derivatives, we explored the [4+2] cycloaddition reactions between arynes generated from tetrayne **1** and oxime derivatives generated from acrolein and other enals (Scheme 2). When these reactions were carried out in acetonitrile as a solvent, we did not observe the expected cycloadduct but only acetonitrile adducts in marginal yield. We inferred that the formation of the Ritter-type[8] product **2** is the consequence of the initial addition of solvent nitrile with the aryne intermediate formed from HDDAR followed by trapping of the nitrilium ion by adventitious water contained in wet solvent.

Scheme 2. Diels-Alder reaction vs. solvent addition

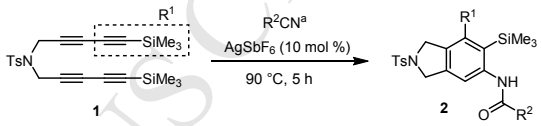


Having recognized the dearth of reports on the addition of nitriles through their nitrogen atom with arynes or benzyne,[9] we further explored the reaction, and reported herein are the results of systematic investigation that leads to the development of aryne-based new three-component coupling reactions to form arylamides and imides. This study also demonstrated the importance of silver species in aryne-based transformation, the exact role of which is yet to be defined.

2. Results and discussion

Our investigation commenced with optimizing reaction conditions for symmetrical tetrayne **1** to form amide adduct **2** (Table 1). In presence of silver hexafluoroantimonate as a catalyst (10 mol %), the reaction of tetrayne **1** in different nitrile solvent heated at 90 °C for 5 h led to the complete consumption

Table 1. Optimization for different amide formation



entry	R^2CN	product	yield (%)[b]
1	CH_3CN	**2a**	72
2	CN	**2b**	75
3	CN	**2c**	56
4	CN	**2d**	47[c]
5	CN	**2e**	69[d]

[a]Non-distilled, used as the solvent. [b]Isolated yiled. [c]Yield from the reaction with extra water (10 equiv). [d]Overall yield after desilylation with TBAF.

of **1**, providing the corresponding amides **2a–d**. Although these products could be obtained without the silver catalyst,[10] lower yields with significantly increased amount of unknown byproducts were resulted. First, with acetonitrile, amide **2a** was obtained in 72% yield (entry 1). With propionitrile, **2b** was obtained in 75% yield (entry 2), whereas only with 24% yield of **2** was observed without the catalyst. With acrylonitrile solvent, the reaction of **1** provided acrylamide derivative **2c** in somewhat lower 56% yield (entry 3). Although addition of extra water was not necessary to form **2a–2c**, the reaction with isobutyronitrile required addition of water. Thus, under the same conditions with 10 equivalents of added water, amide **2d** was generated in 47% yield (entry 4). Aromatic nitrile behaves similarly but provided some desilylated products. Thus, after complete removal of the

silyl groups with TBAF, arylbenzamide **2e** was obtained in 69% yield (entry 5).

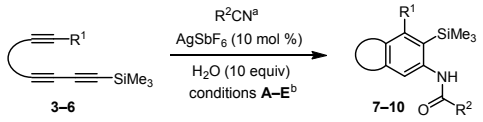
The formation of single regioisomer is most likely the consequence of the strong electronic directing effect of the silyl substituent.[11] The structural identity of these single regioisomeric products was confirmed by nOe experiment.

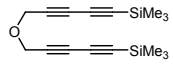
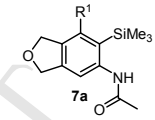
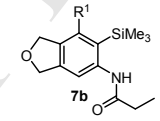
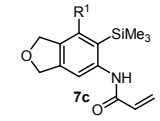
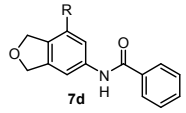
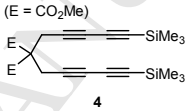
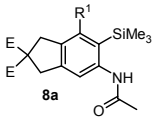
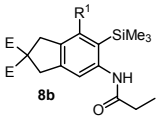
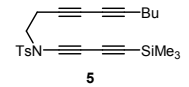
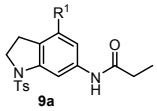
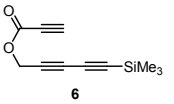
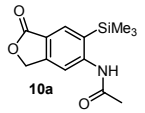
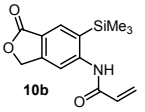
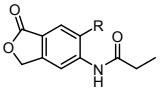
With the successful reaction of NTs-tethered symmetrical tetrayne **1** to generate different amide derivatives, we next explored the reaction of other substrates containing differently tethered tetraynes and triynes (Table 2).[12] In general, because of the structural variation with steric and electronic differences, all-carbon tethered substrate **4** containing a *gem*-dicarboxylate and ester-tethered triyne **5** required higher reaction temperature and extended reaction time. For most of the reactions, addition of water (10 equiv) significantly improved yields of the desired product.

First, the reaction of an oxygen-tethered symmetrical tetrayne **3** was carried out by heating at 90 °C for 5 h, which cleanly afforded acetamide **7a** in 78% yield (entry 1). Similar result was obtained when acetonitrile was replaced by propionitrile and acrylonitrile, where propionamide **7b** and acrylamide **7c** were obtained in 80% and 75% yield, respectively (entries 2 and 3). In benzonitrile medium, arylbenzamide was generated with partial removal of silyl group. After complete desilylation, amide **7d** was obtained in 20% overall yield (entry 4). All-carbon tethered substrate **4** containing a *gem*-dicarboxylate is unreactive at 90 °C, but at 150 °C it readily participate in the reaction with acetonitrile and propionitrile to yield the corresponding amide **8a** and **8b** in 59% and 30% yield (entries 5 and 6). However, with acrylonitrile, no expected amide product was observed, probably because of the instability of acrylonitrile at this high temperature. It is interesting to notice the difference between the reactions with acetonitrile and propionitrile, where addition of 10 equivalents of water significantly improved the yield of **8a** whereas the yield of **8b** was not improved by water additive. An ynamide-tethered non-symmetrical tetrayne **5** afforded propionamide-substituted indoline **9a** in 49% from the reaction with propionitrile at 90 °C (entry 7). An ester-tethered triyne **6** derived from propiolic acid turned out to be less reactive than tetraynes, thus the reaction was carried out at 150 °C. With acetonitrile, the reaction of **6** provided **10a** in 79% yield at 150 °C for 30 h (entry 8). With acrylonitrile, acrylamide derivative **10b** was obtained in 46% yield after 9 h, and extended reaction time did not improve the yield (entry 9). With propionitrile, a mixture of amides products **10c** and **10c'** (2.6:1) was obtained after heating at 150 °C for 18 h (entry 10).

