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Synthetic Methods

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

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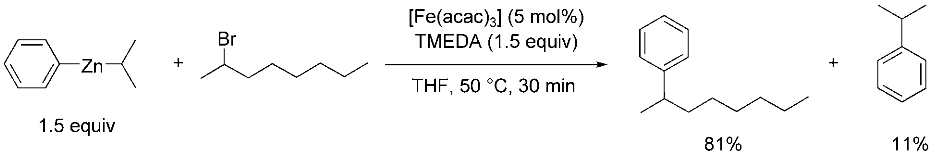
Iron-catalyzed aryl–alkyl coupling reactions have been extensively studied throughout the past ten years.[1–4] These reactions can be performed by coupling aryl Grignard reagents with alkyl halides[2] or alkyl Grignard reagents with aryl halides.[3] Aryl zinc compounds have also been used.[4] We report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

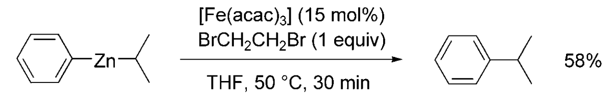
Examples of metal-mediated oxidative heterocoupling reactions have, to date, been rare. Lipshutz and co-workers[5] showed that unsymmetrical biaryls, Ar−Ar′, can be obtained in good yields by oxidation, at low temperature, of a kinetic high-order cyanocuprate $ArAr'Cu(CN)Li_2$ with oxygen. More recently, 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).



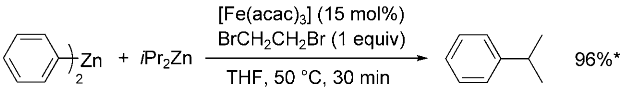
Scheme 1. Iron-catalyzed cross-coupling reaction between PhZnMe and 2-bromooctane.

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



Scheme 2. Iron-catalyzed oxidative heterocoupling of *i*PrZnPh.

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



* Only one Ph group and one *i*Pr group are transferred

Scheme 3. Iron-catalyzed oxidative heterocoupling of Ph_2Zn with iPr_2Zn.

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 Me_3SiCH_2 as the nontransferable group, as proposed by Nakamura and co-workers.[4] The phenyl and the isopropyl groups were selectively transferred from $PhZnCH_2SiMe_3$ and $iPrZnCH_2SiMe_3$ but isopropylbenzene

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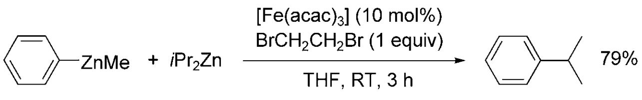
was obtained in only 54 % yield. Various other groups (PhCOO, Et_2N, *t*Bu) were tested as nontransferable groups without success.[10] The reaction generally led to low yields and no selectivity. However, a very interesting result was obtained by using a simple methyl group, which was as efficient as Me_3SiCH_2 but cheaper.[10] As a rule, mixed organozinc reagents, such as $RZnCH_2SiMe_3$ 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.

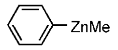
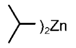
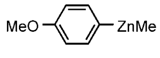
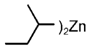
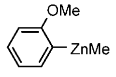
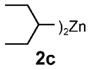
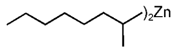
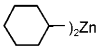
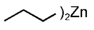
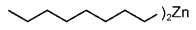
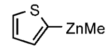
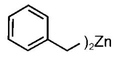
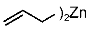
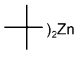
We tried to improve the yields by using an unsymmetrical diorganozinc species bearing a nontransferable methyl group and a more reactive symmetrical diorganozinc species (Scheme 4). This attempt afforded isopropylbenzene in a satisfactory yield of 79 %. Moreover, similar results were obtained by using 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 (R_2Zn) 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).



Scheme 4. Iron-catalyzed oxidative heterocoupling of PhZnMe with *i*Pr_2Zn.

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

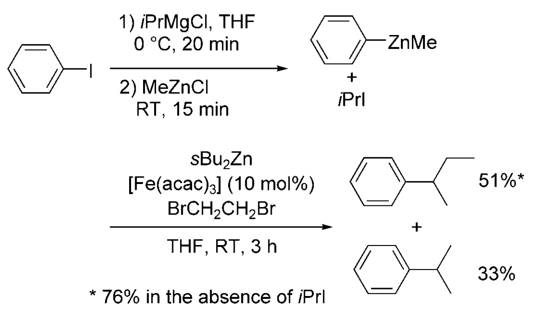
$$\text{Ar-ZnMe} + R_2Zn \xrightarrow[\text{THF, RT, 3 h}]{[\text{Fe(acac)}_3]\ (10\ \text{mol\%}),\ \text{BrCH}_2\text{CH}_2\text{Br}\ (1\ \text{equiv})} \text{Ar-R}$$

