Original Research Proposal: Enantioselective Conjugate Addition of Aldehydes to Nitroarenes Enabled *via* Bifunctional Thiourea-Secondary Amine Catalysis: A Mild Synthesis of α-Aryl Aldehydes

Student's Name

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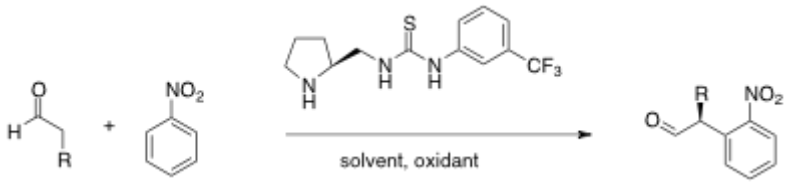
Abstract:

The α-aryl carbonyl functionality is a structural motif found in both pharmaceuticals as well as in naturally occurring bioactive compounds, however, the formation of a C-C bond between an aryl carbon and a carbonyl α-carbon has long posed a challenge to the synthetic community. Reported methods that have been applied to solve this problem revolve around palladium catalysis, and more recently, organocatalysis. Although outstanding work has been performed in the field, a carbonyl α-arylation protocol that can be carried out in both an intermolecular and enantioselective fashion remains largely unexplored.

This document is a proposal to accomplish this task using a chiral bifunctional organocatalytic system. Within the framework of the catalyst are both a hydrogen bond donor and a secondary amine. The strategy involves activation of a nitroaryl compound towards nucleophilic attack via hydrogen bond donation, and condensation of the carbonyl compound to a nucleophilic enamine. Reaction of the two components placed in proximity in a chiral environment ultimately results in the desired C-C bond formation. The type of catalyst necessary for this transformation is well described in the literature. Urea or thiourea, acting as an H-bond donor, and a secondary amine moiety contained within the same molecule constitute the bifunctional catalyst. These catalysts have been used extensively for a variety of processes related to this proposal including α-alkylation and Michael addition. The analogous reactions proceed under mild conditions and avoid the need for metals or strong bases.

Specific Aims:

The formation of a C-C bond between the α-carbon of a carbonyl and an aromatic carbon has been a significant challenge in organic synthesis. This proposal will address the issue by employing a chiral bifunctional catalyst to enable the asymmetric conjugate addition of an aldehyde to a nitroarene (Scheme 1).



Scheme 1. Proposed asymmetric organocatalytic α-arylation of aldehydes.

The specific aims of this proposal are as follows:

1) To develop a general system for the asymmetric conjugate addition of aldehydes to nitroarenes facilitated through bifunctional organocatalysis to form nitronate σ-complexes.

2) To investigate protocols to rearomatize the nitronate intermediates in situ.

3) To compare the versatility and practicality of this method to other known protocols.

Background and Significance:

α-Aryl carbonyls are seen in a variety of compounds including the profen family of drugs,[1] and other biologically active compounds (Figure 1).[2a] Considerable efforts have been made by many research groups to construct this type of functionality through the use of metals, organo-SOMO catalysis, and the addition of silyl enol ethers to nitrobenzenes.

