JOC The Journal of Organic Chemistry

Article

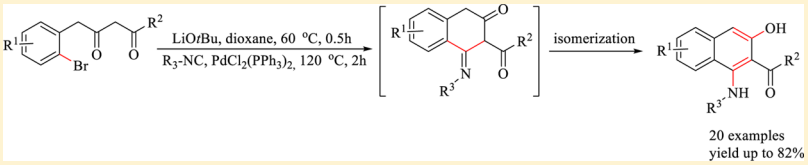
pubs.acs.org/joc

Palladium-Catalyzed Domino Synthesis of 4-Amino-3-acyl-2-naphthols via Isocyanide Chemoselective Insertion

Zhong Chen,[†] Hua-Qing Duan,[†] Xiao Jiang,[†] Yong-Ming Zhu,*[,†] Shun-Jun Ji,*[,‡] and Shi-Lin Yang[†]

[†]College of Pharmaceutical Science and [‡]College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou, 215123, China

Supporting Information



ABSTRACT: A novel and efficient strategy for the synthesis of sterically hindered 4-amino-3-acyl-2-naphthols through a palladium-catalyzed coupling reaction involving isocyanide chemselective insertion and domino isomerization has been developed. The methodology, which is in accordance with the principle of "atom and step economy", efficiently constructs 4-amino-3-acyl-2-naphthols in moderate to good yields.

INTRODUCTION

3-Acyl-2-naphthols are key structural components in a lot of non-naturally and naturally occurring products and have been widely used as building blocks in the chemical and medicinal field.[1] For example, **P1** is useful in preventing disorders mediated by a peroxisome proliferator activated receptor (PPAR) such as type II diabetes,[1d] **P2** is a kind of fluorescent dye,[1c] and **P3** can be used as a chiral catalyst in organic synthesis[1b] (Figure 1). However, as shown in Scheme 1, efficient synthetic methods toward 3-acyl-2-naphthols are surprisingly limited. (1) Friedel−Crafts acylation of 2-naphthol with benzoyl chloride in neat TfOH afforded 3-benzoyl-2-naphthol as a byproduct in very low yield.[2] (2) 2-methoxynaphthalene was first ortholithiated and then treated with Weinreb amide to give 3-benzoyl-2-methoxynaphthalene. Followed by demethylation with BCl_3, the desired 3-benzoyl-2-naphthol was obtained.[1b] The usage of strong base and excessively low reaction temperature may dent the substrate scope and application of this method. (3) Treatment of 2-(4-hydroxy-but-1-ynyl) benzaldehydes with the Jones reagent and subsequent purification through column chromatography on silica gel pre-eluted with Et_3N could synthesize 3-acyl-2-naphthols.[3] (4) Pd-catalyzed coupling reaction of polymericdiaryliodoniumsalts with salicylaldehydes is another choice to synthesize 3-benzoyl-2-naphthol.[4] (5) Reaction of 3-hydroxy-2-napthoic acid with phenyllithium at −78 °C produced 3-benzoyl-2-naphthol in a yield of 36% yield.[1d] With the growing demand for the fine chemicals and pharmaceutical intermediates, the direct synthesis of 3-acyl-2-naphthols becomes more and more desirable.

Isocyanides have been widely used in the world of synthetic chemistry, since the pioneering work of Passerini[5] and Ugi.[6] Recently, palladium-catalyzed reactions involving isocyanide insertion to form C−N, C−O, or C−C bonds have been widely used for the synthesis of various nitrogen-containing heterocycles or carbonyl compounds.[7] Isocyanide can undergo migratory insertion to a Pd (II) intermediate, followed by substitution with various nucleophiles and reductive elimination to generate target products. Furthermore, compared to the traditional preactivation of substrates as halide, palladium-catalyzed isocyanide insertion reaction with the selective activation C−H or N−H bond is a more important research topic in organic chemistry.[8] Transition-metal-catalyzed inert bonds activation and radical oxidative annulation of isocyanides are also attractive for isocyanide insertion chemistry.[9] In 2012, our group reported palladium-catalyzed synthesis of isocoumarins and phthalides via *tert*-butyl isocyanide insertion by forming C−O bond.[7i] In continuation of our interest to develop more convenient isocyanide insertion reactions,[7f,g] herein we report a facile synthesis of 4-amino-3-acyl-2-naphthols, which is a class of sterically crowded compounds, by palladium-catalyzed couple reaction involving isocyanide selective insertion and domino isomerization. To the best of our knowledge, no other protocol has been able to lead three substitutes into the 2, 3, and 4-positions of naphthalene ring in one step.

RESULTS AND DISCUSSION

According to our previous work,[7i] **1a** (1.0 mmol) was treated with LiO*t*Bu (3.0 mmol) in 2.0 mL of dioxane at 60 °C for 0.5 h. Then $PdCl_2(PPh_3)_2$ (0.05 mmol) and *tert*-butyl isocyanide (1.2 mmol) were added, and the reaction was kept at 120 °C for another 2 h under N_2. To our delight, (1-(*tert*-butylamino)-3-hydroxynaphthalen-2-yl) (phenyl)methanone (**2a**) was successfully synthesized in a yield of 82% (Table 1, entry 1).The solvent choice was very important for the reaction (Table 1,

