JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

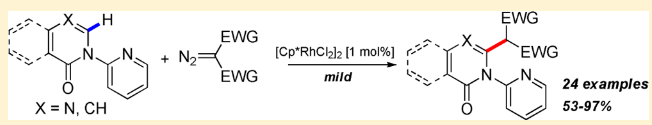
C6-Selective Direct Alkylation of Pyridones with Diazo Compounds under Rh(III)-Catalyzed Mild Conditions

Debapratim Das, Aniruddha Biswas, Ujjwal Karmakar, Santanu Chand, and Rajarshi Samanta*

Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721302, India

S Supporting Information

ABSTRACT: A Rh(III)-catalyzed highly efficient C6-alkylation of 2-pyridones has been achieved successfully with α-diazo carbonyl compounds. The developed method is simple, mild, and highly regioselective with a broad range of substrate scope. The regioselectivity is guided by the pyridyl substituent attached to the nitrogen center of the pyridone ring. The directing group can be easily removed, and the only formed byproduct is nitrogen. Furthermore, other similar heterocyclic scaffolds can also be functionalized regioselectively under the developed conditions.



■ INTRODUCTION

Regioselective direct functionalization of pyridone derivatives is a subject of great interest to synthetic and medicinal chemists due to its presence as the prevalent heterocyclic core structure in many pharmaceuticals and biologically active natural products (Figure 1).[1] In continuation of the recent advances in transition metal-catalyzed direct regioselective C−H bond functionalization,[2] a number of studies were carried out to directly introduce new carbon−carbon bonds regioselectively on pyridone derivatives.[3] Recently, the Hirano and Miura group developed C3-selective alkylation and arylation using catalytic Ni(0) or Mn(III) salt in stoichiometric amounts.[3a,b] Very recently, Maiti and co-workers demonstrated a user-friendly method for C3 arylation using an inexpensive iron catalyst and boronic acid as a coupling partner.[3c] A Pd(II)-catalyzed C3 arylation was achieved by Zografos and co-workers though the method is restricted to the 4-hydroxypyridone moiety.[3d] With a blocked C5 position, carbon−carbon bond formation was achieved at the C3 position of N-protected pyridone using Pd(II) catalysis.[3e,f,4b] After the leading discovery of palladium-mediated oxidative C5-alkenylation of the 2-pyridone moiety by Itahara and co-workers,[4a] recently its substoichiometric version was developed by the Li group.[4b] The Nakao and Hiyama group demonstrated the redox neutral, stereo-, and C6-selective direct alkenylation and alkylation of the 2-pyridone scaffold using seminal Ni(0)/Lewis acid cooperative catalysis (Scheme 1a).[5] Recently, in a great advancement, Miura and Hirano group reported a copper-mediated C6-selective dehydrogenative heteroarylation of 2-pyridones with 1,3-azoles (Scheme 1b).[6]

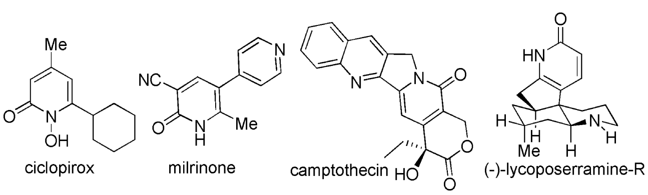
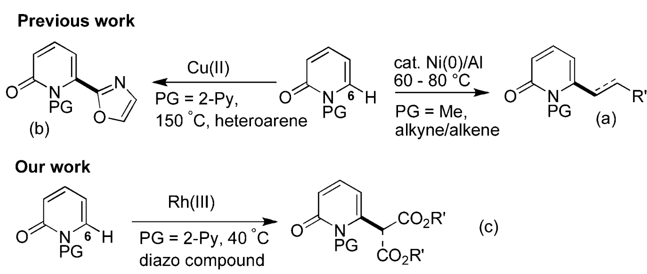


Figure 1. Pharmaceuticals and natural products having a C6-alkylated 2-pyridone core structure.

Scheme 1. C6-Selective Functionalization of 2-Pyridones



Concerted direct metal carbene insertion into unactivated C−H bonds represents a traditional approach.[7] Compared to the well studied classical reactions of carbenoid, C−H metalation, metal−carbene formation followed by migratory insertion with diazo compounds has not yet been well explored.[8] After the report by the Wang group on direct Cu(I)-catalyzed benzylation and allylation of 1,3-azoles with N-tosylhydrazones,[9] the Yu group published the pioneering work on ortho C−H alkylation of nonheteroarenes bearing a directing group with diazomalonates using Rh(III) catalysis in 2012.[10] Since then, promising progress has been observed in Rh(III)-catalyzed directed C−H alkylation using diazo compounds by various groups.[11]

Despite this advancement, mild C6-selective 2-pyridone alkylation is still challenging due to the use of drastic reaction conditions or nonremovable protecting groups. Given these restrictions and the notable importance of pyridone building

Received: October 9, 2015
Published: January 7, 2016

ACS Publications © 2016 American Chemical Society

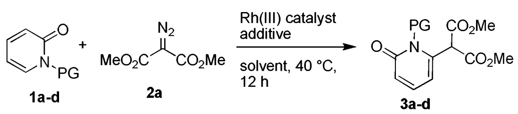
DOI: 10.1021/acs.joc.5b02349
J. Org. Chem. 2016, 81, 842−848

blocks, we started studies on the regioselective alkylation of pyridone scaffolds using diazo compounds as coupling partners. Herein we reveal the Rh(III)-catalyzed C6-selective direct alkylation of 2-pyridone using carbonyl-containing diazo compounds under mild[2c] conditions.

■ RESULTS AND DISCUSSION

Our synthetic attempt began with the search for optimal reaction conditions in the C6-alkylation of 2-pyridone. We investigated the reaction of N-protected 2-pyridone (**1**) with methyl diazomalonate (**2a**) in the presence of $[(Cp^*RhCl_2)_2]$ (1 mol %, Cp* = pentamethylcyclopentadiene) and $AgSbF_6$ (4 mol %) in 1,2-dichloroethane (DCE) at 40 °C. Methyl (**1a**), pivaloyl (**1b**), or carbamoyl (**1c**) as the protecting group did not provide our desired product. Gratifyingly, 1-(2-pyridyl)-2-pyridone (**1d**) afforded the desired C6-alkylated product (**3d**) in excellent yield (92%) (Table 1, entries 1−4).

Table 1. Optimization C6-Selective Alkylation of 2-Pyridones[a]



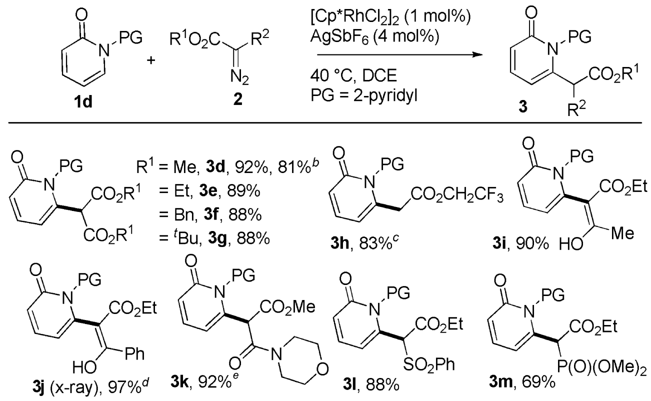
entry	PG	solvent	additive	yield[b]
1	Me (**1a**)	DCE	$AgSbF_6$	n.d.
2	Piv (**1b**)	DCE	$AgSbF_6$	n.d.
3	$CONMe_2$(**1c**)	DCE	$AgSbF_6$	n.d.
4	2-Py (**1d**)	DCE	$AgSbF_6$	92
5	2-Py	DMF	$AgSbF_6$	87
6	2-Py	*tert*-amyl alcohol	$AgSbF_6$	n.d.
7	2-Py	toluene	$AgSbF_6$	trace
8	2-Py	CH_3CN	$AgSbF_6$	67
9	2-Py	DCE	$AgNTf_2$	87
10	2-Py	DCE	$AgNO_3$	65
11	2-Py	DCE	$AgPF_6$	89
12	2-Py	DCE	AgOAc	trace
13	2-Py	DCE	$AgBF_4$	90
14[c]	2-Py	DCE	$AgSbF_6$	62

[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), $[Cp^*RhCl_2]_2$ (1 mol %), additive (4 mol %), 0.1 M. [b]Isolated yields. [c]Reaction conditions: $[Cp^*IrCl_2]_2$ (2 mol %), additive (8 mol %), 0.1 M at 80 °C. DCE = 1,2-dichloroethane. n.d. = not detected.

