Single-atom insertion into indole

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Content

1. Background
2. Single-carbon atom insertion into indole
3. Single-nitrogen atom insertion into indole
4. Summary and outlook

Content

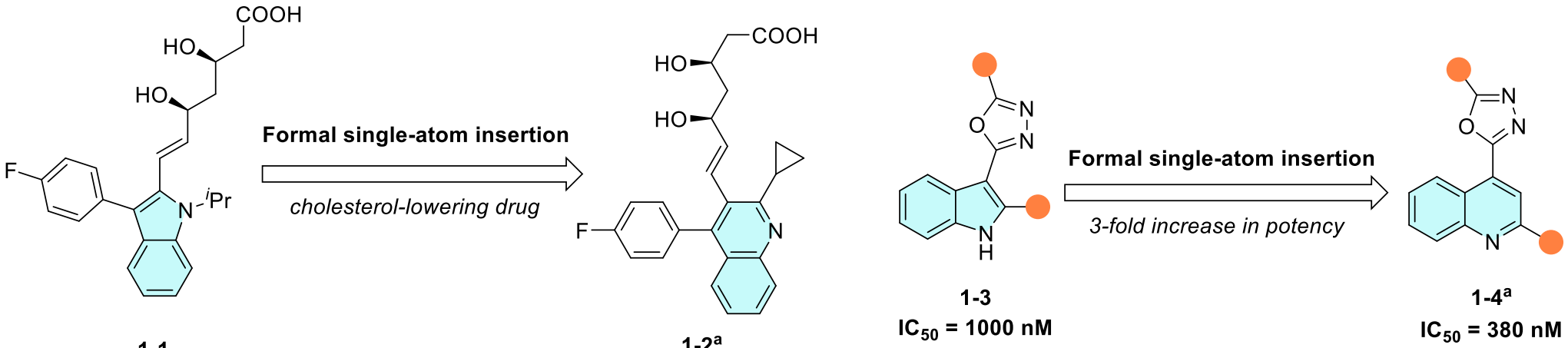
Background

Gisbert Schneider

Scaffold hopping

- ✓ Start with known active compounds
- ✓ End with a novel chemotype
- ✓ By modifying the central core structure of the molecule

Heterocycle replacement



1-1
Fluvastatin

1-2[a]
Pitavastatin

1-3
IC_{50} = 1000 nM

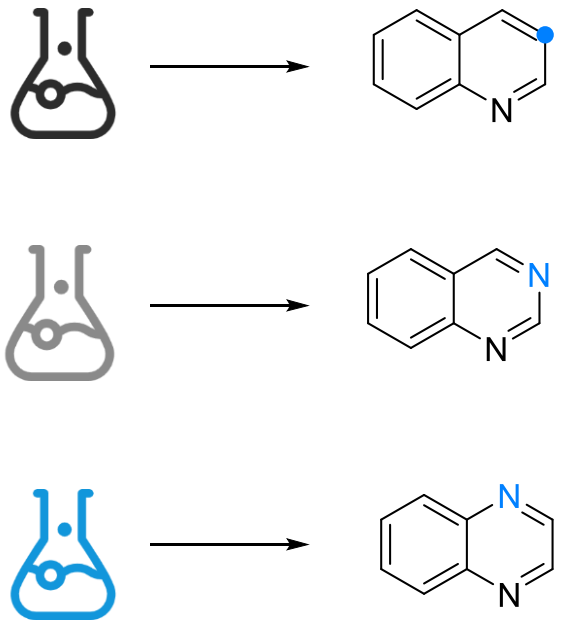
1-4[a]
IC_{50} = 380 nM

[a]*Prepared by traditional multi-step synthesis*

[1] G. Schneider, *et al*. *Angew. Chem. Int. Ed.* **1999**, *38*, 2894–2896. [2] X. Bi, *et al*. *Nat. Commun.* **2024**, *15*, 9998. [3] S. Pang, *et al*. *J. Am. Chem. Soc.* **2026**, *148*, 3672–3680.

Background

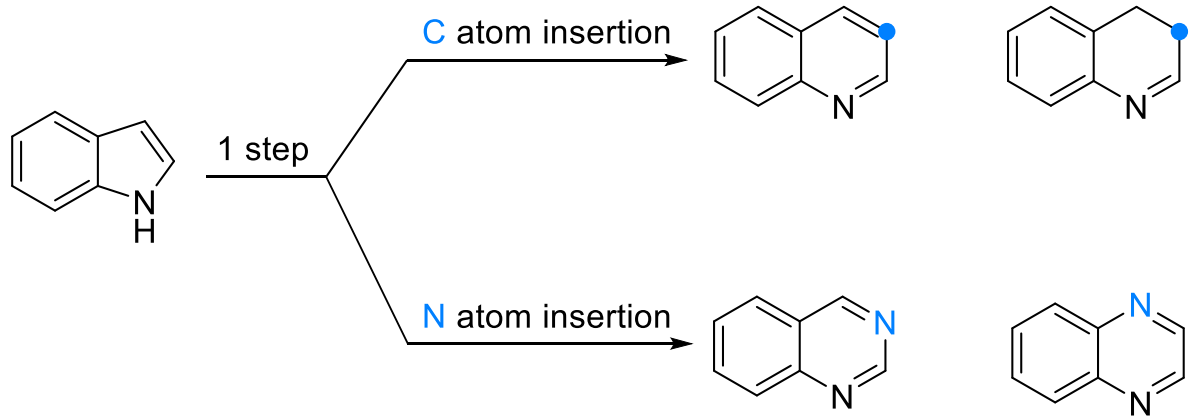
Traditional synthesis:



VS

- **Time-consuming**
- **Not versatile**

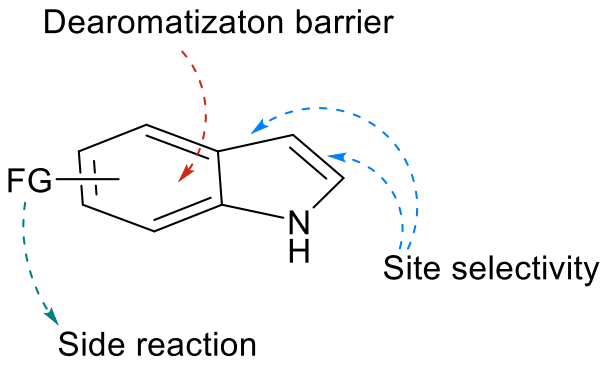
Single-atom insertion:



✓ **Time-saving**

✓ **Versatile**

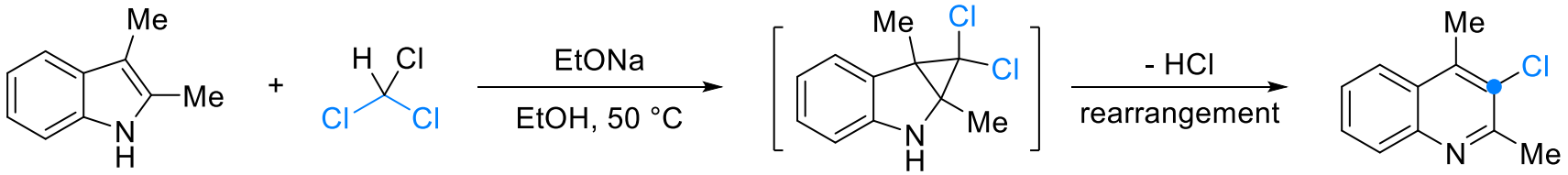
Challenges:



Content

Single-carbon atom insertion into indole

1964 Rees & Smithen

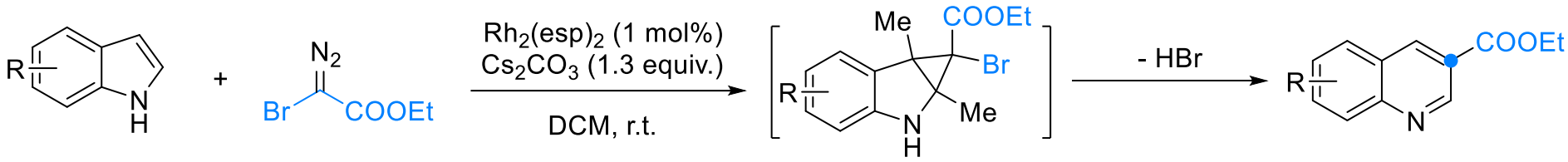


2-1 **2-2** **2-3**

2-4
10% yield

- *limited to halogens*
- *low yield*

2015 Bonge-Hansen



2-5 **2-6** **2-7**

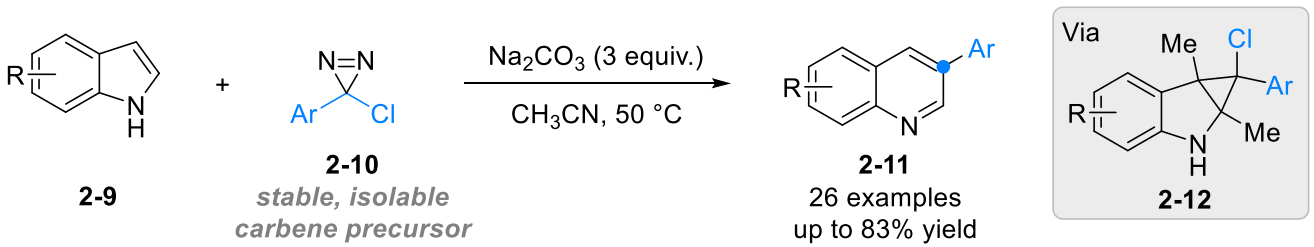
2-8
8 examples
up to 98% yield

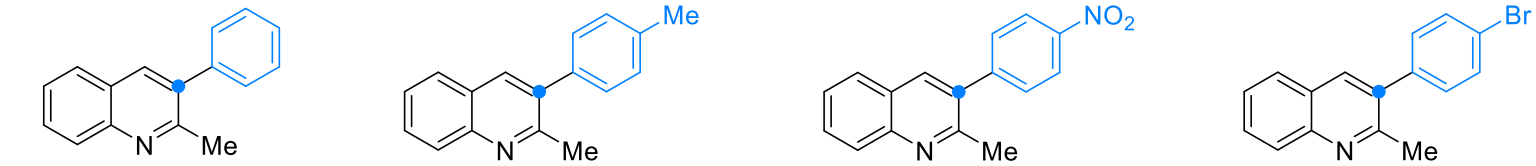
- *poor thermal stability*
- *limited to EWG*

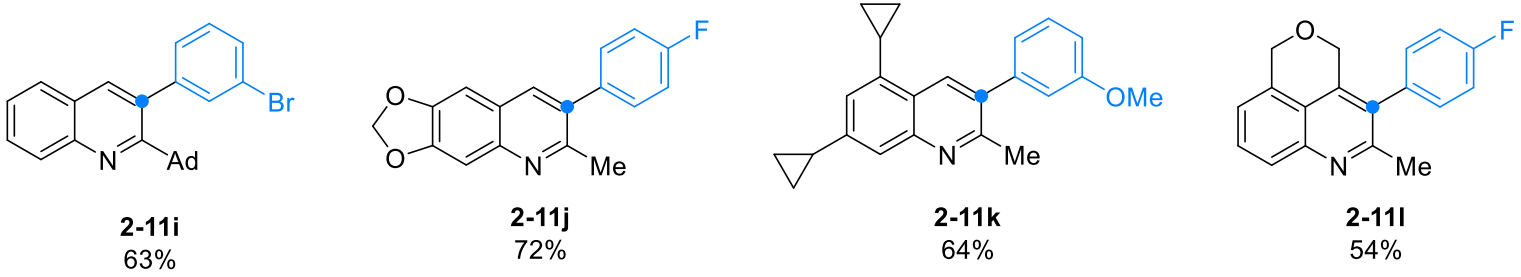
[1] C. E. Smithen, *et al*. *J. Chem. Soc.* **1964**, 928–937.
[2] T. Bonge-Hansen, *et al*. *Beilstein J. Org. Chem.* **2015**, *11*, 1944–1949.

Single-carbon atom insertion into indole

2021 Levin



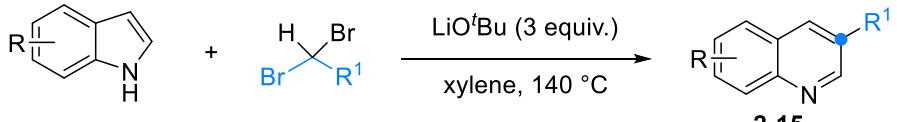




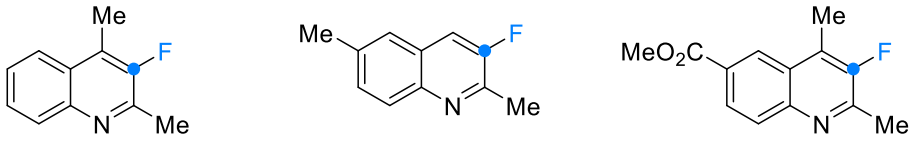
M. D. Levin, *et al*. *J. Am. Chem. Soc.* **2021**, *143*, 11337–11344.

