Literature Report 4

Ni-Catalyzed Carbon-Carbon Bond-Forming Reductive Amination

Reporter: Zhou-Hao Zhu
Checker: Zi-Biao Zhao
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Heinz, G.; Lutz, J. P.; Simmons, E. M.; Miller, M. M.; Ewing, W. R.; Doyle, A. G.*
J. Am. Chem. Soc. **2018**, *140*, 2292

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2 Dialkyl Ether Formation by Nickel-Catalyzed Cross-Coupling

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CV of Prof. Abigail Gutmann Doyle

Abigail Gutmann Doyle

Background:

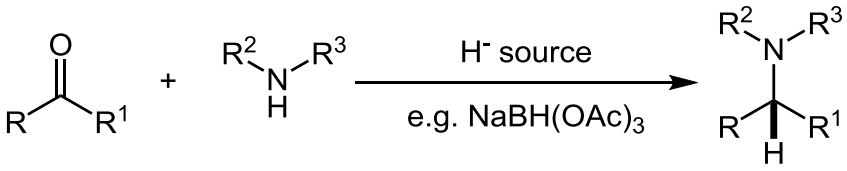
- **1998-2002** B.S., Harvard University
- **2002-2003** Pre-Doctoral Fellow, Stanford University
- **2003-2008** Ph.D., Harvard University (with Prof. Jacobsen)
- **2008-2013** Assistant Professor, Princeton University
- **2013-2017** Associate Professor, Princeton University
- **2017-now** Professor, Princeton University

Research Interests:

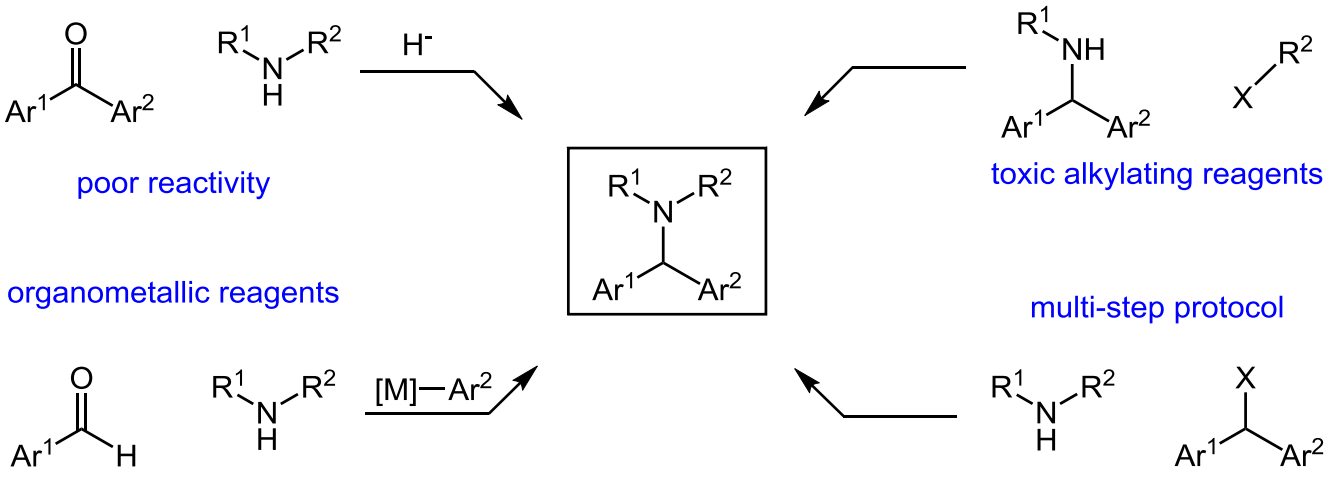
- Ni cross coupling
- Photocatalysis with Ni
- Nucleophilic fluorination
- Machine learning for reaction prediction

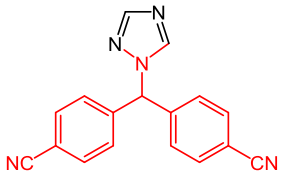
Introduction

a) Traditional reductive amination

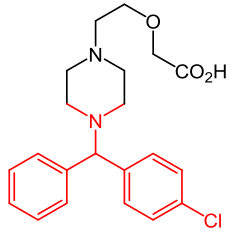


b) Benzhydryl amines: synthetic approaches & pharmaceutical agents

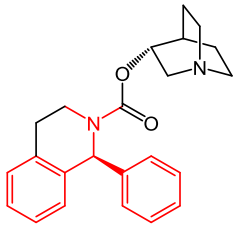




Femara® (Novartis)
antitumor

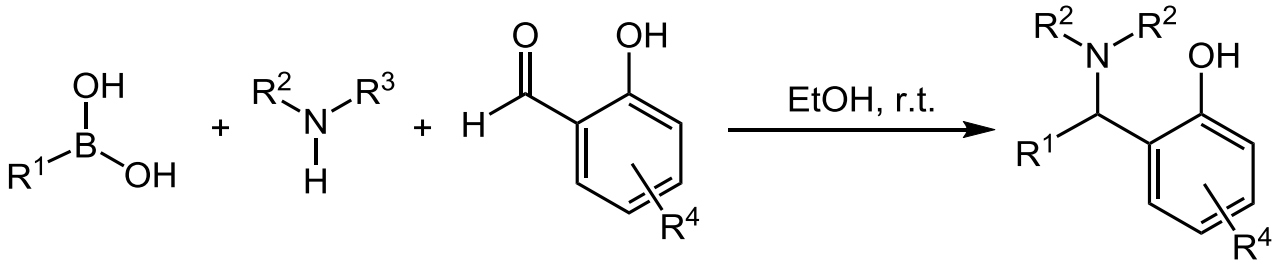


Zyrtec® (Janssen)
antihistamine

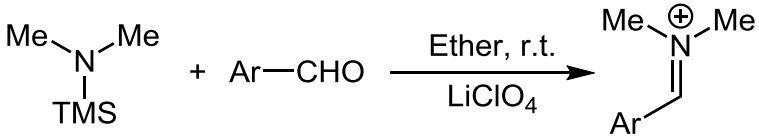


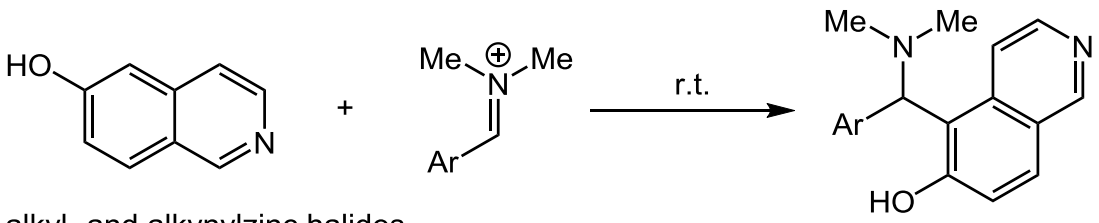
Vesicare® (Astellas)
antimuscarinic

Introduction



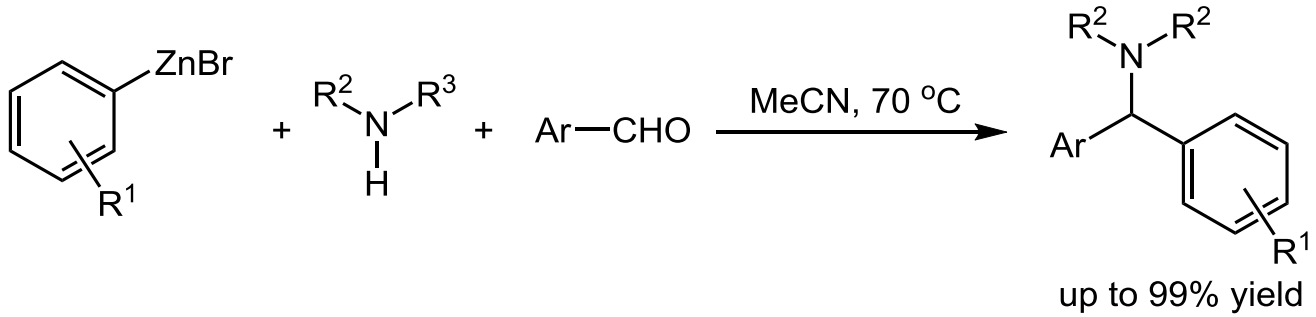
Petasis, N. A. *et. al. Tetrahedron Lett.* **2001**, *42*, 539





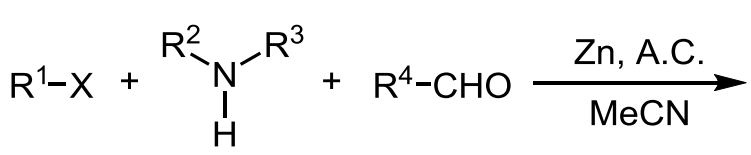
Saidi, M. R. *et. al. Tetrahedron Lett.* **2001**, *42*, 8111

