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Enantioselective Synthesis of β-Aryl-γ-amino Acid Derivatives via Cu-Catalyzed Asymmetric 1,4-Reductions of γ-Phthalimido-Substituted α,β-Unsaturated Carboxylic Acid Esters

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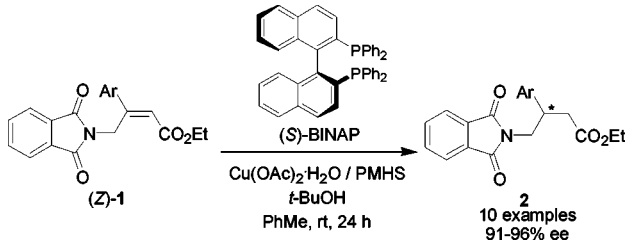

A series of chiral β-aryl-substituted γ-amino butyric acid derivatives were synthesized in good enantioselectivities via the Cu-catalyzed asymmetric conjugate reduction of γ-phthalimido-α,β-unsaturated carboxylic acid esters using $Cu(OAc)_2 \cdot H_2O$ as a catalyst precursor, (*S*)-BINAP as a ligand, PMHS as a hydride source, and *t*-BuOH as an additive. The methodology has been applied successfully to the enantioselective synthesis of a chiral pharmaceutical, (*R*)-baclofen.

γ-Amino butyric acid (GABA) is an important central nervous system neurotransmitter and has a profound impact on many important biological functions.[1] Hence, many GABA analogues, particularly those bearing substituents at the β-position such as 4-amino-3-(4-chlorophenyl)butyric acid (baclofen), have been well explored as medicines to treat various diseases associated with GABA receptors.[2] Studies have disclosed that the biological activities of these GABA analogues resides mainly in the single enantiomer, and therefore the development of an enantioselective method for the synthesis of these compounds is highly desirable. Although some catalytic asymmetric syntheses of β-substituted γ-amino acid derivatives have been reported in the past few years,[3] the search for new and efficient catalytic asymmetric synthetic methods remains a significant challenge.

Very recently, we have reported a Rh-catalyzed asymmetric hydrogenation of γ-phthalimido-α,β-unsaturated carboxylic acid esters, in which a variety of chiral β-aryl-γ-amino acid derivatives can be obtained with good enantioselectivities.[4] However, this method has the disadvantages of demanding reaction conditions (60 atm of H_2 pressure), the use of the expensive Rh catalyst, and the relatively high catalyst loadings (1 mol %). These shortcomings prompted us to seek for an alternative approach to synthesize chiral β-substituted γ-amino acids.

In the past decade, copper hydride (Cu-H) with chiral ligands has emerged as a powerful reagent for effecting asymmetric reductions of various α,β-unsaturated compounds[5] such as enones,[6] α,β-unsaturated esters,[7] nitroalkenes,[8] α,β-unsaturated sulfones,[9] and α,β-unsaturated nitriles.[10] Since the copper salts is very cheap in comparison with the Rh catalyst precursor, we therefore envisioned that an asymmetric 1,4-reduction of γ-phthalimido-α,β-unsaturated esters via copper hydride catalysis should be an attractive alternative to these chiral compounds. Herein, we report our studies on this new strategy for constructing chiral β-aryl substituted γ-amino acid derivatives.

We started our studies on the catalytic asymmetric conjugate reduction of ethyl (*Z*)-4-phthalimido-3-phenylbut-2-enoate (**1a**) by surveying a number of copper salts, silanes, diphosphine ligands, and solvents in order to identify a suitable catalyst

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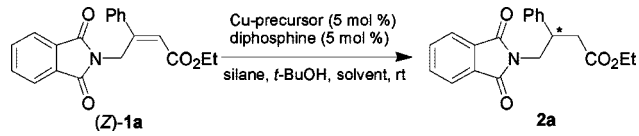
TABLE 1. Enantioselective Conjugate Reduction of (*Z*)-4-Phthalimido-3-phenylbut-2-enoate (1a)[a]



