Dimerization of Benzyl and Allyl Halides via Photoredox-Mediated Disproportionation of Organozinc Reagents

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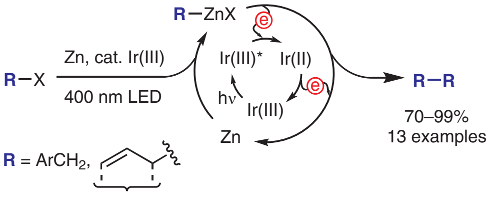

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Abstract Benzyl and allyl halides undergo homocoupling when treated with zinc in the presence of a catalytic amount of a cationic iridium(III) complex under irradiation with 400 nm light-emitting diodes. The reaction proceeds through the intermediate formation of an organozinc reagent, which disproportionates to a free radical and elemental zinc under photoredox conditions.

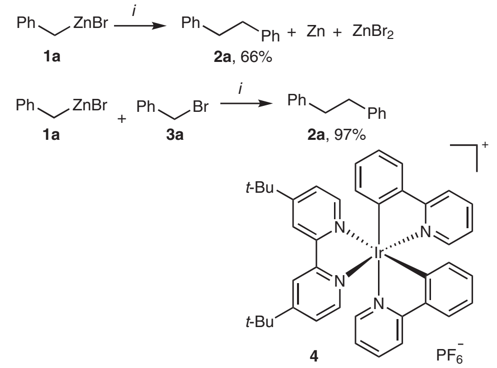
Key words organozinc reagents, homocoupling, photoredox, free radicals, organic halides

Organozinc compounds have emerged as valuable nucleophilic reagents with their applications spanning from carbonyl addition to cross-couplings.[1] A classic method for the preparation of organozincs is the reaction of an organic halide with elemental zinc. The driving force of this transformation is determined by the electropositive nature of the metal, which strives to lose electrons upon moving from a zero-valent to a two-valent state, with the latter being stabilized by solvation. The reverse process of the formation of elemental zinc from organozincs is, apparently, endergonic, and to be effected, the input of energy is required to overcompensate for the thermodynamically disadvantageous reaction.

Photoredox catalysis has gained increasing attention in recent years.[2] The use of visible light provided by readily available light sources such as household bulbs or light-emitting diodes is a key feature of the method. In these reactions, the energy of photons harvested by a sensitizer (a transition-metal complex or an organic dye) is used to drive a reaction either by electron-transfer or energy-transfer mechanisms.

The reduction of zinc(II) salts to zinc using triethylamine as a stoichiometric reducing agent upon irradiation in the presence of a photosensitizer has been reported.[3] Herein, we describe an observation that zinc metal can be formed from organozinc halides in a disproportionation process mediated by light, and apply this phenomenon to reductive coupling of benzyl bromides.[4–6]

Benzylzinc bromide (**1a**) was selected as a model reagent, and its solution in tetrahydrofuran was irradiated with 400 nm light-emitting diodes in the presence of 0.25 mol% of the iridium catalyst, Ir(dtbbpy)(ppy)$_2$ PF$_6$ (**4**) (Scheme 1). Analysis of the reaction mixture allowed the identification of diphenylethane **2a**, which was formed in 66% yield (GC analysis with an internal standard). In addition, a precipitate of elemental zinc was formed! When an additional equivalent of benzyl bromide (**3a**) was added to starting organozinc **1a**, the homocoupling product **2a** was isolated in 97% yield. A blank experiment indicated that the latter reaction does not proceed without light.



Scheme 1 Disproportionation reaction. *Reagents and conditions*: (*i*) Ir(dtbbpy)(ppy)$_2$ PF$_6$ (**4**) (0.25 mol%), 400 nm LED, THF, rt, 5 h.

