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C–N Coupling of Amides with Alcohols Catalyzed by N-Heterocyclic Carbene–Phosphine Iridium Complexes

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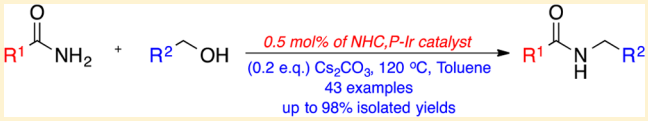
Supporting Information

ABSTRACT: N-Heterocyclic carbene–phosphine iridium complexes (NHC–Ir) were developed/found to be a highly reactive catalyst for N-monoalkylation of amides with alcohols via hydrogen transfer. The reaction produced the desired product in high isolated yields using a wide range of substrates with low catalyst loading and short reaction times.



N-Alkylation of amides is a familiar/useful and important technique in the synthesis of natural products, polymers, and peptides.[1−3] Consequently, there are general methods available for the N-alkylation of amides with aryl and alkenyl halides.[4−8] From a green chemistry perspective, alcohols would be an attractive alternative as alkylating reagents for the C–N bond formation.[9−17] Alcohols are widespread and relatively cheap reagents, they are generally non or less toxic and easier to handle when compared to other reagents used for N-alkylation of amides. However, due to the poor electrophilicity of alcohols, either harsh conditions or extra steps are required.

The metal-catalyzed hydrogen-transfer raction is an elegant way to overcome this problem and has been successfully applied in N-alkylation of amines.[18−21] In this reaction, the alcohol is oxidized by the metal complex to produce an electrophilic aldehyde that undergoes a condensation with the amine. The newly generated C═N bond is finally reduced by the metal hydride complex resulting in a reaction in which only water is generated as a byproduct. Hence, the N-alkylation of amines using alcohols as an alkylating reagent is an environmentally friendly alternative.

The corresponding alkylation of amides has also been studied.[22−30] Because the amide is less nucleophilic than amines, these reactions normally require higher temperatures and/or higher catalyst loadings. Watanabe and Jenner[31,32] reported the successful use of alcohols as alkylating reagents catalyzed by ruthenium and rhodium catalysts at high temperature in the N-alkylation of amides. Fujita and co-workers applied iridium catalysts to develop a method for the N-alkylation of amides using alcohols in 2009.[33] This method required 5 mol % of iridium metal catalysts and a long reaction time under reflux conditions. In 2011, Deng and co-workers reported N-alkylation of amides with alcohols using heterogeneous Ag/Mo oxides.[34] In the same year, alcohols were reported as alkylating reagents in N-alkylation catalyzed by copper,[35] ruthenium,[36] and iridium catalysts.[28] In 2013, Sun and co-workers applied ruthenium/iridium dual catalyst systems in alkylation of aldoximes using alcohols to obtain the N-monoalkylated amide products.[37] Recently, N-alkylation of amides with alcohols was successful using 5 mol % of iridium dimer catalyst under base-free conditions in a microwave reactor.[38] In this study, N-heterocyclic carbene-phosphine iridium catalysts was developed and found to be very active catalysts for the N-monoalkylation of amides using alcohols as alkylation reagents via hydrogen transfer.

Initially, benzamide and benzyl alcohol were chosen as model substrates for the study. The reaction was carried out at 120 °C in toluene with 0.5 equiv of a base and using 0.5 mol % of an iridium catalyst for 5 h (Table 1, entries 2–6). The use of cesium carbonate produced the N-monoalkylated product in the highest isolated yield (Table 1, entry 6). The quantity of cesium carbonate could be decreased to 0.2 equiv, without any significant loss in yield (Table 1, entry 7). An elevated temperature (120 °C) was necessary to complete the reaction in 5 h. At 100 °C, the reaction was incomplete with only 55% yield in 5 h (Table 1, entry 9). A catalyst screening at 100 °C was also performed for the reaction. When the substituent on the imidazole was changed from phenyl to methyl group, 31% of the desired product was obtained (Table 1, entries 11). The best reactivity was obtained for catalyst **D** which resulted in 84% yield (Table 1, entry 13) at 100 °C and 96% isolated yield at 120 °C (Table 1, entry 14). Toluene was found to be the best solvent for the reaction (Table 1, entries 14–17).

Having identified a reactive catalyst and optimized the reaction conditions, a range of alcohols was investigated as electrophiles in the reaction (Table 2, entries 1–13). The benzyl alcohol derivatives bearing electron-donating substituents in the *para* position on the aromatic ring afforded the desired products in excellent yields (Table 2, entries 2 and 3). A slightly lower yield was produced when the substrate has an electron-withdrawing group in the *para* position (Table 2, entry 4). The reaction of benzamide with benzyl alcohols bearing substituents in the *meta* positions were complete after 3 h

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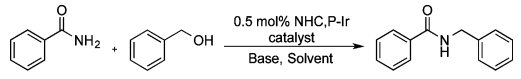
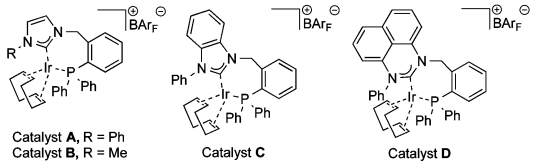
Table 1. Optimization of Reaction Conditions Using NHC,P−Ir Catalysts[a]

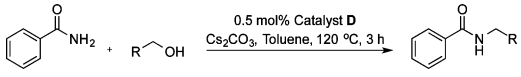


Entry	Base (equiv)	Catalyst	Solvent	Temp (°C)	Time (hour)	yield (%)[b]
1	No Base	**A**	Toluene	120	5	No conversion
2	KOtBu (0.5)	**A**	Toluene	120	5	73
3	NaOtBu (0.5)	**A**	Toluene	120	5	68
4	K_2CO_3 (0.5)	**A**	Toluene	120	5	67
5	KOH (0.5)	**A**	Toluene	120	5	80
6	Cs_2CO_3 (0.5)	**A**	Toluene	120	5	88
7	Cs_2CO_3 (0.2)	**A**	Toluene	120	5	84
8	Cs_2CO_3 (0.2)	**A**	Toluene	80	12	11[c]
9	Cs_2CO_3 (0.2)	**A**	Toluene	100	12	55[c]
10	Cs_2CO_3 (0.2)	**A**	Toluene	120	12	91
11	Cs_2CO_3 (0.2)	**B**	Toluene	100	12	31[c]
12	Cs_2CO_3 (0.2)	**C**	Toluene	100	12	40[c]
13	Cs_2CO_3 (0.2)	**D**	Toluene	100	12	84[c]
14	Cs_2CO_3 (0.2)	**D**	Toluene	120	3	96
15	Cs_2CO_3 (0.2)	**D**	DMF	120	3	84
16	Cs_2CO_3 (0.2)	**D**	DMSO	120	3	78
17	Cs_2CO_3 (0.2)	**D**	1,4-dioxane	120	3	32



[a]Amide (0.25 mmol), benzyl alcohol (0.30 mmol), catalyst (0.5 mol %), base, and 0.25 mL of solvent, heat. [b]Isolated yield. [c]NMR yield using 1,3,5-trimethoxybenzene as internal standard.

