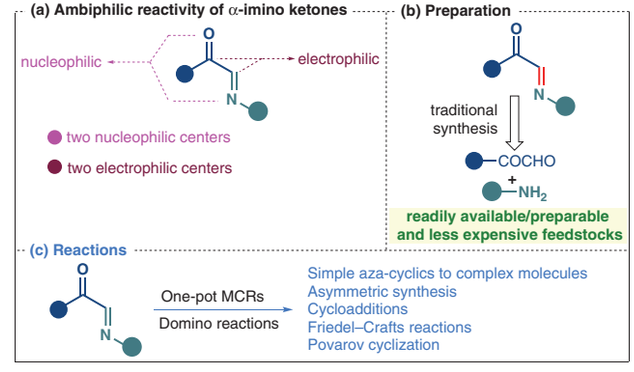
Synthetic Organic Chemistry of α-Imino Ketones: A Graphical Review

Abhishek Pareek[a]
Srinivasarao Yaragorla*[b]

[a] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
[b] School of Chemistry, University of Hyderabad, P.O. Central University, Gachibowli, Hyderabad, 500046, Telangana, India
srinivas.yaragorla@uohyd.ac.in



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Abstract α-Imino ketones are traditionally synthesized through condensing simple and readily available α-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 (–N=C–). 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 α-imino ketones (both cyclic and acyclic) for the synthesis of small molecules and complex systems.

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

Traditionally, α-imino ketones are synthesized from inexpensive α-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 aroylation of aromatic aldehydes with imidoyl chlorides[1] and nitrosobenzene-mediated carbon–carbon bond cleavage using LHMDS.[2] However, in this graphical review, we will focus on the synthetic applications of α-imino ketones rather than their synthesis. It is worth noting that the structure of α-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 β-amino alcohols in a one-pot process.[3] The structure of α-imino ketones includes both imine and ketone functionalities in conjugation, resembling a conjugated ketone where the β-carbon of a 1,4-enone is replaced with nitrogen in α-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 α-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 α-imino ketones as key precursors for constructing aza-(hetero)cyclic compounds.

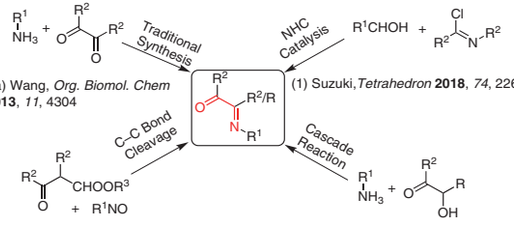
Biographical Sketches

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 subsequently 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 research interests are focused on the cyclizative functionalization of alkynols via allenes, C–H functionalization, multicomponent reactions of α-imino ketones, the Heyns rearrangement and mechanochemistry.

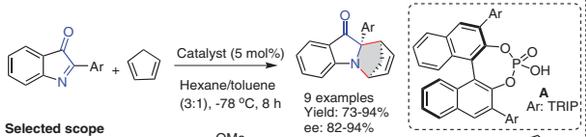
General method for the synthesis of α-imino ketones

- α-Imino ketones are vital in medicinal chemistry and as intermediates for complex molecule synthesis.
- Key synthetic methods include nucleophilic substitutions, reductive aminations, metal-catalyzed N–H insertions, and NHC-mediated C–C bond cleavage reactions.



(4a) Wang, *Org. Biomol. Chem* **2013**, *11*, 4304 (1) Suzuki, *Tetrahedron* **2018**, *74*, 2261 (2) Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 12276 (4b) Zhao, *Org. Lett.* **2021**, *23*, 6819

