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Review

Enantiomers of dimethyl [(2*E*)-1,3-diphenylprop-2-en-1-yl]propanedioate resulting from allylic alkylation reaction: Elution order on major high-performance liquid chromatography chiral columns

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ABSTRACT

Asymmetric allylic alkylation leading to dimethyl [(2*E*)-1,3-diphenylprop-2-en-1-yl]propanedioate **1** is a privileged reaction which has been considered in more than 800 references from 1985 to early 2012. This paper thus begins with a thorough review of the literature with a particular focus on the way the ee's and absolute configuration of the prevailing enantiomer were claimed and reported by the authors. In a large majority of articles chiral chromatography is used for ee's determination. Unfortunately, in too many cases the data, the column or the eluent are not provided. In a significant proportion (5%) the column name is ambiguous. Furthermore, several discrepancies are detected in the assigned order of elution when chiral chromatography data are provided. We therefore decided to firmly establish the chromatographic behavior of the enantiomers of **1**, which were obtained from the corresponding racemate by semi-preparative chiral chromatography and their absolute configuration assigned by ECD and VCD spectroscopies. ORD curves show that optical rotation is very weak at 350 nm with indication of inversion of the sign at lower wavelengths. It results in a low sensitivity for on line JASCO polarimeter detector. Chiroptical detection was nicely performed by on line JASCO CD detector set at 254 nm: (−)-(*S*)-**1** shows a (+)-$CD_{254\,nm}$ sign. Pure enantiomers of authenticated absolute configuration allowed a safe assignment of the order of elution during HPLC or SFC on major chiral stationary phases. Quite interestingly for practical application, the order of elution is reversed on Chiralpak AD-H and IA on going from hexane/EtOH to hexane/2-PrOH in HPLC or on going from CO_2/EtOH (or MeOH) to CO_2/2-PrOH in SFC.

Contents

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1. Introduction

Allylic alkylation of derivatives of *rac*-(2*E*)-1,3-diphenylprop-2-en-1-ol with dimethyl malonate leads to *rac*-dimethyl [(2*E*)-1,3-diphenylprop-2-en-1-yl]propanedioate **1** (Fig. 1).

This time-honored reaction has gained the status of "privileged" reaction [1] in its enantioselective version known as Metal-Catalyzed Asymmetric Allylic Alkylation, where palladium is by far the dominant metal. That reaction has been so widely used as a model reaction that it is named "standard AAA" in a recent review on Palladium-Catalyzed Enantioselective Allylic Substitution [2]. Conversion and ee are the two main indicators of the efficiency of the catalyst in terms of activity and enantioselectivity respectively. Above all, the absolute configuration of the prevailing enantiomer is the cornerstone for all mechanistic studies. The AAA has been largely reviewed by several authors in terms of ligand efficiency, operating conditions and mechanistic issues. The mechanistic considerations in these reviews relied on the reported ee's and the reported configuration of the major enantiomer [3–5]. To the best of our knowledge there is no critical review on the methods which have been employed to establish the ee and the absolute configuration of the prevailing enantiomer for that particular reaction.

During the construction of CHIRBASE database [6–8], we were quite surprised to detect several examples of discrepancy in the reported order of elution of the enantiomers of **1** when the same chiral stationary phase and the same eluting conditions were used (see below). Similar discrepancies were also detected on the recently-introduced immobilized chiral stationary phases such as Chiralpak IA. This casts a doubt on the claimed absolute configuration of the major enantiomer, with all the consequences on the mechanistic considerations.

Our aim is first to review how the ee's and absolute configuration of the major enantiomer in AAA leading to **1** have been established and reported in the literature, and second to provide valid orders of elution of the enantiomers of **1** on the major chiral stationary phases used in HPLC or SFC. The pure enantiomers of **1**, used for that screening study, were obtained by semi-preparative chiral chromatography and their absolute configuration was determined for the first time by vibrational and electronic circular dichroism (VCD and ECD).

