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Carbonylative Hiyama Coupling of Aryl Halides with Arylsilanes under Balloon Pressure of CO

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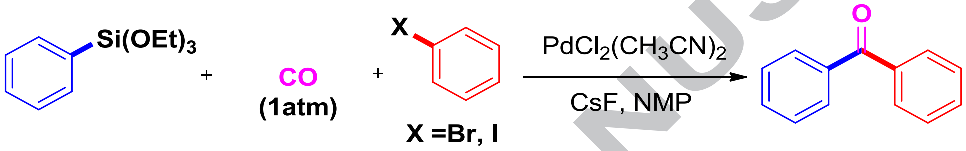

Abstract

An efficient protocol has been developed for the carbonylative Hiyama coupling of aryl halides using the cesium fluoride as a promoter by palladium-catalyzed in NMP. This protocol was applied to a wide variety of functionalized and hindered aryl iodides and bromides with arylsilanes, to afford the desired biaryl ketones in good to excellent yields.

Keywords

carbonylation, Hiyama coupling, Pd-catalyzed, arylsilanes

Introduction

Palladium-catalyzed coupling reactions represent an important toolbox for the functionalization of arene derivatives.[1] Among the various types of coupling processes, the catalytic cross-coupling reaction between aryl electrophiles and organometallic nucleophiles accompanied by insertion of carbon monoxide allow for the straightforward preparation of symmetrical or unsymmetrical diaryl ketones, which represents a powerful tool in organic synthesis.[2] Such structures are key components in a variety of important pharmaceuticals including Tricor,[3] Evistor [4] and

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Sector[5] in addition to being numerous photosensitizers and advanced organic materials.[6] The Pd-catalyzed carbonylative Suzuki−Miyaura reaction represents a viable three-component coupling protocol for rapid access to biaryl ketones and became the most popular protocol among Pd-catalyzed carbonylation method with CO.[7] This is attributed in a large degree to unique properties of organoboron reagents, such as ready availabilities, high stabilities and low toxicities.[8] Otherwise, the carbonylative Negishi, Stille and Hiyama reactions are classical examples of transition metal-catalyzed carbonylation with CO to deliver biaryl ketones.[9] Among them, the Hiyama cross-coupling reaction have attracted much attention and have made great progress in the construction of new C–C bonds.[10] In comparison with Stille coupling using toxic tin reagents and Suzuki coupling with problems in purifying the boron reagents, organosilanes in Hiyama coupling are low toxicity, low cost, ready availability, high chemical stability, and the leaving silicon group can be converted to harmless SiO_2 by incineration, making this method attractive from environmental-friendly points of view.[11] Recently, the cross-coupling of arylsiloxanes with various coupling partners have drawn much attentions, such as tosylates/mesylates,[12] aryldiazonium salts,[13] arylsulfinates,[14] arylsulfonyl chlorides,[15] arylsulfonyl hydrazides,[16] and arylhydrazines.[17] The first carbonylative Hiyama coupling have been reported by Hiyama over twenty years ago,[18] diaryl ketones were produced in good yields via the palladium-catalyzed carbonylative coupling of arylfluorosilanes with aryl iodides in the presence of KF. However, the related Hiyama-type carbonylations has been scarcely studied since then.

Although there is now considerable literature precedence for carbonylative transformation, the majority of the work has been carried out with iodides. Only a handful of reports focus on the use of aryl bromides as viable substrates,[19] and in all cases these transformations were carried out with organoboron reagents as the nucleophilic coupling partner. No doubt that aryl bromides were low cost and ready available reagents, in the meantime the more challenging coupling partner. Herein, we report that the Pd-catalyzed carbonylative Hiyama coupling of aryl bromides using the cesium fluoride as a promoter. This protocol was also applied to a wide variety of

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functionalized and hindered aryl iodides.