With these results in hand, we envisioned that if the putative nitrilium ion could be captured by other nucleophile rather than water, different end products would be generated. One such nucleophile is carboxylic acid.[13] Although carboxylic acid may complicate the reaction because they themselves are excellent reacting counterparts with arynes, we tried to carry out the first reaction in the presence of acetic acid. To our gratitude, the reaction of **1** in acetonitrile and acetic acid in excess provided the corresponding imide **11a** along with amide **2a**. At this point, we assumed that by removing any adventitious water would reduce or eliminate the formation of **2a**. Indeed, addition of 4 Å molecular sieves to reaction improved the formation of **11a**. Optimizing the amount of acetic acid revealed that addition of 3 equivalents provided the highest yield of the desired product. Thus, under the optimized conditions (10 mol % silver catalyst, 90 °C, 3 equivalents of AcOH, 10 wt % 4 Å molecular sieves) the reaction of NTs-tethered symmetrical tetrayne **1** provided arylimide **11a** in 89% overall yield as a mixture with the

Table 2. Aryne-based three-component coupling for the formation of arlyamides

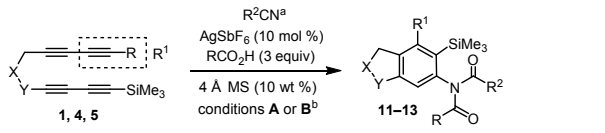


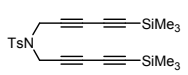
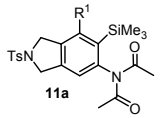
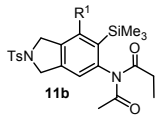
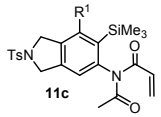
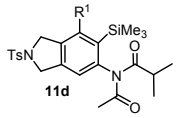
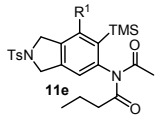
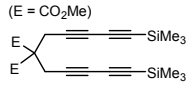
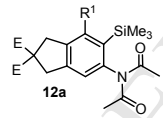
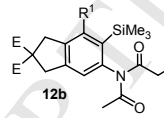
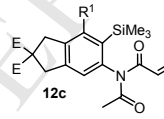
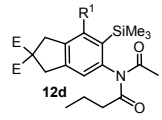
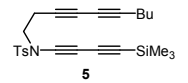
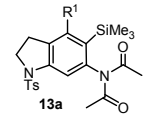
entry	substrate	R^2CN	conditions	product	yield (%)[c]
1	 **3**	CH_3CN	**A**	 **7a**	78
2			**A**	 **7b**	80
3			**A**	 **7c**	75
4			**A**	 **7d**	20[d]
5	 **4**	CH_3CN	**B**	 **8a**	59
6			**B**	 **8b**	30
7	 **5**		**A**	 **9a**	49
8	 **6**	CH_3CN	**C**	 **10a**	79
9			**D**	 **10b**	46
10			**E**	 **10c**, R = $SiMe_3$ (2.7:1) **10c'**, R = H	60

[a]Non-distilled, used as the solvent. [b]Conditions: **A**. 90 °C 5 h; **B**. 150 °C, 1.5 h; **C**. 150 °C, 30 h; **D**. 150 °C, 9 h; **E**. 150 °C, 18 h; [c]Isolated yiled; [d]Overall yield after desilylation with TBAF.

corresponding desilylated product **11a'** in a 10:1 ratio (entry 1). The reaction in propionitrile afforded imide **11b** and desilylated product **11b'** in 75% yield in a 5.2:1 ratio (entry 2). The same product **11b** and **11b'** were obtained from the reaction with the combination of acetonitrile and propionic acid, but with much lower yield (54%) with increased desilylation (entry 3). The reaction of with acrylonitrile and AcOH yielded **11c** and **11c'** in 87% yield (entry 4). Replacing acetonitrile with more sterically demanding isobutyronitrile slightly lower the yield (76%, 1.7:1) and increased the extent of desilylation (entry 5). With acetonitrile and butyric acid, **11e** and the corresponding desilyated product **11b'** were obtained in 45% yield with more pronounced desilylation (entry 6). Similar to the amide forming reaction in Table 2, the reaction of all-carbon tethered substrate **4**, although required higher reaction temperature (150 °C), full conversion was achieved in less than 2 h. Thus, the reaction of **4** with a combination of acetonitrile and AcOH afforded **12a** in 55% yield with no desilylation (entry 7). From the reaction with propionitrile under otherwise identical conditions, **12b** was obtained in 79% yield (entry 8), and the same product was obtained in slightly lower 68% yield by employing acetonitrile and propionic acid (entry 9). With acrylonitrile and AcOH, acrylimide **12c** was obtained as a single product in 78% yield (entry 10), and with the combination of acetonitrile and propionic acid afforded **12d** in 67% yield (entry 11). Finally, unsymmetrical ynamide-tethered substrate **5** provided the corresponding indolinyl imide **13a** in 71% when the reaction was carried out at 90 °C for 5 h (entry 12). With other nitrile such as propionitrile, acrylonitrile and isobutyronitrile, the reaction of **5** provided product **13a** in reasonable yield but contaminated with the corresponding desilylated product.

Table 3. Aryne-based three-component coupling for the formation of arylimides



entry	substrate	R^2CN	R^2CO_2H	conditions	products	yield (%)[c]
1	 **1**	CH_3CN	CH_3CO_2H	**A**	 **11a**	89 10:1[d]
2			CH_3CO_2H	**A**	 **11b**	75 5.2:1[d]
3		CH_3CN		**A**		54 0.91:1[d]
4			CH_3CO_2H	**A**	 **11c**	87 2.6:1[d]
5			CH_3CO_2H	**A**	 **11d**	76 1.7:1[d]
6		CH_3CN		**A**	 **11e**	45 0.27:1[d]
7	(E = CO_2Me)  **4**	CH_3CN	CH_3CO_2H	**B**	 **12a**	55
8			CH_3CO_2H	**B**	 **12b**	79
9		CH_3CN		**B**		68
10			CH_3CO_2H	**B**	 **12c**	78
11		CH_3CN		**B**	 **12d**	67
12	 **5**	CH_3CN	CH_3CO_2H	**A**	 **13a**	71

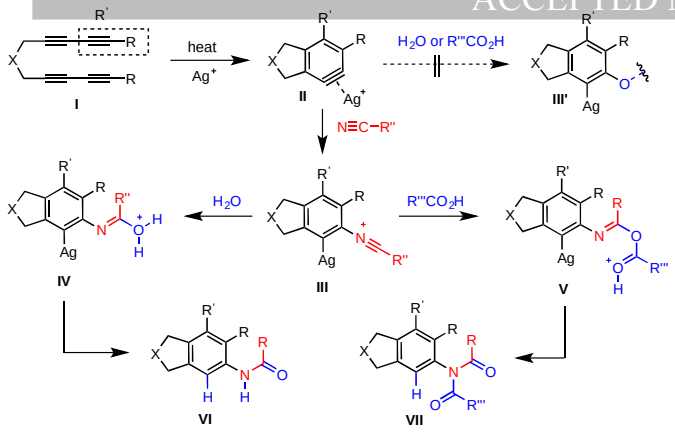
[a]Non-distilled, used as the solvent. [b]Conditions: **A**. 90 °C, 5 h; **B**. 150 °C, 2 h. [c]Isolated yiled. [d]Ratio between the intact and the desilylated product in R^1.

