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C11-Chirasil-Dex as chiral stationary phase in GC: enantioselective separation of cyclopropane derivatives

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Dedicated to Prof. Volker Schurig on the occasion of his 65th birthday.

Abstract

Chirasil-β-Dex containing an undecamethylene spacer (C11-Chirasil-Dex) was used as chiral stationary phase (CSP) in enantioselective gas chromatography (GC). The versatility of the new stationary phase in the simultaneous enantiomeric separation of a set of cyclopropane derivatives is demonstrated. The GC method provides information about the chemical yields of the cyclopropane products, enantioselectivity, substrate specifity, and catalytic activity of the chiral catalysts used in the intermolecular cyclopropanation of olefins and avoids time-consuming work-up procedures.

Keywords: Chirasil-β-Dex; Cyclopropanes; Enantiomeric excess; Gas chromatography; Rhodium complexes

1. Introduction

Substituted cyclopropanes have been characterized with a large spectrum of biological properties ranging from enzyme inhibitions to insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor and antiviral activities [1]. They are used as chiral building blocks in the photodegradable and low mammalian-toxic insecticides namely pyrethroids [2], the antidepressant tranylcypromine [3], papain and cystein protease inhibitors [4], the potential anti-psychotic substances [5], anti-HIV agents [6], and marine lactones [7]. Accordingly, effort has been focused during last decades on the stereo-controlled synthesis of pure and enantioenriched substituted cyclopropanes [8]. Besides the resolution of their racemates [9], a number of synthetic methodologies including asymmetric Simmons–Smith reaction, metal-catalyzed reaction of diazo compounds with olefins, and asymmetric ylide cyclopropanation have been developed [10]. The utility of the ylide approaches is directly related to the level of selectivity of the process, which is believed to proceed in via metal carbenes as intermediates [11,12].

The ways in which efficiency and practicality of this procedure are defined is depending on a large number of factors such as suitable catalyst, scale, reagent costs, time allotted and required. Most importantly, the requirement of suitable equipments and reliable methods for the determination of the enantiomeric excesses (ee) of the resulting products arising from asymmetric catalysis. The development of accurate non-chiroptic methods for the determination of enantiomeric purity has been critical for the development of enantioselective catalysis. Thus, a prerequisite in the metal-catalyzed asymmetric synthesis is a precise and reliable assessment of the enantiomeric purity of the resulting products [13]. Among these methods are: polarimetric methods, gas chromatographic methods, liquid chromatographic methods and NMR spectroscopy. The modern and most sensitive methods used in the determination of enantiomeric purity of the outcome of metal-catalyzed reactions, allowing a detection as little as 0.1% of one enantiomer in the presence of another, are

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chiral GC and HPLC methods. For an efficient monitoring of the reaction progress, enantioselective gas chromatography (GC) was the method of choice for the simultaneous determination of the enantiomeric excesses of the cyclopropane products resulting from the cyclopropanation of olefins catalyzed by dirhodium(II) catalyst.

Although a large number of chiral stationary phases (CSPs) have been developed [14–18], the choice of an appropriate column is still difficult. Modified cyclodextrins (CDs) have been widely used as chiral stationary phases for GC separation of racemic chiral compounds. These CD derivatives are dissolved in polysiloxane phases and are used for preparing efficient capillary columns.

Chirasil-β-Dex, a polysiloxane-anchored permethylated β-cyclodextrin with 3, 5 and 8 spacer have been successfully used as CSP in GC [14]. In this contribution, we report on the investigation of Chirasil-β-Dex with a new 11-spacer as CSP for the gas chromatographic enantiomers separation of a set of cyclopropane derivatives prepared via metal-catalyzed carbene transfer reactions.

2. Experimental

2.1. Chemicals

Meldrum's acid (2,2-dimethyl-1,3-dioxane,4,6-dione) (**4**) and diacetoxyiodobenzene [PhI(OAc)$_2$] (**6**), 1,8-naphthalic anhydride (**12a**) and its 4-Cl-substitued **12b** were purchased from Acros Organics (Belgium). Iodosyl benzene [PhI = O] (**7**) was prepared as described below. $Rh_2(OAc)_4$ was purchased from Pressure Chemical (Pittsburgh, USA). $Rh_2\{(S)\text{-nttl}\}_4$ (**8**) and the ligand used in its preparation *N*-1,8-naphthoyl-(*S*)-*tert*-leucine (**14a**) were prepared as previously reported. Substituted [$Rh_2\{(S)\text{-nttl}\}_4$] catalysts were prepared according to literature procedure [12]. All olefins were commercially available and distilled prior to use.

