Chart I

$IBP \xrightarrow{h\nu} IBP^{S_1}$	$k_d = 2.9 \times 10^7\ s^{-1}$
$IBP^{S_1} \longrightarrow IBP$	$k_{DP} = 8.6 \times 10^6\ s^{-1}$
$IBP^{S_1} \longrightarrow$ **5** (R = CH_3)	$k_c = 3.5 \pm 2 \times 10^8\ s^{-1}$
$IBP^{S_1} \longrightarrow$ **2** (R = CH_3)	$k_{ret} = 3.9 \pm 3 \times 10^8\ s^{-1}$
2 (R = CH_3) $\longrightarrow$ IBP	$k_{po} = 6.3 \pm 3 \times 10^5\ M^{-1}\ s^{-1}$
2 (R = CH_3) + $H_2O \longrightarrow$ **3** (R = CH_3)	
2 (R = CH_3) + $H_3O^+ \longrightarrow$ **3** (R = CH_3)	$k_p = 1 \times 10^{10}\ M^{-1}\ s^{-1}$

using the derived values for c (from the solvent polarity treatment) and k_{DP}. A summary of all of the room temperature rate constants in water is given in Chart I.

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Patrick S. Mariano,*[12] Andrea A. Leone
Department of Chemistry, Texas A&M University
College Station, Texas 77843
Received December 12, 1977

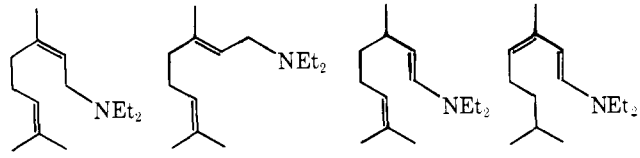
Metal-Assisted Terpenoid Syntheses. 6.[1] Enantioselective Hydrogen Migration in Prochiral Allylamine Systems by Chiral Cobalt Catalysts

Sir:

Transition metal catalyzed double-bond migration has been extensively studied.[2] The isomerization products obtained with efficient catalysts generally reflect thermodynamic control implying effective reversibility of the reaction steps involved. Therefore migration of a multisubstituted inner double bond of an olefin to the less-substituted terminal one would not be possible unless the latter gains relative stability.[3] We are interested in transition metal catalyzed isomerization of substituted allylamines to the corresponding enamines, as the isomerization of prochiral allylamines poses an interesting problem of enantioselection. Organic base catalysts were reported[4-8] to be effective only for unsubstituted allylamines (R_1, R_2 = H), and neither the transition metal catalysis nor the stereospecific reaction has been reported for the isomerization of substituted allylamines. We wish to report here an enantioselective isomerization of prochiral allylamines to chiral enamines, an aldehyde equivalent, a stereospecific hydrogen migration reaction which has never been observed in the entire field of olefin catalysis.

$$R^1R^2C{=}CHCH_2NR_2 \rightleftharpoons R^1R^2CHCH{=}CHNR_2$$

For the nonstereospecific isomerization, a discrete compound $HCo(N_2)(PPh_3)_3$[9] was found to be effective. For example, *N,N*-diethylprenylamine (*N,N*-diethyl-3-methyl-2-butenylamine) was isomerized with 1 mol % of the complex (80 °C, 15 h, THF) to give 95% isolated yield of the *trans*-prenylenamine (*N,N*-diethyl-3-methyl-1(*E*)-butenylamine). Similarly, *N,N*-diethylnerylamine[10] (**1**) and *N,N*-diethylgeranylamine[11] (**2**) were isomerized to give the racemic citronellal-*trans*-enamine[12] (**3**) in 85% yield together with a small amount (<15%) of the 1,3-dienamine[13] (**4**).

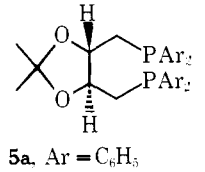


1 2 3 4

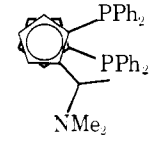
More conveniently, a cobalt catalyst is prepared in situ from cobalt(II) salts, e.g., naphthenate,[14] with $AlEt_3$ or $AlH(i\text{-}Bu)_2$, and PPh_3 (mol ratio, 1:3:3). Comparable yields and similar or slightly higher reaction rates were obtained as compared to $HCo(N_2)(PPh_3)_3$. The enantioselective reaction was effected with this Ziegler type catalyst employing a chiral phosphorus ligand in place of PPh_3.

