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Selective Synthetic Routes to Sterically Hindered Unsymmetrical Diaryl Ketones via Arylstannanes

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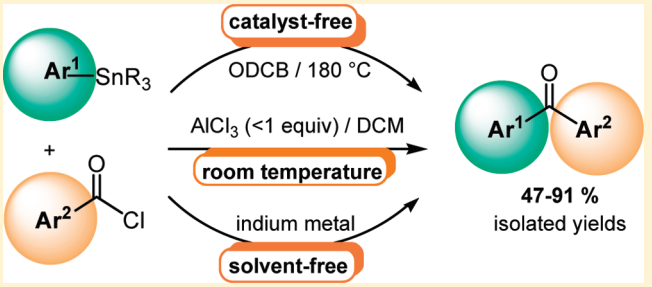
Supporting Information

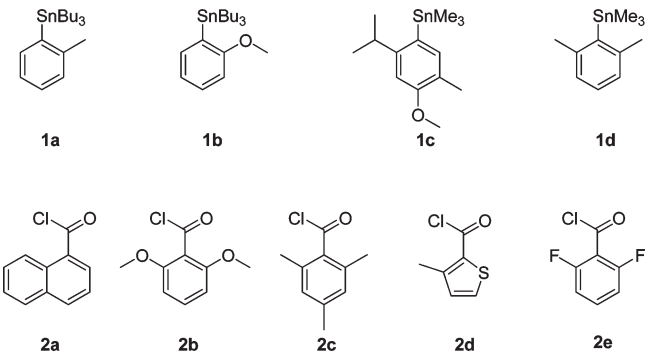
ABSTRACT: Bulky arylstannanes and bulky aroyl chlorides are good reaction partners for the synthesis of two-, three-, and even four-ortho-substituted benzophenones, in good to excellent isolated yields (47−91%). Three simple and direct routes, with differential advantages, are proposed: (i) a catalyst-free protocol, in *o*-dichlorobenzene (ODCB) at 180 °C; (ii) a room temperature protocol, using $AlCl_3$ (0.5 equiv), in dichloromethane (DCM); and (iii) a solvent-free, indium-promoted procedure. A radical mechanism is proposed for the indium-mediated reactions.



INTRODUCTION

Benzophenones are common structures found in organic materials as well as in natural products and pharmaceutical compounds. Most of the biologically active benzophenones are sterically crowded substrates possessing, at least, substituents on both ortho positions to the ketone moiety.[1] These compounds are not readily accessible by conventional routes. Thus, electrophilic aromatic substitution (EAS) such as Friedel−Crafts (F−C) acylation[2] and cross-coupling reactions of acyl chlorides with organometallic reagents[3] are efficient and preferred methods to form ketones in good yields, but they are generally limited to the synthesis of noncrowded ketones. These congested substrates could be synthesized through the addition of aryllithium or arylmagnesium to aldehydes followed by oxidation of the corresponding carbinols.[4] Most recently, there have been proposed two more gentle additional protocols: rhodium-catalyzed oxidative arylation of aldehydes[5] and carbonylative Suzuki−Miyaura couplings of aryl boronics with ortho-disubstituted aryl iodides.[6] In the last years we have been involved in the synthesis of arylstannanes as well as in their application as intermediates in organic synthesis;[7] recently, we have developed new procedures for the regiospecific[8] catalyst-free mono-, bi-, and triaroylation of aromatic rings based on the exceptional leaving group ability of the trialkylstannyl group in EAS.[9] Taking into account our experience and that the proposal of new routes for the synthesis of severely hindered benzophenones would be highly desirable, we considered it interesting to explore the application of the reaction of arylstannanes with aroyl chlorides to the synthesis of these especial ketones. Herein, we are gratified to report the synthetic potential of this pair of reagents, under three different protocols, as well as the special workup carried out in order to recover the trialkyltin chlorides generated (see the Experimental Section).

Chart 1



RESULTS AND DISCUSSION

Reactions in *o*-Dichlorobenzene (ODCB). We prepared a representative series of arylstannanes carrying either one or two substituents attached to the ortho positions of the aromatic ring (**1a**−**d**)[10] and we studied their reaction toward different commercially available ortho-substituted aroyl chlorides (**2a**−**e**) (Chart 1) under the optimized reaction conditions we have previously established, that is, in ODCB as solvent, at 180 °C.[9b] The results obtained are summarized in Table 1.

First, we carried out a series of reactions between 1-naphthoyl chloride (**2a**), carrying only one ortho substituent, and different stannanes (**1a**−**d**) with increasing steric requests; pleasantly, we noticed that all reactions occurred through the *ipso*-substitution

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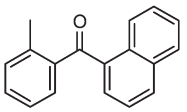
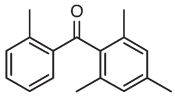
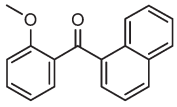
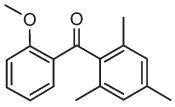
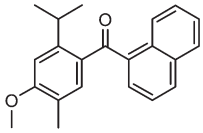
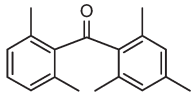
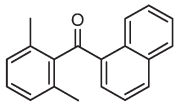
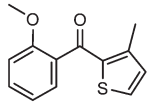
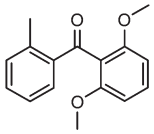
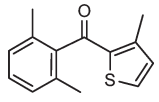
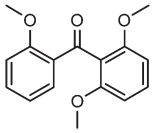
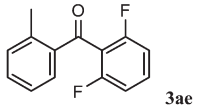
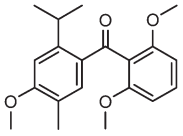
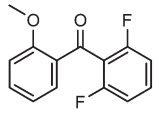
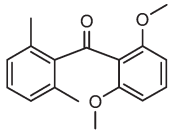
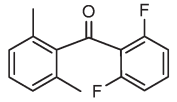
Table 1. Reactions of Arylstannanes with Aroyl Chlorides in ODCB