Table 2. N-Monoalkylation of Benzamide with Various Aromatic Alcohols Using NHC,P−Ir Catalysts[a]



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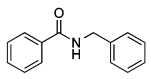
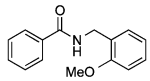
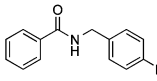
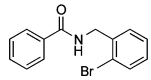
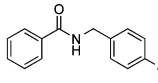
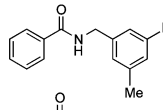
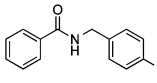
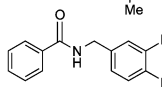
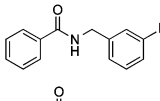
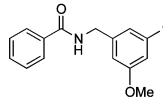
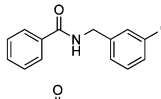
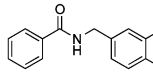
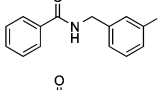
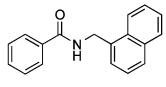
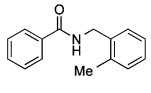
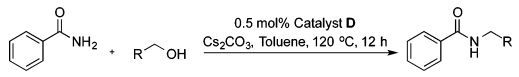
1		96	9[c]		90
2		95	10[c]		82
3		97	11		98
4		82	12		96
5		89	13		90
6[c]		91	14		96
7[c]		97	15[c]		87
8[c]		83			

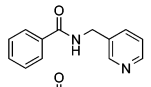
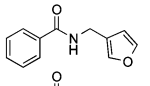
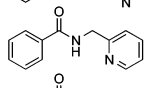
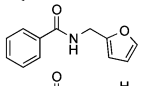
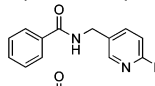
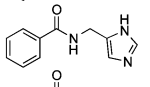
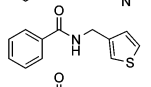
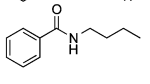
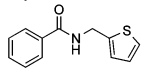
[a]Benzamide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (0.5 mol %), Cs_2CO_3 (0.05 mmol), 120 °C, 3 h. [b]Isolated yield. [c]Benzamide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (0.5 mol %), Cs_2CO_3 (0.05 mmol), 120 °C, 12 h.

(Table 2, entries 5−7). When benzyl alcohols having two substituents on the aromatic ring were used as alkylating reagents, high yields of isolated products were obtained (Table 2, entries 11−13). The napthalenemethanols also resulted in high yields (Table 2, entries 14 and 15).

Alkylation of benzamide with heterocyclic aromatic alcohols as alkylating reagents was also studied (Table 3, entries 1−8).

Table 3. N-Monoalkylation of Benzamide with Various Heterocyclic Alcohols and Butanol Using NHC,P−Ir Catalysts[a]



Entry	Product	yield (%)[b]	Entry	Product	yield (%)[b]
1		95	6[c]		63
2		87	7[c]		72
3		90	8		n.d.
4		97	9[c]		70
5		98			

[a]Benzamide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (0.5 mol %), Cs_2CO_3 (0.05 mmol), 120 °C, 12 h. [b]Isolated yield. [c]Benzamide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (1.0 mol %), Cs_2CO_3 (0.125 mmol), 120 °C, 12 h.

These alcohols showed good to excellent reactivity when applied in the reaction. A longer reaction time was required to give high to excellent yields. The 3-pyridenemethanol and 2-pyridenemethanol were successfully used as substrates (Table 3, entries 1−3). When thiophenenemethanol substrates were used, excellent isolated yields of N-monoalkylated products were obtained (Table 3, entries 4 and 5). Alkylation of benzamide with furan alcohol substrates and aliphatic alcohol butanol as a alkylating reagent also gave the desired N-monoalkylated product in good yields although 1.0 mol % of catalyst loading and 0.5 equiv of base was required (Table 3, entries 6, 7 and 9). For imidazole alcohol (Table 3, entry 8), no conversion was observed.

Benzamide derivatives were also studied in the N-monoalkylation resulting in the desired products in moderate to excellent yields (Table 4). The benzamide derivatives bearing electron-donating substituents, such as methyl and methoxy groups, resulted in the desired products in good yields (Table 4, entries 1 and 5). When *o*-methylbenzamide substrate was used, a slightly lower isolated product yield was obtained (Table 4, entry 6). Benzamides having an electron-withdrawing bromo substituent on the aromatic ring resulted in a slightly lower yield of the isolated product (Table 4, entry 4). The *o*-nitrobenzamide did not result in any desired product (Table 4, entry 5). Finally, the *p*-toluamide successfully reacted with aliphatic alcohols, but more harsher reaction conditions were required to obtain the products in moderate 77% and 72% isolated yields (Table 4, entries 2 and 3).

To investigate the substrate scope further, reactions of heterocyclic and aliphatic amides with various alcohols were studied for the N-alkylation (Table 5, entries 1−10).

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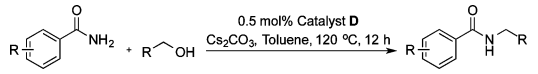
Table 4. N-Monoalkylation of Benzamide Derivatives with Various Alcohols Using NHC,P−Ir Catalysts[a]



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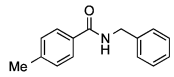
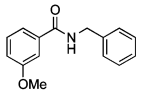
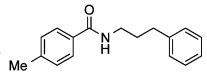
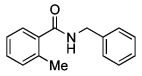
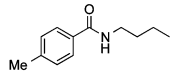
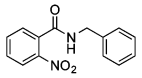
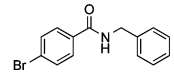
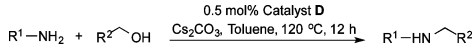
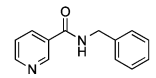
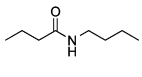
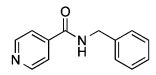
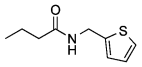
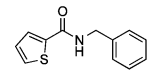
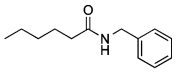
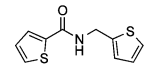
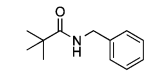
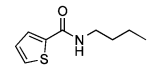
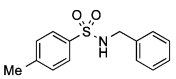
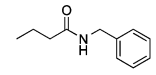
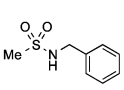
1		93	5		96
2[c]		72	6		84
3[c]		77	7		n.d.
4		78			

[a]Amide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (0.5 mol %), Cs_2CO_3 (0.05 mmol), 120 °C, 12 h. [b]Isolated yield. [c]Amide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (1.0 mol %), Cs_2CO_3 (0.125 mmol), 120 °C, 12 h.

Table 5. N-Monoalkylation of Heterocyclic Aromatic and Aliphatic Amides with Various Alcohols Using NHC,P−Ir Catalysts[a]



Entry	Product	yield (%)[b]	Entry	Product	yield (%)[b]
1		97	7[c,d]		5
2		94	8[e]		62
3		96	9		93
4		73	10		89
5[c]		52	11		98
6		86	12		95

[a]Amide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (0.5 mol %), Cs_2CO_3 (0.05 mmol), 120 °C, 12 h. [b]Isolated yield. [c]Amide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (1.0 mol %), Cs_2CO_3 (0.125 mmol), 120 °C, 12 h. [d]NMR yield using 1,3,5-trimethoxybenzene as internal standard. [e]Amide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (3.0 mol %), Cs_2CO_3 (0.125 mmol), 120 °C, 12 h.

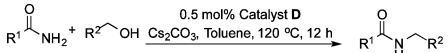
Nicotinamide and isonicotinamide were reacted with benzyl alcohol to obtain excellent isolated yields (Table 5, entries 1 and 2). Alkylation of 2-thiophenecarboxamide gave N-monoalkylated products in 96% isolated yield when reacted with benzyl alcohol and moderate yields when reacted with 2-thiophenemethanol and butanol (Table 5, entries 3−5). The catalyst also provided high efficiency for the alkylation of aliphatic amides, such as butyramide, hexanoamide, and pivalamide with benzyl alcohol (Table 5, entries 6, 9, and 10).