Entry	Ar–ZnMe **1**	R_2Zn **2**[a]	Yield [%][b]
1	 **1a**	 **2a**	79[c]
2	 **1b**	**2a**	67
3	**1a**	 **2b**	76[c]
4	**1b**	**2b**	68
5	 **1c**	**2b**	22[c]
6	**1b**	 **2c**	34
7	**1b**	 **2d**	68
8	**1b**	 **2e**	71
9	**1b**	 **2f**	69
10	**1a**	 **2g**	72
11	 **1d**	**2g**	31
12	**1b**	 **2h**	6[b]
13	**1b**	 **2i**	8[c]
14	**1a**	 **2j**	5[b]

[a] One equivalent of R_2Zn was used. R = alkyl; [b] yield of isolated product; [c] yield determined by GC using decane as an internal standard.

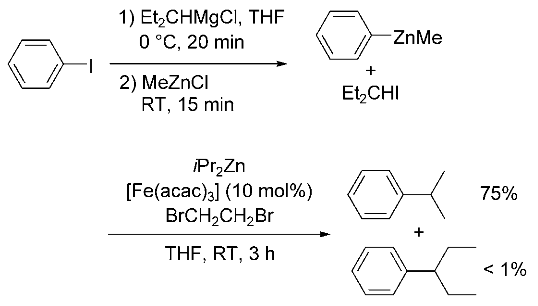
Organozinc compounds are known to be very chemoselective. Nakamura and co-workers recently reported that functionalized arylzinc reagents, $Ar_{FG}ZnCH_2SiMe_3$ (Ar_{FG} = functionalized aryl group), prepared from the Grignard reagents $Ar_{FG}MgCl$, could be coupled with secondary alkyl halides under 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 $ZnCl_2$, 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 reagent, took place competitively, forming isopropylbenzene in 33 % yield.



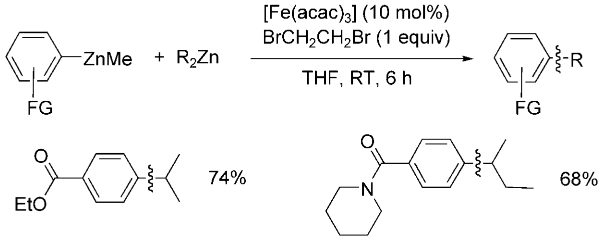
Scheme 5. Use of PhMgCl prepared by I/Mg exchange with *i*PrMgCl.

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



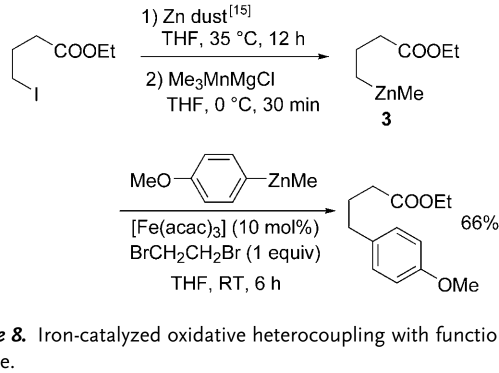
Scheme 6. Use of PhMgCl prepared by I/Mg exchange with Et$_2$CHMgCl.

This procedure was also applied to the coupling of functionalized arylzinc compounds (Scheme 7). It is important to note that functionalized arylmethylzinc reagents reacted more sluggishly, and a 6 h reaction time was necessary. Nevertheless, satisfactory yields were obtained.



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

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 IZn-$(CH_2)_3COOEt$ with methylmagnesium halide or methyllithium 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 [Fe(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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[1] For reviews on iron-mediated coupling reactions, see: a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; b) H. Shinokubo, K. Oshima, *Eur. J. Org. Chem.* **2004**, 2071; c) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624; d) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500; e) G. Cahiez, C. Duplais in *The Chemistry of Organomagnesium Compounds* (Eds.: Z. Rappoport, I. Marek), Wiley-VCH, Weinheim, **2008**, chap. 13, p. 595.

[2] a) T. Nagano, T. Hayashi, *Org. Lett.* **2004**, *6*, 1297; b) R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby, M. Hird, *Chem. Commun.* **2004**, 2822; c) R. B. Bedford, D. W. Bruce, R. M. Frost, M. Hird, *Chem. Commun.* **2005**, 4161; d) R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost, M. Hird, *J. Org. Chem.* **2006**, *71*, 1104; e) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686; f) G. Cahiez, V. Habiak, C. Duplais, A. Moyeux, *Angew. Chem.* **2007**, *119*, 4442; *Angew. Chem. Int. Ed.* **2007**, *46*, 4364. For a desulfinative coupling reaction between aryl Grignard reagents and sulfonyl chlorides, see: g) C. M. Rao Volla, P. Vogel, *Angew. Chem.* **2008**, *120*, 1325; *Angew. Chem. Int. Ed.* **2008**, *47*, 1305.

