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New Chemoselective Metalating Agents for Solid-Phase Synthesis

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Development of new soluble, chemoselective metalating reagents is essential for exploring solid-phase organometallic chemistry. Cuprates and zincates were expected to be potentially usable for solid-phase chemistry, and we started to investigate chemoselective solid-phase halogen–metal exchange reactions using ate complexes. At 0 °C, the halogen–zinc exchange reactions proceeded smoothly in the presence of 2.2 equiv of LTBZ, and the subsequent reaction with an electrophile followed by cleavage with NaOMe/MeOH-THF gave the desired product in an excellent yield. The immobilized organozincate on polymer support was also transformed into the immobilized organocuprate by treatment with lithium cyanothiencuprate. The palladium-catalyzed cross-coupling reaction of the immobilized organozincate with iodobenzene proceeded smoothly at room temperature to give an unsymmetrical biaryl. This methodology is considered to provide a new chemoselective method for solid-phase carbon–carbon bond formation.

Solid-phase synthesis¹ has been recognized as an important methodology for constructing libraries of biologically active small molecules in connection with combinatorial chemistry and automated synthesis oriented for drug discovery research.² Various synthetic methodologies have been applied to solid-phase synthesis; however, organometallic chemistry has not yet sufficiently been explored in this area due to the lack of effective preparative methods of immobilized organometallic compounds for reaction with electrophilic linkages such as esters. Organometallic compounds have played an important role in solution-phase chemistry for selective carbon–carbon bond formations directed toward construction of complex molecules. To develop a new solid-phase carbon–carbon bond forming reaction, we investigated the halogen–metal exchange reaction of organic halides supported on polymer with an electrophilic linkage. Ate complexes turned out to be very effective as solid-phase metalating agents, and various modes of carbon–carbon bond formation were achieved using the resulting immobilized arylmetal ate complexes.

Metalation of an insoluble polymer such as cross-linked polystyrene has been investigated in connection with the preparation of materials for polymer-assisted chemistry,³ and lithiation has routinely been used for the functionalization of polystyrene resin.⁴ However, in this approach the existence of electrophilic functional groups has been limited, and only a few reports on solid-phase lithiation of immobilized small molecules with electrophilic functional groups has appeared so far. Therefore, the development of new ways for the chemoselective metalation of small molecules on polystyrene with an electrophilic functional group is considered to be very important for solid-phase organic synthesis. In solution, reactive organometallic compounds with an alkoxy-carbonyl

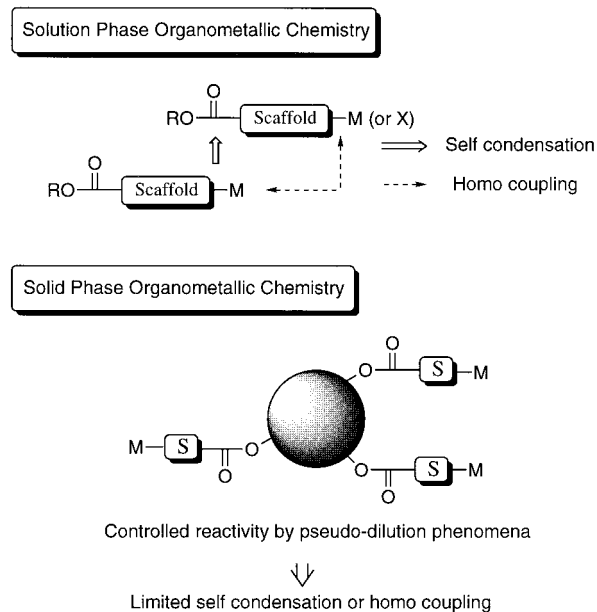


Figure 1.

group are considered to be unstable at an elevated temperature due to self-condensation or homocoupling, depending on the nature of the organometallic species. On the other hand, immobilized organometallic compounds with an electrophilic functional group are expected to have enhanced stability because of the diminished chance of self-condensation and homocoupling by the pseudo-dilution phenomena, compared to the similar chemistry in the solution phase (Figure 1).^{1b}

