Azidation The Next Generation: New Methods for C-H to C-N_3 Bond Formation

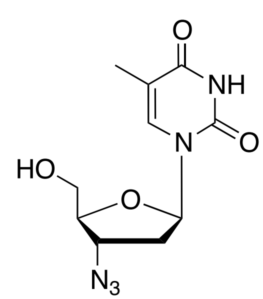
James Johnson
Frontiers in Chemistry
3-14-15

Azidation

- Background
- Enzymes
- Aryl C-H azidation
- Allyl C-H azidation
- Alkyl C-H azidation
- Future directions

Azides

- First azide discovered as phenyl azide by Greiss (1866)
- HN_3 discovered by Curtius in 1890 and NaN_3 in 1892
- Useful synthetic intermediates for the formation of amines, imines, diazo compounds, nitrenes, aziridines, azirines, triazoles, triazolines, tetrazoles etc…
- Bioorthogonal uses "click" chemistry, photocrosslinking and affinity tagging.
- Pseudohalide character
- Azide containing anti HIV drug

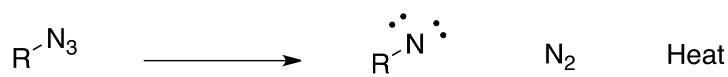


Retrovir
AZT

Greiss, Ann., **1866**, 39
Curtius, Ber., **1890**, 2023

Azides

- Highly energetic functional group
  - Introduction of N_3 group into an organic compound increases its energy content by approx. 290-355 kJ/mol
  - Used in explosives and airbags
- N_3 π-bond is highly polarizable and can result in strong exothermic reactions.



- Sensitivity of metal azides
  - Impact: Cu > Pb, Hg > Ni > Co > Mn > Ba > St > Ca > Ag > Tl > Zn > Na, Li
  - Thermal: Ca > Sr > Ba > Tl > Ag > K > Pb > Na
- Toxicity HN_3
  - High vapor pressure b.p. 36 °C
  - Metabolized to NO, causing neurotoxicity and tachycardia
  - COX inhibitors
  - NaN_3 oral mouse LD_{50} =27 mg/kg (NaCN 6 mg/kg)
  - NaN_3 dermal rabbit LD_{50} = 20 mg/kg (NaCN 8 mg/kg)

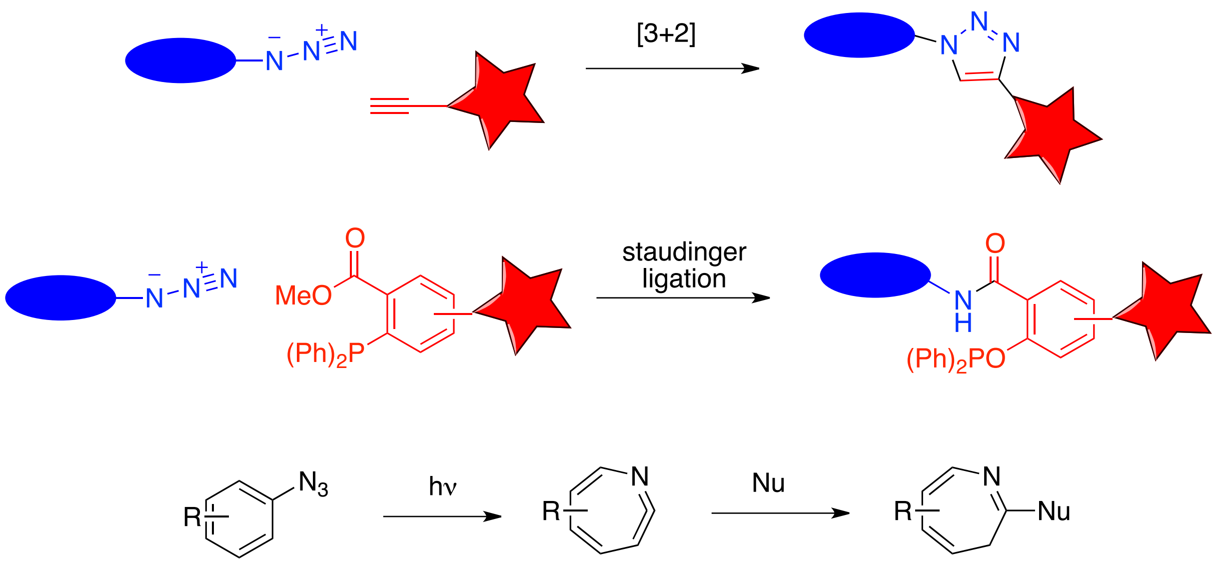
Organic Azides: Synthesis and Applications. 2010 John Wiley and Sons, Ltd

Int. J. Toxicol., **2003**, 175

Thermochimica Acta, **1997**, *179*

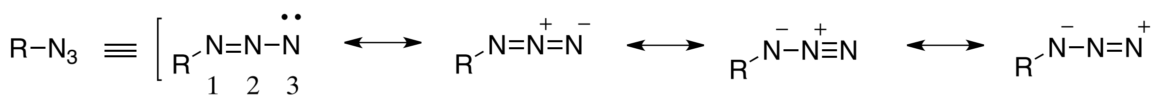
Azides: bioorthogonal labeling

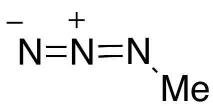
- Used to probe biomolecules in living systems
- Azides are absent in biological systems
- Orthogonal reactivity in biological systems
- Small

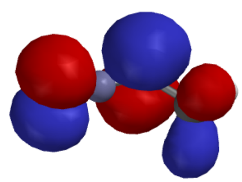


Org. Biomol. Chem. **2014,** 9307
Angew. Chem. Int. Ed., **2009**, 6974

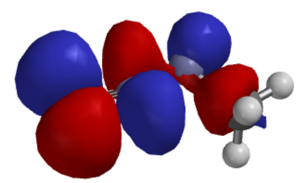
Structure and general reactivity



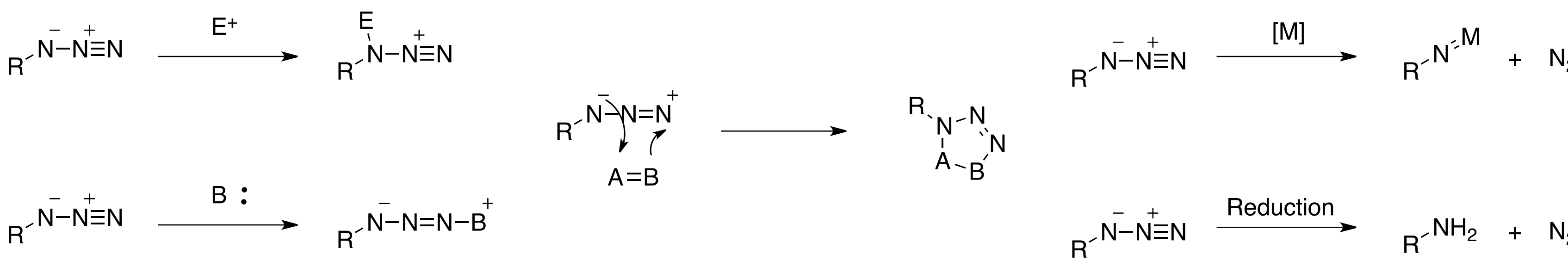


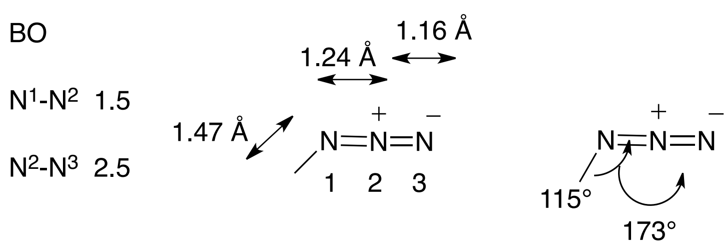


HOMO



LUMO





Strong IR absorption around 2100 cm^{-1}
UV absorption 287 and 216 nm (alkyl azides)

Coord. Chem. Rev. **2006**, 1234

Precursor azides

- Annual consumption 1000 t/yr (\$70/ kg NaN_3)

$$2\ NaNO_2 + 2\ C_2H_5OH + H_2SO_4 \longrightarrow 2\ C_2H_5ONO + Na_2SO_4 + 2\ H_2O$$

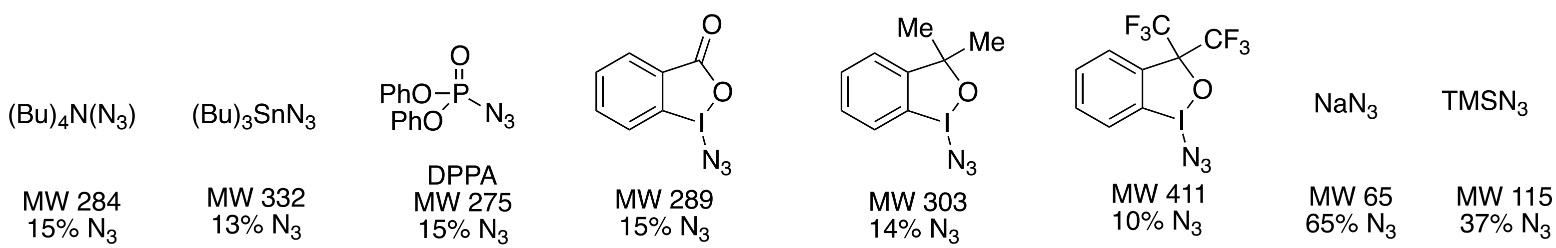
$$C_2H_5ONO + N_2H_4{\bullet}H_2O + NaOH \longrightarrow NaN_3 + C_2H_5OH + 3\ H_2O$$

Curtius synthesis of NaN_3

$$TMSCl \xrightarrow[\text{dyglime, 85\%}]{NaN_3} TMSN_3$$

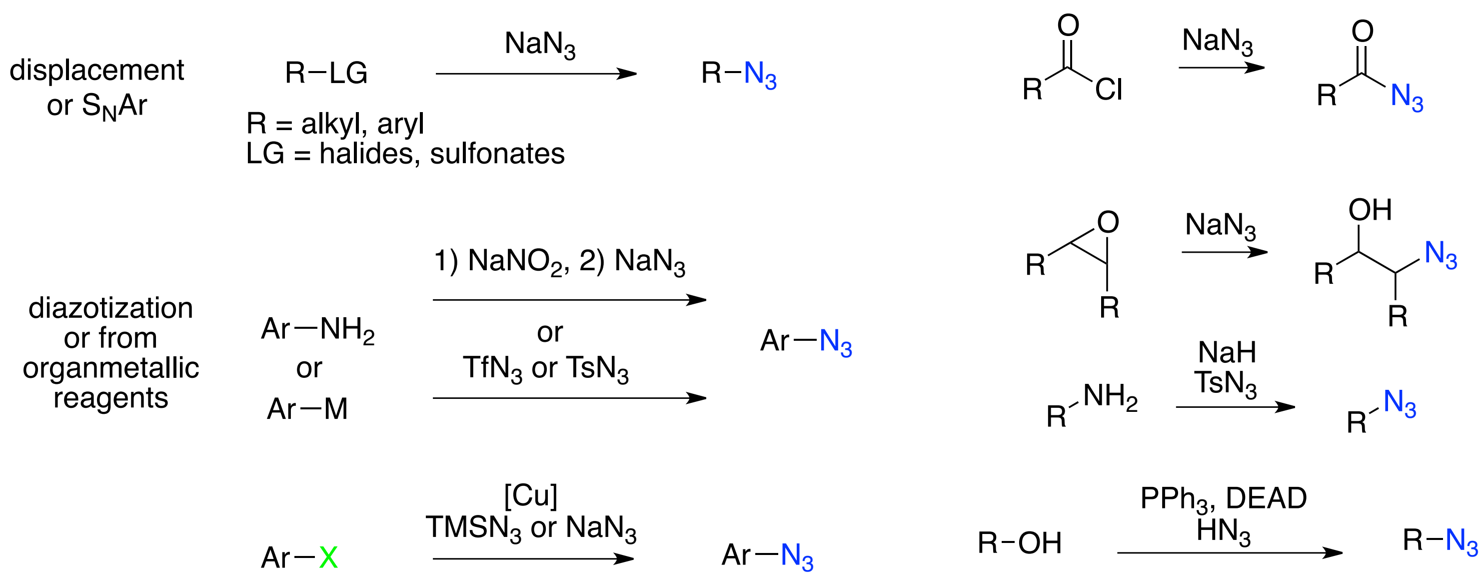
Org. Synth. **1970**, *50*, 107

- Other N_3 containing compounds



Organic Azides: Synthesis and Applications. 2010 John Wiley and Sons, Ltd

Azide formation



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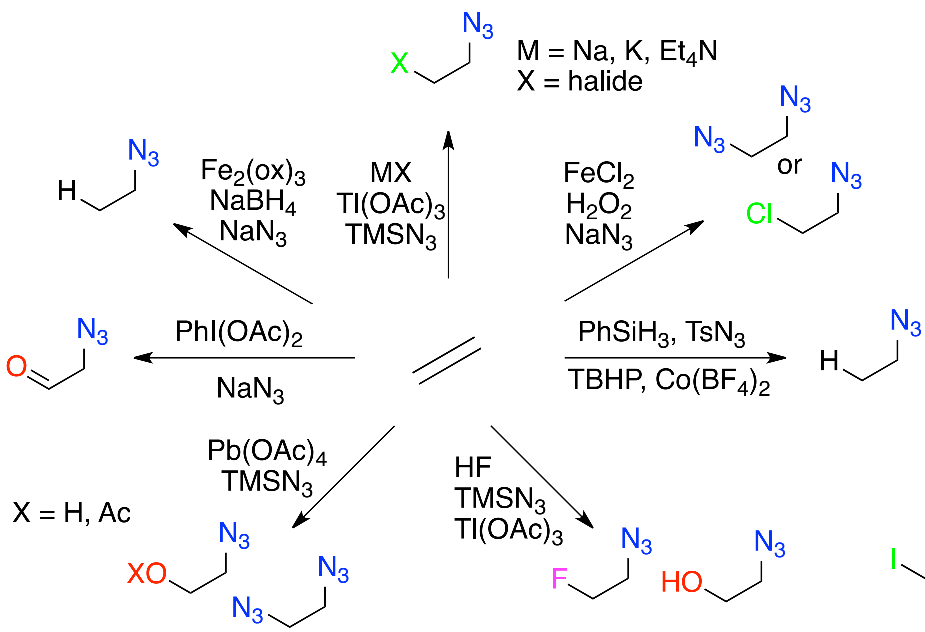
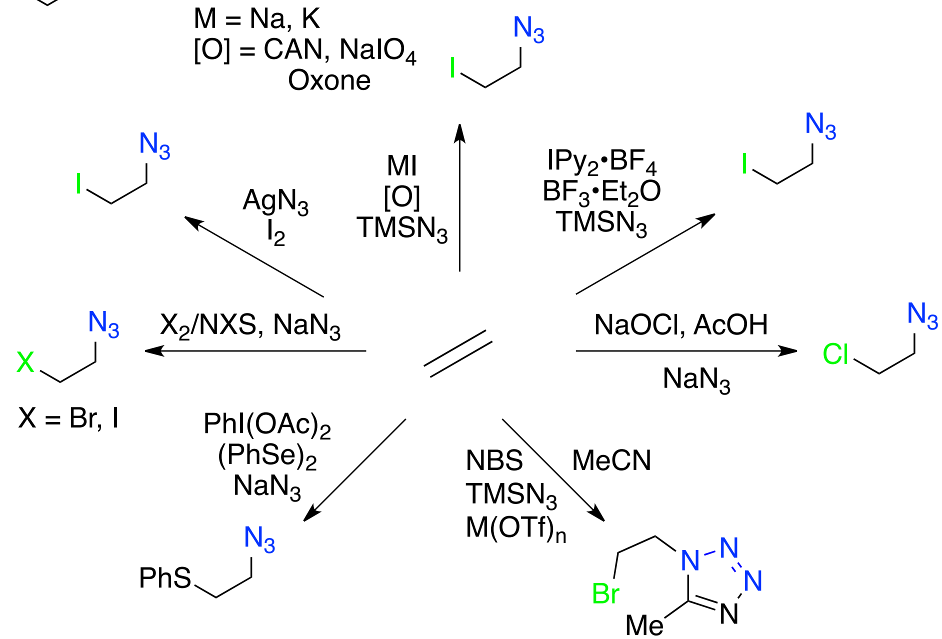
Direct introduction of azides onto olefins





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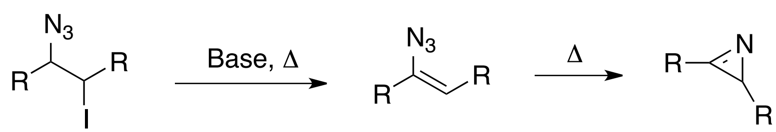
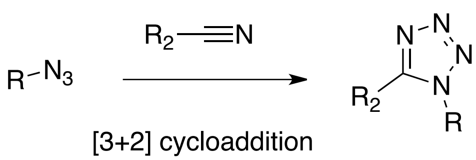
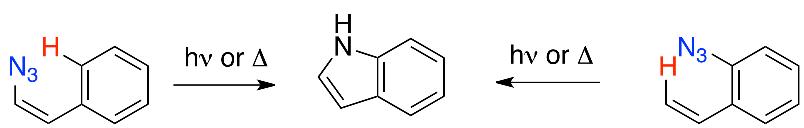
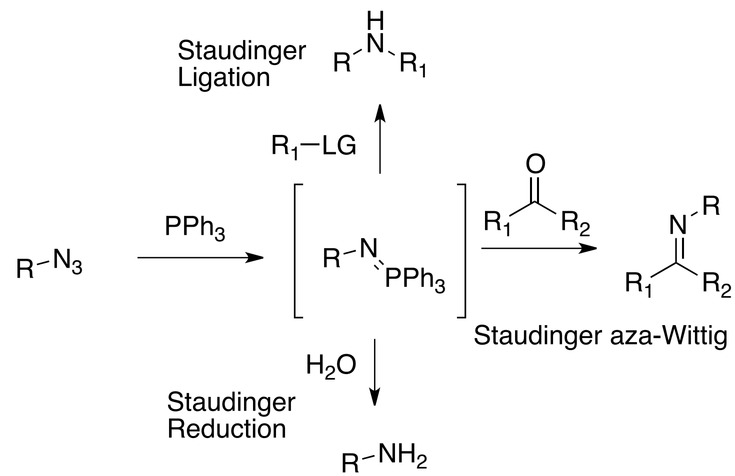
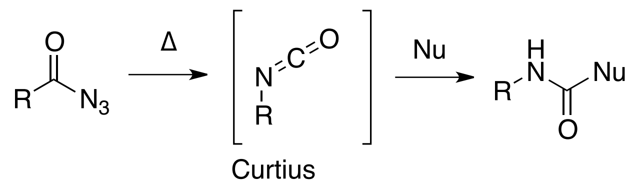
Synthetic uses of azides



