Literature Report 5

A Biphilic Phosphetane Catalyzed N-N Bond Forming

Reporter: Han Wang
Checker: Wen-Jun Huang
Date: 2021.12.06

Radosevich, A. T.* *et al*. *J. Am. Chem. Soc.* **2017**, *139*, 6839.
Radosevich, A. T.* *et al*. *J. Am. Chem. Soc.* **2021**, *143*, 14464.

CV of Dr. Alexander T. Radosevich

Background:

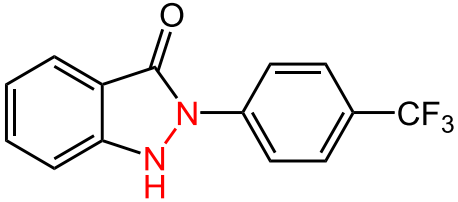
- **1998-2002** B.S., University of Notre Dame
- **2002-2007** Ph.D., University of California, Berkeley
- **2007-2010** Postdoc., MIT (D. G. Nocera)
- **2010-2016** Assistant Professor, The Penn State University
  Associate Professor, The Penn State University
- **2016-now** Associate Professor, MIT

Research:

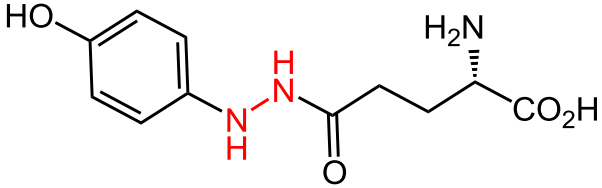
Development of catalytic potential of phosphorus compounds and new methodology

Contents

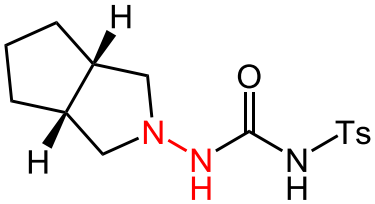
Introduction



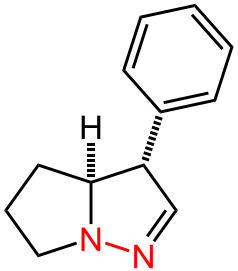
TPRV1 receptor
(antagonists for analgesics)



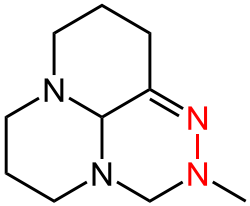
Xanthodermine
(nAChR Inhibitor)



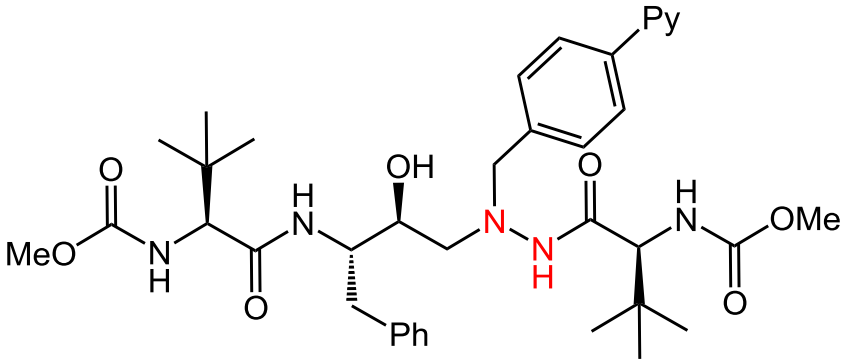
Gliclazide
(hypoglycemic drug)



Newbouldine
(natural product)

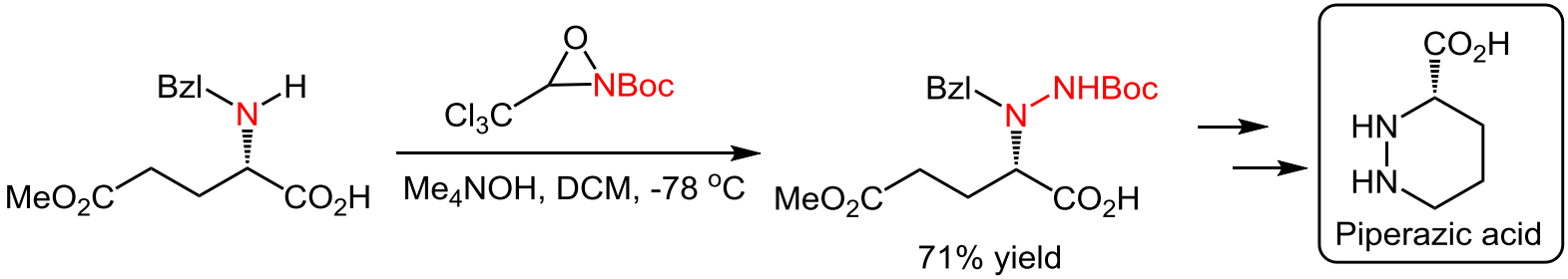


Cinachyramine
(natural product)

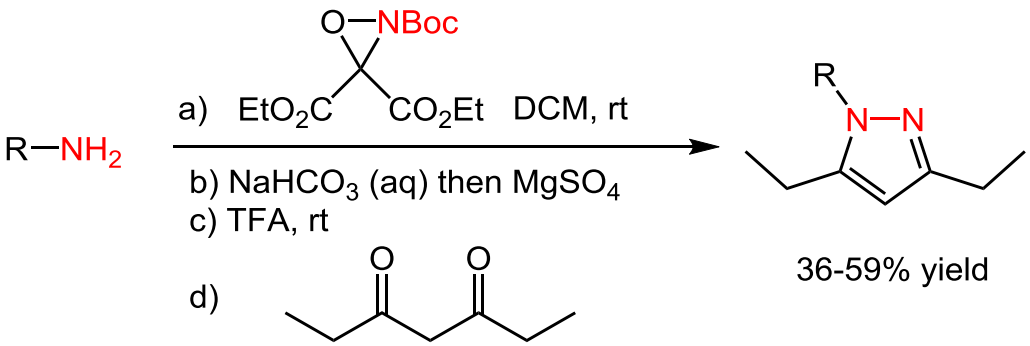


Reyataz
(antiretroviral drug)

Stoichiometric Method

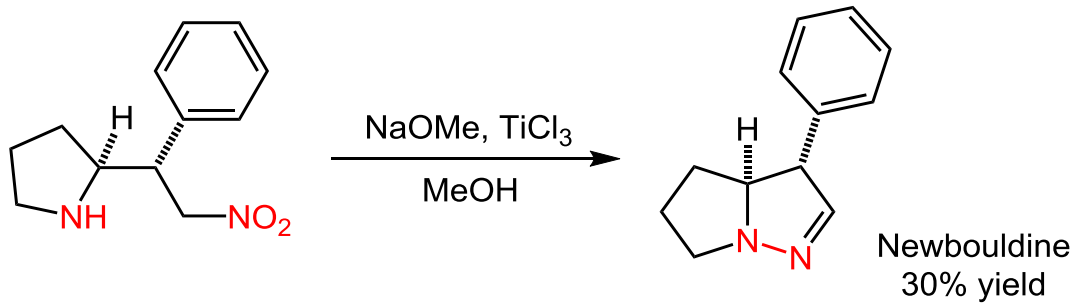


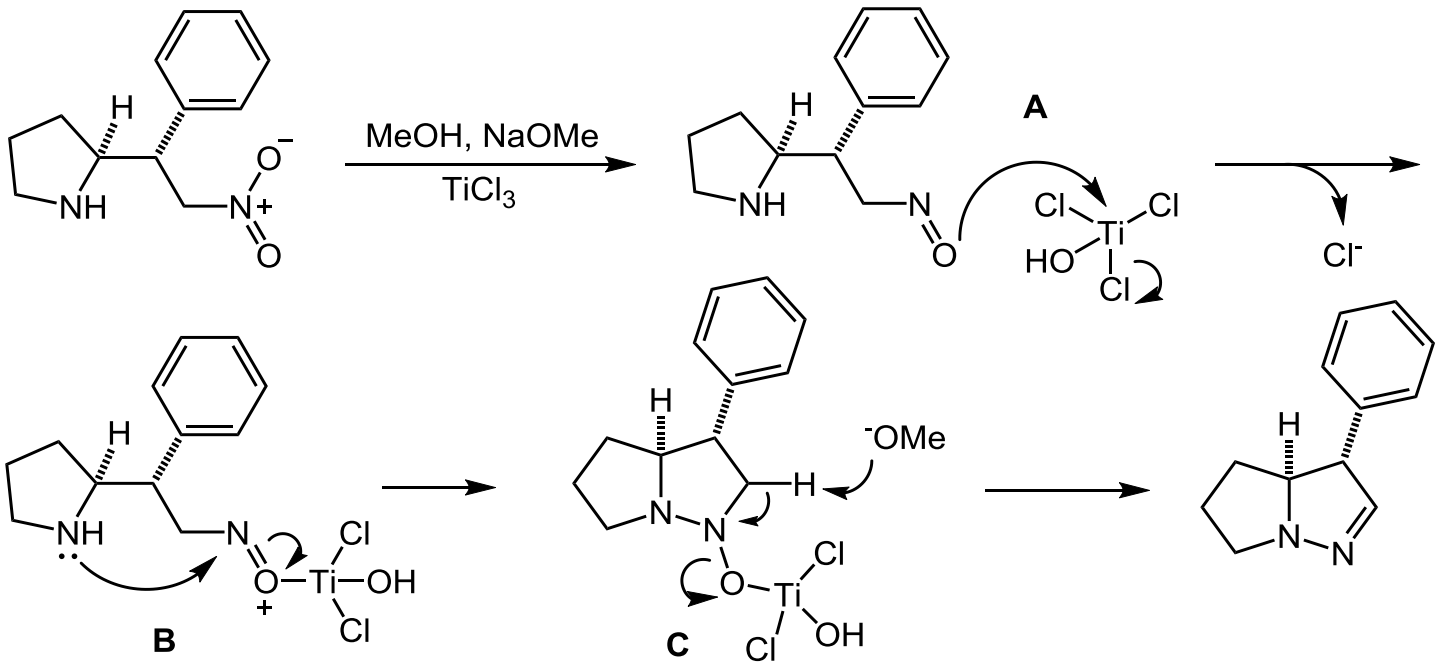
Collet, A. *et al*. *Tetrahedron Lett.* **1998**, *39*, 8845.



