Halogen–Sodium Exchange Revisited

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Sodium is the most abundant alkali metal on Earth. Despite being an attractive choice for sustainable synthesis, organosodium compounds are rarely used in organic synthesis and have been overshadowed to date by organolithium compounds. This situation is largely due to the lack of convenient and efficient methods for the preparation of organosodium compounds. We report herein a halogen–sodium exchange method to prepare a large variety of (hetero)aryl- and alkenylsodium compounds, many of them previously inaccessible by other methods. The key discovery is the use of a bulky alkylsodium lacking a *β*-hydrogen, readily prepared in situ from neopentyl chloride and an easy-to-handle sodium dispersion, which retards undesired reactions such as Wurtz–Fittig coupling and *β*-hydrogen elimination, and enables efficient halogen-sodium exchange. We believe that the efficiency, generality, and convenience of the present method will open new horizons for the use of organosodium in organic synthesis, ultimately contributing to the development of sustainable chemistry by replacing the currently dominant organolithium reagents.

Since its discovery in the early 20th century, organolithium chemistry has played a dominant role in organic synthesis.[1,2,3,4,5,6] Organolithiums are archetypal organometallic compounds that have been used extensively as reactants and reagents (nucleophiles, bases, or reductants) for preparing a diverse range of organic, organometallic, and inorganic compounds. Common methods for preparing aryllithiums and congeners are the following: deprotonation of arenes, two-electron reduction of aryl halides, and halogen–lithium exchange between aryl halides and alkyllithiums (Figure 1a).[3,4,5,6,7,8,9,10] The halogen–lithium exchange method has been extensively used in organic synthesis because it allows rapid preparation of a large variety of organolithium compounds from (hetero)aryl or alkenyl bromides or iodides, typically using butyllithium or *tert*-butyllithium under cryogenic conditions. Because of its versatility and general scope, this method has become the standard entry to organometallic compounds, and found widespread applications in various fields.

From a sustainability point of view, there is a growing demand for alternatives to the less abundant and increasingly expensive lithium. Sodium is the most abundant alkali metal and hence an attractive candidate. However, in contrast to the widespread use of organolithium compounds enabled by the accumulated knowledge of their chemistry, organosodium compounds have met with limited success in synthetic organic chemistry, even though organosodium chemistry first emerged as early as the 1840–50s.[1,2,3,11] Early attempts at halogen–sodium exchange using alkylsodiums such as butylsodium and pentylsodium met with significant challenges.[12,13,14,15] For example, Gilman reported that 1-bromonaphthalene reacted with butylsodium prepared from dibutylmercury and metallic sodium to afford 1-naphthylsodium in 28% yield (Figure 1b);[13] although details were not reported, the low yield was probably due to the formation of side products such as 1-butylnaphthalene and octane.

We have been exploring the potential of organosodium for organic synthesis for a while,[16,17] and have recently reported that arylsodiums can be conveniently prepared by two-electron reduction of aryl chlorides with an easy-to-handle and highly reactive fine dispersion (particle size smaller than 10 mm) of sodium in paraffin oil (sodium dispersion;

SD),[18] and subsequently participate in Negishi, Suzuki–Miyaura, and direct cross-coupling reactions (Figure 1c).[16,19] However, this method could only be applied for the preparation of a narrow range of organosodium compounds. Here, we report that a much broader range of aryl-, heteroaryl, and alkenylsodium compounds are now accessible by halogen–sodium exchange between the corresponding organic bromides or iodides, and neopentylsodium prepared in situ from neopentyl chloride and sodium dispersion, typically at 0 °C (Figure 1d). Alkenyl bromides afforded the corresponding alkenylsodiums with retention of stereochemistry. The resulting organosodiums could be directly reacted with electrophiles, or used as nucleophiles for Negishi and Suzuki–Miyaura cross-coupling.