Received: June 5, 2015
Published: August 6, 2015

DOI: 10.1021/acs.joc.5b01269
J. Org. Chem. 2015, 80, 8183−8188

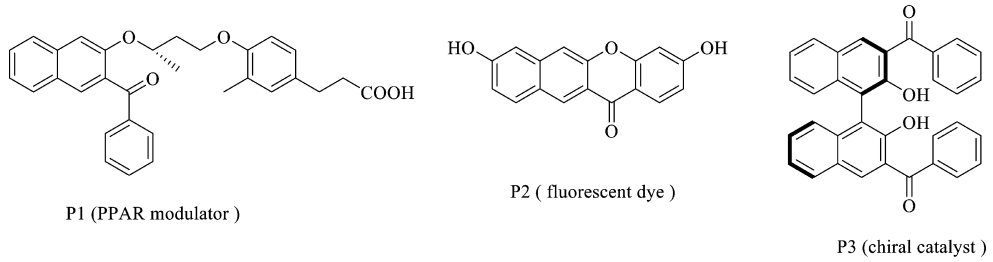
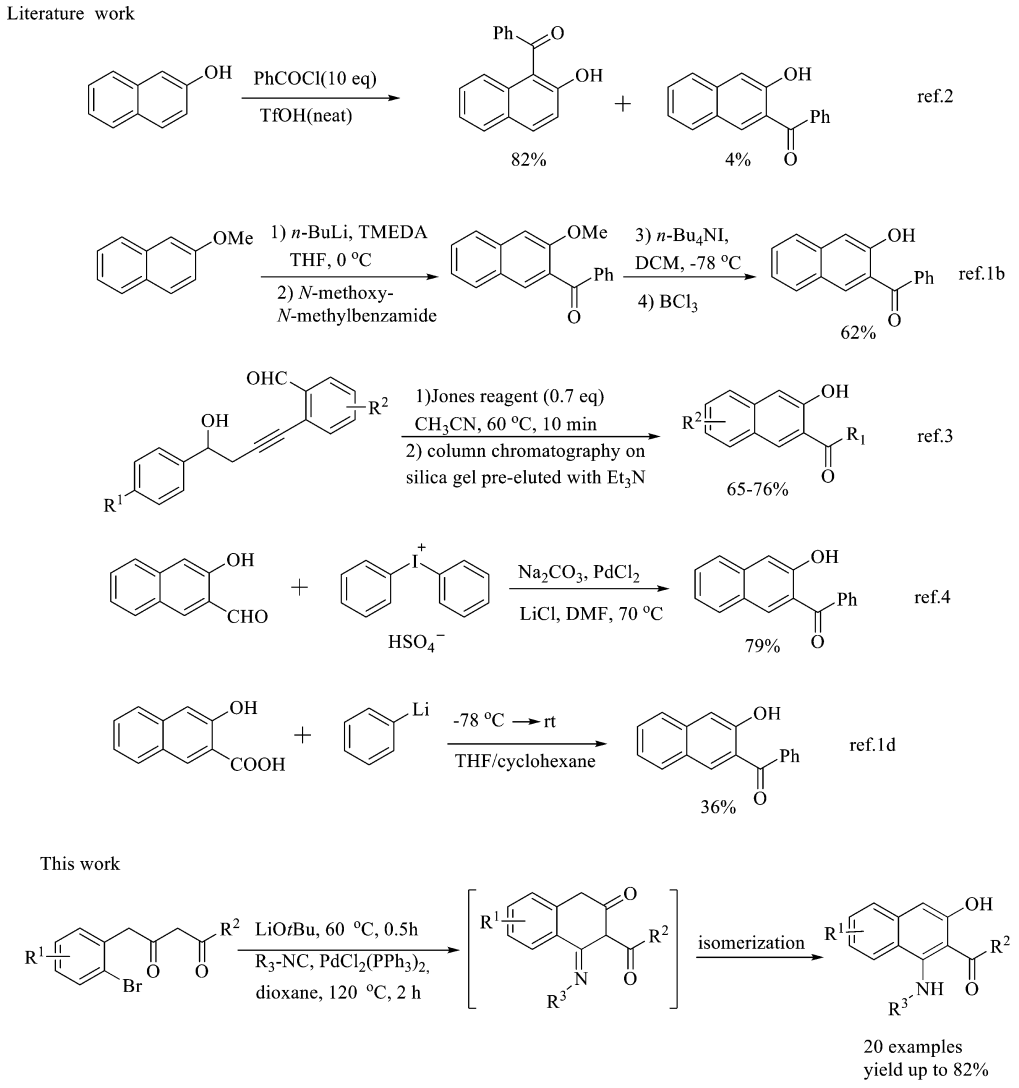


Figure 1. Application examples of 3-acyl-2-naphthol derivatives.

Scheme 1. Synthesis Strategy for 3-Acyl-2-naphthols

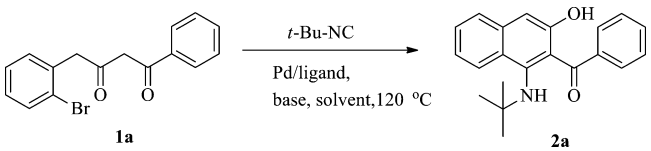


entries 2−4). Especially, when the reaction was run in toluene, only trace target product was produced. Next, the influence of the base on the reaction was investigated. The strong bases (KO*t*Bu, NaO*t*Bu, LiHMDS) were more favorable than the weak base (K_3PO_4) for the reaction, but no significant improvement in the yields was observed (Table 1, entries 5−8). $Pd(OAc)_2$ or $Pd(dba)_2$ was selected as the Pd resource, and the yield of **2a** decreased (Table 1, entries 9−10). Furthermore, other phosphorus ligands such as PCy_3, DPPF, and DPEPhos proved to be less effective (Table 1, entries 11−13). Therefore, the optimal reaction condition was that **1a** (1.0 equiv) was treated with LiO*t*Bu (3.0 equiv) in dioxane at 60 °C for 0.5h. Then *tert*-butyl isocyanide (1.2 equiv) and $PdCl_2(PPh_3)_2$ (5 mmol %) were added, and the contents were kept at 120 °C for 2 h under N_2.

