catalysts

Review

α-Functionalization of Imines via Visible Light Photoredox Catalysis

Alberto F. Garrido-Castro [1], **M. Carmen Maestro** [1,*] and **José Alemán** [1,2,*]

[1] Department of Organic Chemistry, Universidad Autónoma de Madrid, 28049 Madrid, Spain; albertof.garrido@uam.es
[2] Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain
* Correspondence: carmen.maestro@uam.es (M.C.M.); jose.aleman@uam.es (J.A.); Tel.: +34914973875 (J.A.)

Received: 6 May 2020; Accepted: 16 May 2020; Published: 19 May 2020

Abstract: The innate electrophilicity of imine building blocks has been exploited in organic synthetic chemistry for decades. Inspired by the resurgence in photocatalysis, imine reactivity has now been redesigned through the generation of unconventional and versatile radical intermediates under mild reaction conditions. While novel photocatalytic approaches have broadened the range and applicability of conventional radical additions to imine acceptors, the possibility to use these imines as latent nucleophiles via single-electron reduction has also been uncovered. Thus, multiple research programs have converged on this issue, delivering creative and practical strategies to achieve racemic and asymmetric α-functionalizations of imines under visible light photoredox catalysis.

Keywords: amines; imines; photoredox catalysis; radical additions; radical–radical couplings; stereoselectivity; umpolung chemistry; visible light

---

1. Introduction

Visible light photoredox catalysis has been at the forefront of organic chemistry research for over a decade, establishing itself as a sustainable and multifaceted synthetic tool [1]. Irradiation of catalytic amounts of polypyridyl complexes and organic sensitizers under mild conditions has proven to be an excellent activation pathway to access a wide variety of radical intermediates (Figure 1). Spurred by this resurgence, long-standing challenges in the field have been resolved, while a plethora of transformations continue to be developed in an effort to revamp organic synthesis.

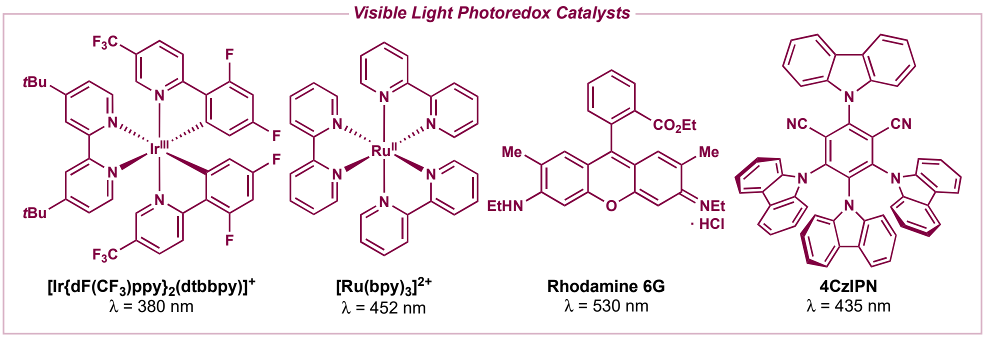
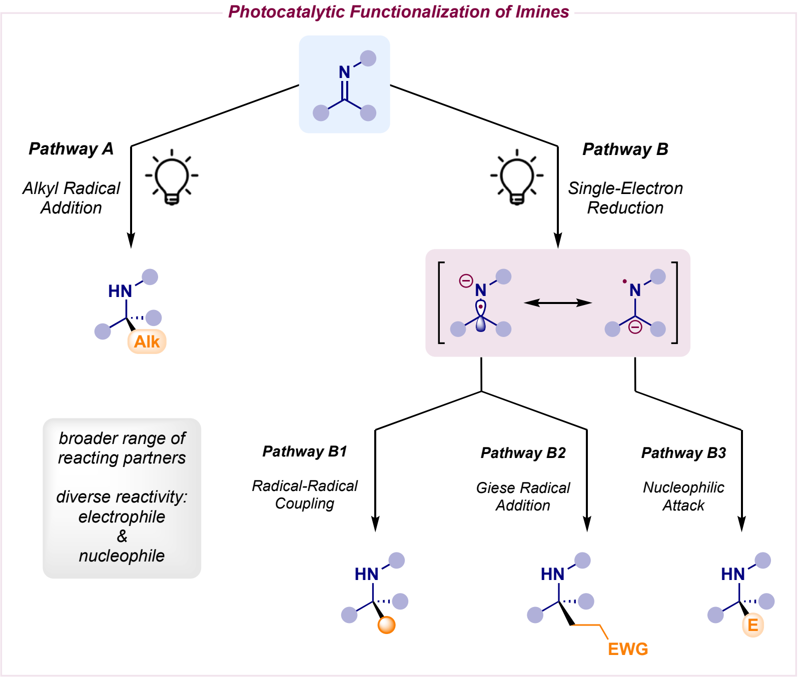


Figure 1. Visible light photoredox catalysts (λ = local absorbance maximum for lowest energy absorption).

The reactivity of imines has certainly undergone a complete makeover, as different strategies involving these key building blocks have been developed (Scheme 1). The classical approach still relies on the innate electrophilic nature of imines to undergo standard alkyl radical addition (pathway A in Scheme 1, left). Thanks to photoredox catalysis, the generation of nucleophilic radicals starting from mild alkylating reagents [2] has provided a broader range to a severely limited transformation in the past due to hazardous reagents and impractical conditions.



Scheme 1. Photocatalytic functionalization of imines: pathway A, alkyl radical addition (left); pathway B, single-electron reduction (right).

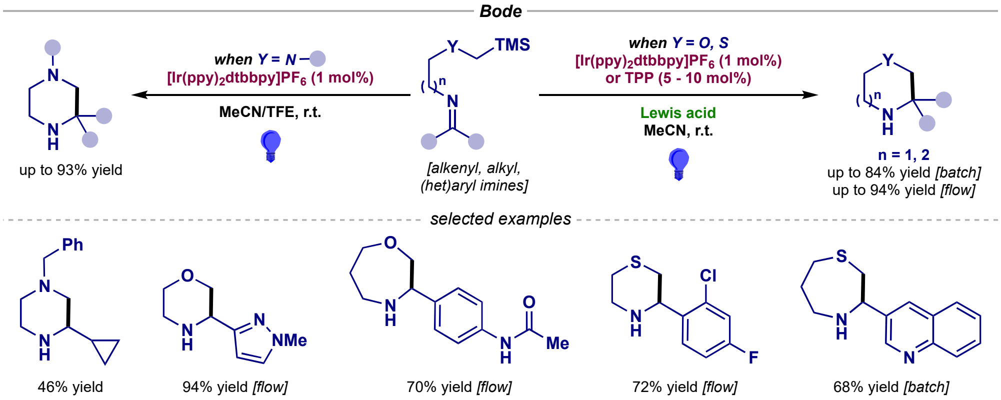
Alternatively, the photocatalytic single-electron reduction of imines has emerged as a powerful technology to generate radical anion intermediates which exist as two different resonant forms (pathway B in Scheme 1, right) [3,4]. The α-amino radical species can engage in radical–radical couplings with a large pool of reacting partners (pathway B1 in Scheme 1), while also displaying a complementary nucleophilic behavior to their corresponding electrophilic imine precursors. Indeed, they can be trapped by electron-deficient π-systems, a combination which would not be feasible using polar chemistry (pathway B2 in Scheme 1). Interestingly, the *N*-centered radical species can be quickly quenched by an H atom donor to yield a stable carbanion capable of reacting with a traditional electrophile in polar fashion (pathway B3 in Scheme 1).

The single-electron reduction event (pathway B in Scheme 1, right) can be a challenging redox process which often requires assistance [4]. While some electron-poor imines can undergo a straightforward photocatalytic reduction (such as *N*-sulfonyl- or α-keto-imines), other neutral imines feature a reduction potential which falls out of range of most photocatalysts. The addition of an external Lewis acid can increase the reduction potential of the imine (less negative) through coordination. Moreover, hydrogen-bonding via Brønsted acid can make this reduction a thermodynamically favorable process thanks to proton-coupled electron transfer (PCET), wherein an electron transfer from the photocatalyst to the imine takes place in concert with a proton transfer from the Brønsted acid to the imine.

2. Photocatalytic Radical Additions to Imines—*Pathway A*

2.1. Racemic Photocatalytic Radical Additions to Imines

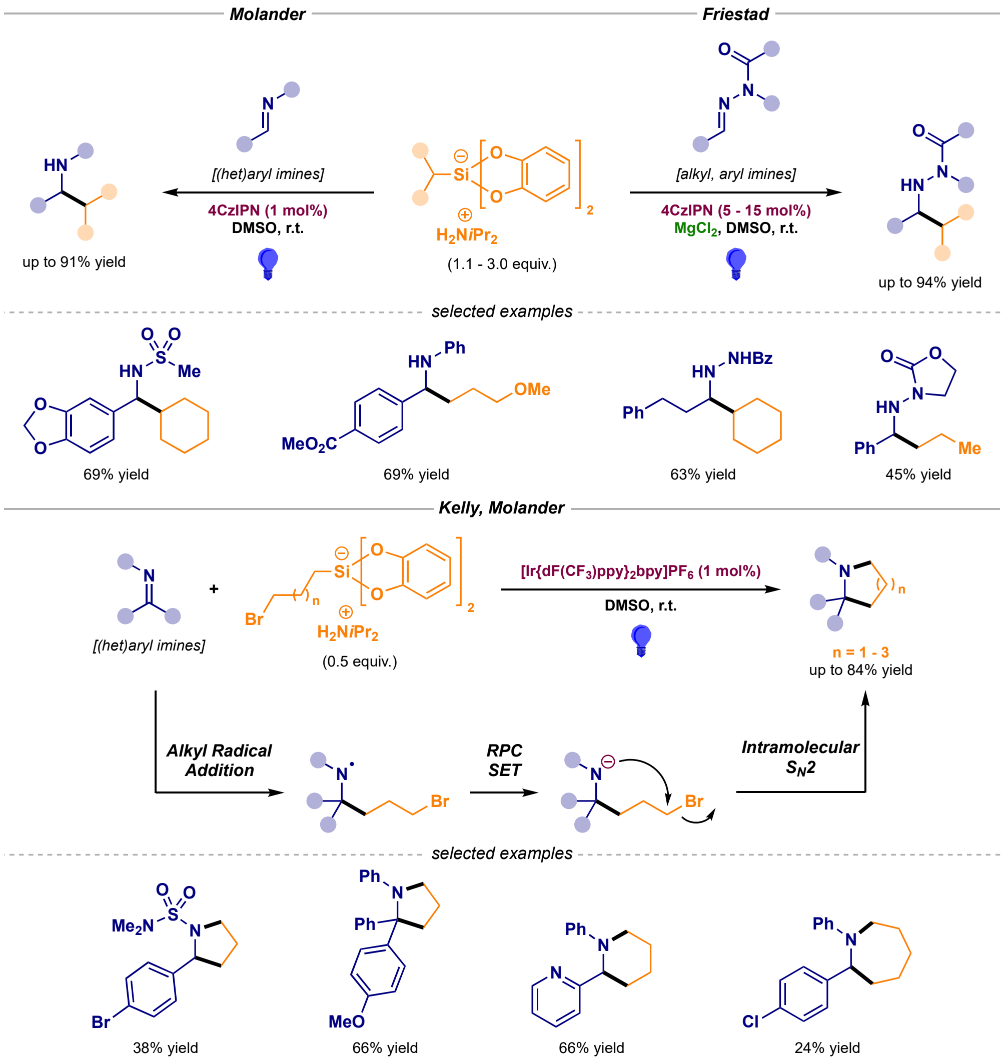
Racemic radical additions to imines under visible light photocatalysis began to appear in 2016, when Bode reported the cyclization of silicon amine protocol (SLAP) reagents with an imine moiety (Scheme 2, left) [5]. These α-silyl amine precursors could undergo mild single-electron oxidation to render α-amino radicals, which could then engage with the imine to yield a wide variety of piperazine derivatives. The protocol was expanded further with α-silyl ether and thioether precursors to access morpholines, oxazepanes, thiomorpholines and thiazepanes (Scheme 2, right) [6,7]. It should be noted that, in this case, a Lewis acid was required to activate the imine, and the photocatalytic cycle could start with an initial Lewis acid-assisted single-electron reduction of the imine.



