Iron-Catalyzed Intermolecular N–H Insertion Using Acceptor–Acceptor Carbenes Derived from Iodonium Ylides.

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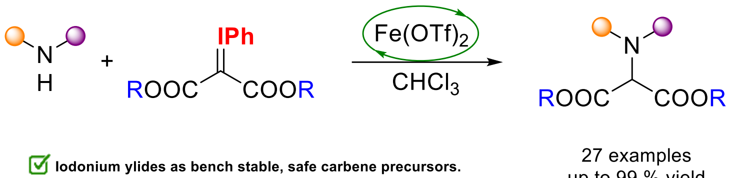
Supporting Information Placeholder



- ☑ Iodonium ylides as bench stable, safe carbene precursors.
- ☑ Use of cheap iron salts as catalysts.
- ☑ Mild reaction conditions, in absence of inert atmosphere.
- ☑ Extremely short reaction times.
- ☑ Primary and secondary aromatic and aliphatic amines.

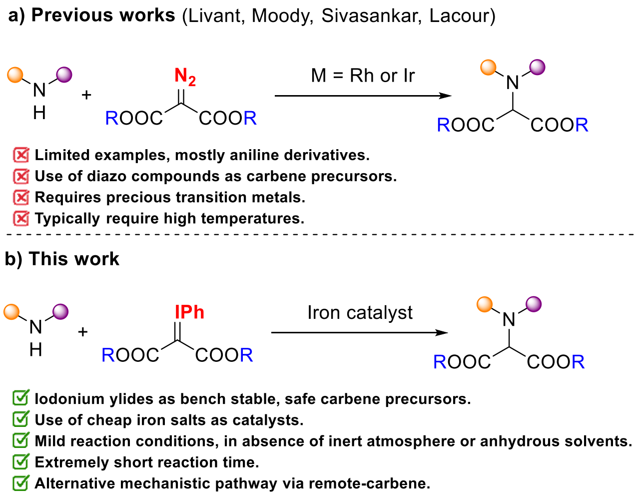
27 examples
up to 99 % yield

ABSTRACT: In this study, we report a general and efficient method for the iron-catalyzed intermolecular N–H insertion at the intercarbonylic position of malonate reagents. Using iodonium ylides and simple iron(II) triflate as the catalyst, the reaction enables the functionalization of a wide range of primary and secondary aromatic and aliphatic amines in excellent yields. The reaction operates under exceptionally mild conditions, without the need for an inert atmosphere or anhydrous solvents, and proceeds in remarkably short reaction times. Mechanistic studies support a non-radical pathway in which an iron(II)-stabilized intermediate having hybrid carbene/carbocationic character undergoes nucleophilic attack by the amine.

Metal carbenes are regarded among the most versatile intermediates in organic chemistry, given their ability to react with a wide range of functional groups, thus enabling the efficient and straightforward construction of diverse chemical bonds.[1,2] Among these, N–H insertion has emerged as especially appealing given the ubiquity of nitrogen heterocycle-containing drugs and small-molecule drugs derived from amino acid derivatives.[3]

Traditionally, diazo compounds have been employed as precursors for generating metal carbenes, with particular emphasis on the generation of donor–acceptor metal carbenes.[4] Instead, the use of acceptor–acceptor carbenes – both in general and particularly in N–H bond insertion reactions – has been largely overlooked in the literature. In the few reported cases, the successful insertion of acceptor–acceptor carbenes into N–H bonds typically require the use of precious metals - Rh(II) or Ir(I) - catalysts (**Scheme 1a**). The groups of Livant[5a] and Moody[5b] reported N–H insertions of diazomalonates under $Rh_2(OAc)_4$ catalysis in refluxing toluene. These transformations are limited to the use of aniline derivatives or sterically hindered secondary alkylamines. Alternatively, the groups of Sivasankar and Lacour employed $[Ir(COD)Cl]_2$ catalyst at room temperature. The substrate scope described by Sivasankar et al.[6] was limited to aromatic amines, while that of Lacour et al.[7] extended to a broader array of aromatic and aliphatic amines.

Scheme 1. N-H insertion reactions with acceptor-acceptor carbenes.



- ☒ Limited examples, mostly aniline derivatives.
- ☒ Use of diazo compounds as carbene precursors.
- ☒ Requires precious transition metals.
- ☒ Typically require high temperatures.