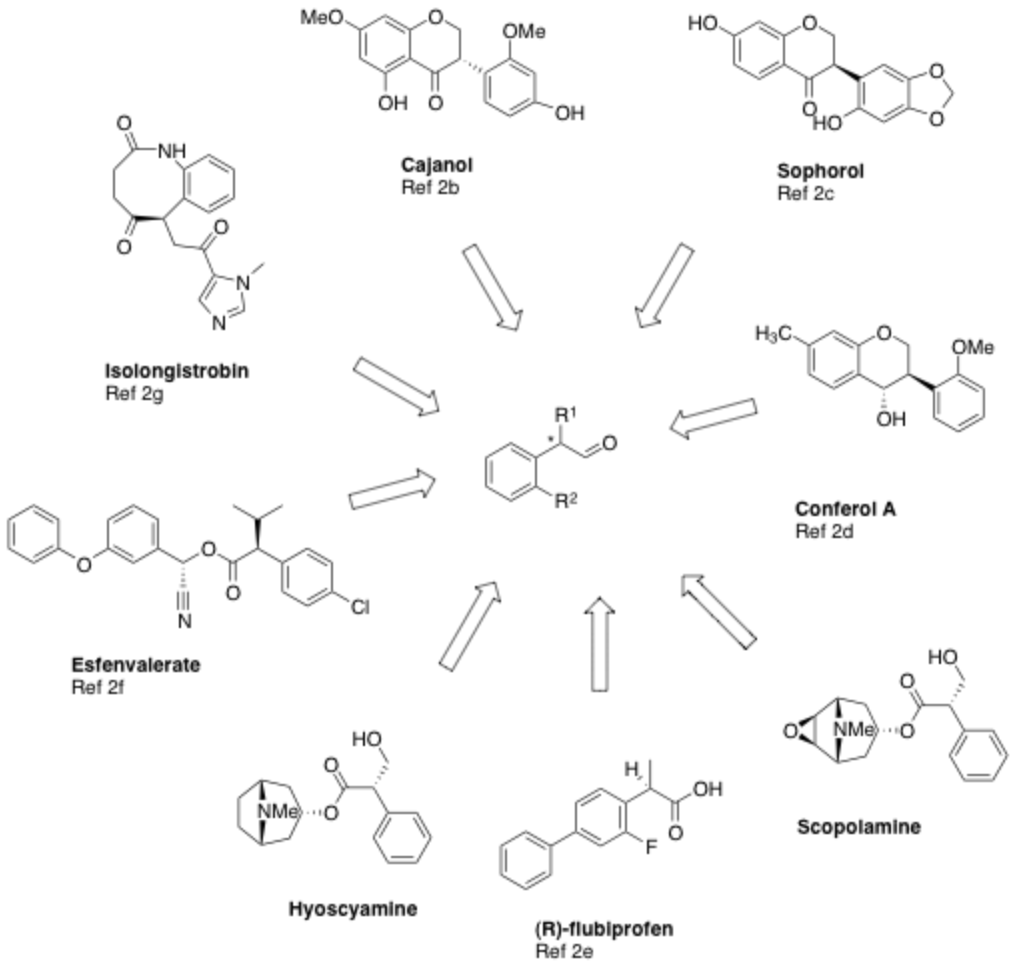


Figure 1. Examples of biologically active compounds derived from of α-aryl aldehydes.

α-Arylation of carbonyl compounds is of interest because it still presents a challenge to chemists, who have gone about several different ways to solve the problem. The mainstay in this area involves palladium catalysis, more specifically, through trapping of an aryl-palladium intermediate with a metal enolate (Figure 2).[3] This method has been applied towards the arylation of esters,[3] amides,[4] imides,[5] ketones[6] and aldehydes.[7a-e] Aside from Pd-catalysis, α-Arylation of aldehydes has also been accomplished using organo-SOMO methodologies.[8a,b] An alternative synthesis of α-aryl esters and nitriles involving oxidative vicarious nucleophilic substitution in nitroarenes by silyl enol ethers was developed as well.[9a-c]

The case of α-arylation of aldehydes versus other carbonyl compounds is more difficult due to the tendency of aldehydes to self-condense under basic conditions. Due to this obstacle, only intramolecular cyclization of haloaryl linked aldehydes had been

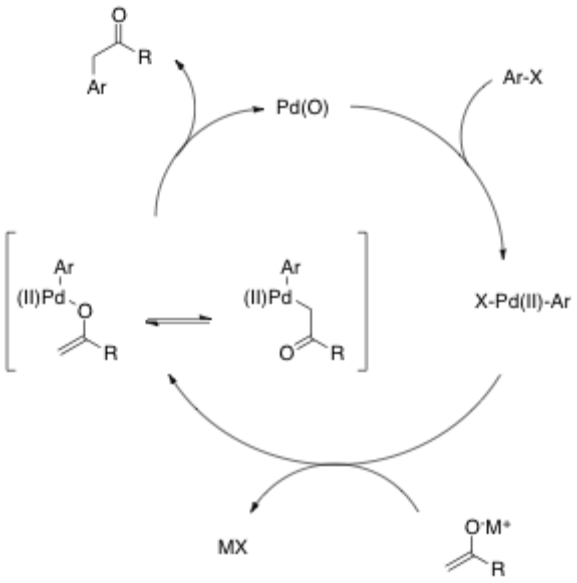
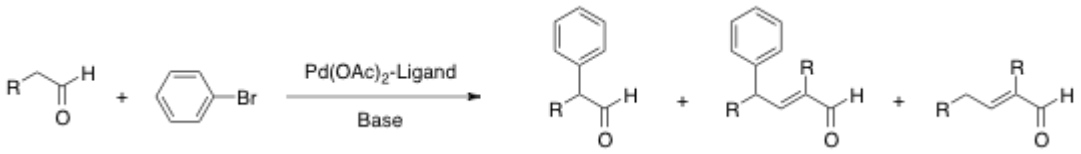
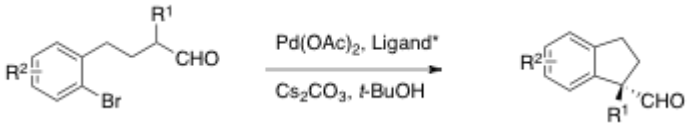


