Kinetic Resolution of an Organozinc Reagent: In Situ Formation of an Enantioenriched Allenylzinc Species

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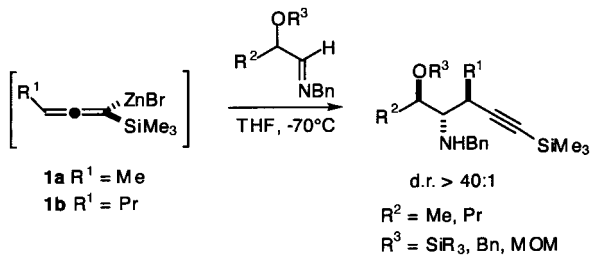
There are very few examples in the literature where an enantioenriched main group organometallic is generated by resolution and further used in a subsequent step. So far, only low enantioselectivities have been obtained.[1] Herein we wish to report the first efficient kinetic resolution of allenylzinc bromide using enantioenriched imines, derived from mandelic and lactic acids, as the resolving agents.

Recently we have shown that allenylzinc bromides **1a**,**b**, derived from propargylic lithium species, react with α-alkoxyimines in a very diastereoselective manner.[2] The anti/anti adduct is obtained in high yield and excellent diastereoselectivity at low temperature (Scheme 1).

Using this electrophile, we addressed the configurational stability of allenylzinc bromide reagent **1**[3] by means of the Hoffmann test.[4] The stability was demonstrated at −60 and −10 °C. In these experiments, the low velocity of the reaction of the mismatched pair of enantiomers was particularly striking. We therefore wondered whether it would be possible to benefit from this slow kinetics using the chiral imine as a resolving agent. Indeed, using 0.5 equiv of imine for 1 equiv of organometallics could lead to the consumption of only one enantiomer of the configurationnally stable allenylzinc, leaving in situ an enantioenriched unreacted allenylzinc. To get direct access to the enantiomeric excess of the organometallic, we decided to trap the remaining organometallic, using pivalaldehyde as electrophile (Scheme 2). The enantiomeric excess of the thus formed anti homopropargylic alcohol[5,6] can be easily determined by chiral GC.[7]

We performed various experiments with (*S*)-lactic and (*R*)-mandelic imine derivatives (*S*)-**2a** and (*R*)-**2b**. The former gave enantiomeric excesses of 50−52% of (+)-**3** (Table 1, entries 1 and 2), quite unsatisfactory but yet better than all previous reports. This result may be due to the slightly lower efficiency of the addition of allenylzinc bromide to lactic imine derivatives (the yield is in the range of 65% as compared to 85% with mandelic derivatives).[3] Therefore, despite the excellent resolution (**4** is obtained as a single diastereomer, Table 1, entries 1 and 2), the control of the conversion of the organometallic is less precise (as indicated by the **4**:**3** ratio, Table 1, entries 1 and 2).

Scheme 1



Scheme 2

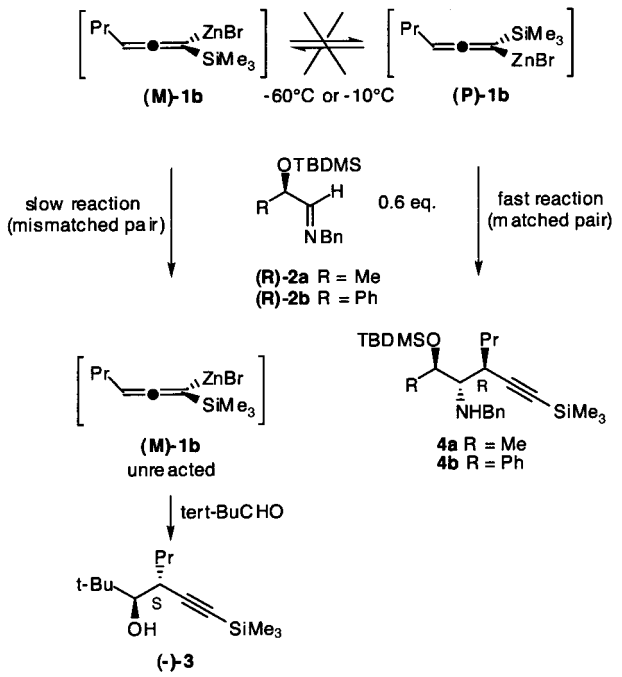


Table 1. Results of Kinetic Resolution

entry	imine	process[a]	**4**:**3**	dr **4**[b]	ee_{max} of **3**[c]	yield of **3**[e]	ee of **3**[d]
1	(*S*)-**2a**	A	34:66	>40:1	52%	65%	49%
2	(*S*)-**2a**	B	41:59	>40:1	69%	60%	52%
3	(*R*)-**2b**	B	64:36	3:1	88%	70%	78.5%
4	(*R*)-**2b**	C	56:44	9:1	100%	75%	87.5%

[a] A: slow addition of the aldimine at −65 °C and 40 min stirring before aldehyde quench. B: slow addition of the aldimine at −65 °C and 120 min stirring before aldehyde quench. C: slow addition of the aldimine (30 min) using a syringe pump at −60 °C and 40 min stirring before aldehyde quench. [b] Entries 1 and 2, *ent*-**4** as the major isomer. [c] Cf. ref 7. [d] Entries 1 and 2, (+)-**3** and entries 3 and 4, (−)-**3**. [e] Corrected to a maximum yield of 40%.