A change in other organic solvents did not improve the isolated yield; rather the yield was decreased (Table 1, entries 5−8). The isolated yields for the other screened halogen scavengers used as additives under mild conditions were also very impressive though the best was $AgSbF_6$ (Table 1, entries 9−13). Another transition metal catalyst $[(Cp^*IrCl_2)_2]$ was also examined (Table 1, entry 14) under more drastic conditions with lower isolated yield. However, the use of additional additive such as NaOAc in catalytic or stoichimetric amounts did not improve the highest isolated yield of the desired product under reduced reaction times (see Supporting Information optimization table for further details).

With the most favorable catalytic system established, we surveyed the scope and limitations of this reaction. Subsequently, the substrate scope of different diazo substrates was explored (Scheme 2). A number of diazomalonates worked smoothly in good to excellent yields (Scheme 2, **3d−h**). To our pleasure, a 13-fold increase in the starting material and 2-fold

Scheme 2. C6-Alkylation of 2-Pyridones with Different Diazo Compounds[a]



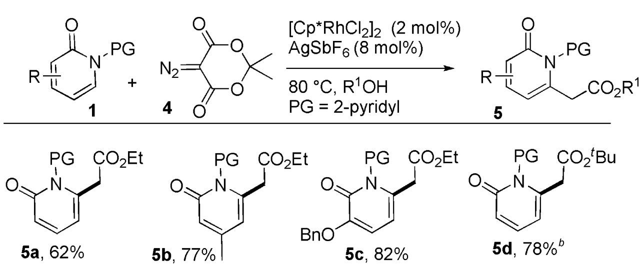
[a]Reaction conditions: **1d** (0.1 mmol), **2** (0.12 mmol), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (4 mol %), 0.1 M, 12 h. [b]Reaction conditions: **1d** (1.35 mmol), **2a** (1.62 mmol), $[Cp^*RhCl_2]_2$ (0.5 mol %), $AgSbF_6$ (2 mol %), 0.1 M at 40 °C for 36 h. [c]Reaction conditions: $[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), 0.1 M at 80 °C for 12 h. [d]Mixture of enol:keto = ∼1.4:1, [e]Reaction conditions: $[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), 0.1 M at 100 °C for 24 h.

decrease in catalyst loading provided an impressive turnover with little increase in reaction time (Scheme 2, **3d**). In general, there is not much difference in yield for electronically variable diazo substrates though when bis(2,2,2-trifluoroethyl)2-diazomalonate was used as a coupling partner, a large amount of decarboxylated product was obtained with the desired product. But elevation of reaction temperature (80 °C) offered solely the decarboxylated product in very good yield (Scheme 2, **3h**). Efficient couplings with diazo keto compounds were also observed (Scheme 2, **3i−j**) under optimized conditions. Additionally, moderate to excellent yield was also obtained when one of the ester groups of the diazomalonate was changed to another electron-deficient group such as amide, sulfonyl, or phosphonate (Scheme 2, **3k−m**).

When α-diazotized Meldrum's acid (**4**) was used as a coupling partner, the reaction proceeded smoothly to the final decarboxylated product (Scheme 3, **5a−d**).[11b,k] Depending upon the alcohol used as solvent, different 6-acetate substituted pyridones were obtained in moderate to good yield (Scheme 3, **5d**).

Satisfactorily, electronically, and sterically variable substituents at the C3, C4, or C5 position of the 2-pyridone scaffold

Scheme 3. C6-Alkylation of 2-Pyridones with the Diazo Derivative of Meldrum's Acid[a]

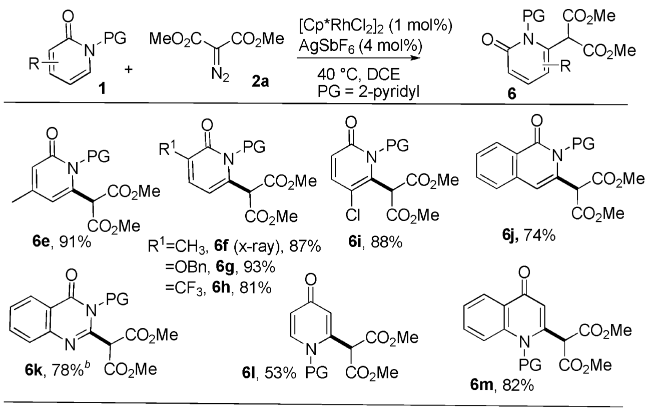


[a]Reaction conditions: **1** (0.1 mmol), **4** (0.12 mmol), $[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), EtOH (0.1 M) at 80 °C for 12 h. [b]The solvent used was ^{t}BuOH.

DOI: 10.1021/acs.joc.5b02349
J. Org. Chem. 2016, 81, 842−848

were well tolerated during the transformation (Scheme 4, **6e**–**i**). An electron-donating group at the C3 position of the 2-

Scheme 4. Regioselective Alkylation of Various Heterocycles with Diazomalonate[a]

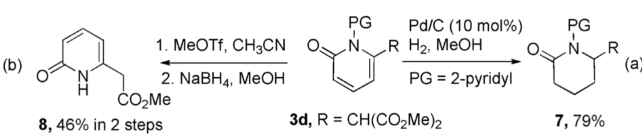


[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), $[Cp^*RhCl_2]_2$ (1 mol %), $AgSbF_6$ (4 mol %), 0.1 M, 12–24 h. [b]Reaction conditions: $[Cp^*RhCl_2]_2$ (2 mol %), $AgSbF_6$ (8 mol %), 0.1 M at 80 °C for 12 h.

pyridone scaffolds (Scheme 4, **6f**, **6g**) works relatively better than an electron-withdrawing group at the same position (Scheme 4, **6h**). To our delight, isoquinolone and quinazolone derivatives also provided the respective alkylated product in good yields (Scheme 4, **6j**–**k**). Though a wide investigation of direct functionalization on enaminone systems was carried out,[12] the transition metal-catalyzed regioselective direct functionalization of quinolones, a privileged motif present in numerous bioactive compounds, is a topic of recent interest.[13] With our optimized catalytic conditions, 2-pyridyl-protected 4-pyridone and quinolone scaffolds were also directly alkylated at its C2 position to provide the corresponding products (Scheme 4, **6l** and **6m**) in moderate to good yield. Interestingly, in the case of quinolone there was no C8 alkylation observed.

Furthermore, hydrogenation of **3d** offered biologically relevant C6-alkylated piperidin-2-one derivative **7**[14] in 79% yield (Scheme 5a). Finally, the 2-pyridyl directing group was

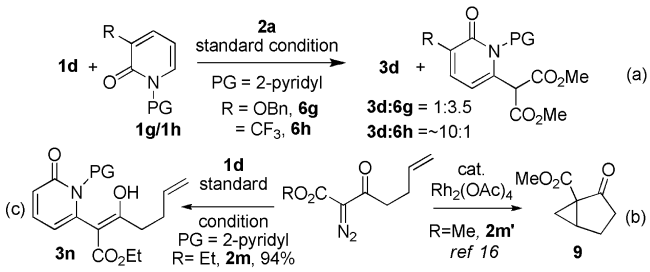
Scheme 5. Transformation of Product Molecule



removed from **3d** via the two-step quaternization–hydride reduction[15] process at room temperature to provide decarboxylated product **8** in acceptable yield with some N-methylated quaternized starting material (Scheme 5b).

