

Transition-Metal-Free Carboxylation of Organozinc Reagents Using CO₂ in DMF Solvent

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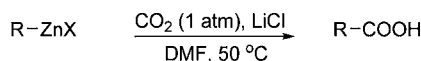
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ABSTRACT

Transition Metal - Free Process



R = Aryl, Alkyl, Alkenyl

An efficient process for the carboxylation of functionalized organozinc reagents with CO₂ under transition-metal-free conditions was developed by employing DMF solvent in the presence of LiCl.

The reaction of nucleophiles with carbon dioxide is one of the most important processes for fixation of CO₂.¹ Highly reactive nucleophiles such as organolithiums and organomagnesium reagents have been used for the reaction with CO₂, which is a relatively less reactive electrophile. Transition-metal-catalyzed addition reaction of carbon nucleophiles toward CO₂ has attracted attention, and recently some important progress has been made toward the carboxylation of organozinc compounds and organoboron compounds.² Oshima et al.^{2a} and Dong et al.^{2b} independently reported nickel- and palladium-catalyzed carboxylation of organozinc reagents with CO₂, and these methods provided a new access to various functionalized aryl and alkyl carboxylic acids. The use of transition-metal catalysts seemed to be essential for

the carboxylation of organozinc compounds in the reports, but we are pleased to report a simple transition-metal-free process by employing a polar aprotic solvent, DMF.

Organozinc reagents have been widely used as soft nucleophiles in organic synthesis, and the control of the nucleophilicity is highly important for desired selective transformations.³ Various methods have been utilized for promoting the reactivity of organozinc compounds, and conventionally ate complexation or transmetalation has been employed.³ On the other hand, solvent is one of the most important parameters in organic reaction. The solvent effects of organometallic reactions have been studied from various viewpoints,⁴ not only on the improvement of solubility of metal salt but also on the change of the oligomeric complex structures, on acceleration of the reaction, and on the reaction selectivity. These effects are considered to depend on the physicochemical nature of solvents (polarity, donor number, and acceptor number, etc.). Therefore, it is an attractive research subject to investigate the relationship between the

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solvents and reactivities of organometallic reagents. We recently reported an allene synthesis using the dramatic effect of DMSO on the reaction of propargyl electrophiles with organozinc reagents, which proceeds in the absence of transition-metal catalyst.⁵ In connection with our recent studies on the reactivity control of organozinc reagents,⁶ we focused our interest on solvent effects for promoting the reactivity of organozinc reagents toward carbon dioxide.

Table 1. Carbonylation of Phenylzinc Iodide

entry	solvent	LiCl (equiv)	<i>T</i> (°C)	yield (%)
1	THF	0	rt	2 ^a
2	THF	2.8	rt	15 ^a
3	CH ₃ CN	2.8	rt	34 ^a
4	DMSO	2.8	rt	40 ^a
5	DMA	2.8	rt	34 ^a
6	DMF	2.8	rt	61 ^b
7	DMF	2.8	50	88 ^b

^a Determined by ¹H NMR. ^b Isolated yield.

First, the reaction of phenylzinc iodide⁷ with CO₂ (1 atm) was examined in various solvents as shown in Table 1. As has been known, the reaction in THF was very slow, and only a trace of benzoic acid (**2a**) was detected after the reaction under CO₂ atmosphere at room temperature for 24 h (entry 1). When LiCl was present as an additive of PhZnI solution which was prepared from PhI and Zn in the presence of LiCl in THF,⁸ the reaction was slightly promoted and the carboxylation proceeded in 15% yield (entry 2). We next focused our attention on solvent effect, and other polar solvents were examined in the presence of LiCl additive. The use of CH₃CN gave a 34% yield of benzoic acid (**2a**) (entry 3), DMSO promoted the reaction, and the yield increased to 40% (entry 4). DMA showed similar promotion in a yield of 34% (entry 5), but to our surprise, DMF showed significant promotion with a yield of 61% (entry 6). When the reaction was carried out at 50 °C, the carboxylic acid (**2a**) was obtained in 88% yield (entry 7).

Using these optimized reaction conditions, the reaction of various functionalized arylzinc iodide with 1 atm of CO₂ was examined. As summarized in Table 2, various arylzinc iodides substituted with an electron-donating or electron-withdrawing group were converted into the corresponding aryl carboxylic acids (**2b–f**) in good to excellent yields (entries 1–5). One of the most important advantages over the transition-metal-catalyzed process is the compatibility of halogen substituents with arylzinc iodides, and halogen-substituted benzoic acids (**2g–i**) were obtained in reasonable yields (entries 6–8).

