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Regioselective, Directed Meta Acylation of Aromatic Compounds

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Abstract: A new method for the directed meta acylation of aromatic compounds is described. This method involves an ortho lithiation procedure combined with zirconocene−benzyne chemistry. 3-Acyl-1-substituted benzene derivatives were obtained by acidic hydrolysis of the azazirconacycle intermediate which results from the coupling of a nitrile with a zirconocene−benzyne complex. Similarly, 3-acyl-2-iodo-1-substituted benzene derivatives were obtained by the iodination of the same intermediate followed by acidic hydrolysis. These procedures, which utilize simple, readily available starting materials, give good yields of regiochemically pure products.

Introduction

There has been much effort in recent years toward the development of methods to introduce carbon substituents onto aromatic rings. The majority of these involve electrophilic aromatic substitution[1] and related rearrangement reactions,[2] directed ortho lithiation procedures,[3] nucleophilic aromatic substitution[4−7] and related rearrangement reactions,[8] and radical cation[9] and transition metal-mediated processes.[10,11]

Typical electrophilic reactions include the Friedel−Crafts reaction[1] and the Fries rearrangement.[2] These reactions are best for electron-rich aromatic compounds and display ortho and para selectivity, but frequently, they are not highly regioselective. Directed ortho lithiation has emerged as a powerful technique

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(1) For reviews, see: (a) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, 1990. (b) Heaney, H. *Comprehensive Organic Chemistry*; Pergamon: Oxford, U.K., 1991; Vol. 2, p 733. (c) Wynberg, H. *Comprehensive Organic Chemistry*; Pergamon: Oxford, U.K., 1991; Vol. 2, p 769. (d) Meth-Cohn, O.; Stanforth. S. P. *Comprehensive Organic Chemistry*; Pergamon: Oxford, U.K., 1991; Vol. 2, p 777. (e) Ishibashi, H.; Ikeda, M. *Rev. Heteroatom Chem.* **1996**, *14*, 59.

(2) For a review, see: Martin, R. *Org. Prep. Proc. Int.* **1992**, *24*, 369.

(3) For reviews, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. See also: (c) Evans, P. A.; Nelson, J. D.; Stanley, A. L. *J. Org. Chem.* **1995**, *60*, 2298.

(4) For reviews of nucleophilic addition to electron-deficient arenes, see: (a) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. (b) Paradisi, C. *Comprehensive Organic Chemistry*; Pergamon: Oxford, U.K., 1991; Vol. 4, p 423. (c) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; Chapter 13.

(5) For reviews of reactions of transition metal−arene complexes, see: (a) Semmelhack, M. F. *Pure Appl. Chem.* **1981**, *53*, 2379. (b) Semmelhack, M. F. *Comprehensive Organic Chemistry*; Pergamon: Oxford, U.K., 1991; Vol. 4, p 517.

(6) For a review of nucleophilic addition to arynes, see: Kessar, S. V. *Comprehensive Organic Chemistry*, Pergamon: Oxford, U.K., 1991; Vol. 4, p 483.

(7) For reviews of vicarious nucleophilic substitution reactions, see: (a) Makosza, M. *Synthesis* **1991**, 103. (b) Makosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282.

(8) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; Chapter 18.

(9) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.*, **1994**, *116*, 3684.

(10) For reviews of transition-metal-catalyzed cross-coupling reactions, see: (a) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (d) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (e) Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y. *Handbook of Palladium-Catalyzed Organic Reactions. Synthetic Aspects and Catalytic Cycles*; Academic Press: San Diego, CA, 1997. (f) Beletskaya, I. P. *Pure Appl. Chem.* **1997**, *69*, 471. (g) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley: New York, 1998.

(11) For a recent review of transition-metal-catalyzed addition of aromatic C−H bonds to multiple bonds, see: Murai, S.; Chatani, N.; Kakiuchi, F. *Pure Appl. Chem.* **1997**, *69*, 589.

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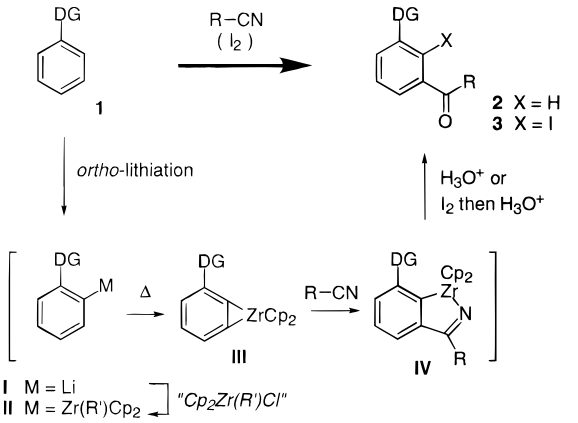
Scheme 1



for the construction of 1,2-disubstituted aromatic compounds due to a wide variety of functional groups which can serve as directing groups.[3] Although nucleophilic aromatic substitution reactions are usually limited to substrates having strong electron-withdrawing groups,[4] reactions of transition metal−arene complexes such as (arene)$Cr(CO)_3$[5] and those of benzyne intermediates[6] allow for the use of the substrates having electron-donating groups.

Unlike the other processes mentioned above which proceed with ipso,[4,10] ortho, or para selectivity,[1−3,7−9,11] carbon−carbon bond forming reactions of arene−metal complexes or benzynes have been reported to take place preferentially at the position meta to a substituent.[5,6] However, satisfactory regioselectivites and yields are obtained only with certain substrates and nucleophiles. In addition, these methods require formation and decomplexation of the metal−arene complex[5] or the preparation of multifunctional precursors for benzyne formation.[6]

Recently, our group has reported a new method for the functionalization of aromatic compounds employing intermediate zirconocene−benzyne complexes.[12] Insertion of an unsaturated compound, such as a nitrile, olefin, alkyne, or isonitrile into the carbon−zirconium bond of the benzyne complex produces a zirconacycle, which can be cleaved with various electrophilic reagents to afford a variety of functionalized aromatic compounds. The reaction of the zirconocene complex with a nitrile is particularly interesting because the product of this reaction (a 3-acyl-1-substituted aromatic compound) is that which would result from an anti-Friedel−Crafts acylation of the arene.