To elucidate the reaction mechanism, several control experiments were carried out. First, a H/D scrambling in DCE/D_2O revealed a reversible C–H bond cleavage in the absence of **2a** (see the Supporting Information for details). When **1d** and **1g** were allowed to react with **2a** under standard conditions, the reaction favored the formation of **6g** over **3d** in a 3.5:1 ratio. In a similar fashion, when **1d** and **1h** were used in an intermolecular competition experiment with **2a**, the product ratio of **3d**:**6h** was ~10:1 which suggested more electron-rich 2-pyridone is kinetically favored and the reaction might proceed through an electrophilic mode of activation (Scheme 6a).

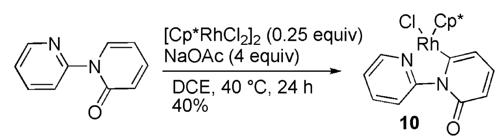
Scheme 6. Control Experiments



In 2002, Sieburth and co-workers demonstrated that **2m′** was a capable substrate to provide cyclopropane **9** under $Rh_2(OAc)_4$ catalysis (Scheme 6b)[16] whereas, under our optimized conditions, we found that **2m** was efficiently giving product **3n** in 94% yield (Scheme 6c).[11c] This can be rationalized when the C–H metalation step is much faster than the metal–carbene formation under our developed conditions.

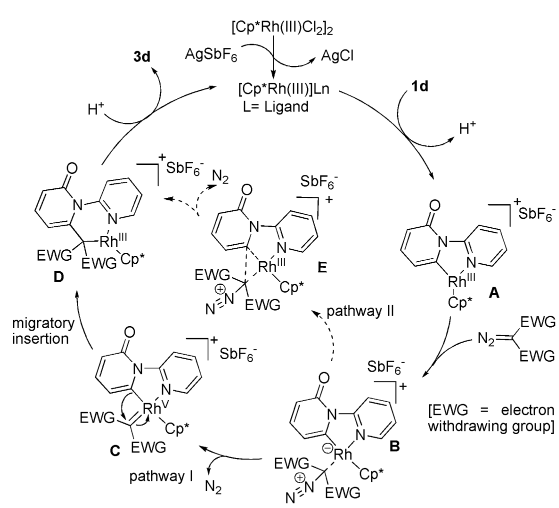
Again we investigated the possibility of a rhodacycle species as an intermediate in the plausible diazomalonate insertion process. A stable cyclometalated Rh(III) complex **10** was prepared through the Jones protocol[17] (Scheme 7). Thus,

Scheme 7. Synthesis of a Stable Rhodacycle



catalytic activity of complex **10** was examined under the previously optimized alkylation conditions. Additionally, stoichiometric conversion of the rhodacycle **10** to compound **3d** was also scrutinized. Gratifyingly, in both cases the desired product formed in excellent yield (see Experimental Section for more details). Based on previous reports[8,10,11,18] and our preliminarily mechanistic experiments, a plausible alkylation pathway is proposed (Scheme 8).

Scheme 8. Proposed Mechanism



DOI: 10.1021/acs.joc.5b02349
J. Org. Chem. 2016, 81, 842–848

First, a cationic Rh(III) catalyst, generated with the help of Ag salt, coordinates to the pyridine nitrogen atom and undergoes electrophilic C−H bond cleavage to form rhodacyclic intermediate **A**. Coordination of the diazonium species to **A** leads to intermediate **B**. Then, via a redox active pathway (pathway I), extrusion of N_2 from **B** provides metal−carbenoid species **C**. Subsequently, the six-membered rhodacycle **D** is obtained from **C** through migratory insertion.

In an alternative redox neutral route (pathway II), species **B** forms intermediate **D** through **E** where alkyl insertion coincides with the loss of N_2 without formation of a distinct metal−carbenoid species. The detailed mechanism of the diazo coupling remains unclear at this stage. Finally, protonation of **D** produces the desired alkylated product with the active Rh(III) catalyst.

CONCLUSION

In summary, we have developed a simple, efficient Rh(III)-catalyzed direct C6-selective C−H alkylation of 2-pyridones with α-diazo compounds under mild conditions. The reaction proceeded with excellent regioselectivity and functional group tolerance. The only byproduct is environmentally benign N_2. The protocol also enables the alkylation of other biologically relevant heterocycles. Furthermore, the footprint of the directing group can smoothly be removed after operation. Current efforts are directed to the total syntheses of natural products having these important heterocyclic scaffolds using the developed method.

EXPERIMENTAL SECTION

General Procedure for Synthesis of Substituted 1-(2-Pyridyl)-2-pyridones.[19] Substituted 2-hydroxypyridine (1 mmol), copper(I) iodide (10 mol %), and potassium carbonate (1 mmol) were added to DMSO (2 mL), and then 2-bromopyridine (2 mmol) was added. The mixture was stirred at 150 °C for 12 h under nitrogen atmosphere. The resulting mixture was allowed to cool to room temperature and then quenched with water. Extraction with ethyl acetate, concentration under reduced pressure, and silica gel column purification with hexane/ethyl acetate afforded 2*H*-[1,2′-bipyridin]-2-one in 50−90% yield.

General Procedure for Synthesis of Diazomalonates.[20] Malonate (1 mmol) was dissolved in dry THF (10 mL), and then Cs_2CO_3 (1 mmol) followed by tosyl azide (1 mmol) was added to it dropwise at room temperature. The reaction was stirred overnight at the same temperature. After completion of the reaction, solvent was evaporated under vacuum. Then the diazomalonates were purified by silica gel column chromatography using hexane/ethyl acetate.

General Procedure for Rhodium(III)-Catalyzed C-6-Selective Alkylation of 2-Pyridones with Diazomalonates. 1-(2-Pyridyl)-2-pyridone (0.1 mmol) was dissolved in 1 mL of dry 1,2-DCE in a 10 mL screw cap vial. Then [(Cp*$RhCl_2)_2$] (1 mol %), $AgSbF_6$ (4 mol %), and dialkyl 2-diazomalonate (0.12 mmol) were added to the reaction mixture at room temperature. Then the reaction mixture was allowed to warm to 40 °C to 100 °C and stirred 6−24 h. After completion of the reaction, the reaction mixture was directly loaded to a silica gel column and fractionated with hexane/ethyl acetate.

Rhodium(III)-Catalyzed C-6-Selective Alkylation of 2-Pyridones with 5-Diazo-2,2-dimethyl-1,3-dioxane-4,6-dione. Substituted 1-(2-pyridyl)-2-pyridone (0.1 mmol) was dissolved in 1 mL of dry alcohol in a 10 mL screw cap vial. Then [(Cp*$RhCl_2)_2$] (2 mol %), $AgSbF_6$ (8 mol %), and 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (0.12 mmol) were added to the reaction mixture at room temperature. Then the reaction mixture was allowed to warm to 100 °C and stirred 12 h. After completion of the reaction, the product was purified by flash chromatography using hexane/ethyl acetate.

Procedure for the Synthesis of Compound 8: Removal of Directing Group.[15] Dimethyl 2-(2-oxo-2*H*-[1,2′-bipyridin]-6-yl)-malonate (**3d**) (120.8 mg, 0.4 mmol) was dissolved in 5 mL of CH_3CN in a 25 mL round-bottom flask, filled with nitrogen. It was cooled to 0 °C. Then MeOTf (66 μL, 0.6 mmol) was added to it. The reaction mixture was allowed to warm to room temperature and stirred 20 h. Volatile materials were evaporated off in vacuum. The residue was dissolved in 5 mL of methanol and cooled to 0 °C. Then $NaBH_4$ (60.5 mg, 1.6 mmol) was added, and the flask was filled with nitrogen again. The reaction mixture was allowed to warm to room temperature and stirred 6 h. The reaction mixture was quenched with water and extracted with ethyl acetate. Organic layer was dried over sodium sulfate, filtered, and concentrated in vaccuo. The product was purified by flash chromatography using NH-bound silica using ethyl acetae/hexane mixture as solvent. Purification afforded methyl 2-(6-oxo-1,6-dihydropyridin-2-yl)acetate (**8**) in 46% yield.

