Pergamon

Tetrahedron Letters 40 (1999) 4765–4768

TETRAHEDRON LETTERS

An asymmetric oxazoline ketenimine rearrangement. Construction of chiral α-quaternary carbon ketones

Michael P. Dwyer, David A. Price, Jason E. Lamar and A. I. Meyers *

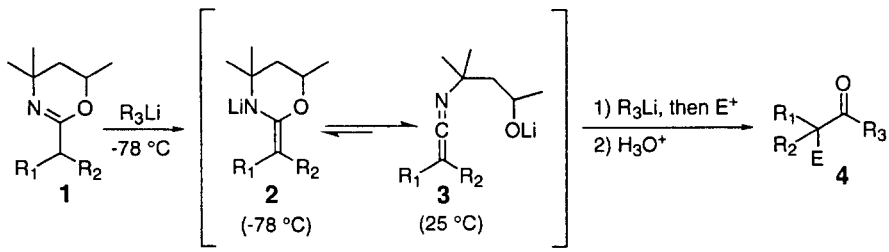
Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

Received 19 March 1999; revised 8 April 1999; accepted 9 April 1999

Abstract

A novel asymmetric oxazoline ketenimine rearrangement has been observed to construct α-quaternary substituted ketones. Levels of asymmetric induction in the ketones, of up to 87% ee, were observed for this unusual rearrangement.

The asymmetric construction of quaternary centers has been an active area of research for the last decade.[1] While several efficient methods are now known, the need for additional methods continues to be investigated. Almost 30 years ago, a novel, reversible oxazine α-carbanion-ketenimine rearrangement (**2** → **3**) was reported by our laboratories.[2] This rearrangement was used to construct racemic ketones **4** bearing an α-quaternary center from achiral oxazines **1** (Scheme 1).



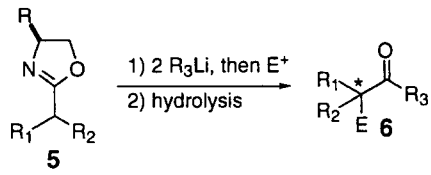
Scheme 1.

During our studies on chiral oxazolines, we investigated an asymmetric version of this reaction to construct ketones bearing an α-quaternary stereocenter (Scheme 2).[3] Besides the elegant use of chiral keteniminium salts by Ghosez,[4] there have been few reports[5] on the use of chiral ketenimines in asymmetric synthesis.

To test the feasibility of using chiral oxazolines in an analogous manner to that shown in Scheme 1, we prepared a series of chiral oxazolines **5**, in accordance with previous reports.[6] Treatment of chiral oxazolines **5** with 2.0 equiv. of organolithium followed by electrophilic quenching and subsequent

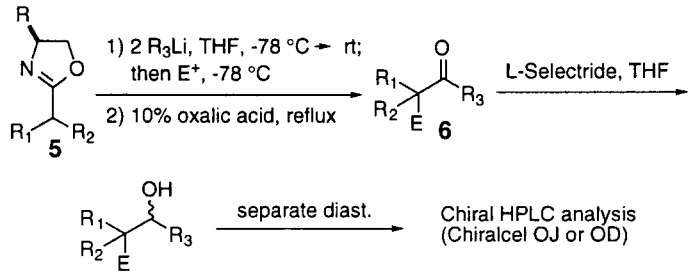
* Corresponding author.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00729-7



Scheme 2.

hydrolysis of the intermediate imines with 10% oxalic acid afforded ketones **6** in good yields (Scheme 3, Table 1).[2] The extent of asymmetric induction for each entry was determined by reduction of the ketone with L-Selectride to give diastereomeric carbinols which were easily separated and subjected to chiral HPLC analysis (Scheme 3). In each example, the corresponding racemic ketone was prepared from an achiral oxazoline and analyzed in similar fashion to insure that no inadvertent resolution had occurred during the reaction.



Scheme 3.

