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Practical Asymmetric Synthesis of Bioactive Aminotetralins from a Racemic Precursor Using a Regiodivergent Resolution

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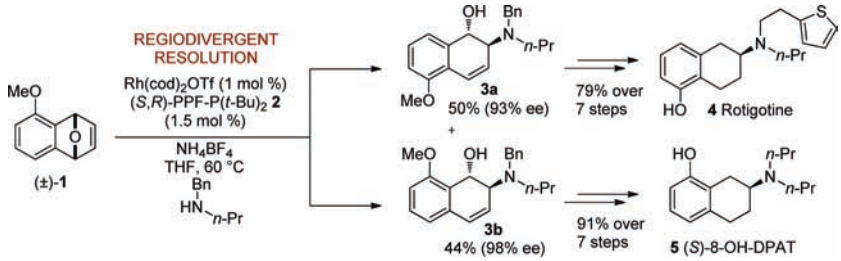
ABSTRACT



Catalyst-controlled asymmetric ring opening of a racemic oxabicyclic alkene leads to two readily separable regioisomeric products both in excellent ee. A cationic Rh catalyst, with added NH_4BF_4 to modulate reactivity, was required to obtain synthetically useful yields. The utility of each substituted aminotetralin product has been demonstrated by their conversion to different biologically relevant molecules in a highly efficient and practical manner.

The Rh(I)-catalyzed asymmetric ring-opening (ARO) reaction of strained oxabicyclic alkenes with heteroatom nucleophiles has been well-studied and demonstrated to be a highly efficient enantioselective process.[1] Although this method affords convenient access to useful compounds of the bioactive dihydronaphthalene class, until recently, the process was limited to *meso*-substrates, i.e., a desymmetrization reaction.

The introduction of substitution at the bridgehead (Scheme 1, R^1 = alkyl) not only results in a significant decrease in reactivity but also removes the plane of symmetry in the parent bicycle, rendering the substrate chiral. Under asymmetric catalysis a complication arises wherein steric and electronic effects could give rise to a *matched*/*mismatched* scenario in which the best outcome would be the kinetic resolution of a racemic substrate.[2] However, we developed a powerful Rh-OTf catalyst system which was able to override the inherent substrate reactivity, transforming each enantiomer of a racemic mixture into two different products in high yield and good enantioselectivity[3]—a regiodivergent resolution (a subset of parallel kinetic resolution).[4]

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(1) (a) Davoust, M.; Kitching, J. A.; Fleming, M. J.; Lautens, M. *Chem.—Eur. J.* **2010**, *16*, 50–54. (b) Fleming, M. J.; Lautens, M. In *Catalyzed Carbon-Heteroatom Bond Formation*; Yudin, A. K., Ed.; John Wiley & Sons Ltd.: Chichester, 2010. (c) Heller, D.; Drexler, H.-J.; Preetz, A.; Torrens Jover, A.; Buschmann, H. H., World Patent WO2009/074496, 2009. (d) Heller, D.; Preetz, A.; Torrens Jover, A.; Garcia Lopez, M.; Drexler, H.-J., World Patent WO2009/074497, 2009. (e) Fleming, M. J.; Lautens, M.; Thommen, M.; Spielvogel, D., European Patent EP2098511, 2009. (f) Lautens, M.; Fagnou, K. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5455–5460. (g) Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194–2196. (h) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48–58, and references cited within.

(2) (a) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291–8327. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26. (c) Kagan, H.; Fiaud, J. *Top. Stereochem.* **1988**, *18*, 249–330.