Figure 2. General catalytic scheme for Buchwald and Hartwig's arylation.



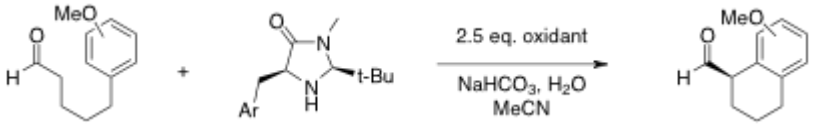
Scheme 2. Typical intermolecular Pd-catalyzed α-arylation reaction.

reported[7a] until 2002, when intermolecular protocols for the reaction of simple aldehydes with aryl bromides (Scheme 2) began to develop. Miura's work was able to overcome to some extent, with careful choice of catalyst and base, the seemingly unavoidable aldol side reaction.[7b] This procedure suffers from some drawbacks such as complex mixtures of racemic products and only modest yields after optimization. Additionally, the reaction was only shown to work with aryl bromides bearing neutral or electron donating *para* substituents. Later, Buchwald and Hartwig independently developed procedures with minor improvements upon Miura's work in terms of scope of substrates and arene electronics.[7c-d] In 2008, Buchwald and Garcia reported the first asymmetric variant of Pd-catalyzed α-arylation of aldehydes with moderate to high yields and enantioselectivities (Scheme 3).[7e] While useful, the reaction is still limited to intramolecular reactions due to competing aldol condensation under the conditions.



Scheme 3. General scheme for Buchwald's intramolecular asymmetric arylation.

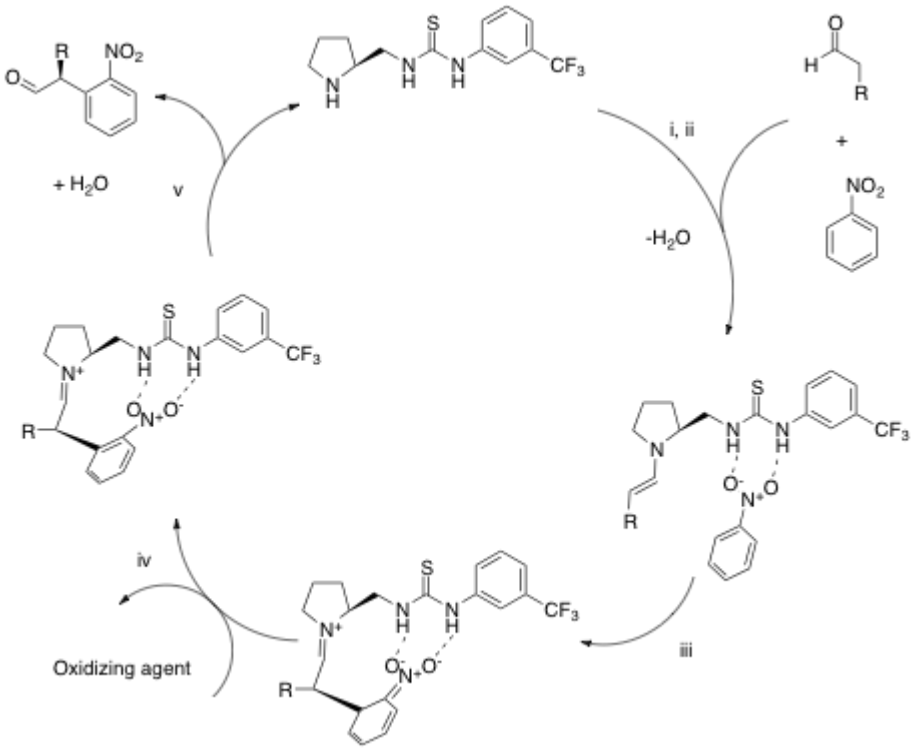
Most recently, asymmetric organocatalytic intramolecular α-arylation of aldehydes was demonstrated by Nicolaou and co-workers in 2009 through the use of organo-SOMO catalysis (Scheme 4).[8a] *Ortho* selective reactions applying the same mode of catalysis was published shortly after by the MacMillan group.[8b] In both cases, the reactions require high catalyst loading (usually 20-30 mol %), an excess of a single electron acceptor, and simple aldehydes tethered to an electron rich arene (Scheme 4).