Single-carbon atom insertion into indole

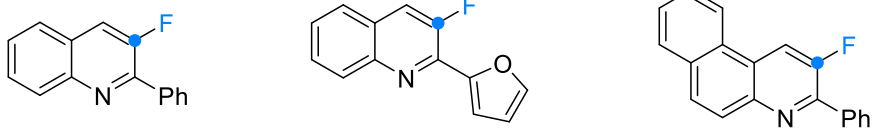
2024 Peng Xu



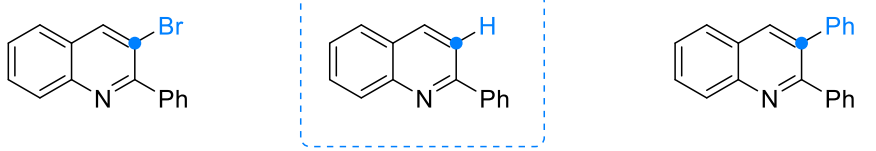
2-13 **2-14** **2-15**
41 examples
up to 87% yield



2-15a 72% **2-15b** 56% **2-15c** 60%

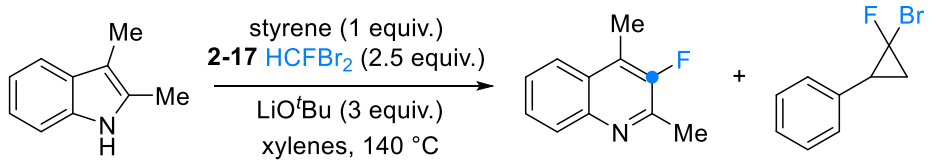


2-15d 75% **2-15e** 51% **2-15f** 58%



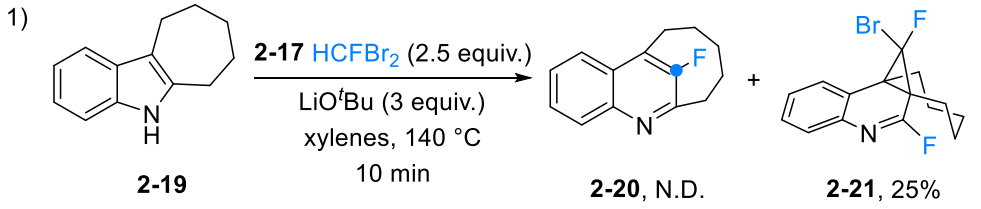
2-15g 87% **2-15h** 56% **2-15i** 61%

a) Detection of carbene intermediate

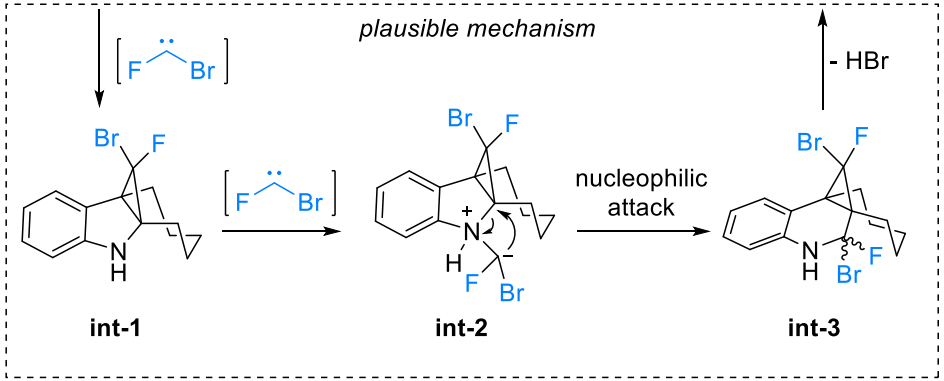


2-16 **2-15a**, 65% **2-18**, 10%

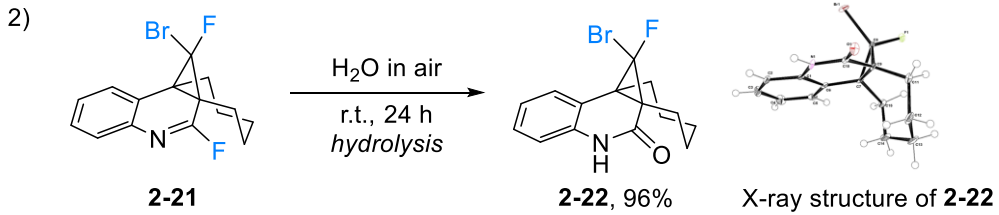
b) Skeletal editing of 7-membered ring-fused indole



2-19 **2-20**, N.D. **2-21**, 25%



int-1 **int-2** **int-3**

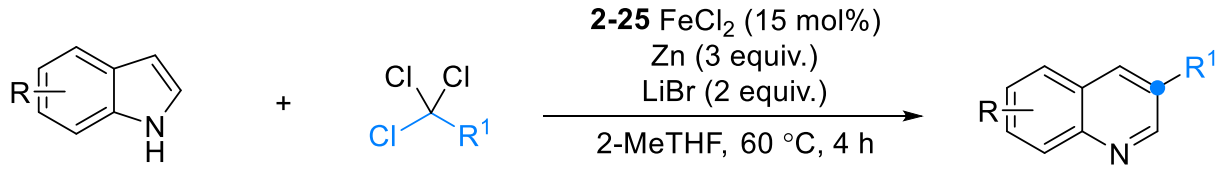


2-21 **2-22**, 96% X-ray structure of **2-22**

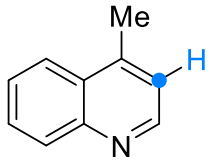
P. Xu, *et al*. *Angew. Chem. Int. Ed.* **2024**, *63*, e202317104.

Single-carbon atom insertion into indole

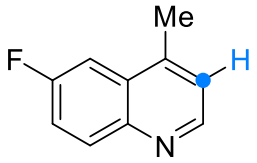
2026 Nagib



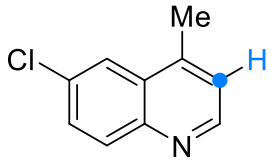
2-23 **2-24** **2-26**
26 examples
up to 77% yield



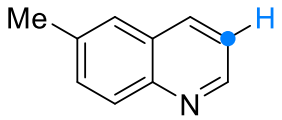
2-26a, 77%



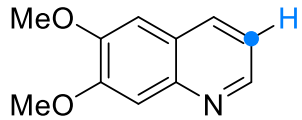
2-26b, 60%



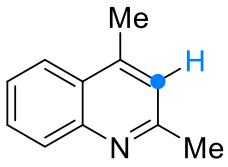
2-26c, 58%



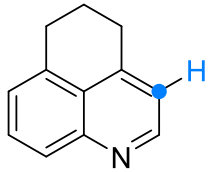
2-26d, 54%



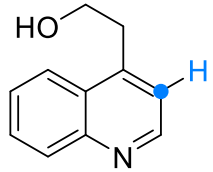
2-26e, 60%



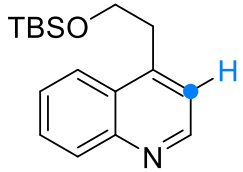
2-26f, 54%



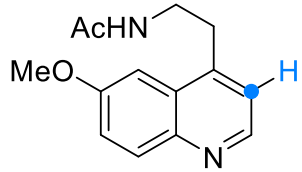
2-26g, 66%



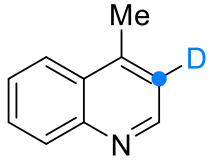
2-26h, 26%



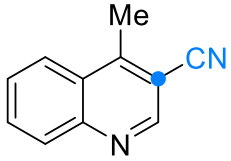
2-26i, 71%



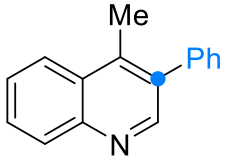
2-26j, 50%



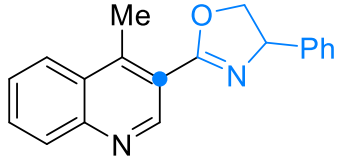
2-26k, 76%



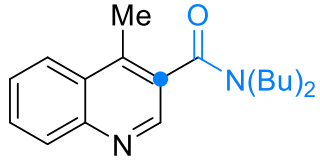
2-26l, 70%



2-26m, 40%



2-26n, 47%

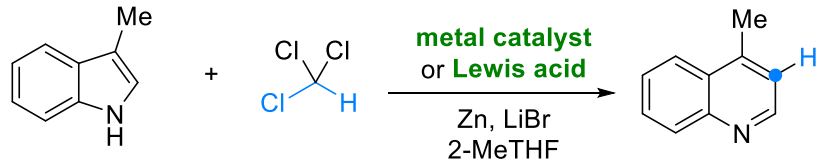


2-26o, 52%

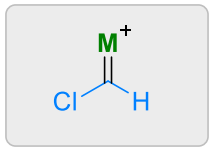
D. A. Nagib, *et al*. *Chem* **2026**, *12*, 102968.

Single-carbon atom insertion into indole

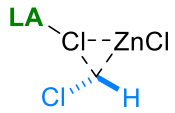
a) Role of Fe catalyst



2-27 **2-28** **2-29**



vs



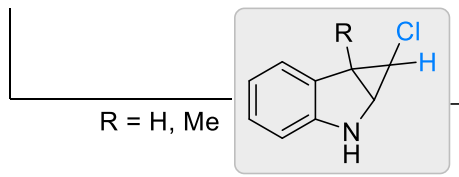
Entry	Fe catalyst	Yield **2-29**
1	**$FeCl_2$**	**77%**
2	$FeBr_2$	53%
3	$Fe(OTf)_2$	48%
4	$FeCl_3$	27%
5	FeTPPCl	0%

Entry	Lewis acid	Yield **2-29**
1	$Cu(OTf)_2$	5%
2	$AuCl_3$	0%
3	$AlCl_3$	0%
4	$In(OTf)_3$	0%
5	$BF_3{\cdot}Et_2O$	0%

