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Regioselectivity in nickel(0)/phosphine catalyzed cycloadditions of alkynes and isocyanates

Hung A. Duong, Janis Louie *

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112-0850, United States

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Abstract

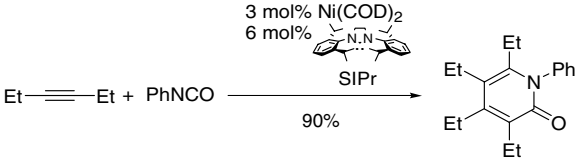
The regioselectivity of Ni(0)-catalyzed cycloadditions of various isocyanates and asymmetrical alkynes to afford pyridones was explored. The use of PEt_3 provided, in most cases, two of the four possible pyridone regioisomers in high overall yields. Mechanistic rationale for the product distribution is provided.

Keywords: Nickel; Phosphine; Catalyst; Isocyanates; Alkynes; Pyridones; Cycloaddition; Regioselectivity

1. Introduction

Transition metal-catalyzed cycloaddition reactions are a powerful strategy used for preparing heterocycles. In particular, diynes may be coupled to isocyanates to produce 2-pyridones, common heterocyclic motifs in a variety of pharmacologically valuable compounds [1]. The ability to control the regio- and chemoselectivity of these cycloadditions is of profound importance. Indeed, much effort has been directed toward evaluating the regioselectivity in Co-catalyzed cycloadditions of asymmetrical alkynes [2].

We recently discovered that the combination of Ni and a suitable σ-donating ligand (such as SIPr, SIPr = 1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene) catalyzes the cycloaddition of alkynes and isocyanates [3,4]. This method allowed for the facile preparation of a variety of pyridones in excellent yields under milder reaction conditions than those employed using either Co [2] or Ru [5] based catalysts. During our investigation, we found our catalyst system facilitates the coupling of 3-hexyne and phenyl isocayante to afford tetraethylpyridone in excellent yield (Eq. (1)) [3]. As part of our program to further develop cycloaddition chemistry [6], we embarked on evaluating the reactivity of a variety of Ni catalysts for the cycloaddition of asymmetrical alkynes to afford highly functionalized pyridones. The regiochemistry of the pyridone products were unambigiously assigned through NMR analysis.



(1)

2. Results

The cycloaddition of an asymmetrically substituted alkyne, 1-trimethylsilyl-1-propyne (**1a**), and phenyl isocyanate (**2a**) was chosen as a model system and a variety of imidazolylidene and phosphine [7,8] based ligands were screened for the formation of pyridone (Eq. (2)).

* Corresponding author. Tel.: +801 581 7309; fax: +801 581 8433.
E-mail address: louie@chem.utah.edu (J. Louie).

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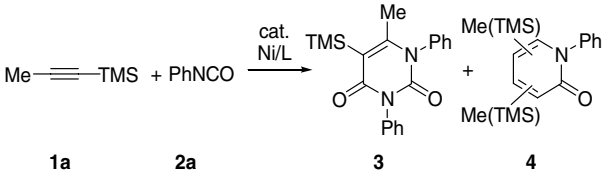
A pronounced difference in reactivity and product distribution was observed. Specifically, imidazolylidenes that were effective for the coupling of 3-hexyne (e.g., IPr and SIPr) did not yield any observable pyridone products. Instead, a single pyrimidine-dione regioisomer (**3**) was obtained [9]. In contrast, a variety of phosphine ligands delivered the desired pyridone (**4**, as a mixture of regioisomers) [8]. Further optimization led to a protocol (5 mol% $Ni(COD)_2$, 20 mol% PEt_3, and isocyanate and alkyne concentrations of 0.1 and 0.2 M, respectively, at room temperature) that afforded excellent yields of pyridone regioisomers (**4**), while concurrently minimizing cyclotrimerization of **1a**, a known side reaction [10].