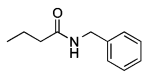
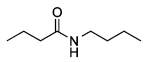
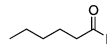
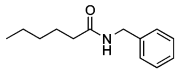
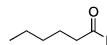
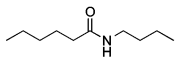
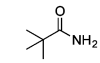
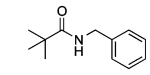
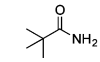
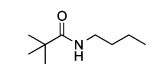
The reactions were completed in 12 h, and higher than 85% of isolated yields were achieved. The iridium catalyst was also successfully applied in N-monoalkylation of sulfonamide compounds with alcohol, such as *p*-tolunesulfonamide and methanesulfonamide, to afford the target products in excellent isolated yields (Table 5, entries 11 and 12). However, when butyramide was reacted with butanol, it showed much lower reactivity than benzyl alcohols (Table 5, entry 7).

The aliphatic amides were less reactive than aryl amides, perhaps because the alkyl substitution on the α-carbon decreased the acidity of the amide. Additionally, in the case of the other reagent, the alcohol, the aliphatic aldehydes generated in the reaction, might be more unstable under the reaction condition than benzyl aldehyde. This reactivity difference was first observed using benzamide, and was much more pronounced in the combination of an aliphatic amide and an aliphatic alcohol.

In order to shed further light on the reactivity difference, several combinations between aliphatic amides and aliphatic alcohols were carried out and summarized in Table 6. Three

Table 6. Comparison of the Reactivity Difference between Benzyl Alcohol and Butanol with Aliphatic Amides[a]



Entry	Amide	Product	yield (%)[b]
1			86
2[c,d]			5
3			93
4[c]			26
5			89
6[c]			n.d.

[a]Amide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (0.5 mol %), Cs_2CO_3 (0.05 mmol), 120 °C, 12 h. [b]Isolated yield. [c]Amide (0.25 mmol) in toluene (0.25 mL), alcohol (0.3 mmol), catalyst **D** (1.0 mol %), Cs_2CO_3 (0.125 mmol), 120 °C, 12 h. [d]NMR yield using 1,3,5-trimethoxybenzene as internal standard.

alkyl amides were chosen as the nucleophiles. Compared with the results from alkylation of benzamide with benzyl alcohol (Table 2, entry 1) which gave 96% yield in 3 h, aliphatic amides were less reactive and required longer reaction time and higher catalytic loading (1.0 mol %). With benzyl alcohol (Table 6, entry 1), the reaction went to completion in 12 h with over 85% yield. However, when the butyramide and butanol, which

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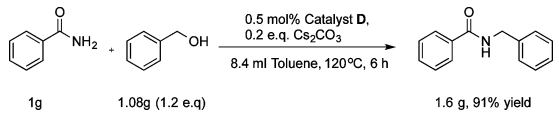
J. Org. Chem. 2015, 80, 11529−11537

are both poor reactants, were combined (Table 6, entry 2), it completely inhibited the alkylation reaction with only 5% of NMR yield. This reactivity difference was also observed with other aliphatic amides such as hexanoamide and pivalamide as well (Table 6, entries 3−6). The alkylation with butanol instead of benzyl alcohol decreased the yields from 93% to 26% (Table 6, entries 3 and 4) for hexanoamide and 89% to 0% (Table 6, entries 5 and 6) for pivalamide, respectively.

Next, the new iridium catalytic system for the alkylation of amide was evaluated in the large-scale reaction using 1 g of the benzamide and 0.5 mol % of the iridium catalyst **D** (Scheme 1). The reaction was completed in 6 h at 120 °C and 91% of the isolated yield was obtained.

Scheme 1. Alkylation of Benzamide with Benzyl Alcohol on a 1 g Scale



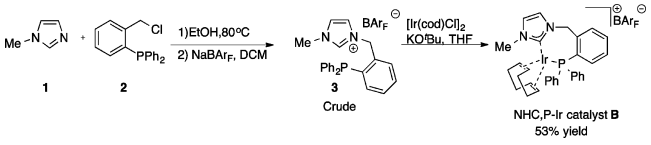
In conclusion, we have developed an efficient NHC−Ir catalyst system for N-monoalkylation of amides with alcohol via a hydrogen transfer reaction. Catalyst **D** exhibited high reactivity and good selectivity. A variety of substrate amides were converted to the desired product with various different alcohols in up to 98% isolated yield with low catalyst loading (only 0.5 mol %) in 3 to 12 h. Catalyst **D** also displayed high reactivity for N-monoalkylation of sulfonamides with alcohol to give the desired product in excellent yield.

EXPERIMENTAL SECTION

General Methods. Iridium-catalyzed alkylation was carried out under nitrogen atmosphere. The glass vessels were dried in the oven (160 °C) overnight and cooled to room temperature under nitrogen. Toluene and 1,4-dioxane were dried over sodium−benzophenone, distilled, and stored under nitrogen. Dimethylformamide and dimethyl sulfoxide were dried with molecular sieves 0.4 nm, followed by distillation under nitrogen. Amides and alcohols substrates were commercially available sources and purified by column chromatography or distillation. Potassium *tert*-butoxide, sodium *tert*-butoxide, potassium carbonate, potassium hydroxide, and cesium carbonate weresublimed grade. The thin-layer chromatography (TLC) was performed on aluminum plates coated with Kieselgel 60 (0.20 mm, UV 254) and visualized under ultraviolet light followed by staining with potassium permanganate solution. ^{1}HNMR spectra were recorded at 400 MHz in $CDCl_3$ and referenced internally to the residual $CHCl_3$ signal (7.26 ppm). ^{13}CNMR spectra were recorded at 100 MHz in $CDCl_3$ and referenced to the central peak of $CDCl_3$ (77.16 ppm). Chemical shifts are reported in ppm (δ scale), and coupling constants (J) are reported in hertz (Hz). IR spectra were obtained from an FT-IR spectrometer. High-resolution mass spectrometric (HRMS) data were obtained from a TOF-Q instrument operated at ambient temperatures.

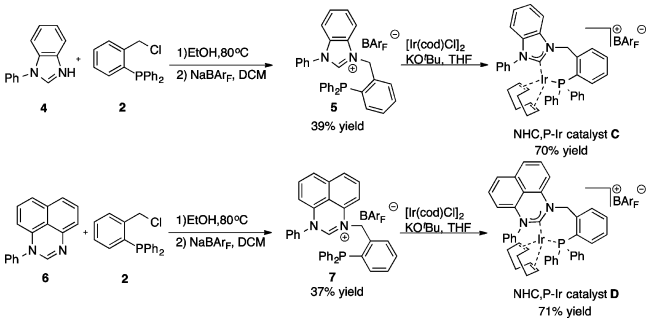
Synthesis of Catalyst A. Synthesis of catalyst **A** was reported by Li and Andersson in 2013.[27]

Synthesis of Catalyst B.



