Phosphazene base-promoted halogen–zinc exchange reaction of aryl iodides using diethylzinc†

Masahiro Ueno,[a] Andrew E. H. Wheatley‡[b] and Yoshinori Kondo*[a]

The use of catalytic *t*-Bu-P4 base dramatically improved the performance of halogen–zinc exchange of aryl iodides, and the arylzinc derivatives were functionalized under copper-free reaction conditions.

Phosphazene bases[1] developed by Schwesinger and proazaphosphatranes[2] developed by Verkade are known to be strong non-metallic organic superbases. Among them, *t*-Bu-P4 base shows extremely high basicity and has been used for various selective deprotonative transformations.[3] The strong affinity of *t*-Bu-P4 base for protons is regarded as synthetically useful, however the ability of *t*-Bu-P4 base to activate organometallic compounds is largely undocumented.[4] Control of the reactivities of organometallic compounds is the key to the success of selective bond formation processes, making the development of reactions of organometallics catalytically promoted by *t*-Bu-P4 base an important subject.
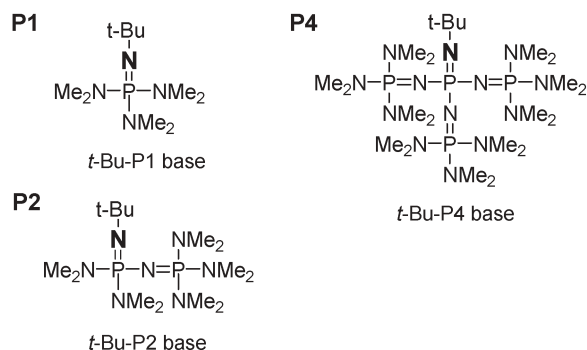

Fig. 1 Phosphazene bases for organic synthesis.

In recent years, organozinc compounds have been widely used in organic synthesis.[5] One of the most powerful methods for the preparation of functionalized organozinc derivatives is the halogen–zinc exchange reaction. Knochel *et al.* recently reported an excellent method for the halogen–zinc exchange reaction of aryl iodides using diisopropylzinc and Li(acac).[6] In connection with our

recent interest on the chemistry of functionalized arylzinc compounds,[7] we focused on the halogen–zinc exchange reaction of aryl iodides promoted by catalytic *t*-Bu-P4 base. Here, we chose diethylzinc for the halogen–zinc exchange reaction from the viewpoint of the availability of organozinc reagents.

In our initial investigation for the halogen–zinc exhange reaction, we chose ethyl 4-iodobenzoate (**1**) as a substrate. When the reaction of **1** and diethylzinc in THF in the presence of 30 mol% *t*-Bu-P4 base was carried out at room temperature, the halogen–zinc exchange reaction proceeded smoothly and the de-iodinated product (**2**) was isolated quantitatively after hydrolysis (Table 1, entry 1). In the absence of *t*-Bu-P4 base, the exchange reaction was very slow and only a trace of de-iodinated product was detected even when the reaction was carried out at 60 °C (Table 1, entry 2). Other phophazene bases with weaker basicity such as *t*-Bu-P2 base and *t*-Bu-P1 base showed less or no effect on the halogen–zinc exchange reaction (Table 1, entries 3,4). DBU also showed no promotive reactivity on the exchange reaction (Table 1, entry 5). When the amount of *t*-Bu-P4 base was reduced to 10 mol%, the exchange reaction became significantly slower in THF and **2** was isolated in only 56% yield (Table 1, entry 6). In order to optimize the reaction conditions further, solvent was switched from THF to DMF. In DMF, 5 mol% of *t*-Bu-P4 base was sufficient for activation of the exchange reaction and **2** was obtained quantitatively (Table 1, entry 7). When 1 mol% of *t*-Bu-P4 base was used, the reaction became slow and after the same reaction time the yield of **2** was 91% (Table 1, entry 9). NMP was also employed as solvent and showed excellent conversion (Table 1, entry 8). In the absence of *t*-Bu-P4 base, the exchange reaction in DMF was quite slow and it was found that *t*-Bu-P4 base

[a] Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki Aza Aoba 6-3, Aoba-ku, Sendai 980-8578, Japan.
E-mail: ykondo@mail.pharm.tohoku.ac.jp; Fax: 81-22-795-6804;
Tel: 81-22-795-6804
[b] Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EH. E-mail: aehw2@cam.ac.uk;
Fax: 44-1223-336362; Tel: 44-1223-763122
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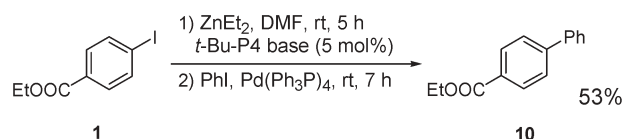‡ (JSPS Fellow 19th January 2006–19th April 2006.)

Table 1 Zincation in the presence of phosphazene base

Entry	Base	Solvent	ZnEt$_2$	Time (h)	Yield (%)
1	*t*-Bu-P4 (30 mol%)	THF	240 mol%	11	quant.
2	—	THF	240 mol%	21	3[a]
3	P2 (30 mol%)	THF	240 mol%	12	33
4	P1 (30 mol%)	THF	240 mol%	12	0
5	DBU (30 mol%)	THF	240 mol%	11	0
6	*t*-Bu-P4 (10 mol%)	THF	200 mol%	11	56
7	*t*-Bu-P4 (5 mol%)	DMF	200 mol%	11	quant.
8	*t*-Bu-P4 (10 mol%)	NMP	200 mol%	11	quant.
9	*t*-Bu-P4 (1 mol%)	DMF	200 mol%	11	91

[a] The reaction was carried out at 60 °C.

Scheme 1

Scheme 2

apparently functions as an activator. The use of dimethylzinc instead of diethylzinc was not effective for the exchange reaction and the reaction was sluggish.

Using this exchange reaction, some functionalizations of aryl halides were examined. As an example of 1,2-addition to a carbonyl group, the arylzinc prepared from **1** and diethylzinc in the presence of *t*-Bu-P4 base in THF was reacted with benzaldehyde to give the benzhydrol derivative **3** in 78% yield. As for the 1,4-addition reaction, the arylzinc prepared similarly in THF was reacted with chalcone and the 1,4-adduct was obtained in 71% yield under copper-free reaction conditions. Allylation was also carried out in the absence of copper additive, and allylbenzoate **5** was obtained in 98% yield. Using the same reaction procedure, the allyl arenes **6**, **7**, **8**, **9** were prepared from the corresponding aryl iodides in excellent yields. It has been reported that arylzinc compounds are inert to 1,4-addition and allylation reaction in the absence of additives and conventionally the employment of copper species has been widely used.[5] However, in this case the *t*-Bu-P4 base is considered to promote the reactivity of arylzinc compounds toward electrophiles.

The arylzinc compounds prepared in DMF can also be used in the palladium catalyzed Negishi coupling reaction[8] and the reaction of the arylzinc with iodobenzene in the presence of palladium catalyst gave the corresponding biarylcarboxylated in 53% yield.

In summary, the use of *t*-Bu-P4 base as a promotor dramatically improves the performance of the halogen–zinc exchange reaction of aryl iodides using commercially available diethylzinc. The 1,4-addition and allylation reaction of the arylzinc prepared in this manner proceeded smoothly under copper-free conditions and the promotor is also considered to enhance the reactivity of arylzinc compounds toward electrophiles. Further investigations on the scope and limitation of the *t*-Bu-P4 base-promoted reaction of organozinc compounds and the mechanistic studies on this activation are underway.

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