ORGANIC LETTERS

2011
Vol. 13, No. 4
788–791

Asymmetric Synthesis of β-Substituted γ-Lactams via Rhodium/Diene-Catalyzed 1,4-Additions: Application to the Synthesis of (*R*)-Baclofen and (*R*)-Rolipram

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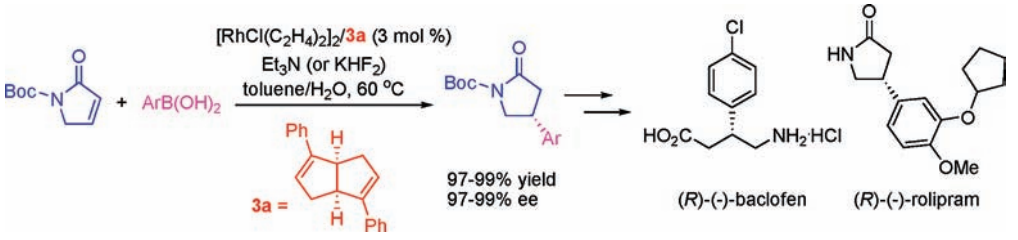
Received December 16, 2010

ABSTRACT



An efficient rhodium/diene-catalyzed asymmetric addition of arylboronic acids to α,β-unsaturated γ-lactams has been developed. The power of this methodology is further demonstrated by the concise synthesis of (*R*)-baclofen and (*R*)-rolipram.

γ-Lactams have attracted considerable attention due to their presence in a large variety of biologically active compounds[1] as well as the synthetic precursors of inhibitory neurotransmitters γ-aminobutyric acids (GABA).[2] Significant efforts have been devoted to the asymmetric synthesis of chiral γ-lactams, and a variety of methods toward introducing C-4 chirality have been developed.[3] However, most existing methods utilize properly substituted acyclic intermediates for lactam formation and usually require multiple structural modifications in the synthesis. A highly enantioselective and straightforward method is still of great interest.

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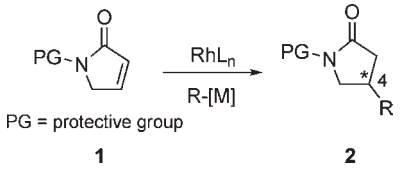
10.1021/ol103054a
Published on Web 01/19/2011

Scheme 1. Chiral γ-Lactams Prepared via 1,4-Addition



The asymmetric rhodium-catalyzed 1,4-addition of organometallic reagents to an α,β-unsaturated lactam is one of the most attractive strategies from a synthetic point of view (Scheme 1). Since the discovery by Miyaura and Hayashi in 1998,[4] rhodium catalyzed asymmetric 1,4-addition of organometallic reagents has been rapidly developed into a powerful tool for the stereoselective formation of a C−C bond.[5] Although Hayashi and co-workers reported asymmetric 1,4-addition reaction to α,β-unsaturated pyridinones in 2001,[6] surprisingly, few reports has been devoted to the addition of α,β-unsaturated γ-lactams, probably due to the problematic isomerization of the carbon−carbon double bond in **1** (Scheme 1).[7] In 2006, He and co-workers reported the asymmetric addition of arylboronic acid to α,β-unsaturated γ-lactams using a rhodium/(*R*)-binap complex as a catalyst.[8] The reaction usually proceeded in moderate yields with less than 90% ee. Therefore, a more effective catalyst system is still highly desirable for this transformation.

The advent of chiral diene ligands offers new opportunities for asymmetric transition-metal catalysis.[9] Compared with phosphane ligands, chiral dienes provide higher reactivities and enantioselectivities in a variety of rhodium-catalyzed asymmetric reactions.[10] Since 2007, our group has developed various diene ligands based on a [3.3.0]-bicyclooctadiene or dicyclopentadiene (DCP) backbone (Figure 1) and successfully applied them in the rhodium-catalyzed enantioselective arylation of imines[11] and the 1,4-addition of arylboronic acids to electron deficient olefins.[12a−c] Herein we describe our new efforts in this catalytic system to α,β-unsaturated γ-lactams to access highly optically pure β-substituted γ-lactams as well as the application on the synthesis of (*R*)-baclofen and (*R*)-rolipram.

