A New Strategy for Deprotonative Functionalization of Aromatics: Transformations with Excellent Chemoselectivity and Unique Regioselectivities Using *t*-Bu-P4 Base

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Deprotonative functionalization of aromatics is one of the most useful transformations in organic synthesis, in which functionalized aromatic rings are directly generated via aromatic carbanions.[1] Traditionally, highly reactive metallic bases such as alkyllithiums or lithium dialkylamides are employed to generate arylmetals that function as aromatic carbanions. A lot of studies have focused on the chemo- and regioselectivity of this reaction. The use of highly reactive metallic bases often has undesirable side reactions such as nucleophilic attack of the intermediary arylmetals on the electrophilic functional groups of the substrate.[2] Therefore, the development of highly chemoselective reactions has been a challenge.[3] More efficient methods to expand chemoselectivity have been developed using magnesium amides[3c−e] or amino zincates.[3f−h] Numerous studies have investigated the regioselectivity of this reaction.[1] Deprotonative metalation of aromatics generally proceeds at the ortho position relative to the heteroatom containing functional groups and/or at the α-position of the heteroatoms in heterocycles. This reaction has been fundamentally understood by the "acid−base mechanism" and the "coordination mechanism".[1] In some cases, the coordination of the Lewis acidic metal cation of metallic base and Lewis basic heteroatoms of substrate has been recognized as an extremely important factor for determining the regioselectivity.[4] However, the situation is much more complex than our understanding, and reactions with incomprehensible regioselectivities have also been reported in particular reaction conditions.[3g,5]
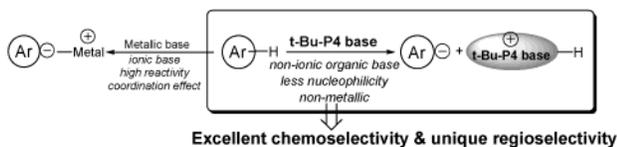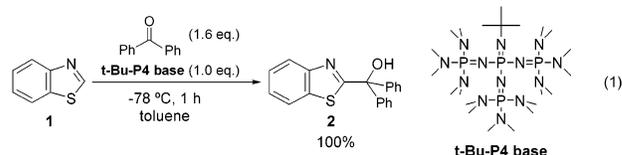

**Figure 1.** New strategy for deprotonative functionalization of aromatics.

In contrast to the traditional reaction using metallic bases, an interesting deprotonative functionalization of aromatics with *t*-Bu-P4 base[6] has been reported in relatively few papers, but detailed reaction conditions were not described.[6a,7] The *t*-Bu-P4 base is an extremely strong nonmetallic organic base (pK_{BH+} = 42.7 in MeCN).[6] Our research has examined the deprotonative functionalization of aromatics with *t*-Bu-P4 base because the base is extremely basic and less nucleophilic,[6b] which allows for highly chemoselective reactions.[8] Also, the nonmetallic *t*-Bu-P4 base cannot function as a Lewis acid. Therefore, the reaction using *t*-Bu-P4 base proceeds without the "coordination mechanism", and the reaction with unique regioselectivity is expected (Figure 1). In this Communication, we wish to report a new reaction with excellent chemoselectivity and unique regioselectivities for deprotonative functionalization of aromatics.

To confirm the adaptability of the *t*-Bu-P4 base in the deprotonative functionalization of aromatics, the reaction of benzothiazole

(**1**) was examined. The 1,2-adduct at the 2-position (**2**) was quantitatively formed when benzothiazole was reacted with *t*-Bu-P4 base in toluene and in the presence of benzophenone as the electrophile (eq 1).[9] Here, the deprotonative functionalization of benzophenone was not observed.

On the basis of these results, we investigated the new strategy for deprotonative functionalization of aromatics. Initially, reactions with π-deficient nitrogen heteroaromatics, which have relatively acidic ring-protons, were examined.
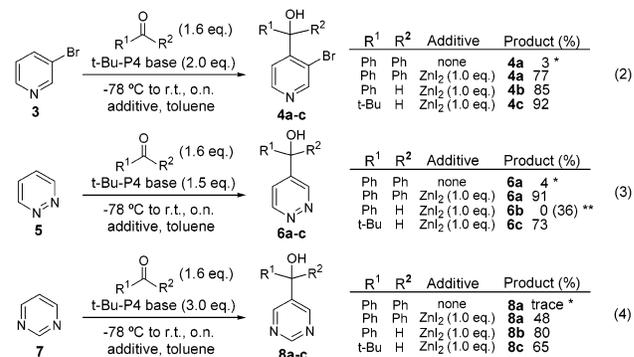