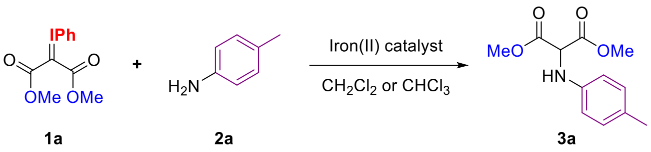
- ☑ Iodonium ylides as bench stable, safe carbene precursors.
- ☑ Use of cheap iron salts as catalysts.
- ☑ Mild reaction conditions, in absence of inert atmosphere or anhydrous solvents.
- ☑ Extremely short reaction time.
- ☑ Alternative mechanistic pathway via remote-carbene.

With these precedents in hand, we envisioned that a methodology that avoids the use of diazo compounds as carbene precursors and precious metals as catalysts will represent a significant advance in the field of acceptor-acceptor carbene N-H insertion. First, iodonium ylides have emerged as promising alternatives to diazo compounds for the generation of acceptor-acceptor carbenes under mild conditions.[8] These reagents are regarded as easily preparable, non-toxic and bench stable solids that bypass the safety issues associated with diazo derivatives.[9] Second, iron constitutes an excellent alternative to precious metals, due to its low toxicity, high natural abundance, and affordability.[10] Nonetheless, iron-catalyzed carbene transfer reactions are underexplored and reports remain scarce.[11] In the particular case of iron-catalyzed carbene N–H insertion reactions, the few reported cases using acceptor carbenes rely on the use of porphyrin derived complexes or highly engineered metalloenzymes.[12]

Herein, we report the N-H insertion of acceptor–acceptor carbenes using iodonium ylides as carbene precursors and simple, commercially available iron catalysts. This highly efficient and straightforward methodology enables the insertion of carbenes into both primary and secondary aromatic and aliphatic amines in high yields and under exceptionally mild conditions, without the need for an inert atmosphere or anhydrous solvents, and in short reaction times.

We began our studies by testing the viability of our hypothesis using iodonium ylide **1a** and 2 equivalents of *p*-toluidine **2a** in the presence of iron(II) acetylacetonate in anhydrous dichloromethane under inert conditions inside a glovebox for 15 min (entry 1, **Table 1**). This initial experiment yielded the desired product **3a** in 54% yield. Encouraged by this result, we repeated the reaction outside the glovebox without employing anhydrous solvents (entry 2, **Table 1**). Remarkably, **3a** was obtained after 45 min. in an improved 74% yield, highlighting the high tolerance and robustness of our transformation. We next evaluated the use of various commercially available iron(II) salts as catalysts. The use of iron(II) acetate resulted in a significantly diminished yield of 17% after 14h (entry 3, **Table 1**). In contrast, iron(II) bromide and chloride afforded **3a** in 77% and 64% yields, respectively (entries 4–5, **Table 1**). Strikingly, when iron(II) triflate was used, immediate solubilization of the iodonium ylide **1a** was observed, with the reaction finished within mixing time, delivering **3a** in 88% yield (entry 6, **Table 1**). Further optimization revealed that the reaction could be carried out with equimolar amounts of the amine partner, affording **3a** in 92% yield (entry 7, **Table 1**). Switching the solvent to chloroform further improved the yield to 99% (entry 8, **Table 1**).[13] We explored the impact of reduction of the catalyst loading to 2.5 mol%, leading to a slightly decreased yield of 84% (entry 9, **Table 1**). Control experiments were conducted to clarify the observed unique reactivity. The use of $Fe(OTf)_3$ or $FeCl_3$ under the optimized conditions afforded **3a** in 54% and 30% yield, respectively. A blank experiment performed in the absence of any iron salt provided **3a** in only 12% yield after 14 hours ~~(entry 10, **Table 1**)~~. Replacement of **1a** with dimethyl 2-diazomalonate led to recovery of starting materials, even upon extending the reaction time to 15 min. Collectively, these results underscore the catalytic role of iron, the superior performance of iron(II) salts, and the essential role of the iodonium ylide as a carbene surrogate in this transformation. Finally, addition of 10 equivalents H_2O under the optimized conditions afforded **3a** in 96% yield, with no detectable water-insertion byproducts, confirming the reaction's tolerance to moisture.

Table 1. Optimization of the reaction conditions[a].