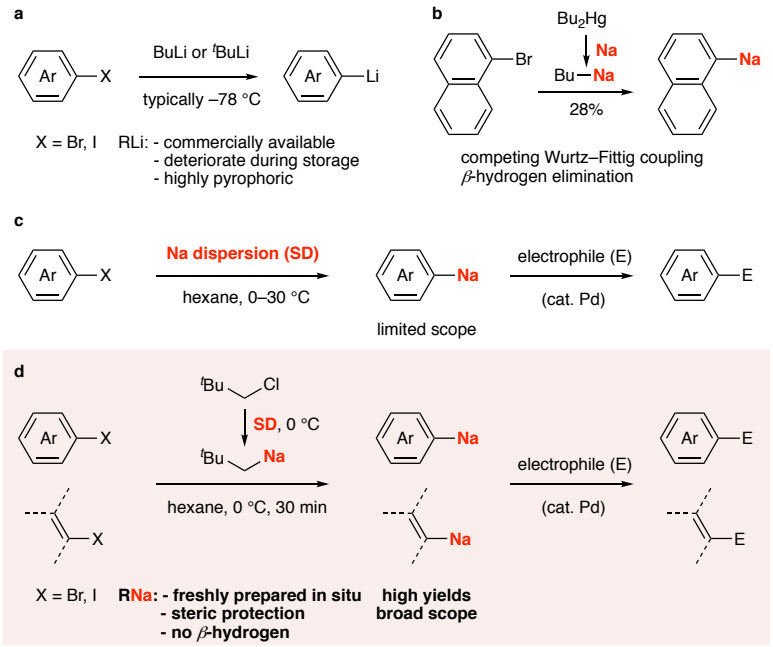


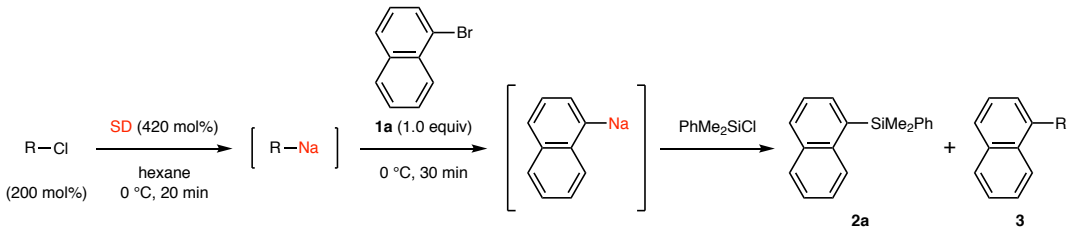
Fig. 1. Preparation of organolithium and organosodium. a, Halogen–lithium exchange. **b**, Halogen–sodium exchange reported by Gilman (ref. 13). **c**, Our previous report: two-electron reduction of aryl halides with sodium dispersion (ref. 16). **d**, This report: halogen–sodium exchange with freshly prepared neopentylsodium.

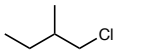
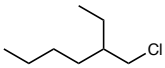
Results

Preparation of aryl- and alkenylsodium by halogen–sodium exchange with alkylsodium.

As depicted in Figure 1b, halogen–sodium exchange is known to proceed with low efficiency, presumably because of the formation of side products from undesired reactions such as the reaction of organosodium with the alkyl halide by the Wurtz–Fittig reaction.[20] We envisioned that to suppress these undesired side reactions and achieve efficient halogen–sodium exchange, an alkylsodium compound should: 1) bear a bulky substituent to kinetically prevent Wurtz–Fittig coupling, 2) lack a β-hydrogen to avoid premature decomposition,[1,2,3,21] 3) be readily and quantitatively prepared in situ from a largely available alkyl halide, 4) be a primary alkylsodium, because it is known that secondary and tertiary alkylsodiums are generated sluggishly from the corresponding halides and undergo faster β-hydrogen elimination.[1,2,3,21] With the above considerations in mind, we commenced our study by identifying an appropriate alkylsodium for the bromine–sodium exchange using 1-bromonaphthalene (**1a**) as a model substrate (Figure 2) to find that neopentylsodium[22] is an optimal reagent that maximizes the formation of 1-naphthylsodium, and minimizes the formation of undesired coupling product **3**. Thus, alkylsodiums were first prepared from the corresponding alkyl chlorides and sodium dispersion (particle size <10 μm)[18] in hexane at 0 °C, then reacted with **1a** and trapped with $PhMe_2SiCl$ to evaluate the efficiency of the reactions. The use of finely dispersed sodium is essential for the efficient and rapid preparation of alkylsodiums. We selected this substrate because 1-naphthylsodium could not be directly obtained (<10% yield) by two-electron reduction of **1a** with sodium dispersion by following the method shown in Figure 1c,[14,16] probably due to the stabilization of the radical anion species generated by one-electron reduction of **1a**. Although the reaction using pentyl chloride and octyl chloride afforded the desired 1-silylnaphthalene (**2a**), this was accompanied by the formation of 1-alkylnaphthalene (**3**) through Wurtz–Fittig coupling as expected (entries 1 and 2). We were delighted to find that primary alkyl chlorides with bulky neighbouring substituents indeed suppressed the side reactions, and neopentyl chloride performed particularly well among others to afford **2a** selectively in good yield (entries 3–5). The amounts of neopentyl chloride and sodium dispersion could be reduced down to 120 and 250 mol%, respectively, but with slightly

