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A Nitrogen-Assisted One-Pot Heteroaryl Ketone Synthesis from Carboxylic Acids and Heteroaryl Halides

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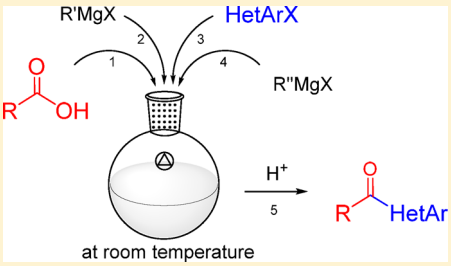
Supporting Information

ABSTRACT: A practical and highly effective one-pot synthesis of versatile heteroaryl ketones directly from carboxylic acids and heteroaryl halides under mild conditions is reported. This method does not require derivatization of carboxylic acids (preparation of acid chlorides, Weinreb amides, etc.) or the use of any additives/catalysts. A wide substrate scope of carboxylic acids with high functional group tolerance has also been demonstrated. The results reveal that the presence of an α-nitrogen on the halide substrate greatly improves the desired ketone formation.



Heteroaryl ketones are common structures in organic and medicinal chemistry,[1] particularly pyridyl ketones such as **1**,[1b] a potent COX-2 selective inhibitor, and **2**, a key intermediate in the synthesis of TGF-β type 1 receptor inhibitor LY580276 (Figure 1).[1c,d]

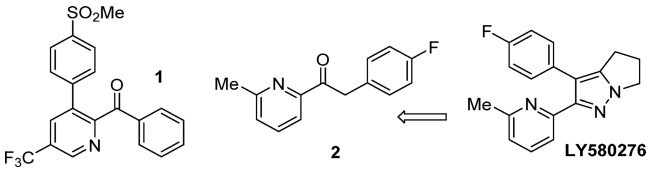


Figure 1. Pyridyl ketones as a pharmaceutically active compound (**1**) and an intermediate (**2**).

Among synthetic methods for heteroaryl ketones, the reactions between organometallic reagents and carboxylic acid derivatives (e.g., acid chloride,[1b,2] anhydride,[3] ester,[1c] amide,[1e,4,5] or nitrile[6]) are most widely used. Direct conversion from carboxylic acids is less frequently employed but is attractive due to its practical advantages: step/atom efficiency, commercial availability of structurally diverse carboxylic acids, and potentially reduced reaction waste. Gilman first reported the direct conversion of carboxylic acids to ketones using excess organolithium reagents in 1933.[7] The method has been applied to heteroaryl ketones, especially 2-pyridyl ketones, by combining with halogen–metal exchange of haloheterocycles.[8] However, the main drawbacks of this method include poor functional group tolerance, an excess amount of reagents required, and cryogenic processing. Although various mild reactions using heteroaryl Grignard reagents with noncarboxylic acid electrophiles have been reported[1e,2,4,5,9−12] with an excellent functional group tolerance,[2] Grignard reagents are less often used directly with carboxylic acids than the analogous lithium reagents.[13−15] This is likely because of the tendency of Grignard reagents to over react, leading to the undesired tertiary alcohol.[13,14] Recent publications have proposed the improved reaction of carboxylic acids and aryl metal species with modified Grignard reagents,[15] nickel-catalyzed reactions with Grignard reagents,[14] and a palladium-catalyzed coupling with aryl boronic acid.[16] These methods require a furnished Grignard reagent, such as alkyl magnesium amide,[15] addition of transition metal catalyst,[14,16] or additives such as di(*N*-succinimidyl)carbonate.[16] Moreover, the two Grignard methods showed only examples using a commercially available phenyl magnesium reagent,[14,15] and the boronic acid reaction requires an extra borylation step.[16] To the best of our knowledge, no example of direct ketone synthesis from a carboxylic acid and pyridyl Grignard reagent has been reported. Therefore, a convenient and functional group tolerant reaction from a carboxylic acid and a heteroaryl (especially pyridyl) halide to the corresponding ketone is still in demand.

Recent development efforts in our laboratories focused on the effective preparation of aryl–pyridyl ketone intermediate **3**. Treatment of 4-(methoxycarbonyl)benzoic acid with in situ generated 2-pyridylmagnesium chloride provided **3** in 96% isolated yield (Scheme 1). This ketone synthesis is specifically attractive due to its practical advantages: tolerance of an ester

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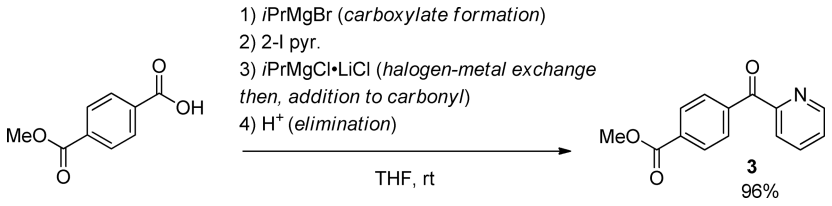
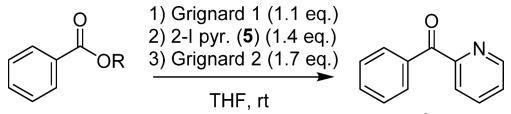
Scheme 1. Highly Effective Synthesis of an Aryl−Pyridyl Ketone



group, no tertiary alcohol formation, one pot synthesis, and ambient reaction temperature. Encouraged by its potential in the preparation of highly valuable heteroaryl ketone moieties, an investigation was carried out to further explore this transformation. Herein, we disclose the reaction scope and limitations.

Our investigation began with a screening of the reaction conditions using benzoic acid inorganic salts or the free acid (**4**) and 2-iodopyridine (**5**) to prepare an aryl−pyridyl ketone (**6**) (Table 1). The primary focus was to identify the optimal R group and Grignard reagent combination for clean conversion from **4** to **6**. Alkaline metal (K, Na, Li) benzoates were treated with *i*PrMgCl·LiCl in the presence of **5** (entries 1−3). HPLC analysis showed clean but incomplete conversion to **6**, likely because of low solubility of the salts in THF. A counterion (K vs Na vs Li) effect was not observed. The coupling reaction from magnesium benzoate generated in situ with *i*PrMgBr was investigated by combining with a halogen−metal exchanging reaction. Compared to various Grignard 2 reagents (EtMgCl, EtMgBr, *i*PrMgBr, vinylMgCl, and vinylMgBr), *i*PrMgCl·LiCl provided the best conversion yield (entry 4 vs 5−9). The method was also superior to the corresponding reaction with the other benzoic acid salts (K, Na, Li, entry 4 vs 1−3). Vinyl magnesium reagents, rarely used for halogen−magnesium exchange, were the least effective (entries 8 and 9).[17] Interestingly,[18] the iodine−lithium exchange reaction with MeLi performed equally well compared to the Grignard reagent (entry 10), and excellent conversion yield was obtained. In addition, the same Grignard reagents (*i*PrMgBr, *i*PrMgCl·LiCl) were confirmed to be applicable to both the salt formation and the iodine−magnesium exchange reaction (entries 11 and 12).

