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Convenient Processes for the Synthesis of Aromatic Ketones from Aryl Bromides and Carboxylic Anhydrides Using a Cobalt Catalysis

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The cross-coupling of various para- and meta-substituted aromatic bromides, mostly bearing sensitive moieties, with several carboxylic acid anhydrides is reported. This reaction can be carried out in two steps, by forming an aromatic organozinc reagent via cobalt catalysis in the first step, or even more interestingly in a single step, also by using a cobalt-based catalyst. The aromatic ketones are obtained by these new, mild, and convenient methods in 30−79% yields versus starting aryl bromide. Results are also disclosed that suggest the role played by cobalt species in the coupling of organozinc reagents with electrophiles could be similar to those of more commonplace transition metal complexes.

Introduction

The acylation of aromatic nuclei has been a long-standing issue in organic chemistry since the first Friedel−Crafts reactions more than a century ago.[1] The past decades have witnessed extensive breakthrough in the field of organometallics and transition-metal catalysis, and numerous efficient methods of synthesis of aromatic ketones have been described.[2] Indeed, whereas the use of strongly nucleophilic reactants such as organomagnesium[3] or organolithium[4] compounds requires low temperatures due to their reactivity with carbonyl bonds, the less reactive organocopper or -manganese reagents can be readily coupled with acyl chlorides[5,6] or anhydrides[6] at room temperature. Still milder reagents such as organotin[7] or -zinc[8] compounds and boronic acids[9] are acylated with an appropriate transition metal catalyst but react only with the most reactive acid derivatives (usually acid chlorides).

However, the main difficulty of these methods is the preliminary preparation of the organometallic reagent, especially when the aromatic ring bears sensitive moieties. Many of the cited organometallics are synthesized by a transmetalation reaction with an organomagnesium or organolithium compound, a method that dramaticaly reduces the range of available functional groups unless working at low temperatures.[10,11] Alternatively, some functionalized aromatic organometallics can be directly prepared from aromatic derivatives. Arylboronic esters can be directly synthesized by palladium-catalyzed borylation of aryl halides or pseudo-halides with a tetra(alkoxy)diboron or dialkoxyborane.[12] Other reagents, namely, organocopper, -manganese, and -zinc compounds, can be accessed with the help of activated metals (Rieke metals[13] or by other methods in the case of manganese[14]). In the case of highly functionalized organozinc compounds, another mild method of synthesis via halogen−

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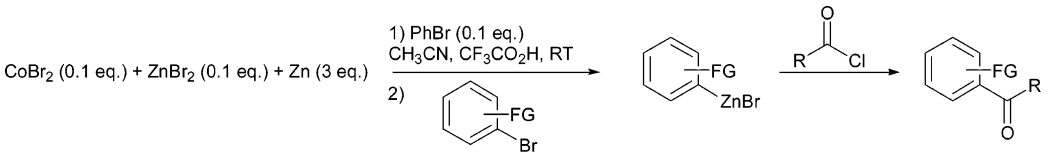
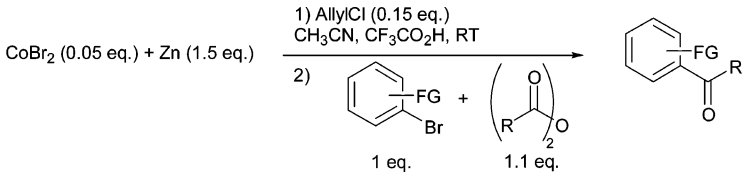
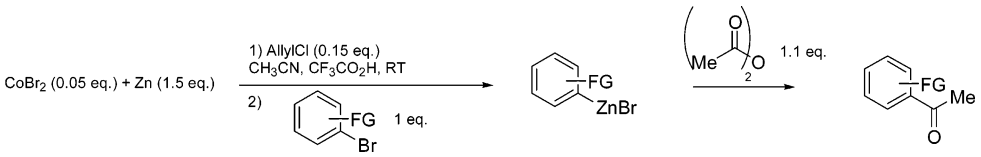
SCHEME 1. Synthesis of Functionalized Arylzinc Reagents and Their Consecutive Reaction with Acid Chlorides (Ref 17)



SCHEME 2. One-Step Synthesis of Aromatic Ketones from Functionalized Aryl Bromides and Acid Anhydrides



SCHEME 3. Two-Step Synthesis of Aromatic Ketones from Functionalized Aryl Bromides and Acetic Anhydride



magnesium exchange followed by transmetalation[15] has also been described.

Recently in our laboratory,[16] a convenient method for the preparation of aromatic organozinc compounds has been discovered. A direct activation of aryl bromides is achieved by low-valent cobalt(I) species arising from the reduction of cobalt(II) halides by zinc dust. This procedure allows the synthesis of a variety of functionalized aryl species in good to excellent yields. The versatility and simplicity of this original method represent an alternative to most described procedures.