lower efficiency (entries 6 and 7). The reactions with secondary and tertiary alkyl chlorides such as cyclohexyl chloride and *tert*-butyl chloride were less efficient, partly because of the inefficient generation of the corresponding alkylsodium (entries 8 and 9).



entry	R—Cl	**2a** (%)	**3** (%)
1	$^{n}C_5H_{11}$—Cl	72	23
2	$^{n}C_8H_{17}$—Cl	61	33
3		93	1
4		90	3
5		>99	0

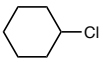
entry	R—Cl	**2a** (%)	**3** (%)
6[a]		93	0
7[b]		88	0
8		75	0
9		46	0

Fig. 2. Bromine–sodium exchange between 1-bromonaphthalene and alkylsodium. Alkylsodium prepared in situ from alkyl chloride (200 mol%) and sodium dispersion (SD: 420 mol%) was reacted with 1-bromonaphthalene (**1a**, 0.25 mmol) in hexane at 0 °C, followed by addition of $PhMe_2SiCl$. Yields were determined using ^1H NMR. [a]Neopentyl chloride (150 mol%) and SD (320 mol%). [b]Neopentyl chloride (120 mol%) and SD (250 mol%). Ph, phenyl; Me, methyl.

We then explored the scope of this procedure to find that a variety of aryl, heteroaryl, and alkenylsodiums were conveniently and rapidly accessible under mild conditions, as probed by trapping with electrophiles such as chlorosilanes and D_2O (Figure 3). In addition to 1-bromonaphthalene (**1a**), 1-iodonaphthalene (**1a'**), 2-bromonaphthalene (**1b**), and larger polycyclic aromatic hydrocarbons such as 9-bromophenanthrene (**1c**) and 1-bromopyrene (**1d**) reacted smoothly to afford the silylated products. Arenes possessing OMe (**1e**, **1f**), Cl (**1g**), F (**1h**), and CF_3 (**1i**) groups could also be converted into the corresponding

arylsodiums, although a lower temperature (–40 °C) was necessary in some cases, to avoid side reactions caused by the deprotonation of the hydrogen adjacent to these functional groups. 4-Bromophenol (**1j**), 4-bromobenzyl alcohol (**1k**), and 5-bromoindole (**1l**) participated in the reaction without requiring protection of the acidic protons, using an additional amount of neopentylsodium for deprotonation. Heteroaryl bromides such as 2-bromopyridine (**1m**), 8-bromoquinoline (**1n**), and 2-bromothiophene (**1o**) reacted within 10 min at –78 to 0 °C. When 1,4-dibromobenzene (**1p**) and 2,2'-dibromo-1,1'-biphenyl (**1q**) were used as substrates, twofold sodiation proceeded, and disilylated benzene and silafluorenes were obtained after quenching the resulting disodioarenes with $PhMe_2SiCl$, Me_2SiCl_2, and Ph_2SiCl_2, respectively. The last reaction could be performed on a gram scale and the silafluorene product (**2r**) was obtained in good yield. Alkenyl bromides (**1s**, **1t**) reacted smoothly under these conditions. The reactions of 1-styryl bromide were stereoretentive, and the *E*/*Z* ratio of the substrate (**1t**) and product (**2t**) were identical. It should be noted that most of the organosodium compounds in Figure 3 are not accessible by the direct reduction of aryl halides with sodium dispersion (Figure 1c)[16] or deprotonative sodiation.

