同济大学 TONGJI UNIVERSITY

The Yang Research Group
Precise Synthesis Lab at Tongji University

张夏衡课题组工作简介

汇 报 人：刘灿祥

时　间　：2026. 10. 28

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04 N-杂环自由基介导的胺化反应

05 Proposal



张夏衡

个人简历

2005.09–2009.07 四川大学化学学院 学士

2009.09–2015.01 中国科学院上海有机化学研究所 博士（导师：俞飚 研究员）

2015.01–2015.11 中国科学院上海有机化学研究所 助理研究员

2015.12–2019.11 美国普林斯顿大学 博士后（合作导师：David W. C. MacMillan 教授）

2019.12–2020.12 美国普林斯顿大学 副研究员

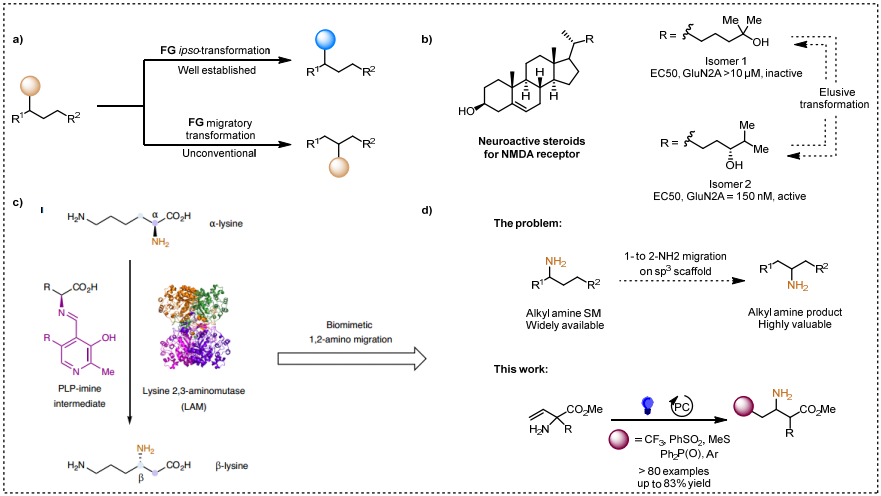
2021.01-2021.09 复旦大学化学系 青年研究员，博士生导师

2021.10 – 至今 国科大杭州高等研究院 研究员

研究方向和兴趣

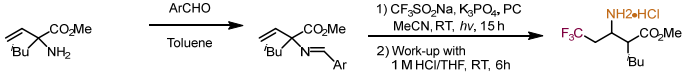
绿色药物合成方法和工艺开发、新颖有机合成方法学研究、可见光催化在有机合成中的应用

光催化仿生1,2-氨基迁移

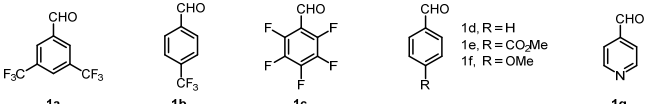


Nat. Chem. **2025**, *17*, 941

光催化仿生1,2-氨基迁移

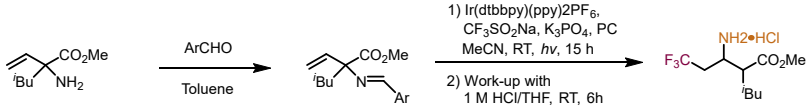


Entry	ArCHO	PC	Yield	Entry	ArCHO	PC	Yield
1	1a	4CzIPN	45	5	1a	$Ir(dtbbpy)(ppy)_2PF_6$	79
2	1b instead of 1a	4CzIPN	32	6	1a	NO PC	ND
3	1c instead of 1a	4CzIPN	30	7	1a	$Ir(dtbbpy)(ppy)_2PF_6$ or dark	ND
4	1d-1g instead of 1a	4CzIPN	trace	8	1a	$Ir(dtbbpy)(ppy)_2PF_6$ (3 mol%)	88% (6.1:1 d.r.)

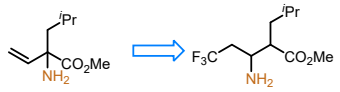


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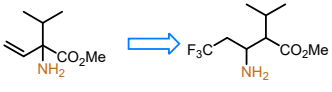
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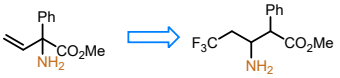
Scope of γ-fluoroalkyl-β-AAs



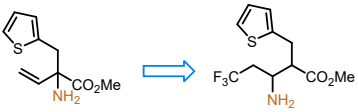
83 yield
6,1:1 d.r.



76 yield
2.9:1 d.r.



69 yield
1.7:1 d.r.

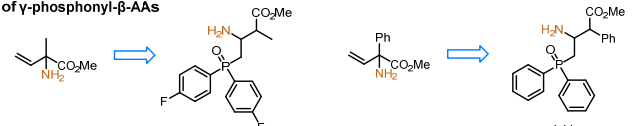


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2.7:1 d.r.

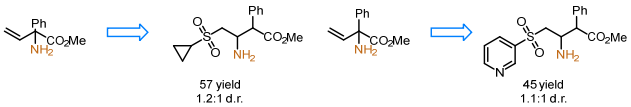
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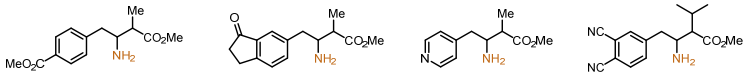
Scope of γ-phosphonyl-β-AAs



