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Diastereoselective arylation of enantiopure 3-bromopiperidin-2-one derived from (*R*)-(−)-2-phenylglycinol with organocuprate reagents

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ABSTRACT

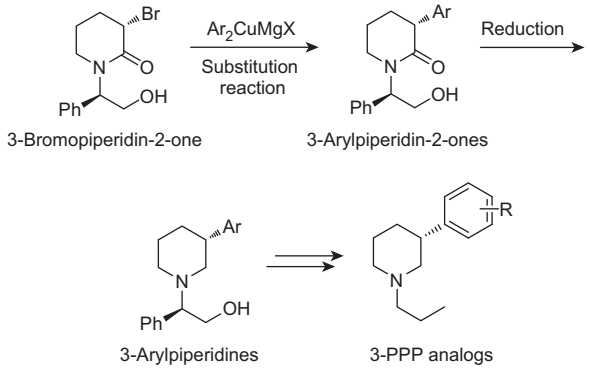
The diastereoselective substitution of 3-bromolactam derived from (*R*)-(−)-2-phenylglycinol with a variety of arylcuprate reagents is presented. The stereochemical outcome of the substitution reaction is discussed. The method provides an efficient and straightforward route to enantiopure 3-arylpiperidines.

A large number of piperidine-containing compounds, either natural or synthetic, are biologically and medicinally interesting.[1] As a consequence, the development of new methods for the enantioselective synthesis of piperidine derivatives by stereoselective introduction of substituents at the carbon positions of the heterocycle constitutes an area of current interest.[2] In the context of the enantioselective synthesis of 3-substituted piperidines, the enolate alkylation of the amide carbonyl of lactams derived from phenylglycinol with alkyl halides takes place with high diastereoselectivity to ultimately give enantiopure 3-alkylpiperidines in good yields.[3] However, this amide-enolate alkylation method cannot be extended to aryl halides, as a consequence the stereoselective arylation at the α-position to the carbonyl group of lactams derived from phenylglycinol has been limited by the lack of a suitable approach.[4] In fact, the preparation of enantiopure 3-arylpiperidines derived from phenylglycinol has been achieved through the condensation of this amino alcohol with a substrate containing the aromatic ring at the beginning of the synthesis, which involves that it is required to follow the entire synthesis to accomplish each derivative.[5a,b]

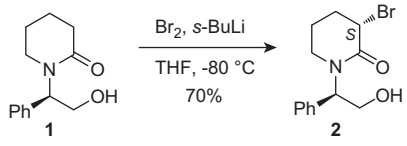
In this communication we present a novel and efficient procedure for the diastereoselective arylation of an enantiopure 3-bromopiperidin-2-one derived from (*R*)-(−)-2-phenylglycinol, involving a substitution reaction with arylcuprate reagents. To illustrate the stereochemical outcome we have prepared enantiopure 3-arylpiperidines derived from phenylglycinol, which had been applied to the synthesis of the alkaloid 3-PPP (Preclamol) and its analogs[5] Scheme 1.

Compound **2** was obtained, starting from lactam **1**,[6] as a epimeric mixture of 3-bromopiperidin-2-ones in 95:5 ratio following the procedure described by Quirion and co-workers.[7] Separation of this mixture by chromatography gave (1′*R*,3*S*)-3-bromolactam **2** in 70% yield as a single diastereoisomer detectable by ^{1}H NMR Scheme 2.

The substitution reaction of 3-bromopiperidin-2-one **2** was initially attempted with phenylmagnesium bromide, as a nucleophile,



Scheme 1. Diastereoselective arylation of an enantiopure 3-bromopiperidin-2-one with arylcuprate reagents.



Scheme 2. Preparation of (1′*R*,3*S*)-3-bromopiperidin-2-one **2**.

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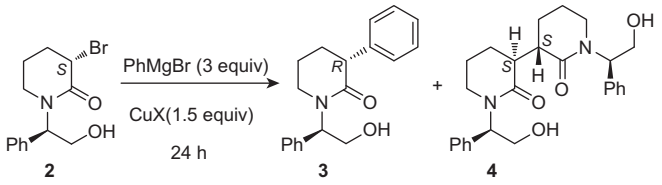
Table 1
Nucleophilic substitution of 3-bromolactam **2**



Entry	Cupper(I) source	*T* (°C)	Solvent [0.05 M]	Ratio[a] **3**:**4**	Yield **3**/**4**(%)
1	0	−57 to 25	THF	0	0[b]
2	CuI·S(Me)$_2$	−57 to 25	THF/S(Me)$_2$	5:95	4/87
3	CuI·S(Me)$_2$	−57 to −25	THF/S(Me)$_2$	40:60	35/53
4	CuI·S(Me)$_2$	−57	THF/S(Me)$_2$	70:30	60/24
5	CuI·S(Me)$_2$	−57	THF/S(Me)$_2$[c]	95:5	80/2
6	CuI	−57	THF[c]	80:20	63/14

[a] Compound **3** was the single diastereoisomer detected by ^{1}H NMR from the reaction mixture.
[b] Only PhMgBr reagent was used as the nucleophile.
[c] The concentration of the reaction was 0.025 M.