Following these discoveries in the field of aromatic organozinc species synthesis, we recently described the synthesis of aromatic ketones by the reaction between a preformed organozinc reagent and a carboxylic acid chloride[17] (Scheme 1). This method relies upon the enhanced reactivity of aromatic organozinc bromides when prepared by our in situ-generated-cobalt(I)-catalysis method and can be efficiently applied to the synthesis of aromatic ketones bearing sensitive functional groups on the aromatic ring, without further addition of a catalyst. Nevertheless, from a practical point of view, acid anhydrides are sometimes preferable to their chloride counterparts, which can be tedious to prepare and to store. Since anhydrides are prepared in milder conditions, they can advantageously replace chlorides in cases where their lower reactivity is not in question, although the use of just one-half of such molecules is an obvious disadvantage considering economic criteria.

The formation of aryl ketones involving an acid chloride requires the formation of the arylzinc species in a first step, taking the high reactivity of the acid chloride into account. The current paper deals with a method inspired by the precedent results obtained with acid chlorides but exploits the lower reactivity of the acid anhydrides in order to carry out the reaction in a single step from aryl bromide (Scheme 2). First, a few reactions in a two-step sequence are described, and the extension of the method to a single-step reaction is then disclosed. Evidence of the role played by the cobalt catalyst in the coupling reaction is also presented.

Results and Discussion

1. Two-Step Synthesis. A preliminary study of the reaction of our organozinc species toward acid anhydrides has been carried in order to confirm the reactivity of these reagents when chemically synthesized by cobalt catalysis, using acetic anhydride as a probe (Scheme 3).

It has been verified that the results obtained in the two-step coupling reaction of aryl bromides and acid chlorides can be easily extended to acid anhydrides,

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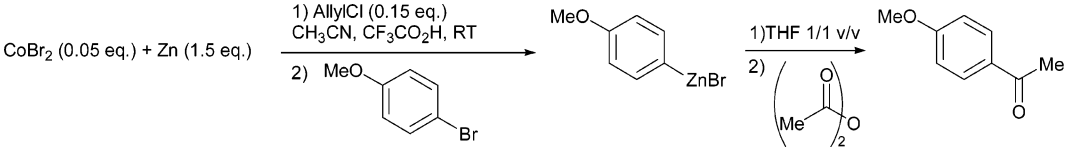
TABLE 1. Two-Step Procedure for the Acylation of Aryl Bromides with Acetic Anhydride

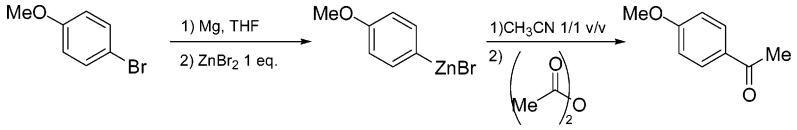
entry	aryl bromide	ArZnBr (%)[a]	conversion of ArBr (%)	reaction time[b]	product	isolated yield[c] (%)
1	4-MeOPhBr	82	97	1 h	4-MeOPhCOMe	71
2	4-NCPhBr	83	100	2 h	4-NCPhCOMe	53
3	3-F_3CPhBr	94	100	2 h	3-F_3CPhCOMe	76

[a] Obtained arylzinc halides are converted into the corresponding aryl iodide by addition of iodine. [b] After addition of the anhydride. [c] Calculated on ArBr.

SCHEME 4. Cobalt-Catalyzed Synthesis of 4-Methoxyphenylzinc Bromide and Coupling with Acetic Anhydride



SCHEME 5. Synthesis of a 4-Methoxyphenylzinc Bromide via Transmetalation of the Corresponding Grignard Reagent and Coupling with Acetic Anhydride



despite their lowered reactivity regarding nucleophilic reagents (Table 1).

1-(4-Methoxyphenyl)ethanone (Table 1, entry 1), 4-acetylbenzonitrile (Table 1, entry 2), and 1-(3-trifluoromethyl)ethanone (Table 1, entry 3) have been readily synthesized in a two-step reaction sequence from the corresponding aryl bromides and acetic anhydride using the optimized reaction conditions detailed elsewhere[18] for the preparation of ArZnBr: 0.05 equiv of $CoBr_2$, 1.5 equiv of zinc dust activated by 50 μL of trifluoroacetic acid, and a 1 M concentration in aryl bromide. Prior to the addition of aryl bromide, a preliminary step of 5 min was carried out using 0.15 equiv of allyl chloride (3 equiv vs cobalt) in order to enhance the yield of the organozinc species and diminish the formation of byproducts, especially ArH. A 1.3-fold excess of zinc dust with regard to the total amount of organic halide (aryl bromide + allyl chloride) was used.

2. Role of the Cobalt Catalyst in the Reactivity of Organozinc Species. As traditional organozinc reagents do not easily react with acid chlorides or anhydrides, we wondered which part the cobalt catalyst played in the reactions studied in our laboratory. Cobalt-catalyzed cross-coupling reactions involving organozinc derivatives have been described in some cases.[19] The role of $CoBr_2$ in the synthesis of the organozinc reagents was also emphasized.[16,20]

Two questions have to be answered. First, does the cobalt catalyst play a role in the subsequent reactions with electrophiles. Second, does it act rather as a cobalt(I)/cobalt(III) couple (as it is described for similar reactions with nickel(0)/nickel(II)[2] or palladium(0)/palladium(II) systems[2,9d]) or as cobalt(II) with the reactive nucleophilic species actually being an organocobalt(II) reagent, the cause of this last hypothesis being that the transmetalation step of the formation of organozinc species is reversible.

