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An Expedient Enantioselective Route to Diaminotetralins: Application in the Preparation of Analgesic Compounds

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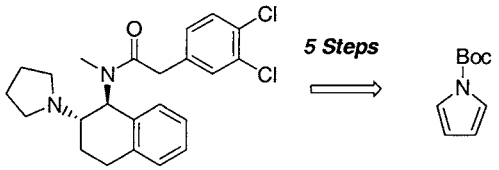
ABSTRACT



Advances to the rhodium-catalyzed asymmetric ring-opening protocol have allowed this methodology to be extended to azabicyclic alkenes, the first time that rhodium has been used in allylic functionalizations with nitrogen leaving groups. The product diaminotetralins are important medicinal compounds. The synthetic utility of this methodology has been demonstrated in the total synthesis of an analgesic compound where the tetralin core, the regiochemistry, and the relative and absolute stereochemistry are all established in the ring-opening step.

We recently reported a rhodium-catalyzed asymmetric ring-opening (ARO) reaction of oxabicyclic alkenes to produce dihydronaphthalenol products in high yield and excellent enantioselectivity (>90% ee).[1] This methodology was also applied to the diastereoselective ring opening of vinyl epoxides.[2] We next focused our attention on expanding the scope of the reaction to include amine-induced ring opening of azabicyclic alkenes so as to have rapid and efficient access to cyclohexyl 1,2-diamino moieties with control of the regio-, diastereo-, and enantioselectivity. A synthetic route to cyclohexyl-1,2-diamines would be valuable and complementary to existing methods that rely on ring-opening reactions of aziridines and aziridinium ions.

Cyclohexyl-1,2-diamines are an important class of compounds for a variety of reasons including their use as scaffolds for chiral ligands[3] and their biological activity. For instance, U-50,488[4,5] **1** and other structural analogues possessing a 1,2-diamino motif (e.g., **2** and **3**) have been reported to be highly selective κ-opioid agonists (Figure 1).[6] In addition to analgesic activity, aminotetralins have been shown to possess a variety of other useful biological properties.[7]

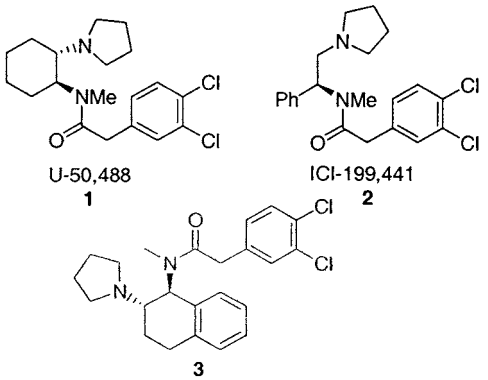


Figure 1. Analgesic diamine compounds.

(1) (a) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650. (b) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677. (c) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259. (d) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170. (e) Lautens, M.; Fagnou, K. *Tetrahedron* **2001**, *57*, 5067.

(2) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319.

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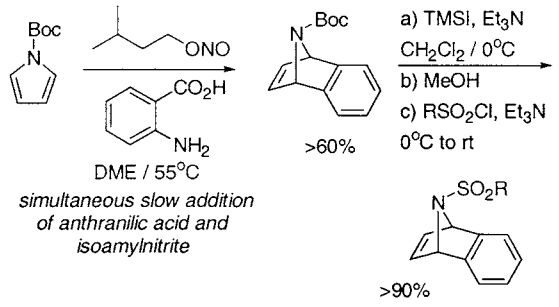
Two main obstacles needed to be overcome before an efficient ring opening of azabicyclic substrates could be achieved. First, nitrogen functionalities are poorer leaving groups than those based on oxygen, and as a result, azabicycles are far less reactive than the corresponding oxabicycles. This diminished reactivity is mirrored in aziridines compared to epoxides. Second, a nucleophilic nitrogen anion is generated during the ring-opening process, which could lead to the formation of oligomerization byproducts.[8]

Our previous results with oxabicyclic alkenes and nitrogen nucleophiles indicated that rhodium catalysis might offer a solution to the challenges associated with nitrogen leaving groups. For example, while benzenesulfonamide is a good nucleophile in the rhodium-catalyzed ring opening of oxabicyclic alkenes,[1a] *N*-benzylbenzenesulfonamide is not, indicating that the reaction is sensitive to the steric bulk of the nucleophile.[9] Amides and carboxamides have also proved to be very poor nucleophiles.[9] Importantly, these functionalities can be considered "activating" groups for the nitrogen functionality. We reasoned that by properly choosing the activating group on the nitrogen of the azabicycle, both the decreased reactivity and the oligomerization problems could be avoided.

