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Enantioselective Hydroarylation of Bridged [3.2.1] Heterocycles: An Efficient Entry into the Homoepibatidine Skeleton

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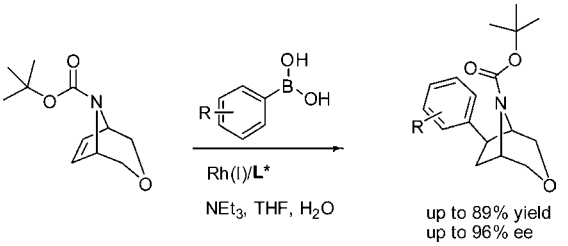
ABSTRACT



Achiral [3.2.1] bridged heterocycles containing a bridging amide can undergo enantioselective hydroarylation reactions under rhodium(I) catalysis. These reactions proceed in high yield and enantioselectivity in most cases, under mild reaction conditions and using commercially available Josiphos ligands. The phosphine ligand structure and the protecting group on the nitrogen both have significant effects on the selectivity and yield of the reactions.

Enantioselective reactions that desymmetrize achiral starting materials are efficient means of forming small molecules with one or more chiral centers.[1] In particular, the enantioselective functionalization of meso-bridged heterocyclic systems provides a rapid entry into chiral building blocks with well-defined conformations which have medicinal chemistry applications, of relevance to the pursuit of higher potency and target selectivity.[2] Despite the utility of these compounds, efficient reactions to form and selectively functionalize such building blocks remain underdeveloped.

One reaction that can be used to efficiently desymmeterize bridged heterocycles is the enantioselective hydroarylation of alkenes.[3] The Lautens group has reported enantioselective hydroarylation reactions of bridged heterocycles that form the desired products in moderate to high yield and enantioselectivity, typically starting from bicyclic hydrazines.[4] One limitation to this chemistry is the lack of examples with a bridging heteroatom, as these examples typically result in the opening of the high energy bridge system.[5] We have recently reported an efficient synthesis of meso [3.2.1] bridged heterocycles through a

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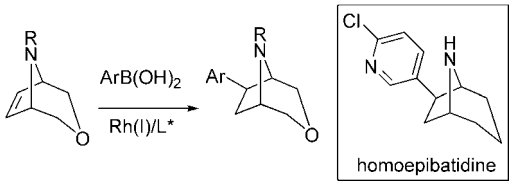
bis-amination/ring closing metathesis sequence.[6] Herein we report an efficient, Rh(I) catalyzed enantioselective hydroarylation of these heterocycles using commercially available ligands under mild reaction conditions. The hydroarylation products are stable to the reaction conditions, and no ring opening is observed (Scheme 1). One application of this methodology is the synthesis of previously unreported analogues of homoepibatidine (Scheme 1, box), a known nicotinic acetylcholine receptor (nAChR) ligand.

Scheme 1. Hydroarylations of [3.2.1] Bridged Heterocycles



The ligands initially screened for the asymmetric hydroarylation reactions were based on the Josiphos ferrocene/diphosphine complex (Table 1, box), previously used by the Lautens group.[4] These ligands are convenient not only because of their previously reported reactivity but also because both enantiomers and a number of different phosphines are commercially available.[7] Other phosphine ligand classes (Walphos, DIOP, BINAP, etc.) typically gave poor conversions to the desired products, even at elevated temperatures. After extensive reaction screening it was found that the phenyl/*tert*-butyl Josiphos ligand (**L1**) gave the highest yields of the desired hydroarylation product. No ring-opening products were observed under any of the reaction conditions screened.

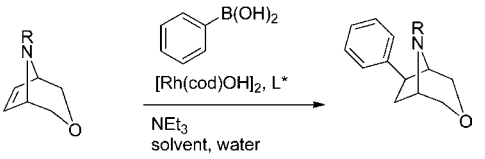
The reactions were optimized using phenylboronic acid along with the rhodium(I) source and ligand (Table 1). Interestingly, the nitrogen protecting group had a major impact on the yield and enantioselectivity of the hydroarylations. The cumyl protecting group previously reported gave rise to modest conversion under a variety of reaction conditions, including at elevated temperatures. Neutralizing the basicity of the nitrogen, by switching to a carbamate, allowed clean conversion to the desired product in high isolated yield under mild reaction conditions.[8] The steric bulk of the carbamate also had a significant impact on enantioselectivity, with the bulky Boc group leading to the product with the highest ee. Clearly the steric bulk on the bridging nitrogen has an effect on the approach of the catalyst to the olefin.