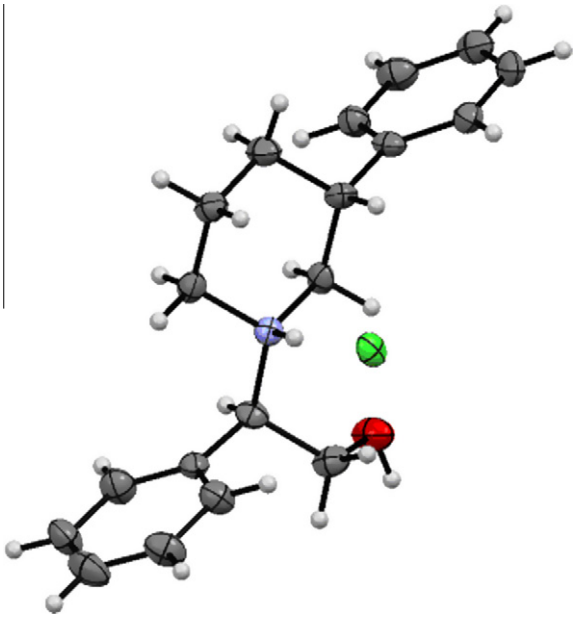
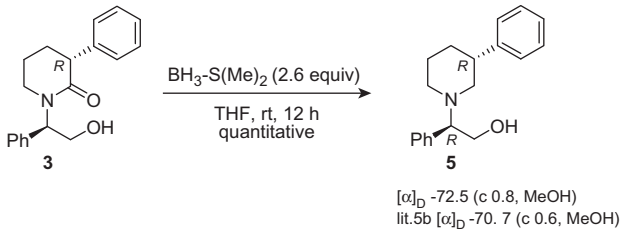
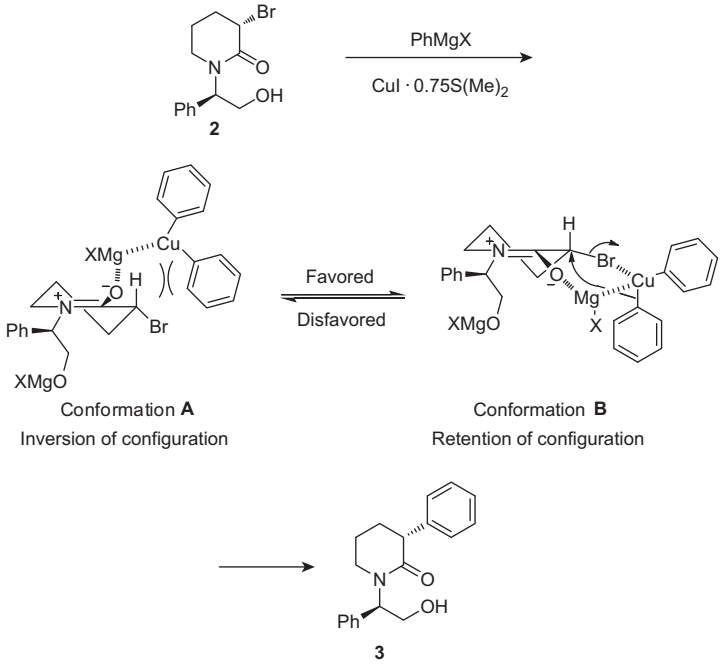


Figure 1. ORTEP of piperidine **5**·**HCl**.



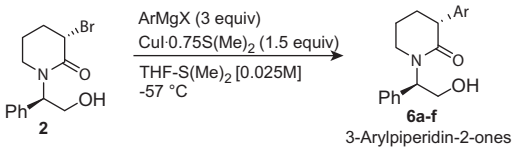
Scheme 3. Reduction of compound **3**.

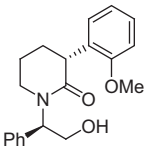
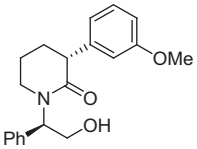
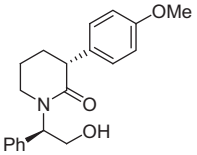
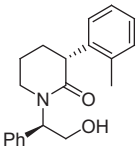
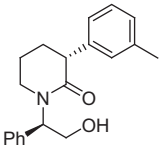
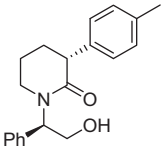
in THF at −57 °C for 12 h.[8] Under these reaction conditions, only starting material was observed, even when the reaction was additionally stirred at room temperature for 12 h (Table 1, entry 1). However, treatment of lactam **2** with phenylmagnesium bromide and CuI·0.75S(Me)$_2$in THF-S(Me)$_2$ solvent under similar reaction conditions gave the desired product 3-phenylpiperidin-2-one **3** although in poor yield (4%).[9] The major product was dimer **4** obtained in 87% yield (entry 2).[10] When this arylation reaction was performed at −57 °C for 24 h, the ratio of products **3**:**4** was 70:30 (entry 4). The best result was achieved when the substitution reaction was carried out at −57 °C for 24 h and the concentration of the reaction was 0.025 M to avoid the formation of dimer **4**. Under these conditions compound **3** was obtained in 80% yield and the ratio **3**:**4** was 95:5 (entry 5).



