


 Very Important Publication


Iron-Catalyzed Radical Zincations of Alkyl Iodides

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Abstract: We report a new iron-catalyzed I/Zn-exchange allowing to convert primary or tailored secondary alkyl iodides into the corresponding alkylzinc iodides. In the presence of a remote double bond at position 5, diastereoselective ring closures are observed. Quenching of these zinc reagents, after transmetalation to copper species (with CuCN·2LiCl) or under Pd-catalysis, with typical electrophiles (allyl bromides, acid chlorides or aryl iodides) gave various polyfunctional products.

Keywords: Carbozincation; Iron-catalysis; Organozinc; Radical cyclization; Diastereoselectivity

The halogen-metal exchange is an important method for the preparation of organometallic reagents.^[1] The rate of such an exchange reaction strongly depends on the nature of the metal. The more electropositive, the faster is the exchange reaction^[2] demonstrated by the I/Li-exchange as one of the fastest reactions in organic synthesis.^[3] However, the I/Mg-exchange, in comparison, is usually much slower^[4] and the I/Zn-exchange even requires polar solvents^[5] or tailored organozinc exchange reagents such as the zincate $s\text{Bu}_2\text{Zn}\cdot 2\text{LiOR}$.^[6] Also, I/Zn-exchange reactions under transition metal catalysis were reported.^[7] Thus, Pd(II) and Ni(II) salts proved to catalyze the I/Zn-exchange under mild conditions.^[7] In the search of a less expensive catalyst, we have examined an iron-catalyzed reaction.^[8] Indeed, iron salts were reported to catalyze a range of radical cyclizations,^[8,9] using organomagnesium^[10] or organozinc reagents followed

by various cross-couplings.^[11] Furthermore, Bertrand has described a non-transition metal catalyzed generation of radicals from alkyl iodides promoted by air.^[12] Herein, we wish to report a new iron-catalyzed I/Zn-exchange reaction allowing the preparation of various alkylzinc organometallics from the corresponding alkyl iodides under mild conditions.

Thus, we have initiated our studies with the cyclic iodohydrin **1**.^[9c] Treatment of iodide **1** with a 1 M solution of diethylzinc in toluene in the presence of catalytic amounts of $\text{Fe}(\text{acac})_3$ and *N*-methylpyrrolidone (NMP; 10 equiv.) in THF at -20°C for 1 h and subsequent aging of the mixture for 15 h at 25°C provided the bicyclic alkylzinc iodide **2**. After aqueous work-up, the bicyclic acetal **3a** was obtained in 80% isolated yield and high diastereoselectivity ($\text{dr} = 95:5$; entry 1 of Table 1). In the absence of iron salts, a low GC-yield of 18% with a decreased dr of 90:10 was obtained (entry 2). Furthermore, using $\text{FeCl}_3\cdot 6\text{H}_2\text{O}$ as an iron source gave only 5% yield of **3a** (entry 3). Lowering the amount of catalyst to 2% $\text{Fe}(\text{acac})_3$ led to 60% GC-yield of **3a** (entry 4). Exchanging NMP for *N,N'*-dimethylpropyleneurea (DMPU) decreased the GC-yield of **3a** to 54% (entry 5). When acetonitrile was used as a solvent, 39% of acetal **3a** was obtained ($\text{dr} = 92:8$; entry 6).^[13] Notably, performing the zincation at 25°C resulted in 75% GC-yield but lower diastereoselectivity ($\text{dr} = 92:8$; entry 7).

