Phase Transfer Catalysis: An Investigation of the Asymmetric Catalytic Capacities of 10,11-Didehydro-Coupled Cinchona Alkaloids in the [2,3]-Wittig Rearrangment

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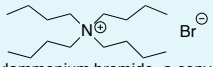
Introduction

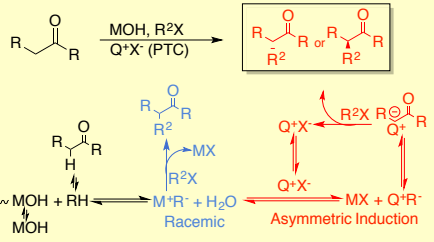
Phase Transfer Catalysis (PTC) facilitates the transport of charged intermediates across immiscible phases, promoting reactant interaction and resulting in rate enhancement. Catalysts very generally consist of hydrophilic quaternary onium cations (i.e. phosphonium or ammonium) with four lipophilic substituents which allows them to be soluble in both aqueous and organic medium. Here, we examine base mediated PTC wherein hydroxide ions in the aqueous phase are bound by PTC and transported into the organic phase to generate a reactive onium-carbanion species Q^+R^- which can facilitate various reactions and rearrangements.



Tetra-n-butylammonium bromide, a conventional PTC

PTC/Asymmetric PTC Mechanism

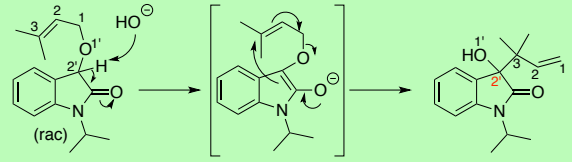
One commonly accepted general PTC mechanism is the Makosza interfacial mechanism shown below. Due to the high lipophilicity of most catalysts, this mechanism reasonably expects PTC to have only interfacial affinity rather than complete aqueous solubility. Intuitively, the use of chiral tetraalkylonium salts can lead to asymmetric induction. The interaction between the onium-carbanion species Q^+R^- is such that one of the enantiotopic faces of the carbanion species is selectively shielded by the chiral onium species so that the carbanion is effectively directed toward an enantioselective alkylation.



Scheme 1. Makosza Interfacial Mechanism (shown for a generic enolate alkylation

Intramolecular APTC

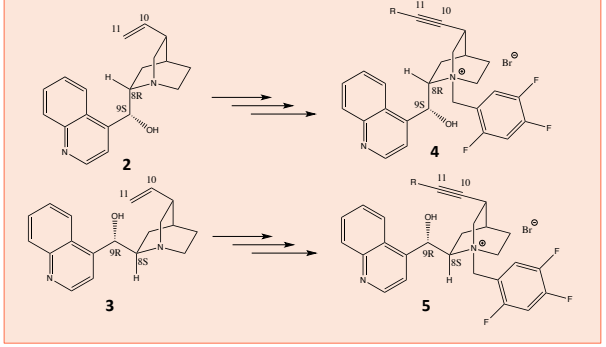
While asymmetric PTC alkylations have been known for several decades, examples of asymmetric PTC rearrangements are virtually nonexistent. Intramolecular rearrangements can also occur through the Makosza interfacial mechanism, however rather than attacking an alkyl halide, the enolate undergoes intramolecular attack on a pendant electrophile. This report will investigate the base mediated asymmetric [2,3]-Wittig rearrangement of 1-isopropyl-3-(3-methylbut-2-enoxy)indolin-2-one **1**. Following rearrangement, a new stereocenter is formed at the 2′ position. The enantiomeric ratio of the rearranged product can be influenced by using a chiral PTC.