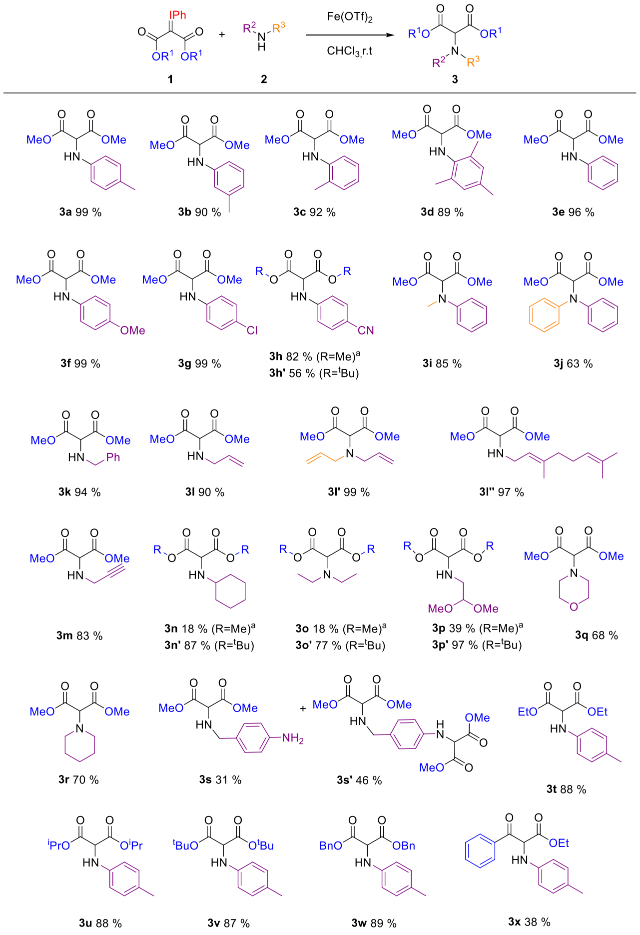


Entry	Catalyst	Reaction time	Yield % (3a)
1[b]	$Fe(acac)_2$	15 min.	54
2	$Fe(acac)_2$	45 min.	74
3	$Fe(OAc)_2$	14 h	17
4	$FeBr_2$	45 min.	77
5	$FeCl_2$	75 min.	64
6	$Fe(OTf)_2$	Mixing time	88
7[c]	$Fe(OTf)_2$	Mixing time	92
8[d]	$Fe(OTf)_2$	Mixing time	99 (99)[e]
9[f]	$Fe(OTf)_2$	Mixing time	84[e]

[a]Reactions were carried out with 0.08 mmol of iodonium ylide **1a**, 0.16 mmol of *p*-toluidine **2a** and 5 mol% catalyst loading, at room temperature in 1 mL of CH_2Cl_2 for the time stated (until complete solubilization of the iodonium ylide). NMR yields calculated via ^1H NMR spectroscopy using CH_2Br_2 as internal standard. [b] Reaction carried out inside of the glovebox using anhydrous solvent [c] Reaction carried out with 0.08 equivalents of *p*-toluidine **2a.** [d] Reaction carried out in $CHCl_3$ as the solvent. [e] Isolated yield. [f] Reaction carried out with 2.5 mol% catalyst loading.

With the optimized conditions in hand, we next explored the scope of the reaction (**Scheme 2**). We began by evaluating the effect of substitution on the aniline moiety. Both *meta*- and *ortho*-toluidine afforded the corresponding insertion products **3b** and **3c** in excellent yields of 90% and 92%, respectively. Notably, the sterically hindered 1,3,5-trimethylaniline also reacted smoothly, delivering **3d** in 89% yield. Unsubstituted aniline could also react efficiently, affording **3e** in an excellent 96% yield. After assessing the tolerance to steric bulk, we next investigated the electronic factors on the aniline ring. *Para*-substituted anilines bearing electron-donating methoxy or electron-withdrawing chlorine groups afforded **3f** and **3g** in quantitative yields. The strong electron-withdrawing (and highly coordinating) nitrile-substituted aniline afforded **3h** in a slightly reduced 82% NMR yield. However, purification was unsuccessful due to co-elution with unreacted *p*-cyanoaniline. Alternatively, we employed a tert-butyl-substituted iodonium ylide, yielding **3h′** in moderate but easily isolable 56% yield. Unfortunately, the reaction with *p*-aminophenol and 2-aminoethanethiol did not proceed and led only to decomposition products. Besides monosubstituted anilines, the reaction was also compatible with aromatic secondary amines bearing methyl and phenyl groups, furnishing **3i** and **3j** in good yields. We then turned our attention to aliphatic amines. Benzylamine reacted cleanly to produce **3k** in 94% yield. Notably, allylamine and propargylamine afforded exclusively the desired insertion products **3l** and **3m**, without any trace of cyclopropanation or cyclopropenation byproducts. Furthermore, the reaction with diallylamine proceeded efficiently, affording the N–H insertion product **3l'** in 99% yield. Interestingly, reaction of geranylamine—a more sterically and electronically demanding substrate bearing both internal and terminal trisubstituted alkenes— also showed excellent selectivity, furnishing the N–H insertion product **3l''** in 97% yield. In contrast, reactions with bulkier aliphatic amines such as cyclohexylamine and diethylamine afforded modest 18% yields of **3n** and **3o** along with the carbene dimerization product (**4**) formed as the major product. We hypothesized that the increased steric bulk of the amines slowed the N-H insertion, thereby allowing the competing iodonium ylide dimerization to dominate. To suppress dimerization, a more sterically hindered tert-butyl derived iodonium was employed. Gratifyingly, the reaction proceeded with significantly improved yields of **3n′** (87%) and **3o′** (77%). Following the same strategy, the reaction with an acetal-derived amine provided **3p′** in an excellent 97% yield.