Having optimized the reaction conditions in hand, we then explored the scope of this method. When 4-(2-bromophenyl)-1-phenylbutane-1,3-dione was selected as the substrate, **2a** was successfully synthesized in high yield of 82% (Table 2, entry 1). It was notable that the yield of **2a** decreased to 43% when the substrate was changed to 4-(2-iodophenyl)-1-phenylbutane-1,3-dione. Furthermore, electron-donating as well as electron-withdrawing substitutes of benzene ring (R_2) were well tolerated, and the target products were in good yields (Table

DOI: 10.1021/acs.joc.5b01269
J. Org. Chem. 2015, 80, 8183−8188

Table 1. Condition Optimizations[a]



1a 2a

entry	catalyst/ligand	base	solvent	yield (%)
1	$PdCl_2(PPh_3)_2$	LiO*t*Bu	dioxane	82
2	$PdCl_2(PPh_3)_2$	LiO*t*Bu	THF	41
3	$PdCl_2(PPh_3)_2$	LiO*t*Bu	anisole	43
4	$PdCl_2(PPh_3)_2$	LiO*t*Bu	toluene	trace
5	$PdCl_2(PPh_3)_2$	KO*t*Bu	dioxane	58
6	$PdCl_2(PPh_3)_2$	NaO*t*Bu	dioxane	61
7	$PdCl_2(PPh_3)_2$	LiHMDS	dioxane	46
8	$PdCl_2(PPh_3)_2$	K_3PO_4	dioxane	trace
9	$Pd(OAc)_2$/ PPh_3	LiO*t*Bu	dioxane	64
10	$Pd(dba)_2$/ PPh_3	LiO*t*Bu	dioxane	62
11	$PdCl_2$/ PCy_3	LiO*t*Bu	dioxane	61
12	$PdCl_2$/DPPF	LiO*t*Bu	dioxane	56
13	$PdCl_2$/DPEPhos	LiO*t*Bu	dioxane	53

[a]Reaction conditions: All reactions were performed with **1a** (1.0 mmol), base (3.0 mmol) in 2.0 mL of solvent at 60 °C for 0.5 h. Then *tert*-butyl isocyanide (1.2 mmol) and catalyst system (0.05 mmol) were added, and the reaction was kept at 120 °C for another 2 h. DPPF = 1,1′- bis(diphenylphosphino)ferrocene, DPEPhos = bis[(2-diphenylphosphino)phenyl]ether. PCy_3 = tricyclohexylphosphine, PPh_3 = triphenyl phosphine, $Pd(dba)_2$ = bis (dibenzylideneacetone) palladium.

2, entries 2−10). The substrate with sensitive functional group such as CN was also transformed smoothly into the target product in the moderate yield (Table 2, entry 9). Good yields were also obtained when R_2 was a naphthalene or heteroaryl group (Table 2, entries 11−13). In addition, when R_2 was an aliphatic group, moderate yields were also obtained (Table 2, entries 14−15). It was interesting that when 4-(2-bromo-3-methylphenyl)-1- phenylbutane-1,3-dione with sterically crowded effect was selected as the substrate, the coupling reaction occurred smoothly in a yield of 69% (Table 2, entry 16).When R_1 was the fluorine atom, the object product was obtained in a yield of 62% (Table 2, entry 17). To further evaluate this practical approach, different substitute isocyanides were investigated. Cyclohexyl isocyanide and 1-adamantyl isocyanide were successfully coupled with the substrate in yields of 51−72% (Table 2, entries18−20).

A plausible mechanism for this reaction is depicted in Scheme 2. Under the assistance of LiO*t*Bu, the intermediate **3** is generated from **1a**. There may be tautomerism of enol form and carbanion form of the intermediate **3**. Oxidative addition of **3** to the Pd (II) catalyst leads to a Pd (IV) complex **4**, and *tert*-butyl isocyanide was inserted to form **5**. Reductive elimination of **5** gives the generation of **6**, which is transformed to the desired product **2a** by isomerization.

CONCLUSION

In summary, we have demonstrated a simple and efficient method for the preparation of 4-amino-3- acyl-2- naphthols from the easily available dicarbonyl substrates and isocyanides, using $PdCl_2(PPh_3)_2$ as the catalyst system and LiO*t*Bu as base. This approach involves isocyanide chemoselective insertion and domino isomerization. Furthermore, this new perspective can expand the application of palladium-catalyzed isocyanide insertion.

EXPERIMENTAL SECTION

General Remarks. All chemicals and reagents were purchased from commercial suppliers and used without further purification. All anhydrous solvents used in the reactions were dried and freshly distilled. TLC was performed on silica HSGF254 plates, and purification was performed using silica gel column chromatography. Melting points were determined with a digital melting point apparatus. ^1H and ^{13}C NMR spectra were obtained from a solution in $CDCl_3$ with TMS as internal standard using a 400/101 MHz ($^1H/^{13}C$) spectrometer. Chemical shifts (δ) are given in ppm and J in Hz. IR spectra were carried out on the FT-IR-spectrometer, and wave numbers were given in cm^{-1}. High-resolution mass spectra were recorded on a chemical ionization (CI) apparatus using time-of-flight mass spectrometry.

General Procedure for the Synthesis of 4-Amino-3-acyl-2-naphthols. The substrate **1** (1.0 mmol), LiO*t*Bu (240 mg, 3.0 mmol) and anhydrous dioxane (2.0 mL) were added to a 15 mL sealed tube equipped with a magnetic stirring bar. The reaction was kept at 60 °C for 0.5 h. Then *tert*-butyl isocyanide (135 μL, 1.2 mmol) and $PdCl_2(PPh_3)_2$ (22 mg, 0.05 mmol) were added. The tube was purged with N_2, and the mixture was stirred at 120 °C for 2 h. After completion of the reaction indicated by TLC, the mixture was filtered through neutral aluminum oxide, and the solvent was removed by a vacuum. The residue was purified on a silica gel column using petroleum ether/EtOAc as the eluate to give the pure target product.

*(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl) (phenyl)-methanone (**2a**).* Yellow solid (262 mg, 82%); 157− 159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H, OH), 8.01 (d, J = 4.0 Hz, 1H), 7.71 (d, J = 4.0 Hz, 1H), 7.65 (d, J = 4.0 Hz, 2H), 7.48−7.54 (m, 2H), 7.38 (t, J = 8.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.17 (s, 1H), 3.44 (s, 1H, NH), 0.94 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 154.0, 145.8, 139.8, 137.3, 132.6, 129.9, 128.6, 128.3, 128.0, 127.3, 124.5, 123.5, 121.8, 107.7, 57.2, 30.7; IR ν = 3255, 3068, 2964, 1657, 1622, 1593, 1448, 1391, 1339, 1314, 1219, 743, 705, 682 cm^{-1}; HRMS-CI (m/z) calcd for $C_{21}H_{22}NO_2[M + H]^+$: 320.1645; found: 320.1646.

