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Copper(I)-Catalyzed Intramolecular Asymmetric [2 + 2] Photocycloaddition. Synthesis of Both Enantiomers of Cyclobutane Derivatives

Niladri Sarkar, Abhijit Nayek, and Subrata Ghosh*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India

ocsg@mahendra.iacs.res.in

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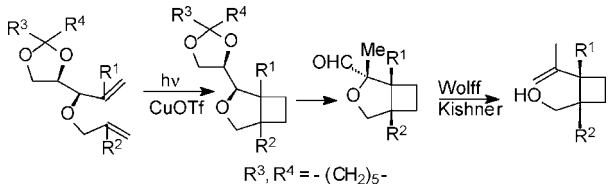
ABSTRACT



A simple approach for asymmetric induction in Cu(I)-catalyzed [2 + 2] photocycloaddition, where asymmetric catalysts or chiral auxiliaries were inefficient, has been developed using the concept of chirality transfer from the readily available 2, 3-di-*O*-cyclohexylidine-(*R*)-(+)-glyceraldehyde. An anion-induced cleavage of the tetrahydrofuran ring of the resulting oxa-bicyclo[3.2.0]heptanes led to a convenient access to the synthetically useful cis-1,2-disubstituted cyclobutanes in enantiomerically pure form.

The [2 + 2] photocycloaddition reaction, giving rise to cyclobutanes, is an extremely useful synthetic tool[1,2] in organic synthesis. Its asymmetric version using a removable chiral auxiliary works efficiently in the case of photocycloaddition[3] between an alkene and an enone. However, copper(I) catalysis[2] required for photocycloaddition between two nonconjugated alkenes proceeds with low des with a variety of chiral auxiliaries.[4] More strikingly, asymmetric catalysis, which is highly successful in inducing high enantioselectivity in a variety of reactions,[5] including many cycloaddition processes, fails to induce significant asymmetry in copper(I)-catalyzed photocycloaddition.[4] The multifaceted application of copper(I)-catalyzed [2 + 2] photocycloaddition in organic synthesis[6] thus necessitates the development of its asymmetric version. We herein report a simple general solution to the problem of asymmetric induction in intramolecular copper(I)-catalyzed [2 + 2] photocycloaddition reaction.

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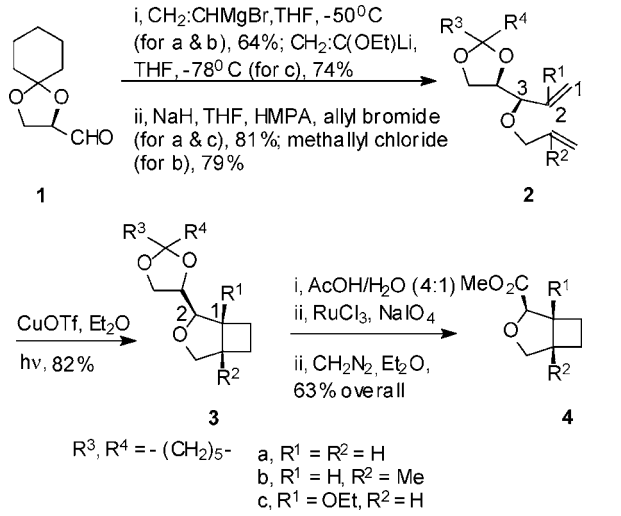
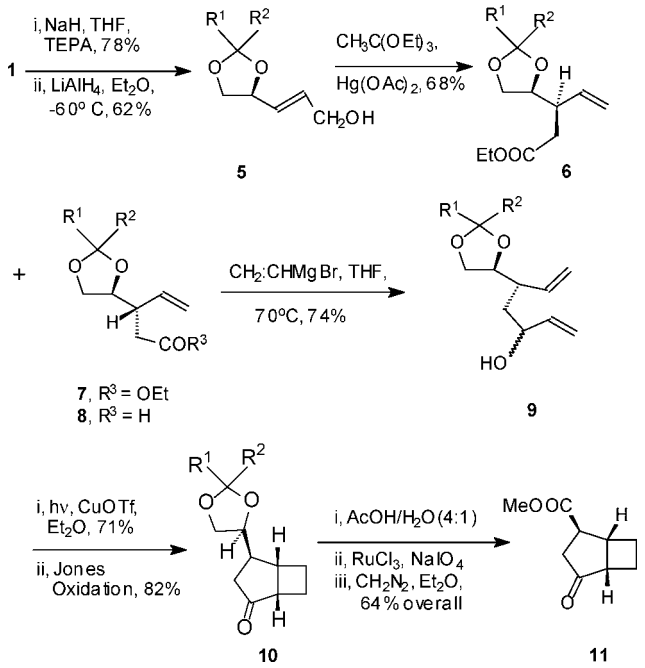
Scheme 1



