Wipf group current literature

Manganese-Catalyzed Late-Stage Aliphatic C−H Azidation

J. Am. Chem. Soc. 2015, 137, 5300−5303

Xiongyi Huang, Tova M. Bergsten, and John T. Groves

Department of Chemistry, Princeton University

Zhizhou Yue 05302015

1

Organic azides:

1 Convenient access to a variety of functionalities such as amines, imines, amides, and triazoles.

2 Broad applications of azide−alkyne Huisgen cycloaddition and Staudinger ligation in “click” chemistry.

3 In materials science, azide-based transformations are widely used for surface modification, macromolecular engineering, and synthesis of novel polymeric materials.

Numerous azidation reactions:
Angew. Chem., Int. Ed. 2005, 44, 5188(Review)

For direct C−H azidation through C−H activation:
James Johnson Fronties in Chemistry, Mar 14 2015

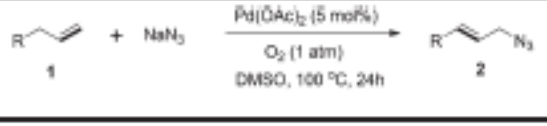
2

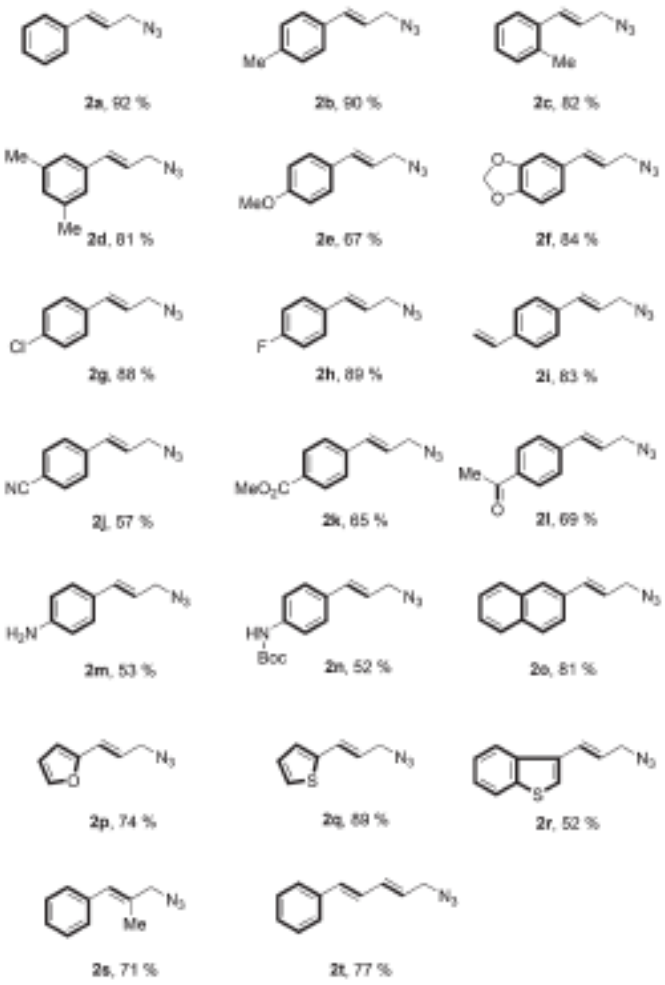
Direct aliphatic C−H azidation reactions

(1) **IN3**: **only for simple hydrocarbons (harsh reaction conditions and/or instability)**

Reaction conditions:
alkenes (0.5 mmol),
NaN3 (0.75 mmol),
Pd(OAc)2 (5 mol%),
2.5 mL DMSO,
O2 (1 atm),
100 °C, 24 h.

Table 1 Pd-catalyzed allylic azidation of alkenes with NaN_3[a,b]

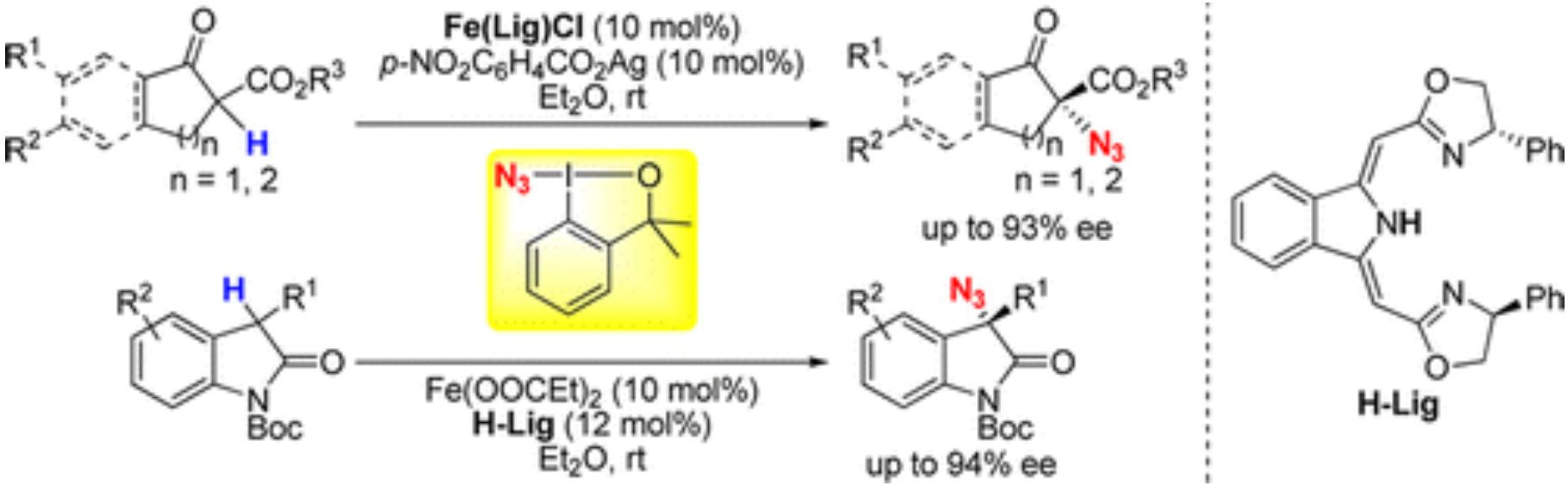


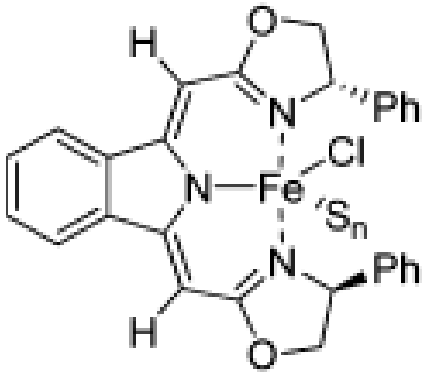


[a] Reaction conditions: alkenes (0.5 mmol), NaN_3 (0.75 mmol), $Pd(OAc)_2$ (5 mol%), 2.5 mL DMSO, O_2 (1 atm), 100 °C, 24 h. [b] Isolated yields are given.