Kelsey, R. D. *et al*. *Org. Lett.* **2005**, *7*, 713.

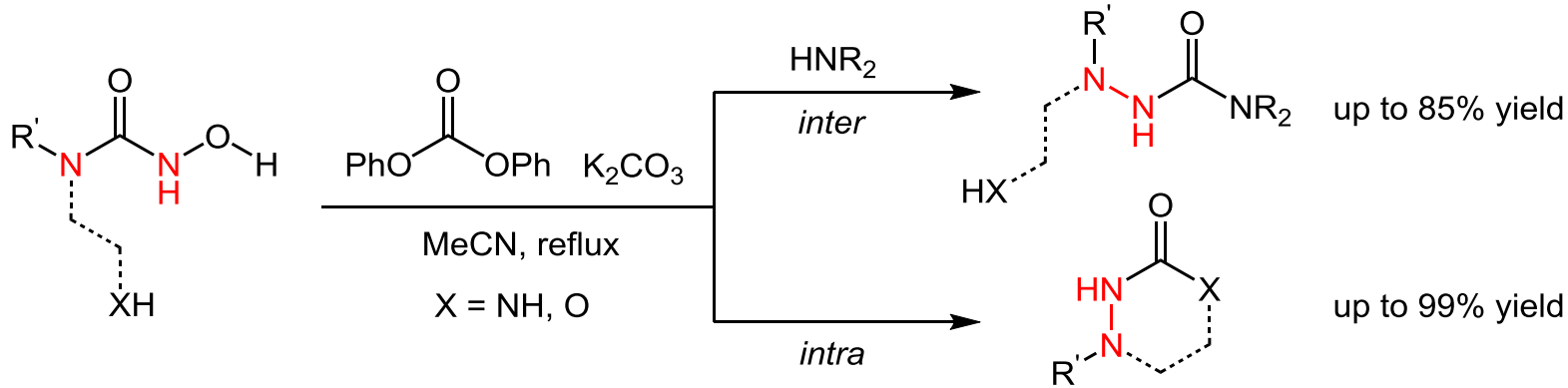
Stoichiometric Method

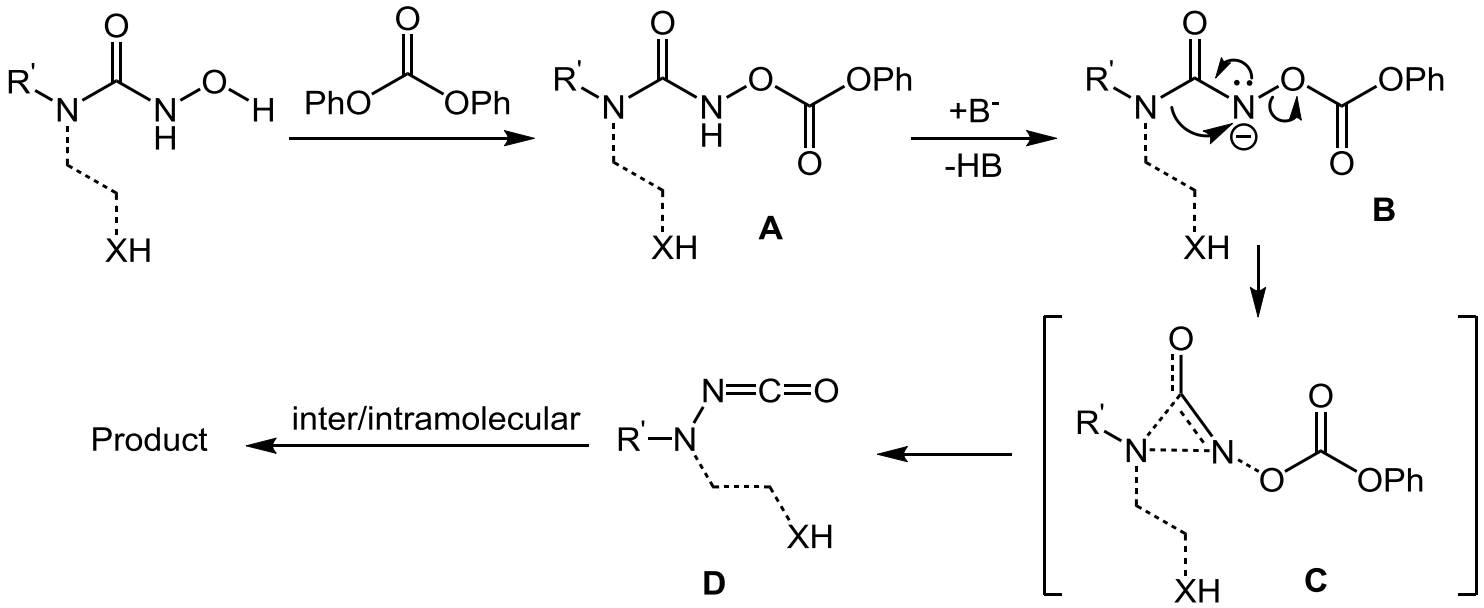




Trauner, D. *et al*. *Tetrahedron* **2010**, *66,* 6626.

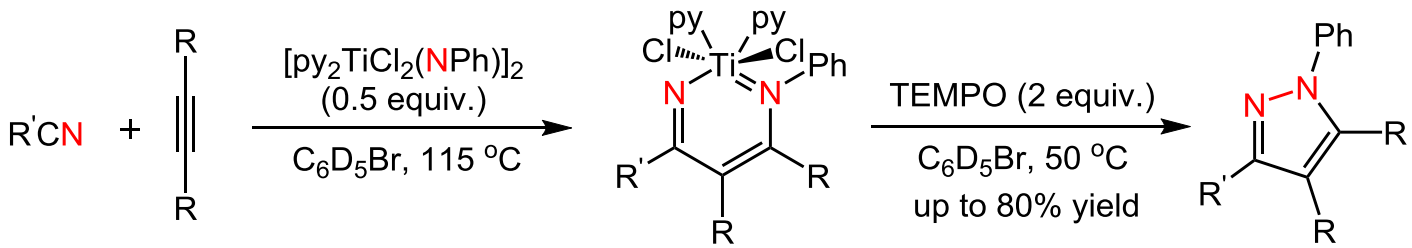
Aza-Lossen Rearrangement

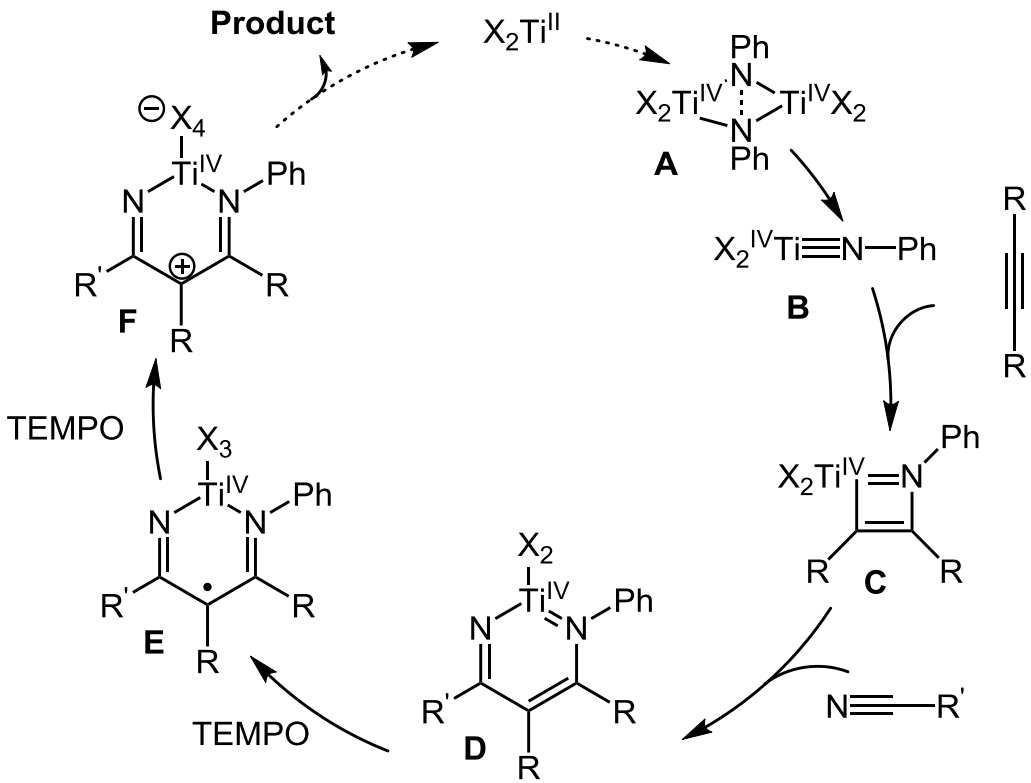




Beauchemin, A. M. *et al*. *Org. Lett.* **2019**, *21*, 4849.