TABLE 2. Comparison of Different Types of 4-Methoxyphenylzinc Bromides toward Coupling with Acetic Anhydride

entry	preparation method of ArZnBr	additional $CoBr_2$[a]	reaction time[b]	yield (%)[c]
1	cobalt catalysis in CH_3CN	no	23 h	76
2	transmetalation in THF	no	20 h	28
3	transmetalation in THF	yes, 5% vs ArBr	30 min	90

[a] Simultaneously with anhydride addition. [b] After addition of acetic anhydride. [c] GC yield calculated on arylzinc bromide.

To answer the first question, a series of experiments was carried out using acetic anhydride and 4-bromoanisole, whose corresponding organozinc reagent can be readily accessed via a transmetalation reaction from the organomagnesium compound. Various two-step coupling reactions have been carried out, either by generating the organozinc reagent by our method (Scheme 4) or by transmetalation (Scheme 5). To be able to compare the results, the zinc reagent was prepared as a 0.5 M solution in a 1:1 tetrahydrofuran/acetonitrile solvent mixture by starting with a 1 M solution of aryl bromide either in CH_3CN (Scheme 4) and diluting with an aliquot of THF or vice versa (Scheme 5). The results are presented in Table 2.

Comparison between entries 1 and 2 of Table 2 demonstrates the enhanced reactivity of our aromatic organozinc reagents even without additional catalyst. On the contrary, in similar concentration and solvent conditions, the same compound, when prepared by transmetalation, only sluggishly undergoes the coupling reaction with acetic anhydride. Remarkably, when 5% $CoBr_2$ is added to this transmetalated organozinc reagent (Table 2, entry 3), the coupling reaction is faster than in the case of entry 1 of Table 2. Our interpretation of these

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TABLE 3. One-Step Procedure for the Synthesis of Aromatic Ketones: Reactions with Acetic Anhydride

entry	aryl bromide	$CoBr_2$ (equiv)	reaction time	product	yield (%) [a]	conversion (%)[a]	ArH (%)[a]	ArAr (%)[a]	ArCOAr (%)[a]
1	4-MeOPhBr	0.05	2 h	4-MeOPhCOMe	81	96	9	1	5
2	4-NCPhBr	0.05	2 h	4-NCPhCOMe	70	99	21	5	2
3	3-F_3CPhBr	0.05	6 days	3-F_3CPhCOMe	45	63	8	4	0
4	3-F_3CPhBr	0.075	29 h	3-F_3CPhCOMe	74	85	11	1	0
5	3-F_3CPhBr	0.1	6 h	3-F_3CPhCOMe	87	97	8	2	0

[a] GC yields.

TABLE 4. One-Step Procedure for the Synthesis of Unsymmetrical Aromatic Ketones: Extension of the Reaction

entry	aryl bromide	acid anhydride	$CoBr_2$ (equiv)	conversion (%)[a]	reaction time	product	isolated yield[b] (%)
1	4-MeOPhBr	Ac_2O	0.05	96	2 h	4-MeOPhCOMe	67
2	4-MeOPhBr	$(C_4H_9CO)_2O$	0.05	98	8 h	4-MeOPhCOC_4H_9	79
3	4-MeOPhBr	$(PhCO)_2O$	0.05	100	6 h	4-MeOPhCOPh	46
4	4-NCPhBr	Ac_2O	0.05	99	2h	4-NCPhCOMe	54
5	4-NCPhBr	$(C_4H_9CO)_2O$	0.05	100	20 h	4-NCPhCOC_4H_9	76
6	4-NCPhBr	$(PhCO)_2O$	0.1	100	30 h	4-NCPhCOPh	30
7	4-EtO_2CPhBr	Ac_2O	0.05	99	1 h	4-EtO_2CPhCOMe	62
8	4-EtO_2CPhBr	$(C_4H_9CO)_2O$	0.05	98	4 h	4-EtO_2CPhCOC_4H_9	78
9	4-EtO_2CPhBr	$(PhCO)_2O$	0.075	100	20h	4-EtO_2CPhCOPh	33
10	4-FPhBr	Ac_2O	0.1	100	22 h	4-FPhCOMe	69
11	4-F_3CPhBr	Ac_2O	0.1	94	4 h	4-F_3CPhCOMe	61
12	3-MeOPhBr	Ac_2O	0.05	97	30 min	3-MeOPhCOMe	72
13	3-NCPhBr	Ac_2O	0.075	61	24 h	3-NCPhCOMe	34
14	3-F_3CPhBr	Ac_2O	0.1	98	6 h	3-F_3CPhCOMe	71

[a] GC Yield. [b] Vs Aryl Bromide.

results is that the unusual reactivity of the organozinc species, when prepared by cobalt catalysis in CH_3CN, could indeed emerge from the presence of cobalt(II) or cobalt(I) species but that the catalyst is already partially exhausted through dismutation of Co(I) when the addition occurs. This would explain why the reaction presented in entry 1 of Table 2 is slower than its counterpart in entry 3 of Table 2. Nevertheless, an evaluation of the quantity of $CoBr_2$ at the end of the cobalt-catalyzed organozinc synthesis would be necessary to support this hypothesis.