Org. Biomol. Chem. 2014, 12, 3340

(2) Allylic, Pd-catalyzed C−H azidation method with NaN3; allylic C−H bonds;

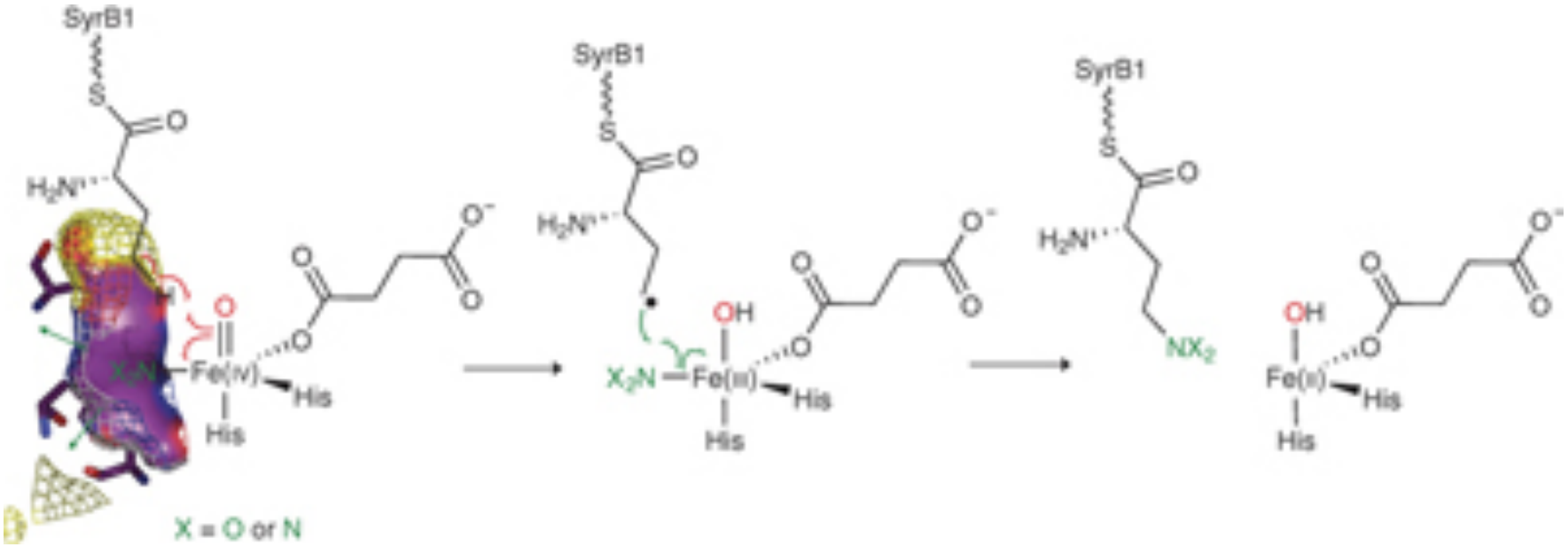




J. Am. Chem. Soc. 2013, 135, 5356

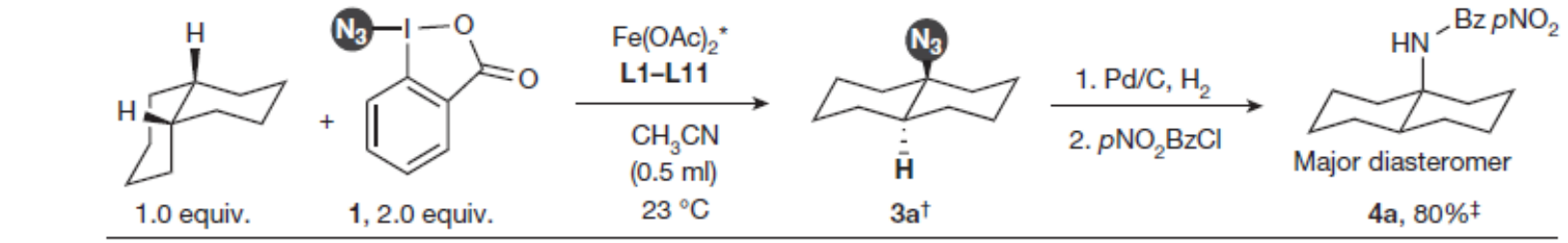
4

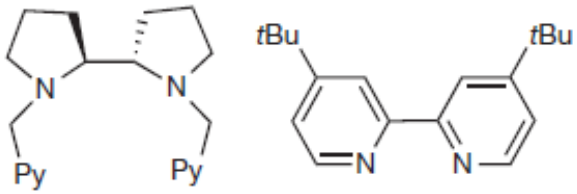
(3) Enantioselective C−H azidation reaction of β-keto esters with an iron boxim catalyst and an azidoiodinane. β-keto ester α-positions; Yield 20 %



Nat. Chem. Biol. 2014, 10, 209.

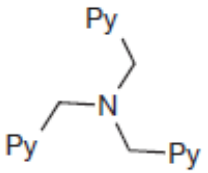
(4) azidation of tertiary and benzylic C−H bonds using an iron catalyst and an azidoiodinane reagent.



