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Nickel-Catalyzed Directed C6-Selective C–H Alkylation of 2-Pyridones with Dienes and Activated Alkenes

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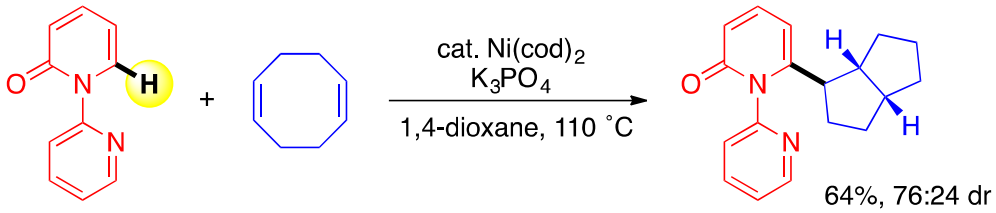


A pyridine-directed, C6-selective nickel-catalyzed ring-contracting C–H alkylation of 2-pyridones with 1,5-cyclooctadiene (cod) has been developed. The reaction proceeds smoothly under external-ligand-free conditions and is accelerated uniquely by a K_3PO_4 base. Preliminary mechanistic investigation with deuterium-labeling substrates and related reactions with some alkenes are also disclosed.

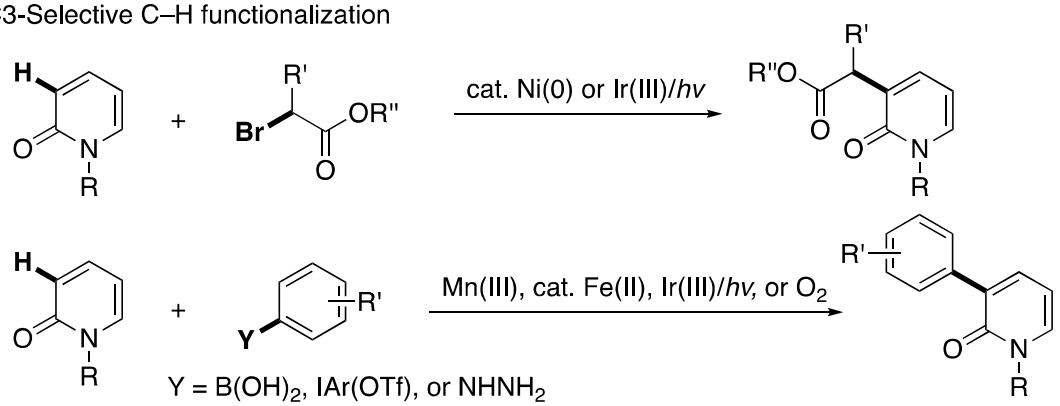
Introduction

A 2-pyridone is one of representative six-membered nitrogen-containing heterocycles, and its nucleus is widely found in natural products, pharmaceutical targets, and biologically active compounds. Such well-known compounds include ciclopirox, milrinone, camptothecin, fredericamycin, perampanel, and cytisine.[1] Thus, synthetic chemists have developed many synthetic methodologies for the preparation and functionalization of 2-pyridone ring. While conventional strategies largely rely on the preactivated starting substrates such as halogenated 2-pyridones, recent advances in metal-mediated C–H activation[2] can provide a potentially more efficient approach to densely functionalized pyridones from the relatively simple starting molecules. The pyridone has four reactive C–Hs (C3, C4, C5, and C6 positions), and thus control of site selectivity is the most important and challenging issue in the C–H functionalization of 2-pyridone. Radical-promoted C3-selective functionalization was independently developed by our group and Maiti (Scheme 1a). In the presence of Ni,[3] Mn,[4] Fe,[5] or Ir[6] salt, C3-alkylated and arylated 2-pyridones were obtained with high site-selectivity. More recently, an O_2-mediated similar reaction with arylhydrazines was also reported.[7] Access to the C4 position still remains underdeveloped, but C–H borylation is possible when the C6 position is blocked by suitable substituents (Scheme 1b).[8] The Pd-mediated C–H alkenylation at the most electron-rich C5 position was first reported by Ouseto and Itahara in 1984,[9] and about 30 years later the catalytic variant was developed by Li[10] (Scheme 1c). The same research group also found the Pd-catalyzed direct arylation with polyfluoroarenes. Although the C–H functionalization at the electron-deficient C6 position was relatively difficult, Nakao and Hiyama overcame such innate electronic biases and achieved C6-selective alkylation and arylation under elegantly designed Ni/Al cooperative catalysis[11] (Scheme 1d). Our research group also introduced a pyridine-based directing group strategy and succeeded in the Cu- and Rh-catalyzed C–H heteroarylation[12] and borylation[13] at the C6 position. Subsequently, several groups reported related catalytic C6-selective alkylation, alkynylation, arylation, and thiolation by using the same directing group strategy.[14] During our continuous studies on the pyridine-directed

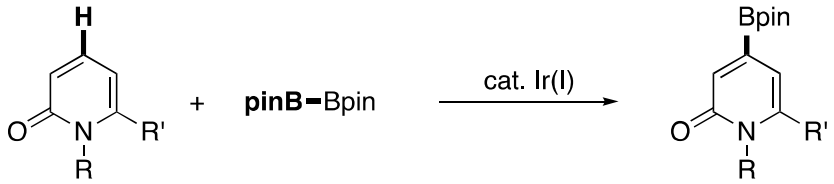
C6-selective functionalization, we have serendipitously found an Ni-catalyzed ring-contracting alkylation with 1,5-cyclooctadiene (cod; Scheme 2). The reaction proceeds smoothly under external-ligand-free conditions and is accelerated uniquely by a K_3PO_4 base. Preliminary mechanistic investigation with deuterium-labeling substrates and related reactions with some alkenes are also reported herein.