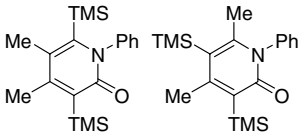
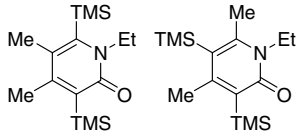
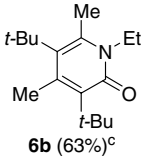
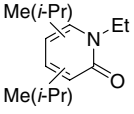
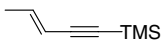
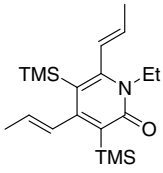
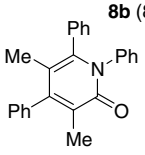


1a **2a** **3** **4** (2)

A variety of asymmetrically substituted alkynes and isocyanates were cocyclized to examine the scope and, more importantly, the regioselectivity of the reaction. The results are summarized in Table 1. 1-Trimethylsilyl-1-propyne (**1a**) underwent clean cycloaddition with both aryl and alkyl isocyanates (e.g., phenyl isocyanate **2a** and ethyl isocyanate **2b**, respectively) to afford pyridones **4** and **5** in excellent overall yields (entries 1–2). In both cases, only two of the possible four regioisomers (**4a** and **4b**, **5a** and **5b**) were obtained in approximately equal amounts. In contrast, alkyl-substituted alkynes such as *tert*-butylpropyne **1b** and *iso*-propylpropyne **1c** required higher catalyst loadings and elevated temperatures to ensure complete conversion (entries 3 and 4, respectively). Nevertheless, the reaction of **1b** afforded pyridone **6b** as the major isomer in 63% yield [11]. In contrast, cycloaddition of the smaller alkyne (**1c**) afforded four pyridone products (**7**). A single regioisomer (**8b**) was obtained in 81% from the cycloaddition of **1d** demonstrating that extended conjugation has an appreciable effect on the regioselectivity [12]. A similar effect was observed in the cycloaddition of phenylpropyne (**1e**) and phenyl isocyanate (**2a**) which afforded pyridone **9** as the major product [13].

The regiochemical assignments of the pyridones were unambigiously assigned by NMR spectroscopy [14]. In general, we found HMBC analysis to be an effective tool for determining the regiochemistry of the isolated pyridones. For example, the HMBC spectrum of **4a** showed coupling between the ring carbons bearing the TMS groups and the TMS protons. Each of these carbons was coupled to the protons *of only one methyl group*. Furthermore, neither methyl groups showed any coupling to the carbonyl carbon. Only isomer **4a** fits this coupling pattern.

Table 1
Ni/PEt_3 catalyzed cycloaddition of asymmetrical alkynes and isocyanates[a]

Entry	Alkyne	Isocyanate	Products (% Yield)[b]	
1	Me—≡—TMS	Ph—NCO		
	1a	**2a**	**4a** (40%)	**4b** (43%)
2	Me—≡—TMS	Et—NCO		
	1a	**2b**	**5a** (42%)	**5b** (50%)
3	Me—≡—*t*-Bu	Et—NCO		
	1b	**2b**	**6b** (63%)[c]	
4	Me—≡—*i*-Pr	Et—NCO		
	1c	**2b**	**7** (94%)[d]	
5		Et—NCO		
	1d	**2b**	**8b** (81%)	
6	Me—≡—Ph	Ph—NCO		
	1e	**2a**	**9c** (80%)[e]	

[a] Reaction conditions: 0.2 M diyne, 0.1 M isocyanate, 5 mol% $Ni(COD)_2$, 20 mol% PEt_3, room temperature.
[b] Isolated yields (average of two runs).
[c] 10 mol% $Ni(COD)_2$, 40% PEt_3, 60 °C.
[d] Reaction run at 80 °C and a mixture of 4 regioisomers were observed by GC/MS spectroscopy.
[e] Isolated as a mixture of two regioisomers; **9c** is the major (90%) regioisomer as determined by NMR spectroscopy.