Results and Discussion

Our study commenced with the decarboxylative Hiyama coupling of bromobenzene with triethoxy(phenyl)silane using KF as the promoter and $Pd(OAc)_2$ as the catalyst under balloon pressure of CO. The reaction could only afford the desired product in very low yield at 80 ^{o}C in NMP. It was found, however, that the desired product could be obtained in 50% yield when iodobenzene and triethoxy(phenyl)silane were mixed and heated at 80 ^{o}C for 12 h (Table 1, entry 1). To explore a more efficient catalytic system for this decarboxylative Hiyama coupling, a model reaction was investigated in detail by varying different parameters such as catalyst, promoter, and solvent to develop appropriate reaction conditions for this transformation (Table 1).

At the outset, different transition metal catalysts, viz. $Cu(OAc)_2$, $Co(OAc)_2$, $RhCl_3$, $RuCl_3$, and $Ni(OAc)_2$, were screened using CsF as a promoter in NMP to determine their catalytic efficacy (Table 1, entries 2-6). We were astonished to see that only the palladium salt could bring about the desired conversion, and therefore the studies were directed to look at the prospective of other palladium salts too. All the palladium salts tried, viz. $Pd(PPh_3)_4$, $Pd_2(dba)_3$, Pd $(dba)_2$, $PdCl_2$, $PdCl_2(PPh_3)_3$, $PdCl_2$(dppf) and $PdCl_2(MeCN)_2$, invariably worked well (Table 1, entries 7-13), but the performance of $PdCl_2(MeCN)_2$ was maximum, providing the carbonylative Hiyama coupling product in 79% yield at 80 ^{o}C (Table 1, entry 13). The experiment under identical conditions without the aid of a catalyst ended with no conversion (Table 1, entry 14). The additive $TBAF{\cdot}3H_2O$ was also found to promote the reaction, allowing a good yield (Table 1, entry 15). As the nature of the promoter is assumed to have a marked impact on the removal of silicon group, different fluorine sources such as NH_4F, NaF and AgF were also examined (Table 1, entries 16-18). Subsequent investigation on the role of promoters for the aforementioned reaction revealed CsF as the most favored one to push the reaction forward (Table 1, entry 19). In the absence of a promoter

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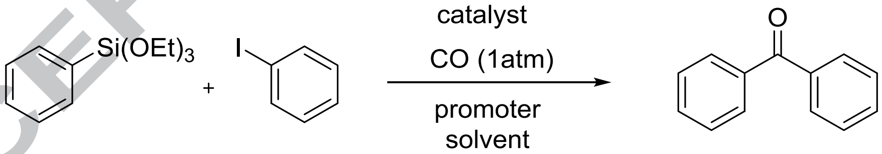
under the same set of conditions, no conversion was observed (Table 1, entry 20). In addition, the solvent effects were tested for this reaction in the presence of CO. Whereas toluene did not afford any product (Table 1, entry 21), the other solvents, viz. 1,4-dioxane, CH_3CN, DMSO and DMF, gave rise to 74%, 78%, 88% and 82% product yields respectively (Table 1, entries 22-25). Finally as concluded above, the optimal reaction conditions for the reaction turned out to be triethoxy(phenyl)silane (0.5 mmol) and iodobenzene (0.5 mmol), at 80 ^{o}C with $PdCl_2(MeCN)_2/CsF$ in NMP (Table 1, entry 19). Then, we optimized the reaction conditions on the basis of triethoxy(phenyl)silane and bromobenzene. The reaction gave a moderate yield in the presence of $PdCl_2(MeCN)_2$ and CsF (Table 1, entry 26). To our delight, the yield was dramatically increased when the reaction temperature was increased to 100 ^{o}C (Table 1, entry 27). In addition, no better results were obtained when the reaction was carried out under higher temperature (Table 1, entry 28). After extensive optimization, it was found that the reaction could perform at 100 ^{o}C with the additive CsF in the presence of an $PdCl_2(MeCN)_2$ catalyst in NMP.