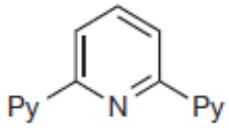


L1, 4%
Py = pyridine

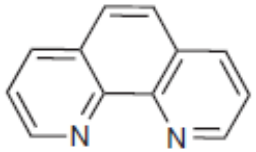
L2, 7%, 3.2:1



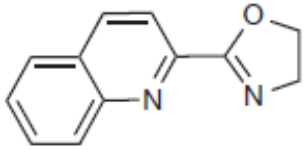
L3, 10%, 3.0:1



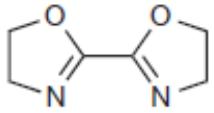
L4,11%, 4.3:1



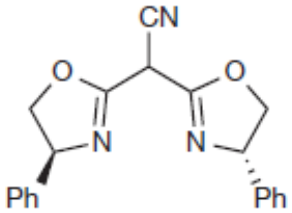
L5, 3%, 2.3:1



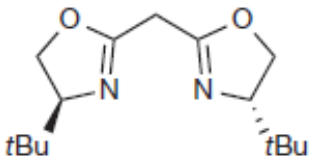
L6, 5%, 3.6:1



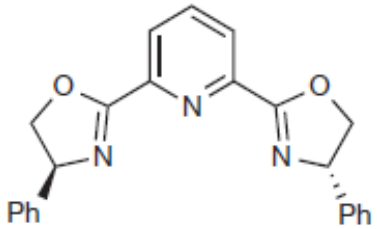
L7, 10%, 2.8:1



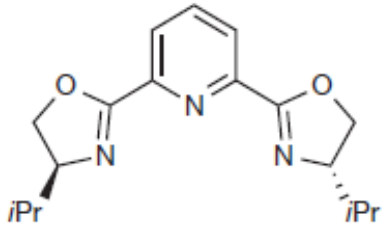
L8, 20%, 4.0:1



L9, 22%, 4.0:1



L10, 35%, 4.1:1



L11, 75%, 4.3:1

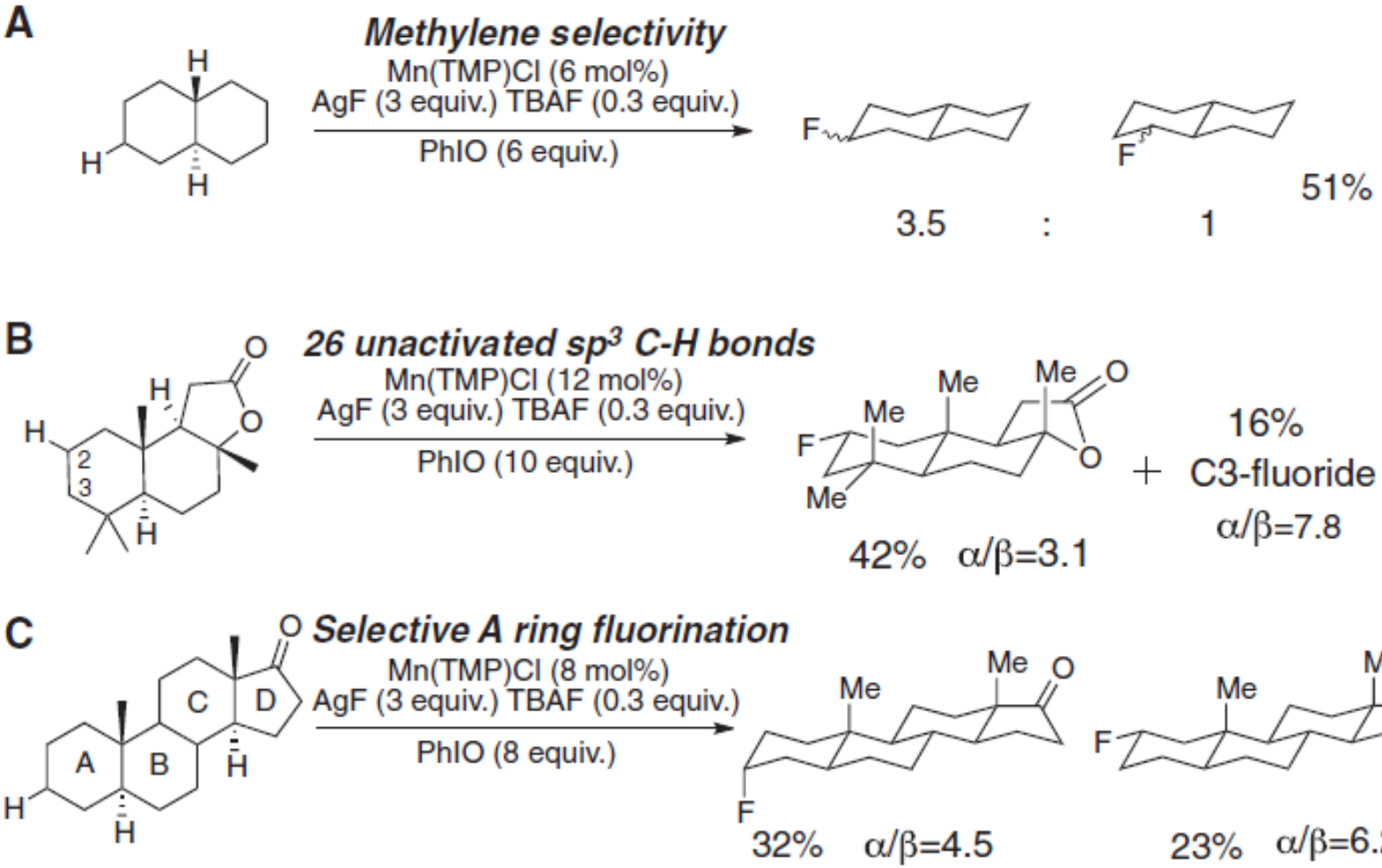
Nature 2015, 517, 600.

This work

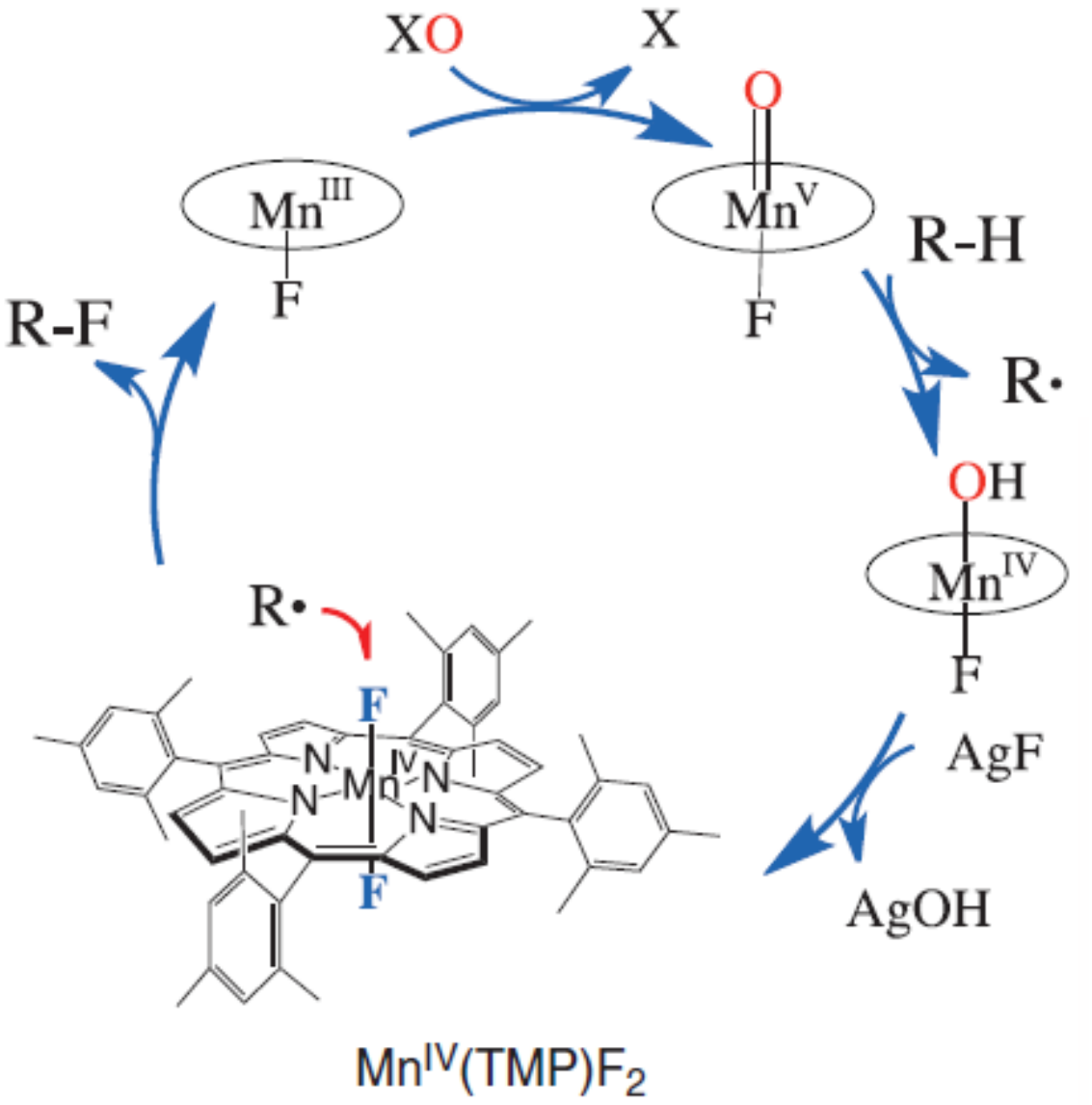
Practical and complementary manganese catalyzed C−H azidation reaction that is applicable to secondary, tertiary, and benzylic C−H bonds.

The method uses easily handled aqueous sodium azide as the azide source.

Oxidative Aliphatic C-H Fluorination with Fluoride Ion Catalyzed by a Manganese Porphyrin



Science 2012, 337, 1322.
J. Am. Chem. Soc. 2014, 136, 6842.



Unusually low barrier to fluorine atom transfer from manganese(IV)-F Species. Manganese porphyrins were capable of mediating low-conversion C−H azidation of simple hydrocarbons along with oxygenation products.

Idea: Replacing fluoride with a suitable azide source might promote the more efficient formation of an analogous MnIV−N3 intermediate, which would trap the substrate radical and form the desired C−N3 bond.

