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Preparation and Stereoselective Additions of Highly Substituted Cyclic Allylzinc Reagents

A Zinc-Ene Cyclization

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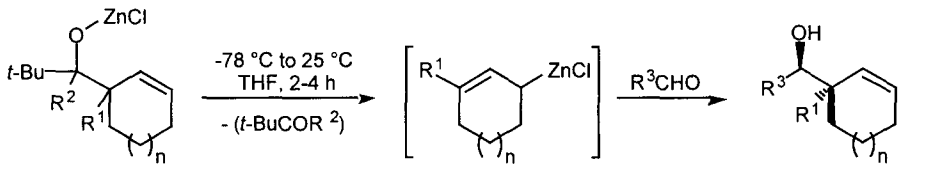
Abstract : Highly substituted cyclic allylzinc reagents 2 have been prepared by fragmentation of sterically hindered homoallylic zinc alcoholates 1. Their reactions with aldehydes proceed under mild conditions and are highly stereoselective (64-86 % ; d.r. up to >98/2). Examples of acylation with benzonitrile and zinc-ene cyclization giving new spirobicyclic zinc reagents are also reported.

The use of allylic organometallics for carbon-carbon bond formation in stereoselective synthesis has received much attention over the past decades.[1] Despite the numerous methods available for performing allylation reactions, there still remains several problems associated with the generation of allyl organometallic reagents. For example, the reaction of allylic halides with a metal such as Li, Mg or Zn gives high proportions of Wurtz homocoupling products. This side reaction becomes a major problem if the generation of highly substituted elaborated allylic organometallics is considered, since the degree of substitution and functionalization dramatically increases the amount of homocoupling products.[2] Recently, we have described a new approach for the generation of allylzinc reagents avoiding these problems based on the fragmentation of sterically hindered homoallylic alcohols.[3] This methodology has also revealed an excellent stereocontrol in the subsequent reaction with aldehydes.[3b] Herein, we wish to disclose a new application of homoallylic zinc alcoholates (masked allylic zinc reagents) for the preparation of highly substituted cyclic allylzinc reagents, their stereoselective addition to aldehydes and the performance of a zinc-ene cyclization.

Homoallylic alcoholates of type **1** undergo a fragmentation in the presence of zinc salts affording highly substituted cyclic allylzinc reagents **2** (Scheme 1). These reagents can be trapped with a range of aldehydes in satisfactory yields (64-86 %) and excellent diastereoselectivities (up to > 98/2). The reactions occurred in very mild conditions (-78 °C to 25 °C) and in short reaction times (2-4 h).



1 : n = 0, 1, 2 **2** **3** : 64-86 %
syn/*anti* up to >98/2

Scheme 1

The 6-membered rings homoallylic alcoholates **1** required for the fragmentation reaction were prepared from cyclohexenyl *tert*-butyl ketone **4** in three steps (Scheme 2). The γ-deprotonation of **4** with LDA in a THF/HMPA mixture leads at -78 °C (3 h) to the expected lithium dienolate. Its methylation at the α-position affords an intermediate β,γ-unsaturated ketone in 88 % yield.[4] Addition of *sec*-BuLi in ether at -78 °C gives the desired alcohol **5a**. Its deprotonation with *n*-BuLi (-78 °C) provides a lithium alcoholate (Procedure A) which proved to be stable at -78 °C for several hours

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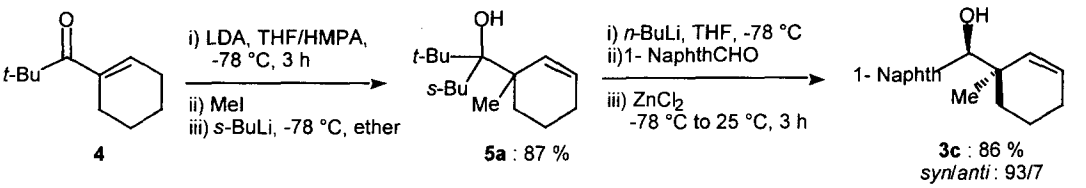
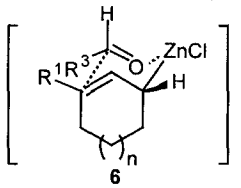
toward fragmentation. The subsequent addition of 1-naphthaldehyde followed by zinc chloride leads to a rapid reaction to afford the *syn* γ-adduct **3c** in 86 % yield (d.r. = 93/7).[5]