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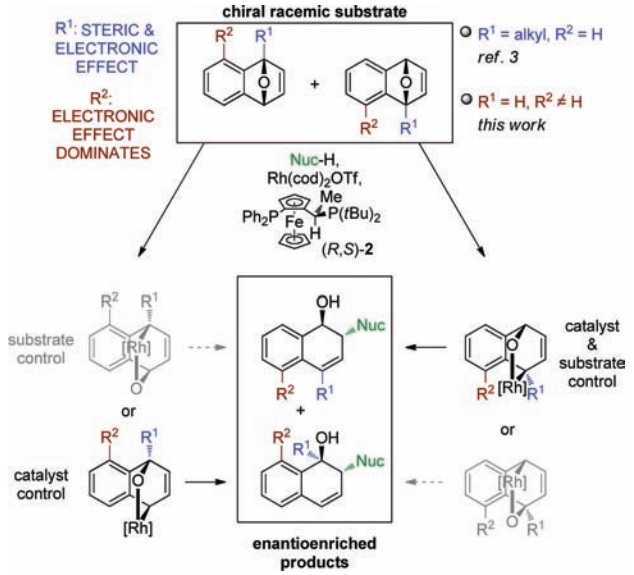
Scheme 1. Regiodivergent Resolution of Unsymmetrical Oxabenzonorbornadienes



When we surveyed the array of biologically privileged 2-aminotetralin compounds in the literature (several of which are APIs currently marketed or under development, Figure 1),[5]

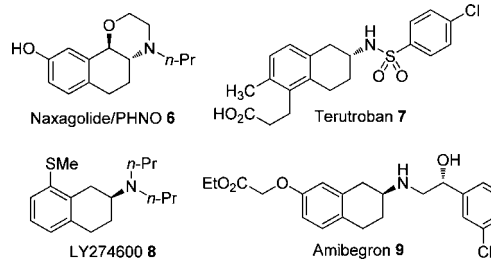
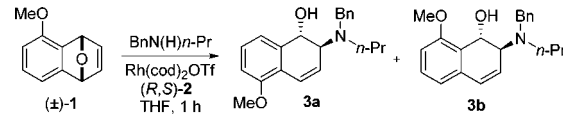


Figure 1. Examples of 2-aminotetralin API structures.

many of them possessed substituents on the aromatic ring. As synthetic targets, they would require the ring opening of an unsymmetrical oxabicyclic substrate with the symmetry-breaking substituent located on the aromatic ring (Scheme 1, $R^2 \neq H$). We have previously shown that the electronic character of these substituents does have a significant effect on the reactivity of these substrates,[6] but despite this, we report here the regiodivergent resolution of racemic unsymmetrical substrates and have demonstrated the power of this process in the efficient synthesis of two bioactive tetralin products.

We first investigated the effects of additive and temperature on the regiodivergent ARO of (±)-**1** (Table 1). Rh-

Table 1. Effect of Additive and Temperature



			yield [%] (% ee)[b]	
entry[a]	temp [°C]	additive	**3a**	**3b**
1	60	n-Bu_4NBr[c]	61 (18)	37 (23)
2	60	n-Bu_4NI[c]	50 (72)	48 (71)
3	60	NH_4I[c]	51 (85)	45 (88)
4	60	none	9 (97)[e]	42 (97)
5	80	none	–[e]	–[e]
6	**60**	**NH_4BF_4**[d]	**47 (97)**	**41 (97)**
7	80	NH_4BF_4[d]	45 (95)	30 (97)

[a] Reagents and conditions: $[Rh(cod)_2OTf]$ (5 mol %), (*S*,*R*)-**2** (6 mol %), THF, 1 h. [b] Yield determined by ^1H NMR using an internal standard; % ee determined by chiral HPLC. [c] 15 mol %. [d] 100 mol %. [e] Starting material was completely consumed.

halide-based catalysts gave low (Br) to modest (I) ee, but this could be improved by using an ammonium halide additive (Table 1, entries 1−3). The Rh-OTf catalyst (no additive) gave excellent ee for both products; however, the highly reactive metal species led to product decomposition, even at 60 °C (Table 1, entries 4 and 5). Reasoning that a cationic rhodium species was required for good ee, and that the reaction proceeded better with a protic additive, we investigated the use of NH_4BF_4 as an additive.

It was found that the catalyst activity was somewhat attenuated with NH_4BF_4, which gave a combination of excellent yield and enantioselectivity for each of the products (Table 1, entry 6).

We specifically investigated *this* process because of the vast array of bioactive aminotetralins, and we reasoned that rather than discarding one of the products both could be used in synthesis.[7] To illustrate this approach, we selected Rotigotine **4**[8] and 8-(OH)-DPAT **5**[9] as two APIs that we envisaged could derive from the same racemic precursor

(3) Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444–445.