Scheme 2



The present approach relies on the transfer of the chirality at C-2 of 2,3-di-*O*-cyclohexylidine-(*R*)-(+)-glyceraldehyde **1**[7] to cis-1,2-disubstituted cyclobutanes through a "relay" process as new chiral centers are generated sequentially. Of the two chirality transfer steps, the first one is illustrated by the synthesis of both enantiomers of the oxa-bicyclo[3.2.0]-heptane derivative **4a** (Scheme 1). Reaction of the aldehyde **1** with vinylmagnesium bromide followed by allylation of the resulting carbinols afforded an inseparable mixture of the diene **2a**[8] and its C-3 epimer in a ca. 3:2 ratio in overall excellent yield. Smooth cycloaddition took place when an ether solution of this diene mixture was irradiated with a Hanovia 450W mercury vapor lamp through a quartz immersion well in the presence of copper(I)trifluoromethane sulfonate (CuOTf) (20−25 mol %) to lead to the photoadduct **3a** and its C-2 epimer. The exo stereochemical assignment of the substituents at C-1, C-2, and C-5 is based on analogy[9] to the formation of the exo adducts from photocycloaddition of 3-alkyl-1,6-dienes. The chiral center present in the chiral auxiliary of the adduct **3a** was then destroyed by a three-step sequence involving acid-induced deketalization (80% aqueous acetic acid)−oxidative cleavage of the resulting diol ($RuCl_3-NaIO_4-CH_3CN-CCl_4-H_2O$) and esterification ($CH_2N_2$) to afford the ester **4a**, $[\alpha]^{25}_D$ + 16.9 (*c* 1.38, $CHCl_3$). Similarly, the C-2 epimer of the adduct **3a** gave the other enantiomer of **4a**, $[\alpha]^{25}_D$ −17.6 (*c* 1.39, $CHCl_3$). In a similar fashion, the dienes **2b** and **2c** and their C-3 epimeric diastereoisomers afforded in each case a pair of the cyclobutanes **4b** and **4c**.

This sequence can also be extended for the synthesis of both enantiomers of the bicyclo[3.2.0]heptane **11**. The required 1,6-diene unit can be crafted conveniently on the glyceraldehyde derivative **1** (Scheme 2). Wittig−Horner reaction of the aldehyde **1** with triethyl phosphonoacetate (TEPA) followed by $LiAlH_4$ reduction of the resulting unsaturated ester afforded the allyl alcohol **5**. Ortho ester Claisen rearrangement of the allyl alcohol **5** on heating with triethyl orthoacetate afforded a 1:1 chromatographically separable mixture of the unsaturated esters **6** (R_t = 2.67 min) and **7** (R_t = 2.87 min). The pure ester **7** was then converted to the aldehyde **8** by $LiAlH_4$ reduction followed by Swern oxidation of the resulting alcohol. Addition of vinylmagnesium bromide to the aldehyde **8** resulted in a diastereoisomeric mixture of the dienols **9**. Irradiation of this diene mixture in the presence of CuOTf followed by Swern oxidation of the photoadducts gave the ketone **10**. The stereochemical assignment of the adduct **10** was based on analogy to earlier works[9] on photocycloaddition of 3-alkyl-substituted dienes. As before, the chirality in the chiral pendant was removed to provide the cyclobutane derivative **11,** $[\alpha]^{25}_D$ +248.1 (*c* 0.8, $CHCl_3$). Similarly, the unsaturated ester **6** gave the other enantiomer of the cyclobutane derivative **11**, $[\alpha]^{25}_D$ −250.2 (*c* 2.4, $CHCl_3$). The CD spectra of each pair of the cyclobutane derivatives of the structures **4c** and **11** confirmed their enantiomeric relationship. The synthesis of both enantiomers of cyclobutane derivatives from 2,3-di-*O*-cyclohexylidine-(*R*)-(+)-glyceraldehyde **1** is noteworthy, as the enantiomer (*S*)-(−)-**1** is not readily available. This concept of asymmetric induction has not been employed earlier[4] in intramolecular Cu(I)-catalyzed [2 + 2] photocycloaddition reactions.