Scope of γ-sulfonyl-β-AAs and γ-thioalkyl-β-AAs

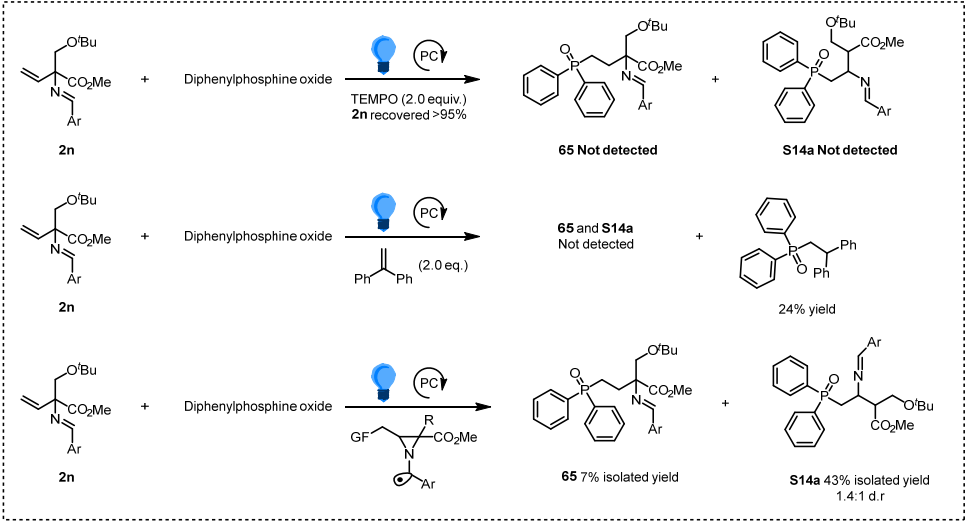


Scope of aryl bromides



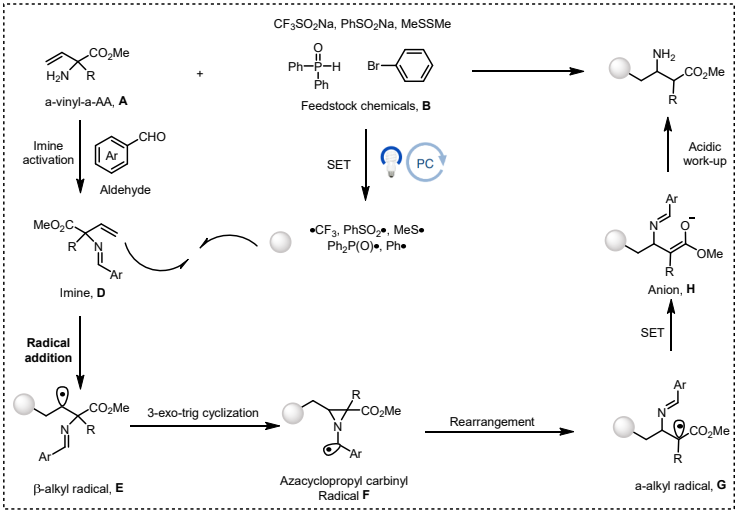
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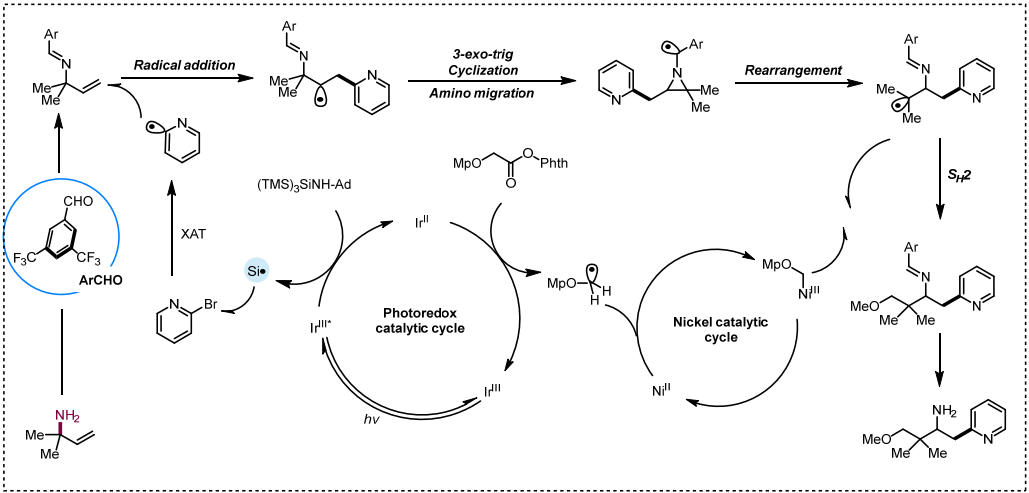
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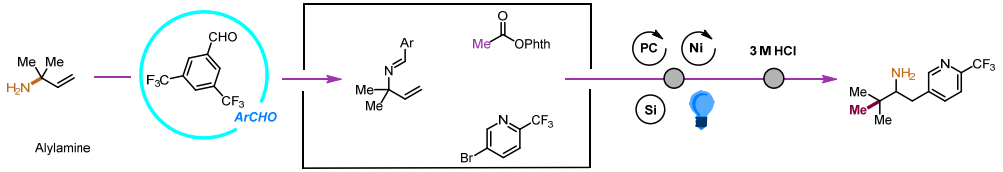
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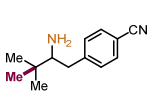
氨基迁移三组分交叉偶联

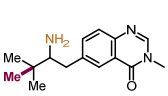


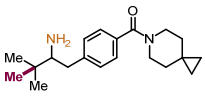
J. Am. Chem. Soc. **2026**, *148*, 41745

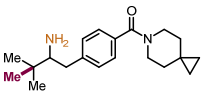
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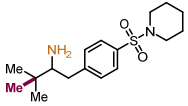


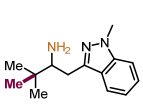

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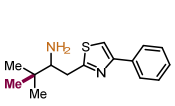

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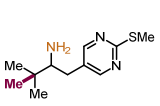

54% yield


54% yield


44% yield

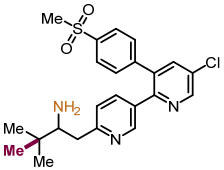

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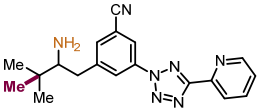

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J. Am. Chem. Soc. **2026**, *148*, 41745

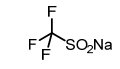
氨基迁移三组分交叉偶联

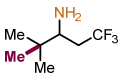


37% yield
from **Etoricoxib**



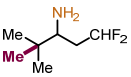
76% yield
from **mGluR5 ligand**



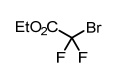


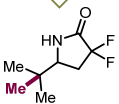
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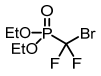


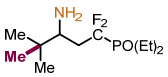
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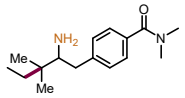




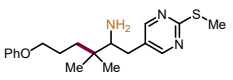
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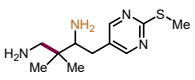
氨基迁移三组分交叉偶联



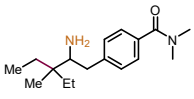
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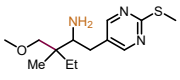
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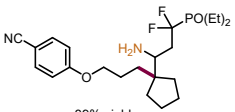
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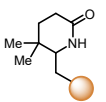
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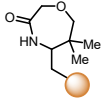
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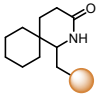
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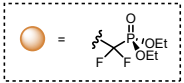
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27% yield

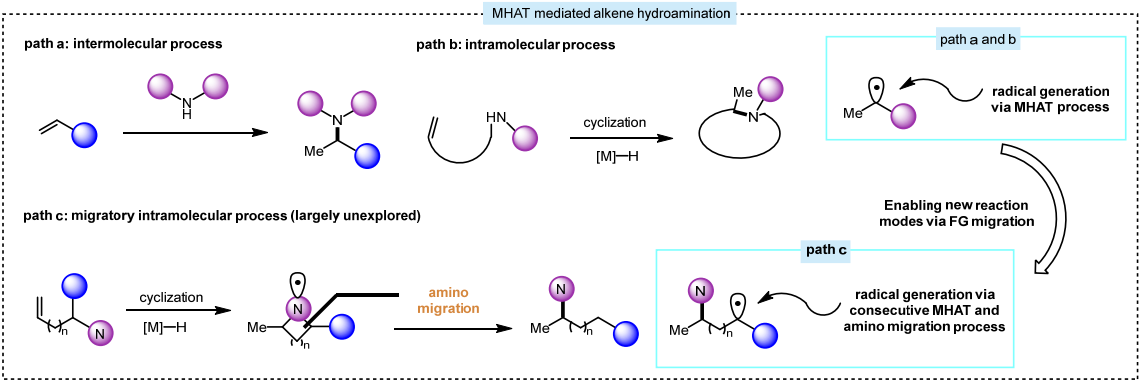


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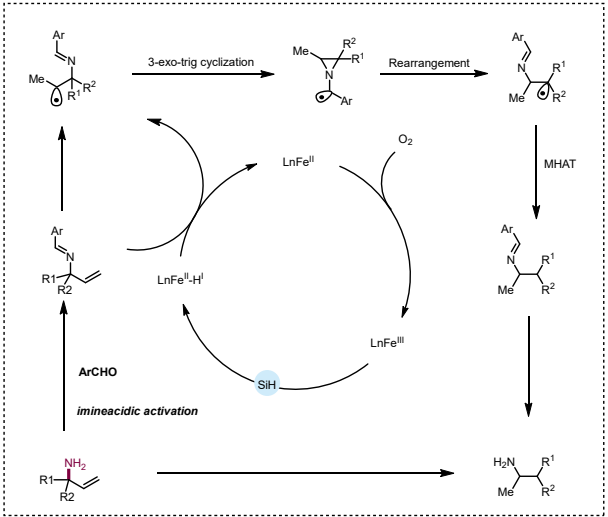
J. Am. Chem. Soc. **2026**, *148*, 41745