[3] a) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856; b) A. Fürstner, A. Leitner, *Angew. Chem.* **2002**, *114*, 632; *Angew. Chem. Int. Ed.* **2002**, *41*, 609; c) R. Martin, A. Fürstner, *Angew. Chem.* **2004**, *116*, 4045; *Angew. Chem. Int. Ed.* **2004**, *43*, 3955; d) G. Seidel, D. Laurich, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3950.

[4] M. Nakamura, S. Ito, K. Matsuo, E. Nakamura, *Synlett* **2005**, 1794.

[5] B. H. Lipshutz, K. Siegmann, E. Garcia, F. Kayser, *J. Am. Chem. Soc.* **1993**, *115*, 9276.

[6] S. R. Dubbaka, M. Kienle, H. Mayr, P. Knochel, *Angew. Chem.* **2007**, *119*, 9251; *Angew. Chem. Int. Ed.* **2007**, *46*, 9093.

[7] a) Y. Zhao, H. Wang, X. Hou, Y. Hu, A. Lei, H. Zhang, L. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 15048; b) L. Jin, Y. Zhao, H. Wang, A. Lei, *Synthesis* **2008**, 649.

[8] a) G. Cahiez, P. Y. Chavant, E. Metais, *Tetrahedron Lett.* **1992**, *33*, 5245; b) G. Cahiez, S. Marquais, *Tetrahedron Lett.* **1996**, *37*, 1773; c) G. Cahiez, S. Marquais, *Pure Appl. Chem.* **1996**, *68*, 53; d) G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199; e) W. Dohle, F. Kopp, G. Cahiez, P. Knochel, *Synlett* **2001**, 1901; f) C. Duplais, F. Bures, T. Korn, I. Sapountzis, G. Cahiez, P. Knochel, *Angew. Chem.* **2004**, *116*, 3028; *Angew. Chem. Int. Ed.* **2004**, *43*, 2968; g) G. Cahiez, C. Chaboche, F. Mahuteau-Betzer, M. Ahr, *Org. Lett.* **2005**, *7*, 1943; h) G. Cahiez, C. Duplais, A. Moyeux, *Org. Lett.* **2007**, *9*, 3253; i) G. Cahiez, A. Moyeux, J. Buendia, C. Duplais, *J. Am. Chem. Soc.* **2007**, *129*, 13788.

[9] Various 1,2-dihalogenoethanes were compared. See the Supporting Information.

[10] See the Supporting Information, Table S4.

[11] In THF, an equilibrium seems to form: $Ar_2Zn + R_2Zn \rightleftarrows ArZnAlk$; see: C. Bolm, N. Hermanns, J. P. Hildebrand, K. Muñiz, *Angew. Chem.* **2000**, *112*, 3607; *Angew. Chem. Int. Ed.* **2000**, *39*, 3465.

[12] a) L. Boymond, M. Rottländer, G. Cahiez, P. Knochel, *Angew. Chem.* **1998**, *110*, 1801; *Angew. Chem. Int. Ed.* **1998**, *37*, 1701. For a review, see: b) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem.* **2003**, *115*, 4438; *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.

[13] For iron catalysis, see references [2f] and [8h]. For cobalt catalysis, see: a) G. Cahiez, C. Chaboche, C. Duplais, A. Giulliani, A. Moyeux, *Adv. Synth. Catal.* **2008**, *350*, 1484; b) G. Cahiez, C. Chaboche, C. Duplais, A. Moyeux, *Org. Lett.* **2009**, *11*, 277.

[14] For a review, see: a) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117. Functionalized alkylzinc bromides can also be prepared from the corresponding bromides by Br/Zn exchange, see: b) I. Klement, P. Knochel, K. Chau, G. Cahiez, *Tetrahedron Lett.* **1994**, *35*, 1177.

[15] Zn dust was activated by treatment with 1,2-dibromoethane (5 mol%) then with trimethylsilyl chloride (3 mol%). For a practical procedure see: B. H. Lipshutz, M. R. Wood, R. Tirado, *Org. Synth.* **1999**, *76*, 252.

[16] For a recent review on organomanganese chemistry, see: G. Cahiez, C. Duplais, J. Buendia, *Chem. Rev.* **2009**, ASAP. For the preparation of manganates, see: G. Cahiez, M. Alami, *Tetrahedron* **1989**, *45*, 4163.