Studies are currently underway in our laboratory in order to try to solve the second problem, i.e., identifying the organometallic species that take part in the reaction.

3. One-Step Synthesis. Acid chlorides could not be coupled to aryl bromides in a one-step sequence with our method, that is, without preforming the organozinc species, because of their high reactivity: we assume that they readily undergo a reaction with cobalt(I) species, resulting in their decomposition. On the other hand, as acid anhydrides are less reactive than acid chlorides, it seemed interesting to develop a convenient method for the one-step synthesis of unsymmetrical aromatic ketones from aryl bromides. This procedure follows the protocol already described, but after the usual preliminary step of 5 min of stirring with 0.3 equiv of allyl chloride, the aryl bromide (1 equiv) and the acid anhydride (1.1 equiv) are added simultaneously (Scheme 2).

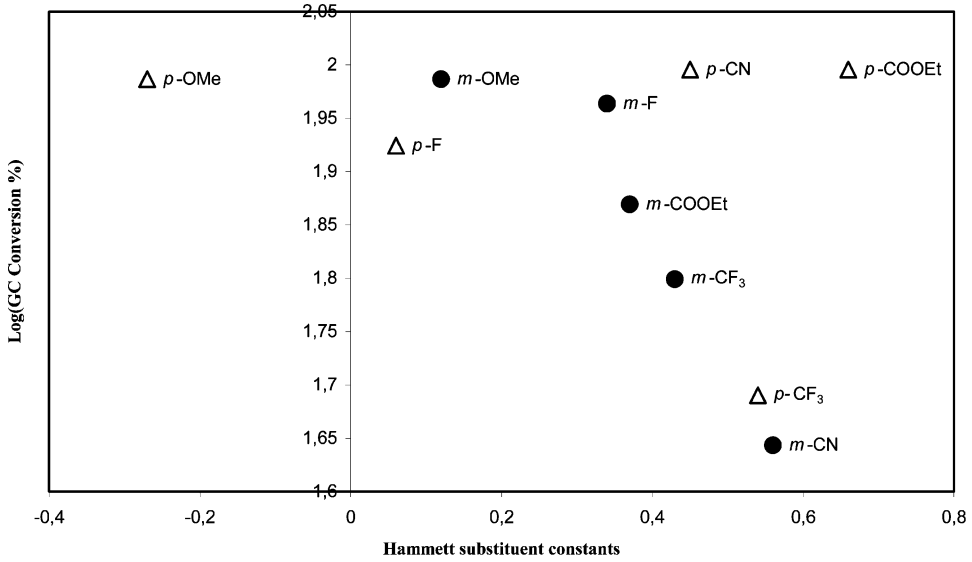
The first reactions between aromatic organozinc reagents prepared in situ from aryl bromides and acetic anhydride are reported in Table 3.

As in the two-step reaction sequence (see Table 1), 4-bromoanisole (Table 3, entry 1) and 4-bromobenzonitrile (Table 3, entry 2) readily react with acetic anhydride and the corresponding products are obtained in satisfying yields and reaction times. Interestingly, a significant quantity of the "ArCOAr" (symmetric ketone) byproduct is obtained with this method in the case of 4-bromoanisole. On the other hand, with 3-bromobenzotrifluoride (Table 3, entry 3), it was found to be very difficult to entirely convert the bromide. Our hypothesis is that there exists a competition between the insertion of cobalt(I) in the carbon−bromine bond[16] and in the carbon−oxygen bond of the anhydride. In this method, the reactivity of aryl bromides thus seems to be more critical with regard to the functional groups they bear than usually observed in the synthesis of organozinc reagents.[18] Whatever the cause of this poor result may be, the problem was solved by gradually increasing the proportion of cobalt(II) bromide, always keeping 3 equiv of allyl chloride versus cobalt and 1.3 equiv of zinc dust versus the total of aryl bromide and allyl chloride. With 0.075 equiv (Table 3, entry 4) and especially with 0.1 equiv (Table 3, entry 5), the reaction proceeds faster and with a better conversion rate. However, it remains slower than the two-step procedure (Table 1, entry 3) in this last case.

Nonetheless, the proof was made that unsymmetrical aromatic ketones could be accessed via this single-step path. We consequently applied the method to other aromatic bromides bearing various functional groups in the para and meta series, coupling them with acetic, valeric, and benzoic anhydrides (Table 4). Optimization of the quantity of the cobalt catalyst was realized as described above when necessary, while always keeping the amount of $CoBr_2$ below 0.1 equiv of aryl bromide.

