

Synthetic Methods

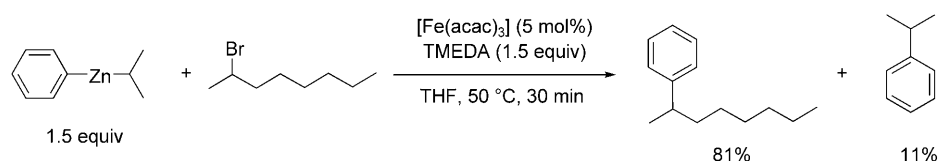
Iron-Catalyzed Oxidative Heterocoupling Between Aliphatic and Aromatic Organozinc Reagents: A Novel Pathway for Functionalized Aryl-Alkyl Cross-Coupling Reactions**

G rard Cahiez,* Laura Foulgoc, and Alban Moyeux

Iron-catalyzed aryl-alkyl coupling reactions have been extensively studied throughout the past ten years.^[1-4] These reactions can be performed by coupling aryl Grignard reagents with alkyl halides^[2] or alkyl Grignard reagents with aryl halides.^[3] Aryl zinc compounds have also been used.^[4] We report herein a new type of aryl-alkyl coupling; the iron-catalyzed oxidative heterocoupling between aliphatic and aromatic diorganozinc reagents.

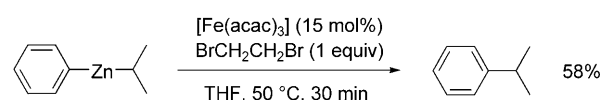
Examples of metal-mediated oxidative heterocoupling reactions have, to date, been rare. Lipshutz and co-workers^[5] showed that unsymmetrical biaryls, Ar-Ar', can be obtained in good yields by oxidation, at low temperature, of a kinetic high-order cyanocuprate ArAr'Cu(CN)Li₂ with oxygen. More recently, Knochel and co-workers^[6] prepared various phenylacetylene derivatives by oxidation of lithium aryl-(alkynyl) cuprates with chloranil. In fact, the palladium-catalyzed oxidative heterocoupling of alkyl zinc halides with alkynylstannanes, using desyl chloride as an oxidant, is the only catalytic procedure of this type reported to date.^[7] No examples of aryl-alkyl oxidative coupling reactions have been reported. Moreover, no examples of oxidative heterocoupling reaction under iron-catalysis are known.

In the course of our investigations on iron-catalyzed cross-coupling reactions,^[8] we obtained an intriguing result. Phenylisopropylzinc reacted with 2-bromooctane in the presence of [Fe(acac)₃] to selectively form 2-phenyloctane in 81 % yield. However, isopropylbenzene was also produced in 11 % yield (Scheme 1).



Scheme 1. Iron-catalyzed cross-coupling reaction between PhZnMe and 2-bromooctane.

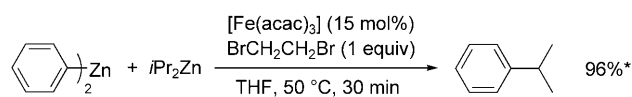
We believed that this unexpected byproduct resulted from an oxidative heterocoupling reaction between an arylzinc and an isopropylzinc species. We confirmed this hypothesis by treating phenylisopropylzinc with 1,2-dibromoethane as an oxidant, in the presence of iron(III) acetylacetonate, which gave isopropylbenzene in 58 % yield (Scheme 2). The pres-



Scheme 2. Iron-catalyzed oxidative heterocoupling of *iPrZnPh*.

ence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in the reaction was not necessary.

Encouraged by this result, we attempted to couple diphenylzinc with diisopropylzinc under the same conditions.^[9] In spite of our efforts, only one phenyl group and one isopropyl group were transferred (Scheme 3). This result was



* Only one Ph group and one *iPr* group are transferred

Scheme 3. Iron-catalyzed oxidative heterocoupling of Ph₂Zn with *iPr*₂Zn.

not surprising, since only 9 % of isopropylbenzene was obtained by coupling phenyl- and isopropylzinc chlorides under the same conditions.