Under argon atmosphere, commercially available 1-methylimidazole **1** (2.0 mmol) was added to the Schlenk tube, followed by **2** (2.05 mmol) in ethanol (8 mL). The mixture was allowed to stir at 80 °C for 48 h. The ethanol was removed under the vacuum. The crude product was dissolved in dichloromethane (5 mL), and $NaBAr_F$ (2.2 mmol) was added. After the reaction mixture was stirred at room temperature for 1 h, the mixture was filtrated through Celite and the solvent was removed under the vacuum. The resulting residue was dissolved in dry THF (10 mL) under argon, followed by addition of $[Ir(cod)Cl]_2$ (1.0 mmol) and KO^{t}Bu (2.1 mmol). The mixture was stirred at room temperature for 3 h under argon atmosphere. After the reaction was complete, the solvent was removed under the vacuum and the residual was purified by flash column chromatography on silica gel with dichloromethane/pentane (3:1) as the eluent to obtain 1.62 g of NHC,P−Ir catalyst B as red solids in 53% yield in three steps. R_f = 0.50 (DCM/pentane = 3/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (m, 2H), 7.72 (m, 8H), 7.50−7.47 (m, 10H), 7.35−7.20 (m, 3H), 6.95−6.90 (m, 2H), 5.03 (m, 1H), 4.75 (d, J = 14 Hz, 1H), 4.60 (m, 1H), 3.97 (m, 1H), 3.12 (m, 1H), 2.80 (m, 1H), 2.50 (m, 2H), 2.30 (m, 2H), 1.65−1.55 (m,5H), 1.26−1.12 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1 (d, J = 11 Hz), 161.9 (dd, J = 101, 50 Hz), 141.2(d, J = 9 Hz), 137.2, 134.8, 133.6, 131.7, 130.5 (d, J = 7 Hz), 129.5−128.6 (m), 126.5,126.1, 125.8, 123.2, 122.7, 122.0, 120.7, 120.5, 117.4 (m), 86.3 (d, J = 11 Hz), 82.0,80.1 (d, J = 13 Hz), 79.7, 56.2 (d, J = 6 Hz), 36.5, 36.3, 36.0, 35.7, 32.0, 31.7, 30.7,30.2, 27.0−25.4 (m). ^{31}P NMR ($CDCl_3$, 100 MHz): δ 2.1. IR (neat, cm^{-1}): ν = 3060, 2924, 1610, 1354, 1278, 1125, 887, 741. HRMS (EI) m/z: $[M - BAr_F]^+$ calcd for $C_{31}H_{33}IrN_2P$ 657.2006, found 657.2025.

Synthesis of Catalysts C and D.



Under argon atmosphere, compound **4**[39] or **6**[40] (0.6 mmol) was added to the Schlenk tube, followed by **2** (0.5 mmol) in ethanol (5 mL). The mixture was allowed to stir at 80 °C for 12 h. The ethanol was then removed under the vacuum. The crude product was dissolved in dichloromethane (5 mL), and then $NaBAr_F$ (0.6 mmol) was added. After the reaction mixture was stirred at room temperature for 1 h, the mixture was filtrated through Celite and the solvent was removed under the vacuum. The resulting residue was purified by column chromatography with dichloromethane/pentane (3:1) as the eluent to obtain compounds **5** and **7** as white solids with 39% and 37% yields, respectively.

Compound **5** or **7** (0.5 mmol) was dissolved in dry THF (10 mL) under argon, followed by addition of $[Ir(cod)Cl]_2$ (0.25 mmol) and KO^{t}Bu (0.525 mmol). The mixture was stirred at room temperature for 3 h under argon atmosphere. After the reaction was completed, the solvent was removed under the vacuum, and the residual was purified by flash column chromatography on silica gel with dichloromethane:-pentane (1:1 to 3:1) as the eluent to obtain NHC,P−Ir catalysts **C** and **D** as red solids with 70% and 71% yields, respectively.

Compound ***5***. White solid, 260 mg, 39% yield. R_f = 0.50 (DCM). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (s, 1H), 7.82 (m, 1H), 7.72 (s, 8H), 7.72−7.49 (m, 13H), 7.26 (m, 2H), 7.21−7.18 (m, 4H), 7.10 (d, J = 8 Hz, 2H), 7.00−6.97 (m, 4H),5.89 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6 (dd, J = 99, 50 Hz), 138.1, 137.9, 137.7 (d, J = 4 Hz), 136.1, 134.8, 134.2, 134.1, 133.6 (d, J = 6 Hz), 133.4, 133.2, 131.9, 131.5 (m), 131.4, 131.3, 130.9, 130.8, 130.7, 129.7, 129.4 (m), 129.0−128.9 (m), 128.7 (m), 128.6, 128.5 (m), 125.9, 124.2, 123.1, 120.6, 117.8, 113.8, 51.4 (d, J = 22 Hz). ^{31}P NMR ($CDCl_3$, 100 MHz): δ −18.4. IR (NaCl, neat, cm^{-1}): ν = 3058, 1610, 1355, 1279, 1126, 877, 742. HRMS (EI) m/z: $[M - BAr_F]^+$ calcd for $C_{32}H_{26}N_2P$ 469.1828, found 469.1830.

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J. Org. Chem. 2015, 80, 11529−11537

Catalyst **C**. Red solid, 571 mg, 70% yield. R_f = 0.50 (DCM/pentane = 3/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (m, 8H), 7.52 (m, 1H), 7.43−7.34 (m, 17H), 7.29−7.21 (m, 7H), 7.17 (m, 1H), 7.02 (m, 1H), 6.55 (d, J = 7.6 Hz, 2H), 5.38 (d, J = 14.8 Hz, 1H), 4.8 (m, 1H), 4.27 (m, 1H), 3.99 (m, 1H), 3.52 (m, 1H), 2.34 (m, 2H), 2.12 (m, 2H), 1.70−1.55 (m, 2H), 1.37 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.5 (d, J = 9 Hz), 161.9 (dd, J = 80, 40 Hz), 140.1 (d, J = 11 Hz), 139.4, 135.7 (d, J = 9 Hz), 134.8, 132.6, 132.5, 132.4, 132.2, 132.0, 131.3, 131.2 (m), 131.1, 130.7, 131.6, 130.2, 129.9, 129.6 (m), 128.8 (m), 128.5−128.3 (m), 127.8, 126.1, 125.6, 124.9, 124.5, 123.5, 117.5, 111.7, 109.8, 88.7 (d, J = 8 Hz), 85.9 (d, J = 10 Hz), 82.2, 82.1, 52.3, 52.2, 34.6, 33.7, 28.1, 28.0. ^{31}P NMR ($CDCl_3$, 100 MHz): δ 4.7. IR (NaCl, neat, cm^{-1}): ν = 3065, 2926, 1610, 1435, 1355, 1278, 1125, 887, 743. HRMS (EI) m/z: $[M - BAr_F]^+$ calcd for $C_{40}H_{37}IrN_2P$ 769.2320, found 769.2278.

Compound **7**. Yellow solid, 255 mg, 37% yield. R_f = 0.40 (DCM). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (m, 8H), 7.70 (m, 1H), 7.67−7.54 (m, 3H), 7.49 (m, 5H), 7.45−7.39 (m, 3H), 7.32−7.17 (m, 11H), 7.13−7.08 (m, 4H), 6.82 (d, J = 7.6 Hz, 1H), 6.23 (d, J = 7.2 Hz, 1H), 5.13 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.0 (dd, J = 99, 49 Hz), 150.8 (d, J = 5 Hz), 137.4 (d, J = 16 Hz), 135.8, 135.4, 135.0, 134.8, 133.7 (d, J = 20 Hz), 133.3 (d, J = 6 Hz), 133.0, 132.84, 131.7, 131.2, 131.0, 130.8 (d, J = 5 Hz), 130.6, 129.8, 129.3 (m), 129.0−129.1, 129.0, 128.8 (m), 128.6 (m), 128.1 (d, J = 8 Hz), 127.8, 125.9, 125.7 (m), 125.6, 123.5, 121.3, 120.9, 117.5, 110.1, 109.1, 56.0 (d, J = 17 Hz). ^{31}P NMR ($CDCl_3$, 100 MHz): δ −16.3. IR (NaCl, neat, cm^{-1}): ν = 3054, 2986, 1659, 1609, 1354, 1278, 1127, 895, 741. HRMS (EI) m/z: $[M - BAr_F]^+$ calcd for $C_{36}H_{28}N_2P$ 519.1985; Found 519.1993.

