Synergistic Catalysis: Highly Enantioselective Acetyl Azaarenes Addition to Enals

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Abstract: We report a novel catalytic enantioselective methodology based on synergistic catalysis for the synthesis of chiral 2-acyl pyridines and pyrazines. The strategy involves the metal Lewis acid activation of acetyl azaarenes and the secondary-amine activation of enals. The proposed mechanism is supported by DFT calculations.

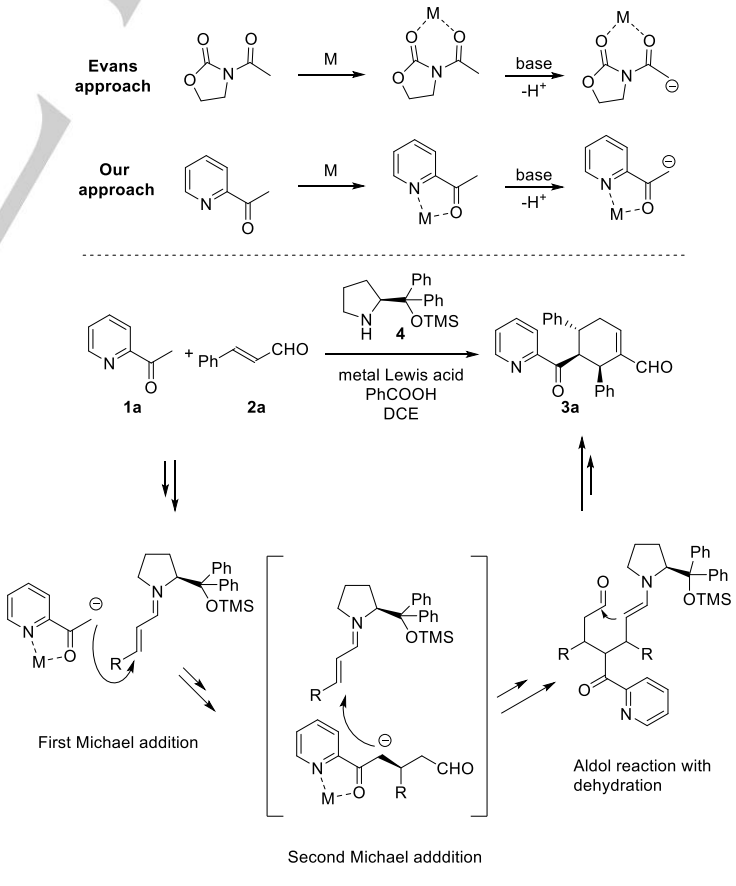
Introduction

In natural products and pharmaceuticals, the presence of pyridines and azaarenes in general is of paramount importance for their biological properties owing to the nature of the nitrogen atom.[1] For this reason, the development of new enantioselective methodologies for the synthesis of chiral molecules containing azaarenes is a valuable and pursued objective in organic chemistry. In this context, in recent years, several research groups have developed new approaches for their synthesis, taking advantage of the possible coordination of the nitrogen atom with Lewis or Brønsted acids.[2] For example, Lam and coworkers reported the activation of azaarenes by increasing their nucleophilicity with chiral Lewis acid complexes, in reactions with nitrostyrenes or imines.[3] Instead, Wei Wang and coworkers reported the use of Brønsted acids to activate azaarenes in a similar fashion.[4] Our research group developed several synergistic approaches for azaarenes' synthesis, combining Lewis acids with secondary amine catalysts or organic Lewis bases.[5] The advantages of synergistic catalysis[6] are that activating the nucleophile and electrophile of a reaction simultaneously by two different catalytic cycles, allows the use of weak nucleophiles and weak electrophiles at the same time, widening the chemical diversity of the reactions.

Results and Discussion

Inspired by the previously mentioned reports, we envisioned the use of 2-acetyl pyridines and pyrazines in a fashion similar to the one used by Evans[7] for the enolate synthesis with acyloxazolidinones (Scheme 1, top). Therefore, we proposed that acetyl azaarenes could coordinate a Lewis metal as bidentate ligand, generating the corresponding enolate. Furthermore, enals react with the chiral secondary amine catalyst forming the iminium ion that reacts with the formed enolate to generate a new C-C bond.