Since zinc reacts readily with benzylic and allylic halides, we decided to carry out reductive homocoupling of these substrates using zinc as a stoichiometric reducing agent (Table 1). Various benzyl bromides provided the corresponding products **2** in good yields. Functional groups such as ester, nitrile, and a boryl fragment, as well as aromatic bromide, were tolerated. Allylic chlorides and bromides also worked well leading to 1,5-dienes **2k** and **2l** (entries 11 and 12). At the same time, secondary and tertiary iodides were notably less efficient. For example, in the reaction of iodocyclohexane, less than 10% of homocoupled product was formed, while for 1-iodoadamantane, no product was detected. However, an α,α-difluorinated iodide (2,2-difluoro-2-iodoethyl)benzene gave product **2m** in reasonable yield (entry 13).

Table 1 Reductive Homocoupling

$$\underset{\mathbf{3}}{\mathrm{R{-}X}} \xrightarrow[\text{THF, 400 nm LED, rt, 5 h}]{\text{Zn (0.75 equiv), } \mathbf{4} \text{ (0.25 mol\%)}} \underset{\mathbf{2}}{\mathrm{R{-}R}}$$

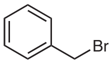
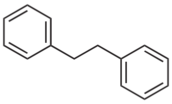
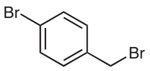
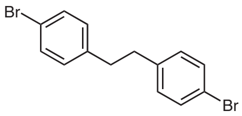
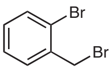
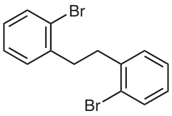
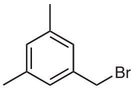
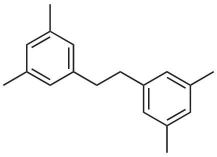
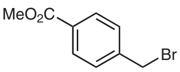
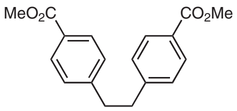
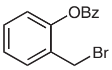
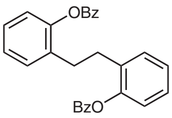
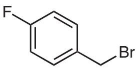
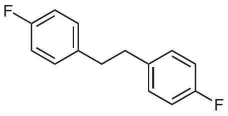
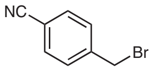
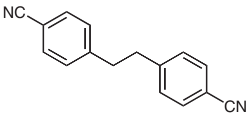
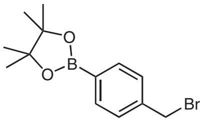
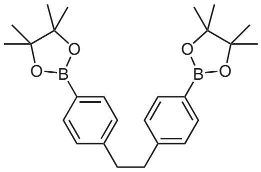
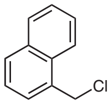
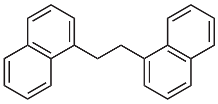
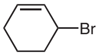
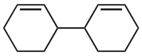
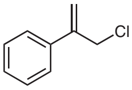
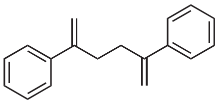
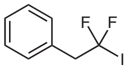
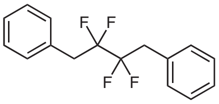
Entry	Substrate	Product		Yield (%)[a]
1		**2a**		85
2		**2b**		75
3		**2c**		87
4		**2d**		77
5		**2e**		86
6		**2f**		78
7		**2g**		80
8		**2h**		70

Table 1 (continued)

Entry	Substrate	Product	Yield (%)[a]
9		**2i** 	71
10		**2j** 	99
11		**2k** 	81
12		**2l** 	95
13		**2m** 	60

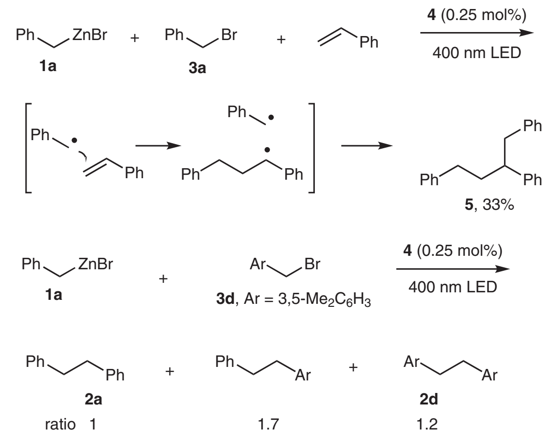
[a] Yield of isolated product.