Table 1. Determining Optimal Reaction Conditions[a]



4 **6**

entry[b]	R	Grignard 1	Grignard 2	**6** (%)[c]
1	K		*i*PrMgCl·LiCl	80
2	Na		*i*PrMgCl·LiCl	87
3	Li		*i*PrMgCl·LiCl	87
4	H	*i*PrMgBr	*i*PrMgCl·LiCl	99
5	H	*i*PrMgBr	EtMgCl	86
6	H	*i*PrMgBr	EtMgBr	93
7	H	*i*PrMgBr	*i*PrMgBr	95
8	H	*i*PrMgBr	vinylMgCl	59
9	H	*i*PrMgBr	vinylMgBr	69
10	H	*i*PrMgBr	MeLi	93
11[d]	H	*i*PrMgBr		90
12[d]	H	*i*PrMgCl·LiCl		89

[a]The reaction mixture was stirred for 15 min after Grignard 1 addition and 1 h after Grignard 2 addition. [b]Reaction scale: **4** (500 mg) in 25 mL of anhydrous THF. [c]Conversion to **6** was based on **4** (% conv = AUC-**6**/(AUC-**4** + AUC-**6**)) and determined by UHPLC (254 nm) of the reaction mixture. [d]Consolidated Grignard reagent (2.75 equiv) was added in one portion.

For the scope of this reaction to be determined, acids **7a** and **b** and halides **8a−j** were reacted under the optimized protocol (Table 1, entry 4). Benzoic acid (**7a**) reacted with 2-iodopyridine (**8a**) and 2-bromopyridine (**8a′**) to afford **9a** in 88% (**8a**) and 83% (**8a′**) yield, respectively.[2] Starting from picolinic acid (**7b**) and iodobenzene (**8b**), **9a** was obtained in a quite lower yield (46%) compared to the yield from **7a**/**8a**. Consistent with the literature,[13,14] the reaction between **7a** and **8b** produced desired product **9b** in a poor yield (26% determined by wt/wt assay) with notable byproduct formation.[19] The remarkable yield difference between **9a** and **9b** led to a hypothesis that the nitrogen in **8** was critical for desired reactivity.[5] The position of the nitrogen relative to the halogen in the heteroaryl halide was also found to be important because **9c** and **9d** were not formed under the same reaction conditions that afforded **9a**. A similar 2-pyridyl effect was also reported for the addition of a pyridyl Grignard reagent to an aldehyde.[12] For other heterocyclic nucleophiles, the reaction went smoothly whenever an α-nitrogen was present, and the desired products were obtained in 79% (**9e**), 70% (**8f** → **9f**), 37% (**8f′** → **9f**), and 47% (**9g**) yield. In contrast, heterocyclic nucleophiles without an α-nitrogen reacted sluggishly (**9i** and **9h**) or not at all (**7a** and **8j**).

Next, the effect of modifying functional groups on the acid substrates **10a−s** was studied under the standard reaction conditions using 2-iodopyridine (**5**) (Table 3). Halogens were tolerated; **11a−c** were isolated with 94, 80, and 64% yields, respectively. The decreasing yields from **11a** to **11c** are in agreement with increasing reactivity of Cl, Br, and I with *i*PrMgCl·LiCl,[20] leading to the undesired competing halogen metal exchange over **5**. The electron-donating methoxy group showed no change of benzoic acid reactivity, and **11d** was isolated in 94% yield. A critical intermediate bearing a methyl group for the marketed allergy drug triprolidine,[21] **11e**, was readily isolated without chromatography in 75% yield. The desired ester (**11f** and **g**) and nitrile (**11h**) products from substituted benzoic acids were obtained in good to excellent yields with high functional group tolerance.[2] Distinctively, diacid **10i** afforded bis-ketone **11i** when excess Grignard reagent was used. The targeted ketones containing an acidic proton for phenol (**11j**), acetamide (**11k**), and indole (**11l**) were also obtained with excess **5** and the Grignard reagents in 62, 82, and 90% yields, respectively. A nitrogen or sulfur atom in carboxylic acid **10** did not interfere with the reaction; **11m** and **11n** were prepared in moderate to good yields. Aliphatic carboxylic acids (**10o** and **10p**) underwent the same reaction to afford mono aryl ketone **11o** and **11p** in 76 and 82% isolated yields, respectively. A methyl ketone was found reactive toward

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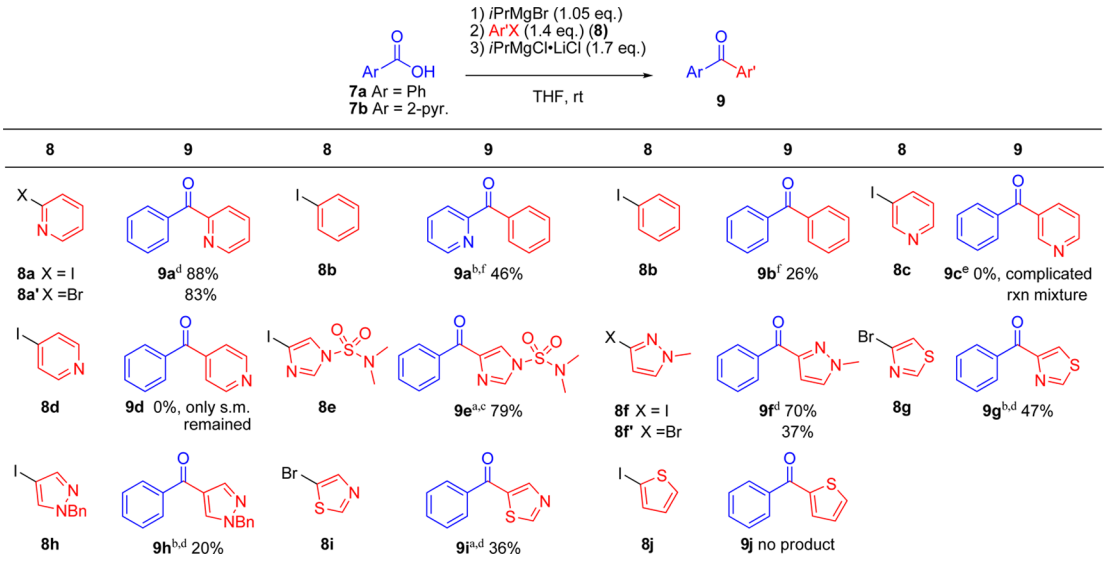
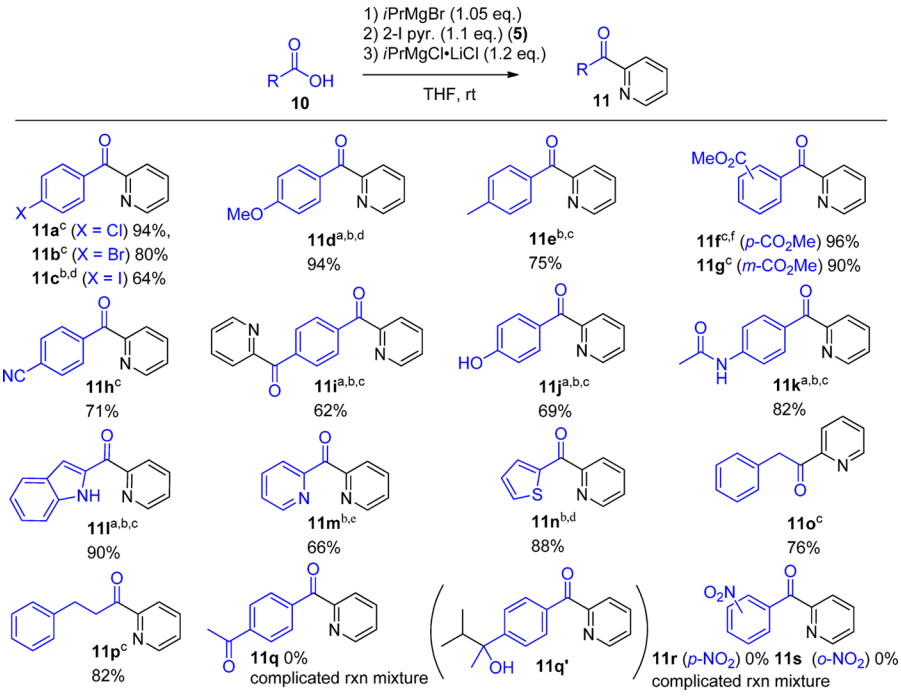
Table 2. Preparation of Heteroaryl Ketones[g]