In this paper, we report the first example of enantioselective addition of acetylazaarenes to enals with synergistic catalysis. This catalytic enantioselective methodology affords highly functionalized chiral azaarenes derivatives and may potentially lead to the development of new scaffolds of potentially great interest for agrochemical and pharmaceutical industries. First, we investigated the reaction of 2-acetyl pyridine **1a** and cinnamaldehyde **2a**. With the combination of a metal Lewis acid and secondary amine catalyst, we obtained exclusively the highly functionalized cyclohexene **3a** through a Michael-Michael-aldol cascade reaction (Scheme 1, bottom).



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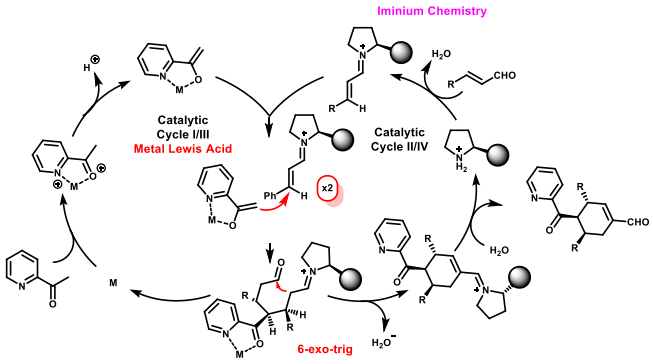
Scheme 1. Previous work and our new synergistic approach with 2-acetyl azaarenes.

The mechanism is shown in Scheme 2. After the initial Michael reaction between the acetylazaarene and the enal, the resulting adduct can form the enolate again and react for the second time with a molecule of enal, followed by an intramolecular aldol reaction through a 6-*exo-trig* cyclization, and subsequent dehydration to afford the final product.



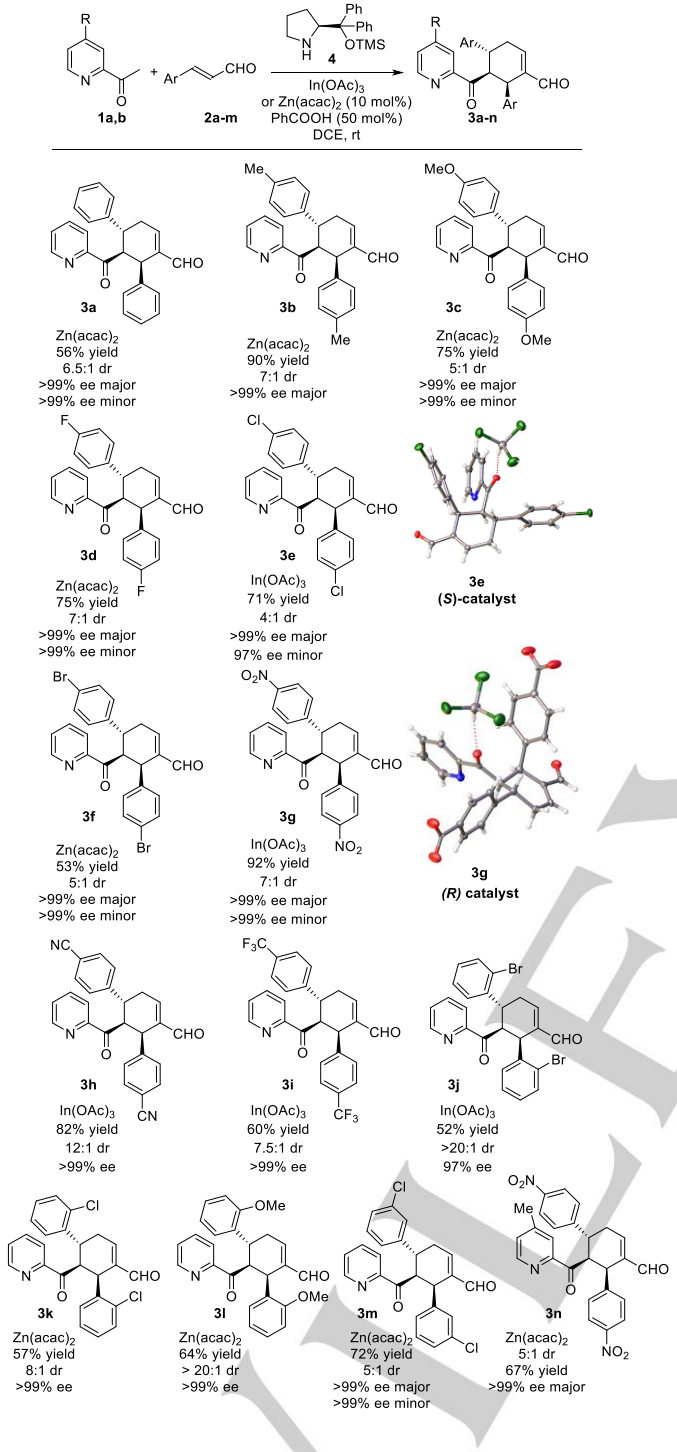
Scheme 2. Proposed mechanism.