While tetrahydrofuran was routinely used as the solvent, the reaction was evaluated in other media. Thus, for the model homocoupling of benzyl bromide **3a**, acetonitrile was similarly effective (85% yield), while in diethyl ether and dimethylformamide product **2a** was formed in decreased yields of 76% and 51%, respectively.

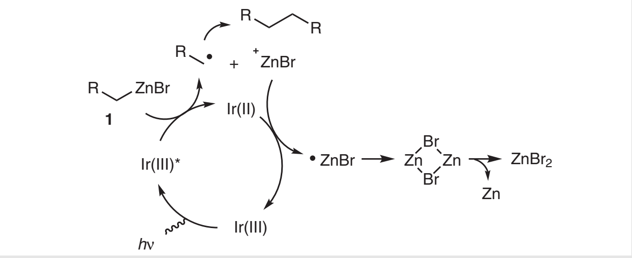
Concerning the mechanism of the formation of the homocoupling products, it is likely that under the reaction conditions the organozinc reagent serves as a source of the corresponding free radical, which is dimerized. In support of this mechanism, when styrene was added to a mixture of **1a** and **3a**, the photochemical reaction furnished compound **5** resulting from the addition of a benzyl radical to styrene with subsequent recombination of two radicals (Scheme 2). Furthermore, GC–MC analysis indicated formation of oligomers arising from consecutive addition of several styrene molecules to benzyl radicals. A crossover experiment verified the scrambling of benzyl fragments when the starting organozinc and bromide possessed different groups. Thus, irradiation of the combination of reagents **1a** and **3d** in the presence of the photocatalyst provided a statistical ratio of the three possible products.

A proposed mechanism for the formation of elemental zinc is shown in Scheme 3. In the first step, the light-activated iridium(III) complex undergoes reductive quenching by oxidation of organozinc reagent **1** generating the free radical and a cationic zinc species.[7] Subsequent reduction of Zn(II) to Zn(I) is effected by the strongly reducing Ir(II) complex [Ir(II)/Ir(III) –1.51 V vs SCE],[2a] thereby completing the redox cycle. Finally, disproportionation of Zn(I), which may proceed through a bridged dimer, affords zero-valent zinc along with the zinc(II) salt.

In summary, a convenient method for the homodimerization of benzylic and allylic halides is described. The reaction involves the use of zinc as a stoichiometric reduc-



Scheme 2 Mechanistic experiments



Scheme 3 Proposed mechanism

ing agent in the presence of a light-activated iridium catalyst. The disproportionation of the organozinc halide under photoredox conditions is believed to be a key feature responsible for the reaction efficiency.

Benzyl bromides **3**,[8] (2,2-difluoro-2-iodoethyl)benzene,[8] benzylzinc bromide,[8] 3-chloro-2-phenyl-1-propene,[9] and the photocatalyst, [Ir(dtbbpy)(ppy)$_2$ PF$_6$],[10] were obtained according to literature procedures. All reactions were performed under an argon atmosphere. Hexane and EtOAc were purchased from commercial suppliers and distilled before use. Tetrahydrofuran was distilled from lithium aluminum hydride prior to use. Column chromatography was performed using Macherey-Nagel silica gel (0.040-0.063 mm). Reactions were irradiated using 400 nm LEDs, the strip of diodes 2x smd 3528 (Arlight RT 2-5000 12V UV400 2X). Melting points were obtained using a Stuart SMP30 apparatus. IR spectra were recorded on a Bruker alpha-T spectrophotometer. NMR spectra were recorded on a Bruker AM 300 MHz spectrometer in CDCl$_3$ using the residual solvent signal as an internal standard. Elemental analysis was performed using a Perkin-Elmer 2400 CHN analyzer.