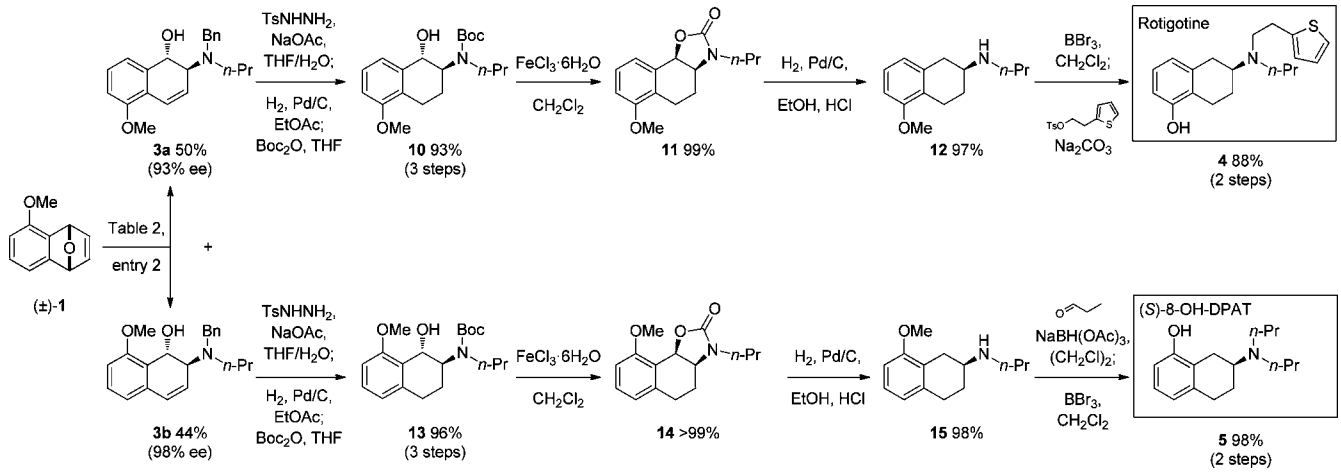
(4) For reviews, see: Kumar, R. R.; Kagan, H. B. *Adv. Synth. Catal.* **2010**, *352*, 231–242. Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365–370. For selected reports, see: Wu, B.; Parquette, J. R.; RajanBabu, T. V. *Science* **2009**, *326*, 1662–1662. Jana, C. K.; Studer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6542–6544. Gansauer, A.; Fan, C. A.; Keller, F.; Keil, J. *J. Am. Chem. Soc.* **2007**, *129*, 3484–3485. Gansauer, A.; Fan, C. A.; Keller, F.; Karbaum, P. *Chem.—Eur. J.* **2007**, *13*, 8084–8090. Pineschi, M.; Del Moro, F.; Crotti, P.; Di Bussolo, V.; Macchia, F. *J. Org. Chem.* **2004**, *69*, 2099–2105. Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 8078–8079. Chen, Y. G.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 11302–11303. Vedejs, E.; Chen, X. H. *J. Am. Chem. Soc.* **1997**, *119*, 2584–2585. Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021–11022. Bolm, C.; Schlingloff, G. *J. Chem. Soc., Chem. Commun.* **1995**, 1247–1248.

(5) (a) Naxagolide/PHNO: Ahlskog, J. E.; Muenter, M. D.; Bailey, P. A.; Miller, P. M. *Clin. Neuropharmacol.* **1991**, *14*, 214–227. (b) Terutroban: Sorbera, L. A.; Serradell, N.; Bolos, J.; Bayes, M. *Drugs Future* **2006**, *31*, 867–873. (c) LY274600: Mendla, K.; Pyke, R.; Eisenreich, W.; Friedl, T., World Patent WO2005/02342, 2005. (d) Amibegron: Overstreet, D. H.; Stemmelin, J.; Griebel, G. *Pharmacol., Biochem. Behav.* **2008**, *89*, 623–626.

(6) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043–8053.