铁氢催化烯烃的迁移型氢胺化



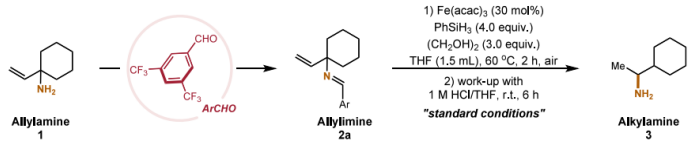
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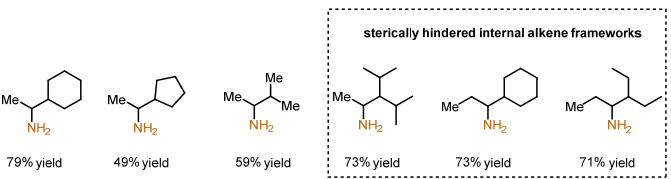
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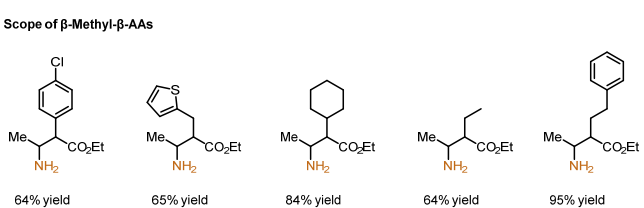


doi.org/10.1021/jacs.6c17662

铁氢催化烯烃的迁移型氢胺化





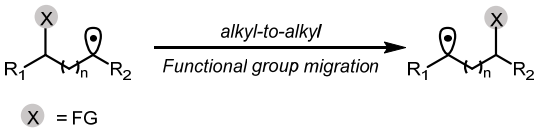


- **首次实现铁氢催化的迁移氢胺化**，将MHAT与1,2-氨基迁移融合；
- **广泛底物范围**：兼容环状/非环状烯丙胺，以及非端烯烃；
- **高区域选择性**：在MHAT和FG迁移过程中均表现出优异的区域选择性；
- **β-氨基酸合成**：从乙烯基-α-氨基酸衍生物直接获取β-甲基-β-氨基酸；
- **复杂分子后期修饰**：应用于多巴胺、西格列汀等药物衍生物

doi.org/10.1021/jacs.6c17662

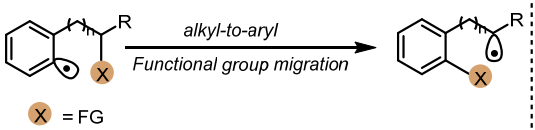
光催化实现烷基到芳基氨基迁

a) Alkyl-to-alkyl FG migration



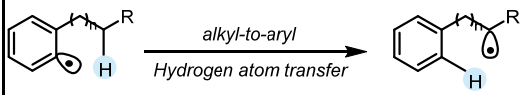
X = cyano, aryl, alkenyl, etc.
Most commonly 1,2-, 1,4-, and 1,5-FG translocation

b) Alkyl-to-aryl FG migration



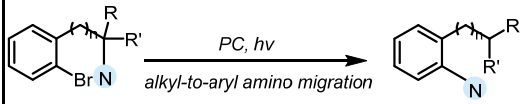
Remain largely unexplored with rare precedents

