Activation of organozinc reagents with *t*-Bu-P4 base for transition metal-free catalytic S_N2' reaction†

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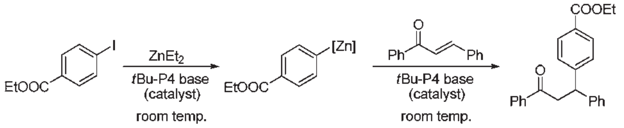
The *t*-Bu-P4 base was found to be an excellent catalyst for activating organozinc reagents and was used to promote the S_N2' reaction of α,β-unsaturated esters bearing a γ-chloride using various organozinc reagents: these reactions proceeded in high yields with excellent chemo-and regioselectivity.

Organozinc reagents are one of the most useful organometallic reagents for organic synthesis.[1] The easy preparation and high functional group compatibility of organozincs allow numerous applications in synthetic chemistry. However, they occasionally require a catalyst to react smoothly with electrophiles. Many organozinc reagent activation methods have been reported and one of the most prevalent methods is transmetalation using transition metal catalysts.[2] However, transition metals are occasionally expensive and sometimes the complete removal of them from the product after the reaction is required, especially in medicinal chemistry research with tricky operations. It is considered very important to provide a novel activation method without the help of transition metal catalysts.

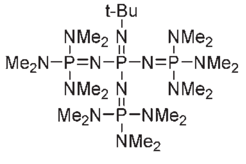
The S_N2' reaction is an important synthetic transformation for creating quaternary carbon centers effectively.[3] Recently, Lee and Hoveyda reported Cu-free asymmetric allylic alkylation reactions with Grignard reagents using *N*-heterocyclic carbenes as Lewis base catalysts.[4] However, the S_N2' reaction of organozinc reagents still required the use of a transition metal catalyst.[5]

We recently reported that the use of catalytic *t*-Bu-P4 base[6] dramatically improves the performance of the halogen–zinc exchange of aryl iodides (Scheme 1).[7] This activation is considered to relate to the donation of the *t*-Bu-P4 base to the zinc atom of dialkylzinc reagents, which increases the electron density of the alkyl group towards high reactivity. Herein we wish to report the S_N2' reaction of organozinc reagents without the use of transition metal catalysts.

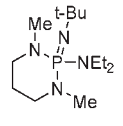


Scheme 1 *t*-Bu-P4 base catalyzed halogen–zinc exchange.

The S_N2' reaction was first examined using α,β-unsaturated esters bearing a γ-chloride (**1**), diethylzinc, and 10 mol% of *t*-Bu-P4 base in various organic solvents (Table 1, entries 1–4). It was suggested that the catalytic activity was solvent dependent and among the solvents tested, DMF was found to be the best for the catalytic activity (Table 1, entry 4). In these cases, no S_N2 reaction product was detected in the NMR analysis of the crude material. By lowering the reaction temperature to 0 °C, the yield of **2** increased to 75% (Table 1, entry 5). The use of a weaker phosphazene base such as BEMP resulted in lower yield (Table 1, entry 6) and the reaction did not proceed in the absence of a phosphazene base (Table 1, entry 7). The use of an additive for facilitating the reaction was then examined. When LiCl was used as an additive, the reaction proceeded more smoothly, and the yield was improved up to 90% (Table 1, entry 7).



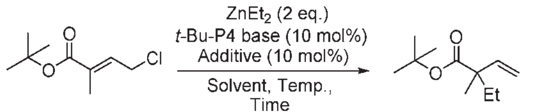
t-Bu-P4 base



BEMP

As shown in Table 1, it was found that the *t*-Bu-P4 base is an excellent catalyst for the S_N2' reaction with organozinc reagents, and the presence of LiCl was also found to be favorable for the smooth conversion. In order to examine further the scope and limitations of the reaction conditions, reactions of other substrates were investigated.