[a]Compound **8** (1.1 equiv), *i*PrMgBr (1.05 equiv), and *i*PrMgCl·LiCl (1.4 equiv) used. [b]Extra **8** and *i*PrMgCl·LiCl used. [c]Yield without chromatography. [d]Yield after chromatography. [e](BINOLate)Bu_2MgLi_2 added as additive. [f]Assay by wt/wt. [g]The reaction was typically run for 4−5 h.

Table 3. Functional Group Tolerance of the Reaction[g]



[a]Extra *i*PrMgBr was used. [b]Extra **5** and *i*PrMgCl·LiCl were used. [c]Yield without chromatography. [d]Yield after chromatography. [e]Assay by wt/wt. [f]**11f** identical to **3**. [g]The reaction was typically run for 2−5 h.

*i*PrMgBr, and a tertiary alcohol **11q′** was the main product. Nitro substitution caused complications; **11r** and **11s** were not observed by LC/MS.

Considering the results of this study, the following reaction mechanism was hypothesized (Scheme 2). The magnesium carboxylate and the second added Grignard reagent could form an aggregated magnesium species **12**, which is mediated by the adjacent nitrogen atom of heteroaryl halides, as explained by other bimetallic magnesium reagents.[12,22] Magnesium species **12** could accelerate the halogen−metal exchange to form the second magnesium complex **13** by bringing the halogen atom closer to the second added Grignard reagent.[3,12] Complex **13** could readily cause an addition of the Grignard reagent to the carboxylate to form dimagnesium tetrahedral intermediate **14**, which was stable to prevent undesirable tertiary alcohol formation.[5,23] The proposed mechanism was supported by the results of a comparison study to prepare **9a** from **8a** versus **8b** as well as the ketone syntheses from 2-iodopyridine (**8a**) versus the corresponding 3- or 4-isomers **8c** or **d** or 2-iodothiophene (**8i**) described in Table 2.[12] The data suggested that the α-nitrogen coordinated to the Grignard reagent more effectively as a hard organometal species as compared to the

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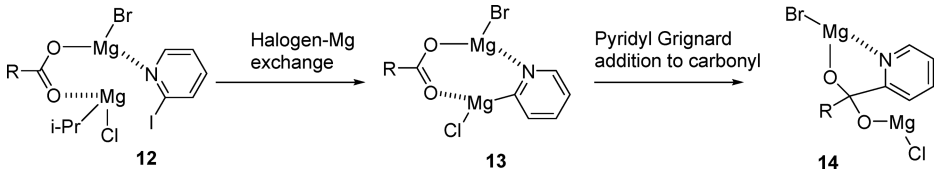
Scheme 2. Proposed Reaction Mechanism



distant nitrogens and the softer sulfur atom. In addition, the formation of aggregated metal species such as **12** might contribute to the promotion of the halogen−metal exchange reaction by vinyl magnesium reagents and MeLi (entries 8−10 in Table 1), which are uncommon for such exchange due to unsuitable reactivity. The fast halogen−metal exchange based on the aggregated magnesium species **12** might also contribute to high functional group tolerance, e.g., ester and nitrile groups (**11f−h** in Table 3).

In conclusion, a one-pot synthesis of heteroaryl ketones from a group of heteroaryl halides and carboxylic acids was demonstrated. It was shown that the presence of an α-nitrogen on the halide substrate greatly improved the reaction. This method allows direct access to ketones without going through additional process intermediates (acid chloride, Weinreb amides, etc.). Other highlights include a wide substrate scope of carboxylic acids with high functional group tolerance and mild reaction conditions.

EXPERIMENTAL SECTION

General. All chemicals were purchased commercially and used without further purification. Melting point was measured on a microscopic melting point apparatus. NMR spectra were taken on a 500 MHz NMR spectrometer with TMS as the internal standard. All UPLC analyses were performed on a UHPLC system equipped with a BEH C18 (1.7 μm, 2.1 × 50 mm) reverse-phase column with a flow rate of 1.0 mL/min. Purification of compounds were performed with an automated chromatography system using prepacked silica columns. High resolution mass spectrometry studies were performed on a Linear Trap Quadropole (LTQ) mass spectrometer using an electrospray ion source in positive mode.

General Procedure for Table 1. For the preparation of phenyl(pyridin-2-yl)methanone (**6**), carboxylic acid **4** (500 mg, 4.094 mmol, 1.0 equiv) dissolved in anhydrous tetrahydrofuran (25.0 mL) was placed in a reaction vessel at room temperature under a nitrogen atmosphere. Grignard 1 (4.299 mmol, 1.05 equiv) was then added dropwise at room temperature and stirred for 15 min. 2-Iodopyridine (5.732 mmol, 1.4 equiv) was added followed by Grignard 2 (6.960 mmol, 1.7 equiv). The resulting solution was stirred at room temperature for 1 h. Conversion to **6** was monitored by UPLC at a wavelength of 254 nm.