2. Review: determination of the ee and absolute configuration of the prevailing enantiomer in asymmetric allylic alkylation leading to dimethyl [(2*E*)-1,3-diphenylprop-2-en-1-yl]propanedioate 1

The Scifinder exact structure match for **1** yielded ca 800 hits for the period between 1985 and early 2012. Twenty of these hits deal with synthesis of (*rac*)-**1**, and seven deal with corrections not connected to ee's or absolute configuration (AC) determinations – they are out of the scope of the review. Ee and AC of the major enantiomer are key issues in all the other reports. Ee's and AC determinations are usually disconnected. Ee's are usually estimated either by NMR using a chiral lanthanide shift reagent (CLSR) or by HPLC on a chiral support, while the prevailing AC is assigned by the sign of the optical rotation of the isolated mixture of the enantiomers of **1**. Two cases in which the ee's were determined by achiral chromatography of diastereomers resulting from chemical transformation of **1** and further derivatization with an optically pure reagent have been found [9,10]. There are only four examples in which the ee's have been determined by polarimetry. Unexpectedly for journals subjected to a refereeing procedure, 44 papers reported the ee and AC of the prevailing enantiomer without mentioning any of the methods used to obtain these key data. Fig. 2 reports the balance between the different methods.

2.1. Chiral lanthanide shift reagents

The use of chiral lanthanide shift reagents (CLSR) for the determination of the ee's is claimed in 151 articles. Seven of them are mentioning both chiral HPLC and CLSR for ee determination. The largely most popular CLSR is tris(3-(heptafluoropropylhydroxymethylene)-*d*-camphorato)-europium(III) ((+)-Eu(hfc)$_3$). In a handful of reports, tris[3-(trifluoromethylhydroxymethylene)-camphorato]-europium (III) also named tris(3-trifluoroacetyl-*d*-camphorato)-europium(III) (Eu(facam)$_3$ or Eu(tfc)$_3$) has been used. The nature of the chiral europium salt is not disclosed in one report [11], and (Eu(hfbc)$_3$), probably a misspelling of (Eu(hfc)$_3$), is found in another report [12]. It is quite unfortunate that some useful description of the actual shift difference and of the assignment of the peaks is specified in only 20 articles out of 151 [13–32]. Among them, two are worth mentioning since they reported the NMR spectra in the presence of (+)-Eu(hfc)$_3$ with a full assignment of the shifts for (*R*)-**1** and (*S*)-**1** [13,24]. In all the other articles, a sentence like "the ee has been determined by NMR using Eu(hfc)$_3$ (or Eu(facam)$_3$)" is the one and only authentication of the reported ee's. The same holds true for the recent use of a chiral di-rhodium complexing agent (Rh$_2$[*R*-(+)-MTPA]$_4$) [33].

The NMR method has a well-documented precision limitation (±2% at best) which may be problematic in the case of high ee's. Interestingly, Dai and Virgil proposed to use ((+)-Eu(hfc)$_3$) for ee's values below 60% and chiral HPLC for higher ee's [34].

The CLSR method can be used not only for ee determination but also for double-checking the AC of prevailing enantiomer gained from the sign of the optical rotation of the purified mixture of enantiomers. In the presence of (+)-Eu(hfc)$_3$, the low field methoxy group is nicely splitted in two signals. If the low field peak of these two is larger than the high field peak, then the prevailing enantiomer is (*R*).

2.2. Chiral chromatography

Chiral HPLC (or SFC in three cases) is by far the most widely used method for ee's determination of the AAA reaction leading to **1** and the technique is referred to in 555 articles. Fig. 3 displays the occurrence of papers reporting the use of chiral stationary phases (CSPs) from 1993 when the first analysis by chiral HPLC appeared toward the end of 2011. In five of them, it is stated that "ee's were determined by Chiral HPLC" without any mention of the column