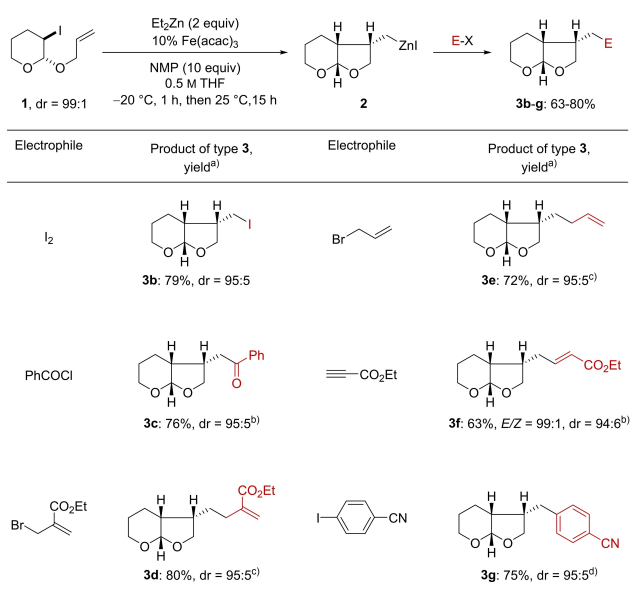
With these optimized conditions in hand, we have treated zinc reagent **2** with various electrophiles (Scheme 1). Thus, iodolysis of **2** furnished the corresponding cyclic iodide **3b** in 79% isolated yield and $\text{dr} = 95:5$. Transmetalation of **2** using $\text{CuCN}\cdot 2\text{LiCl}$ (as 1 M solution in THF; 1 equiv.) and further reaction with benzoyl chloride (3 equiv., -40°C , 3 h) gave the

Table 1. Optimization of the reaction conditions for the iron-catalyzed radical zincation of cyclic iodohydrin **1** leading to the bicyclic acetal **3a**.

Entry	Deviation from standard conditions	GC-Yield of 3a (%) ^[a]	dr (3a) ^[a]
1	None	80 ^[b]	95:5
2	No Fe(acac) ₃	18	90:10
3	10% FeCl ₃ ·6H ₂ O	5	–
4	2% Fe(acac) ₃	60	95:5
5	DMPU instead of NMP as additive	54	95:5
6	MeCN instead of THF	39	92:8
7	Performing reaction at 25 °C	75	92:8

^[a] The reactions were performed on 0.5 mmol scale. Yields and dr (diastereomeric ratio) were determined by GC-analysis using C₁₁H₂₄ as internal standard.

^[b] Isolated yield of analytically pure products.

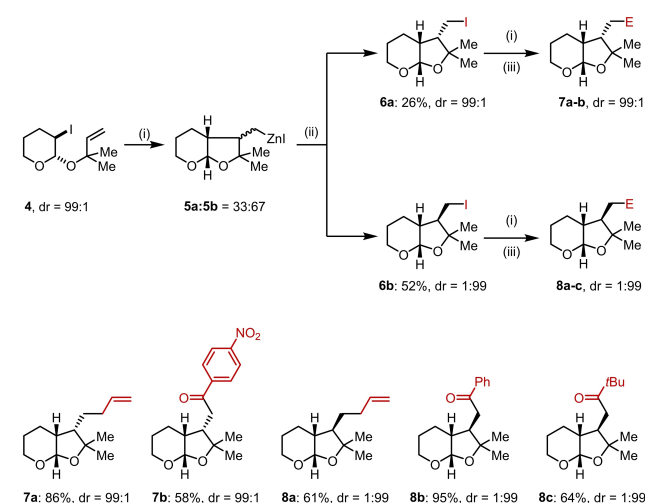


Scheme 1. Products of type **3**, obtained after iron-catalyzed I/Zn-exchange of **1** followed by trapping reactions with electrophiles. Reaction conditions: a) isolated yield of analytically pure products; b) CuCN·2LiCl (1.0 equiv.), electrophile (3.0 equiv.), -40 °C to 25 °C, 2 h; c) allyl bromide (2.1–3.0 equiv.), CuCN·2LiCl (5 mol%), -20 °C to 25 °C, 2 h; d) 5% Pd(OAc)₂, 10% CPhos, 25 °C, 16 h.

ketone **3c** in 76% yield (dr=95:5). Allylation of **2** with ethyl (2-bromomethyl)acrylate or allyl bromide (2.1–3.0 equiv., -20 °C, 2 h) in the presence of 5 mol% CuCN·2LiCl furnished the corresponding allylated products **3d–3e** in 72–80% (dr=95:5). Trapping of **2**, after transmetalation with CuCN·2LiCl

(1.0 equiv.), with ethyl propiolate led to ester derivative **3f** in 63% yield (*E/Z*=99:1; dr=94:6). Furthermore, Pd-catalyzed cross-coupling (5% Pd(OAc)₂, 10% CPhos)^[14] with 4-iodobenzonitrile (25 °C, 16 h) gave the arylated acetal **3g** in 75% yield (dr = 95:5).