Synthesis of Dimethyl 2-(6-Oxo-1-(pyridin-2-yl)piperidin-2-yl)malonate by Hydrogenation.[14] Dimethyl 2-(2-oxo-2*H*-[1,2′-bipyridin]-6-yl)malonate (**3d**) (30.2 mg, 0.1 mmol) was added to methanol in a 25 mL round-bottom flask charged with a magnetic stir bar and filled with nitrogen. Then palladium on carbon was added (10 mol %) to it. The round-bottom flask was evacuated, filled with H_2 gas, and stirred 45 min. The reaction mixture was filtered through a Celite pad and washed with 10 mL of ethyl acetate. The entire organic solution was concentrated in vacuo. The desired product was purified by flash column chromatography using ethyl acetae/hexane mixture as solvent. Purification afforded 2-(6-oxo-1-(pyridin-2-yl)piperidin-2-yl)-malonate (**7**) in 79% yield.

Synthesis of Rhodacycle Complex 10.[17] 1-(2-Pyridyl)-2-pyridone (**1d**) (34.4 mg, 0.2 mmol), [(Cp*$RhCl_2)_2$] (30.9 mg, 0.05 mmol, 0.25 equiv), and NaOAc (65.6 mg, 0.8 mmol, 4 equiv) were placed in a screw cap vial, and then 2 mL of 1,2-DCE was added to it. The reaction mixture was stirred at 40 °C for 24 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated under reduced pressure. The solid residue was washed with dry diethyl ether (2 mL) five times and then dried under vacuum to give a brick-red solid complex (**10**) (40%). The rhodium complex was characterized through analytical data.

Catalytic Alkylation Using Rhodacycle Complex 10. 1-(2-Pyridyl)-2-pyridone (**1d**) (17.2 mg, 0.1 mmol), dimethyl 2-diazomalonate (**2a**) (19 mg, 0.12 mmol), complex **10** (2 mol %), $AgSbF_6$ (8 mol %), and 1 mL of 1,2-DCE were added to a 10 mL screw cap vial, and the reaction was stirred at 40 °C for 12 h. After completion of the reaction, product was isolated through column chromatography using ethyl acetate/hexane mixture as solvent in 94% yield.

Stoichiometric Alkylation with Dimethyl 2-Azomalonates. To a 10 mL screw cap vial were added 8.88 mg of intermediate complex **10** (0.02 mmol) and 6.9 mg of $AgSbF_6$ (0.02 mmol), and then the mixture was dissolved in 0.5 mL of 1,2-DCE under atmospheric conditions. Then 5 mg of dimethyl 2-azomalonate (0.024 mmol) was added to the reaction mixture. The mixture was stirred at 40 °C for 30 min. The crude mixture was quenched 5 N HCl (aq) followed by aq $NaHCO_3$. The organic layer was separated and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure, and product (**3d**) was separated by flash chromatography using ethyl acetae/hexane mixture as solvent in 86% yield.

Competition Experiments for C−H Metalation vs Metal Carbene Formation.[11c] **2m′** is well-known as a precursor of cyclopropane (**9**) in the presence of catalytic $Rh_2(OAc)_4$. But when 1-(2-pyridyl)-2-pyridone (**1d**) was employed under the standard condition with **2m**, **3n** formed exclusively in 94% yield. This proves that the C−H metalation step is much faster than metal−carbene formation in the catalytic cycle.

Dimethyl 2-(2-Oxo-2*H*-[1,2′-bipyridin]-6-yl)malonate (3d). Yellow oil, 27.8 mg (92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.7 Hz, 1H), 7.85 (t, *J* = 7.7, 1H), 7.37 (m, 3H), 6.61 (d, *J* = 9.3 Hz, 1H), 6.30 (d, *J* = 7.0 Hz, 1H), 4.31 (s, 1H), 3.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.1, 150.7, 149.9, 140, 139.8, 138.7, 124.7, 124.5, 121.4, 107.2, 55.0, 53.3. FT-IR: $\tilde{\nu}$ = 3054, 2957, 2927, 2854, 1766, 1734, 1678, 1605, 1545, 1469, 1437, 1396, 1297,

DOI: 10.1021/acs.joc.5b02349
J. Org. Chem. 2016, 81, 842−848

1248, 1205 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{15}H_{15}N_2O_5$: 303.0981, found: 303.1007.

Diethyl 2-(2-Oxo-2*H*-[1,2′-bipyridin]-6-yl)malonate (3e). Yellow oil, 29.4 mg (89%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (m, 1H), 7.84 (td, *J* = 7.8, 2.0 Hz, 1H), 7.41−7.35 (m, 2H), 7.33 (dt, *J* = 7.8, 1.2 Hz, 1H), 6.61 (dd, *J* = 9.4, 1.2 Hz, 1H), 6.31 (dd, *J* = 7.1, 1.2 Hz, 1H), 4.28 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 4H), 1.17 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 163.2, 150.7, 149.9, 140.3, 139.8, 138.6, 124.8, 124.4, 121.2, 107.2, 62.5, 55.3, 13.9; FT-IR: $\tilde{\nu}$ = 3059, 2984, 2927, 2738, 1674, 1602, 1548, 1468, 1435, 1395, 1369, 1308, 1243, 1209 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{17}H_{19}N_2O_5$: 331.1294, found 331.1334.

Dibenzyl 2-(2-Oxo-2*H*-[1,2′-bipyridin]-6-yl)malonate (3f). Yellow oil, 40.0 mg (88%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.70 (td, *J* = 7.7, 1.9 Hz, 1H), 7.42−7.21 (m, 13H), 6.66 (dd, *J* = 9.3, 1.2 Hz, 1H), 6.26 (dd, *J* = 7.1, 1.2 Hz, 1H), 5.20−5.08 (m, 4H), 4.44 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 163.1, 150.6, 149.8, 139.9, 139.7, 138.6, 134.6, 128.7, 128.6, 128.6, 124.7, 124.3, 121.4, 107.4, 68.1, 55.3; FT-IR: $\tilde{\nu}$ = 3063, 3035, 2959, 1738, 1674, 1588, 1498, 1466, 1456, 1434, 1396, 1377, 1304, 1237, 1271, 1211 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{27}H_{23}N_2O_5$: 455.1607, found 455.1615.

Di-^{t}butyl 2-(2-Oxo-2*H*-[1,2′-bipyridin]-6-yl)malonate (3g). Pale yellow oil, 34.0 mg, (88%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 4.9, 1.9 Hz, 1H), 7.88 (td, *J* = 7.8, 1.9 Hz, 1H), 7.50−7.32 (m, 3H), 6.64 (dd, *J* = 9.3, 1.1 Hz, 1H), 6.37 (dd, *J* = 7.1, 1.1 Hz, 1H), 4.14 (s, 1H), 1.42 (s, 18H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 163.4, 151.1, 149.9, 141.3, 139.9, 138.6, 125, 124.3, 121, 106.8, 83.2, 57.4, 27.8; FT-IR: $\tilde{\nu}$ = 2980, 1731, 1675, 1602, 1548, 1467, 1435, 1395, 1370, 1313, 1250 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{21}H_{27}N_2O_5$: 387.1920, found 387.1918.

2,2,2-Trifluoroethyl 2-(2-Oxo-2*H*-[1,2′-bipyridin]-6-yl)-acetate (3h). Pale brown solid, 25.8 mg (83%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 7.87 (td, *J* = 7.7, 1.9 Hz, 1H), 7.46−7.33 (m, 3H), 6.64 (dd, *J* = 9.4, 1.3 Hz, 1H), 6.22 (dd, *J* = 6.8, 1.2 Hz, 1H), 4.31 (q, *J* = 8.4 Hz, 2H), 3.51 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 163.5, 151.1, 149.8, 140.3, 140.0, 138.6, 124.8, 124.4, 122.6 (q, *J* = 278 Hz), 121.3, 108.8, 61.0 (q, *J* = 37.1 Hz), 38.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.6; FT-IR: $\tilde{\nu}$ = 1758, 1670, 1596, 1421, 1269 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{14}H_{12}F_3N_2O_3$: 313.0800, found 313.0793.