Aza-Diels–Alder reaction of cyclic C-acylimines with cyclopentadiene



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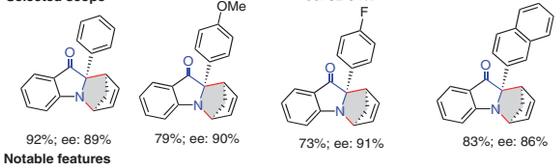
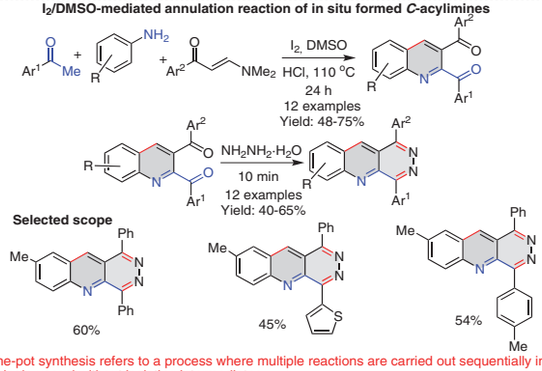


Notable features

- A chiral Brønsted acid catalyzed aza-Diels–Alder reaction efficiently produces aza-tetracycles with high selectivity using a BINOL-derived phosphoric acid catalyst in a hexane/toluene solvent system.

(4c) Raja, *Beilstein J. Org. Chem.* **2012**, *8*, 1819.

I_2/DMSO-mediated annulation reaction of in situ formed *C*-acylimines



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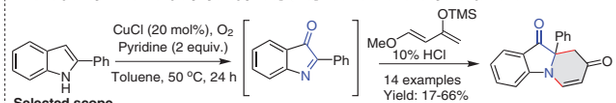
- One-pot synthesis refers to a process where multiple reactions are carried out sequentially in a single vessel without isolating intermediates.
- This reaction uniquely utilizes iodine/DMSO for a one-pot multicomponent process, efficiently generating 1,4-dicarbonyl scaffolds essential for synthesizing complex fused heterocycles.

(4d) Wu, *Org. Lett.* **2019**, *21*, 2708

One-pot synthesis of polyhydropyrido[1,2-*a*]indoles and tetracyclic quinazolinones



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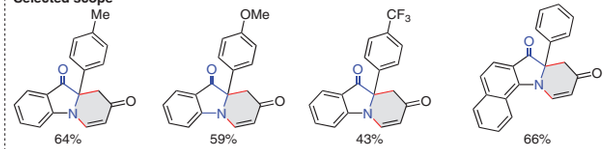
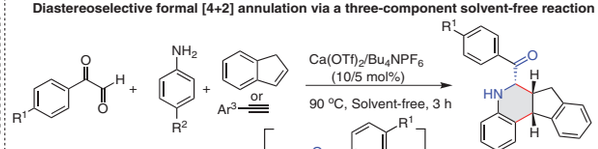


- The method highlights in situ *C*-acylimines generated via copper-catalyzed oxidation, enabling the synthesis of polyhydropyrido[1,2-*a*]indoles and tetracyclic quinazolinones under mild conditions.

(4e) Iida, *Tetrahedron* **2016**, *72*, 4123.

Diastereoselective formal [4+2] annulation via a three-component solvent-free reaction



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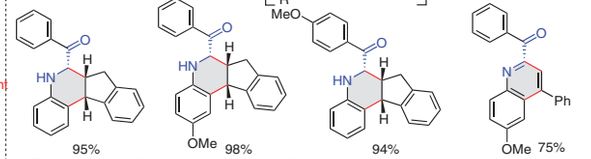
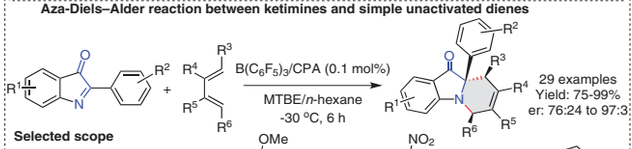


- The reaction highlights the use of chloranil for in situ aromatization, allowing the efficient conversion of tetrahydroindenoquinolines into highly substituted indenoquinolines in one pot.