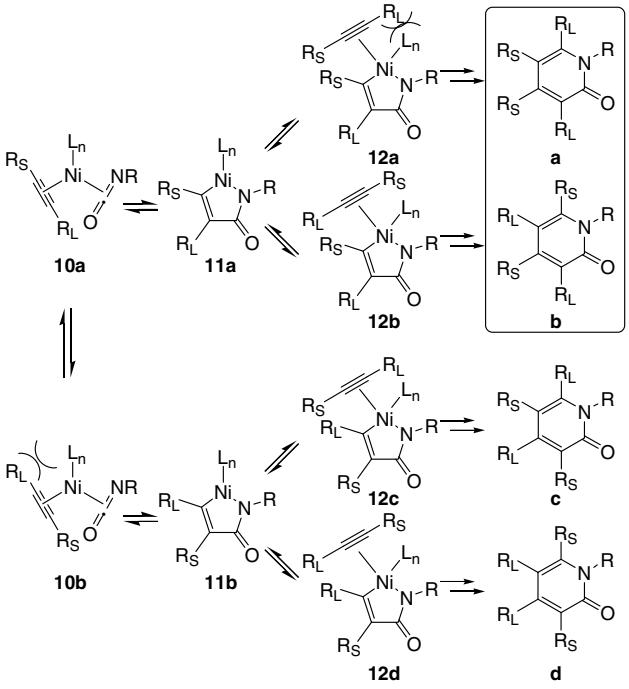
The HMBC spectrum of **4b** also showed coupling between the ring carbons bearing the TMS groups and the TMS protons. A different coupling interaction with the methyl protons was observed. Specifically, one TMS-substituted carbon coupled to both methyl groups and the other TMS-substituted carbon displayed coupling to only one methyl group highly indicative of an alternating substituent pattern on the pyridone ring. Finally, a NOESY spectrum showed an interaction between a methyl group (rather than the TMS group) and the

ortho protons of the *N*-phenyl group. Only isomer **4b** fits this data.

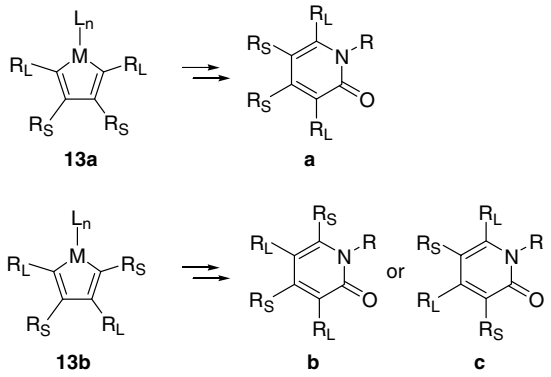
The regiochemistry of **9** (and all other pyridone products) was determined in a similar fashion. The major isomer (90%, **9c**) displayed coupling between one methyl group and the carbonyl carbon (in addition to another ring carbon) while the other methyl was coupled with three ring carbons, but not the carbonyl carbon in the HMBC spectrum. In contrast, one methyl group of the minor regioisomer (10%, **9b**) was coupled to two ring carbons whereas the other was coupled to three ring carbons. Importantly, neither methyl group displayed any coupling to the carbonyl carbon.

3. Discussion

The mechanism of Ni-catalyzed cycloadditions of heterocumulenes is believed to begin with initial oxidative coupling between an alkyne and an isocyanate. Thus, the regioisomers obtained in entries 1–4 in Table 1 can be rationalized by a preference to form nickelacycle **10a** rather than **10b** (Scheme 1). The formation of **10a** circumvents steric interactions between the bulky alkynyl unit (R_L) and the ligand (as observed in **10b**). Futhermore, formation of **10b** is completely inhibited when R_L is sufficiently large (e.g., TMS and *t*-Bu) [15,16]. As the R_L decreases in size, (e.g., *i*-Pr), less selectivity in the oxidative coupling event is observed (see product **7**). The regiochemistry of the subsequent insertion of the second alkyne is also governed by a similar



Scheme 1. Possible mechanisms for the cycloaddition of alkynes and RNCO.



Scheme 2. An alternative mechanism.

steric interaction. However, this interaction is less pronounced as evidenced by the formation of equal molar amounts of both regioisomers **a** and **b** for pyridones **4** and **5** (entry 1–2). Interestingly, if L is a large imidazolylidene (e.g., SIPr), alkyne insertion via **12** is unfavorable due to an increased steric repulsion. Thus, pyimidine-dione (**3**) formation rather than pyridone formation is observed.