Similarly, the sterically hindered dimethyl-substituted iodooxanyl acetal **4**^[9a] underwent the iron-catalyzed zincation at 50 °C giving the diastereomeric zinc species *syn-5a* and *anti-5b*. Iodolysis gave two separable diastereomers *syn-6a* (26%) and *anti-6b* (52%) after column chromatographical purification (Scheme 2). The relative stereochemistry of *syn-6a* and *anti-6b* was proved by NOE-NMR and X-Ray analyses^[15,16] (Figure 1). Subsequent Fe-catalyzed iodine-zinc exchange reaction of *syn-6a* and *anti-6b*



Scheme 2. Diastereomerically enriched products **7a–b** and **8a–c** obtained after an iron-catalyzed zincation of **4** followed by different trapping reactions. Reaction conditions: (i) Et₂Zn (2 equiv.), 10% Fe(acac)₃, NMP (10 equiv.), THF, 50 °C, 8 h. (ii) I₂, 25 °C, 1 h, separation of diastereomers. (iii) Electrophile (3 equiv.).

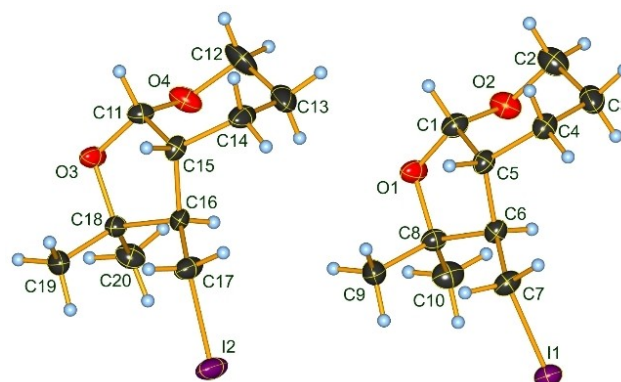
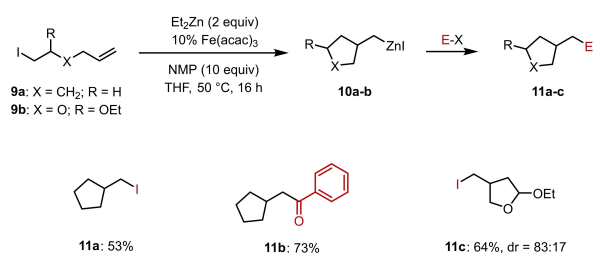


Figure 1. Molecular structure of the alkyl iodide *anti-6b* in the crystal. View of the two crystallographically independent molecules.^[14,15]