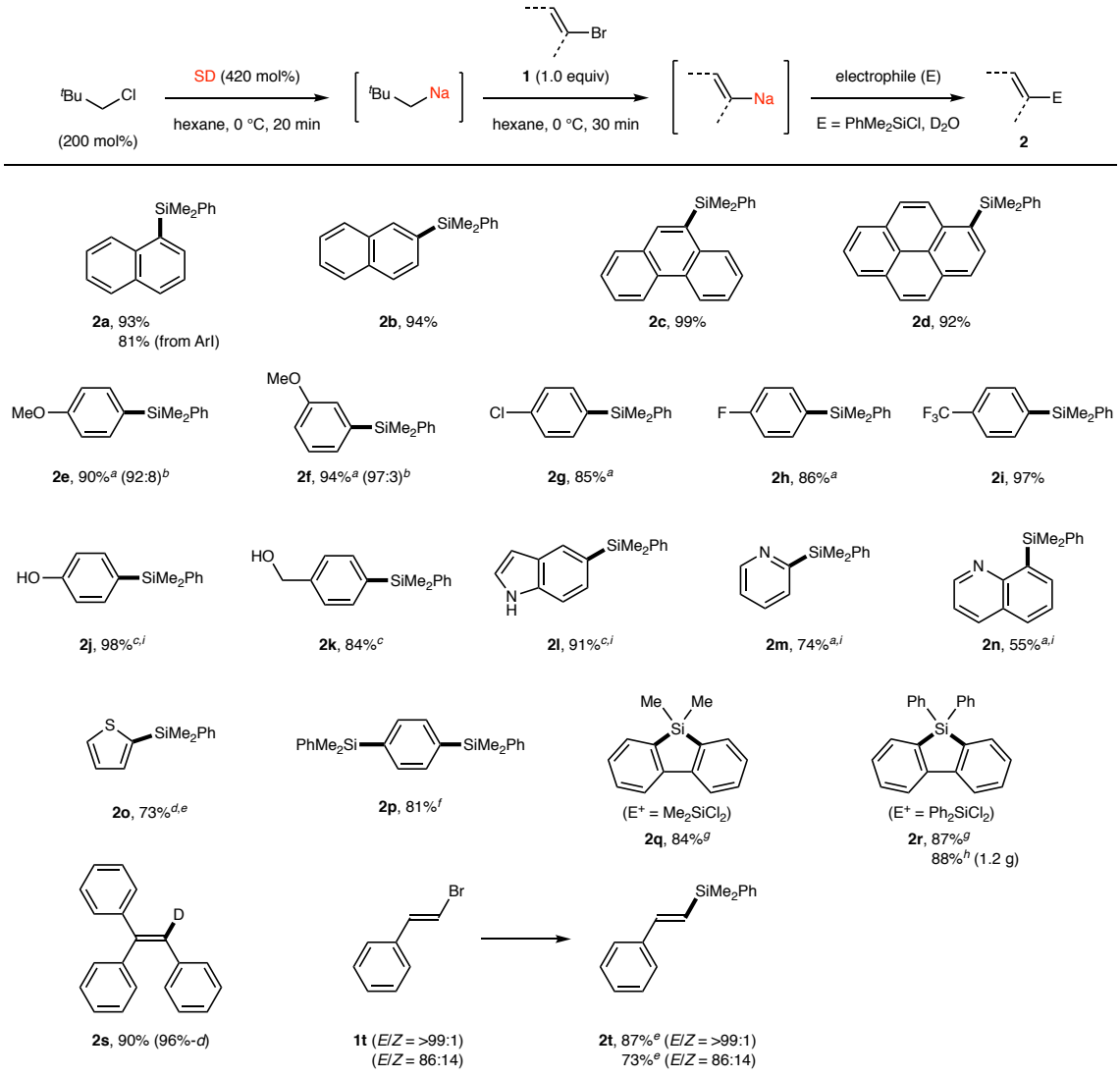


Fig. 3. Bromine–sodium exchange between aryl and alkenyl bromides and neopentylsodium. Neopentylsodium prepared in situ from neopentyl chloride (200 mol%) and sodium dispersion (SD: 420 mol%) was reacted with organic bromide (**1**, 0.25 mmol) in hexane (2.0 mL) at 0 °C, followed by addition of $PhMe_2SiCl$ (1.2 equiv) or D_2O (1.0 mL) as an electrophile. Yields determined by isolation are shown unless otherwise noted. Deuterium content was determined by ^1H NMR. [a]Exchange reaction at –40 °C for 10 min. [b]Ratio of monosilylated and disilylated products determined by ^1H NMR. [c]Neopentyl chloride (300 mol%), SD (630 mol%) in hexane (2.5 mL), and $PhMe_2SiCl$ (3.0 equiv); after reaction, the concentrated crude mixture was reacted with K_2CO_3 (5.0 equiv) in MeOH (3.0

mL) for 1 h. [d]Neopentyl chloride (120 mol%) and SD (250 mol%). [e]Exchange reaction for 10 min. [f]Neopentyl chloride (300 mol%), SD (630 mol%) in hexane (2.5 mL), and $PhMe_2SiCl$ (3.0 equiv). [g]Neopentyl chloride (340 mol%), SD (710 mol%) in hexane (2.5 mL), and R_2SiCl_2 (2.0 equiv). [h]4.0 mmol scale. [i]Yield determined by ^1H NMR. [t]Bu, *tert*-butyl; Ph, phenyl; Me, methyl; MeO, methoxy.

Application to Negishi and Suzuki–Miyaura cross-coupling.

Following our previous studies,[16] we explored whether arylsodium compounds prepared by bromine–sodium exchange could also be used as nucleophilic reagents in the palladium-catalyzed cross-coupling.