Pergamon

Tetrahedron Letters, Vol. 35, No. 25, pp. 4267-4270, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0797-2

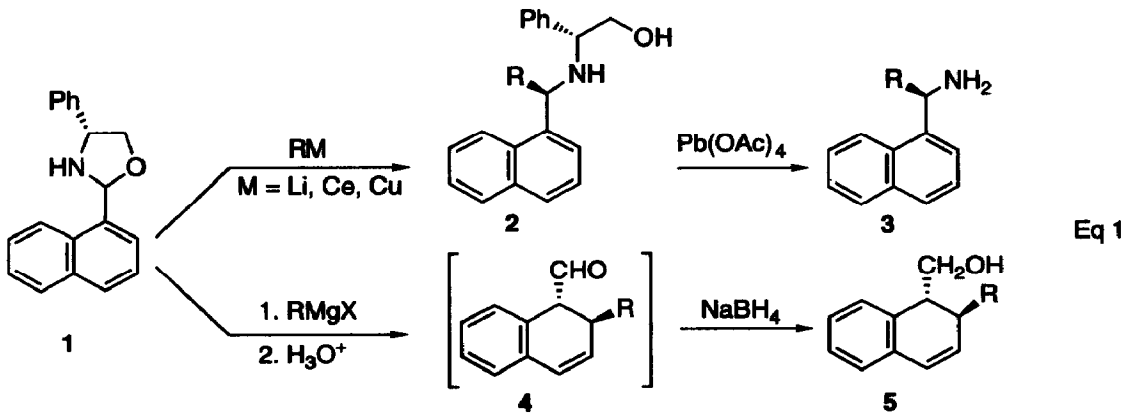
A Single-Pot Synthesis of 1,1,2-Trisubstituted 1,2-Dihydronaphthalenes in High Enantiomeric Purity

Mohamed K. Mokhallalati, K. Raman Muralidharan, and Lendon N. Pridgen*

Synthetic Chemistry Department, SmithKline Beecham Pharmaceuticals,
Post Office Box 1539, King of Prussia, Pennsylvania 19406-0939

Abstract: *A diastereoselective addition of Grignard reagents to nonracemic 2-(1-naphthyl)-4-(4R)-phenyl-1,3-oxazolidines (1) followed by electrophilic trapping of the azaenolate is described. This tandem addition was performed in a single flask producing 1,1,2-trisubstituted 1,2-dihydronaphthalenes 7 in excellent yields and high enantioselectivities.*

This laboratory has reported results of organometallic additions to nonracemic 2-(1-naphthyl)-4-(4*R*)-phenyl-1,3-oxazolidines (**1**) prepared from 1-naphthylcarboxaldehyde. These additions yielded enantiomerically enriched primary amines **3** or 1,2-disubstituted 1,2-dihydronaphthalenes **5**, depending on the choice of metallic nucleophile (equation 1). Both antipodal forms of the resulting nonracemic amines and dihydronaphthalenes are possible by this procedure using, as in our reported examples, the ubiquitous phenylglycinol derived auxiliary.[1,2]