Scheme 1. Concept of Mn-Catalyzed C−H Azidation

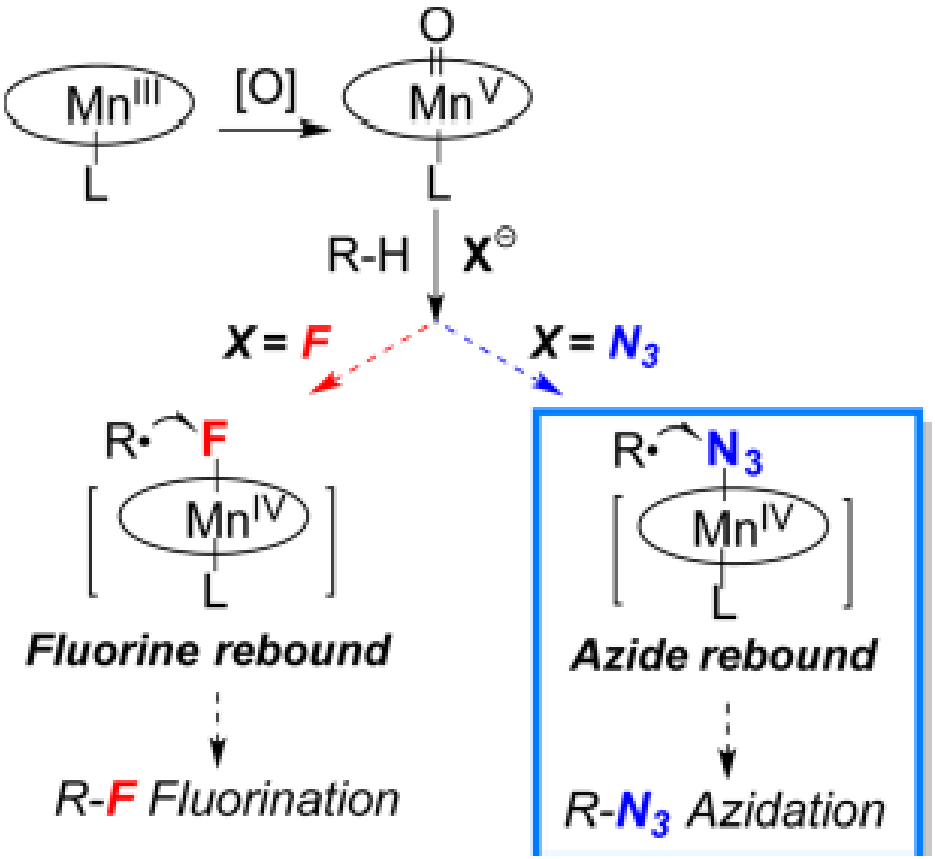
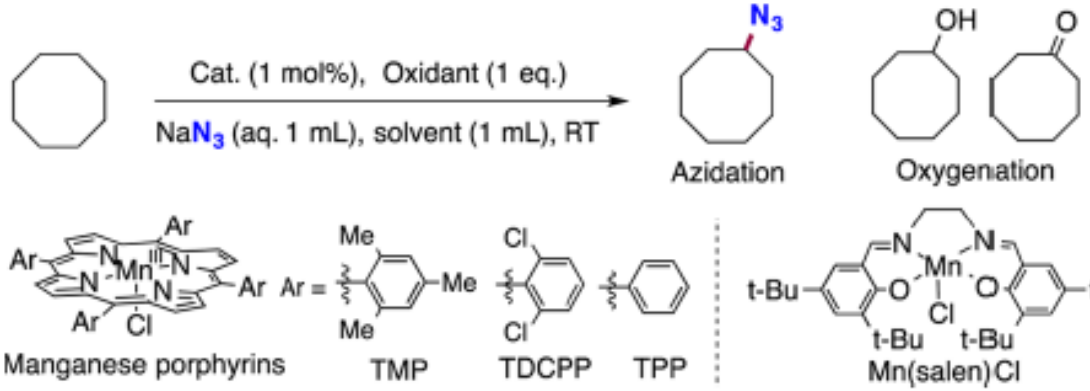


Table 1. Reaction Optimization with Cyclooctane



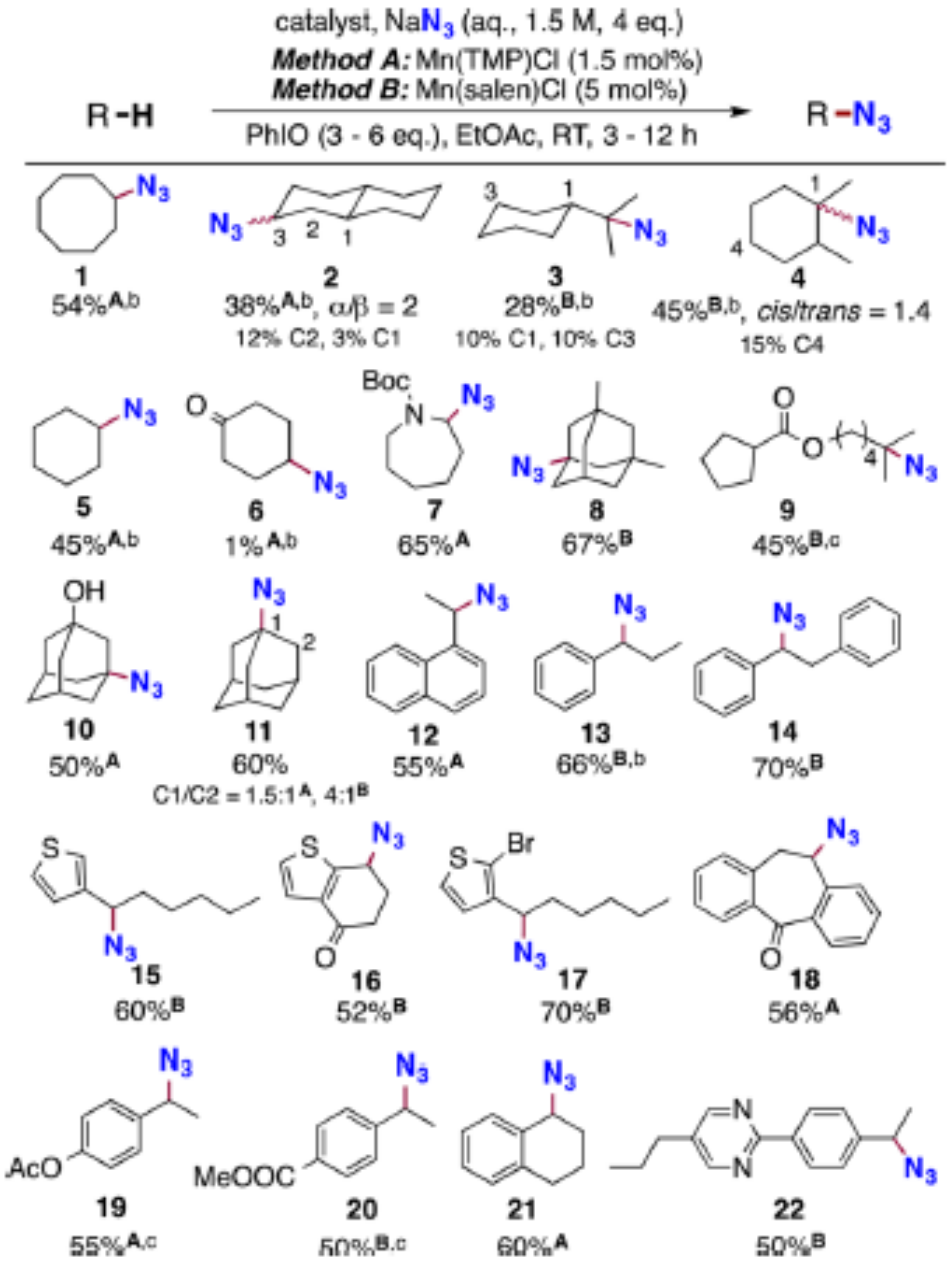
	catalyst	NaN_3 (M)	solvent	yield (%)	Az/Ox
1	Mn(TPP)Cl	6.3	CH_2Cl_2	3	1:1
2	Mn(TMP)Cl	6.3	CH_2Cl_2	26	5:1
3	Mn(TDCPP)Cl	6.3	CH_2Cl_2	18	2:1
4	Mn(TMP)Cl	6.3	$PhCF_3$	20	1.5:1
5	Mn(TMP)Cl	6.3	acetone	3	1:2
6	Mn(TMP)Cl	6.3	benzene	20	2:1
7	Mn(TMP)Cl	6.3	EtOAc	25	4:1
8	Mn(TMP)Cl	1.5	EtOAc	29	5.3:1
9	Mn(TMP)Cl	1.5	EtOAc	55[b]	3.9:1
10	Mn(salen)Cl	1.5	EtOAc	51[b,c]	3.7:1
11	Mn(TMP)Cl	1.5	EtOAc	53[b,d]	3.6:1

[a]Yields, based on starting substrate, and product distributions were determined by GC-MS. [b]4 equiv of PhIO were added sequentially. [c]5 mol % catalyst loading. [d]Reaction was carried out under air.