Monodentate chiral ligands L gave low optical yields for isomerization of **1.** A reaction solution (50:1:3:3 **1**/Co/L/$AlH(i\text{-}Bu)_2$, L = $Ph_2P(O\text{-menthyl})$[15] or Ph_2P-menthyl[16]) gave (80 °C, 15 h, THF) (3*R*)-**3** (~20% yield) in 7% ee.[17] Similarly the catalysts prepared with $Ph_2P(neo\text{-menthyl})$[18] and (*S*)-$PhP(O\text{-}o\text{-}MeC_6H_4)Me$[19] gave (3*S*)-**3** (20 and 5% yield, respectively) in ~5% ee[17] for both cases.

Chiral diphosphines gave better optical yields for the isomerization of **1** and **2.** Thus the reaction of **1** was effected (60 °C, 64–75 h, THF) with the cobalt catalyst prepared from (+)-diop[20] (**5a**) (50:1:1:3 **1**/Co/diop/$AlH(i\text{-}Bu)_2$) to give (3*R*)-**3** (23% yield) in 32% ee. Under the same conditions, the isomerization of **2** gave (3*S*)-**3** (12% yield) in 33% ee. Several



5a, Ar = C_6H_5
b, Ar = *m*-MeC_6H_4



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other chiral diphosphines were tested. A modified (+)-diop (**5b**) having a methyl group at a meta position of the phenyl groups did not improve the enantioselectivity. Substitution of the PPh_2 groups of (+)-diop with $AsPh_2$ reduces both the catalytic activity and the enantioselectivity. (*R,S*)-Aminoethylferrocenyldiphosphine[21] (**6**) is known as a chiral ligand capable of forming a highly enantioselective rhodium(I) hydrogenation catalyst.[21] A cobalt catalyst prepared with this ligand isomerized **1** (50:1:1:3 **1**/Co/**6**/$AlH(i\text{-}Bu)_2$) at 70 °C for 50 h into (3*R*)-**3** (10% yield) in 10% ee, but, at 90 °C for 50 h, **1** was isomerized into (3*S*)-**3** (50% yield) in 17% ee. This reversal in the product configuration and unusual increase in optical yield perhaps reflect the configurational flexibility of the ligand.

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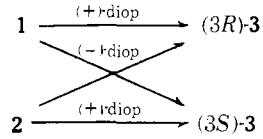
Chart I



It is noteworthy that the (−)-diop cobalt catalyzed isomerization of **1** and **2** exhibits a reaction stereochemistry opposite to that observed with the (+)-diop cobalt catalyst. The stereochemical correlation established is shown in Chart I. As the stereochemical integrity at C-3 remains intact upon acid hydrolysis, the present isomerization provides a practical route to optically active aldehydes, e.g., citronellal.

Unsubstituted allyl ethers (CH_2=$CHCH_2OR$) were isomerized into vinyl ethers by rhodium(I)[22] or ruthenium(II)[23] complexes. Isomerization of unsubstituted[24] or substituted[25] allyl alcohols to the corresponding aldehydes by rhodium(I) was also reported. The present cobalt catalyst lacks the activity for isomerization of allyl ethers and alcohols. Despite this limitation, the applicability to trisubstituted allylamine systems is considered to be quite significant, and the synthetic utility for chiral natural products is obvious. The scope and mechanism are under investigation.