(4f) Yaragorla, *Tetrahedron Lett.* **2019**, *60*, 1043

Aza-Diels–Alder reaction between ketimines and simple unactivated dienes



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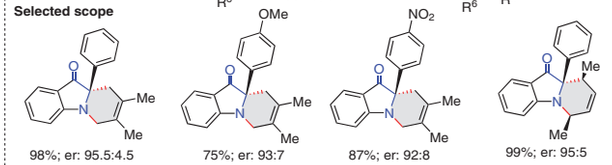
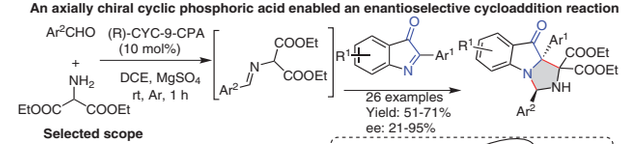


- The authors claim that the acidity of the chiral phosphoric acid increases upon interaction with $B(C_6F_5)_3$, likely due to their cooperative action enhancing the catalytic effectiveness.

(4g) Li, *Angew. Chem. Int. Ed.* **2021**, *60*, 17608.

An axially chiral cyclic phosphoric acid enabled an enantioselective cycloaddition reaction



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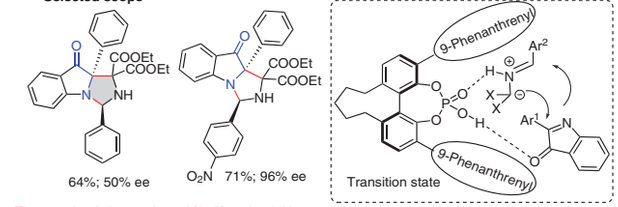
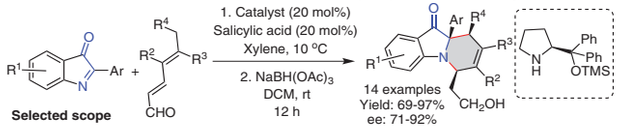


- The reaction follows a formal [3+2] cycloaddition pathway, with enantioselectivity facilitated by the axially chiral cyclic phosphoric acid (R)-CYC-9-CPA through hydrogen bonding.

(4h) Fu, *Org. Lett.* **2019**, *21*, 2498

Normal-electron-demand (NED) aza-Diels–Alder cycloaddition



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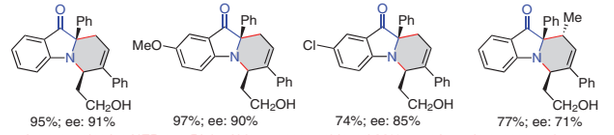
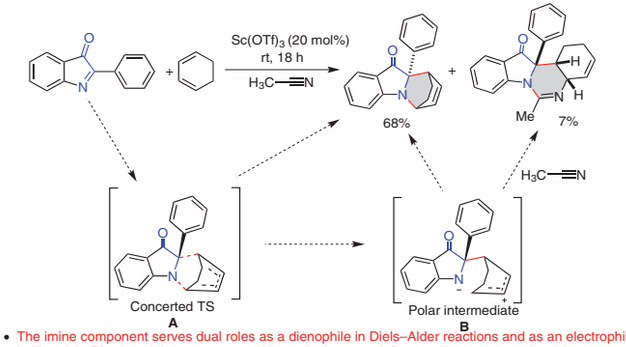


- A stereoselective NED aza-Diels–Alder process achieved 92% enantiomeric excess and >19:1 diastereoselectivity using a trienamine catalyst.

(4i) Chen, *Org. Biomol. Chem.* **2013**, *11*, 8175.

Formation of Diels–Alder (DA) and Mannich–Ritter–amidine (MRA) adducts



- The imine component serves dual roles as a dienophile in Diels–Alder reactions and as an electrophile in Mannich–Ritter–amidine processes, with synthetic output influenced by reactant orientation.

(4j) Luque, *Chem. Eur. J.* **2013**, *19*, 13355.