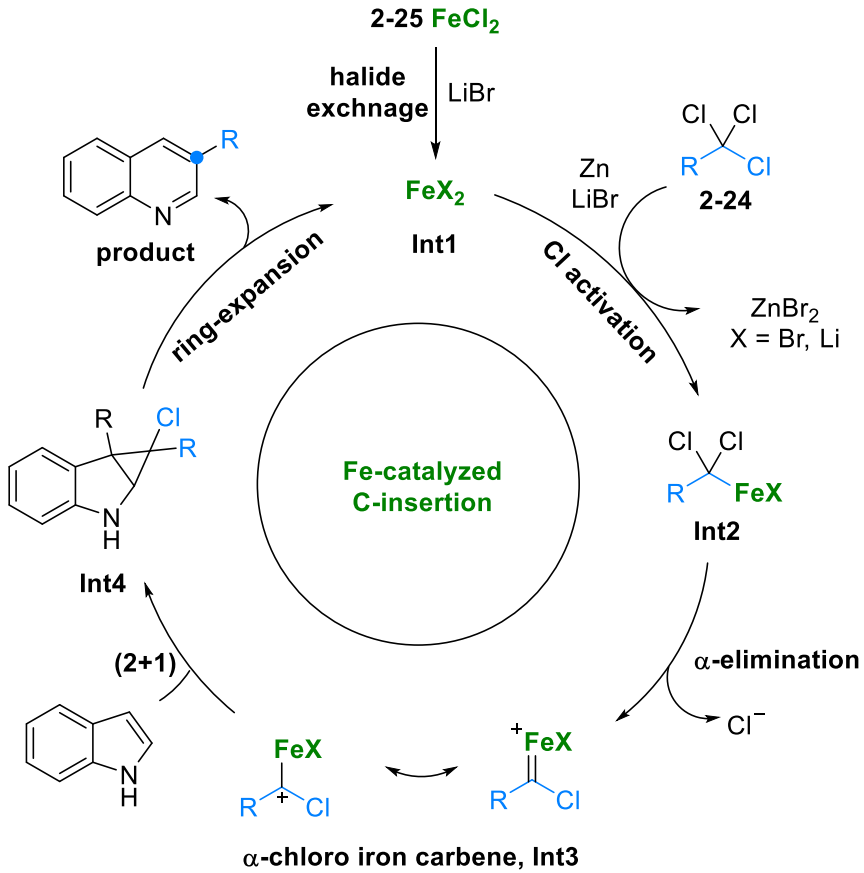
b) Validated intermediates

indole

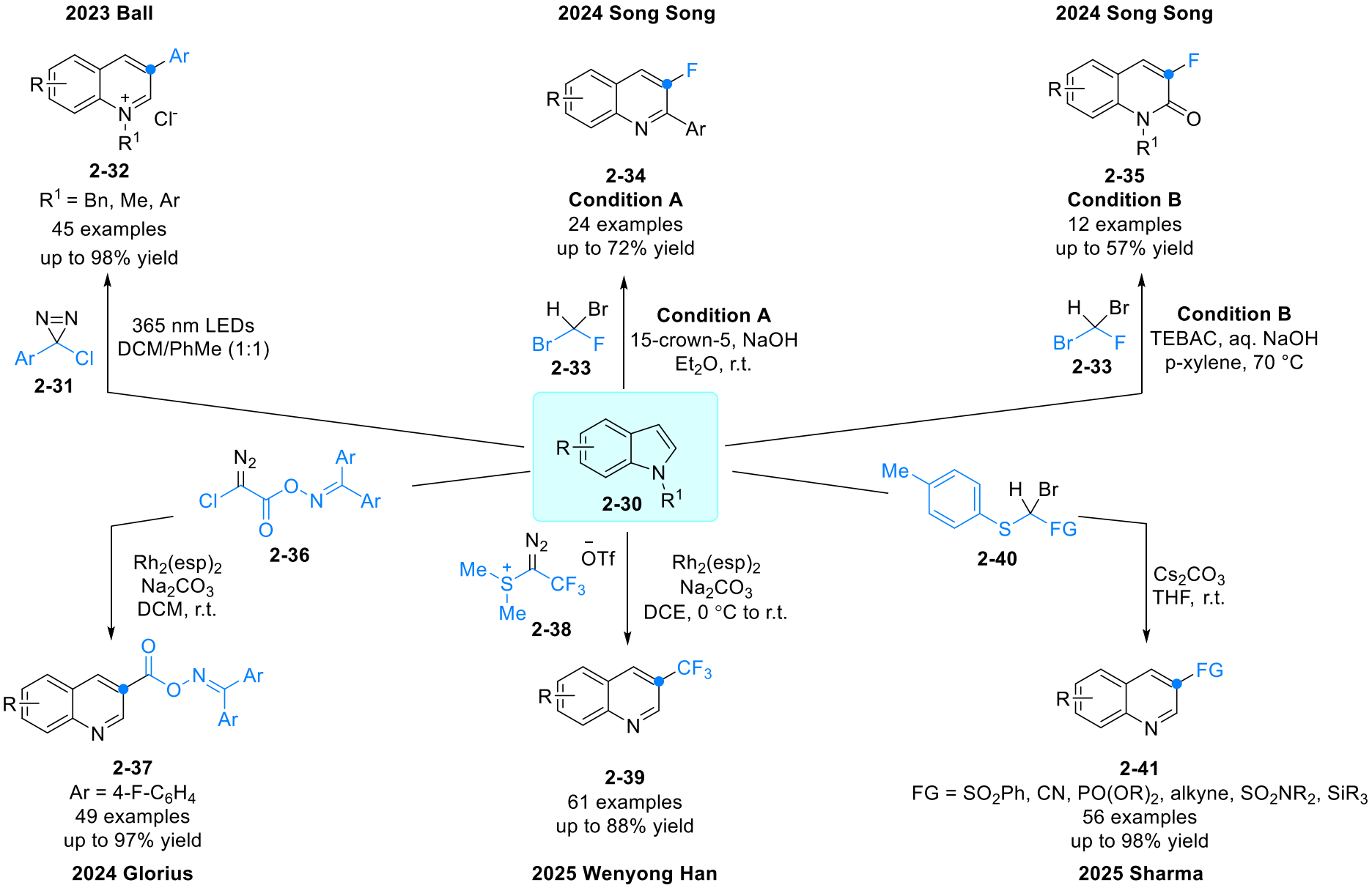
R = H, 8%
R = Me, 77%



c) Plausible mechanism

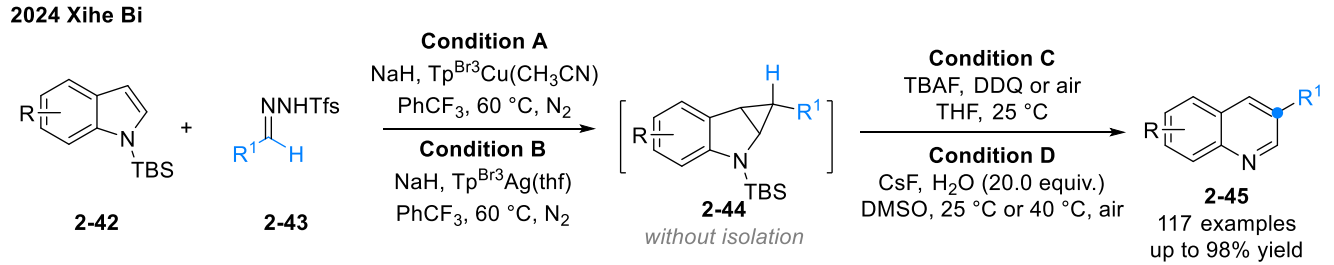


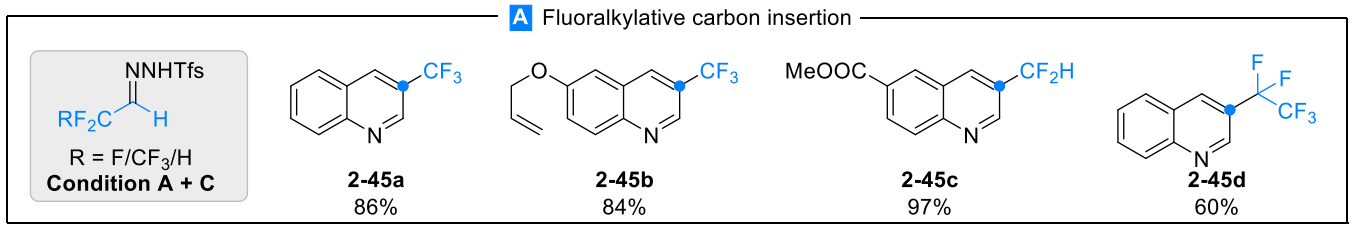
Single-carbon atom insertion into indole

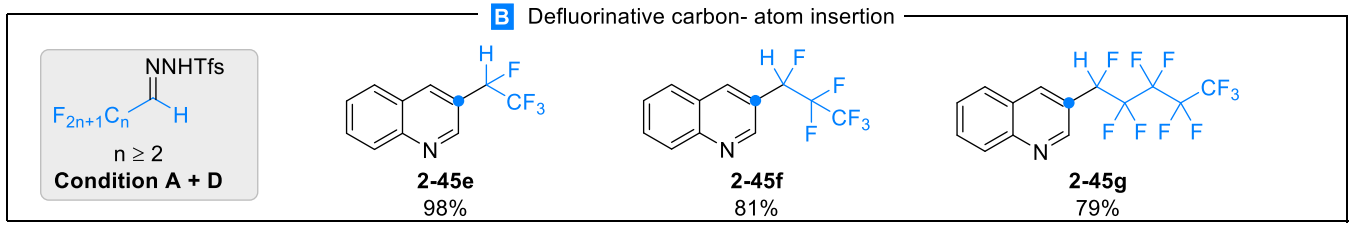


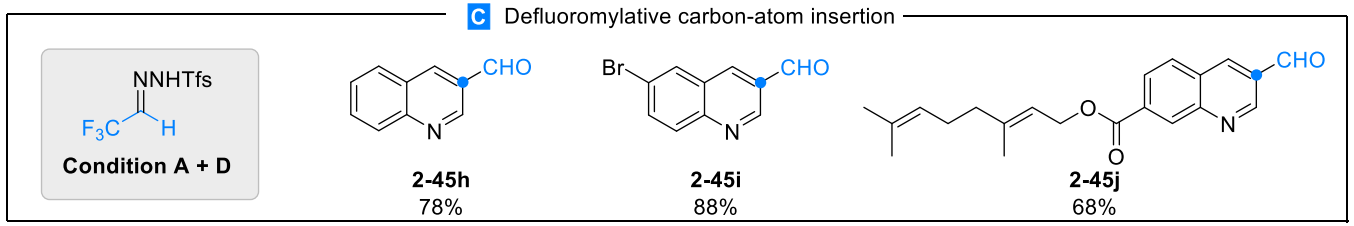
[1] L. T. Ball, *et al*. *Angew. Chem. Int. Ed.* **2023**, *62*, e202305081. [2] S. Song, *et al*. *Chin. J. Chem.* **2024**, *42*, 1128–1132. [3] F. Glorius, *et al*. *ACS Catal.* **2024**, *14*, 13343–13351. [4] W.-Y. Han, *et al*. *Angew. Chem. Int. Ed.* **2025**, *64*, e202501966. [5] I. Sharma, *et al*. *J. Am. Chem. Soc.* **2025**, *147*, 13824–13832.

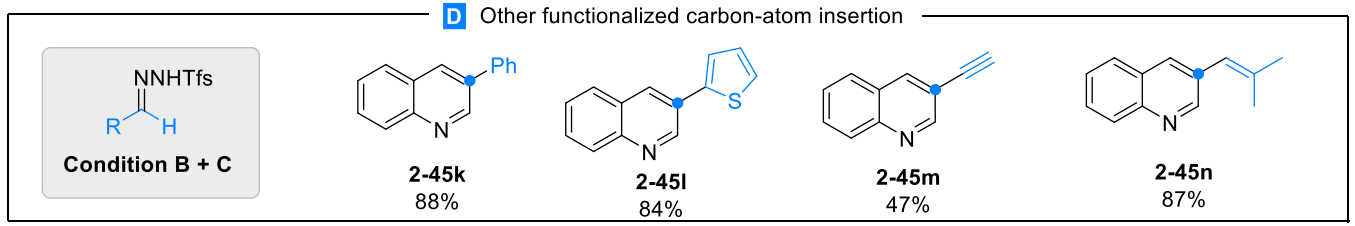
Single-carbon atom insertion into indole







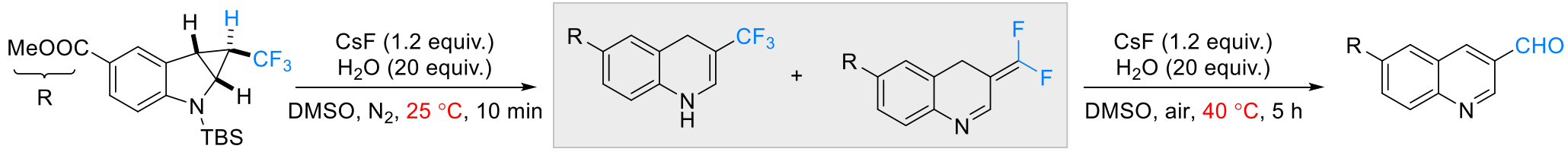




X. Bi, *et al*. *Nat. Commun.* **2024**, *15*, 9998.

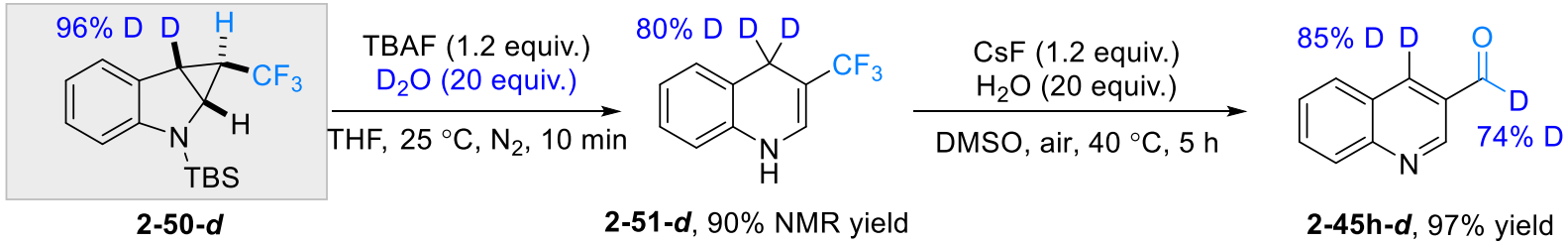
Single-carbon atom insertion into indole

a) Detection of the reaction intermediates

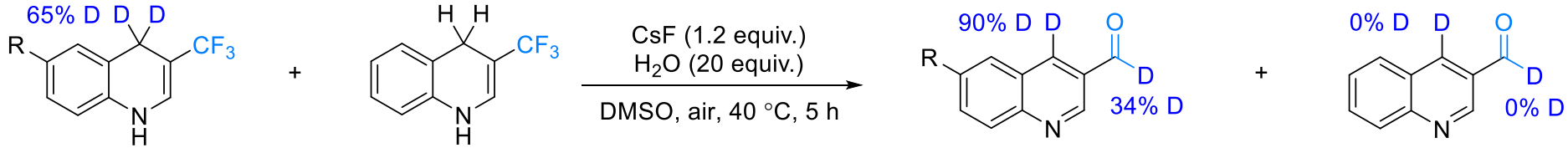


2-46 **2-47**, 40% **2-48**, 42% **2-49**, 80%

b) Experiments to probe the source of the hydrogen atom incorporated in the product