No optimization beyond 0.05 equiv of $CoBr_2$ was needed for 4-bromoanisole coupled with any of the three anhydrides (Table 3, entries 1−3), as these reactions are reasonably fast and the reaction products are obtained in good yields. However, with the poorly reactive benzoic

SCHEME 6. GC Conversions of the Reactions with Ac_2O (0.05 equiv of $CoBr_2$) against Hammett Constants from Ref 22



anhydride (Table 3, entry 3), the yield is lower than in the first two cases, and a significant amount of an ArCOAr byproduct (GC yield 19%) is formed over time, along with a similar quantity of benzophenone.

The reactions between 4-bromobenzonitrile or ethyl 4-bromobenzoate and the two most reactive anhydrides (Table 3, entries 4 and 5 or entries 7 and 8, respectively) proceed in a similar fashion, although the reactions with valeric anhydride are slower in these cases (Table 3, entries 5 and 8). However, the reactions between these two aromatic bromides and benzoic anhydride required larger quantities of the cobalt catalyst and yielded less product than in the case of 4-bromoanisole (Table 3, entries 6 and 9). The formation of benzophenone is also observed in these two cases. Benzophenone formation has already been observed in a similar case, as the result of the decarbonylation of a nickel(II)−benzoyl complex[21] resulting from the oxidative addition of benzoyl chloride to a nickel(0) complex. Similarily, in our case, it can be postulated that the benzophenone results from the decomposition of a cobalt(III)−benzoyl complex formed by the oxidative addition of benzoic anhydride to cobalt-(I). This decarbonylation process may also account for the formation of the ArCOAr byproduct, as its formation is reported in the case of reactions between organozinc reagents and carbon monoxide catalyzed by cobalt(II) complexes.[19]

Other reactions in the para series include coupling between 4-bromofluorobenzene and acetic anhydride (Table 3, entry 10) and between 4-bromobenzotrifluoride and acetic anhydride (Table 3, entry 11). In both cases, the proportion of $CoBr_2$ had to be increased in order to obtain a satisfying yield. It also has to be noted that theses reactions with acetic anhydride are much slower than the corresponding experiments with the other para-substituted aryl bromides (Table 3, entries 1, 4, and 7).

In the meta series, only 3-bromoanisole (Table 3, entry 12) could be readily coupled with acetic anhydride using 0.05 equiv of the cobalt catalyst. Strangely enough, conversion of the 3-bromobenzonitrile (Table 3, entry 13), on the opposite, could not be raised above 61%, even when using 0.1 equiv of $CoBr_2$: the experiment only proceeded faster than in the described case of 0.075 equiv of $CoBr_2$. Finally, full conversion of the aryl bromide could be achieved in the case of 3-bromobenzotrifluoride by using 0.1 equiv of the cobalt catalyst to obtain the desired coupling product in a good yield of 71% (Table 3, entry 14).

It has thus been proved that the one-step reaction between an aryl bromide and an acid anhydride could be efficiently applied to most types of substituents, including sensitive ones such as nitrile and ester groups, at para and meta positions on the aromatic ring. However, differences in reactivity between aryl bromides arose that seemed to have no clear link with the nature of the substituent. To better comprehend the relationship between the structure and the reactivity of the aryl bromides, the decimal logarithm of the final conversion (GC) of the reactions of 0.05 equiv of $CoBr_2$ with acetic anhydride against the Hammett σ_p and σ_m coefficients[22] (respectively) has been plotted (Scheme 6). Final conversion was chosen, since it seemed to better reflect the reactivity of the starting aryl bromide than the yield of product.

The plot shows that there seems to be a good correlation between the electron-withdrawing or -donating power of the substituent and the conversion of the aryl bromide in the meta series. Indeed, results are nearly linear (correlation coefficient 0.969) between *m*-F and *m*-CN substituents. The case of *m*-OMe is interpreted as a "saturation" of the conversion for substituents with σ_m below 0.2. Surprisingly enough, the slope is negative, although the aryl bromide is supposed to be more reactive toward oxidative addition when the substituent is an attractor.

On the contrary, the results from the para series are puzzling because no clear correlation could be deduced

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from the plot. The interpretation of these results is still in question.

Conclusion

The results reported herein prove that the one-step reaction between aromatic bromides and acid anhydrides permits the convenient synthesis of unsymmetrical aromatic ketones. Furthermore, this reaction, derived from our cobalt-catalyzed synthesis of organozinc species, can easily be applied to reagents bearing sensitive functional groups with satisfying isolated yields. As with the two-step reaction with acid chlorides, there is evidence that the formed organozinc reagents display an unexpected reactivity, a fact that was highlighted by a comparison under identical conditions with an organozinc reagent prepared via an organomagnesium transmetalation process. It now seems possible to suppose that cobalt plays a key role not only in the synthesis but also in the reactivity of arylzinc bromides. Further studies will, however, be necessary to pinpoint the exact mechanism of the reaction.

Experimental Section

General Methods. All reagents were purchased and used without further purification. Acetonitrile was used as purchased and stored under argon. Tetrahydrofuran was distilled on sodium/benzophenone under argon. Zinc dust (<10 μm) was purchased from Aldrich.