The loss of half of the starting diorganozinc compounds is clearly a drawback, especially when valuable organic groups are used. Therefore, we turned our attention to mixed diorganozinc compounds bearing an inexpensive nontransferable group.^[10] In theory, these compounds can be obtained by performing two successive transmetalations with two different Grignard reagents.^[11]

Initially, we used Me₃SiCH₂ as the nontransferable group, as proposed by Nakamura and co-workers.^[4] The phenyl and the isopropyl groups were selectively transferred from PhZnCH₂SiMe₃ and *iPrZnCH*₂SiMe₃ but isopropylbenzene

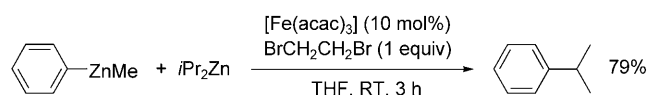
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was obtained in only 54% yield. Various other groups (PhCOO, Et₂N, *t*Bu) were tested as nontransferable groups without success.^[10] The reaction generally led to low yields and no selectivity. However, a very interesting result was obtained by using a simple methyl group, which was as efficient as Me₃SiCH₂ but cheaper.^[10] As a rule, mixed organozinc reagents, such as RZnCH₂SiMe₃ or RZnMe (R = Ph, *i*Pr), are less reactive than the corresponding diorganozinc reagents. Thus, the reaction times are five to ten times longer and the yields of coupling products are lower.

We tried to improve the yields by using an unsymmetrical diorganozinc species bearing a nontransferable methyl group and a more reactive symmetrical diorganozinc species (Scheme 4). This attempt afforded isopropylbenzene in a



Scheme 4. Iron-catalyzed oxidative heterocoupling of PhZnMe with *i*Pr₂Zn.

satisfactory yield of 79%. Moreover, similar results were obtained by using 10 mol% of catalyst instead of 15 mol%. These promising preliminary results prompted us to explore the scope of this reaction (Table 1). The oxidative heterocoupling reaction between arylmethylzinc reagents **1** and secondary dialkylzinc (R₂Zn) reagents **2** generally led to satisfactory yields (Table 1, entries 1–4, 7, and 8). Interestingly, primary dialkylzinc reagents were also used successfully (Table 1, entries 9 and 10). The reaction seemed rather sensitive to steric hindrance, as illustrated by the low yield obtained from the coupling of *o*-anisylmethylzinc **1c** (Table 1, entry 5). Finally, the reaction could not be extended to symmetrical benzyl-, allyl-, or tertiary alkylzinc coupling partners (Table 1, entries 12–14).

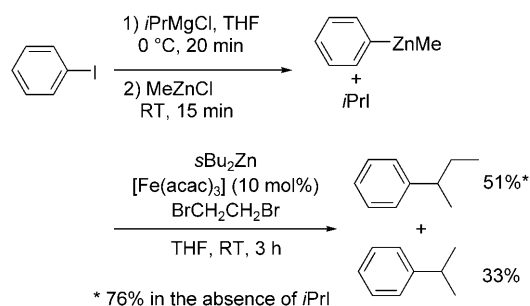
Organozinc compounds are known to be very chemoselective. Nakamura and co-workers recently reported that functionalized arylzinc reagents, Ar_{FG}ZnCH₂SiMe₃ (Ar_{FG} = functionalized aryl group), prepared from the Grignard reagents Ar_{FG}MgCl, could be coupled with secondary alkyl halides under iron catalysis in good yields.^[4] However, this reaction requires two equivalents of the valuable starting Grignard reagent prepared by halogen/magnesium exchange^[12] with *i*PrMgCl. We decided to develop a more economical procedure by using the oxidative heterocoupling method previously disclosed.

Phenylmagnesium chloride was prepared by iodine/magnesium exchange from iodobenzene and isopropylmagnesium chloride, for use in a preliminary experiment.^[11] It was then transmetalated with methylzinc chloride, prepared from MeMgCl and ZnCl₂, to give phenylmethylzinc, which was then coupled with symmetrical *sec*-butylzinc (under the conditions described above) in an oxidative heterocoupling procedure (Scheme 5). Unfortunately, the reaction led to the expected *sec*-butylbenzene in only 51% yield (instead of 76% in the absence of *i*PrI). Moreover, the cross-coupling reaction between phenylmethylzinc and isopropyl iodide, which formed during the preparation of the starting Grignard

Table 1: Oxidative heterocoupling between aromatic and aliphatic diorganozinc reagents.

