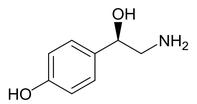
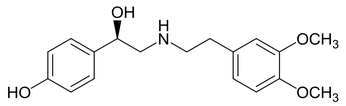
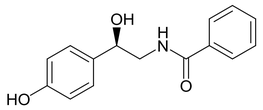
Adrenergic receptors, or adrenoceptors, are protein receptors located on the plasma membrane of an epinephrine-sensitive cell. The hormone epinephrine binds to the receptor, mediating an increase in excitability and conductivity in the tissue. These receptors have various responses and affinities to structural analogs of the epinephrine hormone. One group of structural analogs are called agonists, which bind to the receptor and mimic the effect of epinephrine, while another group of analogs that bind to the receptor without triggering the normal effect produced by the agonists and the natural ligand are called antagonists. By this mechanism, the antagonists effectively block the effects of epinephrine and adrenoceptor agonists.



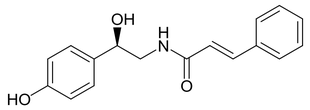
(*R*)-Octopamine



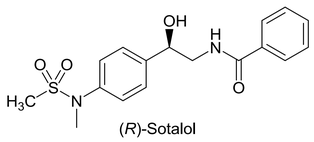
(*R*)-Denopamine



(*R*)-Tembaminde



(*R*)-Aegeline

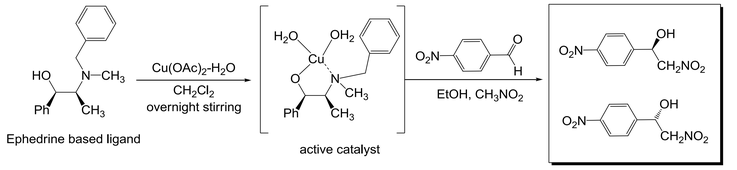


(*R*)-Sotalol

The molecules depicted above are non-cardioselective beta-adrenergic blockers—which means that they block the effects of beta-adrenoceptor agonists in lung and vascular tissue as well as in heart tissue. Optimizing the synthesis of these compounds is the ultimate goal of the present research. While both enantiomers (R,S) of each of these compounds possess reactivity through a separate pathway which mediates prolongation of cardiac action potential duration—only the R enantiomers of these compounds exhibit beta-adrenoceptor blocking activity. This phenomenon is owed to the fact that the blocking ability of each compound is dependent on it's three-dimensional arrangement. In effect, each of the S enantiomers of these compounds represent a non-superimposable mirror image of the correct "puzzle piece" which acts as an antagonist at a beta-adrenoceptor.

Initial Studies—The *Ephedra* Ligands

When a synthesis of denopamine is done in industry today—it yields a racemic (50:50) mixture of the R and S enantiomers of the compound. However, only the R enantiomer exhibits the desired activity.



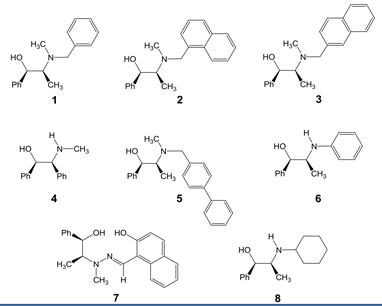
Ephedrine based ligand

active catalyst

One enantiomer will be favored over the other. The identity of the favored enantiomer will be determined by HPLC.

Thus, our research is focused on routes by which the R enantiomer may be produced selectively, to the exclusion of the S enantiomer. To that end, we explored a metal-ion mediated catalytic pathway in our initial studies. The process consisted of complexing a variety of ephedra-based ligands with copper(ii) acetate hydrate to form an active catalyst. Then, *p*-nitro benzaldehyde and nitromethane were reacted in the presence of this catalyst. HPLC analysis was performed to determine the relative amounts of each enantiomer present after the reaction. The identities of the ligands tested as well as the corresponding HPLC analysis results are detailed to the right.

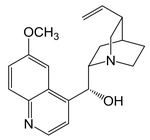
The reactants are drawn to the catalyst before reacting during this process. Because the various *Ephedra* ligands have a fixed three-dimensional shape, they are able to increase selectivity by blocking angles of attack on the substrates.



Ligand	Integration for Enantiomer A	Integration for Enantiomer B	Enantiomeric Excess (%ee)
1	33%	67%	34%
2	35%	65%	30%
3	40%	60%	20%
4	38%	62%	24%
5	36%	64%	28%
6	35%	65%	30%
7	74%	26%	48%
8	52%	48%	4%

Ligand Evaluation

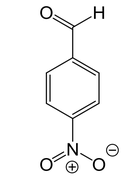
The ephedra ligands under investigation were not proving to be effective enough for the application that was sought in the synthesis of the anti-arrhythmia agents—results were consistently too close to the unwanted 50:50 ratio. Through review of chemical literature, it was determined that the researchers Zielinska-Blajet and Skarzewski had successfully employed the cinchona alkaloid quinine in an asymmetric Henry reaction. Our research is currently focused on optimization of this process towards the synthesis of (R)-denopamine and (R)-sotalol.



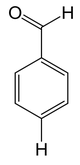
quinine

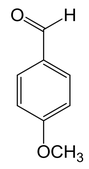
Substrate Evaluation

The low enantioselectivities observed from the ephedra reagents may have been due to the high reactivity of *p*-nitrobenzaldehyde. In response, we began investigating other aldehyde substrates with different substituents.



Highest reactivity

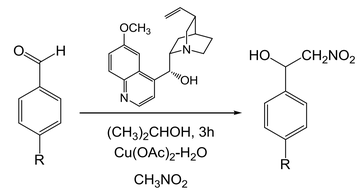




Lowest reactivity

Benzaldehyde and *p*-methoxybenzaldehyde were selected as the reacting substrates in further studies, due to their more favorable electronic properties.

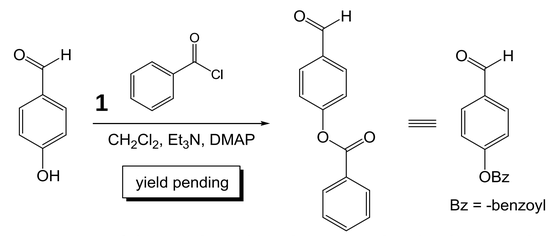
Quinine-Mediated Asymmetric Catalysis



enantiomerically enriched nitroaldol product

R = -H; xx %ee
R = -OCH3; xx %ee

Proposed Denopamine Synthesis



Bz = -benzoyl

The first two steps of this synthesis have been completed—the second step is the quinine/metal active-catalyst mediated step which is presently under study. The following steps are all standard reactions—the key to a successful enantioselective synthesis of (R)-denopamine is the nitro-aldol addition, or the Henry reaction. This is the step which establishes the desired stereochemistry. The HPLC results from the quinine-mediated step in our (R)-denopamine synthesis are pending.