In solution-phase chemistry, many efforts have been made for the preparation of organometallic compounds with electrophilic substituents. For example, Parham investigated the halogen–metal exchange reaction of functionalized arylhalides at low temperature.⁵ As an alternative approach,

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chemoselective oxidative addition of active metals⁶ to organic halides has been investigated intensively. Among various organometallics, organocopper reagents⁷ and organozinc reagents⁸ have been extensively used as soft nucleophilic reagents in organic synthesis. In particular, much of this research has been carried out on organozinc reagents with reactive functional groups prepared by oxidative addition of organohalides to zinc metal activated by various methods. However, for solid-phase chemistry, employing insoluble reagents such as Rieke's active metals is considered generally unfavorable,⁹ and development of new soluble, chemoselective metalating reagents is essential for exploring solid-phase organometallic chemistry. We recently demonstrated that ate complexes such as cuprates¹⁰ and zincates¹¹ which were expected to be potentially usable for solid-phase chemistry can be used as chemoselective metalating agents for various organic halides in solution. On the basis of this background, we started to investigate chemoselective solid-phase halogen–metal exchange reactions, focusing principally on the preparation and transformation of immobilized intermediate organozincate and organocuprate species (Figure 2, **1** and **2**).

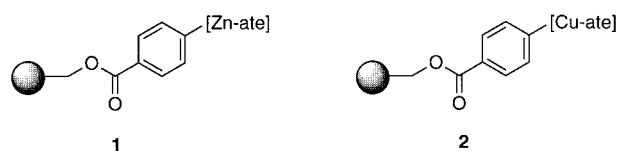


Figure 2.

We first examined Parham's lithiation approach for chemoselective solid-phase metalation; however, the desired halogen–lithium exchange reaction of immobilized 4-iodobenzoate resin **3**¹² did not proceed, and no metalation was observed (Table 1; entries 1 and 2).¹³ We next turned our focus to the halogen–zinc exchange reactions using LTBZ (lithium tri-*tert*-butylzincate). The exchange reaction was found to proceed at $-78\text{ }^{\circ}\text{C}$ to some extent (Table 1; entry 3), but the best result was obtained when the metalation was carried out at $0\text{ }^{\circ}\text{C}$. Compared to the solution-phase reaction, the metalation seemed slow, and a slightly higher reaction temperature was necessary. At $0\text{ }^{\circ}\text{C}$, the metalation proceeded smoothly in the presence of 2.2 equiv LTBZ, and subsequent reaction with PhCHO, followed by cleavage with NaOMe/MeOH-THF, gave the desired hydroxy ester **4a** in 89% yield (Table 1; entry 4). Metalation at room temperature gave the product **4a** in 31% yield, and the cleavage of the ester linkage during the metalation was observed (Table 1; entry 5). Alkylations were also examined using methyl iodide and allyl iodide to give the desired products **4b** and **4c** (Table 1; entries 6 and 7).¹⁴

Scheme 1

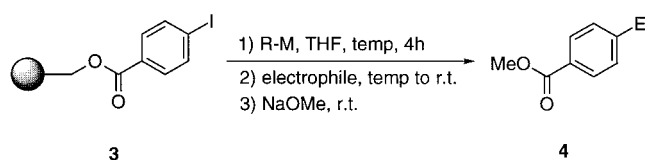
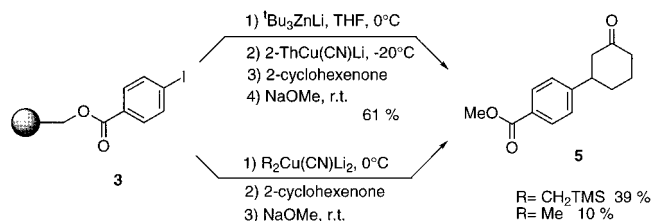


Table 1. Halogen–Metal Exchange Reaction of Immobilized 4-Iodobenzoate

entry	R–M	temp (°C)	electrophile	E	product	yield (%)
1	ⁿ BuLi	-78	PhCHO	CH(OH)Ph		0
2	^t BuLi	-78	PhCHO	CH(OH)Ph		0
3	^t Bu ₃ ZnLi	-78	PhCHO	CH(OH)Ph	4a	47
4	^t Bu ₃ ZnLi	0	PhCHO	CH(OH)Ph	4a	89
5	^t Bu ₃ ZnLi	rt	PhCHO	CH(OH)Ph	4a	31
6	^t Bu ₃ ZnLi	0	MeI	Me	4b	87
7	^t Bu ₃ ZnLi	0	CH ₂ = CHCH ₂ Br	CH ₂ CH= CH ₂	4c	45