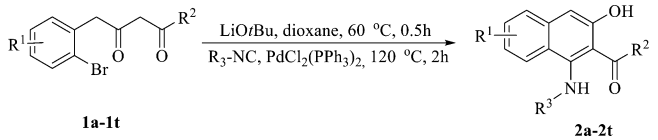
*(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(p-tolyl)-methanone (**2b**).* Yellow solid (216 mg, 65%); 185− 187 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, OH), 8.06 (d, J = 4.0 Hz, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.58 (d, J = 4.0 Hz, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.20 (s, 1H), 7.18 (s, 1H), 7.14 (s, 1H), 3.50 (s, 1H, NH), 2.40 (s, 3H), 0.94 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 153.7, 145.6, 143.7, 137.1 ^{13}C {^1H} NMR, 137.0 ^{13}C {^1H} NMR, 130.0, 129.2, 128.4, 127.5, 127.1, 124.9, 123.2, 122.2, 121.8, 107.6, 57.0, 30.7, 21.9; IR ν = 3299, 3243, 1657, 1626, 1593, 1448, 1339, 1314, 1273, 801, 743, 682 cm^{-1}; HRMS-CI (m/z) calcd for $C_{22}H_{24}NO_2[M + H]^+$: 334.1802; found: 334.1809.

*(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(4-methoxyphenyl)methanone (**2c**).* Yellow solid (202 mg, 58%); 189−191 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H, OH), 8.07 (d, J = 4.0 Hz, 1H), 7.68−7.71 (m, 3H), 7.48 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.15 (s, 1H), 6.88 (d, J = 4.0 Hz, 2H), 3.87 (s, 3H), 3.51 (s, 1H, NH), 0.96 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 163.6, 153.6, 145.1, 137.0, 132.4, 132.0, 128.4, 127.5, 127.1, 124.9, 123.4, 122.2, 113.7, 107.6, 57.0, 55.6, 30.7; IR ν = 3361, 2991, 1763, 1614, 1521, 1274, 1109, 910, 729, 679 cm^{-1}; HRMS-CI (m/z) calcd for $C_{22}H_{24}NO_3[M + H]^+$: 350.1751; found: 350.1758.

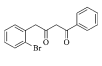
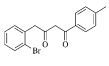
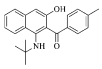
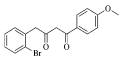
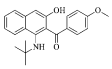
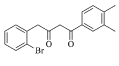
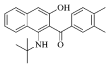
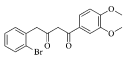
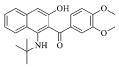
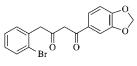
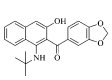
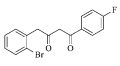
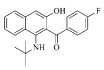
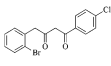
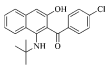
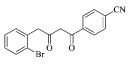
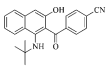
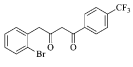
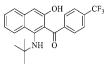
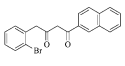
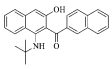
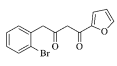
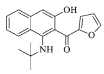
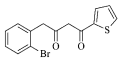
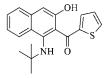
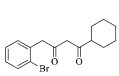
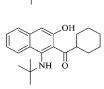
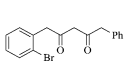
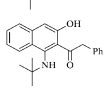
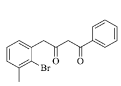
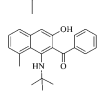
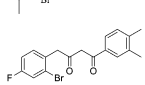
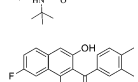
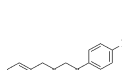
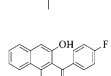
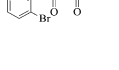
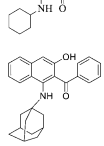
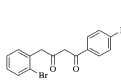
*(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(3,4-dimethylphenyl)methanone (**2d**).* Yellow solid (257 mg, 74%); 157−159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H, OH), 8.11 (d, J = 4.0 Hz, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.52 (s, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 4.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.13−7.15 (m, 2H), 3.55 (s, 1H, NH), 3.32 (s, 3H), 3.28 (s, 3H), 0.95 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 153.0, 145.0, 142.0, 136.8, 136.4, 129.9, 129.2,129.2 127.8, 127.1, 127.1, 126.4, 124.7, 122.6, 121.9, 107.1, 56.3, 30.1, 19.6, 19.3 ; IR ν = 3359, 2966, 1634, 1567,

DOI: 10.1021/acs.joc.5b01269
J. Org. Chem. 2015, 80, 8183−8188

Table 2. Synthesis of 4-Amino-3-acyl-2-naphthols[a]



1a-1t 2a-2t

Entry	Substrate		Product		Yield (%)
1		1a		2a	82 (43)[b]
2		1b		2b	65
3		1c		2c	58
4		1d		2d	74
5		1e		2e	63
6		1f		2f	65
7		1g		2g	68
8		1h		2h	71
9		1i		2i	61
10		1j		2j	72
11		1k		2k	69
12		1l		2l	62
13		1m		2m	64
14		1n		2n	54
15		1o		2o	55
16		1p		2p	69
17		1q		2q	62
18		1r		2r	51
19		1s		2s	68
20		1t		2t	72

[a]All reactions were performed under N_2 on a 1.0 mmol scale, using LiO*t*Bu (3.0 mmol) in dioxane (2.0 mL) at 60 °C for 0.5 h. Then $PdCl_2(PPh_3)_2$ (0.05 mmol) and isocyanide (1.2 mmol) were added, and the reactions were kept at 120 °C for another 2 h. [b]The yield with 4-(2-iodophenyl)-1-phenylbutane-1,3-dione as the substrate.