Scheme 3. Mechanism for the formation of amides and imides via the formation of arynes by HDDAR followed by their trapping with nitriles

From these reactions, a general trend is noted that the reaction with sterically more hindered carboxylic acid provided a product in lower yield. For example, when AcOH was replaced with propionic acid (entry 3) and butyric acid (entry 6), significantly lower yields resulted in with more pronounced desilylation. Another interesting observation is the formation of products devoid of desilylation from the reaction of all-carbon tethered substrate 4 even the reaction was carried out at 150 °C compared to 90 °C for other substrates.

On the basis of these results, we propose a mechanism for the formation of amides and imides (Scheme 3). Upon heating, a tetrayene or triyne substrate **I** undergoes HDDAR to form an aryne species, which then forms silver-aryne complex **II**.[14] Formally, HDDAR is considered to be a pericyclic reaction, but recent theoretical studies suggest that the reaction proceed in a stepwise manner via radical intermediates.[15] Once formed, silver-aryne complex **II**, although water or carboxylic acid can be trapped to form **III'**, under the given reaction conditions, nitrile reacts favorably to form nitrilium species **III**. Trapping of **III** by water or carboxylic acid would form penultimate intermediate **IV** or **V**, respectively. Protonation of the C–Ag bond and proton or acyl shift on **IV** or **V** will generate the observed amide **VI** or imide **VII**. It was proved that under the current reaction conditions, either nitrile did not converted to the corresponding amide, nor the preformed amide reacted with the aryne species, which supports the proposed reaction mechanism. Although carboxylic acid is known to be a good reacting counterpart with arynes[13] the unique combination of their reactivity and concentration of nitrile and carboxylic acid ultimately provides the observed amide products.

In conclusion, we developed aryne-based three-component coupling reactions by forming structurally diverse arynes via HDDAR of tetraynes and triynes. The facile trapping of arynes with nitriles to induce the Ritter-type reaction is a unique aspect of these coupling reactions. Although nitriles are



not strong enough nucleophiles to react with arynes under typical conditions we found that an effective reaction between arynes and nitriles could be promoted by a cationic silver catalyst. Presumably, under these silver-catalyzed conditions, transiently formed aryne-silver complexes initially react with nitriles to form nitrilium ion intermediates, which then subsequently react with either water or carboxylic acid to yield the observed arylamides or arylimides.

3. Experimental section

General procedure for preparation of arylamides (Procedure A): A multiyne substrate (0.1 mmol) and $AgSbF_6$ (0.01 mmol) in nitrile (3 mL) in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 5 h at 90 °C unless otherwise noted. Water (10 equiv) was used as additive in some cases. The reaction mixture was concentrated, and then directly subjected to column chromatography for purification to afford the amide product.

General procedure for preparation of arylimides (Procedure B): A multiyne substrate (0.1 mmol), $AgSbF_6$ (0.01 mmol), AcOH (0.3 mmol), 4 Å MS (10 wt %) in nitrile (3 mL) in a Schlenk tube was flushed with nitrogen. The mixture was stirred for 5 h at 90 °C, unless otherwise noted. The reaction mixture was concentrated, and then purified by flash chromatography to afford the imide product.

4. Characterization data

2a: This compound was obtained (Procedure A) in 72% yield. IR (neat): 3265, 2956, 2924, 2853, 2149, 1663, 1598, 1568, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.73 (m, 3H), 7.54 (s, 1H), 7.36–7.29 (m, 3H), 4.59 (s, 4H), 2.41 (s, 3H), 2.12 (s, 3H), 0.46 (s, 9H), 0.25 (S, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.4, 143.8, 141.8, 137.8, 137.7, 133.7, 132.6, 129.9, 127.6, 124.4, 118.9, 104.9, 102.7, 54.4, 54.1, 24.4, 21.5, 1.7, –0.4; HRMS (ESI) calcd for $C_{25}H_{35}N_2O_3SSi_2$ $[M+H]^+$ 499.1909, found 499.1928.

2b: This compound was obtained (Procedure A) in 75% yield. IR (neat): 3269, 2956, 2899, 2854, 2149, 1657, 1597, 1570, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.73 (m, 2H), 7.58 (s, 1H), 7.38–7.29 (m, 3H), 4.58 (s, 4H), 2.41 (s, 3H), 2.32 (q, 2H, *J* = 7.2 Hz), 1.22 (t, 3H, *J* = 7.4 Hz), 0.45 (s, 9H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.1, 143.8, 142.0, 137.7, 137.4, 133.6, 132.3, 129.9, 127.6, 124.4, 118.7, 104.8, 102.7, 54.4, 54.1, 30.6, 21.5, 9.5, 1.8, –0.4; HRMS (ESI) calcd for $C_{26}H_{37}N_2O_3SSi_2$ $[M+H]^+$ 513.2063, found 513.2068.

2c: This compound was obtained (Procedure A) in 56% yield. IR (neat): 3246, 2956, 2924, 2853, 2148, 1661, 1625, 1597, 1571, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.74 (m, 2H), 7.68 (s, 1H), 7.50 (s, 1H), 7.35–7.30 (m, 2H), 6.41 (d, 1H, *J* = 17.0 Hz), 6.15 (dd, 1H, *J* = 16.5 Hz, *J* = 10.2 Hz), 5.77 (d, 1H, *J* = 10.2 Hz), 4.60 (s, 4H), 2.41 (s, 3H), 0.46 (s, 9H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.6, 143.8, 141.7, 137.8, 137.7, 133.7, 132.4, 130.8, 129.9, 128.4, 127.6, 124.5, 118.6, 105.0, 102.6, 54.4, 54.1, 21.5, 1.8, –0.4; HRMS (ESI) calcd for $C_{26}H_{35}N_2O_3SSi_2$ $[M+H]^+$ 511.1907, found 511.1924.