Introduction



up to 99% yield

Le Gall, E. *et. al. Tetrahedron* **2006**, *62*, 9953



up to 96% yield

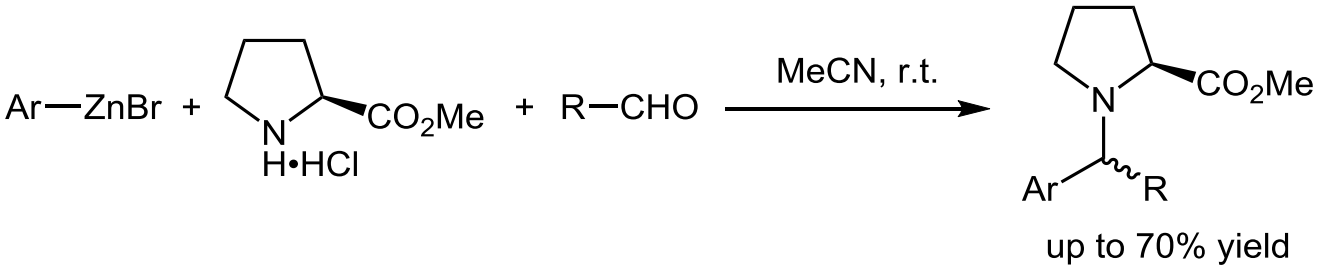
R^1 = Allyl, Aryl, Benzyl, Vinyl, CH_2CO_2R

R^2, R^3 = H, Alkyl, Aryl

R^4 = H, Alkyl, Aryl, Heteroaryl, CO_2R

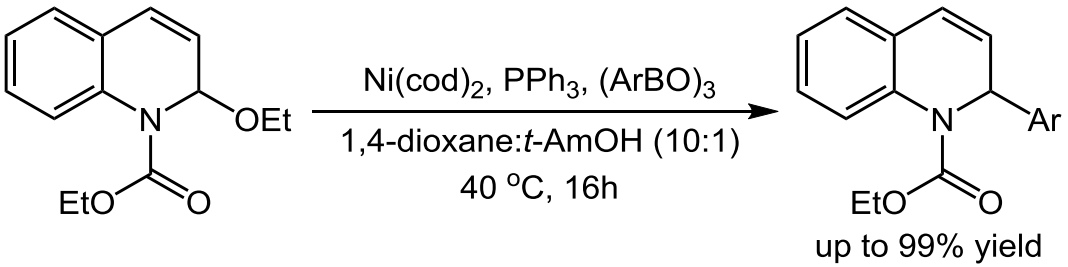
Le Gall, E. *et. al. J. Org. Chem.* **2009**, *74*, 7970

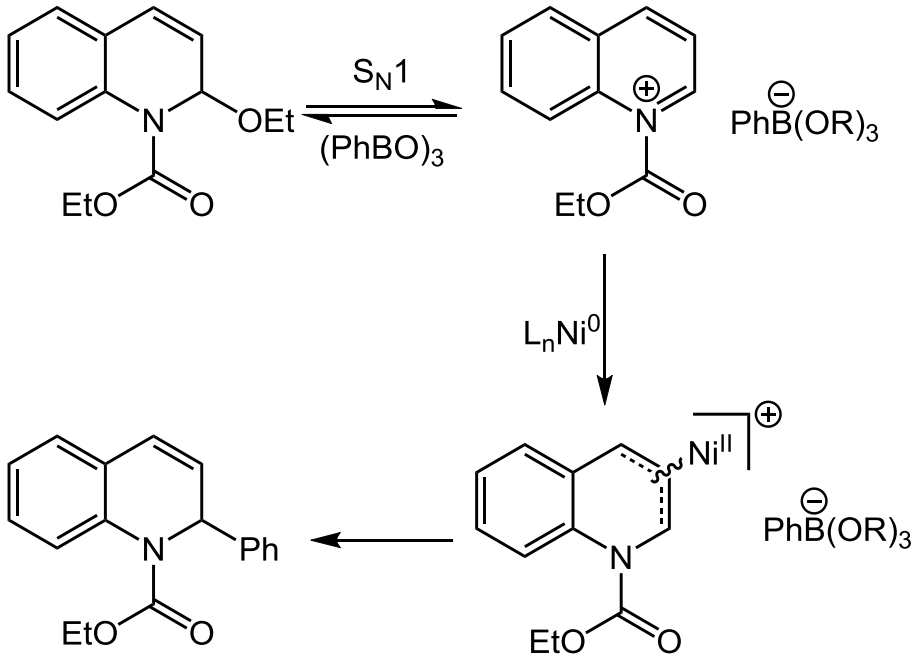
Introduction



Le Gall, E. *et. al. Tetrahedron* **2010**, *66*, 9902

Introduction

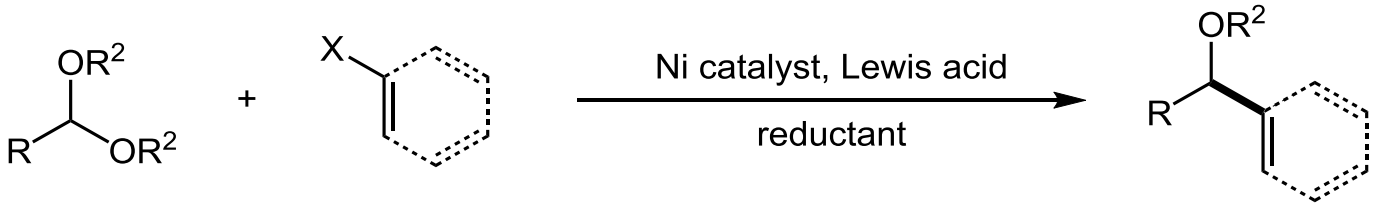




Doyle, A. G. *et. al. Chem. Sci.* **2011**, *2*, 980

Doyle, A. G. *et. al. J. Am. Chem. Soc.* **2012**, *134*, 16967

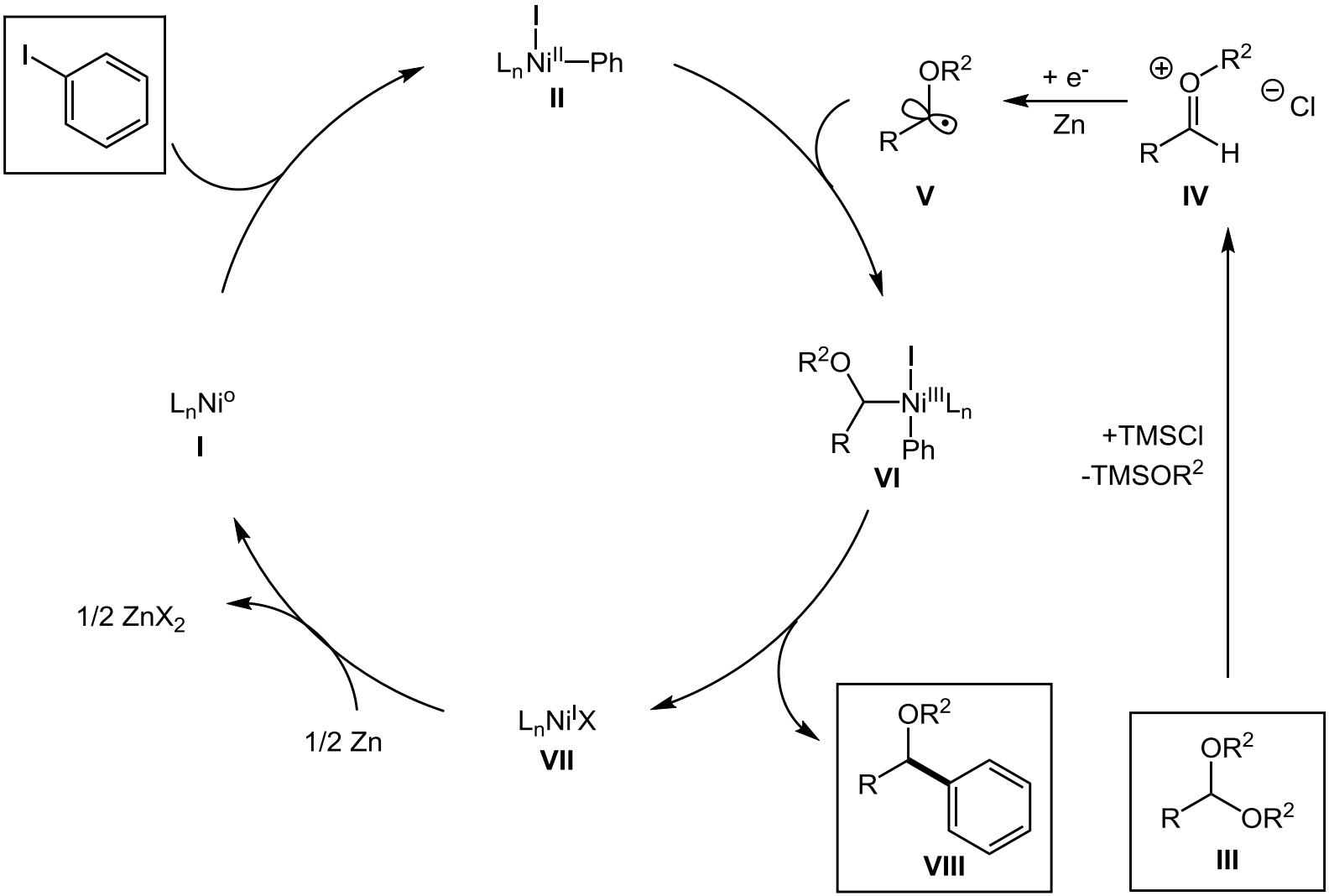
Nickel-Catalyzed Dialkyl Ether Formation