1506, 1260, 970, 769, 678 cm^{-1}; HRMS-CI (m/z) calcd for $C_{23}H_{26}NO_2[M + H]^+$: 348.1958; found: 348.1949.

(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(3,4-dimethoxyphenyl)methanon ***(2e)***. Yellow solid (239 mg, 63%); 143−145 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.12 (d, J = 4.0 Hz, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.24 (s, 1H), 7.14 (s, 1H), 6.80 (d, J = 4.0 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 0.97 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 153.0, 152.6, 148.6, 144.6, 136.3, 131.5, 128.3, 127.8, 127.2,126.4, 124.7, 122.7, 121.9, 110.0, 109.6, 107.1, 56.2, 55.7, 55.6 30.2; IR ν = 2964, 2838, 1700, 1621, 1510, 1267, 1137, 870, 724, 651 cm^{-1}; HRMS-CI (m/z) calcd for $C_{23}H_{26}NO_4[M + H]^+$: 380.1856; found: 380.1862.

Benzo[d][1,3]dioxol-5-yl(1-(tert-butylamino)-3-hydroxynaphthalen-2-yl)methanone ***(2f)***. Yellow solid (236 mg, 65%); 133−135 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.06 (d, J = 4.0 Hz, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.26−7.35 (m, 2H), 7.21 (s, 1H), 7.14 (s, 1H), 6.78 (d, J = 4.0 Hz, 1H), 6.04 (s, 2H), 0.98 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 153.3, 151.8, 148.0, 145.0, 136.9, 133.8, 128.3, 127.5, 127.1, 126.6, 124.8, 123.4, 122.4, 109.6, 108.0, 107.6, 102.0, 57.0, 30.8; IR ν = 3255, 3071, 2968, 1594, 1504, 1442, 1257, 1034, 924, 831, 724, 666 cm^{-1}; HRMS-CI (m/z) calcd for $C_{22}H_{22}NO_4$ $[M + H]^+$: 364.1543; found: 364.1548.

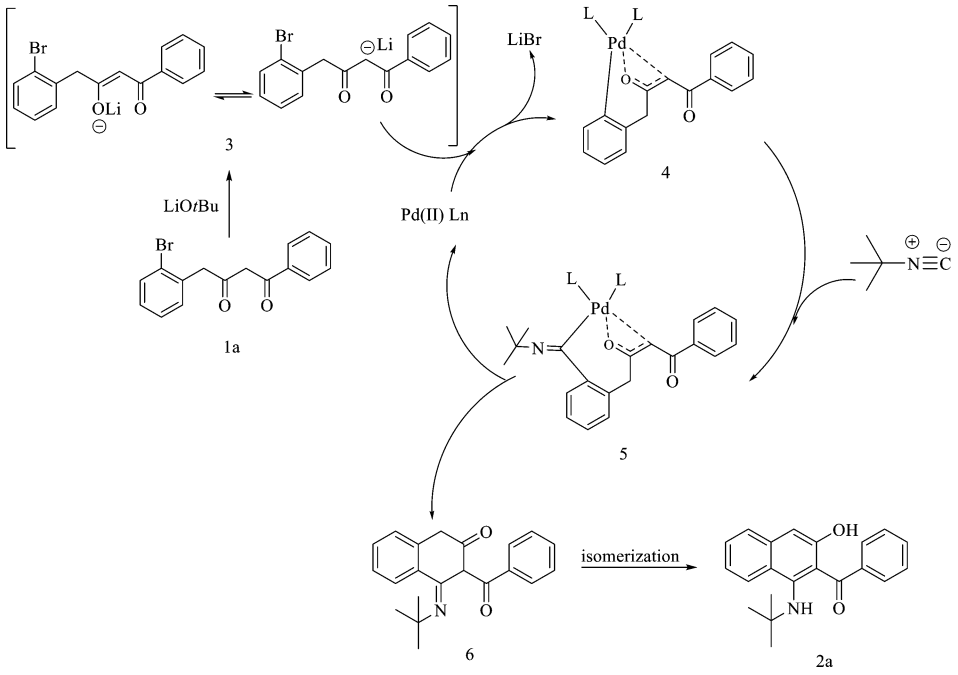
(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(4-fluorophenyl)-methanone ***(2g)***. Yellow solid (229 mg, 68%); 127−129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H, OH), 7.97 (d, J = 4.0 Hz, 1H), 7.66−7.72 (m, 3H), 7.50 (t, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.17 (s, 1H), 7.02−7.06 (m, 2H), 3.49 (s, 1H, NH), 0.96 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 166.7, 164.2, 153.8, 145.4, 137.3, 135.8, 132.7,132.6, 128.6, 127.4, 127.0, 124.1, 123.7, 121.5, 115.4, 115.2, 107.7, 57.3, 30.7; IR ν = 3363, 2995, 2968, 1633, 1573, 1507, 1397, 1265, 1147, 1090, 939, 890, 834, 771, 656 cm^{-1}; HRMS-CI (m/z) calcd for $C_{21}H_{21}NO_2F$ $[M + H]^+$: 338.1551; found: 338.1572.

(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(4-chlorophenyl)methanone ***(2h)***. Yellow solid (250 mg, 71%); 144−146 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H, OH), 7.95 (d, J = 4.0 Hz, 1H), 7.73 (d, J = 4.0 Hz, 1H), 7.58 (d, J = 4.0 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.32−7.37 (m, 3H), 7.17 (s, 1H), 3.50 (s, 1H, NH), 0.95 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 153.8, 145.6, 138.7, 138.1, 137.4, 131.4, 128.7, 128.5, 127.4, 127.0, 123.9, 123.7,121.4, 107.7, 57.2, 30.5; IR ν = 3359, 3065, 2966, 1657, 1589, 1509, 1338, 1265, 1089, 890, 767, 709, 670 cm^{-1}; HRMS-CI (m/z) calcd for $C_{21}H_{21}NO_2Cl$ $[M + H]^+$: 354.1255; found: 354.1262.