2d: This compound was obtained (Procedure A with 10 equiv water additive) in 47% yield. IR (neat): 3270, 2962, 2929, 2900, 2148, 1662, 1597, 1569, 1506 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.72 (m, 2H), 7.64 (s, 1H), 7.37 (s, 1H), 7.34–7.29 (m, 2H), 4.59 (s, 4H), 2.41 (s, 3H), 2.40 (sept, 1H, *J* = 6.8 Hz), 1.22 (d, 6H, *J* = 6.8 Hz), 0.46 (s, H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.4, 143.7, 142.2, 137.7, 137.3, 133.7, 131.9, 129.9, 127.5, 124.3, 118.5, 104.8, 102.8, 54.4, 54.1, 36.8, 21.5, 19.5, 1.9, –0.4; HRMS (ESI) calcd for $C_{27}H_{39}N_2O_3SSi_2$ $[M+H]^+$ 527.2220, found 527.2222.

2e: This compound was obtained (Procedure A followed by TBAF-mediated deprotection) in 69% yield. IR (neat): 3266, 2922, 2853, 2360, 1677, 1605, 1539, 1492 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.96 (s, 1H), 7.86–7.81 (m, 2H), 7.79–7.75 (m, 2H), 7.69 (s, 1H), 7.57–7.51 (m, 1H), 7.50–7.42 (m, 3H), 7.35–7.30 (m, 2H), 4.62 (s, 4H), 3.25 (s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 165.8, 143.9, 137.9, 137.4, 135.2, 134.3, 133.6, 132.2, 129.9, 128.9, 127.6, 127.0, 122.9, 117.6, 115.4, 82.0, 79.8, 54.2, 53.5, 21.5; HRMS (ESI) calcd for $C_{24}H_{19}N_2O_3S$ $[M–H]^-$ 415.1116, found 415.1113.

7a: This compound was obtained (Procedure A) in 78% yield. IR (neat): 3226, 2956, 2899, 2855, 2148, 1643, 1574, 1533 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.60 (s, 1H), 7.39 (s, 1H), 5.15–5.07 (m, 4H), 2.15 (s, 3H), 0.49 (s, 9H), 0.23 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.5, 141.5, 141.1, 141.0, 131.9, 122.8, 117.7, 103.8, 103.2, 74.3, 24.4, 1.8, –0.4; HRMS (ESI) calcd for $C_{18}H_{28}NO_2Si_2$ $[M+H]^+$ 346.1659, found 346.1670.

7b: This compound was obtained (Procedure A) in 80% yield. IR (neat): 3227, 2958, 2897, 2149, 1645, 1604, 1570, 1529 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.67 (s, 1H), 7.36 (s, 1H), 5.13–5.07 (m, 4H), 2.36 (q, 2H, *J* = 7.6 Hz), 1.25 (t, 3H, *J* = 7.6 Hz), 0.49 (s, 9H), 0.23 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.0, 141.7, 141.0, 140.8, 131.4, 122.7, 117.4, 103.7, 103.3, 74.3, 74.1, 30.7, 9.6, 1.9, –0.4; HRMS (ESI) calcd for $C_{19}H_{30}NO_2Si_2$ $[M+H]^+$ 360.1815, found 360.1808.

7c: This compound was prepared (Procedure A) in 75% yield. IR (neat): 3222, 2957, 2898, 2149, 1667, 1650, 1605, 1574, 1535 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.74 (s, 1H), 7.44 (s, 1H), 6.43 (d, 1H, *J* = 16.8 Hz), 6.25–6.12 (m, 1H), 5.78 (d, 1H, *J* = 10.1 Hz), 5.20–5.06 (m, 4H), 0.49 (s, 9H), 0.23 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.7, 141.4, 141.1, 131.7, 131.0, 128.1, 122.8, 117.3, 103.8, 103.2, 74.3, 74.1, 1.8, –0.4; HRMS (ESI) calcd for $C_{19}H28NO_2Si_2$ $[M+H]^+$ 358.1659, found 358.1665.

7d: This compound was obtained (Procedure A followed by TBAF-mediated deprotection) in 20% yield. IR (neat): 3290, 3060, 2923, 2853, 2360, 2341, 1652, 1604, 1579, 1537 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): 7.88–7.84 (m, 3H), 7.75 (s, 1H), 7.59–7.54 (m, 1H), 7.53–7.46 (m, 3H), 5.18–5.12 (m, 4H), 3.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 165.8, 140.6, 138.4, 137.6, 134.6, 132.1, 128.9, 127.0, 122.5, 116.1, 113.9, 81.1, 80.3, 74.1, 73.4; HRMS (ESI) calcd for $C_{17}H_{14}NO_2$ $[M+H]^+$ 264.1025, found 264.1021.

8a: This compound was prepared (Procedure A, but at 150 °C for 1.5 h with 10 equiv of water additive) in 59% yield. IR (neat): 3259, 2955, 2926, 2889, 2147, 1737, 1657, 1563, 1521 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.56 (s, 1H), 3.76 (s, 6H), 3.62 (s, 2H), 3.61 (s, 2H), 2.13 (s, 3H), 0.47 (s, 9H), 0.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.0, 168.4, 141.7, 141.1, 131.6, 125.5, 125.0, 120.9, 104.0, 103.7, 59.3, 53.1, 41.1, 40.8, 24.4. 1.9, –0.3; HRMS (ESI) calcd for $C_{23}H_{34}NO_5Si_2$ $[M+H]^+$ 460.1976, found 460.1975.

8b: This compound was prepared in 30% yield by using Procedure A but at 150 °C for 1.5 h. IR (neat): 3260, 2954, 2926, 2854, 2147, 1737, 1652, 1590, 1564, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.62 (s, 1H), 7.26 (s, 1H), 3.76 (s, 6H), 3.62 (s, 2H), 3.60 (s, 2H), 2.33 (q, 2H, *J* = 7.4 Hz), 1.24 (t, 3H, *J* = 7.4 Hz), 0.47 (s, 9H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.0, 141.6, 141.4, 141.3, 131.2, 125.4, 120.7, 104.1, 103.6, 59.3, 53.1, 41.1, 40.8, 30.7, 9.6, 2.0, –0.3; HRMS (ESI) calcd for $C_{24}H_{36}NO_5Si_2$ $[M+H]^+$ 474.2132, found 474.2139.