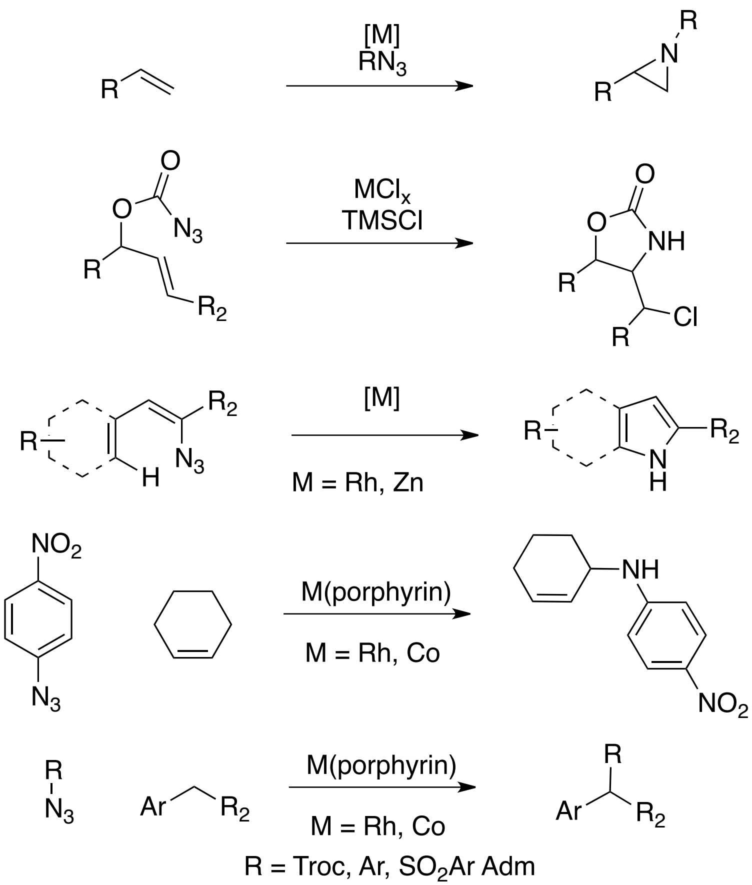


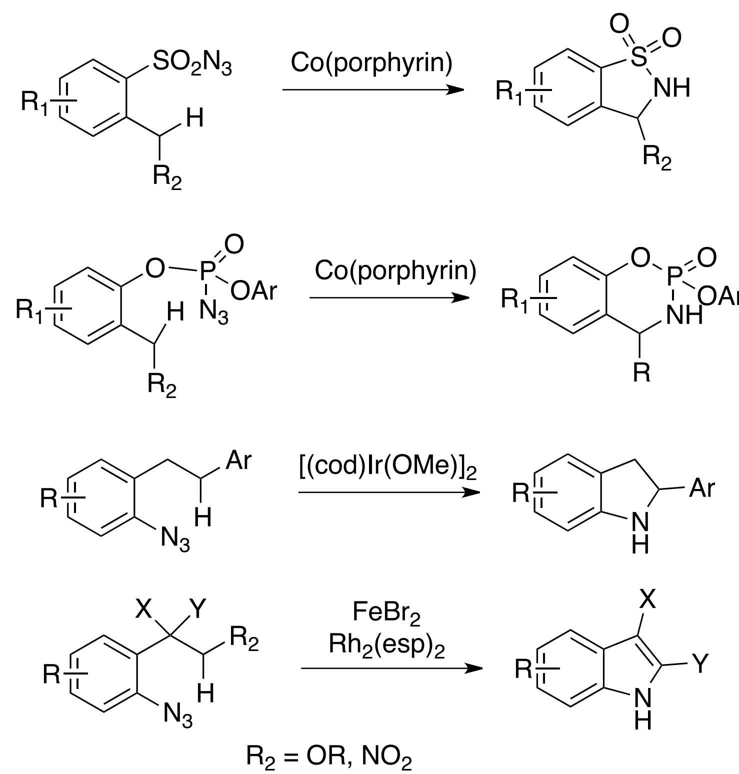






Azides as N sources nitrene chemistry

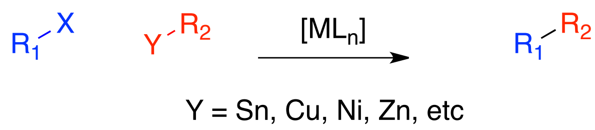




Org. Biomol. Chem., **2010**, 3831

C-H bond transformations

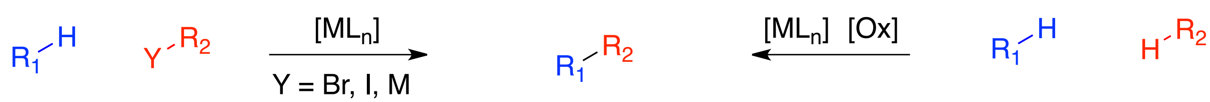
Traditional cross-coupling

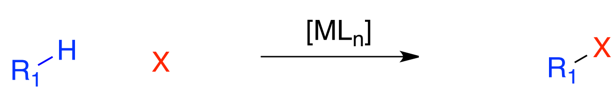


C-H activation

Direct cross-coupling

Dehydrogenative cross-coupling



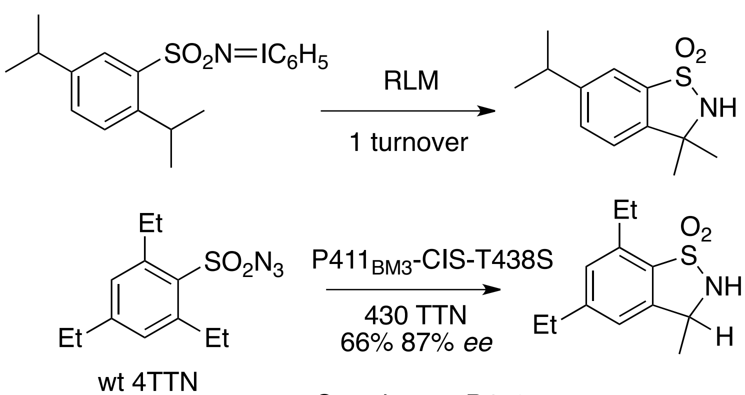


Chem. Soc. Rev., 2011, 40, 5068–5083

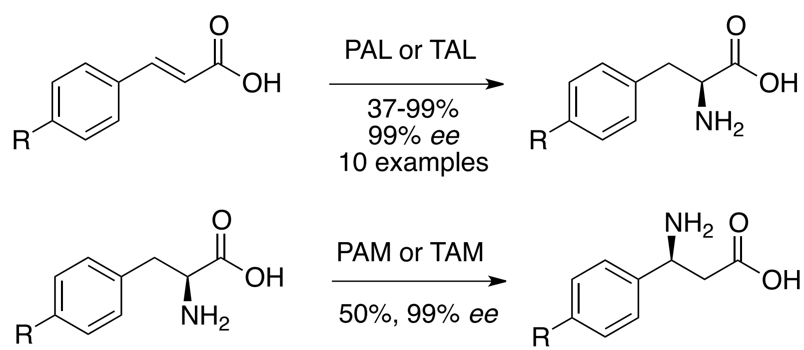
Enzymatic azidation

Enzymatic C-H activation

- Inert C-H bonds converted to C-X (X = C, O, P, S, halogen)
- Late stage functionalization of complex molecules
- Enantiospecific
- Involve free radical or high-valent metal-oxo intermediate
- Few examples of enzymatic C-N bond formation
- N_3 inhibits the activity of many enzymes through binding to metal porphyrin complexes

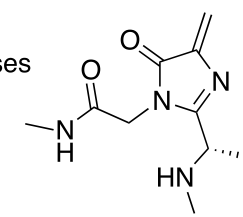


Cytochrome P450



Ammonia Lyases and Mutatases

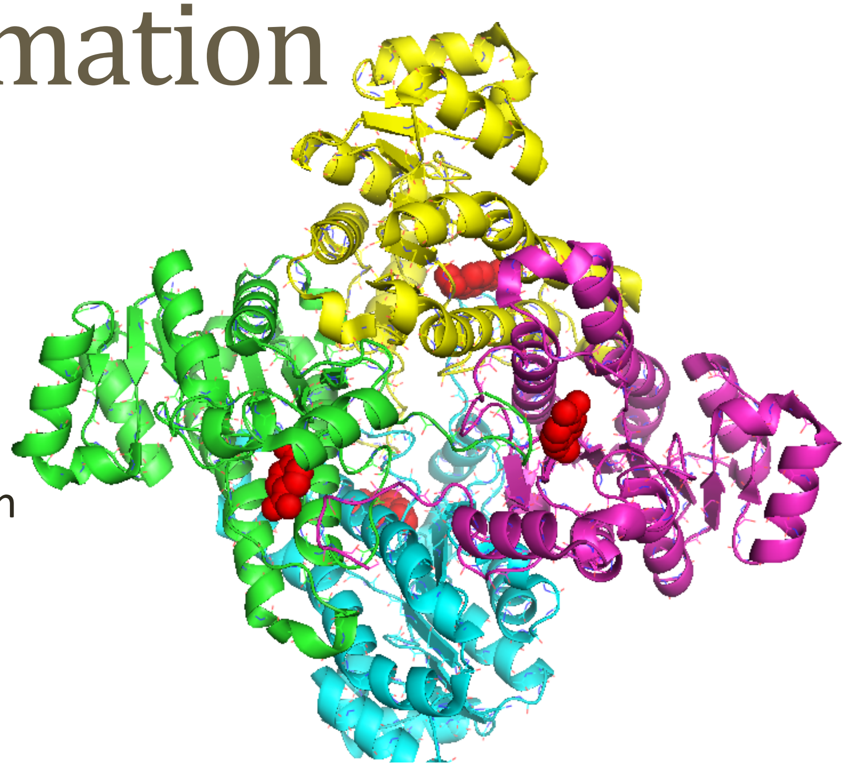
MIO (cofactor)
4-methylidineimidazole-5-one

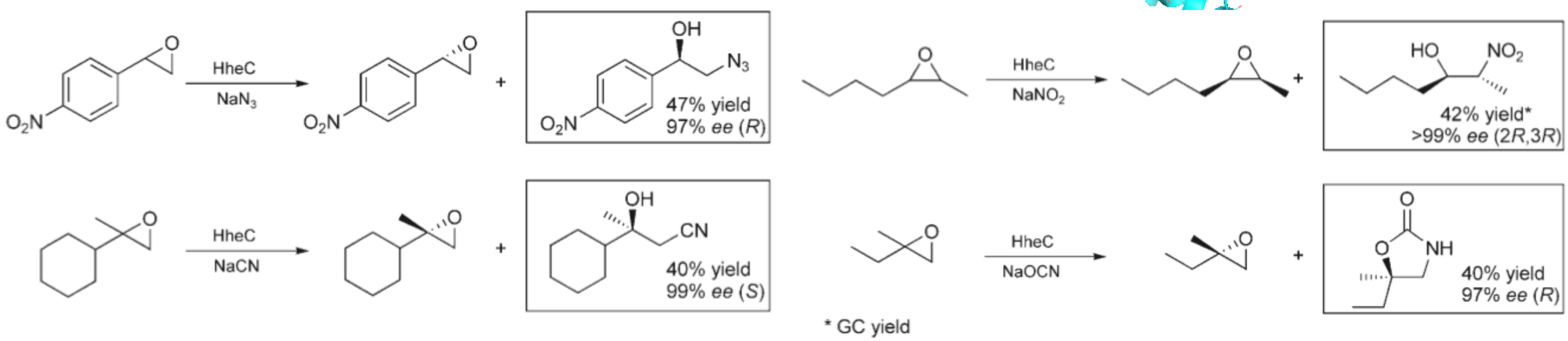


Angew. Chem. Int. Ed., **2013**, 9309
Curr. Opin. Chem. Biol. **2011**, 234
J. Am. Chem. Soc. **1985**, 6427

Harnessing non-specific catalysis for C-N_3 bond formation

- Halohydrin Dehalogenase from *Agrobacterium radiobacter* AD1
- Originally used for the dehalogenation of 1-chloropropan-2,3-diol to form the epoxide
- Homotetramer
- Enantioselective opening of epoxides with CN, NO_2, OCN, N_3
- Scalable cultures

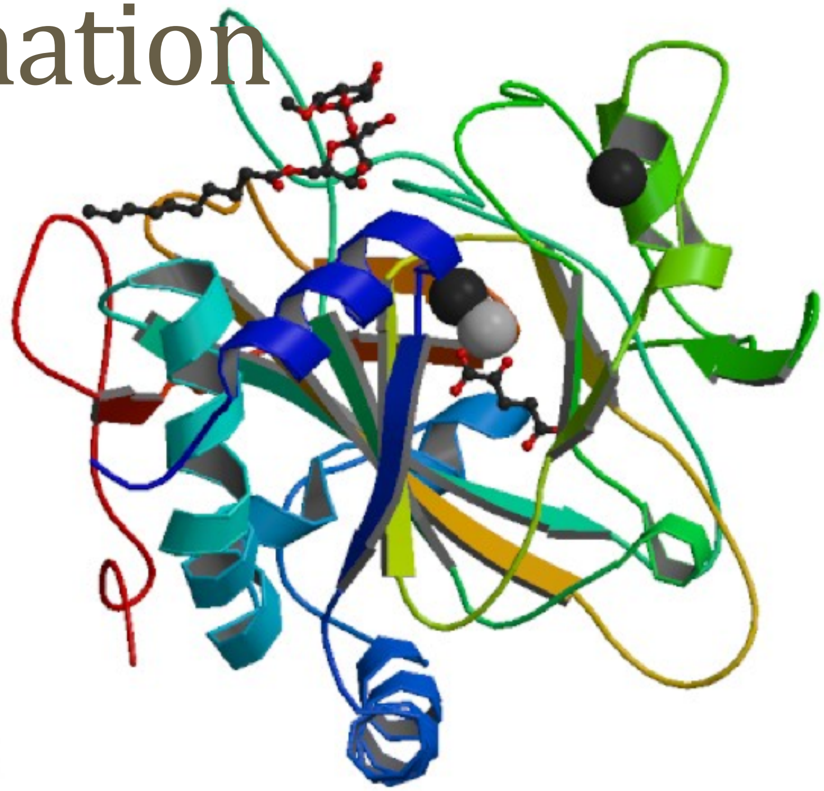


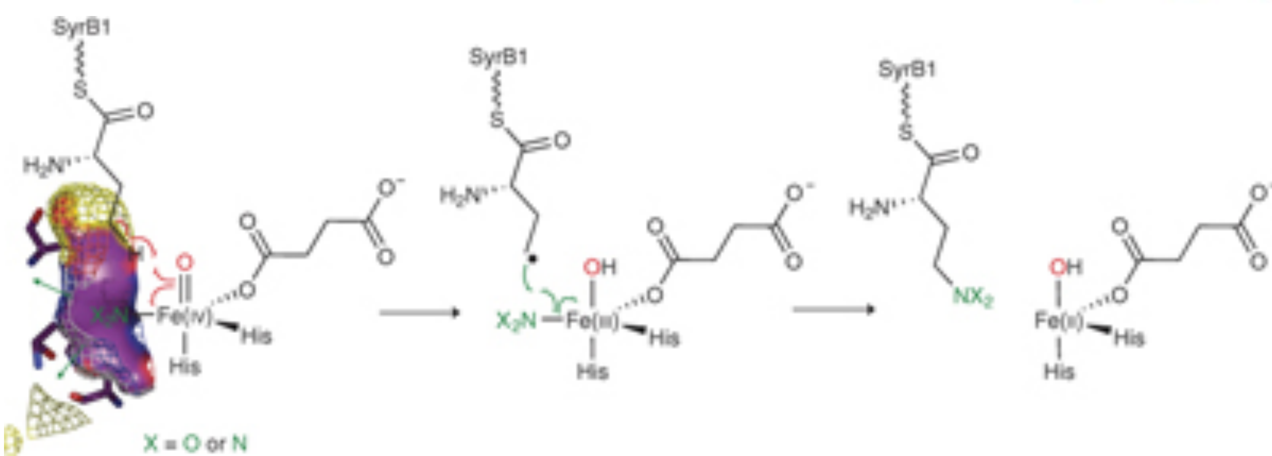


Org. Lett. **2001**, 3, 41-3

Harnessing non-specific catalysis for C-N_3 bond formation

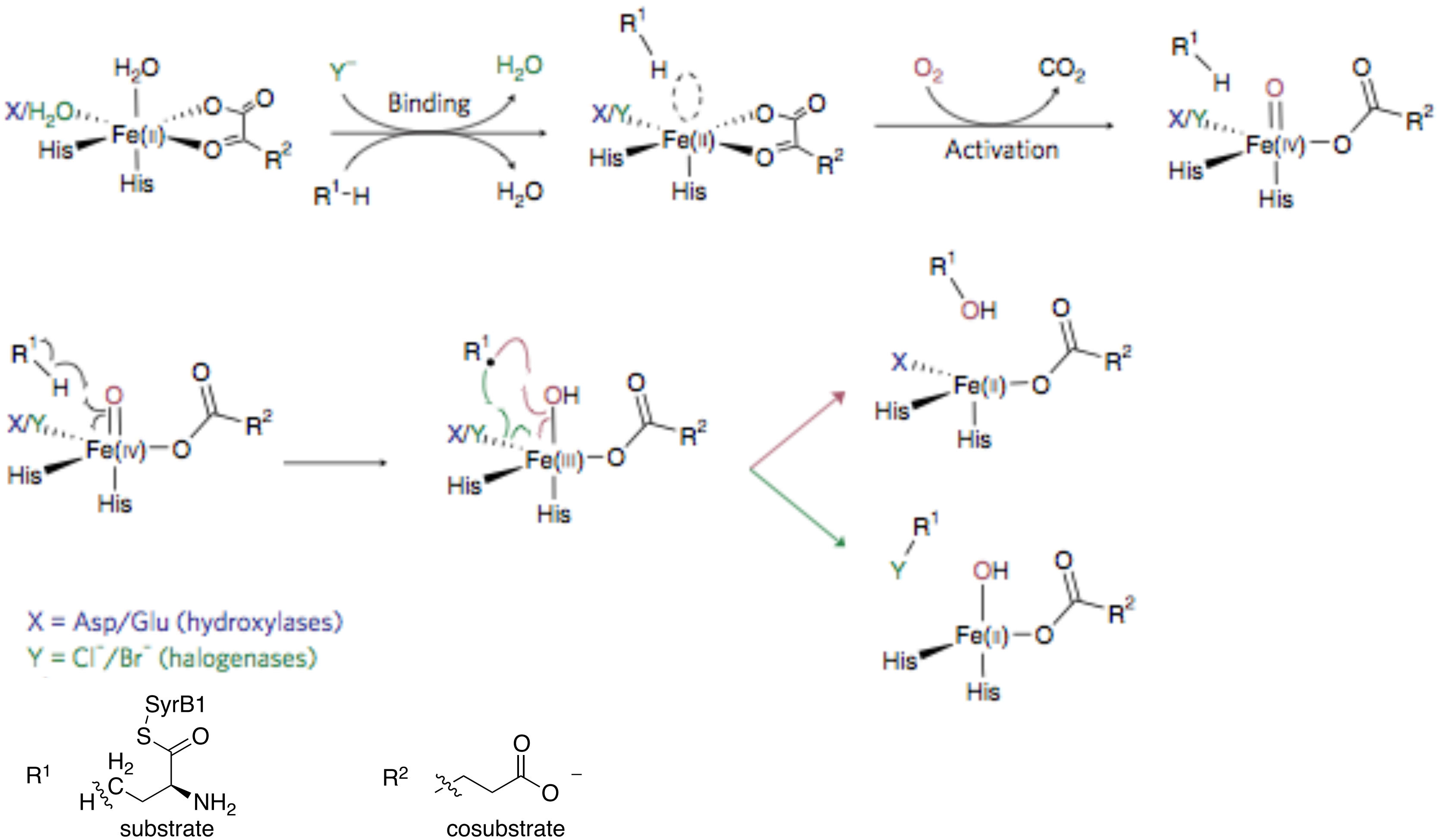
- Halogenase SyrB2 from *Pseudomonas syringae* B301D
- Haloferryl complex facilitates H$^{\bullet}$ abstraction
- Activation of inert aliphatic C-H bonds NO_2 and N_3
- Yields of 20% for azidation and 52% for nitration