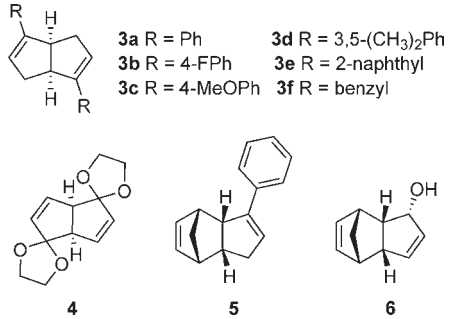
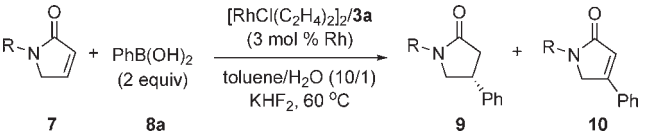


Figure 1. Chiral Dienes Used in This Study.

Table 1. Influence of *N*-Protective Group of **7** on the Asymmetric Rhodium-Catalyzed 1,4-Addition Reaction[a]



entry	substrate	time (h)	product	yield[b] (%)	ee of **9**[c] (%)
1	**7a** R = Bn	6	**9aa**+**10aa**	96[d]	94
2	**7b** R = PMB	10	**9ba**+**10ba**	95[e]	94
3	**7c** R = PMP	10	**9ca**	98	89
4	**7d** R = Boc	6	**9da**	99	97
5	**7e** R = H	10	**9ea**	n.d.	−

[a] The reaction was carried out with **7** (0.2 mmol), phenylboronic acid **8a** (0.4 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0030 mmol), diene **3a** (0.0066 mmol, 1.1 equiv to Rh), and KHF_2 (0.8 mmol) in toluene/H_2O (10/1) at 60 °C for 6−10 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Isolated as a 3.3:1 inseparable mixture of **9aa** and **10aa**. [e] Isolated as a 2.9:1 inseparable mixture of **9ba** and **10ba**. n.d. = not detected.

Initially, we examined the influence of the protective group on nitrogen. Several α,β-unsaturated γ-lactams with different *N*-protective groups were prepared and evaluated in the rhodium-catalyzed addition of phenylboronic acid under the reaction conditions recently developed for nitroalkenes.[12c] The reactions of **7a** and **7b** gave the corresponding addition products with 94% ee accompanied with inseparable byproduct **10** which may be attributed to a Mizoroki−Heck-type reaction (Table 1, entries 1 and 2). A slight decrease in enantioselectivity (89% ee) occurred when PMP (*p*-methoxyphenyl) was used as a protecting group (Table 1, entry 3). To our delight, the best result (99%

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yield, 97% ee) was obtained for **7d** in which the nitrogen was protected by a Boc (*tert*-butoxycarbonyl) group (Table 1, entry 4). When the nitrogen was not masked, the compound **7e** was relatively unstable[7a] and no desired product was observed under the standard conditions (Table 1, entry 5).

Table 2. Optimization of the Experimental Conditions[a]

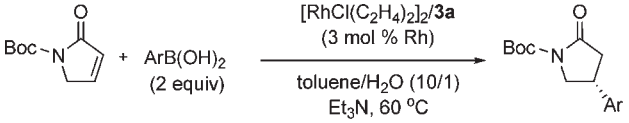
7d **8a** **9da**

entry	diene	solvent	additive[b]	time (h)	yield[c] (%)	ee[d] (%)
1	**3a**	toluene	KHF_2	6	99	97
2[e]	**3a**	toluene	KHF_2	24	52	97
3	**3b**	toluene	KHF_2	5	99	94
4	**3c**	toluene	KHF_2	5	99	96
5	**3d**	toluene	KHF_2	6	99	96
6	**3e**	toluene	KHF_2	6	98	96
7	**3f**	toluene	KHF_2	5	99	69
8	**4**	toluene	KHF_2	2	99	−51
9	**5**	toluene	KHF_2	24	35	37
10	**6**	toluene	KHF_2	24	69	27
11	**3a**	toluene	K_3PO_4	24	65	81
12	**3a**	toluene	KOH	24	58	71
13	**3a**	toluene	Et_3N	6	99	98
14	**3a**	dioxane	Et_3N	10	99	98