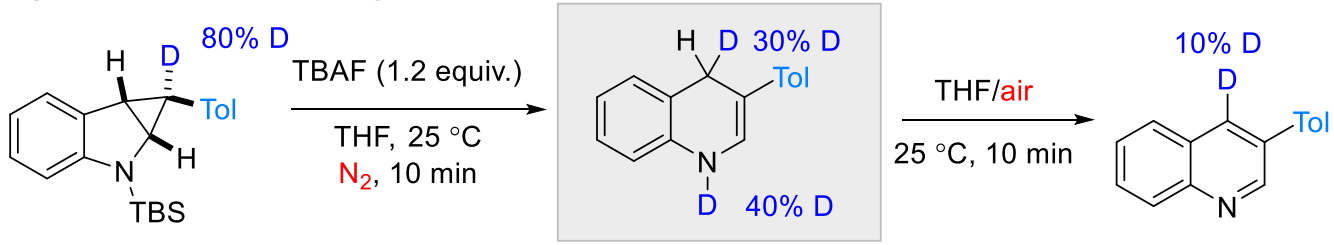


2-50-*d* **2-51-*d***, 90% NMR yield **2-45h-*d***, 97% yield



2-47-*d* **2-51** **2-49-*d*,** 96% **2-45h-*d*,** 90%

c) Experiment to validate the process of imine-enamine tautomerization



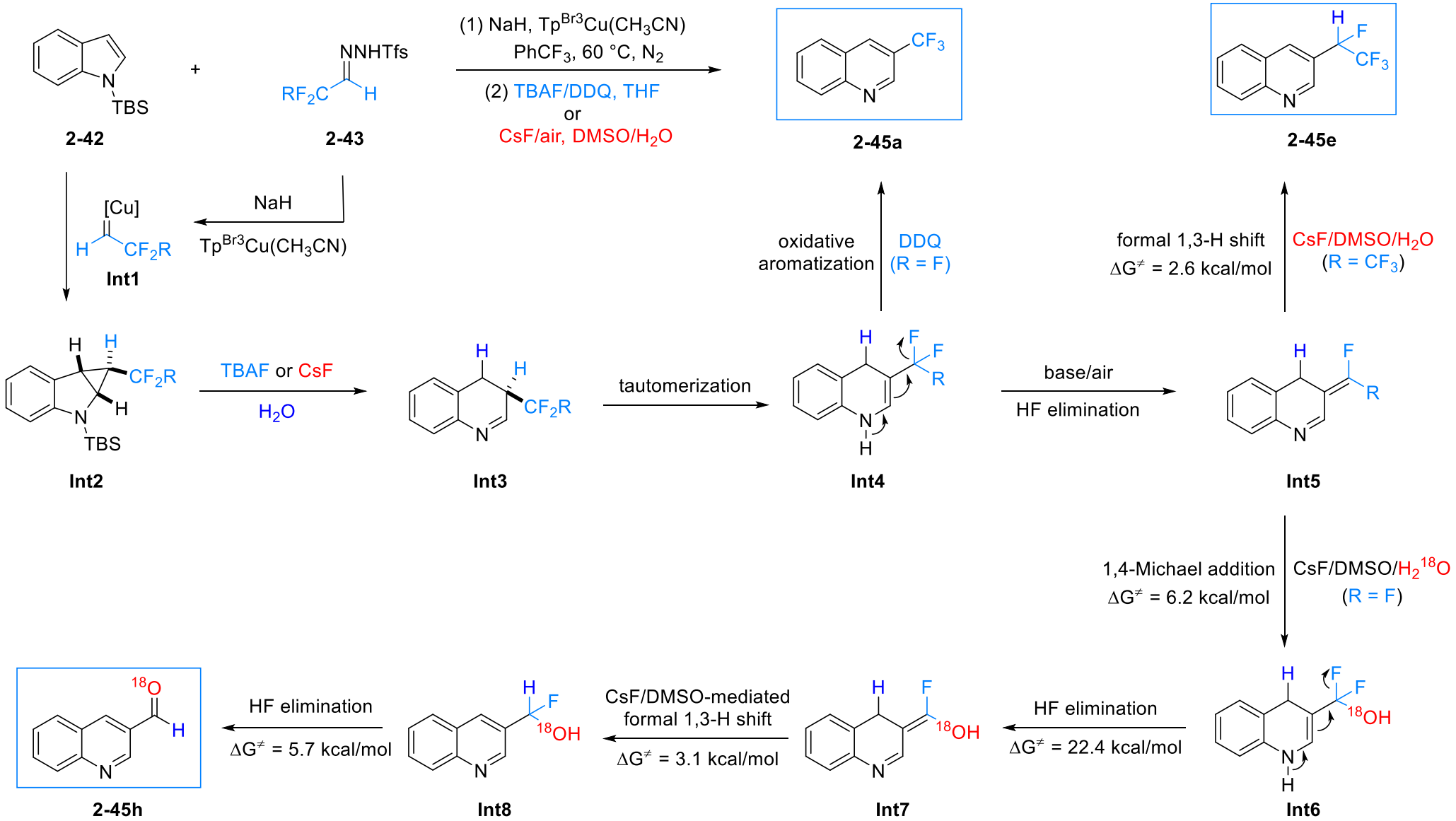
2-52-*d* **2-53**, 98% NMR yield **2-54-*d*,** 97%

d) Probing the source of the oxygen atom

2-50 **2-45h-^{18}O**

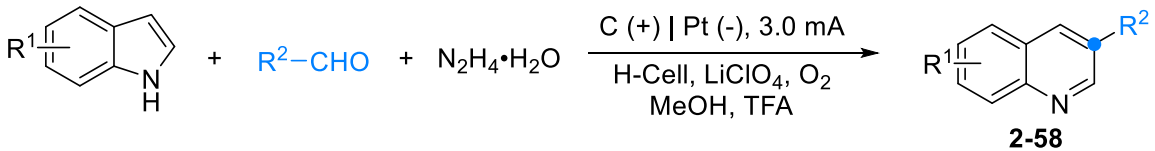
Single-carbon atom insertion into indole

e) Plausible mechanism:

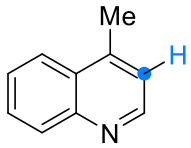


Single-carbon atom insertion into indole

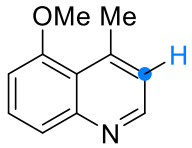
2026 Siping Pang



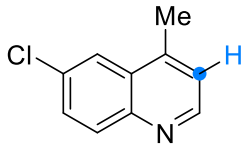
2-55 **2-56** **2-57** **2-58** 68 examples up to 72% yield



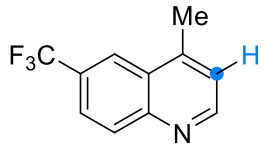
2-58a, 67%



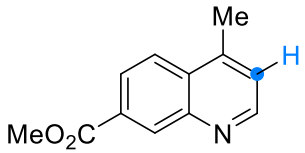
2-58b, 58%



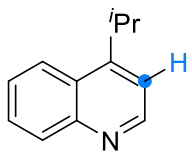
2-58c, 65%



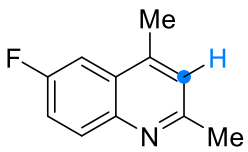
2-58d, 48%



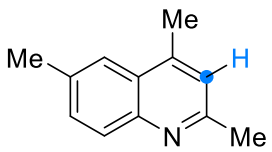
2-58e, 47%



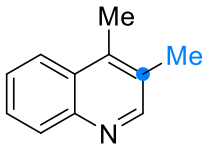
2-58f, 65%



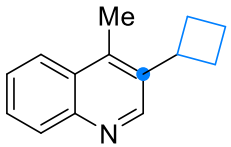
2-58g, 47%



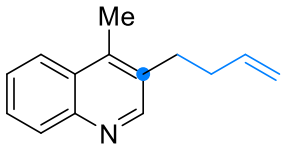
2-58h, 47%



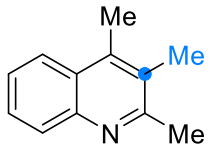
2-58i, 53%



2-58j, 45%



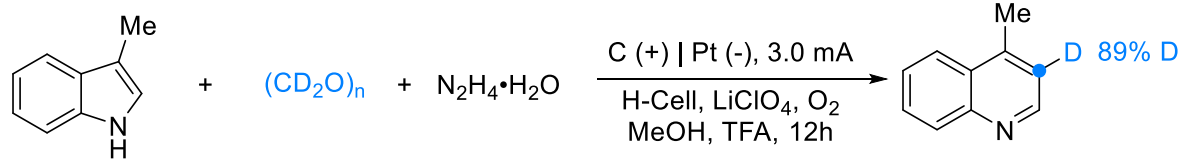
2-58k, 38%



2-58l, 31%

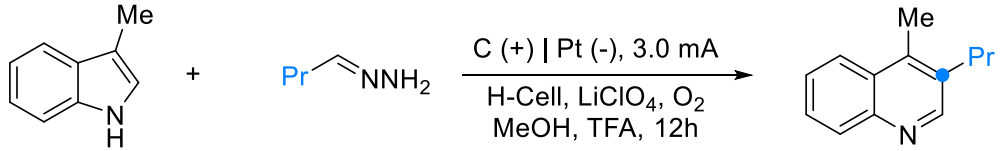
Mechanistic studies:

a) Deuterium labeling experiment

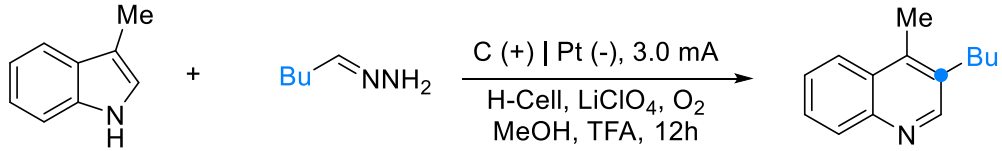


2-59 **2-60** **2-57** **2-61**, 62% yield

b) Hydrazone using as reagents experiments



2-59 **2-62** **2-63**, 40% yield



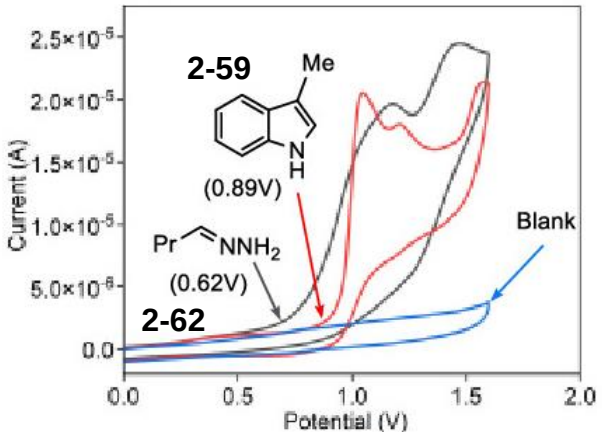
2-59 **2-64** **2-65**, 40% yield

S. Pang, *et al*. *J. Am. Chem. Soc.* **2026**, *148*, 3672–3680

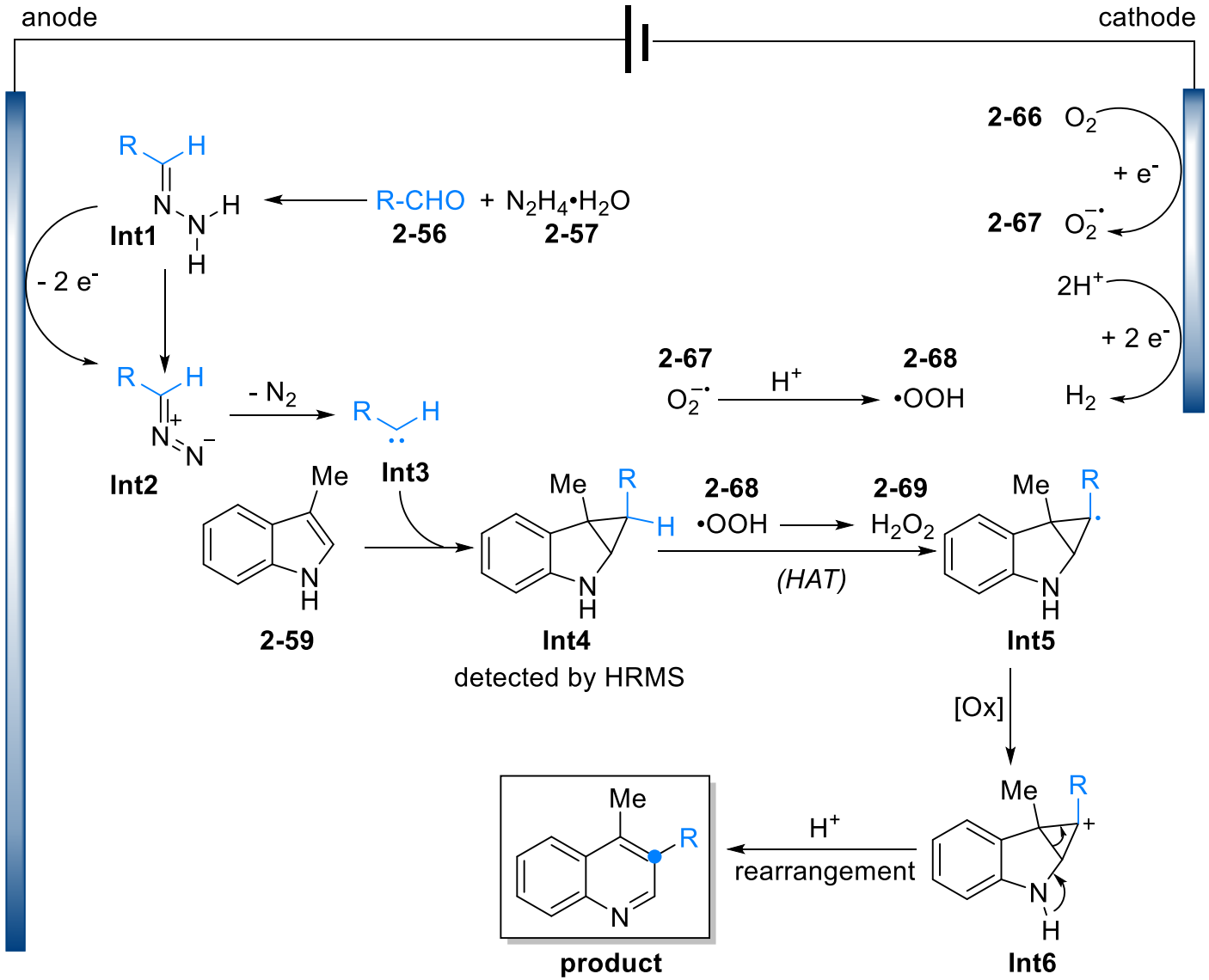
Single-carbon atom insertion into indole

c) H_2O_2 detection experiment

d) CV experiment

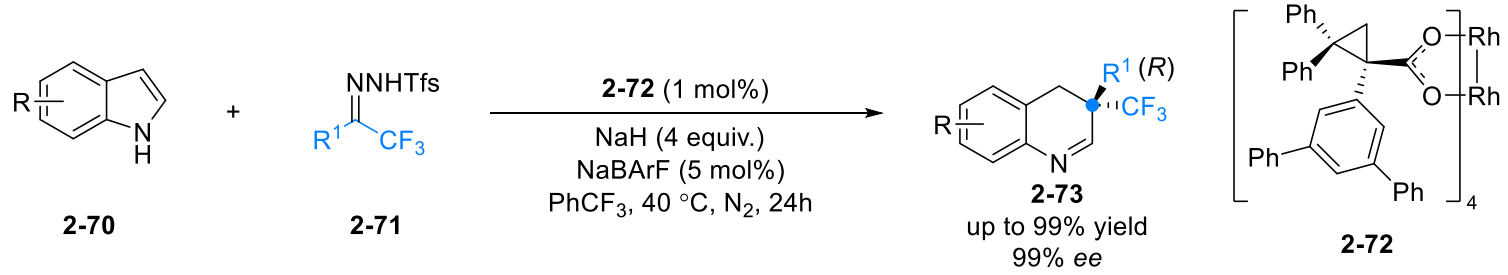


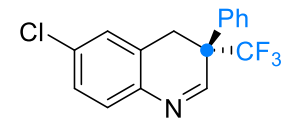
e) Plausible mechanism

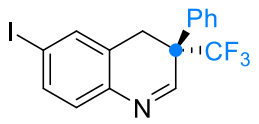


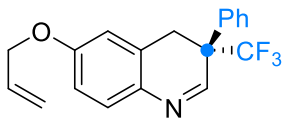
Single-carbon atom insertion into indole