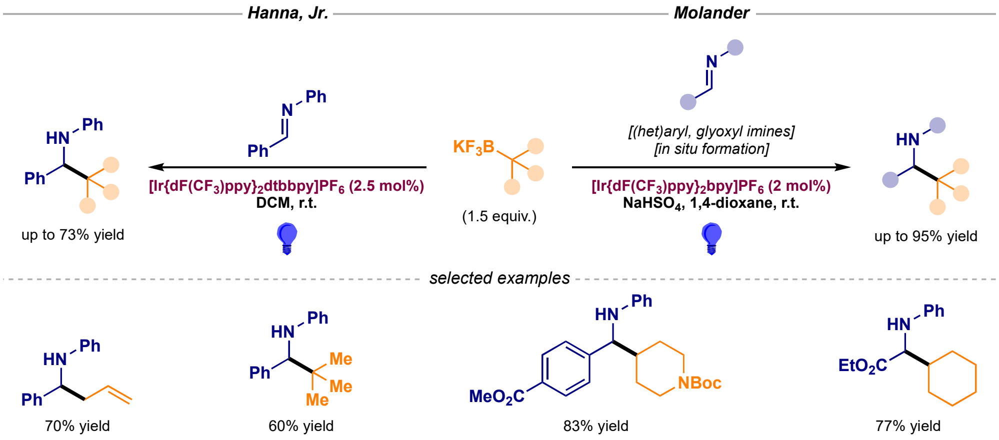
Scheme 2. Cyclization of SLAP reagents developed by Bode for the synthesis of piperazines (left) and morpholines, oxazepanes, thiomorpholines and thiazepanes (right).

The first intermolecular photocatalytic radical addition was published in 2017 by Molander's group [8]. The design of a general and modular approach based on the swift single-electron oxidation of ammonium alkyl bis(catecholato)silicates enabled the alkylation of different *N*-sulfonyl- and *N*-aryl-imines (Scheme 3, top left) [9]. In addition, Friestad employed these silicon reagents to perform the alkylation of *N*-acyl hydrazones in the presence of a Lewis acid (Scheme 3, top right) [10]. Alkyl silicates have also been utilized by Kelly and Molander to achieve the synthesis of various saturated *N*-heterocycles via radical alkylation and subsequent cyclization in a radical polar crossover (RPC) process (Scheme 3, bottom) [11].

More radical precursors have also been deployed in an attempt to expand the synthetic prowess of this transformation. For instance, Hanna, Jr. and Molander disclosed the photocatalytic activation of alkyl trifluoroborates, enabling the radical alkylation of non-activated imines (Scheme 4) [12,13].

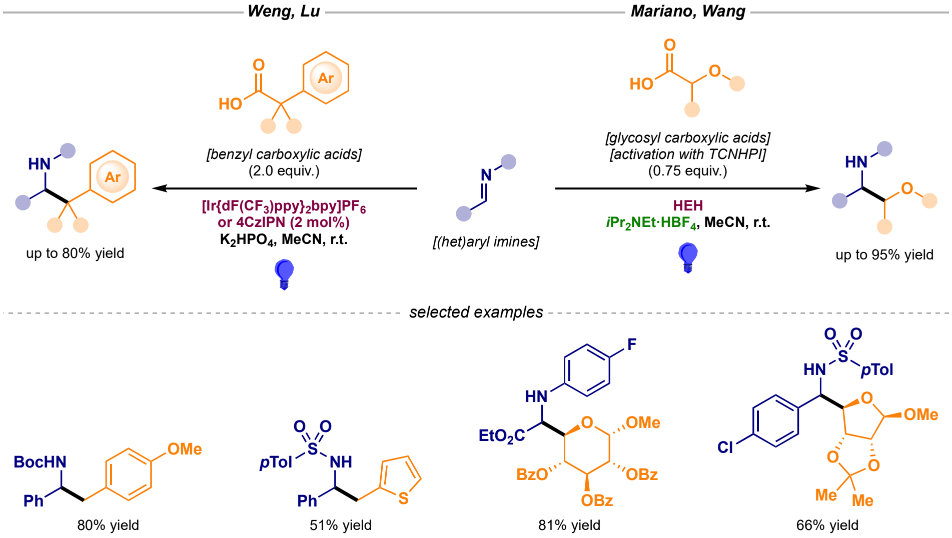


Scheme 3. Intermolecular photocatalytic radical additions to imines using alkyl silicates developed by Molander (top left), Friestad (top right) and Kelly and Molander (bottom).



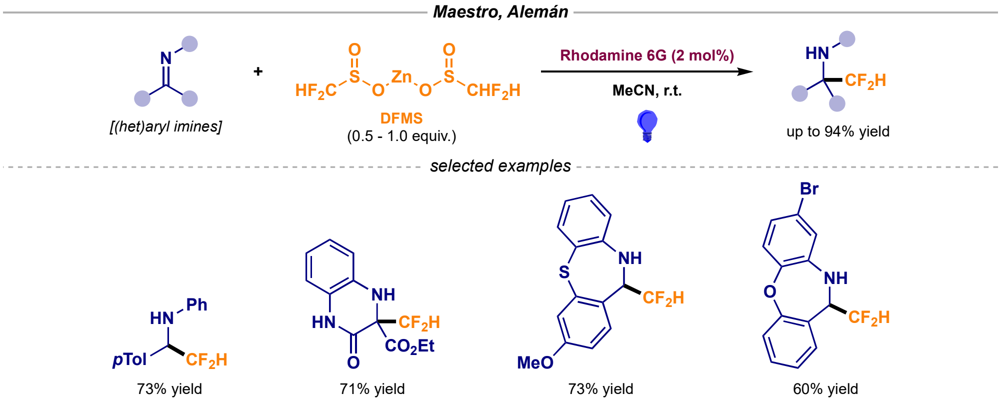
Scheme 4. Photocatalytic radical additions to imines using alkyl trifluoroborates developed by Hanna, Jr (left) and Molander (right).

Alkyl carboxylic acids hold a preferred position among radical precursors due to their versatility and ubiquity. Indeed, these alkylating agents can be implemented into mechanistically distinct photoredox pathways. Deprotonation of the acid can render a carboxylate species which can then undergo single-electron oxidation and subsequent decarboxylation to afford the alkyl radical intermediate. Alternatively, these acids can be activated with *N*-hydroxyphthalimide (NHPI) or its tetrachlorinated derivative (TCNHPI) through a simple esterification process to provide redox-active esters (RAEs). In this case, single-electron reduction can deliver the alkyl radical intermediate. This flexible behavior has been exploited by several research groups attempting to perform the alkyl radical addition to imines (Scheme 5). Weng and Lu reported the decarboxylative benzylation process following the oxidative pathway (Scheme 5, left) [14,15], while Mariano and Wang published a reductive version. In this later case, the decarboxylative glycosylation of imines was featured, although a Hantzsch ester (HEH) derivative was needed as a stoichiometric photosensitizer (Scheme 5, right) [16,17].



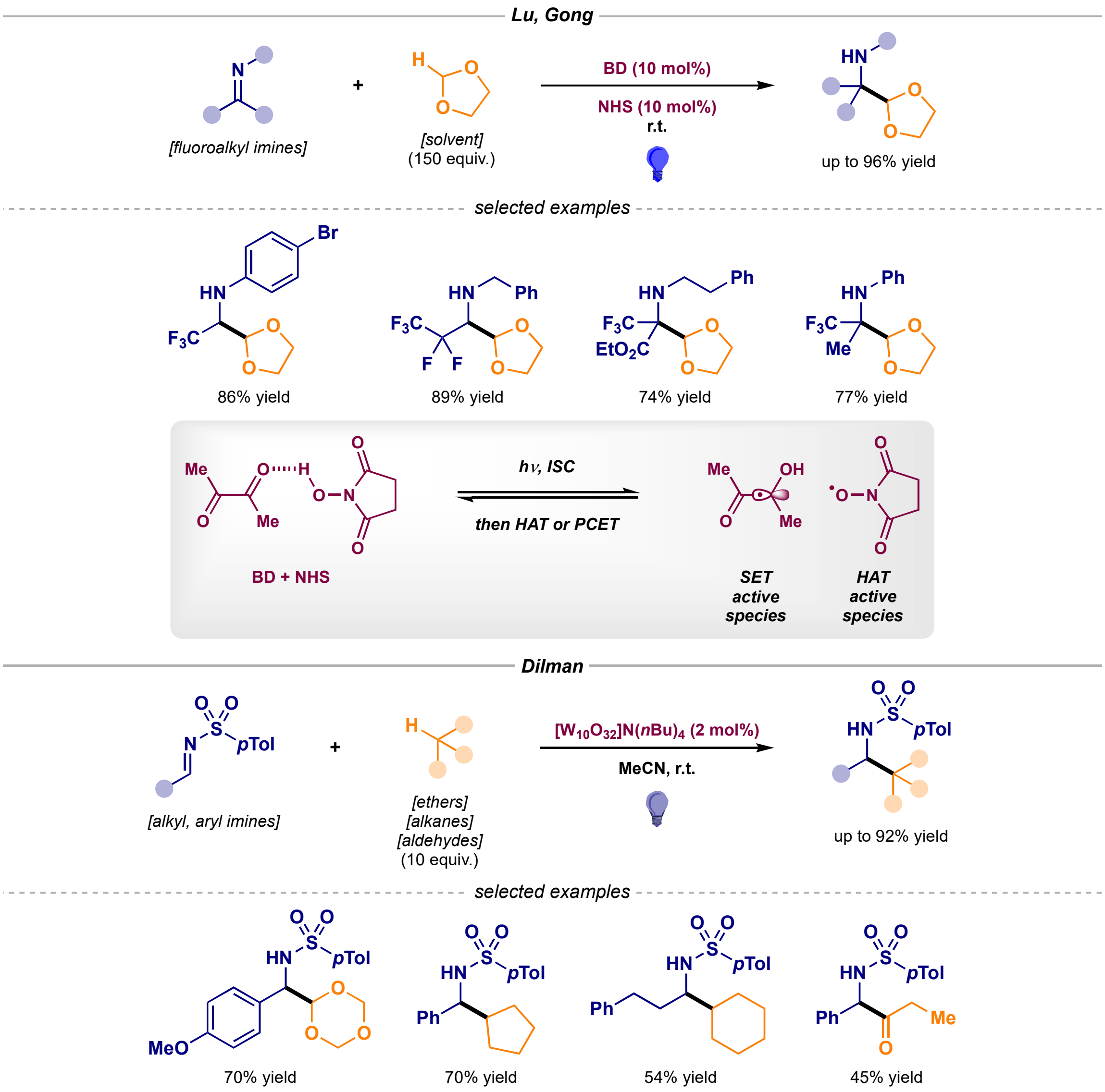
Scheme 5. Photocatalytic radical additions to imines using alkyl carboxylic acids developed by Weng and Lu (left) and Mariano and Wang (right).