2. 3% to26% from Mn(TPP)Cl to Mn(TMP)Cl
3-7: CH2Cl2 to ethyl acetate
8. Decreasing the azide concentration led to a slightly higher yield;
9. More oxidant further increased the yield(4 eq PhIO);
10. Manganese salen-type Jacobsen catalysts (5%)
11. under air :OK

No manganese catalysts, no azidation products

wide range of substrates



1 NO PTC

2 Amide(7), ester(9, 19,20), ketone (16,18), carbamate(7), tertiary alcohol(10), heteroaryl groups thiophene(15-17), and pyrimidine(22) were well tolerated. 3 The reaction of trans-decalin with the bulky Mn (TMP)Cl catalyst afforded mostly secondary azidation products (2-4). 4 The efficiency of C−Hctivation was significantly affected by the electronic properties of the substrate. (5 and 6). 5 The regio-selectivity of C −H activation could be regulated by the electronic and steric properties of the ligand(11). 6 adamantane(8, 10), dibenzocycloheptane (18), tetrahydronaphthalene (21), and other benzylic position

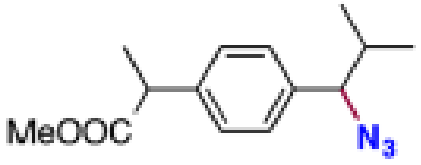
Substrate scope of Mn-catalyzed C−H azidation.

(a)Conditions: catalyst (method A: 1.5 mol % Mn(TMP)Cl; method B: 5 mol % Mn(salen)Cl), substrate (0.6 mmol), 1.5 mL of NaN3 (aq., 1.5 M, 4 equiv), 1 mL of EtOAc, 23 °C. PhIO (3−6 equiv) was added in portions (0.8−1.0 equiv PhIO each portion). The reaction was monitored by TLC, GC-MS or LC-MS. Isolated yields of major products are reported unless notified otherwise. Azide to oxygenated product ratios were 2−4:1.

(b)Yields were determined relative to starting material by GC-MS.

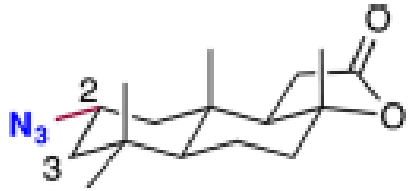
(c)Methyl acetate was used as solvent.

Application in more complex bioactive molecules

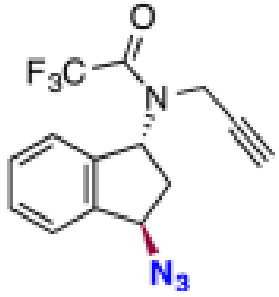


23
N_3-ibuprofen methyl ester
67%[B,a,b]

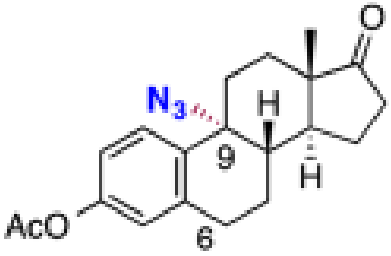
24
pregabalin derivative
60%[A]



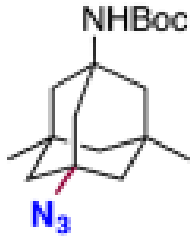
25
N_3-sclareolide
57%[A,b] (α/β = 7.5)



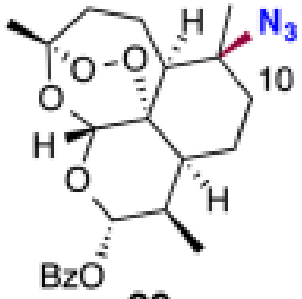
26
N_3-NTFAc-rasagiline
45%[B,a]



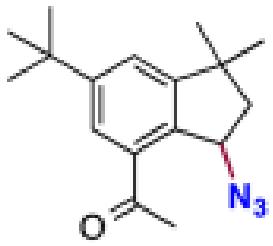
27
N_3-estrone acetate
38%[B,a,b] (+ 18% diazidation)



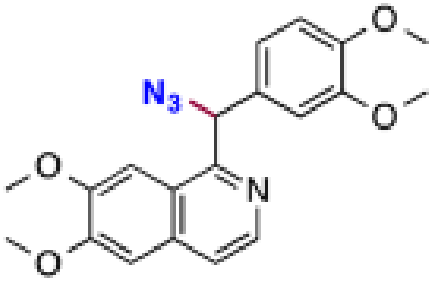
28
N_3-NHBoc-memantine
47%[B,a]



29
N_3-artemisinin-OBz
20%[B,a,b]



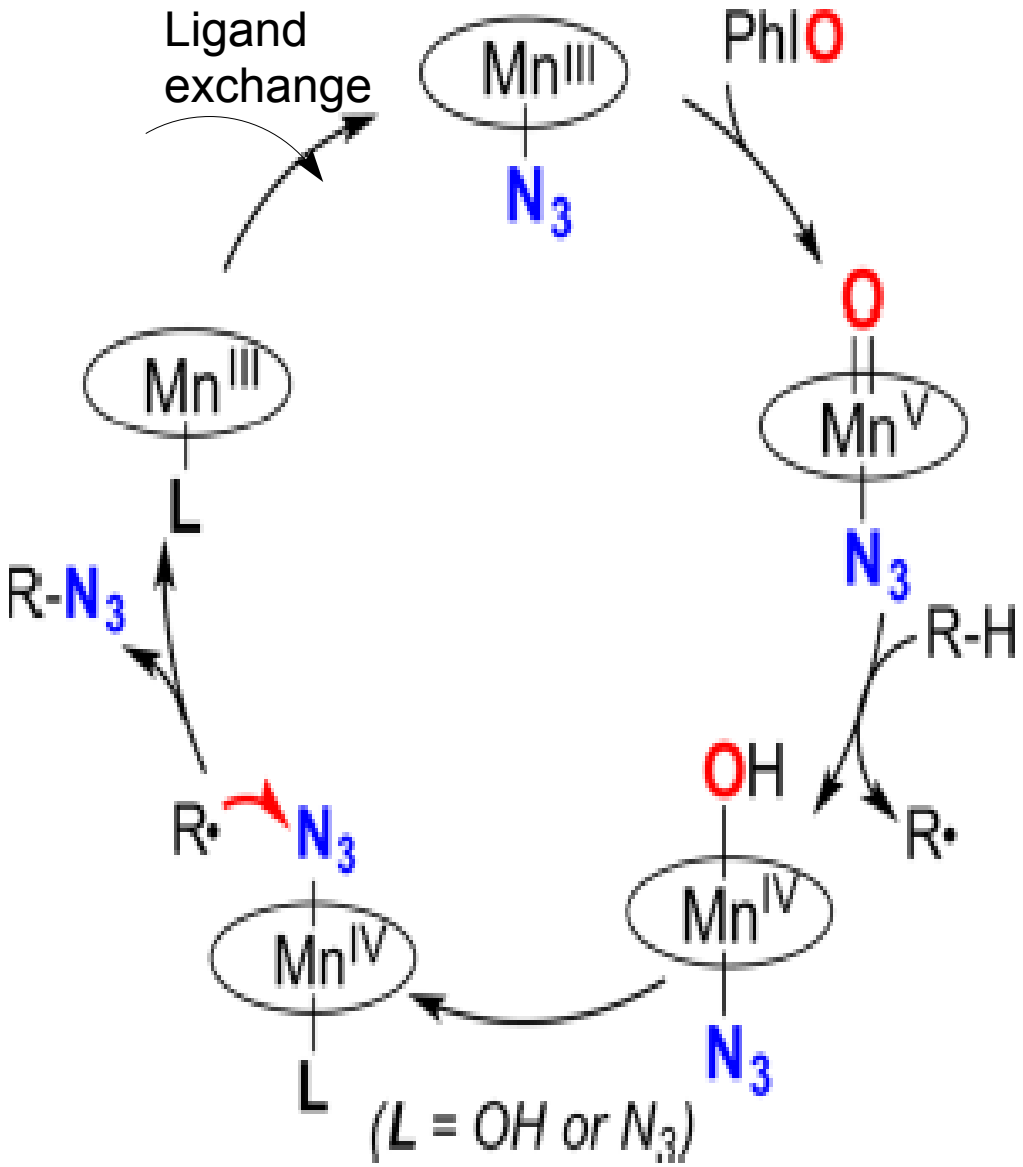
30
N_3-celestolide
74%[B,a]



