Tetrahedron Letters 52 (2011) 830–833

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Rhodium-catalyzed asymmetric addition of arylboronic acids to γ-phthalimido-substituted-α,β-unsaturated carboxylic acid esters: an approach to γ-amino acids

Fuzhong Han, Jun Chen, Xiangyang Zhang, Jibing Liu, Linfeng Cun, Jin Zhu, Jingen Deng, Jian Liao *

Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China
Natural Products Research Center, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China
Graduate School of Chinese Academy of Sciences, Beijing 100049, China

ARTICLE INFO

Article history:
Received 27 October 2010
Revised 30 November 2010
Accepted 10 December 2010
Available online 15 December 2010

Keywords:
Bis-sulfoxide ligand
Rh-catalyzed
1,4-Addition
γ-Aminobutyric acids

ABSTRACT

Efficient Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to ethyl-γ-phthalimidocrotonate by using bis-sulfoxide ligand affords γ-aminobutyric acid (GABA) derivatives with high enantioselectivities (90–96% ee) under mild conditions. Optically pure (*S*)-Baclofen and (*S*)-Rolipram have been prepared successfully through this synthetic route.

1. Introduction

Asymmetric catalyzed synthesis is one of the most powerful tools to obtain enantiomerically pure pharmaceuticals.[1] As a class of important compounds for therapeutic uses in a range of central nervous system disorders and useful building blocks, γ-aminobutyric acids (GABA) and their derivatives, especially those analogs bearing substituents at the β-position, have been the subject of intense investigation.[2] Moreover, studies have indicated that the biological activity of these GABA analogs resides exclusively in a single enantiomer; it is, therefore, desirable to provide an enantioselective method for the synthesis of these molecules. Although much progress has been achieved that uses chiral auxiliaries,[3] organocatalysis,[4] and metal-catalysis,[5] finding a more efficient pathway of a transition-metal-catalyzed asymmetric transformation to prepare chiral GABA is still a challenge. Recently, Zheng and co-workers developed an impressive, highly enantioselective Rh-catalyzed hydrogenation and copper hydride 1,4-reduction route to synthesize a variety of chiral β-substituted γ-amino acid derivatives.[6] Helmchen, on the other hand, described the use of $[Rh(acac)(C_2H_4)_2]$/BINAP as an effective catalyst and afforded a γ-amino ester in 96% yield and 89% ee.[7] This is one of the earliest examples of the application of Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated esters, discovered by Miyaura and co-workers,[8] toward pharmaceutically active compounds.[9]

Chiral bis-sulfoxides have been used as ligands in late-transition-metal catalyzed asymmetric reactions.[10] In particular, Dorta and co-workers disclosed that Rh-disulfoxide complexes can be successfully applied in a number of transformations.[11] Very recently, we demonstrated that simple chiral *tert*-butyl sulfoxide, which is a ubiquitous, privileged structural element of chiral ligands with only sulfur chirality, can be used in asymmetric reactions (especially in rhodium-catalyzed 1,4-addition of arylboronic acids to enones) with excellent enantioselectivities.[12] Inspired by the recent success of chiral sulfoxide (P-SOs and bis-sulfoxide) ligands in asymmetric 1,4-addition, it is anticipated that this protocol would allow preparation of the GABA derivatives with excellent enantioselectivities and reactivities. Herein, we report that alkyl γ-phthalimidocrotonates are excellent substrates for the chiral rhodium bis-*tert*-butylsulfoxide complex catalyzed enantioselective conjugate addition of arylboronic acids under mild conditions, providing β-substituted γ-amino acid derivatives in high yields and enantioselectivities ranging from 90% to 96% ee.

2. Result and discussion

As a starting point in our agenda, we set out to develop an efficient synthetic route to alkyl γ-phthalimidocrotonates. These are

* Corresponding author.
E-mail address: jliao@cib.ac.cn (J. Liao).