Scheme 1. Site-Selective C–H Functionalization of 2-Pyridones

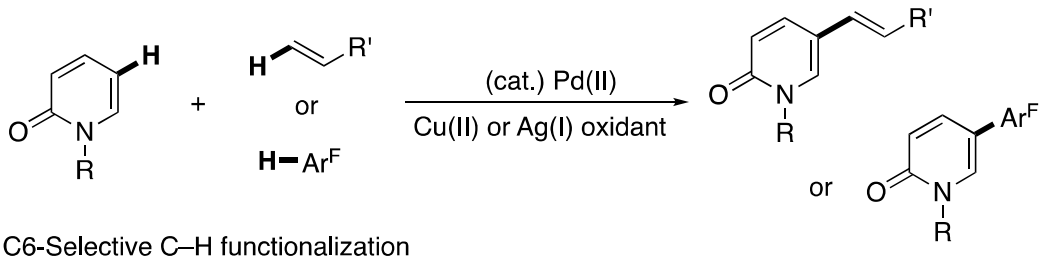
a) C3-Selective C–H functionalization



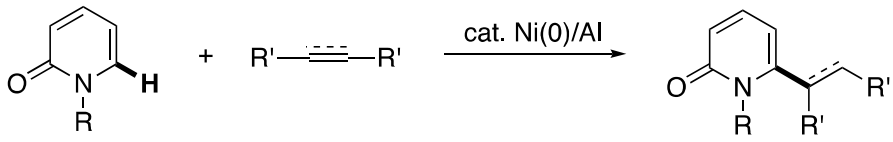
b) C4-Selective C–H functionalization

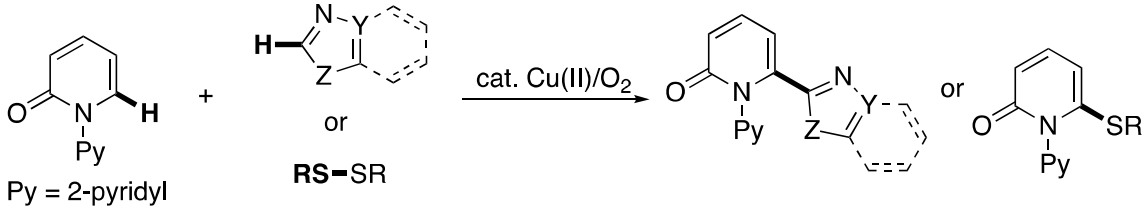


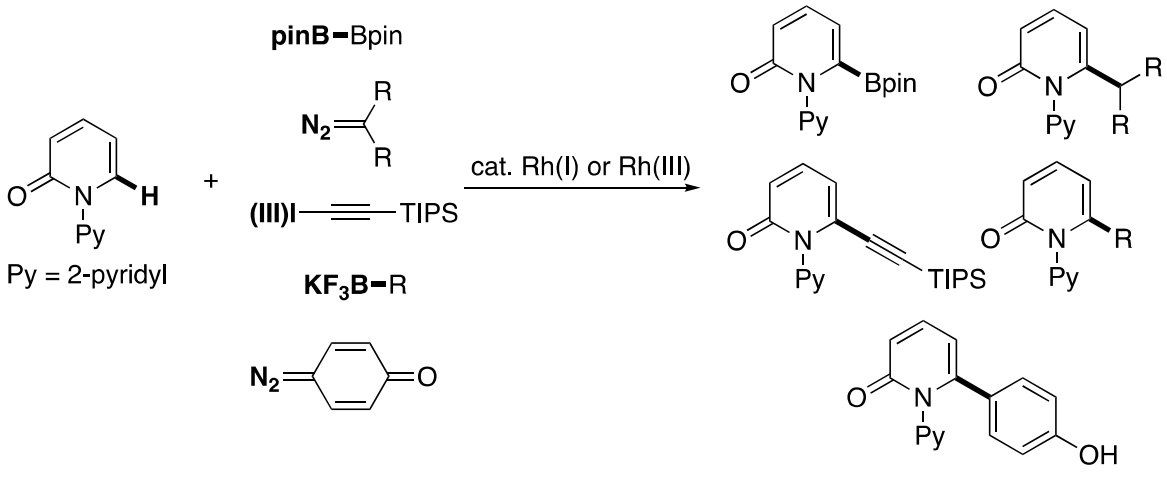
c) C5-Selective C–H functionalization



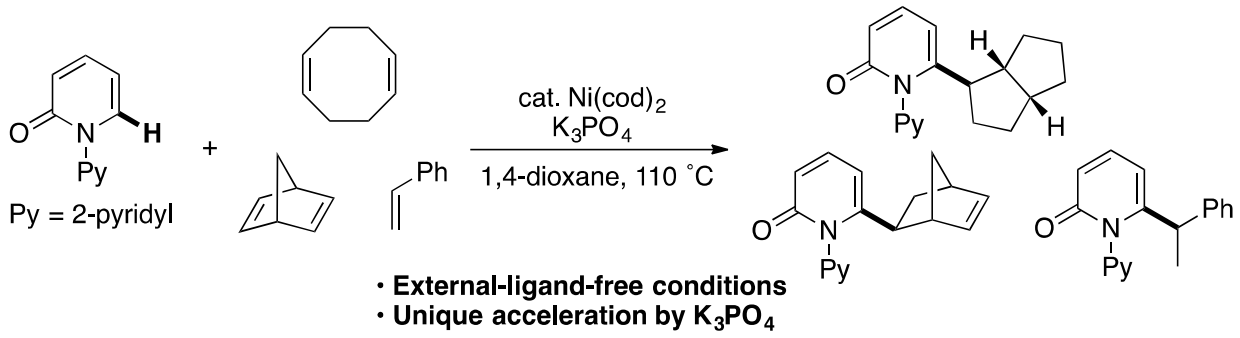
d) C6-Selective C–H functionalization







Scheme 2. Ni-Catalyzed C6-Selective C–H Alkylation of 2-Pyridones with Dienes and Alkenes (This Work)



Results and Discussion

We initially attempted a $Ni(cod)_2$-catalyzed directed C–H arylation of 2-pyridone **1a** with $PhB(OH)_2$ in the presence of Cs_2CO_3/MeOH and cyclohexene as basic additives and oxidant, respectively (Scheme 3). Unfortunately, the desired phenylated product was not detected at all, but we serendipitously detected a small amount of C6-alkylated pyridone **2a**, which apparently arose from the cod ligand in $Ni(cod)_2$ catalyst. Additionally, the unique ring contraction of cod unit concomitantly occurred. The structure of **2a** was first assigned by NMR and HRMS, and finally determined by X-ray crystallographic analysis of the major diastereomer after dibromination with dibromohydantoin.[15] Such a ring-contracting coupling with cod is not trivial.[16] Thus, the preliminary but intriguing result in Scheme 3 prompted us to optimize conditions for the unique catalytic C–H alkylation of 2-pyridone with cod as a coupling partner (Table 1). Initial additive screening (entries 1–4) revealed that neither $PhB(OH)_2$ nor MeOH were necessary but Cs_2CO_3 played a pivotal role in this reaction. Thus, we then tested various inorganic and organic bases (entries 5–10). Several inorganic bases accelerated the reaction, with K_3PO_4 proving to be optimal (entry 5). Finally, with 20 mol % loading of $Ni(cod)_2$, **2a** was obtained in 64% yield (entry 11). Some additional observations are to be noted: addition of external ligands such as pyridine, lutidine, dppe, and IPr•HCl gave negligible or negative impact on the

reaction efficiency as far as we tested. The corresponding *N*-Me- and *N*-Ph-2-pyridones did not react with cod at all, thus suggesting the indispensable coordinating ability of pyridine moiety in **1a**. No reaction of *N*-Me-2-pyridone occurred even under $Ni(cod)_2$/IPr/MAD (MAD = methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)) cooperative catalysis reported by Nakao and Hiyama.[11b] The observed reactivity was unique to the pyridone, and structurally similar 2-phenylpyridine gave no coupling products under conditions identical to entry 11 in Table 1.

Scheme 3. Initial Finding

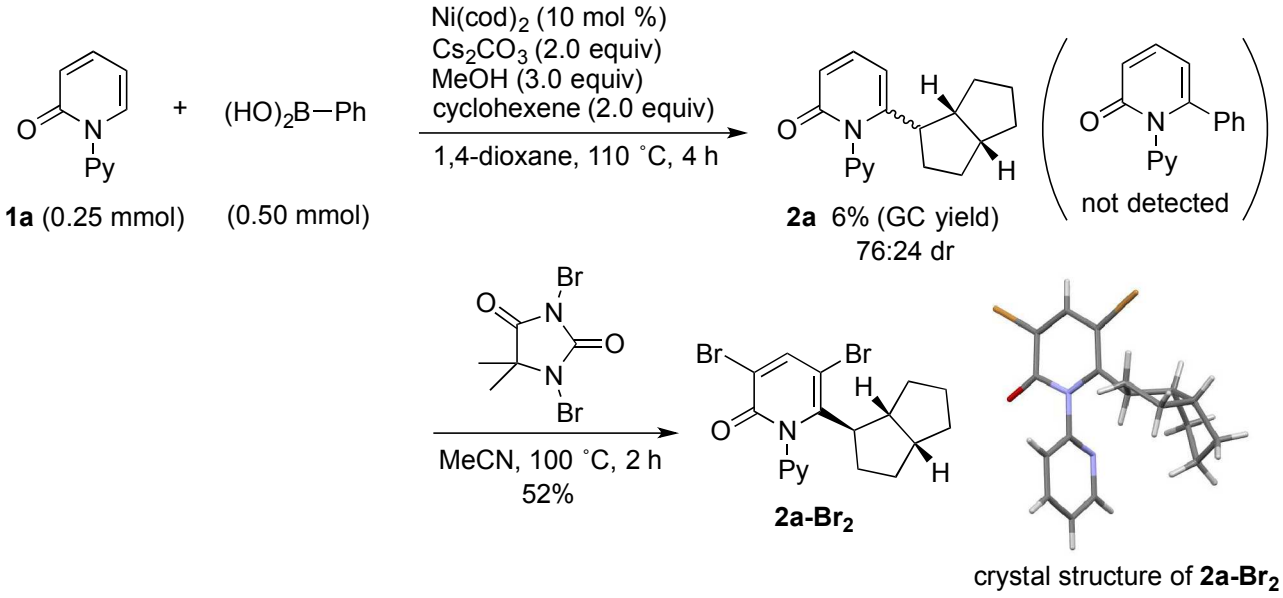
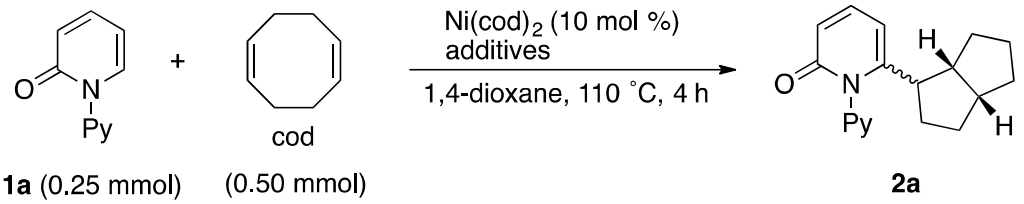


