Highly diastereoselective reactions using masked allylic zinc reagents

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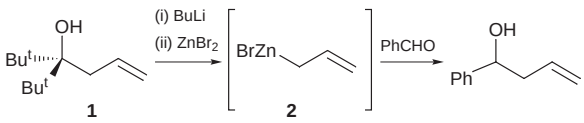
Substituted allylic organozinc reagents have been prepared using a novel fragmentation reaction; the resulting allylic zinc species are configurationally stable and give excellent regio- and diastereo-selectivities.

We have recently documented an entirely new approach for the generation of allylic zinc reagents based on a retro-allylation, an allylation sequence starting from the sterically hindered tertiary alcohol **1** (Scheme 1).[1,2] Generation of the zinc alkoxide of this homoallylic alcohol results in fragmentation and formation of an allyl zinc reagent **2** *in situ*; this is itself able to react with a range of other electrophiles. This method avoids the problems associated with Wurtz coupling.



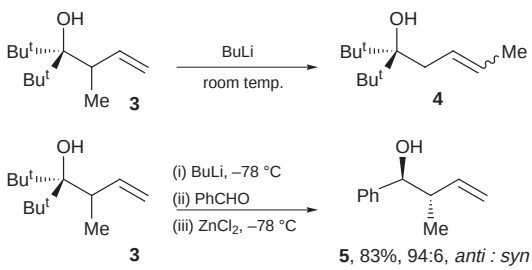
1 **2**

Scheme 1

Substituted allyl zinc reagents had previously been prepared by Tamura from allyl benzoates but with mixed results;[3] we hoped that our mild method would give improved selectivities.

Accordingly, the tertiary alcohol **3** bearing an α-methylallyl group was prepared (Scheme 2).[4] However, we were disappointed to find that upon deprotonation of this material at room temperature with BuLi a rapid isomerisation to the γ-substituted isomer **4** occurred.[5] Undeterred, the deprotonation was attempted at −78 °C, and we were pleased to find no isomerisation. Addition of benzaldehyde followed by a solution of zinc chloride gave within 1 h at −78 °C the benzylic alcohol **5** in 83% isolated yield.† More interestingly, the product was isolated as a 94:6 mixture of *anti*:*syn* diastereomers.[6] This reaction is in stark contrast to the addition of crotylzinc bromide to benzaldehyde, which gives approximately 1:1 mixtures of diastereomers.[7]

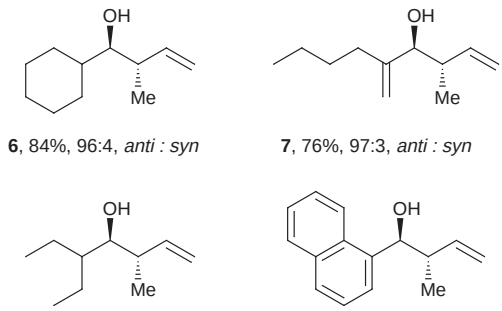
Inspired by this reaction, a range of aldehydes were screened (Fig. 1). Reaction of the homoallylic alcohol with cyclohexanecarbaldehyde gave the alcohol **6** in 84% yield, again with the *anti* diastereomer in excess (96:4). Similarly, reaction with 2-butylacrolein gave solely the product of 1,2-addition, giving the homoallylic alcohol **7** in 76% isolated yield as a 97:3 mixture of diastereomers. The reaction with 2-ethylbutyraldehyde and 1-naphthaldehyde gave the expected products **8** and **9** in 86 and 92% yields, respectively; in both cases only the



3 **4**

3 **5**, 83%, 94:6, *anti : syn*

Scheme 2



6, 84%, 96:4, *anti : syn* **7**, 76%, 97:3, *anti : syn*

8, 86%, >98:2, *anti : syn* **9**, 92%, >98:2, *anti : syn*

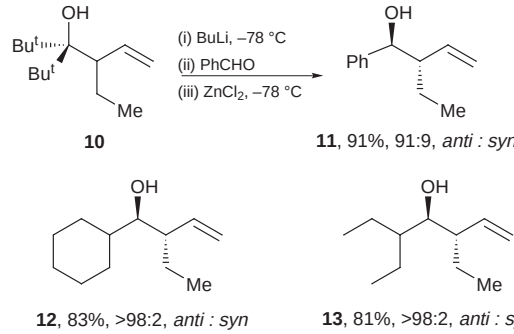
Fig. 1

anti-diastereomer was observed by ^{1}H and ^{13}C NMR spectroscopy. In all cases, none of the γ-substituted product was detected.