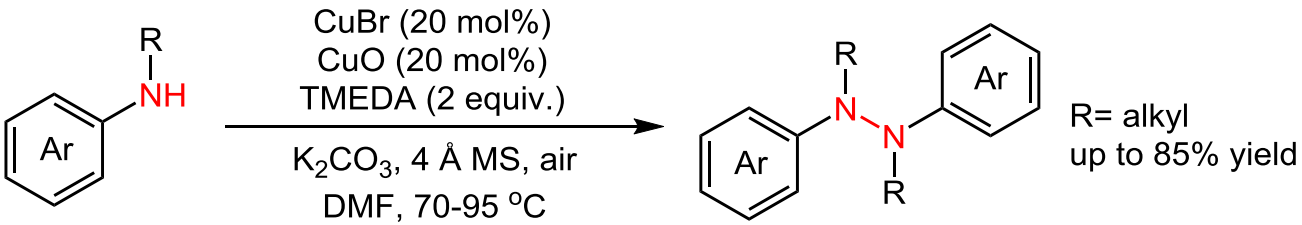
Ti-Induced N-N Formation

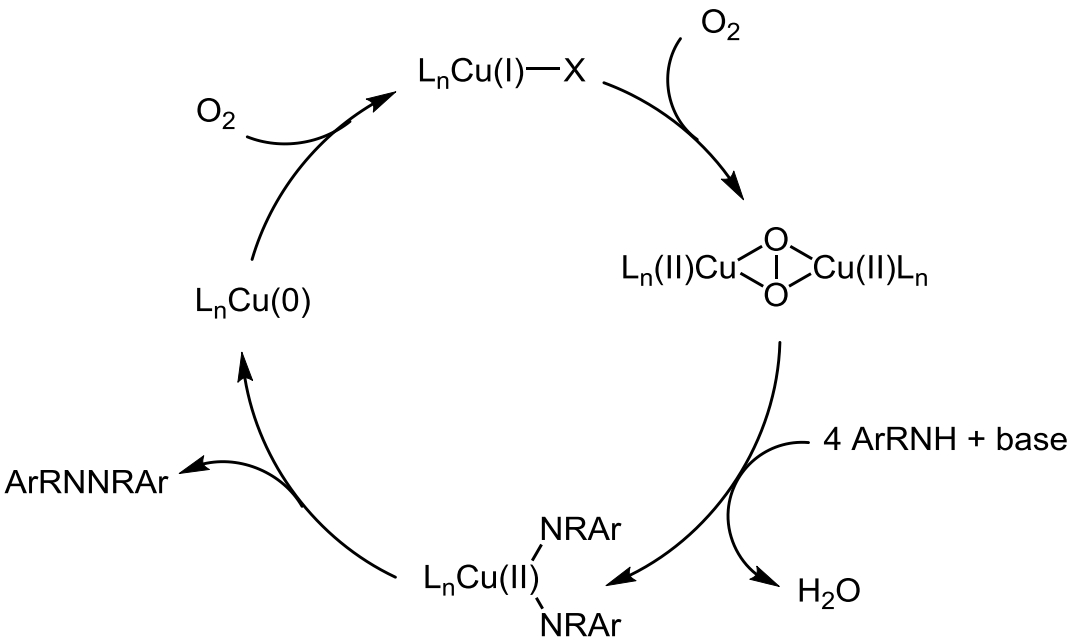




Tonks, I. A. *et al*. *J. Am. Chem. Soc.* **2020**, *142*, 4390.

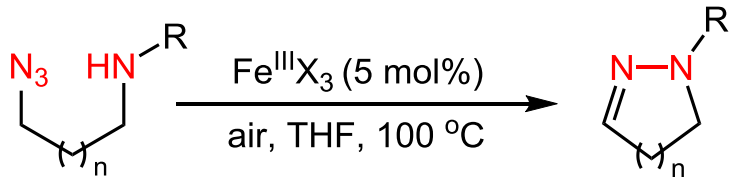
Cu Catalyzed N-N Formation



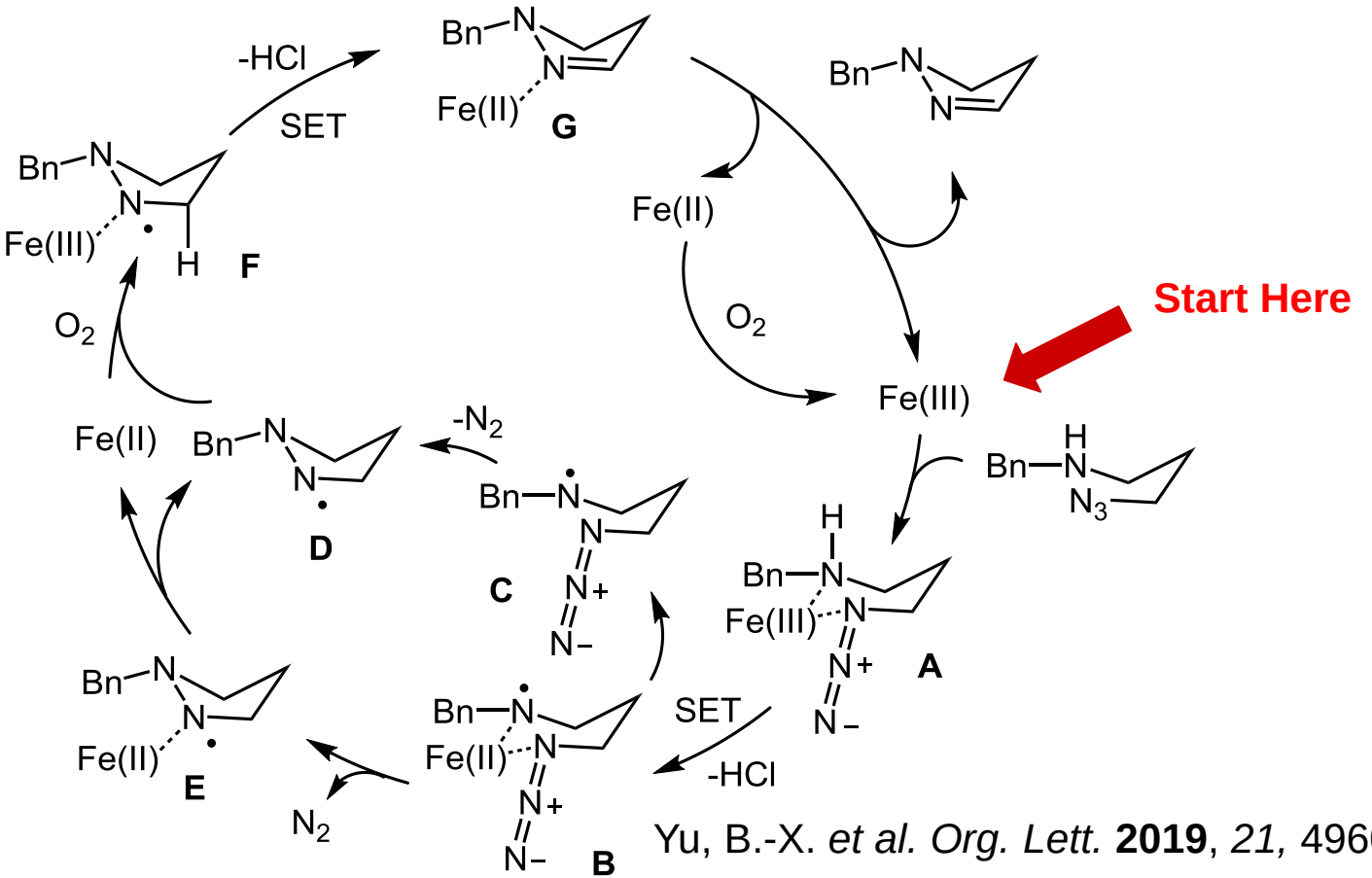


Huang, Z.-Z. *et al. Synlett.* **2011**, *4,* 569.

Fe Catalyzed N-N Formation

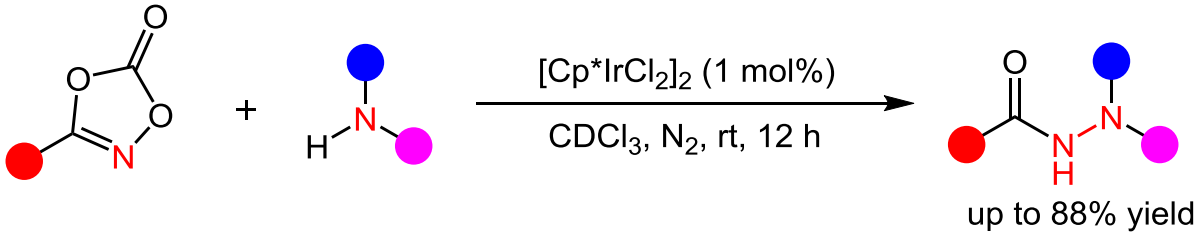


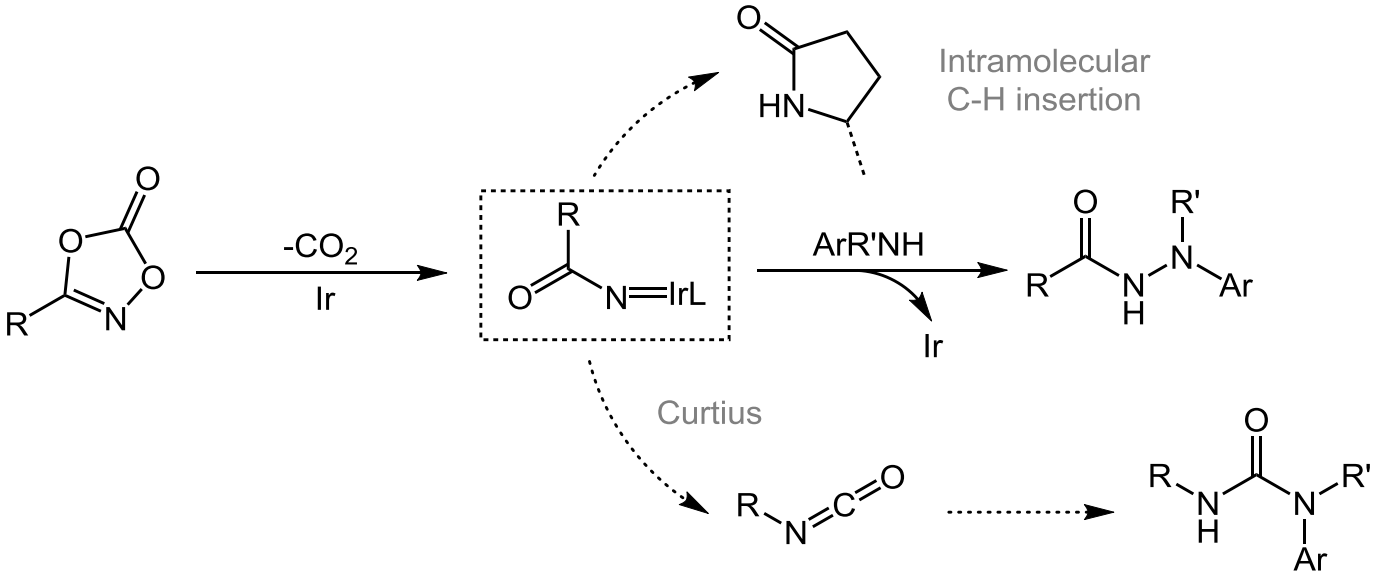
n = 1, X = Cl
n = 2, X = Br
up to 88% yield



Yu, B.-X. *et al. Org. Lett.* **2019**, *21*, 4960.