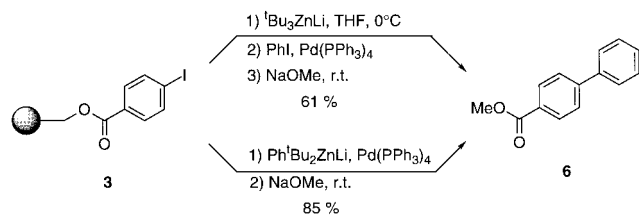
By treatment with lithium cyanothiencuprate, immobilized organozincate on polymer support was transformed into the immobilized organocuprate which was reacted with 2-cyclohexenone followed by cleavage to give the desired 1,4-adduct **5** in 61% yield (Scheme 2).¹⁵ With respect to the transmetalation, the halogen–copper exchange reaction was also examined using Me₂Cu(CN)Li₂ in order to prepare immobilized cuprates directly. The metalation was conducted at $0\text{ }^{\circ}\text{C}$ for 6 h, followed by the treatment with 2-cyclohexenone. Cleavage of the product with NaOMe in THF-MeOH at room temperature gave the 1,4-addition product in 10% yield. This cuprate was not stable enough at $0\text{ }^{\circ}\text{C}$, so the metalating agent was switched to (TMSM)₂Cu(CN)Li₂ to give the 1,4-adduct in 39% yield after similar treatments (Scheme 2). The trimethylsilylmethyl (TMSM) group was reported to work as an excellent dummy group for cuprates,¹⁶ and our result supports the stabilizing effect of the TMSM group in cuprates. However, the yield was not satisfactory, and we need to continue some more optimization studies around the solid-phase halogen–copper exchange reaction conditions.

Scheme 2



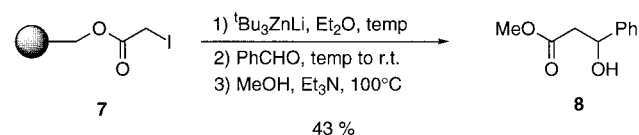
In order to examine further the synthetic utility of the immobilized organozincate species, the palladium-catalyzed cross-coupling reaction with iodobenzene was investigated.¹⁷ The cross-coupling reaction proceeded smoothly at room temperature in the presence of Pd(PPh₃)₄, and methyl 4-biphenylcarboxylate **6** was obtained in 61% yield after cleavage from the resin (Scheme 3). The coupling reaction of the immobilized iodobenzoate with di-*tert*-butylphenylzincate was also found to proceed smoothly, in contrast to our previous studies on the solution-phase palladium-catalyzed reaction of arylzincate with iodobenzene (Scheme 3).^{11b} Thus, the solid-phase coupling reaction is considered to be advantageous for this kind of unsymmetrical biaryl synthesis. We consider the pseudo-dilution effect to also be operative in the above palladium-catalyzed coupling reaction.

Scheme 3



A Reformatsky-type immobilized organozincate was also prepared by a similar procedure using LTBZ as the metalating agent. Immobilized iodoacetate resin **7**¹⁸ was treated with LTBZ in Et_2O , and the immobilized zincate was reacted with benzaldehyde. Cleavage from the polymer was carried out by the treatment with Et_3N and MeOH at 100°C to give the β -hydroxy ester **8** in 43% yield (Scheme 4).

Scheme 4



In summary, we achieved the chemoselective preparation of the immobilized reactive organometallic compounds using ate complexes for metalations. This methodology is considered to provide a new chemoselective method for solid-phase carbon-carbon bond formation, and further investigations toward selective transformations oriented for high-throughput organic synthesis and automated synthesis are underway.

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Supporting Information Available. Representative experimental procedure and ATR FT-IR spectra (11 pages). See any current masthead page for ordering information and Internet access instructions.

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