Figure 1 Cycloaddition reactions of α-imino ketones (part 1)[1,2,4a–j]

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

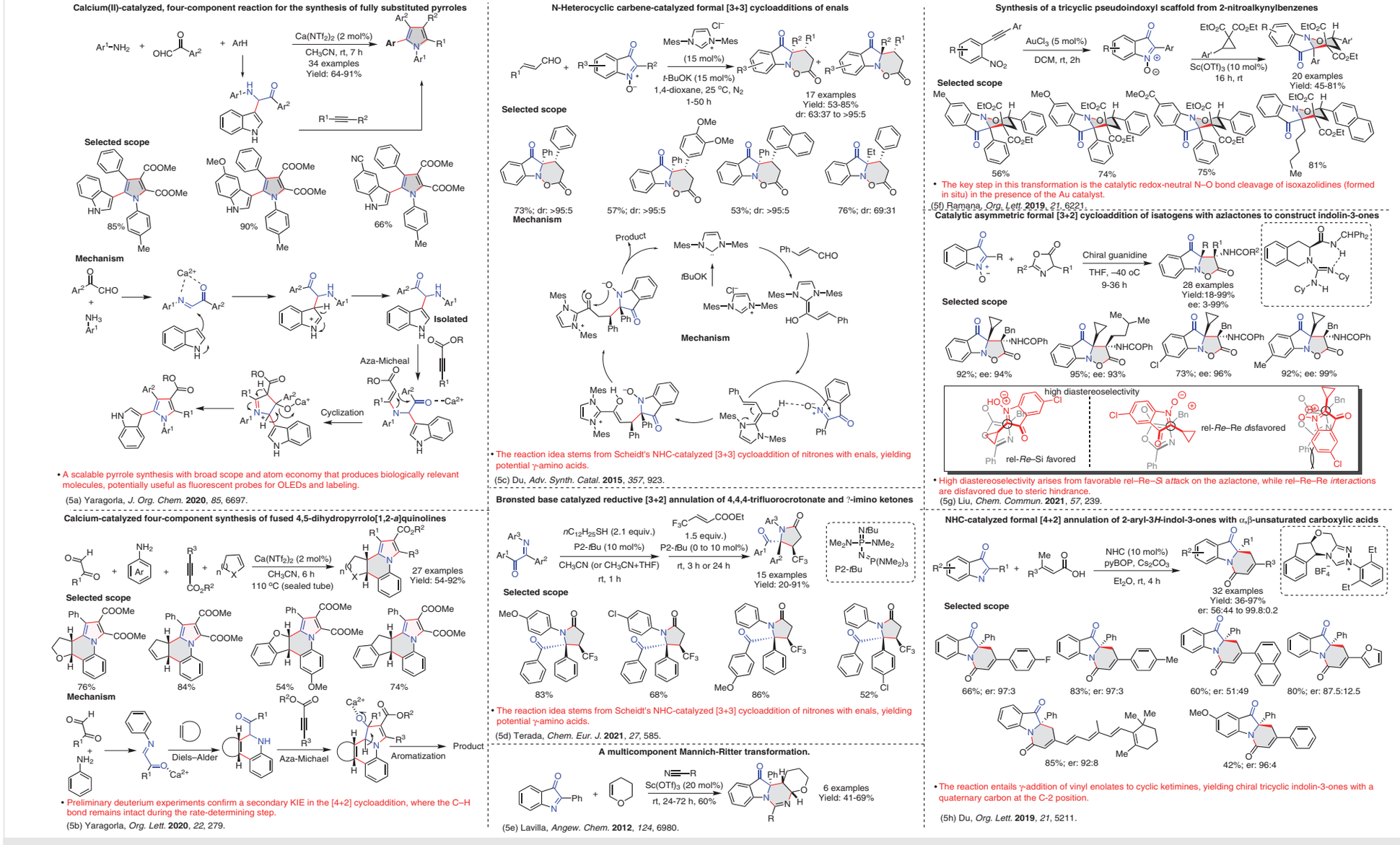


Figure 2 Cycloaddition reactions of α-imino ketones (part 2)[5a–h]