Catalyst **D**. Orange solid, 597 mg, 71% yield. R_f = 0.50 (DCM/pentane = 3/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (brs, 8H), 7.67 (m, 1H), 7.50−7.28 (m, 19H), 7.21−7.20 (m, 3H), 7.18 (m, 1H), 7.11 (m, 1H), 7.10−7.03 (m, 2H), 5.98 (m, 1H), 5.71 (d, J = 7.6 Hz, 1H), 5.34 (d, J = 14.4 Hz, 1H), 5.06 (m, 1H), 4.48 (m, 1H), 4.29 (m, 1H0, 3.56 (m, 1H), 3.26 (m, 1H), 2.27 (m, 1H), 2.14 (m, 2H), 1.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.9, 161.5 (dd, J = 100, 50 Hz), 139.2 (d, J = 14 Hz), 138.1, 137.9, 136.2, 134.8, 133.4, 133.1, 132.5−132.2 (m), 131.8, 131.7, 131.3, 131.1, 130.9, 130.6, 130.5, 130.3 (m), 129.2−129.0 (m), 128.9, 128.8, 128.5, 127.8, 127.3, 127.2, 125.6, 123.5, 122.9, 122.7, 122.4, 122.3, 121.3, 117.5, 107.8, 106.3, 84.5, 83.3, 82.9 (d, J = 6 Hz), 55.3, 39.7, 37.5, 34.9, 29.7, 29.3, 26.2, 25.8, 25.6, 25.4, 24.5. ^{31}P NMR ($CDCl_3$, 100 MHz): δ −4.6. IR (NaCl, neat, cm^{-1}): ν = 3055, 2926, 1601, 1354, 1278, 1126, 887, 743. HRMS (EI) m/z: $[M - BAr_F]^+$ calcd for $C_{44}H_{39}IrN_2P$ 819.2477, found 819.2457.

Procedure for Iridium Catalyzed Alkylation of Amides. To an oven-dried microwave vial (5 mL, tapered style) with magnetic stirring bar were added Cs_2CO_3 (16.3 mg, 0.05 mmol), NHC,P−Ir catalyst **D** (2.10 mg, 5 mol %), and amide reagent (0.25 mmol). Under nitrogen, alcohol (0.3 mmol) and toluene (0.25 mL) were added, followed degassing that used a vacuum pump and refilled with nitrogen three times. The reaction mixture was stirred for 3 or 12 h under 120 °C, and then the mixture was cooled to ambient temperature. The solvent was then removed under the vacuum, and the residue was purified by column chromatography (EtOAc/pentane).

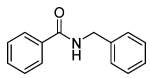


Table 2, Entry 1. White solid, 50.7 mg, 96% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 7.37−7.35 (m = 4H), 7.32−7.28 (m, 1H), 6.44 (s, 1H), 4.65 (d, J = 5.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 138.2, 134.3, 131.5, 128.7, 128.5, 127.9, 127.6, 126.9, 44.1.

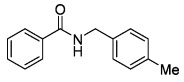


Table 2, Entry 2. White solid, 53.4 mg, 95% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J = 7.3 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.25 (d, J = 4.3 Hz, 2H), 7.16 (d, J = 4.3 Hz, 2H), 6.39 (s, 1H), 4.60 (d, J = 5.7 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 159.2, 134.5, 131.5, 130.2, 129.3, 128.6, 126.9, 114.2, 55.3, 43.7.

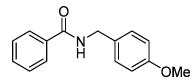


Table 2, Entry 3. Yellow solid, 58.6 mg, 97% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91−7.62 (m, 2H), 7.56−7.44 (m, 1H), 7.39 (td, J = 7.6, 2.2 Hz, 2H), 7.29−7.21 (m, 2H), 6.90−6.81 (m, 2H), 6.59 (d, J = 22.6 Hz, 1H), 4.54 (dd, J = 5.6, 2.9 Hz, 2H), 3.78 (d, J = 1.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 159.2, 134.5, 131.6, 130.43, 130.40, 129.35, 128.6, 127.1, 127.0, 114.2, 55.4, 43.7.

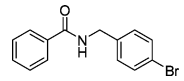


Table 2, Entry 4. White solid, 59.4 mg, 82% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85−7.66 (m, 2H), 7.56−7.45 (m, 1H), 7.41 (td, J = 8.5, 6.8 Hz, 4H), 7.22−7.12 (m, 2H), 6.86−6.69 (m, 1H), 4.54 (d, J = 5.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 137.5, 134.2, 131.9, 131.8, 129.6, 128.7, 127.1, 121.5, 43.5.

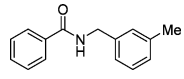


Table 2, Entry 5. Yellow solid, 50.0 mg, 89% yield. Spectral data match those previously reported.[41] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83−7.77 (m, 2H), 7.52−7.46 (m, 1H), 7.41 (dd, J = 8.2, 6.7 Hz, 2H), 7.28−7.21 (m, 1H), 7.17−7.08 (m, 2H), 6.59 (s, 1H), 4.59 (d, J = 5.6 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 138.6, 138.2, 134.5, 131.6, 128.8, 128.6, 128.4, 127.1, 125.0, 44.2, 21.5.

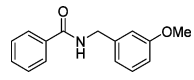


Table 2, Entry 6. Yellow solid, 54.8 mg, 91% yield. Spectral data match those previously reported.[41] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82−7.75 (m, 2H), 7.54−7.46 (m, 1H), 7.41 (ddd, J = 8.7, 4.9, 1.8 Hz, 2H), 7.30−7.23 (m, 1H), 6.97−6.87 (m, 2H), 6.83 (dd, J = 8.3, 2.5 Hz, 1H), 6.50 (s, 1H), 4.61 (d, J = 5.8 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 160.1, 139.9, 134.5, 131.7, 129.9, 128.7, 127.1, 120.2, 113.6, 113.2, 55.4, 44.2.

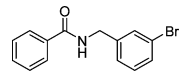


Table 2, Entry 7; N-(3-Bromobenzyl)benzamide. 70.0 mg, 97% yield. white solid; R_f = 0.54 (EtOAc/pentane =3/7), mp 104−105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83−7.74 (m, 2H), 7.55−7.47 (m, 2H), 7.47−7.38 (m, 3H), 7.32−7.26 (m, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.55 (s, 1H), 4.61 (d, J = 5.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 140.7, 134.2, 131.9, 130.9, 130.8, 130.5, 128.8, 127.1, 126.6, 122.9, 43.6. IR (NaCl, neat, cm^{-1}): IR: ν = 3293, 3080, 2931, 1638, 1576, 1546, 1416, 1351, 1255, 990, 750, 695. HRMS (EI) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}BrNO$ 290.0175, found 290.0161.

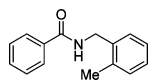
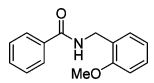


Table 2, Entry 8. White solid, 46.7 mg, 83% yield. Spectral data match those previously reported.[42] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81−7.76 (m, 2H), 7.53−7.47 (m, 1H), 7.45−7.39 (m, 2H), 7.32−7.28 (m, 1H), 7.24−7.17 (m, 3H), 6.30 (s, 1H), 4.64 (d, J = 5.3 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 136.8, 135.9, 134.5, 131.6, 130.8, 128.8, 128.7, 128.0, 127.1, 126.4, 42.5, 19.2.