4 **5a** : 87 % **3c** : 86 %
syn/*anti* : 93/7

Scheme 2

We have applied this method for preparing highly substituted allylic organometallics having 5, 6 and 7-membered rings. The rate of the reaction strongly depends on the steric hindrance of the alcoholate and on the ring size. Thus, for the 6-membered ring series when R^1 = H, two *tert*-Bu groups adjacent to the tertiary alcoholate position were required to induce the fragmentation at 0 °C in the presence of zinc salt (entry 4 of Table 1). When the steric hindrance was increased (R^1 = Me), the presence of one *tert*-Bu and one *sec*-Bu group was sufficient to initiate a fast and clean reaction at -78 °C (see entries 1-3 of Table 1).[5] When R^1 = allyl, the cyclic allylzinc reagent has been generated in a one-pot reaction starting from the corresponding ketone **5c** (entries 5 and 6 of Table 1). Thus, the addition of *n*-BuLi at 0 °C afforded a THF solution of the tertiary lithium alcoholate which was immediately cooled to -78 °C (Procedure B). Addition of the aldehyde followed by zinc chloride gave a clean reaction by slowly warming to 25 °C. Additionally these results showed that diastereoselectivities increased with the steric hindrance of R^1 (compare entries 1, 4 and 5 of Table 1). In the case of the 5-membered ring series,[6] the reaction only occurred in the presence of two *tert*-Bu groups (entry 7 of Table 1). Low diastereoselectivity was observed in this series. The 7-membered ring allylzinc reagent was directly generated from the ketone **5e**[7] according to procedure B and was reacted with benzaldehyde to afford **3h** in 67 % yield and good diastereoselectivity (*syn*/*anti* = 90/10 ; entry 8 of Table 1).



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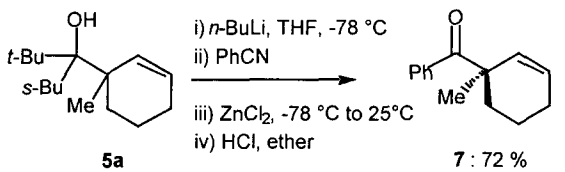
Scheme 3



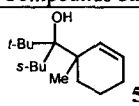
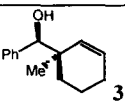
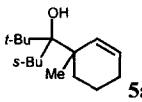
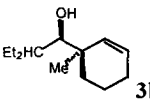
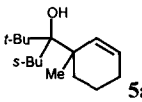
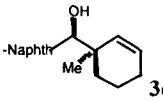
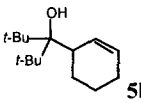
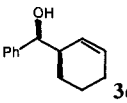
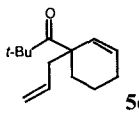
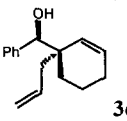
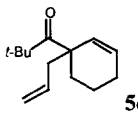
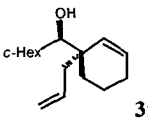
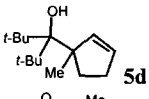
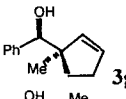
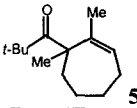
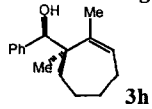
5a **7** : 72 %

Scheme 4

These results suggested that a chair-like transition state like **6** where each substituent would be placed in an equatorial position would explain the observed relative diastereoselectivities (Scheme 3).[8] Acylation reactions were also possible by adding nitriles to cyclic allylzinc reagents. Thus, the zinc alcoholate of **5a** reacted with benzonitrile affording the ketone **7** in 72 % yield after acid hydrolysis (Scheme 4).