[23,24] We found that the arylsodiums smoothly underwent Negishi and Suzuki–Miyaura cross-coupling reactions after being transmetalated to organozinc and organoboron compounds using $ZnCl_2$•TMEDA (TMEDA: *N,N,N',N'*-tetramethylethylenediamine) or MeOBpin, respectively, in the presence of Pd-PEPPSI-IPr as catalyst (Figures 4 and 5).[25] The reactions were performed in a one-pot sequence: preparation of neopentylsodium, preparation of Ar^1Na via bromine–sodium exchange, transmetalation to Ar^1Zn or Ar^1B, and palladium-catalyzed cross-coupling with Ar^2Cl, to afford the coupling products in good to excellent yields. For example, naphthylsodium (**4a**, **5a**), arylsodiums bearing a diphenylamino (**4b**), carbazolyl (**5c**), trifluoromethyl (**4e**, **4f**), fluoro (**5b**), and *tert*-butyl (**4c**) substituent, heteroarylsodiums such as (methyl)thienylsodium (**4d**, **5f**) and quinolylsodium (**5d**), and styrylsodium (**5e**) were prepared in situ and found to function as efficient nucleophilic sources. As expected from the well-recognized functional group compatibility of these cross-coupling reactions, various functional groups on the electrophilic coupling partners such as methoxycarbonyl (**4a**), ketocarbonyl (**4c**), formyl (**5c**), cyano (**5a**), amino (**5d**), nitro (**5e**), trifluoromethyl (**4b**), trifluoromethoxy (**5d**), and methoxy (**5b**, **5e**) groups were tolerated. Overall, the halogen–sodium exchange we developed here greatly expanded the potential of organosodium-based cross-coupling technology.

