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Highly selective and efficient conversion of aryl bromides to *t*-butyl benzoates with di-*t*-butyl dicarbonate

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Abstract

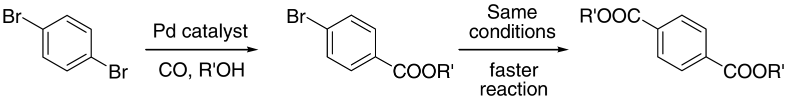
t-Butyl benzoates can be accessed from aromatic compounds bearing multiple halogen substituents via selective metal–halogen exchange with lithium tri-*n*-butylmagnesium ate complex followed by trapping with di-*t*-butyl dicarbonate.

Over the recent years, transition metal-catalyzed carbonylation reactions have become the method of choice to prepare benzoate esters from aryl bromides.[1] These methods represent an improvement over other methodologies in terms of yields and substrate scope. Alternative methods involving metallation or metal–halogen exchange, followed by trapping of the resulting organometallic species with carbon dioxide, methyl chloroformate[2] or dimethyl carbonate,[3] often required cryogenic conditions and afforded products with variable yields.[4]

One of the limitations of transition metal-catalyzed carbonylations has been the lack of selectivity for the monocarbonylation of substrates containing multiple halogen substituents. On these substrates, the product of the first carbonylation reaction is more reactive to carbon–halogen bond insertion than the starting aryl halide and it becomes very difficult to achieve selectivity in the reaction (Scheme 1).[5]

Cassar et al.[6] showed that, under very controlled Pd-catalyzed carbonylation conditions, it was possible to prepare 4-bromobenzoic acid in 90% yield from 1,4-dibromobenzene. The key to obtaining high selectivity in this reaction was a slow addition of the substrate under phase transfer conditions. Under these reaction conditions, the product of the first carbonylation reaction was extracted as a carboxylate salt into the aqueous layer, thus being unavailable for a second palladium insertion (Scheme 2).

Lee et al.[7] recently explored a possible solution to this problem. They carried out the direct metallation of 1,4-dibromobenzene with 2.5 equiv of magnesium under sonication conditions, followed by trapping of the resulting Grignard with diethyl dicarbonate in the presence of Lewis acids. With this method, they obtained ethyl 4-bromobenzoate in 92% yield, with only 3% of diethyl terephthalate. Lower selectivities were obtained with other dibromides studied.



Scheme 1.

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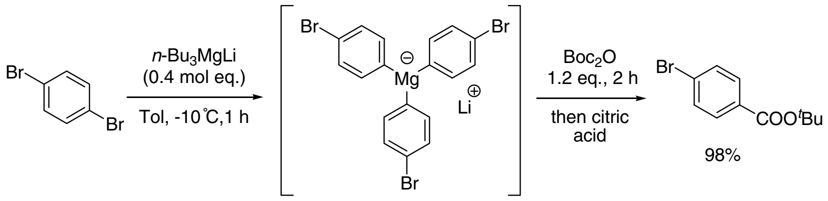
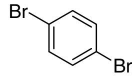
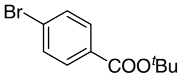
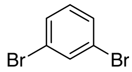
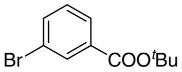
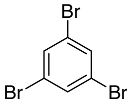
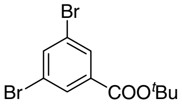
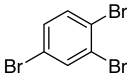
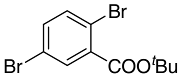
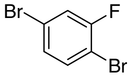
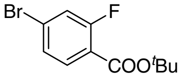
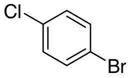
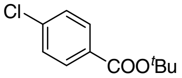
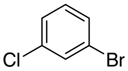
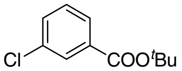
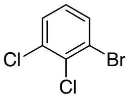
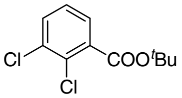
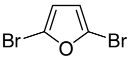
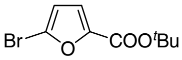
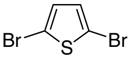
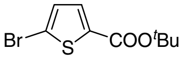
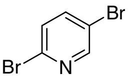
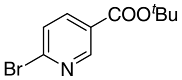
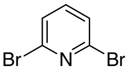
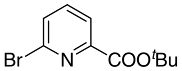
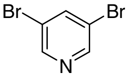
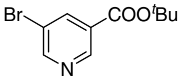
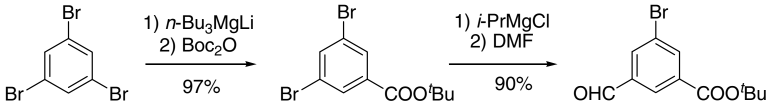


Scheme 2.

