

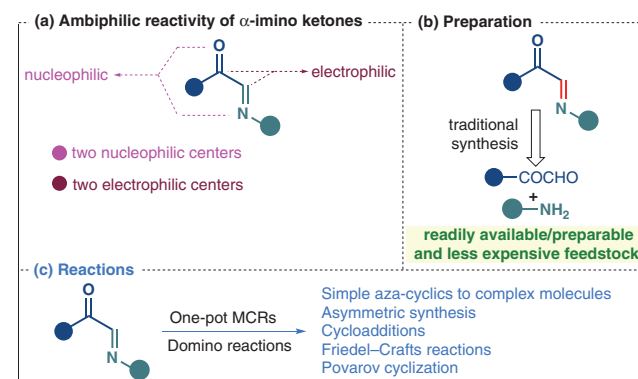
# Synthetic Organic Chemistry of $\alpha$ -Imino Ketones: A Graphical Review

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**Abstract**  $\alpha$ -Imino ketones are traditionally synthesized through condensing simple and readily available  $\alpha$ -keto aldehydes or 1,2-diketones with primary or secondary amines. They are structurally similar to many naturally occurring biological substances due to the presence of the imino group ( $-C=N-$ ). Chemically, *C*-acylimines exhibit ambiphilic reactivity, making their synthetic chemistry particularly attractive and viable for the creation of various aza-cyclic and heterocyclic compounds, including their asymmetric counterparts. Consequently, numerous synthetic strategies have been developed starting from these building blocks. Herein, we provide a graphical review of state-of-the-art synthetic efforts over the past 20 years, focusing on the use of  $\alpha$ -imino ketones (both cyclic and acyclic) for the synthesis of small molecules and complex systems.

**Key words**  $\alpha$ -imino ketones, *C*-acylimines, ambiphilic reactivity, cycloadditions, annulations, asymmetric synthesis

Sustainable synthesis is one of the key concerns for synthetic organic chemists. Amongst several factors, initiating chemical synthesis from readily available and inexpensive starting materials through one-pot, multicomponent approaches contribute significantly to sustainable syn-

thesis. Such reactions are particularly important in the chemical industry because they facilitate scale-up and large-scale synthesis with relative ease.  $\alpha$ -Imino ketones, also known as *C*-acylimines, are key building blocks in organic synthesis.

Traditionally,  $\alpha$ -imino ketones are synthesized from inexpensive  $\alpha$ -keto aldehydes or 1,2-diketones and amines through removal of water via simple mixing under various conditions. Additionally, several other methods have been developed, such as NHC-catalyzed arylation of aromatic aldehydes with imidoyl chlorides<sup>1</sup> and nitrosobenzene-mediated carbon-carbon bond cleavage using LHMDS.<sup>2</sup> However, in this graphical review, we will focus on the synthetic applications of  $\alpha$ -imino ketones rather than their synthesis. It is worth noting that the structure of  $\alpha$ -imino ketones resemble those of certain natural biological substances due to the presence of the imino group ( $-C=N-$ ), which allows these substrates to be converted into biologically relevant  $\beta$ -amino alcohols in a one-pot process.<sup>3</sup> The structure of  $\alpha$ -imino ketones includes both imine and ketone functionalities in conjugation, resembling a conjugated ketone where the  $\beta$ -carbon of a 1,4-enone is replaced with nitrogen in  $\alpha$ -imino ketones. This modification results in completely different reactivity for *C*-acylimines; while 1,4-enones can undergo both 1,2-addition and 1,4-conjugate addition depending on the reaction conditions, *C*-acylimines cannot participate in conjugate addition, though direct 1,2-addition is possible. More intriguingly, the  $\alpha$ -carbon in these substrates demonstrates umpolung reactivity. Thus, they exhibit ambiphilic reactivity, with the two heteroatoms (oxygen and nitrogen) displaying nucleophilic characteristics and the two carbons (the carbonyl carbon and the imine carbon) showing electrophilic properties. Due to these unique reactivity patterns, numerous synthetic groups have utilized  $\alpha$ -imino ketones as key precursors for constructing aza-(hetero)cyclic compounds.