Although the arylzirconocene intermediate **II** (Scheme 1) has usually been prepared from an aryl halide by a halogen−lithium exchange reaction followed by reaction with $Cp_2Zr(Me)Cl$, we envisioned that an approach which combined our zirconocene−benzyne chemistry with ortho lithiation should produce **II** (Scheme 2) and, therefore, would be a more efficient method for the synthesis of meta-acylated arenes **2**. This protocol would benefit from the use of more readily available, less-substituted aromatic precursors **1** (Scheme 1). Herein we describe a general, one-pot, and regioselective procedure for the directed acylation of aromatic compounds at the meta position of a preexisting functional group. As shown in Scheme 1, azazirconacycle intermediate **IV** is hydrolyzed with acid to form **2**, or quenched with I_2 followed by acid hydrolysis to afford *m*-acyl-*o*-iodoarenes **3**. Depending on the choice of reagents, this protocol effects the net increase of ring substituents by one or two.

Results and Discussion

To examine the feasibility of the above-described approach, we first investigated the reaction of the *o*-lithiophenyl ether, generated by the reaction of methoxymethyl (MOM) phenyl ether **1a** with *t*-BuLi, with $Cp_2Zr(Me)Cl$. Intermediates of type **II** could be transformed to product as previously described. In a typical procedure (method A), treatment of **1a** in Et_2O with 1.1 equiv of *t*-BuLi at 0 °C and then at room temperature (RT) afforded **I** (DG = OMOM). The reaction mixture was cooled to −78 °C and a suspension of $Cp_2Zr(Me)Cl$ (1.1 equiv) in Et_2O was added. The mixture was slowly warmed to RT, and benzonitrile was added. Heating the reaction mixture at 80 °C in a resealable Schlenk flask for 15 h, followed by cooling to RT and treatment of the reaction mixture with aqueous HCl, produced the desired 3-benzoylphenyl MOM ether **2a** in 63% yield (Table 1, entry 1). Similar reactions could be carried out with 7-chloroheptanonitrile and 2-cyanothiophene to provide the corresponding 3-acylphenol ethers **2b** and **2c** in 82% and 81% yields, respectively (entries 2 and 3).

In a similar manner, the *o*-lithiobenzamide, prepared in situ by the reaction of the benzamide **1b** with *t*-BuLi, was treated with $Cp_2Zr(Me)Cl$, and the resulting arylzirconocene was heated in the presence of benzonitrile. This reaction required harsher conditions for the formation of the zirconocene−benzyne complex: the intermediate arylzirconocene was heated with the nitrile at 120 °C for 39 h. Workup as above afforded a 72% yield of the desired meta-acylated product **2g** after hydrolysis of the azazirconacycle intermediate (entry 7).[13]

With these initial results in hand we next investigated the use of commercially available Cp_2ZrCl_2 in lieu of $Cp_2Zr(Me)Cl$. The latter reagent is prepared from Cp_2ZrCl_2 by a two-step route, one of which involves the use of $AlMe_3$[14] and must be handled under anhydrous conditions. We have previously shown that $Cp_2Zr(i\text{-Bu})Cl$ can serve as a surrogate for $Cp_2Zr(Me)Cl$ in many procedures.[12a] Two methods which we considered to generate $Cp_2Zr(i\text{-Bu})Cl$ from Cp_2ZrCl_2 involved the reaction of Cp_2ZrCl_2 with either *t*-BuLi (method B)[12a] or *t*-BuMgCl (method C).[15] A preliminary examination of the use of $Cp_2Zr(i\text{-Bu})Cl$ prepared by these two methods for the reaction of lithiated **1a** and benzonitrile was carried out, and the results are summarized in Table 1. To our delight the use of method B gave better yields than did the use of method A (entry 1). A similar reaction using Cp_2ZrCl_2/*t*-BuMgCl was slow and gave a poor yield (approximately 15%) of **2a**. Addition of 2.4 equiv of 1,4-dioxane[16] (method C) to the reaction mixture prior to

(12) (a) Barr, K. J.; Watson, B. T.; Buchwald, S. L. *Tetrahedron Lett.* **1991**, *32*, 5465. (b) Buchwald, S. L.; King, S. M. *J. Am. Chem. Soc.* **1991**, *113*, 258. (c) Tidwell, J. H.; Peat, A. J.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 7164. (d) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11799. (e) de Rege, F. M. G.; Buchwald, S. L. *Tetrahedron* **1995**, *51*, 4291. (f) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028. For reviews of zirconocene−benzyne chemistry, see: (g) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (h) Buchwald, S. L.; Fisher, R. A. *Chem. Scr.* **1989**, *29*, 417. (i) Bennett, M. A.; Schwemlein, H. P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1296. (j) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696. (k) Buchwald, S. L.; Broene, R. D. *Comprehensive Organometallic Chemistry II*; Elsevier: New York, 1995; Vol. 12, p 771.

(13) In this case, the solvent used for the ortho lithiation and subsequent reaction with the zirconocene reagent (a mixture of Et_2O and THF) was replaced with toluene before heating.

(14) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* **1971**, *33*, 181.

(15) (a) Negishi, E.; Miller, J. A.; Yoshida, T. *Tetrahdron Lett.* **1984**, *25*, 3407. (b) Swanson, D. R.; Nguyen, T.; Noda, Y.; Negishi, E. *J. Org. Chem.* **1991**, *56*, 2590.

(16) Addition of 1,4-dioxane to a Grignard reagent is known to form MgX_2·(1,4-dioxane)$_2$, although we have not determined the effect of dioxane in this case. See: Coates, G. E.; Heslop, J. A. *J. Chem. Soc. (A)* **1968**, 514.

