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Iron-Catalyzed Acylation of Polyfunctionalized Aryl- and Benzylzinc Halides with Acid Chlorides

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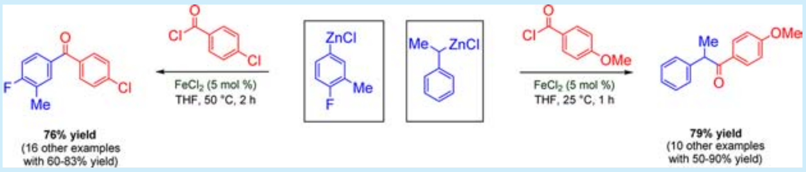
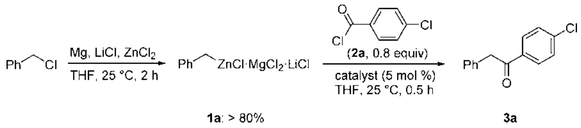
Ⓢ *Supporting Information*



ABSTRACT: $FeCl_2$ (5 mol %) catalyzes a smooth and convenient acylation of functionalized arylzinc halides at 50 °C (2–4 h) and benzylic zinc chlorides at 25 °C (0.5–4 h) with a variety of acid chlorides leading to polyfunctionalized diaryl and aryl heteroaryl ketones.

Organozinc reagents belong to the most useful organometallics for organic synthesis since they show a high tolerance of functional groups and undergo efficient transmetalations to various metallic salts leading to a broad reactivity pattern.[1] The reaction of zinc reagents with acid chlorides is an important method for preparing a range of polyfunctionalized ketones.[2] Although such acylations proceed without catalysts, the yields are usually low due to extensive side reactions.[3] A transmetalation of organozinc reagents to the corresponding copper reagents using $CuCN{\cdot}2LiCl$[4] considerably extends the reaction scope of this acylation procedure and allows the preparation of various highly functionalized ketones.[5] Although this acylation can be performed in many cases using substoichiometric amounts of copper catalyst, lower yields generally result under such conditions. Alternatively, Negishi[6] reported a palladium-catalyzed acylation method of organozinc halides, and Rieke[7] described a related nickel-catalyzed acylation for the preparation of aryl ketones. Recently, Gosmini[8] reported a cobalt-catalyzed acylation of arylzinc bromides. Interestingly, organozinc reagents can also be acylated with thioesters as shown by Fukuyama[9] or with acyl cyanides.[10] Since iron salts are cheap, environmentally friendly, and of moderate toxicity, their use as acylation catalysts would be especially attractive.[11] Marchese[12] and Fürstner[13] already demonstrated that iron-catalyzed reactions of acid chlorides with organomagnesium reagents can be readily performed. In addition, Cahiez[14] showed that organomanganese reagents prepared from the corresponding Grignard species undergo acylation reactions with excellent yields.

Table 1. Screening of Catalysts for the Acylation of Benzylzinc Chloride (1a) with 4-Chlorobenzoyl Chloride (2a)



entry	catalyst	yield[a] (%)	entry	catalyst	yield[a] (%)
1		74	5	$FeBr_3$	85[b]
2	$MnCl_2$	60	6	$Fe(acac)_2$	73
3	$CrCl_2$	65	7	$FeBr_2$	82[b]
4	$Fe(acac)_3$	60	8	$FeCl_2$	90[c] (70)[d]

[a] Isolated yields of pure product. [b] $FeBr_2$ and $FeBr_3$ of 98% purity. [c] $FeCl_2$ of 99.5% purity. [d] $FeCl_2$ of 98% purity.[25]