Notably, the radical fluoroalkylation of imines had remained inaccessible in the field until Maestro and Alemán recently reported the direct difluoromethylation of imine moieties (Scheme 6) [18]. This general procedure was predicated on the single-electron oxidation of readily available zinc difluoromethane sulfinate (DFMS) in the presence of an organophotoredox catalyst (Rhodamine 6G).



Scheme 6. Photocatalytic difluoromethyl radical addition to imines using DFMS developed by Maestro and Alemán.

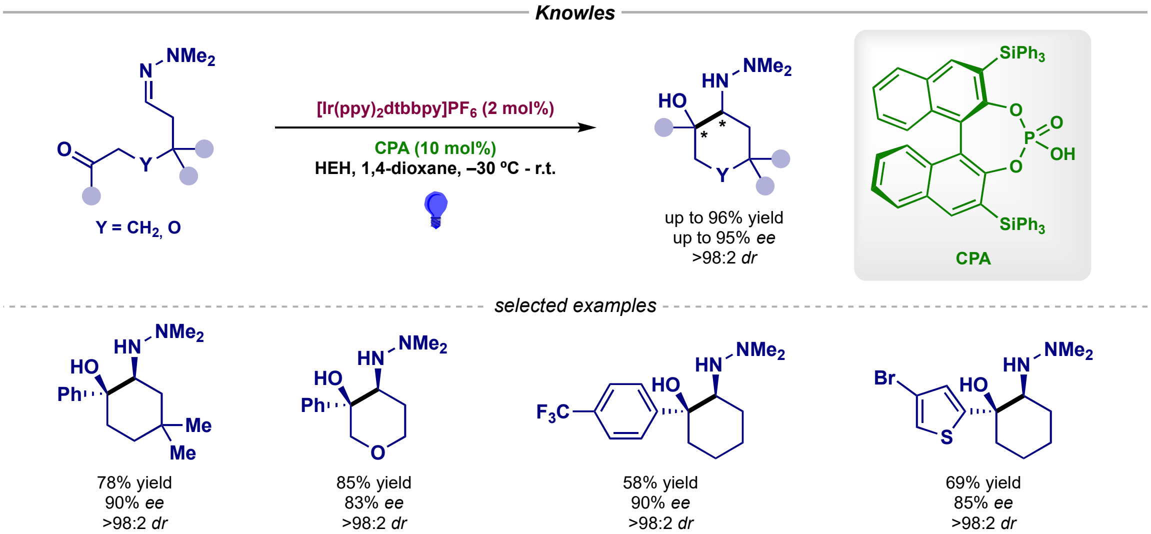
Lastly, hydrogen atom transfer (HAT) has also been used in order to perform the C-H activation of different alkyl radical precursors and perform the desired alkylation reaction with activated imines (Scheme 7). Lu and Gong reported the α-oxyalkyl radical addition of 1,3-dioxolane to fluoroalkyl imines (Scheme 7, top) [19,20], while Dilman managed to install different alkyl and acyl radicals into *N*-sulfonyl imines (Scheme 7, bottom) [21–23].



Scheme 7. Photocatalytic radical additions to imines using HAT developed by Lu and Gong (top) and Dilman (bottom).

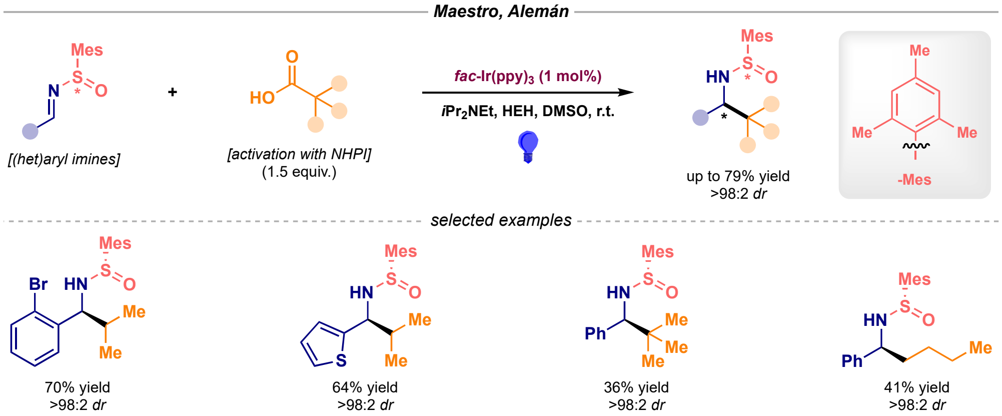
2.2. Stereoselective Photocatalytic Radical Additions to Imines

In the field of asymmetric photocatalytic additions to imines, Knowles first described in 2013 an elegant intramolecular example in which a hydrazone trapped a ketyl radical intermediate—generated by PCET—in enantioselective fashion thanks to the chiral induction exerted by a chiral phosphoric acid (Scheme 8) [24].



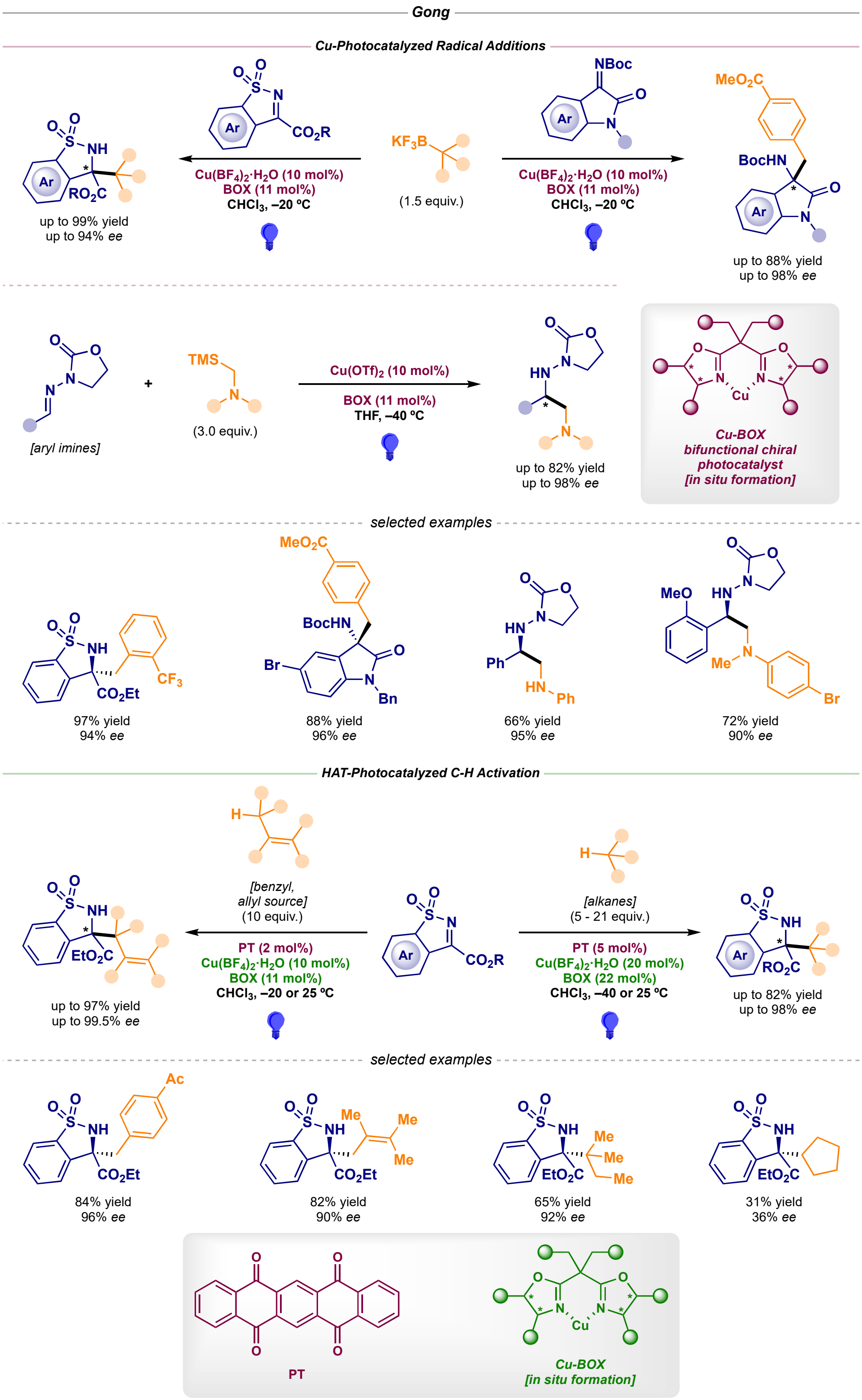
Scheme 8. Asymmetric intramolecular photocatalytic radical addition to hydrazones developed by Knowles.

No further reports were published on this topic until Maestro and Alemán disclosed in 2017 an asymmetric intermolecular radical alkylation of imines based on the use of chiral sulfoxides (Scheme 9) [25]. The photocatalytic reduction of NHPI-derived RAEs delivered the alkyl radical, which then engaged with the enantiopure *N*-sulfinimine in diastereoselective fashion to afford α-branched benzyl amine derivatives.



Scheme 9. Asymmetric intermolecular photocatalytic radical addition to *N*-sulfinimines developed by Maestro and Alemán.

Moreover, Gong's research group developed a series of transformations in 2018 and 2019 based on chiral Lewis acid-catalyzed radical alkylations of different imine scaffolds (Scheme 10, top) [26,27]. When using redox-active alkyl trifluoroborates and silanes, the Cu-BOX complexes acted as bifunctional chiral photocatalysts, performing both the asymmetric induction and the single-electron oxidation of the radical precursors, while suppressing the need for an external photocatalyst. In the latest report published by Gong, an HAT-photocatalyst (5,7,12,14-pentacenetetrone, PT) was required to perform the C-H activation of benzyl and allyl positions, as well as non-activated alkanes (Scheme 10, bottom) [28].



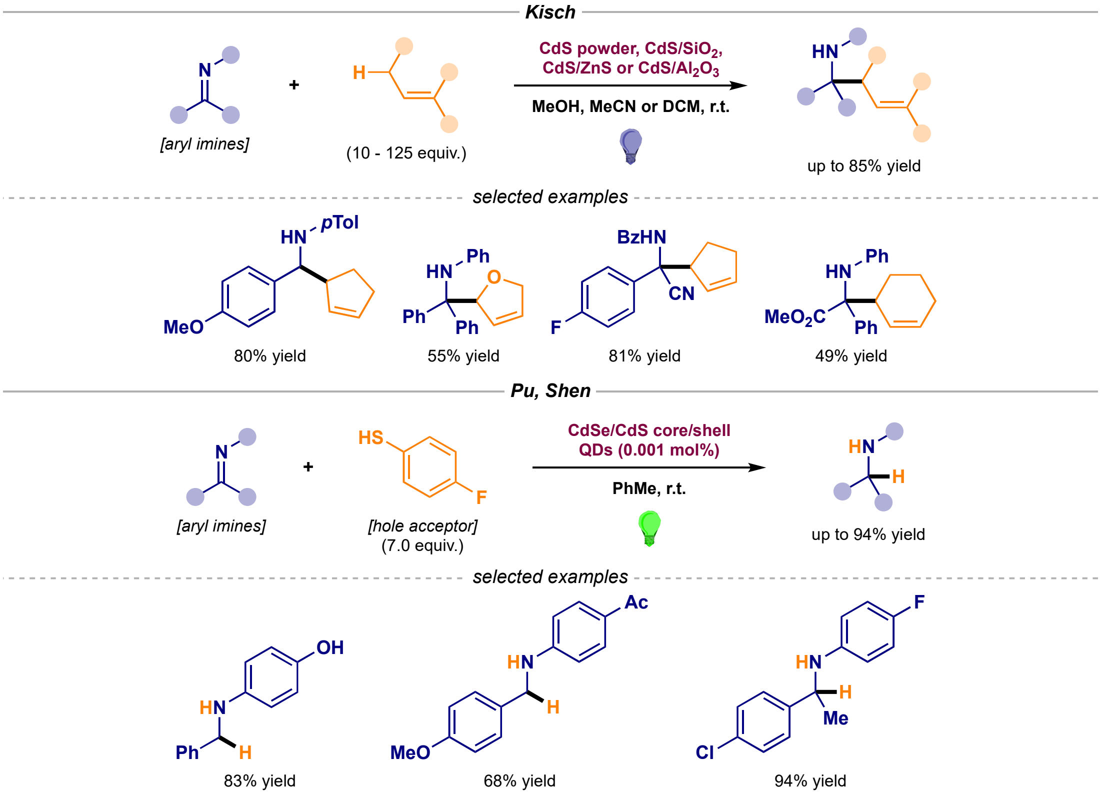
Scheme 10. Asymmetric intermolecular photocatalytic reactions developed by Gong: Cu-photocatalyzed radical additions (top) and HAT-photocatalyzed C-H activation (bottom).