9a: This compound was obtained (Procedure A) in 49% yield. IR (neat): 3295, 2955, 2929, 2871, 1666, 1609, 1593, 1544 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.72–7.68 (m, 2H), 7.49 (s, 1H), 7.26–7.23 (m, 2H), 7.10 (S, 1H), 3.89 (t, 2H, *J* = 8.4 Hz), 2.90 (t, 2H, *J* = 8.4 Hz), 2.40 (q, 2H, *J* = 7.8 Hz), 2.38 (s, 3H), 2.36 (t, 2H, *J* = 7.01 Hz), 1.54–1.48 (m, 2H), 1.46–1.38 (m, 2H), 1.26 (t, 3H, *J* = 7.6 Hz), 0.91 (t, 2H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.8, 144.3, 142.3, 137.6, 133.7, 129.8, 129.6, 127.4, 121.5, 118.1, 106.0, 94.8, 77.7, 50.0, 30.8, 30.7, 27.3, 21.9, 21.6, 19.1, 13.6, 9.6; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_3S$ $[M+H]^+$ 425.1899, found 425.1913.

10a: This compound was prepared in 79% yield by using Procedure A but at 150 °C for 30 h with 10 equiv water additive. IR (neat): 3458, 2968, 2870, 1763, 1693, 1618, 1516, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.27 (s, 1H), 7.97 (s, 1H), 7.50 (s, 1H), 5.28 (s, 2H), 2.23 (s, 3H), 0.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 168.2, 149.4, 147.2, 132.5, 131.1, 121.2, 114.6, 69.4, 28.8, –0.4; HRMS (ESI) calcd for $C_{13}H_{18}NO_3Si$ $[M+H]^+$ 264.1056, found 264.1045.

10b: This compound was prepared in 46% yield by using Procedure A but at 150 °C for 9 h with 10 equiv water additive. IR (neat): 3212, 3016, 2954, 1756, 1674, 1651, 1622, 1578, 1525 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.38 (s, 1H), 7.99 (s, 1H), 7.61 (s, 1H), 6.47 (d, 1H, *J* = 17.0 Hz), 6.23 (dd, 1H, *J* = 16.9 Hz, *J* = 10.3 Hz), 5.88 (d, 1H, *J* = 10.4 Hz), 5.29 (s, 2H), 0.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 163.5, 149.5, 147.2, 132.5, 130.7, 129.1, 121.3, 114.7, 69.5, –0.4; HRMS (ESI) calcd for $C_{14}H_{18}NO_3Si$ $[M+H]^+$ 276.1056 found 276.1057.

10c: This compound was prepared in 44% yield by using Procedure **A** but 150 °C for 18 h with 10 equiv water additive. IR (neat): 3301, 2923, 2853, 1741, 1699, 1682, 1604, 1547 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.33 (s, 1H), 7.97 (s, 1H), 7.49 (s, 1H), 5.27 (s, 2H), 2.44 (q, 3H, *J* = 7.5 Hz), 1.28 (t, 3H, *J* = 7.6 Hz), 0.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.0, 170.8, 149.5, 147.4, 132.4, 130.9, 121.0, 114.4, 69.4, 31.1, 9.5, –0.4; HRMS (ESI) calcd for $C_{14}H_{20}NO_3Si$ $[M+H]^+$ 278.1212, found 278.1222. **10c'** (16%): IR (neat): 3301, 2923, 2853, 1741, 1699, 1682, 1604, 1547 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.15 (s, 1H), 7.84 (d, 1H, *J* = 8.2 Hz), 7.37 (s, 1H), 7.27 (d, 1H), 5.20 (s, 2H), 2.46 (q, 2H, *J* = 7.6 Hz), 1.28 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.5, 170.7, 148.7, 143.4, 126.5, 120.8, 119.9, 112.2, 69.5, 30.9, 9.4; HRMS (ESI) calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$ 206.0817, found 206.0813.

11a: This compound was obtained (Procedure B) in 80% yield. IR (neat): 2956, 2899, 2852, 2150, 1708, 1597, 1567 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.75 (m, 2H), 7.36–7.32 (m, 2H), 6.77 (s, 1H), 4.67–4.60 (m, 4H), 2.43 (s, 3H), 2.22 (s, 3H), 0.33 (s, 9H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.0, 144.3, 144.0, 141.2, 141.0, 138.6, 133.5, 130.0, 127.6, 125.8, 123.5, 106.3, 102.1, 54.1, 27.5, 21.5, 0.5, –0.4; HRMS (ESI) calcd for $C_{27}H_{37}N_2O_4Si_2S$ $[M+H]^+$ 541.2013, found 541.2012. **11a'** (9%, obtained as an inseparable mixture with **11a** in a 1:1 ratio): ^1H NMR ($CDCl_3$, 500 MHz): δ 7.80–7.75 (m, 2H), 7.37–7.31 (m, 2H), 6.81 (s, 1H), 4.70–4.60 (m, 4H), 3.60 (s, 1H), 2.42 (s, 3H), 2.23 (s, 6H), 0.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (all peaks) 173.0, 144.3, 144.0, 141.9, 141.5, 141.2, 141.0, 138.7, 138.6, 133.5, 133.4, 131.3, 130.0, 127.6, 125.8, 124.7, 124.0, 123.5, 123.1, 106.3, 102.1, 88.2, 81.1, 78.8, 54.2, 54.0, 53.9, 27.5, 26.9, 21.5, 0.6, 0.5, –0.4; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_4SiS$ $[M+H]^+$ 469.1617, found 469.1620.

11b: This compound was obtained (Procedure B) in 63% yield. IR (neat): 2956, 2924, 2852, 2149, 1712, 1597, 1567, 1513, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.75 (m, 2H), 7.36–7.32 (m, 2H), 6.75 (s, 1H), 4.70–4.56 (m, 4H), 2.43 (s, 3H), 2.39–2.33 (m, 2H), 2.32 (s, 3H), 1.06 (t, 3H, *J* = 7.3 Hz), 0.31 (s, 9H), 0.26 (S, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.3, 173.2, 144.0, 141.2, 141.1, 138.5, 133.5, 130.0, 127.6, 125.8, 123.6, 106.2, 102.2, 54.1, 32.4, 27.8, 21.5, 8.6, 0.5, –0.4; HRMS (ESI) calcd for $C_{28}H_{39}N_2O_4SSi_2$ $[M+H]^+$ 555.2169, found 555.2151. **11b'** (12%): IR (neat): 3256, 3065, 2954, 2824, 2853, 1712, 1598, 1569, 1493 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.76 (m, 2H), 7.36–7.32 (m, 2H), 6.79 (s, 1H), 4.74–4.57 (m, 4H), 3.60 (s, 1H), 2.43 (s, 3H), 2.39–2.34 (m, 2H), 2.33 (s, 3H), 1.06 (t, 3H, *J* = 7.2 Hz), 0.31 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.3, 173.2, 150.2, 144.0, 141.8, 141.6, 138.6, 133.4, 130.0, 127.6, 124.6, 124.1, 88.2, 81.1, 54.2, 54.0, 32.5, 27.8, 21.5, 8.6, 0.6; HRMS (ESI) calcd for $C_{25}H_{31}N_2O_4SiS$ $[M+H]^+$ 483.1774, found 483.1775.