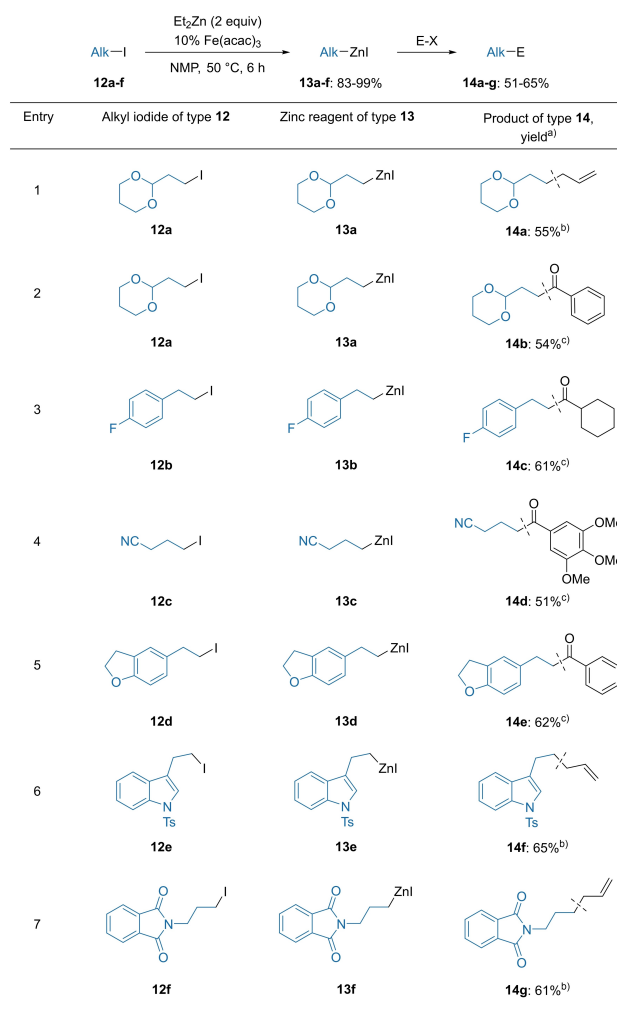
under the same conditions, followed by various trapping reactions led to functionalized dimethyltetrahydrofurans **7a–b** and **8a–c**. Thus, allylation of **5a** or **5b** with allyl bromide in the presence of 20 mol% of $\text{CuCN}\cdot 2\text{LiCl}$ gave alkenes **7a** and **8a** in 61–86% yield ($\text{dr}=99:1$). Transmetalation of **5a** or **5b** with stoichiometric amounts of $\text{CuCN}\cdot 2\text{LiCl}$ followed by the addition of benzoyl chloride, *tert*-butylacetyl chloride or 4-nitrobenzoyl chloride gave the ketones **7b** and **8b–c** in 58–95% yield ($\text{dr}=99:1$).

We have extended this I/Zn-exchange to alkenyl iodides **9a** and **9b**^[7c] (Scheme 3). Thus, 6-iodohex-1-ene (**9a**) underwent the I/Zn-exchange at 50 °C instead of –20 °C in the case of the diastereoselective ring closure (Table 1 and Scheme 1) leading to the corresponding zinc species **10a** which after iodolysis afforded cyclopentylmethyl iodide **11a** in 53% yield. These harsher conditions may be due to the generation of an intermediate primary alkyl radical which is less stable than a secondary alkyl radical. The copper-derivative of **10a** obtained by adding $\text{CuCN}\cdot 2\text{LiCl}$ (as 1 M solution in THF; 1 equiv.) was acylated with benzoyl chloride (3 equiv., –40 °C, 3 h) and gave ketone **11b** in 73% yield. Iodoacetal **9b** provided after an iron-catalyzed I/Zn-exchange the zinc species **10b** which after iodolysis furnished the iodide **11c** in 64% yield ($\text{dr}=83:17$).

Additionally, a range of functionalized primary alkyl iodides **12a–f** underwent an iron-catalyzed zincation within 6 h at 50 °C in NMP as solvent leading to alkylzinc iodides **13a–f** in 83–99% yield.^[15] After various trapping reactions with typical electrophiles, we have obtained the expected products **14a–g** in 51–65% yield (Scheme 4). Thus, (2-(1,3-dioxan-2-yl)ethyl)zinc iodide **13a** was trapped with allyl bromide in the presence of 5 mol% of $\text{CuCN}\cdot 2\text{LiCl}$ giving the allylated product **14a** in 55% yield. Acylation of copper derivatives of **13a–d**, obtained by addition of $\text{CuCN}\cdot 2\text{LiCl}$ (1 M solution in THF; 1 equiv.), with various acyl chlorides gave ketones **14b–e** in 51–62% yield. Interestingly, alkyl iodides containing heteroaryl moieties (**12e–f**) readily underwent the I/Zn-exchange and after allylations with allyl



Scheme 3. Iron-catalyzed I/Zn-exchange of alkenyl iodides of type **9**.