Scheme 2. Methods for Preparation of Arylzirconocene Intermediates **II**

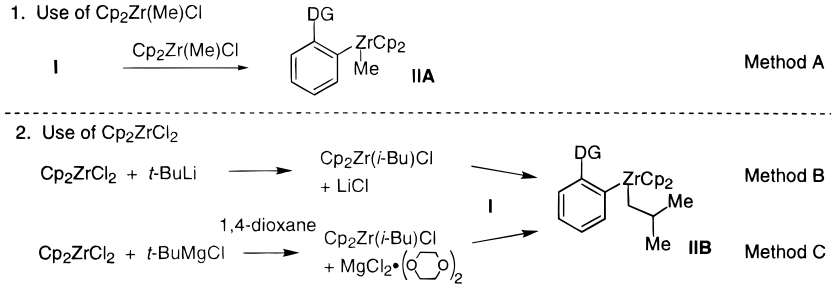
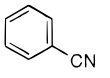
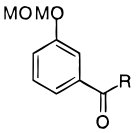
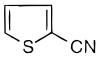
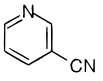
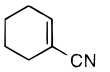
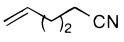
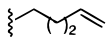
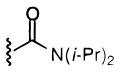
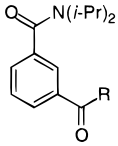
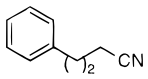
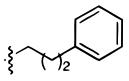
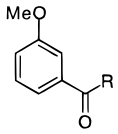
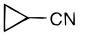
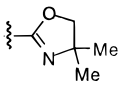
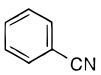
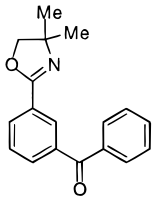


Table 1. Preparation of 3-Acyl-1-Substituted Benzenes **2**[a]

Entry	1, DG =	Nitrile	2		Isolated Yield, %[b] Method A	Method B	Method C
1	–OMOM **1a**			**2a**	63	84	73[c]
2		$Cl(CH_2)_6CN$	$(CH_2)_6Cl$	**2b**	82	62	81
3				**2c**	81[c]	79	
4				**2d**		83	
5				**2e**		48[c]	60
6				**2f**		79	
7	 **1b**			**2g**	72	80	d[c]
8				**2h**		75	
9	–OMe **1c**	*n*-Pr-CN		R = *n*-Pr **2i**		81	
10				**2j**		69	
11	 **1d**			**2k**		59	

[a] Heated at 80−85 °C except for entries 7 and 8 (120 °C). [b] Average of two runs, unless otherwise noted. The yield is based on **1** as the limiting substrate. [c] Single run. [d] GC ratio, 52:48 for **1b**:**2g**.

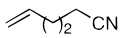
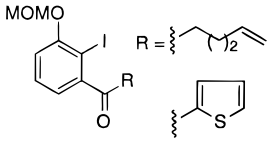
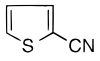
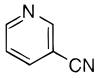
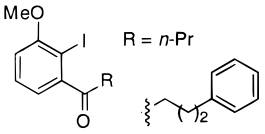
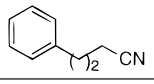
heating eliminated these problems, and **2a** was obtained in good yield (entry 1).

The scope of methods B and C were investigated by examining reactions of a variety of aromatic compounds and nitriles, and the results are summarized in Table 1. In general, method B furnished good yields of the desired meta-acylated products **2**. For reactions with 7-chloroheptanonitrile or 1-cyclohexenecarbonitrile, the use of method B led to the formation of side products.[17] Fortunately, by employing method C, **2b** and **2e** could be isolated in good yield (entries 2 and 5, respectively). The yields reported are for the one-pot conversion of **1** to the final product **2**. It is noteworthy that these procedures require no isolation and little manipulation of any intermediates and that only a single regioisomer is formed in all cases, corresponding to an anti-Friedel−Crafts acylation. Of particular importance is that this method tolerates a reasonable range of functional groups including olefins, heteroaryl, and cyclopropyl groups.

As we have previously reported,[12a,b] the reaction of azazirconacycle intermediates **IV** with 2.5 equiv of I_2, followed by

(17) Formation of cyclohexyl 3-(methoxymethoxy)phenyl ketone **4** was observed for the reaction of entry 2 with the GC ratio 79:21 for **2a** and **4**. Addition of 0.3 equiv of Me_3SiCl before reaction with the nitrile for the same method gave inferior results (**2a**:**4** = 15:85).

Table 2. Preparation of 3-Acyl-2-iodo-1-Substituted Benzenes **3**[a]

Entry	**1**, DG =	Nitrile	**3**		Isolated yield, %[b]
1	–OMOM **1a**			**3a**	45
2				**3b**	72
3				**3c**	74
4	–OMe **1c**	*n*-Pr-CN		**3d**	74
5				**3e**	59

[a] Run by method B. [b] Average of two runs.

hydrolysis affords *m*-acyl-*o*-iodoarenes **3** in good yield (Table 2). These iodinated products are potential precursors to a number of polyfunctionalized aromatic compounds.[10] As in the previous cases, these compounds were produced as single regioisomers.

In summary, we have developed an efficient method for the preparation of 3-acyl-1-substituted benzene derivatives. This method involves the combination of directed ortho lithiation technology with our previously developed zirconocene−benzyne chemistry. The following points are noteworthy: (1) The overall transformation is the synthetic equivalent of a directed meta metalation of an aromatic ring, a process not readily achieved using previously reported methods. Furthermore, both electron-rich and electron-deficient aromatic compounds are compatible with this method. (2) The required compounds for this procedure are an arene bearing a directing group, a nitrile, Cp_2ZrCl_2, and *t*-BuLi and/or *t*-BuMgCl, all of which are commercially or readily available. (3) A number of functional groups are tolerated, providing access to aryl ketones with diverse substituents. However, this technique still suffers from an inability to tolerate several important functional groups such as carbonyls and nitriles. (4) The process gives good to excellent yields of the products. Thus, we believe this new approach complements the powerful techniques already available for the introduction of carbon substituents onto aromatic rings.

Experimental Section

General Considerations. All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques. Transfer and storage of air- or moisture-sensitive zirconocene reagents were performed in a Vacuum Atmospheres Co. drybox under an atmosphere of nitrogen.[18] Resealable Schlenk tubes and round-bottomed resealable Schlenk flasks used in the procedures were single-neck flasks fitted with Teflon O-ring screw valves. *Caution*: reactions performed in sealed tubes should be carried out with suitable precautions such as the use of safety shields.

Tetrahydrofuran (THF), diethyl ether, and toluene were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Anhydrous chemicals, dichloromethane, benzonitrile, 1,4-dioxane, and tetrahydropyran were purchased from Aldrich Chemical Co. and were used without further purification. All other nitriles were available from commercial sources and were passed through a short plug of alumina under an atmosphere of argon immediately prior to use. Cp_2ZrCl_2 was a gift from Boulder Scientific Inc., Mead, CO. Other compounds either were available from commercial sources or were prepared according to published procedures and were used after either distillation or recrystallization. Flash column chromatography was performed using ICN Flash Silica Gel (230−400 mesh). Gas chromatography analyses were performed on a Hewlett-Packard model HP6980 with FID detector using a 25-m capillary column HP-1. Melting points are uncorrected. Yields refer to isolated material of ≥95% purity as determined by ^{1}H NMR, capillary GC, and combustion analyses (performed by E & R Microanalytical Laboratory, Inc.). Yields indicated in this section refer to a single experiment, while those reported in the tables are an average of two runs, so the numbers may differ slightly.

