Pergamon

Tetrahedron Letters 40 (1999) 6137–6139

TETRAHEDRON
LETTERS

Asymmetric dihydroxylations of aromatic cyclopropylidenes

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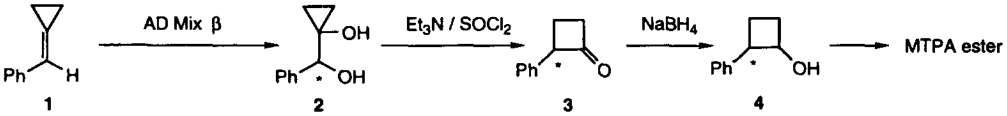
Received 3 March 1999; accepted 11 May 1999

Abstract

A number of aromatic cyclopropylidenes have been converted to diols using the Sharpless asymmetric dihydroxylation (AD) procedure. The enantiomeric ratios were determined by chiral phase HPLC by comparison with their racemates. © 1999 Elsevier Science Ltd. All rights reserved.

Fukumoto and coworkers have reported elegant work with cyclopropylidenes, particularly with regard to their utility in natural product synthesis.[1] During their endeavors, they reported that **2** could be made asymmetrically by exposing styrene **1** to AD mix β. Fukumoto could not determine the enantiomeric excess (ee) of **2** directly (instability complicated MTPA ester formation and employment of chiral shift reagents) and therefore tentatively inferred it after further chemical elaboration. Consequently, diol **2** was exposed to thionyl chloride and triethylamine which initiated rearrangement to cyclobutanone **3**. Sodium borohydride reduction of **3** furnished **4**.[2] The ee of **4** was found to be 29% after analysis (^{1}H NMR) of its MTPA ester and it was unclear to Fukumoto if this low ee was the result of a poor performing AD reaction on **1** or if a loss in ee occurred during the rearrangement of **2** to **3** (Scheme 1).



Scheme 1.

Diol **2** was an important intermediate in a development project at SB, and an accurate ee value was crucial for our purposes. In order to determine this value we utilised the services of chiral HPLC. Guided by the work of Fukumoto, benzaldehyde was exposed to cyclopropyltriphenylphosphonium bromide and NaH in THF to give styrene **1**. The styrene, after purification, was subjected to the commercially available AD mixes (α and β).[3] In addition, styrene **1** was treated with catalytic osmium tetroxide (NMO reoxidant) in order to prepare the racemic diol for analytical purposes (Scheme 2).

HPLC analysis revealed that when **1** was subjected to AD mix β, diol **2** was obtained in 91% yield with an ee of 89%. This allowed us to conclude that Fukumoto's ee of 29% was a result of the conditions

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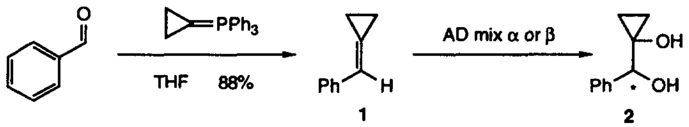
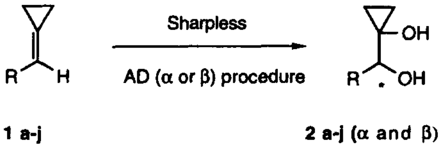
PII: S0040-4039(99)01153-3



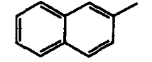
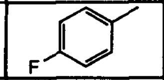
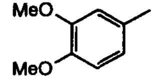
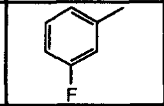
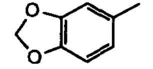
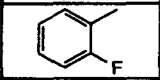
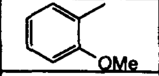
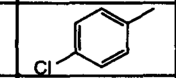
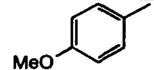
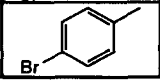
Scheme 2.

he employed to effect the rearrangement to the cyclobutanone and not the Sharpless AD reaction. In addition, when AD mix α was used on styrene 1, the resulting diol was obtained in 55% yield with an ee of 76%. In order to determine the scope of the Sharpless AD reaction on this class of molecules, a group of styrenes was made and subjected to the AD protocol (Scheme 3). To support the study, the racemates were also made and the results from these experiments are presented in Table 1.[4]



Scheme 3.

Table 1
Asymmetric dihydroxylations of cyclopropylidenes

Entry[a]	Substrate R =	AD α %ee[b]	AD β %ee[b]		Entry[a]	Substrate R =	AD α %ee[b]	AD β %ee[b]
2a		79	90		2f		68	86
2b*		0	70		2g*		71	89
2c		47	75		2h		85	98
2d		67	76		2i		70	87
2e		63	84		2j		63	86

a Yields are based on purified (column chromatography) isolated compound and are not optimized.[5]
b % ee based on purified product.
ee's were determined by a Chiralpak AS HPLC column unless stated otherwise.[6]
* ee's were determined by a Chiralcel OD HPLC column.[7]

Conclusion: The AD reaction performed well on the cyclopropylidenes especially when AD mix β was employed. It seems clear from these results that Fukumoto's loss in ee happened subsequent to the AD reaction and occurred during the pinacol rearrangement.

Acknowledgements

We would like to thank Lew Kilmer for mass spectral data, Richard Matsuoka, Robert Maleczka Jr. (Michigan State University), David Stevenson and Ken Tubman for helpful discussions.

References

1. Nemoto, H.; Miyata, J.; Hakamata, H.; Fukumoto, K. *Tetrahedron Lett.* **1995**, *36*, 1055–1058. Nemoto, H.; Fukumoto, K. *Synlett* **1997**, *8*, 863.
2. Fukumoto did not comment on the selectivity of this reduction.
3. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
4. All compounds gave satisfactory ^{1}H NMR, ^{13}C NMR, IR and mass spectra.
5. Chemical yields: (%β)/(%α): **2a** (64/68), **2b** (76/90), **2c** (66/67), **2d** (50/55), **2e** (68/68), **2f** (46/28), **2g** (51/42), **2h** (92/72), **2i** (33/47), **2j** (51/80). The diols convert to the butanone upon contact with silica. Consequently, silica was pre-washed with hexane containing 1% triethylamine. The eluent (hexane/*t*-butyl methyl ether) also contained 1% triethylamine. Drying of the organic layers was accomplished with potassium carbonate.
6. The optical purities were determined by a Chiralpak AS HPLC column (4.6 mm I.D.×25 cm), 1 ml/min, λ=254 nm. Mobile phase 10% IPA/hexane, diols (major/minor ret. times, min): **2a** (16.2/12.7), **2c** (28.5/23.6), **2d** (12.6/18.7), **2e** (18.1/15.3), **2f** (11.1/9.7), **2i** (10.6/9.5), **2j** (11.3/9.7), mobile phase 5% IPA/hexane, diol **2h** (13.8/15.4).
7. The optical purities were determined by a Chiralcel OD HPLC column (4.6 mm I.D.×25 cm) 1 ml/min, λ=254 nm. Mobile phase 10% IPA/hexane. Diols (major/minor peaks ret. times, mins) **2b** (22.8/33.7), **2g** (10.7/9.3).