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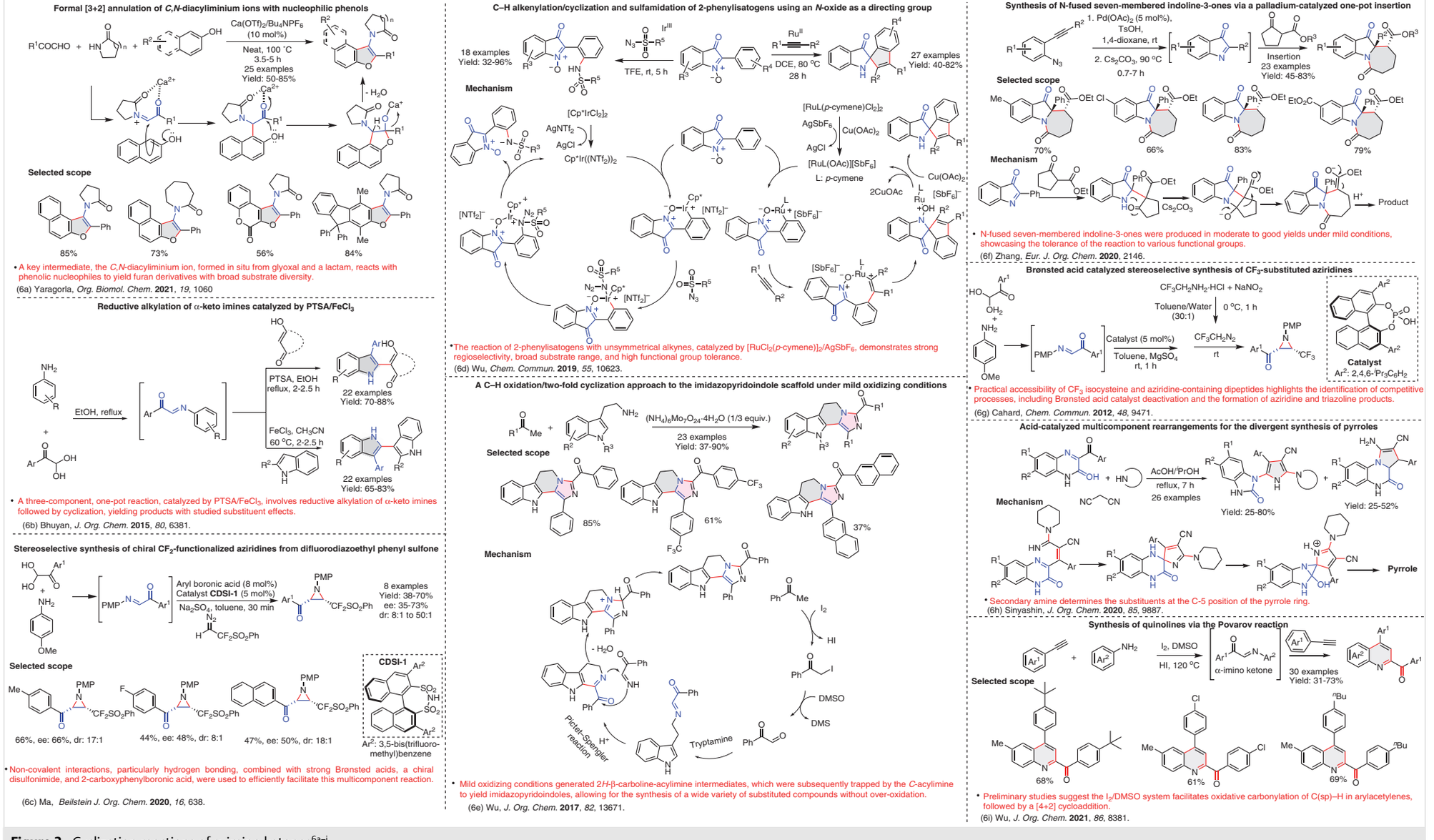

Figure 3 Cyclization reactions of α-imino ketones[6a–i]