In Co catalyzed cycloadditions, an alternative mechanism involves the generation of a cobaltacyclopentadiene (rather than a cobaltazacyclopentadione) intermediate through the oxidative coupling of two alkynes (**13a** and **13b**, Scheme 2). In these reactions, both R_L groups are generally on the α carbon (as in **13a**) and pyridone **a** is the major regioisomer. In contrast, Ni-catalyzed cycloadditions provide pyridone **b** as the major regioisomer which suggests mechanistic differences between Co and Ni catalyzed reactions [2a] (entries 1–3 and 5, Table 1).

Additional differences in selectivity between Co and Ni catalyzed cycloadditions are seen when 1-phenyl-propyl-1-yne (**1d**) is employed. Pyridone **9a** is formed exclusively in Co catalyzed cycloadditions (Fig. 1) [2a]. Interestingly, pyridone **9b** (rather than the observed **9c**) is the expected product, based on steric considerations (**15b**), in Ni catalyzed cycloadditions. Thus, electronic factors seem to override steric interactions in

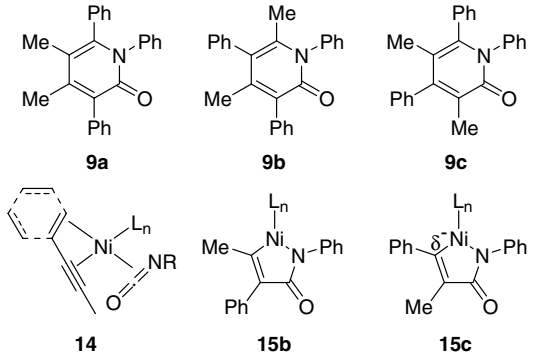


Fig. 1. Possible intermediates for the cycloaddition of **1e**.

these reactions (i.e., 90% **9c** versus 10% **9b**). Although it is possible the phenyl group 'directs' the regiochemistry of oxidative coupling (**14**) [12], the directing effect has only been observed for vinyl groups making this an unlikely explanation. Thus, stabilization of a partial negative charge on the α-carbon (**15c**) [17] best predicts the observed regioselectivity [18–20].

4. Conclusions

The combination of Ni(0) and PEt_3 catalyzed cycloaddition of asymmetrical alkynes and isocyanates afforded regioisomeric mixtures of pyridones. Regioselectivity was highly dependent on the size of the terminal groups. In some cases, electronic factors override steric interactions to ultimately afford a single pyridone regioisomer. NMR analysis indicated that the two regioisomers possessed the large substituent (R_L) at the 3-position on the pyridone ring.

5. Experimental

All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2 filled glove-box. Toluene, pentane, and diethyl ether were dried over neutral alumina under N_2 using a Grubbs-type solvent purification system [21]. $Ni(COD)_2$ was purchased from Strem and used without further purification. Tri-(*n*-butyl)-phosphine, tri-(*tert*-butyl)-phosphine, tricyclohexylphosphine and triethylphosphine were purchased from Aldrich and used without further purification. 1-Trimethylsilyl-1-propyne, 4,4-dimethyl-2-pentyne and 1-phenyl-1-propyne were purchased from GFS chemicals, dried and degassed prior to use. Ethyl isocyanate and phenyl isocyanate were purchased from Aldrich, dried and degassed prior to use. SIPr was prepared as previously reported [22]. All other reagents were purchased and used without further purification unless otherwise noted. ^1H and ^{13}C NMR spectra of pure compounds were acquired at 300 and 75 MHz, respectively, unless otherwise noted and were referenced to residual protiated solvent. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. HRMS were performed at the mass spectrometry facility at the University of Utah. Analytical C&H combustion analyses were performed by Midwest Microlab, LLC, Indianapolis, Indiana.

5.1. General cycloaddition of alkynes and isocynates

In a glove box, a solution of alkyne and isocyanate in toluene was added to an oven-dried vial equipped with a stir bar. To the stirring solution, a solution of $Ni(COD)_2$ and PEt_3 was added and the reaction was stirred at room temperature for 4 h (or until complete consumption of starting material was observed as judged by GC). The mixture was then quenched with acetone, concentrated and purified by silica gel column chromatography, pre-treated with triethyl amine. This procedure was used for the cycloaddition unless otherwise noted.