DOI: 10.1021/acs.joc.5b01324
J. Org. Chem. 2015, 80, 11529−11537

Table 2, Entry 9. White solid, 54.0 mg, 90% yield. Spectral data match those previously reported.[43] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77−7.74 (m, 2H), 7.2−7.48 (m, 4H), 6.96−6.90 (m, 3H), 6.62 (s, 1H), 4.64 (d, J = 5.4 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 157.7, 134.8, 131.4, 129.0, 128.6, 127.0, 120.8, 110.5, 55.5, 40.1.

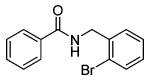


Table 2, Entry 10; N-(2-Bromobenzyl)benzamide. 59.5 mg, 82% yield. White solid. R_f = 0.67 (EtOAc/pentane = 3/7). Mp: 105−107 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84−7.74 (m, 2H), 7.57 (dd, J = 7.9, 1.3 Hz, 1H), 7.54−7.39 (m, 4H), 7.29 (td, J = 7.5, 1.3 Hz, 1H), 7.16 (td, J = 7.7, 1.8 Hz, 1H), 6.69 (s, 1H), 4.71 (d, J = 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 137.4, 134.4, 133.0, 131.8, 130.8, 129.4, 128.7, 127.9, 127.1, 124.0, 44.5. IR (NaCl, neat, cm^{-1}): IR: ν = 3268, 3061, 2925, 1641, 1535, 1498, 1306, 1026, 746, 692. HRMS (EI) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}BrNO$ 290.0175, found 290.0171.

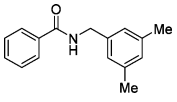


Table 2, Entry 11; N-(3,5-Dimethylbenzyl)benzamide. 58.6 mg, 98% yield. White solid. R_f = 0.69 (EtOAc/pentane = 3/7). Mp: 66−67 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84−7.77 (m, 2H), 7.53−7.46 (m, 1H), 7.42 (ddt, J = 8.3, 6.5, 1.3 Hz, 2H), 6.97 (d, J = 1.6 Hz, 2H), 6.94 (s, 1H), 6.51 (s, 1H), 4.56 (d, J = 5.6 Hz, 2H), 2.31 (d, J = 0.8 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 138.5, 138.2, 134.6, 131.6, 129.3, 128.7, 127.1, 125.9, 44.2, 21.4. IR (NaCl, neat, cm^{-1}): IR: ν = 3312, 3061, 3020, 2919, 1645, 1605, 1538, 1490, 1308, 848, 695. HRMS (EI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{17}NONa$ 262.1202, found 262.1191.

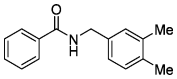


Table 2, Entry 12. White solid, 57.4 mg, 96% yield. Spectral data match those previously reported.[44] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (dd, J = 7.9, 1.5 Hz, 2H), 7.52−7.46 (m, 1H), 7.42 (td, J = 7.3, 1.3 Hz, 2H), 7.17−7.02 (m, 3H), 6.38 (s, 1H), 4.58 (dd, J = 5.5, 1.5 Hz, 2H), 2.26 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 137.2, 136.2, 135.7, 134.6, 131.6, 130.1, 129.5, 128.7, 127.1, 125.6, 44.1, 19.9, 19.6.

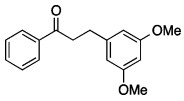


Table 2, Entry 13. White solid, 61.0 mg, 90% yield. Spectral data match those previously reported.[45] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82−7.75 (m, 2H), 7.53−7.45 (m, 1H), 7.45−7.37 (m, 2H), 6.58 (d, J = 5.9 Hz, 1H), 6.49 (d, J = 2.3 Hz, 2H), 6.37 (t, J = 2.2 Hz, 1H), 4.55 (d, J = 5.7 Hz, 2H), 3.76 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 161.2, 140.7, 134.4, 131.6, 128.7, 127.1, 105.9, 104.6, 99.5, 55.5, 44.3.

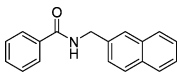


Table 2, Entry 14. White solid, 62.6 mg, 96% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89−7.74 (m, 6H), 7.56−7.39 (m, 6H), 6.51 (s, 1H), 4.81 (d, J = 5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 135.7, 134.5, 133.5, 133.0, 131.7, 128.8, 128.8, 127.9, 127.8, 127.1, 126.7, 126.5, 126.2, 126.1, 44.4.

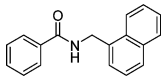


Table 2, Entry 15. White solid, 56.8 mg, 87% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13−8.04 (m, 1H), 7.90 (dd, J = 8.0, 1.6 Hz, 1H), 7.84 (dt, J = 8.2, 1.1 Hz, 1H), 7.78−7.72 (m, 2H), 7.61−7.33 (m, 7H), 6.39 (s, 1H), 5.09 (d, J = 5.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 134.4, 134.1, 133.5, 131.7, 131.6, 129.0, 128.9, 128.8, 128.7, 127.1, 126.9, 126.2, 125.6, 123.6, 42.7.

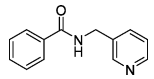


Table 3, Entry 1. Yellow oil, 50.4 mg, 95% yield. Spectral data match those previously reported.[42] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62−8.45 (m, 2H), 7.84−7.78 (m, 2H), 7.72 (d, J = 7.9 Hz, 1H), 7.53−7.46 (m, 1H), 7.41 (tt, J = 7.2, 1.8 Hz, 2H), 7.27 (d, J = 6.7 Hz, 1H), 7.08−6.88 (m, 1H), 4.63 (dt, J = 5.7, 3.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 149.0, 148.6, 136.3, 134.5, 134.1, 131.9, 128.8, 127.2, 123.9, 41.6.

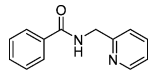


Table 3, Entry 2. Yellow oil, 46.1 mg, 87% yield. Spectral data match those previously reported.[42] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.56 (dt, J = 5.0, 1.3 Hz, 1H), 7.90−7.84 (m, 2H), 7.73−7.57 (m, J = 8.0, 2.3 Hz, 2H), 7.54−7.47 (m, 1H), 7.47−7.40 (m, 2H), 7.32 (d, J = 7.8 Hz, 1H), 7.21 (ddd, J = 7.5, 5.0, 1.1 Hz, 1H), 4.76 (d, J = 4.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 156.3, 149.1, 137.0, 134.5, 131.6, 128.7, 127.2, 122.6, 122.3, 44.8.

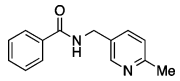


Table 3, Entry 3; N-((6-Methylpyridin-3-yl)methyl)benzamide. 50.9 mg, 90% yield. White solid. R_f = 0.38 (EtOAc/pentane = 3/7). Mp: 103−105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (d, J = 2.3 Hz, 1H), 7.82−7.75 (m, 2H), 7.64 (dd, J = 8.0, 2.3 Hz, 1H), 7.54−7.48 (m, 1H), 7.44 (ddt, J = 8.2, 6.6, 1.3 Hz, 2H), 7.16 (d, J = 7.9 Hz, 1H), 6.49 (s, 1H), 4.63 (d, J = 5.8 Hz, 2H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 157.7, 148.5, 136.5, 134.2, 131.8, 131.2, 128.8, 127.1, 123.4, 41.3, 24.1. IR (NaCl, neat, cm^{-1}): IR: ν = 3263, 3061, 2924, 1641, 1603, 1577, 1539, 1490, 1297, 1032, 705. HRMS (EI) m/z: $[M + H]^+$ calcd for $C_{14}H_{15}N_2O$ 227.1179, found 227.1186.