GC analyses were carried out using a 5 m DB-1 capillary column. Mass spectra were recorded with an ITD spectrometer coupled to a gas chromatograph (DB1, 30 m). Flash column chromatographies were performed on silica gel 60, 35−70 μm. NMR spectra were recorded on a Bruker AC-200 spectrometer using TMS as a standard for ^{1}H and ^{13}C and CF_3Cl as a standard for ^{19}F. Melting points were measured on an Electrothermal IA9100 device.

1. Typical Procedure for the Two-Step Synthesis of Unsymmetrical Aromatic Ketones. In a preliminary step, zinc dust (1.47 g; 1.49 equiv), cobalt(II) bromide (164 mg; 0.05 equiv), allyl chloride (185 μL; 0.15 equiv), 200 μL of dodecane (internal reference for GC), and 50 μL of trifluoroacetic acid (to activate the zinc dust) are stirred under argon in 15 mL of acetonitrile for 5 min at room temperature. 4-Bromoanisole (1.88 mL; 15 mmol) is then added, and the reaction is carried out for 1 h, until complete conversion of the starting aryl bromide (as monitored by GC on iodolyzed aliquots quenched with a sodium thiosulfate solution). Acetic anhydride (1.55 mL; 1,1 equiv) is added to the reaction vessel, and the reaction is carried out for 2 h, until total conversion of the organozinc reagent. The reaction is quenched with 40 mL of 1.5 M HCl and extracted with 3 × 40 mL ether. The organic layer is washed with 20 mL of a saturated solution of $NaHCO_3$ and 20 mL of a saturated solution of NaCl. The crude product is purified by flash chromatography on silica gel eluted with pentane/ether 9/1, yielding 71% of 1-(4-methoxyphenyl)ethanone as a white solid: mp 36 °C, (lit.[23] 38−39 °C); ^{1}H NMR ($CDCl_3$)[24] δ 2.55 (3H, s), 3.85 (3H, s), 6.96 (2H, d, J = 8.8 Hz), 7.97 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$)[24] δ 26.0, 55.0, 113.4 (2C), 130.0, 130.4 (2C), 163.2, 196.2; MS (EI)[24] m/z (relative intensity) 150 ($M^{+\bullet}$, 48), 135 (100), 107 (6), 92 (7), 77 (30). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71; O, 21.31. Found: C, 70.65; H, 6.48; O, 21.52.

4-Acetylbenzonitrile: mp 57−58 °C (lit.[25] 58−59 °C); ^{1}H NMR ($CDCl_3$)[26] δ 2.63 (3H, s), 7.76 (2H, d, J = 8.4 Hz), 8.03 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$)[26] δ 26.8, 116.3, 118.0, 128.7 (2C), 132.5 (2C), 139.9, 196.6; MS (EI)[26] m/z (relative intensity) 145 (M^+, 5), 130 (100), 102 (33), 75(14). Anal. Calcd for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65; O, 11.02. Found: C, 74.26; H, 4.87; N, 9.62; O, 11.29.

1-(3-Trifluoromethylphenyl)ethanone: ^{1}H NMR ($CDCl_3$)[27] δ 2.49 (3H, s), 7.45 (1H, dd, J_a = J_b = 7.5 Hz), 7.65 (1H, d, J = 7.5 Hz), 7.97 (1H, d, J =7.5 Hz), 8.04 (1H, s); ^{13}C NMR ($CDCl_3$)[27] δ 26.4, 125.0, 128.6 (q, J_{C-F} = 240 Hz), 129.2, 129.4, 131.3, 131.7, 137.6, 196.5; ^{19}F NMR ($CDCl_3$)[28] −63.0 (s); MS (EI) m/z (relative intensity) 188 (M^+, 3), 173 (100), 145 (52), 125 (6), 95(6), 75(4). Anal. Calcd for $C_9H_7F_3O$: C, 57.45; H, 3.75; F, 30.29. Found: C, 57.5; H, 3.87; F, 28.83.

2. Typical Procedure for the Preparation of an Organozinc Reagent by Transmetalation of the Correponding Organomagnesium Reagent. Magnesium turnings (500 mg, 1.05 equiv), THF (3 mL), and 10 drops of 4-bromoanisole are gently stirred under argon with a few crystals of iodine. Upon decoloration, the rest of the 4-bromoanisole (2.40 mL; 20 mmol) as a solution in 17 mL of THF is introduced dropwise over 1 h. After total conversion of the aryl bromide (monitored by GC), $ZnBr_2$ (4.50 g; 1 equiv) is added and the reaction medium is vigorously stirred during 1 h. The completion of the reaction is monitored by a coloration test with Michler's ketone.[29] Acetonitrile (20 mL) is added, and the $MgBr_2$ salt is allowed to set. The clear solution contains 60−70% (GC yield of an iodolyzed aliquot) of the organozinc reagent and can be used in further experiments.