## Biographical Sketches



**Abhishek Pareek** was born in Badayali, a village in the Nagaur District of Rajasthan, India. He completed his master's degree at Jai Narain Vyas University in Jodhpur, after which he pursued his Ph.D. at the Central University of

Rajasthan under the mentorship of Prof. Srinivasarao Yaragorla. He subsequently moved to the University of Warsaw in Poland, where he worked as a postdoctoral fellow on the Morita–Baylis–Hillman (MBH) reaction with Dr.

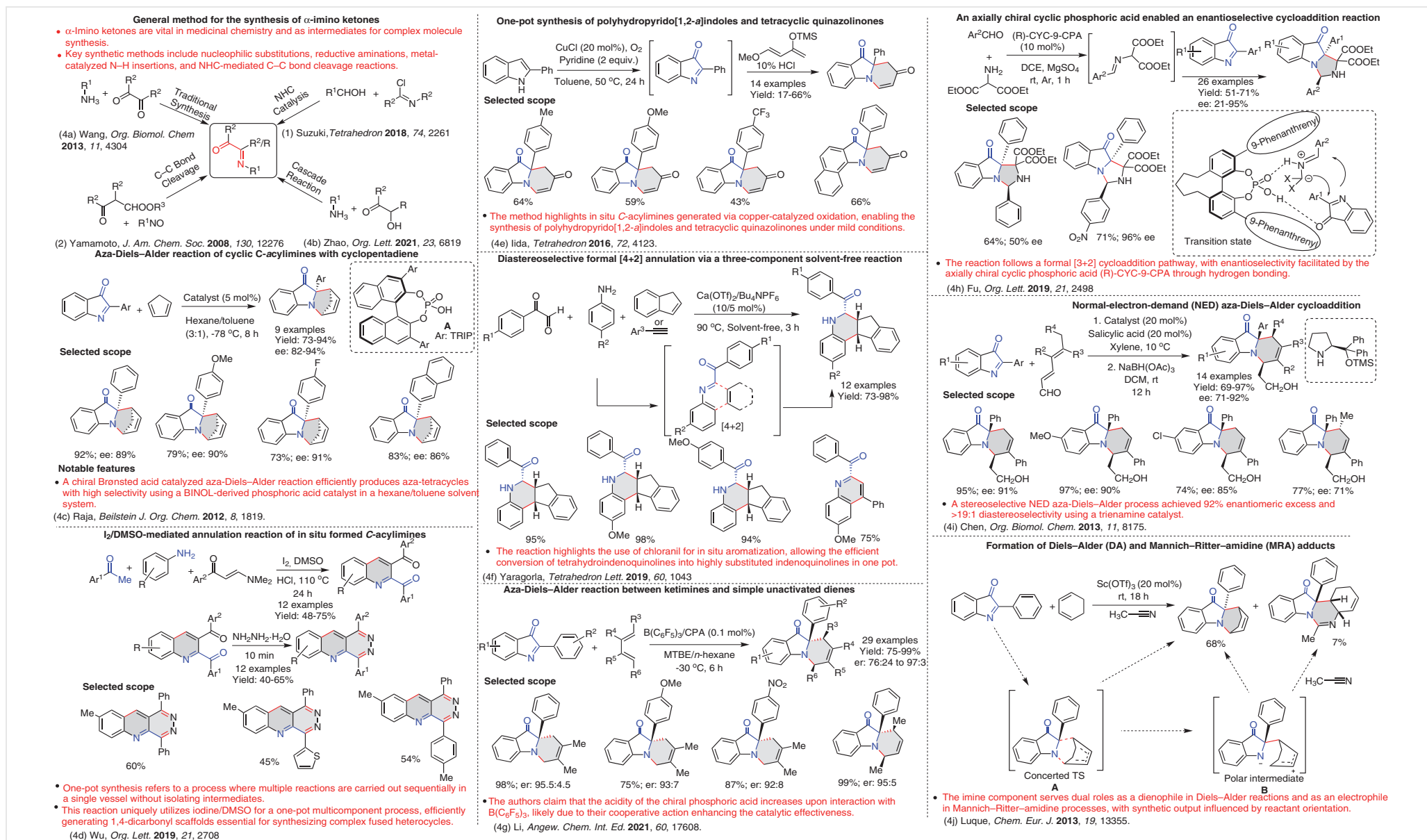
Marcin Kalek. Currently, he is continuing his research at the Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, under the supervision of Dr. Przemyslaw Gawel, focusing on the synthesis of novel optoelectronic materials.