Similar cascade reactions have been reported in organocatalytic reactions with malononitriles,[8] oxindoles,[9] benzofuranones,[10] pyrazonoles,[11] quinolines,[12] but this is the first time that this cascade reaction is reported with acetyl azaarenes in a double synergistic catalysis fashion.

After the optimization, we found that the best conditions involve the use of 10 mol% of $In(OAc)_3$ or $Zn(acac)_2$ as the Lewis acid and 20 mol% of OTMS protected diphenylprolinol as secondary amine catalyst in dichloroethane at room temperature, with 50 mol% of benzoic acid as additive.

In^{+3} and Zn^{+2} are close shell metals, the ligand exchange will be faster for this reason. Moreover, when more oxophilic metals were used, 1,2-addition appears as a byproduct, reducing the yield of the reaction drastically (See SI). Generally $Zn(acac)_2$ works better than $In(OAc)_3$; when $Zn(acac)_2$ gave low yields or stereoselectivities, $In(OAc)_3$ was tested and the best of both results are shown in Scheme 2.

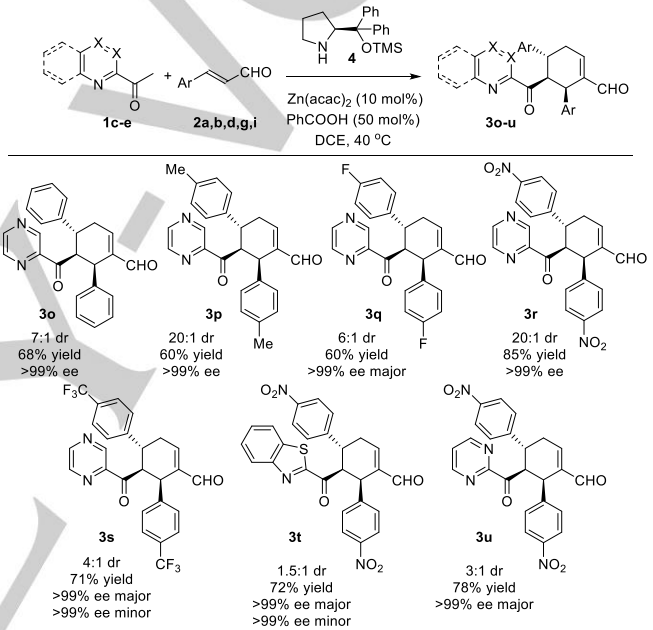
With the optimized conditions in hand, first we studied the scope of the reaction of 2-acetylpyridine with enals (Scheme 3). The product **3a** of the reaction with cinnamaldehyde was obtained in moderate yields and diastereoselectivities and excellent enantioselectivities for both major and minor diastereomers. When the aromatic enal was substituted with an EDG (Me, OMe), the reaction products **3b** and **3c** were obtained with high yields good diastereoselectivities and excellent enantioselectivities. 53-75% yields, up to 7:1 dr and up to >99% ee (**3d-f**) were obtained when 4-halogen substituted aromatic enals were employed. High yields and dr and >99% ee were obtained with EWG 4-substuituted enals (**3g-i**). With the substituent in position 2 of the aromatic ring of the enal, the reaction rendered the products **3j-l** in good yields 8:1->20:1 dr, and excellent enantioselectivities. Similar results but with 5:1 dr, (**3m**) were obtained with a Cl in position 3 of the aromatic ring of the enal. The 4-Me-substituted 2-acetylpyridine, gave the product **3n** in good yield, dr and excellent enantioselectivity.