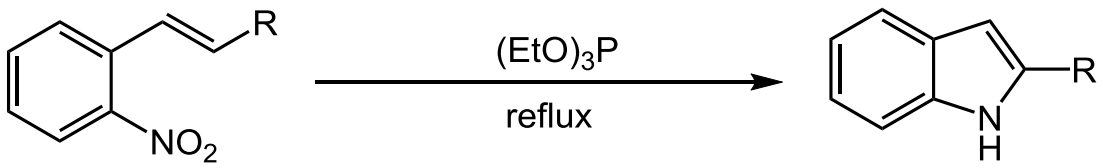
Ir Catalyzed N-N Formation

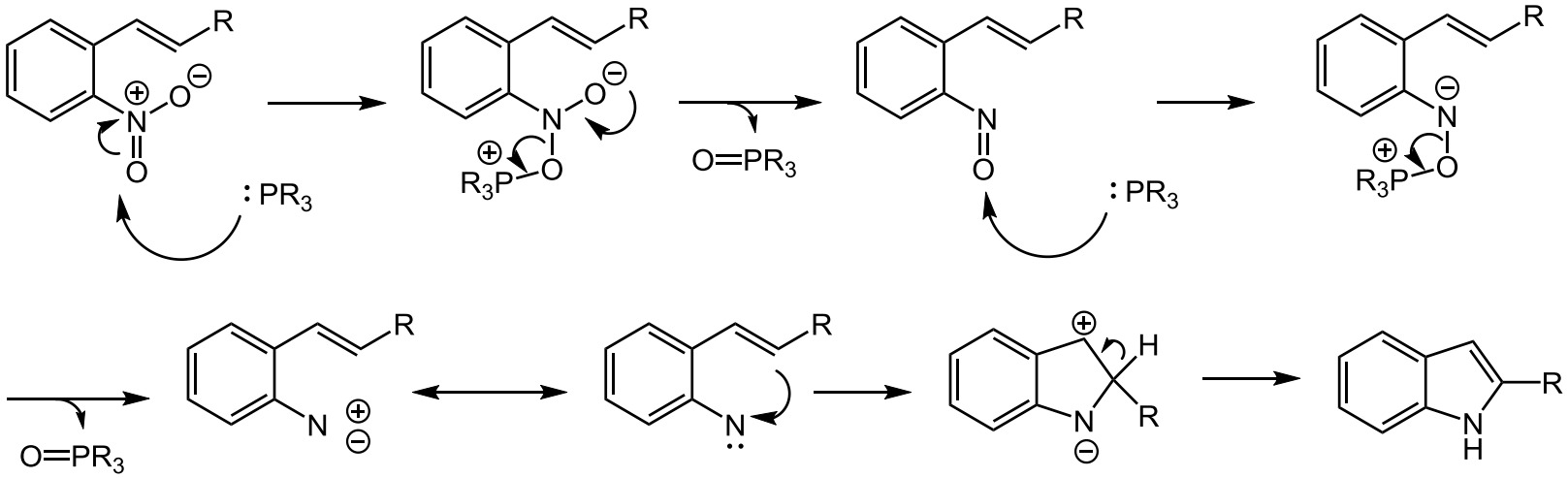


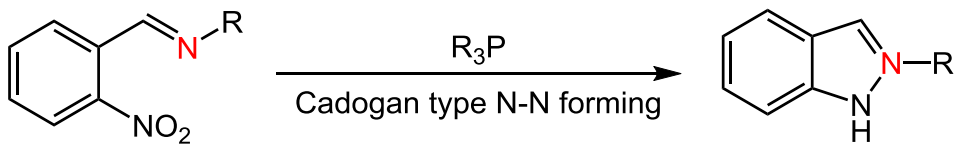


Chen, G. *et al. Nat. Chem.* **2021**, *13*, 378.

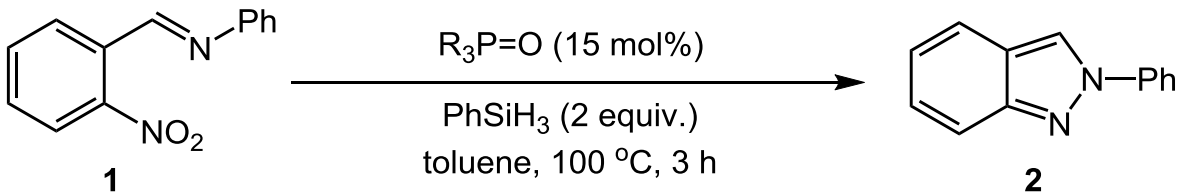
Cadogan Reaction





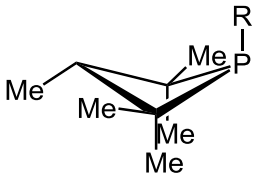


Optimization of Reaction Parameters

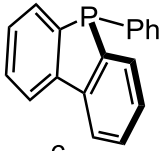


Entry[a]	$R_3P=O$	silane	Conv. [%]	Yield [%]
1	**3[O]**	$PhSiH_3$	49	20
2	**4[O]**	$PhSiH_3$	45	31
3	**5[O]**	$PhSiH_3$	99	83
4	**6[O]**	$PhSiH_3$	21	1
5	**7[O]**	$PhSiH_3$	96	24
6	**8[O]**	$PhSiH_3$	21	6
7	**none**	$PhSiH_3$	14	0
8	**5[O]**	none	12	0
9	**5**	$PhSiH_3$	99	93

[a] Conversion and yield determined via GC vs internal standard..



3: R = pyrrolidino
4: R = Ph
5: R = Me



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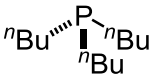

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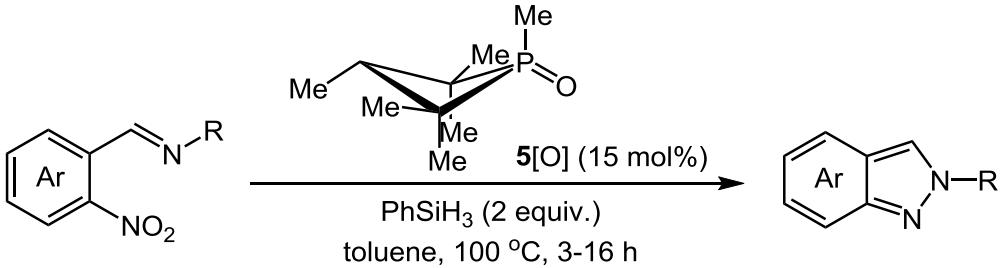
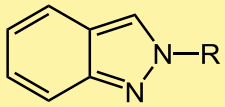
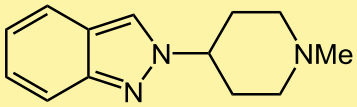
Substrate Scope



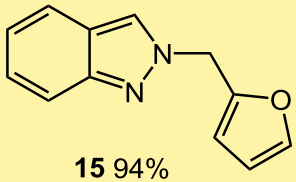
N-alkyl substituents



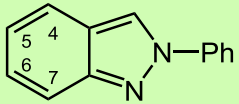
9 R = ^{n}Bu, 83%
10 R = ^{i}Pr, 86%
11 R = ^{t}Bu, 74%
12 R = Cy, 92%
13 R = Bn, 79%



14 98%

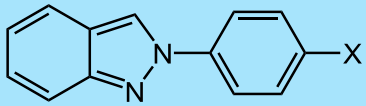


15 94%

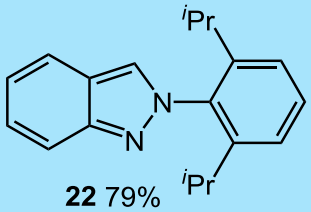


26 R = 5-CO_2Me 73%
27 R = 5-Cl 71%
28 R = 6-NO_2 34%
29 R = 6-Cl 76%
30 R = NMe_2 61%
31 R = 4-Cl 73%

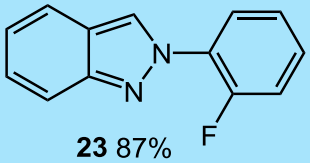
N-aryl substituents



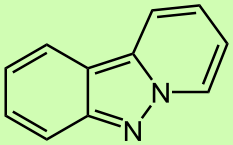
2 R = H 93%
16 R = ^{i}Pr 92%
17 R = Cl 83%
18 R = Br 88%
19 R = OMe 83%
20 R = OH 81%
21 R = CN 86%