Table 1. Optimization Studies for Nickel-Catalyzed Ring-Contracting C–H Alkylation of 2-Pyridone 1a with 1,5-Cyclooctadiene (cod)[a]



entry	additives (mmol)	**2a**, NMR yield (%)[b]
1	none	14

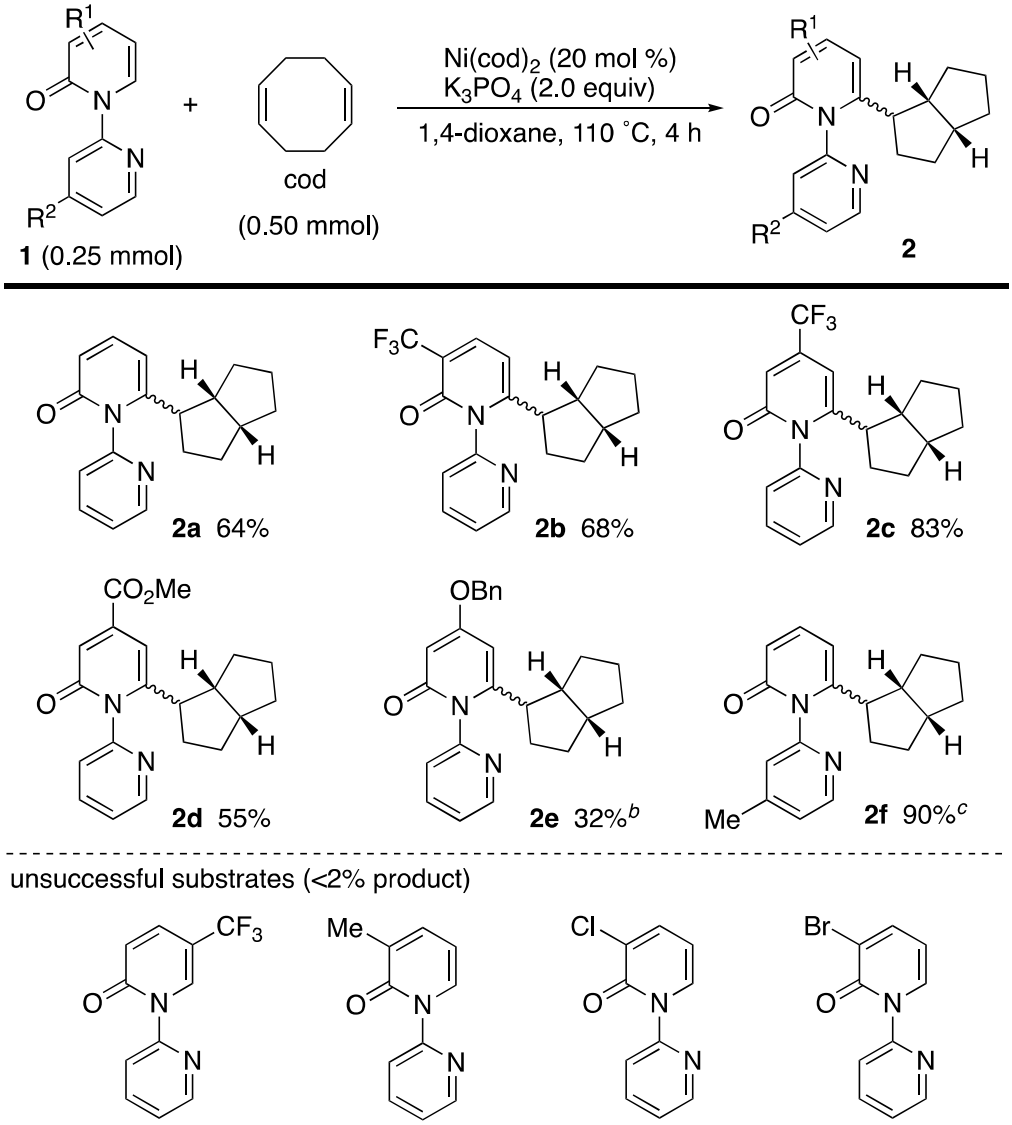
2	$PhB(OH)_2$ (0.50)	0
3	MeOH (0.75)	9
4	Cs_2CO_3 (0.50)	38
5	K_3PO_4 (0.50)	67
6	K_2CO_3 (0.50)	45
7	KOAc (0.50)	33
8	LiO-*t*-Bu (0.50)	32
9	NaO-*t*-Bu (0.50)	5
10	Et_3N (0.50)	20
11[c]	K_3PO_4 (0.50)	81 (64)

[a] Reaction conditions: **1a** (0.25 mmol), cod (0.50 mmol), $Ni(cod)_2$ (0.025 mmol), additives, 1,4-dioxane (1.5 mL), N_2. [b] NMR yield was calculated with dibenzyl ether as an internal standard. Yield is in parentheses. The product **2a** was generally obtained as a 76:24 mixture of diastereomers. [c] With 20 mol % of $Ni(cod)_2$ (0.050 mmol). Py = 2-pyridyl.

With promising conditions in hand, we investigated the scope of 2-pyridone **1** (Scheme 4). Electron-withdrawing CF_3 group at the C3 and C4 positions was tolerated, and the corresponding alkylated products **2b** and **2c** were obtained in 68% and 83% yields, respectively. The ester functionality was also accommodated under the standard conditions to deliver **2d** in a synthetically useful yield. On the other hand, the pyridone bearing an electron-donating benzyloxy substituent showed moderate reactivity (**2e**). As observed in our previous work,[12,13] the present catalysis was sensitive to steric factors: the C5-substituted pyridones did not couple with cod. The introduction of methyl substituent also suppressed the reaction while we have no explanation for the reason at present. The halogenated pyridones were reluctant substrates and a small but significant amount of dehalogenated starting pyridones were detectedbecause of the competitive oxidative addition of

C-halogen bond to low-valent Ni center; however, the latent halogenation could be possible as shown in Scheme 3, which can be a synthetic handle for further manipulations. Notably, the 4-methylpyridyl directing group was found to somewhat improve the reaction efficiency, and the desired alkylated product **2f** was formed in 90% yield even with 10 mol % catalyst loading.[17]

Scheme 4. Nickel-Catalyzed Ring-Contracting C–H Alkylation of Various 2-Pyridones 1 with 1,5-Cyclooctadiene (cod)[a]

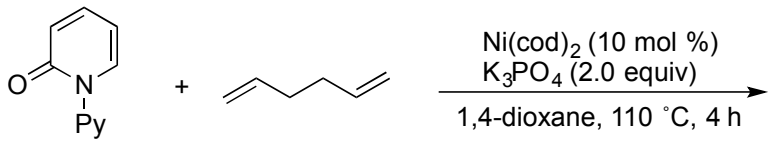


[a] Reaction conditions: **1** (0.25 mmol), cod (0.50 mmol), K_3PO_4 (0.50 mmol), 1,4-dioxane (1.5 mL), N_2, 110 °C, 4 h. All products **2** were obtained as ca. 80:20 mixture of diastereomers. [b] ^1H NMR yield. [c] With 10 mo % of $Ni(cod)_2$ (0.025 mmol).