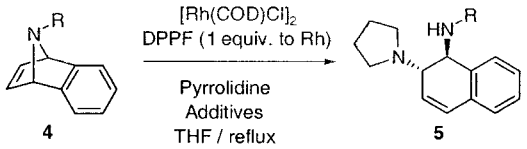
Since no method was available for the practical large-scale preparation of azabicyclic material, our initial efforts focused on this task. We could not determine from the outset which *N*-activating group would be required, so a flexible approach allowing installation of a variety of *N*-substituents was established. Our preferred procedure involves the cycloaddition of benzyne, generated in situ from anthranilic acid and isoamyl nitrite, and commercially available *N*-Boc pyrrole.[10] In this way, *N*-Boc **4** can be produced on a 20 g scale in 60−70% yield. A one-pot exchange of the *N*-group is achieved by treating *N*-Boc **4** dissolved in CH_2Cl_2 with Et_3N and TMSI followed by a slight excess of MeOH and the desired sulfonyl chloride or other electrophile (Scheme 1). Importantly, no recourse to chromatography is required since purification for both steps can be performed by recrystallization.[11]

Scheme 1. Preparation of Azabicyclic Alkenes



The nature of the activating group was found to be an important factor in the reactivity of **4** (Table 1). For example,

Table 1. Effect of Activating Group and Additives on the Rhodium-Catalyzed Ring Opening with Pyrrolidine[e]



4 5

Entry	R-Group	Additives	Time (h)	Yield[a] (%)
1	Me	Et_3N·HCl	24	nr
2	Bn	Et_3N·HCl	24	nr
3	$CO_2{}^tBu$	Et_3N·HCl	24	nr
4[d]	$CO_2{}^tBu$	none	24	50
5[d]	$CO_2{}^tBu$	Et_3N·HCl	24	82
6	Tos	none	24	nr
7	Tos	Et_3N·HCl	24	91
8	Nos	Et_3N·HCl	24	89
9	Nos	Bu_4NI/CSA[b]	4	72
10	Nos	NH_4I	2	94
11[c]	Nos	NH_4I	18	91

[a] Isolated yield. [b] 5 equiv of Bu_4NI and 2.5 equiv of CSA used. [c] 0.5 mol % of $[Rh(COD)Cl]_2$, 1.5 mol % of DPPF, 1.5 equiv of NH_4I, and 3 equiv of pyrrolidine used. [d] Tetrahydropyran was used as the solvent, and the reaction was run at 100 °C. [e] Conditions: $[Rh(COD)Cl]_2$ (2.5 mol %), DPPF (5 mol %), **4** dissolved in THF (0.2 M) followed by the addition of the additive (5 equiv to **4**). Solution heated to reflux followed by the addition of pyrrolidine (10 equiv to **4**). Reacted at reflux until complete as determined by TLC analysis.

N-methyl- and *N*-benzylazabicycles do not react under the standard conditions used with oxabicyclic alkenes. Reaction of *N*-Boc **4** in refluxing THF gives traces of **5** after prolonged reaction time (Table 1, entry 3). By using tetrahydropyran (THP) as solvent and increasing the reaction temperature, however, **5** was obtained in 82% yield (Table 1, entry 6).[12] On the other hand, *N*-tosyl and *N*-nosyl **4** both showed enhanced reactivity, giving **5** in 91 and 89% yields in refluxing THF.[13]

(3) (a) Lucet, D.; LeGall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (c) Mukaiyama, T.; Asami, M. *Top. Curr. Chem.* **1985**,*127*, 133. (c) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (d) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(4) Szmuszkovicz, J.; Vov, Voigtlander, P. F. *J. Med. Chem.* **1982**, *25*, 31.