Scheme 2. Scope of the reaction.

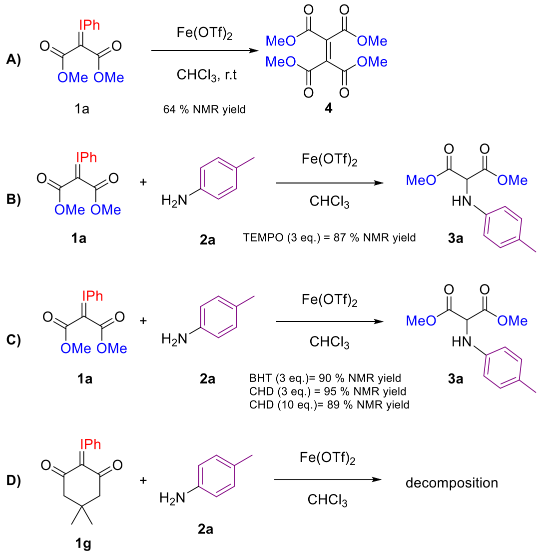


General conditions: Iodonium ylide **1** (0.16 mmol), amine derivative **2** (0.16 mmol, 1.0 equiv), and Fe(OTf)$_2$ (5 mol%) in CHCl$_3$ (2.0 mL) at room temperature. The reactions were complete after mixing time. Isolated yields. [a] NMR yield.

In contrast, when N-Boc protected propargylamine was tested with both methyl and *tert*-butyl iodonium ylides, no N-H insertion was observed in either case, and the reaction resulted predominantly in dimerization of the iodonium ylide. Cyclic secondary amines such as morpholine and piperidine were compatible with the reaction, affording **3q** and **3r** in good yields. To further evaluate the chemoselectivity of the system, we tested *p*-(N-benzylamino)aniline. The reaction yielded a mixture of mono-inserted **3s** and doubly functionalized **3s′**, in 31% and 46% yields, respectively, indicating a preference for the reaction to occur at the benzylic amine over the aromatic one. Finally, we examined the scope of the iodonium ylide partner. Substituents such as ethyl (**3t**), isopropyl (**3u**), tert-butyl (**3v**), and benzyl (**3w**) were all well tolerated, affording the corresponding insertion products in high yields. To evaluate the generality of the method beyond diester-containing substrates, we tested the iodonium ylide derived from methyl 3-oxo-3phenylpropanoate. The reaction proceeded smoothly, affording the desired product **3x** in 38 % yield. When scaling up the reaction for the synthesis of **3a** to 1 mmol mixing the solid reagents prior to solvent addition lead to a spontaneous exothermic event,[14] thus the reagents were dissolved in chloroform before adding the iron catalyst, providing the product in a 71% yield. During the preparation of this manuscript, the group of Song[15] reported the iron-catalyzed insertion of iodonium ylides into B-H and N–H bonds. Unlike in the current report, the reaction relies on a sophisticated iron catalyst, requires strictly inert and anhydrous conditions, significantly longer reaction times and provided lower yields compared to our system, clearly highlighting the advantages of our approach.