Entry[a]	Ar^1SnR_3	Ar^2COCl	Ketone	Time (h)	Yield[b] (%)	Entry	Ar^1SnR_3	Ar^2COCl	Ketone	Time (h)	Yield (%)
1	**1a**	**2a**	 **3aa**	3	80 (77)	9	**1a**	**2c**	 **3ac**	2	69 (62)
2	**1b**	**2a**	 **3ba**	5	66 (61)	10	**1b**	**2c**	 **3bc**	4	31[d]
3	**1c**	**2a**	 **3ca**	2	89 (85)	11	**1d**	**2c**	 **3dc**	2	66 (62)
4	**1d**	**2a**	 **3da**	2	83 (79)	12	**1b**	**2d**	 **3bd**	4	60 (57)
5	**1a**	**2b**	 **3ab**	3	60 (57)	13	**1d**	**2d**	 **3dd**	2	78 (75)
6	**1b**	**2b**	 **3bb**	2	17[c]	14	**1a**	**2e**	 **3ae**	9	71 (66)
7	**1c**	**2b**	 **3cb**	2	75 (71)	15	**1b**	**2e**	 **3be**	12	55 (50)
8	**1d**	**2b**	 **3db**	3	57 (53)	16	**1d**	**2e**	 **3de**	7	73 (69)

[a] All reactions were conducted in 1.0 M Ar^1SnR_3 with 1.2 equiv of Ar^2COCl at 180 °C (oil bath). [b] Determined by GC (using tetradecane as internal standard). Isolated yields from 1.0 mmol scale experiments (column chromatography) are given in parentheses. [c] Together with **4bb** (35%). [d] Together with **4bc** (25%).

of the stannyl group providing the expected ketones in good to excellent isolated yields (61% to 85%, entries 1 to 4) in rather short times (2 to 5 h).

To explore the synthetic potential of this approach to the access to sterically hindered benzophenones we carried out a series of reactions between the arylstannanes and different mono- or di-ortho-substituted aroyl chlorides (**2b**−**e**) (Table 1). With only two exceptions, the reactions were regiospecific affording the desired ketones in good yields (53% to 71%). Moreover, experiments 12 to 16 confirm that it is possible to synthesize heterocyclic benzophenones as well as benzophenones bearing electron-attracting groups such as fluorine in both ortho positions.

Much to our regret, the reaction of **1b** with **2b** gave a mixture of isomeric ketones, i.e., (2,6-dimethoxyphenyl)(2-methoxyphenyl)methanone (**3bb**) and (2,6-dimethoxyphenyl)(4-methoxyphenyl)methanone (**4bb**) (1:2 ratio), generated by acyldestannylation and direct acylation−protodestannylation of the ring, respectively (entry 6). Similarly, the reaction of **1b** and **2c** afforded a mixture of (2,4,6-trimethylphenyl)(2-methoxyphenyl)methanone (**3bc**) and (2,4,6-trimethylphenyl)(4-methoxyphenyl)methanone (**4bc**) in a 1.25:1 ratio (entry 10).[11] So, we set out to investigate the reaction of **1b** and **2b** with the aim of finding the most suitable conditions for reducing the competing non-*ipso*-substitution (Table 2).

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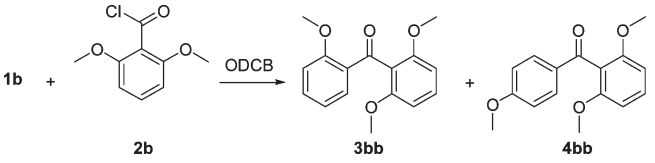
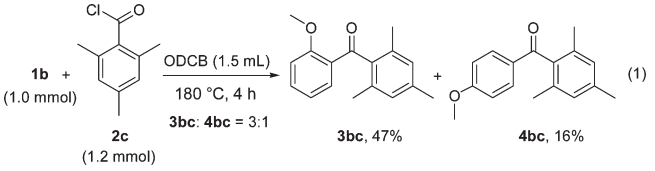
Table 2. Optimization of the Acyldestannylation Reaction of 1b with 2b in ODCB



				products (%)[a]		
entry	**1b** [M]	temp (°C)	time (h)	**3bb**	**4bb**	**3bb**:**4bb**
1	1.00	180	2	17	35	1:2
2	0.66	180	6	52	8	6.7:1
3	1.00	130	9	43	9	5:1
4	0.66	130	12	60	10	6:1

[a] Determined by GC (using tetradecane as internal standard).

We first studied the effect of dilution. The GC analysis of the isomer compositions showed that an increment of dilution produced an increase of ketone **3bb** over **4bb** (6.7:1 ratio) (Table 2, entry 2); unfortunately, we were not able to obtain an isomerically pure product.[12] On the other hand, considering the outstanding leaving group ability of the trialkylstannyl group, we supposed that under lower reaction temperatures, acyldestannylation would be more competitive over direct acylation, so, we carried out a series of reactions at lower temperatures. Once more, we obtained a mixture of ketones although with a sensible increment of the amount of **3bb** over **4bb** (5:1 ratio) (Table 2, entry 3).[13] Taking into account these results we carried out an experiment working both at 130 °C and at lower concentration, but a similar result was obtained (Table 2, entry 4). Thus, it was not possible to avoid the unwanted direct acylation of the ring, with dilution being the most appropriate condition to decrease it although longer reaction time (6 h) was required for completion. Under the optimized conditions the reaction of **1b** with **2c** gave also a mixture of **3bc** and **4bc** in a 3:1 ratio (eq 1).

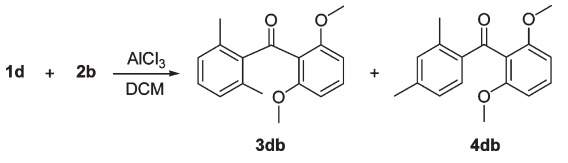


Taking into account the results obtained in the reactions performed between **1b** and different aroyl chlorides, it is probable that the mixtures of isomeric ketones obtained in experiments 6 and 10 (Table 1) are the result of an improvement of the competitiveness of the direct acylation reaction due to steric requirements (ketones **3bb** and **3bc** supported three bulky groups in the ortho-position). On the other hand, experiments 2, 12, and 15 (Table 1) proceed with total selectivity (ketones **3ba** and **3bd** supported only two ortho-groups and in ketone **3be** steric requirements of fluor are small).[14]

On the basis of the results obtained, we can say that the reaction of bulky arylstannanes with bulky aroyl chlorides in ODCB, at 180 °C, is, in general, adequate for the catalyst-free regioselective synthesis of bi-, tri-, and even tetra-ortho-substituted benzophenones in reasonable yields.