31
N_3-papaverine
60%[B,a]

23, two benzylic Position; 24. two a-position; 25. 2 and 3. 2nd H and tertiary H and ester a-position H
26, two benzylic Position; 24 and 26; 27. 6,9, two H, ketone a-position; 29 different tertiary H
30 benzylic H and ketone a-H

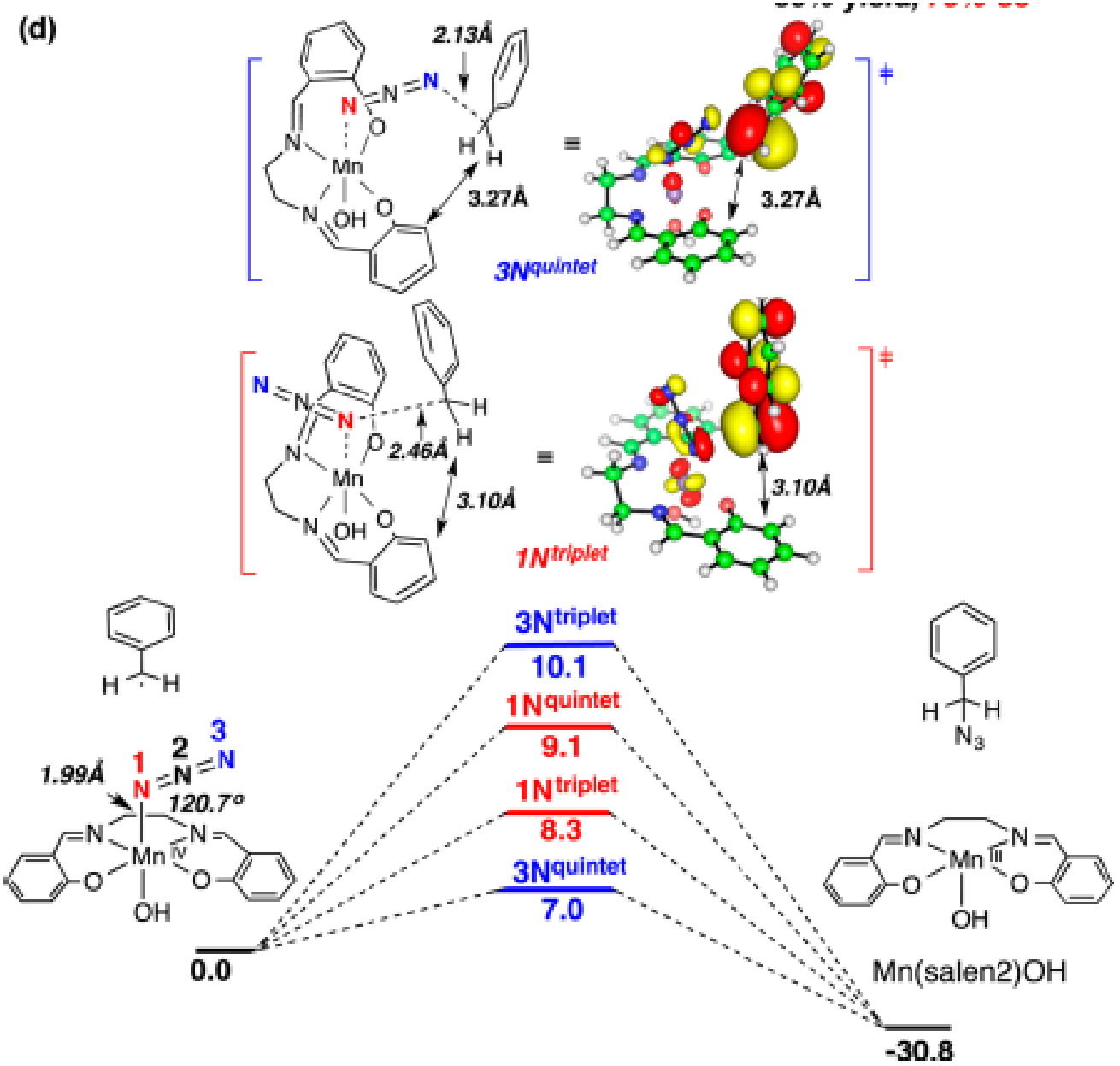
Reaction Mechanism



1, Ligand exchange; Mn(TMP)Cl with NaN3 to form Mn(TMP)N3
2 PhIO oxidation (resting Mn(III) catalyst to the hydrogen-abstracting oxoMn(V) intermediate
3 Hydrogen abstraction (substrate radical formed)
4 possible trans-diazidoMn(IV)
5 C−N3 bond formation(radical captured by Mn(IV)−N3 intermediate); catalyst regeneration