Scheme 3. Scope of the reaction of 2-acetylpyridines **1a,b** and α,β-unsaturated aldehydes **2a-m**. The dr was determined by analysis of the crude reaction mixture by ^{1}H-NMR. The ee was determined by chiral HPLC.

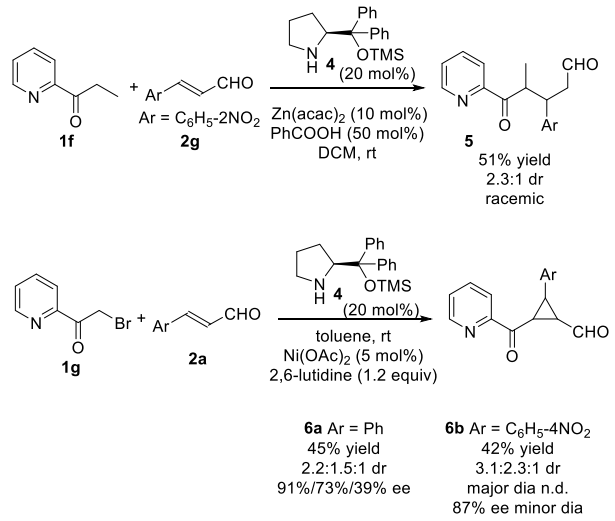
Then, 2-acetylpyrazine was tested in the reaction with aromatic α,β-unsaturated aldehydes (Scheme 4). With EDG, EWG and halogens as substituents on the aromatic ring of the enals, the products **3o-3s** were obtained with good yields (60-85%), good to excellent dr (4:1 to 20:1 dr) and always as enantiopure products (>99% ee). We also tested the reaction with acetylbenzothiophene as azaarene that gave the final product in low dr but high enantioselectivity and yield. Finally, the reaction works with 2-acetylpyrimidine, giving 3:1 dr, high yields and excellent diastereoselectivity.

The relative and absolute configuration of the major diastereomer was confirmed by X-ray crystallography[13] (see ESI), while the same information about the minor diastereomer was inferred by NMR spectroscopy and by TD-DFT simulation of the Electronic Circular Dichroism (ECD) spectra (see ESI).



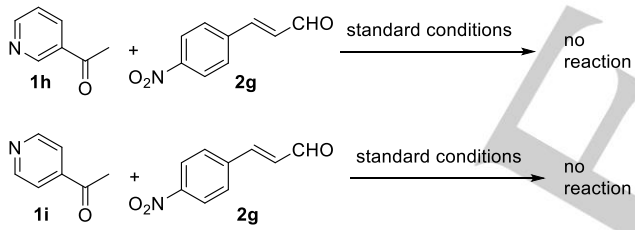
Scheme 4. Scope of the reaction of 2-acetyl azaarenes **1c-e** and α,β-unsaturated aldehydes **2a,b,d,g,i**. The dr was determined by analysis of the crude reaction mixture by ^{1}H-NMR. The ee was determined by chiral HPLC.

Moreover, we studied the scope of the reaction by using substituted 2-propionyl pyridines **1f** (Scheme 5). We expected that the increased bulkiness in the enolate position would allow the formation of the single Michael addition product **5**. As it is shown in Scheme 4, our assumption was correct however, the Michael adduct was obtained in 3% ee and, despite our efforts, it was not possible to increase the enantioselectivities. Finally, we tested the possibility to form cyclopropanes, using 2-(bromoacetyl)pyridine **1g**, moderate yields and enantioselectivities were obtained, probably due to the need of using an external base to trap the HBr formed as byproduct.



Scheme 5. Monoaddition and cyclopropanation

To show the importance of the double coordination between the metal Lewis acid and the *N* and *O* of the acetyl pyridine, we tested the reaction with 3-acetylpyridine **1h**, and 4-acetylpyridine **1i** where a coordination between the metal and the heterocycle is not possible. As expected, no reaction was observed in both cases (Scheme 6).



