# Tandem Asymmetric Transformations: An Asymmetric 1,2-Migration from a Higher Order Zincate Coupled with a Stereoselective Homoaldol Reaction

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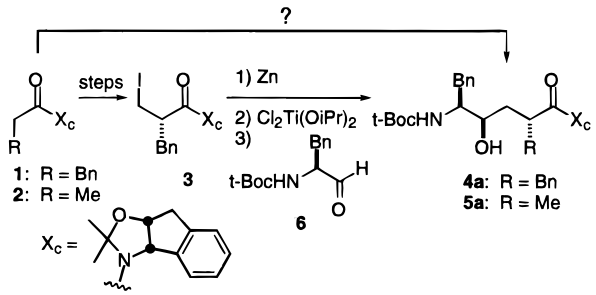
The preparation of organic compounds of high optical purity is becoming an increasingly important objective. To this end, numerous examples of methods involving chiral catalysts (both natural and unnatural) and covalently-bonded chiral auxiliaries can be cited.[1] Although often highly stereoselective, these methods typically embrace a single event in which bond-forming or bond-breaking takes place on a given substrate. For molecules with multiple stereocenters it would be desirable to couple several distinct asymmetric transformations in a single-vessel reaction sequence. In this paper we describe the development of such a tandem asymmetric process, which couples a 1,2-migration with a homoaldol reaction.

The reaction of the titanium homoenolate derived from **3** with *N*-(*tert*-butoxycarbonyl)phenylalaninal (**6**) is known to yield the homoaldol product **4a** as a single isomer (Scheme 1).[2] The overall conversion of **1** to **4a** requires four individual steps, including two stereodefining steps.[3] The recent development of one-carbon, organozinc homologation reagents prompted an exploration into the possibility of streamlining the overall transformation of **1** to **4a**.[4] The success of such a process would require two distinct asymmetric transformations: an asymmetric homologation and an asymmetric homoaldol.

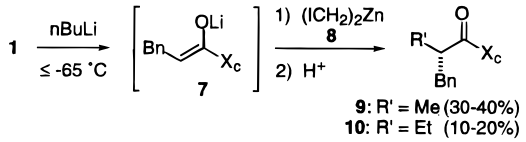
Initial attempts to homologate the preformed lithium enolate **7** with bis(iodomethyl)zinc (**8**) were met with limited success, producing moderate yields of the methyl and ethyl derivatives **9** and **10**, respectively (Scheme 2).[5] The following experimental observations suggested the reactivity of the lithium enolate **7** was attenuated by **8**: The conversions to **9** and **10** were established rapidly upon addition of **8** to **7** at −70 °C, with no change over time. If **7** was added to 1.1 equiv of **8** ("inverse addition"), only 3% of **9** was formed at −70 °C. However, if **7** was added to a solution containing 0.6 equiv of **8**, a 60% conversion to **9** was observed. The deep yellow color indicative of **7** rapidly dissipated upon addition of approximately 0.5 equivalents of **8**. Finally, *in situ* IR spectroscopy clearly indicated the disappearance of the lithium enolate **7** upon addition to **8**, with concurrent formation of a new species.[6] We believe these results are consistent with the formation of carbon-bound enolate zincate **11** (Scheme 3).[7]

Having established **11** was unreactive, a mechanism proceeding through another species must account for the observed reactivity under conditions in which **8** is added to **7**. Since that reaction pathway is only available in the early phases of the addition, we propose that the higher order zincate **12a** is responsible for the formation of **9**.[8] Presumably, this species increases the electron density at the zinc center, driving the 1,2-migration to **13a**.[9] This mechanistic scheme is fully consistent with the observed results. During the initial stages of the addition of **8** to **7**, the presence of a large excess of free lithium enolate **7** can either drive the 1,2-migration through the higher order zincate **12a** or can react with ethyl iodide to produce **10**.[5] As the addition of **8** continues, all lithium enolate **7** has been effectively "quenched" as the zincate species **11** or **13a**. A combined maximum yield of 50% for **9** and **10** would be expected with this order of addition. In contrast, inverse

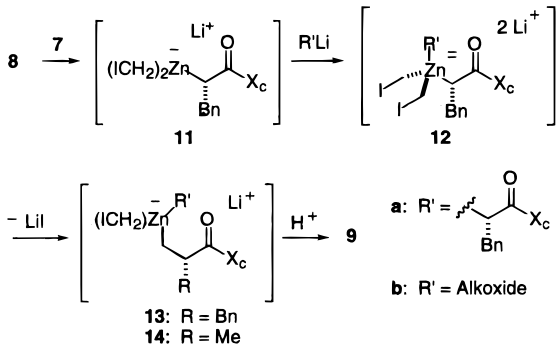
**Scheme 1**




**Scheme 2**




**Scheme 3**




(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1994. (b) Wong, C.-H; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Tetrahedron Organic Chemistry Series; Pergamon Press: Tarrytown, NY, 1994; Vol. 12.