4-(1-(tert-Butylamino)-3-hydroxy-2-naphthoyl)benzonitrile ***(2i)***. Yellow solid (210 mg, 61%); 105−107 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H, OH), 7.90 (d, J = 4.0 Hz, 1H), 7.74 (d, J = 4.0 Hz, 1H), 7.62−7.69 (m, 4H), 7.51−7.55 (m, 1H), 7.35−7.39 (m, 1H), 7.18 (s, 1H), 0.94 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 154.0, 146.0, 143.9,137.7, 131.9, 130.1, 129.0, 128.3, 127.6, 126.7, 124.0, 123.5, 120.9, 118.4,108.0, 57.7, 30.6; IR ν = 2969, 2223,

DOI: 10.1021/acs.joc.5b01269
J. Org. Chem. 2015, 80, 8183−8188

Scheme 2. Plausible Mechanism for the Synthesis of 2a



1700, 1591, 1554, 1329, 1095, 995, 819, 754, 721 cm^{-1}; HRMS-CI (m/z) calcd for $C_{22}H_{21}N_2O_2[M + H]^+$: 345.1598; found: 345.1601.

(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(4-(trifluoromethyl)phenyl)methanone (**2j**). Yellow solid (279 mg, 72%); 127−129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H, OH), 7.92 (d, J = 4.0 Hz, 1H), 7.69−7.75 (m, 3H), 7.60−7.62 (m, 2H), 7.53 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.19 (s, 1H), 3.52 (s, 1H, NH), 0.95 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8,153.9, 145.8, 143.1,137.4, 129.9, 128.8, 127.4, 126.7, 124.9, 124.9, 123.5, 123.8, 123.5,121.0, 107.7, 57.5, 30.5 ; IR ν = 3369, 2969, 1633, 1509, 1319, 1161, 1127, 833, 774, 728, 651 cm^{-1}; HRMS-CI (m/z) calcd for $C_{22}H_{21}NO_2F_3[M + H]^+$: 388.1519; found: 388.1518.

(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(naphthalen-2-yl)methanone (**2k**). Yellow solid (255 mg, 69%); 173−175 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72(s, 1H), 8.19 (d, J = 4.0 Hz, 1H), 8.03 (d, J = 4.0 Hz, 1H), 7.81−7.88 (m, 3H), 7.74 (t, J = 8.0 Hz, 2H), 7.58 (t, J = 8.0 Hz, 1H),7.49−7.55 (m, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.21 (s, 1H), 3.51(s, 1H, NH), 0.94 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 153.7, 145.6, 137.1, 137.0, 135.3, 132.5,131.0, 129.6, 128.4, 128.3, 127.9, 127.7, 127.1,126.6, 125.8, 124.4, 123.4, 122.0, 107.6, 57.1, 30.6; IR ν = 3482, 3371, 3050, 2963, 1645, 1619, 1597, 1561, 1128, 1080, 766, 748, 634 cm^{-1}; HRMS-CI (m/z) calcd for $C_{25}H_{24}NO_2[M + H]^+$: 370.1802; found: 370.1797.

(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(furan-2-yl)-methanone (**2l**). Yellow solid (192 mg, 62%); 170−172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.03 (d, J = 4.0 Hz, 1H), 8.69 (d, J = 4.0 Hz, 1H),7.57 (s, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.12(s, 1H), 6.53 (s, 1H), 1.03 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 153.5, 153.1, 146.4, 145.4, 137.0, 128.3, 127.2, 127.2, 124.1, 123.4, 121.6, 119.8, 112.3, 107.3, 56.7, 30.7; IR ν = 3254, 3071, 2968, 1640, 1594, 1504, 1257, 1033, 832, 724, 666 cm^{-1}; HRMS-CI (m/z) calcd for $C_{19}H_{20}NO_3[M + H]^+$: 310.1438; found: 310.1434.

(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(thiophen-2-yl)-methanone (**2m**). Yellow solid (208 mg, 64%); 180−182 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 4.0 Hz,1H), 7.97 (s, 1H), 7.68−7.71 (m, 2H), 7.55 (d, J = 2.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.05−7.08 (m, 1H), 3.75 (s, 1H, NH), 1.06 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 152.7, 145.1, 144.6, 136.9, 135.4, 134.7, 128.4, 128.0, 127.5, 127.2, 124.7, 123.5, 122.9, 107.7, 56.9, 30.9; IR ν = 3237, 3098, 2965, 1619, 1597, 1405, 1355, 1193, 824, 739, 676 cm^{-1}; HRMS-CI (m/z) calcd for $C_{19}H_{20}NO_2S[M + H]^+$: 326.1209; found: 326.1212.

(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)(cyclohexyl)-methanone (**2n**). Yellow solid (175 mg, 54%); 139−141 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 14.24 (s, 1H),7.86 (d, J = 4.0 Hz, 1H), 7.62 (d, J = 4.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 6.34 (s, 1H), 5.13 (brs, 1H), 3.35−3.40 (m, 1H), 1.91−1.94 (m,2H), 1.82−1.85 (m,2H), 1.67−1.76 (m, 4H), 1.57 (s, 2H), 1.54 (s, 9H, $CH_3 \times 3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 167.1, 148.6, 133.9, 127.7, 125.7, 122.8, 120.3, 120.2, 106.4, 96.8, 51.8, 48.8, 30.3, 29.3, 25.9, 25.8; IR ν = 3304, 3005,1759, 1602, 1414, 1329, 1235, 1117, 895, 756, 683 cm^{-1}; HRMS-CI (m/z) calcd for $C_{21}H_{28}NO_2[M + H]^+$: 326.2115; found: 326.2124.