In an effort to improve the performance and selectivity of this transformation, we turned our attention to a report from Iida et al.[8] who showed good reactivity and very high selectivities for metal–halogen exchange reactions of dibromoarenes using lithium tri-*n*-butylmagnesium ate complex. We later discovered that di-*t*-butyl dicarbonate

Table 1
n-Bu$_3$MgLi-mediated mono-carboxylation of di and tribromoarenes and heteroarenes[9,10]

	Substrate	Conditions	Product	Yield (%)
1		Toluene, −5 °C		98
2		Toluene, −5 °C		98
3		Toluene, −5 °C		97
4		Toluene, −5 °C		71[11]
5		Toluene, −10 °C		92
6		Toluene, 0 °C		95
7		Toluene, −10 °C		99
8		Toluene, −10 °C		80
9		Toluene, −10 °C		84
10		Toluene, −10 °C		96
11		Toluene–THF[12] (1:1), −10 °C		66
12		Toluene–THF (1:1), −10 °C		0
13		Toluene–THF (1:1), −10 °C		0



Scheme 3.

is an excellent electrophile to trap triarylmagnesium ate complexes affording the desired *t*-butyl esters with complete selectivity and in very high yields. Contrary to the report by Lee, our reaction conditions do not require excess organometallics, sonication, or the use of Lewis acids to achieve good yields.

After some reaction optimization, we were able to perform the complete process in a one-pot operation under non-cryogenic conditions. In most cases, the products obtained did not require further purification and were obtained as colorless oils or solids that could be used in subsequent chemical steps. Lithium tri-*n*-butylmagnesium ate complex is generated in situ at −10 °C in toluene by mixing 1/3 mol equiv of *n*-butyl magnesium chloride with 2/3 mol equiv of *n*-butyl lithium. The resulting organometallic species has the capability to transfer all three butyl groups readily, making the process very efficient. A slight excess of organometallic species is typically used in our procedure to compensate for the use of reagent grade solvents rather than anhydrous grade. Despite this excess reagent, we have never observed byproducts arising from a double metal–halogen exchange reaction. Subsequent quenching of the triarylmagnesium ate complex with Boc anhydride also takes place at −10 °C and is typically complete in 2–3 h. Both chemical transformations can be monitored easily by HPLC. Once the reaction is judged complete by HPLC (<1% bromobenzene remaining), the addition of a 10% (w/w) citric acid solution causes the addition intermediate to collapse with evolution of CO_2.

We next examined the application of this protocol to other di- and trihaloarenes and heteroarenes. The results obtained are summarized in Table 1. The reaction performed very well on di- and tribromobenzenes **1**, **2** and **3**. The reaction of tribromobenzene **4** afforded *t*-butyl-2,5-dibromobenzoate as the major product in 71% yield.[11] Complete selectivity was observed on the reaction of 1,4-dibromo-2-fluorobenzene **5** to afford *t*-butyl-4-bromo-2-fluorobenzoate in 92% yield.

Substrates containing both chloro and bromo substituents (**6–8**) showed preference towards the bromide for metal–halogen exchange, affording the corresponding benzoates in high yields. Mixed results were obtained with dibromoheteroaromatic compounds. While furan **9**, thiophene **10** and pyridine **11** behaved well in the reaction, pyridines **12** and **13** decomposed completely upon the addition of Boc anhydride resulting in complex mixtures of products. This was a surprising outcome since both the substrates behaved well when submitted to the same metal–halogen exchange conditions followed by quenching with dimethylformamide.[8]

Although chemists tend to rely mostly on methyl or ethyl esters, the use of *t*-butyl esters may have advantages in some cases. The possibility of *t*-butylester hydrolysis under acidic conditions makes these compounds complimentary to simpler esters such as methyl or ethyl. Within the context of this chemistry, we have successfully used the *t*-butyl moiety as a protecting group for the ester functionality in subsequent Grignard chemistry. This is exemplified by the reaction of *t*-butyl-3,5-dibromobenzoate obtained by our method with *i*-propylmagnesium chloride followed by addition to dimethylformamide (Scheme 3).[13]

In summary, we have demonstrated that di-*t*-butyl dicarbonate is a good electrophile for additions to triarenemagnesium ate complexes. When coupled with the high selectivity for single metal–halogen exchange, this method is a practical solution to the limitation of transition metal-catalyzed carbonylations of arenes bearing multiple halogen substituents.