Table 1 Optimization of S_N2' reaction conditions



1 **2**

Entry	Base	Additive	Solvent	Temp/°C	Time/h	Yield (%)
1	*t*-Bu-P4	—	THF	r.t.	24	32[a]
2	*t*-Bu-P4	—	Toluene	r.t.	24	18[a]
3	*t*-Bu-P4	—	DMF	r.t.	2	71
4	*t*-Bu-P4	—	DMF	0	2	75
5	*t*-Bu-P4	—	DMF	−40	12	63[a]
6	BEMP	—	DMF	0	2	29
7	—	—	DMF	0	2	0
8	*t*-Bu-P4	LiCl	DMF	0	2	90

[a] NMR yields.

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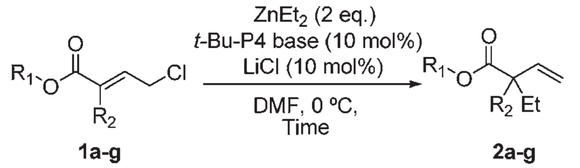
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data for synthesized compounds. See DOI: 10.1039/b807169a

Table 2 S_N2' reaction of functionalized substrates



1a-g → 2a-g

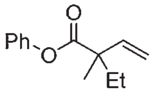
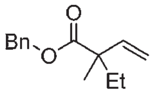
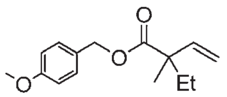
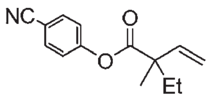
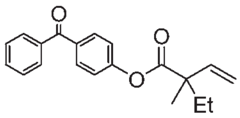
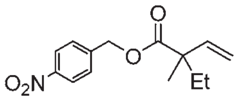
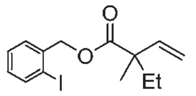
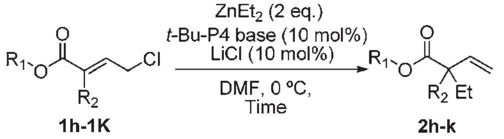
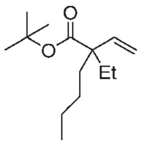
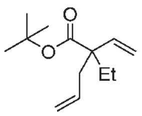
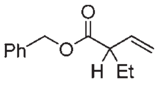
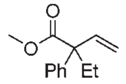
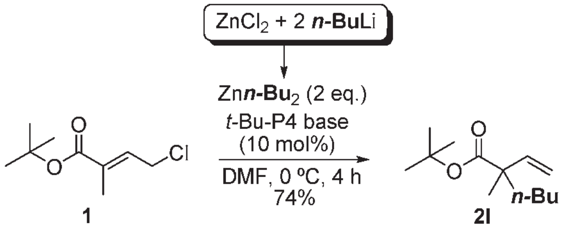
Entry	Product	Time/h	Yield (%)
1		2	87
2		2	93
3		2	91
4		2	84
5		2	88
6		8	66
7		3	88

Table 3 Influence of α-substituents on S_N2' reaction



1h-1K → 2h-k

Entry	Product	Time/h	Yield (%)
1		2	88
2		4	74
3		2	94
4		2	38 (S_N2; 61)



1 → **2l**

Scheme 2 The reaction using dibutylzinc.

As other α,β-unsaturated esters bearing a γ-chloride substrate, phenyl and benzyl esters was reacted with diethylzinc to give the corresponding esters in 87% and 93%, respectivity (Table 2, entries 1,2). Various substituents on α,β-unsaturated esters bearing a γ-chloride were compatible with this S_N2' reaction. The substitution with a metal coordinating group such as a methoxy group did not affect the reaction, and the corresponding ester was obtained in good yield (Table 2, entry 3). The presence of electrophilic functional groups was examined and the tolerance of cyano, carbonyl, nitro and iodo groups during the S_N2' reaction is considered to be synthetically important (Table 2, entries 4–7). These highly selective conversions in the presence of sensitive functional groups are considered to be difficult to achieve using conventional transition metal catalyzed protocols.

Our next interest was focused on the influence of substituents at the α-position of α,β-unsaturated esters. Alkyl, allyl and hydrogen substituted substrates were reacted with diethylzinc under the same reaction conditions and the desired products were obtained in good yields (Table 3, entries 1–3). But, when a phenyl substituted substrate was used, the selectivity was significantly lowered and the desired product was isolated in only 38% yield together with the S_N2 product in 61% yield (Table 3, entry 4).

