Enantioselective α-arylation of aldehydes enabled via a multiple hydrogen bond donating / enamine dual catalyst system.

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. α-Aryl carbonyls are seen in a variety of compounds including the profen family of drugs[1], and other biologically active compounds.[2] Considerable efforts have been made to prepare these compounds, particularly through trapping of an aryl-palladium intermediate with a metal enolate or by arylative transmetallation of a palladium enolate in the case of esters.[3] Arylation of amides,[4] imides,[5] and ketones[6] has also been accomplished using similar methodologies. Recently, intramolecular α-arylation of aldehydes was demonstrated by Nicolaou and co-workers utilizing organo-SOMO catalysis.[7]

I propose that α-arylation of carbonyls can proceed using a dual organocatalytic strategy involving the activation of an aryl nitro-compound via a multiple hydrogen bond donor and subsequent conjugate addition of a chiral enamine (Figure 1) allowing for mild, intermolecular reactions that are not normally accessible according to known protocols. This methodology would circumvent the need for metals and strongly basic conditions associated with the standard palladium-catalyzed procedure, and surpass the current limitations of SOMO catalysis.

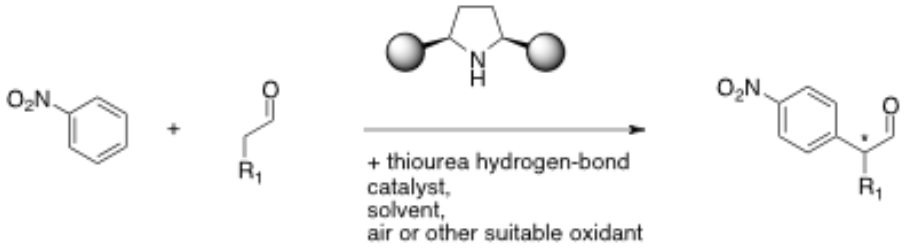

Figure 1: Proposed α-arylation of nitrobenzene via a dual organocatalytic system.

It is known that thioureas act as hydrogen bond donors to activate nitro functionalities, although less so than carbonyls or imines.[8] However, thioureas containing multiple hydrogen bond donor groups have been shown to increase the reactivity of the nitro group and allow for conjugate addition of enamines to nitroolefins.[9] A similar mechanism can be proposed for the alkylation of nitrobenzene in this fashion (Figure 2). This methodology may also be extended to other aromatic nitro compounds.

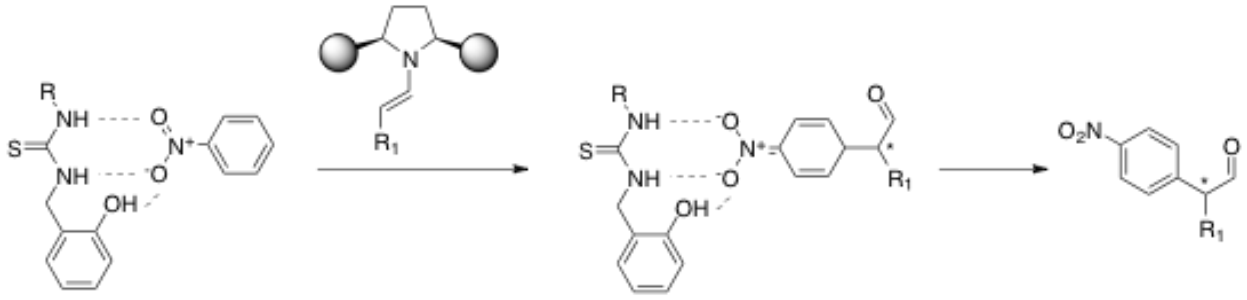

Figure 2: Proposed reaction pathway.

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