$AlCl_3$-Catalyzed Reactions. Neumann has reported that $AlCl_3$ is an effective catalyst in diverse substitution reactions performed with arylstannanes.[15] Looking for alternative reaction conditions for the synthesis of crowded benzophenones, we search the best conditions for the selective reaction of bulky arylstannanes with bulky aroyl chlorides using $AlCl_3$ as catalyst in dichloromethane (DCM) as solvent.

Table 3. Optimization of Conditions for the $AlCl_3$-Catalyzed Reaction of 1d with 2b



			products (%)[b]		
entry[a]	temp (°C)	time (h)	**3db**	**4db**	**3db**:**4db**
1	−10	4	17	−	
2	0	4	19	−	
3	10	4	30	−	
4	RT	4	49	−	
5	40	4	25	25	1:1
6	RT	6	58	−	
7	RT	14	60	20	3:1
8[c]	RT	14	78	−	

[a] All reactions were conducted in DCM at 0.10 M concentration of Ar^1SnR_3, using 1.2 equiv of Ar^2COCl in the presence of 1.2 equiv of $AlCl_3$ unless otherwise stated. [b] Determined by GC (using tetradecane as internal standard). [c] Performed in the presence of 0.5 equiv of $AlCl_3$

First, we optimized conditions for the reaction of **1d** with **2b**, which would give the most crowded ketone **3db**. The results are shown in Table 3.

It was clear that temperature rise (from −10 to 40 °C) produced an increase of the yields (Table 3, entries 1−5); nevertheless, at 40 °C the selectivity fails and both isomeric ketones, **3db** and **4db**, were detected in a 1:1 ratio (GC/MS). Therefore, we worked at room temperature. Experiments 6 and 7, carried out with the main goal of determining the optimal reaction time, showed that although yields increased with time, unexpectedly, after 14 h, a mixture of ketones **3db** and **4db** (3:1) was obtained. Could it be possible to assume that the presence of **4db** is related to the reversibility of the reaction? It is known that F−C acylations are virtually irreversible.[2] Nevertheless, when the resonance stabilization is reduced because the acyl group is tilted out of the plane of the aromatic nucleus by neighboring bulky substituents, as in our case, the pattern of irreversibility of F−C acylation may be confronted.[16] To prove our hypothesis, a mixture of **3db**, $AlCl_3$, and Me_3SnCl, 1:1:1,[17] was stirred at room temperature. After 14 h, the GC/MS of the crude product effectively showed a mixture of **3db** and **4db** (2.3:1), confirming the reversibility of the reaction. On the other hand, a mixture of **3db**, $AlCl_3$, and Me_3SnCl, 1:1:1, was stirred at 40 °C for 4 h; only traces of **4db** were detected in the crude product indicating that the results obtained in experiment 5 were due to the effective competition of the direct acylation of the ring under those conditions.

The results obtained show that the percentage of ketone **4db** increases with reaction time and temperature. This could be explained by considering that the generation of ketone **3db** is a

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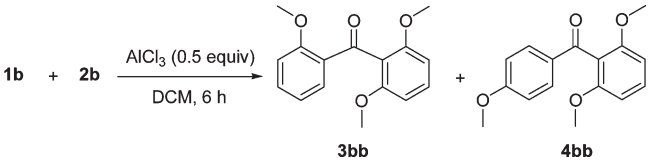
Table 4. Optimization of the $AlCl_3$-Catalyzed Acyldestannylation Reaction of 1b with 2b



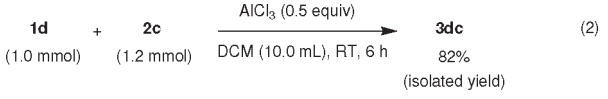
		products (%)[b]		
entry[a]	temp (°C)	3bb	4bb	3bb:4bb
1	0	43	29	1.5:1
2	RT	40	20	2:1
3	40	40	27	1.5:1
4[c]	RT	56 (47)	2.0	10:1

[a] All reactions were conducted in 0.10 M Ar^1SnR_3 with 1.2 equiv of Ar^2COCl in the presence of 0.5 equiv of $AlCl_3$ unless otherwise stated. [b] Determined by GC (using tetradecane as internal standard). Isolated yield from 1.0 mmol scale experiment (column chromatography) is given in parentheses. [c] Performed in 0.05 M Ar^1SnR_3

kinetically controlled process, while the formation of isomer **4db** is the result of low stannyldeacylation of **3db** and the major thermodynamic stability of isomer **4db**.

To minimize the inconvenience caused by the reversibility of the reaction we analyzed the effect of using minor amounts of $AlCl_3$ as catalyst and, pleasantly, we found that 0.5 equiv of $AlCl_3$ was enough for the synthesis of **3db** (14 h), at room temperature, in 78% yield (entry 8). Probably, the Me_3SnCl produced during the reaction may also work as a weak Lewis acid.[18]

The optimized conditions were applied to the reaction of **1d** with **2c**, which afforded isomerically pure ketone **3dc** in high isolated yield (eq 2).

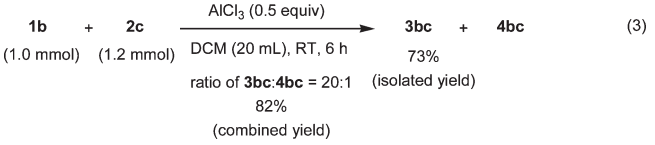


(2)

Our next goal was to find optimal reaction conditions to overcompensate the high para-directing force of the OMe group which had inhibited the selective synthesis of both **3bb** and **3bc** in ODCB (Table 1). With this purpose we carried out a series of reactions between **1b** and **2b** (Table 4). Experiments 1 to 3 are representative of the influence of temperature, showing that there are no relevant changes either in the yield or in the isomer mixtures obtained, working from 0 to 40 °C.

On the other hand, experiment 4 showed that dilution produced a pronounced increment in the selectivity of the reaction providing a mixture of **3bb** and **4bb** in a 10:1 ratio.[12]

The same conditions applied to the reaction of **1b** with **2c** providing 82% of a mixture of **3bc** and **4bc** in a 20:1 ratio (eq 3).