Table 1 Influence of the reaction conditions in carbonylative Hiyama cross-coupling of iodobenzene with triethoxy(phenyl)silane



Entry	Promoter	Catalyst	Solvent	Yield(%) [b]
1	KF	$Pd(OAc)_2$	NMP	50
2	KF	$Cu(OAc)_2$	NMP	-
3	KF	$Co(OAc)_2$	NMP	-
4	KF	$RhCl_3$	NMP	-
5	KF	$RuCl_3$	NMP	-
6	KF	$Ni(OAc)_2$	NMP	-
7	KF	$Pd(PPh_3)_4$	NMP	57
8	KF	$Pd_2(dba)_3$	NMP	54

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9	KF	Pd $(dba)_2$	NMP	59
10	KF	$PdCl_2$	NMP	53
11	KF	$PdCl_2$ $(PPh_3)_3$	NMP	67
12	KF	$PdCl_2(dppf)$	NMP	72
13	KF	$PdCl_2(MeCN)_2$	NMP	79
14	KF	-	NMP	-
15	$TBAF\cdot 3H_2O$	$PdCl_2(MeCN)_2$	NMP	84
16	NH_4F	$PdCl_2(MeCN)_2$	NMP	59
17	AgF	$PdCl_2(MeCN)_2$	NMP	68
18	NaF	$PdCl_2(MeCN)_2$	NMP	82
19	CsF	$PdCl_2(MeCN)_2$	NMP	95
20	-	$PdCl_2(MeCN)_2$	NMP	-
21	CsF	$PdCl_2(MeCN)_2$	toluene	-
22	CsF	$PdCl_2(MeCN)_2$	1,4-dioxane	74
23	CsF	$PdCl_2(MeCN)_2$	CH_3CN	78
24	CsF	$PdCl_2(MeCN)_2$	DMSO	88
25	CsF	$PdCl_2(MeCN)_2$	DMF	82
26[c]	CsF	$PdCl_2(MeCN)_2$	NMP	69
27[d]	CsF	$PdCl_2(MeCN)_2$	NMP	91
28[e]	CsF	$PdCl_2(MeCN)_2$	NMP	90

[a] Reaction conditions: triethoxy(phenyl)silane (0.5 mmol), iodobenzene (0.5 mmol) (0.5 mmol), promoter (0.5 mmol), catalyst (5 mol%), solvent (5.0 ml) at 80 ^{o}C for 6 hours under CO (1 atm) unless otherwise indicated. [b] Isolated yield. [c] Iodobenzene was replaced by bromobenzene (0.5 mmol) at 80 ^{o}C. [d] Iodobenzene was replaced by bromobenzene (0.5 mmol) at 100 ^{o}C. [e] Iodobenzene was replaced by bromobenzene (0.5 mmol) at 120 ^{o}C.

With the optimal conditions in hand, the scope of the transformation was investigated, and the results were summarized in Table 2. As shown in Table 2, both electron-donating and -withdrawing groups attached to triethoxy(phenyl)silane were

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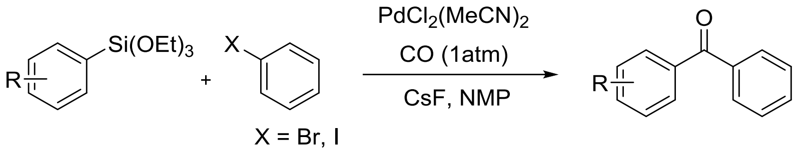
all suitable for this protocol. Aryl silanes with different substituents, such as Me, F, NO_2, and CF_3, could all provide the corresponding products with 88-95% yields (Table 2, column A, entries 1-5). In addition, 3,4-methyl and 2-methyl substituted aryl silanes also reacted with iodobenzene to obtain the desired products in 87% and 84% yields (Table 2, column A, entries 6-7). This indicated that the electronic and steric nature of the aryl silanes had little influence on the reaction efficiency. Notably, chloro-substituent could also tolerant with this method to afford the corresponding products in good to excellent yields (Table 2, column A, entries 8-10). Encouraged by the results obtained with iodobenzene, we focused our attention on the reaction of bromobenzene and aryl silanes with the same functionalized groups for comparison. Delightfully, the results in Table 2 (column B) demonstrated a good functional-group tolerance for different functionalized aryl silanes. The results demonstrated that the electronic nature of the aryl silanes had little influence on the reaction efficiency, as all the desired products were obtained in good yields (Table 2, column B, entries 1-5). The substrate scope of various steric hindrance aryl silanes with bromobenzene was explored (Table 2, column B, entries 6-7), only with slightly decrease of efficiency.