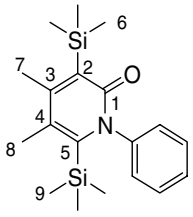
5.2. 4,5-Dimethyl-3,6-bis(trimethylsilyl)-1-phenylpyridin-2(1H)-one (**4a**) and 4,6-dimethyl-3,5-bis(trimethylsilyl)-1-phenylpyridin-2(1H)-one (**4b**)

The general procedure was used with 1-trimethylsilyl-1-propyne (100 mg, 0.89 mmol, 0.2 M), phenyl isocyanate (53 mg, 0.45 mmol, 0.1 M), $Ni(COD)_2$ (6 mg, 0.022 mmol, 5 mol%), triethyl phosphine (11 mg, 0.089 mmol, 20 mol%) and 4.5 mL of toluene. The reaction mixture was quenched with acetone and purified by column chromatography on silica gel pre-treated with triethyl amine (hexane/ethyl acetate 9:1) to afford 3 (62 mg, 41%) and 4 (66 mg, 43%) as white solids.

5.3. Analytical data for **4a**

^1H NMR (500 MHz, $CDCl_3$, ppm): δ 0.35 (9H, s), 2.18 (3H, s), 2.26 (3H, s), 7.21–7.43 (5H, m); ^{13}C {^1H} NMR (125 MHz, $CDCl_3$, ppm) δ 1.9, 2.2, 19.2, 20.7, 125.2, 128.2, 129.1, 129.6, 129.8, 142.6, 148.7, 157.8, 166.0; IR (KBr pellet): 1619, 1490, 1315, 1253; Anal. Calc. for $C_{15}H_{29}NOSi_2$: C, 66.41; H, 8.51; N, 4.08. Found: C, 66.37; H, 8.47; N, 4.07%.

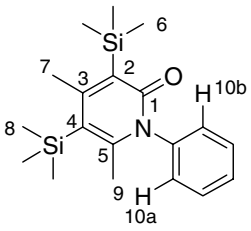
HMBC summary: The following cross peaks were observed: H(6) and C(2); H(7) and C(2), C(3), C(4); H(8) and C(3), C(4), C(5); H(9) and C(5).



5.4. Analytical data for **4b**

^1H NMR (500 MHz, CD_2Cl_2, ppm): δ 0.34 (9H, s), 0.37 (9H, s), 2.01 (3H, s), 2.39, (9H, s), 1.36–1.17 (2H, m), 7.39–7.51 (3H, m); ^{13}C {^1H} NMR (125 MHz, CD_2Cl_2, ppm) δ 2.3, 4.1, 23.8, 26.5, 115.2, 125.9, 128.3, 128.4, 129.9, 140.2, 151.2, 162.7, 166.0; IR (KBr pellet): 1630, 1486, 1249; Anal. Calc. for $C_{15}H_{29}NOSi_2$: C, 66.41; H, 8.51; N, 4.08. Found: C, 66.03; H, 8.25; N, 3.94%.

HMBC summary: The following cross peaks were observed: H(6) and C(2); H(7) and C(2), C(3), C(4); H(8) and C(4); H(9) and C(5).



NOE was observed for H(9) and 10a, 10b.

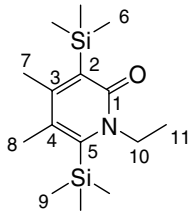
5.5. 1-Ethyl-4,5-dimethyl-3,6-bis(trimethylsilyl)pyridin-2(1H)-one (**5a**) and 1-ethyl-4,6-dimethyl-3,5-bis-(trimethylsilyl)pyridin-2(1H)-one (**5b**)

The general procedure was used with 1-trimethylsilyl-1-propyne (51 mg, 0.45 mmol, 0.2 M), ethyl isocyanate (16 mg, 0.23 mmol, 0.1 M), $Ni(COD)_2$ (3 mg, 0.011 mmol, 5 mol%), triethyl phosphine (5 mg, 0.045 mmol, 20 mol%) and 2.3 mL of toluene. The reaction mixture was quenched with acetone purified by column chromatography on silica gel pre-treated with triethyl amine (hexane/ethyl acetate 9:1) to afford 1 (28 mg, 42%) and 2 (34 mg, 50%) as white solids.