(3)

It is noteworthy that the high selectivity achieved allowed us to isolate isomerically pure ketones **3bb** and **3bc** in 47% and 73% yield, respectively.

On the basis of the results obtained we can say that $AlCl_3$ is an effective catalyst for the synthesis of these highly hindered benzophenones, through the reaction of bulky aroyl chlorides with bulky arylstannanes, at room temperature. Moreover, it is almost possible to compensate the steric hindrance and the para-directing effect of the OMe group. However, one disadvantage is that, although we used a deficiency of catalyst, it cannot be recovered after aqueous workup and a considerable amount of toxic waste is generated.

Indium-Mediated Reactions. In the last years, indium-mediated reactions have expanded in the literature due to the special properties of indium metal.[19] Thus, it is unaffected by air, moisture, or oxygen at ambient temperature and, most importantly, the element itself is without any apparent toxicity. On the basis of the fact that In(0) acts as a Lewis acid catalyst in aromatic F−C reactions,[19] we considered it interesting to examine the possibility of promoting acyldestannylation reactions by means of In(0) as catalyst instead of $AlCl_3$.

First, a mixture of arylstannane **1a**, aroyl chloride **2a**, and In(0) (1:1.2:1) in DCM as solvent was stirred at room temperature. After 8 h no starting material was detected by TLC and the GC/MS analysis of crude showed the presence of low amounts of ketone together with a large amount of toluene, that is, proto-destannylation product. Second, we performed the same reaction but employing α,α,α-trifluortoluene instead of DCM. Once more, only traces of ketone were detected and toluene was the main product. Finally, we decided to carry out the reaction in the absence of solvent. In the course of time the reaction mixture became quite viscous and after 13 h the stirring was not possible. Anyway, the GC/MS analysis of the mixture showed the presence of ketone together with starting material and only traces of toluene. To achieve an efficient stirring throughout the reaction time we carried out a reaction at 60 °C (oil bath). The starting material was consumed after 7 h as shown by TLC. Purification by column chromatography (from independent experiments) gave the desired ketone **3aa**, identified by NMR, in 78% yield (Table 5, entry 1). It is important to note that a control experiment showed that no reaction occurred in the absence of In(0), indicating that the metal acts as a promoter of the reaction. These results encouraged us and we carried out a series of representative experiments which are summarized in Table 5.

It should be mentioned that each reaction was performed at the lowest temperature, which allowed keeping the stirring of the reaction mixture during reaction time. An analysis of the results summarized in Table 5 shows that the indium-mediated selective synthesis of hindered benzophenones **3aa**, **3ca**, **3da**, **3ab**, **3cb**, **3db**, **3ac**, and **3dc** in good to excellent isolated yields (49 to 91%) is possible. Moreover, an increase in reaction temperature causes a sharp reduction of reaction time without affecting the yield (entry 9 vs 10). More significantly, use of substoichiometric amounts (0.2 equiv) of In(0) does not have a major detrimental effect on the yield (entry 7). Unfortunately, the results obtained with the more electrophilic acid chlorides **2d** and **2e** were unsuccessful. At room temperature, the reactions of **1d** with **2d** and **2e** were negative even after long reaction times (entries 11 and 14). The same reactions performed at higher temperature (60 °C) provided the expected ketone but the major products were those derived from the unwanted direct acylation, i.e., **4dd** and **4de**, respectively (entries 12 and 15). Moreover, stannane **1a** did not react with **2e** even after 52 h at 60 °C (entry 13). These unexpected reaction outcomes, in spite of the high

Table 5. Indium-Mediated Reactions of Arylstannanes with Aroyl Chlorides

$Ar^1SnR_3 + Ar^2COCl \xrightarrow[\text{Conditions}]{\text{In(0)}} Ar^1COAr^2$

entry[a]	Ar^1SnR_3	Ar^2COCl	temp (°C)	time (h)	Ar^1COAr^2	yield[b] (%)
1	**1a**	**2a**	60	7	**3aa**	82 (78)
2	**1c**	**2a**	60	2	**3ca**	95 (91)
3	**1d**	**2a**	60	2	**3da**	67 (64)
4	**1a**	**2b**	100	1	**3ab**	52 (49)
5	**1c**	**2b**	80	2	**3cb**	83 (80)
6	**1d**	**2b**	80	2	**3db**	55 (52)
7[c]	**1d**	**2b**	80	2	**3db**	49
8	**1a**	**2c**	RT	27	**3ac**	70 (67)
9	**1d**	**2c**	RT	25	**3dc**	58 (54)
10	**1d**	**2c**	60	3	**3dc**	66 (62)
11	**1d**	**2d**	RT	14	**3dd**	—[d]
12	**1d**	**2d**	60	3	**3dd**	32[e]
13	**1a**	**2e**	60	52	**3ae**	—[d]
14	**1d**	**2e**	RT	55	**3de**	—[d]
15	**1d**	**2e**	60	13	**3de**	15[f]

[a] All reactions were conducted in solvenless conditions with 1.0 equiv of Ar^1SnR_3, 1.2 equiv of Ar^2COCl, and 1.0 equiv of indium metal, unless otherwise stated. [b] Determined by GC (using tetradecane as internal standard). Isolated yields from 1.0 mmol scale experiment (column chromatography) are given in parentheses. [c] Performed with 0.2 equiv of indium metal. [d] Starting material was almost completely recovered. [e] Together with 32% of **4dd**. [f] Together with 30% of **4de**.

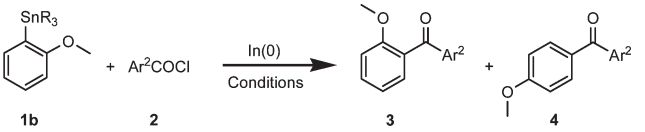
electrophilicity of **2d** and **2e**, led us to suppose that these reactions promoted by indium did not go through a conventional electrophilic attack. So, we it considered interesting to investigate whether this procedure could be suitable for the *ipso*-aroylation of reluctant compound **1b**. The results obtained are displayed in Table 6.