1-(1-(tert-Butylamino)-3-hydroxynaphthalen-2-yl)-2-phenylmethanone (**2o**). Yellow solid (183 mg, 55%); 145−147 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 3.0 Hz, 1H), 7.48 (d, J = 3.0 Hz, 1H), 7.40 (t, J = 6.0 Hz, 1H), 7.35 (t, J = 6.0 Hz, 1H), 7.05 (t, J = 3.0 Hz, 2H), 6.95 (t, J = 3.0 Hz, 1H), 6.90 (s, 1H), 6.85 (t, J = 3.0 Hz, 2H), 5.97 (s, 1 H), 2.32 (s, 2 H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 152.5, 138.8,138.5, 132.6, 129.2, 128.5, 127.2, 127.0, 126.4, 125.8, 125.4, 124.7, 124.1, 109.3,60.7, 28.7, 14.4; IR ν = 3185, 2973, 1734, 1599, 1381, 1344, 1242, 1118, 743, 697 cm^{-1}; HRMS-CI (m/z) calcd for $C_{22}H_{24}NO_2[M + H]^+$: 334.1802; found: 334.1797.

(1-(tert-Butylamino)-3-hydroxy-8-methylnaphthalen-2-yl)(phenyl)methanone (**2p**). Yellow solid (230 mg, 69%); 108−110 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1 H), 7.69−7.71 (m, 2H), 7.55 (d, J = 4.0 Hz, 1H), 7.49−7.51 (m, 1H), 7.39 (t, J = 8.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.12 (s, 1H), 7.06 (d, J = 4.0 Hz, 1H), 2.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 153.8, 149.9, 140.7, 138.1, 133.8, 131.9, 129.5, 128.2, 127.9, 127.7, 127.6, 126.2, 122.4, 108.3, 58.5, 29.9, 25.7; IR ν = 3263, 2976, 1777, 1700, 1656, 1593, 1267, 1088, 900, 725, 666 cm^{-1}; HRMS-CI (m/z) calcd for $C_{22}H_{24}NO_2[M + H]^+$: 334.1802; found: 334.1809.

(1-(tert-Butylamino)-7-fluoro-3-hydroxynaphthalen-2-yl)(3,4-dimethylphenyl)methanone (**2q**). Yellow solid (227 mg, 62%); 160−162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.77−7.80 (m, 1H), 7.65−7.69 (m, 1H), 7.52 (s, 1H), 7.39 (d, J = 4.0 Hz, 1H), 7.27−7.30 (m, 1H), 7.16−7.18 (m, 2H), 3.33 (s, 1H), 2.33 (s, 3H), 2.29 (s, 3H), 0.88 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0,161.1, 157.8, 152.7, 144.6, 143.1, 137.3, 137.1,130.4, 130.1, 129.1, 129.0, 127.6, 123.7, 118.9, 118.6, 109.5, 109.2, 108.0,56.8, 30.7, 20.3, 20.0 ; IR ν = 3338, 2969, 1630, 1603, 1569, 1430, 1230, 1169, 1141, 848, 788, 715,

DOI: 10.1021/acs.joc.5b01269
J. Org. Chem. 2015, 80, 8183−8188

668 cm^{-1}; HRMS-CI (m/z) calcd for $C_{23}H_{25}FNO_2$ $[M + H]^+$: 366.1864; found: 366.1869.

*(1-(Cyclohexylamino)-3-hydroxynaphthalen-2-yl)(4-fluorophenyl)methanone (**2r**).* Blue solid (185 mg, 51%); 160−162 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 4.0 Hz, 2H), 7.39 (d, J = 4.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 6.94 (t, J = 8.0 Hz, 2H), 5.70 (s, 2H), 2.57 (s, 4H), 1.44−1.65 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 187.8, 150.8, 147.0, 136.6, 127.6, 124.7, 124.6, 121.1, 109.7, 57.9, 48.8, 35.4, 25.0, 21.6; IR ν = 3040, 2931, 1721, 1602, 1574, 1466, 1408, 1132, 1059, 789, 627 cm^{-1}; HRMS-CI (m/z) calcd for $C_{23}H_{23}FNO_2[M + H]^+$: 364.1707; found: 364.1719.

*(1-(Adamantan-1-ylamino)-3-hydroxynaphthalen-2-yl)(phenyl)-methanone (**2s**).* Yellow solid (271 mg, 68%); 222−224 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.00 (d, J = 4.0 Hz, 1H), 7.72 (d, J = 4.0 Hz, 1H), 7.58 (s, 1H), 7.56 (s, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.32−7.37(m, 3H), 7.16 (s, 1H), 3.48 (s, 1H),1.94 (s, 3H), 1.51−1.54 (m, 3H), 1.41−1.44 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 153.9, 144.7, 138.5,138.4, 137.3, 131.4, 128.7, 128.5, 127.4, 127.1, 124.0, 123.6, 121.2, 107.6, 57.8, 44.2, 36.1, 30.0; IR ν = 3354, 2892, 2846, 1633, 1587, 1506, 1399, 1306, 1257, 1087, 839, 763, 654 cm^{-1}; HRMS-CI (m/z) calcd for $C_{27}H_{26}NO_2$ $[M - H]^-$: 396.1969; found: 396.1975.

*(1-(Adamantan-1-ylamino)-3-hydroxynaphthalen-2-yl)(4-fluorophenyl)methanone (**2t**).* Yellow solid (299 mg, 72%); 180−182 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.02 (d, J = 4.0 Hz, 1H), 7.65−7.73 (m, 3H), 7.49−7.53 (m, 1H), 7.33−7.37 (m, 1H), 7.16 (s, 1H), 7.02−7.06 (m, 2H), 3.44 (s, 1H), 1.94 (s, 3H), 1.51−1.54 (m, 3H), 1.40−1.44 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 167.0, 163.7, 153.8, 144.5, 137.0, 136.0, 132.7, 132.5, 128.6, 127.3, 127.2, 124.1, 123.6, 121.3, 115.5, 115.2, 107.6, 57.6, 44.2, 36.2, 30.0; IR ν = 3346, 2904, 2845, 1635, 1582, 1505, 1306, 1225, 1146, 1091, 934, 845, 768, 634 cm^{-1}; HRMS-CI (m/z) calcd for $C_{27}H_{27}FNO_2$ $[M + H]^+$: 416.2020; found: 416.2021.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01269.

