nature chemistry

ARTICLES

PUBLISHED ONLINE: 8 JULY 2012 | DOI: 10.1038/NCHEM.1385

Guided desaturation of unactivated aliphatics

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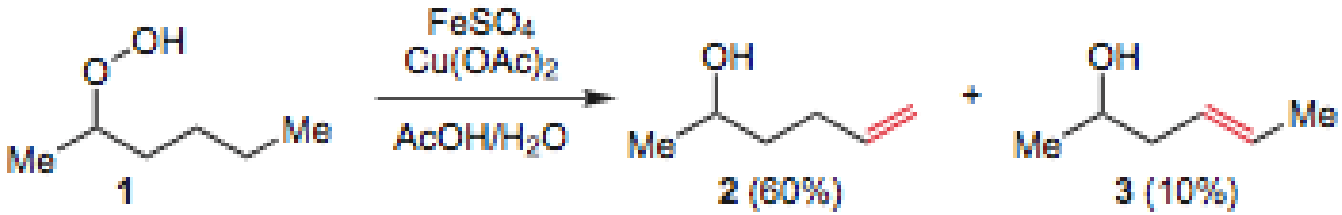
Most olefin forming reaction:

1. Functionalization of ketones or aldehydes (aldol condensation, Wittig olefination).
2. Modification of other alkenes (olefin metathesis, metal-catalysed coupling reactions).
3. Reductive transformations of alkynes (stereoselective reduction, reductive coupling).
4. Synthesis by elimination reactions (from alcohols, halides).

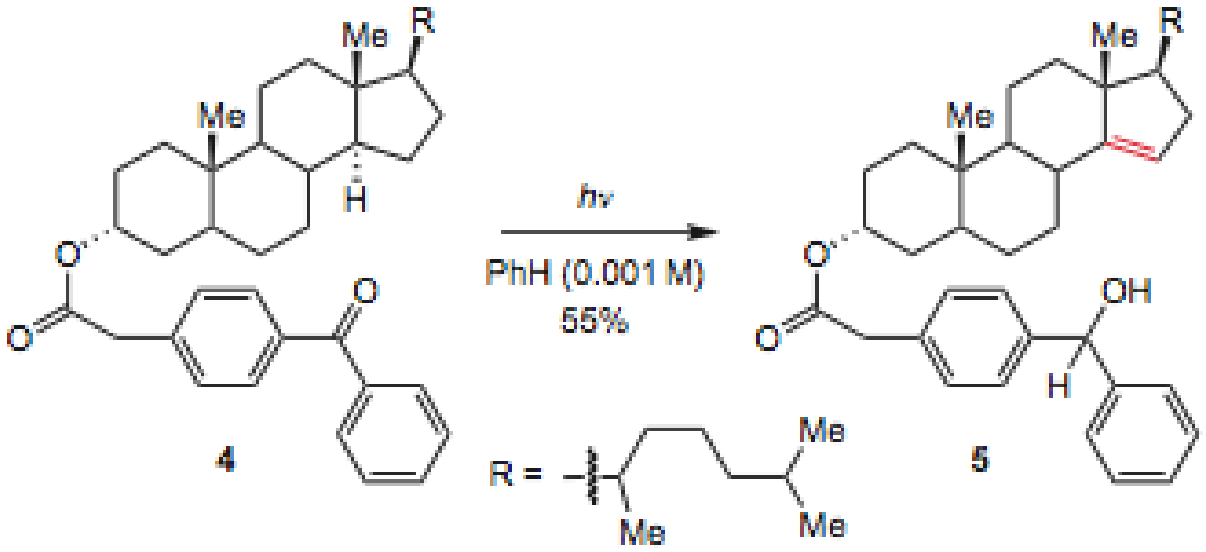
Alkane dehydrogenation:

a O-centred radical abstraction/oxidation – Cekovic, Beckwith, Kochi



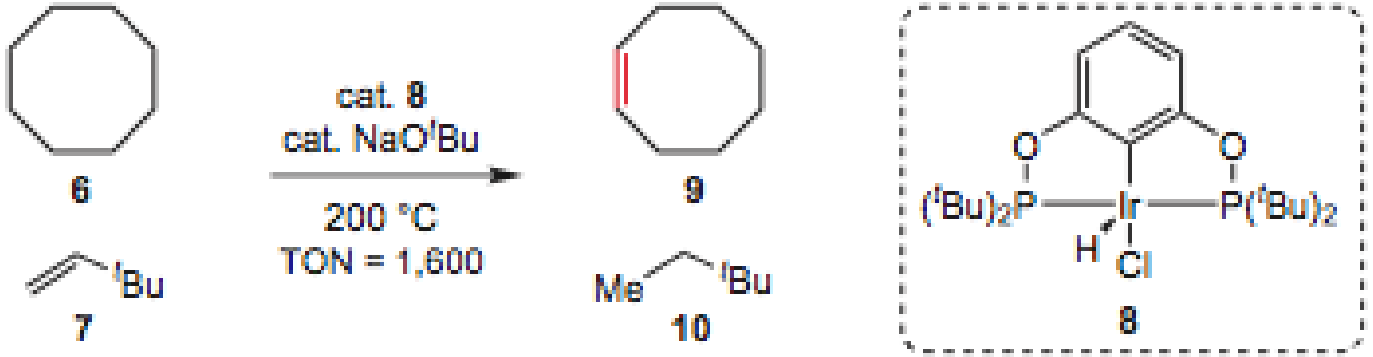
Tetrahedron 35, 2021-2026 (1979).