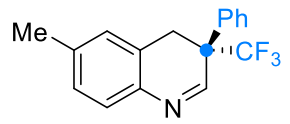
2025 Xihe Bi

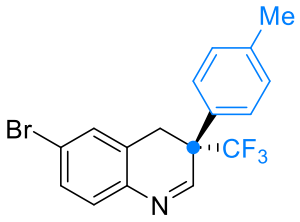


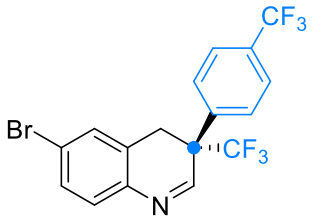


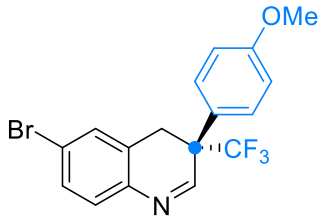


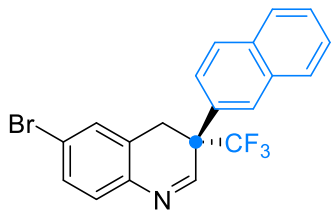






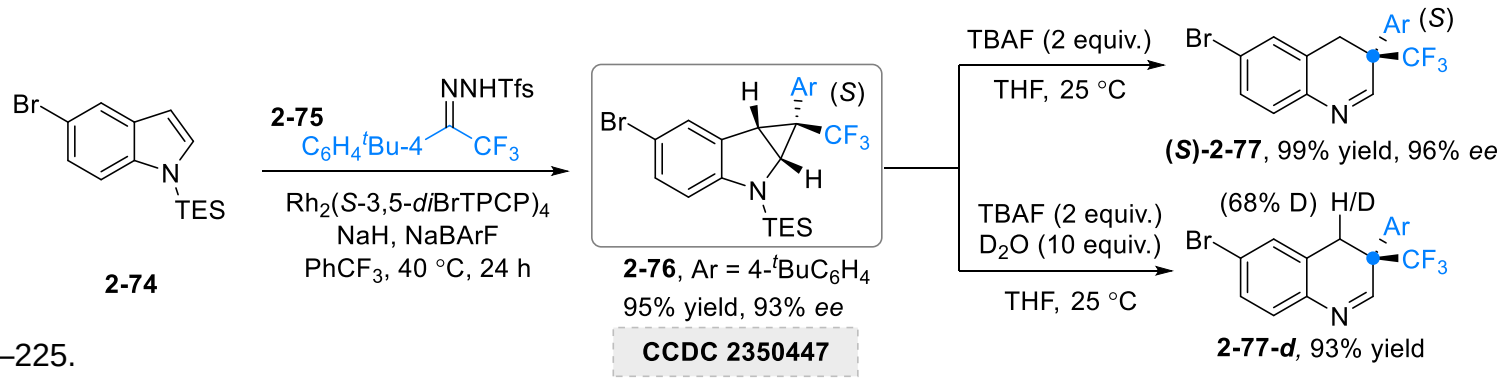






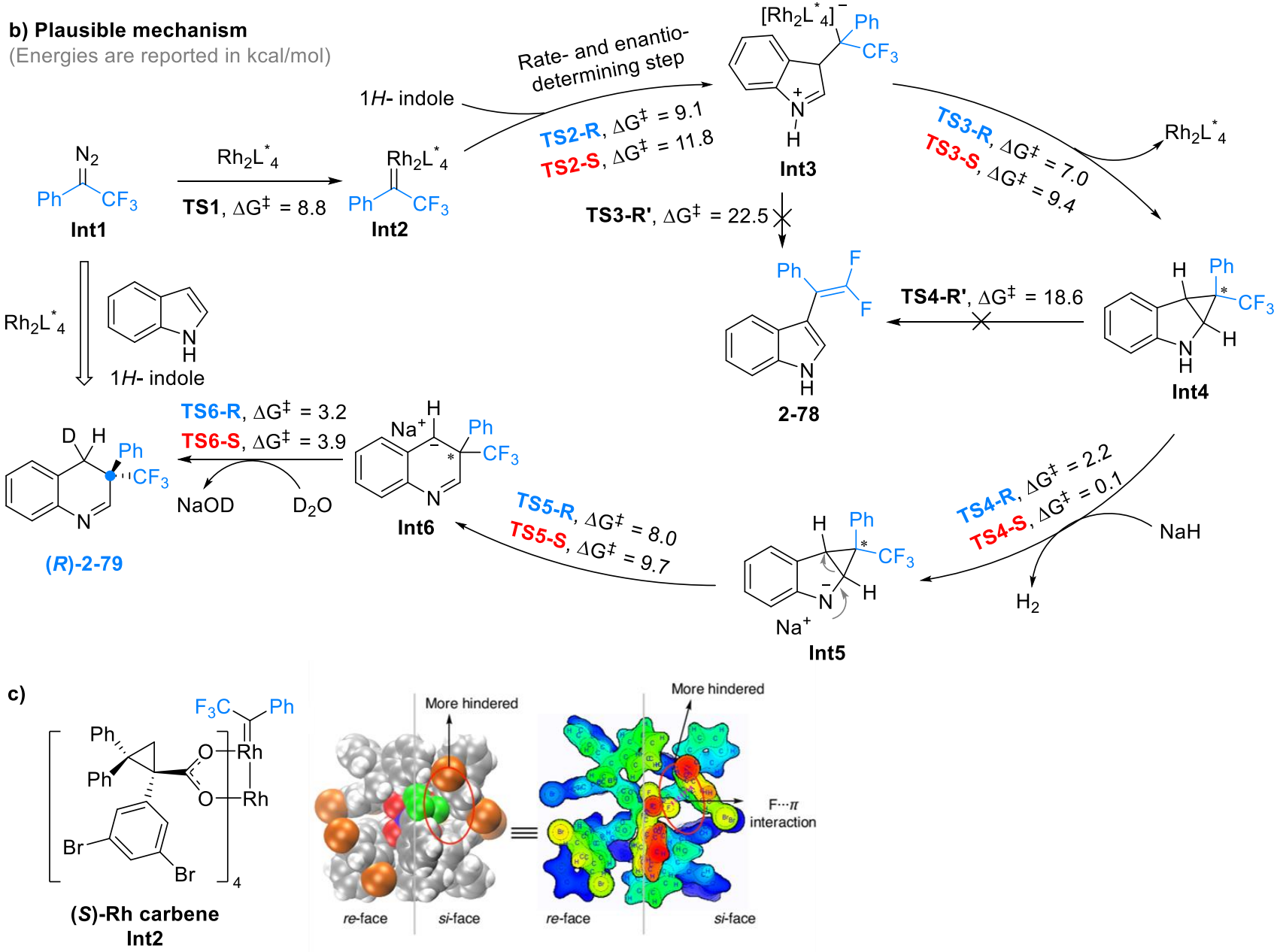
Mechanistic studies

a)



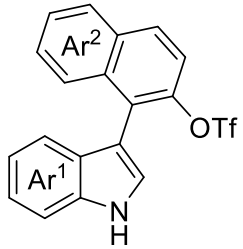
X. Bi, *et al*. *Nat. Chem.* **2025**, *17*, 215–225.

Single-carbon atom insertion into indole



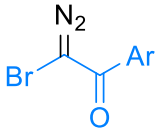
Single-carbon atom insertion into indole

2025 Suero



2-80

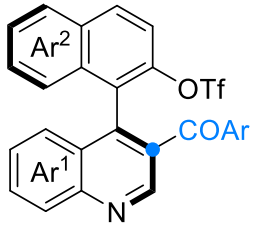
+



2-81

2-82 (1 mol%)

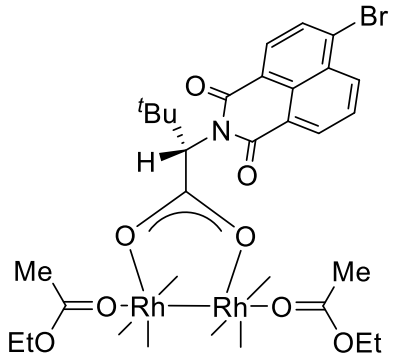
$^{i}Pr_2EtN$ (1.5 equiv.), DCM/PhCl, r.t.



2-83

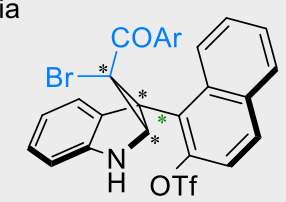
38 examples

up to 98% yield, 99% *ee*



2-82

Via

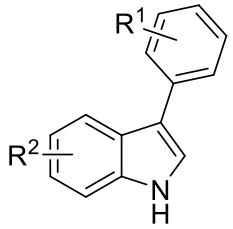


* chiral centers

* chiral axis

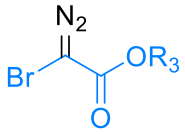
2-84

2026 Gustafson



2-85

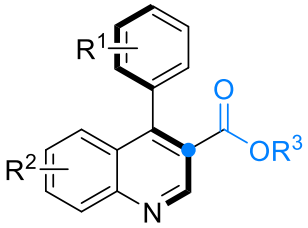
+



2-86

2-87 (1 mol%)

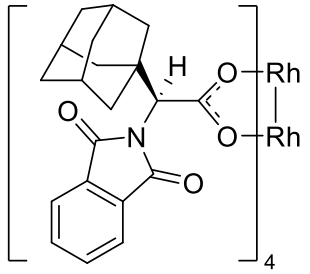
Cs_2CO_3 (1.3 equiv.), DCM, -78 °C



2-88

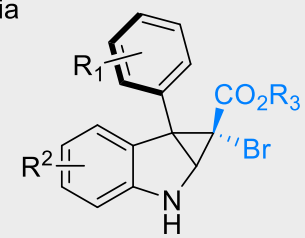
20 examples

up to 98% yield, 98% ee



2-87

Via



2-89

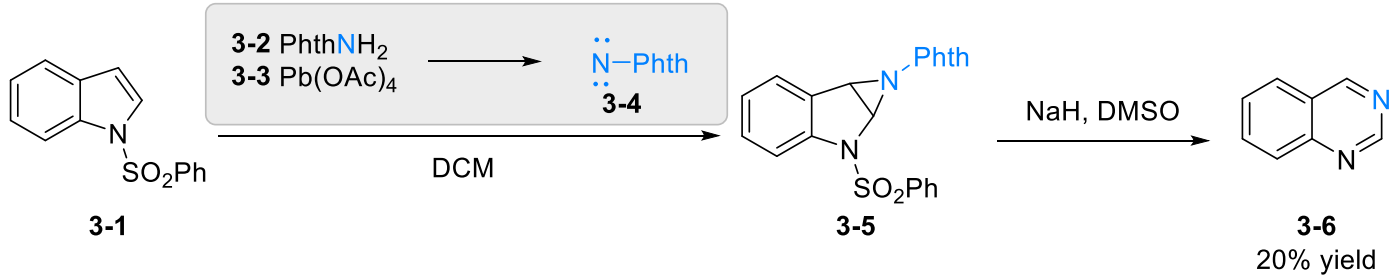
[1] M. G. Suero, *et al*. *J. Am. Chem. Soc.* **2025**, *147*, 24206–24212.

[2] J. L. Gustafson, *et al*. *ACS Catal.* **2026**, *16*, 6067–6076.

