Catalytic Enantioselective Reductive Cyclization of Acetylenic Aldehydes via Hydrogenation

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Received 20 April 2007

Abstract: The reductive cyclization of acetylenic aldehydes is accomplished via rhodium-catalyzed asymmetric hydrogenation. This process provides access to a wide variety of cyclic allylic alcohols in good yields and with high levels of asymmetric induction.

Key words: acetylenic aldehyde, allylic alcohol, hydrogenation, rhodium, reductive cyclization

Introduction

Considerable effort has been invested in the development of new catalytic methods for the reductive cyclization of acetylenic aldehydes.\(^1,2\) This is not surprising as this method provides direct access to allylic alcohols, which are valuable synthetic building blocks. The reductive cyclization of acetylenic aldehydes was first described in 1994 by Ojima.\(^3\) Shortly thereafter, Crowe\(^4\) reported a titanocene-catalyzed variant, and Montgomery\(^5\) reported an analogous nickel-catalyzed reaction. Subsequently, the intermolecular reductive couplings of alkynes and aldehydes were reported by Montgomery\(^6\) and Jamison.\(^7\) Notably, Jamison has developed an asymmetric variant of the intermolecular transformation.\(^8\) Surprisingly, despite impressive advances in this field, catalytic asymmetric intramolecular reductive cyclization of alkynes and aldehydes had not been reported prior to the studies described in this account.\(^9\)

Here, the first catalytic enantioselective reductive cyclization of acetylenic aldehydes is reviewed. The reaction is mediated by a chirally modified cationic rhodium catalyst and utilizes molecular hydrogen as the terminal reductant (Scheme 1). The addition of Brønsted acid was found to enhance both the rate and yield. This effect of Brønsted acid cocatalysts has been observed in related hydrogenative C–C coupling reactions.\(^10\) Cyclic allylic alcohols are generated in good yield and excellent enantiomeric excess. Furthermore, chiral acetylenic aldehydes undergo highly diastereoselective reductive cyclization.

Scope and Limitations

The hydrogen-mediated reductive cyclization was optimized using the acetylenic aldehyde 1a as substrate (Scheme 2). After extensive optimization, it was found that exposure of 1a in 1,2-dichloroethane solution (0.1 M) at 45 °C to hydrogen (1 atm), 2-naphthoic acid (5 mol%), Rh(COD)\(_2\)OTf (5 mol%), and (R)-Cl,MeO-BIPHEP (5 mol%) resulted in the formation of 1b in 67% yield and 98% enantiomeric excess. Notably, when 2-naphthoic acid was excluded, 1b was obtained in 24% yield and 95% enantiomeric excess.

A variety of acetylenic aldehydes were subjected to the optimized reaction conditions (Scheme 3, Figure 1). Electron-deficient α,β-acetylenic amides were first examined. Substrates 2a–4a underwent cyclization smoothly to furnish the desired products 2b–4b in good yield and excellent enantiomeric excess. These examples reveal that the alkyne terminus can be substituted with aryl (2b), alkyl...
(3b), or cyclopropyl (4b) moieties. Next, the reductive cyclization of unactivated alkynes was investigated. An assortment of sulfonamide-tethered alkynes 5a–10b proved to be efficient substrates. Notably, in the case of 9b, it was found that unsubstituted alkynes participate in the reaction. Additionally, geminal substitution adjacent to the aldehyde (5b) or alkyne (10b) is also tolerated. After testing the sulfonamide-tethered substrates, ether-tethered acetylenic aldehydes were examined. Gratifyingly, the ether-tethered acetylenic aldehydes 11b–13b participate in efficient reductive cyclization to furnish the corresponding alkylidene furans. Unfortunately, attempts to form six-membered rings via hydrogen-mediated reductive cyclization were unsuccessful and provided mainly the product of conventional alkyne reduction.

After examining the scope of the enantioselective process, diastereoselective variants of the reductive cyclization were explored. Accordingly, chiral acetylenic aldehydes were subjected to standard conditions for hydrogen-mediated reductive cyclization using the achiral ligand BIPHEP (Figure 2). Gratifyingly, the chiral acetylenic aldehydes 14b–16b were found to engage in highly diastereoselective reductive cyclization to provide the syn-stereoisomers.