3. Typical Procedure for the One-Step Synthesis of Aromatic Ketones. In a preliminary step, zinc dust (1.47 g; 1.49 equiv), cobalt(II) bromide (164 mg; 0.05 equiv), allyl chloride (185 μL; 0.15 equiv), 200 μL of dodecane (internal reference for GC), and 50 μL of trifluoroacetic acid (to activate the zinc dust) are stirred under argon in 15 mL of acetonitrile for 5 min at room temperature. 4-Bromoanisole (1.88 mL; 15 mmol) and acetic anhydride (1.55 mL; 1,1 equiv) are then added simultaneously, and the reaction is carried out for 2 h, until complete conversion of the starting aryl bromide (as monitored by GC). The reaction is quenched with 40 mL of 1.5 M HCl and extracted with 3 × 40 mL of ether. The organic layer is washed with 20 mL of a saturated solution of $NaHCO_3$ and 20 mL of a saturated solution of NaCl. The crude product is purified as described above.

1-(4-Methoxy-phenyl)pentan-1-one: ^{1}H NMR ($CDCl_3$)[30] δ 0.97 (3H, t, J_a = 7.2 Hz), 1.40 (2H, tq, J_a = J_b = 7.2 Hz), 1.70 (2H, tt, J_b = J_c = 7.2 Hz), 2.89 (2H, t, J_c = 7.2 Hz), 3.82 (3H, s), 6.90 (2H, d, J = 8.6 Hz), 7.92 (2H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$)[30] δ 13.7, 22.3, 26.4, 37.6, 55.0, 113.4 (2C), 129.2 (2C), 130.0, 163.0, 198.5; MS (EI)[30] m/z (relative intensity) 192 (M^+, 3), 163 (2), 135 (100), 107 (12), 77 (18). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64. Found: C, 74.58; H, 8.47; O, 16.85.

(4-Methoxy-phenyl)-phenylmethanone: mp 61−63 °C (lit.[31] 67−68 °C); ^{1}H NMR ($CDCl_3$)[31] δ 3.83 (3H, s), 6.91 (2H, d, J = 8.8 Hz), 7.37−7.55 (3H, m), 7.70 (2H, d, J = 7.6 Hz), 7.78 (2H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$)[31] δ 55.4, 113.5, 127.9 (2C), 129.7 (2C), 130.0, 131.6, 132.6 (2C), 138.1, 163.1,

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195.3; MS (EI)[31] *m/z* (relative intensity) 212 (M^+, 54), 181 (11), 135 (100), 107 (9), 77(25). Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70; O, 15.08. Found: C, 79.02; H, 5.32; O, 14.98.

4-Pentanoylbenzonitrile: mp 32−33 °C (lit.[32] 34−36 °C); ^{1}H NMR ($CDCl_3$)[32] δ 0.90 (3H, t, J_a = 7.3 Hz), 1.36 (2H, tq, J_a = J_b = 7.3 Hz), 1.56 (2H, tt, J_b = J_c = 7.3 Hz), 2.95 (2H, t, J_c = 7.3 Hz), 7.72 (2H, d, J = 8.2 Hz), 8.00 (2H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.3, 26.1, 38.6, 116.1, 118.0, 128.4 (2C), 132.3 (2C), 140.0, 199.0; MS (EI)[32] *m/z* (relative intensity) 187 (M^+, 28), 145 (46), 130 (100), 102 (29), 75(7). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48; O, 8.54. Found: C, 76.13; H, 7.16; N, 7.24; O, 9.14.

4-Benzoylbenzonitrile: mp 113 °C (lit.[33] 110−114 °C); ^{1}H NMR ($CDCl_3$)[30] δ 7.46−7.88 (9H, m); ^{13}C NMR ($CDCl_3$)[30] δ 115.6, 118.0, 128.6 (2C), 130.2 (2C+2C), 132.2 (2C), 133.3, 136.3, 141.2, 195.0; MS (EI)[34] *m/z* (relative intensity) 207 (M^+, 93), 130 (23), 105 (100), 102(21), 77(49). Anal. Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.30; N, 6.76; O, 7.72. Found: C, 80.59; H, 4.47; N, 6.57; O, 7.93.

Ethyl 4-Acetylbenzoate: mp 54−55 °C (lit.[35] 55−56 °C); ^{1}H NMR ($CDCl_3$)[35] δ 1.33 (3H, t, J = 7.1 Hz), 2.56 (3H, s), 4.31 (2H, q, J = 7.1 Hz), 7.92 (2H, d, J = 8.4 Hz), 8.04 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$)[35] δ 14.1, 26.6, 61.1, 128.0 (2C), 129.4 (2C), 133.9, 139.8, 165.3, 197.1; MS (EI)[35] *m/z* (relative intensity) 192 (M^+, 19), 177 (100), 149 (85), 147 (39), 121 (11), 91(15), 76 (7). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; O, 24.97. Found: C, 68.65; H, 6.20; O, 24.21.