From Table 1, the levels of asymmetric induction observed range from fair to quite good, and several trends became evident. Firstly, subtle changes in the overall asymmetric induction were observed when the electrophile (entry b), the organolithium (entry c), and the chiral auxiliary (entry d) were varied

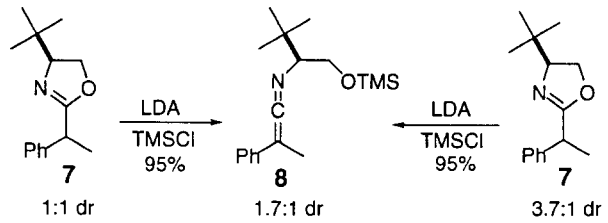
Table 1
Construction of α-quaternary ketones **6** from oxazolines **5**

Entry	R	R_1	R_2	R_3	Electrophile	yield (%)	ee (%)
a	*t*-Bu	Me	Ph	*n*-Bu	BnBr	72	73[b]
b	*t*-Bu	Me	Ph	*n*-Bu	AllylBr	69	63[b]
c	*t*-Bu	Me	Ph	Ph	BnBr	50	59[b]
d	*i*-Pr	Me	Ph	*n*-Bu	BnBr	72	56[b]
e	*t*-Bu	Et	Ph	*n*-Bu	BnBr	73	8[b]
f	*t*-Bu	*n*-Bu	Ph	*n*-Bu	BnBr	52	0[b]
g	*t*-Bu	thn[a]		*n*-Bu	BnBr	64	54[c]
h	*t*-Bu	*n*-Bu	Me	*n*-Bu	BnBr	69	35[b]
i	*t*-Bu	*n*-Bu	Me	Ph	BnBr	53	87[c]
j	*t*-Bu	*i*-Pr	Me	*n*-Bu	BnBr	71	55[c]
k	*t*-Bu	*i*-Pr	Me	Ph	BnBr	50	49[b]

[a]thn = 1,2,3,4-tetrahydronaphthyl
[b]Chiralcel OJ column; 97:3 hex/IPA, 1.0 ml/min, UV detector λ = 254 nM.
[c]Chiralcel OD column; 99:1 hex/IPA, 0.75 ml/min, UV detector λ = 254 nM.

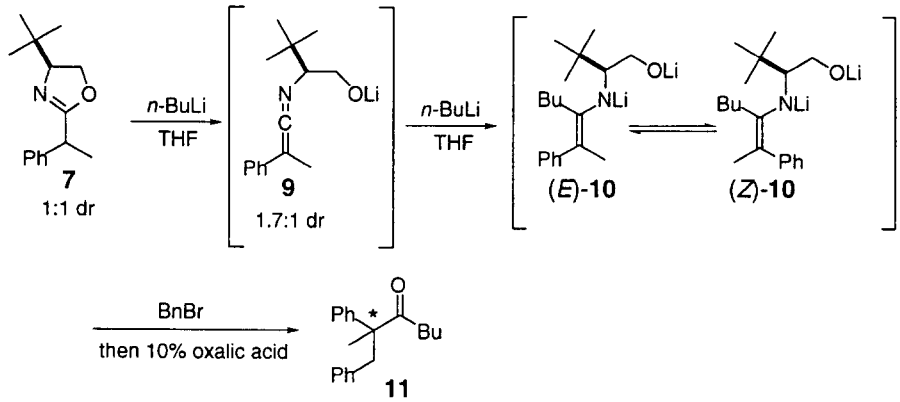
from entry a. Secondly, in the case of phenyl-substituted oxazolines (R_2=Ph), the yield and level of asymmetric induction dropped off drastically as the R_1 group became larger (entries e, f). Thirdly, a lower level of asymmetric induction was observed for a cyclic species (entry g) versus its acyclic counterpart (entry a). Lastly, dramatic effects on the overall asymmetric induction were observed in dialkyl oxazoline precursors which were highly dependent on both the substituents on the oxazoline as well as the organolithium employed (entries h–k).

In an effort to understand the factors that control asymmetric induction, oxazoline **7** of varying diastereomeric ratios (1:1 to 3.7:1) was treated with LDA followed by TMSCl to afford the silylated ketenimine **8**. Both routes gave a 1.7:1 mixture of diastereomers (Scheme 4).[7] While this experiment proves that the initial diastereomeric ratio of oxazolines is not important to the ee of the ketone, it also suggests that the diastereomeric ratio of the intermediate ketenimines **8** does not influence the final asymmetric enantiomeric ratio observed in this process since the overall level of asymmetric induction was 73% ee (6.7:1) (entry a).



Scheme 4.