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(14) Technical grade, Nakarai Chemicals Ltd.
(15) Prepared by treating Ph_2PCl with *l*-menthol in pyridine; colorless liquid, bp 160 °C (0.01 Torr), $[\alpha]^{16}_D$ −56.5° (*c* 2.1, *n*-hexane).
(16) Prepared by reacting menthyl lithium with diphenylchlorophosphine; bp 139–142 °C (1.8 × 10^{-2} Torr), $[\alpha]^{24}_D$ −64.7° (*c* 3.4, *n*-hexane).
(17) The optical purity was assessed by comparing the $[\alpha]^{25}_D$ value (−64.7°, (*c* 3.4, *n*-hexane) of an authentic sample of *N*-[(3*R*),7-dimethyl-1(*E*),6-octadienyl]diethylamine.
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Hidenori Kumobayashi, Susumu Akutagawa
Central Research Laboratory, Takasago Perfumery Co. Ltd. 31-36, 5-chome, Kamata, Ohta-ku, Tokyo 144

Sei Otsuka*
Department of Chemistry, Faculty of Engineering Science Osaka University, Toyonaka, Osaka, Japan 560

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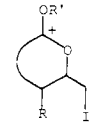
Stereoselective Epoxidation of Acyclic Olefinic Carboxylic Acids via Iodolactonization

Sir:

Many macrocyclic natural products pose a considerable synthetic challenge because of their stereochemical complexity. Our interest in the synthesis of these compounds has focussed initially on the stereoselective introduction of chiral centers in appropriate acyclic precursors. Recent work in this area has led to several novel and general methods for doing this; however, many of these approaches serve only to establish a specific relationship between the newly generated chiral centers and do not provide for relative asymmetric induction from preexisting ones.[1] In contrast, hydroxyl-directed epoxidation can be used to introduce two chiral centers with high 1,2- or 1,3-asymmetric induction in acyclic systems.[2] Iodolactonization has been used to functionalize double bonds in a regio- and stereoselective manner in a large number of cyclic cases,[3] but its potential for similar selectivity in acyclic systems has remained largely unexplored. Recently, Terashima and Jew reported an asymmetric synthesis of α-hydroxy acids in which the stereochemistry is established by a bromolactonization.[4] In this communication, we describe the development of iodolactonization as a means of epoxidizing acyclic olefinic acids with very high 1,2-asymmetric induction.

Under conditions involving kinetic control (I_2, aqueous $NaHCO_3$, and ether[5] or *N*-iodosuccinimide and $CHCl_3$), iodolactonization of several acyclic γ,δ- and δ,ε-unsaturated acids exhibits only moderate asymmetric induction.[6] Equilibration of a cyclic intermediate and therefore thermodynamic control over the stereochemistry can be achieved by reaction of the carboxylic acid with iodine in acetonitrile in the *absence* of base. Under these conditions, cis to trans equilibration occurs, via the protonated lactones **1a,** and affords the more stable

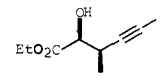


1a: R' = H
1b: R' = CH_3

trans isomers with very high stereoselectivity and in good yield. A high concentration of this protonated intermediate ($pK_a \approx -7$) is required, as shown by the fact that substitution of dimethylformamide ($pK_a \approx -1$) for acetonitrile ($pK_a \approx -10$) as solvent in the cyclization of **2b** leads to a kinetic mixture of **3b** and **4b** (3:4), even after a prolonged period.

As Table I indicates, this stereoselective iodolactonization procedure is general for a variety of γ,δ- and δ, ε-unsaturated acids. In the case of the disubstituted olefins **5a–c,** only γ-lactones are obtained, as would be expected from the greater stability of γ- over δ-lactones.[11] Understandably, little stereoselectivity is seen in the cyclization of 2-phenyl-4-pentenoic acid (**11**),[12] although the possibility that 1,3- or even 1,4-asymmetric induction may occur in the formation of appropriate six-membered lactones cannot be excluded.

The hydroxy acid derivatives **5** were prepared by conventional elaboration of the acetylenic ester **13,** which is formed in 69% yield from the reaction of ethyl *trans*-2,3-epoxybutanoate with 1-propynyldiethylalane. The δ,ε-unsaturated acids **8** were prepared from *meso*-2,4-dimethylglutaric anhydride[13]



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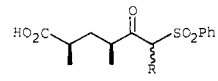
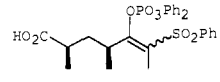


14a: R = H
14b: R = CH_3



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