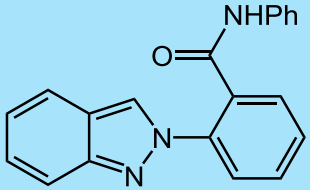
22 79%



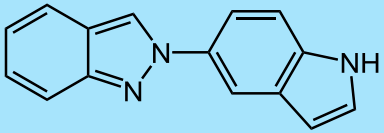
23 87%



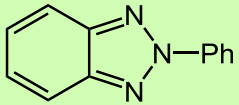
32 99%



24 50%

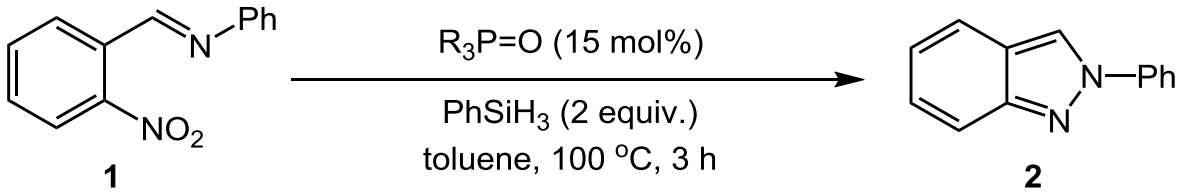


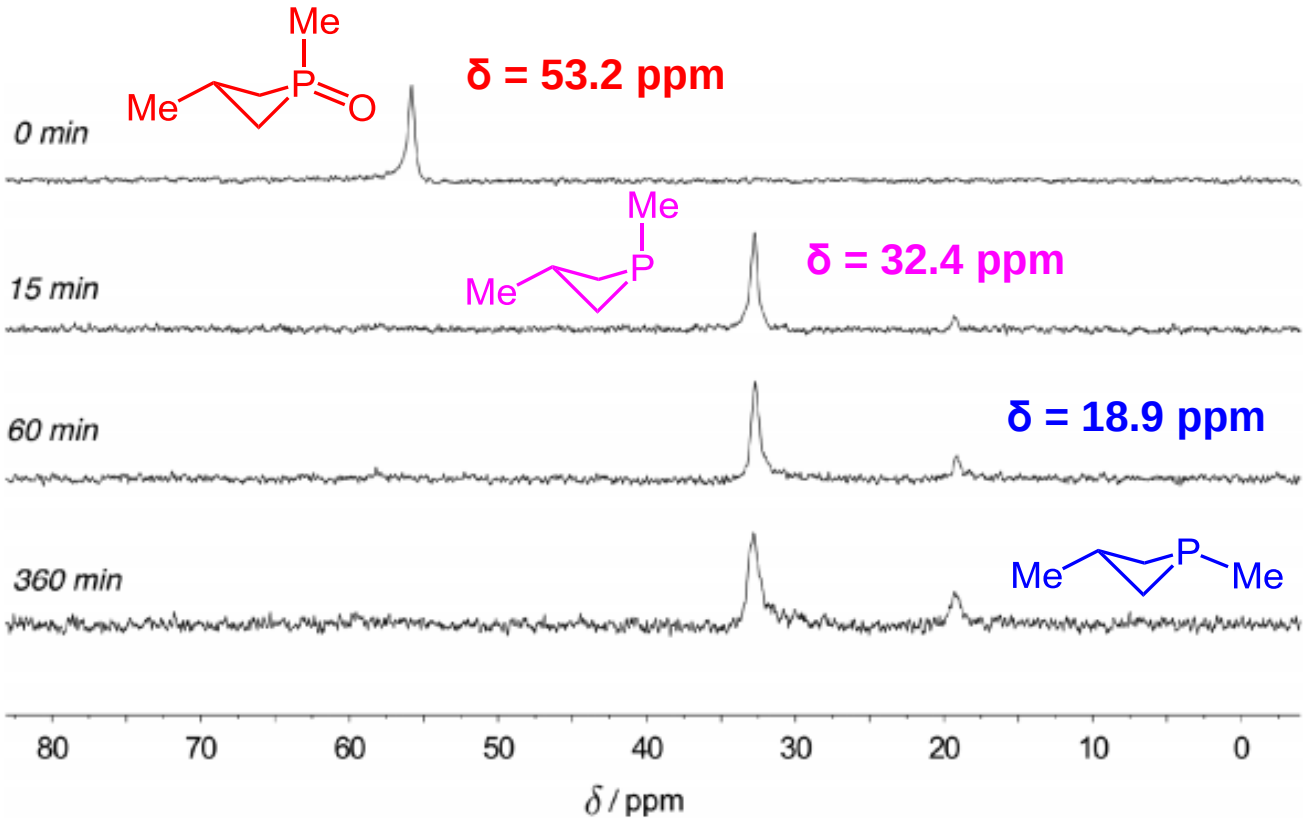
25 91%



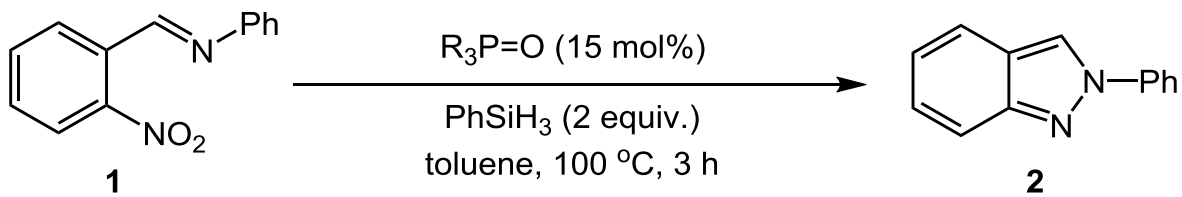
33 71%

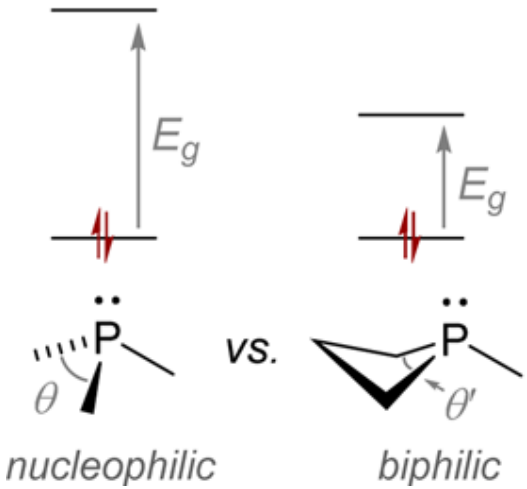
Mechanistic Study



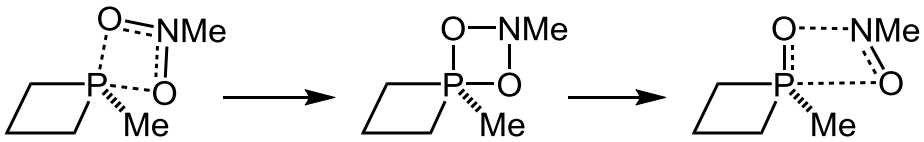


Mechanistic Study

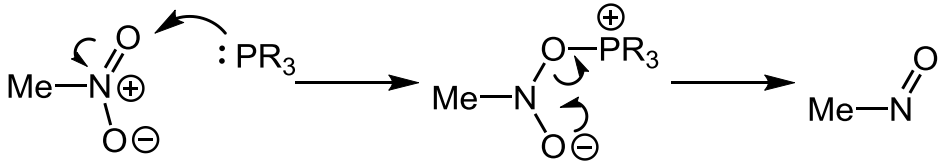




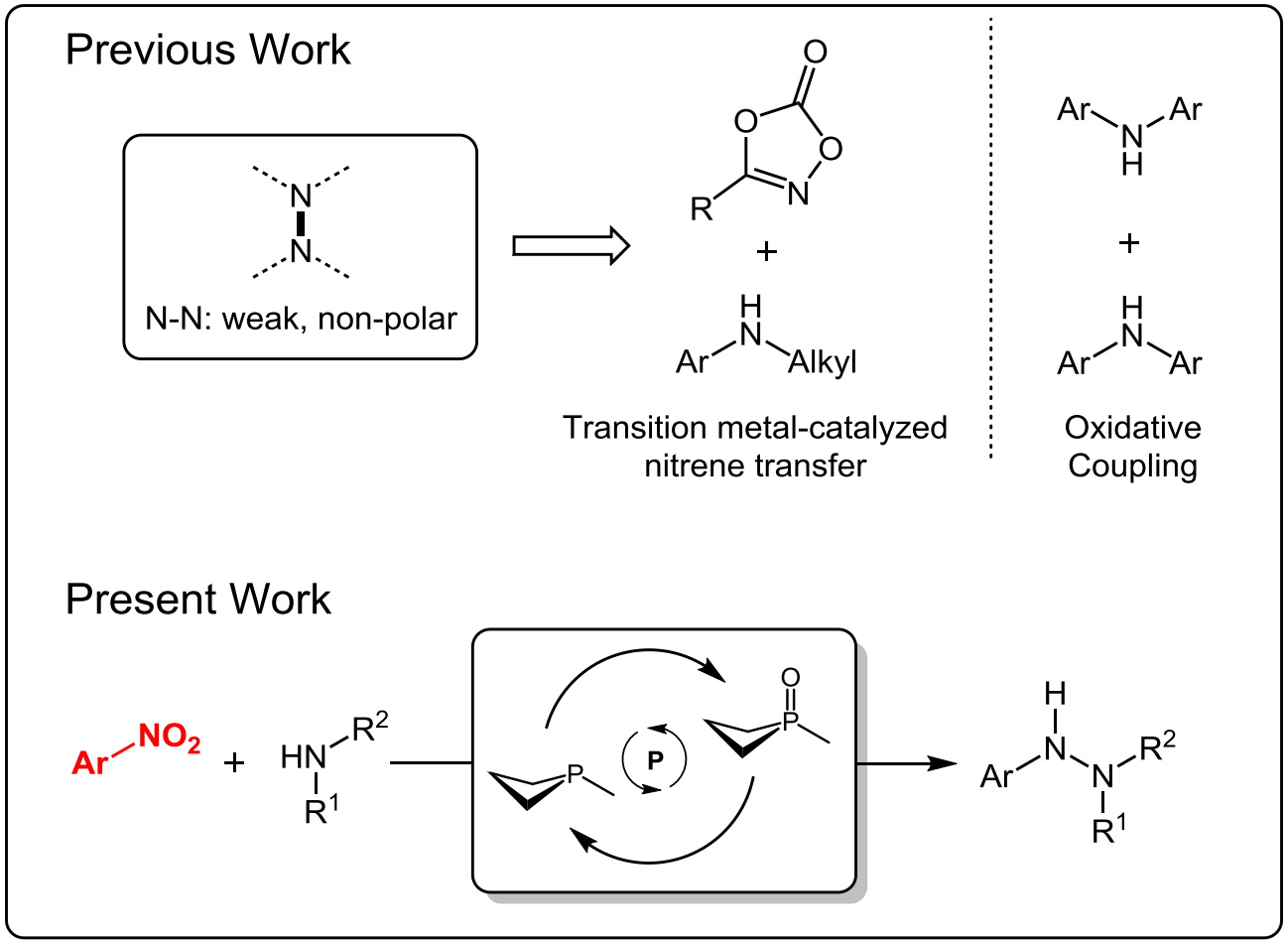
(3+1)/retro(2+2) Pathway



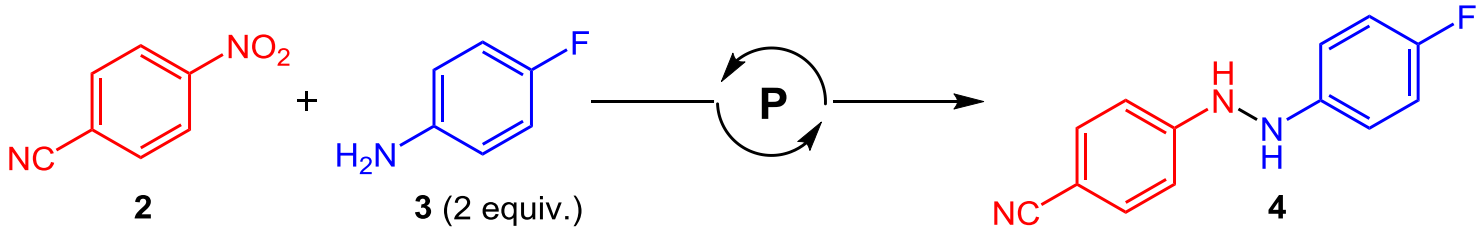
Cadogan Pathway (PR_3 melting)



Intermolecular N-N formation



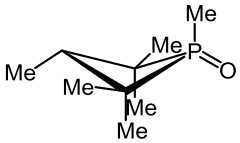
Optimization of Reaction Parameters



Entry [a]	Change from standard conditions	Yield [%]
1	None	86 (81)
2	**1** (15 mol%)	86
3	**1[O]** (5 mol%)	84 [b]
4	No catalyst **1[O]**	0
5	No silane	0
6	No 2,4,6-trimethylbenzoic acid	Trace
7	Under ambient air	82
8	100 °C	79
9	THF (0.5 M)	41

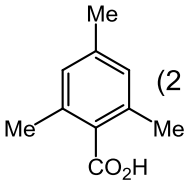
[a] Yields were determined through ^{19}F NMR with 4-fluorotoluene as an internal standard. [b] 72 h reaction time.

Standard Conditions



1[O] (15 mol%)

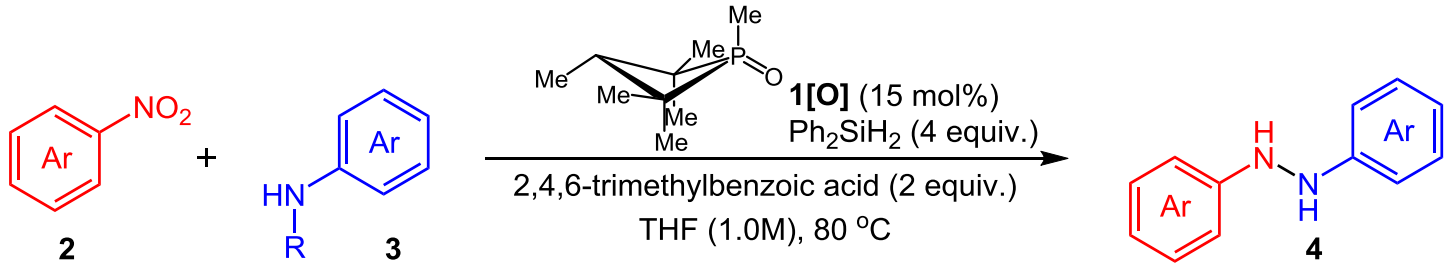
Ph_2SiH_2 (4 equiv.)



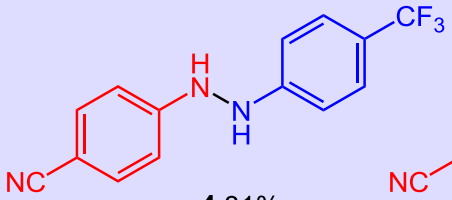
(2 equiv.)

THF (1.0M)
80 °C, 24 h

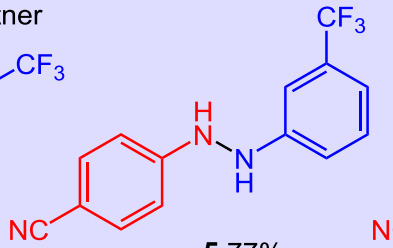
Substrate Scope