Herein, we report an efficient iron-catalyzed acylation of polyfunctionalized aryl- and benzylzinc halides with acid chlorides. Thus, benzylzinc chloride (**1a**, 1.0 equiv), prepared by the insertion of Mg turnings and $ZnCl_2$, reacts with 4-chlorobenzoyl chloride (**2a**, 0.8 equiv) in THF (25 °C, 0.5 h) in the presence of various transition-metal salts (Table 1).[15a] This rapid screening indicated that iron(II) chloride is an excellent catalyst (Table 1, entry 8) in THF as solvent.[16] Additives like 4-(dimethylamino)pyridine,[17] $Sc(OTf)_3$,[18] $InCl_3$,[19] $BF_3{\cdot}OEt_2$,[20] and $LaCl_3{\cdot}2LiCl$[21] did not lead to an improvement.[22] In addition, the testing of various solvent mixtures showed that THF was the ideal solvent for this acylation reaction since the ketone **3a** was obtained after 0.5 h reaction time in 90% isolated yield.[23] To ensure that $FeCl_2$ is the true catalyst of this acylation, we have used $FeCl_2$ of high purity (99.5%).[24] The coupling experiment with $FeCl_2$ of lower purity (98%) proceeded somewhat less cleanly and gave 70% yield of product.

This iron-catalyzed acylation proved to be quite general. Thus, the reaction of (3-trifluoromethylbenzyl)zinc chloride (**1b**) with 4-*tert*-butylbenzoyl chloride (**2b**) provides within 0.5 h at 25 °C the desired ketone **3b** in 65% yield (Table 2, entry 1). In the absence of an iron catalyst, the yield leveled at 38% yield. Similarly, the acylation of **1b** with 4-chlorobenzoyl chloride (**2a**) gave the ketone **3c** in 71% yield (entry 2). Furthermore, (3-fluorobenzyl)zinc chloride (**1c**) reacted in the presence of $FeCl_2$

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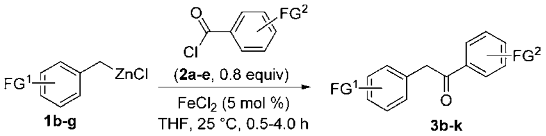
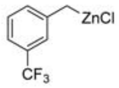
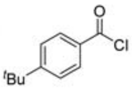
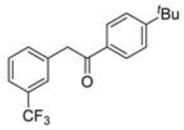
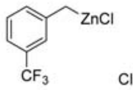
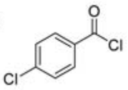
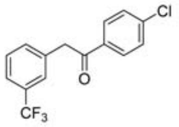
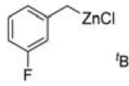
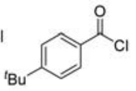
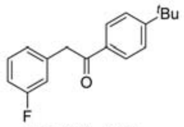
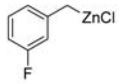
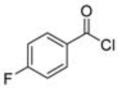
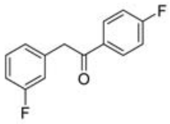
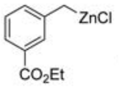
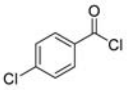
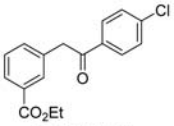
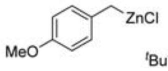
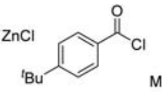
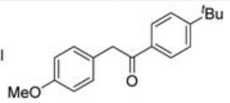
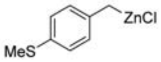
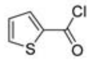
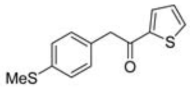
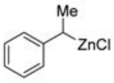
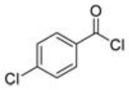
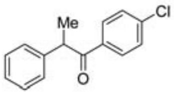
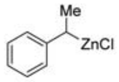
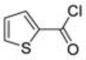
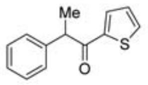
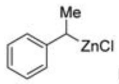
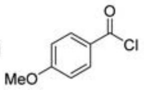
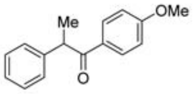
Table 2. Iron-Catalyzed Acylations of Benzylic Zinc Reagents (**1b**–**g**) with Acid Chlorides (**2a**–**e**)



