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S_N2'-Regio- and Diastereoselective Allylation of Organozinc Reagents

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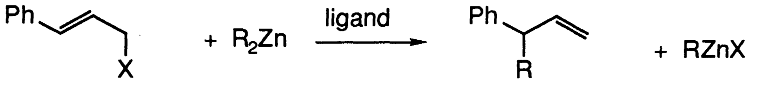
Dialkylzinc reagents, R_2Zn and $R_2Zn{\cdot}LiCl$, undergo an S_N2'-regio- and diastereoselective allylation reaction with substituted allylic chlorides and phosphates in the presence of a coordinating additive.

While the S_N2'-allylation reactions of organocopper reagents have proven to be useful for acyclic stereocontrol,[1)] their synthetic value still appears to be grossly underestimated. In addition, the reagents available for this reaction have been limited entirely to the copper-based ones.[2)] In this context, we felt it necessary to find new organometallics in order to further explore the potential of the S_N2'-reactions. We wish to report that, in the presence of a suitable ligand, dialkylzinc reagents act as a thermally stable, regio- and stereoselective alkyl donor to allylic chlorides and phosphates.



(1)

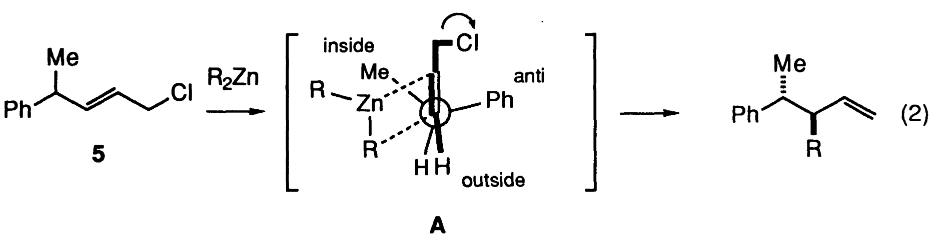
1: X = Cl
2: X = Br
3: X = OP(O)(OEt)$_2$

ligand = DMF, HMPA, TMEDA etc.

Alkylzinc compounds, RZnCl, R_2Zn, and R_3ZnLi,[3)] are a poor alkyl donor to an allylic halide.[4)] We found, however, that they do undergo smooth allylation reaction in the presence of a polar ligand (Table 1). Thus, in the presence of two equivalents of HMPA in THF, dialkylzinc reagents (Et_2Zn, $Bu_2Zn{\cdot}2LiCl$, or $Me_2Zn{\cdot}2LiCl$) smoothly undergo selective allylation at room temperature, giving the desired S_N2'-product in excellent yield with high regioselectivity (entries 2, 6-9, and 13). In contrast, alkylzinc chloride reagents ($BuZnCl{\cdot}LiCl$) are poorly reactive, yet highly S_N2'-selective (entry 1), and trialkylzincate reagents, $Bu_3ZnLi{\cdot}LiCl$, are very reactive yet poorly regioselective (entry 3).[5)] HMPA could be replaced by equally effective additives such as excess DMF (entry 8) or one equivalent of TMEDA (entries 7 and 9-11). A monodentate amine, Et_3N was found to be ineffective. The presence of LiCl has no consequence on the allylation reaction, and pure Et_2Zn in HMPA/THF/hexane also reacted smoothly (entry 9). Interestingly, the nature of the bulk solvent was found to be important for the regio- and diastereoselectivities as well as for the reaction rate. Thus, the reaction in pure hexane was immensely slow, and the reaction in TMEDA/hexane (entry 10)

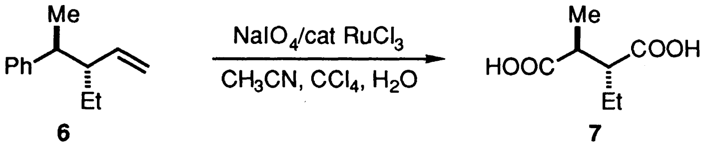
was found to be much less selective and much slower than in TMEDA/THF (cf. entry 9). The use of high pressure (11 kbar, 25 °C), however, was found to significantly improve both the selectivities and the reaction rate (cf. entry 11). The reaction in pure hexane under high pressure was neither regio- nor diastereoselective.[6)]

As observed for organocopper reagents,[1e)] the nature of the leaving group influences the regioselectivity. Thus, allylic chloride and phosphate[7)] showed high S_N2'-selectivity (entry 5), and more reactive allylic bromide exhibited poor selectivity (entry 4).