Similar results were obtained when we placed other substituents in the α-position. 3-(*tert*-Butyl)-2,2-dimethyl-4-ethylhex-5-en-3-ol **10** was prepared using identical chemistry as used in the preparation of homoallylic alcohol **3**.[4] This too was found to exhibit high levels of *anti*-selectivity. Reaction with BuLi, benzaldehyde and zinc chloride (Scheme 3) gave 2-ethyl-1-phenylbut-3-en-1-ol **11** in 91% as a 91:9 mixture of *anti*:*syn* isomers. Likewise, reaction with cyclohexanecarbaldehyde and 2-ethylbutyraldehyde gave rise to the homoallylic alcohols **12** and **13** in 83 and 81% yields, respectively, both solely as the *anti*-diastereomers.

Further synthetic investigation revealed that a benzyl group could easily be incorporated into the α-position of the homoallylic alcohol (Scheme 4). The precursor was readily prepared form 2, 2-dimethylhex-5-en-3-one **14** by deprotonation with LDA at −78 °C, followed by α-alkylation with BnBr in THF–HMPA in 65% yield. Subsequent reaction with Bu^{t}Li gave the required precursor **15** in 85% yield. As in all previous cases, deprotonation and reaction with benzaldehyde in the presence of zinc chloride gave the desired benzylic alcohol **16** in 89%, again with excellent diastereoselectivity (95:5). Aliphatic aldehydes also reacted well giving the homoallylic alcohols **17** and **18** in 88 and 80% yields, respectively.

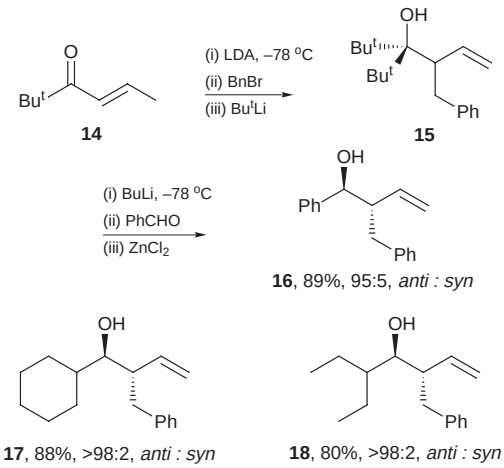
Surprised by these results we were interested to investigate the outcome of placing substituents in the γ-position of the



10 **11**, 91%, 91:9, *anti : syn*

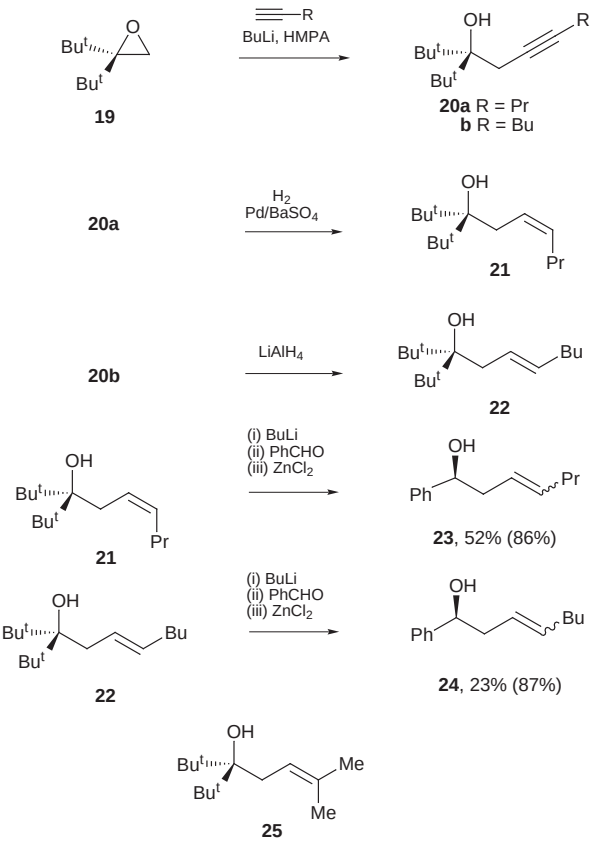
12, 83%, >98:2, *anti : syn* **13**, 81%, >98:2, *anti : syn*