b Photochemical transfer hydrogenation – Breslow



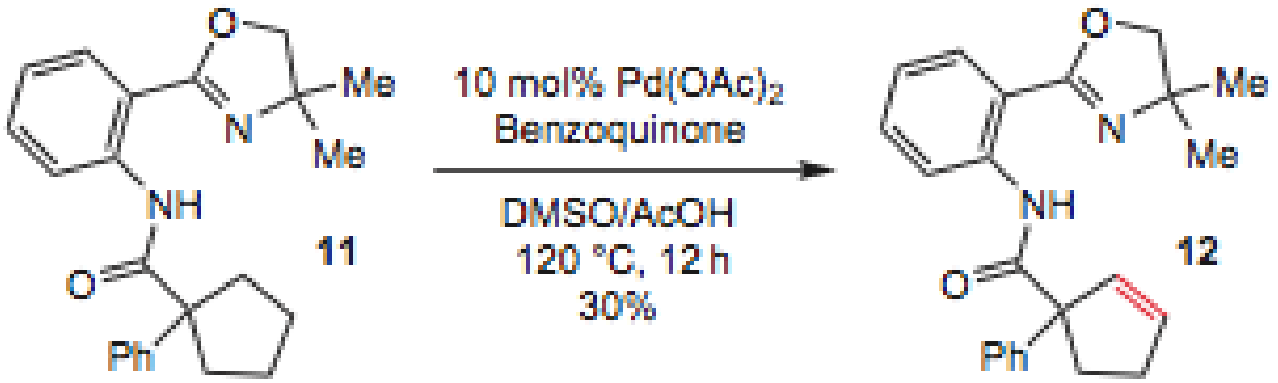
J. Am. Chem. Soc. 95, 3251-3262 (1973).

c Oxidative addition/β-H elimination – Brookhart, Crabtree, Goldman, Bergman



J. Am. Chem. Soc. 126, 1804–1811 (2004).

d Cyclometallation/β-H elimination – for Pd: Yu, Catellani, Boudoin; for Pt: Sames

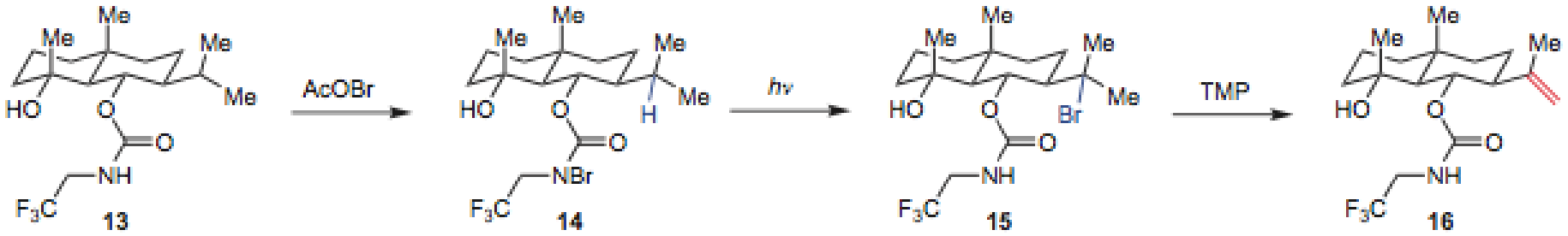


Organometallics 27, 1667–1670 (2008).

Important limitations include:

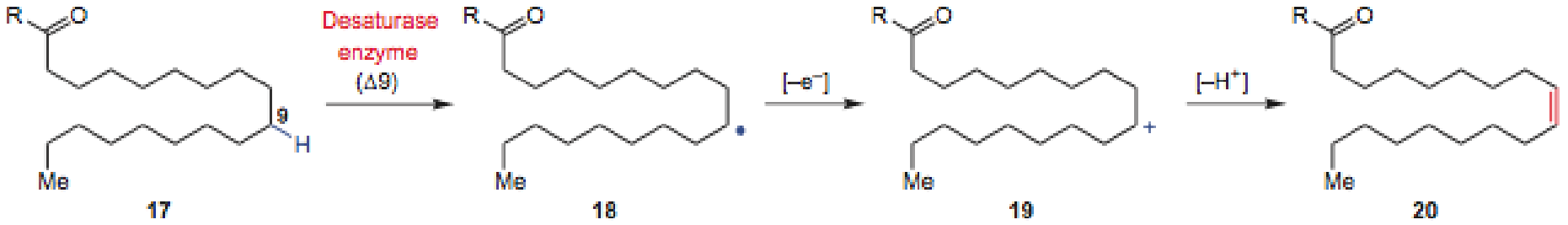
1. The use of inconvenient starting materials (for example, peroxides).
2. Poor substrate scope.
3. Overoxidation of the resulting olefin.
4. Large substrate excesses.
5. Harsh reaction conditions.

a A formal desaturation via C–H oxidation: application in total synthesis



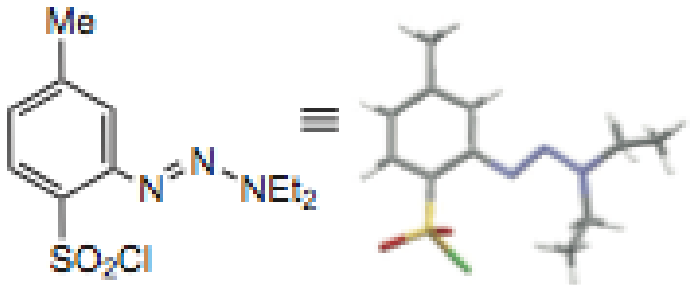
Nature 459, 824-828 (2009).

b One postulated mechanism for enzymatic desaturation



Annu. Rev. Plant Physiol. Plant Mol. Biol. 49, 611-641 (1998).