To gain a deeper understanding, several mechanistic experiments were conducted (**Scheme 3**). First, we subjected **1a** to the optimized reaction conditions in the absence of any amine partner, leading to dimerized product **4** in 64% NMR yield (**Scheme 3A**). Previous studies by Betley[16] and Groysman[17] have proposed the involvement of vinyl radical intermediates in reactions involving 1,3-dicarbonyl-derived carbene precursors and iron catalysts. DFT calculations by Groysman et al.[17] suggest that the reaction of iodonium ylides with iron(II) alkoxide proceeds via κ^2 coordination through both carbonyl esters and concurrent oxidation, which activates the C-I bond, resulting in the formation of an iron(III) remote carbene/vinyl radical intermediate **A** (**Scheme 4**). This intermediate reacts with alkenes in a stepwise manner to undergo cyclopropanation. On the other hand, the mechanism that Betley et al.[16] describe for their intramolecular C-H alkoxylation of α-diazo-β-ketoesters using Fe(acac)$_2$ as catalyst also involves a radical intermediate. Again, via κ^2 coordination through the keto and ester carbonyls, a single electron transfer from iron to the substrate generates a vinyl carbon radical intermediate **B** (**Scheme 4**), which further evolves via hydrogen atom transfer (HAT). However, several experiments argue against the implication of such a carbon-centered radical intermediate in our system. First, the reaction is not perturbed by the presence of O$_2$. Moreover, when the reaction was carried out in the presence of three equivalents of radical trapping agents such as TEMPO (**Scheme 3B**), the insertion product **3a** was obtained in 87% yield. Furthermore, the addition of BHT or 1,4-cyclohexadiene, well-established hydrogen atom donors, had no apparent effect on the reaction outcome (**Scheme 3C**), suggesting the absence of a competitive hydrogen atom transfer process typically associated with radical species. Altogether, these results point to a mechanistic pathway in which intermediates with radical character are not implicated.

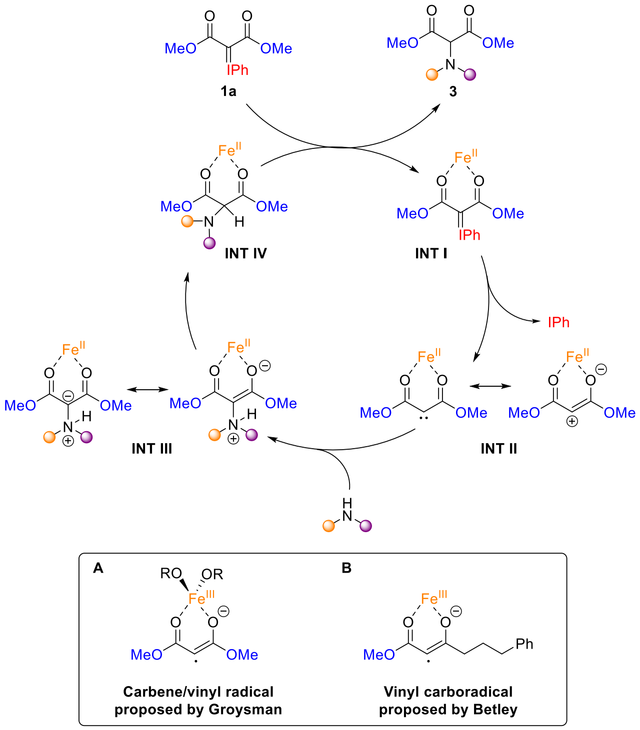
Scheme 3. Mechanistic experiments



The fast reaction rates of the current catalytic system, combined with the low solubility of the iodonium ylides, prevented the identification of reaction intermediates that could support the characterization of the actual catalytic species or provide meaningful guidance to enable computational studies. Under these conditions, we propose a tentative alternative pathway—compatible with the available mechanistic information—in which the catalyst remains in the iron(II) oxidation state (**Scheme 4)**. Consistent with the precedents reported by Groysman and Betley, the iron center is κ^2-coordinated to the two ester carbonyl groups. Supporting this coordination-based mechanism, the reaction with dimedone-derived iodonium ylide **1g** (**Scheme 3D**) failed and led exclusively to decomposition, likely due to the rigid cyclic structure preventing proper coordination to the iron center. This coordination, instead or promoting oxidation, stabilizes an intermediate that can be viewed as a hybrid between a vinyl carbocation and a "remote" carbene (**INT II**). Differences in the ligand set, which in the current case is less donating that in Groysman and Betley's catalysts may upshift the Fe(III)/Fe(II) red-ox potential, favoring the ferrous state. To the best of our knowledge, this would represent the first example of a remote carbene intermediate operating in a metal-carbene-type transformation. The carbocationic character of this intermediate accounts for its high reactivity towards nucleophilic amines, as well as the chemoselectivity observed with substrates bearing alkenes (**3l**) and alkynes (**3m**). This hypothesis was further supported by a control experiment using styrene under otherwise analogous conditions, which showed no evidence of cyclopropanation product formation, but only dimerization of the iodonium ylide.

To sum up, the proposed reaction mechanism (**Scheme 4**) begins with the initial coordination of the iron catalyst to iodonium ylide **1a**, forming intermediate **INT I**. This intermediate undergoes extrusion of iodobenzene to generate the iron remote carbene (**INT II**). Nucleophilic attack by the amine at the carbenic/carbocationic carbon yields ylide intermediate **INT III**, which undergoes a proton transfer followed by dissociation of final product **3a** from the iron center.