Copies of ^1H, ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhuyongming@suda.edu.cn.

*E-mail: chemjsj@suda.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support by PAPD (a project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions).

■ REFERENCES

(1) (a) Kozlowski, M. C.; Dugan, E. C.; DiVirgilio, E. S.; Maksimenka, K.; Bringmann, G. *Adv. Synth. Catal.* **2007**, *349*, 583. (b) Li, X. L.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500. (c) Azuma, E.; Kuramochi, K.; Tsubaki, K. *Tetrahedron* **2013**, *69*, 1694. (g) Arnaud, P.; Emmanuel, C.; Christine, M.; Yves, G.; Andrew, E. G. *Org. Lett.* **2002**, *18*, 3139. (d) Gonzalez, V. I. C. ; Mantlo, N. B.; Shi, Q.; Wang, M. M.; Winneroski, L. L. J.; Xu, Y. P.; York, J. S. PCT patent WO2005019151 A1, March 3, 2005. (e) Lucas, S.; Heim, R.; Negri, M.; Antes, I.; Ries, C.; Schewe, K. E.; Bisi, A.; Gobbi, S.; Hartmann, R. W. *J. Med. Chem.* **2008**, *51*, 6138. (f) Koch, S. S. C.; Dardashti, L. J.; Hebert, J. J.; White, S. K.; Croston, G. E.; Flatten, K. S.; Heyman, R. A.; Nadzan, A. M. *J. Med. Chem.* **1996**, *39*, 3229.

(2) Murashige, R.; Hayashi, Y.; Ohmori, S.; Torii, A.; Aizu, Y.; Muto, Y.; Murai, Y.; Oda, Y.; Hashimoto, M. *Tetrahedron* **2011**, *67*, 641.

(3) He, Y.; Zhang, X. Y.; Shen, N. N.; Fan, X. S. *J. Org. Chem.* **2013**, *78*, 10178.

(4) Chen, J.; Chen, Z. C. *Synlett* **2000**, *2000*, 1175.

(5) (a) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Passerini, M.; Ragni, G. *Gazz. Chim. Ital.* **1931**, *61*, 964.

(6) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Steinbruckner, C. *Angew. Chem.* **1960**, *72*, 267. (c) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8.

(7) (a) Lang, S. *Chem. Soc. Rev.* **2013**, *42*, 4867. (b) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084. (c) Qiu, G. Y. S.; Ding, Q. P.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257. (d) Lygin, A. V.; Meijere, A. de. *Angew. Chem., Int. Ed.* **2010**, *49*, 9094. (e) Li, J.; He, Y. M.; Luo, S.; Lei, J.; Wang, J.; Xie, Z. Q.; Zhu, Q. *J. Org. Chem.* **2015**, *80*, 2223. (f) Jiang, X.; Wang, J. M.; Zhang, Y.; Chen, Z.; Zhu, Y. M.; Ji, S. J. *Org. Lett.* **2014**, *16*, 3492. (g) Jiang, X.; Tang, T.; Wang, J. M.; Chen, Z.; Zhu, Y. M.; Ji, S. J. *J. Org. Chem.* **2014**, *79*, 5082. (h) Tang, T.; Fei, X. D.; Ge, Z. Y.; Chen, Z.; Zhu, Y. M.; Ji, S. J. *J. Org. Chem.* **2013**, *78*, 3170. (i) Fei, X. D.; Ge, Z. Y.; Tang, T.; Zhu, Y. M.; Ji, S. J. *J. Org. Chem.* **2012**, *77*, 10321. (j) Boissarie, P. J.; Hamilton, Z. E.; Lang, S.; Murphy, J. A.; Suckling, C. J. *Org. Lett.* **2011**, *13*, 6256. (k) Geden, J. V.; Pancholi, A. K.; Shipman, M. *J. Org. Chem.* **2013**, *78*, 4158. (l) Tobisu, M.; Imoto, S.; Ito, S.; Chatani, N. *J. Org. Chem.* **2010**, *75*, 4835. (m) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698.

(8) (a) Wang, H.; Xu, B. *Youji Huaxue* **2015**, *35*, 588. (b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (c) Kukl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (d) Peng, J.; Liu, L.; Hu, Z.; Huang, J.; Zhu, Q. *Chem. Commun.* **2012**, *48*, 3772. (e) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 4966. (f) Wang, Y. Y.; Zhu, Q. *Adv. Synth. Catal.* **2012**, *354*, 1902. (j) Liu, Y. J.; Xu, H.; Kong, W. J.; Shang, M.; Dai, H. X.; Yu, J. Q. *Nature* **2014**, *515*, 389. (g) Vlaar, T.; Cioc, R. C.; Mampuys, P.; Maes, B. U. W.; Orru, R. V.A.; Ruijter, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 13058. (h) Xia, Z.; Zhu, Q. *Org. Lett.* **2013**, *15*, 4110. (i) Fang, T.; Tan, Q.; Ding, Z.; Liu, B.; Xu, B. *Org. Lett.* **2014**, *16*, 2342.

(9) (a) Wang, H.; Yu, Y.; Hong, X.; Xu, B. *Chem. Commun.* **2014**, *50*, 13485. (b) Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 3990. (c) Tu, H. Y.; Liu, Y. R.; Chu, J. J.; Hu, B. L.; Zhang, X. G. *J. Org. Chem.* **2014**, *79*, 9907. (d) Cao, J. J.; Zhu, T. H.; Wang, S. Y.; Gu, Z. Y.; Wang, X.; Ji, S. J. *Chem. Commun.* **2014**, *50*, 6439. (e) Pan, C.; Han, J.; Zhang, H.; Zhu, C. *J. Org. Chem.* **2014**, *79*, 5374.

DOI: 10.1021/acs.joc.5b01269
J. Org. Chem. 2015, 80, 8183−8188