[a] The reaction was carried out with **7d** (0.2 mmol), phenylboronic acid **8a** (0.4 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0030 mmol), diene (0.0066 mmol, 1.1 equiv to Rh), and additive in toluene/H_2O at 60 °C. [b] Used 4 equiv for entries 1−10, 13, and 14 and 2 equiv for entries 11 and 12. [c] Yield of isolated product. [d] Determined by chiral HPLC analysis. [e] The reaction was carried out at 40 °C.

Next, several reaction parameters including ligand, temperature, additive, and solvent were screened in order to further improve the enantioselectivity. Some representative results are shown in Table 2. The application of dienes **3b**−**e** as ligands, which bear two more sterically hindered aromatic groups on the double bonds than **3a**, resulted in a small erosion of the enantioselectivity (Table 2, entries 3−6). When a flexible benzyl substituted diene **3f** was used, a significant loss of enantioselectivity was observed although the high reactivity was maintained (Table 2, entry 7). Low stereoselectivity were also observed using diene **4**, **5**, or **6** as a ligand (Table 2, entries 8−10). The reduction of temperature to 40 °C gave a lower yield albeit keeping the same enantioselectivity (Table 2, entry 2). It was found that a base or acid additive had a significant impact on both yields and enantioselectivities (Table 2, entries 11−13). The best result (99% yield, 98% ee) was achieved with Et_3N as an additive. Replacement of toluene by dioxane gave the same yield and enantioselectivity (Table 2, entry 14).

Table 3. Rhodium-Catalyzed Asymmetric 1,4-Addition Reaction of Arylboronic Acids to **7d**[a]



7d **8** **9**

entry	Ar	time (h)	**9**	yield[b] (%)	ee[c] (%)
1	Ph (**8a**)	6	**9da**	99	98
2	4-$MeOC_6H_4$ (**8b**)	5	**9db**	99	98
3	4-MeC_6H_4 (**8c**)	5	**9dc**	99	98
4	3-$MeOC_6H_4$(**8d**)	6	**9dd**	99	98
5	3-MeC_6H_4 (**8e**)	6	**9de**	98	98
6	2-$MeOC_6H_4$ (**8f**)	8	**9df**	99	99
7	2-MeC_6H_4 (**8g**)	8	**9dg**	99	99
8	1-naphthyl (**8h**)	6	**9dh**	99	99
9	2-naphthyl (**8i**)	5	**9di**	99	98
10[d]	4-$CF_3C_6H_4$ (**8j**)	24 (10)	**9dj**	56 (97)	98 (97)
11[d]	4-ClC_6H_4 (**8k**)	24 (6)	**9dk**	78 (99)	98 (97) (*R*)
12[d]	4-BrC_6H_4 (**8l**)	24 (6)	**9dl**	72 (99)	97 (97)

[a] The reaction was carried out with **7d** (0.2 mmol), arylboronic acid **8** (0.4 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0030 mmol), diene (0.0066 mmol, 1.1 equiv to Rh), and Et_3N (4 equiv) in toluene/H_2O at 60 °C, unless otherwise noted. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The data in the brackets are results when KHF_2 was used as additive (0.8 mmol, 4 equiv).