(5) (a) Cowan, A.; Gmerek, D. E. *Trends Pharmacol. Sci.* **1986**, *7*, 69. (b) Millan, M. J. *Trends. Pharmacol. Sci.* **1990**, *11*, 70.

(6) Costello, G. F.; James, R.; Shaw, J. S.; Slater, A. M.; Stutchbury, N. C. J. *J. Med. Chem.* **1991**, *34*, 181.

(7) For example, see: (a) van Vliet, L. A.; Tepper, P. G.; Dijkstra, D.; Damsma, G.; Wikström, H.; Pugsley, T. A.; Akunne, H. C.; Heffner, T. G.; Glase, S. A.; Wise, L. D. *J. Med. Chem.* **1996**, *39*, 4233 and references therein. (b) Degnan, A. P.; Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3503 and references therein.

(8) These challenges likely contribute to the diminished focus on vinylaziridines in π-allylmetal chemistry compared to vinyl epoxides.

(9) Lautens, M.; Fagnou, K. Unpublished results.

(10) Use of high reaction concentration (~2.5 M) is key to obtaining high yields. Under lower concentrations, yields of 10−20% are typically obtained. See the Supporting Information.

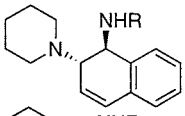
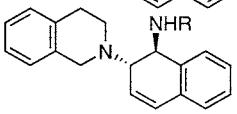
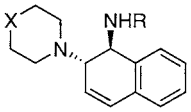
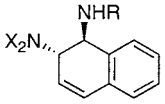
(11) Yields of up to 80% can be obtained with recourse to chromatographic purification techniques.

(12) This temperature effect has previously been observed in the ring opening of oxabicycles: Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170−7171.

(13) The relative *trans* stereochemistry was proven for *N*-Tos **5** by X-ray crystallography.

As with oxabicyclic substrates, the effect of protic and halide additives played an important role in the ring opening with aliphatic amines. Reaction times were extremely slow, and several substrates failed to react completely in the absence of an additive (Table 1, entries 4 and 6). The nature of the halide was also found to influence the time required for complete conversion.[14] For example, slow reactions occurred with $Et_3N{\cdot}HCl$, whereas a combination of Bu_4NI and camphorsulfonic acid (CSA) resulted in much faster reactions (Table 1, entry 8 vs entry 9). The use of excess tetraalkylammonium salts is not practical, however, since they lead to emulsions that greatly impede the isolation of **5**. Gratifyingly, NH_4I, which is soluble in water, can be used in place of Bu_4NI.[1d,15] A wide variety of amines reacted in high yield, allowing rapid access to a range of diaminotetralins including cyclic amines (Table 2, entries 1−6) and secondary aliphatic amines (Table 2, entries 7−9).

Table 2. Scope of Amine Ring-Opening Reactions[e]

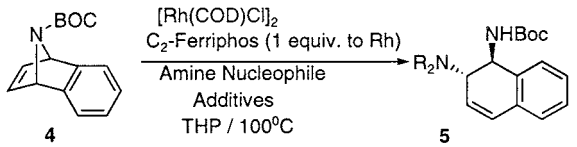
Entry	Product		R-Group	Product	Yield(%)[a]
1[d]			Boc	**7**	70
2			Tos	**8**	89
3			Tos	**9**	81
4[d]		X=NPh	Boc	**10**	76
5[d]		X=O	Boc	**11**	67
6[b]		X=O	Nos	**12**	92
7[b,c]		X= Et	Nos	**13**	91
8[d]		X= Bn	Boc	**14**	78
9		X= Bn	Nos	**15**	89

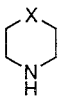
[a] Isolated yield. [b] These reactions were performed on a 4−5 g scale. [c] Et_2NH (10 equiv) used due to volatility of the amine. [d] Reaction performed at 100 °C in tetrahydropyran. [e] Conditions: $[Rh(COD)Cl]_2$ (0.5−1 mol %), DPPF (1.5−3 mol %), **4** dissolved in THF (0.2 M) followed by the addition of the NH_4I (1.5 equiv to **4**). Solution heated to reflux followed by the addition of the amine (3 equiv to **4**). Reacted at reflux until complete as determined by TLC analysis.