References and notes

1. See for example: (a) Skoda-Foldes, R.; Kollar, L. *Curr. Org. Chem.* **2002**, *6*, 1097–1119; (b) Beller, M.; Indolese, A. F. *Chimia* **2001**, *55*, 684–687.
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8. Iida, T.; Wada, T.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2001**, *42*, 4841–4844.
9. All compounds isolated gave consistent ^{1}H NMR, ^{13}C NMR and GCMS or LCMS data.
10. *Typical reaction procedure*; *Synthesis of t-butyl-3,5-dibromobenzoate*: *n*-Butyl lithium (7.2 mL, 18.0 mmol, 2.5 M in hexanes) was added to a 100 mL flask under nitrogen atmosphere containing 9 mL of toluene at −10 °C. *n*-Butylmagnesuim chloride (4.5 mL, 9.0 mmol, 2 M in THF) was then added at such a rate to keep the temperature <−5 °C. The resulting milky slurry was aged at −10 °C for 30 min. To this slurry was added 1,3,5-tribromobenzene (6.67 g, 21.2 mmol) dissolved in 20 mL of toluene. The rate of addition was such that the temperature did not increase above −5 °C. After the addition was complete, the mixture was kept at −10 °C until the metal–halogen reaction was complete (30 min to 2 h depending on the substrate). A solution of di-*t*-butyl dicarbonate (5.89 g, 27 mmol) in 7.5 mL of toluene was then charged such at a rate to keep the temperature <−5 °C. After the addition was complete, the mixture was kept at −10 °C until the aryl-Mg intermediate was completely

consumed (2–3 h). The mixture was quenched by the addition of 40 mL of a 10% (w/w) aqueous solution of citric acid, which resulted in an exotherm and generation of carbon dioxide. The phases were separated and the organic layer was washed with another 40 mL of citric acid solution. The organic extracts were then dried with $MgSO_4$ and the solvents were removed at reduced pressure. 6.93 g of *t*-butyl-3,5-dibromobenzoate (97% yield) were obtained as a brown oil which crystallized on standing. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.60 (s, 9H), 7.80 (d, $J = 1.7$ Hz, 1H), 8.03 (d, $J = 1.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 27.8, 82.4, 122.7, 131.1, 135.1, 137.6, 162.9.

11. 4.4% of an isomeric *t*-butyl-dibromobenzoate was detected in the crude reaction mixture by GCMS.
12. THF was required to dissolve the substrate.
13. *Synthesis of t-butyl-5-bromo-3-carboxybenzoate*: To a solution of *t*-butyl-3,5-dibromobenzoate (7.5 g, 20 mmol) in 50 mL of THF cooled in an ice bath to 3 °C was added *iso*-propyl magnesium chloride (17 mL, 34 mmol, 2 M in THF). The mixture turned dark and the temperature increased to 17 °C during the addition. When the addition was complete, the ice batch was removed and the mixture was kept at room temperature until the starting material was completely consumed (30 min to 1 h). The dark solution was cooled down to 3 °C with an ice bath and dimethylformamide (3.9 mL, 50 mmol) was added such at a rate to keep the temperature below 25 °C. The resulting mixture was aged for 30 min and then diluted with 50 mL of *t*-butylmethylether. The mixture was washed twice with 80 mL of a 20% (w/w) solution of citric acid. The organic layer was dried with $MgSO_4$ and the solvents were removed at reduced pressure. The crude red oil was purified by chromatography on silica gel (hexanes/*t*-butylmethylether) to obtain 5.15 g of *t*-butyl-5-bromo-3-carboxybenzoate (90% yield) as a pale yellow oil that crystallized on standing. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.61 (s, 9H), 8.15 (t, $J = 1.6$ Hz, 1H), 8.33 (t, $J = 1.6$ Hz, 2H), 8.37 (t, $J = 1.6$ Hz, 2H), 10.00 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 28.0, 82.6, 123.2, 129.5, 134.8, 135.0, 137.7, 137.8, 163.1, 189.9.