11c and **11c'** (inseparable mixture): A nixture of these compounds was obtained (Procedure B) in 87% yield with a 2.6:1 ratio. IR (neat): 3254, 2956, 2924, 2900, 2854, 2150, 1703, 1615, 1597, 1567, 1493, 1467; (major isomer) ^1H NMR (500 MHz, $CDCl_3$): δ 7.80–7.75 (m, 2H), 7.37–7.33 (m, 2H), 6.76 (s, 1H), 6.46–6.41 (m, 1H), 6.20–6.11 (m, 1H), 5.69–5.64 (m, 1H), 4.76–4.52 (m, 4H), 2.47 (s, 3H), 2.43 (s, 3H), 0.30 (s, 9H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (all peaks) 173.9, 167.2, 144.0, 143.3, 141.9, 141.5, 141.2, 138.7, 138.6, 133.6, 131.3, 131.2, 130.0, 129.8, 127.5, 125.8, 124.7, 124.3, 123.8, 109.8, 106.3, 102.2, 88.3, 81.1, 54.1, 54.0, 27.7, 21.5, 0.6, 0.5, –0.4; HRMS (ESI) calcd for $C_{28}H_{37}N_2O_4Si_2S$ $[M+H]^+$ 553.2013, found 553.2018.

11d: This compound was obtained (Procedure B) in 48% yield. IR (neat): 2959, 2933, 2900, 2873, 2151, 1707, 1597, 1567 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.78–7.76 (m, 2H), 7.36–7.33 (m, 2H), 6.75 (s, 1H), 4.71–4.55 (m, 4H), 2.43 (s, 3H), 2.32 (s, 3H), 2.87–2.79 (m, 1H), 2.43 (s, 3H), 2.32 (s, 3H), 1.10 (d, 3H, *J* = 6.7 Hz), 1.04 (d, 3H, *J* = 6.6 Hz), 0.32 (s, 9H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 180.2, 173.5, 144.1, 144.0, 141.5, 141.1, 138.3, 133.6, 130.0, 127.6, 125.7, 123.5, 106.2, 102.2, 54.1, 54.0, 35.0, 27.8, 21.5, 19.5, 19.4, 0.6, –0.4; HRMS (ESI) calcd for $C_{29}H_{41}N_2O_4Si_2S$ $[M+H]^+$ 569.2326, found 569.2300. **11d'** (28%): IR (neat): 3255, 2956, 2920, 2850, 1708, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.79–7.76 (m, 2H), 7.36–7.33 (m, 2H), 6.79 (s, 1H), 4.74–4.56 (m, 4H), 3.60 (s, 1H), 2.87–2.80 (m, 1H), 2.43 (s, 3H), 2.32 (s, 3H), 1.11 (d, 2H, *J*

= 6.7 Hz), 1.05 (d, 2H, *J* = 6.8 Hz), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 180.2, 173.5, 144.1, 144.0, 142.0, 141.7, 138.4, 130.0, 127.6, 124.6, 124.0, 88.2, 81.2, 54.2, 54.0, 35.0, 27.8, 21.5, 19.5, 19.4, 0.6; HRMS (ESI) calcd for $C_{26}H_{33}N_2O_4SiS$ $[M+H]^+$ 497.1930, found 497.1916.

11e: This compound was obtained (Procedure B) in 10% (in the table it is 45% as a total yield of the mixture) yield. IR (neat): 2958, 2927, 2901, 2872, 2850, 2152,1713, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80–7.76 (m, 2H), 7.36–7.32 (m, 2H), 6.74 (s, 1H), 4.72–4.54 (m, 4H), 2.43 (s, 3H), 2.34–2.28 (m, 5H), 1.64–1.54 (m, 2H), 0.88 (t, 3H, *J* = 7.4 Hz), 0.32 (s, 9H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.4, 173.3, 144.0, 141.2, 141.1, 138.5, 133.6, 130.0, 127.6, 125.7, 123.6, 106.2, 102.2, 54.1, 40.8, 27.8, 21.5, 17.7, 13.6, 0.5, –0.4; HRMS (ESI) calcd for $C_{29}H_{41}N_2O_4Si_2S$ $[M+H]^+$ 569.2326, found 569.2310. **11e'** (35%) IR (neat): 3261, 2958, 2929, 2873, 2853, 1712, 1597, 1493 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80–7.76 (m, 2H), 7.36–7.32 (m, 2H), 6.78 (s, 1H), 4.74–4.54 (m, 4H), 3.60 (s, 1H), 2.43 (s, 3H), 2.35–2.29 (m, 5H), 1.63–1.57 (m, 2H), 0.89 (t, 3H, *J* = 7.0 Hz), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.4, 173.3, 144.0, 141.8, 141.7, 138.6, 133.4, 130.0, 127.6, 124.6, 124.1, 88.2, 81.1, 54.2, 54.0, 40.8, 27.8, 21.5, 17.7, 13.6, 0.6; HRMS (ESI) calcd for $C_{26}H_{33}N_2O_4SiS$ $[M+H]^+$ 497.1930, found 497.1946.

12a: This compound was obtained (Procedure B, but at 150 °C for 2 h) in 55% yield. IR (neat): 2955, 2900, 2148, 1736, 1708, 1590, 1562, 1432 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.79 (s, 1H), 3.78 (s, 6H), 3.71 (s, 2H), 3.64 (s, 2H), 2.24 (s, 3H), 0.35 (s, 9H), 0.25 (S, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.2, 171.8, 144.9, 143.6, 142.5, 139.6, 104.9, 103.5, 59.1, 53.2, 40.9, 40.8, 27.5, 0.6, –0.4; HRMS (ESI) calcd for $C_{25}H_{36}NO_6Si_2$ $[M+H]^+$ 502.2081, found 502.2068.

12b: This compound was obtained (Procedure B, but at 150 °C for 2 h) in 79% yield. IR (neat): 2955, 2901, 2149, 1736, 1708, 1589, 1561 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.76 (s, 1H), 3.78 (s, 6H), 3.71 (s, 2H), 3.63 (s, 2H), 2.41–2.35 (m, 2H), 2.34 (s, 3H), 1.06 (t, 3H, *J* = 7.3 Hz), 0.33 (s, 9H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.6, 173.4, 171.9, 171.8, 144.8, 143.3, 142.4, 139.7, 104.8, 103.6, 59.1, 53.2, 40.9, 40.8, 32.4, 27.8, 8.6, 0.6, –0.4; HRMS (ESI) calcd for $C_{26}H_{38}NO_6Si_2$ $[M+H]^+$ 516.2238, found 516.2247.