Inspiration: aryl radical-mediated alkyl-to-aryl HAT



Well-established and many applications
Most commonly 1,5-HAT

This work: photocatalytic alkyl-to-aryl amino migration

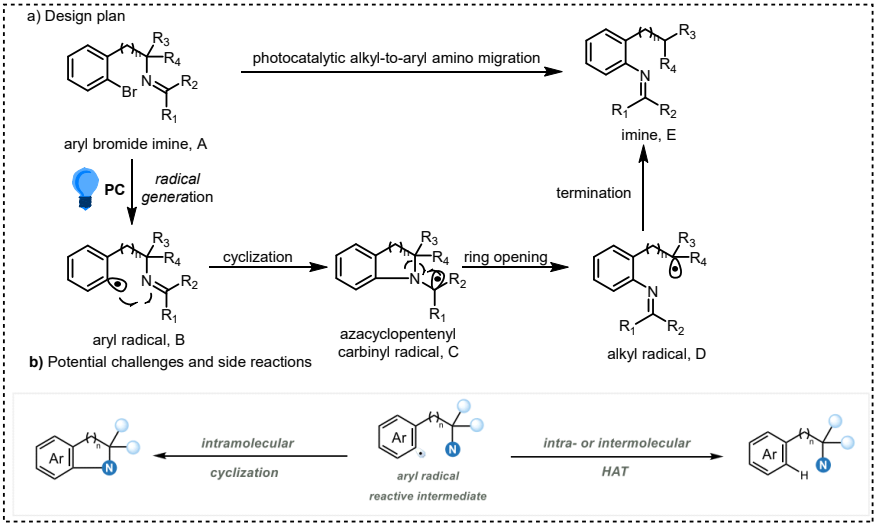


1,4- & 1,5-Amino migration
Excellent chemoselectivity

Good compatibility
DFT computation

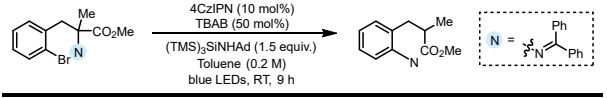
ACS Catal. **2026**, *16*, 9447

光催化实现烷基到芳基氨基迁

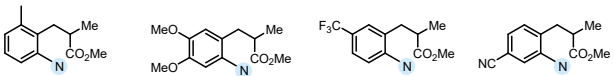


ACS Catal. **2026**, *16*, 9447

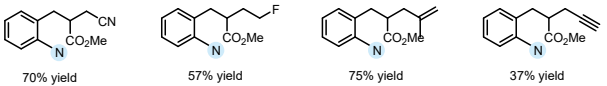
光催化实现烷基到芳基氨基迁

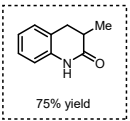


Scope of aryl ring



Scope of alkyl chain

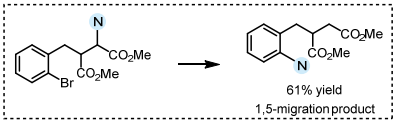




芳环：兼容给电子基、吸电子基，多环芳烃、杂环；

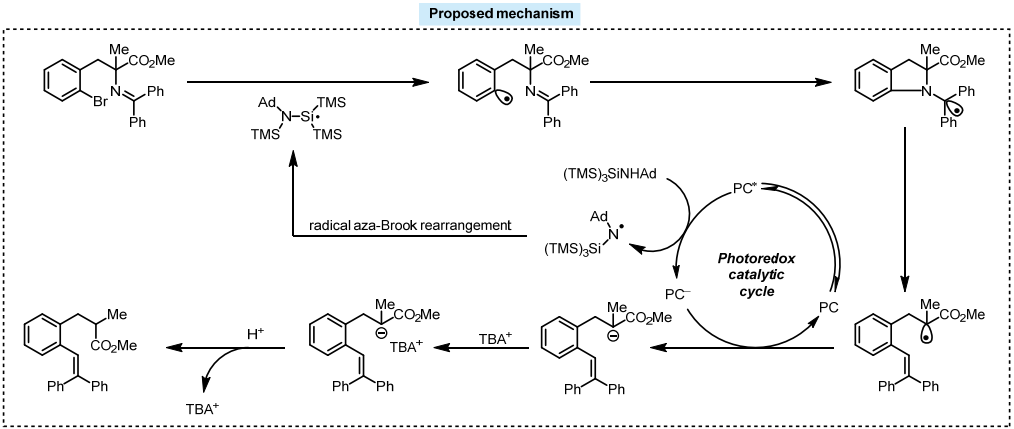
烷基链：酯基、烷基、苄基、硫醚、吲哚、烯基、炔基等均耐受；

迁移类型：实现1,4 - 氨基迁移与1,5 - 氨基迁移。



ACS Catal. **2026**, *16*, 9447

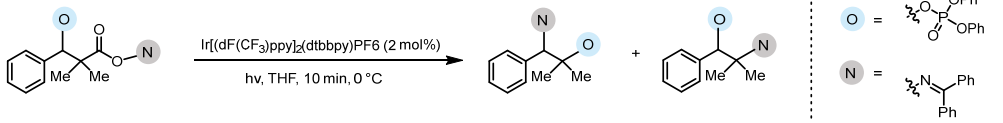
光催化实现烷基到芳基氨基迁



ACS Catal. **2026**, *16*, 9447

能量转移光催化策略实现N-O双官能团移位反应

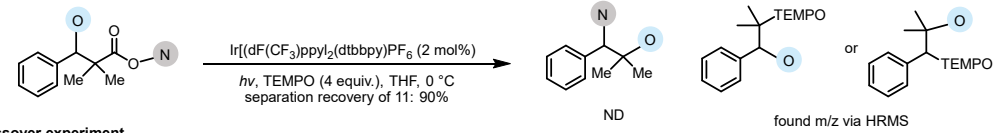
Reaction optimizations



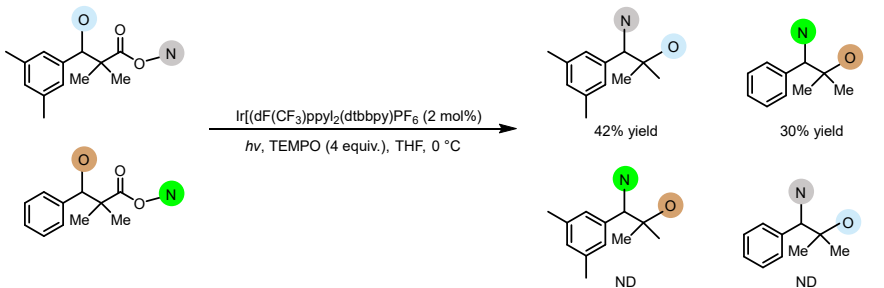
Entry	Variations from standard conditions	Yield	Entry	Variations from standard conditions	Yield
1	none	72	6	acetone instead of THF	43
2	thioxanthone as PC	64	7	EtOAc instead of THF	71
3	4CzIPN as PC	15	8	DME instead of THF	65
4	$Ir(ppy)_2(dtbbpy)PF_6$ as PC	ND	9	R.T. instead of 0 °C	46
5	fac-$Ir(ppy)_3$ as PC	trace	10	no PC or in dack	ND

能量转移光催化策略实现N-O双官能团移位反应

Radical inhibition experiment



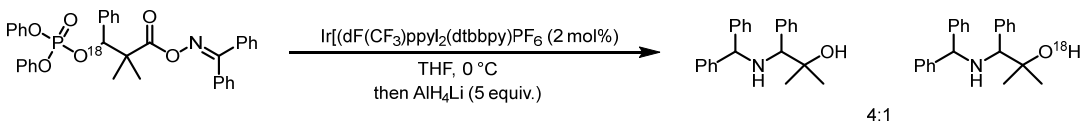
Crossover experiment



Adv. Sci. **2026**, *13*, e76772

能量转移光催化策略实现N-O双官能团移位反应

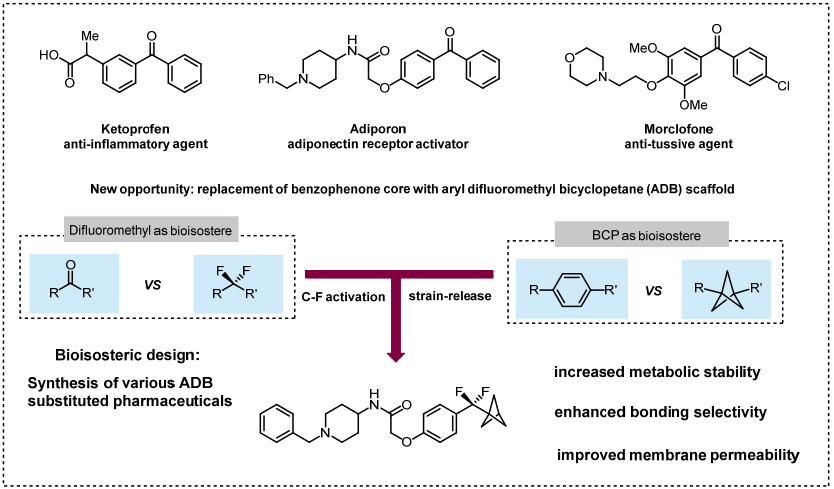
O^{18}-labeling experiment



底物与光敏剂发生EnT，引发脱羧，生成短寿命的β-磷酸氧基烷基自由基和持久亚胺自由基；
短寿命自由基先发生分子内 1,2-磷酸氧基迁移；
迁移后生成的碳中心自由基再与持久亚胺自由基发生自由基-自由基偶联，得到N–O双转位产物。
该策略的特别之处是不依赖烯烃作为自由基受体，不同于经典 EnT 双官能化中“两个自由基依次加成到烯烃”的路线。

Adv. Sci. **2026**, *13*, e76772

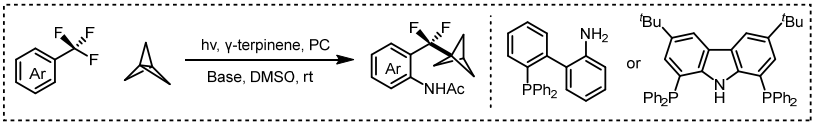
光诱导C-F键活化构建芳基二氟甲基双环烷烃

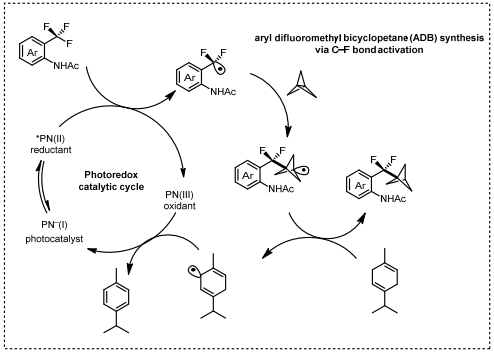


电子等排指两个原子、基团或分子在大小、形状、电子分布、偶极矩、氢键性质等方面相似，因而可能表现出相似的物理化学或生物性质。它描述的是一种关系或设计原则。

Nat. Commun. **2024**, *15*, 419[24]

光诱导C–F键活化构建芳基二氟甲基双环烷烃





文章亮点

直接以商品化 $ArCF_3$ 为起点，避免预制备 $ArCF_2Br$ 等昂贵/难得试剂；

新设计强还原 N-阴离子有机光催化剂 PCN，空气稳定、可克级制备；

C–F 活化与张力释放合并，一锅构建 ADB 骨架；

底物范围广，>70 例，含杂芳、多氟芳烃、复杂药物后期修饰；

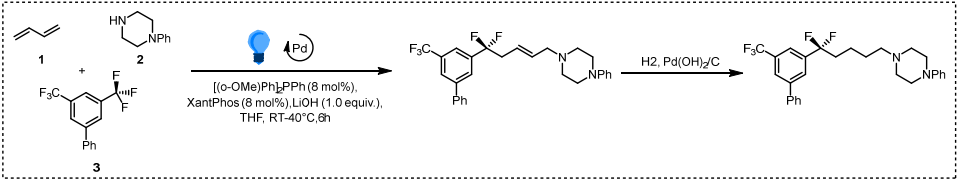
可扩展至 [3.1.1]/[4.1.1]propellane，获得不同几何形状的双环等排体；