The generality observed throughout this section noticeably stands out, wherein an assortment of radical precursors has been inserted into mechanistically similar protocols based on their photocatalytic activation to render the nucleophilic radical intermediate. Most notably, the range of imine building blocks employed in these reactions is quite impressive, as both activated and non-activated substrates have proven to be suitable acceptors to the different radical additions.

3. Photocatalytic α-Amino Radical Reactivity via Single-Electron Reduction of Imine Derivatives—*Pathway B*

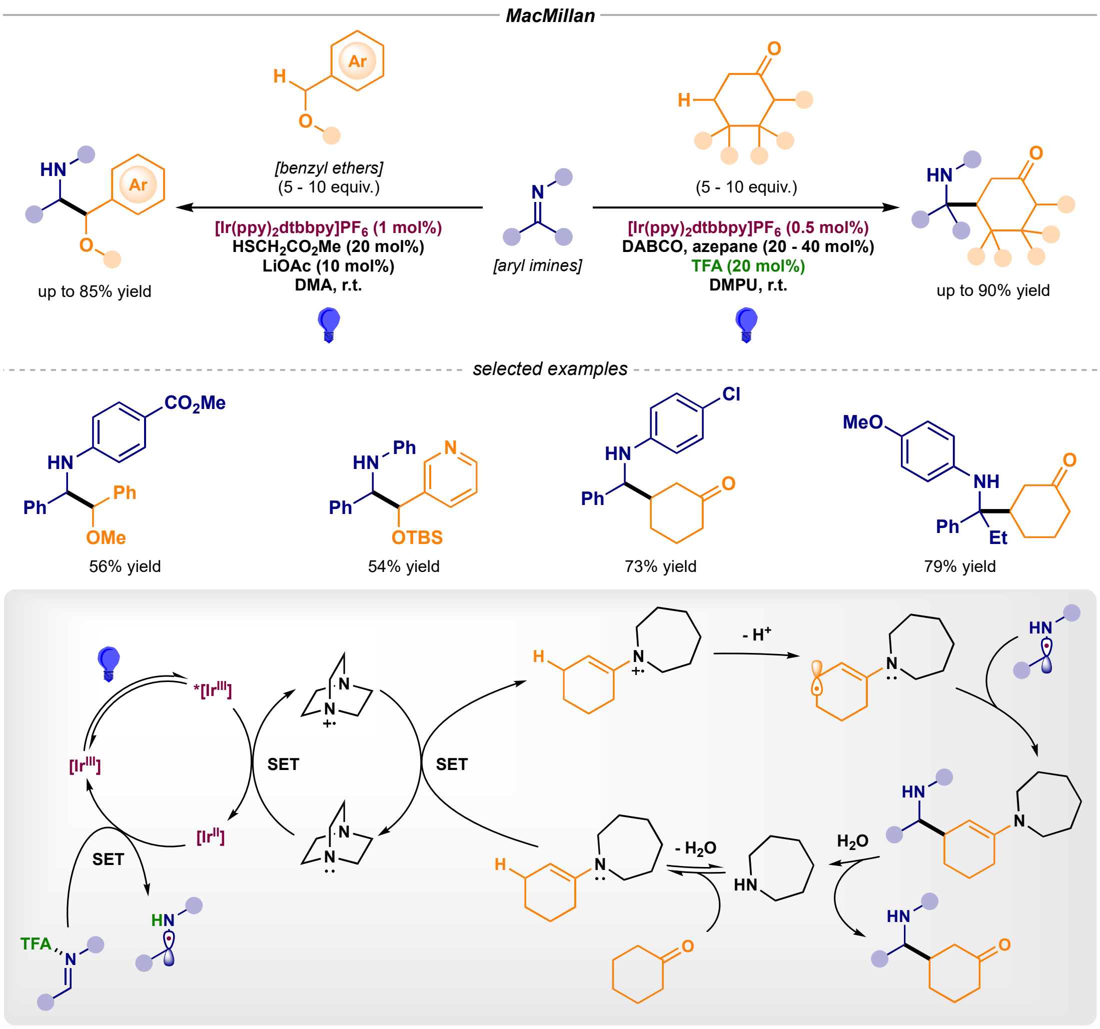
3.1. Racemic α-Amino Radical–Radical Couplings—Pathway B1

The generation of α-amino radical intermediates derived from imine building blocks was first reported by Kisch (Scheme 11, top) [29,30]. By means of a family of heterogeneous photocatalyst semiconductors, their group developed a series of transformations involving the coupling of α-amino radicals and allyl radicals (pathway B1 in Scheme 1) [31]. CdS powder as well as supported versions on SiO_2, ZnS, and Al_2O_3 can behave as the photocatalyst semiconductor which features a surface with the ability to engage in interfacial electron transfer (IFET). Upon visible light absorption, the semiconductor can generate an electron-hole pair—essentially reducing and oxidizing surface centers. These sites can then perform IFET with the adsorbed substrates, delivering the two radical intermediates that eventually afford the recombination product (known as semiconductor photocatalysis B). Later on, Pu and Shen used CdSe/CdS core/shell quantum dots (QDs) as photocatalysts for the transfer hydrogenation of diaryl imines with a thiophenol as H atom donor (Scheme 11, bottom) [32,33].



Scheme 11. Heterogeneous photocatalytic α-amino radical–radical couplings developed by Kisch (top) and Pu and Shen (bottom).

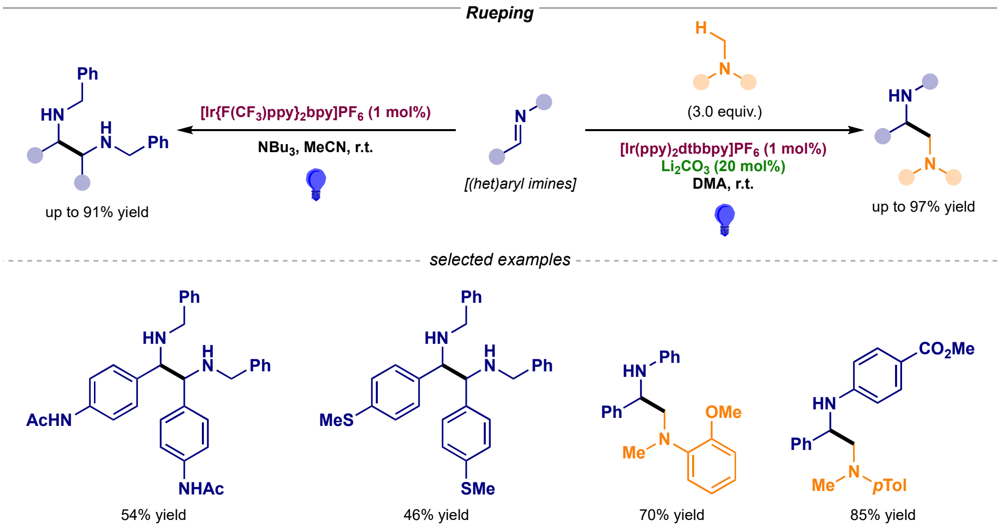
In the field of homogenous photocatalysis, MacMillan first reported the coupling of α-amino radicals with α-oxybenzyl and β-enaminyl radicals, giving access to pinacol-type products and the formal β-Mannich reaction, respectively (Scheme 12, top) [34,35]. Notably, the generation of the radical reacting partners required elegant multicatalytic approaches. The pinacol-type coupling reaction relied on the initial photocatalytic oxidation and deprotonation of methyl thioglycolate to produce a thiyl radical. Then, this *S*-centered radical could perform the H atom abstraction from the benzyl ether to afford the α-oxybenzyl radical and regenerate the thiol catalyst. On the other hand, the β-enaminyl radical could be accessed following: i) initial condensation of a cyclic ketone with a simple aminocatalyst (azepane), ii) subsequent oxidation of the catalytic enamine, and iii) final allylic deprotonation (Scheme 12, bottom).



Scheme 12. Photocatalytic α-amino radical–radical couplings (top) and mechanistic proposal for the formal β-Mannich reaction (bottom) developed by MacMillan.

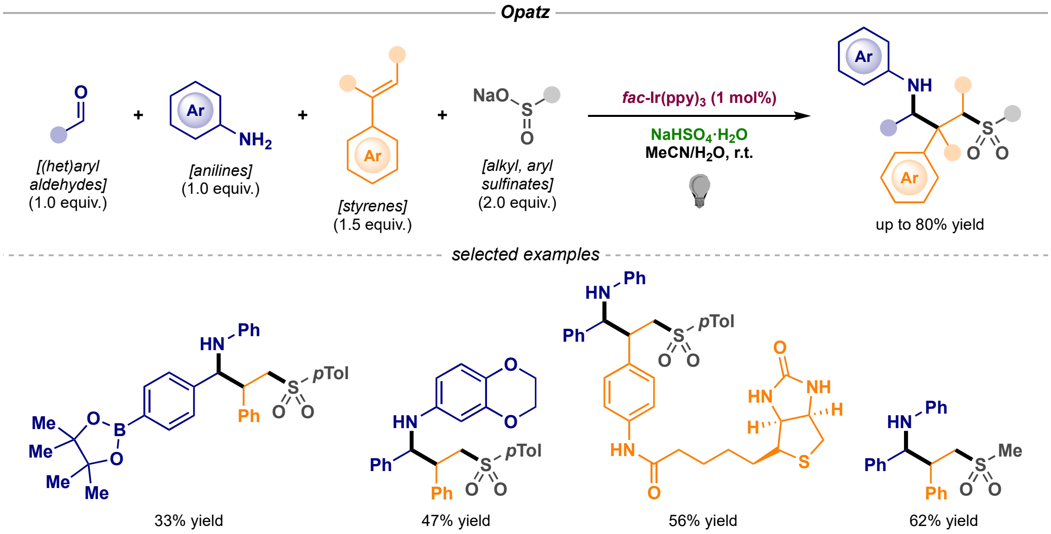
Concurrently, Rueping displayed the ability of these α-amino radicals to react with each other to render symmetrical and unsymmetrically substituted 1,2-diamines (Scheme 13) [36,37].

Following the development of these transformations, different variants of the radical–radical coupling of α-amino radicals began to appear. Sudo successfully employed an organophotoredox catalyst in a similar symmetrical coupling [38], whereas Gilmore obtained vicinal primary diamine products through *in situ* formation of the imines with aldehydes and ammonia [39]. Regarding unsymmetrical adducts, Wang reported the coupling of imine-derived α-amino radicals with tetrahydroisoquinoline-derived α-amino radicals [40]. In most cases, the imine reduction is believed to be assisted by coordination to an external acidic species.



