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Direct Formation of Secondary and Tertiary Alkylzinc Bromides

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

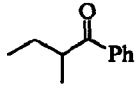
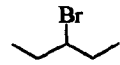

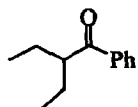

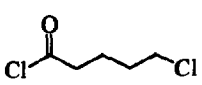
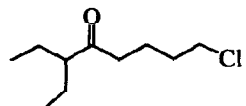
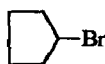

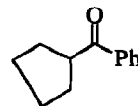
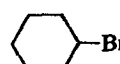

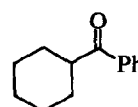
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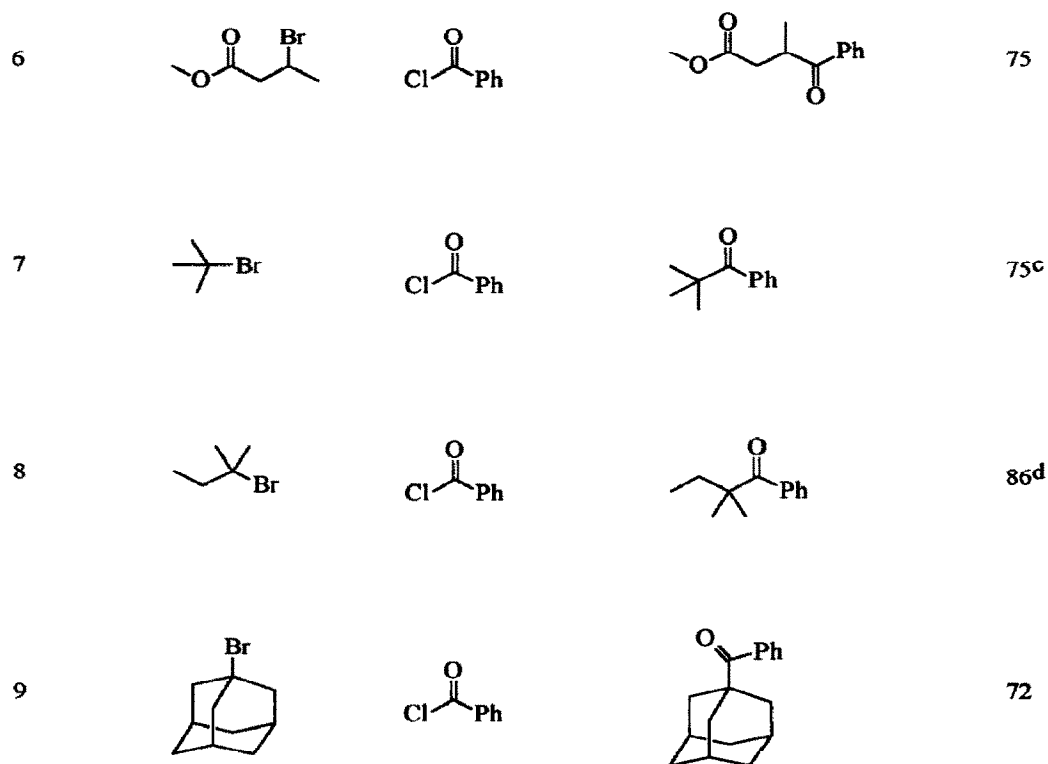
Abstract: The direct formation of secondary and tertiary alkylzinc bromides can be accomplished under mild conditions from the direct oxidative addition of Rieke zinc to secondary and tertiary alkyl bromides including remote functionalized halides.

In 1973, we reported a general approach for the preparation of highly reactive zinc.¹ This zinc allowed for the first time the oxidative addition to all primary alkyl bromides as well as to aryl iodides and even aryl bromides. In 1991, we published an improved method which was not only safer but also yielded a more reactive zinc.² Significantly, this approach provided a direct route to highly functionalized organozinc halide reagents from alkyl bromides, aryl iodides and bromides as well as vinyl iodides and bromides. A number of approaches for the direct reaction of alkyl iodides have been reported³ including some novel metathesis reactions.⁴ In this paper, we would like to report that Rieke zinc reacts directly with secondary and tertiary alkyl bromides to yield the corresponding organozinc reagents in near quantitative yields under mild conditions. Significantly, these bromides can contain a wide range of remote functional groups.