5.6. Analytical data for **5a**

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 0.35 (9H, s), 0.47 (9H, s), 1.23 (3H, t, J = 6.8 Hz), 2.11 (3H, s), 2.18 (3H, s), 4.11–4.13 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm) δ 2.1, 3.8, 15.7, 19.1, 20.5, 43.7, 125.0, 129.4, 148.3, 156.6, 165.8; IR (KBr pellet): 1609, 1554, 1498, 1325, 1254; Anal. Calc. for $C_{15}H_{29}NOSi_2$: C, 60.95; H, 9.89; N, 4.74. Found: C, 60.94; H, 9.87; N, 4.60%.

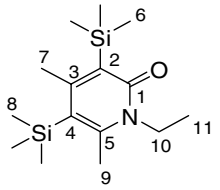
HMBC summary: The following cross peaks were observed: H(6) and C(2); H(7) and C(2), C(3), C(4); H(8) and C(3), C(4), C(5); H(9) and C(5); H(10) and C(1), C(5), C(11); H(11) and C(10).



5.7. Analytical data for **5b**

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.24 (3H, s), 0.30 (3H, s), 1.18 (3H, t, J = 7.1 Hz), 2.23 (3H, s), 2.38 (3H, s), 3.99 (2H, q, J = 6.99 Hz); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm): δ 1.8, 3.6, 13.5, 21.5, 25.9, 38.9, 21.5, 25.9, 38.9, 115.4, 124.2, 151.0, 161.1, 165.0; IR (KBr pellet): 1618, 1497, 1442; Anal. Calc. for $C_{15}H_{29}NOSi_2$: C, 60.95; H, 9.89; N, 4.74. Found: C, 61.04; H, 9.77; N, 4.68%.

HMBC summary: The following cross peaks were observed: H(6) and C(2); H(7) and C(2), C(3), C(4); H(8) and C(4); H(9) and C(4), C(5); H(10) and C(1), C(5), C(11); H(11) and C(10).



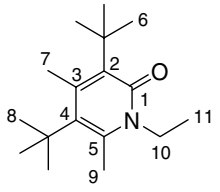
5.8. 3,5-Di-tert-butyl-1-ethyl-4,6-dimethylpyridin-2(1H)-one (**6b**)

In a glove box, a solution of 4,4-dimethyl-2-pentyne (51 mg, 0.53 mmol, 0.2 M) and ethyl isocyanate (19 mg, 0.27 mmol, 0.1 M) in toluene (2.7 mL) was added to an oven-dried vial equipped with a stir bar. To the stirring solution, a solution of $Ni(COD)_2$ (7 mg, 0.027 mmol, 10 mol%)and triethyl phosphine (13 mg, 0.106 mmol, 40 mol%) was added and the reaction was stirred at 60 °C for 4 h. The mixture was then quenched with acetone, concentrated and purified by silica gel column chromatography (hexane/ethyl acetate 9:1) to afford a white solid (44 mg, 63%).

5.9. Analytical data for **6b**

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.25 (3H, t, J = 7.0 Hz), 1.43 (9H, s), 1.47 (9H, s), 4.08 (2H, q, J = 7.1 Hz); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm) δ 14.2, 20.3, 25.8, 31.1, 33.0, 36.3, 38.2, 39.5, 127.9, 136.0, 137.1, 147.8, 160.7; IR (KBr pellet): 1620, 1562, 1435; Anal. Calc. for $C_{17}H_{29}NO$: C, 77.51; H, 11.1; N, 5.32, found: C, 77.33; H, 11.01; N, 5.39.

HMBC summary: The following cross peaks were observed: H(6) and C(2); H(7) and C(2), C(3), C(4); H(8) and C(4); H(9) and C(5); H(10) and C(1), C(5), C(11).