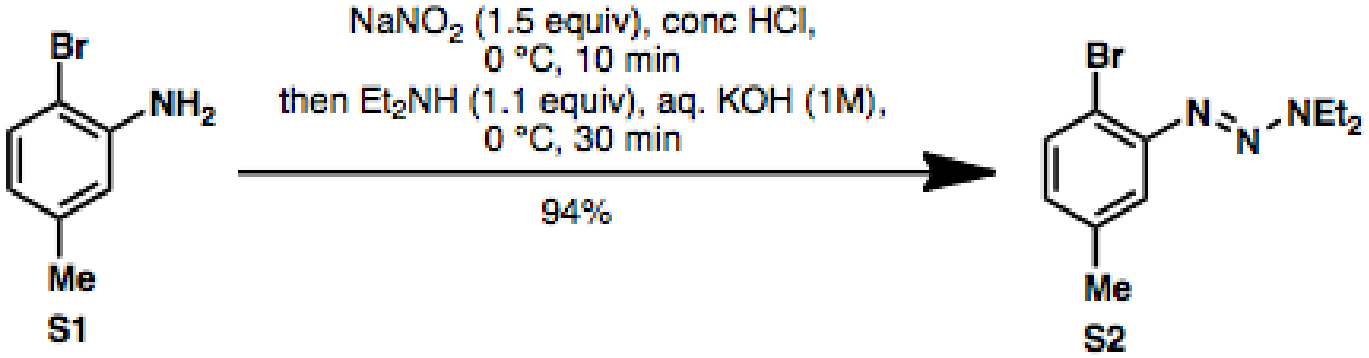
Design of a ‘portable’ desaturase:

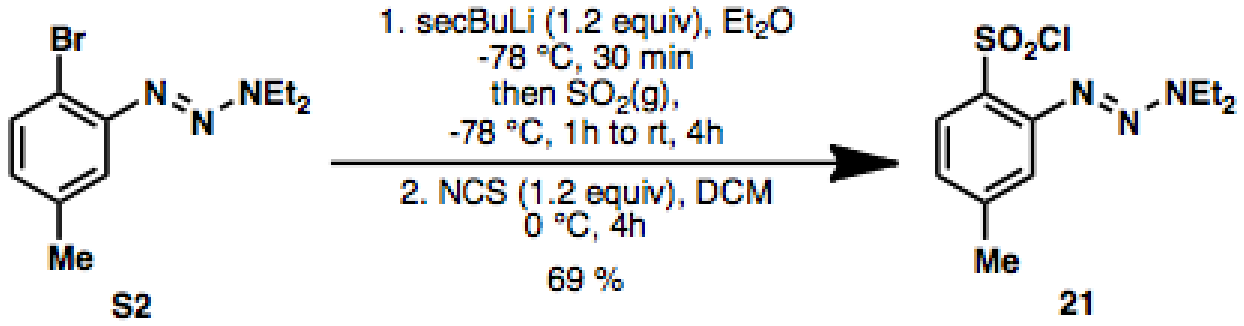


Tz^{o}Cl (21)

Portable desaturase
Commercially available from Aldrich,
catalogue number L510092

- Bench stable
- Easily prepared (>100 g)
- Facile installation


NaNO2 (1.5 equiv), conc HCl,
0 °C, 10 min
then Et2NH (1.1 equiv), aq. KOH (1M),
0 °C, 30 min
94%
Br
NH2
Me
S1
Br
N=N
NEt2
Me
S2


1. secBuLi (1.2 equiv), Et2O
-78 °C, 30 min
then SO2(g),
-78 °C, 1h to rt, 4h
2. NCS (1.2 equiv), DCM
0 °C, 4h
69 %
Br
N=N
NEt2
Me
S2
SO2Cl
N=N
NEt2
Me
21

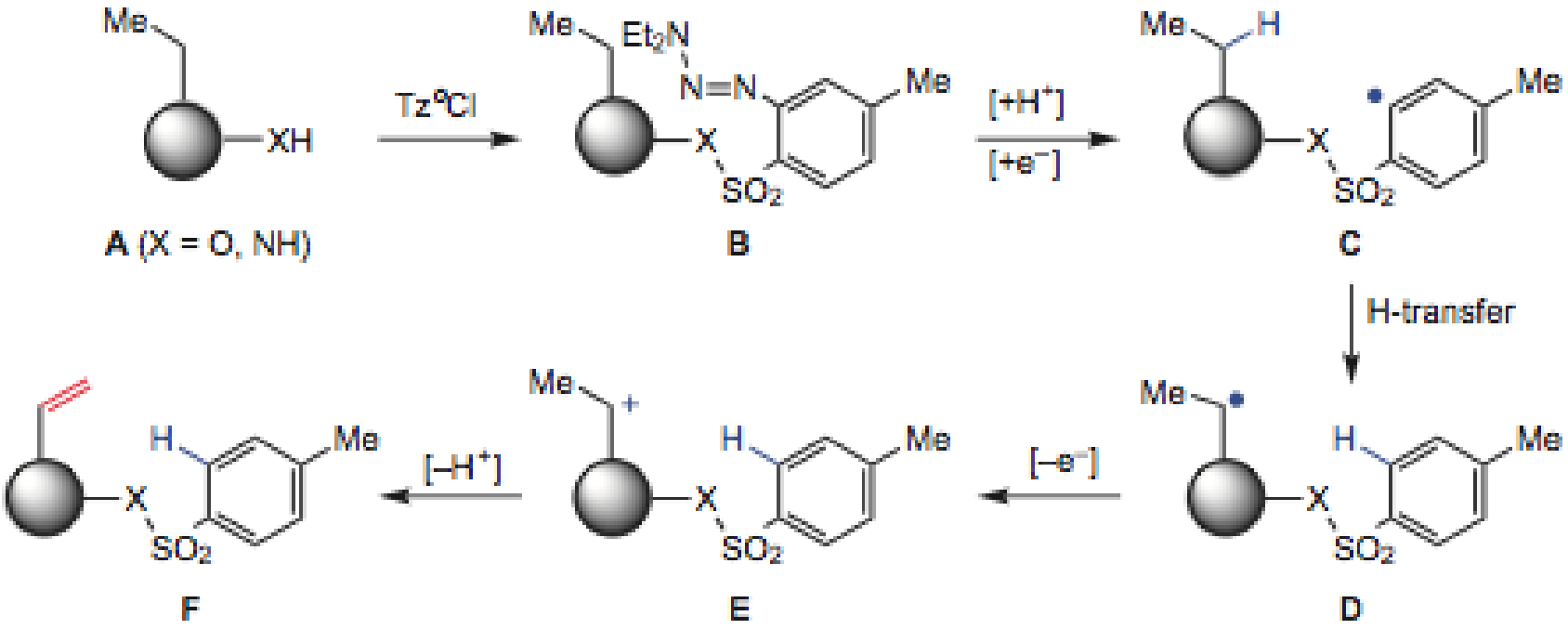
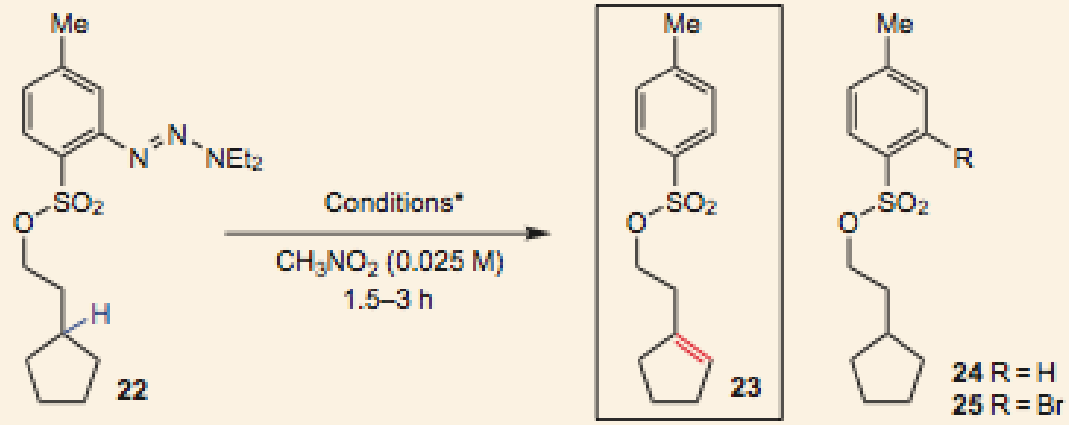