(*Z*)-**1a** **2a**

entry	Cu-precursor	ligand	silicon reagent	solvent	yield (%)[b]	ee (%)[c] (config)[d]
1	CuCl/*t*-BuONa	(*S*)-BINAP	PMHS	toluene	60	96[e]
2	$CuF(PPh_3)_3 \cdot MeOH$	(*S*)-BINAP	PMHS	toluene		*f*
3	CuF_2	(*S*)-BINAP	PMHS	toluene		*f*
4	$Cu(OAc)_2 \cdot H_2O$	(*S*)-BINAP	PMHS	toluene	78	96 (*S*)
5	$Cu(OAc)_2 \cdot H_2O$	(*S*)-Tol-BINAP	PMHS	toluene	57	92
6	$Cu(OAc)_2 \cdot H_2O$	(*R*)-MeO-BIPHEP	PMHS	toluene	61	94
7	$Cu(OAc)_2 \cdot H_2O$	(*S*)-SYNPHOS[7e]	PMHS	toluene	20	60
8	$Cu(OAc)_2 \cdot H_2O$	(*S*)-BINAP	TMDS	toluene	24	91
9	$Cu(OAc)_2 \cdot H_2O$	(*S*)-BINAP	Ph_2SiH_2	toluene		*f*
10	$Cu(OAc)_2 \cdot H_2O$	(*S*)-BINAP	$PhSiH_3$	toluene	32	97
11	$Cu(OAc)_2 \cdot H_2O$	(*S*)-BINAP	PMHS	THF	40	98
12	$Cu(OAc)_2 \cdot H_2O$	(*S*)-BINAP	PMHS	xylene	72	96
13	$Cu(OAc)_2 \cdot H_2O$	(*S*)-BINAP	PMHS	CH_2Cl_2		*f*

[a] All reactions were conducted using 0.25 mmol of substrate, 5 mol % Cu, 5 mol % ligand, 1.0 mmol of *t*-BuOH, and 1.0 mmol of silane in 2 mL of solvent at room temperature for 24 h, unless otherwise specified. [b] Isolated yields. [c] Values were determined by HPLC on a chiral column (Chiralpak AD or AD-H). [d] Absolute configuration was determined by comparison of the sign of the optical rotation with the reported data. [e] No added *t*-BuOH. [f] Not determined because of low reactivity.

system. The results are summarized in Table 1. Initially, we employed the published procedure[7a] for the preparation of the catalyst formed between CuCl, BINAP, and NaO*t*-Bu. To our delight, this catalyst promoted the reaction in good enantioselectivity and moderate yield by using PMHS as the stoichiometric hydride donor (entry 1). Other copper salts were then screened (entries 1−4).[11] The results suggested that $Cu(OAc)_2 \cdot H_2O$[12] is the best catalyst precursor in terms of yield and enantioselectivity, providing the reduction product in 78% yield and 96% ee (entry 4). Since BINAP has proved to be an efficient ligand for this transformation, some structurally similar diphosphines were next investigated (Figure 1). Although good enantioselectivities were obtained in some cases, no results surpassed that obtained with BINAP (entries 4−7). Subsequent experiments in an effort to increase yield and enantioselectivity by the variation of the silane reagents proved unsuccessful. We found that the use of TMDS, diphenylsilane or phenylsilane in the reaction resulted in dramatically decreased reaction rates (entries 8−10). Solvent-screening experiments revealed that the nature of the solvents had a profound effect on the catalytic reaction. The reactions performed in THF gave an increased enantioselectivity, but decreased reaction rate (entry 11). Using xylene as the solvent, a comparable result was achieved (entry 12). However, very low reaction rate was observed when the reaction was carried out in CH_2Cl_2 (entry 13).

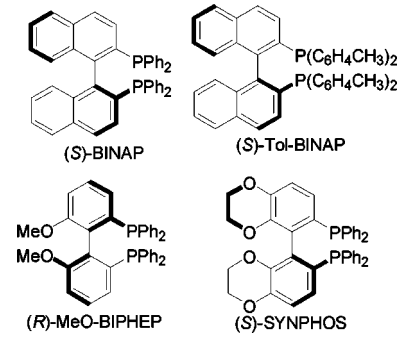


FIGURE 1. Representative ligands for asymmetric 1,4-reduction.