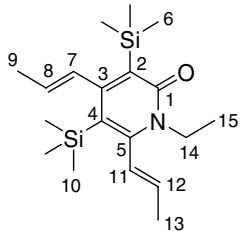
5.10. 4,6-Dimethyl-3,5-bis(trimethylsilyl)-1-phenylpyridin-2(1H)-one (**8b**)

The general procedure was used with 1-trimethylsilyl-pent-3-en-1-yne (54 mg, 0.39 mmol, 0.2 M), ethyl

isocyanate (16 mg, 0.19 mmol, 0.1 M), $Ni(COD)_2$ (3 mg, 0.010 mmol, 5 mol%), triethyl phosphine (5 mg, 0.039 mmol, 20 mol%) and 2.0 mL of toluene. The reaction mixture was quenched with acetone and purified by column chromatography on silica gel pre-treated with triethyl amine (hexane/ethyl acetate 9:1) to afford 7 (55 mg, 81%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.12 (9H, s), 0.24 (9H, s), 1.23 (3H, t, J = 7.1 Hz), 1.80 (3H, dd, J = 1.7 and 5.7 Hz), 1.90 (3H, dd, J = 1.7 and 5.8 Hz), 3.99 (2H, q, J = 7.0 Hz), 5.41–5.48 (1H, m), 5.80–5.87 (1H, m), 6.34 (1H, dd, J = 1.7 and 15.6 Hz), 6.50 (1H, dd, J = 1.7 and 15.9 Hz); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$, ppm) δ 2.0, 4.2, 14.0, 18.3, 18.5, 40.1, 115.2, 125.2, 127.9, 129.9, 135.3, 135.4, 153.7, 163.2, 165.1; IR (KBr pellet): 1619, 1477, 1444, 1245; HRMS (*m*/*z*): calcd for $C_{19}H_{33}NOSi_2$ (M^+) 347.2101, found 347.2112.

HMBC summary: The following cross peaks were observed: H(6) and C(1), C(2), C(3); H(7) and C(2), C(3), C(4), C(8), C(9); H(8) and C(3), C(7), C(9); H(9) and C(7), C(8); H(10) and C(4); H(11) and C(4), C(5), C(12), C(13); H(12) and C(11), C(13); H(13) and C(11), C(12); H(14) and C(1), C(5), C(15).



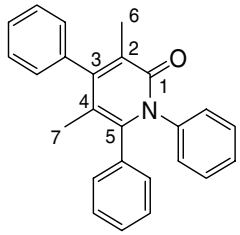
5.11. 3,5-Dimethyl-1,4,6-triphenylpyridin-2(1H)-one (**9c**) [7]

The general procedure was used with 1-phenyl-1-propyne (58 mg, 0.50 mmol, 0.2 M), phenyl isocyanate (30 mg, 0.25 mmol, 0.1 M), $Ni(COD)_2$ (3 mg, 0.012 mmol, 5 mol%), triethyl phosphine (6 mg, 0.050 mmol, 20 mol%) and 2.5 mL of toluene. The reaction mixture was quenched with acetone purified by column chromatography on silica gel (hexane/ethyl acetate 3:2) to afford **9c** [7] and its regioisomer (less than 10% by ^{1}H NMR) (76 mg, 87%) as white solid.

5.12. Analytical data for **9c**

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.53 (3H, s), 1.98 (3H, s), 6.92–7.56 (15H, m).

HMBC summary: The following cross peaks were observed: H(6) and C(1), C(2), C(3); H(7) and C(3), C(4), C(5).



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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.jorganchem.2005.03.027.

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[13] Pyridone **9** could not be separated from the other regioisomer, formed in 10% as determined by both GC and ^1H NMR spectroscopy, that is generated through the Ni-catalyzed cycloaddition chemistry. Nevertheless, the regiochemistry of **9** was unambigiously assigned through NMR analysis. See Section 5 and supporting information.
[14] It is important to note that the regiochemistry of the pyridone products cannot be assigned through standard ^1H spectroscopy alone. Volhardt used substituent corrections and non-^1H-decoupled ^{13}C NMR data for the assignment of the pyridone isomers. (See Ref. [2a]).
[15] We have observed a similar phenomenon in the Ni-catalyzed cycloaddition of asymmetrical diynes and carbon dioxide. When difference between Me and R_L is sufficiently large, 3-R_L-pyrones were formed *exclusively*. See Ref. [6b].
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