Scheme 2. [2,3]-Wittig Rearrangment

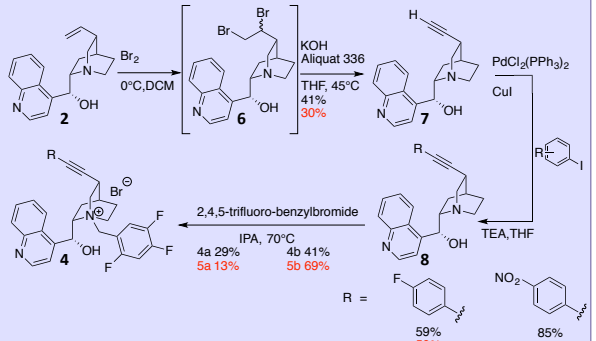
Cinchona PTC Analogs

From the inception of asymmetric PTC development, catalysts derived from the *Cinchona* alkaloid family have achieved stellar enantioselectivity and rate enhancement. Scaffolds derived from *Cinchonas* cinchonidine **2** and cinchonine **3** are lucrative for PTC development due to their complex structure, varied functionality, pseudo-enantiomeric availability, and low cost. Several generations of *Cinchona* PTC analogs have been developed for a variety of targeted asymmetric organic syntheses, each appending distinct moieties to the original scaffold. In efforts to determine structure-activity relationships for this class of catalyst, previous work has investigated the asymmetric catalytic effect of various quaternizing agents, *O*-alkylations, diquats, and dimers. In this investigation, we endeavor to report the asymmetric catalytic effect of the 10,11-didehydro-coupled catalysts **4** and **5**.



Catalyst Synthesis

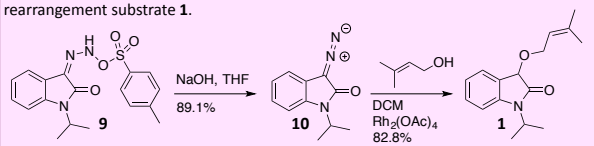
Cinchona alkaloid **2** was reacted with bromine to yield 10,11-dibrominated epimeric intermediate **6**. Subsequent reaction with potassium hydroxide yielded the doubly eliminated terminal alkyne **7**. Aryl-iodides were appended to the terminal alkyne employing a Sonogashira cross-coupling reaction to yield the coupled product **8**. Quaternization was achieved through the benzylation of the tertiary quinuclidine amine with 2,4,5-trifluoro-benzylbromide to produce the active catalyst **4**.



Synthesis of cinchonine catalysts **5a** and **5b** followed the same procedure (yields shown in red).

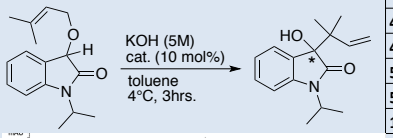
Substrate Synthesis

N-Tosyl hydrazide starting material **9** was available from a previous two-step synthesis from isatin. After detosylation to yield the diazo compound **9**, expulsion of nitrogen and subsequent carbene O-H insertion led to the [2,3]-Wittig rearrangement substrate **1**.



Results

Catalyst **4a** was the most selective, yielding a 61:39 enantiomeric ratio. Catalyst **5a** was the least selective yielding essentially racemic product. All trials were run in duplicate. Previously synthesized catalyst **11** was run as a control for the coupled cinchonidine catalysts.



Catalyst	e.r.
4a	61:39
4b	54:46
5a	49:51
5b	43:57
11	73:27

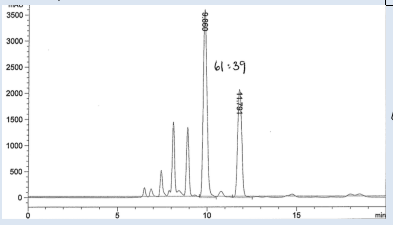
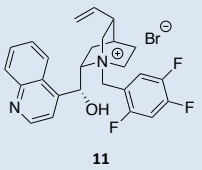


Figure 1. Catalyst **4a** HPLC trace. Peaks at 8 and 9 minutes are unreacted starting material.



11

It is difficult to draw conclusions from this set of five catalysts, yet it is notable that the uncoupled catalyst achieved a better e.r. than all other catalysts. The e.r. for catalyst **11** was achieved in a prior study from these laboratories.

Future Work

Extensions of this project will investigate the effect of various steric moieties at the 10,11 position. A thorough screening of quaternizing agents will also be necessary to understand catalyst structure-activity relationships.

Acknowledgements

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References

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