(2)

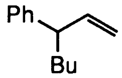
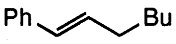
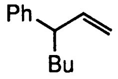
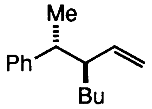
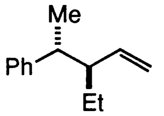
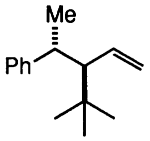
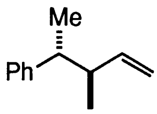
We next examined the diastereoselectivity of the reaction. Structure **5** represents prototypical substrate for the studies of the selectivity in relation to the Cram's rule (Eq. 2). The reaction of **5** with an R_2Zn reagent proceeded smoothly with excellent S_N2'-regioselectivity and with high diastereoselectivity (entries 6-9). Both R_2Zn and $R_2Zn \cdot 2LiCl$ reagents reacted with **5** to give the *anti* products as a major product with 87-89% ds. The regioselectivity eroded for a bulky (*t*-Bu)$_2$Zn reagent (entry 12), but the level of diastereoselectivity remained unchanged. Oxidative degradation of the vinyl and the phenyl groups of the allylation product **6** gave the known diacid (*2R**,*3S**)-2-ethyl-3-methylsuccinic acid (**7**, Eq. 3), revealing the *anti* stereochemistry of the allylation reaction.



(3)

The observed selectivity profile conforms to the standard Cram's rule (**A**) proposed for carbonyl additions. While the mechanisms of the present allylation reaction and the carbonyl addition may seem different from each other, similarity may become rational if the allylation reaction is viewed as a pseudo-carbometalation reaction as suggested in the structure **A**. Recent theoretical calculations have demonstrated the close kinship between the transition structures of carbometalation and carbonyl addition,[8)] and there is experimental evidence that a certain type of S_N2'-allylation reaction of organocuprates does proceed via a carbometalation mechanism.[9,10)]

Table 1. Regio- and Stereoselective Allylation of Organozinc Reagents[a)]

Entry	Allyl-X	"RZn(II)"	Additive	Yield/%	%S_N2'	%ds	Major product[b)]
1	**1**	BuZnCl·LiCl	HMPA	20	98	-	
2	**1**	Bu_2Zn·2LiCl	HMPA	93	98	-	
3	**1**	Bu_3ZnLi·2LiCl	HMPA	91	4	-	
4	**2**	Bu_2Zn·2LiCl	HMPA	88	72	-	
5	**3**	Bu_2Zn·2LiCl	HMPA	45	98	-	
6	**5**	Bu_2Zn·2LiCl	HMPA	87	97	89	
7	**5**	Bu_2Zn·2LiCl	TMEDA	83	97	87	
8	**5**	Bu_2Zn·2LiCl	DMF	48	96	87	
9	**5**	Et_2Zn	TMEDA	87	97	87	
10	**5**	Et_2Zn (hexane)	TMEDA	9	50	67	**6**
11	**5**	Et_2Zn (hexane/11 kbar)	TMEDA	79	90	78	
12	**5**	*t*-Bu_2Zn·2LiCl	HMPA	52	49	87	
13	**5**	Me_2Zn·2LiCl	HMPA	68	83	84	

a) See footnote 6 for the procedure. Reaction period is 4 h, 12-24 h, and 72 h in entries 1-5, 6-12, and 13, respectively. Reactions were carried out in hexane/THF, except in entries 10 and 11, 12, and 13 in hexane, pentane/THF, and ether/THF, respectively.

b) The stereochemistry of the product in entry 9 has been determined as shown in Eq. 3, and that in entry 13 has been similarly correlated to 2,3-dimethylsuccinic acid. Others were assigned by analogy.