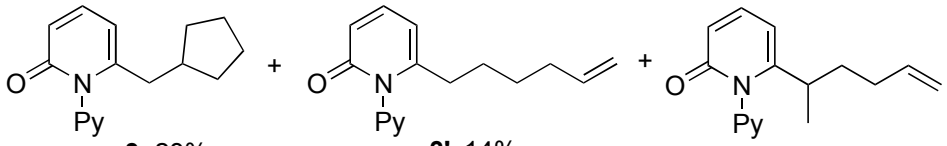
The reactivity of some dienes and alkenes were also investigated (Scheme 5). In addition to cod (1,5-diene), 1,4- and 1,3-dienes also reacted with **1a** under identical conditions (Scheme 5a). The former afforded a mixture of ring-forming (**3**) and simple addition products (**3'** and **3"**), but each product could be easily separated and a combined yield was also good (84%). No double addition product was detected; chemoselectivity of which is completely different from that of the reported Ni/Al catalysis.[11b] On the other hand, the latter formed the simple linear adduct **4** exclusively. However, conjugated 1,3-diene, 1,6-diene that bears longer methylene tether, and simple aliphatic terminal alkene did not give any detectable amount of coupling products. Several strained alkenes were also reactive, and norbornadiene and norbornene furnished the corresponding *exo*-adducts **5** and **6** in good yields (Scheme 5b). The structure of **5** was unambiguously confirmed by X-ray analysis.[15] Notably, in the case of norbornene, the addition of K_3PO_4 was not necessary. Additionally, electronically activated styrene coupled with **1a** to produce the branched adduct **7** selectively, where the positive effect of H_2O (4.0 equiv) was observed (Scheme 5c). In all cases, a small amount of cod-coupled **2a** was observed, but it could be readily separated from the desired product by column chromatography.

Scheme 5. Nickel-Catalyzed C–H Alkylation of 2-Pyridone 1a with Several Dienes and Alkenes

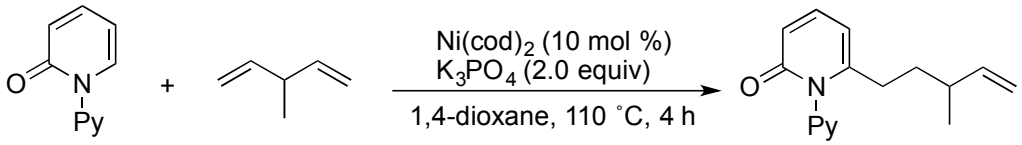
a) Reaction with 1,n-dienes



1a (0.25 mmol) (0.50 mmol)

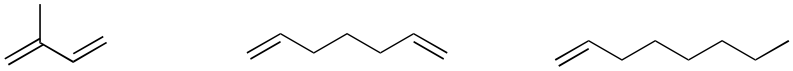


3 28% **3'** 14% **3"** 42%

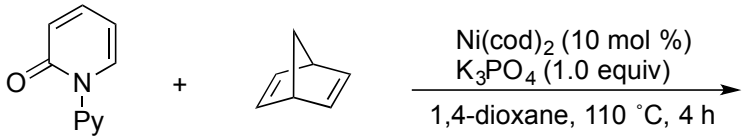


1a (0.25 mmol) (0.50 mmol) **4** 54%

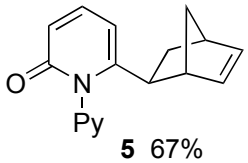
unsuccessful substrates (<2% product)



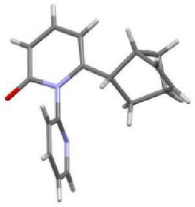
b) Reaction with strained alkenes



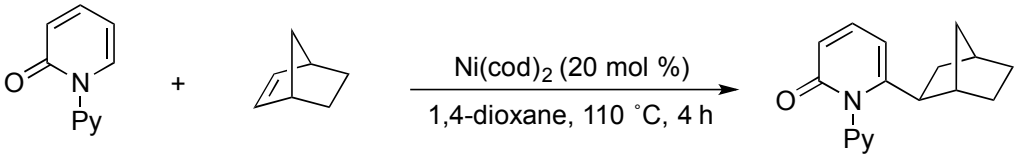
1a (0.25 mmol) (0.50 mmol)