Nature Chem. Biol., **2014**, 209

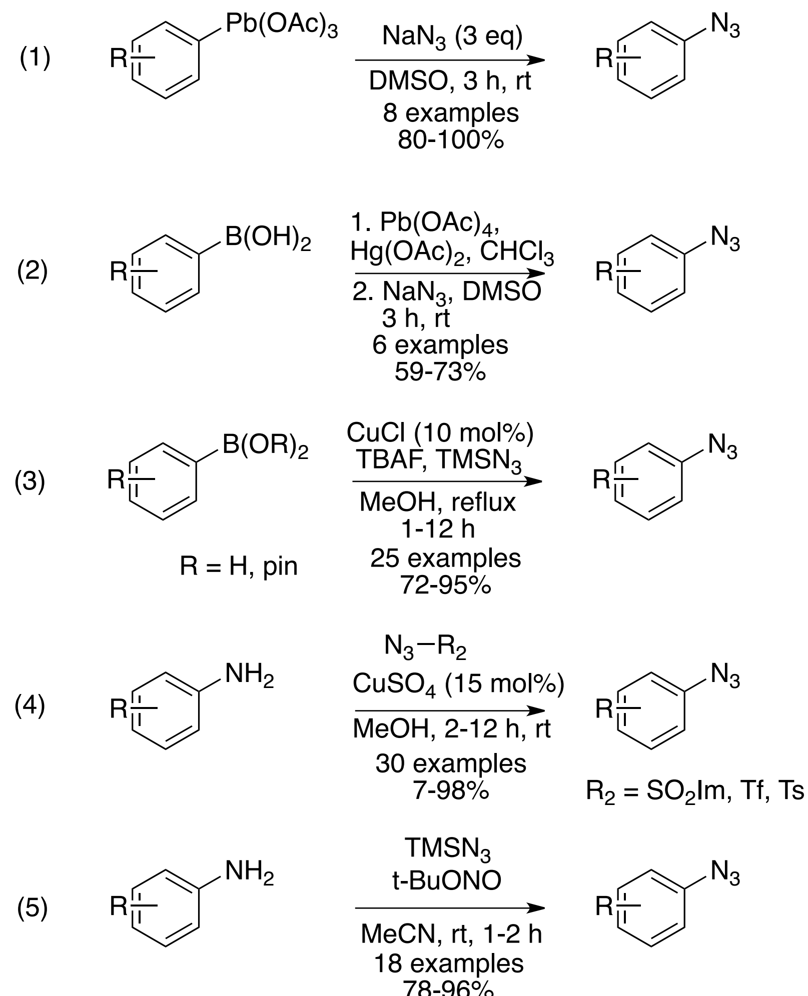
Mechanism



Nature Chem. Biol., **2014**, 209

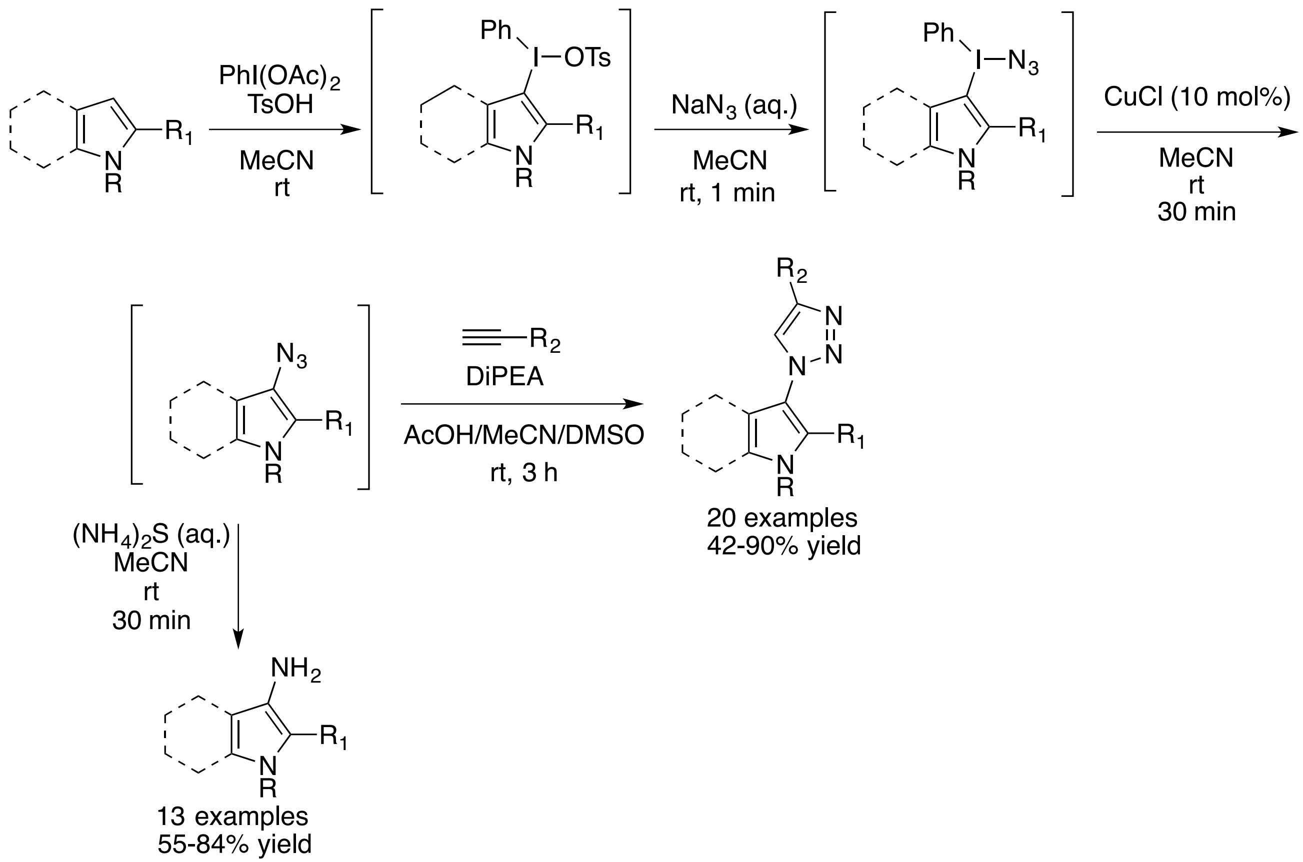
Aryl C-H azidation

Indirect C-H azidation

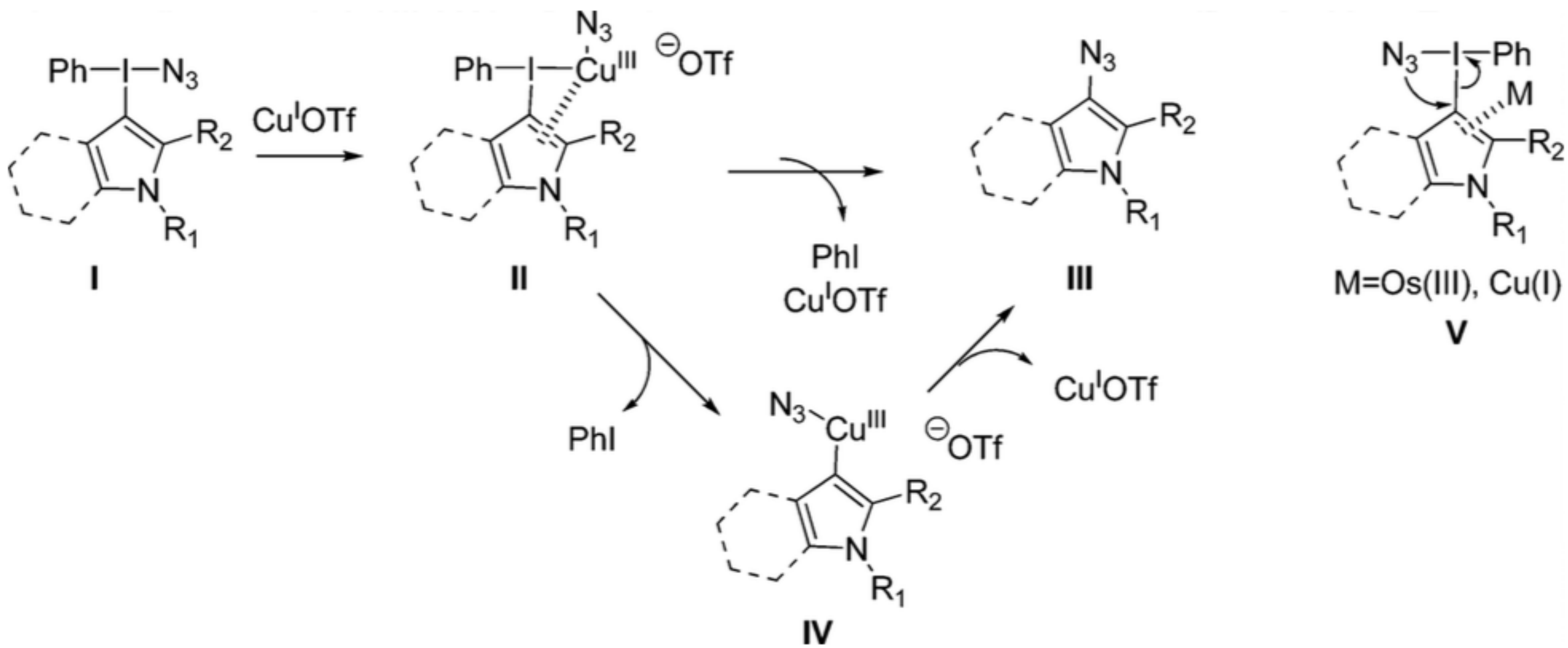


J. Chem. Soc., Perkin Trans 1. **1990**:721
Org. Lett., **2007**, 3797
Chem. Eur. J. **2010**, 7969

C-H to C-N bond formation via C-N_3

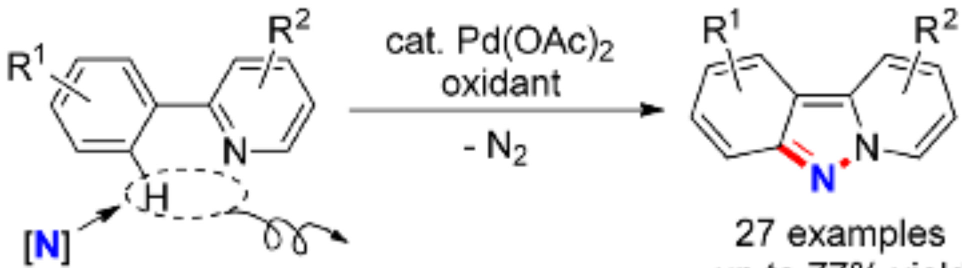


J. Am. Chem. Soc. 2012, 134, 15436–15442


Ph—I—N3
CuIOTf
R2
N
R1
I
N3
Ph—I—CuIII
⊖OTf
II
PhI
CuIOTf
III
M=Os(III), Cu(I)
V
N3—I—Ph
M
N3 CuIII
⊖OTf
IV

C-H to C-N bond formation via C-N_3

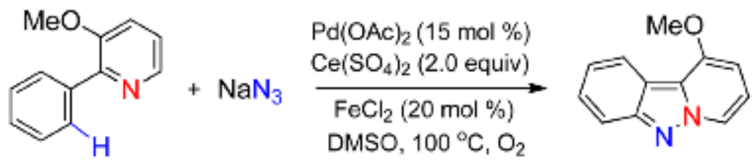
Pd-catalyzed relay of C-H azidation and N-N formation



27 examples
up to 77% yield

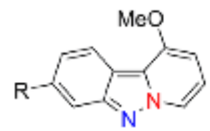
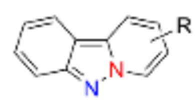
Org. Lett., **2013**, 4262

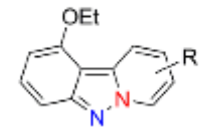
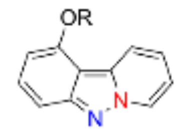
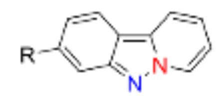
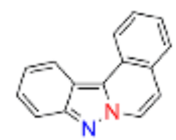
Scope



1a "standard conditions" **2a**

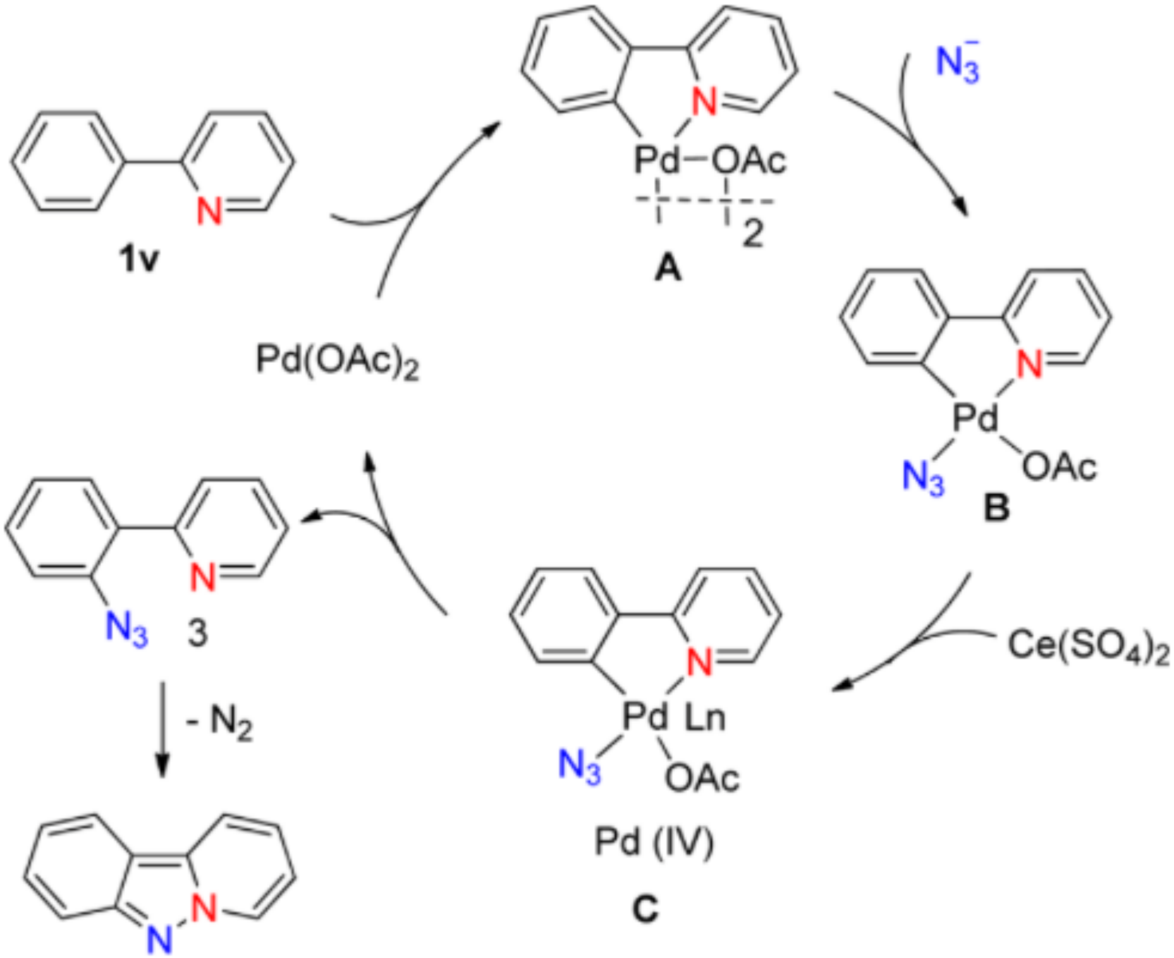
entry	change from the "standard conditions"	yield of **2a** (%)[b]
1	none	77
2	no $Pd(OAc)_2$	0
3	no $Ce(SO_4)_2$ [with 1.0 equiv of $Pd(OAc)_2$]	0
4	no $FeCl_2$	56
5	Ar instead of O_2	61
6	Selectfluor instead of $Ce(SO_4)_2$	10
	dioxane instead of DMSO	
7	CAN instead of $Ce(SO_4)_2$	15
8	DDQ instead of $Ce(SO_4)_2$	0
9	$TMSN_3$ instead of NaN_3	0
10	DMF instead of DMSO	0

entry	product	yield [%][b]
		
1	**2a**: R = H	77
2	**2b**: R = Me	71
3	**2c**: R = *i*Pr	71
4	**2d**: R = *t*Bu	75
5	**2e**: R = F	52
6	**2f**: R = Cl	48
7	**2g**: R = CF_3	41
8	**2h**: R = COOMe	60
		
9	**2i**	70
		
10	**2j**: R = 4-Me	44
11	**2k**: R = 5-Me	35
12	**2l**: R = 3,5-diMe	48
		
13	**2m**: R = H	70
14	**2n**: R = 4-Me	61
15	**2o**: R = 5-Me	61

entry	product	yield (%)[b]
		
16	**2p**: R = H	72
17	**2q**: R = 4-Me	60
18	**2r**: R = 5-Me	62
		
19	**2s**: R = *i*Pr	62
20	**2t**: R = *n*Bu	65
21	**2u**: R = Ph	55
		
22	**2v**: R = H	45
23	**2w**: R = Me	51
24	**2x**: R = *t*Bu	50
25	**2y**: R = F	32
26	**2z**: R = Cl	42
		