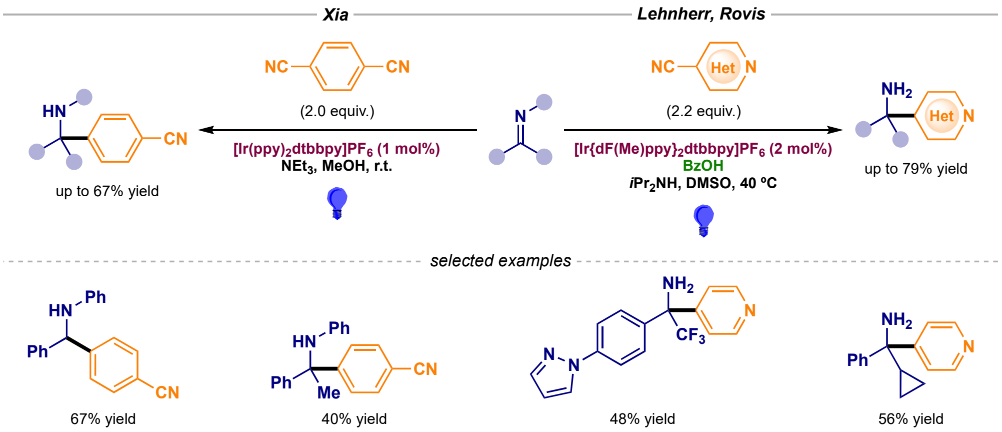
Scheme 13. Photocatalytic α-amino radical–radical couplings developed by Rueping.

A unique example based on the reactivity of these α-amino radicals was reported by Opatz featuring a four-component reaction which gave access to structurally diverse products (Scheme 14) [41]. The protocol involved the simultaneous construction of three new bonds: C-N (via *in situ* formation of the imine), C-S (via sulfonyl radical addition to styrene) and C-C (via α-amino radical-benzyl radical coupling).



Scheme 14. Photocatalytic α-amino radical-benzyl radical coupling developed by Opatz.

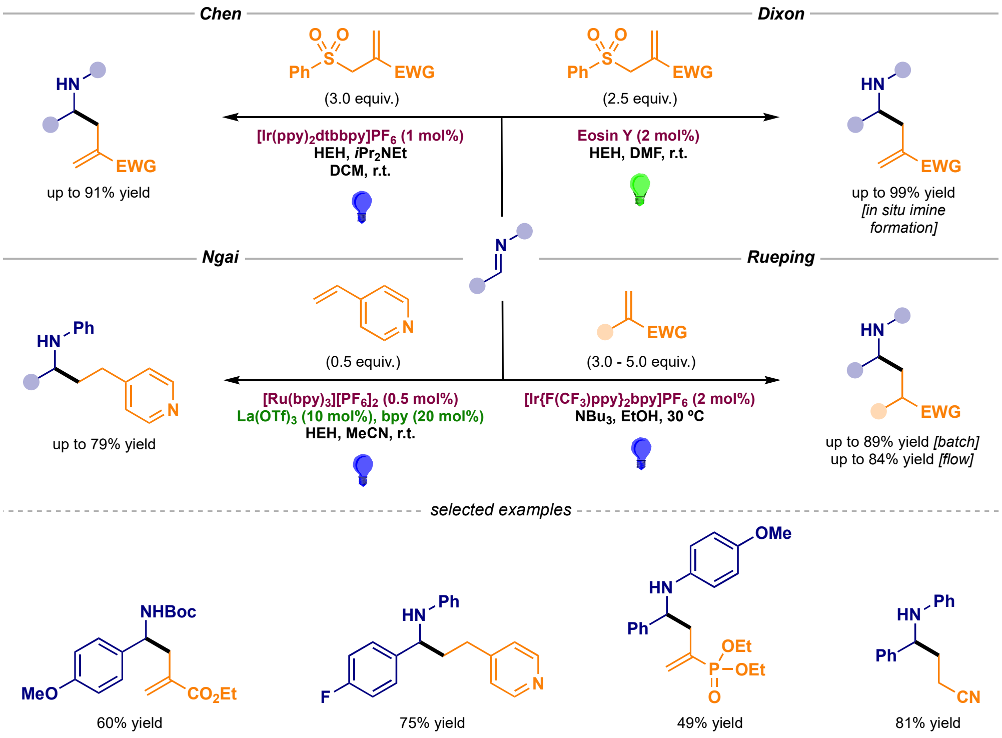
Arylation reactions, which had remained elusive in the context of radical chemistry with imines, were achieved by Xia and Lehnherr and Rovis (Scheme 15) [42,43]. Through generation of stabilized aryl radical intermediates, the radical–radical coupling became feasible with 1,4-dicyanobenzene and 4-cyanopyridine precursors, respectively.



Scheme 15. Photocatalytic α-amino radical-aryl radical couplings developed by Xia (left) and Lehnherr and Rovis (right).

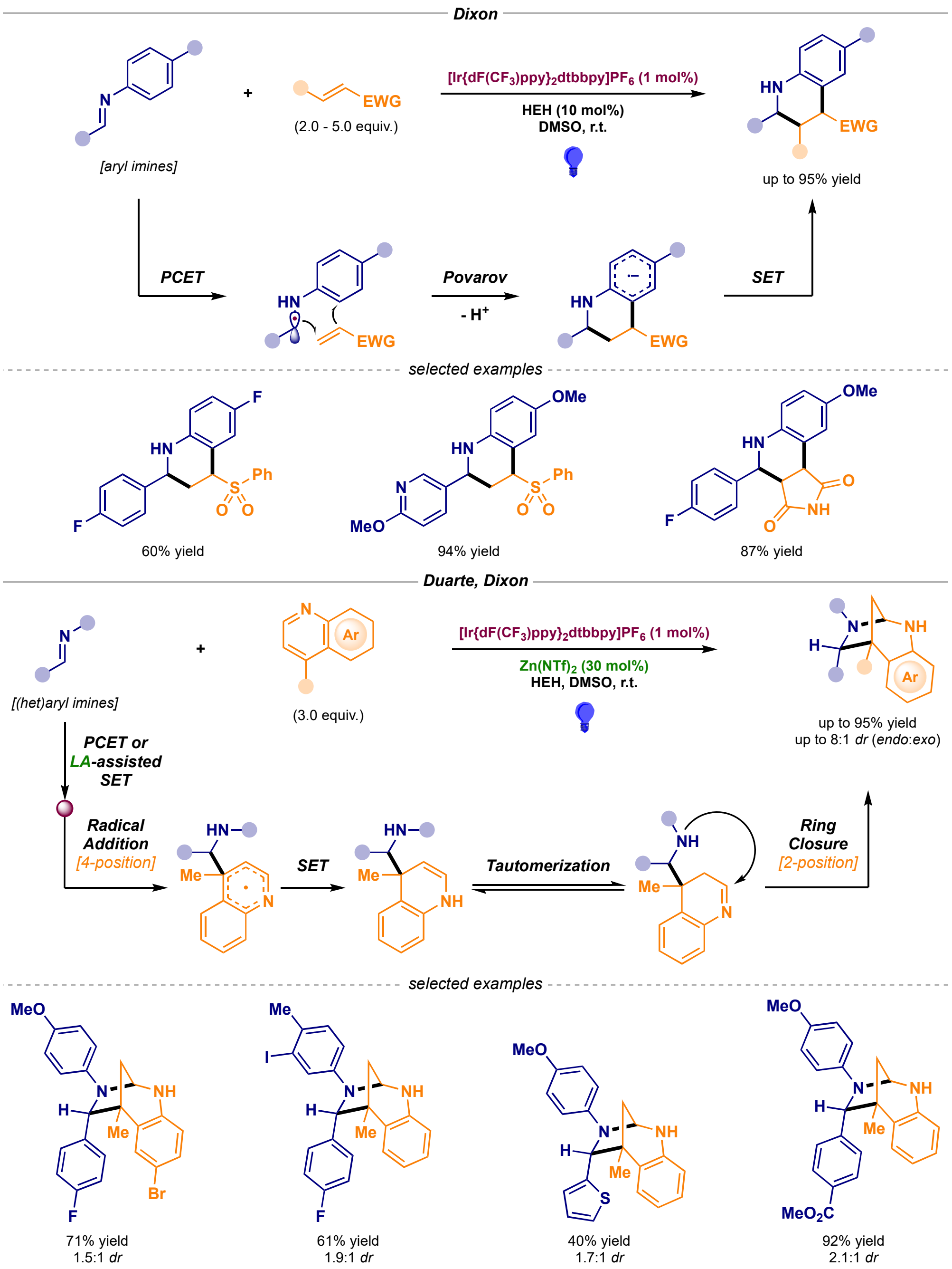
3.2. Racemic α-Amino Radical Additions to Activated Olefins—Pathway B2

The development of the single-electron reduction of imines to produce new radical–radical couplings has undoubtedly revamped this area. Furthermore, the polarity reversal displayed in this redox process served as a platform upon which an even greater challenge could be tackled. The new nucleophilic character of the α-amino radical was exploited in a series of Giese radical additions (pathway B2 in Scheme 1) reported by several groups. Indeed, Chen [44], Dixon [45,46], Ngai [47], and Rueping [48] independently worked on the addition of these intermediates to different activated olefins (Scheme 16).



Scheme 16. Photocatalytic α-amino radical additions to activated olefins developed by Chen (top left), Dixon (top right), Ngai (bottom left), and Rueping (bottom right).

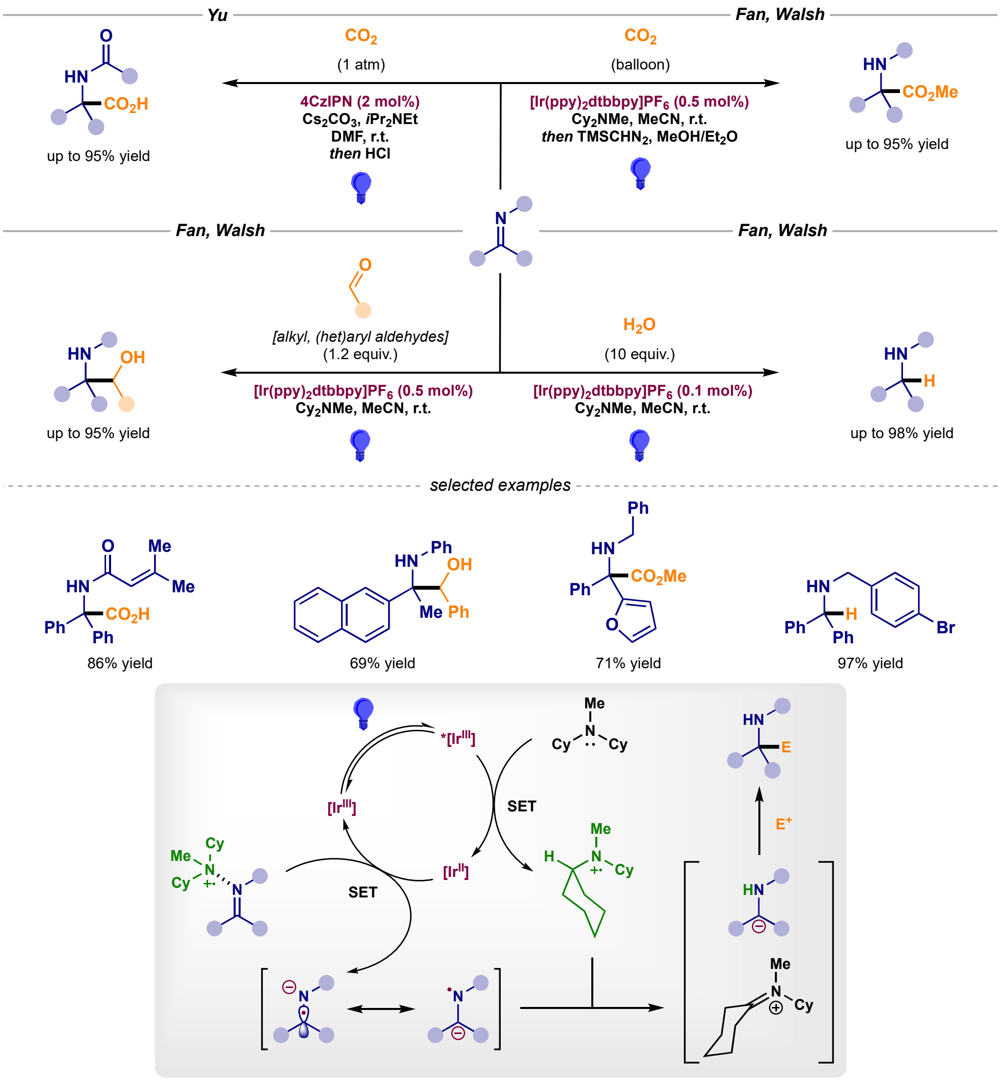
In addition, Dixon's lab described two procedures built on these radical additions to electrophilic partners followed by cyclization events, thus granting access to molecules of higher structural complexity (Scheme 17) [49,50]. Notably, the addition of the α-amino radical to vinyl sulfones led to a reverse polarity Povarov reaction (Scheme 17, top), while bridged 1,3-diazepanes could be prepared via α-amino radical addition to the 4-position of a quinoline core and subsequent ring closure at the 2-position (Scheme 17, bottom).