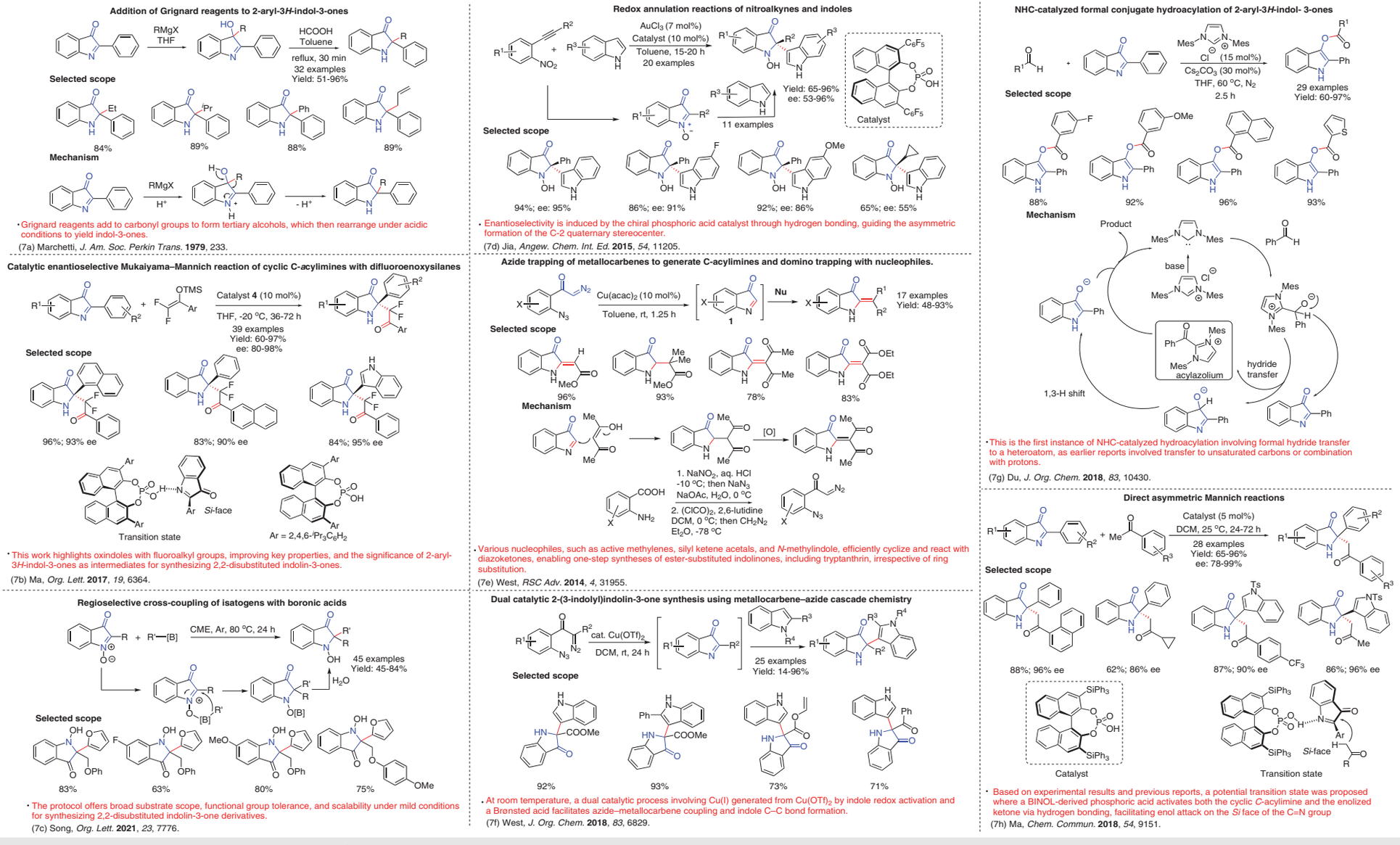

Figure 4 Formation of C–C bonds using α-imino ketones[7a–h]