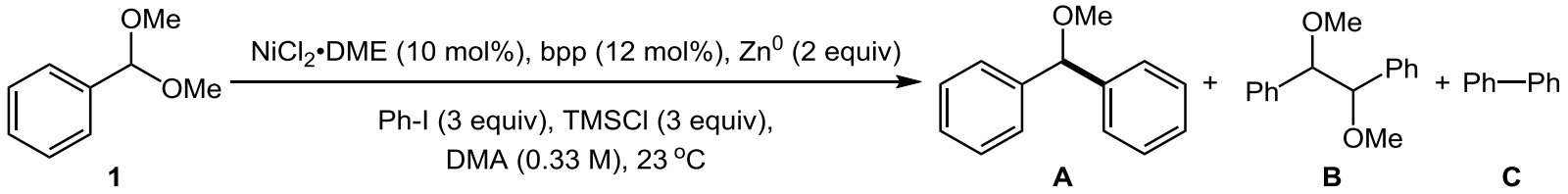
- formal C(sp^3)-O bond activation
- stable, abundant starting materials
- C-C bond-forming synthesis of ethers

Doyle, A. G. *et. al. Angew. Chem. Int. Ed.* **2015**, *54*, 9876

Proposed Mechanism



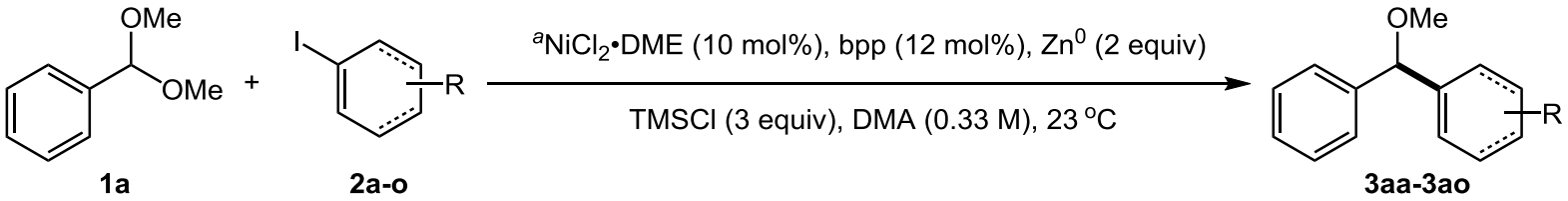
Reaction Optimization Studies

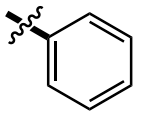


entry	deviation from standard conditions	yield (%)[a]		
		A	B	C
1	none	91	3	3
2	no $NiCl_2$·DME	0	13	0
3	no Zn^0	0	0	0
4	no TMSCl	0	0	25
5	1 equiv PhI	55	2	2
6	PPh_3 instead of bpp[b]	5	30	35
7	Dppbz instead of bpp	4	28	10
8	bpy instead of bpp	38	10	31
9	terpy instead of bpp	10	11	35
10	Ph-Box instead of bpp	2	39	0
11	Ph-PyBox instead of bpp	0	27	38

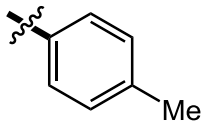
[a] Determined by GC using dodecane as a quantitative internal standard. [b] 20 mol% ligand loading. Box = bis(oxazoline), DMA = *N,N*-dimethylacetamide, DME = dimethoxyethane.

Scope of Aryl Iodides

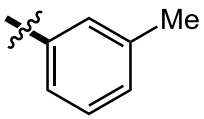




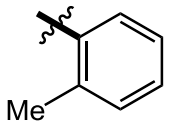
3aa
91% yield



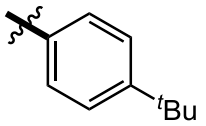
3ab
71% yield



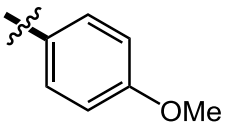
3ac
82% yield



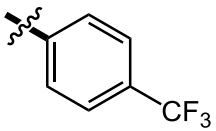
3ad
9% yield



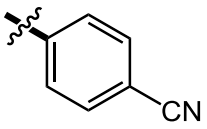
3ae
85% yield



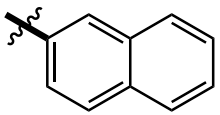
3af
77% yield



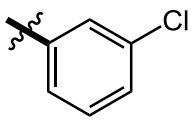
3ag
50% yield



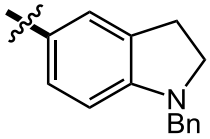
3ah
89% yield



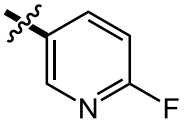
3ai
80% yield



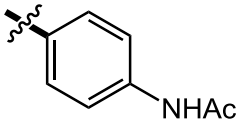
3aj
78% yield



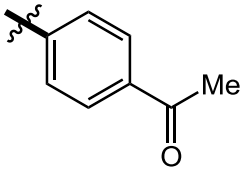
3ak
60% yield



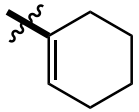
3al
44% yield



3am
65% yield



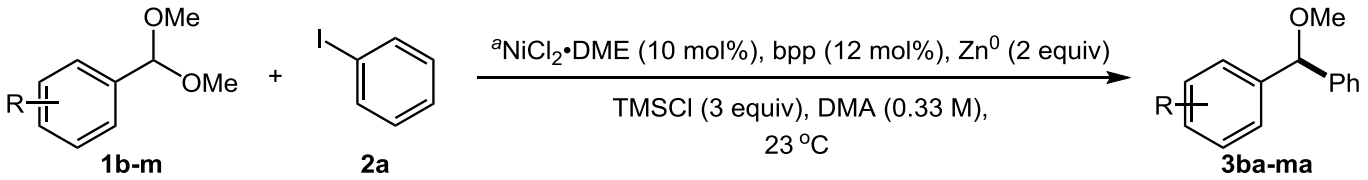
3an
60% yield

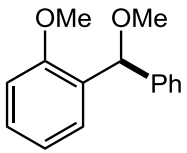


3ao
60% yield

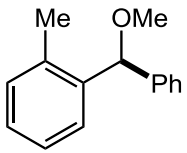
[a]Yield is that of the isolated product (0.50 mmol).

Scope of Acetals

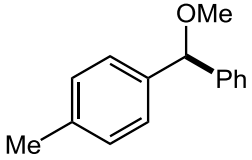




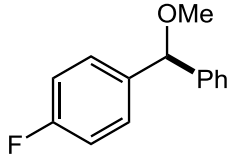
3ba
83% yield



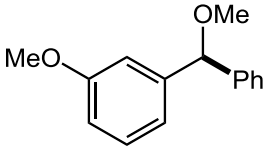
3ca
10% yield



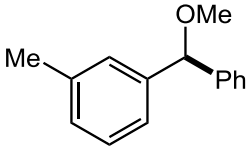
3da
84% yield



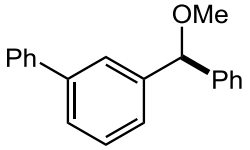
3ea
54% yield



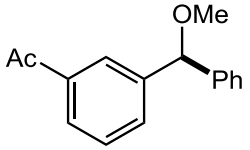
3fa
79% yield



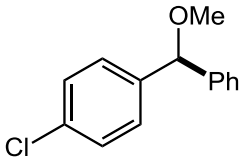
3ga
86% yield



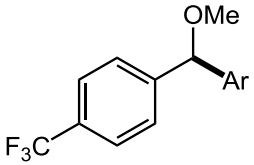
3ha
78% yield



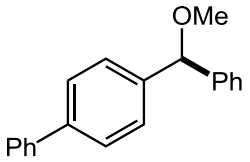
3ia
64% yield



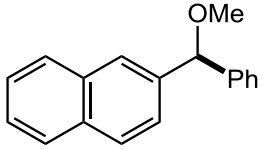
3ja
49% yield



3ka
64% yield[b]