With the optimal reaction conditions in hand, the scope of rhodium-catalyzed 1,4-addition was investigated using a variety of boronic acids with diverse steric and electronic properties. The results are summarized in Table 3. All arylboronic acids with an electron-donating group on the phenyl ring were added successfully to **7d**, giving the desired products in excellent yields (98−99%) and enantioselectivities (98−99% ee) (Table 3, entries 2−7). Excellent ee's (98−99%) and yields (99%) were also obtained when 1-naphthyl or 2-naphthyl boronic acid was used (Table 3, entries 8 and 9). When the phenyl ring was substituted with electron-withdrawing groups, the reaction afforded the addition products in moderate yields even after prolonged reaction time, but enantioselectivies were still excellent (Table 3, entries 10−12). A possible reason may be attributed to the relatively lower reactivity and faster hydrolysis of the electron-deficient boronic acids.[6] To our delight, this problem was solved by applying the original reaction conditions (with KHF_2 as an additive). The yields were greatly improved to 99% (Table 3, entries 10−12, data in brackets). The absolute configuration of **9dk** was assigned as *R* by comparing the optical rotation of its deprotected product **11** (see below, Scheme 2) with the literature value,[13] which is consistent with the stereochemical model proposed by Hayashi.[9a]

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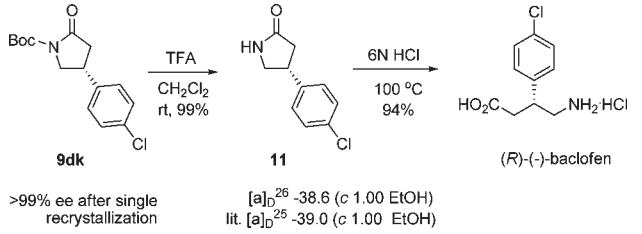
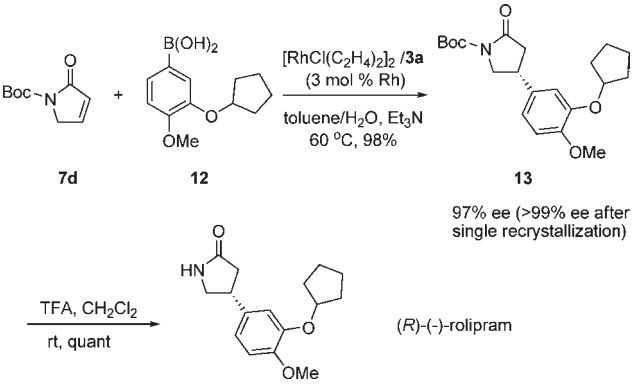
Scheme 2. Synthesis of (*R*)-Baclofen



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



Notablely, the corresponding chiral β-substituted γ-lactams are very useful building blocks for assembling some bioactive compounds. For example, with the treatment of 6 N HCl, **9dk** underwent deprotection and subsequent hydrolysis to afford a selective $GABA_B$ receptor agonist, (*R*)-baclofen hydrochloride,[14] in high yield (Scheme 2).

The synthetic utility of this methodology is also demonstrated by a two-step synthesis of antidepressant (*R*)-rolipram.[15] With the complex of rhodium/**3a** as catalyst, the key enantioselective addition of **12** to **7d** gave the desired product **13** in 98% yield with 97% ee. A higher ee value (>99%) for **13** was easily obtained after a single recrystallization. Deprotection of **13** with TFA afforded (*R*)-rolipram in quantitative yield (Scheme 3).

In summary, we have developed a rhodium-catalyzed asymmetric addition of arylboronic acids to α,β-unsaturated γ-lactams using chiral diene as ligands. Under optimal conditions, the reaction proceeded with excellent yields and enantioselectivities, affording a variety of synthetically useful chiral β-substituted γ-lactams. The power of this methodology is demonstrated by the concise synthesis of (*R*)-baclofen and (*R*)-rolipram. Extension of the methodology to other related substrates and further synthetic applications are currently underway.

Acknowledgment. Financial support from the National Natural Science Foundation of China (21002112), the Major State Basic Research Development Program (2010CB833302), and the Shanghai Municipal Committee of Science and Technology (09JC1417300) is greatly acknowledged.

Supporting Information Available. Experimental procedures and characterization data; copies of ^1H and ^{13}C NMR spectra and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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