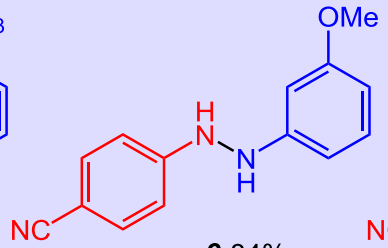
Variation of amine coupling partner



4 81%



5 77%



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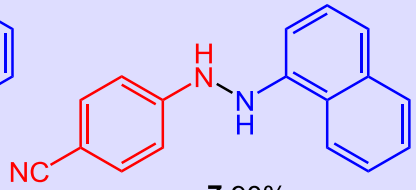

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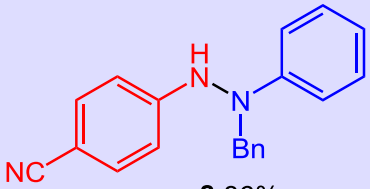

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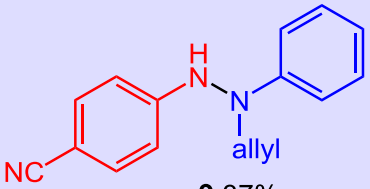

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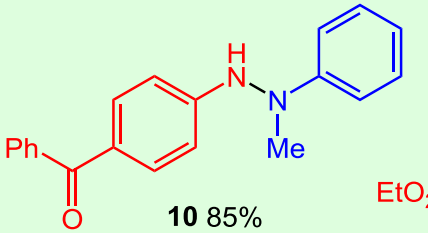

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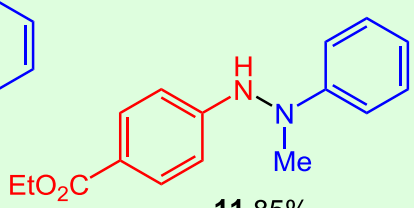

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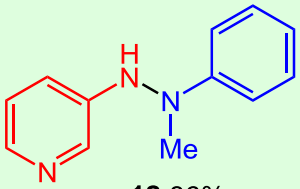

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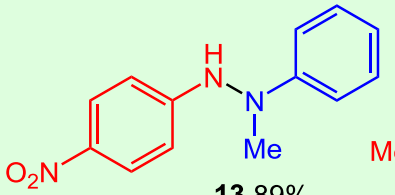

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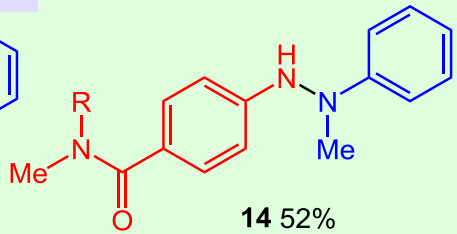
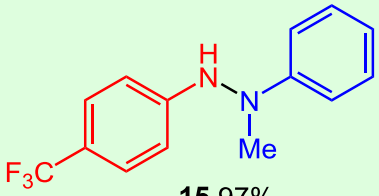


14 52%

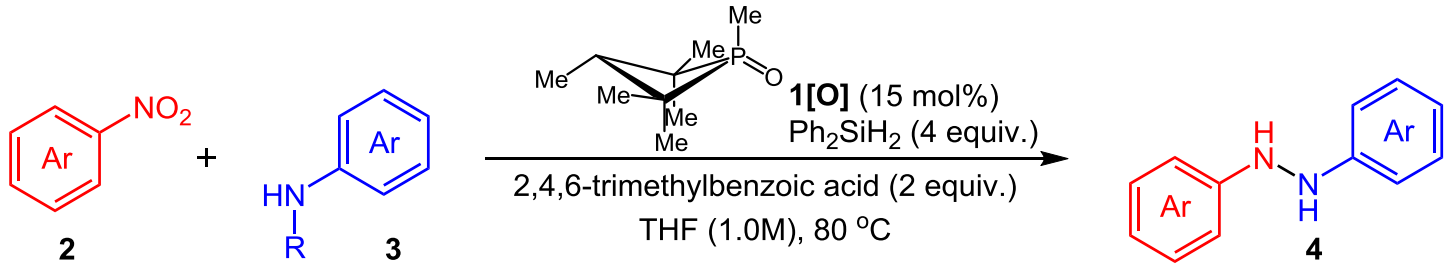
R = 4-(Ph-N=N)-C_6H_4



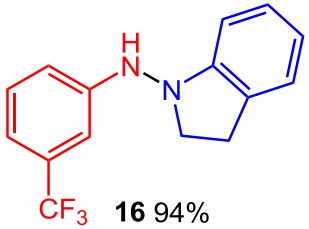
15 97%

Variation of nitro coupling partner

Substrate Scope



Variation of amine and nitro coupling partner



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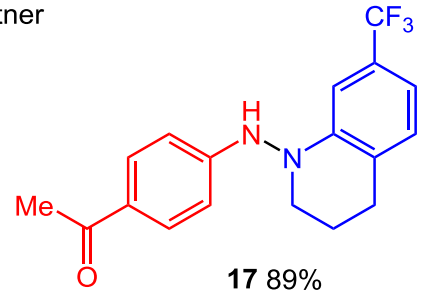

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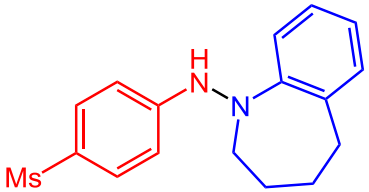

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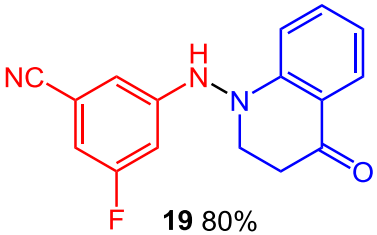