Scheme 6. Test reactions of 3- and 4-acetyl pyridine **1h,i** and α,β-unsaturated aldehyde **2g**.

A DFT computational study[14] was performed to rationalize the whole catalytic cycle (see ESI for full details). The best geometry obtained for the zinc enolate involves the loss of a ligand from $Zn(acac)_2$, and the coordination of zinc with 2-acetylpyridine with "seesaw" geometry at zinc. The zinc enolate can then approach the iminium ion in an "endo" geometry driven by a more favorable interaction between the HOMO of the enolate and the LUMO of the iminium ion (Figure 1), with the Zinc and the nitrogen of the iminium ion involved in the HOMO-LUMO interaction.

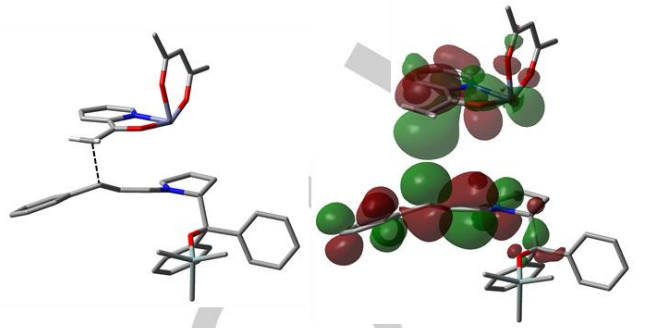


Figure 1. Left: optimized geometry for the addition of the zinc enolate to the iminium ion. Right: shapes of the HOMO of enolate and the LUMO of iminium ion (the distance between the two reagents has been enlarged to show the MOs).

The distance between the two carbons forming the new bond is 2.06 Å (the single imaginary frequency calculated is related to the formation of the C-C bond), with *E* geometry of the iminium ion. This geometry is more stable than the "*exo*" (zinc far from the nitrogen of the iminium ion) by more than 3 kcal/mol, and it accounts for the formation of the *S* enantiomer when *R*-catalyst is used.

The TS involving the second addition is similar to that of the first step (C-C distance 2.05 Å, see the geometries in the ESI), with *E* geometry of the iminium ion. Again the *endo* geometry with zinc over the nitrogen is favored with respect to the *exo*, and the most stable TS involves the attack of the *Re* face of the zinc enolate (Figure 2). This TS forges the second stereocenter with *S*-configuration.

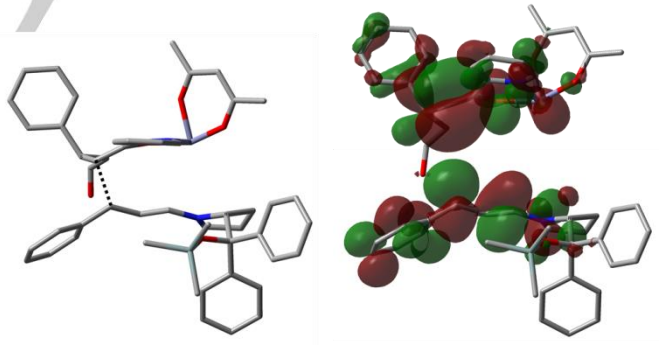
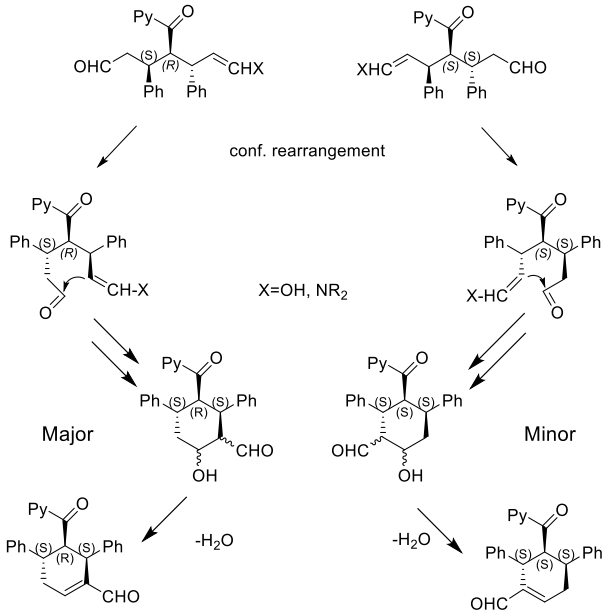


Figure 2. Left: optimized geometry for the addition of the zinc enolate to the iminium ion. Right: shapes of the HOMO of enolate and the LUMO of iminium ion (the distance between the two reagents has been enlarged to show the MOs).