9a: Phenyl(pyridin-2-yl)methanone. For the preparation of phenyl(pyridin-2-yl)methanone (**9a**), benzoic acid (500 mg, 4.094 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.299 mmol, 1.05 equiv) was added at a rate that kept the temperature below 15 °C. 2-Iodopyridine (0.61 mL, 5.732 mmol, 1.4 equiv) or 2-bromopyridine (0.55 mL, 5.732 mmol, 1.4 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 5.4 mL, 6.960 mmol, 1.7 equiv). After 10 min (2-iodopyridine) or 4 h (2-bromopyridine) of stirring, the reaction was quenched with saturated ammonium chloride aqueous solution (25 mL). The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford a light yellow liquid. The residue was purified via column chromatography with a gradient mobile phase of 0−60% ethyl acetate in hexanes to afford compound **9a** (from 2-iodopyridine (658 mg, 88%) or 2-bromopyridine (624 mg, 83%)) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.50−7.59 (m, 2H), 7.61−7.75 (m, 2H), 7.92−8.03 (m, 3H), 8.07 (t, J = 7.73 Hz, 1H), 8.72 (br d, J = 4.40 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 124.6, 127.2, 128.7, 131.0, 133.4, 136.5, 138.1, 149.0, 155.0, 193.9 ppm. HRMS calculated for $C_{12}H_9NO$ $[M + H]^+$ 184.0762, found 184.0757.

9a: Phenyl(pyridin-2-yl)methanone. For the preparation of phenyl(pyridin-2-yl)methanone (**9a**), 2-picolinic acid (500 mg, 4.061 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.264 mmol, 1.05 equiv) was added at a rate that kept the temperature below 15 °C. Iodobenzene (0.50 mL, 4.468 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.7 mL, 4.874 mmol, 1.2 equiv). After 1 h of stirring, some starting material still remained, and then iodobenzene (0.14 mL, 1.218 mmol, 0.3 equiv) and isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.6 mL, 2.032 mmol, 0.5 equiv) were added. After another 3 h of stirring, an additional amount of isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.6 mL, 2.032 mmol, 0.5 equiv) was added. A calibration curve of the reference material was created, and after 5 h of stirring, a weight/weight assay was carried out in order to determine the yield of compound **9a** (344.7 mg, 46%). The NMR data were consistent with those of **9a**.

9b: Benzophenone. For the preparation of benzophenone (**9b**), benzoic acid (500 mg, 4.094 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.299 mmol, 1.05 equiv) was added at a rate that kept the temperature below 15 °C. 2-Iodopyridine (918.8 mg, 4.504 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.8 mL, 4.913 mmol, 1.2 equiv). After 2 h of stirring, it was determined that starting material was remaining; then, the reaction was cooled to 10 °C, and 2-iodopyridine (75.2 mg, 1.228 mmol, 0.3 equiv) was added to

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the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.6 mL, 2.047 mmol, 0.5 equiv). The reaction mixture was stirred for an additional 3 h and quenched with saturated sodium chloride solution (25 mL). The mixture was washed with saturated ammonium chloride solution (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford a light yellow liquid. A calibration curve with the reference material was created, and a weight/weight assay was carried out to determine the yield of compound **9b** (26%). NMR data were consistent with reference standards and those reported in the literature.

9e: 4-Benzoyl-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide. For the preparation of 4-benzoyl-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (**9e**), benzoic acid (500 mg, 4.094 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.229 mmol, 1.05 equiv) was added at a rate that kept the temperature below 10 °C. 4-Iodo-*N*,*N*-dimethyl-imidazole-1-sulfonamide (1.356 g, 4.504 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.8 mL, 4.913 mmol, 1.2 equiv). After 3.5 h of stirring, the reaction was quenched with water with saturated ammonium chloride solution (25 mL). The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **9e** (905.7 mg, 79%) as a yellow solid; mp 130−131 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.91 (s, 6H), 7.53−7.59 (m, 2H), 7.67 (t, J = 7.34 Hz, 1H), 8.17 (d, J = 7.83 Hz, 2H), 8.31 (s, 1H), 8.40 (s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 38.4, 125.0, 128.8, 130.3, 133.3, 137.4, 138.0, 141.6, 186.9 ppm. HRMS calculated for $C_{12}H_{13}N_3O_3S$ $[M + H]^+$ 280.0756, found 280.0749.

9f: (1-Methyl-1*H*-pyrazol-3-yl)(phenyl)methanone. For the preparation of (1-methyl-1*H*-pyrazol-3-yl)(phenyl)-methanone (**9f**), benzoic acid (500 mg, 4.094 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.299 mmol, 1.05 equiv) was added at a rate that kept the temperature below 15 °C. 3-Iodo-1-methyl-pyrazole (936.8 mg, 4.504 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.8 mL, 4.913 mmol, 1.2 equiv). At 1.5 h, there was still starting material remaining, and additional amounts of 3-iodo-1-methyl-pyrazole (211.3 mg, 1.118 mmol, 0.3 equiv) and isopropyl-magnesium chloride−lithium chloride complex (1.3 M in THF, 1.6 mL, 2.047 mmol, 0.5 equiv) were added. After 4 h of stirring, the reaction was quenched with saturated ammonium chloride solution (25 mL). The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford **9f** (533 mg, 70% yield) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.99 (s, 3H), 6.88 (d, J = 2.45 Hz, 1H), 7.50−7.57 (m, 2H), 7.59−7.69 (m, 1H), 7.90 (d, J = 1.96 Hz, 1H), 8.16 (s, 1H), 8.17−8.18 (m, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 39.8, 109.2, 128.7, 130.4, 133.0, 133.1, 137.7, 150.3, 187.2 ppm. HRMS calculated for $C_{11}H_{10}N_2O$ $[M + H]^+$ 187.0871, found 187.0866.

9f: (1-Methyl-1*H*-pyrazol-3-yl)(phenyl)methanone. For the preparation of (1-methyl-1*H*-pyrazol-3-yl)(phenyl)-methanone (**9f**), benzoic acid (500 mg, 4.094 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.299 mmol, 1.05 equiv) was added at a rate that kept the temperature below 15 °C. 3-Bromo-1-methyl-pyrazole (725.1 mg, 4.504 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.8 mL, 4.913 mmol, 1.2 equiv). After 27 h of stirring, the reaction was quenched with saturated ammonium chloride solution (25 mL). The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford a yellow liquid. The residue was purified via column chromatography with a gradient mobile phase of 0−60% ethyl acetate in hexanes to afford compound **9f** (282.2 mg, 37% yield) as a colorless oil. The NMR data were consistent with those of **9f.**

9g: Phenyl(thiazol-4-yl)methanone. For the preparation of phenyl(thiazol-4-yl)methanone (**9g**), benzoic acid (500 mg, 4.094 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.229 mmol, 1.05 equiv) was added at a rate that kept the temperature below 10 °C. 4-Bromothiazole (0.40 mL, 4.504 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.8 mL, 4.913 mmol, 1.2 equiv). After 18.5 h, starting material was still remaining, and 4-bromothiazole (0.11 mL, 1.228 mmol, 0.3 equiv) and isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.6 mL, 2.047 mmol, 0.5 equiv) were added. At 19.5 h, isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.8 mL, 4.913 mmol, 1.0 equiv) was added. The reaction mixture was stirred for a total of 24 h and was then quenched with water (25 mL) with some saturated ammonium chloride solution. The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford a dark oil. The residue was then was purified via column chromatography with a gradient mobile phase of 0−60% ethyl acetate in hexanes to afford compound **9g** (360 mg, 47%) as a dark yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.54−7.59 (m, 2H), 7.65−7.70 (m, 1H), 8.07−8.12 (m, 2H), 8.65 (d, J = 1.96 Hz, 1H), 9.29 (d, J = 1.96 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 128.8, 130.3, 130.5, 133.4, 137.5, 154.7, 155.6, 187.1 ppm. HRMS calculated for $C_{10}H_7NOS$ $[M + H]^+$ 190.0327, found 190.0321.