It can be seen that whatever the aroyl chloride employed, even using a deficiency or an excess of In(0) (experiments 3 and 4) or working at different temperatures (entries 5 to 7) it was not possible to overcome the strong para-directing effect of the OMe group. These reactions led to a mixture of the expected ketone together with that generated by direct acylation of the ring. It should be mentioned that in experiment 6, carried out at 0 °C, the presence of the direct acylation product supporting the tributyltin group, i.e., mesityl(3-(tributylstannyl)-4-methoxyphenyl)methanone was detected (GC/MS), indicating that this ketone acts as an intermediate in the generation of **4bc**. It should be mentioned that, once more, reactions performed with **2e** were negative even at 60 °C recovering starting materials.

It is known that, because of its low first ionization potential, In(0) is capable of promoting single-electron transfer (SET) processes.[19] To prove whether acyldestannylations proceeded through a polar or a free radical pathway, we performed the reaction of **1d** and **2b** in the presence of 0.5 equiv of di-*tert*-butylnitroxide (DTBN) as radical scavenger. Compared with a blank reaction, we noticed that the addition of DTBN had a dramatic retardation effect and only traces of ketone were detected recovering the starting substrate.

On the basis of these results, we believe that the reaction proceeds initially through a SET from In(0) to the aroyl chloride

Table 6. Indium-Mediated Reactions of 1b with Aroyl Chlorides

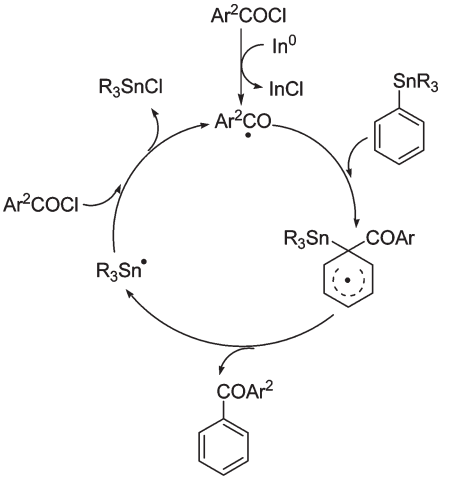


1b **2** **3** **4**

entry[a]	Ar^2COCl	temp (°C)	time (h)	products, yield (%)[b]	
1	**2a**	60	4	**3ba**, 26	**4ba**, 52
2	**2b**	80	4	**3bb**, 29	**4bb**, 41
3[c]	**2b**	80	5	**3bb**, 3	**4bb**, 29
4[d]	**2b**	80	3	**3bb**, 30	**4bb**, 42
5	**2c**	RT	4	**3bc**, 16	**4bc**, 33
6	**2c**	0	2	**3bc**, 14	**4bc**, 43
7	**2c**	80	2	**3bc**, 19	**4bc**, 26

[a] All reactions were conducted in solvenless conditions using 1.0 equiv of Ar^1SnR_3, 1.2 equiv of Ar^2COCl and 1.0 equiv of indium metal, unless otherwise stated. [b] Determined by GC (using tetradecane as internal standard). [c] Performed with 0.5 equiv of indium metal. [d] Performed with 2.0 equiv of indium metal

Scheme 1. Proposed Mechanistic Pathways for the Indium-Mediated Homolytic Aromatic *ipso*-Substitution of Aryltins



with generation of an acyl radical and In(I) chloride salt. The acyl radical thus formed reacts with the arylstannane through a homolytic *ipso* aromatic substitution affording the ketone. The selective *ipso*-substitution is a consequence of the enhanced hyperconjugation of the unpaired electron with the β-carbon—tin bond, namely, the β-effect.[20] The tin radical should be rapidly lost and reacts with the aroyl chloride, regenerating an acyl radical (Scheme 1). Thus, In(0) acts as an initiator of the radical process. This is supported by the fact that 0.2 equiv of In(0) is enough to promote the acyldestannylation reaction.

CONCLUSIONS

Our results enable us to affirm that bulky arylstannanes and bulky aroyl chlorides are good reaction partners for the synthesis of two-, three-, and even four-ortho-substituted benzophenones, in good to excellent yields. We proposed three different procedures which broaden the applicability of these transformations.

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Initially, we have demonstrated the effectiveness of the catalyst-free reaction of these reagents carried out in ODCB, at 180 °C. Thus, highly hindered benzophenones were regiospecifically synthesized in good yields (53 to 85%) in generally short times. Nevertheless, the high leaving group ability of tin was not enough to overcompensate the steric bulk and the para-directing effect of the OMe group in the synthesis of **3bb** and **3bc** from **1b**.

This drawback could be reversed working in DCM, using $AlCl_3$ as catalyst. Thus, we have been able to find optimal reaction conditions not only for the synthesis of highly hindered benzophenones but also for the highly selective synthesis of ketones **3bb** and **3bc**. It is important to mention that these reactions were carried with a substoichiometric amount of catalyst (0.5 equiv) and at room temperature.

Finally, we have established that In metal acts as a promoter in these reactions and that even substoichiometric amounts (0.2 equiv) of In(0) are enough to promote them. The ketones are synthesized in good to excellent yields (49−91%) at relatively low temperatures and in the absence of solvent. Unfortunately, these conditions were not suitable for the regiospecific aroylation of the *o*-methoxy-substituted aryltin **1b**; furthermore, highly electrophilic acid chlorides like **2d** and **2e** give a mixture of the desired ketones together with important amounts of the unwanted direct acylation products. As far as we know, these are the first reported examples of In(0)-catalyzed-reactions connected with substitution reactions on organostannanes. We believe that these reactions proceed through a SET process. A detailed investigation on the mechanism and on the scope and limitations of this method for the synthesis of carbonyl compounds via organostannanes is currently in progress in our laboratory.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were carried out under a dry nitrogen atmosphere. Acid chlorides were commercially available and fractionally distilled under nitrogen before use except for 2,6-dimethoxybenzoyl chloride, which was recrystallized from hexane. Aryltributylstannanes **1a** and **1b** were prepared by transmetalation of the appropiate Grignard reagents with tributyltin chloride in anhydrous THF. Aryltrimethylstannanes **1c** and **1d** were obtained from the corresponding commercial aryl chlorides by photostimulated reaction with Me_3SnNa in liquid ammonia, according to the literature procedures.[21] Physical and spectroscopic characteristics of compounds **1a**,[22] **1b**,[21] and **1d**[23] are consistent with those previously reported. For unknown compound **1c** evidence of identity and purity are shown below. 1,2-Dichlorobenzene and dichloromethane were distilled from calcium hydride under dry nitrogen atmosphere and stored over 4A molecular sieves. Reactions were monitored by thin-layer chromatography carried out on silica gel plates (60F-254) and visualized under UV light or using 5% phosphomolybdic acid in ethanol. Column chromatography was performed over silica gel 60 (70−230 mesh) doped with 10% of potassium fluoride.[24] The NMR spectra were recorded on a 300 MHz spectrometer (300.1 MHz for ^{1}H, 75.5 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane, with residual nondeuterated solvent resonance as internal reference ($CDCl_3$: δ 7.27 for ^{1}H and δ 77.0 for ^{13}C) and coupling constants (J) are in Hz. Identity and purity of the products (crude or purified) were established by using a GC/MS instrument (HP5-MS capillary column, 30 m × 0.25 mm ×0.25 μm) equipped with a 5972 mass selective detector operating at 70 eV (EI). Program: 50 °C for 2 min with an increase of 10 deg/min to 280 °C. For gas−liquid chromatography (GLC) an instrument equipped with a flame-ionization detector and a HP5 capillary column (30 m × 0.25 mm ×0.25 μm) was used.