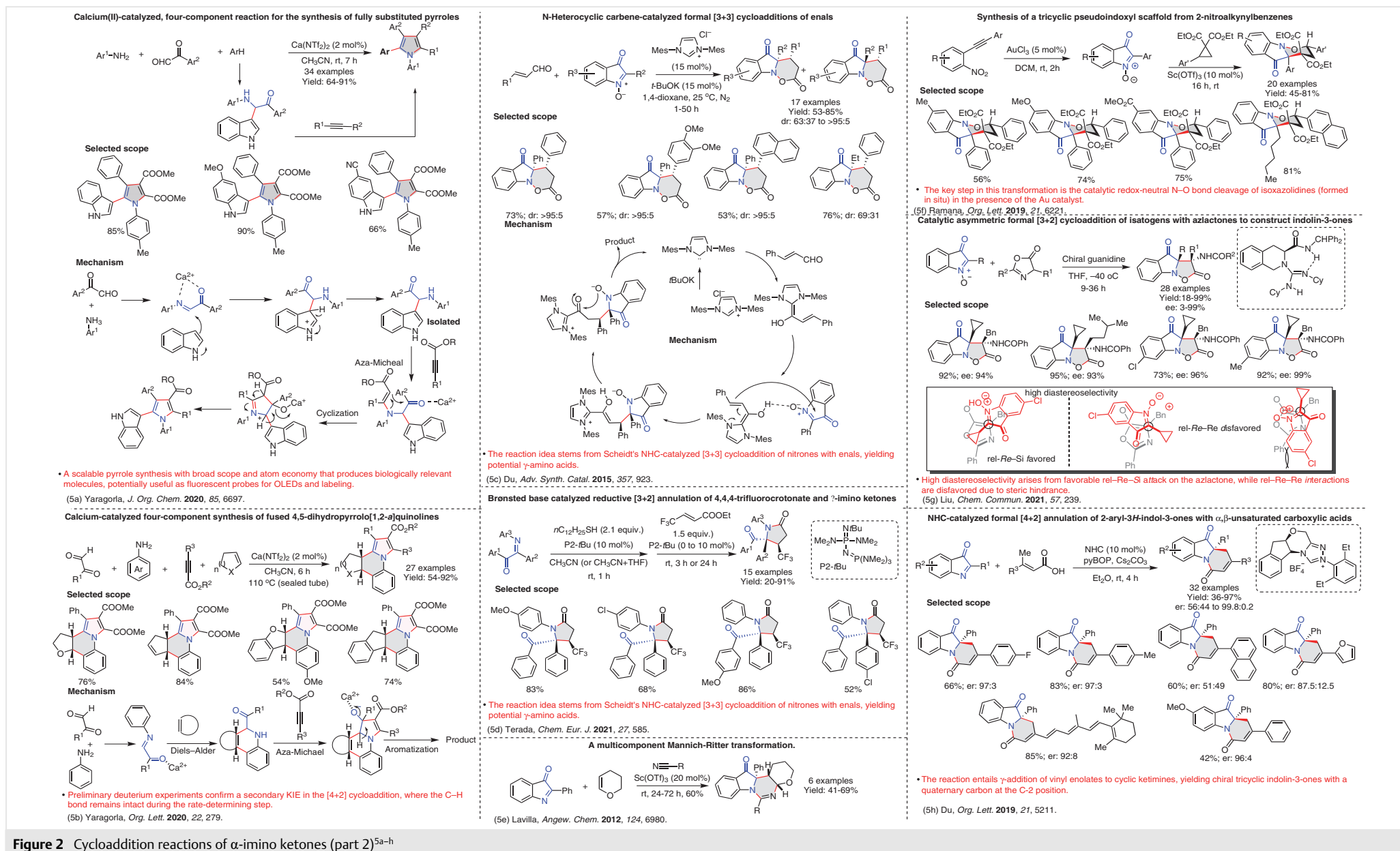


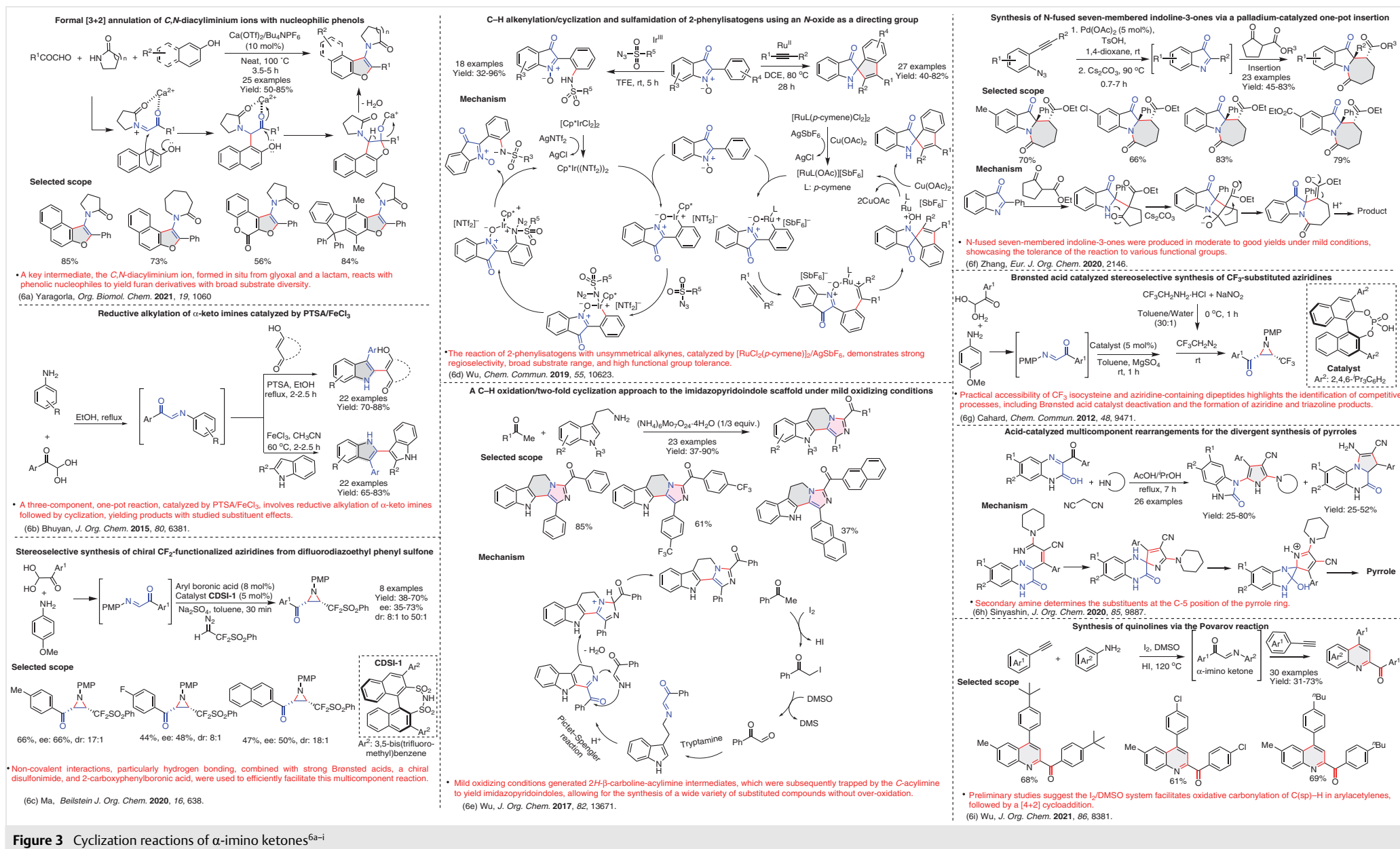
**Srinivasarao Yaragorla** was born in the village of Sitharamapuram in Telangana state, India. He obtained his master's degree (M.Sc.) in chemistry from the University of Hyderabad and his Ph.D. (2008) from the Indian Institute of Chemical Technology (IICT), Hyderabad. He subsequent-

ly undertook postdoctoral studies at the University of Minnesota, USA, and the University of Hyderabad. He then started his independent research career as an assistant professor at the Central University of Rajasthan. Currently, he is a full professor at the University of Hyderabad. His re-

search interests are focused on the cyclizative functionalization of alkynols via allenes, C–H functionalization, multicomponent reactions of  $\alpha$ -imino ketones, the Heyns rearrangement and mechanochemistry.