We have found that Rieke zinc readily yields alkylzinc bromides under mild conditions from the direct oxidative addition of Rieke zinc to secondary and tertiary alkyl bromides. This procedure obviates the need for the proximal functional group activation of the carbon-bromine bond⁵ and zinc insertion proceeds readily under mild conditions. 2-Butylzinc bromide can be generated from 2-bromobutane and Rieke zinc at ambient temperature, but the reaction time is conveniently reduced in refluxing THF to 2.5 h. This zinc reagent coupled with benzoyl chloride in high yield (95%) using the soluble copper cyanide/lithium bromide complex^{3c} catalytically (Table 1, entry 1). 2-Bromobutane was sufficiently reactive that Rieke zinc could be used stoichiometrically. For most cases, better success was achieved if 1.1 equivalents of the highly reactive zinc to the alkyl halide was used. After complete consumption of the alkyl halide the zinc was allowed to settle (ca. 4-6 h) and the cross-

Table 1. Formation and Coupling Reactions of *sec*- and *t*-Alkylzinc Bromides.

| Entry | Alkyl Bromide | Electrophile | Product ^a | Yield ^b |
|-------|---|---|--|--------------------|
| 1 |  |  |  | 95 |
| 2 |  |  |  | 87 |
| 3 |  |  |  | 62 |
| 4 |  |  |  | 84 |
| 5 |  |  |  | 99 |



a) ¹H NMR, ¹³C NMR, FTIR, HRMS, and elemental analysis were consistent with structure or in agreement with the literature. b) Isolated yields c) Coupling performed at rt. d) Coupling performed at 0 °C.

coupling was then conducted. 3-Bromopentane (0.9 equiv) readily underwent oxidative insertion in refluxing THF to form the organozinc bromide reagent and likewise coupled with benzoyl chloride (0.9 equiv) and 5-chlorovaleryl chloride (0.9 equiv) to give good yields of the product ketones (Table 1, entries 2-3). Cycloalkyl bromides reacted similarly (Table 1, entries 4-5, 0.9 and 0.7 equiv benzoyl chloride respectively). *t*-Butyl bromide easily reacted at rt in 1 h to form the zinc reagent. The tertiary alkylzinc bromides (Table 1, entries 7-9) coupled slowly with benzoyl chloride (0.7 equiv), taking 4-8 h for completion. These results are significant, in that tertiary alkylzinc bromides can be formed

readily from active zinc insertion in high yield, which would be difficult or impossible by other methodologies which do not tolerate functionality. The scope of this method is currently under investigation.

As a representative procedure: to a slurry of Rieke zinc⁶ (7.98 mmol) in THF (25 mL) under argon was added 2-bromobutane (7.95 mmol) and the mixture was refluxed for 2.5 h. The resulting light brown solution was cooled to rt and was transferred via cannula to a THF (10 mL) solution of CuCN (1.5 mmol) and LiBr (1.5 mmol) at -45 °C. Benzoyl chloride (7.95 mmol) was added neat and the mixture was warmed slowly to rt over 4 h. The reaction mixture was quenched with 3 M HCl (20 mL), extracted with ether (3×20 mL), and the combined organic layers were washed with water (20 mL), dried over MgSO₄, and concentrated. 2-Methyl-1-phenylbutanone (7.52 mmol, 95%) was isolated from the crude reaction mixture by flash chromatography (hexanes/ethyl acetate).

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References and Notes

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6. To a flask charged with finely cut (0.75×1.0×5.0 mm) Li (0.1108 g, 15.96 mmol), naphthalene (0.20 g, 1.6 mmol), and THF (10 mL) under argon was transferred via cannula a THF (15 mL) solution of zinc chloride (1.088 g, 7.982 mmol) dropwise so as addition was complete in ca. 1.5 h. An egg-type stirbar was used with light to moderate stirring.

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