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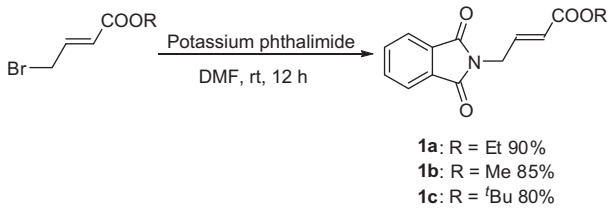
doi:10.1016/j.tetlet.2010.12.044

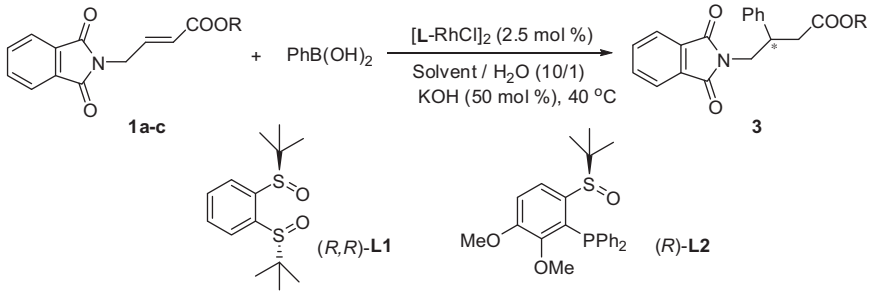


Scheme 1. Synthesis of alkyl γ-phthalimidocrotonates **1**.

interesting substrates mainly due to their excellent properties as Michael acceptors, which allows efficient functionalization at the β position by treatment with arylboronic acids. In addition, substrates with the phthalimido group can make the purification of the crude substrates convenient and promote the ee of addition products because of their high crystallinity. From a synthetic point of view, this type of substrate, alkyl γ-phthalimidocrotonates, can be easily prepared from the commercially available (*E*)-alkyl 4-bromobut-2-enoate and phthalimide potassium salt through a one step transformation (Scheme 1).[13]

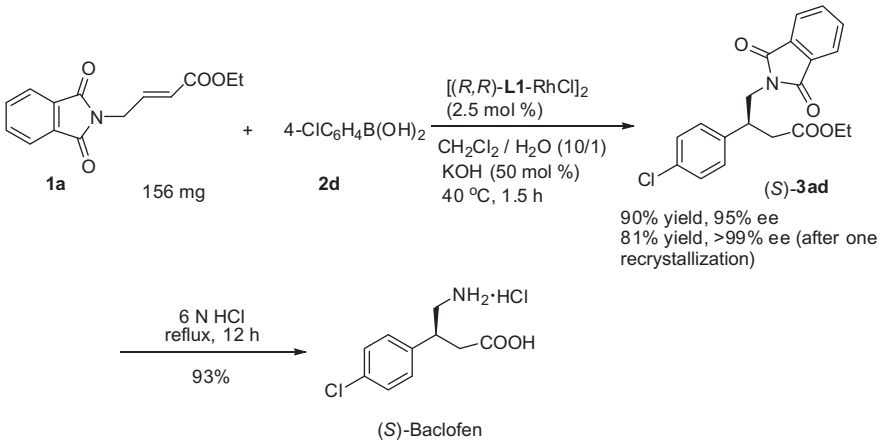
With the substrates in hand, we began our investigation by studying Rh(I)-catalyzed asymmetric 1,4-addition of arylboronic acids to alkyl γ-phthalimidocrotonates. The results are summarized in Table 1. In the first set of experiments, addition of phenylboronic acid (**2a**) to ethyl ester **1a** was examined under several reaction conditions. Treatment of **1a** with **2a** (3.0 equiv) in CH_2Cl_2/H_2O (10:1) at 40 °C for 7 h using [**L**-RhCl]$_2$ (2.5 mol %) and

Table 1
Rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acid to alkyl γ-phthalimidocrotonates[a]



Entry	Substrate	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	CH_2Cl_2	7	92	95(*S*)
2[d]	**1a**	CH_2Cl_2	7	60	21
3	**1b**	CH_2Cl_2	7	88	93
4	**1c**	CH_2Cl_2	7	70	95
5	**1a**	MeOH	7	20	89
6	**1a**	Toluene	7	Trace	n.d.
7	**1a**	THF	7	n.r.	n.d
8	**1a**	1,4-Dioxane	7	Trace	n.d.
9	**1a**	$ClCH_2CH_2Cl$	7	Trace	n.d.
10	**1a**	CH_2Cl_2	1.5	92	95
11	**1a**	CH_2Cl_2	1.0	83	94
12	**1a**	CH_2Cl_2	0.5	67	94

[a] All reactions were carried out with 0.2 mmol of substrate, 0.6 mmol $PhB(OH)_2$ and KOH (1.0 M, 0.1 mL) at 40 °C in 1 mL of the indicated solvent with 2.5 mol % catalyst ([(*R*,*R*)-**L1**-RhCl]$_2$).
[b] Isolated yield.
[c] The ee values were determined by HPLC on a chiral AD-H column and the absolute configuration was determined by comparison to the literature data.[6a]
[d] (*R*)-**L2** as ligand.