Figure 1 Cycloaddition reactions of  $\alpha$ -imino ketones (part 1)<sup>1,2,4a-j</sup>

Figure 2 Cycloaddition reactions of  $\alpha$ -imino ketones (part 2)<sup>5a-h</sup>

Figure 3 Cyclization reactions of  $\alpha$ -imino ketones<sup>6a-i</sup>

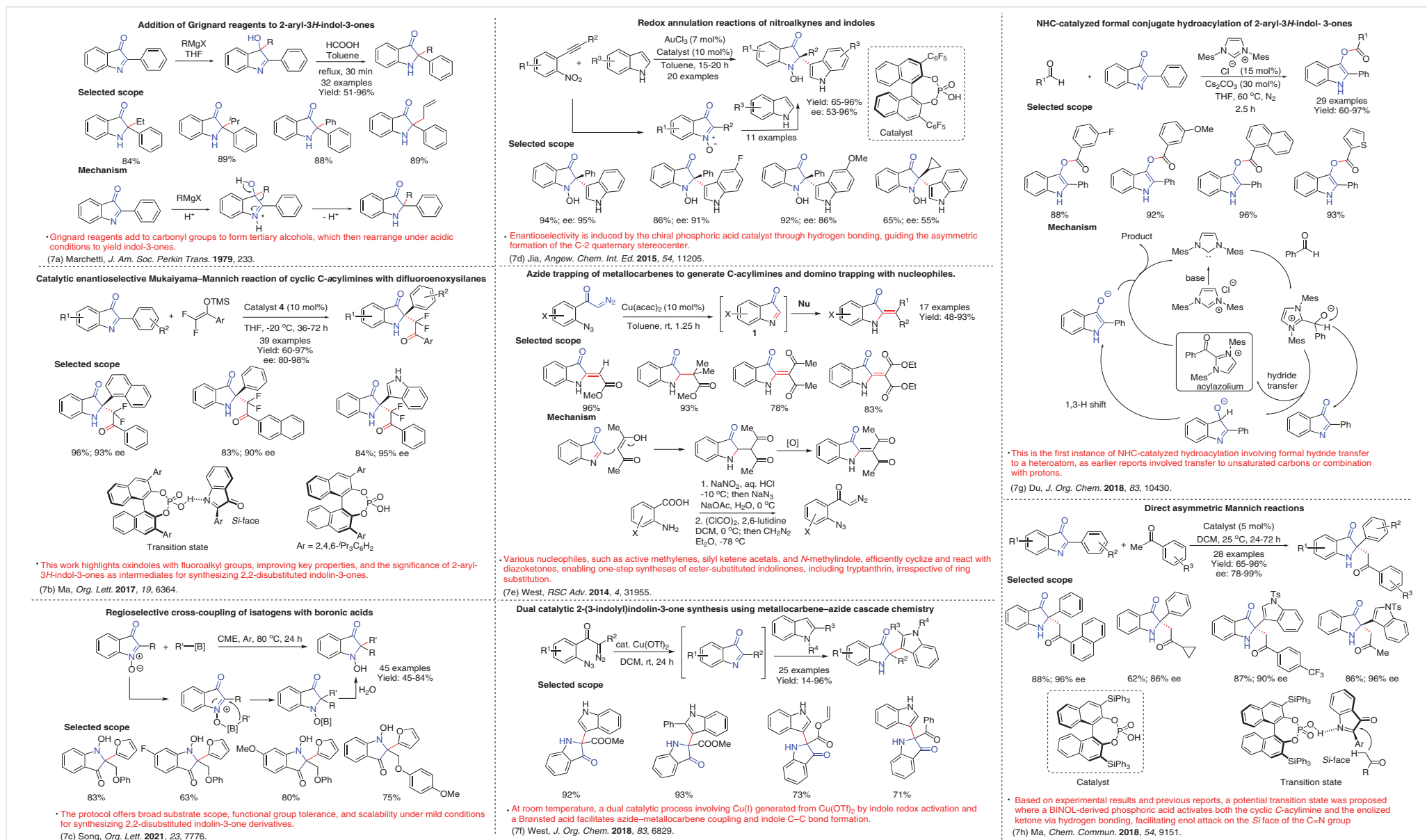
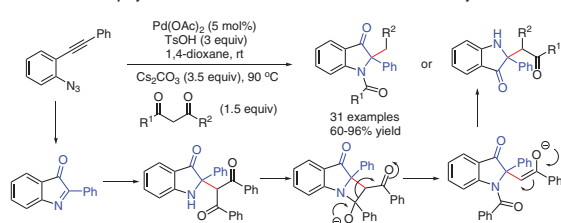