The phosphines on the Josiphos ligands also had a significant impact on the yield and ee of the reactions, again due to steric factors. Higher steric bulk on the phosphine (**PR_2**) gave lower yields. A bulky *tert*-butyl

(7) The ligands used in this paper were purchased from Aldrich and Strem.

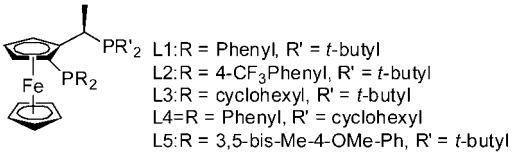
(8) See Supporting Information for details on formation of the carbamate protected bridged heterocycles.

Table 1. Optimization of Hydroarylation Conditions



R	ligand	solvent	temp	yield[a] (%)	ee[b] (%)	product[c]
Cbz	L1	THF	rt	80	84	**2a**
Cbz	L2	THF	rt	38	78	**2a**
Cbz	L3	THF	rt	0	N/A	**2a**
Cbz	L4	THF	rt	47	30	**2a**
Boc	**L1**	**THF**	**rt**	**76**	**95**	**2b**
Boc	L2	THF	rt	17	78	**2b**
Boc	L3	THF	rt	trace	NA	**2b**
Boc	L5	THF	rt	trace	NA	**2b**
CO_2Me	L1	THF	rt	83	78	**2c**
cumyl	L1	THF	rt	0	N/A	N/A

[a] Yields refer to isolated products after purification over silica. [b] Ee determined by chiral HPLC. [c] All reactions run with 5 mol % rhodium, 10 mol % ligand, 2.0 equiv of NEt_3, and 1.5 equiv of boronic acid at rt for 16 h.



Josiphos Ligands

group on the phosphine next to the chiral center (**PR'_2**) was necessary for high enantioselectivity, suggesting that this center is key to the facial selectivity of the nucleophilic addition. In all cases a single diastereomer (*exo*) was observed. The base used in the reaction had little effect, as other mild bases (Hunig's base, K_2CO_3) gave similar results as triethylamine.

These observations could be further explained by *in silico* modeling of the reaction transition state. The starting configuration for the Josiphos ligand **L1**, the one that provided the best yields and enantioselectivities, was built using a small-molecule crystal structure obtained from the Cambridge Structural Database (CSD) (refcode = CAQSAP). The ligand in CSD has R = cyclohexyl and R′ = *tert*-butyl. In that structure, the rhodium ion is coordinated with the phenyl anion and iodide, in addition to the two phosphine groups. To build models for the transition states (TSs) that lead to the observed stereochemistry using the Josiphos ligand **L1** as the catalyst, the cyclohexyl groups were changed to phenyl and the iodide ion was deleted. The bridged heterocycle protected by the Boc group was positioned in two vectors, approaching the reaction center adjacently to the phenyl (TS1) or the *tert*-butyl groups (TS2) (Figure 1). The phenyl anion was built in the remaining vector of the rhodium(I) square planar coordination geometry in each case. The bridged

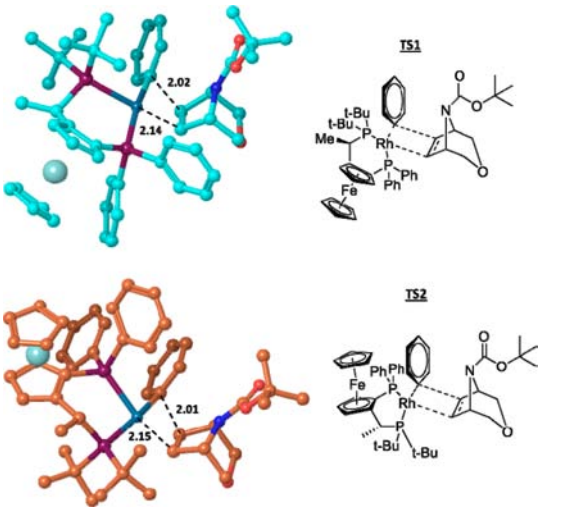
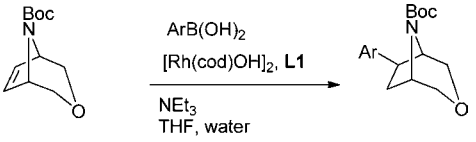


