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Enantioselective Synthesis of (*R*)-Tolterodine via CuH-Catalyzed Asymmetric Conjugate Reduction

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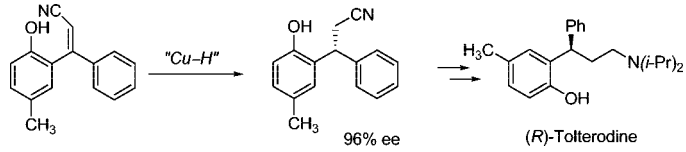


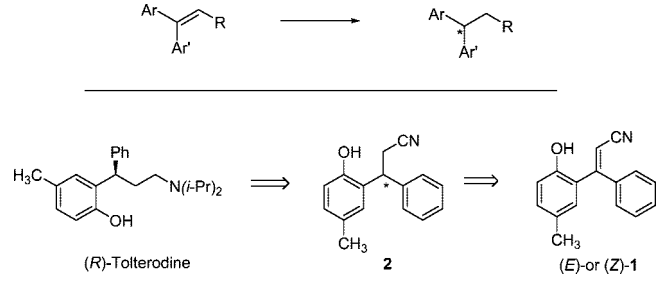
An efficient and highly enantioselective method for the preparation of (*R*)-tolterodine is described. The synthesis was performed by CuH-catalyzed asymmetric conjugate reduction of a β,β-diaryl-substituted unsaturated nitrile as a key step, which is prepared by a stereoselective hydroarylation of alkynenitrile with aryl boronic acid. The synthesis was accomplished without employing the protection−deprotection sequence.

Introduction

(*R*)-Tolterodine, a potent muscarinic antagonist, is an important urological drug used for the treatment of an overactive bladder.[1] Several different approaches have been reported for the asymmetric synthesis of tolterodine so far, utilizing asymmetric hydrogenation,[2] conjugate addition of arylboronic acids,[3] and CBS reduction[4] as a key step. In most of the syntheses, cyclic precursors such as coumarins[2,3a] and indenones[4] were used in the key catalytic enantioselective step except for the early approaches based on chiral auxiliaries[5] or hydroformylation reaction.[6] Although some of the syntheses achieved high levels of enantioselectivity,[3,4] a more efficient method with no extra steps for manipulating unnecessary functionalities is still required.

Tolterodine has the structural element with two aryl groups attached to a chiral center. One attractive route to this type of target molecule would be catalytic asymmetric reduction of a suitable acyclic alkenyl precursor (Scheme 1). However, this approach has not been realized possibly due to a difficult control

SCHEME 1. Retrosynthetic Analysis



of the double bond configuration and to the lack of appropriate asymmetric reduction methods. On the other hand, asymmetric hydrogenations of a coumarin intermediate catalyzed by rhodium or ruthenium were reported, but only a moderate level (80% ee) of enantioselectivity was obtained under optimized conditions.[2]

Copper hydride (Cu−H) ligated by nonracemic ligands has rapidly developed into a powerful catalyst for the enantioselective reduction of various electron-deficient olefins, including α,β-unsaturated carbonyl compounds, nitroalkenes, and alkenyl sulfones.[7] One of the applications of the copper hydride catalysis is the asymmetric reduction of α,β-

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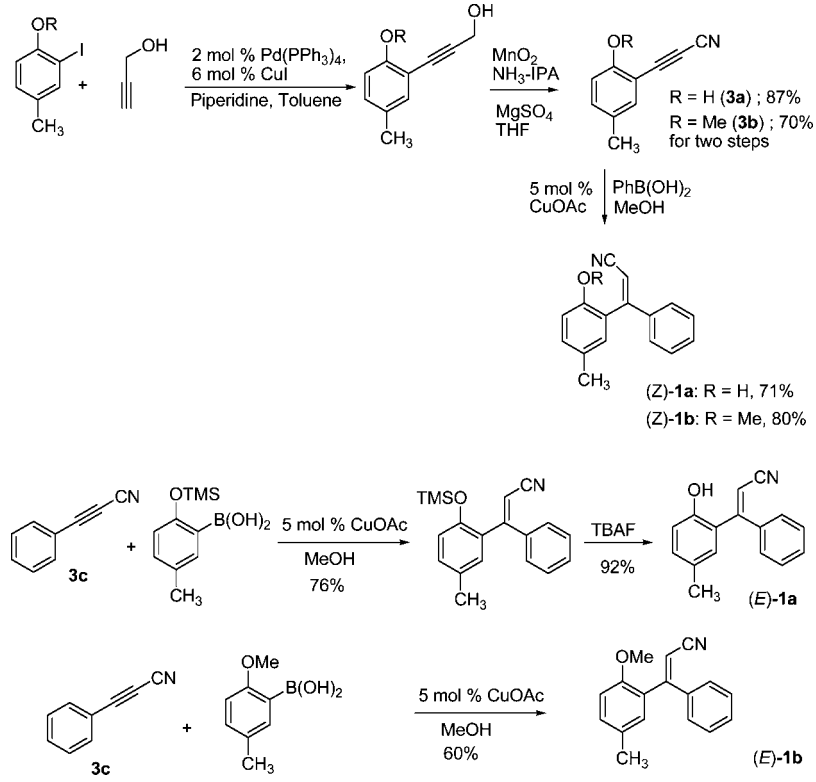
SCHEME 2. Preparation of (*Z*)- and (*E*)-Nitriles via Stereoselective Hydroarylation