Scheme 17. Photocatalytic reactions of α-amino radicals for the synthesis of polycyclic structures developed by Dixon: reverse polarity Povarov reaction (top) and bridged 1,3-diazepane construction (bottom).

3.3. Racemic α-Amino Carbanion Nucleophilic Attacks—Pathway B3

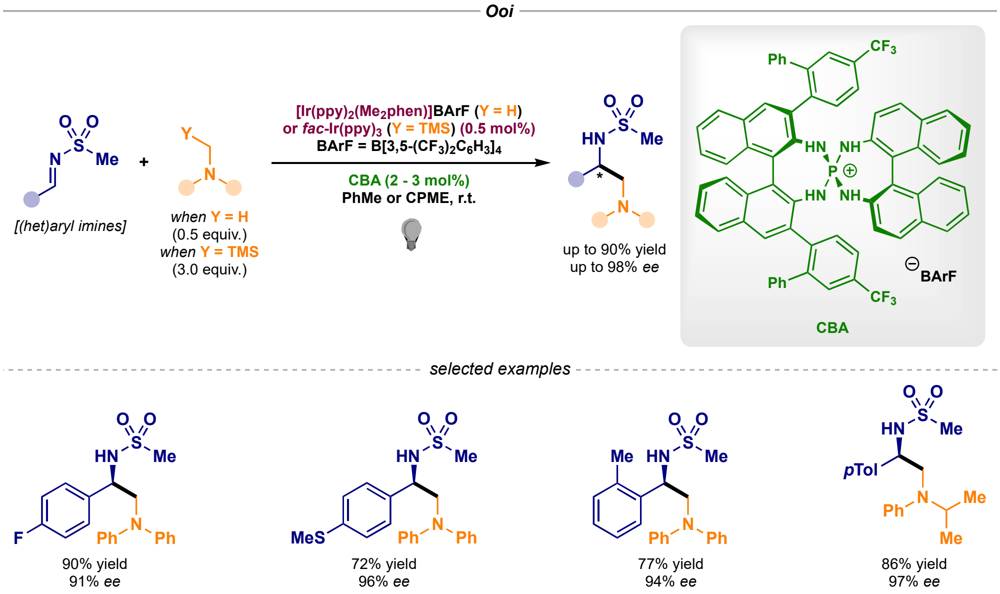
After thorough evaluation of the results outlined above, it could be assumed that the single-electron reduction of imine scaffolds usually delivers a radical anion that can exist as two different resonant forms. As mentioned previously, the *N*-radical resonant form can engage in an HAT to yield a stable carbanion (pathway B3 in Scheme 1). This behavior has been exploited by Yu and Fan and Walsh to achieve polar nucleophilic attacks on numerous electrophiles, such as CO_2 and aldehydes, as well as the direct hydrolysis of these anionic intermediates to afford the formal reduction to benzyl amines (Scheme 18) [51–54].



Scheme 18. Photocatalytic carbanion additions to electrophiles developed by Yu and Fan and Walsh: carboxylation (top), reaction with aldehydes (middle left) and hydrolysis (middle right).

3.4. Stereoselective Photocatalytic α-Amino Radical Reactivity via Single-Electron Reduction of Imine Derivatives—Pathway B

Controlling the stereochemical outcome of transformations involving the single-electron reduction of imines has proven to be an outstanding challenge. An exceptional solution to this problem was developed by Ooi's lab in 2015 and 2016 (Scheme 19) [55,56], wherein the radical anion derived from this redox process was ion-paired with a chiral phosphonium salt, rendering an asymmetric radical–radical coupling with α-amino radicals (pathway B1 in Scheme 1).

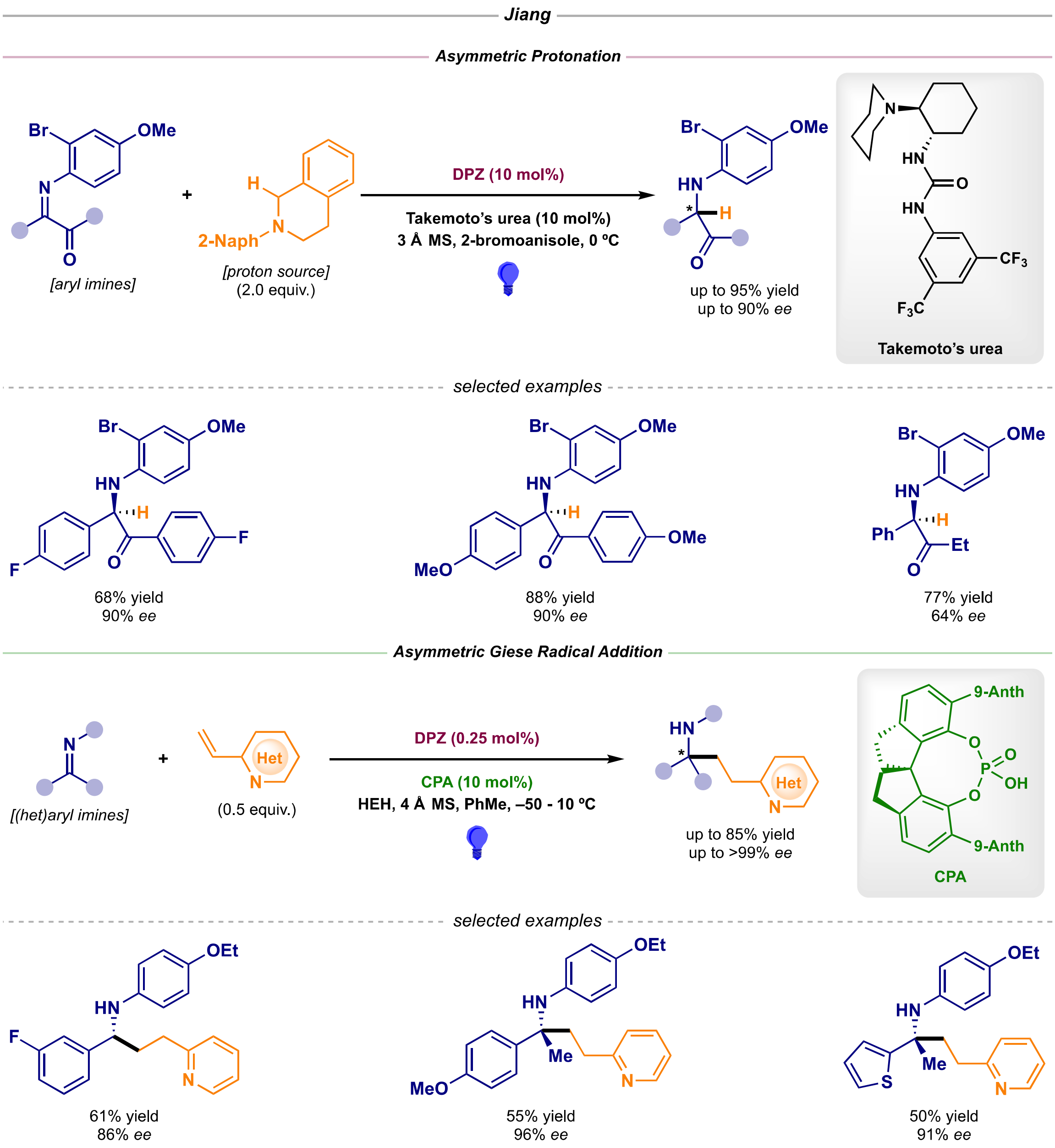


Scheme 19. Asymmetric photocatalytic α-amino radical–radical couplings developed by Ooi.

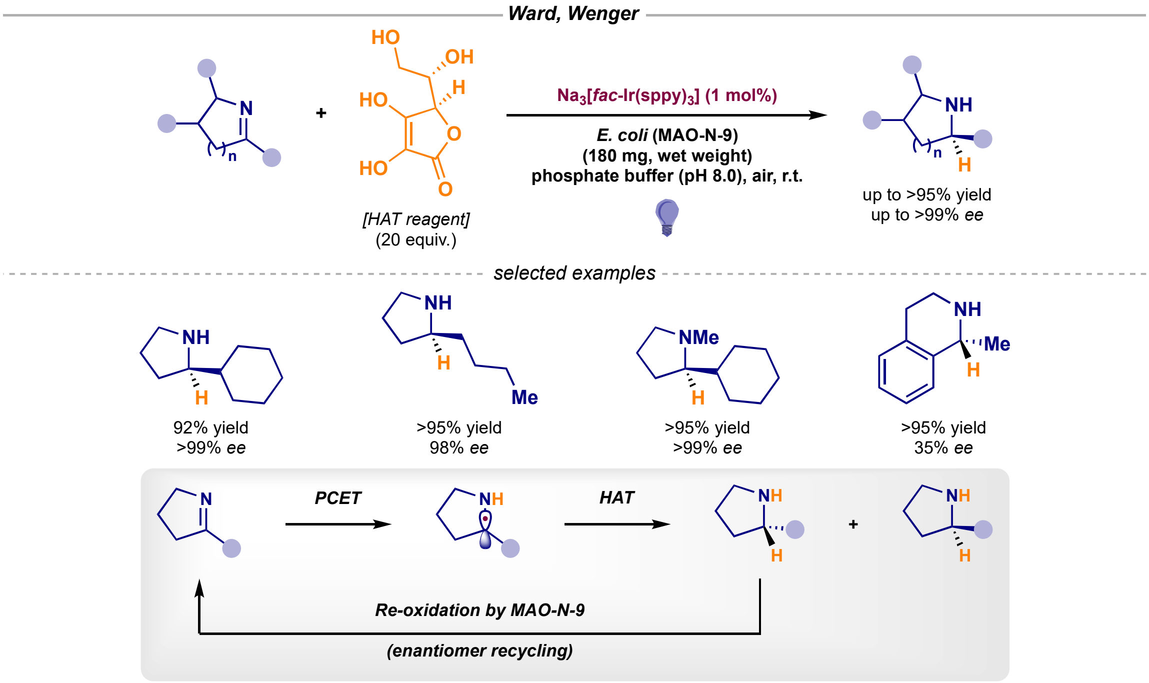
Moreover, Jiang's lab reported two transformations involving the use of traditional organocatalysts (Scheme 20) [57,58]. In the first one, the formal reduction of activated ketimines was achieved via coordination of Takemoto's urea catalyst to the radical anion and ensuing asymmetric HAT (pathway B1 in Scheme 1). In the second one, a chiral Brønsted acid managed to activate vinyl pyridines—acting as acceptors in a Giese radical addition—while exerting stereocontrol through H-bond interactions (pathway B2 in Scheme 1).