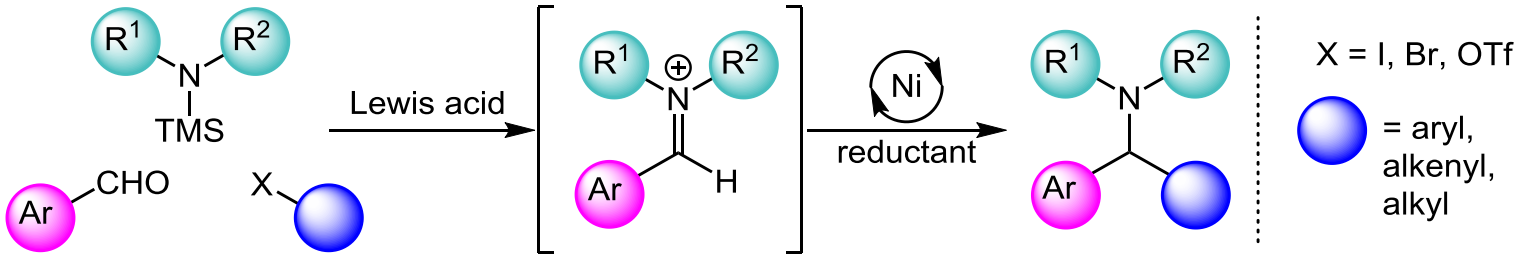
3la
59% yield



3ma
73% yield

[a]Yield is that of the isolated product (0.50 mmol). [b]*p*-Iodoanisole was employed as the coupling partner.

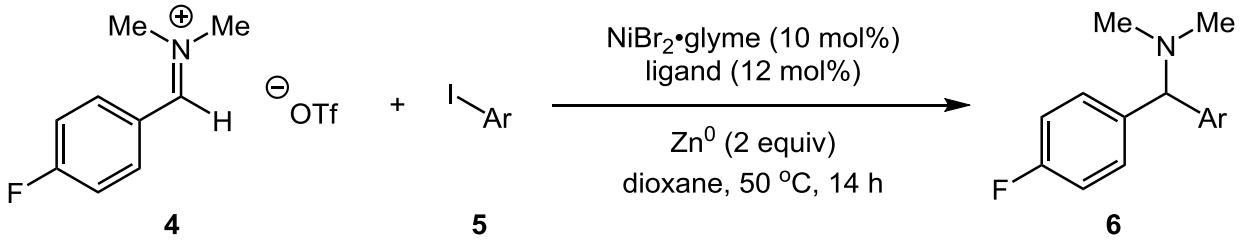
Ni-Catalyzed Reductive Amination



- modular, three-component coupling
- cyclic/acyclic benzhydrylamines
- in situ generated electrophile

Doyle, A. G. *et al. J. Am. Chem. Soc.* **2018**, *140*, 2292

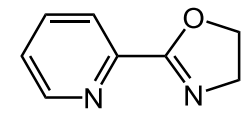
Ligand Evaluation



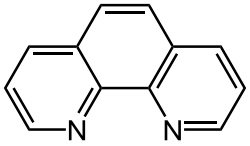
4 **5** **6**

conv. 4[b,c] / yield[b] / biaryl[b] (%)

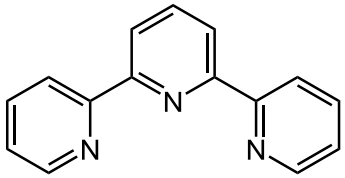
no Ni / ligand: 77 / 0 / 0
no ligand: 70 / 20 / 1



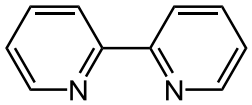
L1: 55 / 46 / 4



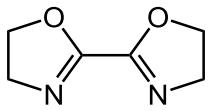
L2: 75 / 49 / 4



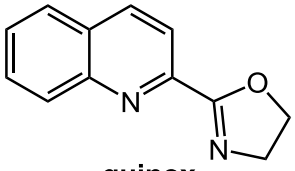
L3: 69 / 53 / 4



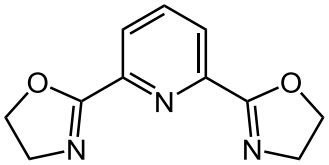
L4: 75 / 63 / 3



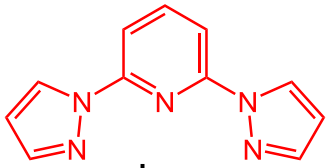
L5: 73 / 67 / 20



quinox
L6: 92 / 87 / 29



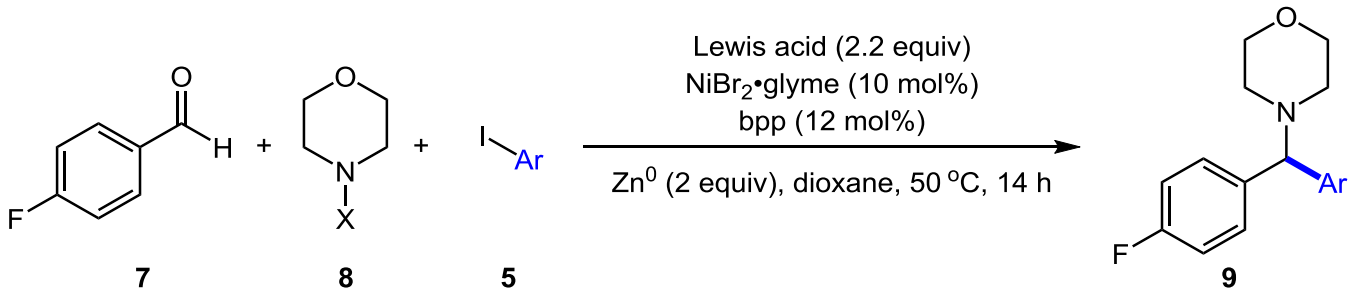
L7: 95 / 94 / 6



bpp
L8: 94 / 88 / 3

[a]Reactions run on 0.2 mmol scale with 3.0 equiv ArI (Ar = 4-fluorophenyl). [b]Determined using ^{19}F NMR analysis versus 1-fluoronaphthalene as a quantitative external standard. [c]Determined from the yield of 4-fluorobenzaldehyde (**7**) following aqueous workup.

Development of a Three-Component Coupling

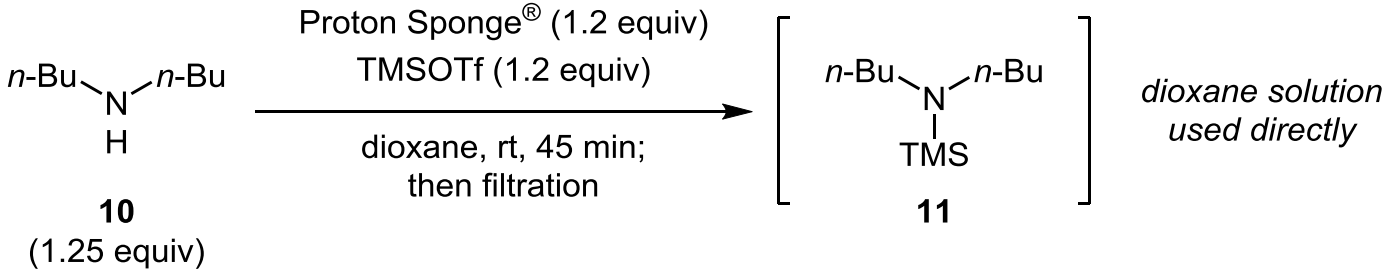


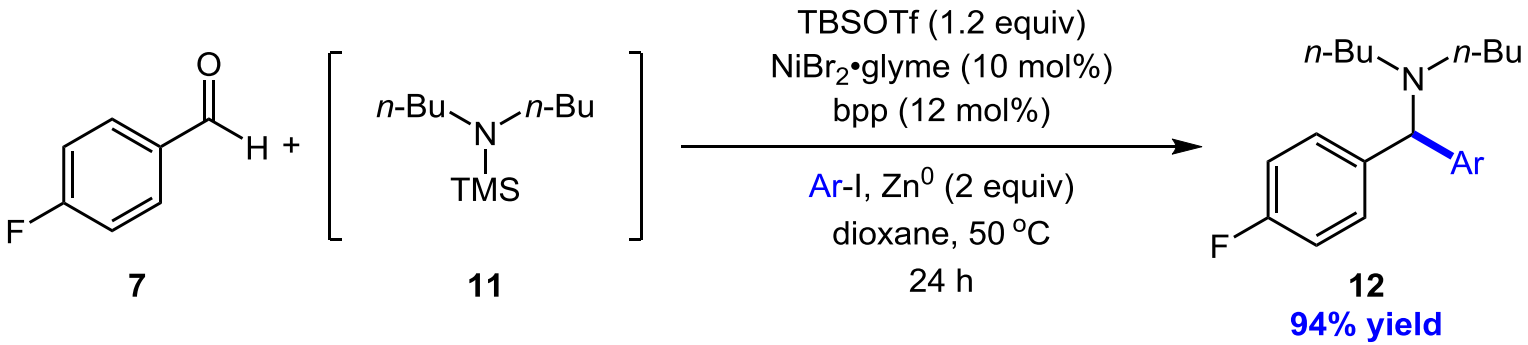
7 8 5 9

entry	X	Lewis acid	conv 7 (%)[b]	yield (%)[b]	biaryl (%)[b]	dimer (%)[b,c]
1	H	TMSCl	87	1	0	20
2	H	TBSOTf	78	43	2	1
3	TMS	TMSCl	99	37	9	7
4	TMS	TBSOTf	99	90	1	0

[a] Reactions run on 0.25 mmol scale with 3.0 equiv ArI (Ar = 4-fluorophenyl). [b] Determined using ^{19}F NMR analysis versus 1-fluoronaphthalene as a quantitative external standard. [c] Yield of 1,2-bis(5-fluorophenyl)-1,2-dimorpholinoethane (dimerized iminium ion).