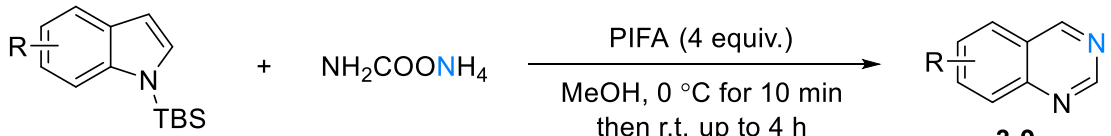
Content

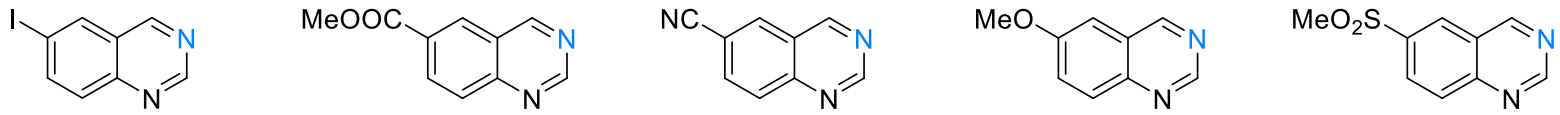
Single-nitrogen atom insertion into indole

1987 Kumar



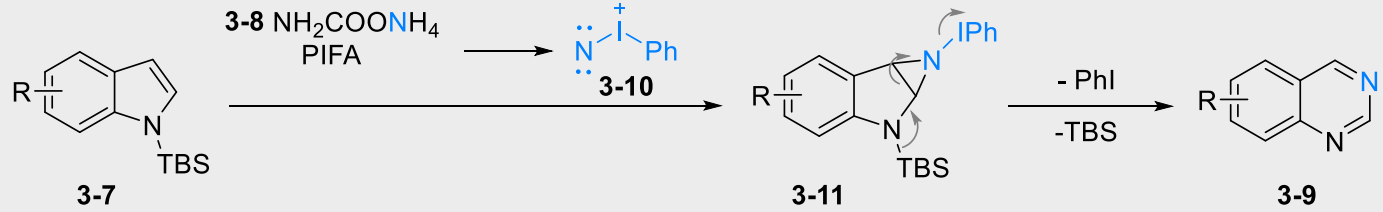
2022 Morandi





3-9a, 74% **3-9b**, 66% **3-9c**, 39% **3-9d**, 63% **3-9e**, 66%

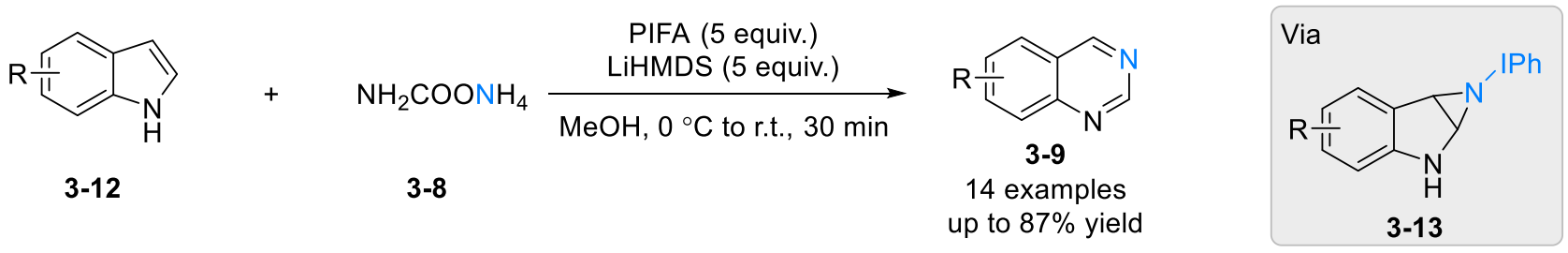
Plausible mechanism



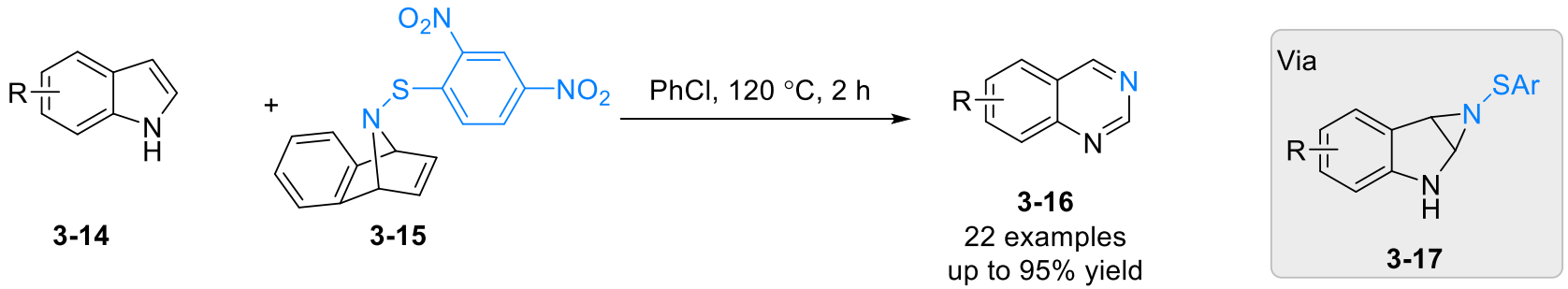
[1] P. Kumar, *Heterocycles* **1987**, *26*, 1257–1262.
[2] B. Morandi, *et al*. *Science* **2022**, *377*, 1104–1109.

Single-nitrogen atom insertion into indole

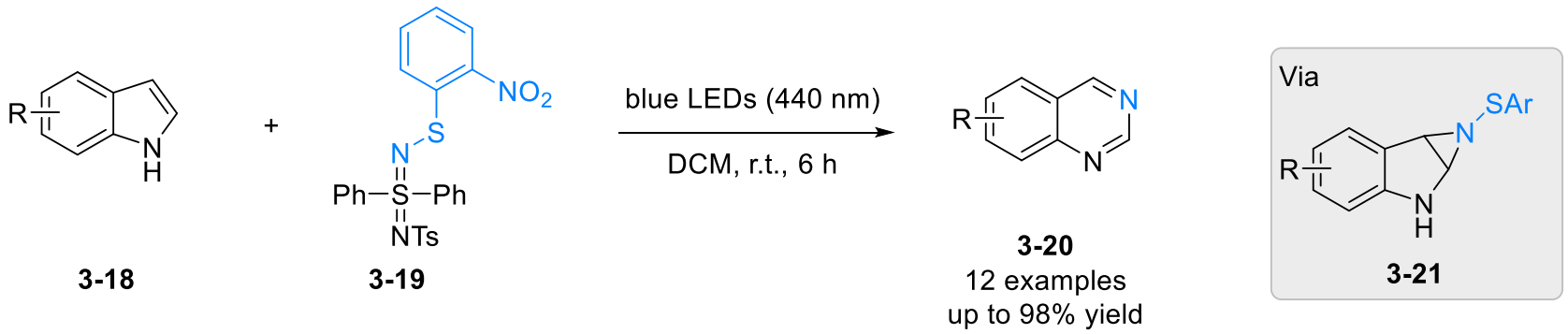
2023 Morandi



2025 Sharma



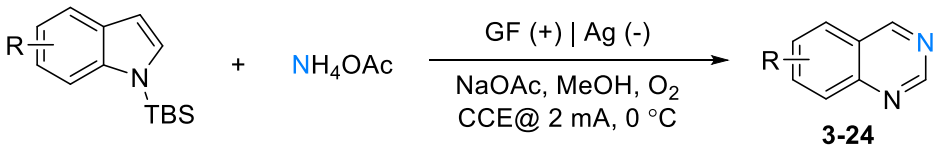
2026 Sharma



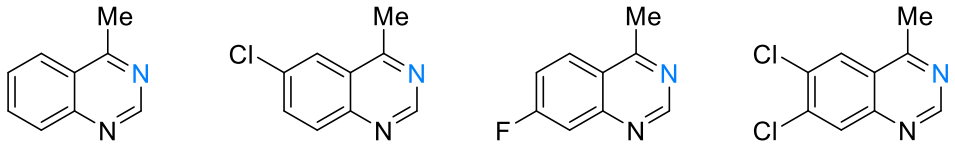
[1] B. Morandi, *et al*. *Org. Lett.* **2023**, *25*, 8419–8423. [2] I. Sharma, *et al*. *Science* **2025**, *387*, 102–107. [3] I. Sharma, *et al*. *Chem* **2026**, *12*, 102753.

Single-nitrogen atom insertion into indole

2024 Ackermann

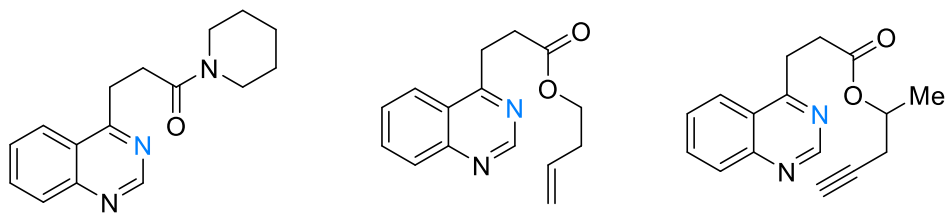


3-22 **3-23** **3-24**
35 examples
up to 75% yield



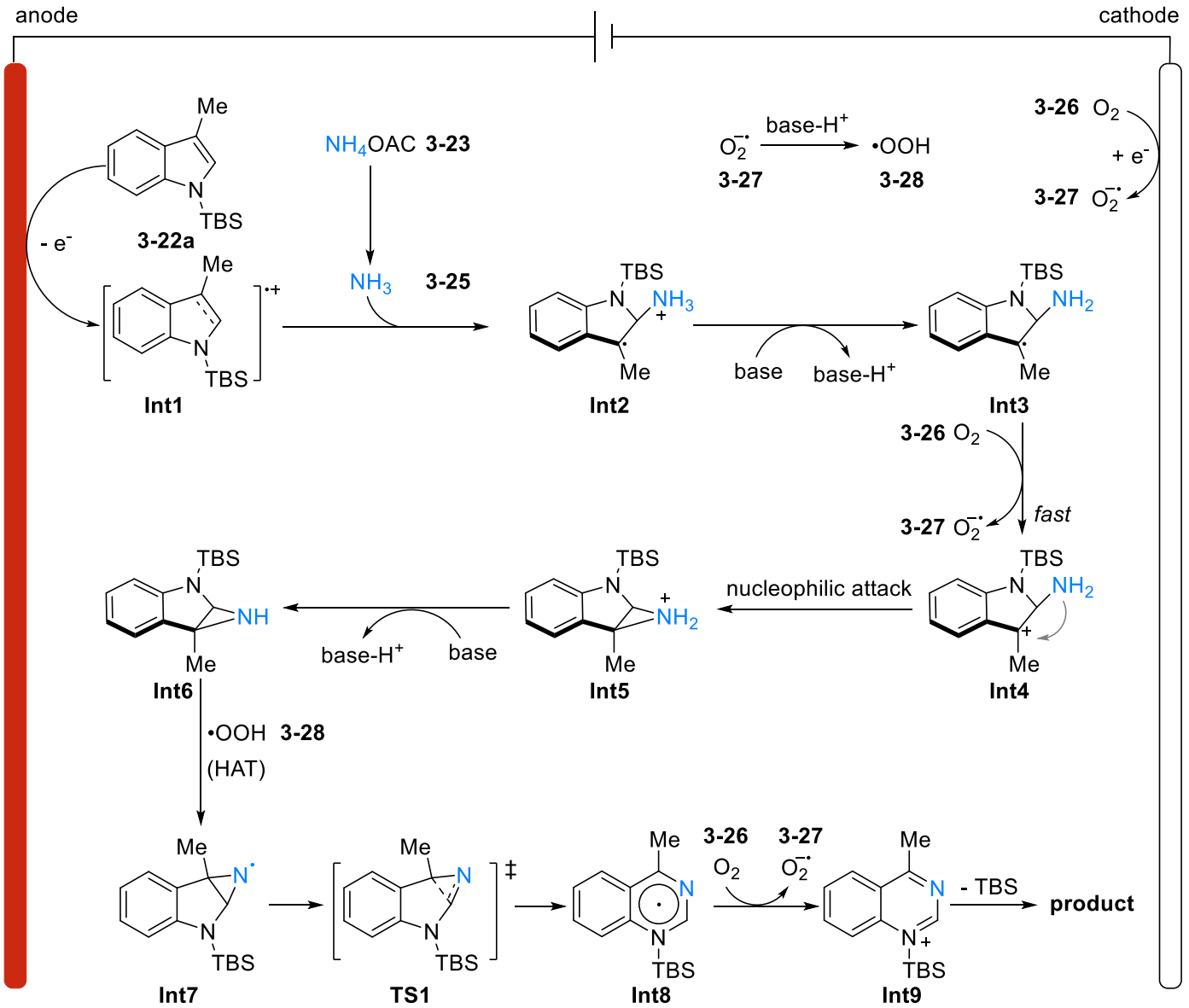
3-24a, 62% **3-24b**, 47% **3-24c**, 72% **3-24d**, 47%

3-24e, 75% **3-24f**, 62% **3-24g**, 55% **3-24h**, 49%



3-24i, 39% **3-24j**, 38% **3-24k**, 42%

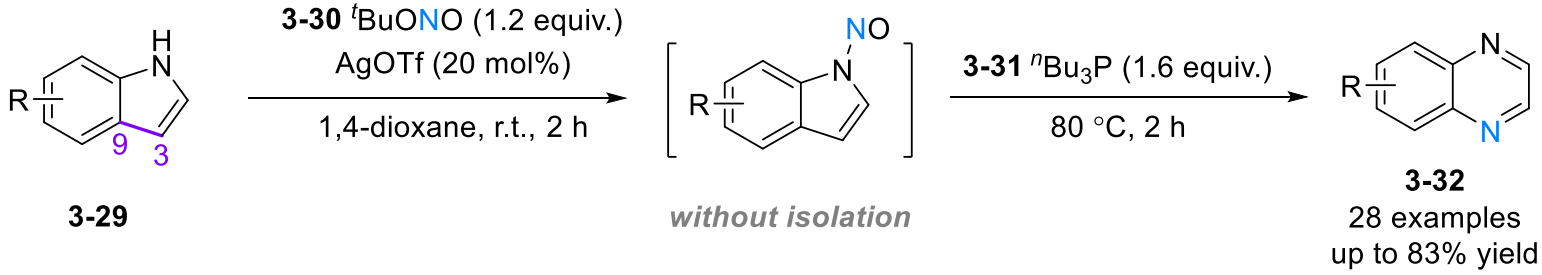
Plausible mechanism:



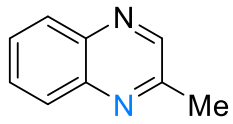
L. Ackermann, *et al*. *Angew. Chem. Int. Ed.* **2024**, *63*, e202407384.