Homocoupling of Benzylzinc Bromide (1a)

In a test tube, a solution of benzylzinc bromide (**1a**) (0.5 mL of a 2.0 M solution in THF, 1.0 mmol) was diluted with THF (0.5 mL) followed by addition of Ir(dtbbpy)(ppy)$_2$ PF$_6$ (2 mg, 0.0025 equiv). The reaction mixture was stirred under irradiation with a strip of 400 nm LEDs for 5 h, with water cooling to maintain the reaction temperature around 23–25 °C. The mixture was analyzed by GC (using 4-fluorotoluene as the internal standard) which indicated a 66% yield of **2a**. To isolate zinc, the mixture was centrifuged and the zinc dust was washed twice with EtOH and dried (43 mg, 65% yield).

Coupling of Benzyl Bromide with Benzylzinc Bromide

Benzylzinc bromide (**1a**) (0.6 mL of a 2.0 M solution in THF, 1.2 mmol, 1.2 equiv), THF (0.6 mL), benzyl bromide (**3a**) (1.0 mmol, 1.0 equiv) and Ir(dtbbpy)(ppy)$_2$ PF$_6$ (2 mg, 0.0025 equiv) were successively added to a test tube equipped with a stir bar. The reaction mixture was stirred under irradiation with a strip of 400 nm LEDs for 5 h, with water cooling to maintain the reaction temperature around 23–25 °C. For the work-up, H$_2$O (5 mL) was added and the mixture was extracted with hexane (3 × 7 mL). The combined extracts were filtered through Na$_2$SO$_4$, concentrated under vacuum, and the residue was purified by column chromatography on silica gel eluting with hexane to afford 1,2-diphenylethane (**2a**) (177 mg, 97% yield).[11]

Homocoupling of Organic Halides; General Procedure

THF (1.5 mL), organic halide **3** (1.5 mmol, 1.0 equiv) and Ir(dtbbpy)(ppy)$_2$ PF$_6$ (3.5 mg, 0.0025 equiv) were successively added to a test tube containing Zn dust (73 mg, 1.125 mmol, 0.75 equiv). The reaction mixture was stirred under irradiation with a strip of 400 nm LEDs for 5 h, with water cooling to maintain the reaction temperature around 23–25 °C. For the work-up, H$_2$O (5 mL) was added and the mixture was extracted with hexane (3 × 7 mL). The combined extracts were filtered through Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified by flash chromatography eluting with hexane/EtOAc.

1,2-Diphenylethane (2a)[11]

Yield: 116 mg (85%); white solid; mp 52–53 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.25 (m, 10 H), 2.95 (s, 4 H).

1,2-Bis(4-bromophenyl)ethane (2b)[5e]

Yield: 191 mg (75%); white solid; mp 108–112 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.40 (d, *J* = 8.3 Hz, 4 H), 7.00 (d, *J* = 8.3 Hz, 4 H), 2.86 (s, 4 H).

1,2-Bis(2-bromophenyl)ethane (2c)[5e]

Yield: 221 mg (87%); white solid; mp 82–83 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.46 (d, *J* = 7.8 Hz, 2 H), 7.15–7.06 (m, 4 H), 7.02–6.94 (m, 2 H), 2.95 (s, 4 H).

1,2-Bis(3,5-dimethylphenyl)ethane (2d)[12]

Yield: 137 mg (77%); white solid; mp 75–76 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.87 (s, 6 H), 2.82 (s, 4 H), 2.33 (s, 12 H).

Dimethyl 4,4′-(Ethane-1,2-diyl)dibenzoate (2e)[5e]

Yield: 192 mg (86%); yellowish crystalline solid; mp 119–120 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.95 (d, *J* = 8.1 Hz, 4 H), 7.20 (d, *J* = 8.1 Hz, 4 H), 3.91 (s, 6 H), 3.00 (s, 4 H).

Ethane-1,2-diylbis(2,1-phenylene) Dibenzoate (2f)[13]

Yield: 247 mg (78%); white solid; mp 123.5–125.5 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.15 (d, *J* = 7.8 Hz, 4 H), 7.71–7.43 (m, 6 H), 7.18–7.03 (m, 8 H), 2.90 (s, 4 H).