General Procedure for the Preparation of 2a−f,i,j from 1a or 1c. Method A. To an oven-dried 100-mL round-bottomed resealable Schlenk flask fitted with a rubber septum were added **1a** (0.40 mL, 3.0 mmol) and Et_2O (15 mL), and the resulting solution was cooled to 0 °C. To this solution was added *t*-BuLi (1.7 M solution in pentane, 1.95 mL, 3.3 mmol) dropwise over a period of 3 min. The resulting yellow suspension was stirred at 0 °C for 30 min and then at RT for 2.5 h. $Cp_2Zr(Me)Cl$ (0.92 g, 3.4 mmol) was placed in an oven-dried 50-mL Schlenk tube in the drybox, and the Schlenk tube was sealed with a glass stopper. The Schlenk tube was taken out of the drybox and connected to the Schlenk line, and the glass stopper was replaced with a rubber septum. Et_2O (10 mL) was added, and the resulting suspension was transferred via cannula over a period of 5 min to the flask containing the ortho-lithiated compound which had been cooled to −78 °C. The Schlenk tube was rinsed with Et_2O (5 mL), and the washings were added to the reaction flask. The reaction mixture was stirred at −78 °C for 20 min, gradually warmed to RT over a period of 40 min, and stirred at RT for 1 h. The nitrile (4.1−4.5 mmol, 1.35−1.5 equiv) was added, the septum was replaced with a Teflon screw valve, and the flask was sealed and heated at 80 °C for 15 h. After being cooled to RT, the reaction mixture was concentrated in vacuo and THF (15 mL) was added. The resulting solution was cooled to 0 °C, 1 N HCl (12 mL) was added, and the resulting mixture was stirred at RT for 5 h. At this time it was poured into a separatory funnel containing Et_2O (20 mL) and saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was separated and extracted with Et_2O (20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash column chromatography.

Method B. In a drybox,[18] Cp_2ZrCl_2 (1.05 g, 3.6 mmol) was placed in an oven-dried 100-mL Schlenk tube and the tube was sealed with a glass stopper. The Schlenk tube was taken out of the drybox, connected to the Schlenk line, and placed under vacuum (0.1 Torr) at RT for 20 min. The Schlenk tube was flushed with argon, the glass stopper was replaced with a rubber septum, THF (18 mL) was added, and the resulting clear solution was cooled to −78 °C. To this solution was added *t*-BuLi (1.7 M solution in pentane, 2.12 mL, 3.6 mmol) dropwise over a period of 3 min. The resulting dark red mixture was stirred at −78 °C for 15 min, the cooling bath was removed, and the reaction

(18) Cp_2ZrCl_2 was kept in the drybox for convenience, as it is very slightly hygroscopic. The use of a drybox is not necessary, but we recommend that Cp_2ZrCl_2 be stored in the absence of moisture (e.g., in a desiccator), particularly during humid periods of the year.[12a]

mixture was warmed to RT and then stirred at RT for 1 h to give a solution of $Cp_2Zr(i\text{-Bu})Cl$. This solution was cooled to −78 °C and was added via cannula to a suspension of the ortho-lithiated **1a** (3.0 mmol), prepared as shown in method A, which had been cooled to −78 °C. The reaction mixture was stirred at −78 °C for 20 min, gradually warmed to RT over a period of 40 min, and stirred at RT for 1 h. The nitrile (3.9−4.5 mmol, 1.3−1.5 equiv) was added, the septum was replaced with a Teflon screw valve, and the flask was sealed and heated at 85 °C for 16−18 h. Upon cooling to RT, the reaction mixture was concentrated in vacuo to half its original volume, diluted with THF (10 mL), cooled to 0 °C, and treated with 1 N HCl (12 mL) [0.2 N HCl (30 mL) for entry 10]. The remainder of the procedure is the same as described in method A.

Note: the ortho lithiation of **1c** (0.33 mL, 3.0 mmol) was run as shown in method A except for the following modification: a mixture of Et_2O (5 mL) and anhydrous tetrahydropyran[19] (0.88 mL, 9 mmol) was used as solvent, and *t*-BuLi (1.7 M solution in pentane, 1.95 mL, 3.3 mmol) was added at −30 °C. The resulting yellow suspension was stirred at −30 °C for 10 min and then at RT for 2 h (during warming the suspension changed to a solution). The remainder of the procedure is the same as described above.

Method C. In a drybox,[18] Cp_2ZrCl_2 (0.96 g, 3.3 mmol) was placed in an oven-dried 100-mL Schlenk tube and the tube was sealed with a glass stopper. The Schlenk tube was taken out of the drybox, connected to the Schlenk line, and placed under vacuum (0.1 Torr) at RT for 20 min. The Schlenk tube was flushed with argon, and the glass stopper was replaced with a rubber septum. Toluene (20 mL) was added, and to the resulting suspension was added *t*-BuMgCl (2.0 M solution in Et_2O, 1.65 mL, 3.3 mmol) dropwise over a period of 5 min to give a mixture of an orange solution and a white precipitate. The reaction flask was covered with aluminum foil,[15b] and the mixture was stirred at RT for 10 min and then at 50 °C for 1 h. The reaction mixture was cooled to RT, and the aluminum foil was removed. Anhydrous 1,4-dioxane (0.62 mL, 7.3 mmol) was added, and the mixture was stirred at RT for 20 min. The reaction mixture was cooled to −78 °C and was transferred via cannula to a suspension of the ortho-lithiated **1a** (3.0 mmol), prepared as shown in method A, which had been cooled to −78 °C. The resultant reaction mixture was stirred at −78 °C for 20 min, gradually warmed to RT over a period of 40 min, and stirred at RT for 40 min. The nitrile (3.6−4.5 mmol, 1.2−1.5 equiv) was added, and the flask was sealed and heated at 85 °C for 19 h. The reaction mixture was cooled to RT, concentrated in vacuo, and diluted with THF (20 mL). The mixture was cooled to 0 °C and 1 N HCl (12 mL) [0.2 N HCl (20 mL) for entry 5] was added. The remainder of the procedure is the same as described in method A.