27	**2aa**	43

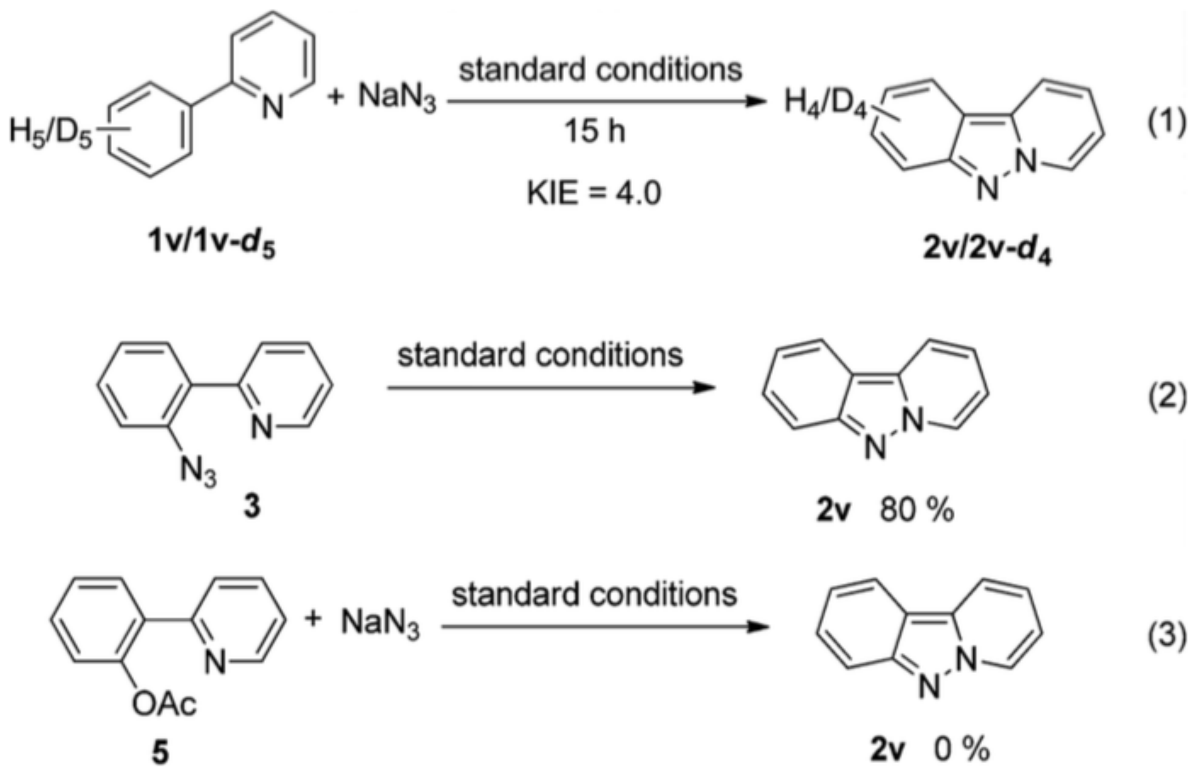
Org. Lett., **2013**, 4262

Aromatic C-H Azidation



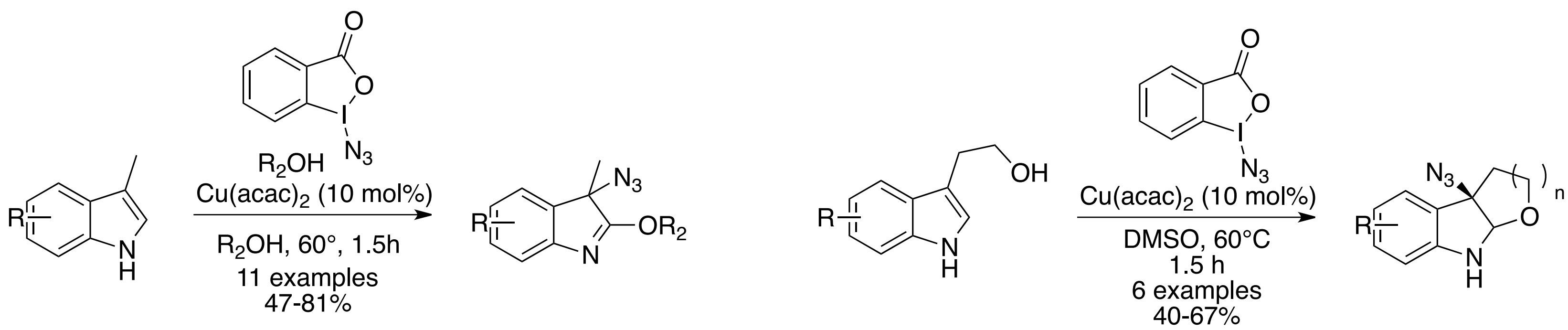
Org. Lett., **2013**, 4262

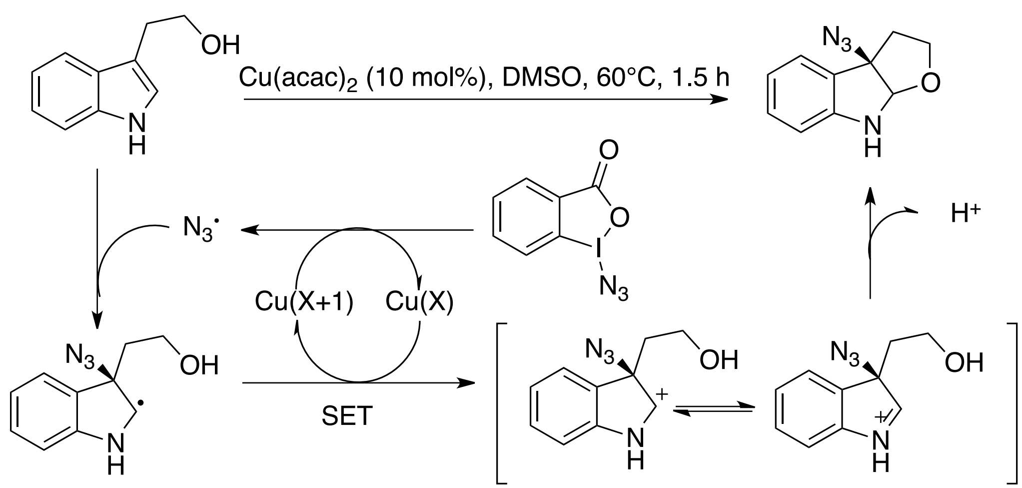
Aromatic C-H Azidation



Org. Lett., **2013**, 4262

Indole oxoazidation





Org. Lett., **2014**, 2302

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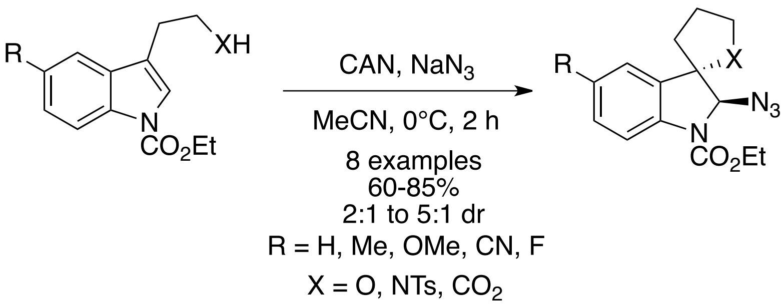
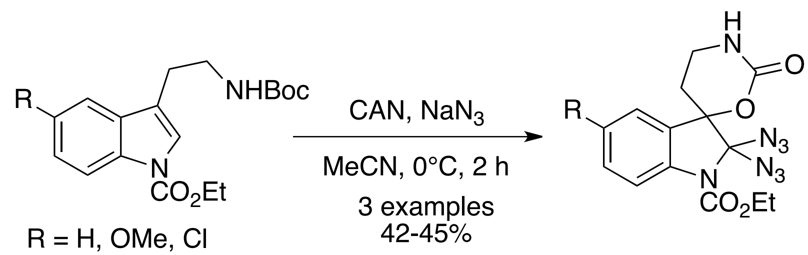
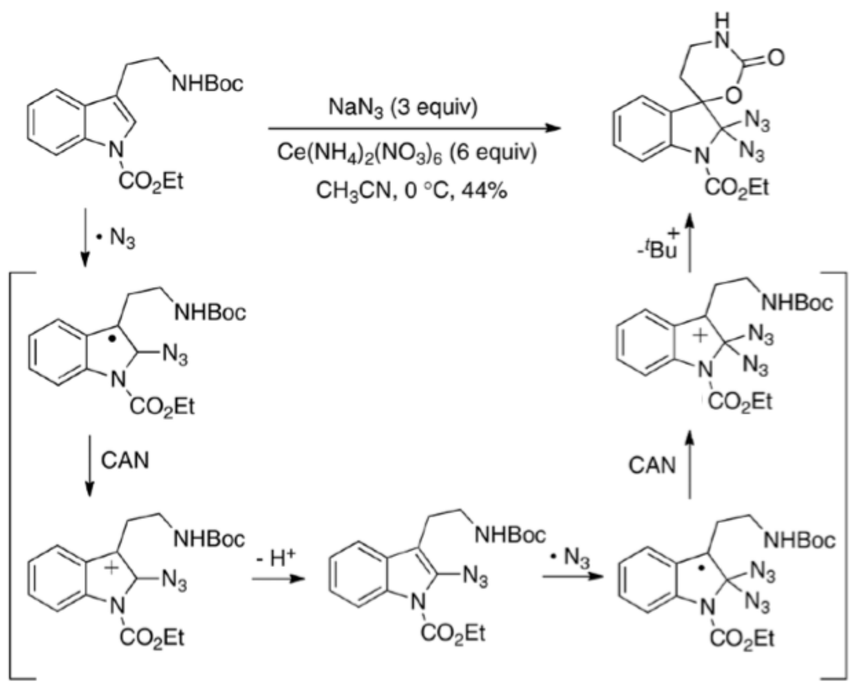
Indole oxoazidation







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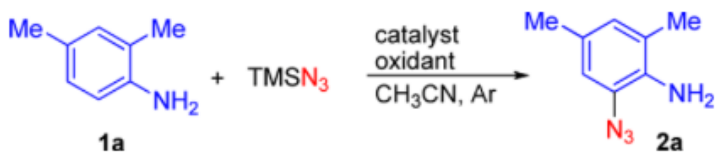
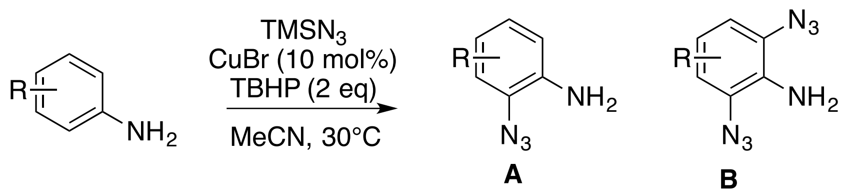
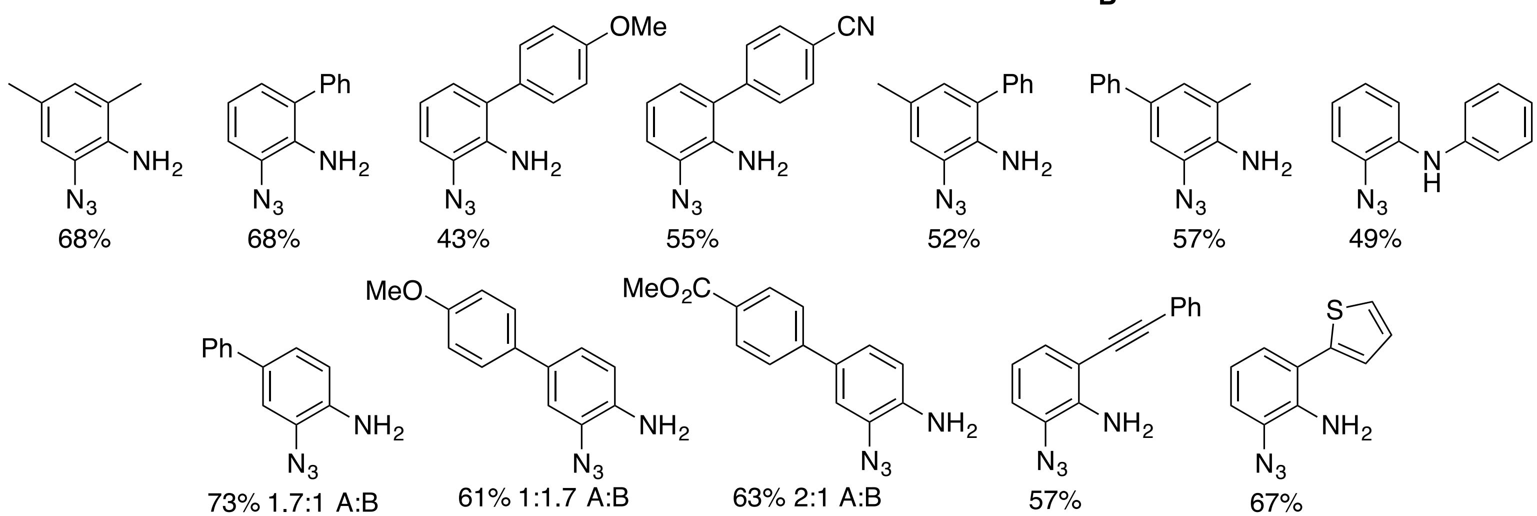
C-H azidation of anilines



entry	catalyst (mol %)	oxidant (equiv)	*T* (°C)	time (h)	yield (%)[b]
1	CuBr (10)	TBHP (2.0)	60	12	28
2	CuBr (10)	TBHP (2.0)	30	12	27
3	CuBr (10)	TBHP (2.0)	30	1	56
4	**CuBr (10)**	**TBHP (2.0)**	**30**	**2**	**68**
5	CuBr (10)	TBHP (1.2)	30	2	54
6	CuBr (5)	TBHP (2.0)	30	2	40
7	CuCl (10)	TBHP (2.0)	30	2	48
8	$CuBr_2$ (10)	TBHP (2.0)	30	2	34
9	–	TBHP (2.0)	30	2	0
10	$FeCl_2$ (10)	TBHP (2.0)	30	2	0





J. Am. Chem. Soc., **2010**, 18924

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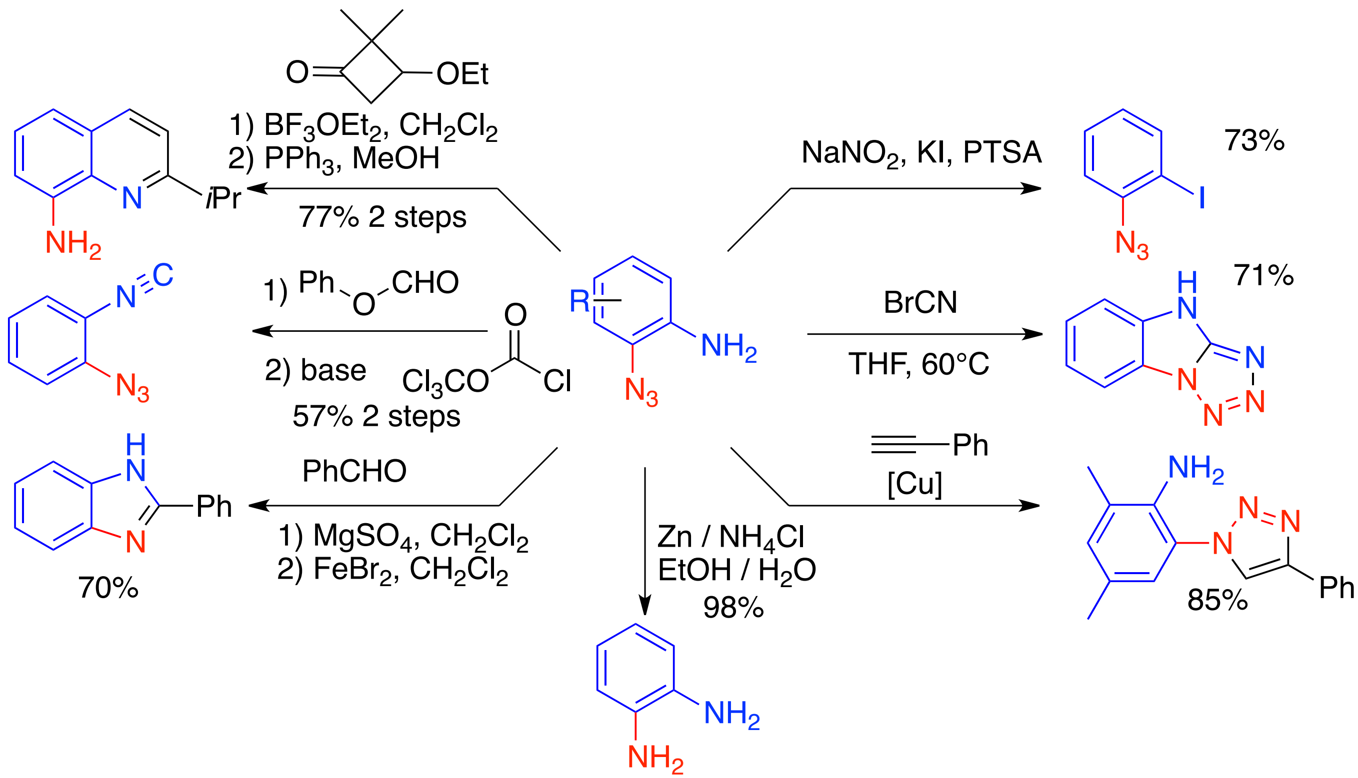
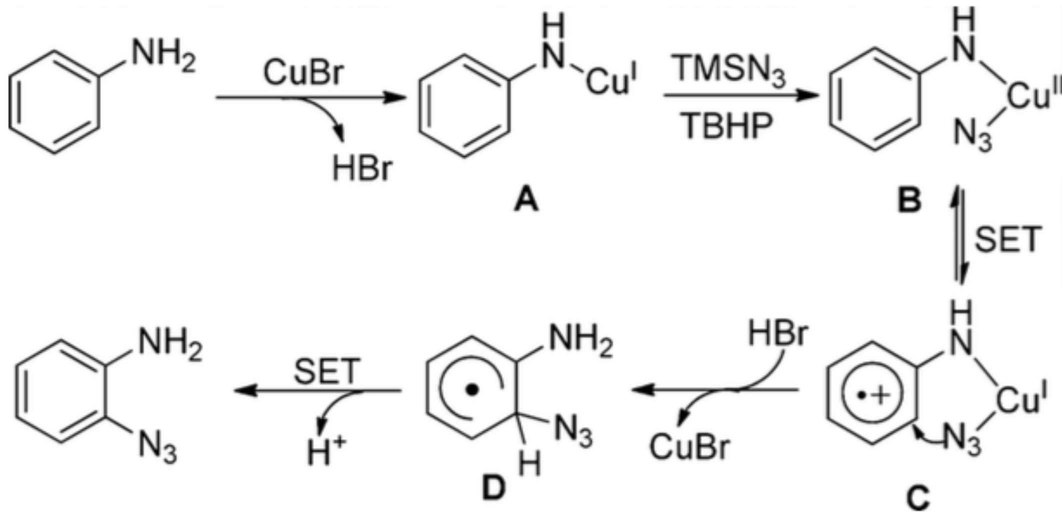
Further modifications



J. Am. Chem. Soc., **2010**, 18924

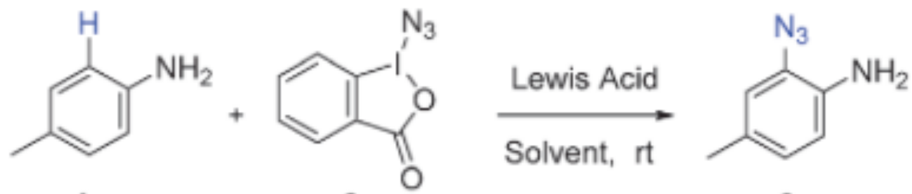
Proposed mechanism



J. Am. Chem. Soc., **2010**, 18924

Mild C-H azidation of anilines

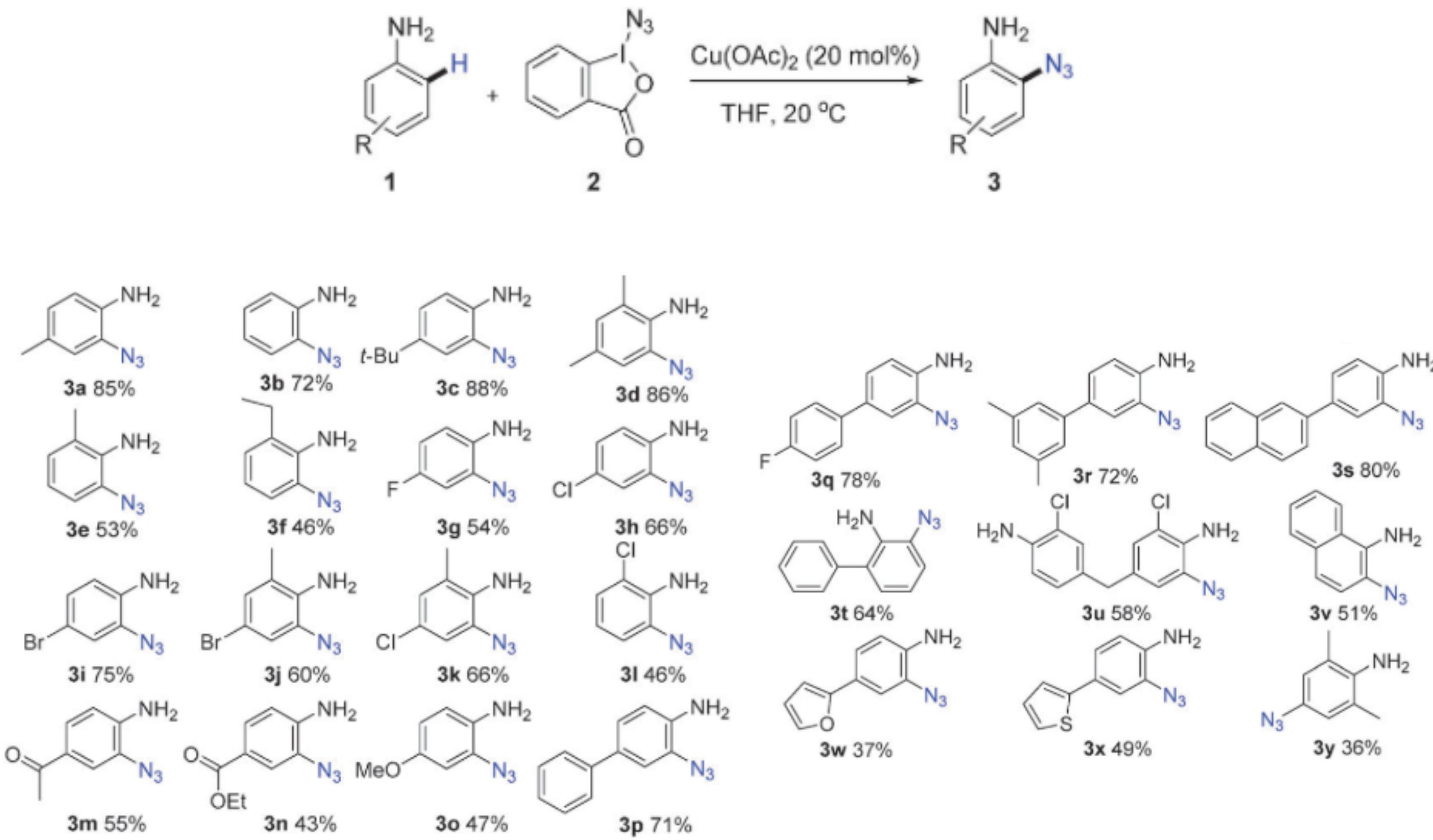
2:1 ratio **1a**:**2**



Entry	**1a** (equiv.)	Lewis acid (mol%)	Solvent	*T* (°C)	Yield[b]
1	1.0	None	CH_3CN	20	0
2	2	CuI (10)	CH_3CN	20	67
3	2	CuBr (10)	CH_3CN	20	59
4	2	CuCl (10)	CH_3CN	20	57
5	2	CuOAc (10)	CH_3CN	20	52
6	2	$Fe(ClO_4)_3$ (10)	CH_3CN	20	0
7	2	$Zn(ClO_4)_2 \cdot 6H_2O$ (10)	CH_3CN	20	0
8	2	ZnI_2 (10)	CH_3CN	20	63
9	2	$ZnCl_2$ (10)	CH_3CN	20	57
10	2	$CuCl_2$ (10)	CH_3CN	20	45
11	2	$CuSO_4$ (10)	CH_3CN	20	57
12	2	$Cu(OAc)_2$ (10)	CH_3CN	20	72
13	2	$Cu(OAc)_2$ (10)	CH_2Cl_2	20	69
14	2	$Cu(OAc)_2$ (10)	THF	20	79
15	2	$Cu(OAc)_2$ (10)	MeOH	20	0
16	2	$Cu(OAc)_2$ (20)	THF	20	85
17	2	$Cu(OAc)_2$ (20)	THF	30	86
18	1.0	$Cu(OAc)_2$ (20)	THF	20	57