1,2-Bis(4-fluorophenyl)ethane (2g)[5e]

Yield: 130 mg (80%); white solid; mp 92–93 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.09 (dd, *J* = 8.6, 5.5 Hz, 4 H), 6.96 (dd, *J* = 8.6, 8.6 Hz, 4 H), 2.88 (s, 4 H).

^{19}F NMR (282 MHz, CDCl$_3$): δ = 118.2 (tt, *J* = 8.6, 5.5 Hz, 2 F).

1,2-Bis(4-cyanophenyl)ethane (2h)[14]

Yield: 122 mg (70%); white crystals; mp 199–202 °C.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.57 (d, *J* = 8.1 Hz, 4 H), 7.23 (d, *J* = 8.1 Hz, 4 H), 3.01 (s, 4 H).

1,2-Bis[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethane (2i)[15]

Yield: 231 mg (71%); white crystals; mp 219–220 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.7 Hz, 4 H), 7.21 (d, *J* = 7.7 Hz, 4 H), 2.95 (s, 4 H), 1.37 (s, 24 H).

1,2-Di(naphthalen-1-yl)ethane (2j)[16]

Yield: 207 mg (99%); white solid; mp 150–157 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.9 Hz, 2 H), 7.92 (d, *J* = 7.1 Hz, 2 H), 7.78 (d, *J* = 7.9 Hz, 2 H), 7.61–7.49 (m, 4 H), 7.48–7.34 (m, 4 H), 3.55 (s, 4 H).

[1,1′-Bi(cyclohexane)]-2,2′-diene (2k)[17]

Yield: 115 mg (81% yield); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (1:1 mixture of diastereoisomers) = 5.79–5.68 (m, 2 H), 5.67–5.52 (m, 2 H), 2.22–2.06 (m, 2 H), 2.05–1.92 (m, 4 H), 1.84–1.64 (m, 4 H), 1.62–1.44 (m, 2 H), 1.43–1.25 (m, 2 H).

2,5-Diphenyl-hexa-1,5-diene (2l)[18]

Yield: 166 mg (95%); yellowish solid; mp 41–43 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.20 (m, 10 H), 5.30 (s, 2 H), 5.06 (s, 2 H), 2.67 (s, 4 H).

(2,2,3,3-Tetrafluorobutane-1,4-diyl)dibenzene (2m)

Yield: 127 mg (60%); white crystalline solid; mp 127.0–127.5 °C.

IR (film): 3031, 1496, 1456, 1438, 1352, 1246, 1158, 1085, 1051, 973, 903, 767, 708, 540, 530 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 10 H), 3.35 (tt, *J* = 20.2, 6.3 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 130.9, 128.4, 127.7, 118.0 (tt, *J* = 250.5, 37.7 Hz), 36.4 (m).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –114.0 (m, 4 F).

Anal. Calcd for $C_{16}H_{14}F_4$: C, 68.08; H 5.00. Found: C, 67.97; H, 5.04.

1,2,4-Triphenylbutane (5)

Benzylzinc bromide (**1a**) (0.6 mL of a 2.0 M solution in THF, 1.2 mmol, 1.2 equiv), THF (0.6 mL), styrene (180 μL, 1.2 mmol, 1.2 equiv), benzyl bromide (**3a**) (1.0 mmol, 1.0 equiv) and Ir(dtbbpy)$(ppy)_2$ PF_6 (1.75 mg, 0.0025 equiv) were successively added to a test tube equipped with a stir bar. The reaction mixture was stirred under irradiation with a strip of 400 nm LEDs for 5 h, with water cooling to maintain the reaction temperature around 23–25 °C. For the work-up, H_2O (5 mL) was added and the mixture was extracted with hexane (3 × 7 mL). The combined extracts were filtered through Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography eluting with hexane to afford 1,2,4-triphenylbutane (**5**)[19] (94 mg, 33% yield) as a colorless oil, which solidified on storage; mp 28–29 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.01 (m, 15 H), 3.01–2.86 (m, 3 H), 2.61–2.40 (m, 2 H), 1.93 (m, 2 H).

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