FG$_1$ = 3-CF$_3$; 3-F; 3-CO$_2$Et; 4-OMe; 4-SMe
FG$_2$ = 4-F; 4-Cl; 4-^{t}Bu; 4-OMe

entry	benzylzinc reagent	acid chloride[a]	product[b,c]
1	 **1b**	 **2b**	 **3b**: 65% (38%)[d], 0.5 h
2	 **1b**	 **2a**	 **3c**: 71%, 0.5 h
3	 **1c**	 **2b**	 **3d**: 88%, 0.5 h
4	 **1c**	 **2c**	 **3e**: 74%, 0.5 h
5	 **1d**	 **2a**	 **3f**: 50%, 4 h
6	 **1e**	 **2b**	 **3g**: 58%, 0.5 h
7	 **1f**	 **2d**	 **3h**: 60%, 4 h
8	 **1f**	 **2a**	 **3i**: 78%, 1 h
9	 **1g**	 **2d**	 **3j**: 65%, 1 h
10	 **1g**	 **2e**	 **3k**: 79%, 1 h

[a] 0.8 equiv of the acid chloride was used. [b] Isolated yield of pure product. [c] Up to 20% of homocoupling was observed. [d] Isolated yield of pure product without catalyst.

(5 mol %) with 4-*tert*-butylbenzoyl chloride (**2b**) within 0.5 h, furnishing the expected diaryl ketone (**3d**) in 88% yield (entry 3). The acylation of the benzylic zinc chloride (**1c**) with the electron-deficient 4-fluorobenzoyl chloride (**2c**) afforded the bis-fluorinated ketone **3e** in 74% yield (entry 4). Remarkably, the readily available benzylic zinc reagent **1d**[15a] bearing an ester moiety underwent an efficient acylation with 4-chlorobenzoyl chloride (**2a**) leading to the functionalized diaryl ketone **3f** in 50% yield (entry 5).

Additionally, the electron-rich (4-methoxybenzyl)zinc chloride (**1e**) reacted with 4-*tert*-butylbenzoyl chloride (**2b**) to afford ketone **3g** in 58% yield (entry 6). Interestingly, the acylation of the sulfur-containing benzylic zinc chloride (**1f**) with 2-thiophenecarbonyl chloride (**2d**) succeeded within 4 h at 25 °C to give the desired aryl heteroaryl ketone (**3h**) in 60% yield (entry 7). Finally, the reaction of a secondary benzylzinc reagent (**1g**) with selected acid chlorides (**2a**,**d**,**e**) provides the diaryl ketones **3i**–**k** in 65–79% yield (entries 8–10). In all of these acylations, less than 20% homocoupling of the benzylic moiety was observed.

Additionally, we have extended this cross-coupling to arylzinc chlorides. Compared to benzyliczinc reagents, the carbon–zinc bond of arylzinc halides has a much lower ionic character and, therefore, is significantly less reactive. Thus, the direct acylation of the electron-poor arylzinc halide **4a**, conveniently prepared via an I/Mg exchange using *i*PrMgCl·LiCl[26] followed by transmetalation with ZnCl$_2$, proceeds only sluggishly with 4-chlorobenzoyl chloride (**2a**) at 50 °C in THF providing the ketone **5a** in 34% yield even after a prolonged reaction time of 12 h. In contrast, when FeCl$_2$ (5 mol %, 99.5% pure) was used, the acylation with **2a** was complete after 4 h reaction time at 50 °C and the desired ketone **5a** was isolated in 62% yield (Table 3, entry 1).[27] Similarly, the arylzinc reagent **4a** underwent several acylations with the functionalized acid chlorides **2b**,**c**,**f** leading to the diaryl ketones **5b**–**d** in 65–83% (entries 2–4). Furthermore, the related arylzinc reagent (**4b**), bearing an ester moiety in meta position, reacted rapidly with the acid chlorides **2a**,**b**,**h** to afford the ketones **5e**–**g** within 4 h in 60–75% yield (entries 5–7). Performing such acylations using the ortho-substituted arylzinc chloride (**4c**) in combination with the two electron-poor acid chlorides 4-chlorobenzoyl chloride (**2a**) and 4-cyanobenzoyl