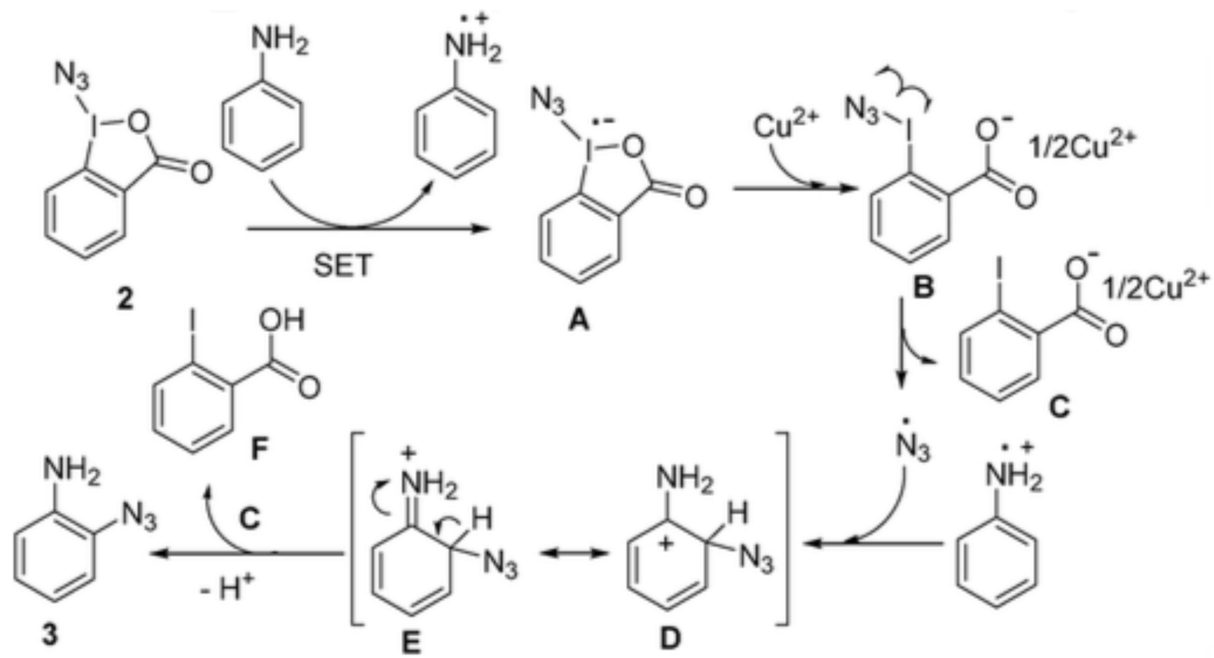
[a] Reagent **2** (0.3 mmol), 4-methyl aniline, catalyst, solvent, temperature and indicated solvents under N_2. [b] Isolated yield.

Chem. Commun., **2014**, 5733



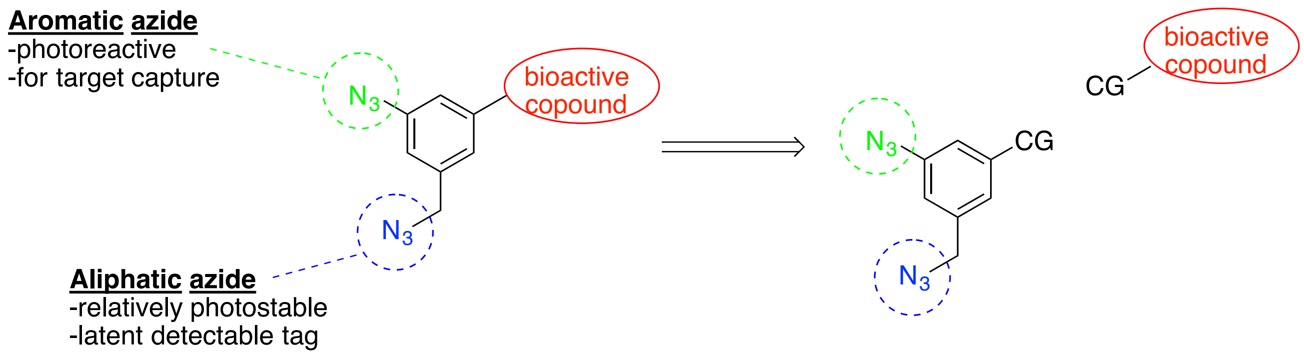
Chem. Commun., **2014**, 5733

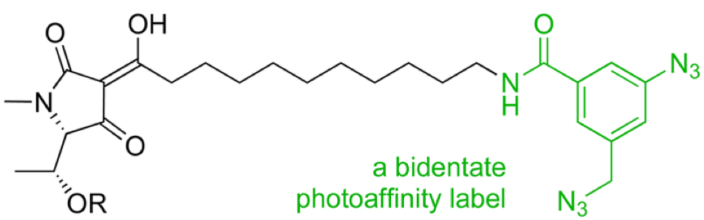
Proposed mechanism



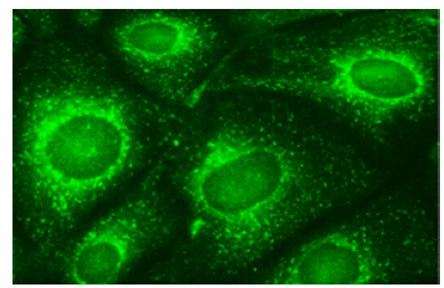
Chem. Commun., **2014**, 5733

Azides for photoaffinity labeling

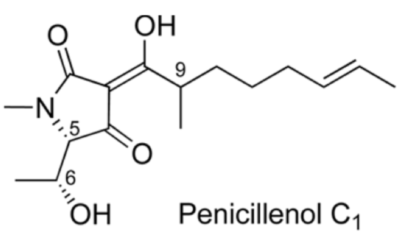




Penicillenol C_1 bis-azide analog



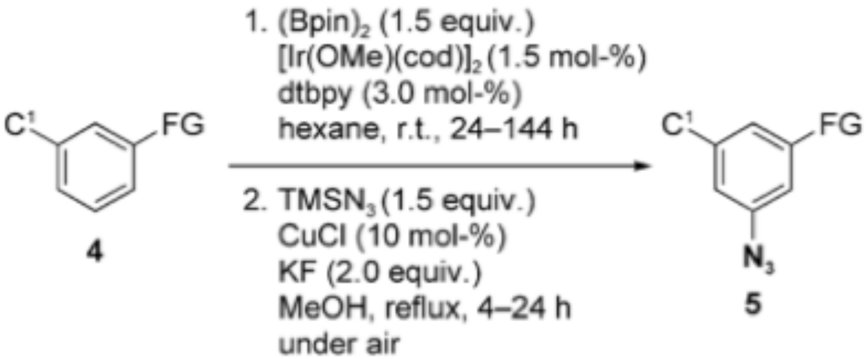
DyLight488- phosphine



Penicillenol C_1

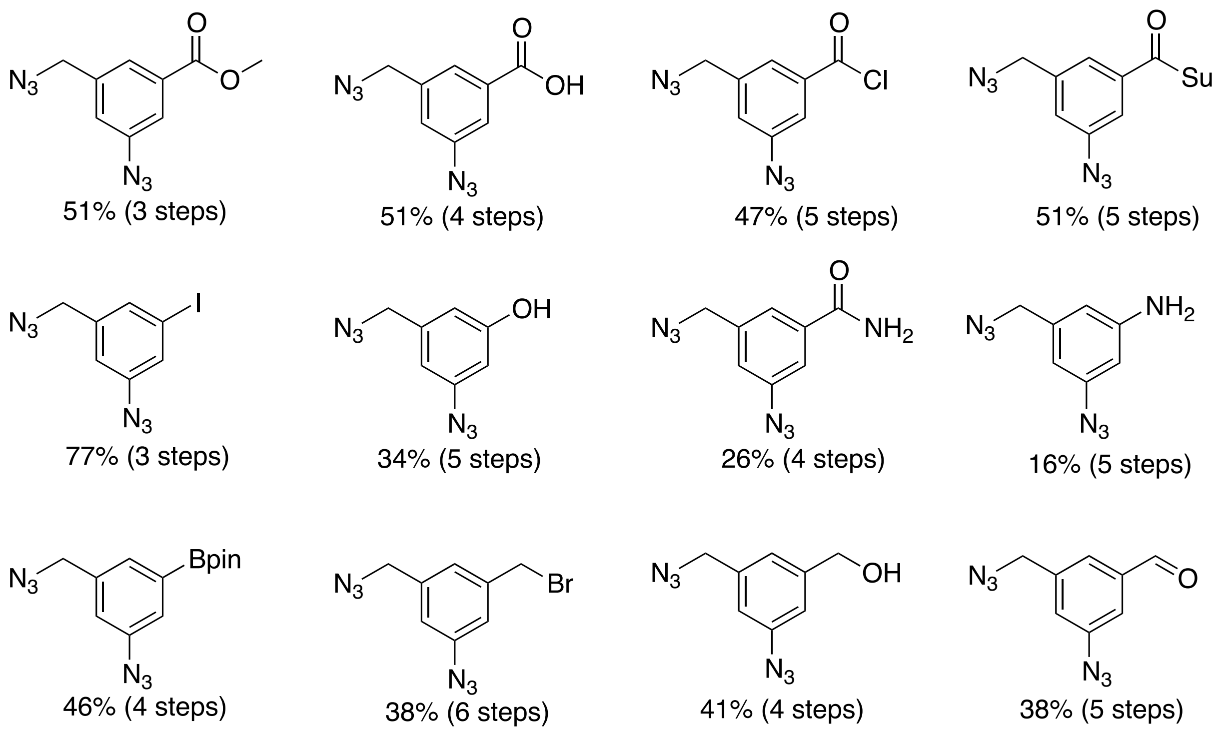
Eur. J. Org. Chem. **2014**, 3991
J. Org. Chem. **2013**, 2455

PAL diazide synthesis



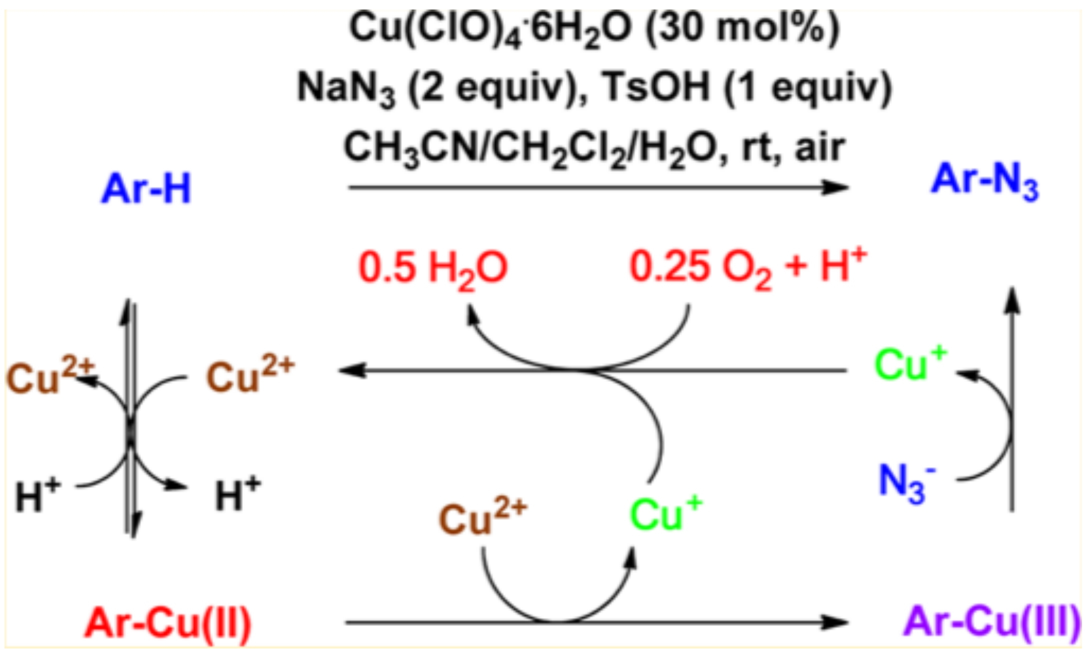
Entry	4	C^1	FG	5	Yield [%][a]
1	**4a**	CO_2Et	I	**5a**	91
2	**4b**	CO_2Me	Br	**5b**	96
3	**4c**	CH_3	CO_2Me	**5c**	95
4	**4d**	CH_3	CN	**5d**	70
5	**4e**	CO_2Et	$SCPh_3$	**5e**	0[b]
6	**4f**	CH_3	CH_2OH	**5f**	0[b]

[a] Yield of isolated product. [b] The borylation did not proceed and the starting material was not consumed.