3-(Methoxymethoxy)benzophenone (2a). Using method B, benzonitrile (0.40 mL, 3.9 mmol, 1.3 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:EtOAc = 10:1) yielded 0.58 g (80%) of a pale orange oil (**2a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (2 H, br d, J = 7 Hz), 7.58 (1 H, br t, J = 7.5 Hz), 7.50−7.44 (3 H, m), 7.42−7.35 (2 H, m), 7.30−7.23 (1 H, m), 5.22 (2 H, s), 3.48 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 157.1, 138.9, 137.5, 132.4, 130.0, 129.3, 128.3, 123.8, 120.4, 117.4, 94.5, 56.2. IR (film): 1660, 1598, 1583, 1482, 1447, 1316, 1282, 1227, 1200, 1154, 1081, 1015, 957, 726 cm^{-1}. MS (EI): *m*/*z* (%) 242 (M^+, 100), 212 (15), 135 (18), 105 (86). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.58; H, 5.96. Using method A, benzonitrile (0.46 mL, 4.5 mmol, 1.5 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to 0.46 g (63%) of **2a**. Using method C, benzonitrile (0.46 mL, 4.5 mmol, 1.5 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to 0.53 g (73%) of **2a**.

7-Chloro-1-[(3-methoxymethoxy)phenyl]heptan-1-one (2b). Using method C, 7-chloroheptanonitrile (0.56 g, 3.6 mmol, 1.2 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:EtOAc = 15:1) yielded 0.70 g (82%) of a colorless oil (**2b**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62−7.57 (2 H, m), 7.38 (1 H, t, J = 7.5 Hz), 7.25−7.21 (1 H, m), 5.22 (2 H, s), 3.54 (2 H, t, J = 7 Hz), 3.49 (3 H, s), 2.96 (2 H, t, J = 7 Hz), 1.84−1.70 (4 H, m), 1.55−1.35 (4 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.7, 157.4, 138.5, 129.6, 121.6, 121.0, 115.5, 94.5, 56.3, 45.2, 38.7, 32.6, 28.7, 26.9, 24.3. IR (film): 1687, 1586, 1486, 1444, 1254, 1154, 1081, 1007, 988 cm^{-1}. MS (EI): *m*/*z* (%) 284/286 (M^+, 6/2), 180 (100), 165 (55). Anal. Calcd for $C_{15}H_{21}ClO_3$: C, 63.26; H, 7.43. Found: C, 63.08; H, 7.32. Using method A, 7-chloroheptanonitrile (0.60 g, 4.1 mmol, 1.35 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to 0.75 g (86%) of **2b**. Using method B, 7-chloroheptanonitrile (0.60 g, 4.1 mmol, 1.35 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to 0.57 g (65%) of **2b**.

3-(Methoxymethoxy)phenyl 2-Thienyl Ketone (2c). Using method B, 2-cyanothiophene (0.43 mL, 4.6 mmol, 1.5 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:EtOAc = 10:1 → 3:1) yielded 0.58 g (78%) of a pale brown oil (**2c**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (1 H, dd, J = 5, 1 Hz), 7.67 (1 H, dd, J = 4, 1 Hz), 7.53−7.48 (2 H, m), 7.41 (1 H, t, J = 7.5 Hz), 7.28−7.24 (1 H, m), 7.16 (1 H, dd, J = 5, 4 Hz), 5.23 (2 H, s), 3.50 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 157.1, 143.5, 139.4, 134.9, 134.3, 129.5, 128.0, 122.7, 120.3, 116.8, 94.5, 56.3. IR (film) 1637, 1583, 1413, 1289, 1154, 1081, 1011 cm^{-1}. MS (EI): *m*/*z* (%) 248 (M^+, 65), 111 (100). Anal. Calcd for $C_{13}H_{12}O_3S$: C, 62.88; H, 4.87. Found: C, 63.13; H, 4.67. Using method A, 2-cyanothiophene (0.43 mL, 4.6 mmol, 1.5 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to 0.61 g (81%) of **2c**.

3-(Methoxymethoxy)phenyl 3-Pyridyl Ketone (2d). Using method B, 3-cyanopyridine (0.44 g, 4.2 mmol, 1.4 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:EtOAc:Et_3N = 100:100:1) yielded 0.62 g (85%) of a pale brown oil (**2d**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.01 (1 H, d, J = 1.5 Hz), 8.82 (1 H, dd, J = 5, 1.5 Hz), 8.13 (1 H, dt, J = 8, 2 Hz), 7.51−7.41 (4 H, m), 7.31 (1 H, dt, J = 7, 2.5 Hz), 5.24 (2 H, s), 3.49 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.4, 157.4, 152.9, 150.9, 138.0, 137.2, 133.1, 129.7, 123.7, 123.4, 121.2, 117.2, 94.4, 56.2. IR (film): 1664, 1583, 1285, 1154, 1081, 1015 cm^{-1}. MS (EI): *m*/*z* (%) 243 (M^+, 100), 106 (23). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39. Found: C, 69.33; H, 5.43.

1-Cyclohexenyl 3-(Methoxymethoxy)phenyl Ketone (2e). Using method C, 1-cyclohexenecarbonitrile (0.43 g, 4.0 mmol, 1.3 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:EtOAc = 10:1) yielded 0.48 g (65%) of a pale yellow oil (**2e**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.23 (3 H, m), 7.19−7.15 (1 H, m), 6.63−6.59 (1 H, m), 5.02 (2 H, s), 3.48 (3 H, s), 2.44−2.37 (2 H, m), 2.30−2.22 (2 H, m), 1.77−1.63 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9, 157.1, 144.5, 140.3, 138.7, 129.2, 122.8, 119.2, 116.9, 94.6, 56.2, 26.3, 24.1, 22.1, 21.8. IR (film): 1644, 1583, 1482, 1436, 1278, 1258, 1154, 1081, 1015, 980 cm^{-1}. MS (EI): *m*/*z* (%) 246 (M^+, 42), 214 (49), 201 (100), 185 (53). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.37; H, 7.63. Using method B, 1-cyclohexenecarbonitrile (0.43 g, 4.0 mmol, 1.3 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to 0.36 g (48%) of **2e**.