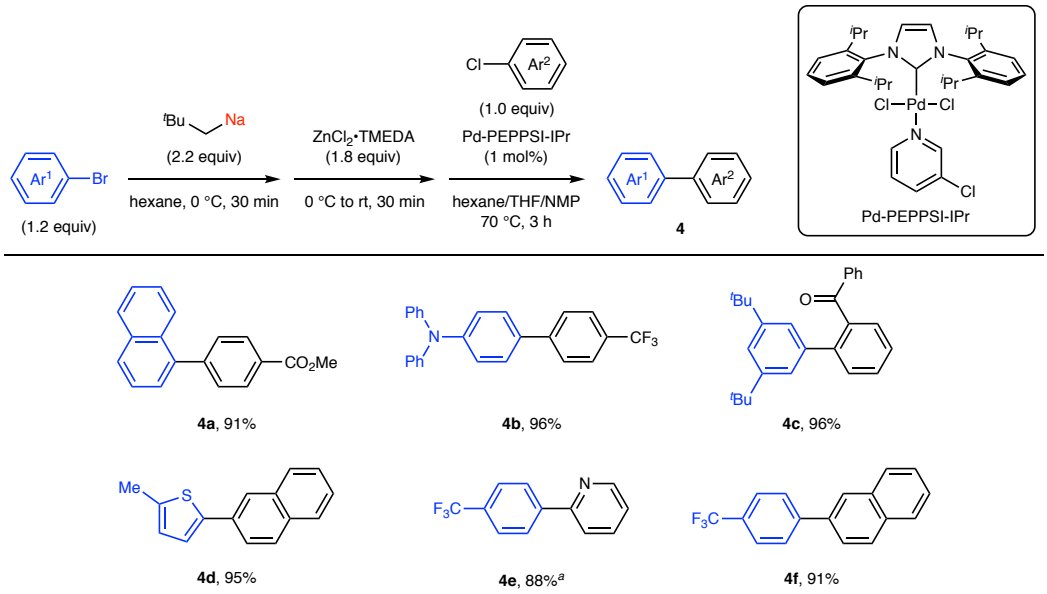


Fig. 4. Palladium-catalysed Negishi cross-coupling reactions using arylsodiums. Conditions: step 1, neopentyl chloride (220 mol%) and SD (450 mol%) in hexane (2.0 mL) at 0 °C, 20 min; step 2, Ar^1Br (1.2 equiv) was added at 0 °C, 30 min; step 3, $ZnCl_2$•TMEDA (1.2 equiv) was added at 0 °C, stirred at rt for 30 min; step 4, Pd-PEPPSI-IPr (1 mol%), Ar^2Cl (0.30 mmol, 1.0 equiv), THF (0.80 mL) and *N*-methylpyrrolidone (NMP, 0.40 mL) were added and the cross-coupling reaction was performed at 70 °C for 3 h. Yields determined by isolation are shown. [a]$ZnCl_2$•TMEDA (2.2 equiv). SD, sodium dispersion; Ar, aryl; ^{t}Bu, *tert*-butyl; TMEDA, *N*,*N*,*N*',*N*'-tetramethylethylenediamine; THF, tetrahydrofuran; NMP, *N*-methyl-2-pyrrolidone; ^{i}Pr, isopropyl; Me, methyl; Ph, phenyl.