With these encouraging results, we then selected $Cu(OAc)_2 \cdot H_2O$ as the catalyst precursor, BINAP as the ligand, PMHS as the silane reagent, and toluene as the solvent for investigating the scope of this new method on various ethyl (*Z*)-4-phthalimido-3-arylbut-2-enoate (**1**), and the results are summarized in Table 2. Initially, a variety of substituted (*Z*)-4-phthalimido-3-phenylbut-2-enoates (**1b**−**h**) were examined, and the results indicated that the electronic properties of the substituent in the phenyl ring had little effect on the enantioselectivity. All of the substrates were reduced in 93−96% ee (entries 1−7). These reduction products can be easily upgraded via recrystallization to higher level of ee values because of their high crystallinity conferred by the phthalimido group. Good enantioselectivities were also obtained in the conjugate reduction of β-2-naphthyl- and β-2-thiophenyl-substituted substrates (**1i**−**j**, entries 8 and 9). These results demonstrated the applicability of this new method in the enantioselective synthesis of γ-amino acid derivatives.

To explore the potential synthetic utility of this new method, we attempted its application in the synthesis of the chiral pharmaceuticals (*R*)-baclofen (Scheme 1). Although baclofen is commercialized in its racemic form, pharmacological studies have shown that its biological activity resides exclusively in its (*R*)-enantiomer.[2a] As we have reported, the requisite substrate (*Z*)-3-(4-chlorophenyl)-4-phthalimidobut-2-enoate (**1c**) was pre-

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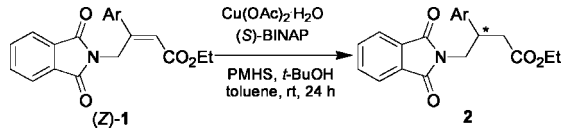
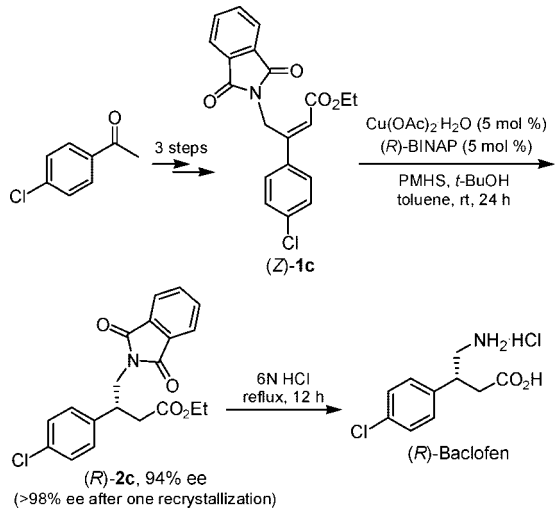
TABLE 2. Enantioselective Conjugate Reduction of (*Z*)-4-Phthalimido-3-arylbut-2-enoate (1) with a $Cu(OAc)_2 \cdot H_2O$/(*S*)-BINAP/PMHS Catalytic System[a]



entry	substrate (Ar)	yield (%)[b]	ee (%)[c] (config)[d]
1	**1b**: Ar = 4-FC_6H_4	91	94(−)
2	**1c**: Ar = 4-ClC_6H_4	94	93 (*S*)
3	**1d**: Ar = 4-BrC_6H_4	71	93(−)
4	**1e**: Ar = 4-$MeOC_6H_4$	77	95(−)
5	**1f**: Ar = 4-$CF_3C_6H_4$	94	94(−)
6	**1g**: Ar = 3-$MeOC_6H_4$	92	96(−)
7	**1h**: Ar = 3-cyclopentoxy-4-$MeOC_6H_3$	86	94 (*S*)
8	**1i**: Ar = 2-naphthyl	88	95(−)
9	**1j**: Ar = 2-thiophenyl	92	91(−)

[a] Reactions were carried out with 0.5 mmol of substrate in 2 mL of toluene at room temperature for 24 h, with a substrate/$Cu(OAc)_2 \cdot H_2O$/(S)-BINAP/PMHS/t-BuOH ratio of 1/0.05/0.05/4/4. [b] Isolated yields. [c] Values were determined by HPLC on a chiral column (Chiralpak AD-H or chiralcel OD-H). [d] Absolute configuration was determined by comparison of the sign of the optical rotation with the reported data.