3-Bromopyridine (**3**)[10] was reacted with *t*-Bu-P4 base in the presence of benzophenone in toluene, and the deprotonative functionalization proceeded at the 4-position (**4a**) in only 3% yield. Some additives for facilitating the reaction were then examined. When ZnI$_2$ was used as an additive, the reaction dramatically proceeded, and the yield increased to 77% (eq 2). ZnI$_2$ also enhanced reactions with diazines. Pyridazine (**5**)[11] was reacted under the ZnI$_2$-free conditions, and a 4% yield of the 1,2-adduct at the 4-positon (**6a**) was obtained, but the presence of ZnI$_2$ resulted in a 91% yield (eq 3). Similarly, only a trace amount of the 1,2-adduct at the 5-position (**8a**) was obtained when pyrimidine (**7**)[11] was reacted under the ZnI$_2$-free conditions, but a 48% yield was achieved with the recovery of some unreacted **7** when ZnI$_2$ was added (eq 4). In these reactions, no regioisomer was detected. The addition of ZnI$_2$ resulted in efficient and chemoselective deprotonative

functionalizations of π-deficient nitrogen heteroaromatics.[12] Reactions with other electrophiles (benzaldehyde and pivalaldehyde) also proceeded maintaining the regioselectivities (**4b**,**c**, **6b′**,**c**, **8b**,**c**, eqs 2−4).[13] Benzaldehyde functioned only as an electrophile, and deprotonative functionalization of benzaldehyde was not observed. The regioselectivities of these reactions with azines are quite noteworthy. The reactions proceeded at the most remote position from the ring nitrogens, and pyridazine and pyrimidine display unique regioselectivities in deprotonative functionalization, which is the opposite of the directed ortho metalation.[1,11] In H−D exchange of azines, similar kinetic acidities have been reported. The pair−pair electron repulsion is present in the transition state for deprotonation, and that is considered to be a reason for the acidity pattern.[14] We have a speculation that unique regioselectivities of reactions with *t*-Bu-P4 base may be the result of the same effect of pair−pair electron repulsions.

Intrigued by the exciting results of azines, we then investigated the deprotonative functionalization of benzene derivatives. 4-Bromobenzonitrile (**9**) was treated with *t*-Bu-P4 base in the presence of benzophenone and ZnI$_2$ in toluene, and the reaction proceeded chemoselectively at the 3-position (**10a**)[15] in 55% yield (60% yield in THF). Without ZnI$_2$, the reaction did not proceed (eq 5, Table 1). Surprisingly, the orientation of the reaction is the opposite of the deprotonative metalation using TMP-zincate.[16] Reactions with other electrophiles were also examined. Benzaldehyde and pivalaldehyde were used as electrophiles in the reaction of 4-bromobenzonitrile (**9**) in THF, and the appropriate 1,2-adducts (**10b**,**c**)[15] were obtained in 86%, 87% yield, respectively (eq 5, Table 1).

(5)
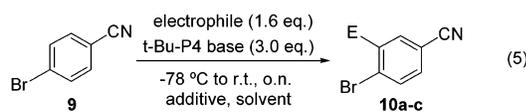
Table 1. Deprotonative Functionalization of 4-Bromobenzonitrile

Electrophile	Solvent	Additive	Product	Yield(%)
	Toluene	none		0[a]
	Toluene	ZnI$_2$ (1.0 eq.)	**10a**	55
	THF	ZnI$_2$ (1.0 eq.)		60
	THF	ZnI$_2$ (1.0 eq.)	**10b**	86
	THF	ZnI$_2$ (1.0 eq.)	**10c**	87

[a] One equivalent of *t*-Bu-P4 base was uitilized.

In summary, a novel type of deprotonative functionalization of aromatics was achieved with unique regioselectivities and excellent chemoselectivity using *t*-Bu-P4 base and ZnI$_2$ in the presence of an electrophile. Further investigations on the scope and limitations of this reaction and mechanistic studies, especially on the role of ZnI$_2$, are underway.

Supporting Information Available: Experimental details and spectroscopy of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The deprotonative metalation of 4-bromobenzonitrile with TMP-zincate and subsequent treatment with benzaldehyde yielded 5-bromo-3-phenylphthalide via deprotonative zincation at the 2-position with a trace amount of the 3-adduct: Imahori, T.; Kondo, Y., unpublished data.

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