Figure 1. Models for the TS structures that lead to the observed stereochemistry.

heterocycle double bond was oriented in a way to provide the observed stereochemistry when the newly C−C bond with the phenyl anion is formed. Two TS models were obtained (Figure 1). The energy difference at the B3LYP/LACV3P**+ //B3LYP/LACV3P* level between the two TS models is −0.32 kcal/mol favoring the one where the bridged heterocycle approaches the reaction center adjacently to the phenyl groups (cyan). Addition of zero-point vibrational energies and thermal contributions to enthalpy at 25 °C increased the difference to −1.60 kcal/mol. Addition of entropic contributions led to a reduced free-energy energy difference in the gas phase of −0.29 kcal/mol. Incorporation of THF solvent effects provided a final value of −0.79 kcal/mol. The TS1 model, the more stable transition state, helps explain some of the results listed in Table 1. For example, the electron-withdrawing CF_3 group at the 4-position of the phenyl rings (**L2**) would reduce the electron density of the phenyl anion, negatively impacting the carborhodation step. Higher steric bulk on one phosphine (R) in **L3** makes the catalyst too crowded for the bridged heterocycle to approach the reaction center. In the case of **L5**, the model suggests that the addition of several substituents to the phenyl groups would lead to clashes with the protecting groups.

The hydroarylation reaction worked for a variety of aryl boronic acids, giving high yields and enantioselectivities in most cases. *Para*- and *meta*-substituted boronic acids typically gave high yields, although cases with an electron-withdrawing group necessitate the addition of extra equivalents of boronic acid to push the reaction to completion (Table 2, entries 2−9). All of these examples gave high enantioselectivity using the commercially available Josiphos ligand **L1**. The only functional group issue observed was with the strongly withdrawing *meta*-nitro substituent, which gave no reaction, even with extra equivalents of the boronic acid and elevated temperatures. The model in Figure 1 also

Table 2. Hydroarylation Reactions



entry	Ar	yield[a]	ee[b]	product[c]
1	Ph	76	95	**2b**
2	*p*-CF_3Ph	89[d]	90	**3a**
3	*p*-BrPh	73	92	**3b**
4	*p*-CO_2MePh	85[d]	90	**3c**
5	*p*-Tol	81	89	**3d**
6	*p*-NHAcPh	82	93	**3e**
7	*m*-OMePh	87	96	**3f**
8	*m*-BrPh	82	88	**3g**
9	*m*-CO_2MePh	69[d]	94	**3h**
10	*o*-FPh	36[d]	50	**3i**
11	*o*-FPh	55[e]	42	**3i**
12	*o*-Tol	17[e]	76	**3j**
13	3-thiophene	83	77	**3k**
14	*m*-NO_2Ph	0	N/A	N/A
15	*o*-COoMePh	0	N/A	N/A

[a] Yields refer to isolated products after purification over silica. [b] Ee determined by chiral HPLC. [c] All reactions run with 5 mol % rhodium, 10 mol % ligand, 2.0 equiv of NEt_3, and 1.25 equiv of boronic acid at rt for 16 h. [d] Reaction run with 2.5 equiv of boronic acid. [e] Reaction run at 50 °C with 2.5 equiv of boronic acid.

explains the reduced yields obtained with the *ortho*-substituted phenyl boronic acids. These groups would lead to rotation of the phenyl anion and consequently worse orbital overlap with the bridged heterocycle double bond carbon in the transition state. The *ortho*-fluorophenyl boronic acid gave a moderate yield and low enantioselectivity at rt and only a slightly higher yield when the temperature was raised. The *ortho*-tolylboronic acid gave a low yield and the *ortho*-methyl ester gave no reaction, showing a clear trend based on the size of the substituent at the *ortho* position. Heating the reaction helped the yields slightly, but resulted in slightly lower levels of enantioselectivity. One heterocycle, 3-thiophene boronic acid, gave the desired product in high yield and moderate enantioselectivity (**3k**, Table 2).