9h: (1-Benzyl-1*H*-pyrazol-4-yl)(phenyl)methanone. For the preparation of (1-benzyl-1*H*-pyrazol-4-yl)(phenyl)-methanone (**9h**), benzoic acid (500 mg, 4.094 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.299 mmol, 1.05 equiv) was added at a rate that kept the temperature below 10 °C. 1-

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J. Org. Chem. 2016, 81, 3447−3456

Benzyl-4-iodo-1*H*-pyrazole (1280 mg, 4.504 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.8 mL, 4.913 mmol, 1.2 equiv). After 3 h, there was still starting material remaining, and additional amounts of 1-benzyl-4-iodo-1*H*-pyrazole (350 mg, 1.228 mmol, 0.3 equiv) and isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.6 mL, 2.047 mmol, 0.5 equiv) were added. At 24 h, there was still starting material remaining, and additional amounts of 1-benzyl-4-iodo-1*H*-pyrazole (350 mg, 1.228 mmol, 0.3 equiv) and isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.6 mL, 2.047 mmol, 0.5 equiv) were added. At 27 h, there was still starting material remaining, and additional amounts of 1-benzyl-4-iodo-1*H*-pyrazole (581 mg, 2.047 mmol, 0.5 equiv) and isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.6 mL, 2.047 mmol, 0.5 equiv) were added. The reaction mixture was stirred for a total of 28 h and was then quenched with water (25 mL) with some saturated ammonium chloride solution. The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford a yellow oil. The residue was purified via column chromatography with a gradient mobile phase of 0−55% ethyl acetate in hexanes, followed by separation by prep HPLC to afford compound **9h** (200 mg, 20%) as a colorless oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.41 (s, 1H), 6.27−6.37 (m, 1H), 7.28−7.49 (m, 4H), 7.51−7.72 (m, 3H), 7.74−7.85 (m, 1H), 7.85−8.07 (m, 2H), 8.39 (s, 1H), 8.56 (s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 69.1, 106.3, 129.0, 129.1, 129.2, 129.3, 129.5, 130.7, 134.1, 135.3, 135.6, 139.6, 194.1 ppm. HRMS calculated for $C_{17}H_{14}N_2O$ $[M + H]^+$ 263.1184, found 263.1180.

9i: Phenyl(thiazol-5-yl)methanone. For the preparation of phenyl(thiazol-5-yl)methanone (**9i**), benzoic acid (500 mg, 4.094 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.299 mmol, 1.05 equiv) was added at a rate that kept the temperature below 10 °C. 5-Bromothiazole (738.7 mg, 4.504 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.8 mL, 4.913 mmol, 1.2 equiv). The reaction mixture was stirred for a total of 4.5 h and was then quenched with water (25 mL) with some saturated ammonium chloride solution. The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford a brown oil. The residue was purified via column chromatography with a gradient mobile phase of 0−50% ethyl acetate in hexanes to afford compound **9i** (275 mg, 36%) as an orange oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.56−7.66 (m, 2H), 7.66−7.81 (m, 1H), 8.21−8.31 (m, 2H), 8.35−8.43 (m, 2H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 128.8, 129.0, 131.2, 134.3, 135.2, 145.8, 167.3, 184.1 ppm. HRMS calculated for $C_{10}H_7NOS$ $[M + H]^+$ 190.0327, found 190.0324.

11a: (4-Chlorophenyl)(pyridin-2-yl)methanone. For the preparation of (4-chlorophenyl)(pyridin-2-yl)methanone (**11a**), 4-chlorobenzoic acid (500 mg, 3.193 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.2 mL, 3.353 mmol, 1.05 equiv) was added at a rate that kept the temperature below 10 °C. 2-Iodopyridine (0.37 mL, 3.513 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 4.2 mL, 5.429 mmol, 1.7 equiv). The reaction mixture was stirred at room temperature for 1 h. Saturated ammonium chloride solution (25 mL) was added to quench the reaction. The mixture was washed with saturated ammonium chloride solution (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11a** (653.4 mg, 94% yield) as a yellow solid; lit. mp 60−61 °C.[24] ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55−7.63 (m, 1H), 7.63−7.64 (m, 1H), 7.67−7.72 (m, 1H), 8.00−8.11 (m, 4H), 8.64−8.84 (m, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 124.7, 127.5, 128.8, 133.0, 135.1, 138.3, 138.4, 149.1, 154.5, 192.5 ppm. HRMS calculated for $C_{12}H_8ClNO$ $[M + H]^+$ 218.0373, found 218.0368.

11b: (4-Bromophenyl)(pyridin-2-yl)methanone. For the preparation of (4-bromophenyl)(pyridin-2-yl)methanone (**11b**), 4-bromobenzoic acid (500 mg, 2.487 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 0.90 mL, 2.162 mmol, 1.05 equiv) was added at a rate that kept the temperature below 20 °C. 2-Iodopyridine (0.29 mL, 2.736 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.3 mL, 4.228 mmol, 1.7 equiv). The reaction mixture was stirred at room temperature for 2 h. Water (25 mL) with a few drops of saturated ammonium chloride solution was added to quench the reaction, and the organic layer was then extracted with water (2 × 25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11b** (518.7 mg, 80% yield) as a white solid; lit. mp (45−47 °C).[25] ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68−7.79 (m, 3H), 7.89−8.10 (m, 4H), 8.73 (dd, J = 4.89, 0.98 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 124.7, 127.5, 127.6, 131.8, 133.1, 135.5, 138.2, 149.1, 154.4, 192.7 ppm. HRMS calculated for $C_{12}H_8BrNO$ $[M + H]^+$ 261.9868, found 261.9863.