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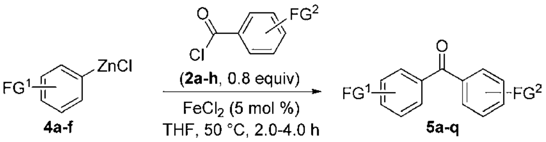
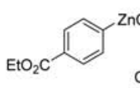
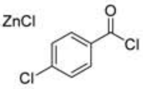
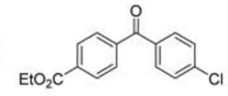
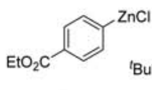
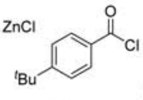
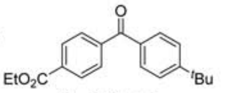
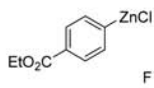
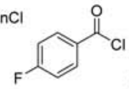
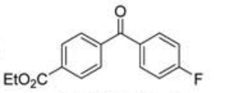
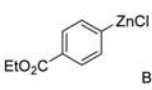
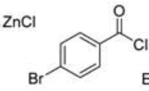
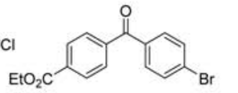
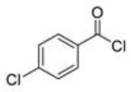
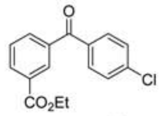
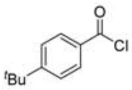
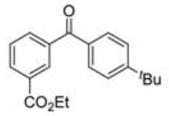
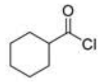
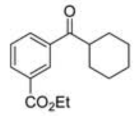
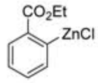
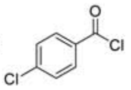
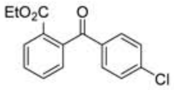
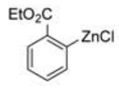
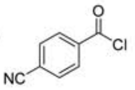
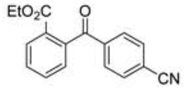
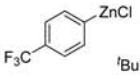
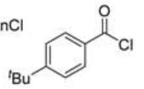
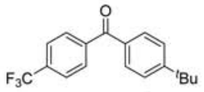
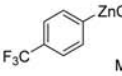
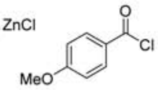
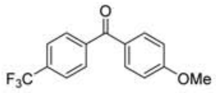
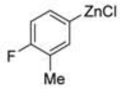
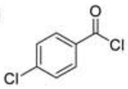
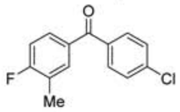
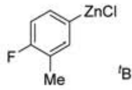
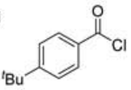
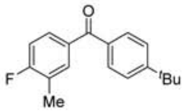
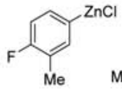
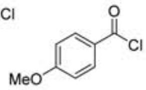
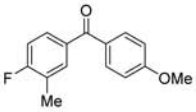
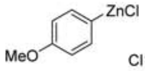
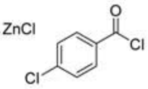
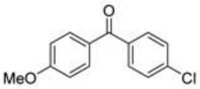
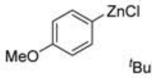
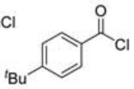
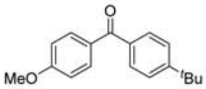
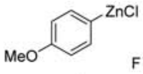
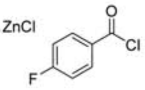
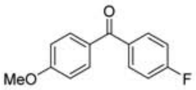
Table 3. Iron-Catalyzed Acylations of Arylzinc Reagents (4a−f) with Acid Chlorides (2a−h)