Metallo-ene cyclizations have been used as key steps in natural products synthesis.[9] However their applications are limited due to the difficulties encounted for the preparation of the starting allylic metal reagents. The use of homoallylic alcohols as masked allylzinc reagents allows a straightforward preparation of precursors for the zinc-ene reaction. Thus, the enone **8** was treated with *n*-BuLi at 0 °C in THF giving the corresponding tertiary lithium alcoholate (Scheme 5). After cooling to -78 °C, zinc chloride (1 equiv.) was added to promote the fragmentation. By slowly warming to 25 °C

Table 1 : Products **3a-h** obtained by the fragmentation of the zinc alcoholates **1** derived from compounds **5a-e** and subsequent trapping with aldehydes.

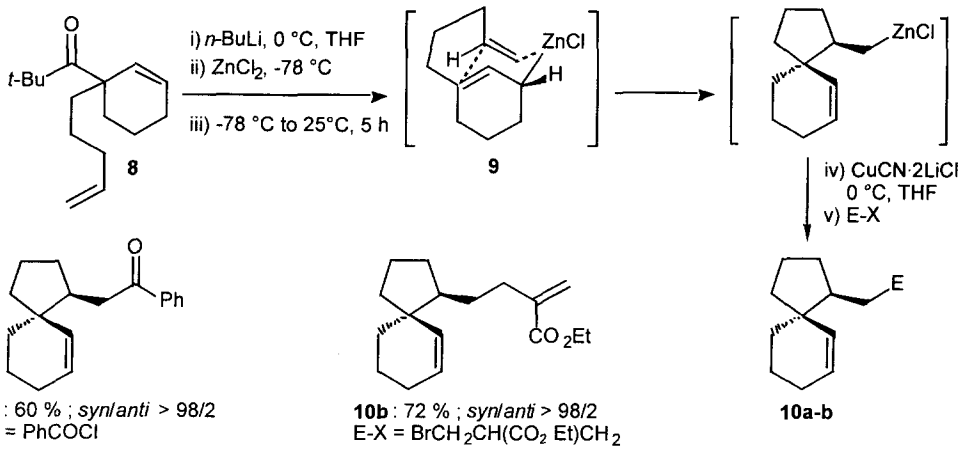
Entries	Compounds **5a-e**	R^{3a}	Procedure[b]	Products **3a-h**	*syn/anti*[c]	Yields (%)[d]
1	 **5a**	Ph	A	 **3a**	92/8	77[e]
2	 **5a**	Et_2CH	A	 **3b**	90/10	81
3	 **5a**	1-Naphth	A	 **3c**	93/7	86
4	 **5b**	Ph[f]	A	 **3d**	90/10	64[g]
5	 **5c**	Ph	B	 **3e**	5/95	77
6	 **5c**	*c*-Hex	B	 **3f**	> 2/98	76
7	 **5d**	Ph	A	 **3g**	75/25	81[h]
8	 **5e**	Ph[f]	B	 **3h**	90/10	67

[a] Aldehyde : 0.9 eq ; [b] Procedure A : i) *n*-BuLi, THF, -78 °C ii) R^3CHO iii) $ZnCl_2$; Procedure B : i) *n*-BuLi, THF, 0 °C, ii) R^3CHO, -78 °C iii) $ZnCl_2$; [c] ^1H NMR determined ratio ; [d] Isolated yields ; [e] The reaction was also run with $InCl_3$ using the same conditions (52 % yield ; *syn/anti* = 80/20) ; [f] Benzaldehyde : 0,7 eq ; [g] Reaction time 60 h at 0 °C ; [h] The reaction was also run with $InCl_3$ using the same conditions (54 % yield ; *syn/anti* = 52/48).

over 4 h, complete fragmentation was observed and further cyclization of the resulting unsatured allylzinc reagent **9** was achieved. Transmetallation with CuCN·2LiCl followed by addition of benzoyl chloride or ethyl 2-(bromomethyl)acrylate afforded 1-substituted spiro-[4,5]dec-6-ene **10a** and **10b** respectively in 60 % and 72 % yield. Only one diastereoisomer was observed by ^1H and ^{13}C NMR analysis. The relative stereochemistry of the products were determined by X-Ray analyses of compound **10a**.[10]

In summary, we have shown that zinc alcoholates of type **1** are versatile masked zinc reagents[3] allowing the convenient preparation of substituted cyclic allylzinc reagents not previously available by simple methods. No formation of Wurtz homocoupling products was observed. The method has also been applied in a stereoselective zinc-ene cyclization to

prepare new spirobicyclic zinc reagents. It illustrates the potential of this chemistry in natural product synthesis. Further applications are currently underway in this direction.