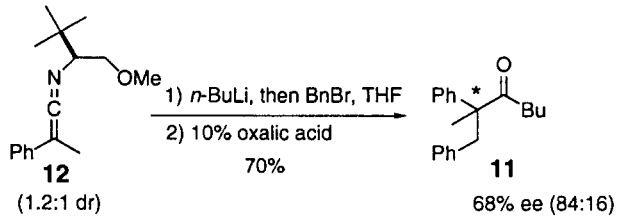
Based upon these observations, the overall asymmetric induction of this process may be controlled by two factors: (1) the ratio of the intermediate *E*- and the *Z*-metalloenamines **10** as well as (2) the facial alkylation on *E,Z*-**10** (Scheme 5). Efforts were then focused upon investigating variables that might ultimately effect these two factors.



Scheme 5.

Initial experiments focused upon trying to equilibrate the metalloenamines **10** by either thermal or chemical means.[8,9] Efforts to improve the asymmetric induction in a number of entries described above by use of higher reaction temperatures or the use of additives (HMPA, LiBr, etc.) were unsuccessful. However, the use of THF as a reaction solvent was imperative to maintaining asymmetric induction in this process. In addition, transmetallation of the intermediate dilithiometalloenamine **10** to either the zinc or magnesio derivatives afforded intermediates that were unreactive to further alkylation even at elevated temperatures.

In an effort to control the facial selectivity of the alkylation step by use of an internal ligand,[10] methoxy ketenimine **12** was prepared as a 1.2:1.0 mixture of diastereomers according to earlier reports.[5c,d] Metallation–alkylation as described above afforded the ketone in roughly the same overall yield and ee as the oxazoline, **7** (entry a, Table 1) as shown in Scheme 6.



Scheme 6.

The asymmetric oxazoline α-carbanion-ketenimine rearrangement has been briefly studied and produced chiral α-quaternary ketones in up to 87% ee. The necessary key elements were found to be a highly coordinating solvent (THF), a bulky chiral auxiliary, and ultimately the substituents on the intermediate metalloenamine. The use of a pendant internal ligand did not seem to have any effect on the overall asymmetric induction of this process. Current work continues to study the controlling features for the asymmetric induction and will be reported in due course.

Acknowledgements

The authors are grateful to the National Institute of Health for generous financial support of this program.

References

1. (a) Meyers, A. I.; Romo, D. *Tetrahedron* **1991**, *47*, 9503. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. See also an earlier review on quaternary carbon syntheses: (c) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.
2. (a) Meyers, A. I.; Smith, E. M. *Tetrahedron Lett.* **1970**, 4355. (b) Meyers, A. I.; Smith, E. M.; Jurjevich, A. F. *J. Am. Chem. Soc.* **1971**, *93*, 2314. (c) Meyers, A. I.; Smith, E. M.; Ao, M. S. *J. Org. Chem.* **1973**, *38*, 2129. (d) Meyers, A. I.; Kovelesky, A. C.; Jurjevich, A. F. *J. Org. Chem.* **1973**, *38*, 2136.
3. Dubois, J. E.; Lion, C. *R. Acad. Sci.* **1972**, *274*, 203.
4. Marko, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192.
5. For reviews of ketenimines in synthesis, see: (a) Krow, G. R. *Angew. Chem., Int. Ed.* **1971**, *10*, 435. (b) Michael, J. P.; De Koning, C. B. Ketenimines and their P, As, Sb, and Bi Analogues; in *Comprehensive Organic Functional Group Transformations*; Pattenden, G., Ed.; Elsevier: Tarrytown, New York, 1995; Vol 3, pp. 555–610. For related examples, see: (c) Hiroi, K.; Sato, S. *Chem. Pharm. Bull.* **1985**, *33*, 2331. (d) Hiroi, K.; Sato, S. *Chem. Pharm. Bull.* **1985**, *33*, 4691.
6. (a) Meyers, A. I.; Knaus, G. *J. Am. Chem. Soc.* **1974**, *96*, 6508. (b) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.
7. The diastereomeric ratio was determined by ^{1}H NMR analysis in C_6D_6 by integrating the methyl signals of the TMS ketenimine.
8. For examples of thermal equilibration of metalloenamines, see: (a) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081. (b) Meyers, A. I.; Williams, D. R.; White, S.; Erickson, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 3088.
9. Lee, J. Y.; Lynch, T. J.; Mao, D. T.; Bergbeiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1981**, *103*, 6215.
10. Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032.