news & views

CROSS-COUPLING REACTIONS

Is sodium finally coming of age?

Given the fact that sodium is the most abundant alkali metal on Earth, the direct and indirect use of organosodium compounds in palladium-catalysed carbon–carbon bond forming reactions is an attractive alternative for sustainable organic synthesis.

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The formation of carbon–carbon single bonds is one the most important fundamental chemical reactions in organic synthesis, finding numerous applications in pharmaceutical and materials sciences. Conventionally, carbon–carbon single bonds can be constructed by many well-established organic transformations; especially those named metal-catalysed cross-coupling reactions, for example, Heck–Mizoroki, Migita–Kosugi–Stille, Negishi, and Suzuki–Miyaura reactions. In these reactions, organometallic reagents such as organotin, organozinc or organoboron are employed as nucleophiles, whose preparations often involve transmetallation of organolithium compounds. The use of sodium in cross-coupling reactions has been considered inferior to lithium, despite the fact that sodium is also an alkali metal, and is the most abundant such metal in the Earth's crust and oceans. However, since the first direct preparation of 3-furylsodium from 3-iodofuran in 1933 by Gilman and Wright[1], and of phenylsodium from chlorobenzene in 1935 by Bockmühl and Ehrhart[2], organosodium reagents have been overlooked for more than 80 years.

Now, writing in *Nature Catalysis*, Asako, Nakajima and Takai — chemists from Okayama University in Japan — demonstrate that organosodium compounds can be easily prepared from aryl chlorides or (hetero)arenes and an easily handled sodium dispersion[3]. These organosodium compounds can be converted further into coupling partners for palladium-catalysed Negishi or Suzuki–Miyaura cross-coupling reactions. Direct palladium-catalysed cross-coupling reactions employing these organosodium compounds are also demonstrated.

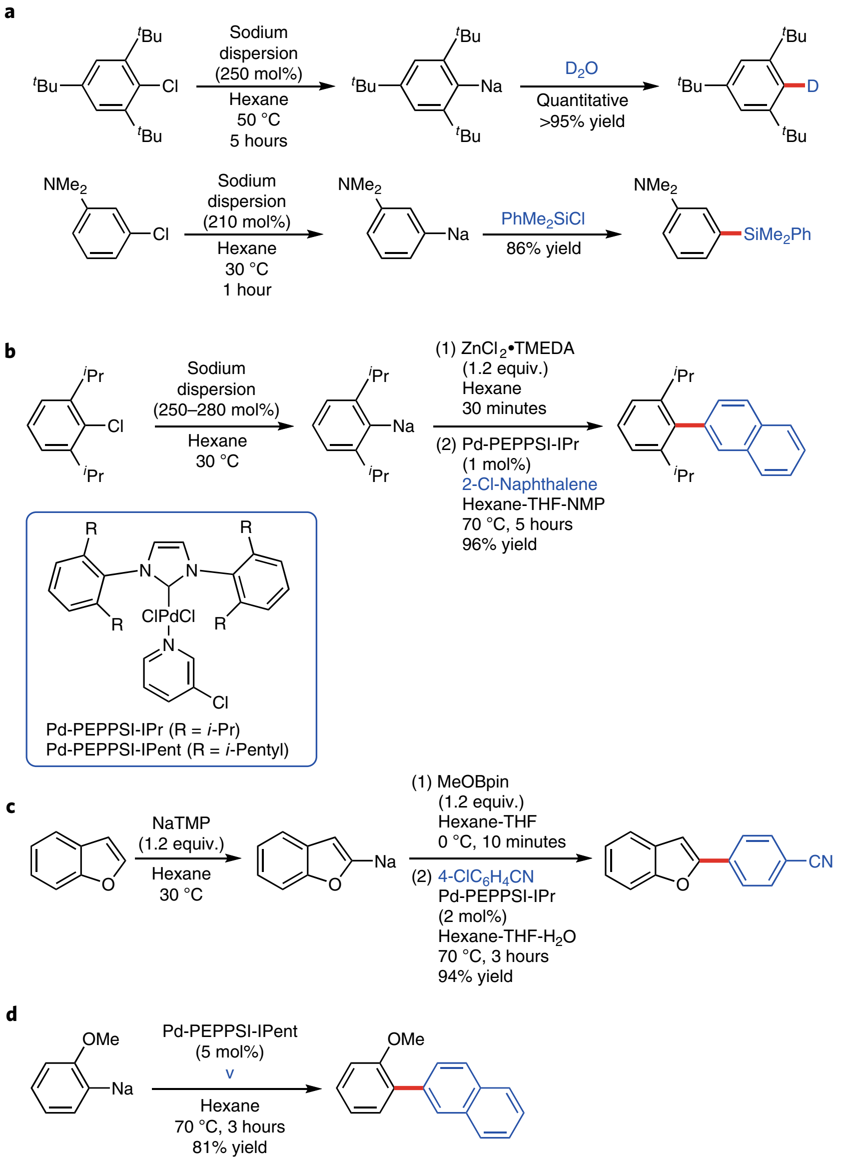

Fig. 1 | Reactions of organosodium compounds. **a**, Preparation and quenching of organosodium compounds. **b**, Negishi reaction. **c**, Suzuki–Miyaura reaction. **d**, Direct cross-coupling reaction.