Scheme 4. Organo-SOMO catalytic arylation of aldehydes.

To date, Pd-catalyzed methods of coupling aryl halides and enolates have only been shown to work well intramolecularly and with simple substrates. Although asymmetric examples have been studied, they suffer the same limitations. The organo-SOMO approach is constrained by requiring specific arene electronics (electron donating substituents) and a tethered aldehyde as well.

Herein I propose that asymmetric α-arylation of aldehydes with nitroarenes can proceed in an intermolecular fashion using a bifunctional organocatalytic strategy (Figure 3).



i) Coordination of an aryl nitro-compound to a hydrogen bond donor. ii) Formation of an enamine from the aldehyde and secondary amine. iii) Conjugate addition of the enamine to the activated arene to form a nitronate σ-complex. iv) Oxidation of the σ-complex. v) hydrolysis of the iminium ion to form the product and regenerate the catalyst.

Figure 3. Proposed catalytic cycle.

The proposed strategy is a mild asymmetric intermolecular synthesis of α-aryl aldehydes that are not readily accessible according to known protocols. This methodology would provide a greener alternative by circumventing the need for metals, and avoid base promoted aldol reactions associated with the standard Pd-catalyzed procedure. It should also surpass the current intramolecular restrictions of Pd-catalyzed and organo-SOMO catalysis. The proposed methodology relies on an electron withdrawing group on the arene, contrary to the organo-SOMO strategy. The withdrawing functionality, in this case $–NO_2$, is capable of further transformations.

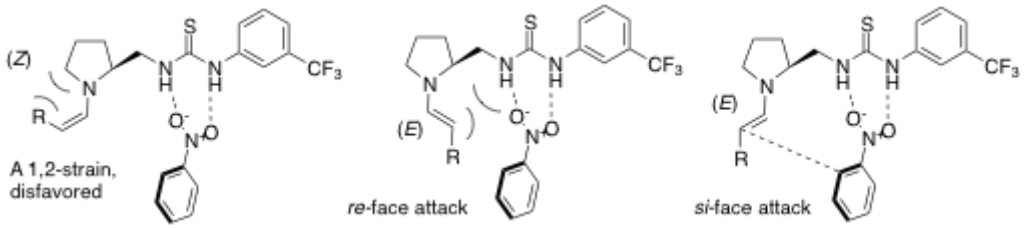


Figure 4. Model for stereochemical induction.

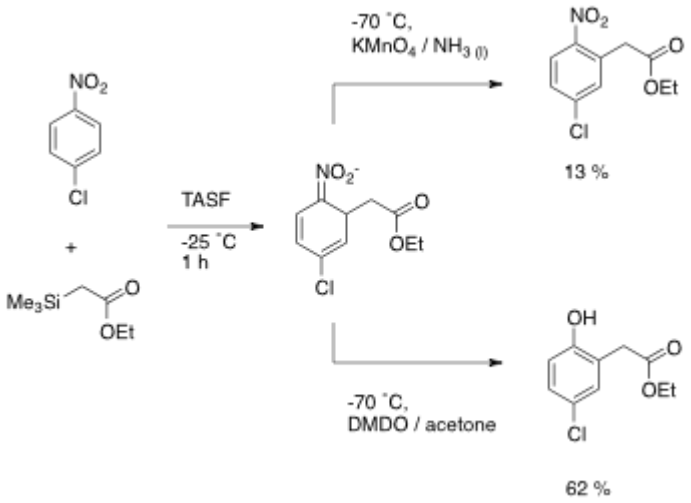
The proposed reaction is also enantioselective. Stereochemistry of the product is set by attack from the *si*-face of the (*E*)-enamine double bond. The (*E*) conformation is preferred to minimize 1,2-allylic strain between the R group and the pyrrolidine. The R group is directed away from the bulky thiourea scaffold of the catalyst, which promotes attack by the *si*-face of the olefin (Figure 4).