11c: (4-Iodophenyl)(pyridin-2-yl)methanone. For the preparation of (4-iodophenyl)(pyridin-2-yl)methanone (**11c**), 4-iodobenzoic acid (500 mg, 2.016 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. Isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 0.73 mL, 2.117 mmol, 1.05 equiv) was added dropwise, and the reaction mixture was stirred for 15 min. 2-Iodopyridine (0.30 mL, 2.822 mmol, 1.4 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 2.6 mL, 3.427 mmol, 1.7 equiv). The reaction mixture was stirred at room temperature for 2 h. Saturated ammonium chloride solution (25 mL) was added to quench the reaction. The mixture was washed with saturated ammonium chloride solution (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified via column chromatography with a gradient mobile phase of 0−50% ethyl acetate in hexanes

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to afford compound **11c** (395.5 mg, 64% yield) as an orange oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.63−7.74 (m, 1H), 7.75 (d, J = 7.34 Hz, 2H), 7.90−8.03 (m, 3H), 8.04−8.13 (m, 1H), 8.64−8.80 (m, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 102.1, 124.7, 127.4, 132.8, 135.8, 137.6, 138.2, 149.1, 154.5, 193.1 ppm. HRMS calculated for $C_{12}H_8INO$ $[M + H]^+$ 309.9729, found 309.9732

11d: (4-Methoxyphenyl)(pyridin-2-yl)methanone. For the preparation of (4-methoxyphenyl)(pyridin-2-yl)methanone (**11d**), 4-methoxybenzoic acid (500 mg, 3.286 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. Isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 2.4 mL, 6.901 mmol, 2.1 equiv) was added dropwise, and the reaction mixture was stirred for 15 min. 2-Iodopyridine (0.49 mL, 4.601 mmol, 1.4 equiv) was added followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 4.3 mL, 5.587 mmol, 1.7 equiv). The reaction mixture was stirred at room temperature for 4 h. Saturated ammonium chloride solution (25 mL) was added to quench the reaction. The mixture was washed with saturated ammonium chloride solution (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified via column chromatography with a gradient mobile phase of 0−55% ethyl acetate in hexanes to afford compound **11d** (650 mg, 94% yield) as a white solid; lit. mp 60−61 °C.[26] ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.86 (s, 3H), 7.08 (d, J = 8.80 Hz, 2H), 7.65 (t, J = 6.17 Hz, 1H), 7.89−7.97 (m, 1H), 7.97−8.10 (m, 3H), 8.71 (dd, J = 4.89, 0.98 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 56.0, 114.1, 124.5, 126.8, 128.9, 133.6, 138.0, 148.9, 155.7, 163.7, 192.0 ppm. HRMS calculated for $C_{13}H_{11}NO_2$ $[M + H]^+$ 214.0868, found 214.0863.

11e: Pyridin-2-yl(*p*-tolyl)methanone. For the preparation of pyridin-2-yl(*p*-tolyl)methanone (**11e**), 4-methylbenzoic acid (500 mg, 3.672 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.3 mL, 3.856 mmol, 1.05 equiv) was added at a rate that kept the temperature below 10 °C. 2-Iodopyridine (0.43 mL, 4.040 mmol, 1.1 equiv) was added to the reaction mixture. Isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.4 mL, 4.407 mmol, 1.2 equiv) was then added at a rate that kept the temperature below 10 °C. The reaction mixture was stirred at room temperature for 2.5 h. Starting material was still present so additional 2-iodopyridine (0.12 mL, 1.102 mmol, 0.3 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.4 mL, 1.836 mmol, 0.5 equiv). The reaction mixture was stirred at room temperature for an additional 2 h. Water (25 mL) with a few drops of saturated ammonium chloride solution was added to quench the reaction, and the organic layer was then extracted with water (2 × 25) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11e** (563 mg, 78% yield) as a brown oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.40 (s, 3H), 7.35 (d, J = 7.75 Hz, 2H), 7.62−7.68 (m, 1H), 7.86−7.96 (m, 3H), 8.06 (td, J = 7.70, 1.71 Hz, 1H), 8.72 (dq, J = 4.89, 0.98 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.7, 124.5, 127.0, 129.3, 131.2, 133.8, 138.1, 144.0, 149.0, 155.3, 193.4 ppm. HRMS calculated for $C_{13}H_{11}NO$ $[M + H]^+$ 198.0919, found 198.0915.

11f: Methyl 4-Picolinoylbenzoate. For the preparation of methyl 4-picolinoylbenzoate (**11f**), monomethyl terephthalate (500 mg, 2.775 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.0 mL, 2.914 mmol, 1.05 equiv) was added at a rate that kept the temperature below 15 °C. 2-Iodopyridine (0.33 mL, 3.053 mmol, 1.1 equiv) was added to the reaction mixture. Isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 2.6 mL, 3.330 mmol, 1.2 equiv) was then added at a rate that kept the temperature below 15 °C. The reaction mixture was stirred at room temperature for 3 h 30 min. Starting material remained so additional isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.1 mL, 1.388 mmol, 0.5 equiv) was added. After a total of 4.5 h, water (25 mL) with a few drops of saturated ammonium chloride solution was added to quench the reaction, and the organic layer was extracted with water (2 × 25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11f** (642 mg, 96% yield) as an off-white solid; mp 117−119 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.91 (s, 3H), 7.70−7.73 (m, 1H), 8.06−8.12 (m, 6H), 8.74 (d, J = 4.88 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 53.0, 124.7, 127.7, 129.3, 131.2, 133.3, 138.3, 140.4, 149.2, 154.2, 166.1, 193.5 ppm. HRMS calculated for $C_{14}H_{11}NO_3$ $[M + H]^+$ 242.0817, found 242.0811.

11g: Methyl 3-Picolinoylbenzoate. For the preparation of methyl 3-picolinoylbenzoate (**11g**), monomethyl isophthalate (500 mg, 2.775 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.0 mL, 2.914 mmol, 1.05 equiv) was added at a rate that kept the temperature below 10 °C. 2-Iodopyridine (0.33 mL, 3.053 mmol, 1.1 equiv) was added to the reaction mixture. Isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 2.6 mL, 3.330 mmol, 1.2 equiv) was then added at a rate that kept the temperature below 10 °C. The reaction mixture was stirred at room temperature for 30 min. Water (25 mL) with a few drops of saturated ammonium chloride solution was added to quench the reaction, and the organic layer was extracted with water (2 × 25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11g** (600 mg, 90% yield) as a white solid. Purity was determined by a wt/wt NMR assay, as some pyridine was present in the sample; mp 108−109 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.89 (s, 3H), 7.66−7.77 (m, 2H), 8.02−8.16 (m, 2H), 8.19−8.30 (m, 2H), 8.53 (s, 1H), 8.75 (dd, J = 4.89, 0.98 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 52.9, 124.8, 127.6, 129.3, 130.0, 131.6, 133.5, 135.6, 136.9, 138.3, 149.1, 154.3, 166.0, 192.8 ppm. HRMS calculated for $C_{14}H_{11}NO_3$ $[M + H]^+$ 242.0817, found 242.0810.