unsaturated nitriles,[8] which produce a different coordination environment from α,β-unsaturated carbonyl compounds due to its linear CN group. Recently, we have also reported an efficient CuH-catalyzed enantioselective conjugate reduction of 3-aryl-3-pyridylacrylonitriles.[9] In this study, we found that the copper system did not require a secondary coordinating functionality for catalytic reactivity unlike Rh- and Ru-catalyzed asymmetric hydrogenation.[10]

For the development of a new synthetic route to tolterodine, we became interested in applying the CuH asymmetric reduction method to sterically demanding 3,3-diarylacrylonitriles having an ortho substitution on the aryl group. Herein, we report an efficient asymmetric synthesis of (*R*)-tolterodine that was successfully achieved by performing highly enantioselective CuH catalysis of isomerically pure 3,3-diaryl-substituted acrylonitriles.

Results and Discussion

In the beginning of our study, we found that attaining geometrically pure 3,3-diarylacrylonitriles was of great importance because the CuH reduction of (*E*)- and (*Z*)-olefin isomers was known to supply opposite enantiomers.[8,9] Our initial attempts to stereoselectively synthesize the unsaturated nitrile compounds via a Heck[11] or a Suzuki−Miyaura cross-coupling[12] reaction by following the known literature procedures were not successful; with ortho-substituted coupling partners, the coupling reactions resulted in incomplete conversion and production of an inseparable mixture of (*E*)- and (*Z*)-isomers.[13] Then, we turned our attention to the copper-catalyzed hydroarylation of alkynoates reported by Yamamoto and co-workers.[14] To our satisfaction, the reaction of phenyl boronic acid with properly substituted aryl alkynenitriles **3a** and **3b** gives (*Z*)-3,3-diarylacrylonitriles (**1a** and **1b**) with high stereoselectivity (Scheme 2).[15] The corresponding (*E*)-isomers were also prepared by the reaction of phenyl alkynenitrile (**3c**) with ortho-substituted boronic acids. However, the addition of the boronic acid possessing an unprotected ortho-phenolic hydroxyl group proceeded very poorly, and thus (*E*)-**1a** was obtained after deprotection of the TMS group of the intermediate adduct. The stereochemistry of (*Z*)-**1b** and (*E*)-**1b** was assigned based on the mechanism of the hydroarylation and corroborated by NOE experiments.[16]

Then, we examined the conjugate reduction of these substrates with 2 mol % of catalyst in the presence of excess polymethylhydrosiloxane (PMHS) as a stoichiometric reducing agent in toluene. As expected, this type of diarylacrylonitrile with an ortho substitution (**1**) generates more steric congestion around the reactive site than simple 3-phenyl-3-pyridylacrylonitriles, and thus most of the catalyst−ligand[17] combinations that had given complete conversion of the latter substrates displayed inferior reactivity (Table 1, entries 1 and 2). However, to our delight, the reduction of (*Z*)-**1a** smoothly proceeded to completion at room temperature in 12 h with 2

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(13) See the Supporting Information for details.
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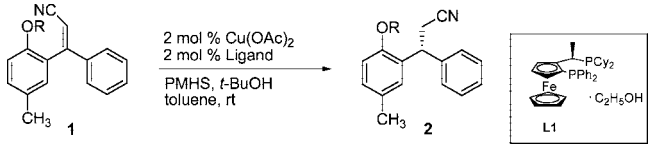
(15) These are first examples of 3,3-diarylacrylonitriles synthesized from alkynenitriles via copper-catalyzed hydroarylation with aryl boronic acids.
(16) See the Supporting Information for details.