The synthetic potential of this protocol could be enhanced if fragmentation of the relatively inert tetrahydrofuran ring in the oxa-bicyclo[3.2.0]heptanes could be achieved. We anticipated that generation of a radical **12** or an anion **13**

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(8) Stereochemical assignment of the dienes **2** and **9** will be described in a full account of this work.

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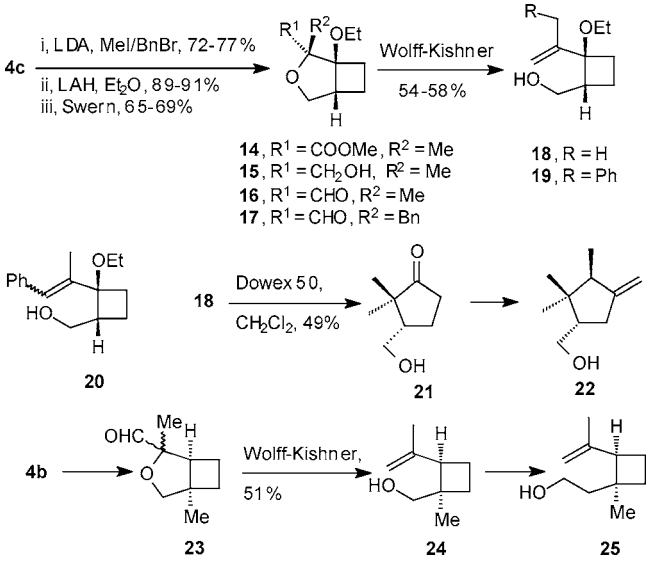
12 **13**

might trigger fragmentation of the tetrahydrofuran ring. Toward this end, the lithium enolate generated from the ester **4c** was methylated to produce exclusively the exo methylated product **14** (Scheme 3).

Scheme 3



The ester **14** was then reduced to the alcohol **15**. Transformation of the alcohol **15** to the corresponding bromide or xanthate, probable precursors for the radical **12**, could not be achieved. Wolff−Kishner reduction of aldehyde group to methyl is known to proceed through a carbanionic intermediate. Thus, we anticipated that the aldehyde **16** could be a precursor for the anion equivalent to **13**. Swern oxidation of the alcohol **15** afforded the aldehyde **16**. The aldehyde **16**, when subjected to Wolff−Kishner condition, underwent smooth fragmentation to deliver the disubstituted cyclobutane **18** in 54% yield. The fragmentation process is general. The aldehydes **17** and **23** prepared from the esters **4c** and **4b** gave the disubstituted cyclobutanes **20** and **24** in 51 and 58% yields, respectively. The product **20** appears to arise from isomerization of the initially formed olefin **19**. To the best of our knowledge, the present protocol for the fragmentation[10] of tetrahydrofuran rings is unprecedented. Cis-1,2-disubstituted cyclobutanes obtained in this way are of considerable synthetic use. For example, the cyclobutane dervative **18**, when treated with Dowex-50, smoothly rearranged to the known cyclopentanone **21**[6f] $[\alpha]^{25}_{D}$ −63 (*c* 0.8, $CHCl_3$), an intermediate in our synthesis[6i] of the monoterpene *β*-necrodol **22**. The cyclobutane derivative **24** $[\alpha]^{25}_{D}$ −4.1 (*c* 0.9, $CHCl_3$) has already been transformed to (−)-grandisol **25**[11a] by one-carbon homologation.

In conclusion, we developed a simple approach for asymmetric induction in intramolecular Cu(I)-catalyzed [2 + 2] photocycloaddition where asymmetric catalysts or chiral auxiliaries were inefficient. This, in combination with the new protocol developed for the cleavage of tetrahydrofuran rings present in oxa-bicyclo[3.2.0]heptanes, resulted in the synthesis of useful cis-1,2-disubstituted cyclobutanes in enantiomerically pure form.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **2**−**4**, **9**, and **10** along with their diastereoisomers, **11**, **14**, **16**−**18**, **20**, and **23**, ^{1}H NMR spectrum of the compound **24**, CD spectra of compounds **4c** and **11**, and a representative experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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