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References

1) a) T. Ibuka, H. Habashita, S. Funakoshi, N. Fujii, Y. Oguchi, T. Uyehara, and Y. Yamamoto, *Angew. Chem., Int. Ed. Engl.*, **29**, 801 (1990) and refs therein; b) S. L. Denmark and L. K. Marble, *J. Org. Chem.*, **55**, 1984 (1990); c) J. P. Marino and A. Viso, *ibid.*, **56**, 1349 (1991); d) J. A. Marshall, T. D. Crute III, and J. D. Hsi, *ibid.*, **57**, 115 (1992); e) E. Nakamura, K. Sekiya, M. Arai, and S. Aoki, *J. Am. Chem. Soc.*, **111**, 3091 (1989).

2) M. Arai, E. Nakamura, and B. H. Lipshutz, *J. Org. Chem.*, **56**, 5489 (1991); M. Bourgain-Commerçon, J.-F. Normant, and J. Villieras, *J. Chem. Res. (synopses)*, **1977**, 183; S. Araki and Y. Butsugan, *J. Chem Soc., Perkin Trans. 1*, **1984**, 969; A. Yanagisawa, Y. Noritake, N. Nomura, and H. Yamamoto, *Synlett*, **1991**, 251; A. Yanagisawa, N. Nomura, Y. Noritake, and H. Yamamoto, *Synthesis*, **1991**, 1130; K. Bannai, T. Tanaka, N. Okamura, A. Hazato, S. Sugiura, K. Manabe, K. Tomimori, Y. Kato, S. Kurozumi, and R. Noyori, *Tetrahedron*, **46**, 6689 (1990).

3) The reagents examined in these reactions, $BuZnCl \cdot LiCl$, $Bu_2Zn \cdot 2LiCl$, and $Bu_3ZnLi \cdot 2LiCl$, were prepared in situ by the reaction of BuLi with $ZnCl_2$.

4) They undergo allylation only in the presence of a suitable transition metal catalyst. K. Sekiya and E. Nakamura, *Tetrahedron Lett.*, **29**, 5155 (1988).

5) Diallyl and diphenylzinc reagents predominantly gave S_N2 products.

6) Typical procedure is as follows. To a solution of $ZnCl_2$ (1.0 M THF, 1.5 mmol, 1.5 mL) was added *n*-BuLi (1.58 M hexane, 3 mmol) at -70 °C. After addition of HMPA (3 mmol), an allylic chloride (1 mmol) was added at -70 °C. The reaction mixture was warmed to room temperature, and was stirred for 4 h. After addition of ca. 2 mL of hexane saturated with water, the reaction mixture was passed through a pad of silica gel. Capillary GC analysis (HR-1) of the filtrate indicated the S_N2'/S_N2 ratio. Purification of the crude product by silica gel column chromatography afforded the allylation product.

7) Cf. J. A. Miller and H. C. S. Wood, *J. Chem. Soc., C*, **1968**, 1837.

8) E. Nakamura, M. Nakamura, Y. Miyachi, N. Koga, and K. Morokuma, *J. Am. Chem. Soc.* in press.

9) a) A. Alexakis, I. Marek, P. Mangeney, and J. F. Normant, *J. Am. Chem. Soc.*, **112**, 8042 (1990). See also: J. Berlan, Y. Besace, G. Pourcelot, and P. Cresson, *J. Organomet. Chem.*, **256**, 181 (1983); M. Huche, J. Aubouet, G. Poucelot, and J. Berlan, *Tetrahedron Lett.*, **24**, 585 (1983); P. Mangeney, A. Alexakis, and J. F. Normant, *ibid.*, **24**, 373 (1983). b) A fundamentally different mechanism involves an initial nucleophilic attack of Cu(I) metal leading to a Cu(III) intermediate followed by reductive elimination to give the S_N2'-allylation product. This mechanism, however, is improbable for organozinc compounds,. Cf. J. M. Dollat, J. L. Luche, and P. Crabbé, *J. Chem. Soc., Chem. Commun.*, **1977**, 761.

10)Professor Keiji Yamamoto of this Institute has also found regioselective allylation of organozinc species. We thank Prof. Yamamoto for this information prior to publication.

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