Experimental Design and Methods:

Conjugate addition to nitroarenes and rearomatization

The proposed α-arylation depends primarily on the conjugate addition of a carbon nucleophile to nitrobenzene and subsequent rearomatization (oxidation of the σ-complex). Cases of nucleophilic addition to nitroarenes followed by rearomatization are well documented in the literature.[9a-d] Grignard or alkyllithium reagents can be added in a 1,4- and/or 1,6- fashion to nitroarene compounds to form nitronate adducts. These unstable intermediates are then converted in situ to aromatic alkylnitro derivatives with the use of a suitable oxidant such as O_2, DDQ, bromine and triethylamine, or potassium permanganate.[9a-d] Vicarious nucleophilic substitution is another relevant reaction typically encountered with nitroarenes. It features a nucleophile, especially a carbanion,

replacing a hydrogen rather than an aromatic substituent such as a halogen as is usually seen in nucleophilic aromatic substitution reactions.[10] Complementary to the proposed system is the addition of silyl enol ethers to unactivated nitroarenes. In this reaction, ketone enolates generated by treatment of silyl enol ethers with fluoride ion add to the *ortho* position of a nitrobenzene (Scheme 6).[11a-c] Interestingly, depending on the oxidant, different products are accessible. Potassium permanganate presumably attacks at the addition site of the enolate to furnish the substituted nitroarene, while DMDO attacks at the carbon *ipso* to the nitro group, producing the substituted phenol. These transformations may be applied to the proposed system to afford a variety of useful building blocks (Figure 5).



Scheme 6. Addition of a silyl enol ether to a nitroarene and σ-complex oxidation.

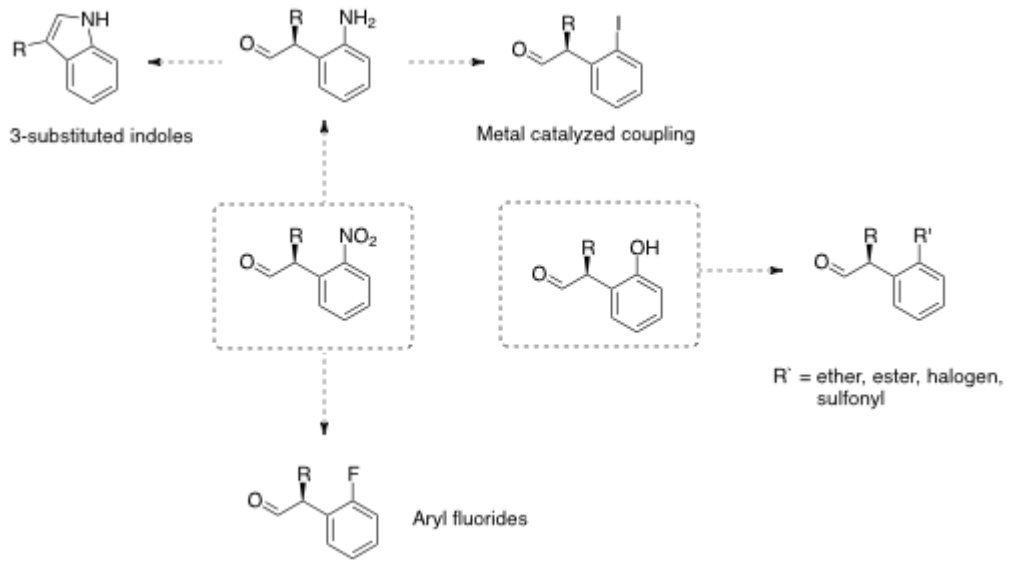


Figure 5. Building blocks accessible though functional group interconversion.