15

Reaction Mechanism



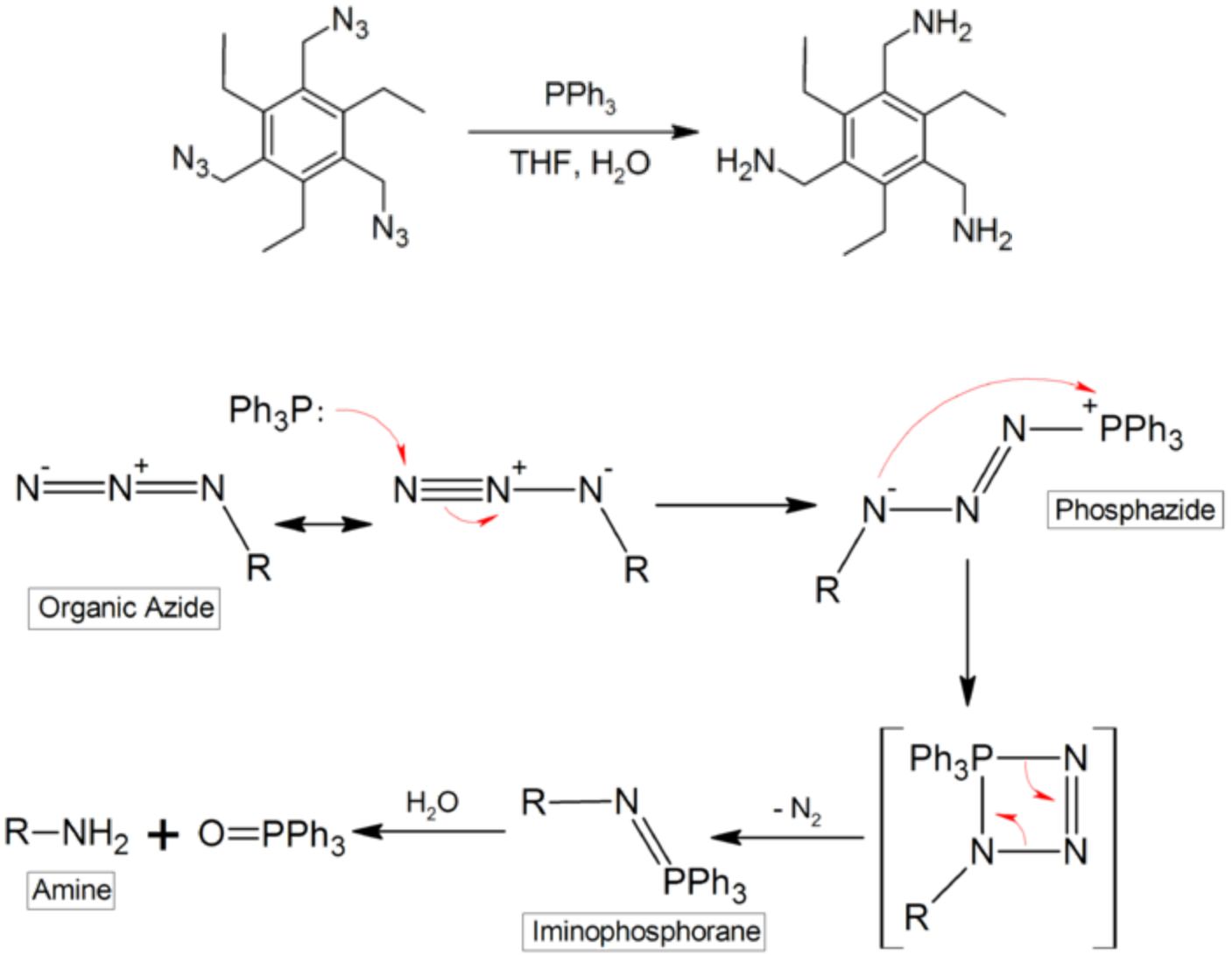
16

Conclusion

- A facile and convenient manganese-catalyzed aliphatic C−H azidation reaction.
- The easily handled aqueous NaN3 solutions as the azide source and operationally simple.
- Applications in organic synthesis, chemical biology and drug discovery(late stage azidation of several bioactive molecules).
- Initial high enatioselectivity with chiral manganese salen catalyst,
- Introduction other pseudohalogen functional groups to molecules via manganese-catalyzed C −H activation.

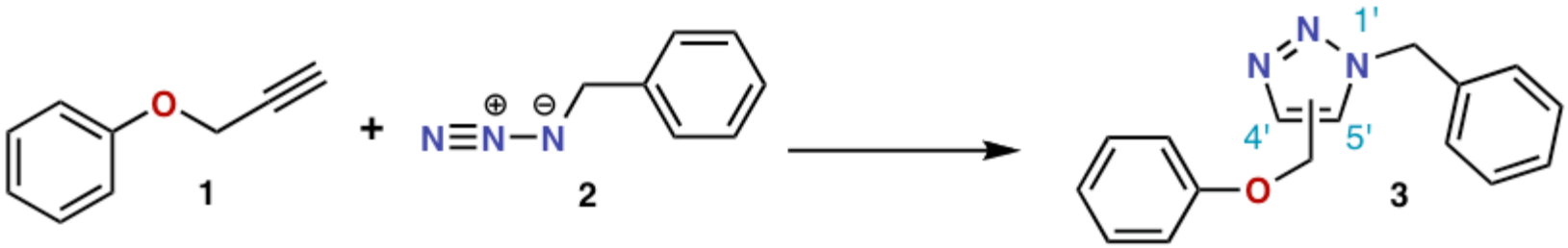
Thank You

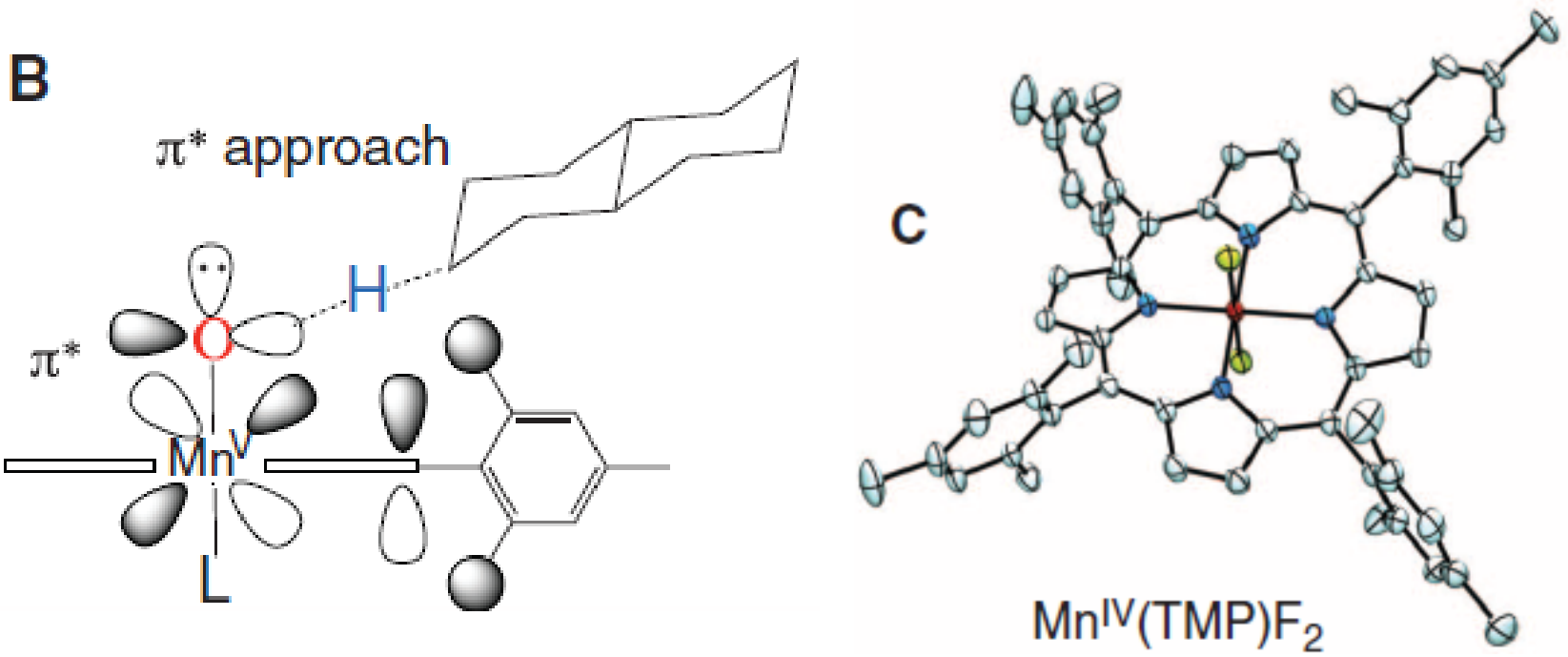
- Staudinger ligation



- azide−alkyne Huisgen cycloaddition

  1,3-dipolar cycloaddition between an azide and a terminal or internal alkyne to give a 1,2,3-triazole.