$\text{Ar-ZnMe} + \text{R}_2\text{Zn} \xrightarrow[\text{THF, RT, 3 h}]{[\text{Fe}(\text{acac})_3] (10 \text{ mol}\%), \text{BrCH}_2\text{CH}_2\text{Br} (1 \text{ equiv})} \text{Ar-R}$			
Entry	Ar-ZnMe 1	R ₂ Zn 2 ^[a]	Yield [%] ^[b]
1			79 ^[c]
2		2a	67
3	1a		76 ^[c]
4	1b	2b	68
5		2b	22 ^[c]
6	1b		34
7	1b		68
8	1b		71
9	1b		69
10	1a		72
11		2g	31
12	1b		6 ^[b]
13	1b		8 ^[c]
14	1a		5 ^[b]

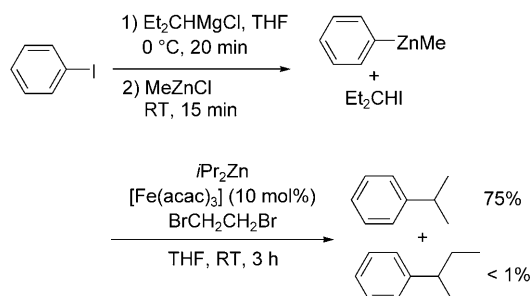
[a] One equivalent of R₂Zn was used. R = alkyl; [b] yield of isolated product; [c] yield determined by GC using decane as an internal standard.



Scheme 5. Use of PhMgCl prepared by I/Mg exchange with *i*PrMgCl.

reagent, took place competitively, forming isopropylbenzene in 33% yield.

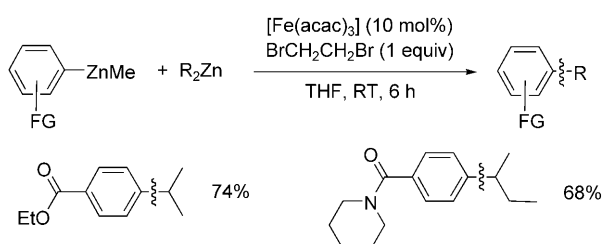
Owing to our experience in the field of iron-catalyzed coupling reactions involving secondary alkyl halides, we knew the reactivity of these species to be very sensitive to steric factors.^[13] Thus, we performed the iodine/magnesium exchange by using 3-pentylmagnesium chloride, instead of isopropylmagnesium chloride. This attempt was successful since the oxidative heterocoupling reaction was not perturbed by the presence of 3-iodopentane (Scheme 6). To our knowl-



Scheme 6. Use of PhMgCl prepared by I/Mg exchange with Et_2CHMgCl .

edge, it is the first use of this Grignard reagent to achieve an iodine/magnesium exchange.

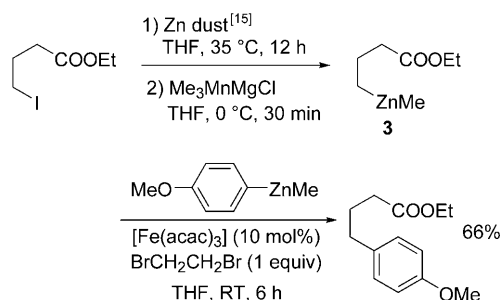
This procedure was also applied to the coupling of functionalized arylzinc compounds (Scheme 7). It is important to note that functionalized arylmethylzinc reagents



Scheme 7. Iron-catalyzed oxidative heterocoupling with functionalized ArZnMe .

reacted more sluggishly, and a 6 h reaction time was necessary. Nevertheless, satisfactory yields were obtained.

Furthermore, functionalized alkylzinc compounds, easily prepared by insertion of zinc to the C–I bond of functionalized alkyl iodides,^[14] were also used successfully (Scheme 8).



Scheme 8. Iron-catalyzed oxidative heterocoupling with functionalized ArZnMe .

The preparation of the functionalized alkylmethylzinc **3** (Scheme 8) was not obvious and requires some clarification. Indeed, the reaction of the alkylzinc iodide $\text{IZn}(\text{CH}_2)_3\text{COOEt}$ with methylmagnesium halide or methyl-lithium was not chemoselective and afforded poor yields of **3**. Interestingly, we discovered that the addition of trimethylmanganate Me_3MnMgCl (0.33 equivalents) led to quantitative yields of **3**.^[16]

In summary, we have disclosed herein the first iron-catalyzed oxidative cross-coupling reaction. The coupling product was obtained by treating a mixture of aryl- and alkylzinc reagents with 1,2-dibromoethane in the presence of $[\text{Fe}(\text{acac})_3]$. Primary or secondary aliphatic diorganozinc reagents were both applicable to this reaction. Good yields were obtained under mild conditions (no ligand, room temperature, 3–6 h). Notably, functionalized aryl- or alkylzinc reagents were both used successfully. Such a reaction paves the way to a new class of coupling reactions, complementary to the classical cross-coupling procedures between an organometallic reagent and an organic halide.

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