Me
XH
A (X = O, NH)
Tz°Cl
Me
Et2N
N=N
Me
X
SO2
B
[+H+]
[+e−]
Me
H
Me
X
SO2
C
H-transfer
Me
H
Me
X
SO2
D
[−e−]
Me
+
H
Me
X
SO2
E
[−H+]
H
Me
X
SO2
F

Table 1 | Development of a method for guided desaturation.



Entry	Copper source	Additive (equiv.)	Acid (equiv.)	Temperature (°C)	Yield% (ratio 23:24:25)[†]
1	$CuBr_2$ (5 mol%)	-	TFA (2)	80	34 (20:13:1)[‡]
2	$CuBr_2$ (5 mol%)	-	TFA (2)	80	31 (5:1:2)
3	$CuBr_2$ (5 mol%)	TEMPO (1)	TFA (2)	80	40 (6:1:1)
4	-	TEMPO (1)	TFA (2)	80	50 (4.5:1:0)
5	-	-	TFA (3)	80	12 (20:1:0)
6	-	TEMPO (1)	-	80	NR
7	**-**	**TEMPO (1)**	**TFA (3)**	**60**	**68 (10:1:0)[§]**
8	**-**	**TEMPO (1)**	**TfOH (2)**	**r.t.**	**54 (20:1:0) (45[||])**
9	-	AZADO (1)	TFA (3)	60	15 (20:1:0)
10	-	$Ad_2NO^•$ (1)	TFA (3)	60	24 (20:1:0)

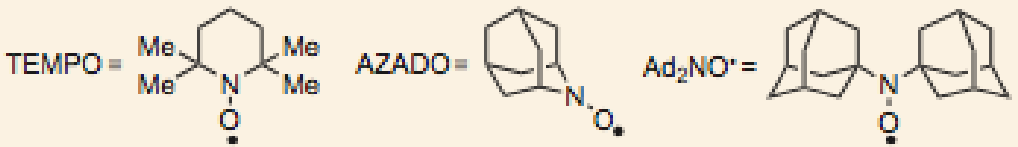
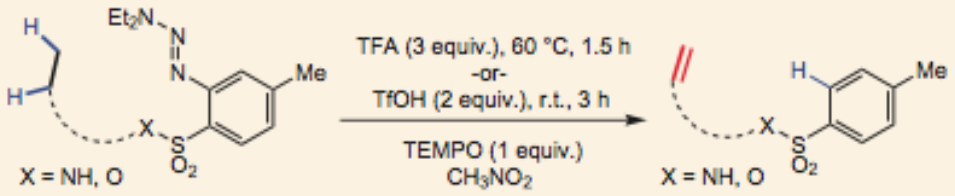
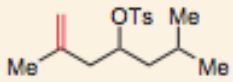


Table 2 | Substrate scope for the guided desaturation reaction.

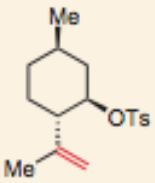


- 20 examples
- No metal required
- Predictable dehydrogenation site
- No overoxidation observed
- Good functional group tolerance
- No strong oxidants required

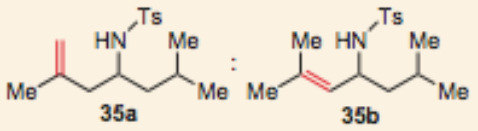


26 (44%)*

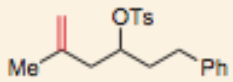
30 (55%)*



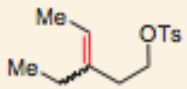
33 (92%)*
(74%, >1 g scale)
[X-ray]



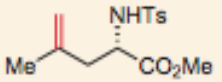
35a **35b**
(60%, **35a**:**35b** = 10:1)†