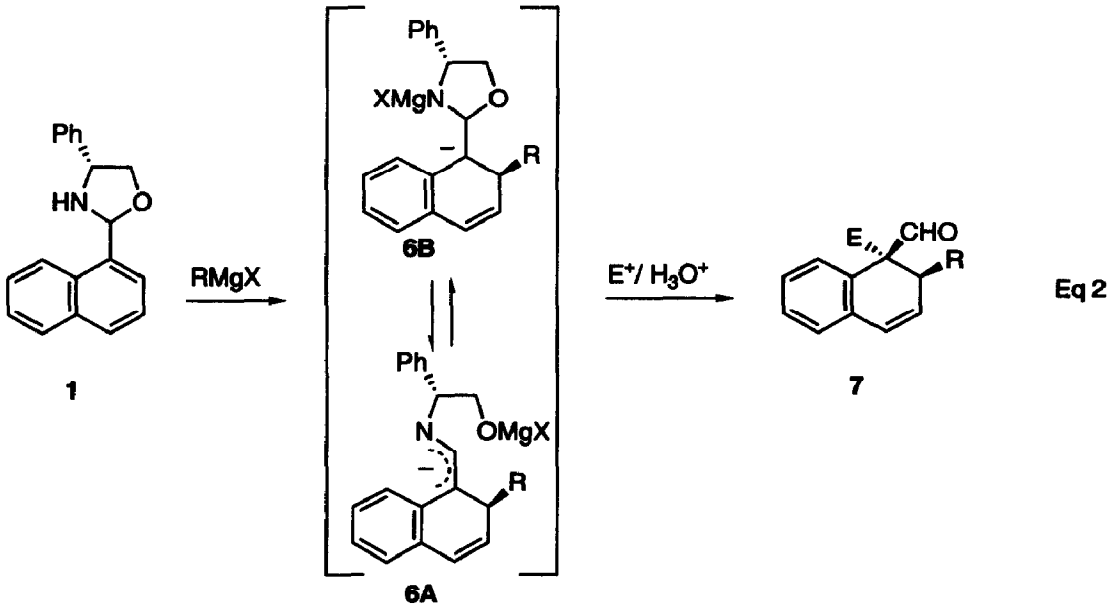


Eq 1

In 1984, Meyers demonstrated a tandem organolithium/electrophile addition procedure on nonracemic 1-naphthyloxazolines yielding stereoselectively nonracemic 1,1,2-trisubstituted 1,2-dihydronaphthalenes.[3] The intermediate oxazolinyl 1,2-dihydronaphthalene derivative was subjected to nitrogen alkylation, sodium borohydride reduction and/or a second reduction which yielded either nonracemic trisubstituted naphthyl aldehydes or carbinols in >95% ee.[4] The absolute configuration of the adducts was confirmed by X-ray crystallography and was thought to be dependent on the configuration of the C-4 substituent on the oxazolinyl ring.

More recent reports from that laboratory have described the successful use of other 4-substituted oxazolines as chiral auxiliaries which do not possess the pendant C-4 methoxymethyl group but give even higher levels of diastereofacial selectivities (*e.g.* valinol and *t*-leucinol derived auxiliaries).[5] The *t*-leucinol derived auxiliary consistently yielded the highest selectivity ~99:1, but suffers from the disadvantage of not being readily available in both enantiomeric forms. A later report[6] by them describes the use of *l*-serine derived auxiliaries to overcome this disadvantage.[7]

From our earlier reported examples, the apparent mode of conjugate Grignard addition to the naphthalene ring to form the disubstituted naphthalene parallels very closely to that reported by Meyers.[3-6] We, therefore, sought to determine if a Grignard tandem addition procedure could be applied to the oxazolidinyl/imino system with its potential multi-sites of alkylation (equation 2).



There are several advantages for choosing an oxazolidinyl system over the oxazolines for the synthesis of chiral 1,2-dihydronaphthalenes **7**: (1) In most cases, the more easily prepared organomagnesium reagents are sufficiently nucleophilic to effect the initial diastereomeric carbon-carbon bond formation. This avoids the necessity of having to form, through stannyl transmetalation, the lithium reagent which is required in the oxazolinyl series; (2) The C-2 oxazolidinyl carbon is in the appropriate oxidation level for simple hydrolysis to an aldehyde. Consequently, the

alkylation/BH_4^- reduction sequence used to lower the oxidation level at C-2 of oxazolines is no longer a requirement. Facile acidic hydrolysis of the reaction mixture after sequential addition of the Grignard and electrophile as specified in Table I is all that is required to transform achiral 1-naphthalenecarboxaldehyde to nonracemic trisubstituted **7** in the same flask; (3) The low temperature restraints typically required to achieve highest stereoselectivity for oxazolines are not required for the oxazolidines. A temperature range of –45 °C to ambient was found to be optimum.

Table I. Organometallic Additions to 2-(1-naphthyl)-4-(4*R*)-phenyl-1,3-oxazolidines (**1**).

Entry	R	E^+	Reaction Conditions, THF	Yield **7**,[a] (%)	ee **7**,[b] (%)	$[\alpha]_D^{25}$ ($CHCl_3$)
1	Et	Me	–45 °C (2 h) → 0 °C (18 h); MeI (0 °C) → rt (18 h)	86	97	–80.2 (c 1.0)
2	Et	allyl	–45 °C (2 h) → 0 °C (18 h); allyl iodide (–45 °C) → rt (18 h)	82	98[c]	+19.1 (c 0.8)
3	Et	CO_2Et	–45 °C (2 h) → 0 °C (18 h); $ClCO_2Et$ (–45 °C) → rt (18 h)	89	98	+167.3 (c 1.3)
4	Me	Me	–45 °C (2 h) → rt (18 h); MeI (–60 °C) → rt (18 h)	31	98	-[d]
5	Bu	Me	–45 °C (2 h) → 0 °C (4 h); MeI (0 °C) → rt (18 h)	87	98	–36.5 (c 1.0)
6	Ph	Me	–45 °C (2 h) → rt (24 h); MeI (0 °C) → rt (18 h)	84	99	+213.0 (c 0.8)
7	Vinyl	Me	–45 °C (2 h) →0 °C (18 h); MeI (0 °C) → rt (18 h)	70	74	+60.8 (c 1.1)[c,d]