12c: This compound was obtained (Procedure B, but at 150 °C for 2 h) in 78% yield. IR (neat): 2955, 2900, 2149, 1737, 1703, 1615, 1590, 1562 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.79 (s, 1H), 6.43 (dd, 1H, *J* = 1.6 Hz, *J* = 16.7 Hz), 6.19 (dd, 1H, *J* = 10.2 Hz, *J* = 16.6 Hz), 5.65 (dd, 1H, *J* = 1.6 Hz, *J* = 10.3 Hz), 3.78 (s, 6H), 3.72 (s, 2H), 3.64 (s, 2H), 2.48 (s, 3H), 0.32 (s, 9H), 0.25 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.0, 172.0, 171.8, 167.5, 145.0, 142.6, 142.4, 140.1, 130.8, 130.3, 126.8, 125.5, 105.0, 103.5, 59.1, 53.2, 41.0, 40.8, 27.8, 0.6, –0.4; HRMS (ESI) calcd for $C_{26}H_{36}NO_6Si_2$ $[M+H]^+$ 514.2081, found 514.2068.

12d: This compound was obtained (Procedure B) in 67% yield. In this reaction, butanoic acid was used instead of acetic acid and the reaction mix was stirred at 150 °C for 2 h. IR (neat): 2957, 2901, 2875, 2854, 2149, 1737, 1710, 1589, 1562 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.77 (s, 1H), 3.78 (s, 6H), 3.72 (s, 2H), 3.64 (s, 2H), 2.35 (t, 2H, *J* = 7.2 Hz), 2.33 (s, 3H), 1.66–1.57 (m, 2H), 0.90 (t, 3H, *J* = 7.4 Hz), 0.34 (s, 9H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.7, 173.4, 171.9, 171.8, 144.8, 143.3, 142.4, 139.8, 126.7, 125.4, 104.8, 103.6, 59.1, 53.2, 41.0, 40.8, 40.7, 27.8, 17.8, 13.7, 0.7, –0.4; HRMS (ESI) calcd for $C_{27}H_{40}NO_6Si_2$ $[M+H]^+$ 530.2394, found 530.2377.

13a: This compound was obtained (Procedure B) in 71% yield. IR (neat): 2956, 2929, 2872, 2224, 1711, 1580, 1493 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69–7.65 (m, 2H), 7.29–7.25 (m, 2H), 7.21 (S, 1H), 3.91 (t, 2H, *J* = 8.7 Hz), 3.02 (t, 2H, *J* = 8.6 Hz), 2.41 (t, 2H, *J* = 7.0 Hz), 2.39 (s, 3H), 2.28 (s, 6H), 1.59–1.51 (m, 2H), 1.48–1.39 (m, 2H), 1.48–1.39 (m, 2H), 0.91 (m, 3H, *J* = 7.4 Hz), 0.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.0, 144.6, 144.5, 143.6, 135.6, 134.4, 133.4, 129.9, 128.1, 127.4, 114.6, 100.8, 79.1, 49.6, 30.4, 28.1, 27.4, 22.1, 21.6, 19.3, 13.5, 0.7; HRMS (ESI) calcd for $C_{28}H_{37}N_2O_4SSi$ $[M+H]^+$ 525.2243, found 525.2253.

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References and notes

1. (a) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. (b) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. (c) Sanz, R. *Org. Prep. Proc. Int.* **2008**, *40*, 215–291. (d) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550–3577. (e) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140–3152. (f) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191–218. (g) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116–125. (h) Yoshida, S.; Hosoya, T. *Chem. Lett.* **2015**, *44*, 1450–1460.
2. (a) Wittig, G.; Hoffmann, R. W. *Org. Synth.* **1967**, *47*, 4. (b) Campbell, C. D.; Rees, C. W. *J. Chem. Soc. C.* **1969**, 742. (c) Gilchrist, T. L.; Graveling, F. J.; Rees, C. W. *J. Chem. Soc. C.* **1971**, 977.
3. Berthelot, M. *Liebigs Ann. Chem.* **1867**, *141*, 173.
4. (a) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943–3946. (b) Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917–9918. (c) Ueda, I.; Sakurai, Y.; Kawano, T.; Wada, Y.; Futai, M. *Tetrahedron Lett.* **1999**, *40*, 319–322. (d) Kociolek, M. G.; Johnson, R. P. *Tetrahedron Lett.* **1999**, *40*, 4141. (e) Miyawaki, K.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **2000**, *41*, 1447–1451. (f) Kimura, H.; Torikai, K.; Miyawaki, K.; Ueda, I. *Chem. Lett.* **2008**, *37*, 662. (g) Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Li, W. H. H.; Daoust, K. J.; Bovee, L. B.; DiRico, K. J.; Johnson, R. P. *J. Org. Chem.* **2011**, *76*, 9320.
5. Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208–212.
6. Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *1211–1214*.
7. (a) Tsui, J. A.; Sterenberg, B. T. *Organometallics* **2009**, *28*, 4906–4908. (b) Wang, K.; Yun, S. Y.; Mamidipalli, P.; Lee, D. *Chem. Sci.* **2013**, *4*, 3205–3211. (c) Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P.; Hoye, T. R. *Nat. protocols* **2013**, *8*, 503–508. (d) Niu, D.; Willoughby, P. H.; Woods, B. P.; Baire, B.; Hoye, T. R. *Nature* **2013**, *501*, 531–534. (e) Niu, D.; Wang, T.; Woods, B. P.; Hoye, T. R. *Org. Lett.* **2014**, *16*, 254–257. (f) Holden, C.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 5746–5749. (g) Willoughby, P. H.; Niu, D.; Wang, T.; Haj, M. K.; Cramer, C. J.; Hoye, T. R. *J. Am. Chem. Soc.* **2014**, *136*, 13657−13665. (h) Woods, B. P.; Baire, B.; Hoye, T. R. *Org. Lett.* **2014**, *16*, 4578−4581. (i) Chen, J.; Baire, B.; Hoye, T. R. *Heterocycles* **2014**, *88*, 1191–1200. (j) Niu, D.; Wang, T.; Woods, B. P.; Hoye, T. R. *Org. Lett.* **2014**, *16*, 254–257. (k) Zhang, H.; Hu, Q.; Li, L.; Hu, Y.; Zhou, P.; Zhang, X.; Xie, H.; Yin, F.; Hu, Y.; Wang, S. *Chem. Commun.* **2014**, *50*, 3335–3337. (l) Baire, B.; Wang, T.; Hoye, T. R. *Chem. Sci.* **2014**, *5*, 545–550. (m) Pogula, V. D.; Wang, T.; Hoye, T. R. *Org. Lett.* **2015**, *17*, 856−859. (n) Kerisit, N.; Toupet, L.; Larini, P.; Perrin, L.; Guillemin, J. C.; Trolez, Y. *Chem.–Eur. J.* **2015**, *21*, 6042–6047. o) Nguyen, Q. L.;