1-[3-(Methoxymethoxy)phenyl]-5-hexen-1-one (2f). Using method B, 5-cyano-1-pentene (0.40 g, 4.2 mmol, 1.4 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:EtOAc = 10:1) yielded 0.57 g (81%) of a pale yellow oil (**2f**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62−7.57 (2 H, m), 7.37 (1 H, t, J = 8 Hz), 7.25−7.21 (1 H, m), 5.82 (1 H, ddt, J = 17, 10.5, 6.5 Hz), 5.22 (2 H, s), 5.22−4.98 (2 H, m), 3.49 (3 H, s), 2.96 (2 H, t, J = 7.5 Hz), 2.16 (2 H, q, J = 7.5 Hz), 1.84 (2 H, quintet, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 157.6, 138.6, 138.2, 129.8, 121.8, 121.0, 115.6, 115.4, 94.5, 56.3, 38.0, 33.3, 23.4. IR (film): 1687, 1640, 1586, 1486, 1444, 1409, 1251, 1154, 1081, 1004, 923 cm^{-1}. MS (EI): *m*/*z* (%) 234 (M^+, 19), 180 (100), 165 (41). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.52; H, 7.63.

1-[3-(Methoxyphenyl)]butan-1-one (2i). Using method B, butyronitrile (0.39 mL, 4.5 mmol, 1.5 equiv) and **1c** (0.33 mL, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:Et_2O = 15:1) yielded 0.43 g (81%) of a colorless oil (**2i**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56−7.49 (2 H, m), 7.37 (1 H, t, J = 8 Hz), 7.10 (1 H, ddd, J = 8, 2.5, 1 Hz), 3.86 (1 H, s), 2.94 (2

(19) Use of tetrahydropyran was reported to be effective for the ortho lithiation of phenol. See: (a) Posner, G. H.; Canella, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 2571. (b) Talley, J. J.; Evans, I. A. *J. Org. Chem.* **1984**, *49*, 5267.

H, t, $J = 7.5$ Hz), 1.77 (2 H, sextet, $J = 7.5$ Hz), 1.00 (3 H, t, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.3, 159.9, 138.6, 129.6, 120.8, 119.4, 112.4, 55.5, 40.7, 18.0 14.0. IR (film): 1686, 1681, 1598, 1584, 1256, 1046 cm^{-1}. MS (EI): *m*/*z* (%) 178 (M^+, 19), 135 (100), 107 (27). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.16; H, 7.69.

Cyclopropyl 3-Methoxyphenyl Ketone (2j). Using method B, cyclopropyl cyanide (0.33 mL, 4.5 mmol, 1.5 equiv) and **1c** (0.33 mL, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:Et_2O = 15:1 → 5:1) yielded 0.38 g (72%) of a pale yellow oil (**2j**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (1 H, d, J = 8 Hz), 7.51 (1 H, br s), 7.38 (1 H, t, $J = 8$ Hz), 7.11 (1 H, dd, J = 8, 2.5 Hz), 3.85 (3 H, s), 2.70−2.62 (1 H, m), 1.27−1.21 (2 H, m), 1.07−1.01 (2 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.5, 159.9, 139.5, 129.6, 120.8, 119.3, 112.4, 55.5, 17.4, 11.9. IR (film): 1671, 1597, 1582, 1261, 1035, 1008, 898 cm^{-1}. MS (EI): *m*/*z* (%) 176 (M^+, 41), 135 (100), 107 (26). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.08; H, 7.07.

General Procedure for the Preparation of 2g,h from 1b. Method A. A 100-mL round-bottomed resealable Schlenk flask was charged with **1b** (615 mg, 3.0 mmol), sealed with a Teflon screw valve, and evacuated (0.1 Torr) for 5 h at RT. The flask was flushed with argon, the Teflon screw valve was replaced with a rubber septum, Et_2O (18 mL) and THF (2 mL) were added, and the resulting solution was cooled to −78 °C. To this solution *t*-BuLi (1.7 M solution in pentane, 1.85 mL, 3.15 mmol) was added dropwise over a period of 3 min. The resulting bright yellow suspension was stirred at −78 °C for 1.5 h. To this suspension was added a solution of $Cp_2Zr(Me)Cl$ (0.90 g, 3.3 mmol) in Et_2O (10 mL) and THF (2 mL) as described in method A for **1a**. The reaction mixture was stirred at −78 °C for 20 min, gradually warmed to RT over a period of 40 min, and stirred at RT for 1 h. Toluene (20 mL) was added, and the mixture was concentrated in vacuo to one-third of the original volume. Toluene (20 mL) and the nitrile (3.6 mmol, 1.2 equiv) were added, the septum was replaced with a Teflon screw valve, and the flask was sealed and heated at 120 °C for 39 h. After being cooled to RT, the reaction mixture was concentrated in vacuo and the resulting residue was suspended in THF (20 mL). The suspension was cooled to 0 °C, and 1 N HCl (12 mL) was added, followed by stirring at RT for 5 h. The reaction mixture was worked up as described for the reaction of **1a** (EtOAc was used as an extracting solvent). The product was purified by flash column chromatography.

Method B. To a suspension of the ortho-lithiated **1b** (3.0 mmol), prepared as above, was added the solution of $Cp_2Zr(i\text{-}Bu)Cl$ (3.6 mmol) in THF as described in method B for **1a**. The reaction mixture was stirred at −78 °C for 20 min, gradually warmed to RT over a period of 40 min, and stirred at RT for 1 h. Toluene (15 mL) was added, and the mixture was concentrated in vacuo to one-third of the original volume. Toluene (20 mL) and the nitrile (4.5 mmol, 1.5 equiv) were added, and the flask was sealed and heated at 120 °C for 18 h. The reminder of the procedure is the same as described for method A.

***N,N*-Diisopropyl-3-benzoylbenzamide (2g).** Using method B, benzonitrile (0.46 mL, 4.5 mmol, 1.5 equiv) and **1b** (615 mg, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:EtOAc = 5:1 → 3:1) yielded 0.78 g (84%) of a yellow powder (**2g**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (3 H, d, $J = 8$ Hz), 7.73 (1 H, s), 7.61 (1 H, t, $J = 7.5$ Hz), 7.56−7.47 (4 H, m), 3.95−3.42 (2 H, m), 1.72−1.00 (12 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.3, 170.0, 139.2, 138.0, 137.3, 132.9, 130.4, 130.2, 129.7, 128.8, 128.6, 127.2, 51.3, 46.2, 20.9. IR ($CHCl_3$): 1660, 1625, 1451, 1347 cm^{-1}. MS (EI): *m*/*z* (%) 309 (M^+, 10), 266 (15), 209 (100). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49. Found: C, 77.86; H, 7.33. Recrystallization of the above product from Et_2O−hexane gave an off-white powder. Mp: 83−85 °C. Using method A, benzonitrile (0.37 mL, 3.6 mmol, 1.2 equiv) and **1b** (615 mg, 3.0 mmol) were converted to 0.67 g (72%) of **2g**.