Finally, Ward and Wenger published an interesting asymmetric reduction of cyclic imines in which enzymatic catalysis played a fundamental role (Scheme 21) [59]. Initial photocatalytic reduction and HAT would deliver a racemic mixture of both amines (pathway B1 in Scheme 1), yet, in the presence of monoamine oxidase MAO-N-9, only one enantiomer could undergo subsequent re-oxidation (enantiomer recycling). Therefore, the combination of photocatalysis and biocatalysis yielded an elegant dynamic kinetic resolution (DKR) en route to chiral amines.

In this section, the pool of radical precursors employed in reactions following pathway B1 may not be as diverse when compared to conventional radical additions (pathway A). However, thanks to the nucleophilic character of the imine-derived radical anion, pathways B2 and B3 have widened the scope of reacting partners since they no longer require photocatalytic activation. Remarkably, common electrophiles used in polar methodologies find a smooth transition into these new radical processes thanks to the inspired polarity reversal enforced upon the imine substrates.



Scheme 20. Asymmetric photocatalytic α-amino radical-mediated reactions developed by Jiang: asymmetric protonation (top) and asymmetric Giese radical addition (bottom).



Scheme 21. Asymmetric bio- and photo-catalytic reduction of cyclic imines developed by Ward and Wenger.

4. Conclusions

The development of new methodologies to perform the α-functionalization of imine building blocks has proven to be a subject of intense research during the past decade, as numerous approaches featuring outstanding versatility have surfaced in the context of visible light photoredox catalysis. Most importantly, the complimentary nature to the different photocatalytic strategies employed in imine chemistry has provided immense flexibility, since the imine reagent can now be used as both an electrophile and, strikingly, a nucleophile. This multifaceted behavior has delivered a wide array of racemic transformations in this area. However, asymmetric functionalization of the C=N moiety has remained a great challenge in photoredox catalysis. Nevertheless, brilliant activation strategies have been deployed to achieve stereoselectivity, although an increase in generality and modularity can be expected as the field continues to grow.

Author Contributions: Conceptualization, A.F.G.-C. and M.C.M.; literature search, A.F.G.-C. and M.C.M.; writing—original draft preparation, A.F.G.-C.; writing—review and editing, A.F.G.-C., M.C.M., and J.A.; supervision, M.C.M. and J.A.; project administration, M.C.M. and J.A.; funding acquisition, M.C.M. and J.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the European Research Council, grant number 647550; the Spanish Government, grant number RTI2018-095038-B-I00; the "Comunidad de Madrid" and European Structural Funds, grant number S2018/NMT-4367.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

For uncommon abbreviations outlined throughout the manuscript, see the following list:

abbreviation	full description
4CzIPN	2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile
Ac	acyl
Alk	alkyl
Anth	anthracenyl
Ar	aryl
BArF	$B[3,5\text{-}(CF_3)_2C_6H_3]_4$
BD	2,3-butanedione
Boc	*tert*-butyloxycarbonyl
BOX	bis(oxazoline)
bpy	2,2′-bipyridine
Bu	butyl
Bz	benzoyl
CBA	chiral Brønsted acid
CPA	chiral phosphoric acid
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DFMS	zinc difluoromethanesulfinate
DKR	dynamic kinetic resolution
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMPU	*N,N′*-dimethylpropyleneurea
DMSO	dimethylsulfoxide
DPZ	5,6-bis(5-methoxythiophen-2-yl)pyrazine-2,3-dicarbonitrile
dr	diastereomeric ratio
dtbbpy	4,4′-di-*tert*-butyl-2,2′-dipyridyl
E	electrophile
ee	enantiomeric excess
Et	ethyl
EWG	electron withdrawing group
HAT	hydrogen atom transfer
HEH	Hantzsch ester
Het	heteroaryl
IFET	interfacial electron transfer
*i*Pr	*iso*-propyl
MAO	monoamine oxidase
Me	methyl
Mes	mesityl
MS	molecular sieves
Naph	naphthyl
NHPI	*N*-hydroxyphthalimide
NHS	*N*-hydroxysuccinimide
PCET	proton-coupled electron transfer
Ph	phenyl
phen	1,10-phenanthroline
ppy	2-phenylpyridine
PT	5,7,12,14-pentacenetetrone
*p*Tol	*para*-tolyl
QD	quantum dot
RAE	redox-active ester
RPC	radical polar crossover

SET	single-electron transfer
SLAP	silicon amine protocol
S_N2	bimolecular nucleophilic substitution
sppy	3-(pyridin-2-yl)benzenesulfonate
TBS	*tert*-butyldimethylsilyl
TCNHPI	*N*-hydroxytetrachlorophthalimide
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TMS	trimethylsilyl
TPP	2,4,6-triphenylpyrylium tetrafluoroborate

References

1. *Visible Light Photocatalysis in Organic Chemistry*, 1st ed; Stephenson, C.R.J.; Yoon, T.P.; MacMillan, D.W.C. (Eds.) Wiley-VCH: Weinheim, Germany, 2018.
2. Matsui, J.K.; Lang, S.B.; Heitz, D.R.; Molander, G.A. Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development. *ACS Catal.* **2017**, *7*, 2563–2575. [CrossRef]
3. Lee, K.N.; Ngai, M.-Y. Recent developments in transition-metal photoredox-catalysed reactions of carbonyl derivatives. *Chem. Commun.* **2017**, *53*, 13093–13112. [CrossRef] [PubMed]
4. Leitch, J.A.; Rossolini, T.; Rogova, T.; Maitland, J.A.P.; Dixon, D.J. α-Amino Radicals via Photocatalytic Single-Electron Reduction of Imine Derivatives. *ACS Catal.* **2020**, *10*, 2009–2025. [CrossRef]
5. Hsieh, S.-Y.; Bode, J.W. Silicon Amine Reagents for the Photocatalytic Synthesis of Piperazines from Aldehydes and Ketones. *Org. Lett.* **2016**, *18*, 2098–2101. [CrossRef] [PubMed]
6. Jackl, M.K.; Legnani, L.; Morandi, B.; Bode, J.W. Continuous Flow Synthesis of Morpholines and Oxazepanes with Silicon Amine Protocol (SLAP) Reagents and Lewis Acid Facilitated Photoredox Catalysis. *Org. Lett.* **2017**, *19*, 4696–4699. [CrossRef] [PubMed]
7. Hsieh, S.-Y.; Bode, J.W. Lewis Acid Induced Toggle from Ir(II) to Ir(IV) Pathways in Photocatalytic Reactions: Synthesis of Thiomorpholines and Thiazepanes from Aldehydes and SLAP Reagents. *ACS Cent. Sci.* **2017**, *3*, 66–72. [CrossRef]
8. Patel, N.R.; Kelly, C.B.; Siegenfeld, A.P.; Molander, G.A. Mild, Redox-Neutral Alkylation of Imines Enabled by an Organic Photocatalyst. *ACS Catal.* **2017**, *7*, 1766–1770. [CrossRef]
9. Prieto, A.; Bouyssi, D.; Monteiro, N. Radical-Mediated Formal C(sp^2)–H Functionalization of Aldehyde-Derived *N*,*N*-Dialkylhydrazones. *Eur. J. Org. Chem.* **2018**, 2378–2393. [CrossRef]
10. Cullen, S.T.J.; Friestad, G.K. Alkyl Radical Addition to Aliphatic and Aromatic *N*-Acylhydrazones Using an Organic Photoredox Catalyst. *Org. Lett.* **2019**, *21*, 8290–8294. [CrossRef]
11. Pantaine, L.R.E.; Milligan, J.A.; Matsui, J.K.; Kelly, C.B.; Molander, G.A. Photoredox Radical/Polar Crossover Enables Construction of Saturated Nitrogen Heterocycles. *Org. Lett.* **2019**, *21*, 2317–2321. [CrossRef]
12. Plasko, D.P.; Jordan, C.J.; Ciesa, B.E.; Merrill, M.A.; Hanna, J.M., Jr. Visible light-promoted alkylation of imines using potassium organotrifluoroborates. *Photochem. Photobiol. Sci.* **2018**, *17*, 534–538. [CrossRef] [PubMed]
13. Yi, J.; Badir, S.O.; Alam, R.; Molander, G.A. Photoredox-Catalyzed Multicomponent Petasis Reaction with Alkyltrifluoroborates. *Org. Lett.* **2019**, *21*, 4853–4858. [CrossRef] [PubMed]
14. Guo, J.; Wu, Q.-L.; Xie, Y.; Weng, J.; Lu, G. Visible-Light-Mediated Decarboxylative Benzylation of Imines with Arylacetic Acids. *J. Org. Chem.* **2018**, *83*, 12559–12567, The reaction pathway could not be confirmed; both the radical addition and the radical–radical coupling are most likely taking place. [CrossRef] [PubMed]
15. Zhang, H.-H.; Yu, S. Radical Alkylation of Imines with 4-Alkyl-1,4-dihydropyridines Enabled by Photoredox/Brønsted Acid Cocatalysis. *J. Org. Chem.* **2017**, *82*, 9995–10006, The reaction pathway could not be confirmed; both the radical addition and the radical–radical coupling are most likely taking place. [CrossRef]