SCHEME 1. Synthesis of (*R*)-Baclofen



pared through a three-step transformation from 4′-chloroacetophenone in good yields (over 60% in total yields). With the catalysis of Cu/(*R*)-BINAP, **1c** was reduced in 92% yield and 94% ee. The resulting reduction product **2c** was further upgraded via recrystallization to over 98% ee and then converted in one step to (*R*)-baclofen in a nearly quantitative yield, demonstrating the potential utility of this method in the synthesis of chiral pharmaceuticals.

In conclusion, we have developed a method for the asymmetric conjugate reduction of α,β-unsaturated esters containing γ-phthalimido groups, which has led to the asymmetric synthesis of various β-aryl-substituted γ-amino acid derivatives in good enantioselectivities. Interestingly, the results disclosed that the heteroatom in the γ-position seems to be no impact on the direction of hydride delivery. High crystallinity conferred by the phthalimido group made the upgrade of ee values of the reduction products possible. This method has been successfully applied in the enantioselective synthesis of the chiral pharmaceuticals (*R*)-baclofen.

Experimental Section

Ethyl (*Z*)-4-phthalimido-3-arylbut-2-enoates **1a**−**j** were prepared according to the known methods.[4]

General Procedure for Catalytic Asymmetric 1,4-Reduction. $Cu(OAc)_2 \cdot H_2O$ (5 mg, 0.025 mmol), (*S*)-BINAP (15.6 mg, 0.025 mmol), and toluene (1.0 mL) were added into an oven-dried Schlenk tube. The resulting mixture was stirred at room temperature for 30 min. Then, PMHS (0.12 mL, 2.0 mmol) was added to the reaction mixture, which was stirred for 30 min. A solution of ethyl (*Z*)-3-(4-chlorophenyl)-4-phthalimidobut-2-enoate (**1c**) (185 mg, 0.5 mmol) in toluene (1.0 mL) was added, followed by *t*-BuOH (0.191 mL, 2.0 mmol). The reaction vessel was sealed, and the mixture was stirred for 24 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The product was purified by chromatography on silica gel.

Ethyl (*S*)-3-(4-Chlorophenyl)-4-phthalimidobutanoate (2c). ^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, *J* = 7.2 Hz, 3H), 2.68−2.72 (m, 2H), 3.72−3.75 (m, 1H), 3.86−3.91 (m, 2H), 3.92 (q, *J* = 7.2 Hz, 2H), 7.20−7.26 (m, 4H), 7.69−7.71 (m, 2H), 7.79−7.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 38.6, 40.2, 42.9, 60.6, 123.3, 128.8, 129.1, 131.8, 133.0, 134.1, 138.9, 168.1, 171.2. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{18}NO_4ClNa^+$ 394.0822, found 394.0836. $[\alpha]^{25}_D$ −60.4 (*c* 0.5, $CHCl_3$). 93% ee was determined by chiral HPLC (Chiralpak AD-H (0.46 cm × 25 cm), *i*-PrOH/hexane = 15/85, UV 254 nm, 40 °C, 1.0 mL/min), retention times (min) 16.4 (major, *S*) and 22.2 (minor, *R*).

Synthesis of (*R*)-Baclofen. [13] A mixture of (*R*)-**2c** (186 mg, 0.5 mmol, 94% ee) and 6 M HCl (10 mL) was heated under reflux for 12 h. The solution was cooled, and the precipitated phthalic acid was filtered off. The filtrate was evaporated to dryness, and the resulting solid was resuspended in water (10 mL). The filtrate was evaporated to dryness under reduced pressure and then dried under vacuum to give 112 mg (90.2% yield) of (*R*)-baclofen as a colorless solid, mp 198−199 °C; $[\alpha]^{25}_D$ −2.17 (c 0.6, H_2O), lit.[13b] −2.0 (c 0.6, H_2O). ^1H NMR (400 MHz, D_2O): δ 2.73−2.90 (m, 2H), 3.24−3.47 (m, 3H), 7.35−7.48 (m, 4H). ^{13}C NMR (100 MHz, D_2O): δ 38.3, 39.4, 43.7, 129.3, 129.5, 133.4, 137.1, 175.3.

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Supporting Information Available: Experimental details, and analysis of ee-values of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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