Ethyl 3-Hydroxy-2-(2-oxo-2*H*-[1,2′-bipyridin]-6-yl)but-2-enoate (3i). White solid, 27.0 mg (90%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.70 (s, 1H), 8.51 (dd, *J* = 5.1, 1.9 Hz, 1H), 7.75 (td, *J* = 7.7, 1.9 Hz, 1H), 7.39 (dd, *J* = 9.3, 6.7 Hz, 1H), 7.28 (m, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 6.64 (dd, *J* = 9.3, 1.2 Hz, 1H), 6.13 (dd, *J* = 6.7, 1.2 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.00 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9, 170.6, 163.8, 152.1, 149.6, 142.6, 140.0, 137.9, 123.9, 123.2, 121.1, 109.8, 99.1, 61.1, 20.6, 14.3; FT-IR: $\tilde{\nu}$ = 2984, 1667, 1644, 1595, 1548, 1467, 1434, 1382, 1337, 1277, 1234 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{16}H_{17}N_2O_4$: 301.1188, found 301.1171.

(*E*)-Ethyl 3-Hydroxy-2-(2-oxo-2*H*-[1,2′-bipyridin]-6-yl)-3-phenylacrylate Compound and Ethyl 3-Oxo-2-(2-oxo-2*H*-[1,2′-bipyridin]-6-yl)-3-phenylpropanoate (1.37:1) (3j). Yellow solid, 35.1 mg (97%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.37 (s, 1H), 8.65 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.46 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.95−7.80 (m, 2H), 7.77−7.65 (m, 3H), 7.59−7.53 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.40−7.34 (m, 3H), 7.33−7.28 (m, 3H), 7.26−7.22 (m, 2H), 7.05 (s, 1H), 6.61 (ddd, *J* = 10.5, 9.2, 1.2 Hz, 2H), 6.19−6.06 (m, 1H), 6.06−5.93 (m, 1H), 5.31 (s, 1H), 4.19 (m, 1H), 4.10 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.2, 173.2, 173.1, 171.4, 166.6, 163.8, 151.8, 151.1, 150.1, 149.0, 139.9, 139.8, 137.1, 134.2, 130.9, 129, 128.9, 128.0, 124.8, 124.5, 123.6, 121.3, 120.7, 111.5, 108.2, 99.2, 98.9, 62.3, 61.5, 57.7, 14.2, 14.0; FT-IR: $\tilde{\nu}$ = 3056, 2928, 2854, 1743, 1665, 1613, 1595, 1584, 1545, 1492, 1468, 1446, 1434, 1408, 1372, 1316, 1291, 1273, 1228 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{21}H_{19}N_2O_4$: 363.1345, found 363.1340.

Methyl 3-Morpholino-3-oxo-2-(6-oxo-1-(pyridin-2-yl)-1,6-dihydropyridin-2-yl)propanoate (3k). Pale yellow solid, 32.8 mg (92%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.9, 2, 0.9 Hz, 1H), 7.89 (td, *J* = 7.7, 2.0 Hz, 1H), 7.48−7.39 (m, 2H), 7.34−7.28 (m, 1H), 6.67 (dd, *J* = 9.4, 1.2 Hz, 1H), 6.27 (dd, *J* = 7.0, 1.2 Hz, 1H), 4.60 (s, 1H), 3.70 (m, 2H), 3.67−3.57 (m, 5H), 3.54−3.44 (m, 2H), 3.42−3.28 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.9, 164.4, 163.3, 151.1, 150.1, 140.4, 139.9, 139, 125, 124.8, 121.8, 107.1, 66.6, 66.3, 53.7, 53.2, 46.7, 42.8; FT-IR: $\tilde{\nu}$ = 3040, 2946.5, 2858.8, 1742.9, 1651.9, 1598, 1547, 1436, 1253 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{18}H_{20}N_3O_5$: 358.1403, found 358.1407.

Ethyl 2-(2-Oxo-2*H*-[1,2′-bipyridin]-6-yl)-2-(phenylsulfonyl)-acetate (3l). White solid, 35.1 mg (88%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.85 (td, *J* = 7.8, 1.9 Hz, 1H), 7.67 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.53−7.46 (m, 2H), 7.43−7.37 (m, 2H), 7.15 (dt, *J* = 8, 1.1 Hz, 1H), 6.90 (dd, *J* = 7.1, 0.9 Hz, 1H), 6.67 (dd, *J* = 9.3, 1.1 Hz, 1H), 4.74 (s, 1H), 4.16 (qd, *J* = 7.1, 2.6 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 162.4, 150.4, 149.9, 139.2, 138.6, 137.0, 134.9, 134.7, 129.6, 129.2, 125.5, 124.5, 123.1, 110.4, 69.7, 63.4, 13.9; FT-IR: $\tilde{\nu}$ = 2985, 1745, 1674, 1600, 1543, 1466, 1448, 1435, 1395, 1368, 1312, 1237 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{20}H_{18}N_2O_5S$: 399.1014, found 399.0997.

Ethyl 2-(Dimethoxyphosphoryl)-2-(2-oxo-2*H*-[1,2′-bipyridin]-6-yl)acetate (3m). Brown oil, 25.2 mg (69%); ^{1}H NMR (600 MHz, $CDCl_3$) δ8.64 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.89 (td, *J* = 7.7, 2.0 Hz, 1H), 7.42 (dt, *J* = 7.4, 5.6 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 6.86 (dd, *J* = 7.4, 2.8 Hz, 1H), 6.62 (d, *J* = 9.4 Hz, 1H), 4.23−4.08 (m, 2H), 3.84 (d, *J* = 25.9 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1 (d, *J* = 4.3 Hz), 163.5, 151.1, 150.1, 139.8 (d, *J* = 3.1 Hz), 138.8, 138.2 (d, *J* = 3.9 Hz), 124.8, 124.6, 121.3, 108.8 (d, *J* = 6.1 Hz), 62.8, 54.3 (d, *J* = 6.8 Hz), 54.1 (d, *J* = 6.8 Hz), 47.8 (d, *J* = 137.1 Hz), 14.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.1; FT-IR: $\tilde{\nu}$ = 3058, 2959, 2854, 1737, 1671, 1596, 1544, 1467, 1435, 1394, 1367, 1302, 1241, 1210 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{16}H_{20}N_2O_6P$: 367.1059, found 367.1048.

(*E*)-Ethyl 3-Hydroxy-2-(6-oxo-1-(pyridin-2-yl)-1,6-dihydropyridin-2-yl)hepta-2,6-dienoate (3n). Pale yellow oil, 31.9 mg (94%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.83 (s, 1H), 8.51 (m, 1H), 7.75 (td, *J* = 7.7, 1.9 Hz, 1H), 7.40 (dd, *J* = 9.4, 6.8 Hz, 1H), 7.29 (ddd, *J* = 7.7, 4.8, 1.1 Hz, 1H), 7.23 (dt, *J* = 7.9, 1.1 Hz, 1H), 6.66 (dd, *J* = 9.4, 1.2 Hz, 1H), 6.12 (dd, *J* = 6.8, 1.2 Hz, 1H), 5.77 (m, 1H), 5.11−4.92 (m, 2H), 4.11 (qd, *J* = 7.2, 1.8 Hz, 2H), 2.50−2.23 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 163.9, 152.1, 150, 149.5, 142.3, 139.9, 137.8, 137, 124, 123.3, 121.2, 115.8, 110.1, 98.9, 61.2, 33.3, 29.9, 14.3; FT-IR: $\tilde{\nu}$ = 2986, 2366, 1665, 1411, 1377, 1343, 1269, 1234 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{19}H_{21}N_2O_4$: 341.1501, found 341.1498.