Scheme 4. A proposed mechanism for the nucleophilic substitution of compound **2**.

Table 2
Diastereoselective arylation of compound **2** with arylcuprate reagents



Entry	Ar	Time (h)	Product[a]	Yield (%)
1	2-Methoxyphenyl	36	 **6a**	45[c]
2	3-Methoxyphenyl	12	 **6b**	82[b]
3	4-Methoxyphenyl	12	 **6c**	85[b]
4	2-Tolyl	24	 **6d**	50[c]
5	3-Tolyl	12	 **6e**	85[b]
6	4-Tolyl	12	 **6f**	85[b]

[a] Onlythe (3*R*)diastereoisomers **6a–f** were observed by ^{1}H-NMR from the crude reaction mixtures.
[b] Ratio product/dimer **4** was 95:5.
[c] In this case, the ratio product/dimer**4** was 90:10.

Additionally, in order to examine the reactivity of the phenylcuprate reagent in the absence of $S(Me)_2$, lactam **2** was treated with phenylmagnesium bromide and CuI, as a cooper (I) source, in THF without $S(Me)_2$ at −57 °C for 24 h. In this case, compound **3** was achieved in 60% yield and the ratio of compounds **3**:**4** was 80:20 (entry 6).[11]

The absolute configuration at the C-3 of piperidin-2-one **3** was determined by reduction of the lactam carbonyl group to give the known piperidine **5** (absolute configuration at the piperidine 3-position had previously assigned as *R*)[5b] Scheme 3.

In addition, compound **5**·**HCl** was crystallized and its X-ray crystallographic analysis confirmed the (*R*) configuration at C-3[12] Figure 1.

The stereochemical outcome of the arylation reaction can be explained by coordination of the amide oxygen to magnesium atom of the phenylcuprate reagent in half-chair conformation **A** or **B**. In the conformation **A** the attack of the phenylcuprate reagent is hindered by the axial hydrogen at the C-3. Whereas, in the conformation **B** the delivery of the phenyl group takes place from the same face of the C–Br bond, affording 3-phenylpiperidone **3** with retention of the configuration at C-3 Scheme 4.

Following our finding, the efficiency of diastereoselective arylation of 3-bromopiperidin-2-one **2** with various arylcuprate reagents under optimized reaction conditions was investigated. All results are summarized in Table 2.

It is worth nothing that treatment of lactam **2** with sterically demanding nucleophiles, such as 2-methoxyphenyl- and 2-tolylcuprate gave the corresponding products in moderate yields (entries 1 and 4). Additionally, less sterically hindered arylcuprate reagents provided similar yields (entries 2, 3, 5, and 6) than when employing the phenylcuprate reagent. It is also worth mentioning that in all cases only the (3*R*) diastereoisomers were identified by ^{1}H NMR from the crude reaction mixtures.

Finally, compound **6b** was employed in the synthesis of the alkaloid (+)-3-PPP. Thus, treatment of **6b** with BH_3-$S(Me)_2$ in THF afforded compound **7** in quantitative yield. The spectroscopic data of compound **7** are in good agreement with the data reported in the literature for the (1*R*,3*R*) enantiomer.[5a] Then, starting from **7** and following the methodology described by Marazano and co-workers the synthesis of (+)-3-PPP was achieved in two steps in 96% yield[5a] Scheme 5.

In conclusion, an efficient method for the diastereoselective arylation of 3-bromopiperidin-2-one derived from (*R*)-(−)-2-phenylglycinol with arylcuprate reagents has been developed.

The stereochemical outcome has been studied and we showed that the nucleophilic substitution occurs with the retention of configuration via a coordinated transition state. Finally, to the best of our knowledge this is the first example of a nucleophilic substitution of an enantiopure α-bromolactam with an arylcuprate reagent.

Acknowledgments

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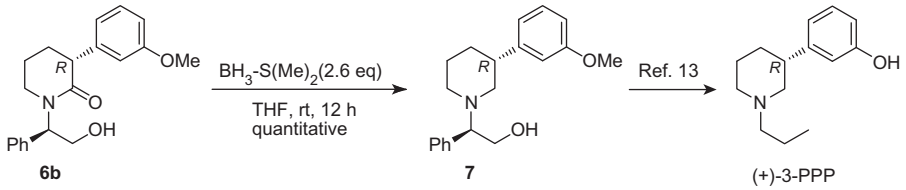

Scheme 5. Synthesis of (+)-3-PPP.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.124.

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10. Dimer **4** was crystallized and its X-ray crystallographic analysis confirmed as (*S*) the absolute configuration at the two new stereo centers created. Crystal structure was deposited at the Cambridge Crystallographic Data Centre. Deposit number: CCDC 831757.
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