Science 2012, 337, 1322

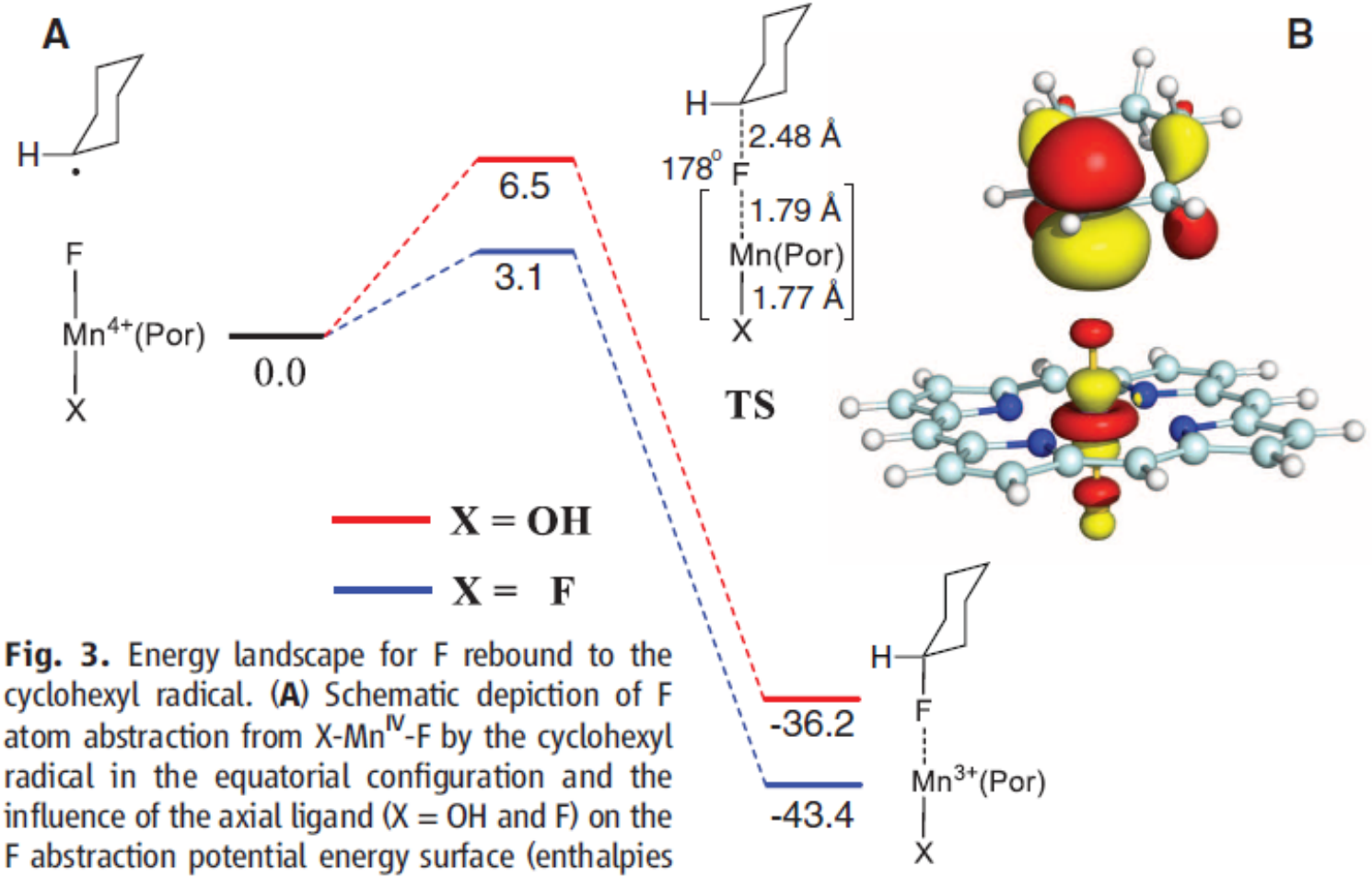


Fig. 3. Energy landscape for F rebound to the cyclohexyl radical. (**A**) Schematic depiction of F atom abstraction from X-Mn^{IV}-F by the cyclohexyl radical in the equatorial configuration and the influence of the axial ligand (X = OH and F) on the F abstraction potential energy surface (enthalpies in kilocalories per mole at 298 K). Bond distances shown are calculated for X = F. (**B**) Frontier orbital depiction of the transition state (TS) for F transfer.

Science 2012, 337, 1322

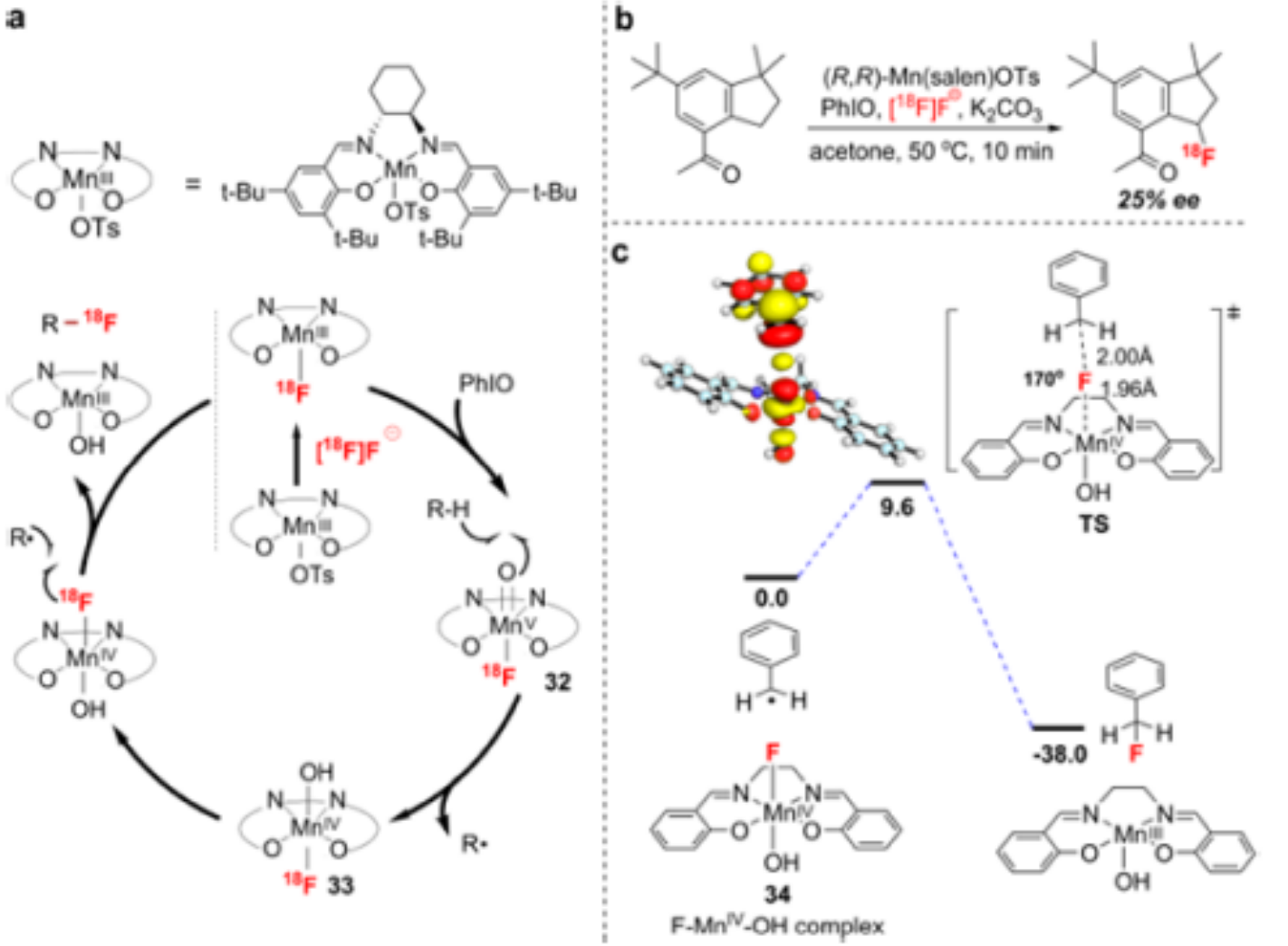


Figure 5. (a) Proposed mechanism for ^{18}F labeling of benzylic C–H bonds catalyzed by a manganese salen catalyst. (b) Detection of enantioselectivity of labeling products of celestolide by chiral radio-HPLC analysis. (c) Energy landscape of fluorine transfer from F–Mn^{IV}–OH intermediate (34) to a benzyl radical.

J. Am. Chem. Soc. 2014, 136, 6842−6845