***N,N*-Diisopropyl-3-(4-phenylbutyryl)benzamide (2h).** Using method B, 4-phenylbutyronitrile (0.67 mL, 4.5 mmol, 1.5 equiv) and **1b** (615 mg, 3.0 mmol) were converted to the title compound. Purification by flash chromatography (hexane:EtOAc = 5:1 → 3:1) yielded 0.85 g (81%) of a brown powder (**2h**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (1 H, dt, $J = 7$, 2 Hz), 7.87 (1 H, br s), 7.52−7.44 (2 H, m), 7.32−7.17 (5 H, m), 3.85−3.45 (2 H, m), 2.98 (2 H, t, $J = 7.5$ Hz), 2.72 (2 H, t, $J = 7.5$ Hz), 2.09 (2 H, quintet, $J = 7.5$ Hz), 1.65−1.05 (12 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.6, 170.1, 141.7, 139.4, 137.3, 130.1, 129.0, 128.6, 128.5, 128.3, 126.1, 125.4, 51.2, 46.1, 37.9, 35.2, 25.7, 20.8. IR ($CHCl_3$) 1687, 1625, 1455, 1370, 1343 cm^{-1}. MS (EI): *m*/*z* (%) 351 (M^+, 12), 308 (15), 251 (100). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32. Found: C, 78.72; H, 8.48. Recrystallization of the above product from EtOAc−hexane gave an off-white powder. Mp: 91−92 °C.

Preparation of 2k from 1d by Method B. To an oven-dried 100-mL round-bottomed resealable Schlenk flask fitted with a rubber septum were added **1d** (0.51 mL, 3.0 mmol) and Et_2O (15 mL), and the resulting solution was cooled to −78 °C. To this solution was added *n*-BuLi (1.6 M solution in hexane, 1.95 mL, 3.15 mmol) dropwise over a period of 3 min. The resulting pale yellow clear solution was gradually warmed to 0 °C over a period of 40 min with stirring and stirred at 0 °C for 3 h to give the ortho-lithiated **1d**. The remainder of the procedure is the same as described for method B for **1a** [benzonitrile (0.40 mL, 3.9 mmol, 1.3 equiv) was used], except the acid hydrolysis of the crude reaction mixture was conducted as follows. After being heated at 85 °C for 16 h, the reaction mixture was cooled to RT and concentrated in vacuo to one-half its original volume. THF (20 mL) was added, the resulting suspension was cooled to 0 °C, and 0.1 N HCl (40 mL) was added. The reaction mixture was stirred at RT for 2.5 h and neutralized with saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was separated and extracted with Et_2O (20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and filtered, and the solvents were removed using a rotary evaporator. The residue was dissolved in THF (40 mL), and the resulting solution was cooled to 0 °C. HCl (0.01 N, 40 mL) was added, and the mixture was stirred at RT for 3 d. Saturated aqueous $NaHCO_3$ (20 mL) was added. Extractive workup, as shown immediately above, followed by purification by flash chromatography (hexane:EtOAc = 5:1 → 2:1) yielded 0.47 g (56%) of a reddish orange gum (**2k**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (1 H, br t, $J = 2$ Hz), 8.18 (1 H, dt, $J = 8$, 1.5 Hz), 7.90 (1 H, dt, $J = 8$, 1.5 Hz), 7.83−7.79 (2 H, m), 7.63−7.47 (4 H, m), 4.13 (2 H, s), 1.39 (6 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.2, 161.4, 138.1, 137.4, 132.9, 132.6, 132.1, 130.2, 129.7, 128.6, 79.4, 68.0, 28.6. IR ($CHCl_3$): 1650, 1598, 1448, 1325, 1067, 986, 974 cm^{-1}. MS (EI): *m*/*z* (%) 279 (M^+, 3), 264 (100), 208 (30), 105 (55). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13. Found: C, 77.55; H, 6.09.

General Procedure for the Preparation of 3 in Table 2 by Method B. **1a** or **1b** (3.0 mmol) was ortho-lithiated and converted to the corresponding zirconocene intermediate **II** as described in method B for the preparation of **2**. The nitrile (4.2−4.5 mmol, 1.4−1.5 equiv) was added, and the reaction mixture was heated at 85 °C for 16 h. After being cooled to RT, the reaction mixture was concentrated in vacuo, and anhydrous CH_2Cl_2 (10 mL) was added to give a suspension. A solution of I_2 (1.90 g, 7.5 mmol) in THF (2 mL) and anhydrous CH_2Cl_2 (20 mL) was prepared in a 50-mL Schlenk tube. This was added via cannula to the suspension, prepared above, which had been cooled to 0 °C. Anhydrous CH_2Cl_2 (5 mL) was added to rinse the Schlenk tube, and the washings were added to the reaction flask. The reaction mixture was stirred at RT for 7 h, then poured into a 200-mL round-bottomed flask. THF (30 mL) was used to rinse the reaction residue into the round-bottomed flask. The reaction mixture was cooled to 0 °C, 1 N HCl (12 mL) was added, and the reaction mixture was stirred at RT for 14−40 h. Saturated aqueous Na_2SO_3 (50 mL) was added, and the mixture was stirred vigorously at RT for 30 min and then was filtered through a pad of Celite. The filtrate was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (50 mL), and the aqueous layer was separated off and extracted with EtOAc. The combined organic layers were washed successively with saturated aqueous Na_2SO_3 (50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered. The solvents were removed using a rotary evaporator, and the product was purified by flash column chromatography.

1-[2-Iodo-3-(methoxymethoxy)phenyl]-5-hexen-1-one (3a). Using the general procedure, 5-cyano-1-pentene (0.40 g, 4.2 mmol, 1.4 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to the title compound. In this example, the hydrolysis with HCl was carried out for 20 h.