Having demonstrated the incorporation of heterocycles in such hydroarylations, we decided to apply this chemistry to a previously unreported oxygen-containing analogue of homoepibatidine.[9] Reaction of **1b** with 4-chloro-3-pyridine boronic acid gave the desired product (−)-**4** in moderate yield and selectivity upon heating (Scheme 2). The absolute stereochemistry of the products was assigned by X-ray crystallography of two antipodes of hydroarylation product **4** (Figure 2).[10]

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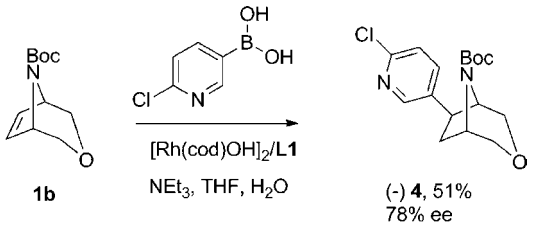
(10) See Supporting Information for detailed X-ray analysis.

Scheme 2. Synthesis of Homoepibatidine Analogue **4**[a]



[a] Ee determined by chiral HPLC. Reaction run with 5 mol % rhodium, 10 mol % ligand, 2.0 equiv of NEt_3 at 50 °C with 2.5 equiv of boronic acid.

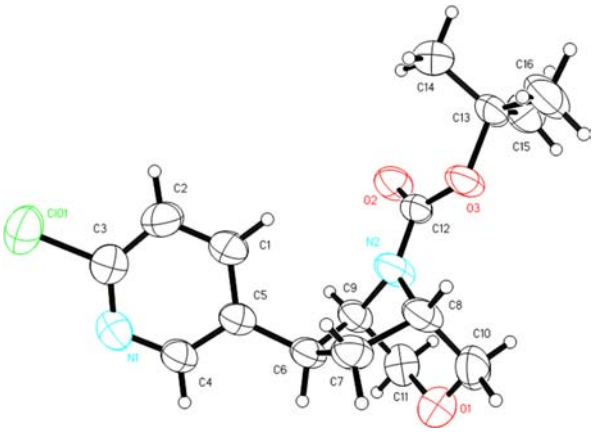
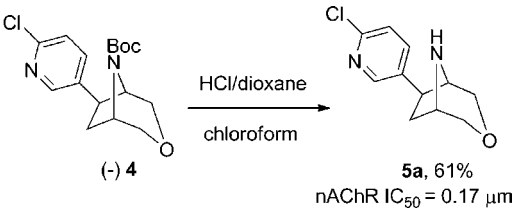


Figure 2. X-ray structure of (−)-**4**.

Deprotection of the Boc group in **4** led to the desired homoepibatidine analogue **5a** (Scheme 3). Compound **5a** showed dose dependent inhibition of the flow of current resulting fron 1 μM acetylcholine, with an IC_{50} of 0.17 μm

Scheme 3. Synthesis of Homoepibatidine Analogue **5a**



in an $\alpha4\beta2$ nAChR assay.[11] Interestingly, **5a** showed minimal binding to several other receptors, including the muscarinic acetylcholine receptor mAChR M1.[12]

In conclusion an enantioselective hydroarylation of heterobicyclic olefins has been achieved, using examples containing a bridging nitrogen. The majority of the reactions proceeded in high yield and enantioselectivity using commercially available Josiphos ligands under mild conditions. No ring-opening byproducts were observed in any of the cases screened. Modeling work helped explain the stereochemical course of the reactions as well as the effects of different ligands and protecting groups on nitrogen. One of the products formed is a previously unreported analogue of the biologically active product homoepibatidine.

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Supporting Information Available. Preparation and characterization of all new compounds is included. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) See Supporting Information for a complete table of receptors and binding results.

The authors declare no competing financial interest.