16. Ji, P.; Zhang, Y.; Wei, Y.; Huang, H.; Hu, W.; Mariano, P.A.; Wang, W. Visible-Light-Mediated, Chemo- and Stereoselective Radical Process for the Synthesis of *C*-Glycoamino Acids. *Org. Lett.* **2019**, *21*, 3086–3092. [CrossRef]
17. Jia, J.; Lefebvre, Q.; Rueping, M. Reductive coupling of imines with redox-active esters by visible light photoredox organocatalysis. *Org. Chem. Front.* **2020**, *7*, 602–608. [CrossRef]
18. Garrido-Castro, A.F.; Gini, A.; Maestro, M.C.; Alemán, J. Unlocking the direct photocatalytic difluoromethylation of C=N bonds. *Chem. Commun.* **2020**, *56*, 3769–3772. [CrossRef]
19. Yang, S.; Zhu, S.; Lu, D.; Gong, Y. Formylation of Fluoroalkyl Imines through Visible-Light-Enabled H-Atom Transfer Catalysis: Access to Fluorinated α-Amino Aldehydes. *Org. Lett.* **2019**, *21*, 2019–2024. [CrossRef]
20. For a photoinduced α-oxyalkylation of imines generated in situ, see: Zhang, L.; Deng, Y.; Shi, F. Light promoted aqueous phase amine synthesis via three-component coupling reactions. *Tetrahedron Lett.* **2013**, *54*, 5217–5219.
21. Supranovich, V.I.; Levin, V.V.; Dilman, A.D. Radical Addition to *N*-Tosylimines via C−H Activation Induced by Decatungstate Photocatalyst. *Org. Lett.* **2019**, *21*, 4271–4274. [CrossRef]
22. For an inverse hydroboration of imines wherein the boryl radical is generated from *N*-Heterocyclic Carbene (NHC) boranes via HAT, see: Zhou, N.; Yuan, X.-A.; Zhao, Y.; Xie, J.; Zhu, C. Synergistic Photoredox Catalysis and Organocatalysis for Inverse Hydroboration of Imines. *Angew. Chem., Int. Ed.* **2018**, *57*, 3990–3994, The reaction pathway could not be confirmed; both the radical addition and the radical–radical coupling are most likely taking place.
23. Zhang, H.-H.; Yu, S. Visible-Light-Induced Radical Acylation of Imines with α-Ketoacids Enabled by Electron-Donor−Acceptor Complexes. *Org. Lett.* **2019**, *21*, 3711–3715, A radical–radical coupling is most likely taking place. [CrossRef] [PubMed]
24. Rono, L.J.; Yayla, H.G.; Wang, D.Y.; Armstrong, M.F.; Knowles, R.R. Enantioselective Photoredox Catalysis Enabled by Proton-Coupled Electron Transfer: Development of an Asymmetric Aza-Pinacol Cyclization. *J. Am. Chem. Soc.* **2013**, *135*, 17735–17738. [CrossRef] [PubMed]
25. Garrido-Castro, A.F.; Choubane, H.; Daaou, M.; Maestro, M.C.; Alemán, J. Asymmetric radical alkylation of *N*-sulfinimines under visible light photocatalytic conditions. *Chem. Commun.* **2017**, *53*, 7764–7767. [CrossRef]
26. Li, Y.; Zhou, K.; Wen, Z.; Cao, S.; Shen, X.; Lei, M.; Gong, L. Copper(II)-Catalyzed Asymmetric Photoredox Reactions: Enantioselective Alkylation of Imines Driven by Visible Light. *J. Am. Chem. Soc.* **2018**, *140*, 15850–15858. [CrossRef]
27. Han, B.; Li, Y.; Yu, Y.; Gong, L. Photocatalytic enantioselective α-aminoalkylation of acyclic imine derivatives by a chiral copper catalyst. *Nat. Commun.* **2019**, *10*, 3804–3812. [CrossRef]
28. Li, Y.; Lei, M.; Gong, L. Photocatalytic regio- and stereoselective C(sp^3)–H functionalization of benzylic and allylic hydrocarbons as well as unactivated alkanes. *Nat. Catal.* **2019**, *2*, 1016–1026, The reaction pathway could not be confirmed; both the radical addition and the radical–radical coupling are most likely taking place. [CrossRef]
29. Schindler, W.; Knoch, F.; Kisch, H. Semiconductor-Catalysed Photoaddition: γ,δ-Unsaturated Amines from Cyclopentene and Schiff Bases. *Chem. Ber.* **1996**, *129*, 925–932. [CrossRef]
30. Keck, H.; Schindler, W.; Knoch, F.; Kisch, H. Type B Semiconductor Photocatalysis: The Synthesis of Homoallyl Amines by Cadmium Sulfide-Catalyzed Linear Photoaddition of Olefins and Enol/Allyl Ethers to *N*-Phenylbenzophenone Imine. *Chem. Eur. J.* **1997**, *3*, 1638–1645. [CrossRef]
31. Kisch, H. Semiconductor Photocatalysis for Chemoselective Radical Coupling Reactions. *Acc. Chem. Res.* **2017**, *50*, 1002–1010. [CrossRef]
32. Xi, Z.-W.; Yang, L.; Wang, D.-Y.; Pu, C.-D.; Shen, Y.-M.; Wu, C.-D.; Peng, X.-G. Visible-Light Photocatalytic Synthesis of Amines from Imines via Transfer Hydrogenation Using Quantum Dots as Catalysts. *J. Org. Chem.* **2018**, *83*, 11886–11895. [CrossRef] [PubMed]
33. Van As, D.J.; Connell, T.U.; Brzozowski, M.; Scully, A.D.; Polyzos, A. Photocatalytic and Chemoselective Transfer Hydrogenation of Diarylimines in Batch and Continuous Flow. *Org. Lett.* **2018**, *20*, 905–908. [CrossRef] [PubMed]
34. Hager, D.; MacMillan, D.W.C. Activation of C−H Bonds via the Merger of Photoredox and Organocatalysis: A Coupling of Benzylic Ethers with Schiff Bases. *J. Am. Chem. Soc.* **2014**, *136*, 16986–16989. [CrossRef] [PubMed]

35. Jeffrey, J.L.; Petronijević, F.R.; MacMillan, D.W.C. Selective Radical−Radical Cross-Couplings: Design of a Formal β-Mannich Reaction. *J. Am. Chem. Soc.* **2015**, *137*, 8404–8407. [CrossRef]
36. Nakajima, M.; Fava, E.; Loescher, S.; Jiang, Z.; Rueping, M. Photoredox-Catalyzed Reductive Coupling of Aldehydes, Ketones, and Imines with Visible Light. *Angew. Chem., Int. Ed.* **2015**, *54*, 8828–8832. [CrossRef]
37. Fava, E.; Millet, A.; Nakajima, M.; Loescher, S.; Rueping, M. Reductive Umpolung of Carbonyl Derivatives with Visible-Light Photoredox Catalysis: Direct Access to Vicinal Diamines and Amino Alcohols via α-Amino Radicals and Ketyl Radicals. *Angew. Chem., Int. Ed.* **2016**, *55*, 6776–6779. [CrossRef]
38. Okamoto, S.; Kojiyama, K.; Tsujioka, H.; Sudo, A. Metal-free reductive coupling of C=O and C=N bonds driven by visible light: Use of perylene as a simple photoredox catalyst. *Chem. Commun.* **2016**, *52*, 11339–11342. [CrossRef]
39. Rong, J.; Seeberger, P.H.; Gilmore, K. Chemoselective Photoredox Synthesis of Unprotected Primary Amines Using Ammonia. *Org. Lett.* **2018**, *20*, 4081–4085. [CrossRef]
40. Xia, Q.; Tian, H.; Dong, J.; Qu, Y.; Li, L.; Song, H.; Liu, Y.; Wang, Q. *N*-Arylamines Coupled with Aldehydes, Ketones, and Imines by Means of Photocatalytic Proton-Coupled Electron Transfer. *Chem. Eur. J.* **2018**, *24*, 9269–9273. [CrossRef]
41. Kammer, L.M.; Krumb, M.; Spitzbarth, B.; Lipp, B.; Kühlborn, J.; Busold, J.; Mulina, O.M.; Terentev, A.O.; Opatz, T. Photoredox-Catalyzed Four-Component Reaction for the Synthesis of Complex Secondary Amines. *Org. Lett.* **2020**, *22*, 3318–3322. [CrossRef]
42. Chen, M.; Zhao, X.; Yang, C.; Xia, W. Visible-Light-Triggered Directly Reductive Arylation of Carbonyl/Iminyl Derivatives through Photocatalytic PCET. *Org. Lett.* **2017**, *19*, 3807–3810. [CrossRef] [PubMed]
43. Nicastri, M.C.; Lehnherr, D.; Lam, Y.; DiRocco, D.A.; Rovis, T. Synthesis of Sterically Hindered Primary Amines by Concurrent Tandem Photoredox Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 987–998. [CrossRef] [PubMed]
44. Qi, L.; Chen, Y. Polarity-Reversed Allylations of Aldehydes, Ketones, and Imines Enabled by Hantzsch Ester in Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 13312–13315. [CrossRef] [PubMed]
45. Fuentes de Arriba, A.L.; Urbitsch, F.; Dixon, D.J. Umpolung synthesis of branched α-functionalized amines from imines via photocatalytic three-component reductive coupling reactions. *Chem. Commun.* **2016**, *52*, 14434–14437. [CrossRef]
46. Rossolini, T.; Leitch, J.A.; Grainger, R.; Dixon, D.J. Photocatalytic Three-Component Umpolung Synthesis of 1,3-Diamines. *Org. Lett.* **2018**, *20*, 6794–6798. [CrossRef]
47. Lee, K.N.; Lei, Z.; Ngai, M.-Y. β-Selective Reductive Coupling of Alkenylpyridines with Aldehydes and Imines via Synergistic Lewis Acid/Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 5003–5006. [CrossRef]
48. Lefebvre, Q.; Porta, R.; Millet, A.; Jia, J.; Rueping, M. One Amine–3 Tasks: Reductive Coupling of Imines with Olefins in Batch and Flow. *Chem. Eur. J.* **2020**, *26*, 1363–1367. [CrossRef]
49. Leitch, J.A.; Fuentes de Arriba, A.L.; Tan, J.; Hoff, O.; Martínez, C.M.; Dixon, D.J. Photocatalytic reverse polarity Povarov reaction. *Chem. Sci.* **2018**, *9*, 6653–6658. [CrossRef]
50. Leitch, J.A.; Rogova, T.; Duarte, F.; Dixon, D.J. Dearomative Photocatalytic Construction of Bridged 1,3-Diazepanes. *Angew. Chem., Int. Ed.* **2020**, *59*, 4121–4130. [CrossRef]
51. Ju, T.; Fu, Q.; Ye, J.-H.; Zhang, Z.; Liao, L.-L.; Yan, S.-S.; Tian, X.-Y.; Luo, S.-P.; Li, J.; Yu, D.-G. Selective and Catalytic Hydrocarboxylation of Enamides and Imines with CO_2 to Generate α,α-Disubstituted α-Amino Acids. *Angew. Chem., Int. Ed.* **2018**, *57*, 13897–13901. [CrossRef]
52. Fan, X.; Gong, X.; Ma, M.; Wang, R.; Walsh, P.J. Visible light-promoted CO_2 fixation with imines to synthesize diaryl α-amino acids. *Nat. Commun.* **2018**, *9*, 4936–4943. [CrossRef] [PubMed]
53. Wang, R.; Ma, M.; Gong, X.; Fan, X.; Walsh, P.J. Reductive Cross-Coupling of Aldehydes and Imines Mediated by Visible Light Photoredox Catalysis. *Org. Lett.* **2019**, *21*, 27–31. [CrossRef] [PubMed]
54. Wang, R.; Ma, M.; Gong, X.; Panetti, G.B.; Fan, X.; Walsh, P.J. Visible-Light-Mediated Umpolung Reactivity of Imines: Ketimine Reductions with Cy_2NMe and Water. *Org. Lett.* **2018**, *20*, 2433–2436. [CrossRef] [PubMed]
55. Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. Synergistic Catalysis of Ionic Brønsted Acid and Photosensitizer for a Redox Neutral Asymmetric α-Coupling of *N*-Arylaminomethanes with Aldimines. *J. Am. Chem. Soc.* **2015**, *137*, 13768–13771. [CrossRef]
56. Kizu, T.; Uraguchi, D.; Ooi, T. Independence from the Sequence of Single-Electron Transfer of Photoredox Process in Redox-Neutral Asymmetric Bond-Forming Reaction. *J. Org. Chem.* **2016**, *81*, 6953–6958. [CrossRef]

57. Lin, L.; Bai, X.; Ye, X.; Zhao, X.; Tan, C.-H.; Jiang, Z. Organocatalytic Enantioselective Protonation for Photoreduction of Activated Ketones and Ketimines Induced by Visible Light. *Angew. Chem., Int. Ed.* **2017**, *56*, 13842–13846. [CrossRef]
58. Cao, K.; Tan, S.M.; Lee, R.; Yang, S.; Jia, H.; Zhao, X.; Qiao, B.; Jiang, Z. Catalytic Enantioselective Addition of Prochiral Radicals to Vinylpyridines. *J. Am. Chem. Soc.* **2019**, *141*, 5437–5443. [CrossRef]
59. Guo, X.; Okamoto, Y.; Schreier, M.R.; Ward, T.R.; Wenger, O.S. Enantioselective synthesis of amines by combining photoredox and enzymatic catalysis in a cyclic reaction network. *Chem. Sci.* **2018**, *9*, 5052–5056. [CrossRef]