11h: 4-Picolinoylbenzonitrile. For the preparation of 4-picolinoylbenzonitrile (**11h**), 4-cyanobenzoic acid (500 mg, 3.398 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide

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(2.9 M in 2-methyltetrahydrofuran, 1.2 mL, 3.568 mmol, 1.05 equiv) was added at a rate that kept the temperature below 10 °C. 2-Iodopyridine (0.40 mL, 3.738 mmol, 1.1 equiv) was added to the reaction mixture. Isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 4.4 mL, 5.777 mmol, 1.7 equiv) was then added at a rate that kept the temperature below 10 °C. The reaction mixture was stirred at room temperature for 3 h. Water (25 mL) with a few drops of saturated ammonium chloride solution was added to quench the reaction, and the organic layer was then extracted with water (2 × 25) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11h** (502 mg, 71% yield) as a white solid; lit. mp 118−121 °C.[5] ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64−7.80 (m, 1H), 7.96−8.06 (m, 2H), 8.06−8.19 (m, 4H), 8.68−8.80 (m, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 115.1, 118.7, 124.8, 127.9, 131.5, 132.5, 138.4, 140., 149.2, 153.7, 192.9 ppm. HRMS calculated for $C_{13}H_8N_2O$ $[M + H]^+$ 209.0715, found 209.0708.

11i: 1,4-Phenylenebis(pyridin-2-ylmethanone). For the preparation of 1,4-phenylenebis(pyridin-2-ylmethanone) (**11i**), terephthalic acid (500 mg, 3.010 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 2.2 mL, 6.320 mmol, 2.1 equiv) was added at a rate that kept the temperature below 10 °C. 2-Iodopyridine (0.71 mL, 6.621 mmol, 2.2 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 5.6 mL, 7.223 mmol, 2.4 equiv). After 1 h of stirring, it was determined that starting material remained; thus, the reaction mixture was cooled to 10 °C, and 2-iodopyridine (0.32 mL, 3.010 mmol, 1 equiv) was added followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 2.5 mL, 3.311 mmol, 1.1 equiv). The reaction mixture was stirred for an additional 19 h, cooled in an ice bath, and then quenched with water (25 mL), causing a white solid to crash out. The pH of the solution was adjusted to 9 with saturated ammonium chloride solution, and an additional 10 mL of water was added. The reaction was then filtered to afford compound **11i** (540 mg, 62%) as a white solid; lit. mp 172−174 °C.[25] ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.72 (ddd, J = 6.85, 4.89, 1.96 Hz, 2H), 8.01−8.17 (m, 8H), 8.75 (dt, J = 4.52, 1.41 Hz, 2H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 124.2, 127.2, 130.0, 137.8, 139.3, 148.7, 153.8, 193.2 ppm. HRMS calculated for $C_{18}H_{12}N_2O_2$ $[M + H]^+$ 289.0977, found 289.0968.

11j: (4-Hydroxyphenyl)(pyridin-2-yl)methanone. For the preparation of (4-hydroxyphenyl)(pyridin-2-yl)methanone (**11j**), 4-hydroxybenzoic acid (500 mg, 3.620 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 2.6 mL, 7.602 mmol, 2.1 equiv) was added at a rate that kept the temperature below 15 °C. 2-Iodopyridine (0.42 mL, 3.982 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.3 mL, 4.344 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 3 h. Starting material remained, and additional 2-iodopyridine (0.65 mL, 6.154 mmol, 1.7 equiv) and isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 6.1 mL, 7.964 mmol, 2.2 equiv) were added. The reaction mixture was heated to 30 °C and stirred for 16 h. Water (25 mL) with a few drops of saturated ammonium chloride solution was added to quench the reaction, and the organic layer was then extracted with water (2 × 25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11j** (500 mg, 69% yield) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.87 (s, 1H), 6.88 (s, 1H), 7.57−7.66 (m, 1H), 7.84−7.97 (m, 3H), 7.99−8.07 (m, 1H), 8.70 (dt, J = 5.14, 1.10 Hz, 1H), 10.46 (br s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 115.5, 124.3, 126.5, 127.4, 133.9, 137.9, 148.8, 156.1, 162.8, 191.9 ppm. HRMS calculated for $C_{12}H_9NO_2$ $[M + H]^+$ 200.0712, found 200.0709.

11k: *N*-(4-Picolinoylphenyl)acetamide. For the preparation of *N*-(4-picolinoylphenyl)acetamide (**11k**), 4-acetamidobenzoic acid (500 mg, 2.7906 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 2.0 mL, 5.8604 mmol, 2.1 equiv) was added at a rate that kept the temperature below 15 °C. 2-Iodopyridine (0.42 mL, 3.9069 mmol, 1.4 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.6 mL, 4.7441 mmol, 1.7 equiv). The reaction mixture was stirred at room temperature for 20 h. Starting material was still present, and additional 2-iodopyridine (0.42 mL, 3.9069 mmol, 1.4 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.6 mL, 4.7441 mmol, 1.7 equiv). The reaction mixture was stirred a room temperature for an additional 2 h. Water (25 mL) with a few drops of saturated ammonium chloride solution was added to quench the reaction, and the organic layer was then extracted with water (2 × 25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11k** (550 mg, 82% yield) as a light brown solid; mp (dec) 143−145 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.10 (s, 3H), 7.65 (dd, J = 6.60, 5.62 Hz, 1H), 7.73 (d, J = 8.80 Hz, 2H), 7.84−7.97 (m, 1H), 7.97−7.98 (m, 1H), 8.00 (s, 1H), 8.02−8.18 (m, 1H), 8.63−8.79 (m, 1H), 10.32 (s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 24.7, 118.3, 124.5, 126.8, 130.7, 132.6, 138.0, 144.2, 148.9, 155.6, 169.5, 192.2 ppm. HRMS calculated for $C_{14}H_{12}N_2O_2$ $[M + H]^+$ 241.0977, found 241.0959.

11l: (1*H*-Indol-2-yl)(pyridin-2-yl)methanone. For the preparation of (1*H*-indol-2-yl)(pyridin-2-yl)methanone (**11l**), indole-2-carboxylic acid (500 mg, 3.103 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 2.2 mL, 6.516 mmol, 2.1 equiv) was added at a rate that kept the temperature below 10 °C. 2-Iodopyridine (0.36 mL, 3.413 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 2.9 mL, 3.723 mmol, 1.2 equiv) at a rate that kept the temperature below 5 °C. After 3 h and 30 min, starting material remained; thus, isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 2.9 mL, 3.723 mmol, 1.2 equiv) was added. After another 1 h, 2-

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J. Org. Chem. 2016, 81, 3447−3456

iodopyridine (0.10 mL, 0.9308 mmol, 0.3 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.2 mL, 1.551 mmol, 0.5 equiv). After another 1 h, 2-iodopyridine (0.10 mL, 0.9308 mmol, 0.3 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.2 mL, 1.551 mmol, 0.5 equiv). The reaction mixture was stirred for a total of 22 h and was then quenched with water (25 mL) with some saturated ammonium chloride solution. The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11l** (617.6 mg, 90%) as an orange solid; mp 146−148 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.09 (ddd, J = 8.19, 6.97, 0.98 Hz, 1H), 7.25−7.38 (m, 1H), 7.47−7.59 (m, 1H), 7.65−7.81 (m, 2H), 7.86 (dd, J = 1.96, 0.98 Hz, 1H), 8.06−8.12 (m, 2H), 8.80−8.91 (m, 1H), 11.96 (br s, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-$d6$) δ 113.3, 114.6, 120.8, 123.6, 124.0, 126.4, 127.5, 127.6, 134.3, 138.1, 138.5, 149.4, 154.8, 183.3 ppm. HRMS calculated for $C_{14}H_{10}N_2O$ $[M + H]^+$ 223.0871, found 223.0866.