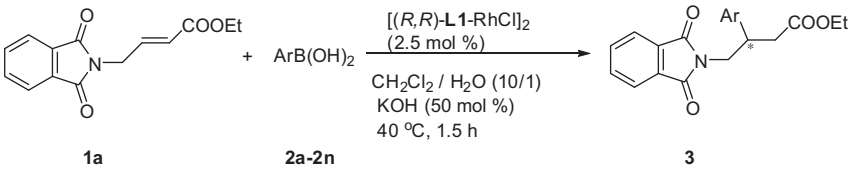


Scheme 2. Synthesis of (*S*)-Baclofen.

50 mol % of KOH. First, we studied the enantioselectivity of the process in the presence of structurally different chiral sulfoxide ligands. The [(*R*,*R*)-**L1**-RhCl]$_2$ (**L1** = 1,2-bis(*tert*-butylsulfinyl)benzene, which was reported by us previously[12d]), provided the best result in terms of ee value (95%) and yield (92%) (Table 1, entry 1). In contrast, (*R*)-**L2** (also developed by us), which is one of the best ligands for the Rh-catalyzed asymmetric conjugate addition of arylboronic acids to enones,[12e] gave the addition product **3aa** with low yield (60%) and poor enantioselectivity (21% ee) (Table 1, entry 2). Next, the ester group of **1** showed a 93% ee, and *tert*-butyl ester (**1c**) gave **3ca** with high ee (95%) but lower yield (70%) (Table 1, entries 3 and 4).

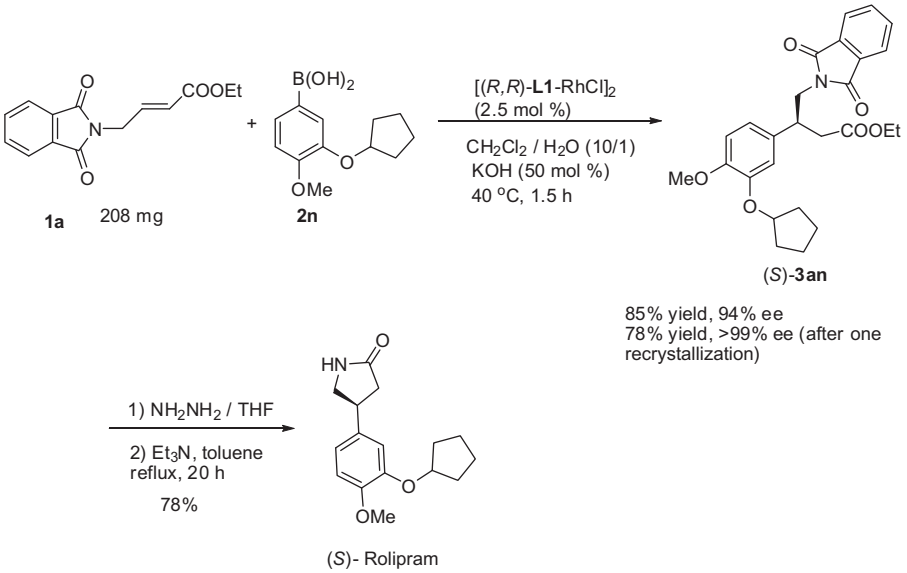
Then, ethyl γ-phthalimidocrotonate (**1a**) and phenylboronic acid (**2a**) were chosen as standard substrates, and some common factors, such as solvent, reaction time were examined. The enantioselectivities and reactivities were found to be quite sensitive to the solvent used. When the reaction was carried out at 40 °C in toluene, MeOH, THF, 1,4-dioxane, $ClCH_2CH_2Cl$, and CH_2Cl_2, the results ranged from no reaction to high yield and excellent ee (Table 1, entries 1 and 5–9). When protic MeOH was used, good enantioselectivity (89% ee) but low yield (20%) was afforded. CH_2Cl_2 was found to be the most favorable solvent for this reaction. Thus, thorough screening experiments were performed to find the best reaction time. The results indicated that 1.5 h is enough to obtain high yield.