The research team initially explored the preparation of arylsodium compounds by making use of sodium particles dispersed in paraffin oil with an average size smaller than 10 μm. The concentration of approximately 26 wt% also renders this sodium dispersion stable and easy to handle in air. Following the method of Nobis and Moormeier[4], 15 organosodium compounds were prepared and, upon quenching with either D_2O or $PhMe_2SiCl$, deuterioarenes or phenyldimethylsilanes were afforded in yields ranging from 60% to quantitative yield. Two examples of these conversions are shown in Fig. 1a. For the sterically hindered aryl chloride, 250 mol% of sodium dispersion is required (though considering that sodium is a one-electron donor, this is only 1.25 equivalents), and the reaction temperature is also higher.

Next, the authors converted organosodium compounds into the corresponding organozinc reagents for Negishi reaction (Fig. 1b). Organosodium compounds underwent transmetallation reactions by addition of $ZnCl_2$•TMEDA (TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) to form arylzinc compounds in situ, which then were allowed to react with a second aryl chloride with 0.1–3 mol% of a Pd-pyridine-enhanced precatlyst preparation stabilization and initiation (PEPPSI)-IPr catalyst, to form the carbon(sp^2)–carbon(sp^2) bond. In this way, a total of 21 cross-coupled products were prepared with yields ranging from 70% to 98%. Noteworthy is that the turnover number (TON) of 920 was also obtained for one of these Negishi reactions. Suzuki–Miyaura reactions were also performed and, as shown in Fig. 1c, 2-arylbenzo[*b*]furan was achieved in 94% yield. In this palladium-catalysed Suzuki–Miyaura cross-coupling reaction, benzo[*b*]furan-2-sodium was prepared by a direct metallation of benzo[*b*]furan, making use of the unusual α-hydrogen acidity of benzo[*b*]furan. A total of eight examples were reported, with yields ranging from 78% to 94%. Finally, a direct cross-coupling reaction with arylsodium compounds was also carried out. As can be seen in Fig. 1d, the organosodium compound was allowed to couple directly with an aryl chloride to provide the product with a new carbon(sp^2)–carbon(sp^2) bond in 81% yield. Aryl bromides can also be used, and the reaction temperature and time for cross-coupling can be lowered to 30 °C and 1 hour, respectively. A slightly structurally different palladium catalyst, Pd-PEPPSI-IPent (5 mol%) was used instead. In this direct cross-coupling reaction, eight examples were reported, with yields ranging generally from 60% to 96% (yields were typically increased if 10 mol% of zinc salt was added). A 2.5 mmol scale reaction was also performed, resulting in an almost similar yield, thereby pointing to the possibility that these reactions can be scaled up to multi-gram quantities.

One interesting implication of the work is the potential for adoption by industry. As pointed out by the authors[3]: "Because of the lower reactivity of the sodium dispersion at this concentration upon contact with water, the permitted amount of sodium per designated quantity of the sodium dispersion is about 45 times larger than that of a sodium lump in Japan, which would make industrial applications more feasible". The fact that the sodium dispersion can be measured precisely using a syringe, while the same is not true for sodium lump, makes the use of sodium dispersion much more attractive and convenient. As such, organosodium compounds would be readily accessible under very mild conditions in chemistry laboratories, and presumably also at industrial settings. These organosodium compounds would then undergo transmetallation processes to form organozinc or organoboron species for palladium-catalysed Negishi or Suzuki–Miyaura reactions, or a direct palladium-catalysed cross-coupling reaction with aryl chlorides or bromides, leading to the formation of new carbon(sp^2)-carbon(sp^2) bonds. Nonetheless, unlike organolithium chemistry, chemists so far have not focused so much attention on organosodium chemistry. Therefore, suffice it to say that more efforts are still needed in order to widen the synthetic scope of organosodium compounds. In view that the current investigation still has some limitations, future efforts should be focussed on issues such as avoiding unwanted arylsodium-induced dehydrochlorination of aryl chlorides, the direct use of organosodium in metal-catalysed cross-coupling reactions, as well as in the formation of C–N, C–O and C–S bonds, and the use of abundant metal catalysts such as iron, zinc and nickel. Notwithstanding, this *Nature Catalysis* paper from Asako, Nakajima and Takai[3] serves as an inspiration to replace scarce elements such as lithium with the terrestrially abundant, inexpensive and non-toxic sodium, for the sake of the sustainable future of the planet Earth, on which we all reside. ❒

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