Scheme 3

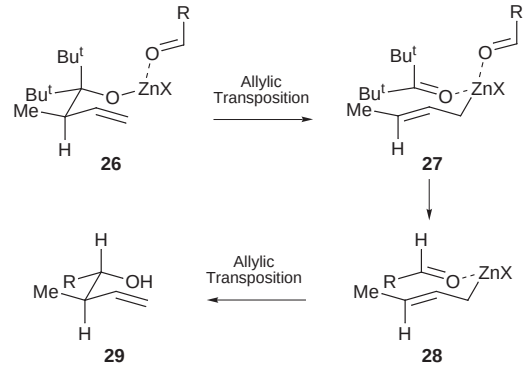


Scheme 4

allylic system. A new synthetic route needed to be adopted and oxirane **19** was prepared and opened with a variety of lithium acetylides to give the homopropargyl compounds **20a**,**b** in reasonable yields (84 and 65%) (Scheme 5). Hydrogenation with palladium on barium sulfate gave the *Z*-isomer **21** quantitatively, whilst treatment with $LiAlH_4$ gave the required *E*-isomer **22**. With these two compounds to hand the migration was investigated. The resulting zinc alkoxides were found to be less reactive. Whereas the α-substituted compounds migrated at −78 °C, these compounds required warming to room temperature before migration could be observed. With **21** migration occurred in 52% yield after 48 h (86% based on recovered starting material) to give the desired homoallylic alcohol **23**, while the *E*-isomer **22** gave the corresponding alcohol **24** in 23% yield after 12 h (87% based on recovered starting material). In both cases the products were isolated as 2:1 mixture of *Z*:*E* isomers. The γ-disubstituted compound **25** was also prepared; however, this compound proved to be stable and no migration was detected.



Scheme 5



Scheme 6

These results suggest a plausible mechanism involving a double allylic transposition. Generation of the zinc alkoxide of the alcohol **26** results in a cyclic six-membered intermediate where the zinc is complexed to the reacting carbonyl compound (Scheme 6). Allylic transposition gives rise to a crotylzinc reagent **27** complexed to the parent bis(*tert*-butyl) ketone and the reaction partner, the zinc reagent bearing solely a *trans*-configuration. At −78 °C this species is stable and undergoes no isomerisation.[8] Owing to the complexation of the reacting partner with the zinc, a new six-centred intermediate **28** is possible, whereby all the substituents lie in equatorial positions; allylic transposition then gives rise to the product **29**, predominately as the *anti*-diastereomer. This mechanism is supported by the unreactive nature of the γ-substituted isomer, whereby steric congestion prevents the first allylic transposition from occurring.

In summary, we have developed a novel method for the preparation of substituted allylic zinc reagents. This method is extremely selective, giving both excellent regiochemical selectivity and excellent diastereoselectivity. The method is extremely mild and avoids Wurtz coupling products.[9]

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Notes and references

† Typical procedure: *anti*-2-methyl-1-phenylbut-3-en-1-ol **5**: A solution of BuLi (2.52 mmol) in pentane (1.6 M, 1.58 ml) was added dropwise over 5 min to a stirred solution of 3-*tert*-butyl-2,2,4-trimethylhex-5-en-3-ol (ref. 4) **3** (500 mg, 2.52 mmol) in THF (4 ml) at −78 °C under argon. The resulting solution was then stirred for 15 min and benzaldehyde (256 μl, 2.52 mmol) was added and stirred for a further 15 min; finally a solution of zinc chloride (343 mg, 2.52 mmol) in THF (2 ml) was added over 3 min. The reaction was stirred at −78 °C for 1 h then allowed to warm to room temperature. The reaction was worked up as usual to give a crude residue, which was then purified by column chromatography on silica using 10% Et_2O–light petroleum as eluent to give the desired alcohol (ref. 10) **5** (341 mg, 83%) as a pale yellow oil.

1 Y. Yamamoto and N. Asao, *Chem. Rev*., 1993, **93**, 2207.
2 P. Jones, N. Millot and P. Knochel, *Chem. Commun*., 1998, 2405.
3 M. Shimizu, M. Kimura, S. Tanaka and Y. Tamaru, *Tetrahedron Lett.* 1998, **39**, 609 and references cited therein.
4 R. A. Benkeser, M. P. Siklosi and E. C. Mozdzen, *J. Am. Chem. Soc*., 1978, **100**, 2134.
5 F. Gérard and P. Miginiac, *Bull. Chim. Soc. Fr*., 1974, 2527; F. Barbot and P. Miginiac, *Bull. Chim. Soc. Fr*., 1977, 113.
6 All diastereomeric excesses were determined by ^1H NMR analysis.
7 S. R. Wilson and M. E. Guazzaroni, *J. Org. Chem*., 1989, **54**, 3087.
8 bis (3-Methylallyl)zinc is known to be a rapidly isomerising system at room temperature, hence explaining the 1:1 *anti*:*syn* selectivity in additions to aldehydes. R. Benn, E. G. Hoffmann, H. Lehmkuhl and H. Nehl, *J. Organomet. Chem*., 1978, **146**, 103.
9 A patent has been filed with Chemetall GmbH (Frankfurt).
10 S. Kobayashi and K. Nishio, *J. Org. Chem*., 1994, **59**, 6620.

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