We have also achieved asymmetric ring opening of the *N*-Boc-protected azabicycle.[16] Under optimized conditions for the analogous oxabicyclic alkene using (*R*,*S*)-PPF-P^{t}Bu$_2$ as the chiral ligand with NH_4I as the additive, **5** was obtained in 65% yield and only 25% ee. Changing to C_2-Ferriphos[17] and examining the effect of an additive revealed that the use of $Et_3N{\cdot}HCl$ in THP[18] at 100 °C gives **5** in 77% yield and 86% ee. While the reaction can take place without an additive,[19] higher product yields and enantioselectivities are obtained with $Et_3N{\cdot}HCl$. The reasons for the lower selectivities with azabicyclic alkenes compared to oxabicycle substrates may be due to the availability of different binding modes of the rhodium to the *N*-activating group on the substrate.

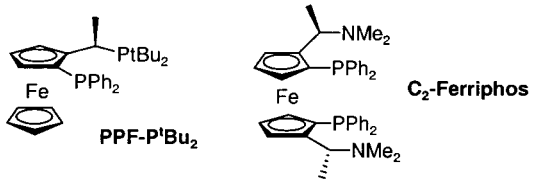
The nature of the nucleophile was found to influence the reaction outcome, but by varying the reaction conditions excellent results can be obtained in all cases. For example, with simple aliphatic amines, best results are obtained with $Et_3N{\cdot}HCl$ (Table 3, entries 6, 8, and 9). In contrast, amines possessing a second heteroatom, such as *N*-phenylpiperazine

Table 3. Asymmetric Ring Opening of *N*-Boc-azabenzonorbornadiene[e]



Entry	Nucleophile		Additives	Yield(%)[a]	ee(%)[b]
1[d]			NH_4I	65	25
2			NH_4I	94	44
3			Bu_4NI	70	26
4			Et_3N/NH_4I	94	36
5			$Et_3N.HCl$	75	78
6			$Et_3N.HCl/Et_3N$	60	85
7			none	50	59
8[c]			$Et_3N.HCl$	77	86
9		X = CH_2	$Et_3N.HCl$	85	84
10		X = N-Ph	none	70	68
11[d]		X = N-Ph	none	75	96
12		X = O	none	90	80
13	Bn_2NH		none	80	89

[a] Isolated yield. [b] ee determined by CSP HPLC with a Chiralcel AD column. [c] Two equivalents of ligand to rhodium metal was used. [d] (*R*,*S*)-PPF-P^{t}Bu$_2$ used as the chiral ligand.



[e] Conditions: $[Rh(COD)Cl]_2$ (2.5 mol %), ligand (5 mol %), **4** dissolved in THP (0.2 M) followed by the addition of the additive (5 equiv to **4**). Solution heated to 100 °C followed by the addition of pyrrolidine (10 equiv to **4**). Reacted at 100 °C until complete as determined by TLC analysis.

(14) For a review on halide effects in transition metal catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

(15) Application of these new conditions to the asymmetric ring opening of oxabicyclic alkenes will be reported in due course.

(16) The absolute stereochemistry of the ring opened products was shown to be (1*S*,2*S*) by X-ray crystallography. Crystals suitable for X-ray analysis were obtained by deprotecting *N*-Boc **10**, followed by protection of the free amine with 4-bromobenzenesulfonyl chloride. This is the opposite sense of induction that we have observed for the oxabicyclic series using the same sense of chirality in the ligands.

(17) This ligand was prepared from (*R*)-2-methyl-CBS-oxazaborilidine: Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, No.5, 950.

(18) We screened a variety of typical high boiling solvents and found that while DMF and toluene gave the product in decent ee (80% and 79% ee, respectively), THP was the preferred solvent.