三组分模块化偶联，可安装 Bpin 等后续转化手柄；

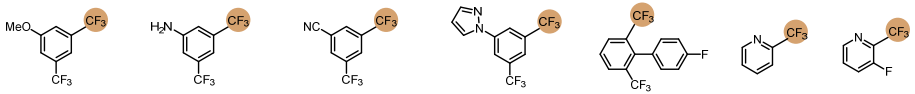
初步生物评价显示 ADB 可改善二苯甲酮类药物的代谢稳定性。

Nat. Commun. **2024**, *15*, 419

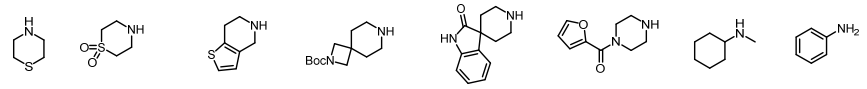
光激发钯催化下三氟甲基芳烃脱氟多组分串联反应



Scope of Trifluoromethylarenes

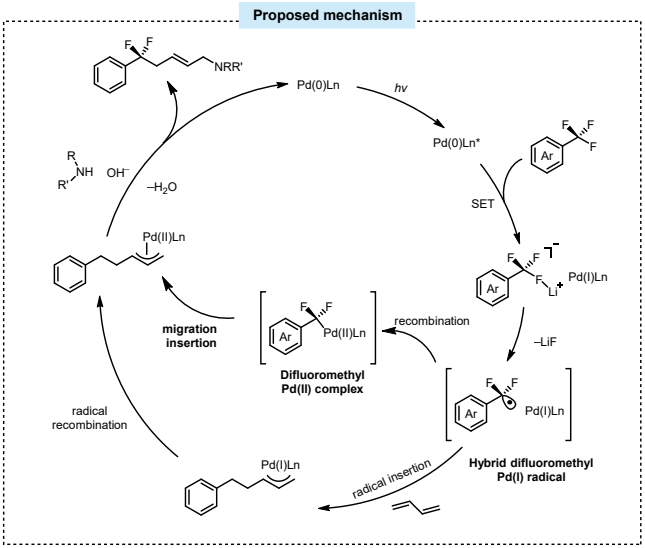


Scope of Nucleophiles



JACS Au 2024, 4, 4223

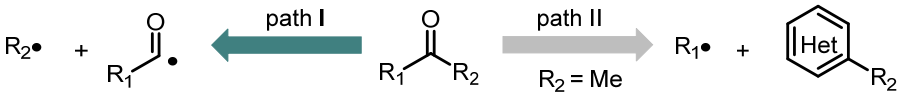
光激发钯催化下三氟甲基芳烃脱氟多组分串联反应



JACS Au 2024, 4, 4223

非张力酮的脱酰芳基化和炔基化反应

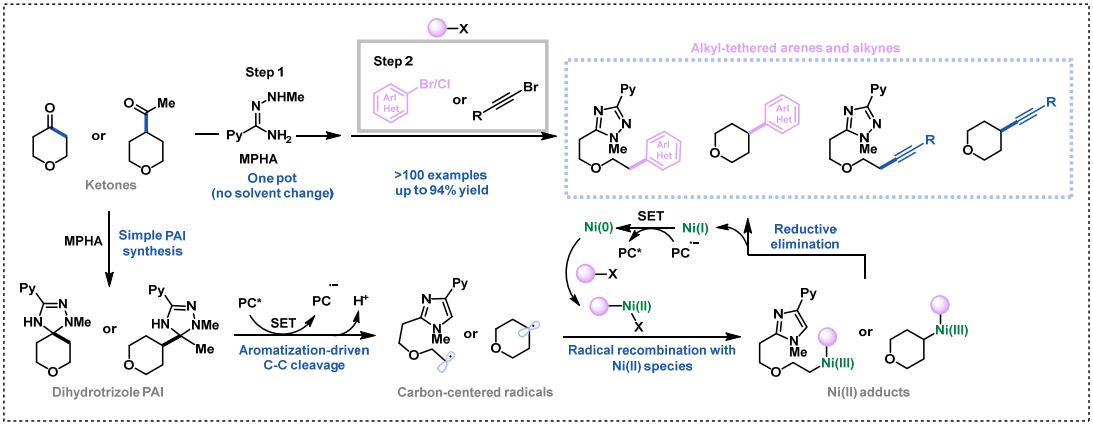
C-C activation of ketones via radical-mediated strategy



High-energy UV light	Aromatization as sole driving force
Radical recombination	Harsh reaction conditions (high temperature)
Decarbonylation	Limited substrate scope (methyl ketones)

Sci. Adv., **2024** ,*10*, eado0225.

非张力酮的脱酰芳基化和炔基化反应

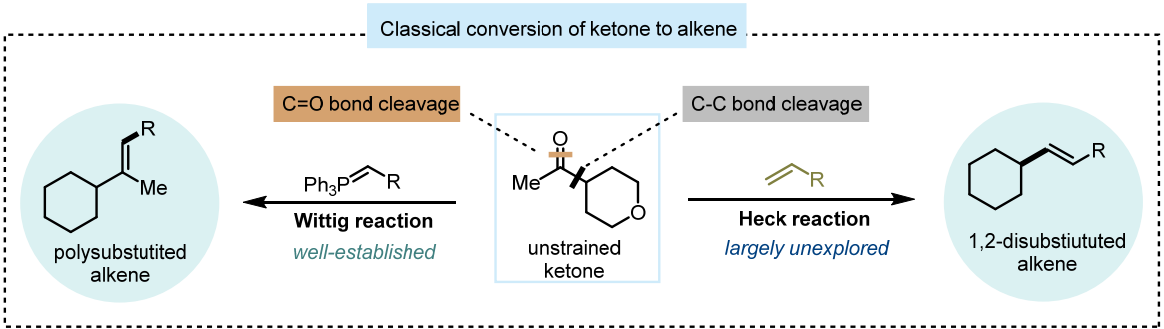


Broad ketone scope: cyclic, methyl and drug-derived ketones
Mild conditions with excellent functional group compatibility

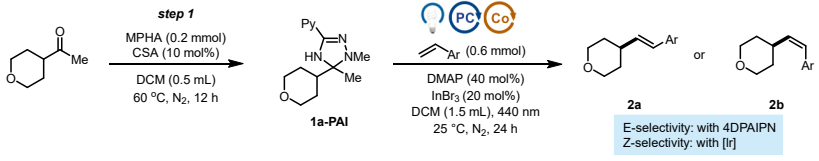
Scalable to gram quantity
Suitable for one-pot procedure

Sci. Adv., **2024** ,*10*, eado0225.

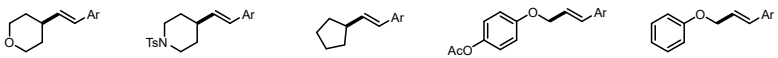
非张力酮的立体发散性脱酰基Mizoroki–Heck反应



非张力酮的立体发散性脱酰基Mizoroki–Heck反应



Scope of ketones



63% yield, 94:6 E/Z
82% yield, 83:17 Z/E

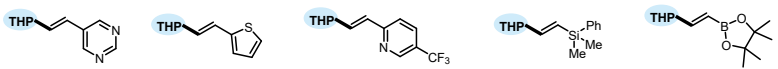
83% yield, 93:7 E/Z
76% yield, 85:15 Z/E

50% yield, 92:8 E/Z
56% yield, 81:19 Z/E

47% yield, 99:1 E/Z
53% yield, 88:12 Z/E

47% yield, 98:2 E/Z
53% yield, 78:22 Z/E

cope of alkenes



64% yield, 90:10 E/Z
72% yield, 86:14 Z/E

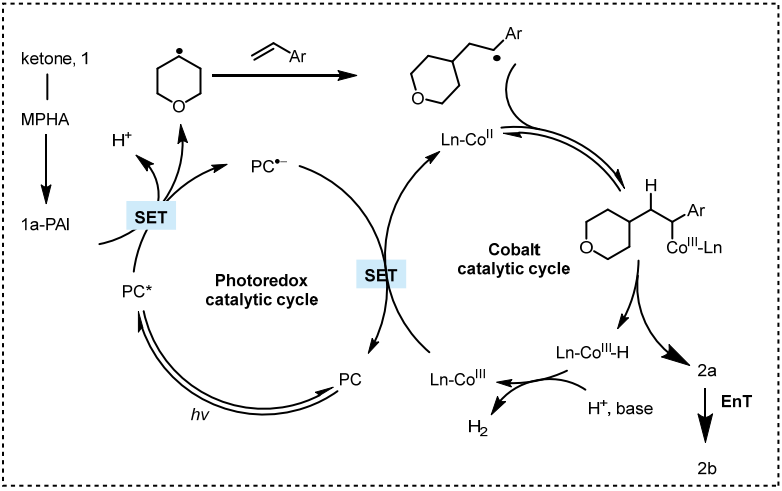
42% yield, 86:14 E/Z
46% yield, 76:24 Z/E