11m: Di(pyridin-2-yl)methanone. For the preparation of di(pyridin-2-yl)methanone (**11m**), benzoic acid (500 mg, 4.061 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.5 mL, 4.264 mmol, 1.05 equiv) was added at a rate that kept the temperature below 20 °C. 2-Iodopyridine (0.61 mL, 5.686 mmol, 1.4 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 5.3 mL, 6.904 mmol, 1.7 equiv). After 2 h of stirring, starting material remained; thus, isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.6 mL, 2.031 mmol, 0.5 equiv) was added. A calibration curve of the reference material was created, and after 5 h of stirring, a wt/wt assay was carried out to determine the yield of compound **11m** (496.4 mg, 66%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (t, J = 6.23 Hz, 2H), 7.95−8.00 (m, 2H), 8.04 (t, J = 7.58 Hz, 2H), 8.64−8.73 (m, 2H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 124.8, 127.1, 137.5, 149.4, 154.7, 194.1 ppm. HRMS calculated for $C_{11}H_8N_2O$ $[M + H]^+$ 185.0715, found 185.0710.

11n: Pyridin-2-yl(thiophen-2-yl)methanone. For the preparation of pyridin-2-yl(thiophen-2-yl)methanone (**11n**), thiophene-2-carboxylic acid (500 mg, 3.902 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.4 mL, 4.097 mmol, 1.05 equiv) was added at a rate that kept the temperature below 10 °C. 2-Iodopyridine (0.46 mL, 4.292 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.6 mL, 4.682 mmol, 1.2 equiv). After 1 h and 30 min, starting material remained; thus, 2-iodopyridine (0.21 mL, 1.171 mmol, 0.3 equiv) and isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.5 mL, 1.951 mmol, 0.5 equiv) were added. After another 2 h, isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.5 mL, 1.951 mmol, 0.5 equiv) was added. After another 1 h, 2-iodopyridine (0.21 mL, 1.171 mmol, 0.3 equiv) and isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.5 mL, 1.951 mmol, 0.5 equiv) were added. At the 5 h time mark, additional amounts of 2-iodopyridine (0.21 mL, 1.171 mmol, 0.3 equiv) and isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 1.5 mL, 1.951 mmol, 0.5 equiv) were added. The reaction mixture was stirred for a total of 24 h and was then quenched with water (25 mL) with some saturated ammonium chloride solution. The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford a dark orange liquid. The residue was purified via column chromatography with a gradient mobile phase of 0−60% ethyl acetate in hexanes to afford compound **11n** (648 mg, 88%) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29 (dd, J = 5.14, 3.67 Hz, 1H), 7.70−7.73 (m, 1H), 8.06−8.13 (m, 3H), 8.32−8.35 (m, 1H), 8.79−8.82 (m, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 123.9, 127.9, 128.5, 137.3, 138.1, 138.4, 139.8, 149.1, 153.7, 183.4 ppm. HRMS calculated for $C_{10}H_7NOS$ $[M + H]^+$ 190.0327, found 190.0326.

11o: 2-Phenyl-1-(pyridin-2-yl)ethanone. For the preparation of 2-phenyl-1-(pyridin-2-yl)ethanone (**11o**), 2-phenylacetic acid (500 mg, 3.672 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.3 mL, 3.856 mmol, 1.05 equiv) was added at a rate that kept the temperature below 15 °C. 2-Iodopyridine (0.43 mL, 4.040 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.4 mL, 4.407 mmol, 1.2 equiv) at a rate that kept the temperature below 10 °C. After 3 h of stirring, the reaction was quenched with water that contained some saturated sodium ammonium solution (25 mL). The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11o** (550.1 mg, 76%) as a brown oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.53 (s, 2H), 7.21−7.44 (m, 5H), 7.69 (t, J = 5.97 Hz, 1H), 7.88−8.09 (m, 2H), 8.79 (dd, J = 4.89, 0.98 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 43.86, 122.3, 126.9, 128.3, 128.7, 130.4, 135.6, 138.1, 149.7, 153.0, 199.2 ppm. HRMS calculated for $C_{13}H_{11}NO$ $[M + H]^+$ 198.0919, found 198.0913.

11p: 3-Phenyl-1-(pyridin-2-yl)propan-1-one. For the preparation of 3-phenyl-1-(pyridin-2-yl)propan-1-one (**11p**), 3-phenylpropanoic acid (500 mg, 3.330 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (25.0 mL, 308 mmol) were added to a reaction vessel at room temperature under a nitrogen atmosphere. The reaction was then cooled in an ice bath, and isopropylmagnesium bromide (2.9 M in 2-methyltetrahydrofuran, 1.2 mL, 3.496 mmol, 1.05 equiv) was added at a rate that kept the temperature below 15 °C. 2-Iodopyridine (0.39 mL, 3.663 mmol, 1.1 equiv) was added to the reaction mixture followed by isopropylmagnesium chloride−lithium chloride complex (1.3 M in THF, 3.1 mL, 3.995 mmol, 1.2 equiv). After 2 h of stirring, the reaction was quenched with saturated ammonium chloride aqueous solution (25 mL). The mixture was washed with water (25 mL) and brine (25 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford compound **11p** (577.7 mg, 82%) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.96 (t, J = 7.58 Hz, 2H), 3.51 (t, J = 7.58 Hz, 2H), 7.01−7.35 (m, 5H), 7.65 (ddd, J = 7.34, 4.40, 1.47 Hz, 1H), 7.89−8.10 (m, 2H),

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J. Org. Chem. 2016, 81, 3447−3456

8.71 (d, J = 5.07 Hz, 1H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 29.8, 39.2, 121.7, 126.3, 128.2, 128.7 (2C), 138.0, 141.8, 149.6, 153.2, 200.8 ppm. HRMS calculated for $C_{14}H_{13}NO$ $[M + H]^+$ 212.1075, found 212.1071.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00194.

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

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

In Table 2, the I was changed to Br in structures **8g** and **8i**; the correct version reposted April 6, 2016.

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