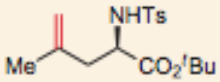
27 (36%)*



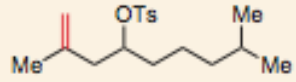
31 (69%, *E*:*Z*=1:1)*



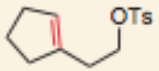
36 (47%)*



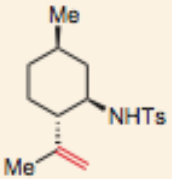
37 (40%)*



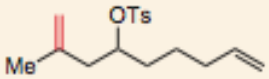
28 (41%)*



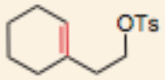
23 (68%)*,‡



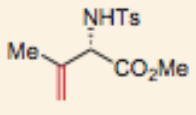
34 (59%)†



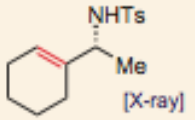
29 (32%)*



32 (51%)*,‡

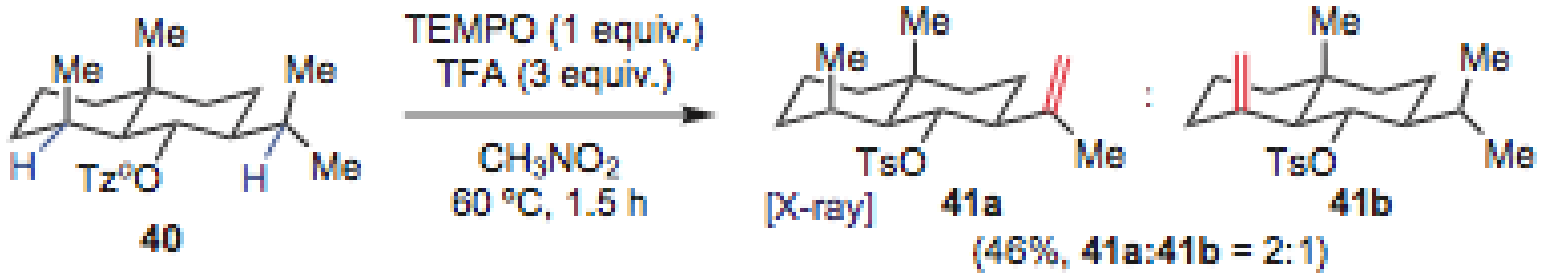


38 (51%)*,§

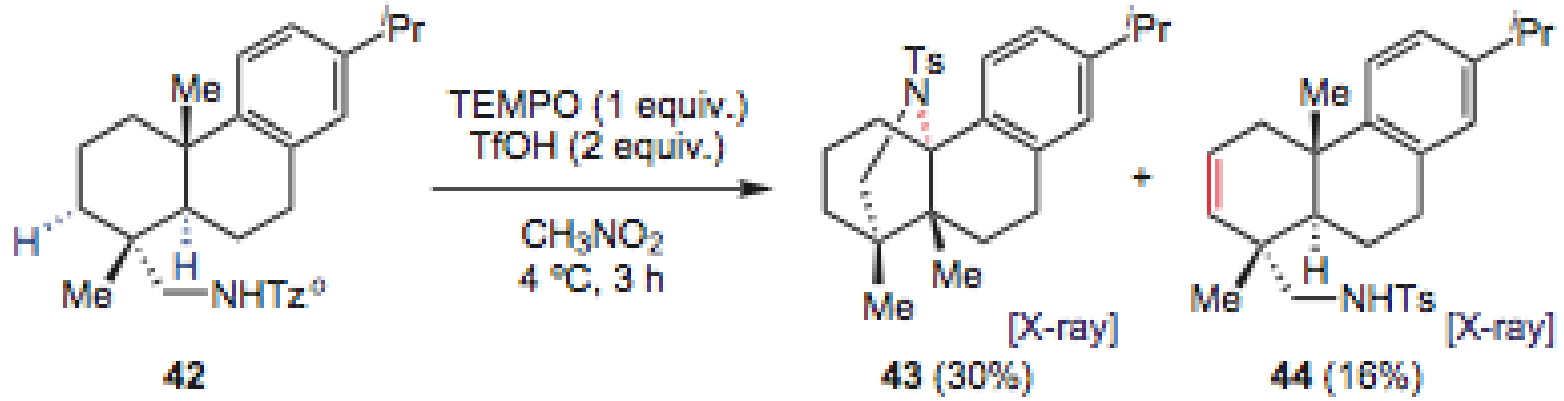


39 (50%)†

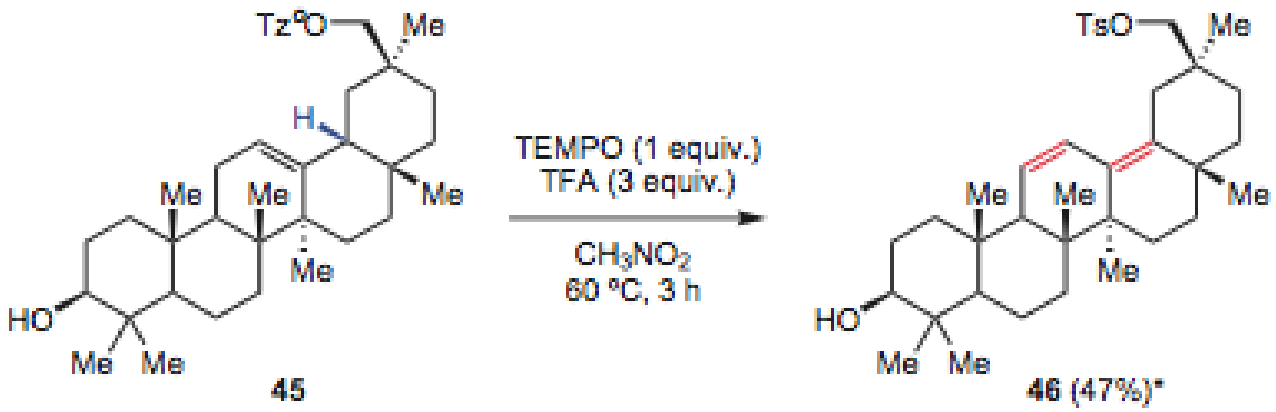
a Desaturation of eudesmane derivative **40**