53% yield, 98:2 E/Z
66% yield, 88:12 Z/E

46% yield, >99:1 E/Z

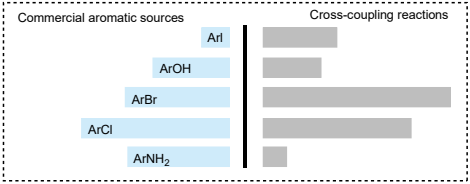
43% yield, >99:1 E/Z

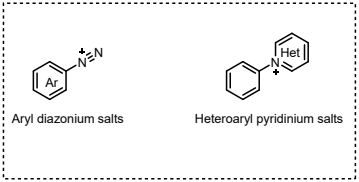
非张力酮的立体发散性脱酰基Mizoroki–Heck反应

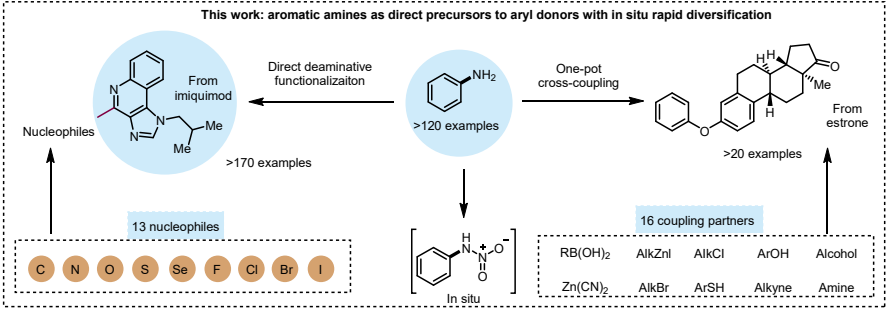


Angew. Chem. Int. Ed. 2026, 65, e18599[32]

N-硝胺介导的直接脱氨官能团化

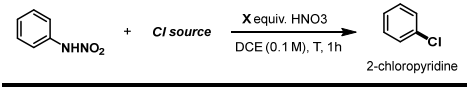


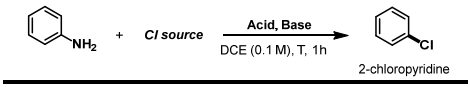




Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化





- **以N-吡啶基硝胺 1 为底物筛选氯源和碱：**

$MgCl_2$(3.0 equiv) + HNO_3(3.0 equiv), 100 °C: 42% yield；
不加HNO_3或$MgCl_2$减量：检测不到；
$MgCl_2$ 3.0 equiv, 50 °C : 68%；
LiCl替代$MgCl_2$：30%。

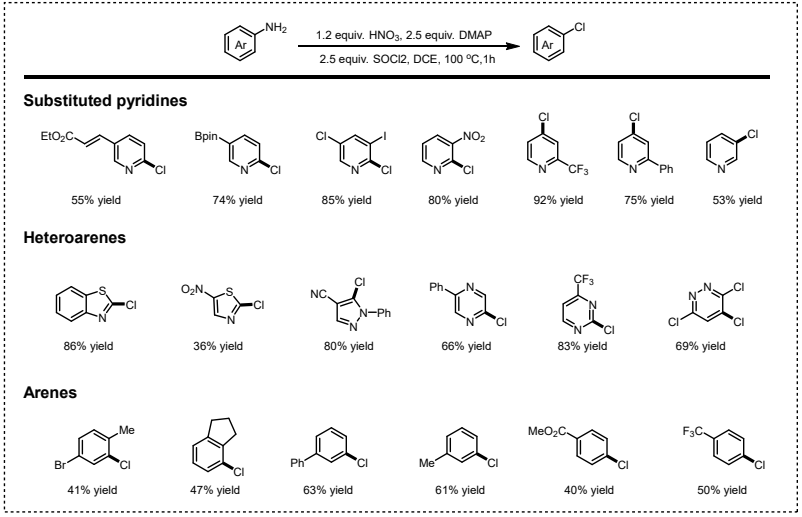
- **碱筛选（1.8 equiv base, DCE, 70 °C ）：**

DMAP: 74%；
DBU:55%；2-吡咯烷酮:65%；奎宁环：60%；NBn_3：67%；2,6-二叔丁基吡啶：61%。

- **酸筛选**：只有 HNO_3 有效（16%→74%），HCl、H_2SO_4、TfOH、TFA、AcOH 均检测不到；
- **氯源筛选：**$SOCl_2$ 最优，$POCl_3$、AcCl、BzCl、TsCl 次之，LiCl/NaCl/$MgCl_2$/NH_4Cl/$^nBu_4NCl$ 单独使用无效；
- **碱筛选：**DMAP 最优（57%），DMF、DBU、TMEDA、咪唑、Et_3N 等均较低；
- **溶剂筛选：**DCE 最优（57%），DCM 55%，THF 35%，正己烷 44%，MeCN 仅 trace，甲苯/DMF/DMSO 无效；
- **温度：**50 °C, 39%; 70 °C, 57%; 100 °C, 57%；
- **化学计量优化：**$SOCl_2$ 2.5 equiv、HNO_3 1.5 equiv、DMAP 2.5 equiv 时达 70–74%；最终标准条件定为 1.2 equiv HNO_3、2.5 equiv DMAP、2.5 equiv $SOCl_2$、DCE、100 ° C、1 h，2-氯吡啶 74%。

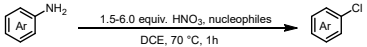
Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化

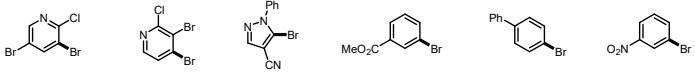


Nature 2025, 648, 341.

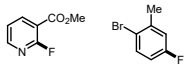
N-硝胺导介导的直接脱氨官能团化



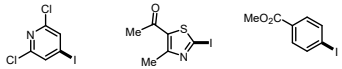
C–Br bond formation



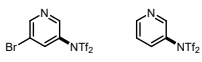
C–F bond formation



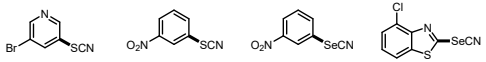
C–I bond formation



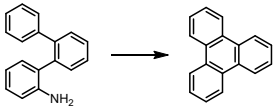
C–N bond formation



C–S/Se bond formation



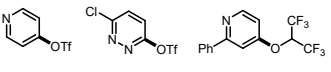
Intramolecular C-C(sp^2) bond formation



Intramolecular C-C(sp^3) bond formation

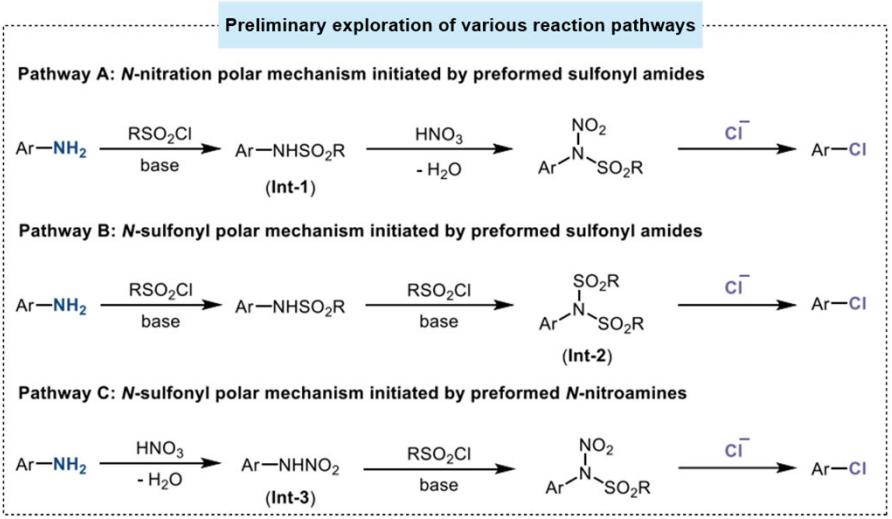


C–O bond formation



Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化

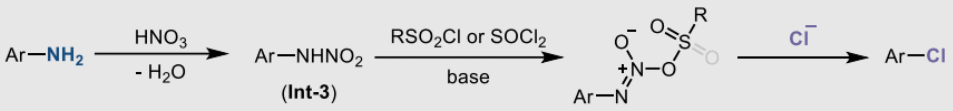


Nature 2025, 648, 341.