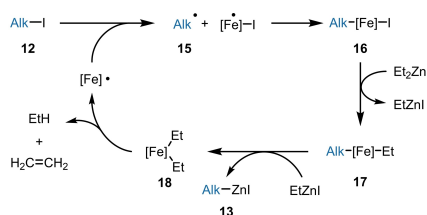


Scheme 4. Iron-catalyzed zincation of primary alkyl iodides (**12a–f**) followed by quenching reactions with electrophiles leading to products **14a–g**. Reaction conditions: a) isolated yield of analytically pure products; b) allyl bromide (1.5 equiv.), $\text{CuCN}\cdot 2\text{LiCl}$ (5 mol%), –20 °C to 25 °C, 2 h; c) $\text{CuCN}\cdot 2\text{LiCl}$ (1.0 equiv.), acyl chlorides (1.2–3.0 equiv.), –40 °C to 25 °C, 3 h.

bromide in the presence of 5 mol% of $\text{CuCN}\cdot 2\text{LiCl}$ gave the expected alkenes **14f–g** in 61–65% yield.

Although no detailed mechanistic studies have been performed, we propose the following mechanism in which the iron-catalyst converts the alkyl iodide **12** into an alkyl radical **15** which by recombination afforded alkyl-iron intermediate **16**. Subsequently, iron species **17** was produced *via* ligand exchange with Et_2Zn which after transmetalation generated the diethyl iron intermediate **18** (which decomposed to ethane and ethylene) and alkylzinc iodide **13** (Scheme 5).

In summary, we have reported a new practical iron-catalyzed I/Zn-exchange reaction allowing the conversion of primary and tailored secondary alkyl iodides^[17] to the corresponding alkylzinc reagents. In



Scheme 5. Tentative radical mechanism for the iron-catalyzed preparation of alkylzinc iodides (**13**) from alkyl iodides (**12**).

the presence of a remote double bond at position 5, a highly diastereoselective cyclization took place. All the prepared zinc reagents were trapped with allylic bromides, acid chlorides or aryl iodides in the presence of copper- or palladium catalysts.

Experimental Section

Typical Experimental Procedure for the Synthesis of **14d**

A dry and argon flushed Schlenk-tube, equipped with a magnetic stirring bar and a septum, was charged with 4-iodobutyronitrile (**12c**; 98 mg, 0.5 mmol), Fe(acac)₃ (18 mg, 0.05 mmol) and dry NMP (1.0 mL). Then a 1.0 M solution of Et₂Zn in toluene (1.0 mL, 1.0 mmol) was added *via* syringe at 50 °C. After the zincation was complete as checked by GC-analysis of reaction aliquots (6 h, 83% GC-yield), a 1.0 M CuCN·2LiCl solution in THF (0.5 mL, 0.5 mmol) was added at –40 °C and the mixture was stirred for 30 min. Then, 3,4,5-trimethoxybenzoyl chloride (231 mg, 1.0 mmol) was added and the reaction mixture was allowed to warm to room temperature within 3 h. After the reaction was completed, the mixture was quenched with an aq. sat. NH₄Cl solution and extracted with ethyl acetate (3 × 20 mL). The organic phase was then dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica (hexanes/ethyl acetate 7:3 → 6:4) to afford the desired product **14d**. Colorless crystals (56 mg, 51%); m.p.: 92.2–93.9 °C. ¹H-NMR (400 MHz, CDCl₃): δ = 7.20 (s, 2H), 3.91 (d, *J* = 1.4 Hz, 9H), 3.14 (t, *J* = 6.8 Hz, 2H), 2.52 (t, *J* = 6.9 Hz, 2H), 2.10 (p, *J* = 6.8 Hz, 2H). ¹³C-NMR (100 MHz, CDCl₃): δ = 197.1, 153.2, 142.9, 131.8, 119.6, 105.5, 61.1, 56.4, 36.1, 20.0, 16.7. HRMS (EI, 70 eV) *m/z*: [M]⁺ Calcd for C₁₄H₁₇NO₄: 263.1158; found: 263.1149.

Acknowledgements

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- [15] See Supporting Information.
- [16] CCDC-2201809 (*anti-6b*) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.
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