Single-nitrogen atom insertion into indole

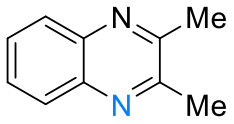
2026 Won-Jin Chung



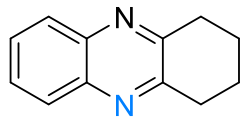
3-29 | *without isolation* | **3-32** 28 examples up to 83% yield



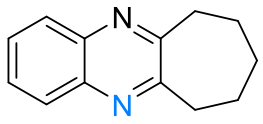
3-32a, 71%



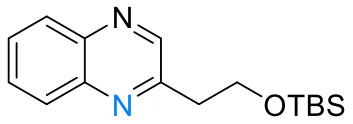
3-32b, 73%



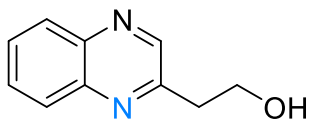
3-32c, 61%



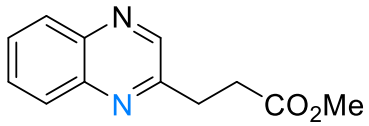
3-32d, 64%



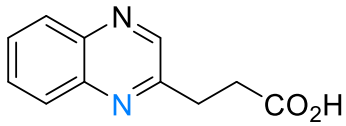
3-32e, 81%



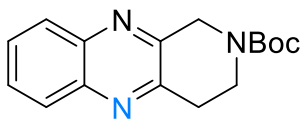
3-32f, 26%



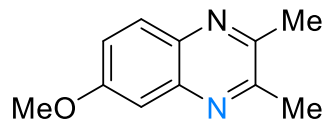
3-32g, 72%



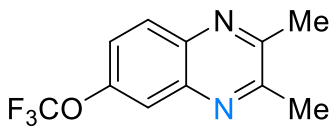
3-32h, 26%



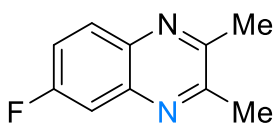
3-32i, 68%



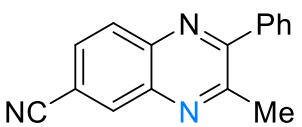
3-32j, 80%



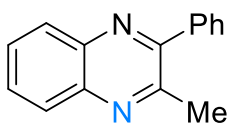
3-32k, 79%



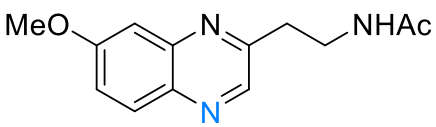
3-32l, 83%



3-32m, 46%



3-32n, 46%

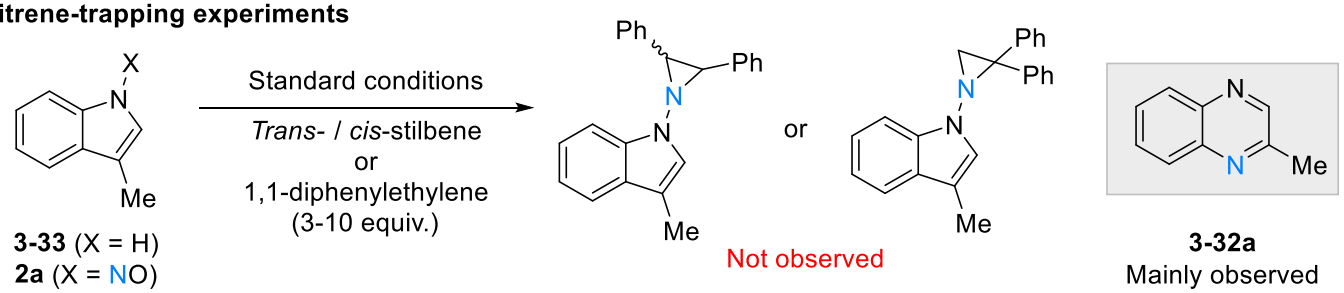


3-32o, 72%

W.-j. Chung, *et al*. *Nat. Synth.* **2026.** https://doi.org/10.1038/s44160-026-01046-z

Single-nitrogen atom insertion into indole

a) Nitrene-trapping experiments

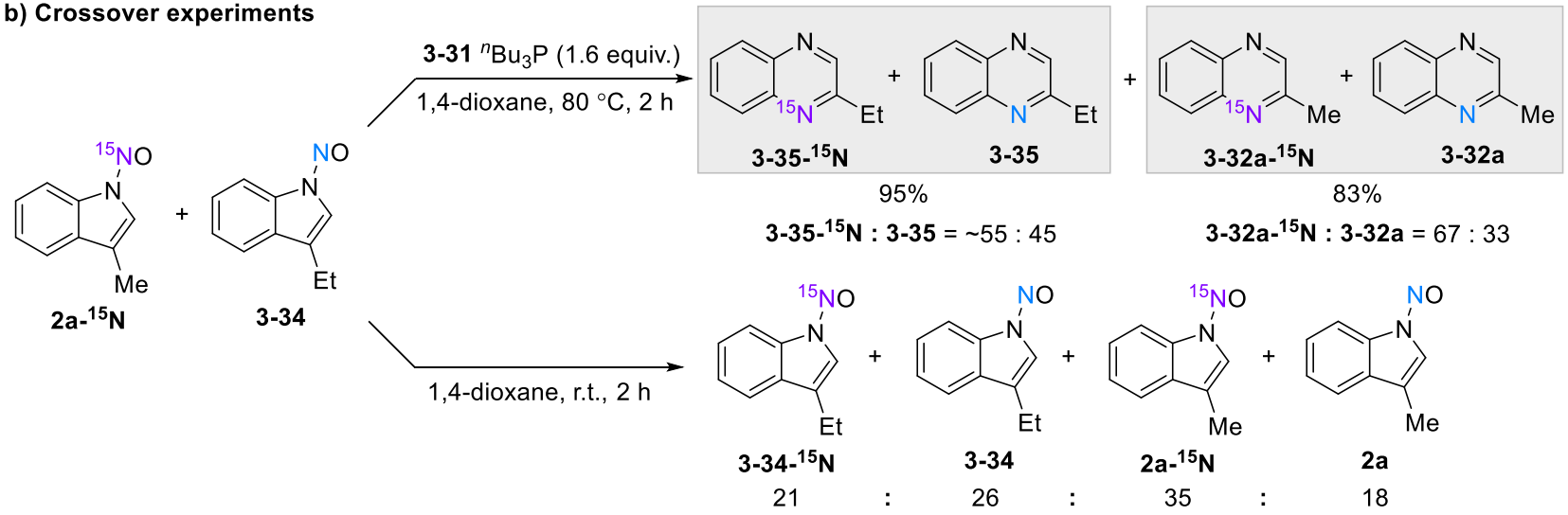


3-33 (X = H)
2a (X = NO)

Not observed

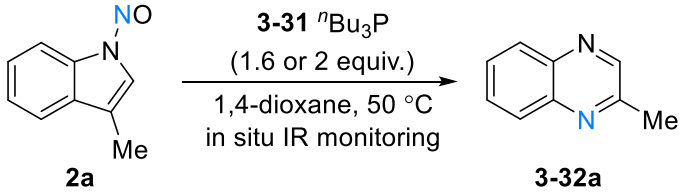
3-32a
Mainly observed

b) Crossover experiments



2a-^{15}N
3-34

c) Kinetic study via variable time normalization analysis



2a
3-32a

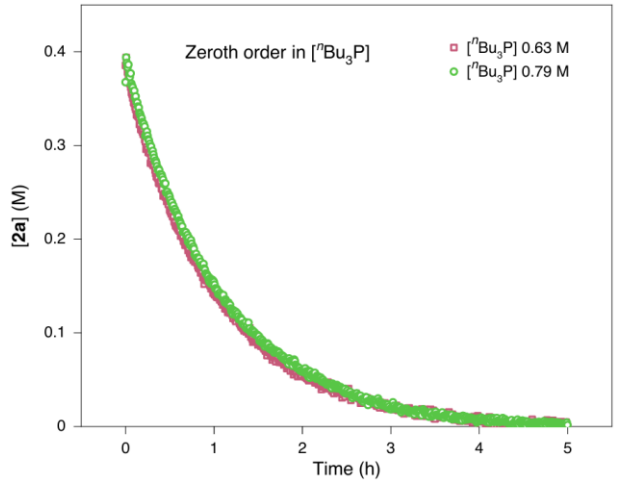
Symbol	[**2a**] (M)	[**3-31**] (M)	[xs] (M)
□	0.39	0.63	0.24
○	0.39	0.79	0.40
△	0.31	0.79	0.18

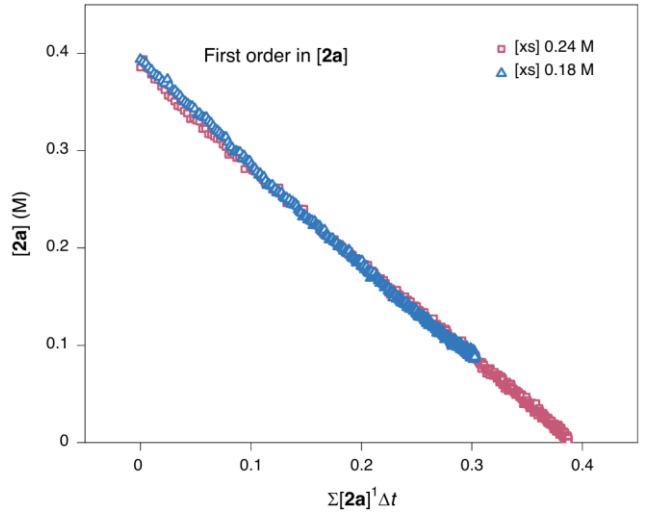
[xs] = [**3-31**] - [**2a**]

rate = k [**2a**]^1[**3-31**]^0

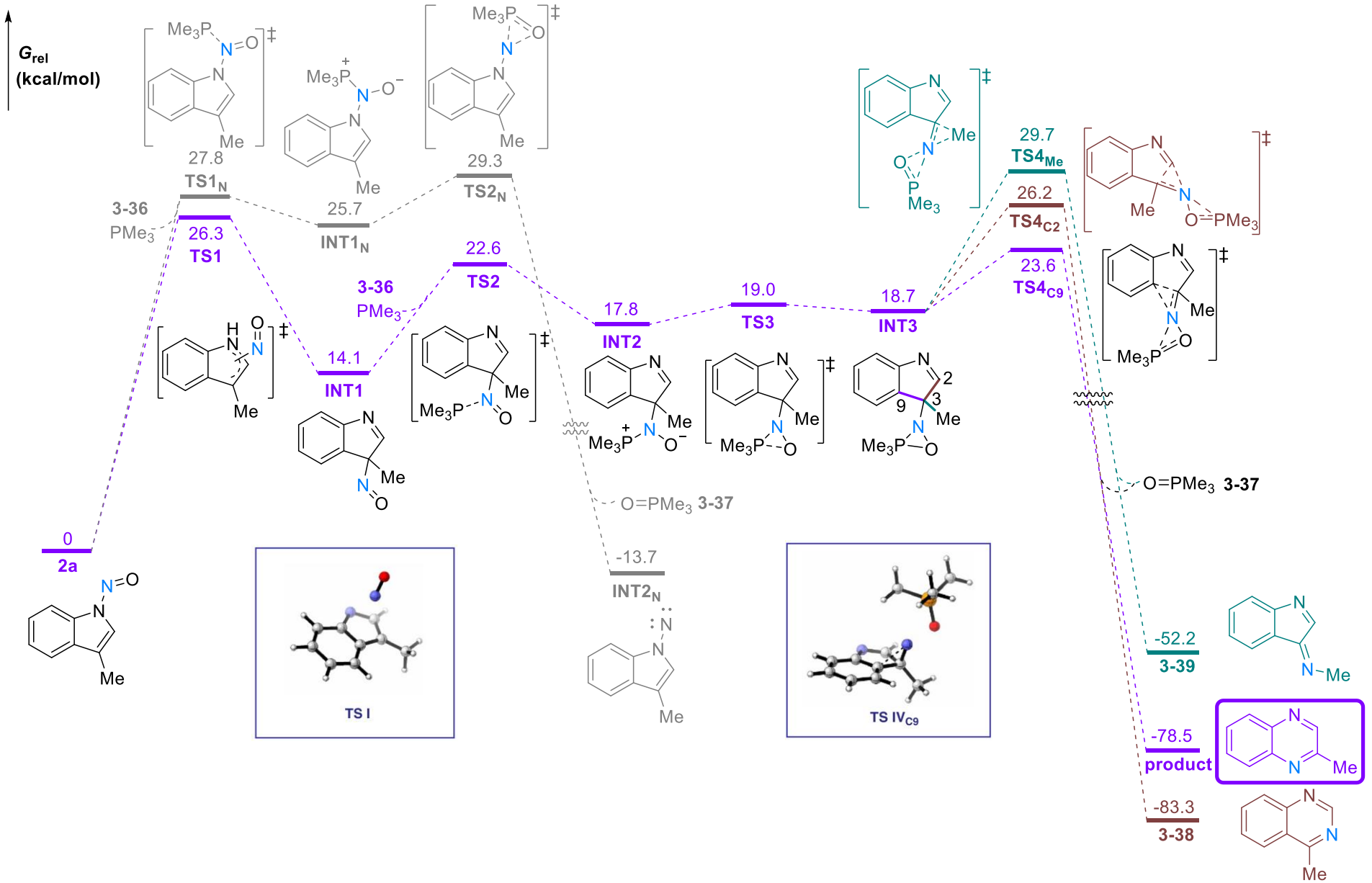
k_{obs} = 0.97 h^{-1}

k_{obs}, obesrved rate constant





Single-nitrogen atom insertion into indole



1,3-nitroso group migration	Phosphine addition	Deoxygenative single nitrogen atom insertion