Scheme 4. Proposed mechanism



In conclusion, we have developed a novel method for the N-H insertion of acceptor–acceptor carbenes, utilizing iodonium ylides as carbene precursors and readily available, inexpensive iron(II) triflate as the catalyst. The reaction proceeds efficiently under mild conditions, without the need for an inert atmosphere or anhydrous solvents, in remarkably short reaction times. Mechanistic studies support a non-radical pathway in which an iron(II)-stabilized intermediate having hybrid carbene/carbocationic character undergoes nucleophilic attack by the amine.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details and spectral data for all unknown compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Jia, M.; Ma, S. New Approaches to the Synthesis of Metal Carbenes. *Angew. Chem. Int. Ed.* **2016,** *55*, 9134-9166. DOI: 10.1002/anie.201508119. (b) Cheng, Q. Q.; Doyle, M. P. The Selection of Catalysts for Metal Carbene Transformations. In *Advances in Organometallic Chemistry*, Pérez, P. J., Ed. Academic Press: 2016; Vol.

66, chapter 1, pp 1-31. DOI: 10.1016/bs.adomc.2016.07.002. (c) He, Y.; Huang, Z.; Wu, K.; Ma, J.; Zhou, Y.-G.; Yu, Z. Recent Advances in Transition-Metal-Catalyzed Carbene Insertion to C–H Bonds. *Chem. Soc. Rev.* **2022,** *51*, 2759-2852. DOI: 10.1039/D1CS00895A. (d) Zhang, L.; DeMuynck, B.M.; Paneque, A.N.; Rutherford, J.E.; Nagib, D.A. Carbene Reactivity from Alkyl and Aryl Aldehydes, *Science*, **2022**, *377*, 649-654. DOI: 10.1126/science.abo6443.

(2) (a) Bergstrom, B. D.; Nickerson, L. A.; Shaw, J. T.; Souza, L. W. Transition Metal Catalyzed Insertion Reactions with Donor/Donor Carbenes. *Angew. Chem. Int Ed*. **2021**, *60*, 6864-6878. DOI: 10.1002/anie.202007001. (b) Huang, M.-Y.; Zhu, S.-F. Uncommon Carbene Insertion Reactions. *Chem. Sci.* **2021**, *12*, 15790-15801. DOI: 10.1039/D1SC03328J. (c) Balhara, R.; Chatterjee, R.; Jindal, G. Mechanism and Stereoselectivity in Metal and Enzyme Catalyzed Carbene Insertion into X–H and C(sp_2)–H Bonds. *Chem. Soc. Rev*. **2024**, *53*, 11004-11044. DOI: 10.1039/D4CS00742E.

(3) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257-10274. DOI: 10.1021/jm501100b. (b) Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T. An Update on the Nitrogen Heterocycle Compositions and Properties of U.S. FDA-Approved Pharmaceuticals (2013-2023). *J. Med. Chem.* **2024**, *67*, 11622–11655. DOI: acs.jmedchem.4c01122. (c) Lui, A.; Han, J.; Nakano, A.; Konno, H.; Moriwaki, H.; Abe, H.; Izawa, K., Soloshonok, V. A. New Pharmaceuticals Approved by FDA in 2020: Small-Molecule Drugs Derived from Amino Acids and Related Compounds. *Chirality* **2021**, *34*, 86-103. DOI: 10.1002/chir.23376. (d) Han, J.; Konno, H.; Sato, T.; Soloshonok, V. A.; Izawa, K. Tailor-Made Amino Acids in the Design of Small-Molecule Blockbuster Drugs. *Eur. J. Med. Chem.* **2021**, *220*, 113448. DOI: 10.1016/j.ejmech.2021.113448.

(4) (a) Davies, H. M. L.; Denton, J. R. Application of Donor/Acceptor-Carbenoids to the Synthesis of Natural Products. *Chem. Soc. Rev.* **2009**, *38*, 3061-3071. DOI: 10.1039/B901170F. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. Catalytic Carbene Insertion into C−H Bonds. *Chem. Rev.* **2010**, *110*, 704-724. DOI: 10.1021/cr900239n. (c) Davies, H. M. L.; Morton, D. Guiding Principles for Site Selective and Stereoselective Intermolecular C–H Functionalization by Donor/Acceptor Rhodium Carbenes. *Chem. Soc, Rev.* **2011**, *40*, 1857-1869. DOI: 10.1039/C0CS00217H. (d) Cheng, Q.-Q.; Deng, Y.; Lankelma, M.; Doyle, M. P. Cycloaddition Reactions of Enoldiazo Compounds. *Chem. Soc. Rev.* **2017**, *46*, 5425-5443. DOI: 10.1039/C7CS00324B. (e) Zhu, D.; Chen, L.; Fan, H.; Yao, Q.; Zhu, S. Recent Progress on Donor and Donor–Donor Carbenes. *Chem. Soc. Rev.* **2020**, *49*, 908-950. DOI: 10.1039/C9CS00542K.