[a] Flash chromatographed yields. All new compounds gave satisfactory combustion analyses and/or spectral data. [b] The enantiomeric purity was determined in most cases using the chiral HPLC on a CHIRALCEL OD or OJ column. The opposite enantiomer was prepared for each example to be certain of proper peak assignments. [c] The enantiomeric purity was determined by ^1H NMR (400 MHz) using [Eu(hfc)$_3$] shift reagent on the acetate of the $NaBH_4$ reduced aldehyde. [d] Contained isomeric material.

As evident from the results in Table I, the selectivity of the tandem additions are both exceptionally high. Furthermore, the isolated yields are remarkably high for this combined two-step reaction. We found that adherence to the temperature constraints as described in Table I to be crucial since it was observed that the diastereoselectivity for the Grignard addition eroded at higher temperatures. At much lower temperatures Grignard addition did not occur. In all examples, the diastereofacial selectivity for the Grignard addition as well as electrophilic trapping appears to be almost totally selective. This method of forming nonracemic trisubstituted 1,2-dihydronaphthalenes

appears to be quite general and highly efficient. We did, however, observe that *t*-butyl and *s*-butyl Grignards gave complex mixtures while methyl Grignard gave lower than expected yields. For the latter, about 5% of an unidentified diastereomeric isomer was detected, although enantioselectivity still remained high (entry 4).

It is assumed, based on the similarity of the stereochemical outcome, that the stereoselectivity of the Grignard addition as well as the electrophilic trapping of the azaenolate react as previously reported by Meyers.[3-6] Namely, the overall result is net *trans* addition beginning with the Grignard adding on the face remote from the stereogenic center on the magnesium complexed chiral auxiliary.

Typical procedure (Table I, entry 1): To a stirred solution of 1-naphthyloxazolidine **1** (1.93 g, 0.007 mol) in 20 mL of THF under Argon was added 3 equiv of ethylmagnesium chloride (1.84 M THF soln) dropwise at –45 °C. The resulting solution was stirred at –45 °C for 2h, warmed to 0 °C and stirred for 18h. Neat methyl iodide (3.48 g, 0.0243 mol) was added dropwise and the mixture was allowed to warm to rt and was stirred for 18h. The reaction mixture was then cooled *via* an ice bath and 15 mL of 3M HCl was added dropwise over a period of 15 min. After stirring at rt for 1h, 50 mL of ether was added and the organic phase was separated. The aqueous phase was extracted with 3 x 25 mL of ether. The combined organic phase was washed with 20 mL of 10% $Na_2S_2O_3$ solution, brine, then dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography (eluant: 3% EtOAc / hexane) to afford 1.2 g (86% yield) of the product; 97% ee as determined by Chiral HPLC (CHIRALCEL OD column, eluant: 2% EtOH/hexane, flow rate: 1 mL/min, photodiode array detector: λ 210 nm).

Acknowledgements: The authors are indebted to the SmithKline Beecham post-doctoral program for financial support of this work . We wish to thank Mr. J. Dougherty for his assistance in determining the enantiomeric purities by HPLC.

References and Notes

1. Pridgen, L. N.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237 and references therein.
2. Pridgen, L. N., Presentation in "Organometallic Reagents in Organic Synthesis", 25-26 March 1993, Robinson College, Cambridge, UK. Sponsored by the SmithKline Beecham Research Symposium.
3. (a) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865. (b) Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1984**, *25*, 3667.
4. Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.
5. Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292.
6. Meyers, A. I.; Schmidt, W.; McKennon, M. J. *Synthesis.* **1993**, 250.
7. For other examples of tandem additions to nonracemic 1-naphthyloxazolines see: (a) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607. (b) Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592. (c) Meyers, A. I.; Licini, G. *Tetrahedron Lett.* **1989**, *30*, 4049.

(*Received in USA* 1 *March* 1994; *accepted* 15 *April* 1994)