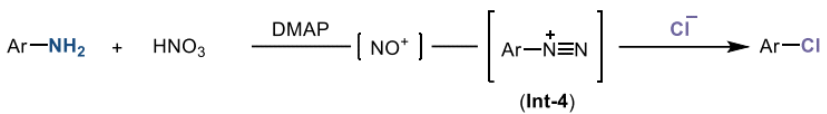
N-硝胺介导的直接脱氨官能团化

Preliminary exploration of various reaction pathways

Pathway D: *O*-sulfonation polar mechanism initiated by preformed *N*-nitroamines (favored)



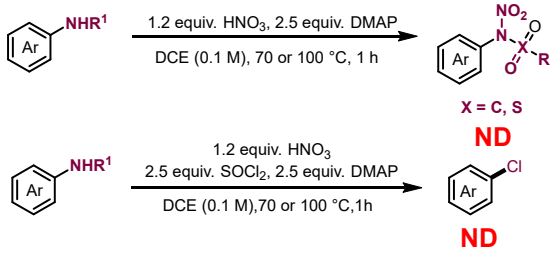
Pathway E: Transient aryldiazonium generation facilitaed by DMAP promoting nitrate reduction



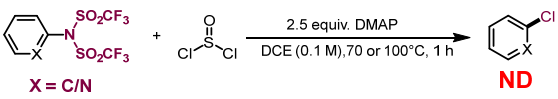
Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化

Experimental verification of pathway A:



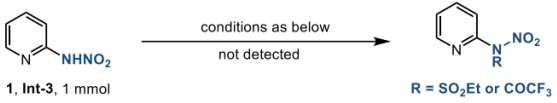
Experimental verification of pathway B:



Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化

Experimental verification of pathway C：



1, **Int-3**, 1 mmol

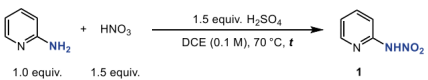
R = SO_2Et or $COCF_3$

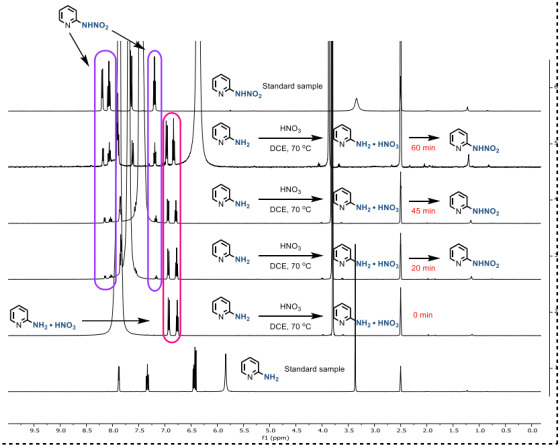
condition	yield
$EtSO_2Cl$ (1.2 equiv), LiHMDS (2 equiv, 1 M in THF), THF or DCE, 70 °C, 2 h	n.d.
1) LiHMDS (2 equiv, 1 M in THF), THF, 0 °C, N_2, 5 min; 2) **$EtSO_2Cl$** (1.2 equiv), THF, 0 °C, N_2, 12 h	n.d.
1) ^{n}BuLi (2.5 equiv), THF, -78 °C, N_2, 5-10 min; 2) **$EtSO_2Cl$** (3 equiv), THF, -78 °C, N_2, 10 min-3 h	n.d.
1) ^{n}BuLi (2.5 equiv), THF, 0 °C, N_2, 30 min; 2) **$EtSO_2Cl$** (3 equiv), THF, 0 °C, N_2, 12 h	n.d.
$EtSO_2Cl$ (3 equiv), Et_3N or Pyridine (3 equiv), DCM, 0 °C, 12 h	n.d.
TFAA (2 equiv), Et_3N (3 equiv), DCM, r.t., 12 h	n.d.
CF_3CO_2H (2 equiv), EDCI (3 equiv), DMAP (3 equiv), DCM, r.t., 12 h	n.d.

Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化

N-硝胺是关键中间体：

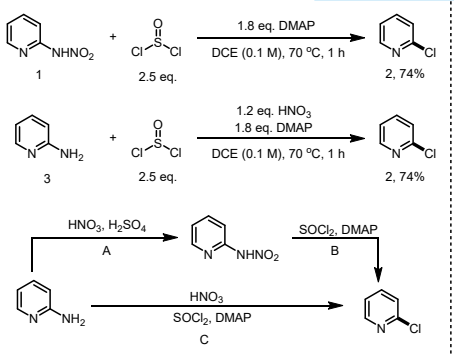


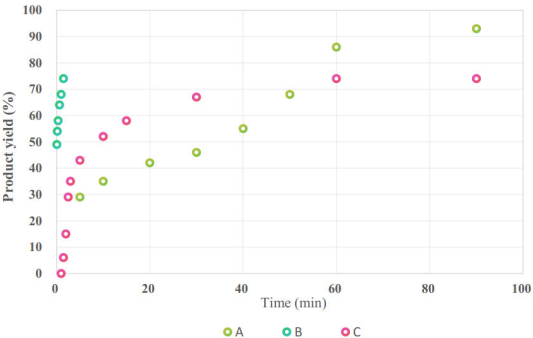


Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化

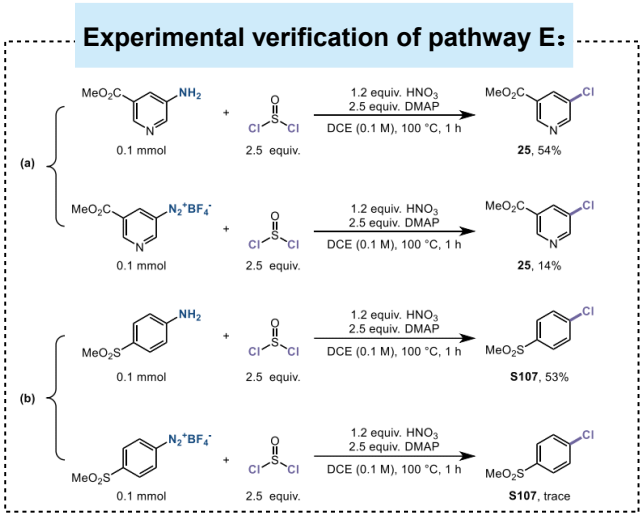
Reaction kinetics experiments：





Nature 2025, 648, 341.

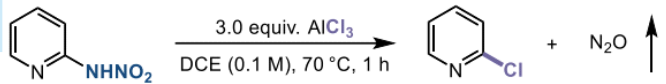
N-硝胺介导的直接脱氨官能团化



Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化

Detected by GC-MS



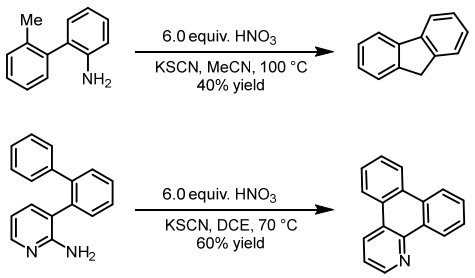
1.0 equiv. 75%

To a 20 mL vial equipped with a stir bar was added *N*-pyridylnitroamine (139.0 mg, 1.0 mmol, 1.0 equiv.), $AlCl_3$ (400.0 mg, 3.0 mmol, 3.0 equiv.) and DCE (10.0 mL). The vial was sealed and the solution was degassed by sparging with argon for 10 minutes. Subsequently, the reaction was heated to 70 ℃ for 1 hour. The reaction mixture was cooled to room temperature and analyzed by GC-MS.

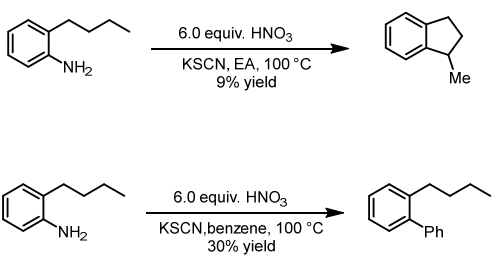
Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化

C－H insertion and electrophilic substitution：



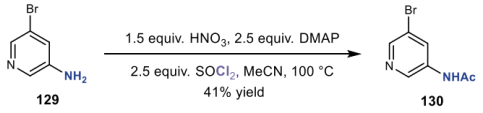
Control experiments



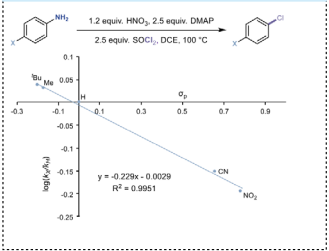
Nature 2025, 648, 341.