5 67%

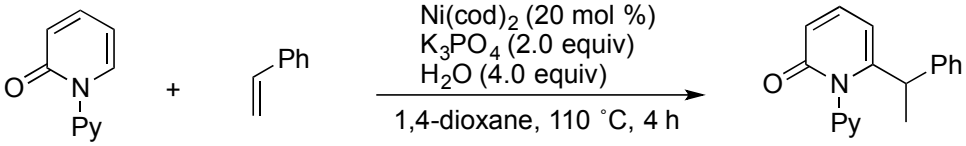


crystal structure of **5**



1a (0.25 mmol) (0.50 mmol) **6** 78%

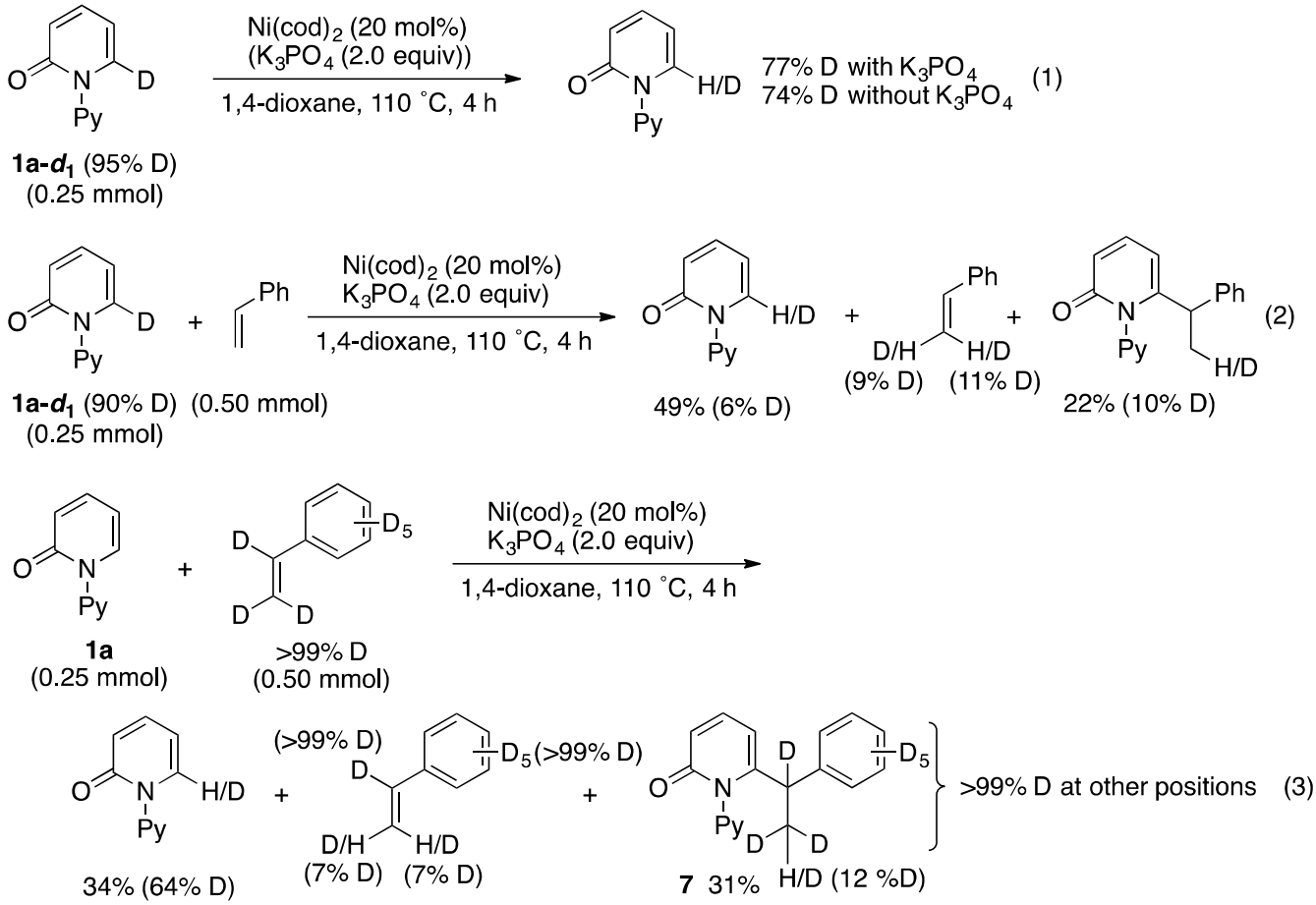
c) Reaction with styrene



1a (0.25 mmol) (0.50 mmol) **7** 70% (49% w/o H_2O)

To get mechanistic insight, several control experiments with deuterium-labeled **1a-*d*$_1$** (90–95% D) and styrene-d_8 (>99% D) were performed (Scheme 6). In the absence or presence of styrene, the deuterium content of recovered **1a-*d*$_1$** decreased considerably (eqs 1 and 2). Additionally, in the latter case the recovered styrene[18] as well as alkylated product **7** was partially deuterated (eq 2). Also in the reaction of **1a** with styrene-d_8, the deuterium incorporation into alkylated product **7** was observed whereas some deuteriums were distributed to the recovered **1a** and the remaining styrene partially lost the deuterium (eq 3). Additionally notable is that the addition of K_3PO_4 showed negligible effect on the H/D exchange of **1a-*d*$_1$** (eq 1).[19]

Scheme 6. Deuterium-Labeling Experiments

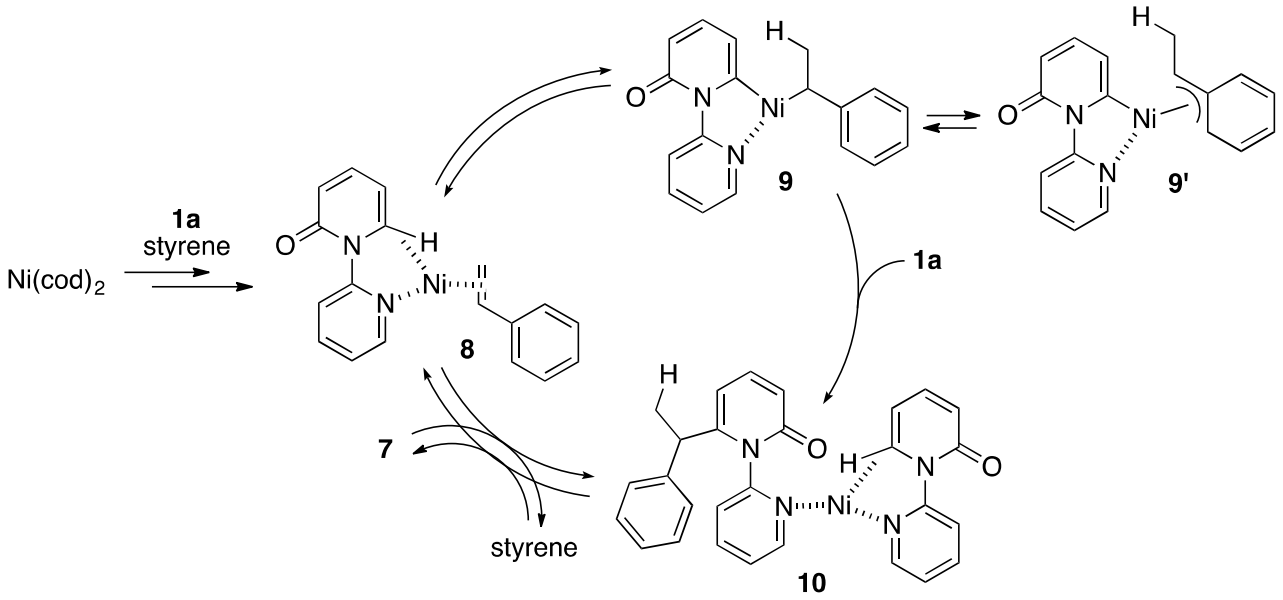


On the basis of our findings and literature information, we propose the reaction mechanism of **1a** with styrene as shown in Scheme 7. The starting $Ni(cod)_2$ initially undergoes the ligand exchange with **1a**[20]

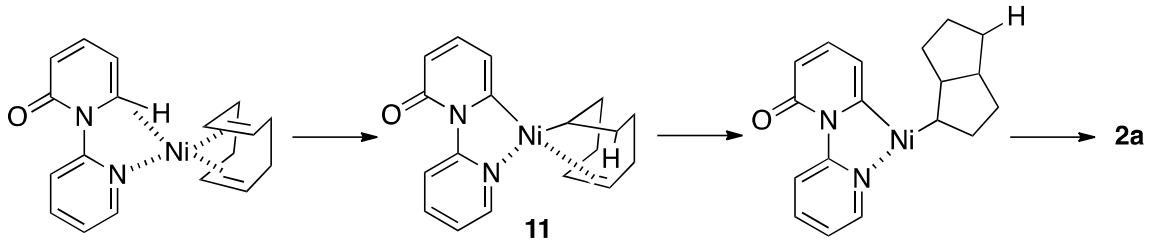
and styrene to form a tricoordinated Ni σ-complex **8** including the pyridone C–H at the C6 position. Subsequent concerted proton transfer occurs (**8** to **9**), in which one C–H is cleaved and two C–Ni bonds are formed.[21] The resulting σ-benzyl Ni intermediate **9** is in equilibrium with more thermodynamically stable π-benzyl Ni **9'**.[22] Productive reductive elimination and coordination of another **1a** generates the product-containing complex **10**. Final ligand exchange with additional styrene releases the alkylated pyridone **7** to close the catalytic cycle. The results of deuterium-labeling experiments in Scheme 6 suggest that the proton transfer process (**8** to **9**) is facile and reversible, and reductive elimination (**9** to **10**) is the irreversible rate-determining step. Although the exact role of K_3PO_4 is not clear at this stage, it can work as an additional anionic ligand to Ni[23] and accelerate the rate-limiting reductive elimination.

Given the reactivity trend of alkenes observed in Scheme 5, suitable binding nature to Ni center is essential for the successful reaction: highly strained norbornadienes and norbornene and moderately electronically activated styrene meet such a demand. In the case of 1,n-dienes, their bidentate coordination ability can be a major driving force.[24] However, the reaction pattern is dependent on the tether length; particularly, cod might be more tightly coordinated to Ni and second olefin moiety undergoes insertion into the alkyl–Ni bond of intermediate **11** following the proton transfer process (Scheme 8).