Aryl silanes bearing a chloro- group afforded the corresponding 4-chlorobenzophenone, 3-chlorobenzophenone and 2-chlorobenzophenone in 90%, 85% and 81% yields, respectively (Table 2, column B, entries 8-10).

Table 2 Pd-catalyzed carbonylative Hiyama coupling of aryl silanes with iodobenzene or bromobenzene [a]



Entry	R	Yield (%) [b]	Yield (%) [c]
1	4-CH_3	93	89
2	H	95	91
3	4-F	89	92

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4	4-NO_2	92	88
5	4-CF_3	88	84
6	3,4-CH_3	87	83
7	2-CH_3	84	78
8	4-Cl	93	90
9	3-Cl	87	85
10	2-Cl	88	81

[a] Reaction conditions: aryl silanes (0.5 mmol), CsF (0.5 mmol), $PdCl_2(MeCN)_2$ (5 mol%), NMP (5.0 ml) for 6 hours under CO (1 atm) unless otherwise indicated. [b] Iodobenzene (0.5 mmol) at 80 ^{o}C with isolated yield. [c] Bromobenzene (0.5 mmol) at 100 ^{o}C with isolated yield.

We next explored the substrate scope of the palladium-catalyzed carbonylative Hiyama coupling reactions. The substrate scope of various aryl iodines with triethoxy(phenyl)silane was explored (Table 3). Delightfully, the results in Table 3 demonstrated a good functional-group tolerance for different aryl iodines, such as methyl, trifluoromethyl, nitro, fluoro, and chloro were suitable for this transformation (Table 3, entries 1-5). Bromo-contained substrate, such as 1-bromo-4-iodobenzene and 1-bromo-2-iodobenzene, which is sensitive in many coupling reactions, survived well under this carbonylative Hiyama conditions, giving the corresponding bromobenzophenones in good to excellent yields (Table 3, entries 6-7). We did not observe the by-products of the coupling with bromated arenes in these reactions. 3-chloro-substituted were converted to the corresponding products in good yield (Table 3, entry 8). Ortho-position substituted aryl iodines such as 2-methyl-iodobenzene and 2-chloro-iodobenzene proceeded smoothly to generate corresponding ketones in good yields (Table 3, entries 9-10). When a highly steric

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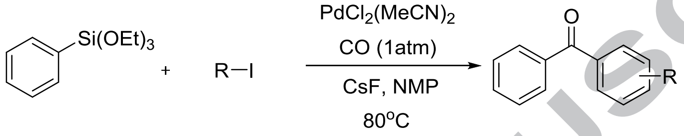
hindrance halides such as pentamethyl-iodobenzene and pentafluoro-iodobenzene was used as substrates, 73% and 75% yield of products were obtained (Table 3, entries 11-12). It is noteworthy that 2-iodopyridine was also proved to be reactive (Table 3, entry 13).

Table 3 Pd-catalyzed carbonylative Hiyama coupling of triethoxy(phenyl)silane with various aryl iodines [a]



Entry	R	Yield (%) [b]
1	4-CH_3-C_6H_5	92
2	4-CF_3-C_6H_5	85
3	4-NO_2-C_6H_5	89
4	4-F-C_6H_5	93
5	4-Cl-C_6H_5	91
6	4-Br-C_6H_5	94
7	2-Br-C_6H_5	87
8	3-Cl-C_6H_5	86
9	2-CH_3-C_6H_5	80
10	2-Cl-C_6H_5	83
11	2,3,4,5,6-CH_3-C_6H_5	73
12	2,3,4,5,6-F-C_6H_5	75
13	2-pyridinyl	72

[a] Reaction conditions: triethoxy(phenyl)silane (0.5 mmol), aryl iodine (0.5 mmol), CsF (0.5 mmol), $PdCl_2(MeCN)_2$ (5 mol%), NMP (5.0 ml) at 80 °C for 6 hours under CO (1 atm) unless otherwise indicated. [b] Isolated yield.