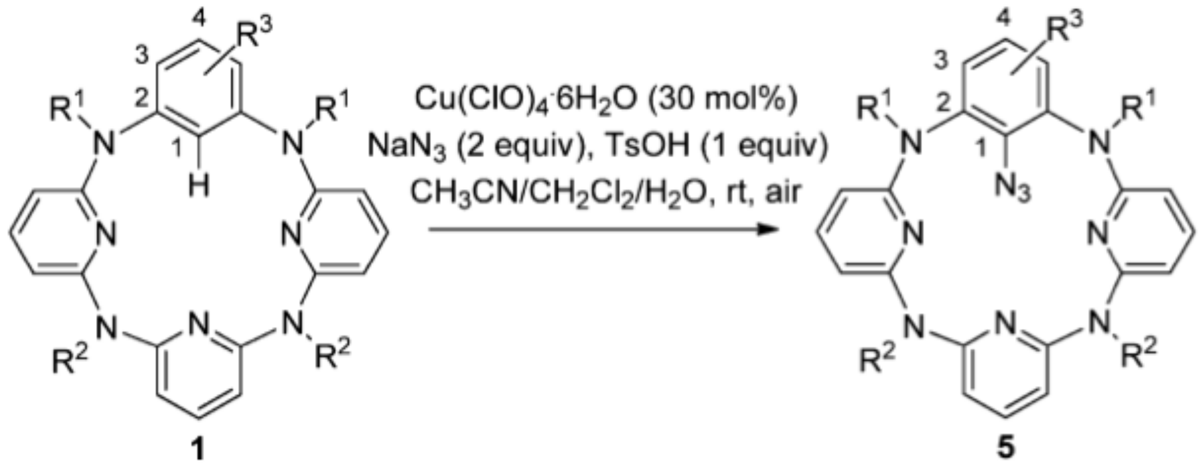


Eur. J. Org. Chem. **2014**, 3991

Cu(III)-catalyzed C-H azidation



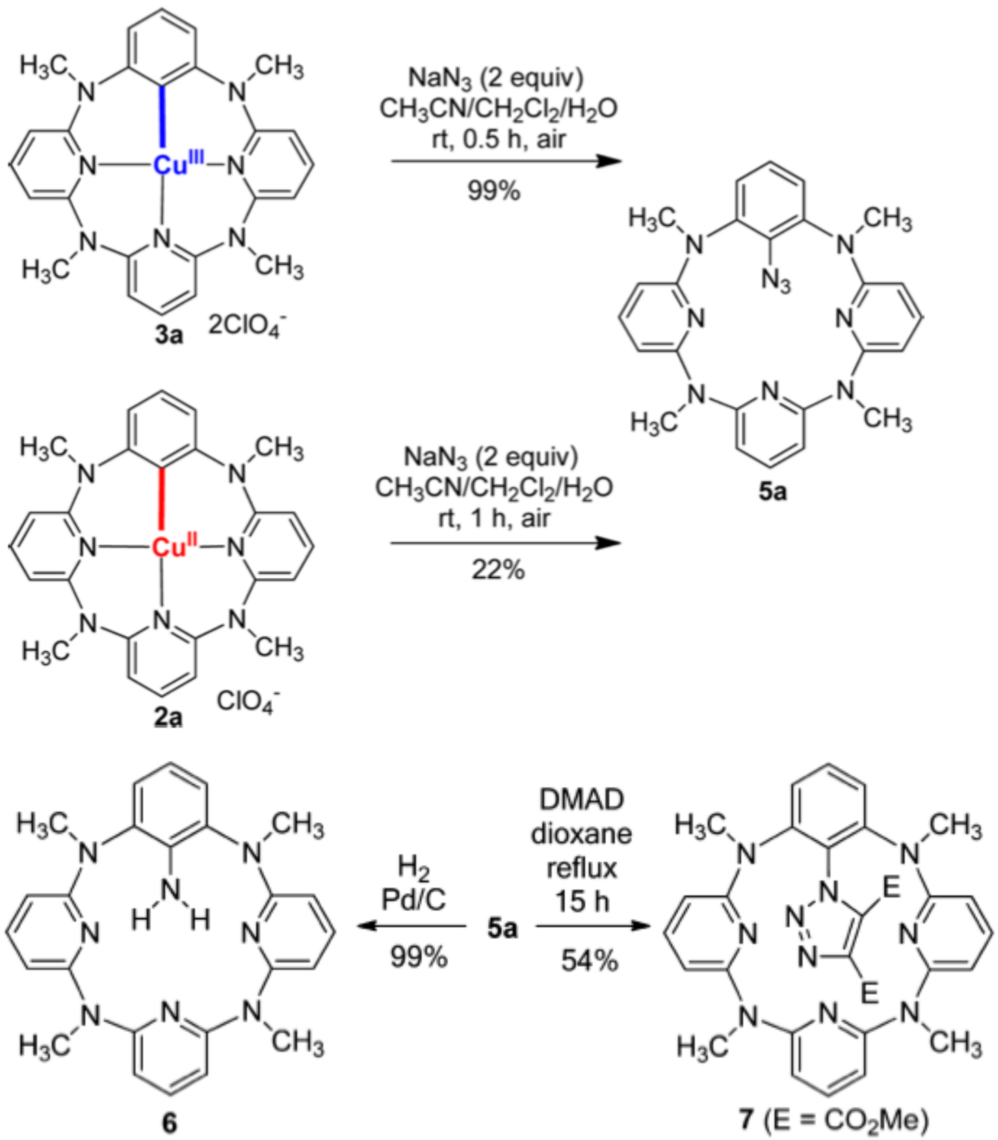
J. Org. Chem. **2014**, 11139



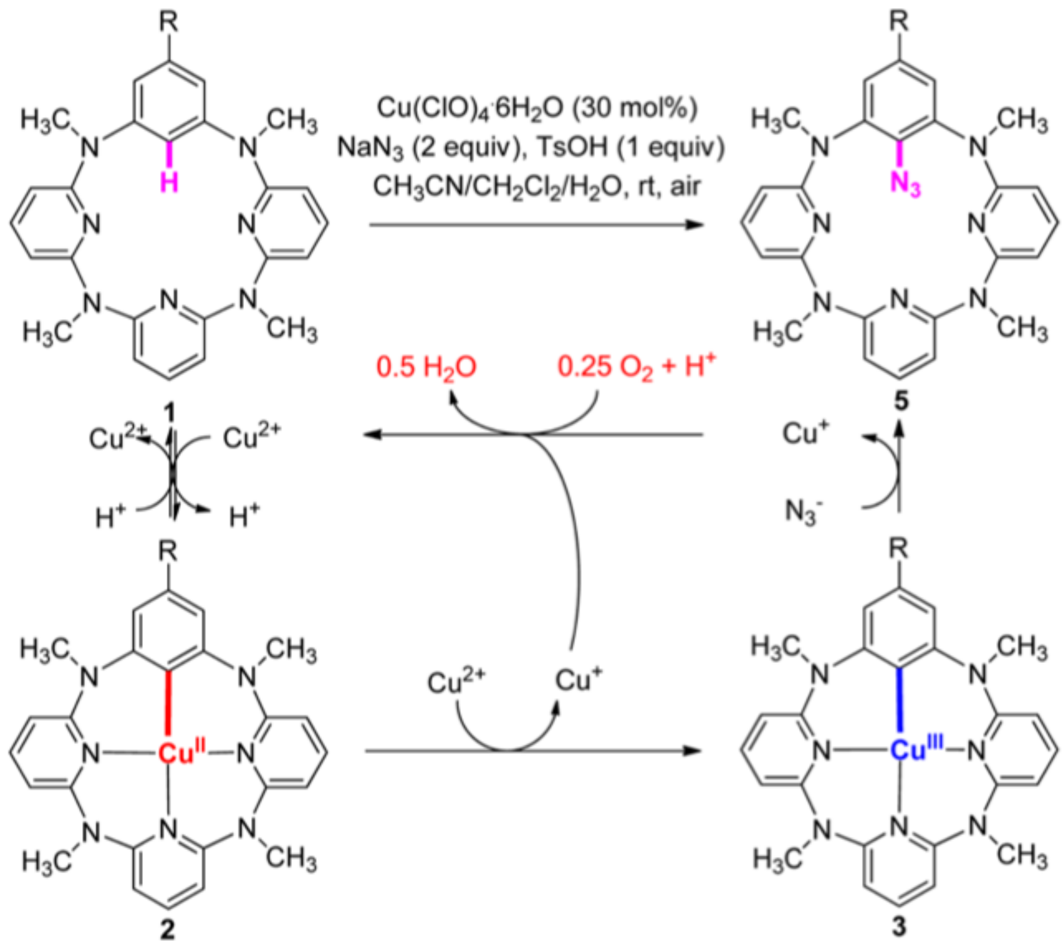
entry	1	substituents	*t* (h)	yield of **5** (%)
1[a]	**1a**	$R^1 = R^2 = CH_3$, R^3 = H	16	**5a** (94)
2	**1a**	$R^1 = R^2 = CH_3$, R^3 = H	24	**5a** (98)
3	**1b**	$R^1 = R^2 = CH_3$, R^3 = 4-Me	24	**5b** (99)
4	**1c**	$R^1 = R^2 = CH_3$, R^3 = 3-Me	24	**5c** (94)
5	**1d**	$R^1 = R^2 = CH_3$, R^3 = 4-Cl	24	**5d** (90)
6	**1e**	$R^1 = R^2 = CH_3$, R^3 = 3-Cl	48	**5e** (93)
7[b]	**1f**	$R^1 = CH_3$, $R^2 = CH_2Ph$, R^3 = H	20	**5f** (87)
8	**1f**	$R^1 = CH_3$, $R^2 = CH_2Ph$, R^3 = H	20	**5f** (83)
9	**1g**	$R^1 = CH_2Ph$, $R^2 = CH_3$, R^3 = H	24	**5g** (96)
10	**1h**	R^1 = H, R^2 = Boc, R^3 = H	20	**5h** (80)
11	**1i**	R^1 = H, R^2 = Boc, R^3 = 3-Br	20	**5i** (88)

[a]Aqueous perchloric acid (1 M, 0.1 mL) was used as an additive.
[b]Aqueous perchloric acid (1 M, 0.1 mL) and 0.1 mL water were used.

J. Org. Chem. **2014**, 11139



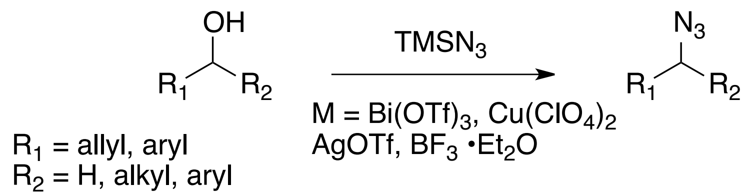
J. Org. Chem. **2014**, 11139



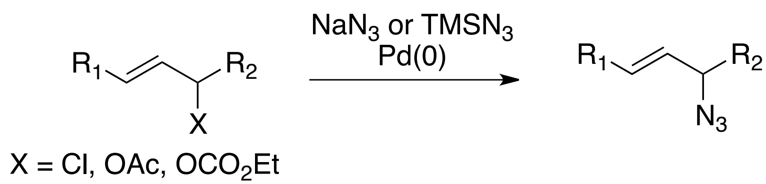
Cu(ClO)4·6H2O (30 mol%)
NaN3 (2 equiv), TsOH (1 equiv)
CH3CN/CH2Cl2/H2O, rt, air
0.5 H2O
0.25 O2 + H+
Cu2+
H+
Cu+
N3-
Cu2+
Cu+
CuII
CuIII
1
2
3
5

Allylic C-H Azidation

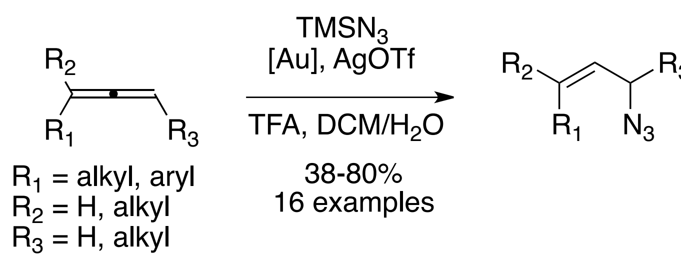
Allylic azidations



Carbocation mechanism



π-allyl mechanism



Au(I) allene

Org. Lett., **2012**, 768; Tet. Lett. **2013**, 2382; Eur. J. Org. Chem. **2015**, ASAP
Tet. Lett., **1986**, 227; Chem. Commun., **2014**, 1494

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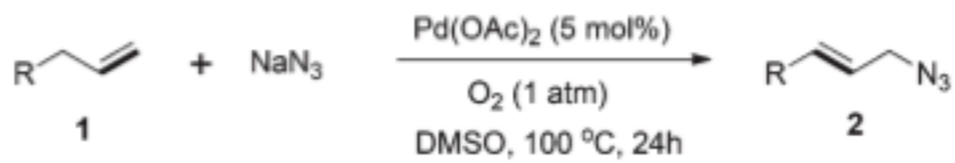
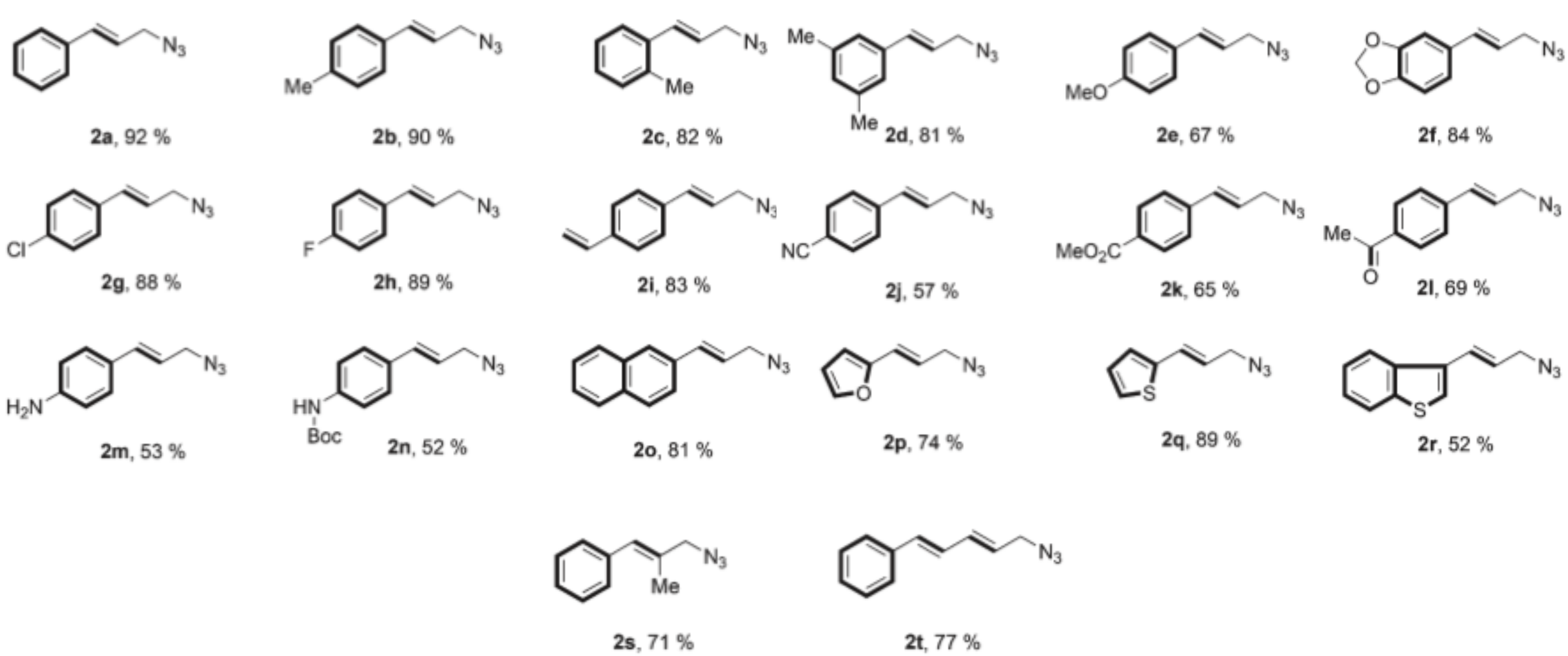
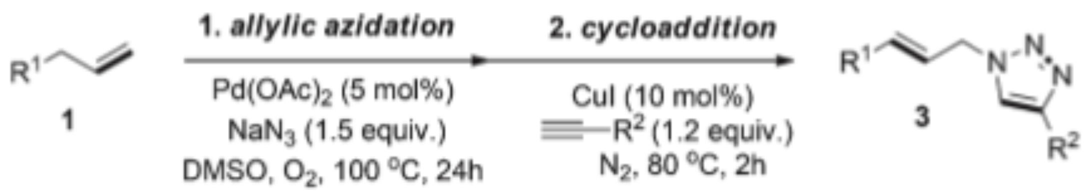
Pd-catalyzed allylic C-H azidation

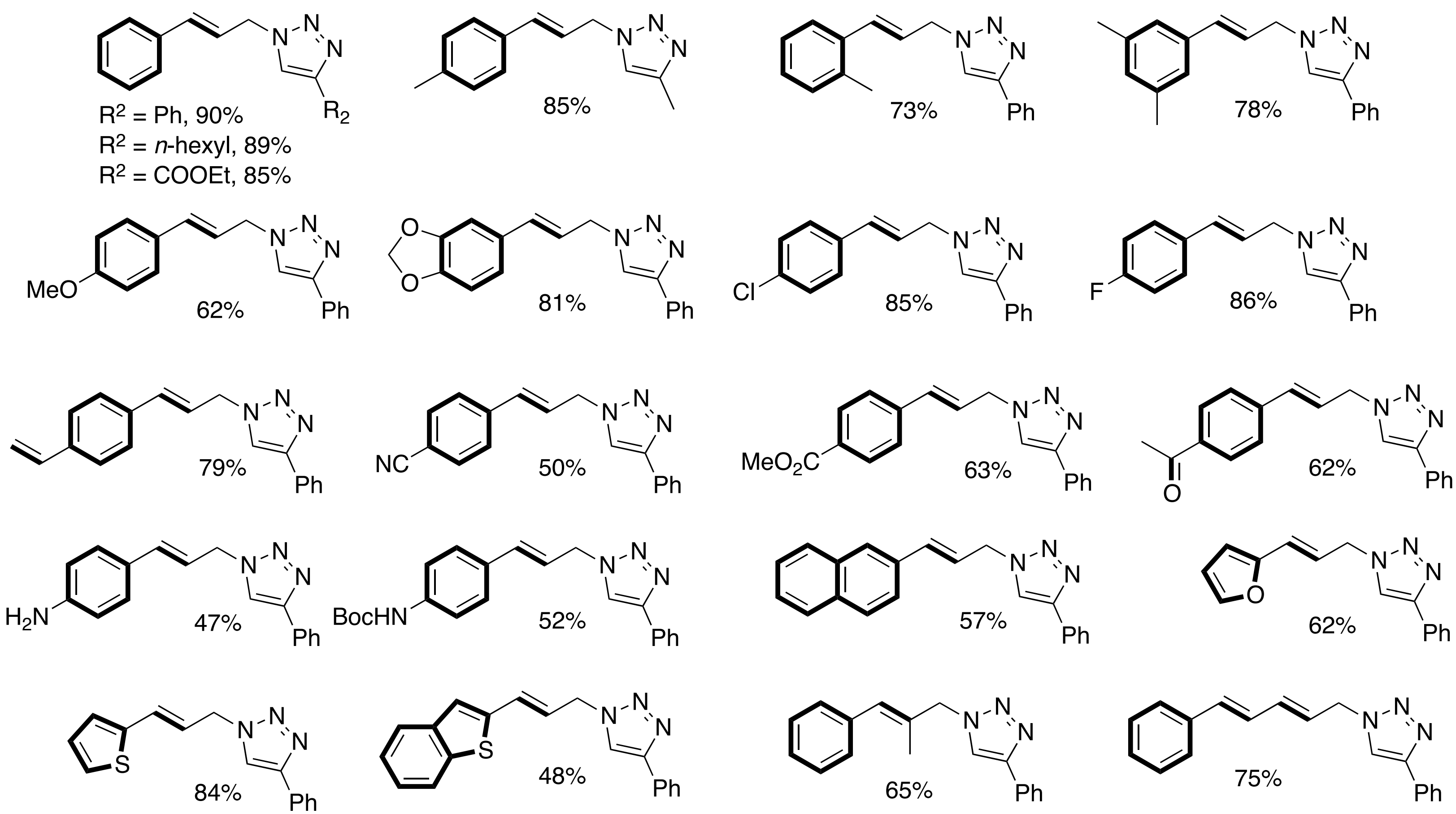




Org. Biomol. Chem., 2014, 12, 3340–3343

Pd-catalyzed allylic C-H azidation

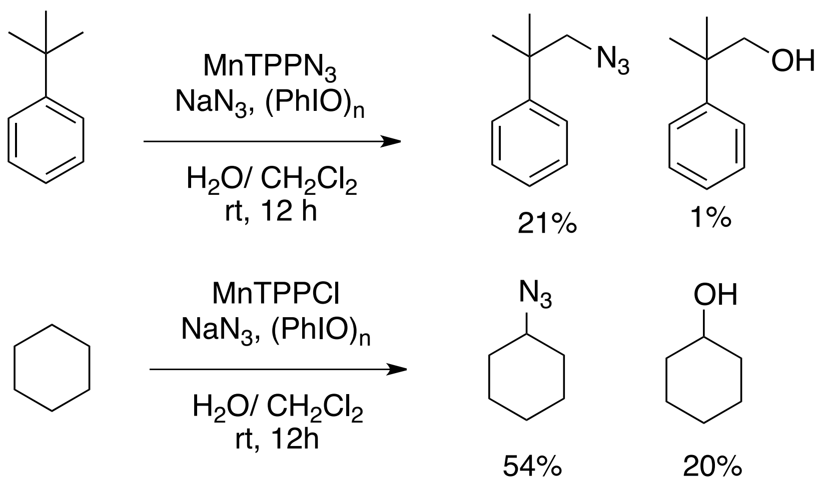




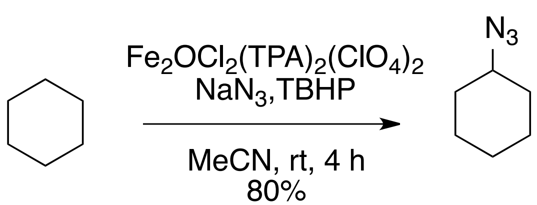
C_{sp3}-H azidation

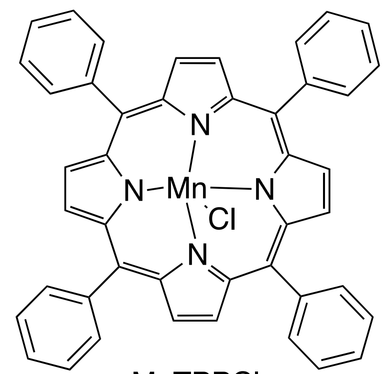
Transition metal C-H azidation

(1)

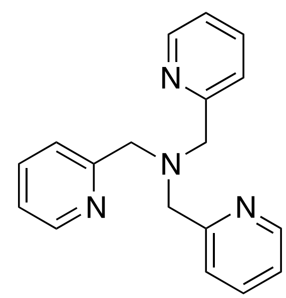


(2)