Purification by flash chromatography (hexane:EtOAc = 10:1) yielded 0.50 g (46%) of a pale brown oil (**3a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (1 H, dd, J = 8.5, 7.5 Hz), 7.10 (1 H, dd, J = 8.5, 1.5 Hz), 6.88 (1 H, dd, J = 7.5, 1.5 Hz), 5.81 (1 H, ddt, J = 17, 10.5, 6.5 Hz), 5.27 (2 H, s), 5.08−4.97 (2 H, m), 3.52 (3 H, s), 2.88 (2 H, t, J = 7 Hz), 2.17 (2 H, br q, J = 7 Hz), 1.85 (2 H, quintet, J = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 156.4, 148.5, 138.1, 129.7, 120.4, 115.7, 115.6, 95.2, 84.4, 56.7, 42.0, 33.2, 23.1. IR (film): 1702, 1640, 1564, 1458, 1421, 1257, 1203, 1154, 977, 921, 783 cm^{-1}. MS (EI): *m*/*z* (%) 360 (M^+, 15), 306 (100), 291 (38), 274 (14), 261 (18), 247 (53). Anal. Calcd for $C_{14}H_{17}IO_3$: C, 46.68; H, 4.76. Found: C, 47.02; H, 4.60.

2-Iodo-3-(methoxymethoxy)phenyl 2-Thienyl Ketone (3b). Using the general procedure, 2-cyanothiophene (0.43 mL, 4.5 mmol, 1.5 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to the title compound. In this example, the hydrolysis with HCl was carried out for 17 h. Purification by flash chromatography (hexane:EtOAc = 5:1 → 3:1) yielded 0.86 g (76%) of a brown solid (**3b**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (1 H, br d, J = 5.5 Hz), 7.34 (1 H, br t, J = 8 Hz), 7.11 (1 H, br d, J = 8 Hz), 7.02−6.94 (3 H, m), 5.29 (2 H, s), 3.54 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 156.5, 147.3, 143.2, 132.4, 130.8, 129.7, 127.9, 121.6, 114.8, 95.2, 87.8, 56.7. IR (film): 3274, 1594, 1562, 1460, 1360, 1143, 1086, 1049, 1004, 912, 874 cm^{-1}. MS (EI): *m*/*z* (%) 373 ($M^+ - 1$, 100), 342 (7), 214 (84), 186 (66), 110 (66). Anal. Calcd for $C_{13}H_{11}IO_3S$: C, 41.73; H, 2.96. Found: C, 41.97; H, 3.16. Recrystallization of the above solid from EtOAc−hexane gave a brown powder. Mp: 91−92 °C.

2-Iodo-3-(methoxymethoxy)phenyl 3-Pyridyl Ketone (3c). Using the general procedure, 3-cyanopyridine (0.44 g, 4.2 mmol, 1.4 equiv) and **1a** (0.40 mL, 3.0 mmol) were converted to the title compound. In this example, the hydrolysis with HCl was carried out for 16 h. Purification by flash chromatography (hexane:EtOAc:Et_3N = 300:200:1) yielded 0.82 g (74%) of an orange oil (**3c**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.94 (1 H, dd, J = 2.5, 1 Hz), 8.81 (1 H, dd, J = 4.5, 1 Hz), 8.17 (1 H, dt, J = 8, 2 Hz), 7.47−7.39 (2 H, m), 7.21 (1 H, dd, J = 8, 1 Hz), 6.95 (1 H, dd, J = 7.5, 1.5 Hz), 5.31 (2 H, s), 3.54 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 226.4, 195.9, 156.5, 153.9, 151.9, 145.6, 137.3, 131.1, 129.9, 123.8, 121.7, 116.0, 95.2, 56.7. IR ($CHCl_3$): 1677, 1584, 1565, 1458, 1297, 1152, 1087, 1047, 1029, 1011, 954 cm^{-1}. MS (EI): *m*/*z* (%) 369 (M^+, 100), 370 (14). Anal. Calcd for $C_{14}H_{12}INO_3$: C, 45.55 H, 3.28. Found: C, 45.75; H, 3.38.

1-(2-Iodo-3-methoxyphenyl)butan-1-one (3d). Using the general procedure, butyronitrile (0.39 mL, 4.5 mmol, 1.5 equiv) and **1c** (0.33 mL, 3.0 mmol) were converted to the title compound. In this example, the hydrolysis with HCl was carried out for 40 h. Purification by flash chromatography (hexane:EtOAc = 13:1 → 8:1) yielded 0.69 g (76%) of a reddish orange oil (**3d**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (1 H, t, J = 8 Hz), 6.85 (1 H, d, J = 8 Hz), 6.83 (1 H, d, J = 8 Hz), 3.90 (3 H, s), 2.85 (2 H, t, J = 7.5 Hz), 1.75 (2 H, sextet, J = 7.5 Hz), 1.01 (3 H, t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 158.3, 148.5, 129.8, 119.2, 111.8, 83.1, 56.8, 44.7, 17.6, 13.9. IR (film): 1702, 1562, 1462, 1421, 1295, 1269, 1020, 1005, 780 cm^{-1}. MS (EI): *m*/*z* (%) 304 (M^+, 22), 261 (100), 218 (11), 203 (21). Anal. Calcd for $C_{11}H_{13}IO_2$: C, 43.44; H, 4.31. Found: C, 43.55; H, 4.14.

1-(2-Iodo-3-methoxyphenyl)-4-phenylbutan-1-one (3e). Using the general procedure, 4-phenylbutyronitrile (0.67 mL, 4.5 mmol, 1.5 equiv) and **1c** (0.33 mL, 3.0 mmol) were converted to the title compound. In this example, the hydrolysis with HCl was carried out for 14 h. Purification by flash chromatography (hexane:EtOAc = 15:1 → 5:1) yielded 0.69 g (61%) of an orange oil (**3e**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.19 (6 H, m), 6.84 (1 H, dd, J = 8, 1.5 Hz), 6.79 (1 H, dd, J = 7.5, 1.5 Hz), 3.90 (3 H, s), 2.88 (2 H, t, J = 7 Hz), 2.72 (2 H, t, J = 7 Hz), 2.07 (2 H, quintet, J = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 158.4, 148.4, 141.7, 129.8, 128.6, 128.5, 126.1, 119.3, 111.9, 83.2, 56.8, 42.0, 35.2, 25.6. IR (film): 1702, 1602, 1583, 1562, 1462, 1417, 1296, 1266, 1018, 1001, 780, 748, 715 cm^{-1}. MS (EI): *m*/*z* (%) 380 (M^+, 0.6), 276 (100), 261 (41), 253 (27). Anal. Calcd for $C_{17}H_{17}IO_2$: C, 53.70; H, 4.51. Found: C, 53.71; H, 4.67.

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