b Desaturation of dihydroabietylamine derivative **42**

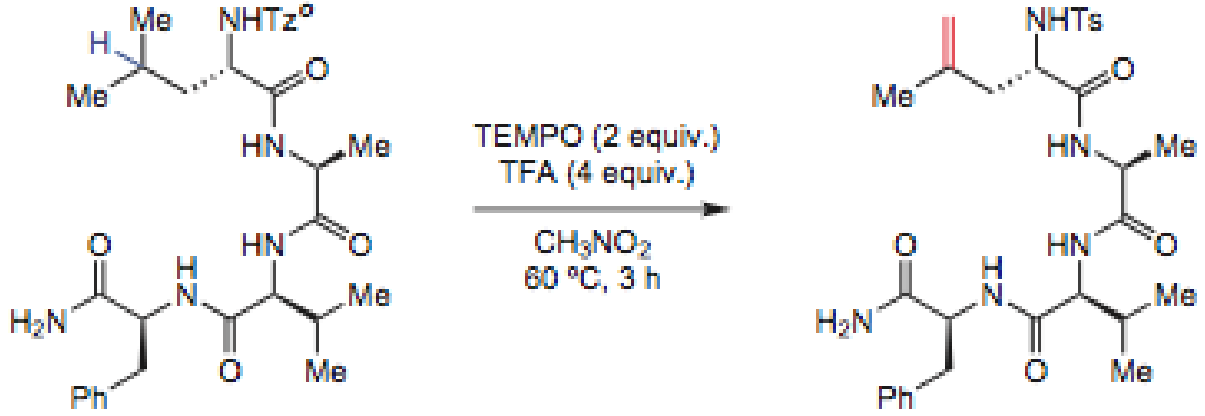


c Desaturation of 18-β-glycyrrhetinic acid derivative **45**

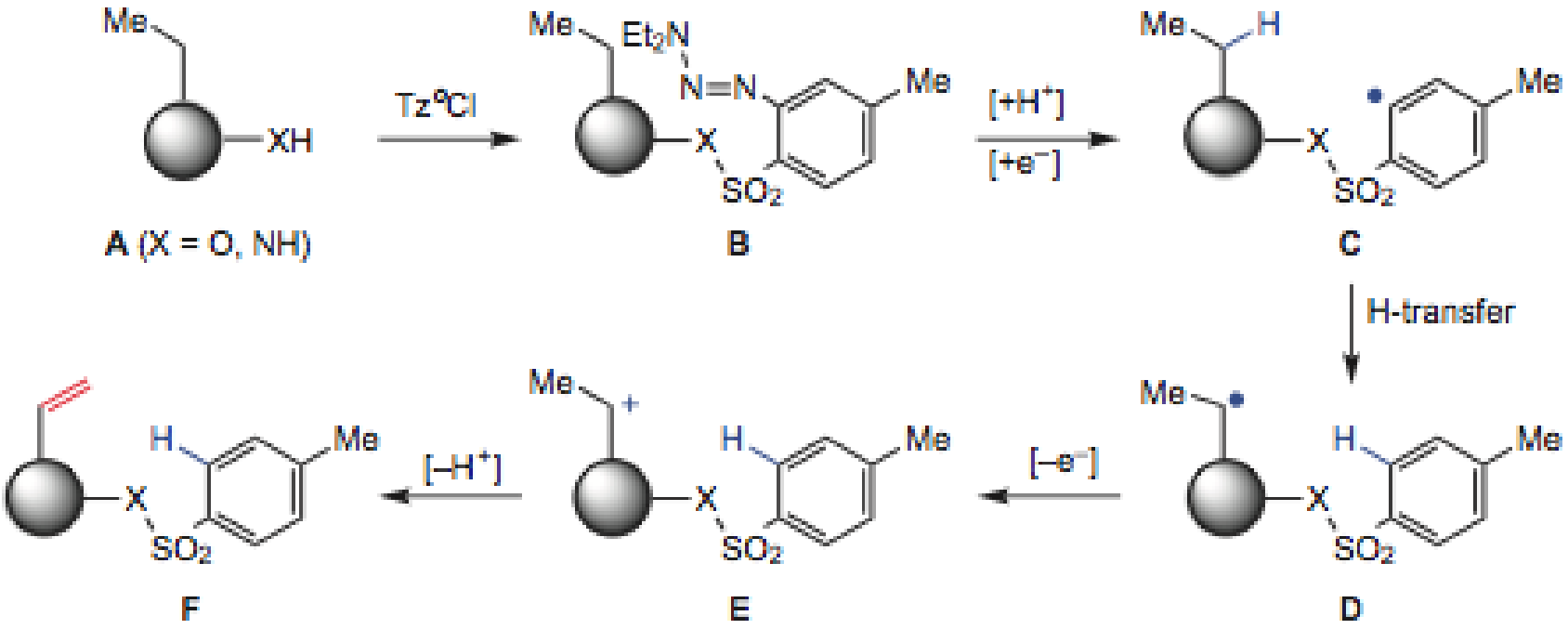


45 **46** (47%)*

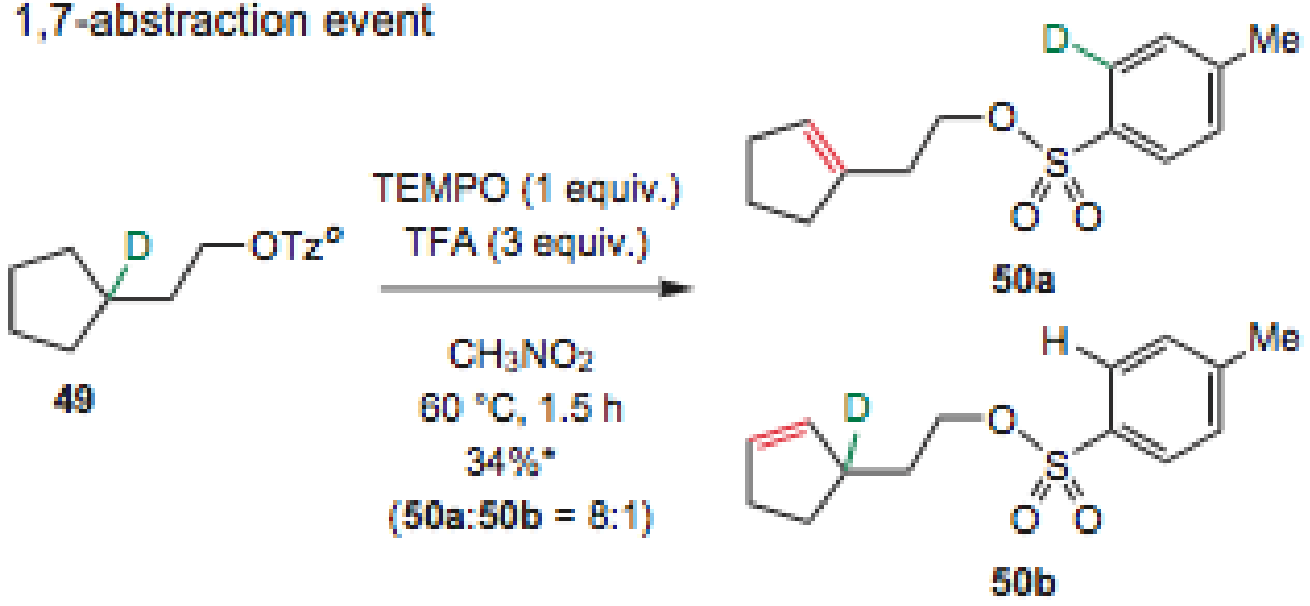