We next examined the reaction of another alkylzinc with α,β-unsaturated esters bearing a γ-chloride. When di-*n*-butylzinc, prepared from *n*-butyllithium and zinc chloride, was used, the corresponding ester was obtained in 74% yield (Scheme 2).

^{1}H-NMR spectra of dimethylzinc in the presence of the *t*-Bu-P4 base were measured for the preliminary estimation of the activation mechanism. As a result, the methyl signal of dimethylzinc in the presence of *t*-Bu-P4 base in THF at −20 °C was observed as sharp singlet at −1.06 ppm, while the methyl signal of dimethylzinc in the absence of the *t*-Bu-P4 base appears at −0.89 ppm. (see ESI†). This result suggests that dimethylzinc exists as the more anionic form in the presence of the *t*-Bu-P4 base by electron donation from the coordinated *t*-Bu-P4 base to dimethylzinc. It has been known that the coodination of donors to alkylzinc compounds causes higher-field shifts of alkyl protons in ^{1}H-NMR spectra.[8] It is assumed that the high reactivity in presence of *t*-Bu-P4 base is attributed to this complexation.

In conclusion, the use of *t*-Bu-P4 base as a catalysts dramatically improves the performance of S_N2' reaction with organozinc reagents. ^{1}H-NMR study suggested that this high reactivity of *t*-Bu-P4 base catalyis originates from the coordination of the *t*-Bu-P4 base to diethylzinc. Futher investigation on the scope and limitation of the *t*-Bu-P4 base promoted reaction of organozinc compounds and mechanistic studies are underway.

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Notes and references

1 P. Knochel and P. Jones, *Organozinc Reagents*, Oxford University Press, Oxford, 1999.

2 P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93** 2117–2188.

3 (*a*) O. Riant and J. Hannedouche, *Org. Biomol. Chem.*, 2007, **5**, 873–888; (*b*) P. G. Cozzi, R. Hilgraf and N. Zimmermann, *Eur. J. Org. Chem.*, 2007, 5969–5994; (*c*) D. Ramon and M. Yus, *Curr. Org. Chem.*, 2004, **8**, 149–183; (*d*) I. Denissova and L. Barriault, *Tetrahedron*, 2003, **59**, 10105–10146; (*e*) R. M. Magid, *Tetrahedron*, 1980, **36**, 1901–1930, and references therein.

4 Y. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2006, **128**, 15604–15605.

5 (*a*) A. O. Larsen, W. Leu, C. Nieto-Oberhuber, J. F. Campbell and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2004, **126**, 11130–11131; (*b*) J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2005, **127**, 6877–6882; (*c*) K. E. Murphy and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, 4690–4691; (*d*) K. E. Murphy and A. H. Hoveyda, *Org. Lett.*, 2005, **7**, 1255–1258; (*e*) H. Malda, A. W. van Ziji, L. A. Arnold and B. L. Feringa, *Org. Lett.*, 2001, **3**, 1169–1171; (*f*) F. Dübner and P. Knochel, *Tetrahedron Lett.*, 2000, **41**, 9233–9237; (*g*) F. Dübner and P. Knochel, *Angew. Chem., Int. Ed.*, 1999, **38**, 379–381.

6 (*a*) R. Schwesinger and H. Schlemper, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 1167–1169; (*b*) R. Schwesinger, H. Schlemper, C. Hasenfratz, J. Willaredt, T. Dambacher, T. Breuer, C. Ottaway, M. Fletschinger, J. Boele, H. Fritz, D. Putzas, H. W. Rotter, F. G. Bordwell, A. V. Satish, G.-Z. Ji, E.-M. Peters, K. Peters, H. G. von Schnering and L. Walz, *Liebigs Ann.*, 1996, 1055–1081.

7 M. Ueno, A. E. H. Wheatley and Y. Kondo, *Chem. Commun.*, 2006, 3549–3550.

8 (*a*) M. Uchiyama, M. Koike. M. Kameda, Y. Kondo and T. Sakamoto, *J. Am. Chem. Soc.*, 1996, **118**, 8733–8794; (*b*) M. Ishimori and T. Tsuruta, *Kogyo Kagaku Zasshi*, 1967, **70** 152–158.