Baire, B.; Hoye, T. R. *Tetrahedron Lett.* **2015**, *56*, 3265–3267. (p) Watanabe, T.; Curran, D. P.; Taniguchi, T. *Org. Lett.* **2015**, *17*, 3450–3453. (q) Karmakar, R.; Ghorai, S.; Xia, X.; Lee, D. *Molecules* **2015**, *20*, 15862–15880. (r) Zhang, M. X.; Shan, W.; Chen, Z.; Yin, J.; Yu, G. A.; Liu, S. H. *Tetrahedron Lett.* **2015**, *56*, 6833–6838. (s) Zhang, M. X.; Shan, W.; Chen, Z.; Yin, J.; Yu, G. A.; Liu, S. H. *Tetrahedron Lett.* **2015**, *56*, 6833–6838. (t) Chen, J.; Palani, V.; Hoye, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 4318–4321. (u) Karmakar, R.; Wang, K. P.; Yun, S. Y.; Mamidipalli, P.; Lee, D. *Org. Biomol. Chem.* **2016**, 14, 4782–4788.

8. (a) Ritter, J. J.; Inieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045–4048. (b) Martinez, A. G.; Alvarez, R. M.; Vilar, E. T.; Frailea, A. G.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *30*, 581–582. (c) Chen. H. G.; Goel, P.; Kesten, S.; Knobelsdorf, J. *Tetrahedron Lett.* **1996**, *37*, 8129–81332. (d) Nair, V.; Rajan, R.; Rath, N. P. *Org. Lett.* **2002**, *4*, 1575–1577. (e) Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453–1455. (f) Gullickson, G. C.; Lewis, D. E. *Synthesis* **2003**, 681–684. (g) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 1431. (h) Okada, I.; Kitano, Y. *Synthesis* **2011**, 3997–4002. (i) Hazarika, N.; Baishya, G.; Phukan, P. *Synthesis* **2015**, *47*, 2851–2859. (j) Dokli, I.; Gredi˘cak, M. *Eur. J. Org. Chem.* **2015**, 2727. (k) Karimian, E.; Akhlaghinia, B.; Ghodsinia, S. S. E. *J. Chem. Sci.* **2016**, *128*, 429–439.
9. (a) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Kusama, O.; Wakisaka, K.; Zasshi, Y. *Yakugaku Zasshi* **1969**, *89*, 1212–1217. (b) Bunnett, J. F.; Gloor, B. *J. Org. Chem.* **1973**, *38*, 4156–4163. (c) Buchwald, S. L.; Sayers, A.; Watson, B. T.; Dewan, J. C. *Tetrahedron Lett.* **1987**, *28*, 3245–3248. (d) Jeganmohan, M.; Cheng, C. H. *Chem. Commun*., **2006**, 2454–2456. As opposed nitriles, the facile addition of isonitriles to arynes are amply demonstrated: (e) Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1998,** *63*, 6742–6744. (f) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem. Int. Ed*. **2004**, *43*, 3935–3938. (g) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Letters* **2004**, *45*, 8659–8662. (h) Yoshida, H.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, A. *Tetrahedron* **2007**, 63, 4793–4805. (i) Sha, F.; Huang, X. *Angew. Chem. Int. Ed.* **2009**, *48*, 3458–3461. (j) Yoshida, H.; Okada, K.; Kawashima, S.; Tanino, K.; Ohshita, J. *Chem. Commun*., **2010**, *46*, 1763–1765. (k) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem. Int. Ed*. **2011**, *50*, 4488–4491. (l) Sha, F.; Wu, L.; Huang, X.; *J. Org. Chem.* **2012**, *77*, 3754−3765. (m) Gesù, A.; Pozzoli, C.; Torre, E.; Aprile, S.; Pirali, T. *Org. Lett*. **2016**, *18*, 1992−1995.
10. Karmakar, R.; Lee, D. *Chem. Soc. Rev*. **2016**, *45*, 4459–4470.
11. (a) Ikawa, T.; Nishiyama, T.; Shigeta, T.; Mohri, S.; Morita, S.; Takayanagi, S.; Terauchi, Y.; Morikawa, Y.; Takagi, A.; Ishikawa, Y.; Fujii, S.; Kita, Y.; Akai, S. *Angew. Chem., Int. Ed*. **2011**, *50*, 5674–5677. (b) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 13966–13969. (c) Ikawa, T.; Takagi, A.; Goto, M.; Aoyama, Y.; Ishikawa, Y.; Itoh, Y.; Fujii, S.; Tokiwa, H.; Akai, S. *J. Org. Chem.*, **2013**, *78*, 2965–2983. (d) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 15798−15805.
12. Liang, Y.; Hong, X.; Yu, P.; Houk, K. N. *Org. Lett.* **2014**, *16*, 5702−5705.
13. Karmakar, R; Yun, S. Y.; Wang, K. P.; Lee, D. *Org. Lett*. **2014**, *16*, 6−9.
14. (a) Yun, S. Y.; Wang, K.; Lee, N.; Mamidipalli, P.; Lee, D. *J. Am. Chem. Soc*. **2013**, *135*, 4668–4671. (b) Wang, K.; Yun, S. Y.; Mamidipalli, P.; Lee, D. *Chem. Sci*. **2013**, *4*, 3205–3211 (c) Mamidipalli, P.; Yun, S. Y.; Wang, K.; Zhou, T.; Xia, Y.; Lee, D. *Chem. Sci.* **2014**, *5*, 2362–2367.
15. (a) Liang, Y.; Hong, X.; Yu, P.; Houk, K. N. *Org. Lett.* **2014**, *16*, 5702−5705. (b) Marell, D. J.; Furan, L. R.; Woods, B. P.; Lei, X.; Bendelsmith, A. J.; Cramer, C. J.; Hoye, T. R.; Kuwata, K. T. *J. Org. Chem.* **2015**, *80*, 11744−11754. (c) Wang, T.; Niu, D.; Hoye, T. R. *J. Am. Chem. Soc*. **2016**, *138*, 7832−7835.

Supplementary material

that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office