Scheme 7. Plausible Mechanism for Reaction of 1a with Styrene



Scheme 8. Proposed Pathway in Reaction of 1a with cod



Conclusion

We have developed a pyridine-directed, Ni-catalyzed C6-selective C–H alkylation of 2-pyridones with dienes and alkenes. The reaction proceeds under external-ligand-free conditions and is uniquely accelerated by the addition of K_3PO_4 base. Additionally, a non-trivial ring-contracting coupling with cod is observed. The Ni catalysis can provide additional access to relatively challenging C–H at the C6 position of 2-pyridone ring. Moreover, this is a rare example of Ni-catalyzed sp^2 C–H functionalizations by using monodentate directing groups.[25]

Experimental Section

Instrumentation and Chemicals ^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ NMR spectra were recorded at 400, 100, 376 MHz, respectively, for $CDCl_3$ or DMSO-d_6 solutions. Note: products **2**, **3"**, **5**, and **6** contained rotamers associated with the C–N axis, and thus ^{1}H and $^{13}C\{^{1}H\}$ NMR analysis of **2a**, **5**, and **6** were performed in DMSO-d_6 at higher temperature. HRMS data were obtained by APCI using TOF. GC analysis was carried out using a silicon OV-17 column (2.6 mm i.d. x 1.5 m) or a CBP-1 capillary column (0.5 mm i.d. x 25 m). TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel $60F_{254}$. Silica gel was used for column chromatography. Gel permeation chromatography (GPC) was performed with a $CHCl_3$ or an ethyl acetate eluent (UV detector). Unless otherwise noted, materials obtained from commercial suppliers were used as received. 1,4-Dioxane was dried on a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.) prior to use. The starting pyridones **1** were prepared according to the reported procedure.[12] The diastereomeric ratios of **2a**, **2b**, **2c**, **2d**, and **2a-Br$_2$** were assigned by ^{1}H or ^{19}F NMR spectrum. On the other hand, we could not determine the isomeric ratio of **2f**.

Preparation of 1a-d_1. 6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-[1,2'-bipyridin]-2-one (343 mg, 1.2 mmol) prepared by our previous method[13] and Cs_2CO_3 (562 mg, 1.7 mmol) were place in a 50 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. THF (6.0 mL) and D_2O (0.62 mL, 35 mmol) were injected via a syringe, and the mixture was stirred for 24 h at 40 □. The resulting mixture was allowed to cool to room temperature and then quenched with water. The mixture was extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, GPC purification with EtOAc eluent afforded 6-deuterio-2*H*-[1,2'-bipyridin]-2-one (**1a-d_1**; 115 mg, 0.66 mmol, 90-95% D) in 58% yield.

Typical Procedure for Ni-Catalyzed Alkylation of 2-Pyridones. The synthesis of **2a** is representative (Scheme 4). In a glovebox filled with nitrogen, 2*H*-[1,2'-bipyridine]-2-one (**1a**; 43 mg, 0.25 mmol), K_3PO_4 (106 mg, 0.50 mmol), and $Ni(cod)_2$ (14 mg, 0.050 mmol) were placed in a Schlenk flask. The flask was then sealed with a septum and taken out of the glovebox. 1,5-Cyclooctadiene (cod; 61 μL, 0.50 mmol) and 1,4-dioxane (1.5 mL) were sequentially injected via a syringe. The mixture was stirred for 4 h at 110 °C. The resulting mixture was allowed to cool to room temperature and then quenched with water. The mixture was extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) followed by GPC with $CHCl_3$ eluent afforded a 76:24 diastereomixture of 6-(octahydropentalen-1-yl)-2*H*-[1,2'-bipyridin]-2-one (**2a**; 45 mg, 0.16 mmol) in 64% yield.

A 76:24 diastereomixture of 6-((3a*R,6a*R**)-octahydropentalen-1-yl)-2*H*-[1,2'-bipyridin]-2-one (2a)**. Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC ($CHCl_3$); 45 mg (64%), white solid; mp 93.1-95.1 °C (from $CDCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6 at 60 ℃): δ 0.63 (br, 0.24×2H), 0.93-2.46 (m, 11H), 3.15-3.18 (m, 1.52H), 6.27 (dd, J = 1.0, 6.9 Hz, 0.24×1H), 6.29-6.34 (m, 0.24×1H and 0.76×2H), 7.43-7.54 (m, 0.76×3H and 0.24×3H), 8.01 (m, 0.76×1H and 0.24×1H), 8.63 (dd, J = 1.0, 5.0 Hz, 0.76×1H and 0.24×1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6 at 60 ℃): δ 23.7, 24.8, 25.0, 26.3, 26.4, 31.6, 31.7, 32.8, 32.9, 34.0, 34.69, 34.71, 41.3, 42.4, 48.3, 50.4, 101.7, 102.2, 116.9, 117.2, 123.8, 123.9, 124.2, 124.3, 138.3, 138.4, 140.3, 140.5, 148.9, 149.1, 151.7, 151.8, 152.7, 154.1, 162.3, 162.4. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{18}H_{21}N_2O$ 281.1648, found 281.1653.

An 82:18 diastereomixture of 6-((3a*R,6a*R**)-octahydropentalen-1-yl)-3-(trifluoromethyl)-2*H*-[1,2'-bipyridin]-2-one (2b)**.

Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent; 59 mg (68%), oil; ^1H and ^{13}C NMR spectra of **2b** are complicated by the presence of diastereomers and rotamers associated with the C-N axis. Thus, all observed signals are described. ^1H NMR (400 MHz, $CDCl_3$): δ 0.54-1.12 (m, 2H), 1.16-1.44 (m, 4H), 1.57-1.71 (m, 3H), 1.98-2.19 (m, 2H), 2.46-2.63 (m, 2H), 6.26-6.30 (m, 1H), 7.34-7.39 (m, 1H), 7.42-7.46 (m, 1H), 7.75-7.79 (m, 1H), 7.90-7.94 (m, 1H), 8.68 (d, *J* = 3.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 25.6, 27.0, 32.5, 32.8, 33.5, 33.6, 33.7, 34.6, 34.78, 34.81, 34.85, 35.5, 35.6, 39.6, 40.4, 42.0, 42.1, 43.3, 43.5, 49.0, 49.7, 50.9, 51.9, 101.3, 101.9, 122.92 (q, *J* = 269.8 Hz), 122.95 (q, *J* = 269.7 Hz), 124.1, 124.4, 124.5, 138.5, 138.7 (q, *J* = 2.5 Hz), 139.5 (q, *J* = 4.3 Hz), 149.8, 150.1, 151.0, 151.2, 158.4, 159.8, 160.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ -65.63, -65.58. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{19}H_{20}F_3N_2O$ 349.1522 , found 349.1529.

A 72:28 diastereomixture of 6-((3a*R,6a*R**)-octahydropentalen-1-yl)-4-(trifluoromethyl)-2*H*-[1,2'-bipyridin]-2-one (2c)**. Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent; 72 mg (83%), brown solid; mp 93.8-95.8 °C (from $CDCl_3$); ^{13}C NMR spectrum of **2c** is complicated by the presence of diastereomers and rotamers associated with the C-N axis. Thus, all observed signals are described. ^1H NMR (400 MHz, $CDCl_3$): δ 0.54-2.18 (m, 11H), 2.46-2.64 (m, 2H), 6.30 (d, *J* = 1.8 Hz, 0.28×1H), 6.32 (d, *J* = 1.7 Hz, 0.72×1H), 6.78 (d, *J* = 1.7 Hz, 0.72×1H), 6.80 (d, *J* = 1.8 Hz, 0.28×1H), 7.31-7.38 (m, 1H), 7.43-7.48 (m, 1H), 7.94 (ddd, *J* = 1.9, 7.7, 7.7 Hz, 1H), 8.69 (dd, *J* = 1.9, 4.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 25.5, 26.9, 32.4, 32.8, 33.4, 33.50, 33.53, 33.6, 34.6, 34.8, 35.5, 35.6, 39.6, 40.2, 41.8, 42.0, 43.1, 43.4, 48.9, 49.6, 50.9, 51.7, 98.0 (q, *J* = 12.2 Hz), 98.5 (q, *J* = 10.3 Hz), 115.5 (q, *J* = 3.7 Hz), 115.9 (q, *J* = 4.3 Hz), 122.4 (q, *J* = 272.6 Hz), 122.5 (q, *J* = 272.6 Hz), 123.9, 124.2, 124.4, 138.6, 138.8, 141.66 (q, *J* = 33.1 Hz), 141.70 (q, *J* = 33.2 Hz), 149.8, 150.1,

151.3, 151.4, 155.7, 157.1, 157.3, 163.0. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ -66.95, -66.87. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{19}H_{20}F_3N_2O$ 349.1522, found 349.1510.