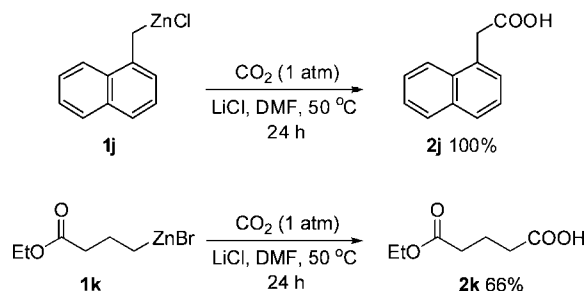
Table 2. Carbonylation of Substituted Arylzinc Iodides

entry	R	time (h)	yield ^a (%)
1	<i>p</i> -OMe (b)	24	73
2	<i>p</i> -Me (c)	24	89
3	<i>m</i> -Me (d)	24	78
4	<i>o</i> -Me (e)	24	56
5	<i>p</i> -COOEt (f)	48	53
6	<i>p</i> -Cl (g)	24	69
7	<i>p</i> -Br (h)	48	98
8	<i>p</i> -I (i)	48	70

^a Isolated yield.

In order to examine further scope and limitations, the carboxylation reactions of other alkyl- and alkenylzinc halides were investigated. These organozinc reagents were prepared from organic halides and Zn in the presence of LiCl.⁸ 1-Naphthylmethylzinc chloride (**1j**) was smoothly converted to the corresponding carboxylic acid (**2j**) in 100% yield (Scheme 1).

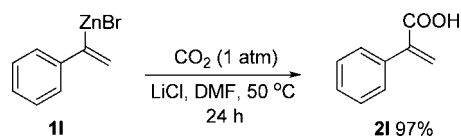
Scheme 1. Carbonylation of Alkylzinc Halides



The carboxylation of the alkylzinc reagent bearing an ethoxycarbonyl group also proceeded smoothly in DMF to give the carboxylic acid (**2k**) in 66% yield (Scheme 1).

Reaction of alkenylzinc reagents also proceeded under similar reaction conditions, and α -styrylzinc bromide (**1l**) was converted to the corresponding carboxylic acid (**2l**) in 97% yield (Scheme 2).

Scheme 2. Carbonylation of Alkenylzinc Bromide

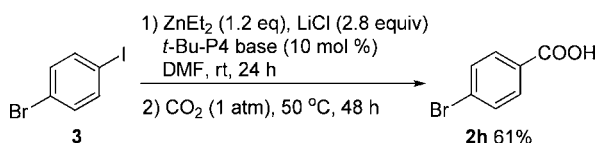


Halogen–zinc exchange has also been used for selective zincation of functionalized aromatic halides, and we recently

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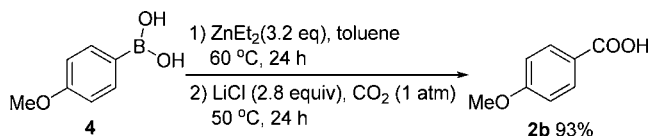
reported phosphazene base-promoted zincation using diethylzinc.^{6c} Using this method, *p*-bromiodobenzene (**3**) was selectively monozincated, and the bromophenylzinc was carboxylated smoothly in DMF in the presence of LiCl to give *p*-bromobenzoic acid (**2h**)(Scheme 3).

Scheme 3. Carbonylation of Aromatic Zinc Compound Prepared by Halogen–Zinc Exchange Reaction



Arylboronic acids have been known as important precursors for the preparation of arylzinc compounds, and the boron–zinc exchange reaction with diethylzinc has been employed.⁹ The *p*-methoxyphenylzinc compound derived from *p*-methoxyphenylboronic acid (**4**) was also easily carboxylated to give *p*-methoxybenzoic acid (**2b**) in excellent yield (Scheme 4).

Scheme 4. Carbonylation of Aromatic Zinc Compound Prepared by Boron–Zinc Exchange Reaction



The solvent polarity (E_T)¹⁰ of DMF (43.8) is largely similar to CH_3CN (45.6) and DMSO (45.1). On the other hand, the donor numbers (DN)¹¹ of DMF (26.6) and DMSO (29.8) are higher values than that of CH_3CN (14.1). The higher DN solvents gave the better results than the lower DN solvents,

but DMF showed further better performance than DMSO, contrary to our expectations. The anionic character of organozinc in DMF is considered to be lower than that in DMSO,¹² and the solubility of CO_2 in a solvent may also relate to the effectiveness of the carboxylation.

In conclusion, the carboxylation of organozinc reagents using 1 atm of CO_2 was achieved under transition-metal-free conditions in DMF solvent. Further investigations on the scope and limitation of the carboxylation and mechanistic studies are underway.

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Supporting Information Available: Experimental details and spectra of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) ^1H NMR Chemical shifts of Me_2Zn δ ppm: –0.99 (DMSO), –0.88 (DMF), –0.84 (THF).