Scheme 5

References and Notes

1) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
2) Knochel, P. *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, **1991**; Vol. 1, p. 211.
3) a) Jones, P.; Millot, N.; Knochel, P. *Chem. Commun.* **1998**, 2405 ; b) Jones, P.; Knochel, P. *Chem. Commun.* **1998**, 2407 ; c) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186.
4) a) Herrmann, J.L.; Kieczykowski, G.R., Schlessinger, R.H. *Tetrahedron Lett.* **1973**, 26, 2433 ; b) Rathke, M.W., Sullivan, D. *Tetrahedron Lett.* **1972**, 41, 4249.
5) *Typical procedure A* : preparation of *syn*-3-((hydroxynaphthyl)methyl)-3-methylcyclohexene of type **2c** : A two-necked flask equipped with an argon inlet was charged with **5a** (0.30 g, 1. 26 mmol) and THF (2 mL). This solution was cooled to -78 °C and a solution of *n*-butyllithium (0.80 mL, 1.26 mmol, 1.57 M in hexane) was added. After stirring for 15 min., 1-naphthaldehyde (0.15 mL, 1.13 mmol) was added via syringe followed by a solution of zinc chloride (0.17 g, 1.26 mmol) in THF (2 mL). The reaction mixture was slowly warmed to room temperature and stirred for 3 h. The reaction mixture was quenched with a saturated aqueous solution of ammonium chloride and extracted with ether. The combined organics were washed with brine and dried ($MgSO_4$). The solvents were evaporated and the crude residue was purified by flash chromatography (pentane/ether : 90/10) to afford 0.24 g (0.97 mmol ; 86 % ; *syn/anti* : 93/7) of **3c** as a colorless oil. ^1H NMR ($CDCl_3$) δ: 8.08-8.04 (1H, m), 7.75-7.66 (3H, m), 7.46-7.37 (3H, m), 5.71 (1H, dt, J = 10.2 Hz, J = 3.7 Hz), 5.45 (1H, s, CH *syn*), 5.40 (1H, s, CH *anti*), 5.32 (1H, d, J = 10.2 Hz), 1.94-1.32 (6H, m), 0.93 (3H, s, CH_3 *syn*), 0.70 (3H, s, CH_3 *anti*). HRMS calcd. for $C_{18}H_{20}O$: 252.1509, found : 252.1525.
6) The 5-membered ring alcohol **5d** was prepared in three steps from cyclopentenyl *tert*-butyl ketone according to Scheme 2.
7) The synthesis of 3-(2,2-dimethylpropionyl)-2,3-dimethylcycloheptene **5e** has been achieved in two steps from 2-(2,2-dimethylpropionyl)-2-methylcycloheptanone : i) LDA, THF, -78 °C, 15 min. ii) $PhNTf_2$ (80 % yield) then $Me_2Cu(CN)Li_2$, THF, -78 °C to rt, 3 h (70 % yield).
8) The relative diastereoselectivity of compounds **2** was assigned according to the previously published NMR data : Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620.
9) a) Oppolzer, W. *Comprehensive Organic Synthesis*; Trost, B.M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, **1991**; Vol. 5, p. 29 ; b) Oppolzer, W.; Ando, A.; *Chimia* **1992**, *46*, 122 ; c) Oppolzer, W.; Bienaymé, H.; Genevois-Borelle, A. *J. Am. Chem. Soc.* **1991**, *113* , 9660 ; d) Meyer, C.; Marek, I.; Normant, J.-F. *Tetrahedron Lett.* **1996**, *37*, 857.
10) X-Ray analyses were performed by measuring intensity data on a Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Cu Kα radiation and the ω scan technique up to θ = 70°. Lists of atomic coordinates, bond distances, bond angles, torsional angles have been deposited at the Cambridge Crystallographic Data Center (n° CCDC 125015).