(19) We have previously observed that halide and protic additives were necessary for the addition of pyrrolidine to oxabicycles. The higher temperatures used in our present reaction conditions most likely facilitate reversible binding of the basic amine to the metal center. See ref 10.

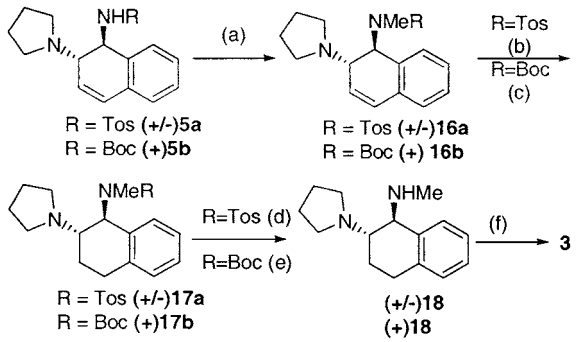
and -morpholine, react best in the absence of additive and can be performed with or without solvent (Table 3, entries 10−12). The more sterically hindered dibenzylamine also reacts well in the absence of additive (Table 3, entry 13). Current efforts are directed at understanding the possible interactions of the protic and halide additives as well possible interactions of the nucleophiles at the metal center.

Having established a new route to the diaminotetralin core, we sought an efficient synthesis of analgesic **3**. A first approach commenced with the methylation of sulfonamide **5a** with iodomethane and K_2CO_3 in acetone followed by hydrogenation with catalytic Pt/C to give **17a** (both steps occur in 96% isolated yield) Photolytic cleavage of the tosyl group according to the method of Hamada and co-workers[20] provides **18** in 91% yield. DCC coupling of the corresponding arylacetic acid gives **3** in 86% yield. This approach has the added benefit that the sulfonyl group makes many of the products crystalline and easy to handle.

Our efforts were then directed toward an enantioselective synthesis of **3**. Asymmetric ring opening of **4** with pyrrolidine proceeded smoothly in the presence of $[Rh(COD)Cl]_2$, C_2-Ferriphos, and Et_3NHCl to produce **5b** in 77% isolated yield and 86% ee (Table 3). Methylation of *N*-Boc **5b** with iodomethane and KH in THF generates **16b** in 96% yield. A diimide hydrogenation of the olefin (>95% yield) followed by deprotection of the BOC group with trifluoroacetic acid gives **18** in 91% yield, and an EDCI coupling of the corresponding arylacetic acid provides enantiomerically enriched **3** in 86% yield (Scheme 2).

In conclusion, we have established a new and efficient route to the diaminotetralin core that can now be obtained in two steps and in high yield from commercially available *N*-Boc-pyrrole. The key step in this approach is the rhodium-catalyzed ARO of azabenzonorbornadienes that establishes the diaminotetralin core, the regiochemistry, and the relative and absolute stereochemistry of the diamine moiety simultaneously. The successful application of rhodium catalysis to this substrate class demonstrates that rhodium catalysis can be successfully applied to allylic systems with nitrogen leaving groups and may provide a solution to the problems encountered with other catalysts and analogous substrates. This methodology has been applied to the preparation of a previously reported analgesic compound **3**. The flexibility and high variability of nitrogen substituents make this methodology ideal for the preparation of compound libraries.

Scheme 2. Synthesis Designed for Maximum Variability[a]



[a] Key: (a) MeI, K_2CO_3, acetone, rt, >95% or KH, THF, rt, >95%; (b) H_2, Pt/C, EtOAc, 96%; (c) $NaIO_4$, H_2NNH_2, EtOH, THF, H_2O, >95%; (d) *hν*/$NaBH_4$, *p*-$MeOC_6H_4OMe$, 80% $EtOH_{(aq)}$, 91%; (e) TFA/CH_2Cl_2 (1:4), rt, 1 h, 90%; (f) $ArCH_2CO_2H$, EDCl, 86%.

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Supporting Information Available: Full characterization details including ^{1}H and ^{13}C NMR, IR, HRMS. and elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026579I

(20) Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140.