Bifunctional catalysts for asymmetric organocatalytic Michael addition to nitroolefins

Bifunctional catalysts, as applied to the asymmetric organocatalytic Michael addition to nitroolefins, bear a primary or secondary amine and a hydrogen bond donating moiety in the same molecule (Figure 6). Although less accepting to hydrogen bond donation than carbonyl or imine groups, the nitro functionality still holds a favored position among the groups that may be activated by hydrogen bond donation catalysis.[12] Recently, this lower reactivity has been found to be mitigated through the use of thiourea catalysts. These catalysts are capable of activating nitroolefins towards the conjugate addition of carbon nucleophiles by donating hydrogen bonds to the $-NO_2$ group.[13a-e]

It is well known and documented that carbonyls, upon condensation with a secondary amine, form nucleophilic enamines. By incorporating an amine and thiourea in one catalyst, simultaneous activation of both carbonyl and nitro functional groups is possible. Numerous examples of high yielding and highly enantioselective Michael

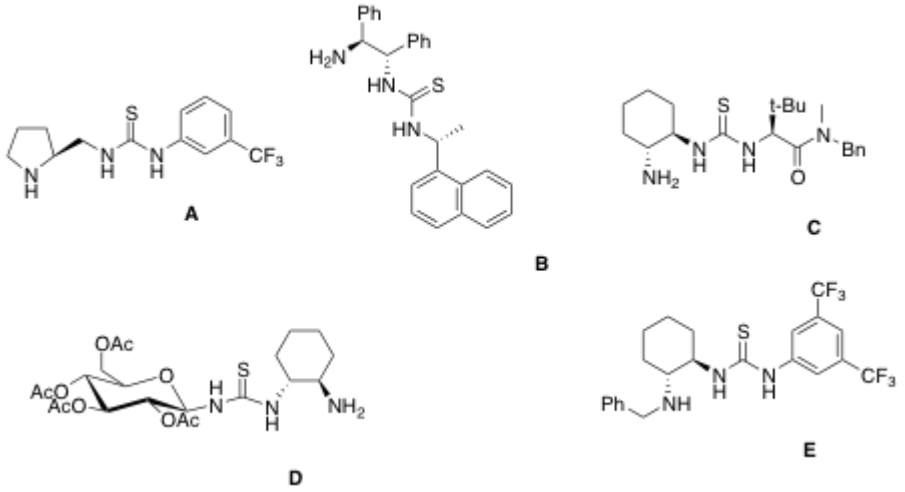
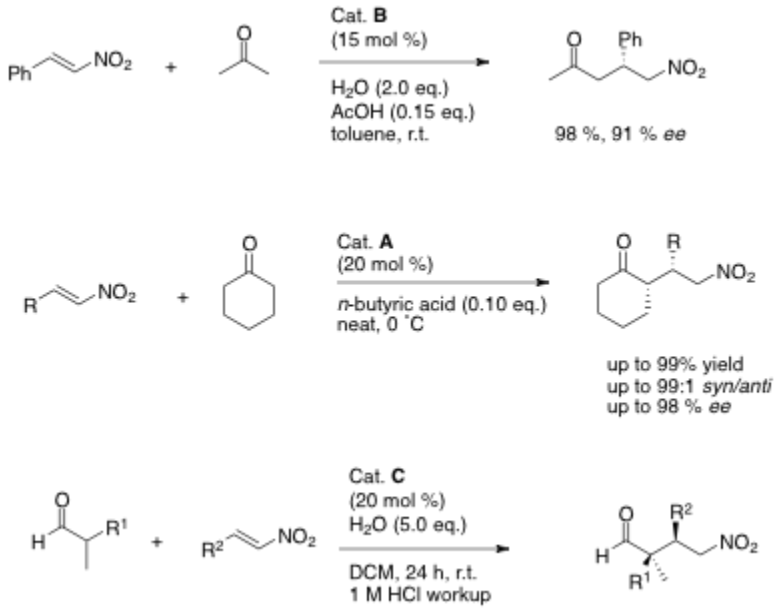


Figure 6: Examples of bifunctional thiourea-amine catalysts.[12,13e-g]

addition enabled by these catalysts (Scheme 7) are disclosed in the literature.[14a-c] However, no instances of the enantioselective addition of enamines to nitrobenzenes have been reported. Through use of a bifunctional catalyst incorporating both a thiourea and a secondary amine it is likely that the analogous conjugate addition to nitroarenes is possible.



Scheme 7. Examples of bifunctional organocatalytic Michael addition to nitroolefins.[13e]

Rationale

The proposed reaction is an improvement upon existing methods for many reasons. Asymmetric α-arylation reactions of aldehydes and intermolecular α-arylation reactions of aldehydes are mutually exclusive. This method is the first to have reacting groups in different molecules combine in an asymmetric manner. Another advantage is the use of environmentally benign bifunctional thiourea catalysts. Contrary to most metal complexes, thioureas are bench stable and easy to handle. They are also water tolerant, and work under mild, almost neutral conditions.[12] This methodology avoids basic conditions, which promote undesired side reactions. Lastly, the closest related precedence reported in the literature support the claims of this proposal without indications that it should be unsuccessful.