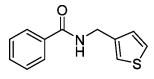


Table 3, Entry 4; N-(Thiophene-3-ylmethyl)benzamide. 52.7 mg, 97% yield. White solid. R_f = 0.50 (EtOAc/pentane = 3/7). Mp: 103−105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82−7.73 (m, 2H), 7.52−7.45 (m, 1H), 7.45−7.36 (m, 2H), 7.30 (dd, J = 5.0, 2.9 Hz, 1H), 7.19 (qd, J = 3.0, 2.0, 1.3 Hz, 1H), 7.07 (dd, J = 4.9, 1.4 Hz, 1H), 6.60 (s, 1H), 4.62 (d, J = 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 139.1, 134.4, 131.7, 128.7, 127.5, 127.08, 127.07, 126.59, 126.57, 122.6, 77.5, 77.2, 76.8, 39.4. IR (NaCl, neat, cm^{-1}): IR: ν = 3301, 3053, 2933, 1637, 1543, 1422, 1333, 1254, 987, 760, 690. HRMS (EI) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}NOS$ 218.0634, found 218.0626.

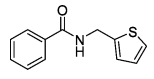


Table 3, Entry 5. Yellow solid, 53.2 mg, 98% yield. Spectral data match those previously reported.[42] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83−7.74 (m, 2H), 7.54−7.47 (m, 1H), 7.43 (dd, J = 8.3, 6.8 Hz, 2H), 7.27−7.23 (m, 1H), 7.05 (dd, J = 3.4, 1.1 Hz, 1H), 6.97 (dd, J = 5.1, 3.4 Hz, 1H), 6.46 (s, 1H), 4.82 (d, J = 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 140.9, 134.3, 131.8, 128.8, 127.1, 126.4, 125.5, 39.0.

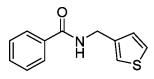


Table 3, Entry 6; N-(Furan-3-ylmethyl)benzamide. 31.7 mg, 63% yield. Brown solid. R_f = 0.44 (EtOAc/pentane = 3/7). Mp: 68−70 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80−7.75 (m, 2H), 7.54−7.47 (m, 1H), 7.47−7.39 (m, 4H), 6.43 (dd, J = 1.9, 0.9 Hz, 1H), 6.24 (s, 1H),

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J. Org. Chem. 2015, 80, 11529−11537

4.50 (dd, J = 5.6, 0.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 143.8, 140.5, 134.5, 131.7, 128.8, 127.0, 122.3, 110.5, 35.2. IR (NaCl, neat, cm^{-1}): IR: ν = 3309, 3058, 2940, 1636, 1545, 1491, 1311, 1262, 1156, 991, 777, 692. HRMS (EI) m/z: $[M + H]^+$ calcd for $C_{12}H_{12}NO_2$ 202.0863, found 202.0857.

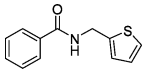


Table 3, Entry 7. Yellow solid, 36.2 mg, 72% yield. Spectral data match those previously reported.[46] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82−7.74 (m, 2H), 7.54−7.46 (m, 1H), 7.46−7.39 (m, 2H), 7.38 (dd, J = 1.9, 0.8 Hz, 1H), 6.42 (s, 1H), 6.35 (dd, J = 3.3, 1.9 Hz, 1H), 6.32−6.29 (m, 1H), 4.65 (d, J = 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 151.3, 142.5, 134.3, 131.8, 128.7, 127.1, 110.7, 107.9, 37.2.

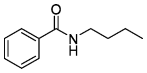


Table 3, Entry 9. Yellow oil, 31.0 mg, 70% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79−7.72 (m, 2H), 7.52−7.45 (m, 1H), 7.45−7.39 (m, 2H), 6.14 (s, 1H), 3.50−3.38 (m, 2H), 1.71−1.53 (m, 2H), 1.42 (h, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 135.0, 131.4, 128.7, 126.9, 39.9, 31.9, 20.3, 13.9.

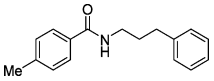


Table 4, Entry 1. White solid, 52.4 mg, 93% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72−7.67 (m, 2H), 7.35 (d, J = 4.4 Hz, 4H), 7.32−7.27 (m, 1H), 7.22 (d, J = 7.9 Hz, 2H), 6.48 (s, 1H), 4.63 (d, J = 5.7, 1.0 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.4, 142.1, 138.4, 131.6, 129.3, 128.9, 128.0, 127.7, 127.1, 44.2, 21.6.

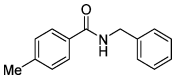
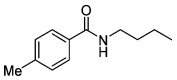


Table 4, Entry 2: 4-methyl-N-(3-phenylpropyl)benzamide. 45.6 mg, 72% yield. Yellow solid. R_f = 0.63 (EtOAc/pentane = 3/7). Mp: 64−66 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63−7.52 (m, 2H), 7.33−7.27 (m, 3H), 7.25−7.16 (m, 5H), 6.06 (s, 1H), 3.50 (td, J = 7.1, 5.8 Hz, 2H), 2.73 (t, J = 7.5 Hz, 2H), 2.38 (s, 4H), 2.03−1.88 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 141.8, 141.7, 132.0, 129.3, 128.7, 128.5, 126.9, 126.2, 39.9, 33.7, 31.3, 21.6. IR (NaCl, neat, cm^{-1}): IR: ν = 3308, 3027, 2925, 1634, 1547, 1505, 1453, 1306, 1187, 838, 750, 699. HRMS (EI) m/z: $[M + H]^+$ calcd for $C_{17}H_{20}NO$ 254.1539, found 254.1535.



,*Table 4, Entry 3.* Yellow oil, 36.8 mg, 77% yield. Spectral data match those previously reported.[47] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69−7.62 (m, 2H), 7.24−7.19 (m, 2H), 6.12 (s, 1H), 3.44 (td, J = 7.1, 5.7 Hz, 2H), 2.38 (s, 3H), 1.64−1.53 (m, 2H), 1.48−1.32 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 141.8, 132.2, 129.3, 126.9, 39.9, 31.9, 21.5, 20.30, 13.9.

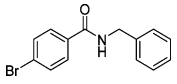


Table 4, Entry 4. White solid, 56.6 mg, 78% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69−7.62 (m, 2H), 7.58−7.51 (m, 2H), 7.39−7.27 (m, 5H), 6.47 (s, 1H), 4.62 (d, J = 5.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.5, 138.0, 133.3, 131.9, 129.0, 128.7, 128.07, 127.9, 126.4, 44.4.

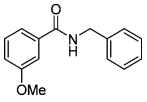


Table 4, Entry 5. Yellow solid, 58.0 mg, 96% yield. Spectral data match those previously reported.[41] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41−7.37 (m, 1H), 7.35 (d, J = 4.4 Hz, 4H), 7.32−7.27 (m, 3H), 7.03 (dt, J = 6.9, 2.5 Hz, 1H), 6.50 (s, 1H), 4.63 (d, J = 5.7 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 160.0, 138.3, 136.0, 129.7, 128.9, 128.0, 127.7, 118.8, 117.9, 112.5, 55.6, 44.3.