An 84:16 diastereomixture of methyl 6-((3a*R,6a*R**)-octahydropentalen-1-yl)-2-oxo-2*H*-[1,2'-bipyridine]-4-carboxylate (2d)**. Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC ($CHCl_3$); 46 mg (55%), oil; ^{13}C NMR spectrum of **2d** is complicated by the presence of diastereomers and rotamers associated with the C-N axis. Thus, all observed signals are described. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88-1.02 (m, 1H), 1.15-1.82 (m, 8H), 1.96-2.36 (m, 2H), 2.50-2.60 (m, 2H), 3.93 (s, 3H), 6.70 (d, *J* = 1.4 Hz, 0.16×1H), 6.72 (d, *J* = 1.5 Hz, 0.84×1H), 7.13 (d, *J* = 1.5 Hz, 0.84×1H), 7.15 (d, *J* = 1.4 Hz, 0.16×1H), 7.32-7.38 (m, 1H), 7.41-7.44 (m, 1H), 7.92 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.68 (d, *J* = 2.3 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 25.5, 27.0, 32.4, 32.6, 32.8, 33.5, 33.6, 33.7, 34.7, 34.9, 35.6, 39.7, 39.8, 40.1, 42.0, 43.1, 43.3, 48.8, 49.5, 50.8, 51.7, 52.9, 101.3, 101.8, 120.0, 120.3, 124.0, 124.2, 138.5, 138.7, 140.86, 140.88, 149.8, 150.0, 151.7, 151.9, 154.0, 155.3, 155.5, 163.80, 163.84, 165.5, 165.6. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{20}H_{23}N_2O_3$ 339.1703, found 339.1709.

A diastereomixture of 4'-methyl-6-((3a*R,6a*R**)-octahydropentalen-1-yl)-2*H*-[1,2'-bipyridin]-2-one (2f)**. (The diastereometric ratio cannot be determined.). Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC ($CHCl_3$); 66 mg (90%), oil; ^{1}H and ^{13}C NMR spectra of **2f** are complicated by the presence of diastereomers and rotamers associated with the C-N axis. Thus, all observed signals are described. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.57-2.20 (m, 12H), 2.44-2.45 (m, 3H), 2.48-2.60 (m, 1H), 6.17-6.20 (m, 1H), 6.47-6.51 (m, 1H), 7.13-7.23 (m, 2H), 7.36 (ddd, *J* = 7.1, 9.5, 9.5 Hz, 1H), 8.51 (d, *J* = 4.8 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 21.2,

25.7, 27.1, 32.7, 32.9, 33.4, 33.6, 33.8, 33.9, 34.7, 35.0, 35.4, 40.0, 42.0, 42.2, 43.2, 43.4, 48.6, 49.2, 50.8, 51.9, 102.8, 103.3, 118.2, 118.6, 124.8, 125.09, 125.13, 140.2, 149.3, 149.6, 150.0, 150.1, 152.3, 152.4, 153.3, 164.1. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{19}H_{23}N_2O$ 295.1805, found 295.1817.

6-(Cyclopentylmethyl)-2*H*-[1,2'-bipyridin]-2-one (3). Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC ($CHCl_3$); 18 mg (28%), white solid; mp 105.8-107.8 ^oC (from $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (br, 2H), 1.43-1.53 (m, 4H), 1.59-1.66 (m, 2H), 1.89 (dt, *J* = 7.3, 7.9 Hz, 1H), 2.23 (d, *J* = 7.3 Hz, 2H), 6.12 (dd, *J* = 1.0, 7.0 Hz, 1H), 6.52 (dd, *J* = 1.0, 9.2 Hz, 1H), 7.33-7.37 (m, 2H), 7.41 (ddd, *J* = 1.0, 4.9, 7.6 Hz, 1H), 7.90 (ddd, *J* = 1.9, 7.6, 7.6 Hz, 1H), 8.67 (ddd, *J* = 1.0, 1.9, 4.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 24.9, 32.6, 37.9, 39.3, 105.8, 118.6, 124.1, 124.2, 138.6, 140.2, 149.5, 149.9, 152.0, 164.0. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{16}H_{19}N_2O$ 255.1492, found 255.1502.

6-(Hex-5-en-1-yl)-2*H*-[1,2'-bipyridin]-2-one (3'). Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC ($CHCl_3$); 9.0 mg (14%), white solid; mp 66.2-68.2 ^oC (from $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (dt, *J* = 7.3, 7.6 Hz, 2H), 1.44 (br, 2H), 1.92 (ddd, *J* = 6.8, 6.8, 7.4 Hz, 2H), 2.22 (t, *J* = 7.6 Hz, 2H), 4.90-4.95 (m, 2H), 5.69 (dddd, *J* = 6.8, 6.7, 10.4, 17.0, 1H), 6.11 (d, *J* = 6.9 Hz, 1H), 6.52 (d, *J* = 9.2 Hz, 1H), 7.33-7.37 (m, 2H), 7.41 (ddd, *J* = 1.0, 4.9, 7.6 Hz, 1H), 7.90 (ddd, *J* = 1.9, 7.6, 7.6 Hz, 1H), 8.67 (ddd, *J* = 1.0, 1.9, 4.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 27.3, 28.3, 32.9, 33.3, 105.1, 114.9, 118.7, 124.1, 124.2, 138.3, 138.6, 140.3, 149.9, 150.0, 151.9, 164.0. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{16}H_{19}N_2O$ 255.1492, found 255.1480.

6-(Hex-5-en-2-yl)-2*H*-[1,2'-bipyridin]-2-one (3''). Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC ($CHCl_3$); 27 mg (42%), oil; ^1H

and ^{13}C NMR spectra of **3''** are complicated by the presence of rotamers associated with the C-N axis. Thus, all observed signals are described. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (br, 1H), 1.18 (br, 1.4H), 1.43 (br, 1H), 1.60-1.65 (m, 1.6H), 1.86-2.00 (m, 2H), 2.18 (br, 1H), 4.83-4.92 (m, 2H), 5.47-5.59 (m, 1H), 6.14 (dd, *J* = 1.0, 7.0 Hz, 1H), 6.50 (dd, *J* = 1.0, 9.2 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.38-7.42 (m, 2H), 7.89 (ddd, *J* = 1.9, 7.8 Hz, 1H), 8.67 (dd, *J* = 1.9, 4.0 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 20.5, 31.3, 35.0, 35.1, 35.6, 36.1, 102.7, 102.9, 115.0, 115.2, 118.3, 123.9, 124.1, 124.4, 137.4, 137.7, 138.5, 138.6, 140.4, 150.0, 151.9, 155.5, 163.9. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{16}H_{19}N_2O$ 255.1492, found 255.1482.