Table 2
Rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to ethyl γ-phthalimidocrotonates **1a**[a]



Entry	Ar (**2**)	Yield[b] (%)	ee[c] (%)
1	Ph (**2a**)	92 (**3aa**)	95 (*S*)[d]
2	4-MeC_6H_4 (**2b**)	91 (**3ab**)	94 (—)
3	4-FC_6H_4 (**2c**)	90 (**3ac**)	95 (—)
4	4-ClC_6H_4 (**2d**)	90 (**3ad**)	95 (*S*)[d]
5	4-MeOC_6H_4 (**2e**)	96 (**3ae**)	94 (—)
6	1-Naphthyl (**2f**)	90 (**3af**)	90 (—)
7	2-Naphthyl (**2g**)	94 (**3ag**)	94 (—)
8	3-MeOC_6H_4 (**2h**)	95(**3ah**)	94 (—)
9	3,5-di MeC_6H_3 (**2i**)	80 (**3ai**)	94 (—)
10	3-MeC_6H_4 (**2j**)	93 (**3aj**)	94 (—)
11	2-MeC_6H_4 (**2k**)	60 (**3ak**)	94 (—)
12	4-^{t}BuC_6H_4 (**2l**)	95 (**3al**)	94 (—)
13	4-$CF_3C_6H_4$ (**2m**)	85 (**3am**)	96 (—)
14	3-Cyclopentoxy-4-MeOC_6H_3 (**2n**)	85 (**3an**)	94 (*S*)[d]

[a] All reactions were carried out with 0.2 mmol of substrate, 0.6 mmol Ar$B(OH)_2$ and KOH (1.0 M, 0.1 mL) at 40 °C in 1 mL of CH_2Cl_2 with 2.5 mol % catalyst ([(*R*,*R*)-**L1**-RhCl]$_2$) for 1.5 h.
[b] Isolated yield.
[c] The ee values were determined by HPLC on a chiral AD-H or OD-H column. The signs of the optical rotations are indicated in parentheses.
[d] The absolute configuration was determined by comparison to literature data.[6a]



Scheme 3. Synthesis of (*S*)-Rolipram.

Reducing the reaction time from 1.5 h to 0.5 h decreases the yield to 67%, although a high ee was maintained (Table 1, entries 10–12).

With these optimized reaction conditions identified, we evaluated the scope of this method for various arylboronic acids, applying (*R*,*R*)-**L1** as the ligand and **1a** as the substrate (Table 2). Several conclusions are drawn from this study: (a) substituents at the *meta*- and *para*-position do not have an effect on the excellent enantioselectivity of the reaction. Enantiomeric excesses up to 96% are achieved, which is comparable to the values found in the unsubstituted case. (b) For each tested arylboronic acid, trifluoromethyl as the electron-withdrawing group slowed the reaction, leading to incomplete conversions (Table 2, entry 13). (c) The steric hindrance of substituents (Table 2, entries 9, 11, and 14) restricted the insertion of the substrate and resulted in lower reactivity for the 1,4-addition.

To showcase the utility of the asymmetric 1,4-addition products, we decided to take advantage of the functional groups present in the conjugate addition products for subsequent synthetic elaboration. In particular, the adduct of 4-chlorophenylboronic acid (**2d**) and ethyl γ-phthalimidocrotonates (**1a**) provided the opportunity to prepare optically pure Baclofen, an antispasmodic agent, using 1,4-adducts as a key step. Thus, subjection of **3ad** (Table 2, entry 4), which can be upgraded via recrystallization to over 99% ee, to subsequent hydrolysis (6 N HCl) afforded the (*S*)-Baclofen in nearly quantitative yield (Scheme 2), demonstrating the potential utility of this method in the synthesis of chiral pharmaceuticals.

Furthermore, we used this method to the synthesis of Rolipram, which has been known as a cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase and is employed as an anti-inflammatory agent and antidepressant.[14] Deprotection of the imide and subsequent preparation of (*S*)-Rolipram were accomplished in 78% overall yield by treatment of **3an** (99% ee after one crystallization) with aqueous hydrazine followed by refluxing with Et_3N in toluene (Scheme 3).

3. Conclusion

In summary, we document that the asymmetric 1,4-addition of arylboronic acids to ethyl γ-phthalimidocrotonate proceeds with high enantioselectivity (90–96% ee) under mild reaction conditions by using a Rh/(*R*,*R*)-1,2-bis(*tert*-butylsulfinyl)benzene complex as the catalyst. The method has been successfully applied to obtain chiral pharmaceuticals, such as enantiomerically enriched Baclofen and Rolipram.

Acknowledgments

We are grateful for support from the NSFC (20872139 and 21072186), the West Light Foundation of CAS, the National Basic Research Program of China (973 Program, 2010CB833300) and Chengdu Institute of Biology, CAS (Y0B1051100).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.044.

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