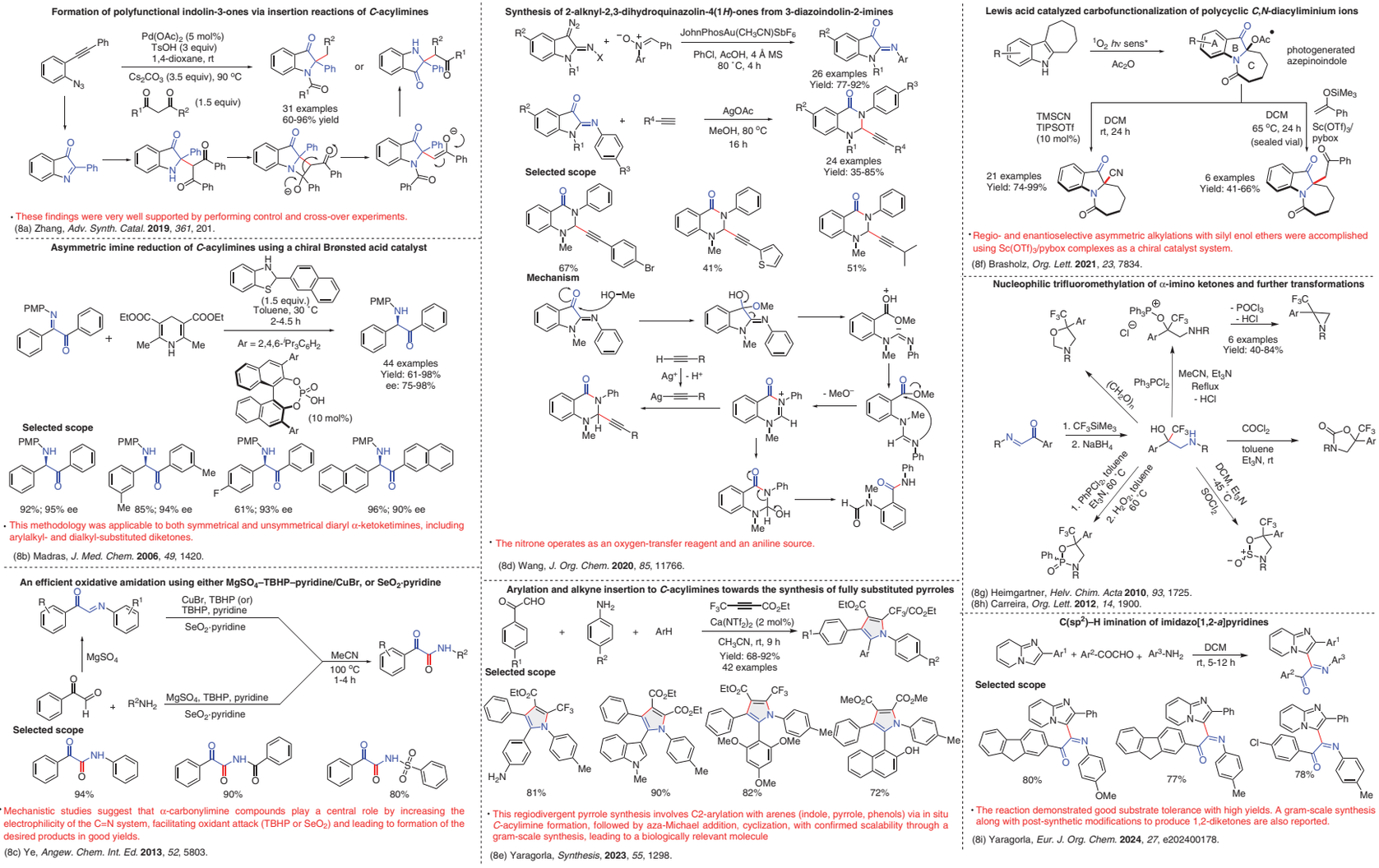

Figure 5 Other reactions of α-imino ketones[8a–i]

Conflict of Interest

The authors declare no conflict of interest.

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