(7) A substructure search for 2-aminotetralin in the Reaxys Database results in over 10 000 compounds with reported biological activity (Search performed 03-Sep-2010).

Scheme 2. Regiodivergent Synthesis of Rotigotine **3** and (*S*)-8-OH-DPAT **4** from a Common Racemic Precursor

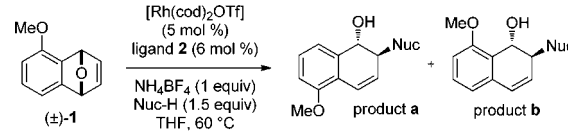


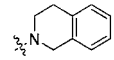
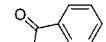
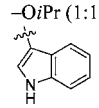
(±)-**1** (Scheme 2). To this end, diimide reduction of the ARO products **3a/b** proceeded without incident, but subsequent removal of the benzylic alcohol (from **10**/**13**) proved challenging. None of the standard conditions tried were successful (catalytic hydrogenation in the presence of Lewis/Brønsted acids, trifluoroacetic acid/triethylsilane, hydride reduction of benzylic tosylate or halide, radical methods) and instead resulted in elimination, over-reduction, and decomposition. We speculated that poor alignment of the C−O bond was responsible for the recalcitrant deoxygenation, so we developed an efficient deoxygenation protocol from *cis*-oxazolidinones **11**/**14** which were generated by using a catalytic amount of $FeCl_3$ to mediate an intramolecular "S_N1-type" cyclization of the carbamate with concomitant loss of isobutene.

Catalytic hydrogenolysis in the presence of HCl liberated CO_2 to form compounds **12** and **15**, respectively.[10] A known two-step demethylation/alkylation sequence from **11** then gave Rotigotine in a total of 7 steps and 79% overall yield from **1a** (using only two chromatographic purifications).[11] Reductive amination of **15** with propionaldehyde followed by demethylation furnished (*S*)-8-(OH)-DPAT **5** in 7 steps and 92% overall yield from **3b** without recourse to a single chromatographic purification. To the best of our knowledge, this constitutes the first time a regiodivergent resolution has been successfully applied in target-oriented synthesis.

A variety of amine and alcohol nucleophiles were investigated and found to participate very well in the reaction (Table 2). Using this new catalytic system, both regioisomers are generally obtained in high ee and close to the theoretical maximum yield,

Table 2. Nucleophile Scope



entry	Nuc	*t* [h]		yield [%] (% ee)[a]	
				a	**b**
1		3	**3**	50 (93)	46 (98)
2[b]		96	**3**	50 (93)	44 (98)
3		3	**16**	40 (94)	43 (97)
4		3	**17**	45 (97)	33 (>98)
5		3	**18**	29 (96)	26 (>98)
6		3	**19**	47 (97)	48 (95)
7[c]		3		-	-
8[c,d]		3	**20**	45 (>98)	42 (98)
10	–OMe (solvent)	3	**21**	44 (74)	38 (96)
11	–OMe (1:1 THF)	3	**21**	48 (78)	40 (91)
12	–OMe (1:10 THF)	24	**21**	47 (83)	44 (93)
13	–O*i*Pr (solvent)	3	**22**	50 (84)	37 (97)
15	–O*i*Pr (1:10 THF)	24	**22**	46 (95)	39 (98)
16		6	**23**	44 (88)	decomp.

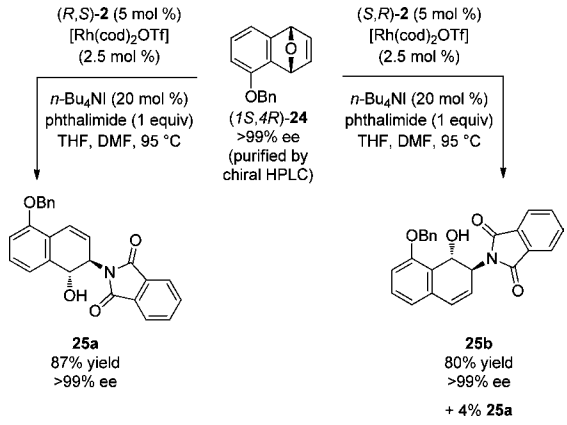
[a] % isolated yield following column chromatography; % ee in parentheses determined by chiral HPLC. [b] Reaction performed on a 5 g scale of **1** with $[Rh(cod)_2OTf]$ (1 mol %) and (*S*,*R*)-**2** (1.5 mol %). [c] DMF added for solubility, reaction performed at 95 °C. [d] *n*-Bu_4NI (20 mol %) in place of NH_4BF_4.