2.2. Instruments

Infrared (IR) spectra were measured on a Shimadzu FT-IR-9100 spectrometer. ^{1}H and ^{13}C NMR and spectra were recorded on a Brucker (400 MHZ) spectrometere. Chemical shifts of ^{1}H NMR are expressed in ppm downfield relative to internal standard (tetramethysilane at 0 ppm). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak and for IR weak (w), medium (m) and strong (s).

2.3. Synthesis of mono-undec-10-enylated β-cyclodextrin [13]

In nitrogen atmosphere, 90 g (80 mmol) of anhydrous β-cyclodextrin (Fluka, Buchs, Switzerland), dried in vacuo at 80 °C over P_4O_{10} for 48 h, were placed into 4 l three-necked, round-bottomed flask equipped with a nitrogen inlet, dropping funnel and reflux condenser fitted with a mercury valve, and were dissolved in 2 l anhydrous DMSO. To the solution was added 10 g (0.25 mol) of dried powdered sodium hydroxide and stirring was continued for 1 h at room temperature. To the vigorously stirred solution, was added 45 ml (0.2 mol) 11-Bromo-undec-1-ene. Stirring was continued for 60 h at room temperature. The reaction mixture was separated from sodium bromide and from unreacted sodium hydroxide by filtration and subsequently concentrated almost to dryness in vacuo and 60 °C. The residue was diluted with methanol and the product was precipitated by adding 200 ml diethyl ether. Purification was performed using silica (ethanol/toluene 2:1).

2.4. Synthesis of permethyl-mono-undec-10-enyl β-cyclodextrin

In nitrogen atmosphere, 1.43 g (59.6 mmol) sodium hydride (55–60% in paraffin oil (Fluka, Buchs, Switzerland) was repeatedly washed with *n*-hexane to remove paraffin oil and then transferred into an ice-cooled three necked, round-bottomed flask equipped with a nitrogen inlet, a dropping funnels, and reflux condenser fitted with a mercury valve. A 1.35 g (1.08 mmol) of 11-undec-1-enylated β-cyclodextrin was dissolved in 30 ml DMF and added slowly via the dropping funnel to the sodium hydride in nitrogen atmosphere, whereupon the vigorous reaction with evolution of hydrogen (caution!) started. After the vigorous reaction has ceased half the amount of 5.25 ml (84.15 mmol) of methyl iodide was added slowly at a bath temperature of 20 °C. After stirring for 30 min, the second half of the reagent was added to the reaction mixture. After stirring for one hour, the reaction mixture was decanted from unreacted sodium hydride and was carefully poured into 200 ml water. The aqueous phase was extracted three times with 100 ml ether. The combined ether layers were washed three times with 20 ml water to remove residual DMF. The organic layer was subsequently dried over anhydrous sodium sulphate, then filtrated and washed with THF. The solid yellowish residue was dried, purified by silica yielding 0.47 g of pure product. MS (positive FAB, in methanol/H_2O 10:1) *m* (nominal mass)/*z* 1568.86 $[M+H]^+$, calcd: $M_r = 1567.81\ g\ mol^{-1}$. ^{1}H NMR ($CDCl_3$) δ 5.74 (m, 1H, olefinic CH-group), 5.11 (d, 1H, anomeric H), 5.02 (m, 2H, olefinic CH_2), 4.7 (t, 1H, H-2), 4.32 (m, 2H, H-6), 3.37 (t, 2H, CH_2), 3.81 (t, 1H, H-4), 3.61 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 1.99 (m, 2H, CH_2 in allylic position), 1.23 (br, 14H, 7^*CH_2). ^{13}C NMR ($CDCl_3$) δ 139.24 (olefinic CH-group), 114.12 (olefinic CH_2), 98.98 (C-1), 77.53 (C-4), 71.39 (C-3), 71.03 (C-2), 70.83 (C-5), 61.319 (C-6), 67.99 (CH_2), 61.39 (CH_3), 58.99 (CH_3), 58.57 (CH_3), 33.83 (CH_2), 30.11 (CH_2), 29.61 (CH_2), 29.53 (CH_2), 29.16 (CH_2), 28.96 (CH_2), 26.01 (CH_2), 25.64 (CH_2) [13].

2.5. Preparation of Chirasil-Dex by hydrosilylation

In nitrogen atmosphere, 0.56 g (approximately 0.19 mmol) dimethylpolysiloxane containing 9.3% CH_3–Si–H