d Desaturation of tetrapeptide **47**



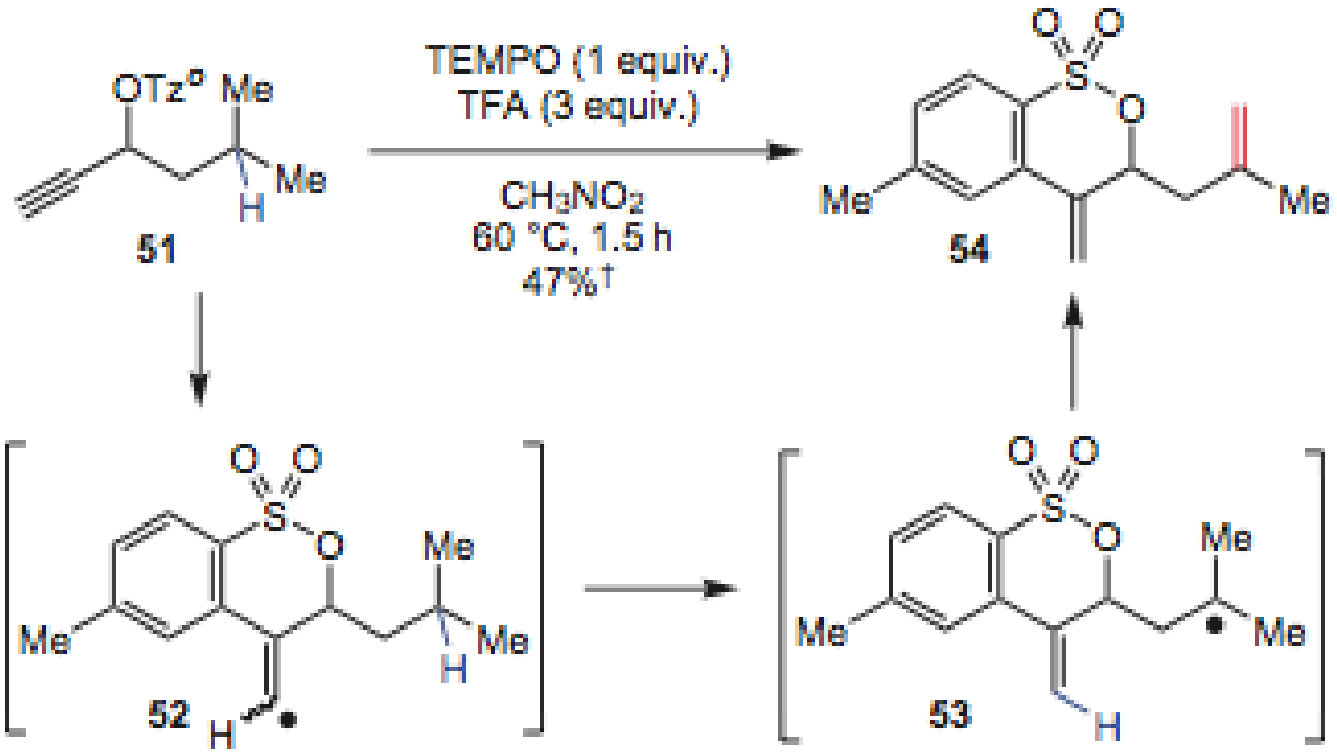
47 **48** (35%)


Me
XH
A (X = O, NH)
Tz°Cl
Me
Et2N
N=N
Me
X
SO2
B
[+H+]
[+e−]
Me
H
Me
X
SO2
C
H-transfer
Me
H
Me
X
SO2
D
[−e−]
Me
+
H
Me
X
SO2
E
[−H+]
H
Me
X
SO2
F