The last step involves the intramolecular aldol reaction. The reaction can take place either on the hydrolyzed bis-aldehyde, or via the enamine resulting from the second addition to the iminium ion (Scheme 7). DFT calculations support the second hypothesis, because the transition state for the addition of the enol to the second CHO moiety cannot be found.



Scheme 7. Transition states by DFT calculations

The two epimers are generated by two different TS where the enamine site can be either in a *syn* relationship with the CO-Py moiety (Scheme 7, left) leading to the *S*,*R*,*S* configuration of the cyclized compound, or in the *anti* relationship (Scheme 7, right) yielding the *S*,*S*,*S* configuration. The first derives from the addition of the *Si* face of the enolate in the second addition, while the second pathway derives from the attack of the *Re* face of the enolate. An explicit molecule of benzoic acid is required in both the two TS to activate the carbonyl towards addition of the enamine.[15]

The origins of the experimentally observed diastereomeric ratio could be found in the second addition step, in the last cyclization step, or in the final dehydration. In the first hypothesis, the second addition would be the rate-determining step, while in the second option the cyclization TS determines the final diastereomeric ratio. DFT calculations suggest that the relative energies of the two TSs yielding the two diastereomers in the intramolecular cyclization well reproduces the experimental ratio (7.6:1 *vs* the experimental 6.5:1 of **3a**, see ESI for details). On the contrary, the calculated energies of the TS in the second addition step would drive the reaction toward the opposite diastereomeric ratio. However, since no intermediates were observed during the reactions, the last hypothesis where dehydration is the driving force of the whole reaction is the more plausible.[9]

Conclusions

In summary, we have developed a new methodology for the synthesis of chiral 2-acetyl pyridines and pyrazines, based on the concept of synergistic catalysis. For first time, the metal activation of 2-acetyl azaarenes was combined with an organocatalytic cascade reaction, pushing the boundaries of this synergistic approach, forming chiral cyclohexenes derivatives with three consecutive chiral centers by a double synergistic Michael addition followed by intramolecular aldol reaction with dehydration. Two different catalytic cycles, (i) the metal Lewis acid activation of 2-acetyl azaarenes and (ii) the secondary amine activation of enals, synergistically worked to afford the final products in high yields, high diastereoselectivity and with 97->99% *ee* in all the examples. We proved the importance of the proposed bidentate coordination of the metal Lewis acid with 2-acetylpyridine, to afford the final compounds. DFT calculations suggest that zinc coordination has a key role also in the addition of the enolate to iminium ion by favoring the interaction of the HOMO of the enolate with the LUMO of the iminium ion.

Experimental Section

In a screw cap vial were added in this sequence: the organic catalyst 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (20 mol%), the α,β-unsaturated aldehyde (2 equiv), acetyl pyridine or acetyl pyrazine (0.1 mmol, 1 equiv), $Zn(acac)_2$ or $In(OAc)_3$ (10 mol%), benzoic acid (50 mol%) and dichloroethane (1.5 ml). The reaction mixture was stirred at room temperature and followed by NMR, then concentrated *in vacuo*. The crude mixture was purified by silica-gel flash column chromatography (hexane/EtOAc) to obtain the desired product.

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Keywords: synergistic catalysis • secondary amine catalysis • Michael addition • acetyl azaarenes • enals

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Layout 1:

FULL PAPER

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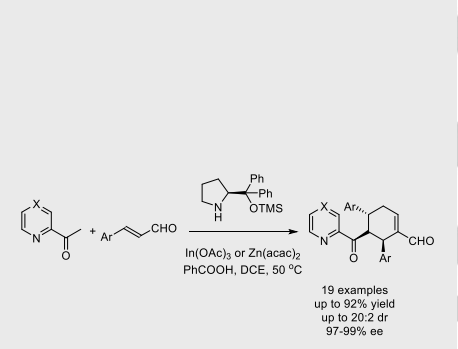

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