The use of (*R*)-mandelic derivatives (*R*)-**2b** (Scheme 2) was expected to be more gratifying and led to much better results: the homopropargylic alcohol was obtained with an enantiomeric excess up to 78.5% for (−)-**3** (entry 3). Performing the inverse addition with a syringe pump over 30 min, led to our best result: alcohol (−)-**3** was obtained with an ee. of 87.5% (entry 4). The high configurational stability of reagent **1b** must be pointed out since very little epimerization occurred even after more than 2 h of stirring at −65 °C (entries 2 and 3). Indeed, in every case the enantioselectivity is well correlated to the maximum enantiomeric excess, and is found to be 10% lower than the theoretical value (Table 1, entries 1−4):[8] this drop may be the result of the exothermicity during the trapping by the electrophile. The absolute

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(1) (a) Hayashi, T.; Kanehira, K.; Hioki, T.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 137−140. (b) de Graaf, G.; Boersma, J.; van Koten, G.; Elsevier: C. J. *J. Organomet. Chem.* **1989**, *378*, 115−124. Such resolutions have been used successfully with configurationally stable allyl stannanes: Marshall, J.; Yashunsky, D. *J. Org. Chem.* **1991**, *56*, 5493−5495.

(2) Poisson, J. F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553−6560.

(3) Poisson, J. F.; Chemla, F.; Normant, J. F. *Synlett* **2001**, 305−307.

(4) Hoffmann, R. W.; Lanz, J.; Hoppe, D.; Metternich, R.; Tarrana, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1145−1146.

(5) (a) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565−4567. (b) Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377−11390.

(6) For enantioenriched related homopropargyl alcohol see: (a) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163−3185. (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812−3813.

(7) enantiomeric excesses were determined on the desilylated derivatives (using 1 equiv of TBAF) by chiral GC using a Lipodex-E colunm (see Supporting Information).

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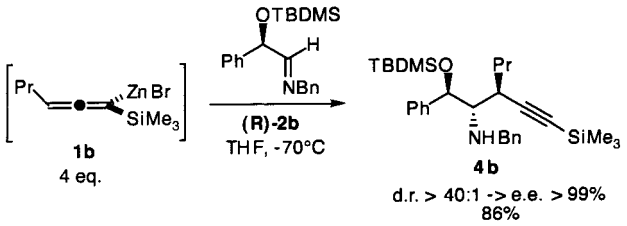
Scheme 3



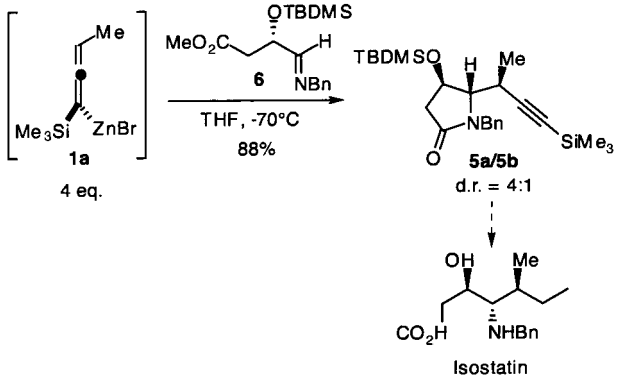
configuration of **3** has not been determined but is secured by the fact that starting from (*S*) or (*R*) imines led to (+)- or (−)-**3**, respectively.

We then decided to extend the scope of this reaction by taking advantage of the high resolution another way. In the preceding case, cheap or easily accessible imines are used. With a more precious imine, it would be profitable to obtain a high yield of a single diasteromer from a racemic allenylzinc bromide. Reacting 4 equiv of allenylzinc bromide **1b** with enantiopure imine (*R*)-**2b** cleanly yields a single diastereomer in an enantioenriched form (Scheme 3).

With the more functionalized imine **6**, a disappointing 4:1 ratio of diastereomers **5** was obtained (Scheme 4). This drop in selectivity may be due to the lower steric hindrance of the methyl group in **1a** as compared to *n*-propyl in **1b**, and/or to the presence of a carbomethoxy moiety in **6**. However, both isomers were easily separated, the major one being a straightforward precursor for the synthesis of the non-natural enantiomer of Isostatin.[9]

In conclusion we have shown that a chiral imine can be used as an efficient resolving agent for an allenylzinc bromide. This

Scheme 4



organozinc reagent could be obtained in situ in an enantioenriched form with ee up to 88%. This reaction can still be optimized and the scope must be expanded to other electrophiles. We have also described an easy access to optically active amino alcohols from enantioenriched imines. Further insight into this methodology will be reported in due course.

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Note Added after ASAP: Text references 2−5 were incorrectly numbered and graphics did not clearly indicate the stereochemistry in the version posted ASAP April 24, 2001; the corrected version was posted May 9, 2001.

Supporting Information Available: Spectral data for all compounds and GC analysis of the enantioenriched homopropargylic alcohol (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The theoretical maximum enantiomeric excess is calculated considering the **3**:**4** ratio and the diastereomeric ratio of **4** (each diastereomer comes from the reaction of one enantiomer of the allenylzinc). The overall formula can be simplified to the following: ee (maximum theoretical value) = **4** × (de-(**3**))/**3**.

(9) (a) Kazmaier, U.; Krebs, A. *Tetrahedron Lett.* **1999**, *40*, 479−482. (b) Rinehart, K. L.; Sakai, R.; Kishore, V.; Sullins, D. W.; Li, K. M. *J. Org. Chem.* **1992**, *57*, 3007−3013.