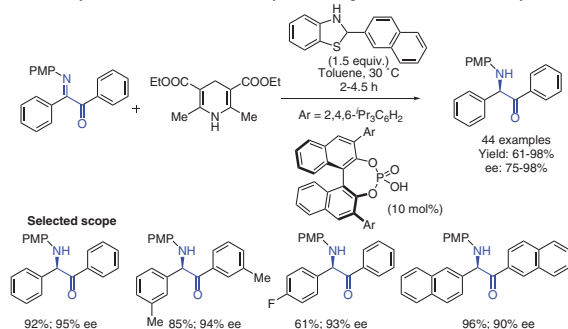
Figure 4 Formation of C–C bonds using  $\alpha$ -imino ketones<sup>7a–h</sup>

### Formation of polyfunctional indolin-3-ones via insertion reactions of C-acylimines



• These findings were very well supported by performing control and cross-over experiments.  
(8a) Zhang, *Adv. Synth. Catal.* **2019**, *361*, 201.

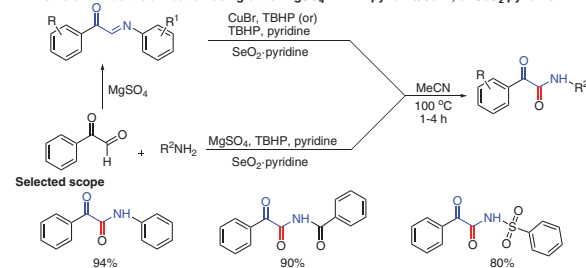
### Asymmetric imine reduction of C-acylimines using a chiral Brønsted acid catalyst



• This methodology was applicable to both symmetrical and unsymmetrical diaryl  $\alpha$ -ketoketimines, including arylalkyl- and dialkyl-substituted diketones.

(8b) Madras, *J. Med. Chem.* **2006**, *49*, 1420.

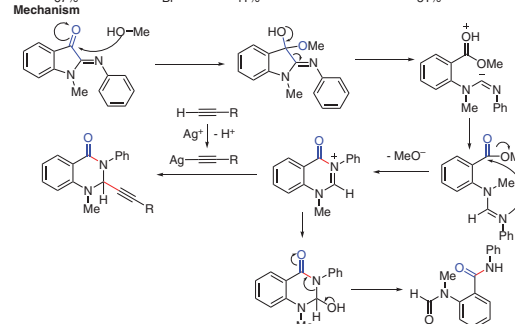
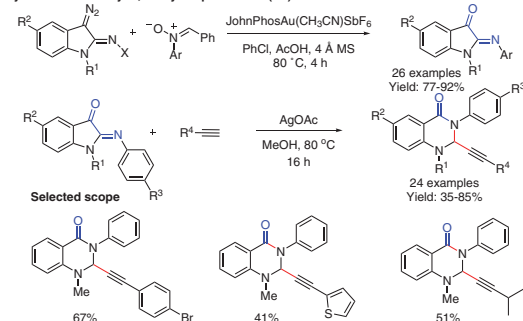
### An efficient oxidative amidation using either MgSO<sub>4</sub>-TBHP-pyridine/CuBr, or SeO<sub>2</sub>-pyridine



• Mechanistic studies suggest that  $\alpha$ -carbonylimine compounds play a central role by increasing the electrophilicity of the C=N system, facilitating oxidant attack (TBHP or SeO<sub>2</sub>) and leading to formation of the desired products in good yields.