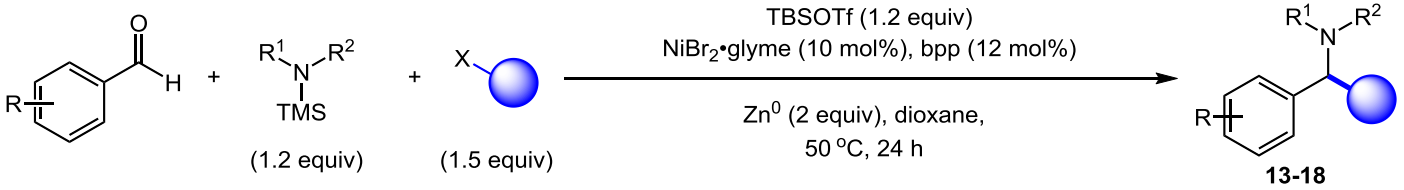
N-Trimethylsilyl Amine Preparation[a]



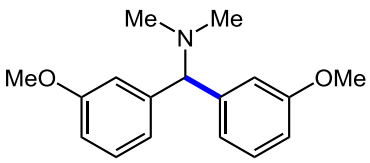


[a] Isolated yield on 0.5 mmol scale with 1.5 equiv ArI (Ar = 4-chlorophenyl).

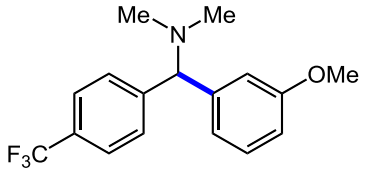
Substrate Scope (Intermolecular)



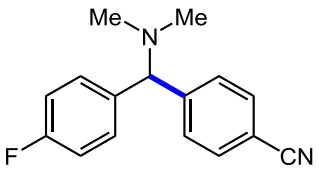
Coupling of aryl iodides with iminium ions derived from commercial *N*-trimethylsilyl amines



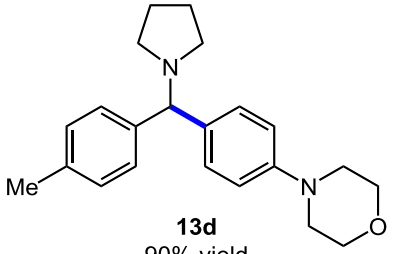
13a
92% yield



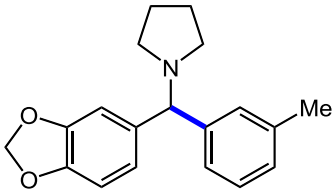
13b
68% yield



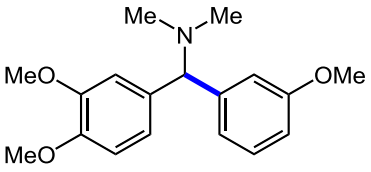
13c
54% yield



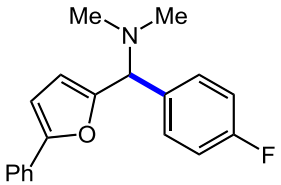
13d
90% yield



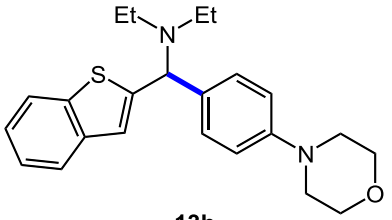
13e
93% yield



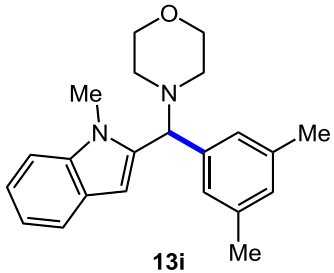
13f
67% yield



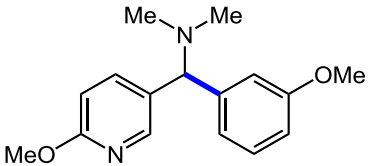
13g
83% yield



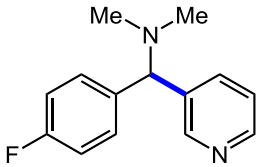
13h
73% yield



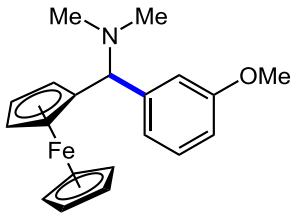
13i
62% yield



13j
99% yield



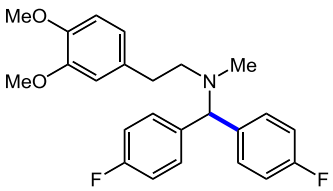
13k
62% yield



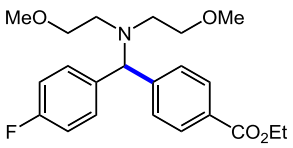
13i
38% yield

Substrate Scope

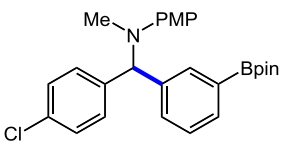
Coupling of aryl iodides with iminium ions derived from non-commercial *N*-trimethylsilyl amines