Ethyl 4-Pentanoylbenzoate: mp 45 °C (lit.[36] 47.5−48 °C); ^{1}H NMR ($CDCl_3$)[36] δ 0.95 (3H, t, J_a = 7.2 Hz), 1.39 (2H, tq, J_a = J_b = 7.2 Hz), 1.39 (3H, t, J = 7.1 Hz), 1.73 (2H, tt, J_b = J_c = 7.2 Hz), 2.99 (t, J_c = 7.2 Hz, 2H), 4.38 (2H, q, J = 7.1 Hz), 7.99 (2H, d, J = 8.4 Hz,), 8.11 (2H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$)[36] δ 13.6 (2C), 22.1, 25.8, 38.1, 60.9, 127.5 (2C), 129.2 (2C), 133.6, 139.8, 165.5, 199.7; MS (EI) *m/z* (relative intensity) 234 (M^+, 6), 205 (11), 192 (55), 177 (100), 149 (99), 147 (25), 121(8), 104 (8), 91 (6), 76(8). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; O, 20.49. Found: C, 71.56; H, 7.78; O, 19.96.

Ethyl 4-Benzoylbenzoate: ^{1}H NMR ($CDCl_3$)[30] δ 1.40 (3H, t, J = 7.1 Hz), 4.40 (2H, q, J = 7.1 Hz), 7.47 (1H, d, J_a = 7.5 Hz), 7.38−7.64 (2H, m), 7.72−7.79 (4H, 2d, J_a = J_b = 7.5 Hz), 8.10 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$)[30] δ 14.1, 61.3, 128.4 (2C), 129.5 (2C), 129.8 (2C), 130.2 (2C), 132.8, 133.3, 136.8, 141.1, 165.7, 195.8; MS (EI) *m/z* (relative intensity) 254 (M^+, 100), 226 (39), 209 (63), 181 (61), 177 (55), 149 (48), 105 (80), 77 (34). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; O, 18.88. Found: C, 75.65; H, 4.49; O, 18.89.

1-(4-Fluorophenyl)-ethanone: ^{1}H NMR ($CDCl_3$)[37] δ 2.47 (3H, s), 7.01 (2H, dd, J_{H-H} = J_{H-F} = 8.7 Hz), 7.87 (2H, dd, J_{H-H} = 8.7 Hz, J_{H-F} = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 26 0.4, 115.6 (2C), 131.1 (2C), 133.3, 165.8 (d, J_{C-F} = 253 Hz), 196.4; ^{19}F NMR ($CDCl_3$)[38] −105.6 (s); MS (EI)[38] *m/z* (relative intensity) 138 (M^+, 10), 123 (100), 95 (46), 75 (20). Anal. Calcd for C_8H_7FO: C, 69.56; H, 5.11; F, 13.75. Found: C, 69.28; H, 5.18; F, 12.40.

1-(4-Trifluoromethylphenyl)-ethanone: ^{1}H NMR ($CDCl_3$)[39] δ 2.56 (3H, s), 7.63 (2H, d, J = 8.0 Hz), 7.97 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 26.8, 123.7 (q, J_{C-F} = 271 Hz), 125.7 (2C), 128.7 (2C), 134.4 (q, J_{C-F} = 32 Hz), 139.8, 196.9; ^{19}F NMR ($CDCl_3$)[28] −63.1 (s); MS (EI) *m/z* (relative intensity) 188 ($M^{+\bullet}$, 3), 173 (100), 145 (46), 125 (4), 95 (5), 75 (3). Anal. Calcd for $C_9H_7F_3O$: C, 57.45; H, 3.75; F, 30.29. Found: C, 57.5; H, 3.87; F, 28.83.

1-(3-Methoxyphenyl)-ethanone: ^{1}H NMR ($CDCl_3$)[40] δ 2.50 (3H, s), 3.75 (3H, s), 7.02 (1H, dd, J_a = 7.9 Hz, ^4J = 2.5 Hz), 7.28 (1H, dd, J_a = J_b = 7.9 Hz), 7.41 (1H, d, ^4J = 2.5 Hz,), 7.45 (1H, d, J_b = 7.9 Hz); ^{13}C NMR ($CDCl_3$)[40] δ 26.5, 55.2, 112.3, 119.3, 120.9, 129.4, 138.7, 159.6, 197.6; MS (EI) *m/z* (relative intensity) 150 (M^+, 48), 135 (100), 107 (35), 92 (8). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71; O, 21.31. Found: C, 71.13; H, 6.62; O, 20.50.

3-Acetyl-benzonitrile: mp 97−98 °C (lit.[41] 98 °C); ^{1}H NMR ($CDCl_3$) δ 2.56 (3H, s), 7.54 (1H, dd, J_a = J_b = 7.7 Hz), 7.75 (d, J_a = 7.7 Hz), 8.09 (1H, d, J_b = 7.7 Hz), 8.12 (1H, s); ^{13}C NMR ($CDCl_3$)[42] δ 26.5, 112.9, 117.8, 129.6, 131.9, 132.2, 135.7, 137.5, 195.7; MS (EI) *m/z* (relative intensity) 145 (M^+, 5), 130 (100), 102 (27), 75 (9). Anal. Calcd for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65; O, 11.02. Found: C, 73.02; H, 4.95; N, 9.10; O, 11.33.

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