Ethyl 2-(2-Oxo-2*H*-[1,2′-bipyridin]-6-yl)acetate (5a). Pale yellow oil, 16.0 mg (62%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73−8.53 (m, 1H), 7.86 (td, *J* = 7.7, 2.0 Hz, 1H), 7.44−7.31 (m, 3H), 6.62 (d, *J* = 9.4 Hz, 1H), 6.20 (d, *J* = 6.7 Hz, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.41 (s, 2H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.6, 163.6, 151.4, 149.8, 141.8, 140.1, 138.4, 125, 124.3, 120.7, 108.4, 61.5, 39.6, 14.1; FT-IR: $\tilde{\nu}$ = 3058, 2983, 1734, 1669, 1596, 1549, 1467, 1435, 1396, 1369, 1333, 1297, 1276, 1248 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{14}H_{15}N_2O_3$: 259.1082, found 259.1075.

Ethyl 2-(4-Methyl-2-oxo-2*H*-[1,2′-bipyridin]-6-yl)acetate (5b). Yellow oil, 20.9 mg (77%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68−8.53 (m, 1H), 7.84 (td, *J* = 7.7, 2.0 Hz, 1H), 7.37 (dd, *J* = 7.7, 3.3 Hz, 2H), 6.42 (s, 1H), 6.05 (s, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 3.38 (s, 2H), 2.21 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8, 163.6, 151.8, 151.3, 149.7, 140.4, 138.3, 125.1, 124.1, 118.8, 111.3, 61.5, 39.5, 21.6, 14.1; FT-IR: $\tilde{\nu}$ = 2983, 1735, 1670, 1549, 1467, 1436, 1361, 1329, 1246, 1219 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{15}H_{17}N_2O_3$: 273.1239, found 273.1241.

Ethyl 2-(3-(Benzyloxy)-2-oxo-2*H*-[1,2′-bipyridin]-6-yl)-acetate (5c). Yellow oil, 29.8 mg (82%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68−8.55 (m, 1H), 7.85 (t, *J* = 7.7 Hz, 1H), 7.45−7.28 (m, 7H), 6.70 (d, *J* = 7.7 Hz, 1H), 6.05 (d, *J* = 7.7 Hz, 1H), 5.15 (s, 2H),

DOI: 10.1021/acs.joc.5b02349
J. Org. Chem. 2016, 81, 842−848

3.94 (q, J = 7.2 Hz, 2H), 3.35 (s, 2H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 159.3, 151.3, 149.7, 148.4, 138.3, 136.4, 132.9, 128.7, 128.1, 127.4, 125.1, 124.2, 116.5, 107.2, 71, 61.4, 39.1, 14.1; FT-IR: $\tilde{\nu}$ = 2927, 1735, 1664, 1611, 1467, 1436, 1284, 1220 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{21}H_{21}N_2O_4$: 365.1501, found 365.1497.

^{t}-Butyl 2-(2-Oxo-2*H*-[1,2′-bipyridin]-6-yl)acetate (5d). Yellow oil, 22.3 mg (78%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.71−8.59 (m, 1H), 7.88(dt, J = 7.5, 4.5 Hz, 1H), 7.40 (m, 3H), 6.62 (d, J = 9.4 Hz, 1H), 6.20 (d, J = 6.9 Hz, 1H), 3.35 (s, 2H), 1.32 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 163.7, 151.5, 149.8, 142.2, 140.1, 138.5, 125.1, 124.2, 120.5, 108.3, 82.0, 40.6, 28.0; FT-IR: $\tilde{\nu}$ = 2979, 2931, 1734, 1671, 1598, 1550, 1467, 1435, 1395, 1369, 1334, 1275, 1252, 1208 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{16}H_{19}N_2O_3$: 287.1395, found 287.1399.

Dimethyl 2-(4-Methyl-2-oxo-2*H*-[1,2′-bipyridin]-6-yl)-malonate (6e). Yellow oil, 28.7 mg (91%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69−8.52 (m, 1H), 7.84 (td, J = 7.7, 1.9 Hz, 1H), 7.45−7.29 (m, 2H), 6.44 (s, 1H), 6.16 (s, 1H), 4.32 (s, 1H), 3.68 (s, 6H), 2.21 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 163.2, 151.7, 150.7, 149.8, 138.7, 138.6, 124.9, 124.4, 119.5, 110, 54.8, 53.3, 21.7; FT-IR: $\tilde{\nu}$ = 2955, 1741, 1674, 1608, 1587, 1547, 1436, 1384, 1357, 1311, 1244, 1201 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{16}H_{17}N_2O_5$: 317.1137, found 317.1137.

Dimethyl 2-(3-Methyl-2-oxo-2*H*-[1,2′-bipyridin]-6-yl)-malonate (6f). Pale yellow solid, 27.5 mg (87%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (dd, J = 5.0, 1.9 Hz, 1H), 7.86 (td, J = 7.9, 1.9 Hz, 1H), 7.45−7.29 (m, 2H), 7.30−7.18 (m, 1H), 6.25 (d, J = 7.1 Hz, 1H), 4.31 (s, 1H), 3.68 (s, 6H), 2.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 163.2, 150.7, 149.9, 140.3, 139.8, 138.6, 124.8, 124.4, 121.2, 107.2, 62.5, 55.3, 13.9; FT-IR: $\tilde{\nu}$ = 2955, 1741, 1664, 1612, 1563, 1467, 1435, 1312, 1263, 1220 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{16}H_{17}N_2O_5$: 317.1137, found 317.1147.

Dimethyl 2-(3-(Benzyloxy)-2-oxo-2*H*-[1,2′-bipyridin]-6-yl)-malonate (6g). Yellow solid, 37.9 mg (93%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (dd, J = 5.0, 2.5 Hz, 1H), 7.86 (m, 1H), 7.43−7.31 (m, 6H), 7.31−7.25 (m, 1H), 6.71 (dd, J = 7.8, 2.5 Hz, 1H), 6.21 (dd, J = 7.8, 2.5 Hz, 1H), 5.12 (s, 2H), 4.28 (s, 1H), 3.67 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 158.8, 150.7, 149.8, 148.9, 138.6, 136.1, 131.0, 128.7, 128.0, 127.3, 124.9, 124.5, 115.3, 106.4, 70.9, 54.5, 53.3; FT-IR: $\tilde{\nu}$ = 3643, 1955, 1739, 1669, 1616, 1590, 1571, 1467, 1435, 1291, 1364, 1227 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{22}H_{21}N_2O_6$: 409.1399, found 409.1388.

Dimethyl 2-(2-Oxo-3-(trifluoromethyl)-2*H*-[1,2′-bipyridin]-6-yl)malonate (6h). Pale yellow solid, 30.0 mg (81%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (ddd, J = 4.9, 1.9, 0.8 Hz, 1H), 7.91 (td, J = 7.6, 1.9 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.46−7.40 (m, 2H), 6.45 (d, J = 7.6 Hz, 1H), 4.38 (s, 1H), 3.73 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 159.0, 150.2, 149.8, 144.6, 139.2 (q, J = 4.5 Hz), 138.9, 125.0, 124.8, 122.4 (q, J = 271 Hz), 121.2 (q, J = 31.3 Hz), 105.6, 55.3, 53.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −66.14; FT-IR: $\tilde{\nu}$ = 2959, 2853, 1758, 1690, 1566, 1437, 1321, 1249 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{16}H_{14}F_3N_2O_5$: 371.0855, found 371.0842.