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To further expand the scope of the substrates, aryl bromides were also investigated. To our delight, aryl bromides could easily be reacted with triethoxy(phenyl)silane, to afford the corresponding products (Table 4). The results indicated that aryl bromides, bearing either an electron-donating or -withdrawing group on the aromatic ring, performed smoothly with triethoxy(phenyl)silane at 100^{o}C, and all the desired products were obtained in good yields (82-90%)(Table 4, entries 1-6). To our delight, cyano was also compatible for the transformation and the corresponding product was afforded in moderate to good yields (77-90%, Table 4, entries 6-7). Meanwhile, aryl bromide bearing a sterically hindered group, such as chloro at their ortho-/meta-positions, also underwent the reaction with triethoxy(phenyl)silane smoothly, providing the corresponding products in slightly lower yields (78–80%) compared with their corresponding para-substituted ones (Table 4, entries 8-9). However, a weak ortho position effect was observed in the reaction of 2-methyl-bromobenzene (Table 4, entry 10). When pentamethyl-bromobenzene and pentafluoro-bromobenzene were used, the desired product was obtained in 76% and 79% yield, upon isolation (Table 4, entries 11-12). This poor yield may be due to steric hindrance. The thienyl and pyridinyl group survived well under the standard conditions, giving the corresponding products in moderate yields (Table 4, entries 13-14). Importantly, structurally challenging nitrogen heterocyclic moiety in a number of bioactive natural products, such as oxazole and pyrimidine derivatives, were also coped with this conditions (Table 4, entries 15-16).

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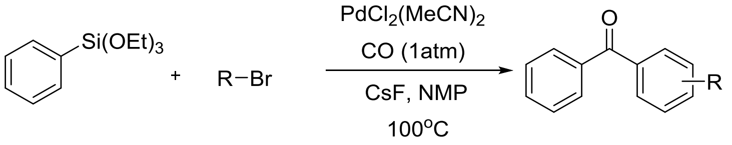
Table 4 Pd-catalyzed carbonylative Hiyama coupling of triethoxy(phenyl)silane with various aryl bromides [a]



Entry	R	Yield (%) [b]
1	4-CH_3-C_6H_5	87
2	4-CF_3-C_6H_5	84

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3	4-NO_2-C_6H_5	82
4	4-F-C_6H_5	88
5	4-Cl-C_6H_5	86
6	4-CN-C_6H_5	90
7	2-CN-C_6H_5	77
8	3-Cl-C_6H_5	80
9	2-Cl-C_6H_5	78
10	2-CH_3-C_6H_5	85
11	2,3,4,5,6-CH_3-C_6H_5	76
12	2,3,4,5,6-F-C_6H_5	79
13	2-thienyl	70
14	3-pyridinyl	75
15	oxazol-2-yl	68
16	3,5-pyrimidinyl	71

[a] Reaction conditions: triethoxy(phenyl)silane (0.5 mmol), aryl bromide (0.5 mmol), CsF (0.5 mmol), $PdCl_2(MeCN)_2$ (5 mol%), NMP (5.0 ml) at 100 °C for 6 hours under CO (1 atm) unless otherwise indicated. [b] Isolated yield.

Mechanism

A possible mechanism for the carbonylative Hiyama coupling is proposed in Scheme 1. It is suggested that the Pd(II) pre-catalyst is first reduced by the generated CO to Pd(0).[20] Oxidative addition of the carbon-halide bond (C-Br or C-I) to the generated Pd(0) generates the corresponding acyl palladium species (I) which followed by CO coordination and insertion to generate the intermediate (II). Attack of fluoride ion to arylsilanes followed by migration of a aryl group generates the intermediate (III) , and the terminal unsymmetrical diaryl ketones are produced after the reductive elimination with the concomitant generation of Pd(0), which finishes the catalytic