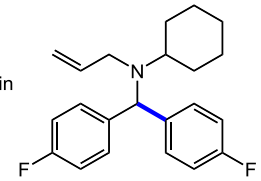
14a
93% yield



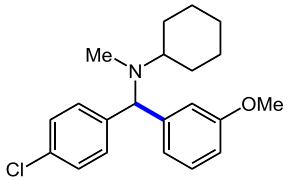
14b
41% yield



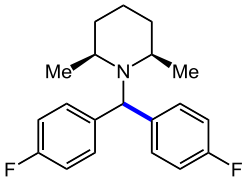
14c
77% yield



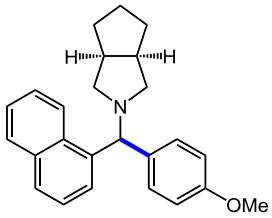
14d
47% yield



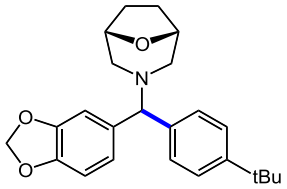
14e
99% yield



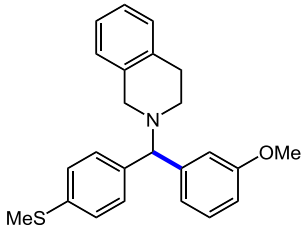
14f
82% yield



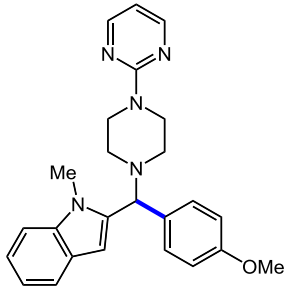
14g
93% yield



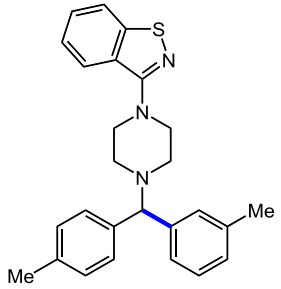
14h
95% yield



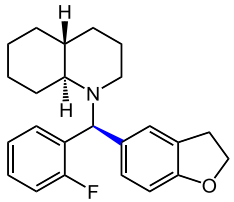
14i
79% yield



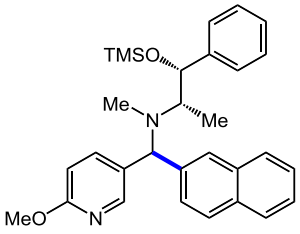
14j
68% yield



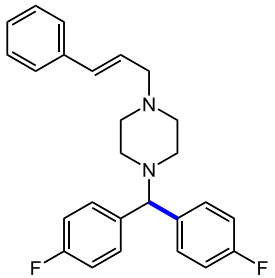
14k
92% yield



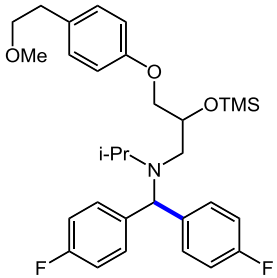
(±)-**14l**
80% yield
>20:1 dr



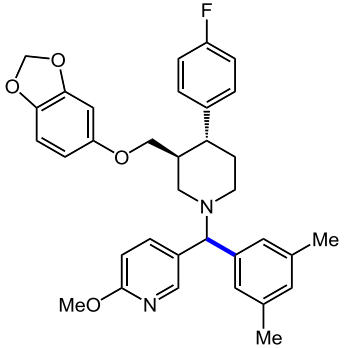
(+)-**14m**
81% yield
>20:1 dr



14n (flunarizine)
86% yield



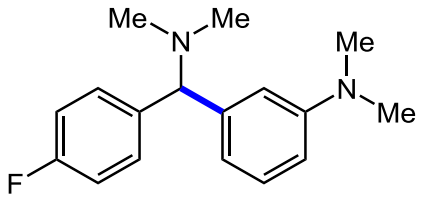
14o [from (±)-metoprolol]
74% yield



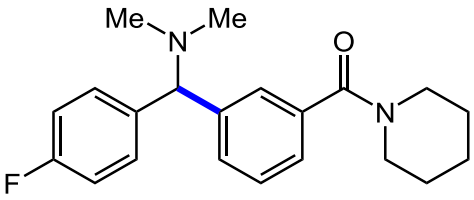
14p [from (-)-paroxetine]
79% yield
1.5:1 dr

Substrate Scope

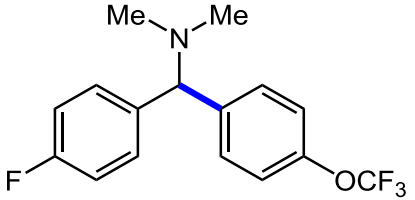
Coupling of aryl bromides



15a
66% yield

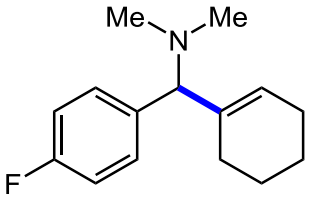


15b
97% yield

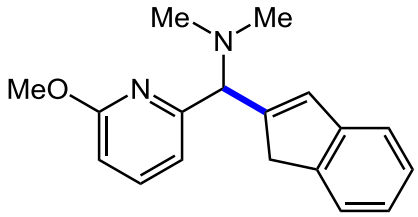


15c
81% yield

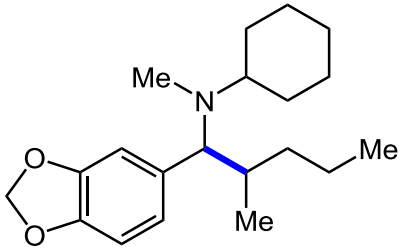
Coupling of vinyl triflates/bromides & alkyl bromides



16 (X = OTf)
61% yield



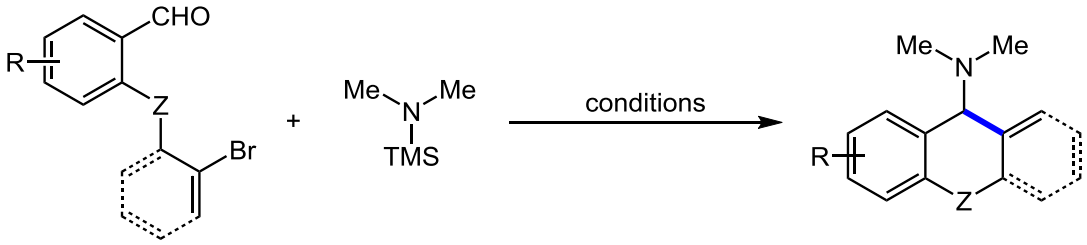
17 (X =Br)
66% yield



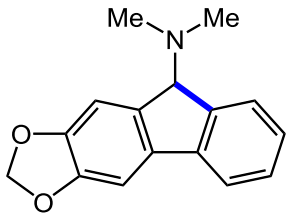
18 (X =Br)
88% yield
1:1 dr

Substrate Scope (Intramolecular)

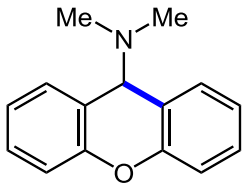
a) Exocyclic amine synthesis via tethered bromoaldehydes[a]



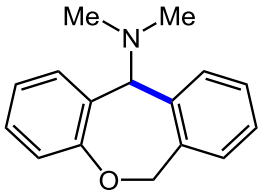
18a-d **19a-d**



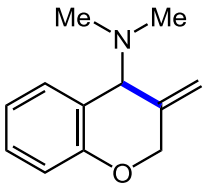
19a
75% yield



19b
70% yield

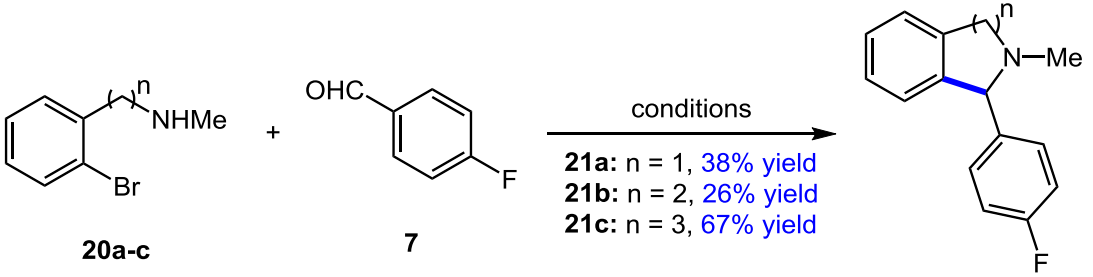


19c
79% yield



19d
50% yield

b) Endocyclic amine synthesis via tethered bromoamines[b]

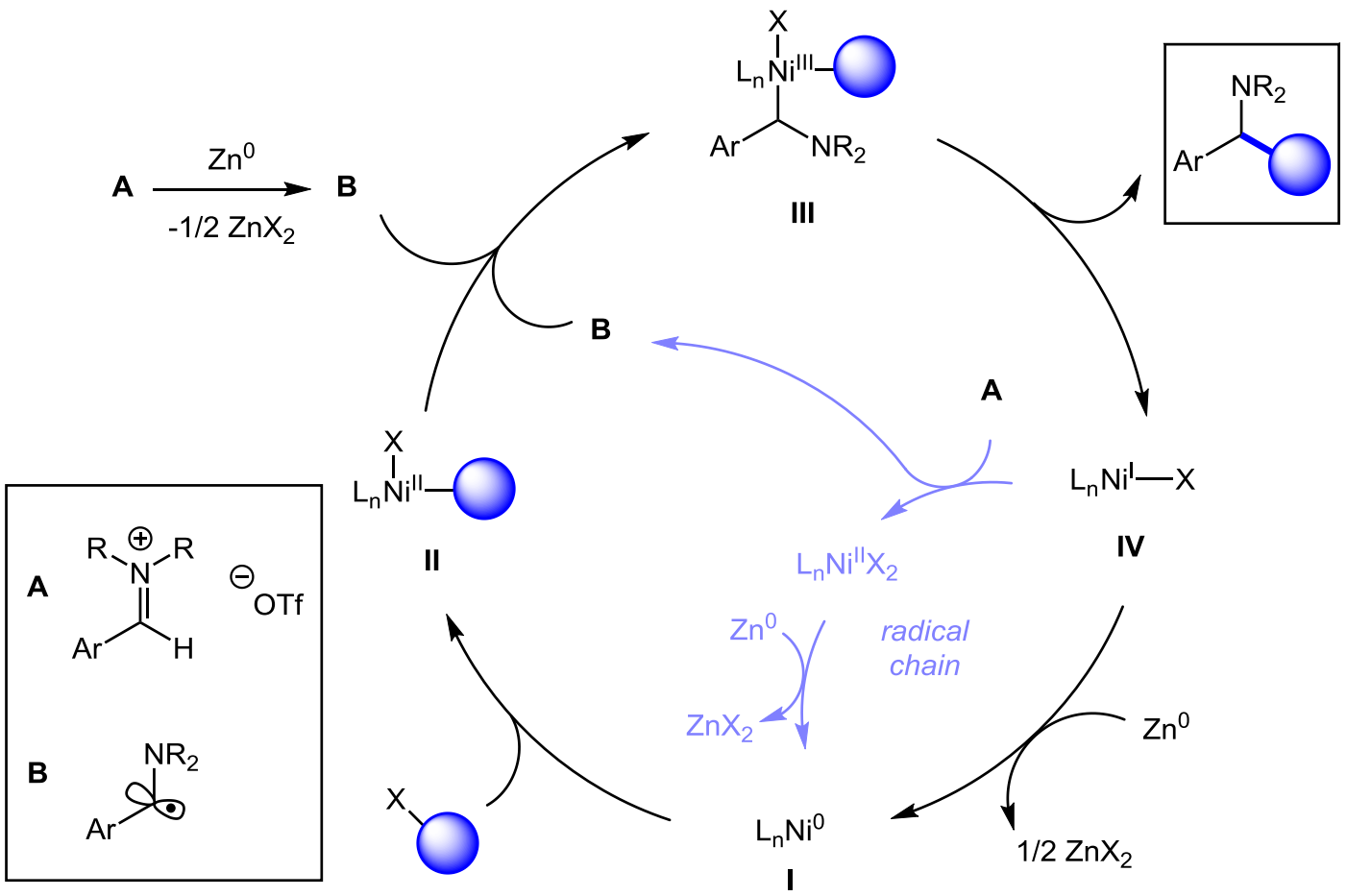


20a-c **7**

[a]Reactions run in THF (0.05 M). [b]Reactions run in dioxane (0.1 M) with quinox (12 mol %) in place of bpp.