Content

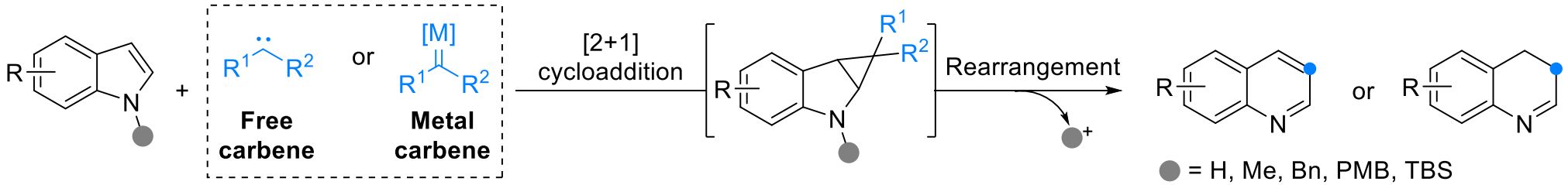
1. Background

2. Single-carbon atom insertion into indole

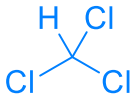
3. Single-nitrogen atom insertion into indole

4. **Summary and outlook**

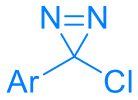
Summary: single-carbon atom insertion into indole



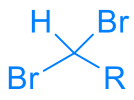
Free carbene sources



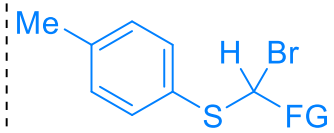
Rees & Smithen (1964)



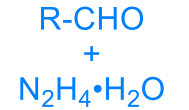
Levin (2021)
Ball (2023)



Xu (2024)
Song (2024)



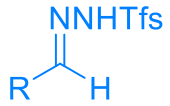
Sharma (2025)



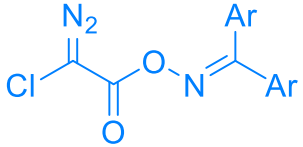
Pang (2026)

Metal carbene sources

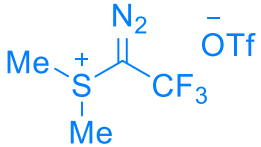
Bonge-Hansen (2015)
Suero (2025)
Gustafson (2026)



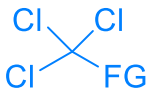
Bi (2024)



Glorius (2024)



Han (2025)

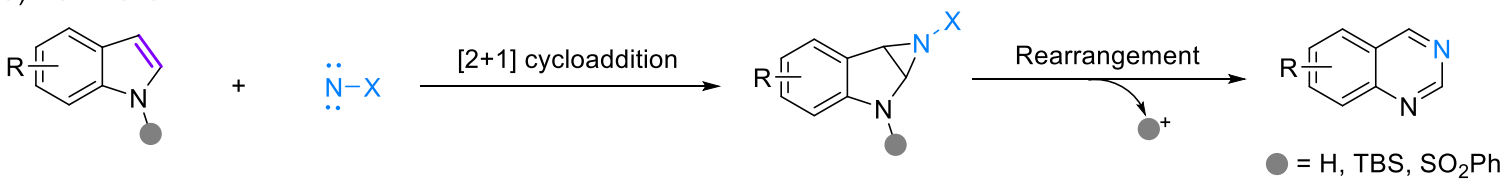


Nagib (2026)

Summary: single-nitrogen atom insertion into indole

C2-C3 bond insertion:

a) Via nitrene



Oxidant-required

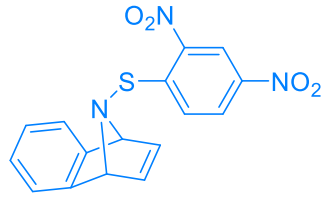
$PhthNH_2$
$Pb(OAc)_4$

Kumar (1987)

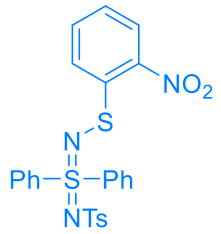
NH_2COONH_4
PIFA

Morandi (2022)

Oxidant-free

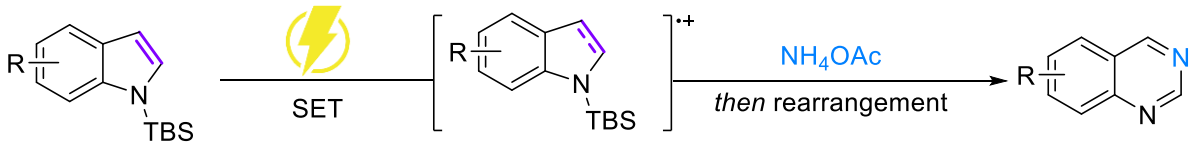


Sharma (2025)



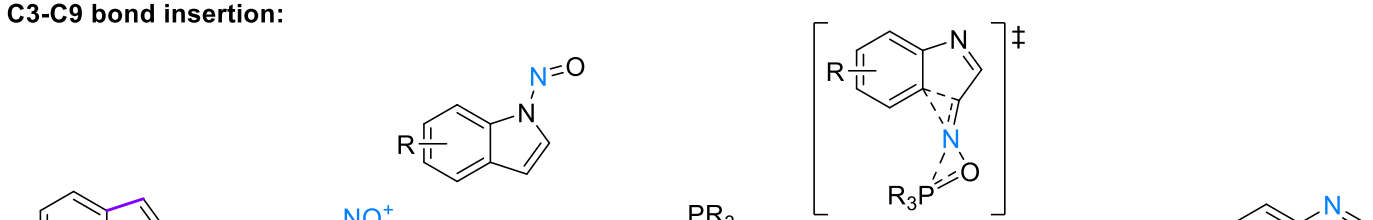
Sharma (2026)

b) Via single electron oxidation



Ackermann (2024)

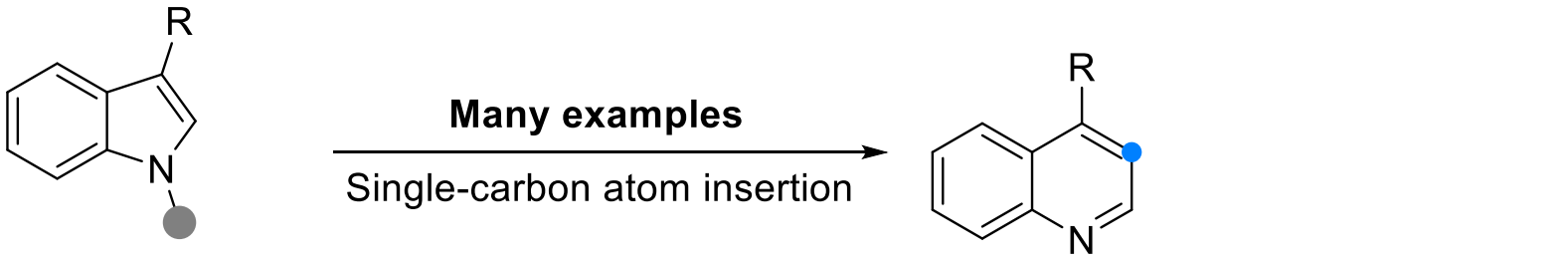
C3-C9 bond insertion:

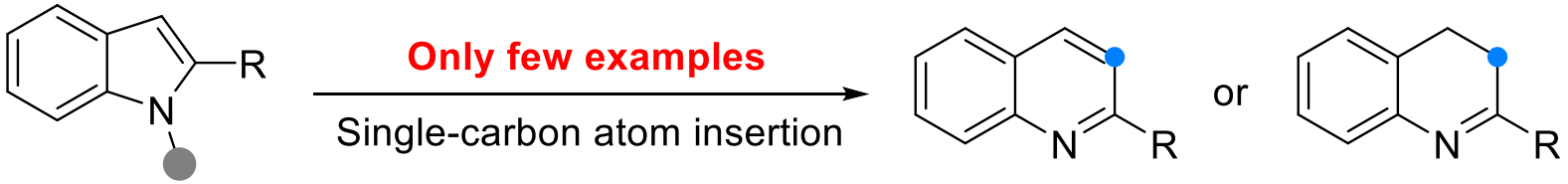


Chung (2026)

Outlook

Ring-forming then reorganization strategy

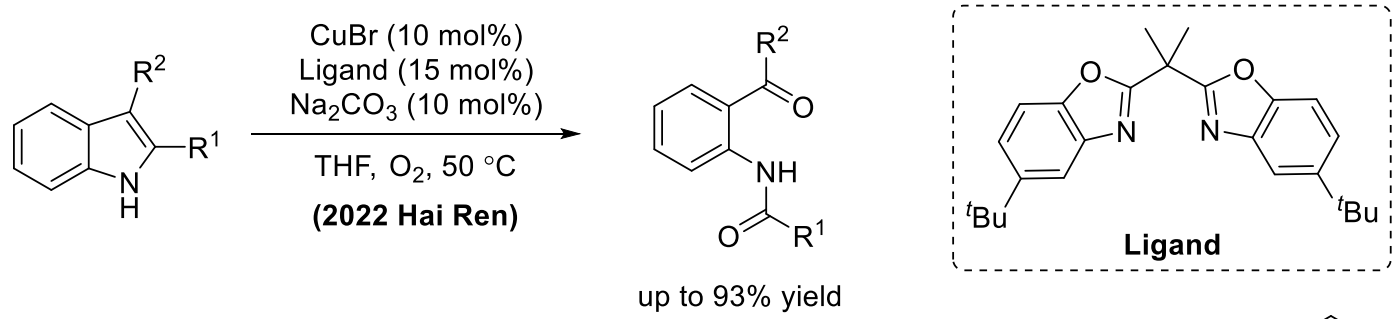


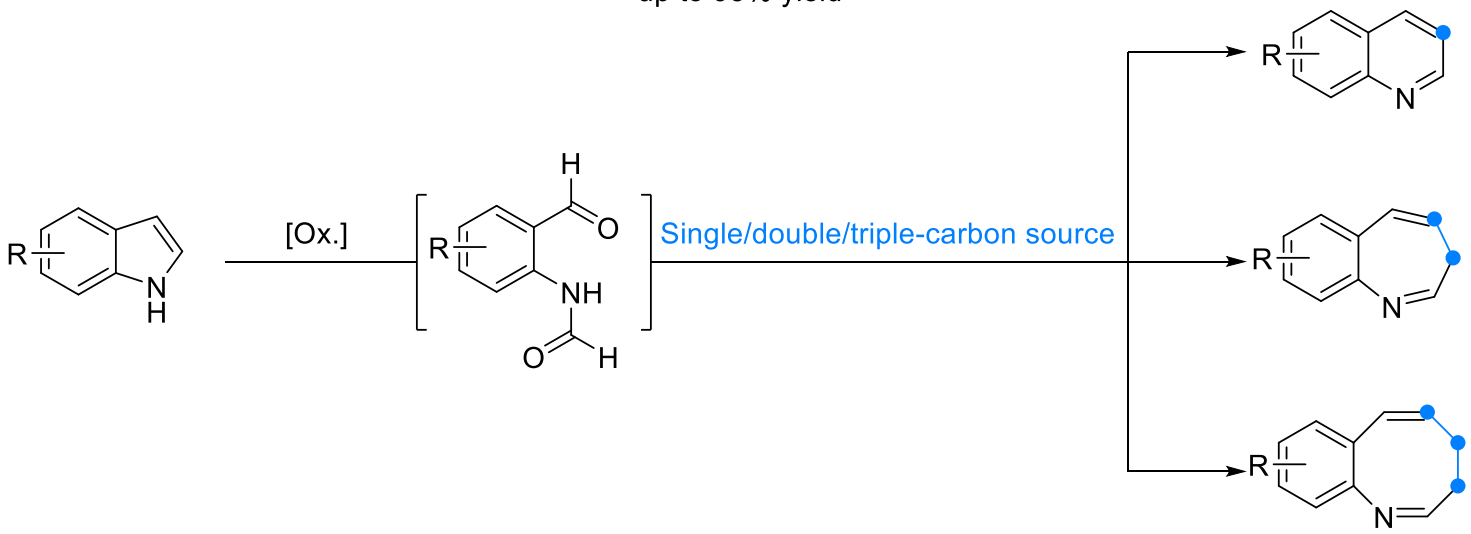


Poor functional group compatibility

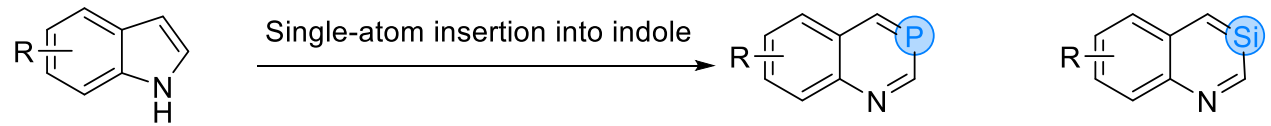
Outlook

1. Ring-opening then reorganization strategy





2. Insertion of other heteroatoms



H. Ren, *et al*. *Org. Lett.* **2022**, *24*, 3358–3362.

Thank you!