(2) (a) Armstrong, J. D., III; Hartner, F. W., Jr.; DeCamp, A. E.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1992**, *33*, 6599. See also: (b) DeCamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867. (c) Reetz, M. R.; Karin, R.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969. (d) Reetz, T. R.; Fox, D. N. A.; *Tetrahedron Lett.* **1993**, *34*, 1119. (e) Reetz, M. R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (f) Kano, S.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **1991**, *32*, 233.

(3) The first step in the sequence is a non-stereoselective aldol between **7** and formaldehyde.

(4) (a) Sidduri, A.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694 and references cited therein. (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. For an early example of the use of a zinc carbenoid with a lithium enolate, see: (c) Whitlick, H. W., Jr.; Overman, L. E. *J. Org. Chem.* **1969,** *34*, 1962.

(5) The formation of **10** may arise from alkylation of ethyl iodide, which is a byproduct of the *in situ* generation of **8**: $2CH_2I_2 + Et_2Zn \rightarrow 7 + 2EtI$. For preparation of **8**, see ref 4a and Supporting Information.

(6) The lithium enolate **7** is identified by IR absobances at 1595 and 1575 $cm^{-1}$. Upon addition to diethylzinc or **8**, new absorbances (1536 and 1567 $cm^{-1}$, respectively) are observed with the disappearance of the lithium enolate absorbances.

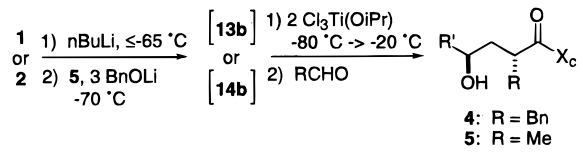
(7) The assignment of a carbon-bound (as opposed to oxygen-bound) zincate species for **11** is based upon low-temperature NMR observations. Enolate zincate **11** is drawn as a monomer for clarity. Prior stuctural studies on zinc enolates suggest **11** may exist in aggregate forms through dative Zn−C or Zn−O bonding. For related examples, see: (a) Bolm, C.; Müller, J.; Zehnder, M.; Neuburger, M. A. *Chem. Eur. J.* **1995**, *1*, 312 and references sited therein. (b) Fabicao, R. M.; Pajerski, A. D.; Richey, G. H., Jr.; *J. Am. Chem. Soc.* **1991**, *113*, 6680.

(8) The involvement of higher order zincates in 1,2-migrations has been previously implicated: Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958.

(9) Although implied as a short-lived intermediate in Scheme 3, **12a** may exist only as a transition state structure.

S0002-7863(96)02123-3 CCC: $12.00 

**Scheme 4**




addition of the lithium enolate **7** to **8** yields negligible amounts of **9** and **10** because **7** is rapidly quenched in the presence of excess **8**.

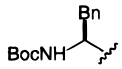
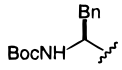
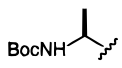
With a reasonable mechanistic hypothesis in hand, effecting good conversions to homoenolate depended upon finding an appropriate enolate surrogate to serve as the driving force in the 1,2-migration. It has been established that α-halocyclopropylzincs undergo 1,2-migrations in the presence of mono- and dialkoxides.[8,10] Indeed, several alkoxides induced good conversions to the homologated product **9**.[11] Lithium benzylalkoxide gives the most consistent conversions. Presumably, the homologation to an alkoxy zincate **13b** proceeds through the higher order alkoxy zincate **12b**.[12] The stereoselectivity of the 1,2 migration is excellent, proceeding with ≥98% de.[13] The corresponding methyl derivative **2** underwent homologation to **14b** with similar stereoselectivity (≥97% de).

With a viable asymmetric route to the zinc homoenolate **13b**, transmetalation was affected with (*i*PrO)$TiCl_3$ (Scheme 4). The homoaldol reaction with *N*-(*tert*-butoxycarbonyl)phenylalaninal (**6**) proceeded as previously described, yielding **4a** as the only homoaldol product in 59% yield.[2a] The overall two-step transformation to **4a** occurred with ≥98% de.[14]

Several aldehydes were examined as homoaldol substrates in this transformation (Table 1).[15,16] The highest diastereoselectivity in the homoaldol reaction is observed for *N*-*tert*-Boc (butoxycarbonyl) aldehydes derived from L-amino acids and the titanium homoenolate derived from **13b** (entries A and C). Diastereoselectivity in the homoaldol reaction with aryl and aliphatic aldehydes decreased with decreasing steric bulk α to the aldehyde.