FG_1 = 2-CO_2Et; 3-CO_2Et; 4-CO_2Et; 4-CF_3; 3-Me, 4-F; 4-OMe
FG_2 = 4-F; 4-Cl; 4-Br; 4-CN; 4-^{t}Bu; 4-OMe

entry	arylzinc reagent	acid chloride[a]	product[b,c]
1	 **4a**	 **2a**	 **5a**: 62% (56%[d], 34%[e]), 4 h
2	 **4a**	 **2b**	 **5b**: 65%, 4 h
3	 **4a**	 **2c**	 **5c**: 83% (21%)[e], 4 h
4	 **4a**	 **2f**	 **5d**: 68%, 4 h
5	 **4b**	 **2a**	 **5e**: 75%, 4 h
6	 **4b**	 **2b**	 **5f**: 72%, 4 h
7	 **4b**	 **2h**	 **5g**: 60%, 4 h
8	 **4c**	 **2a**	 **5h**: 74%, 4 h
9	 **4c**	 **2g**	 **5i**: 62%, 4 h
10	 **4d**	 **2b**	 **5j**: 83%, 3 h
11	 **4d**	 **2e**	 **5k**: 62%, 3 h
12	 **4e**	 **2a**	 **5l**: 76%, 2 h
13	 **4e**	 **2b**	 **5m**: 70%, 2 h
14	 **4e**	 **2e**	 **5n**: 79%, 2 h
15	 **4f**	 **2a**	 **5o**: 74%, 3 h
16	 **4f**	 **2b**	 **5p**: 82%, 3 h
17	 **4f**	 **2c**	 **5q**: 82%, 3 h

[a] 0.8 equiv of the acid chloride was used. [b] Isolated yield of pure product. [c] Up to 10% of homocoupling was observed. [d] $FeCl_2$ with a purity of 99.99% was used. [e] Isolated yield of pure product without catalyst.

chloride (**2g**) proceeded smoothly at 50 °C, yielding the functionalized diaryl ketones **5h,i** in 62−74% yield (entries 8 and 9).

The scope of this acylation procedure proved to be quite general for a range of other functionalized arylzinc reagents. Thus, the reaction of (4-(trifluoromethyl)phenyl)zinc chloride (**4d**) with acid chlorides bearing electron-donating substituents, like 4-*tert*-butylbenzoyl chloride (**2b**) and 4-methoxybenzoyl chloride (**2e**), gave the desired ketones **5j,k** in 62−83% yield (entries 10 and 11). In addition, (4-fluoro-3-methylphenyl)zinc chloride (**4e**) underwent efficient acylations with the acid chlorides **2a,b,e** to afford the functionalized diaryl ketones (**5l**−**n**) in 70−79% yield (entries 12−14). Finally, the electron-rich (4-methoxyphenyl)zinc chloride (**4f**) reacted with selected acid

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chlorides bearing a chlorine (**2a**), a *tert*-butyl (**2b**), or a fluorine substituent (**2c**) in the para position leading to the ketones **5o−q** within 3 h at 50 °C in 74−82% yield (entries 15−17).

In summary, we have shown that various benzylic zinc and arylzinc halides react with a broad range of acid chlorides at 25−50 °C leading to polyfunctionalized diaryl and aryl heteroaryl ketones within 0.5−4 h. Further extensions of this methodology are currently underway in our laboratories.[28]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01677.

Detailed experimental procedures and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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(22) For an additive screening, see the Supporting Information.

(23) For a solvent screening, see the Supporting Information.

(24) For the use of $\mathrm{FeCl_2}$ of even higher purity (99.99%), see Table 3, entry 1.

(25) The uncatalyzed reaction proceeds always in ca. 20−30% lower yield as in the presence of 5 mol% of $\mathrm{FeCl_2}$ (see also Table 2, entry 1, or Table 3, entries 1 and 3).

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(27) Although a yield of 62% of pure product was isolated, indicating that some side reactions may occur, the GC-analysis of the crude reaction mixture showed a clean reaction with only small amounts of side products.

(28) The Fe-catalyzed acylation of alkylzinc halides proceeds under similar conditions (THF, 25 °C). For preliminary experiments, see the Supporting Information.