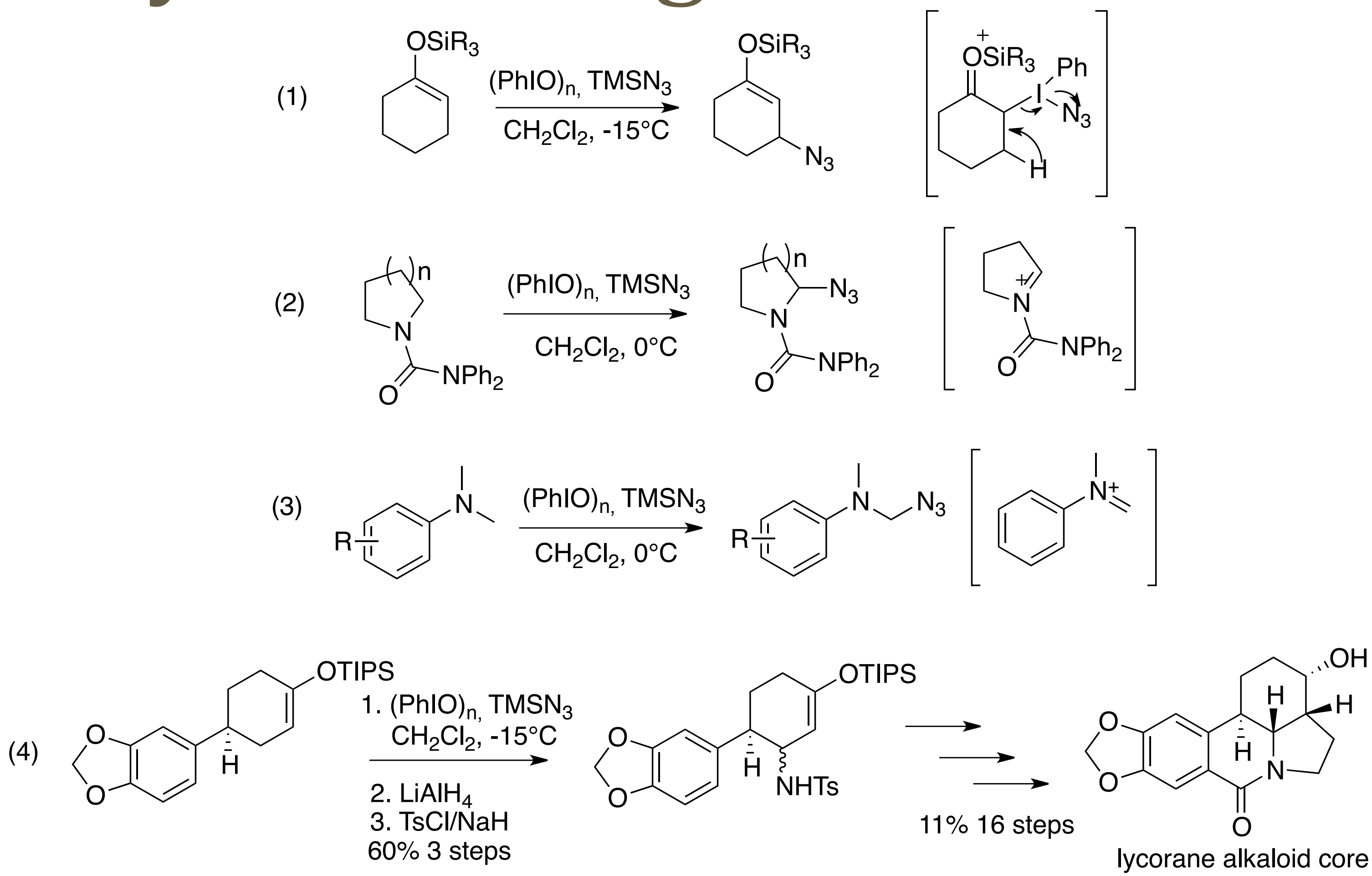
MnTPPCl



TPA

1. J. Org. Chem., **1983**, 48, 3277-3281
2. J. Am. Chem. Soc., **1993**, 115, 11328-11335

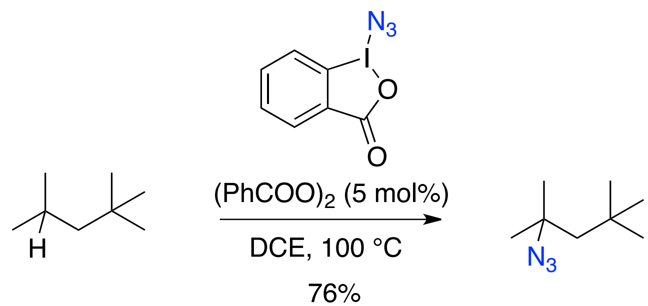
Early work: Magnus

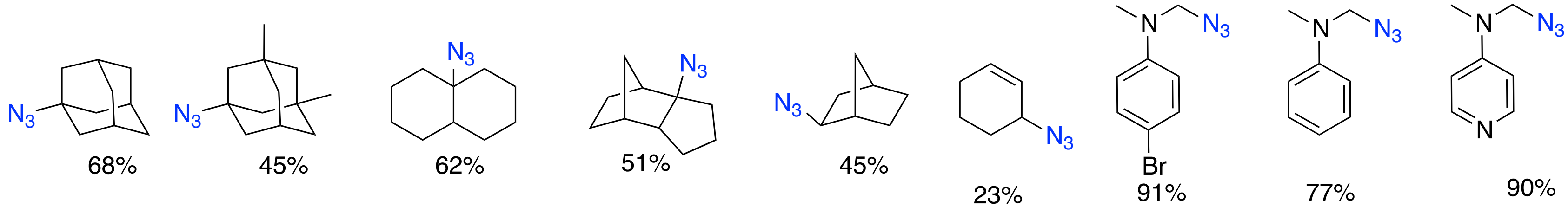


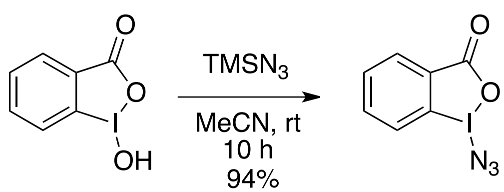
instability of $PhI(N_3)_2$ above 0°C

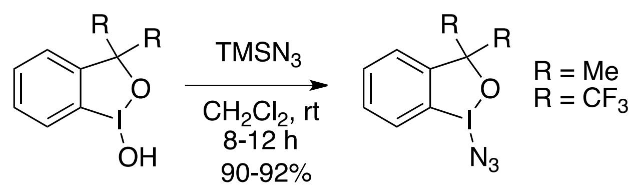
1. J. Am. Chem. Soc. **1992**, 767
2. J. Am. Chem. Soc. **1994**, 4301
3. Synthesis **1998**, 547
4. Tetrahedron **1999**, 13927
J. Am. Chem. Soc., **1998**, 12486

Zhdankin's Iodinanes





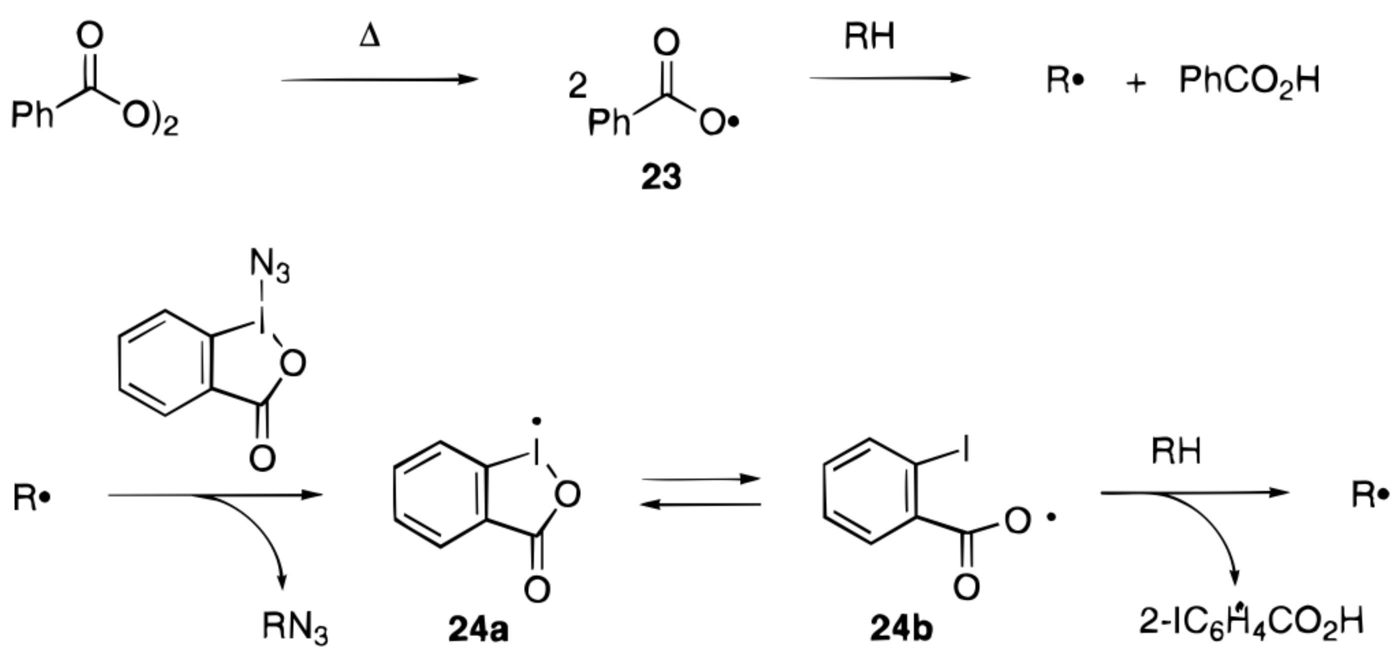




-thermally stable up to 130°C
-readily prepared
-crystalline solids

Tet. Lett. **1994**, 9677
Synlett, **1995**, 1081
J. Am. Chem. Soc. **1996**, 5192

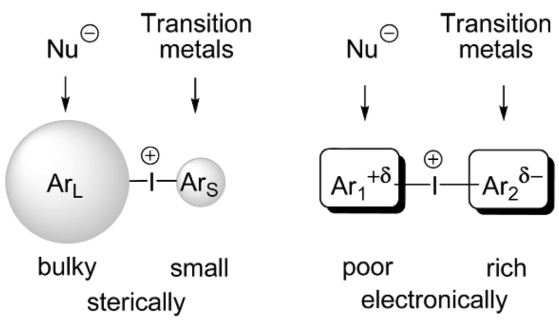
Mechanism



J. Am. Chem. Soc. **1996**, 5192

Hypervalent Iodine reagents

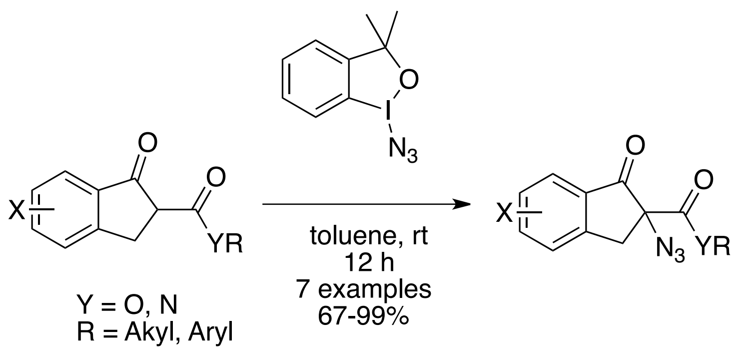
- Used in general oxidations of alcohols (IBX, DMP)
- Oxidative cleavage of diols ($NaIO_4$, DMP, $PhI(OAc)_2$)
- Halogenation/trifluoromethylation (Togni's Reagent, $PhIF_2$, $PhICl_2$)
- Equivalent to organohalide in transition metal-catalyzed coupling of aryl and alkynyl iodonium salts