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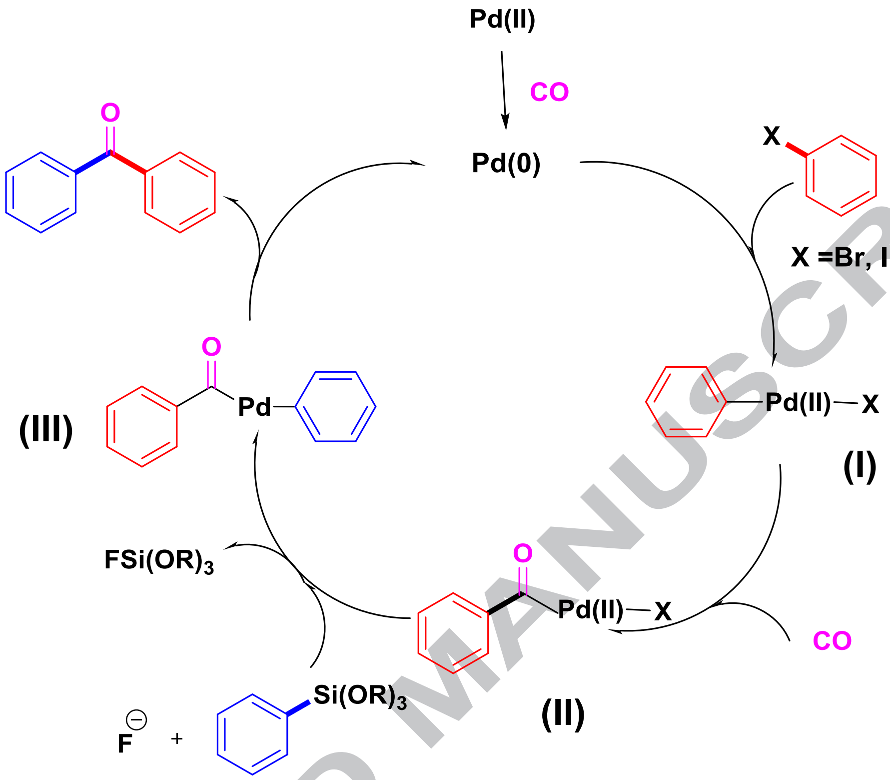
cycle. In addition, a base such as Cesium fluoride reacts with PhSi(OR)$_3$ to facilitate transmetalation step (Scheme 1).



Scheme 1. The plausible mechanism for the carbonylative Hiyama coupling of aryl halides

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Conclusion

In conclusion, a new procedure for the preparation of biaryl ketone compounds through the Pd-catalyzed carbonylative Hiyama cross-coupling of aryl iodines or aryl bromides with various organosilicon reagents was developed. This novel method provides easy access to biaryl ketone compounds by using commercially available and inexpensive aryl halides. The reaction did not require too much time, harsh reaction conditions, an high-pressure carbon monoxide atmosphere, or the exclusion of air. This cost-effective methodology will be very attractive for both academia and industry because commercially available aryl halides are used as the coupling partners. This new reaction may be used in the future as a complement to the classical carbonylative Hiyama cross-coupling reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version

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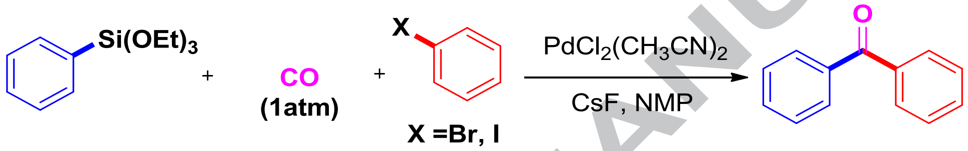
Graphical Abstract



An efficient protocol has been developed for the carbonylative Hiyama coupling of aryl halides using the cesium fluoride as a promoter by palladium-catalyzed in NMP. This protocol was applied to a wide variety of functionalized and hindered aryl iodides and bromides with arylsilanes, to afford the desired biaryl ketones in good to excellent yields.