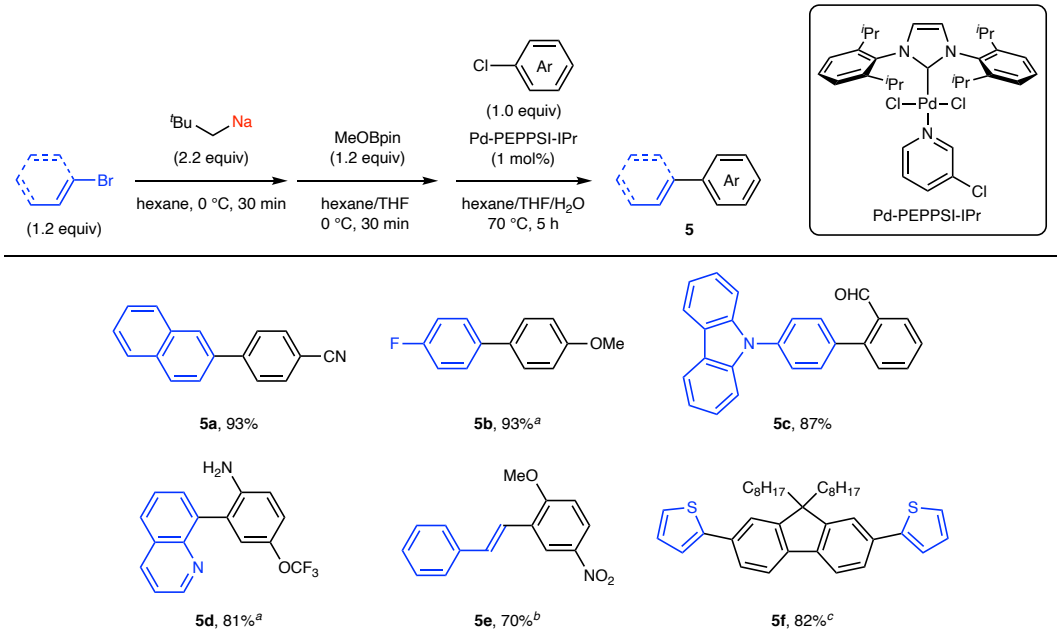


Fig. 5. Palladium-catalysed Suzuki–Miyaura cross-coupling reactions using arylsodiums. Conditions: step 1, neopentyl chloride (220 mol%) and SD (450 mol%) in hexane (2.0 mL) at 0 °C, 20 min; step 2, RBr (1.2 equiv) was added at 0 °C, 30 min; step 3, MeOBpin (1.2 equiv) and THF (0.8 mL) were added at 0 °C, 30 min; step 4, H_2O (0.40 mL), ArCl (0.30 mmol, 1.0 equiv) and Pd-PEPPSI-IPr (1 mol%) were added and the cross-coupling reaction was performed at 70 °C for 5 h. Yields determined by isolation are shown. [a]Nucleophile (1.4 equiv); neopentyl chloride (250 mol%), SD (530 mol%), ArBr (1.4 equiv), and MeOBpin (1.4 equiv). [b]Pd-PEPPSI-IPr (2 mol%). [c]Neopentyl chloride (300 mol%), SD (630 mol%), hexane (2.5 mL), 2-bromothiophene (2.6 equiv), bromine–sodium exchange was performed for 10 min; MeOBpin (2.9 equiv), THF (1.0 mL), H_2O (0.50 mL), 9,9-dioctyl-2,7-dibromofluorene (1.0 equiv) and Pd-PEPPSI-IPr (2 mol%). SD, sodium dispersion; ^{t}Bu, *tert*-butyl; Ar, aryl; MeOBpin, 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; MeO, methoxy; THF, tetrahydrofuran; ^{i}Pr, isopropyl.

Conclusion

Organosodium chemistry has long been overshadowed by the well-established organolithium chemistry. While there has been some recent renewed interest in the use of organosodium compounds for organic synthesis,[26,27,28,29,30,31,32] the lack of general and

reliable preparation methods has hindered the development of truly useful reactions. To change this status quo, we demonstrate in this paper that efficient halogen–sodium exchange reactions are now possible nearly 80 years after the seminal study,[13] using neopentylsodium as a key metalating reagent, to expand the repertoire of available organosodium compounds greatly. This exchange reaction has several attractive features: 1) the alkylsodium reagent can be conveniently and freshly prepared in situ using an inexpensive alkyl chloride and an easy-to-handle sodium dispersion, circumventing the need for hazardous storage; 2) the sodium dispersion in paraffin at 26 wt% concentration is easy to handle and less hazardous;[18] this is a practical advantage, considering that organolithiums are highly pyrophoric and hazardous to use and store, and are the cause of many accidents in organic laboratories; 3) the reactions proceed typically at 0 °C using an ice bath; 4) sodium is ubiquitous, abundant, inexpensive, and therefore less vulnerable to supply risks. Thus, we believe that the reaction described here has the potential to replace the textbook halogen–lithium exchange, and open new frontiers for establishing organosodium-based sustainable organic chemistry.

Acknowledgements

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Author Contributions

S.A., H.N., and K.T. started the project and later I.T. and L.I. joined. S.A. and K.T. directed the project. S.A., I.T., and H.N. conceived and designed the experiments. I.T. and H.N. performed the experiments. S.A., I.T., L.I, and K.T. co-wrote the manuscript. All authors contributed to discussions.

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