(2-Isopropil-4-methoxy-5-methylphenyl)trimethylstannane (1c).. Colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (s, 1H), 6.78 (s, 1H), 3.86 (s, 3H), 3.32 (m, 1H), 2.45 (s, 3H), 1.27 (d, J = 6.8 Hz, 6H), 0.31 (s, $^2J_{HSn}$ = 26 Hz, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) 157.5, 143.1, 133.5, 133.2, 131.6, 111.8, 55.2, 26.8, 24.6, 22.7, −8.7 ($^1J_{CSn}$ = 165/173 Hz); MS (EI, 70 eV) m/z (% rel intensity, ion) 328 (4, M^+), 313 [60, (M^+ − Me), Sn pattern], 298 [100, (M^+ − 2Me), Sn pattern], 297 [17, (M^+ − OMe), Sn pattern], 283 [40, (M^+ − 3Me), Sn pattern]. Anal. Calcd for $C_{14}H_{24}OSn$: C, 51.41; H, 7.40. Found: C, 51.55; H, 7.38.

The experimental procedure employed in the reactions carried out in ODCB has been reported in our previous paper.[9b]

Representative Procedure for $AlCl_3$-Catalyzed Reactions: Synthesis of (2,6-Dimethylphenyl)(2,4,6-trimethylphenyl)-methanone (3dc; eq 2).[5] To a flame-dried two-necked round-bottomed flask loaded with $AlCl_3$ (0.056 g, 0.5 mmol) and dry DCM (5 mL) was added 1.2 mmol (0.220 g) of 2,4,6-trimethylbenzoyl chloride (**2c**) under an atmosphere of nitrogen. The mixture was stirred until the suspension had fully dissolved and then was added via syringe to a stirred solution of 1.0 mmol (0.270 g) of (2,6-dimethylphenyl)trimethylstannane (**1d**) in 5 mL of dry DCM contained in a septum-sealed round-bottomed flask. The system (immersed in a cooling bath of liquid nitrogen) was purged with nitrogen by means of three pump-fill cycles. After addition of 10 μL of tetradecane (internal standard) the reaction mixture was stirred at room temperature for 6 h and then hydrolyzed by adding it to ice (5 g). The aqueous phase was extracted with DCM (3 × 5 mL) and the organic layers were washed with brine (5 mL). The resulting aqueous solution was reserved for further treatment described below. The combined organic layers were dried over Na_2SO_4, filtered, analyzed by GC, and then concentrated in vacuo. The residue was chromatographed on silica gel (60 Å, 70−230 mesh) eluting with hexanes/DCM (90:10) to afford 0.207 g (82%) of **3dc** as a white solid: mp 77−79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.09 (t, J = 7.6 Hz,1H), 6.93 (d, J = 7.6 Hz, 2H), 6.76 (s, 2H), 2.20 (s, 3H), 2.07 (s, 6H), 2.04 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 202.5, 141.3, 140.2, 138.0, 136.9, 136.3, 129.9, 129.8, 128.9, 21.1, 20.7, 20.6. (**3dc** is also found in Table 1, entry 11.)

Representative Procedure for Indium-Mediated Reactions: Synthesis of (2-methylphenyl)-1-naphthylmethanone (3aa; Table 5, Entry 1).[25]. In a flame-dried Schlenk tube (fitted with a Teflon plug valve) 1.2 mmol (0.230 g) of 1-naphtoyl chloride (**2a**) was added to a stirred mixture of 1.0 mmol (0.382 g) of tributyl(2-methylphenyl)stannane (**1a**) and indium powder (0.148 gr, 1.0 mmol) under a nitrogen gas stream. After the purge procedure, the tube was capped and the heterogeneous reaction mixture was stirred at 60 °C (oil bath) for 7 h. After addition of a 10% (m/v) solution of NaOH (2 mL) and 10 μL of tetradecane, the mixture was stirred at room temperature for 15 min and then diluted with DCM (5 mL). The organic phase was successively washed with water and brine, dried over Na_2SO_4, filtered, analyzed by GC, and then concentrated in vacuo. Purification by column chromatography on silica gel (60 Å, 70−230 mesh) doped with 10% of KF (hexanes/DCM 90:10) gave 0.189 g (77%) of **3aa** as a white solid: mp 45−47 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.73 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 7.4 Hz, 1H), 7.74−7.65 (m, 3H), 7.57−7.50 (m, 3H), 7.43 (d, J = 7.3 Hz, 1H), 7.32 (t, J = 7.3 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 200,1, 139.5, 138.1, 136.4, 133.8, 132.4, 131.3, 130.9, 130.3, 130.1, 128.4, 127.7, 126.4, 125.7, 125.3, 124.2, 20.5. (**3aa** is also found in Table 1, entry 1.)