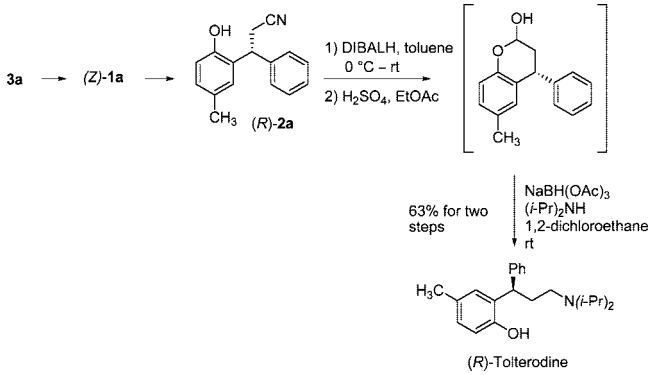
TABLE 1. Copper-Catalyzed Asymmetric Conjugate Reduction



entry	substrates (**1**)	ligand	*t* (h)	conversion (%)	yield (%)	ee[a] (%)
1	(*Z*)-**1a**	(*R*)-(*R*)-Walphos	24	NR		
2	(*Z*)-**1a**	(*R*)-MeOBIPHEP	24	92	60	25 (*S*)
3	(*Z*)-**1a**	(*R*)-(*S*)-cy$_2$PF-Pcy$_2$	18	100	83	41 (*R*)
4	(*Z*)-**1a**	L1	12	100	86	96 (*R*)
5	(*E*)-**1a**	L1	12	100	91	86 (*S*)
6	(*Z*)-**1b**	L1	12	100	87	92 (*R*)
7	(*E*)-**1b**	L1	12	100	85	90 (*S*)

[a] Determined by chiral HPLC analysis.

SCHEME 3. Asymmetric Synthesis of (*R*)-Tolterodine



mol % of Cu(OAc)$_2$ and (*R*)-(*S*)-Josiphos (L1) as the chiral ligand, giving the desired product (*R*)-**2a** in 86% yield and 96% ee (entry 4). The (*E*)-isomer of **1a** gave a lower enantioselectivity of 86% under the same conditions (entry 5). Both of the methoxy derivatives, (*Z*)- and (*E*)-**1b**, were reduced with similar enantioselectivities, 92% and 90% ee, respectively (entries 6 and 7). Overall, with Josiphos as the ligand, the (*Z*)-isomers gave better enantioselectivity than the (*E*)-isomers and increasing steric bulk of the ortho substituent[18] resulted in a slight decrease in ee for the (*Z*)-isomer.

It turned out that the best route to the key intermediate (*R*)-**2a** for tolterodine is the most convenient method starting from **3a** bearing the free hydroxyl group without using the protection−deprotection sequence (Scheme 3). To complete the synthesis of (*R*)-tolterodine, the propionitrile (*R*)-**2a** was reduced to lactol **4** with DIBALH. The crude product was subsequently submitted to reductive amination with diisopropylamine and NaBH(OAc)$_3$ in 1,2-dichloroethane to give (*R*)-tolterodine in 63% yield for the two steps.

In summary, we have developed a short, efficient catalytic asymmetric total synthesis of (*R*)-tolterodine without protecting the phenolic hydroxylic group throughout the synthesis. Two successive copper-catalyzed conjugate additions were stereoselectively carried out to give enantiomerically enriched diarylpropanenitriles (**2**). (*R*)-Tolterodine was produced in 6 steps from commercially available starting materials with an excellent level of enantioselectivity (96% ee).

Experimental Section

For experimental details, see the Supporting Information.

General Procedure for the Copper-Catalyzed Hydroarylation (1). To a solution of alkynenitrile **3a**−**c** (5 mmol) and arylboronic acid (10 mmol) in methanol (10 mL) was added CuOAc (30.5 mg, 0.25 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 6 h. After filtration of the reaction mixture through a pad of Celite, the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (SiO$_2$, hexane/EtOAc = 20:1).

(*Z*)-3-(2-Hydroxy-5-methylphenyl)-3-phenylacrylonitrile ((*Z*)-1a). 3a (786 mg, 5 mmol) and phenylboronic acid (1.2 g, 10 mmol) were employed to afford 830 mg of the desired product as a pale yellow solid (71%): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.55−7.53 (m, 3H), 7.48−7.43 (m, 2H), 7.38−7.32 (m, 2H), 7.25 (s, 1H), 6.35 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 161.1, 155.8, 152.4, 135.4, 134.0, 133.0, 129.7, 129.0, 128.5, 126.8, 118.8, 117.2, 115.3, 21.1; IR (neat) 2211 cm^{-1}. Anal. Calcd for C$_{16}$H$_{13}$NO: C 81.68; H 5.57. Found: C 81.42; H 5.58. HRMS (EI) calcd for C$_{16}$H$_{13}$NO 235.0997, found 235.0988.