N-硝胺介导的直接脱氨官能团化

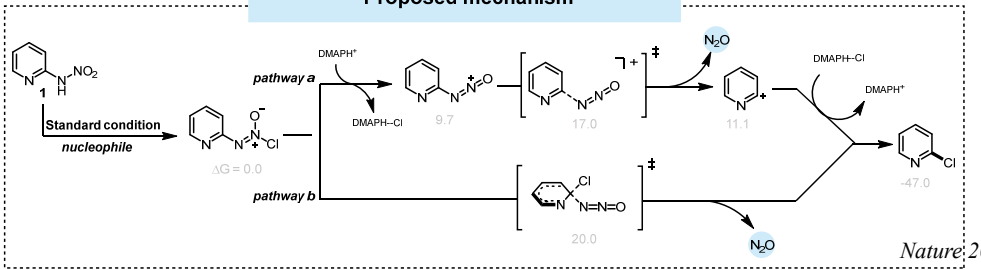
Ritter-type reaction



Hammett analysis

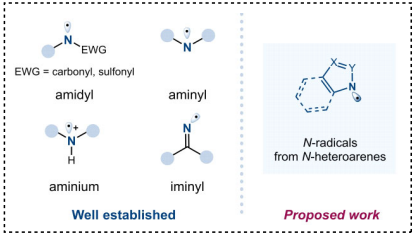


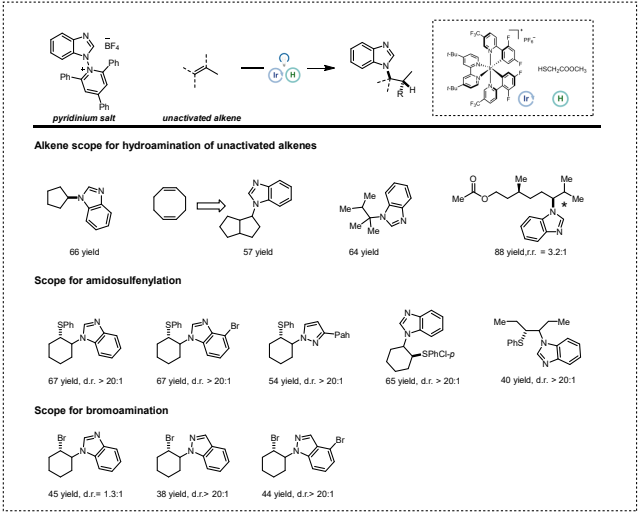
Proposed mechanism



Nature, *2025*, *648*, 341.

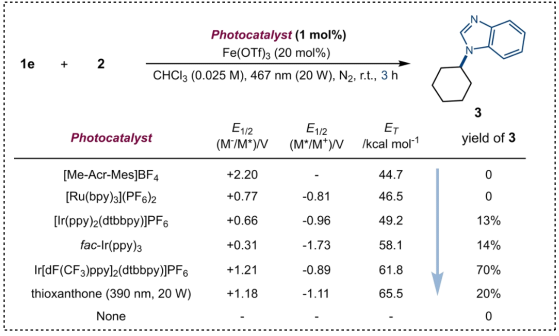
基于芳香杂环氮自由基实现未活化烯烃官能团化



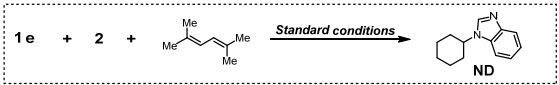


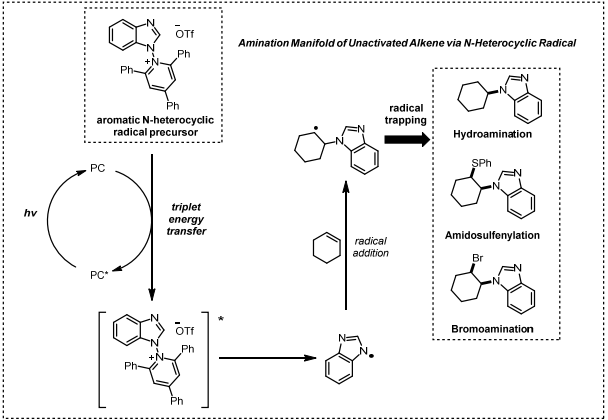
Angew. Chem. Int. Ed. 2023, 62, e202314312.

基于芳香杂环氮自由基实现未活化烯烃官能团化



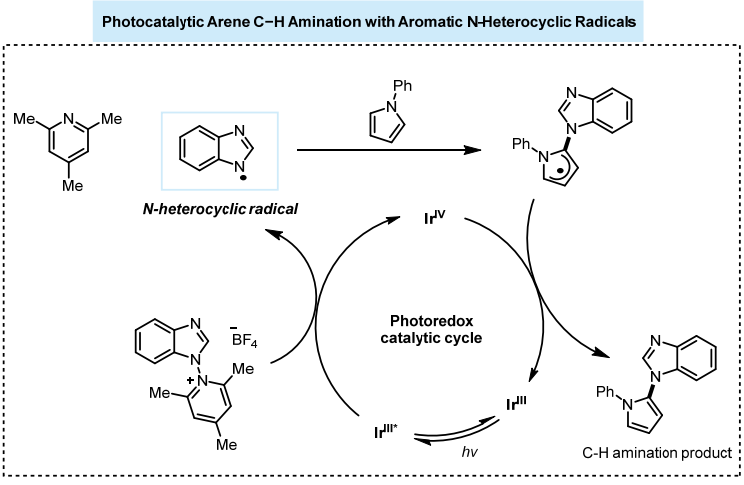
Photocatalyst	$E_{1/2}$ (M^{-}/M^{*})/V	$E_{1/2}$ (M^{*}/M^{+})/V	E_T /kcal mol^{-1}	yield of 3
[Me-Acr-Mes]BF_4	+2.20	-	44.7	0
[Ru(bpy)$_3$](PF_6)$_2$	+0.77	-0.81	46.5	0
[Ir(ppy)$_2$(dtbbpy)]PF_6	+0.66	-0.96	49.2	13%
fac-Ir(ppy)$_3$	+0.31	-1.73	58.1	14%
Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)]PF_6	+1.21	-0.89	61.8	70%
thioxanthone (390 nm, 20 W)	+1.18	-1.11	65.5	20%
None	-	-	-	0





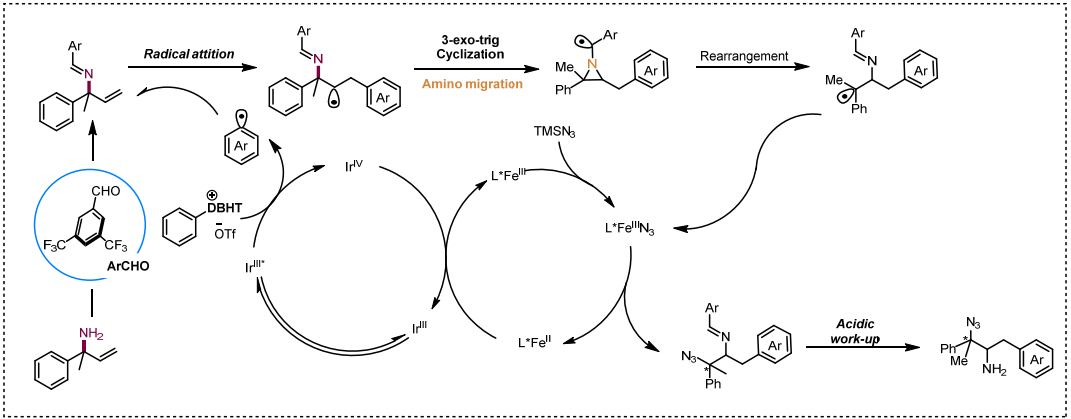
Angew. Chem. Int. Ed. 2023, 62, e202314312.

利用芳香氮杂环自由基实现芳环碳氢胺化反应



ACS Catal. **2025**, *15*, 16863.

光铁催化非端位1,2-二胺化反应



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