Dimethyl 2-(5-Chloro-2-oxo-2*H*-[1,2′-bipyridin]-6-yl)-malonate (6i). Pale Yellow oil, 29.6 mg (88%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68−8.53 (m, 1H), 7.90 (td, J = 7.8, 1.9 Hz, 1H), 7.42 (m,3H), 6.65 (d, J = 9.9 Hz, 1H), 4.32 (s, 1H), 3.75 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 161.8, 151.0, 150.2, 142.3, 139.0, 137.6, 124.9, 124.5, 122.5, 115.5, 54.6, 53.5; FT-IR: $\tilde{\nu}$ = 3058, 2959, 2854, 1737, 1671, 1596, 1545, 1467, 1435, 1394, 1367, 1302, 1241, 1210 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{15}H_{14}{}^{35}ClN_2O_5$: 337.0591, found 337.0584.

Dimethyl 2-(1-Oxo-2-(pyridin-2-yl)-1,2-dihydroisoquinolin-3-yl)malonate (6j). Pale yellow solid, 26.1 mg (74%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72−8.55 (m, 1H), 8.46−8.32 (m, 1H), 7.89 (td, J = 7.7, 1.9 Hz, 1H), 7.69 (ddd, J = 8.3, 7.3, 1.4 Hz, 1H), 7.63−7.47 (m, 2H), 7.47−7.34 (m, 2H), 6.67 (s, 1H), 4.45 (s, 1H), 3.73 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 163.2, 151.3, 149.9, 138.5, 136.3, 133.7, 133.2, 128.2, 127.7, 126.7, 125.8, 125.4, 124.2, 107.9, 55.1, 53.4; FT-IR: $\tilde{\nu}$ = 2956, 1752, 1667, 1630, 1588, 1566, 1484, 1469, 1433, 1398, 1302.6, 1240 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{19}H_{17}N_2O_5$: 353.1137, found 353.1130.

Dimethyl 2-(4-Oxo-3-(pyridin-2-yl)-3,4-dihydroquinazolin-2-yl)malonate (6k). White solid, 27.5 mg (78%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.64 (dd, J = 5.0, 2.0 Hz, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.91 (td, J = 8.0 Hz, 2.0 Hz, 1H), 7.77 (m, 2H), 7.52 (m, 1H), 7.48−7.39 (m, 2H), 4.78 (s, 1H), 3.74 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 161.9, 150.1, 149.7, 148.1, 146.9, 138.7, 134.9, 128.3, 127.9, 127.1, 124.9, 124.8, 121.4, 58.8, 53.4; FT-IR: $\tilde{\nu}$ = 3069, 3010, 2957, 1759, 1740, 1697, 1637, 1610, 1589, 1567, 1508, 1474, 1466, 1433, 1354, 1322, 1305, 1292, 1235, 1202 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{18}H_{16}N_3O_5$: 354.1090, found 354.1100.

Dimethyl 2-(4-Oxo-4*H*-[1,2′-bipyridin]-2-yl)malonate (6l). Yellow oil, 16.0 mg (53%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (dd, J = 4.9, 2.0 Hz, 1H), 7.96 (td, J = 7.7, 1.9 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.45 (dd, J = 7.7, 4.9 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 6.50 (s, 1H), 6.44 (dd, J = 7.7, 2.6 Hz, 1H), 4.62 (s, 1H), 3.73 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.3, 166.1, 153.3, 149.4, 142.5, 140.9, 140.1, 124.6, 120.6, 120.5, 118.1, 55.2, 54.5; FT-IR: $\tilde{\nu}$ = 1752, 1636, 1438, 1280 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{15}H_{15}N_2O_5$: 303.0981, found 303.0981.

Dimethyl 2-(4-Oxo-1-(pyridin-2-yl)-1,4-dihydroquinolin-2-yl)malonate (6m). Yellow oil, 28.8 mg (82%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82−8.75 (m, 1H), 8.44 (d, J = 8.1 Hz, 1H), 8.03 (t, J = 7.8 Hz, 1H), 7.59 (t, J = 6.6 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 6.55 (d, J = 8.7 Hz, 1H), 6.50 (s, 1H), 4.32 (s, 1H), 3.73 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.2, 165.9, 151.4, 151.3, 144.7, 142.2, 139.9, 132.5, 126.5, 125.8, 125.6, 125.2, 124.4, 117.4, 112.1, 55.7, 53.6; FT-IR: $\tilde{\nu}$ = 3050, 2960, 2853, 1758, 1742, 1627, 1604, 1487, 1464, 1427, 1316, 1299, 1221 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{19}H_{17}N_2O_5$: 353.1137, found 353.1143.

Dimethyl 2-(6-Oxo-1-(pyridin-2-yl)piperidin-2-yl)malonate (7). Colorless oil, 24.1 mg (79%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48−8.43 (m, 1H), 7.68 (td, J = 7.8, 1.9 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.12 (m, 1H), 5.39 (q, J = 6.3 Hz, 1H), 3.68 (s, 3H), 3.67 (d, J = 6.8 Hz, 1H), 3.51 (s, 3H), 2.66−2.52 (m, 2H), 2.19 (q, J = 6.3 Hz, 2H), 1.95 (m, 1H), 1.87 (m, 1H); ^{13}C NMR (150 MHz, CDCl3) δ 171.2, 167.7, 167.6, 153.0, 148.4, 137.1, 123.5, 121.6, 55.4, 54.0, 52.62, 52.61, 32.7, 25.3, 18.1; FT-IR: $\tilde{\nu}$ = 2955, 1736, 1665, 1588, 1467, 1435, 1402, 1281 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_{15}H_{19}N_2O_5$: 307.1294, found 307.1308.

Methyl 2-(6-Oxo-1,6-dihydropyridin-2-yl)acetate (8). Pale brown solid, 30.8 mg (46%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.71 (br, 1H), 7.39 (dd, J = 9.2, 6.8 Hz, 1H), 6.48 (d, J = 9.2 Hz, 1H), 6.16 (d, J = 6.8 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ:169.2, 165.5, 141.7, 141.2, 118.8, 107.0, 52.7, 38.3; FT-IR: $\tilde{\nu}$ = 3037, 2951, 2766, 1733, 1660, 1552, 1475, 1348, 1227, 1202 cm^{-1}; HRMS: calculated for [M + H]$^+$ $C_8H_{10}NO_3$: 168.0660, found 168.0657.

Analytical Data for the Rhodacycle 10. Brick-red solid, 35.6 mg (40%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.38 (d, J = 9 Hz, 1H), 8.58 (d, J = 5.7, 1.9 Hz, 1H), 7.86 (t, J = 1.9 Hz, 1H), 7.26−7.23 (m, 1H), 7.15 (dd, J = 9, 6.8 Hz, 1H), 6.56 (dd, J = 6.8, 1.4 Hz, 1H), 6.18 (dd, J = 9.0, 1.4 Hz, 1H), 1.64 (s, 15H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.9 (d, J = 37 Hz), 166.4, 158.5, 150.2, 139.8, 139.2, 122.5, 119, 115.4, 114.5, 97.7 (d, J = 6.2 Hz), 9.2; FT-IR: $\tilde{\nu}$ = 3434, 2956, 2925, 2851, 1629, 1457, 1375 cm^{-1}; HRMS: calculated for [$C_{20}H_{22}N_2ORh$]$^+$: 409.0709, found 409.0739.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02349.

Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data, NMR spectra, and general procedures along with results from optimization, control, and deuteration experiments (PDF)

DOI: 10.1021/acs.joc.5b02349
J. Org. Chem. 2016, 81, 842−848

AUTHOR INFORMATION

Corresponding Author

*E-mail: rsamanta@chem.iitkgp.ernet.in.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank for the generous financial support for this project from the Indian Institute of Technology Kharagpur through ISIRD project grant (IIT/SRIC/CHY/QBE/2013-14/170) and the Science & Engineering Research Board (SERB), India through Start Up Research Grant (Young Scientists) YSS/2014/000383. The authors thank CSIR, New Delhi (D.D. and A.B.) and IIT Kharagpur (U. K. and S. C.) for their research fellowships. We thank Dr. S. K. Patra and Dr. M. C. Das, Department of Chemistry, IIT Kharagpur for helpful discussions.