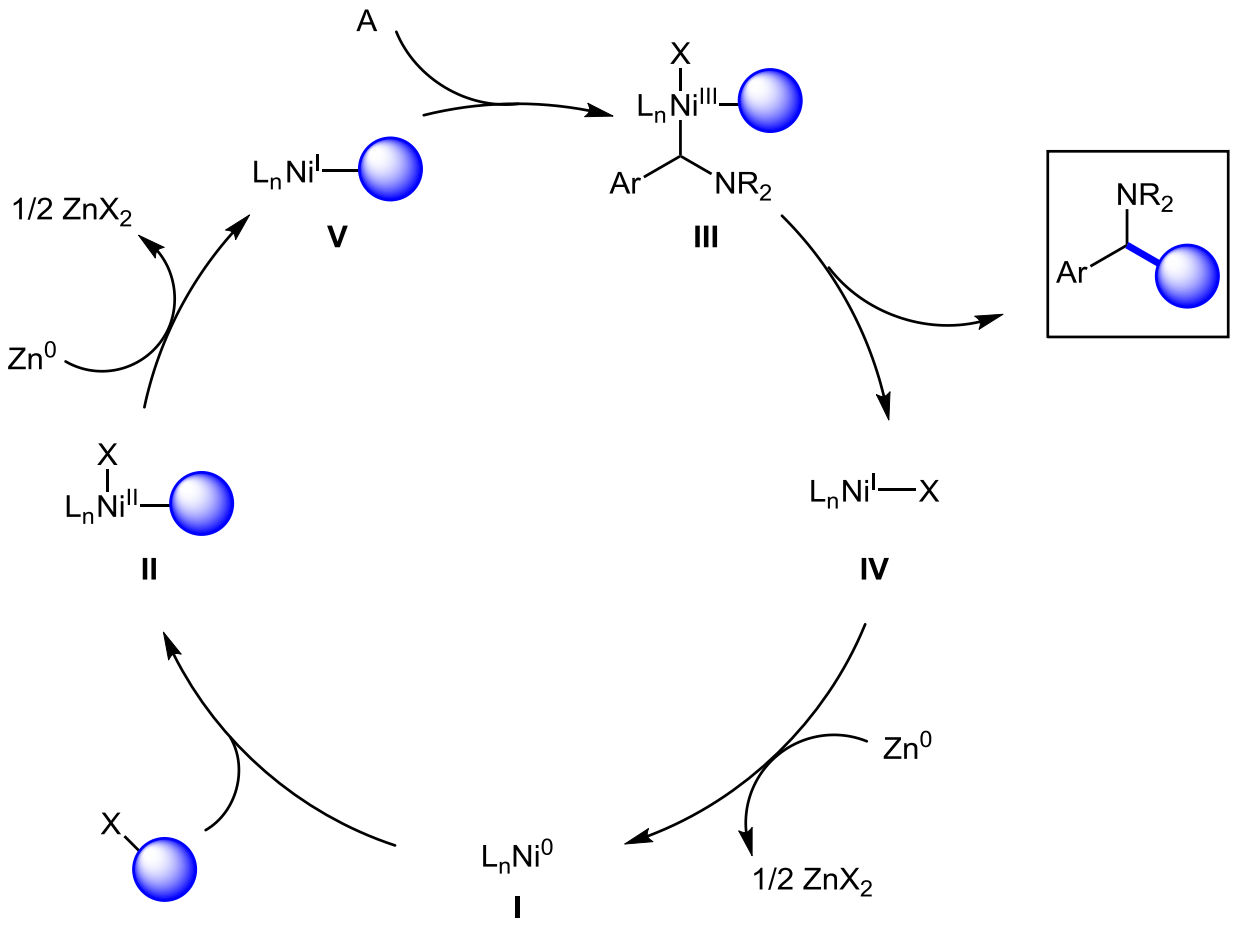
Mechanistic Investigations

a) Mechanisms proceeding via α-amino radical formation

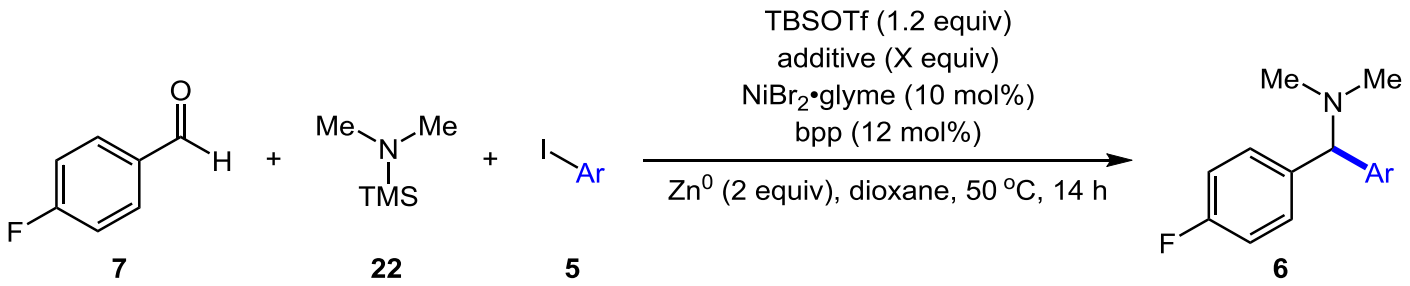


Mechanistic Investigations

b) Sequential oxidative addition mechanism



Additives as Mechanistic Probes

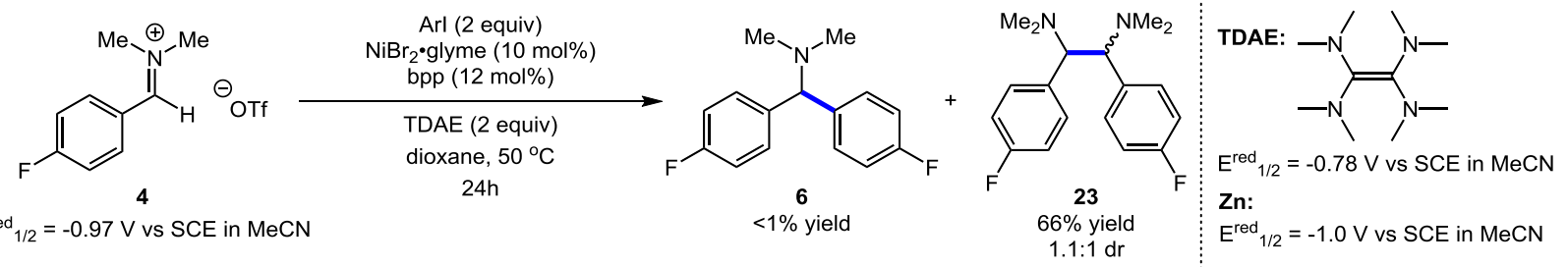


entry	additive (equiv)	conversion 7 (%)[b]	yield (%)[b]
1	none	97	95
2	ArZnBr (2 equiv)[c]	100	85
3	TEMPO (1 equiv)	52	1
4	styrene (3 equiv)	87	80
5	1,1-diphenylethyene (5 equiv)	96	89

[a]Reactions run on 0.5 mmol scale with 1.5 equiv ArI (Ar = 4-fluorophenyl). [b]Determined using ^{19}F NMR analysis versus 1-fluoronaphthalene as a quantitative external standard. [c]No ArI was added.