A plausible catalytic mechanism is proposed for the cyclization of acetylenic aldehyde 8a (Scheme 4). This involves oxidative coupling of 8a to produce the oxa-metallacyclic intermediate 17. Protonolytic cleavage of the metal–oxygen bond produces 18, which hydrogenolytically cleaves to generate 19. Reductive elimination delivers 8b with regeneration of the cationic rhodium catalyst. This mechanism is consistent with the results of deuterium labeling. Protonolytic cleavage of 17 by the Brønsted acid cocatalyst circumvents a highly energetic four-centered transition structure for hydrogenolysis of the rhodium–oxygen bond embodied by 17. This allows hydrogenolysis to occur at the stage of the rhodium carboxylate 18 through a lower energy six-centered transition structure.11

In summary, the catalytic asymmetric reductive cyclization of acetylenic aldehydes has been accomplished via rhodium-catalyzed hydrogenation. This process furnishes cyclic allylic alcohols in good yields with excellent enantiomeric excesses. Related hydrogen-mediated fragment couplings are currently under investigation in our laboratory.
Asymmetric Reductive Cyclization via Hydrogenation

PRACTICAL SYNTHETIC PROCEDURES

Asymmetric Reductive Cyclization via Hydrogenation

All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe, and flasks were flame-dried and cooled under a stream of N₂. DCE was purchased from Fisher Co. and freshly distilled from CaH₂. Other chemicals were purchased from Aldrich Chemical Co. or Across Co. and used without further purification. Analytical TLC was carried out using 0.2 mm commercial silica gel plates (EM Science precoated 60 F 254). ¹H NMR spectra were routinely recorded on Varian Gemini 300 (300 MHz), Varian Mercury 400 (400 MHz), and Varian Inova 500 (500 MHz) spectrometers. Chemical shifts are reported in delta (δ) parts per million (ppm) relative to the central line of CDCl₃ (δ = 7.26 ppm) unless otherwise mentioned. ¹³C NMR spectra were recorded with Varian Gemini 300 (75 MHz), Varian Mercury 400 (100 MHz), and Varian Inova 500 (125 MHz) spectrometers. Chemical shifts are reported in delta (δ) units, parts per million (ppm) down field from TMS, and Hertz (Hz) is used for the coupling constants. HRMS data were obtained on a Perkin-Elmer 1600 infrared spectrometer. Chemical shifts are expressed as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+1, M–1) or a suitable fragment ion.

**Scheme 4  Plausible catalytic cycle**

[Diagram of a plausible catalytic cycle involving Rh(I) complexes and hydrogenation reactions]

**References**


(8) Johnson & Johnson, and the NIH-NIGMS (RO1-GM69445) for partial support of this research.

Acknowledgment

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**Compound 2b; Typical Procedure**

To a solution of 3-phenylpropionic acid (4-bromobenzyl)(2-oxoethyl)amide (2a; 0.15 mmol, 53 mg) in dichloroethane (1.5 mL, 0.1 M) at r.t., were added Rh(COD)OTf (5 mol%, 7.5 µmol, 3.5 mg), 2-naphthoic acid (5 mol%, 7.5 µmol, 1.3 mg), and (R)-ClMeO-BIPHEP (6 mol%, 9.0 µmol, 5.9 mg). The mixture was purged with H₂ and allowed to stir at 45 °C under an atmosphere of H₂ until complete consumption of 2a was observed. The mixture was concentrated via rotary evaporation and the desired product 2b was isolated by column chromatography (SiO₂, hexane–EtOAc, 1:1); yield: 45 mg (85%). HPLC: Chiral OJ-H column, 15% i-PrOH–hexane, 1.0 mL/min, 254 nm, t₁ (major) = 38.5 min, t₂ (minor) = 45.2 min; ee = 97%.

IR (neat): 3380 (br s), 3065 (m), 3030 (m), 2925 (m), 1910 (w), 1670 (s), 1590 (m), 1575 (m), 1490 (s), 1435 (s), 1405 (s), 1350 (m), 1260 (s), 1200 (s), 1130 (m), 1105 (m), 1070 (s), 1010 (s), 910 (s), 835 (m), 800 (s), 730 (s), 690 cm⁻¹ (s).

HRMS (CI): m/z calculated for C₁₈H₁₇BrNO₂ [M+ + 1]: 358.0443; found: 358.0442.

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