REFERENCES

(1) (a) Crozet, M. D.; George, P.; Crozet, M. P.; Vanelle, P. *Molecules* **2005**, *10*, 1318. (b) Magedov, I. V.; Manpadi, M.; Ogasawara, M. A.; Dhawan, A. S.; Rogelj, S.; Van Slambrouck, S.; Steelant, W. F. A.; Evdokimov, N. M.; Uglinskii, P. Y.; Elias, E. M.; Knee, E. J.; Tongwa, P.; Antipin, M. Y.; Kornienko, A. *J. Med. Chem.* **2008**, *51*, 2561. (c) Heeb, S.; Fletcher, M. P.; Chhabra, S. R.; Diggle, S. P.; Williams, P.; Camara, M. *FEMS Microbiol Rev.* **2011**, *35*, 247.

(2) Recent reviews on transition metal-catalyzed C−H functionalization: (a) Yu, J. Q.; Shi, Z. J., Eds. *C−H Activation: Topics in Current Chemistry*; Springer: Heidelberg, 2010 and references cited therein. (b) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (c) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (d) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (e) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (f) Zhang, X.-S.; Chen, K.; Shi, Z.-J. *Chem. Sci.* **2014**, *5*, 2146. (g) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (h) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (i) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. and references cited therein. (j) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986. (k) Yadav, M. R.; Rit, R. K.; Shankar, M.; Sahoo, A. K. *Asian J. Org. Chem.* **2015**, *4*, 846.

(3) (a) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *Chem. - Eur. J.* **2013**, *19*, 7691. (b) Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2014**, *79*, 1377. (c) Modak, A.; Rana, S.; Maiti, D. *J. Org. Chem.* **2015**, *80*, 296. (d) Anagnostaki, E. E.; Fotiadou, A. D.; Demertzidou, V.; Zografos, A. L. *Chem. Commun.* **2014**, *50*, 6879. (e) Min, M.; Kim, Y.; Hong, S. *Chem. Commun.* **2013**, *49*, 196. (f) Cheng, D.; Gallagher, T. *Org. Lett.* **2009**, *11*, 2639.

(4) (a) Itahara, T.; Ouseto, F. *Synthesis* **1984**, *1984*, 488. (b) Chen, Y.; Wang, F.; Jia, A.; Li, X. *Chem. Sci.* **2012**, *3*, 3231.

(5) (a) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 15996. (b) Tamura, R.; Yamada, Y.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5679.

(6) Odani, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10784.

(7) Recent reviews on metal−carbene insertion in C−H bonds: (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (b) Slattery, C. N.; Ford, A.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 6681. (c) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857.

(8) (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (b) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 775. (c) Liu, Z.; Wang, J. *J. Org. Chem.* **2013**, *78*, 10024. (d) Xia, Y.; Zhang, Y.; Wang, J. *ACS Catal.* **2013**, *3*, 2586. (e) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986. (f) Xia, Y.; Liu, Z.; Feng, S.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 223. (g) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508. (h) Kim, J. H.; Gensch, T.; Zhao, D.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 10975. (i) Mishra, N. K.; Choi, M.; Jo, H.; Oh, Y.; Sharma, S.; Han, S. H.; Jeong, T.; Han, S.; Lee, S.-Y.; Kim, I. S. *Chem. Commun.* **2015**, *51*, 17229.

(9) Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296.

(10) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565.

(11) (a) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. (b) Yu, X.; Yu, S.; Xiao, J.; Wan, B.; Li, X. *J. Org. Chem.* **2013**, *78*, 5444. (c) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (d) Cui, S.; Zhang, Y.; Wang, D.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3912. (e) Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1364. (f) Jeong, J.; Patel, P.; Hwang, H.; Chang, S. *Org. Lett.* **2014**, *16*, 4598. (g) Shi, J.; Yan, Y.; Li, Q.; Xu, H. E.; Yi, W. *Chem. Commun.* **2014**, *50*, 6483. (h) Liang, Y.; Yu, K.; Li, B.; Xu, S.; Song, H.; Wang, B. *Chem. Commun.* **2014**, *50*, 6130. (i) Zhang, Y.; Zheng, J.; Cui, S. *J. Org. Chem.* **2014**, *79*, 6490. (j) Ai, W.; Yang, X.; Wu, Y.; Wang, X.; Li, Y.; Yang, Y.; Zhou, B. *Chem. - Eur. J.* **2014**, *20*, 17653. (k) Sharma, S.; Han, S. H.; Han, S.; Ji, W.; Oh, J.; Lee, S.-Y.; Oh, J. S.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2015**, *17*, 2852. (l) Yang, Y.; Wang, X.; Li, Y.; Zhou, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 15400. (m) Zhou, J.; Shi, J.; Liu, X.; Jia, J.; Song, H.; Xu, H. E.; Yi, W. *Chem. Commun.* **2015**, *51*, 5868. (n) Yu, S.; Liu, S.; Lan, Y.; Wan, B.; Li, X. *J. Am. Chem. Soc.* **2015**, *137*, 1623. (o) Li, X. G.; Sun, M.; Liu, K.; Jin, Q.; Liu, P. N. *Chem. Commun.* **2015**, *51*, 2380. (p) Shi, J.; Zhou, J.; Yan, Y.; Jia, J.; Liu, X.; Song, H.; Xu, H. E.; Yi, W. *Chem. Commun.* **2015**, *51*, 668. (q) Son, J.-Y.; Kim, S.; Jeon, W. H.; Lee, P. H. *Org. Lett.* **2015**, *17*, 2518.

(12) Direct functionalization of enaminone system: (a) Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, *130*, 3708. (b) Kim, Y. W.; Niphakis, M. J.; Georg, G. I. *J. Org. Chem.* **2012**, *77*, 9496. (c) Bi, L.; Georg, G. I. *Org. Lett.* **2011**, *13*, 5413. (d) Yu, Y.-Y.; Bi, L.; Georg, G. I. *J. Org. Chem.* **2013**, *78*, 6163. (e) Yu, Y.-Y.; Niphakis, M. J.; Georg, G. I. *Org. Lett.* **2011**, *13*, 5932. (f) Kim, Y. W.; Georg, G. I. *Org. Lett.* **2014**, *16*, 1574. (g) Carrër, A.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Org. Lett.* **2013**, *15*, 5606.

(13) Recent direct quinolone functionalization: (a) Li, M.; Li, L.; Ge, H. *Adv. Synth. Catal.* **2010**, *352*, 2445. (b) Moon, Y.; Kwon, D.; Hong, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11333. (c) Kang, D.; Hong, S. *Org. Lett.* **2015**, *17*, 1938. (d) Metal-free version for C2 alkylation in chromone: Narayan, R.; Antonchick, A. P. *Chem. - Eur. J.* **2014**, *20*, 4568.

(14) Meissner, R. S.; Perkins, J. J.; Duong, L. T.; Hartman, G. D.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; Nagy, R. M.; Naylor-Olsen, A.; Rodan, G. A.; Rodan, S. B.; Whitman, D. B.; Wesolowski, G. A.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 25.

(15) Smout, V.; Peschiulli, A.; Verbeeck, S.; Mitchell, E. A.; Herrebout, W.; Bultinck, P.; Vande Velde, C. M. L.; Berthelot, D.; Meerpoel, L.; Maes, B. U. W. *J. Org. Chem.* **2013**, *78*, 9803.

(16) Lim, Y.-H.; McGee, K. F., Jr.; Sieburth, S. M. *J. Org. Chem.* **2002**, *67*, 6535.

(17) (a) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (b) Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492.

(18) (a) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492. (b) Zhou, T.; Guo, W.; Xia, Y. *Chem. - Eur. J.* **2015**, *21*, 9209.

(19) Sughara, M.; Ukita, T. *Chem. Pharm. Bull.* **1997**, *45*, 719.

(20) Lee, J. C.; Yuk, J. Y. *Synth. Commun.* **1995**, *25*, 1511.

DOI: 10.1021/acs.joc.5b02349
J. Org. Chem. 2016, 81, 842−848