(8) Rotigotine is used in the treatment of Parkinson's disease and restless legs syndrome. (a) Davies, S. *Drugs Today* **2009**, *45*, 663–668. (b) Zareba, G. *Drugs Today* **2006**, *42*, 21–28.

(9) 8-(OH)-DPAT is a 5-HT_{1A} and 5-HT_7 receptor agonist shown to possess antidepressant, anxiolytic, hyperventilative, and analgesic effects. (a) Sprouse, J.; Reynolds, L.; Li, X. F.; Braselton, J.; Schmidt, A. *Neuropharmacology* **2004**, *46*, 52–62. (b) Assie, M. B.; Koek, W. *Br. J. Pharmacol.* **1996**, *119*, 845–850. (c) Larsson, L. G.; Renyi, L.; Ross, S. B.; Svensson, B.; Angebymoller, K. *Neuropharmacology* **1990**, *29*, 85–91.

(10) It was necessary to use a *cis*-fused oxazolidinone. The *trans*-fused oxazolidinone was inert under identical hydrogenolysis conditions and could be reisolated in 100% yield. For similar reactions see: (a) Buisson, D.; Cecchi, R.; Laffitte, J. A.; Guzzi, U.; Azerad, R. *Tetrahedron Lett.* **1994**, *35*, 3091–3094. (b) Sheehan, J. C.; Guziec, F. S. *J. Org. Chem.* **1973**, *38*, 3034–3040.

Scheme 3. Regiodivergent Reaction of an Optically Pure Oxabicyclic Alkene



which is in contrast to our earlier report.[3] Furthermore, the reaction conditions were also highly compliant to scale-up and could be run on a multigram scale with low catalyst loading (1 mol %) with no loss of yield or enantioselectivity (Table 2, entry 2). Notably, phthalimide did not give either of the desired products with NH_4BF_4 as an additive, but excellent results were achieved with *n*-Bu_4NI (Table 2, entries 7 and 8). Interestingly, lower ee was observed when the reaction medium was an alcoholic solvent (Table 2, entries 10−15), but this problem could be solved by simply decreasing the amount of alcohol present.

To demonstrate the power of this reaction further, the optically pure oxabicyclic alkene **24** was subjected to each enantiomer of the catalyst to give two regioisomeric products in excellent yield and optical purity (Scheme 3).

In summary, a practical regiodivergent resolution was developed using a novel cationic Rh(I)-**2** catalyst complex with protic additive. To illustrate the utility of the method, Rotigotine **4** and (*S*)-8-OH-DPAT **5** were both synthesized from oxabicycle (±)-**1** in 80% combined overall yield (39% and 41%, respectively). We are currently investigating catalytic methods to access enantiomerically pure oxabicyclic alkenes which in combination with this chemistry will open up a new realm of efficiency in the synthesis of many valuable bioactive aminotetralins.

Acknowledgment. This research was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Merck Frosst Centre for Therapeutic Research, and the University of Toronto. We thank Solvias for the generous donation of chiral ligands (*R*,*S*)-**2** and (*S*,*R*)-**2**, substrate (1*S*,4*R*)-**24**, and a postdoctoral fellowship (M.J.F.).

Supporting Information Available: Experimental procedures, characterization data for new compounds, and additional data tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Biswas, S.; Zhang, S. H.; Fernandez, F.; Ghosh, B.; Zhen, J.; Kuzhikandathil, E.; Reith, M. E. A.; Dutta, A. K. *J. Med. Chem.* **2008**, *51*, 101–117. (b) Minaskanian, G.; Rippel, K., World Patent WO2001/038321, 2001.