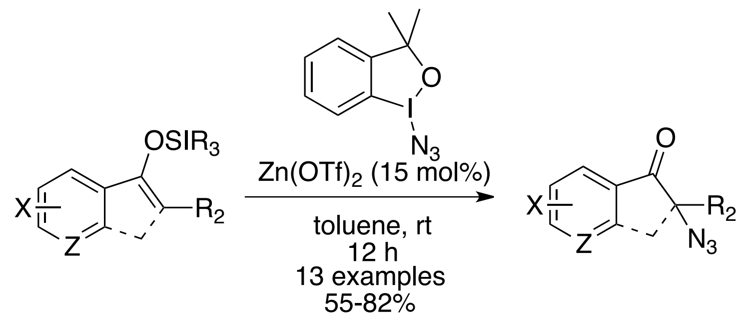


Nu = N_3 w/ TM catalysis

ARKIVOC **2009**, (i) 1-62

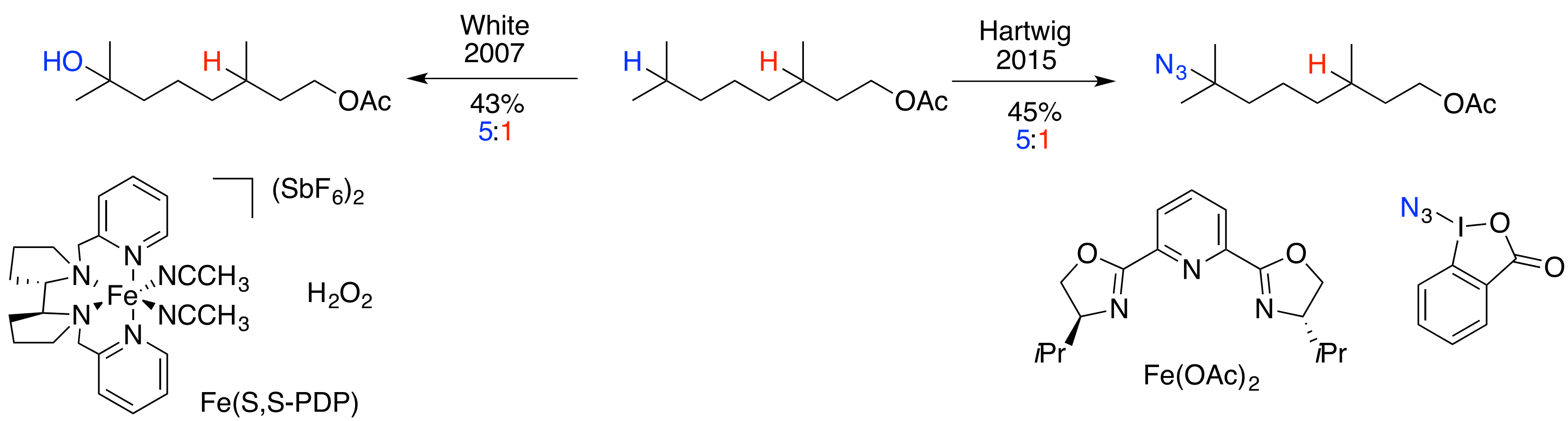
Azidation of activated C-H bonds



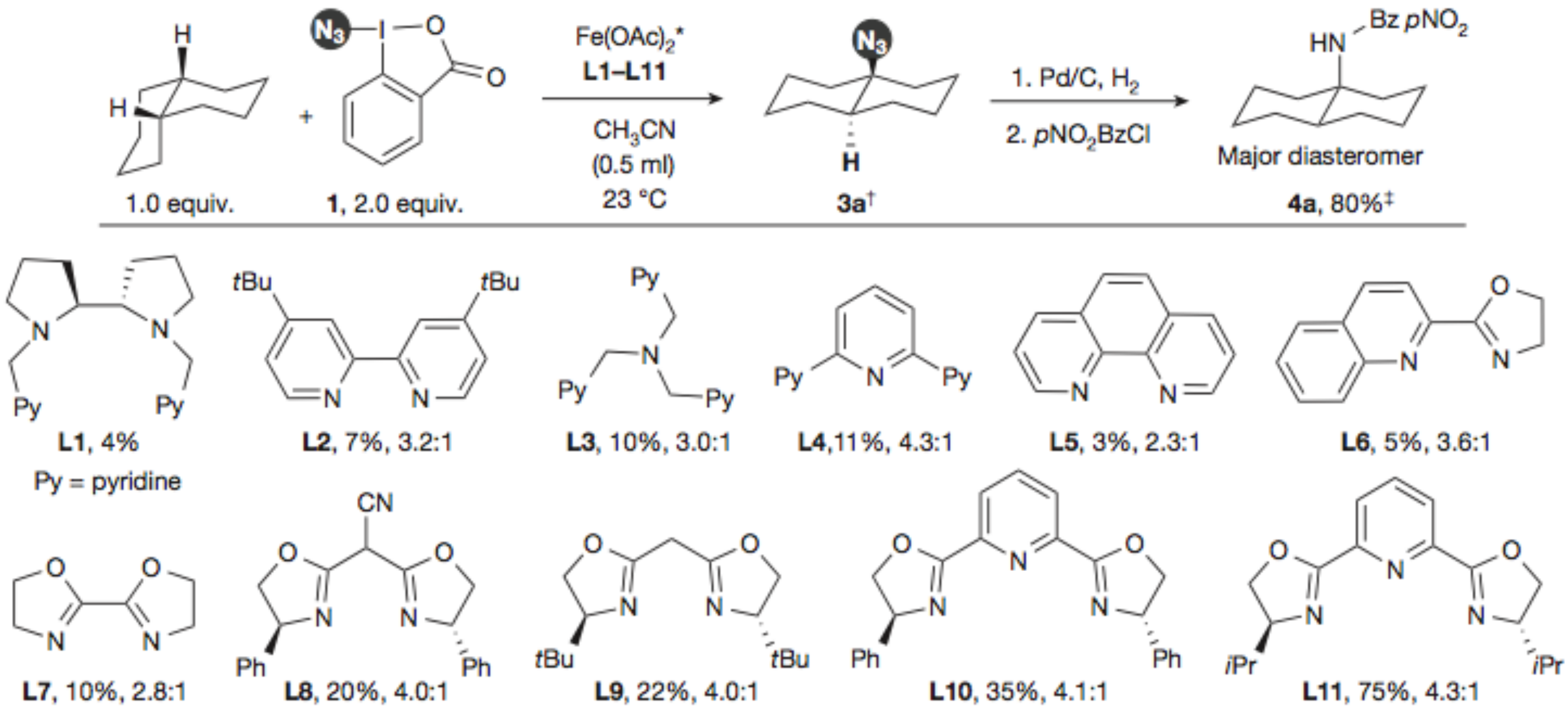


Org. Lett., **2013**, 3246

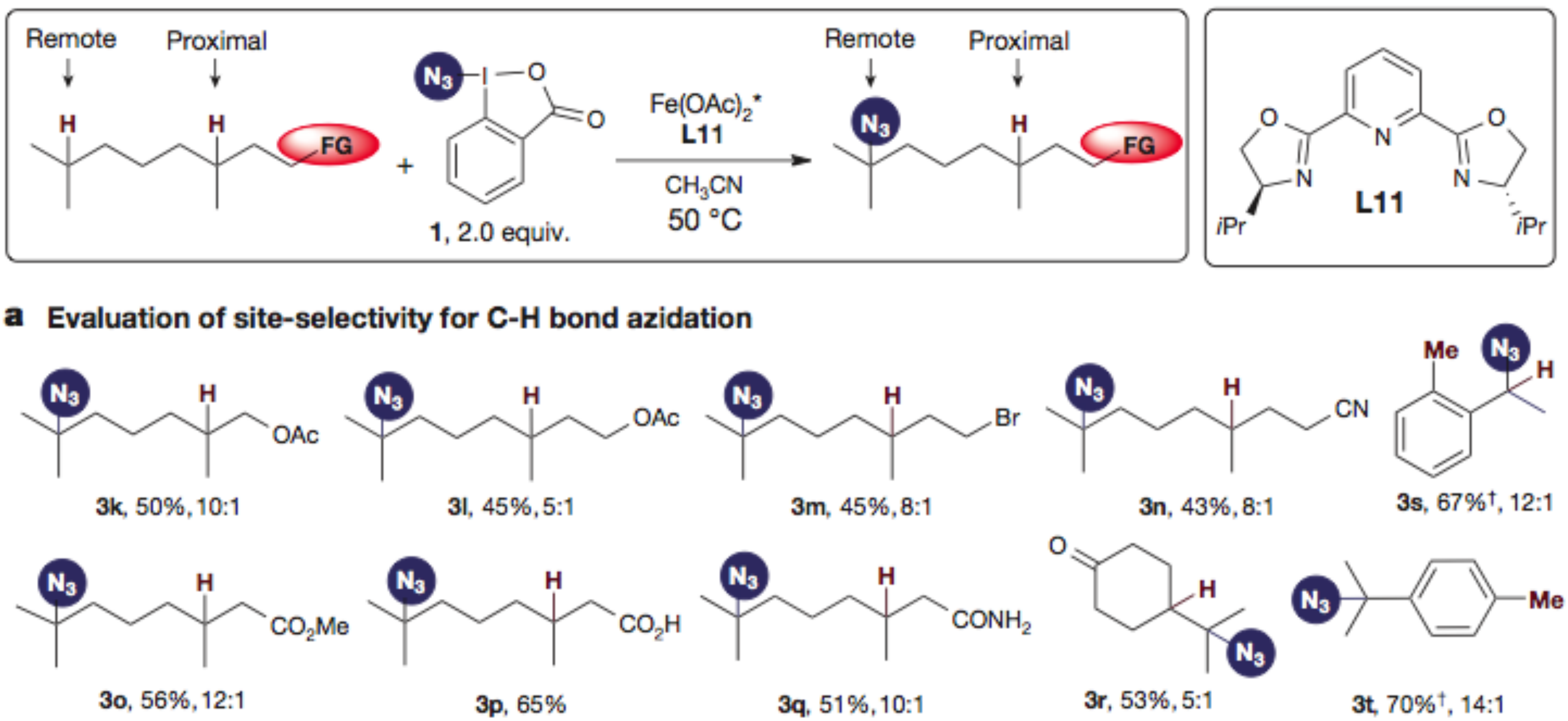
Late stage C_{sp3}-H azidation

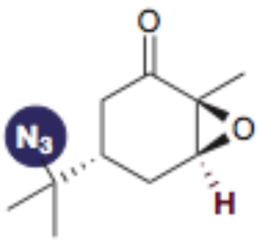


Azidation of C_{sp3} via C-H activation

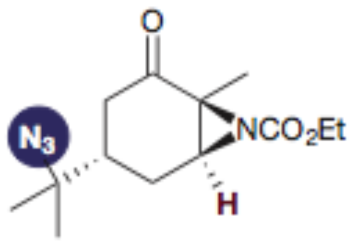


Site-selectivity

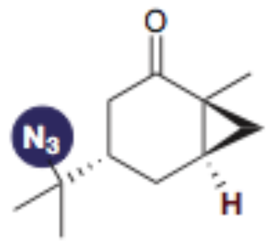




3u, 50%, 11:1:1
20%, 2:1:1‡

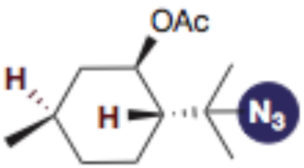


3v, 52%, 10:1:1
15%, 3:1:1‡

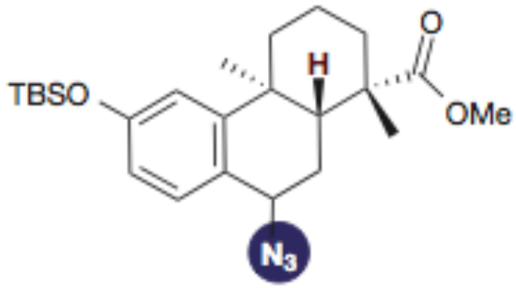


3w, 53%, 10:1:1
10%, 3:1‡

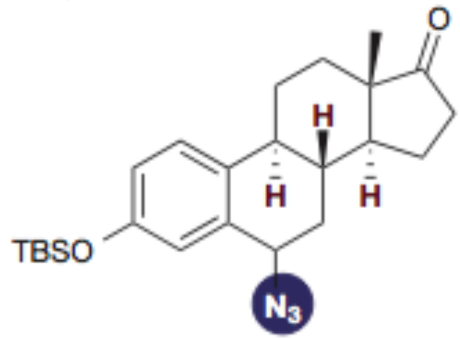
3b, 80%
10%, 1:1‡



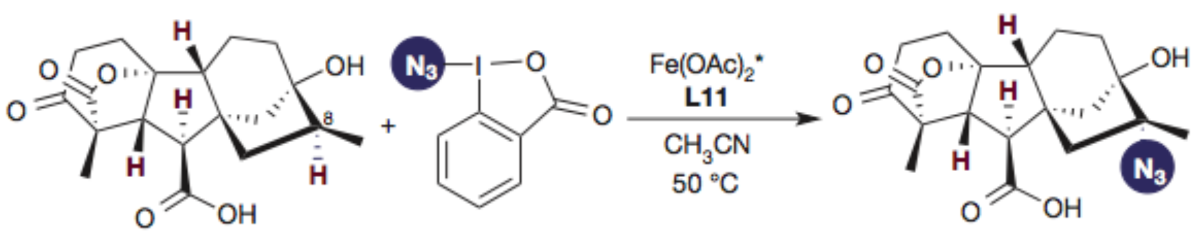
3x, 35%, 8:2:1
25%, 2:1:1‡



3y, 75%, 6:1†§
7%, 2:1‡



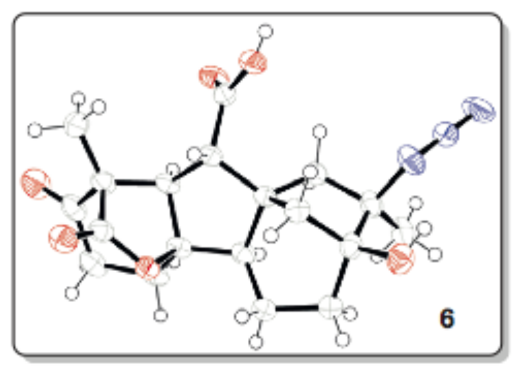
3z, 24%, 5:1†§
5%, 1:1‡



5, 6:1

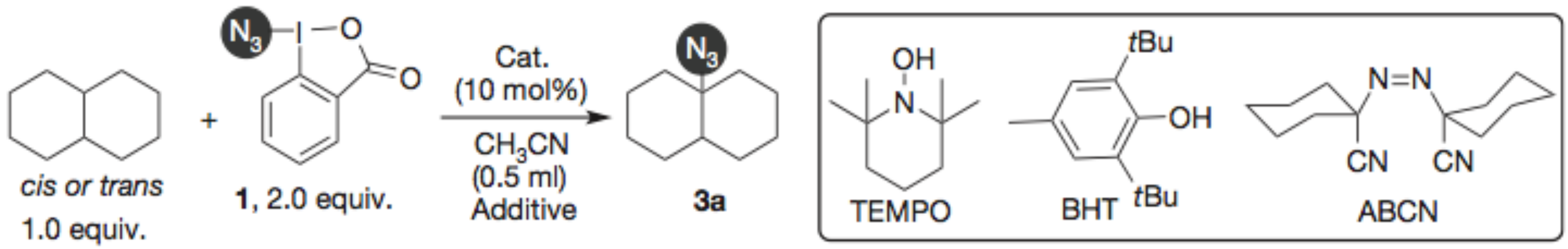
2.0 equiv.

6, 75%
15%‡‖



Yields compared to benzoyl peroxide initiated reaction

Some mechanistic insights



Entry	Substrate	Catalyst	Temperature (°C)	Additive	Yield (%)	Selectivity
1	*cis*	$Fe(OAc)_2$/**L11**	23	TEMPO*	3	NA
2	*cis*	$Fe(OAc)_2$/**L11**	23	BHT*	3	NA
3†	*cis*	$Fe(OAc)_2$/**L11**	80	NA	55	3.2
4†	*trans*	$Fe(OAc)_2$/**L11**	80	NA	43	3.2
5†	*cis*	BzOOBz	80	ABCN‡	40	1.7
6†	*trans*	BzOOBz	80	ABCN‡	33	1.7

Conditions: 10.0 mol% catalyst, *cis*- or *trans*-decalin (0.2 mmol, 1.0 equiv.) and **1** (0.4 mmol, 2.0 equiv.), 2 h. The yield and ratios of isomers were determined by gas chromatography analysis with dodecane as internal standard and not corrected for response factors of minor isomers. NA, not applicable.
* 1.0 equiv. was added.
† EtOAc was used as solvent.
‡ 1.0 mol% was added.

KIE = 5 cleavage of C-H bond is the turnover limiting step

Summary

- Applications of enzymatic C-H azidation
- New methods for the formation of C-N_3 bonds through direct C-H activation
  - Aryl
  - Allylic
  - C_{sp3}-H bond azidation
- Further development of chemistry to access photoaffinity labels in high yields

Future Directions

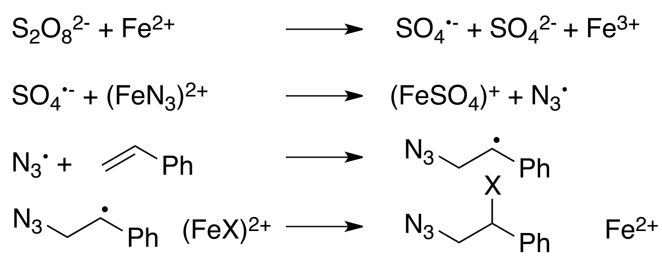
- Relatively new field open to expansion of scope
- Insights into catalytic mechanisms
- Applications in total synthesis
- The next chapter in “oxidase” chemistry

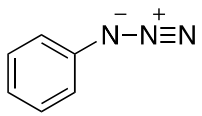
Thanks

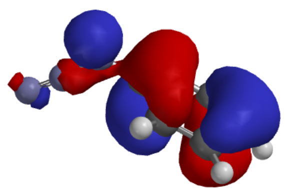
- Dr. Peter Wipf
- Wipf group past and present

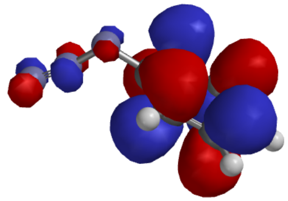
Questions

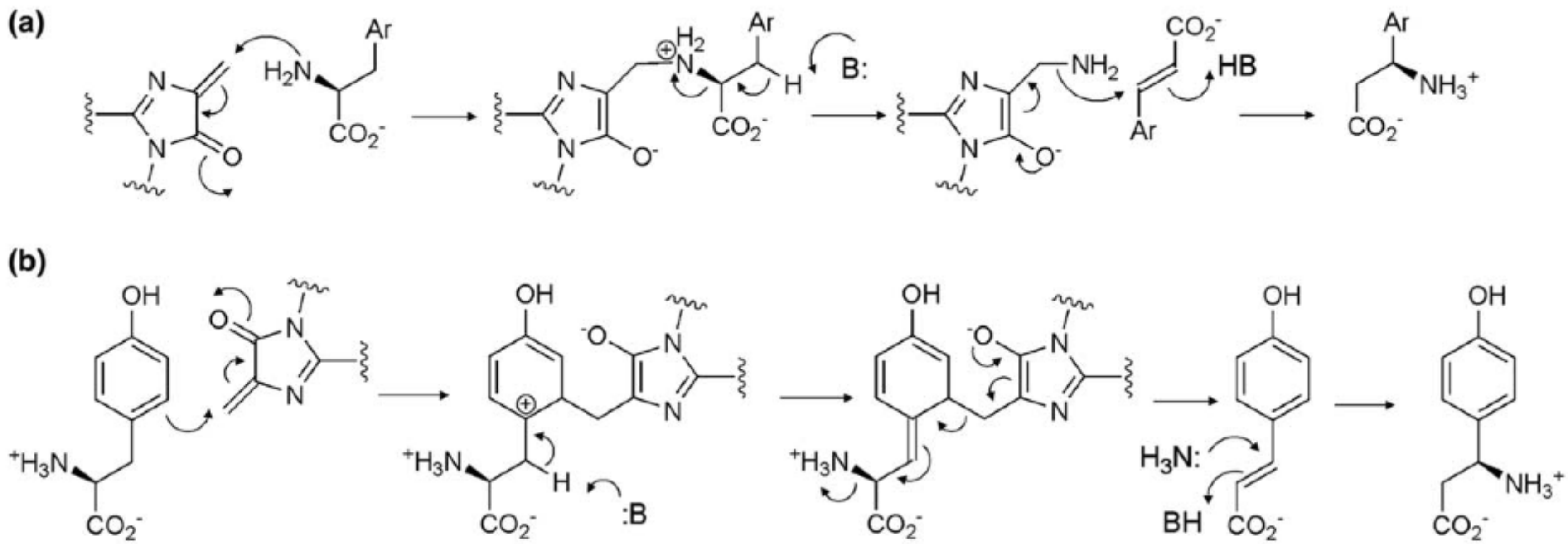
Azides and transition metals











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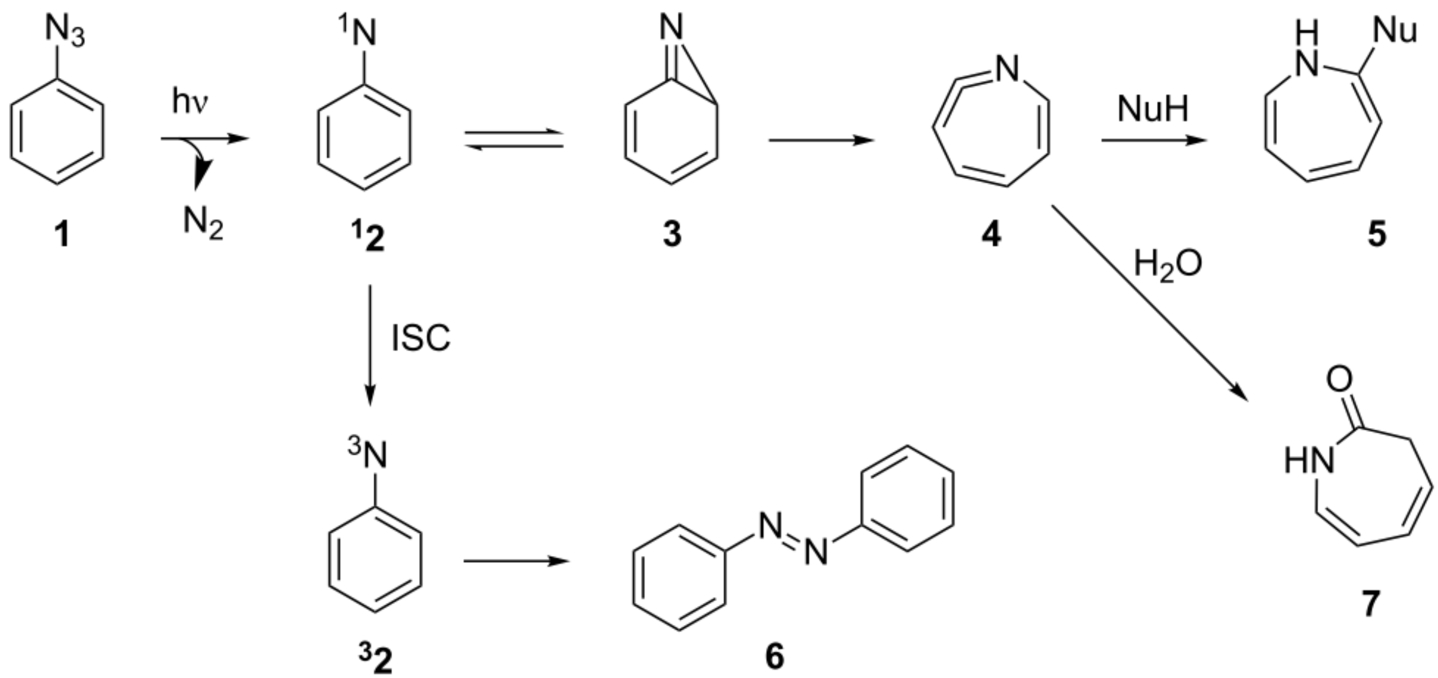

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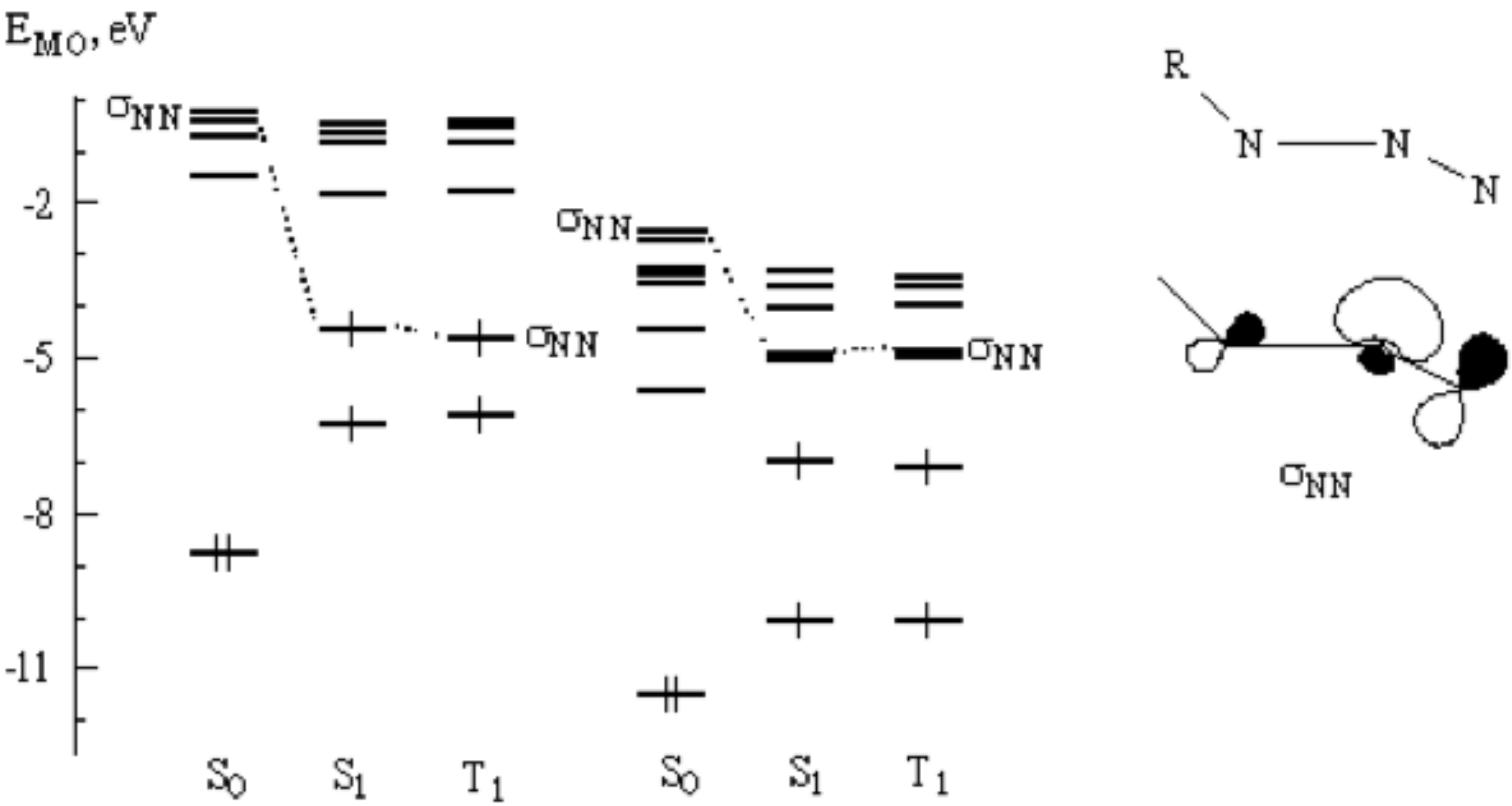

7 Photoactive

8 Nonphotoactive