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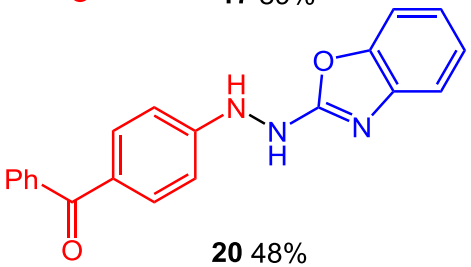

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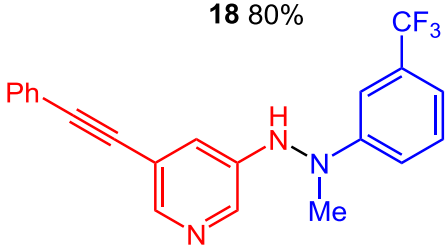
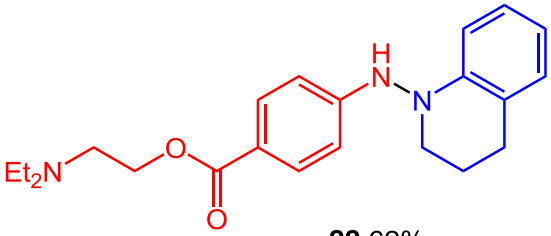
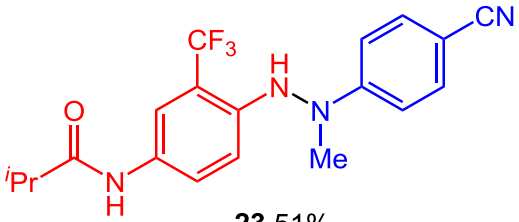