Assessing the Role of Ni and Zn

a) Use of TDAE in place of Zn



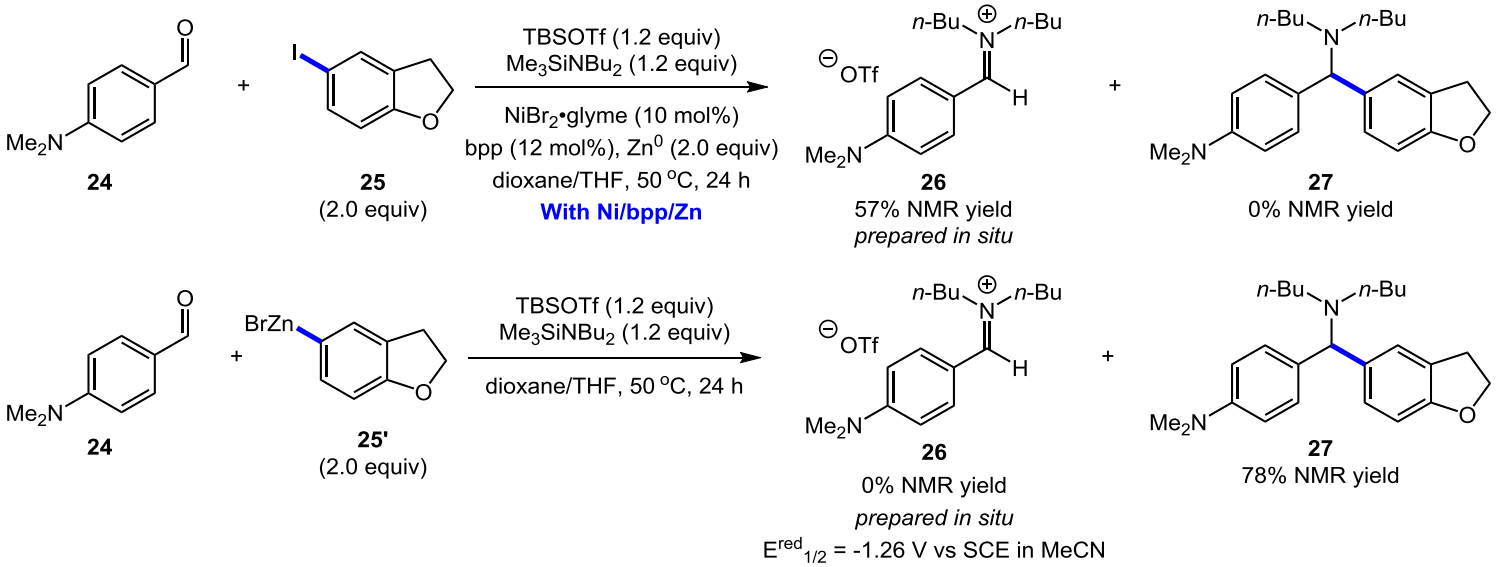
$E^{red}_{1/2}$ = -0.97 V vs SCE in MeCN

$E^{red}_{1/2}$ = -0.78 V vs SCE in MeCN

Zn:

$E^{red}_{1/2}$ = -1.0 V vs SCE in MeCN

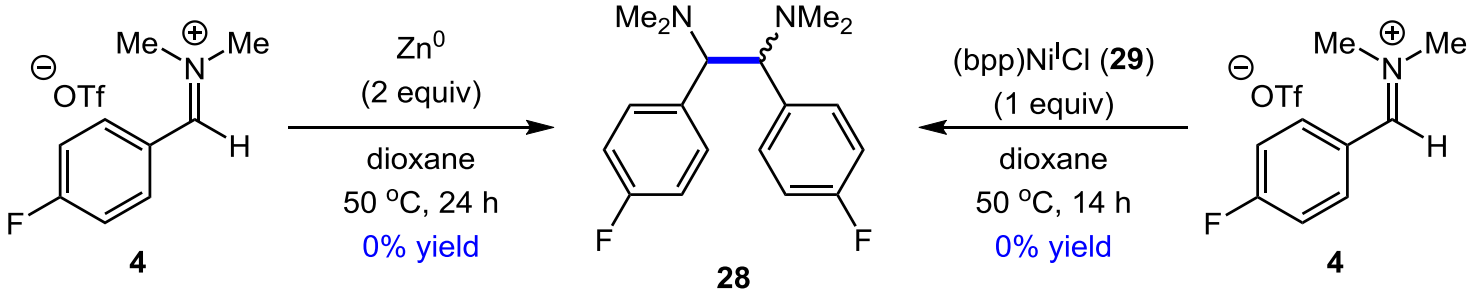
b) Electron-rich iminium ion



$E^{red}_{1/2}$ = -1.26 V vs SCE in MeCN

Assessing the Role of Ni and Zn

c) Iminium reduction



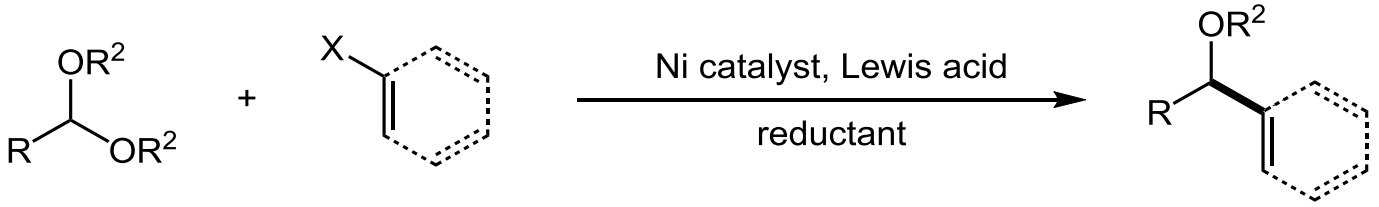
(bpp)Ni^{I}Cl:

$E^{red}_{1/2}$ = -0.8 V vs SCE in MeCN

Zn:

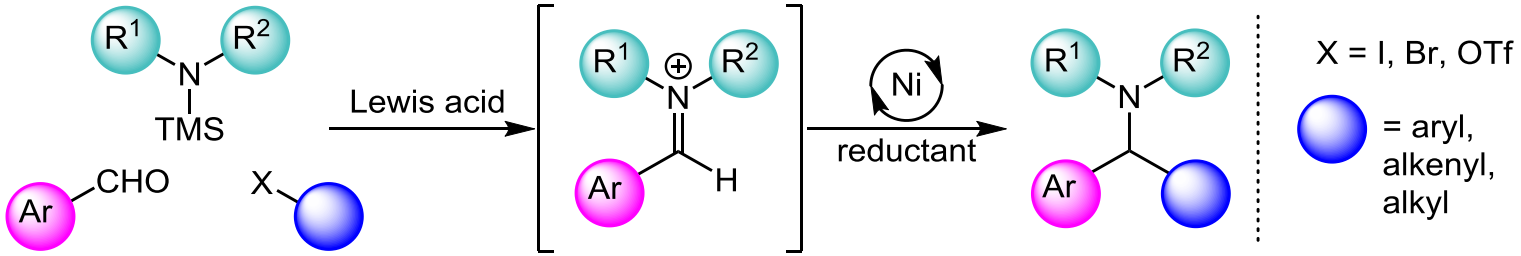
$E^{red}_{1/2}$ = -1.0 V vs SCE in MeCN

Summary



- formal C(sp^3)-O bong activation
- stable, abundant starting materials
- C-C bond-forming synthesis of ethers

Doyle, A. G. *et. al. Angew. Chem. Int. Ed.* **2015**, *54*, 9876



- modular, three-component coupling
- in situ generated electrophile
- cyclic/acyclic benzhydrylamines

Doyle, A. G. *et al. J. Am. Chem. Soc.* **2018**, *140*, 2292

The first paragraph

Reductive amination is among the most important methods for the synthesis of alkylamines and has been widespread application in the preparation of bioactive compounds. A recent analysis of drug candidate syntheses published by three pharmaceutical companies revealed that reductive amination is the sixth most frequently used transformation in medicinal chemistry, representing 5.3% of the data set and accounting for approximately one-quarter of all heteroatom alkylations/arylations. Reductive amination has been carried out on large scale for the industrial manufacture of a number of pharmaceutical agents.

The first paragraph

Notably, it was the process chemistry group at Johnson & Johnson that developed sodium triacetoxyborohydride (STAB), the reducing agent of choice for reductive amination, when they found that previously reported reagents either were not selective for imine over carbonyl reduction or resulted in the formation of toxic and inseparable byproducts. Using STAB, a wide range of aldehydes/ketones and 1° /2° amines proved amenable to reductive amination, which provided a reliable and modular method to access complex alkylamine products.

The last paragraph

In conclusion, we have developed a Ni-catalyzed, three component reductive coupling for the synthesis of tertiary alkylamines from benzaldehydes, organic electrophiles, and N-trimethylsilyl amines, which are conveniently prepared and used without isolation. We have demonstrated C-C bond formation with several distinct classes of organic electrophiles including aryl iodides/bromides, vinyl bromides/triflates, and alkyl bromides. We anticipate that this reaction will prove useful in circumstances where the ketone precursor to a desired amine product is not commercially available or does not readily undergo reductive amination. Furthermore, the convergent nature of this approach should make it ideal for library synthesis. While the precise details of the reaction mechanism remain under active study, preliminary experiments advocate a sequential oxidative addition mechanism and strongly mitigate against in situ organozinc formation. We are optimistic that an increased understanding of the role of Ni in this reaction can lead to the development of an enantioselective reductive amination.

Thanks for your attention