(2,6-Dimethoxyphenyl)(2-methylphenyl)methanone (3ab; Table 1, Entry 5 and Table 5, Entry 4). White solid: mp 115−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37 (d, J = 7.7 Hz, 1H), 7.25 (m, 2H), 7.19 (t, J = 5.8 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.52 (d, J = 8.3 Hz, 2H), 3.62 (s, 6H), 2.59 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 197.3, 157.5, 139.7, 137.6, 131.7, 131.6, 130.6, 125.4, 120.3, 104.2,

55.9, 21.5; MS (EI, 70 eV) m/z (% rel intensity, ion) 256 (1, M^+), 241 [2, (M^+ − Me)], 225 [100, (M^+ − OMe)]. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.26; H, 6.31.

(2-Methylphenyl)(2,4,6-trimethyl)methanone (3ac; Table 1, Entry 9 and Table 5, Entry 8).[5]. Pale yellow solid: mp 99−101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.31−7.21 (m, 2H), 7.19 (d, J = 7.4 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 6.77 (s, 2H), 2.59 (s, 3H), 2.22 (s, 3H), 1.99 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 202.5, 139.9, 138.5, 138.4, 137.1, 134.3, 132.2, 132.1, 131.8, 128.5, 125.8, 21.6, 21.1, 19.3.

(2,6-Difluorophenyl)(2-methylphenyl)methanone (3ae; Table 1, Entry 14). Pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.53−7.38 (m, 3H), 7.35−7.19 (m, 2H), 6.98 (t, J = 7.8 Hz, 2H), 2.66 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 190.7, 159.8 (dd, J = 252, 7.1 Hz), 140.1, 136.5, 132.7, 132.2, 132.1, 131.8 (t, J = 9.6 Hz), 125.8, 120.6 (t, J = 18.3 Hz), 111.8 (m), 21.6; MS (EI, 70 eV) m/z (% rel intensity, ion) 232 (30, M^+), 212 [100, (M^+ − HF)], 183 (67), 141 [66, (M^+ − Tol)], 113 (65). Anal. Calcd for $C_{14}H_{10}F_2O$: C, 72.41; H, 4.34. Found: C, 72.62; H, 4.35.

(2-Methoxyphenyl)-1-naphthylmethanone (3ba; Table 1, Entry 2). White solid: mp 70−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 7.0 Hz, 1H), 7.52−7.29 (m, 6H), 6.93 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 3.48 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.8, 158.3, 136.9, 133.8, 132.8, 132.2, 130.8, 130.1, 129.6, 128.3, 127.5, 126.2, 125.9, 124.3, 120.5, 112.0, 55.7; MS (EI, 70 eV) m/z (% rel intensity, ion) 262 (45, M^+), 247 [13, (M^+ − Me)], 231 [16, (M^+ − OMe)], 135 [80, (M^+ − Naph)], 127 (100). Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.33; H, 5.40.

(2,6-Dimethoxyphenyl)(2-methoxyphenyl)methanone (3bb; Table 4, Entry 4).[26]. White solid: mp 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.71−7.67 (dd, J = 8.0, 2.0 Hz, 1H), 7.43 (m, 1H), 7.26 (t, J = 8.4 Hz, 1H), 6.97−6.91 (m, 2H), 6.56 (d, J = 8.4 Hz, 2H), 3.72 (s, 3H), 3.67 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 193.7, 159.6, 157.3, 133.8, 132.1, 130.0, 128.1, 121.4, 120.1, 112.3, 104.1, 55.9.

(2-Methoxyphenyl)(2,4,6-trimethylphenyl)methanone (3bc; eq 3).[27]. Pale yellow solid: mp 110−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.53 (d, J = 7.5 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 6.98−6.91 (m, 2H), 6.83 (s, 2H), 3.76 (s, 3H), 2.29 (s, 3H), 2.10 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 199.7, 159.5, 139.4, 138.0, 134.2, 133.9, 132.2, 128.2, 128.1, 120.4, 112.3, 55.9, 21.1, 19.4.

(2-Methoxyphenyl)(3-methylthiophen-2-yl)methanone (3bd; Table 1, Entry 12). White solid: mp 72−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35 (t, J = 7.8 Hz, 2H), 7.26 (d, J = 7.4 Hz,1H), 6.95−6.80 (m, 3H), 3.70 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 188.9, 156.7, 145.5, 137.6, 132.3, 131.6, 131.5, 130.8, 128.5, 120.4, 111.5, 55.7, 16.3; MS (EI, 70 eV) m/z (% rel intensity, ion) 232 (39, M^+), 231 [90, (M^+ − H)], 217 [100, (M^+ − Me)], 201 [33, (M^+ − OMe)]. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21. Found: C, 67.01; H, 5.25.

(2,6-Difluorophenyl)(2-methoxyphenyl)methanone (3be; Table 1, Entry 15). White solid: mp 52−54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.78 (dd, J = 7.1, 2.0 Hz, 1H), 7.52 (m, 1H), 7.34 (m, 1H), 7.04 (t, J = 7.3 Hz, 1H), 6.94−6.87 (m, 3H), 3.64 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 187.7, 159.9 (dd, J = 252, 7.5 Hz), 159.6, 134.9, 131.3, 131.1 (t, J = 10.2 Hz), 127.7, 120.7, 120.3 (t, J = 20.0 Hz), 112.0, 111.4 (m), 55.7; MS (EI, 70 eV) m/z (% rel intensity, ion) 248 (30, M^+), 141 [63, (M^+ − Ans)], 135 [100, (M^+ − $C_6H_3F_2$)]. Anal. Calcd for $C_{14}H_{10}F_2O_2$: C, 67.74; H, 4.06. Found: C, 67.95; H, 4.10.

(2-Isopropyl-4-methoxy-5-methylphenyl)-1-naphthylmethanone (3ca; Table 1, Entry 3 and Table 5, Entry 2). Pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.21 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.45−7.35 (m, 3H), 7.29 (t, J = 7.6 Hz, 1H), 7.16 (s, 1H), 6.60 (s, 1H), 3.72 (s, 3H), 3.07 (m, 1H), 2.38 (s, 3H), 0.92 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 199.1, 159.2, 139.1, 138.0, 133.8, 131.4, 131.1, 131.0, 130.4, 130.3, 128.6, 128.3, 127.2, 126.2, 125.9, 124.3, 113.2, 55.3, 26.4, 22.3, 21.3; MS (EI, 70 eV) m/z (% rel intensity, ion) 318 (66, M^+), 317 [50, (M^+ − H)], 303 [17, (M^+ − Me)], 275 [55, (M^+ − i-Pr)], 191 [25, (M^+ − Naph)], 127 (100). Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 83.22; H, 6.97.