21 83%



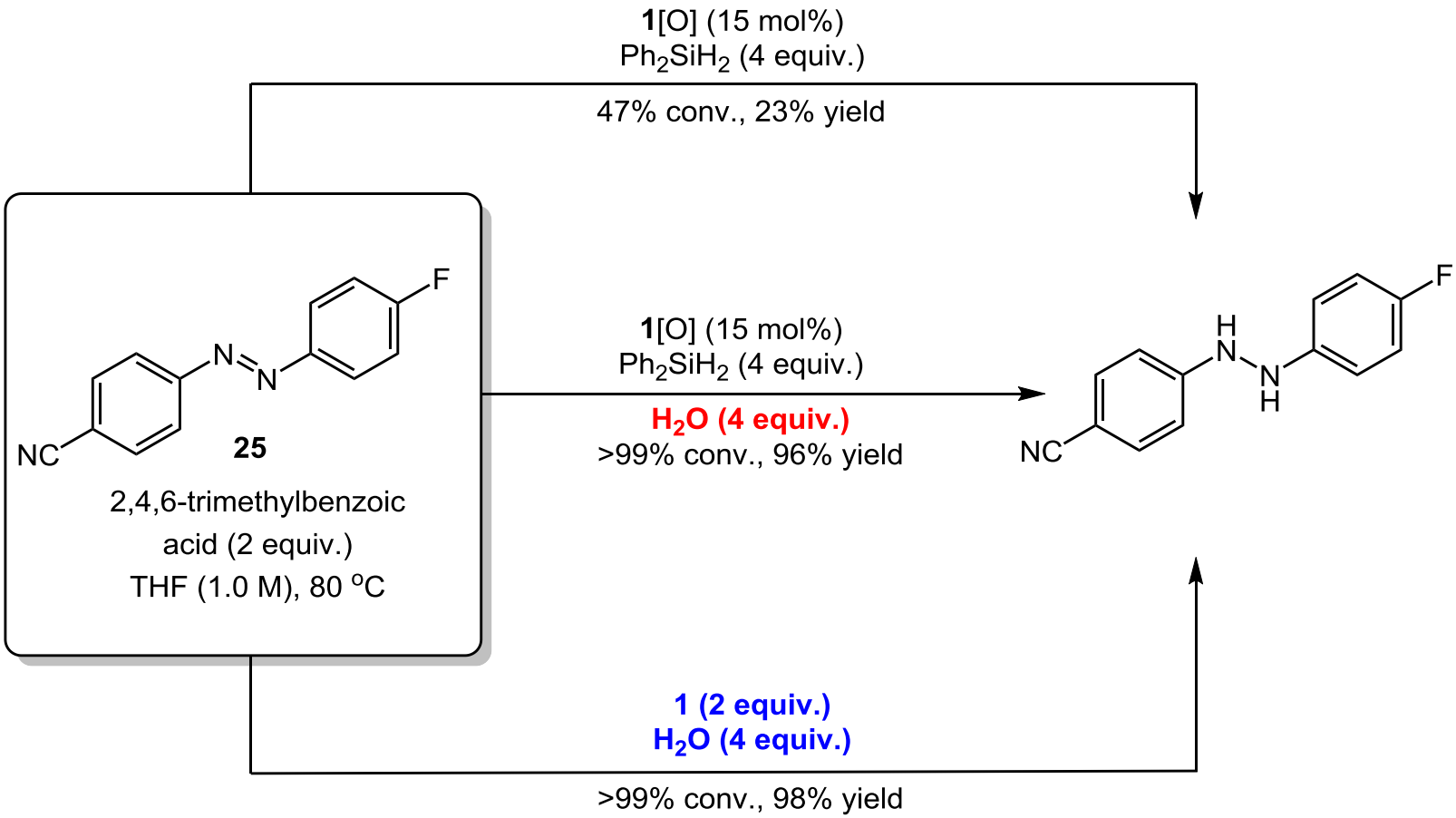
22 62%



23 51%

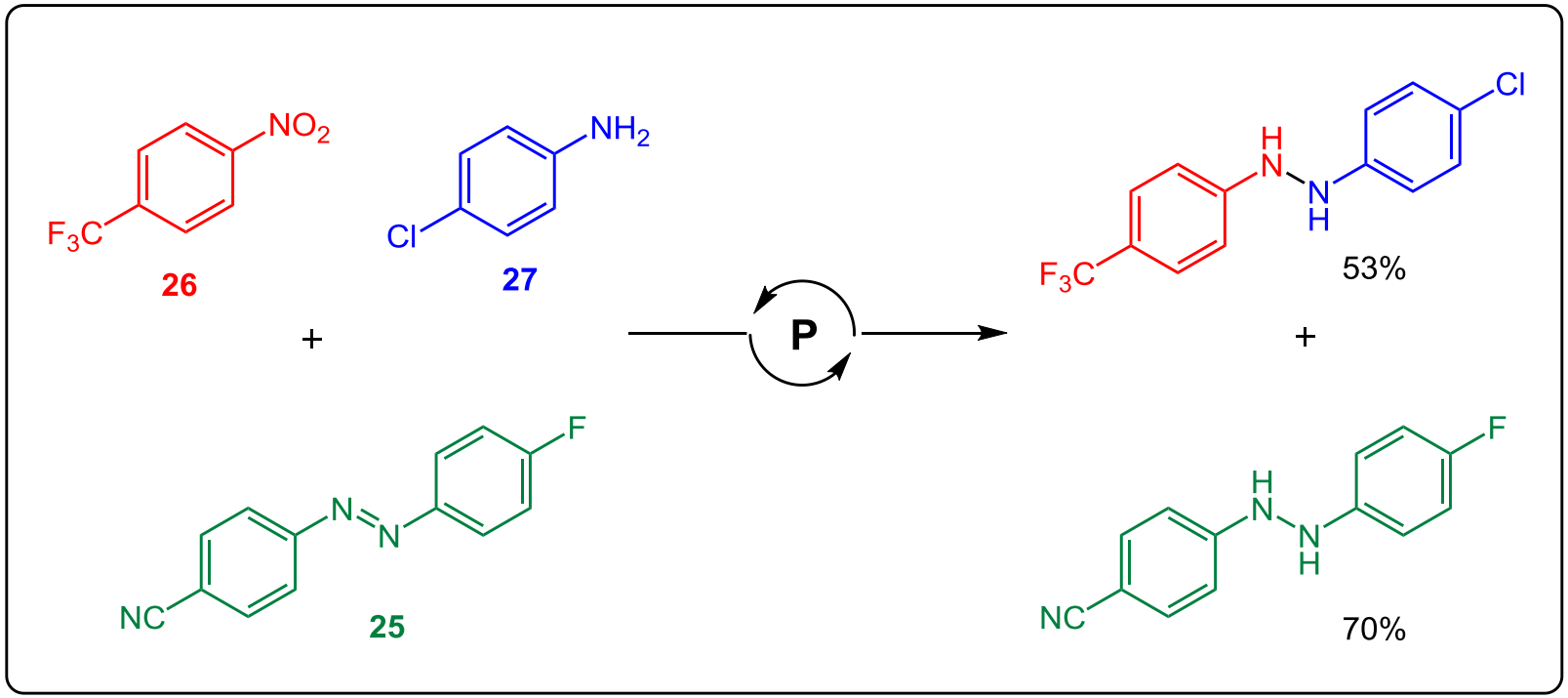
Mechanism Study

Azoarene reduction

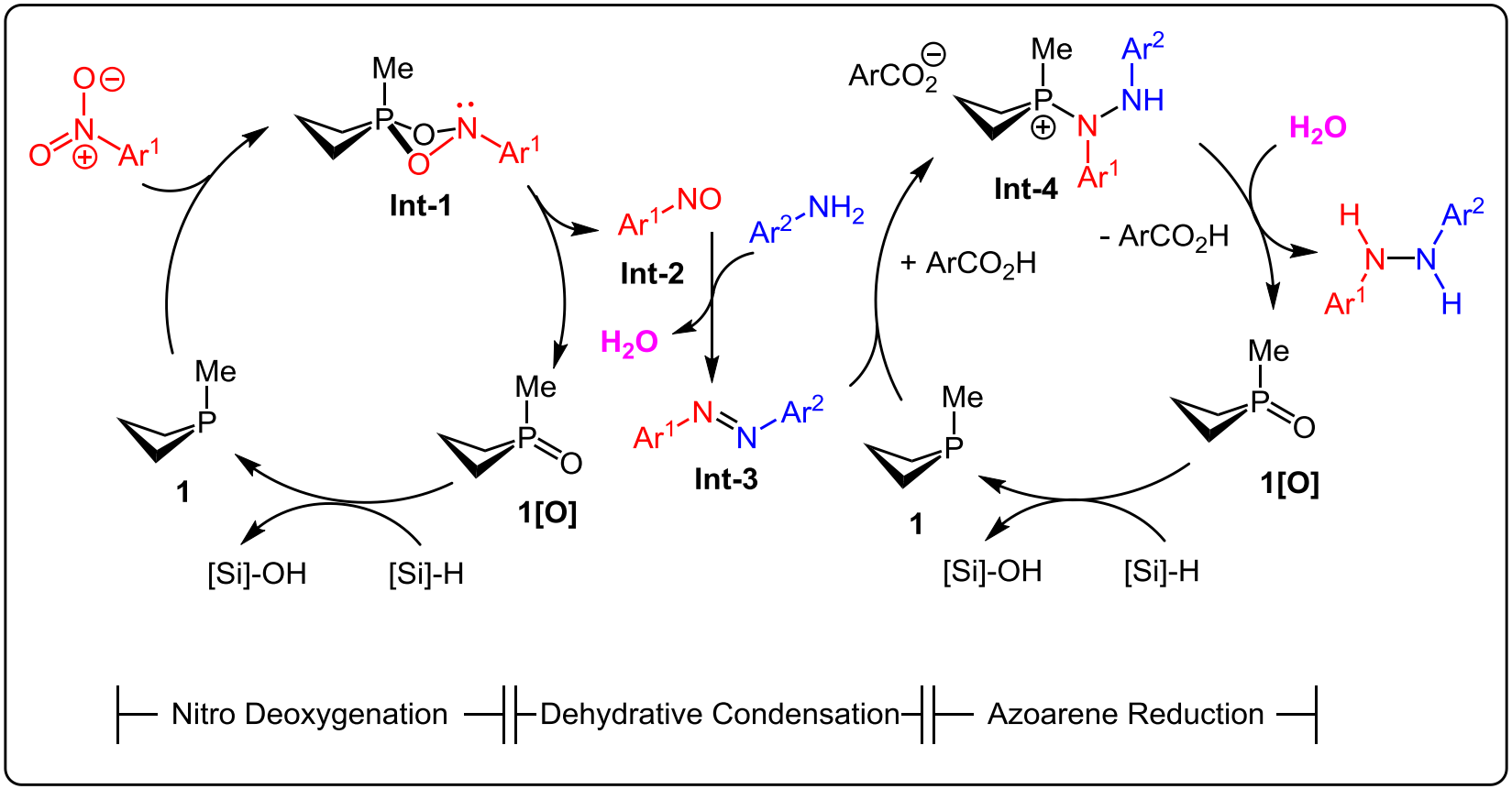


Mechanism Study

Crossover Competition

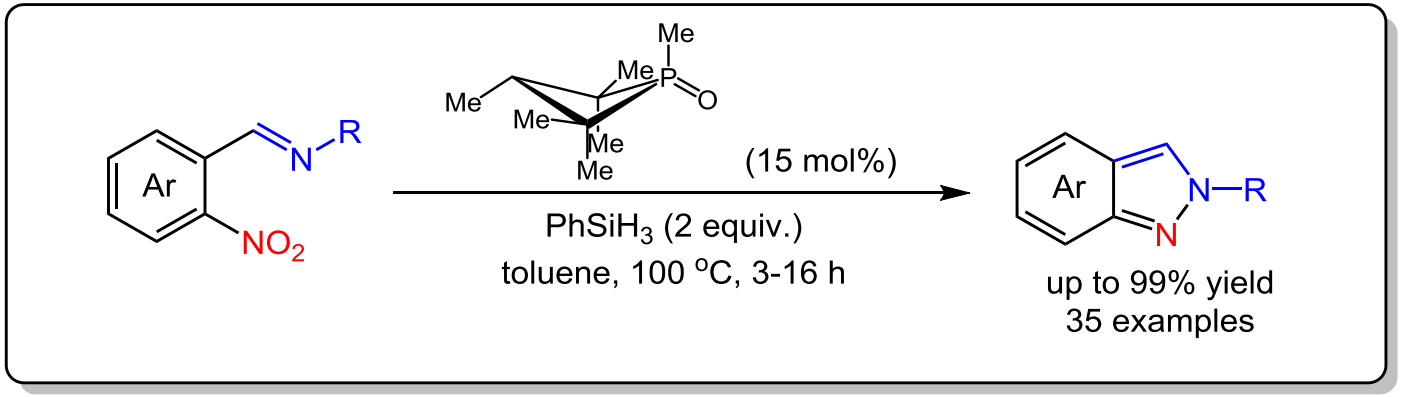


Proposed Mechanism



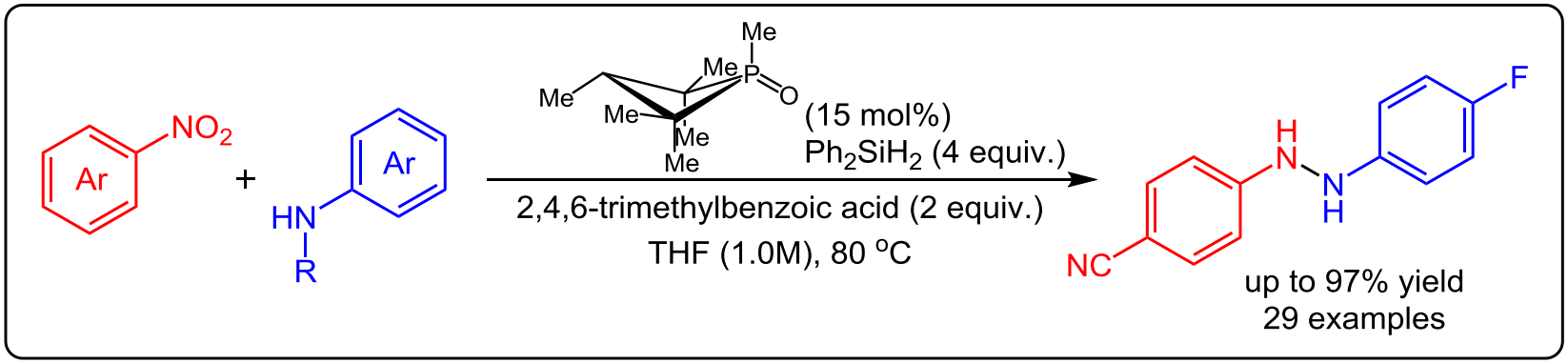
Summary

Intramolecular N-N Formation



Radosevich, A. T. *et al*. *J. Am. Soc. Chem.* **2017**, *139*, 6839.

Intermolecular N-N Formation



Radosevich, A. T. *et al*. *J. Am. Soc. Chem.* **2021**, *143*, 14464.

The First Paragraph

写作思路

N-N键结构重要性

↓

传统构建N-N键方法

↓

构建N-N键的挑战

↓

引出催化方法构建N-N键

The First Paragraph

Hydrazines and related N−N containing derivatives have significant value in organic chemistry, including as natural products and pharmaceuticals. Although the N−N bond presents a potential strategic site for synthesis-especially within medical chemistry-it is only infrequently targeted for retrosynthetic disconnection. In part, this state of play reflects certain constraints in the methods for N−N bond formation, particularly in an intermolecular sense. Stoichiometric methods employ prefunctionalized N-based reagents whose stability and structural variation are intrinsically bracketed by the high electronegativity of the nitrogen atom. Complementarily, several notable advances have recently been achieved in catalytic intermolecular N−N bond formation, despite the inherent challenges associated with synthesis of such a weak and nonpolar bond.

The First Paragraph

Transition-metal-catalyzed nitrene transfer has successfully been applied to the imination of tertiary amines and the N−H insertion of acylnitrene equivalents to N-alkylanilines, specifically by decomposition of bespoke nitrene donors such as 1,4,2-dioxazol-5-ones. Among unfunctionalized precursors, simple diarylamine/carbazole substrates have been subject to intermolecular oxidative N−N coupling under aerobic Cu-catalyzed, Fe-catalyzed or anodic electrochemical conditions, although the realization of cross selectivity remains substrate dependent.

The Last Paragraph

写作思路

工作总结：$P^{III}/P^{V}=O$催化N-N偶联

↓

工作特点：高化学选择性，广泛底物范围

↓

工作展望：方法学得到应用

The Last Paragraph

In summary, the results described above constitute a new and robust organophosphorus-catalyzed protocol for cross-selective intermolecular N−N coupling via $P^{III}/P^{V}=O$ redox cycling that makes use of readily accessible coupling partners in the construction of valuable hydrazine products. Despite the potential lability of the N−N bond under reducing conditions, the high chemoselectivity of the catalytic reductive system allows the synthesis of the target bond with excellent functional group tolerance even among other reductively sensitive functionalities. Critical to the success of this method is the versatility of the $P^{III}/P^{V}=O$ redox couple to manage diverse reductive transformations, which is manifest in the two-stage, autotandem catalytic reaction process.

The Last Paragraph

Given the ready accessibility of nitroarene and aniline partners, we envision that these results might enable a fragment coupling approach to the preparation of highly functionalized hydrazines and related N−N containing derivatives with potential utility in medicinal chemistry and other applications.

Representative Examples

In this vein, prior work has established the viability of organophosphorus-catalyzed reductive N-functionalization of nitroarenes ... (vein 静脉，in this vein 在这种情况下)

Reactions at either higher temperature (entry 8) or higher dilution (entry 9) resulted in erosion of yield. (侵蚀，表示收率降低)

Taken together with literature precedent, these experimental findings are best accommodated by an autotandem catalytic reaction mechanism for the intermolecular N-N reductive coupling involving two sequential and mechanistically distinct reduction events, as illustrated. (结合文献中的先例)

Acknowledgement

Thanks
for your attention