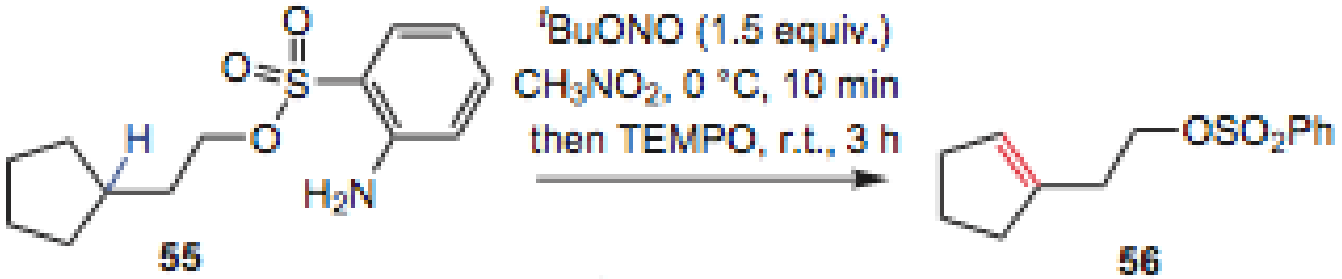
a 1,7-abstraction event



b *In situ* trapping of the aryl radical intermediate



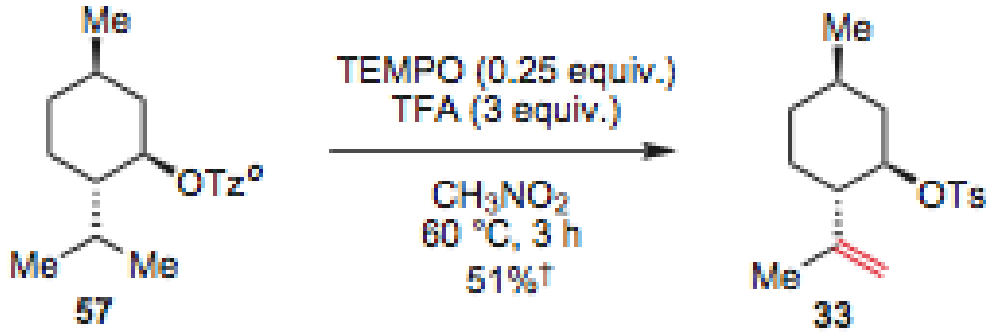
c TEMPO-promoted desaturation from a diazonium intermediate



55 56

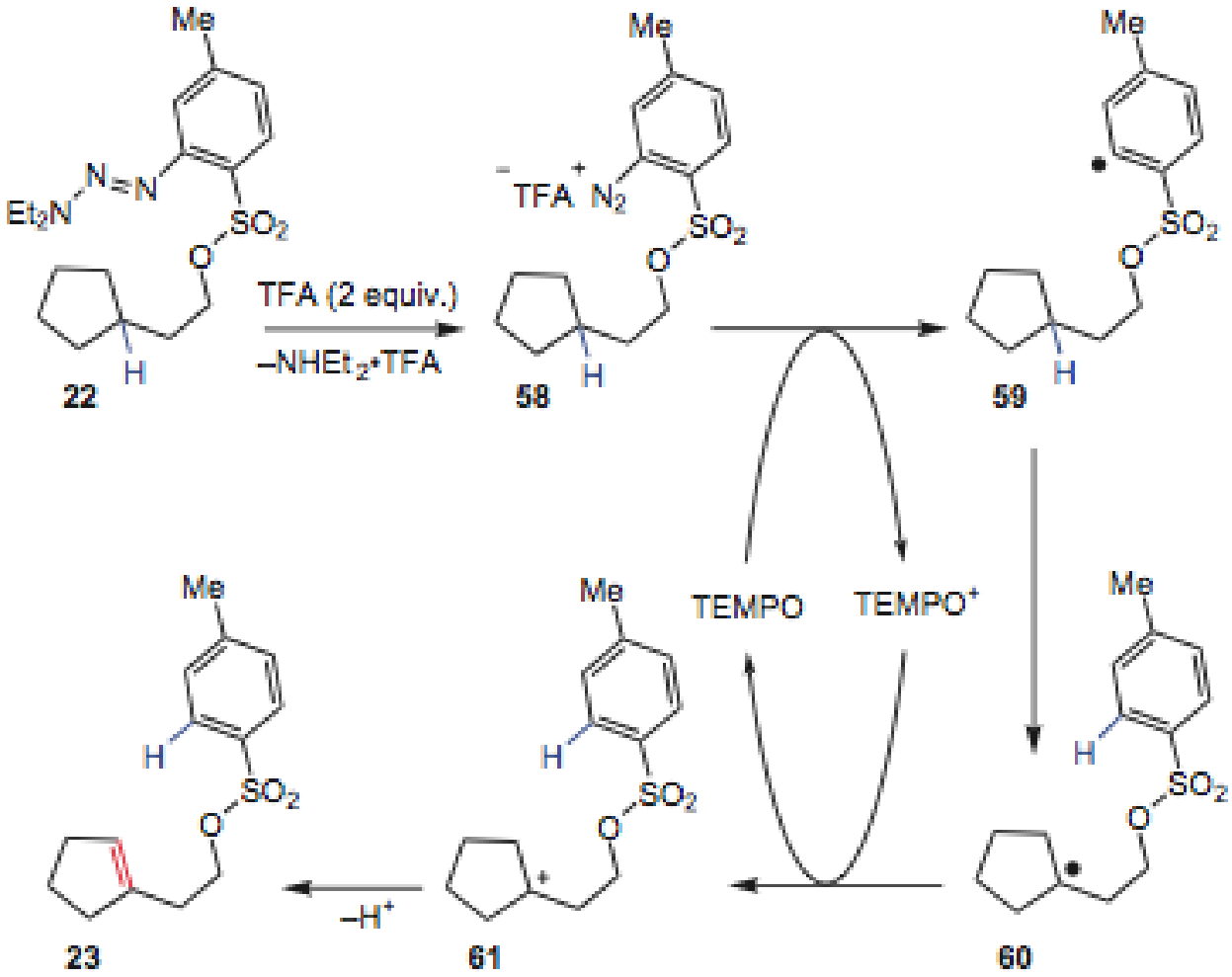
Entry	TEMPO (equiv.)	Yield (%)*
1	1	44
2	0.1	31
3	0	<5‡

d Preliminary result of a TEMPO-catalysed desaturation reaction



57 33

e Proposed reaction mechanism for the guided desaturation reaction



Conclusion:

1. A new chemical moiety, TzºCl (21), has been designed to mimic processes observed in nature and leads to desaturated aliphatics.
2. The chemistry performed by this directing group is centred on the high reactivity of an aryl radical masked as an aryl triazene.
3. The desaturation reaction is applicable on simple substrates derived from saturated alcohols and amines, to give olefin products in a predictable fashion without any overoxidation.
4. Some of the drawbacks of this method are the modest product yields, the formation of minor amounts of inseparable reduction products and the occasional difficulties in purification.