(5) (a) Yang, M.; Wang, X.; Li, H.; Livant, P. A New Route To Hindered Tertiary Amines. *J. Org. Chem.* **2001**, *66*, 6729-6733. DOI: 10.1021/jo010583a. (b) Bashford, K. E.; Cooper, A. L.; Kane, P. D.; Moody, C. J.; Muthusamy, S.; Swann, E. N–H Insertion Reactions of Rhodium Carbenoids. Part 3.1 The Development of a Modified Bischler Indole Synthesis and a New Protecting-Group Strategy for Indoles. *J. Chem. Soc., Perkin Trans. 1* **2002**, *14*, 1672-1687. DOI: 10.1039/B202666J.

(6) Ramakrishna, K.; Sivasankar, C. Iridium Catalyzed Acceptor/Acceptor Carbene Insertion Into N–H Bonds in Water. *Org. Biomol. Chem.* **2017**, *15*, 2392-2396. DOI: 10.1039/C7OB00177K.

(7) Zhong, Z.; Besnard, C.; Lacour, J. General Ir-Catalyzed N–H Insertions of Diazomalonates into Aliphatic and Aromatic Amines. *Org. Lett.* **2024**, *26*, 983-987. DOI: 10.1021/acs.orglett.3c03929.

(8) (a) Tong, M.; Zhang, X.; Wang, Y.; Wang, Z. Advances in Reactions of Iodonium Ylides. *Chin. J. Org. Chem* **2021**, *41*, 126–143. DOI: 10.6023/cjoc20200602 (b) Mi, X.; Pi, C.; Feng, W.; Cui, X. Recent Progress in the Application of Iodonium Ylides in Organic Synthesis. *Org. Chem. Front.* **2022**, *9*, 6999–7015. DOI: 10.1039/D2QO01332K. (c) Díaz-Jiménez, À.; Kennington, S. C. D.; Roglans, A.; Pla-Quintana, A. Copper(I) Iodide Catalyzed [3 + 3] Annulation of Iodonium Ylides with Pyridinium 1,4-Zwitterionic Thiolates for the Synthesis of 1,4-Oxathiin Scaffolds. *Org. Lett.* **2023**, *25*, 4830-4834. DOI: 10.1021/acs.orglett.3c01538

(9) Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. Solvolysis of Cyclohexenyliodonium Salt, a New Precursor for the Vinyl Cation: Remarkable Nucleofugality of the Phenyliodonio Group and Evidence for Internal Return from an Intimate Ion-Molecule Pair. *J. Am. Chem. Soc.* **1995**, *117*, 3360-3367. DOI: 10.1021/ja00117a006.

(10) Enthaler, S.; Junge, K.; Beller, M. Sustainable Metal Catalysis with Iron: From Rust to a Rising Star? *Angew. Chem. Int. Ed.* **2008**, *47*, 3317-3321.DOI: 10.1002/anie.200800012.

(11) (a) Zhu, S.-F.; Zhou, Q.-L. Iron-Catalyzed Transformations of Diazo Compounds. *Nat. Sci. Rev.* **2014**, *1*, 580-603. DOI: 10.1093/nsr/nwu019. (b) Bauer, I.; Knölker, H.-J. Iron Catalysis in Organic Synthesis. *Chem. Rev.* **2015**, *115*, 3170-3387. DOI: 10.1021/cr500425u. (c) Shang, R.; Ilies, L.; Nakamura, E. Iron-Catalyzed C–H Bond Activation. *Chem. Rev.* **2017**, *117*, 9086-9139. DOI: 10.1021/acs.chemrev.6b00772. (d) Hernán-Gómez, A.; Rodríguez, M.; Parella, T.; Costas, M. Electrophilic Iron Catalyst Paired with a Lithium Cation Enables Selective Functionalization of Non-Activated Aliphatic C−H Bonds via Metallocarbene Intermediates. *Angew. Chem. Int. Ed.* **2019**, *58*, 13904-13911. DOI: 10.1002/anie.201905986. (e) Empel, C.; Jana, S.; Koenigs, R.M. C-H Functionalization via Iron-Catalyzed Carbene-Transfer Reactions. *Molecules* **2020**, *25*, 880. DOI: 10.3390/molecules25040880. (f) Rodríguez, M.; Font, G.; Nadal-Moradell, J.; Hernán-Gómez, A.; Costas, M., Iron-Catalyzed Intermolecular Functionalization of Non-Activated Aliphatic C−H Bonds via Carbene Transfer. *Adv. Synth. Catat.* **2020**, *362*, 5116-5123. DOI: 10.1002/adsc.202000817. (g) Damiano, C.; Sonzini, P.; Gallo, E. Iron Catalysts with N-Ligands for Carbene Transfer of Diazo Reagents. *Chem. Soc. Rev.* **2020**, *49*, 4867-4905. DOI: 10.1039/D0CS00221F.