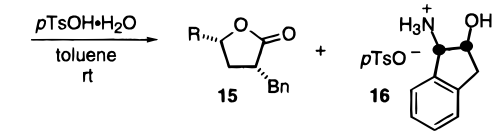
In most cases, the major isomers from the tandem 1,2-migration/homoaldol transformation were isolated in pure form by simple flash chromatography. Conditions for removal of the auxiliary were quite mild. Treating representative γ-hydroxyamides **4** with *p*-toluenesulfonic acid monohydrate induces cyclization to the lactones **15** in good yield (Scheme 5).

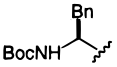
**Table 1.** Tandem Asymmetric 1,2-Migration/Homoaldol Reactions[a]

| Entry | Aldehyde (R') | Product | T (°C) | de (%)[b] | Yield (%)[c] |
|---|---|---|---|---|---|
| A |  | **4a** | -20 | ≥ 99 | 59[d] |
| B |  | **5a** | -20 | 82 | 58[d] |
| C |  | **4b** | -20 | ≥ 99 | 53[d] |
| D | phenyl | **4c** | -40 | 82 | 50 (76)[e] |
| E | phenyl | **5c** | -40 | 80 | 44 (60) |
| F | 2-propenyl | **4d** | -40 | 76 | 55[f] |
| G | cyclohexyl | **4e** | -40 | 86 | 55 (73)[g] |
| H | cyclohexyl | **5e** | -40 | 86 | 41 (56) |
| I | iso-propyl | **4f** | -50 | 76 | 53 (74) |
| J | n-butyl | **4g** | -20 | 64 | 53 (68) |

[a] Reactions were run with 5 equiv of aldehyde, except for entries A−C, in which 0.5 equiv of the corresponding aldehydes was employed.[2] [b] Refers to stereoselectivity of homoaldol reaction as determined by GLC after silylation of the crude mixtures or by HPLC. [c] Isolated yield. Yields in parentheses are based upon homoenolates **13b** or **14b**. The molarities of **13b** and **14b** were determined by HPLC and corrected for response factors. [d] Yield based upon aldehyde.[2] [e] Transmetalation with $TiCl_4$. [f] Based upon recovered **9**. [g] Yield of major isomer only.

**Scheme 5**




| Entry | Amide | R | Lactone | Yield[a] |
|---|---|---|---|---|
| A | **4a** |  | **15a** | 82 |
| B | **4c** | Ph | **15c** | 80 |
| C | **4f** | iso-propyl | **15f** | 85 |

[a]Isolated Yield.

Furthermore, the (1*R*, 2*S*)-*cis*-aminoindanol crystallizes from the toluene solution as the *p*-toluenesulfonate salt **16** and is recovered by simple filtration. Thus, this method provides access to a variety of optically pure γ-lactones.

In conclusion, we have presented a novel approach to the asymmetric synthesis of organic molecules containing multiple stereocenters. Our strategy centers on the asymmetric formation of reactive intermediates, which are further subjected to asymmetric transformations. A single chiral controlling element (*cis*-aminoindanol) is responsible for asymmetric induction in both disparate transformations. Further studies on the scope and mechanism of this and related transformations are in progress.

**Acknowledgment.** We thank Professor David A. Evans and Professor Paul Knochel for helpful discussions.

**Supporting Information Available:** Full experimental details for all compounds (11 pages). See any current masthead page for ordering and Internet access instructions.

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(10) For migrations of halogen-substituted triorganozincates, see: Harada, T.; Wada, H.; Oku, A. *J. Org. Chem.* **1995**, *60*, 5370 and references cited therein.

(11) The following is a list of representative lithium alkoxides and percent conversions, respectively: (EtOLi, 35), (*n*PrOLi, 74−88), (BnOLi, 70−82, 78% isolated yield), ($LiO(CH_2)_2OLi$, 31). Low conversions for the dialkoxide and lithium ethoxide likely reflects the limited solubility of these species at −70 °C. Low temperatures and inverse addition of **7** to **8** (thereby preventing free lithium enolate **7** attack on ethyl iodide) are necessary to minimize formation of **10** (typically, 3−6% of **10** is still observed).

(12) The alkoxy zincate **13b** is drawn as one species for clarity. *In situ* IR spectroscopy indicates at least three species in solution, represented by absorbances at 1637, 1621, and 1602 $cm^{-1}$.

(13) Ratios were determined by GLC analysis (experimental details are described in the Supporting Information).

(14) Only the homoaldol product **4a** was detected in the crude mixture (HPLC).

(15) For a recent example of diastereoselective homoaldol reactions of zinc homoenolates, see: (a) Houkawa, T.; Ueda, T.; Sakami, S.; Asaoka, M.; Takei, H. *Tetrahedron Lett.* **1996**, *37*, 1045. See also: (b) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.

(16) The stereoselectivity of the homoaldol reaction was determined by transformation to the lactones (*vide infra*) and examination of coupling constants and NOE effects.