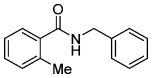


Table 4, Entry 6. White solid, 47.3 mg, 84% yield. Spectral data match those previously reported.[48] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39−7.27 (m, 7H), 7.24−7.15 (m, 2H), 6.10 (s, 1H), 4.62 (d, J = 6.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0, 138.3, 136.4, 136.3, 131.2, 130.1, 128.9, 128.0, 127.7, 126.8, 125.8, 44.0, 20.0.

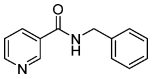


Table 5, Entry 1. White solid, 51.5 mg, 97% yield. Spectral data match those previously reported.[48] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.94 (d, J = 2.6 Hz, 1H), 8.67 (q, J = 3.1, 2.0 Hz, 1H), 8.12 (dq, J = 8.0, 1.9 Hz, 1H), 7.42−7.25 (m, 6H), 6.75 (s, 1H), 4.64 (dd, J = 6.0, 2.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 152.4, 148.0, 137.8, 135.3, 130.2, 129.0, 128.1, 127.9, 123.6, 44.3.

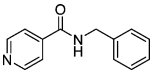


Table 5, Entry 2. Yellow oil, 49.9 mg, 94% yield. Spectral data match those previously reported.[49] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74−8.63 (m, 2H), 7.65−7.56 (m, 2H), 7.41−7.28 (m, 5H), 6.74 (s, 1H), 4.63 (d, J = 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6, 150.7, 141.6, 137.6, 129.0, 128.1, 128.0, 121.0, 44.4.

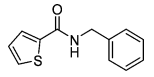


Table 5, Entry 3. White solid, 52.2 mg, 96% yield. Spectral data match those previously reported.[50] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (dd, J = 3.9, 1.1 Hz, 1H), 7.47 (dd, J = 5.0, 1.2 Hz, 1H), 7.35 (d, J = 4.4 Hz, 4H), 7.32−7.27 (m, 1H), 7.06 (dd, J = 5.0, 3.7 Hz, 1H), 6.34 (s, 1H), 4.62 (d, J = 5.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 138.9, 138.2, 130.1, 128.9, 128.3, 128.1, 127.8, 127.8, 44.2.

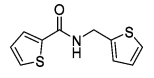


Table 5, Entry 4. Yellow solid, 40.7 mg, 73% yield. Spectral data match those previously reported.[44] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53−7.45 (m, 2H), 7.27−7.22 (m, 1H), 7.10−7.03 (m, 2H), 6.97 (dd, J = 5.1, 3.5 Hz, 1H), 6.32 (s, 1H), 4.79 (d, J = 5.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 140.7, 138.6, 130.3, 128.5, 127.8, 127.1, 126.5, 125.6, 38.8.

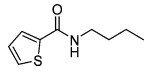


Table 5, Entry 5. White solid, 23.8 mg, 52% yield. Spectral data match those previously reported.[47] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (dq, J = 3.6, 1.1 Hz, 1H), 7.45 (dt, J = 5.0, 1.1 Hz, 1H), 7.06 (ddd, J = 5.0, 3.7, 1.3 Hz, 1H), 5.99 (s, 1H), 3.52−3.37 (m, 2H), 1.73−1.52 (m, 2H), 1.47−1.33 (m, 2H), 0.95 (td, J = 7.3, 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.0, 129.7, 127.9, 127.7, 39.9, 31.9, 20.3, 13.9.

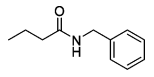


Table 5, Entry 6. White solid, 38.1 mg, 86% yield. Spectral data match those previously reported.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.30 (m, 2H), 7.27 (dd, J = 7.1, 2.7 Hz, 3H), 5.81 (s, 1H), 4.43 (d, J = 5.7 Hz, 2H), 2.23−2.13 (m, 2H), 1.69 (h, J = 7.4 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.9, 138.6, 128.8, 127.9, 127.6, 43.7, 38.8, 19.3, 13.93.

DOI: 10.1021/acs.joc.5b01324
J. Org. Chem. 2015, 80, 11529−11537

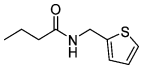


Table 5, Entry 8; N-(thiophen-2-ylmethyl)butyramide. 17.0 mg, 37% yield. Brown solid. R_f = 0.37 (EtOAc/pentane = 3/7). Mp: 53−55 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (dd, J = 4.9, 1.5 Hz, 1H), 6.99−6.92 (m, 2H), 5.76 (s, 1H), 4.62 (d, J = 5.6 Hz, 2H), 2.18 (t, J = 7.4 Hz, 2H), 1.68 (h, J = 7.4 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.7, 141.3, 127.0, 126.1, 125.3, 38.7, 38.4, 19.2, 13.9. IR (NaCl, neat, cm^{-1}): IR: ν = 3289, 3053, 2963, 2931, 1646, 1545, 1424, 1366, 1265, 1219, 738, 701. HRMS (EI) m/z: $[M + Na]^+$ calcd for $C_9H_{13}NOS$ 206.0610, found 206.0609.

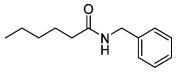


Table 5, Entry 9. White solid, 47.7 mg, 93% yield. Spectral data match those previously reported.[51] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.31 (m, 2H), 7.31−7.24 (m, 3H), 5.70 (s, 1H), 4.44 (d, J = 5.7 Hz, 2H), 2.26−2.12 (m, 2H), 1.72−1.57 (m, 2H), 1.40−1.19 (m, 4H), 0.94−0.84 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 138.6, 128.9, 128.0, 127.6, 43.8, 36.9, 31.6, 25.60, 22.5, 14.1.

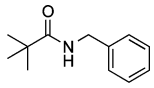


Table 5, Entry 10. Yellow solid, 42.6 mg, 89% yield. Spectral data match those previously reported.[29] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23−7.40 (m, 5H), 5.93 (br, 1H), 4.43 (d, J = 5.6 Hz, 2H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.5 (3C), 38.6, 43.4, 127.2, 127.5 (2C), 128.5 (2C), 138.6, 178.2.

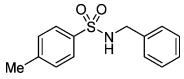


Table 5, Entry 11. White solid, 64.0 mg, 98% yield. Spectral data match those previously reported.[36] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (dd, J = 8.3, 1.7 Hz, 2H), 7.33−7.23 (m, 5H), 7.19 (dd, J = 7.5, 2.1 Hz, 2H), 4.79 (t, J = 6.4 Hz, 1H), 4.12 (d, J = 5.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 137.0, 136.4, 129.9, 128.8, 128.0, 128.0, 127.3, 47.4, 21.7.

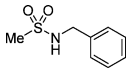


Table 5, Entry 12. White solid, 44.0 mg, 95% yield. Spectral data match those previously reported.[36] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39−7.28 (m, 5H), 4.92 (s, 1H), 4.30 (d, J = 6.2 Hz, 2H), 2.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.8, 129.0, 128.2, 128.0, 47.3, 41.2.

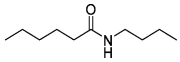


Table 5, Entry 4. Yellow oil, 11.1 mg, 26% yield. Spectral data match those previously reported.[52] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.42 (s, 1H), 3.24 (td, J = 7.1, 5.7 Hz, 2H), 2.20−2.08 (m, 2H), 1.76−1.55 (m, 2H), 1.56−1.42 (m, 2H), 1.40−1.19 (m, 6H), 0.95−0.88 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.2, 39.3, 37.0, 31.9, 31.6, 25.7, 22.6, 20.2, 14.1, 13.9.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01324.

^{1}H and ^{13}C NMR spectra for new compounds; ^{1}H NMR spectra for known N-monoalkylated amides(PDF)

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Notes

The authors declare no competing financial interest.

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