(12) (a) Aviv, I.; Gross, Z. Iron Porphyrins Catalyze the Synthesis of Non-Protected Amino Acid Esters from Ammonia and Diazoacetates. *Chem. Commun.* **2006**, 4477-4479. DOI: 10.1039/B609265A. (b) Wang, Z. J.; Peck, N. E.; Renata, H.; Arnold, F. H. Cytochrome P450-Catalyzed Insertion of Carbenoids into N–H Bonds. *Chem. Sci.* **2014**, *5*, 598-601. DOI: 10.1039/C3SC52535J. (c) Sreenilayam, G.; Fasan, R. Myoglobin-Catalyzed Intermolecular Carbene N–H Insertion with Arylamine Substrates. *Chem. Commun.* **2015**, *51*, 1532-1534. DOI: 10.1039/C4CC08753D. (d) Liu, Z.; Calvó-Tusell, C.; Zhou, A. Z.; Chen, K.; Garcia-Borràs, M.; Arnold, F. H. Dual-Function Enzyme Catalysis for Enantioselective Carbon–Nitrogen Bond Formation. *Nat. Chem.* **2021**, *13*, 1166-1172. DOI: 10.1038/s41557-021-00794-z. (e) Calvó-Tusell, C.; Liu, Z.; Chen, K.; Arnold, F. H.; Garcia-Borràs, M. Reversing the Enantioselectivity of Enzymatic Carbene N−H Insertion Through Mechanism-Guided Protein Engineering. *Angew. Chem. Int. Ed.* **2023**, *62*, e202303879. DOI: 10.1002/anie.202303879. (f) Ma, C.; Wang, S.; Sheng, Y.; Zhao, X.-L.; Xing, D.; Hu, W. Synthesis and Characterization of Donor–Acceptor Iron Porphyrin Carbenes and Their Reactivities in N–H Insertion and Related Three-Component Reaction. *J. Am. Chem. Soc.* **2023**, *145*, 4934-4939. DOI: 10.1021/jacs.2c12155.

(13) As suggested during peer review, we considered the origin of the improved yields observed in chloroform versus dichloromethane. Since both solvents exhibit similar polarity, the difference is likely due to the slightly better solubility of the iodonium ylide in chloroform, which may enhance its availability and reaction efficiency.

(14) **Cautionary note:** When scaling up this reaction to 1 mmol or higher, mixing the solid reagents prior to solvent addition may lead to a spontaneous exothermic event accompanied by gas evolution. To minimize potential hazards, we recommend dissolving the reagents in solvent before adding the iron catalyst, as detailed in the Supporting Information.

(15) An, H.; Cui, Z.; Liang, J.; Ma, X.; Chen, J.; Song, Q. Fe-Catalyzed B–H and N–H Insertion Reactions of Iodonium Ylides. *Org. Chem. Front.* **2025**, DOI: 10.1039/D4QO01916D

(16) Dong, Y.; Wrobel, A. T.; Porter, G. J.; Kim, J. J.; Essman, J. Z.; Zheng, S.-L.; Betley, T. A. O-Heterocycle Synthesis via Intramolecular C–H Alkoxylation Catalyzed by Iron Acetylacetonate. *J. Am. Chem. Soc.* **2021**, *143*, 7480-7489. DOI: 10.1021/jacs.1c02074.

(17) Kulathungage, L. W.; Kurup, S. S.; Browne, E. A.; Spalink, G. H.; Ward, C. L.; Lord, R. L.; Groysman, S. Efficient Carbene Transfer

Reactivity Mediated by Fe(II) Complexes Supported by Bulky Alkoxides. *Chem. Commun.* **2024**, *60*, 7033-7036. DOI: 10.1039/D4CC02108H.