(8c) Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 5803.

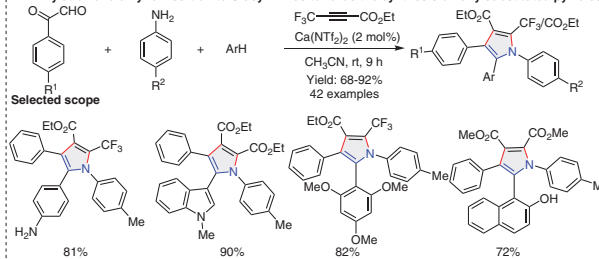
### Synthesis of 2-alkynyl-2,3-dihydroquinazolin-4(1*H*)-ones from 3-diazoindolin-2-imines



• The nitrene operates as an oxygen-transfer reagent and an aniline source.

(8d) Wang, *J. Org. Chem.* **2020**, *85*, 11766.

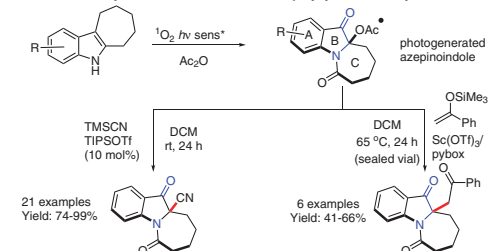
### Arylation and alkyne insertion to C-acylimines towards the synthesis of fully substituted pyrroles



• This regiodivergent pyrrole synthesis involves C2-arylation with arenes (indole, pyrrole, phenols) via in situ C-acylimine formation, followed by aza-Michael addition, cyclization, with confirmed scalability through a gram-scale synthesis, leading to a biologically relevant molecule

(8e) Yaragorla, *Synthesis*, **2023**, *55*, 1298.

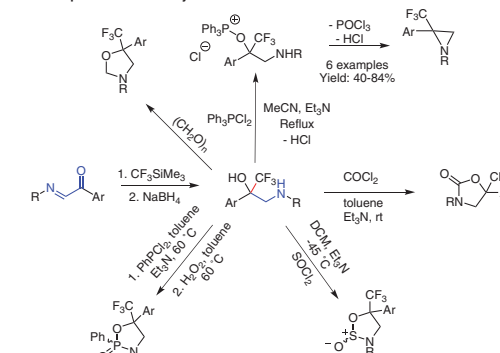
### Lewis acid catalyzed carbofunctionalization of polycyclic C,N-diazylium ions



• Regio- and enantioselective asymmetric alkylations with silyl enol ethers were accomplished using Sc(OTf)<sub>3</sub>/pybox complexes as a chiral catalyst system.

(8f) Brasholz, *Org. Lett.* **2021**, *23*, 7834.

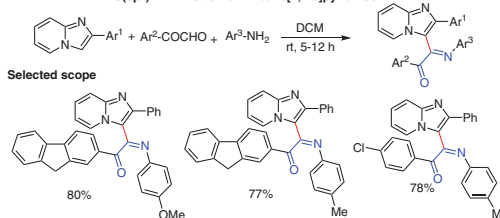
### Nucleophilic trifluoromethylation of $\alpha$ -imino ketones and further transformations



(8g) Heimgartner, *Helv. Chim. Acta* **2010**, *93*, 1725.

(8h) Carreira, *Org. Lett.* **2012**, *14*, 1900.

### C(sp<sup>2</sup>)-H imination of imidazo[1,2-a]pyridines



• The reaction demonstrated good substrate tolerance with high yields. A gram-scale synthesis along with post-synthetic modifications to produce 1,2-diketones are also reported.

(8i) Yaragorla, *Eur. J. Org. Chem.* **2024**, *27*, e202400178.

Figure 5 Other reactions of  $\alpha$ -imino ketones<sup>8a-i</sup>

## Conflict of Interest

The authors declare no conflict of interest.

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