The proposal described here addresses the aims by:

1) Using thiourea-secondary amine organocatalysts to simultaneously activate aldehydes and nitroarenes to undergo conjugate addition at the *ortho* position forming nitronate σ-adducts.
2) Exploiting the selectivities of oxidizing agents to arrive at *o*-substituted nitrobenzenes or phenols from nitronates.
3) Presenting possibilities for functional group interconversion of nitroarenes or phenols, as well as selected examples of chiral biologically active compounds containing α-aryl aldehyde derivatives not accessible through current α-arylation methodologies. The strategy is metal free and both asymmetric and intermolecular.

However, there are some potential difficulties associated with the proposed strategy. As mentioned earlier, basic conditions catalyze the self-condensation of aldehydes. The reaction may be slightly basic due to the amine on the catalyst. This problem can be remedied by buffering the reaction media.

It is worth noting as well that many of the oxidizing agents used to rearomatize nitronates work via radical mechanisms. Sulfur compounds readily participate in radical reactions thus the presence of the thiourea catalyst and oxidizing agent in the same reaction mixture may result in unwanted side reactions. This may be remedied either by using a bifunctional oxo-urea instead of thiourea, or by a two-stage reaction. Protic acids are known to convert nitronates to nitro cyclohexadienes by protonation at the nitronate carbon. The first stage, conjugate addition, could be performed under acidic conditions

to generate the nitro cyclohexadiene. The second stage, after removal of the thiourea catalyst, would be to aromatize the nitro compound to furnish the α-aryl aldehyde.

Problems with enantioselectivity may arise as well. Choice of a bulky substituent on the amine moiety of the catalyst would be advantageous to preferentially form *E* over *Z* enamines and promote greater selectivity for the attack by the *re* or *si* face of the enamine double bond.

Control experiments can be performed to help identify any potential problems. These include:

1) Having only the catalyst and the aldehyde in the reaction mixture. If aldol condensation is observed, measures can be taken to suppress it.
2) Carrying out the reaction in the presence of acid, and the absence of an oxidizing agent. This would help to determine if conjugate addition occurs, without the possibility of radical side reactions.
3) Performing the Michael addition of an aldehyde to a nitroolefin using an amine-thiourea catalyst according to a published procedure, with the addition of oxidant to the reaction mixture. This would be useful to observe what side reactions, if any, occur between the oxidant and catalyst.

<u>Experimental Approach</u>

- Catalyst system: Features common to thiourea catalysts are electron poor, rigid structures, and non-coordinating electron withdrawing substituents at the 3 and/or 5 positions of a phenyl ring. Catalysts **A-E** would be screened for their ability to carry out the reaction based on experimental yield and enantioselectivity.

- Oxidant: The choice of oxidizing agent should be compatible with the other reagents in the reaction mixture, in particular, the thiourea. The first and simplest approach would be conducting the reaction under an oxygen atmosphere.

- Solvent: Reactions with bifunctional catalysts are often run non-polar aprotic solvents with a catalytic amount of aqueous acid. A system must be chosen to allow for the acid catalyzed condensation of the aldehyde and amine, as well as avoid excess water to prevent saturation of the H-bond donor/acceptor sites. Unfavorable interactions with aromatic solvents may also be a concern. A reasonable starting point would be to use dichloromethane and a catalytic amount of acetic acid.

- Temperature: in order to obtain high enantioselectivities, organocatalytic reactions are typically conducted at low temperature, sometimes at the cost of yield and reaction time. We would begin the reactions at 0˚ C and explore variations in temperature to optimize yield and enantioselectivity.

- Substituents: For initial tests, a simple, inexpensive, enolizable aliphatic aldehyde would be used, such as isovaleraldehyde, in combination with unsubstituted nitrobenzene. This would allow for easy distinction between products, side reactions, and starting materials by ^{1}H-NMR. Later experiments on more complex systems with varying arene electronics would be carried out. α,α-Disubstituted aldehydes would be explored as well, to generate chiral quaternary centers.

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