(2-Isopropyl-4-methoxy-5-methylphenyl)(2,6-dimethoxyphenyl)methanone (3cb; Table 1, Entry 7 and Table 5, Entry 5). White solid: mp 125−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.61 (s, 1H), 7.55 (t, J = 8.3 Hz, 1H), 6.94 (s, 1H), 6.85 (d, J = 8.3 Hz, 2H), 4.11 (s, 3H), 3.95 (s, 6H), 3.43 (m, 1H), 2.93 (s, 3H), 1.31 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 195.7, 159.4, 157.2, 140.3, 133.5, 131.2, 130.1, 129.5, 120.7, 113.6, 104.2, 55.9, 55.3, 26.4, 22.3, 22.2; MS (EI, 70 eV) m/z (% rel intensity, ion) 328 (2, M^+), 313 [2, (M^+ − Me)], 297 [100, (M^+ − OMe)], 191 (9), 165 (44). Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.33; H, 7.39.

(2,6-Dimethylphenyl)-1-naphtylmethanone (3da; Table 1, Entry 4 and Table 5, Entry 3). Pale yellow solid: mp 145−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.35 (d, J = 7.7 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 7.7 Hz, 1H), 7.73−7.65 (m, 2H), 7.47 (t, J = 7.7 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.17 (d, J = 7.4 Hz, 2H), 2.26 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 202.4, 141.4, 134.6, 134.3, 134.2, 133.9, 132.5, 130.8, 128.8, 128.6, 127.7, 126.6, 126.2, 124.6, 19.5; MS (EI, 70 eV) m/z (% rel intensity, ion) 260 (75, M^+), 259 [49, (M^+ − H)], 245 [13, (M^+ − Me)], 127 (100). Anal. Calcd for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.42; H, 6.17.

(2,6-Dimethoxyphenyl)(2,6-dimethylphenyl)methanone (3db; Table 1, Entry 8; Table 3, Entry 8 and Table 5, Entry 6).[6]. White solid: mp 140−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.23 (t, J = 8.4 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 7.5 Hz, 2H), 6.47 (d, J = 8.4 Hz, 2H), 3.59 (s, 6H), 2.13 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 199.1, 158.8, 142.4, 135.4, 132.1, 128.5, 127.7, 120.9, 104.7, 56.0, 19.6.

(2,6-Dimethylphenyl)(3-methylthiophen-2-yl)methanone (3dd; Table 1, Entry 13). White solid: mp 94−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39 (d, J = 4.8 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.5 Hz, 2H), 6.86 (d, J = 4.9 Hz, 1H), 2.23 (br, 3H), 2.12 (s, 6H); ^{13}C NMR: (75.5 MHz, $CDCl_3$) δ (ppm) 192.7, 145.5, 141.2, 138.0, 133.8, 132.8, 132.5, 128.9, 127.6, 19.1, 16.0; MS (EI, 70 eV) m/z (% rel intensity, ion) 230 (16, M^+), 215 [100, (M^+ − Me)], 200 [31, (M^+ − 2Me)]. Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13. Found: C, 72.86; H, 6.10.

(2,6-Difluorophenyl)(2,6-dimethylphenyl)methanone (3de; Table 1, Entry 16). White solid: mp 109−11 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.35 (m, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.5 Hz, 2H), 6.91 (m, 2H), 2.22 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm) 194.1, 160.8 (dd, J = 257, 6.3 Hz), 141.1, 134.6, 133.3 (t, J = 10.8 Hz), 129.6, 128.1, 119.0 (t, J = 16.0 Hz), 112.3 (m), 19.5; MS (EI, 70 eV) m/z (% rel intensity, ion) 246 (11, M^+), 226 [100, (M^+ − HF)], 211 (37), 141 (54), 133 (28). Anal. Calcd for $C_{15}H_{12}F_2O$: C, 73.16; H, 4.91. Found: C, 73.33; H, 4.92.

Recovering Method for Trialkyltin Chlorides

Trimethyltin Chloride. The aqueous solution (~10 mL for 1.0 mmol scale reaction) was saturated with KF, 10 mL of Et_2O was added, and the mixture was vigorously shaken, then the precipitated trimethyltin fluoride (0.297 g, 81%) was removed by filtration at reduced pressure and stored for future reconversion to the chloride by treatment with an excess of NaCl in THF, according to the method reported by Mitchell.[28]

Tributyltin Chloride. After chromatographic procedure (10.0 g of silica gel for a 1.00-mmol scale reaction) the column was eluted with 100 mL of THF. The silica was dried with compressed air and poured

into a 100-mL round-bottomed flask fitted with a condenser and a nitrogen T-joint. NaCl (293 mg, 5.00 mmol) and 50 mL of dry THF were added and the mixture was heated at reflux with stirring for 4 days. It was then allowed to cool and poured into a chromatography column plugged with a small piece of cotton wool. All of the THF was drained with air pressure and then the column was eluted with ether (2 × 50 mL). The combined ethers were concentrated in vacuo giving tributyltin chloride in ca. 80% with respect to the starting aryltributylstannane.

■ ASSOCIATED CONTENT

Supporting Information. General experimental methods, physical and spectroscopic data of compound **1c**, ^{1}H and ^{13}C NMR spectra of compounds **1c**, **3ab**, **3ae**, **3ba**, **3bd**, **3be**, **3ca**, **3cb**, **3da**, **3dd**, and **3de**, and ^{1}H NMR spectra of compounds **3aa**, **3ac**, **3bb**, **3bc**, **3db**, and **3dc**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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(10) The starting arylstannanes were prepared by known procedures (see the Supporting Information).

(11) Anisole reacted with **2b** and **2c** under similar reaction conditions. After 2 h at 180 °C, ketones **4bb** or **4bc** were obtained as the only products.

(12) We inform the best result obtained after working at different concentrations.

(13) We inform the best result obtained after working at different temperatures.

(14) It should be mentioned that anisole reacted with **2a**, **2d**, and **2e**, under similar reaction conditions, giving the corresponding *p*-isomers as main products.

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