6-(3-Methylpent-4-en-1-yl)-2*H*-[1,2'-bipyridin]-2-one (4). Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC ($CHCl_3$); 34 mg (54%), oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, *J* = 6.8 Hz, 3H), 1.42 (br, 2H), 1.65 (dddq, *J* = 6.8, 6.8, 6.9, 7.0 Hz, 1H), 2.13-2.28 (m, 2H), 4.79 (ddd, *J* = 1.0, 1.7, 10.3 Hz, 1H), 4.81-4.83 (m, 1H), 5.38 (ddd, *J* = 7.6, 10.3, 17.5 Hz, 1H), 6.10 (dd, *J* = 1.0, 6.9 Hz, 1H), 6.52 (dd, *J* = 1.0, 9.2 Hz, 1H), 7.32-7.36 (m, 2H), 7.41 (ddd, *J* = 1.0, 4.9, 7.6 Hz, 1H), 7.90 (ddd, *J* = 1.9, 7.6, 7.6 Hz, 1H), 8.67 (ddd, *J* = 1.0, 1.9, 4.9 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 20.0, 31.0, 35.0, 37.5, 105.3, 113.7, 118.7, 124.1, 124.3, 138.6, 140.3, 143.3, 150.0, 150.2, 151.9, 164.0. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{16}H_{19}N_2O$ 255.1492, found 255.1496.

6-((1*R,2*S**,4*R**)-Bicyclo[2.2.1]hept-5-en-2-yl)-2*H*-[1,2'-bipyridin]-2-one (5)**. White solid. Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC ($CHCl_3$); 38 mg (57%). mp 151.9-153.9 °C (from $CDCl_3$). X-ray quality crystals were grown from CH_2Cl_2/heptane. ^{1}H NMR (400 MHz, DMSO-d_6 at 120 °C): δ 0.78-0.83 (m, 1H), 1.37 (d, *J* = 8.7 Hz, 1H), 1.53-1.59 (m, 2H), 2.11 (dd, *J* = 5.0, 8.7 Hz, 1H), 2.85 (d, *J* = 2.7 Hz, 1H), 2.93 (d, *J* = 2.7 Hz, 1H), 5.89 (dd, *J* = 2.7, 5.5 Hz, 1H), 5.98 (dd, *J* = 2.7, 5.5 Hz, 1H), 6.25 (d, *J* = 7.3 Hz, 1H), 6.33

(d, J = 9.2 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.43-7.47 (m, 2H), 7.96 (ddd, J = 1.8, 7.8, 7.8 Hz, 1H), 8.59 (ddd, J = 1.0, 1.8, 5.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 at 120 ℃): δ 32.6, 40.1, 41.1, 45.3, 45.7, 101.4, 117.0, 123.2, 124.2, 135.7, 137.0, 137.6, 139.5, 148.5, 151.5, 153.3, 162.2. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{17}H_{17}N_2O$ 265.1335, found 265.1337.

6-((1*R,2*R**,4*S**)-Bicyclo[2.2.1]heptan-2-yl)-2*H*-[1,2'-bipyridin]-2-one (6)**. Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC ($CHCl_3$); 52 mg (78%), oil; ^1H NMR (400 MHz, DMSO-d_6 at 120 ℃): δ 0.65-0.69 (m, 1H), 0.88-0.99 (m, 1H), 1.06-1.16 (m, 2H), 1.28-1.45 (m, 2H), 1.47-1.54 (m, 2H), 2.18-2.22 (m, 2H), 2.34 (s, 1H), 6.18 (d, J = 7.3 Hz, 1H), 6.31 (d, J = 9.6 Hz, 1H), 7.39-7.50 (m, 3H), 7.98 (ddd, J = 1.4, 7.8, 7.8 Hz, 1H), 8.62 (d, J = 5.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6 at 120 ℃): δ 27.2, 29.0, 35.2, 35.3, 37.3, 40.9, 43.1, 101.2, 116.9, 123.2, 124.2, 137.6, 139.4, 148.6, 151.6, 153.6, 162.2. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{17}H_{19}N_2O$ 267.1492, found 267.1480.

6-(1-Phenylethyl)-2*H*-[1,2'-bipyridin]-2-one (7). Purified by column chromatography on silica gel with CH_2Cl_2/EtOAc/Et_3N (1/1/0.02, v/v/v) as an eluent followed by GPC (EtOAc); 48 mg (70%), oil; ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, J = 7.0 Hz, 3H), 3.96 (q, J = 7.0 Hz, 1H), 6.41 (d, J = 6.8 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 6.58-6.62 (m, 3H), 7.07-7.09 (m, 3H), 7.22-7.24 (m, 1H), 7.37 (dd, J = 6.3, 7.6 Hz, 1H), 7.47 (dd, J = 7.9, 8.1 Hz, 1H), 8.62 (d, J = 3.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 22.2, 41.7, 104.6, 119.7, 123.6, 125.5, 125.6, 126.8, 126.9, 128.6, 137.4, 139.9, 143.3, 149.1, 152.1, 164.0. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{18}H_{17}N_2O$ 277.1335, found 277.1353.

Typical Procedure for Dibromination of 2a. 1,3-Dibromo-5,5-dimethylhydantoin (53 mg, 0.18 mmol) was place in a 20 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. A 76:24 diastereomixture of

6-(octahydropentalen-1-yl)-2*H*-[1,2'-bipyridin]-2-one (**2a**; 43 mg, 0.15 mmol) in acetonitrile (1.5 mL) was injected via a syringe, and the mixture was stirred for 4 h at 100 □. The resulting mixture was allowed to cool to room temperature and then quenched with water. The mixture was extracted with EtOAc three times. The combined organic layer was dried over anhydrous Na_2SO_4. After concentration under reduced pressure, silica gel column purification with hexane/EtOAc/Et_3N (2/1/0.02, v/v/v) afforded a diastereomixture of 3,5-dibromo-6-(octahydropentalen-1-yl)-2*H*-[1,2'-bipyridin]-2-one (**2a-Br$_2$**; 35 mg, 0.080 mmol) in 52% yield. X-ray quality crystals were grown from CH_2Cl_2/heptane.

A 76:24 diastereomixture of 3,5-dibromo-6-((3a*R,6a*R**)-octahydropentalen-1-yl)-2*H*-[1,2'-bipyridin]-2-one (2a-Br$_2$)**. Purified by column chromatography on silica gel with hexane/EtOAc/Et_3N (2/1/0.02, v/v/v) as an eluent; 35 mg (52%), white solid; mp 165.8-167.8 ^oC (from CH_2Cl_2/heptane); ^1H and ^{13}C NMR spectra of **2a-Br$_2$** are complicated by the presence of diastereomers and rotamers associated with the C-N axis, and all observed signals are thus described. ^1H NMR (400 MHz, $CDCl_3$): δ 0.59-0.63 (m, 0.5H), 0.79-0.89 (m, 1H), 1.03-1.09 (m, 1H), 1.13-1.25 (m, 2H), 1.42-1.50 (m, 3H), 1.54 (br, 0.1H), 1.57-1.59 (m, 0.3H), 1.70 (br, 0.5H), 1.78-1.84 (m, 0.4H), 1.91-2.06 (m, 1.5H), 2.21-2.30 (m, 0.7H), 2.43-2.45 (m, 1H), 2.58-2.62 (m, 0.7H), 3.15-3.19 (m, 0.7H), 7.23-7.25 (m, 0.4H), 7.30-7.34 (m, 0.6H), 7.42-7.47 (m, 1H), 7.89-7.94 (m, 2H), 8.63-8.69 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 24.8, 27.1, 32.1, 32.6, 34.2, 34.8, 35.0, 36.0, 36.1, 42.4, 42.8, 44.2, 47.1, 47.3, 51.0, 51.6, 53.6, 97.9, 98.2, 114.2, 114.5, 123.3, 123.5, 124.3, 124.5, 124.6, 138.7, 138.9, 139.1, 147.2, 147.28, 147.33, 148.1, 149.4, 149.4, 150.2, 152.5, 152.597, 152.640, 159.27, 159.30. HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{18}H_{19}Br_2N_2O$ 436.9864, found 436.9848.

Associated Content

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Notes

The authors declare no competing financial interest.

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Supporting Information: ^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ NMR spectra for products, ORTEP drawings of **2a-Br$_2$** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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