General Procedure for the Copper-Catalyzed Enantioselective Reduction. Cu(OAc)$_2$ (1.82 mg, 0.010 mmol) and Josiphos ligand (6.41 mg, 0.010 mmol, ethanol adduct) were placed in an oven-dried Schlenk tube. Toluene (0.5 mL) was added under a nitrogen atmosphere and the reaction mixture was stirred for 10 min at room temperature. PMHS (75 μL, 1.25 mmol) was added to the reaction mixture, which was then stirred for 5 min for catalyst activation. The unsaturated nitrile (0.5 mmol) and toluene (0.5 mL) were added, followed by *t*-BuOH (191 μL, 2.0 mmol). The reaction was sealed and stirred until the starting material was completely consumed as judged by TLC. The reaction mixture was quenched with water and transferred to a round-bottomed flask with the aid of EtOAc (10 mL), then NaOH (2.5 M, 1.2 mL) was added. The biphasic mixture was stirred vigorously for 0.5 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The product was purified by chromatography.

(*R*)-3-(2-Hydroxy-5-methylphenyl)-3-phenylpropanenitrile ((*R*)-2a). Using the general procedure for the enantioselective reduction, (*Z*)-**1a** (118 mg, 0.5 mmol) was employed to afford 102 mg of the desired product as a pale yellow oil (86%): ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.37−7.25 (m, 3H), 7.17−7.03 (m, 4H), 6.78 (s, 1H), 4.29 (t, J = 6.7 Hz, 1H), 3.02 (sept, J = 7.5 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 154.6, 141.0, 129.9, 129.4, 128.8, 128.6, 127.8, 127.0, 119.0, 110.9, 55.5, 40.9, 22.7, 20.7; IR (neat) 2245 cm^{-1}. Anal. Calcd for C$_{16}$H$_{15}$NO: C 80.98; H 6.37; N 5.90. Found: C 80.84; H 6.69; N 5.78. The ee (96% ee) was measured by chiral HPLC on an OD-H column (*i*-PrOH/hexane 10:90, 0.5 mL/min); (*R*)-isomer t_r = 16.8 min and (*S*)-isomer t_r = 18.9 min.

(*R*)-Tolterodine. To a solution of (*R*)-**2a** (100 mg, 0.42 mmol) in anhydrous toluene (3 mL) was added dropwise a solution of 1 M DIBAL-H in toluene (500 μL, 0.5 mmol) at 0 °C under a nitrogen atmosphere. The reaction was quenched after 5 h with EtOAc and a solution of sulfuric acid was added. The solution was stirred at room temperature overnight. The aqueous phase was extracted with EtOAc (3 × 20 mL), then the organic phases were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. To a solution of the crude product in 1,2-dichloroethane (3 mL) were added diisopropylamine (280 μL, 2 mmol) and sodium triacetoxyborohydride (59.4 mg, 2 mmol), then the reaction mixture was

(17) Lower conversion and enantioselectivity was obtained except for Josiphos ligand. (*R*)-(*R*)-Walphos = (*R*)-1-[(*R*)-2-(2′-diphenylphosphinophenyl)-ferrocenyl]ethyldi(bis-3,5-trifluoromethylphenyl)phosphine; (*R*)-MeOBIPHEP = (*R*)-(+)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine); (*R*)-(*S*)-cy$_2$PF-Pcy$_2$ = (*R*)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine.

(18) Increasing further the size of a protecting group of the OH resulted in a lower reaction rate. The reaction of a benzyl-protected derivative of (*Z*)-**1a** proceeded to 60% conversion in 24 h under the same conditions.

stirred at room temperature for 16 h. Aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (SiO_2, hexane/EtOAc = 9:10) afforded 86 mg of product as a colorless oil (63%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.29 (m, 4H), 7.24−7.20 (m, 1H), 6.84 (dd, J = 8.2, 2.0 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.54 (s, 1H), 4.48 (dd, J = 11.1, 3.8 Hz, 1H), 3.21 (sept, J = 6.7 Hz, 2H), 2.72−2.69 (m, 1H), 2.40−2.30 (m, 2H), 2.11 (s, 3H), 2.11−2.04 (m, 1H), 1.12 (d, J = 6.7 Hz, 6H), 1.06 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 153.0, 144.7, 132.3, 129.1, 128.5, 128.3, 128.2, 127.6, 125.9, 117.8, 47.9, 42.2, 39.5, 33.5, 20.6, 19.9, 19.5; $[\alpha]^{23}_D$ +19.6 (c 0.5, MeOH) [lit. value: $[\alpha]^{20}_D$ +22.0 (c 0.32, MeOH) for (*R*)-tolterodine].

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Supporting Information Available: Experimental details, characterization data, and HPLC, ^{1}H, and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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