Introduction to Clandestine Chemistry: Comparison to Traditional Laboratory Methods

Luke Oxtoby

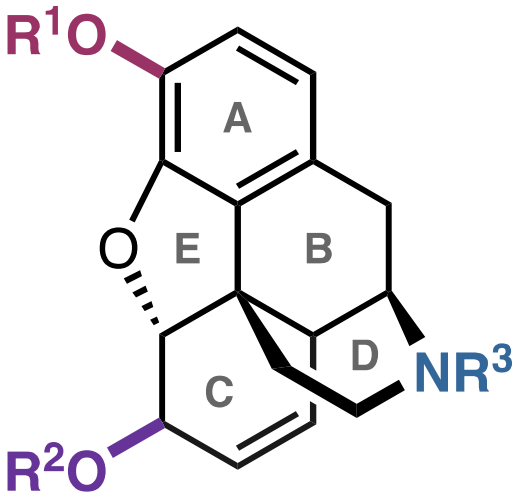
Engle Lab

10/17/2019

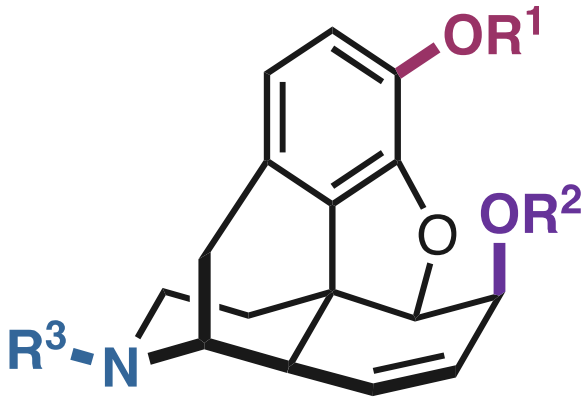
Introduction to Opiates

Pain Physician **2008**, 105–120; *J. Hist. Biol.* **1975**, 95–114; *Historical J.* **2015**, 1009–1029; *PNAS* **1993**, 5391–5393; *Appl. Econ. Lett.* **2008**, 911–913

Natural Opiates

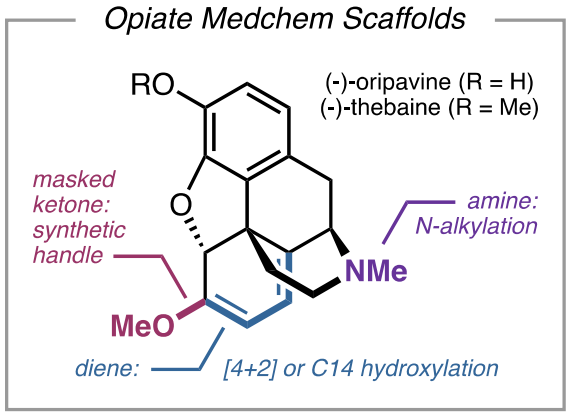


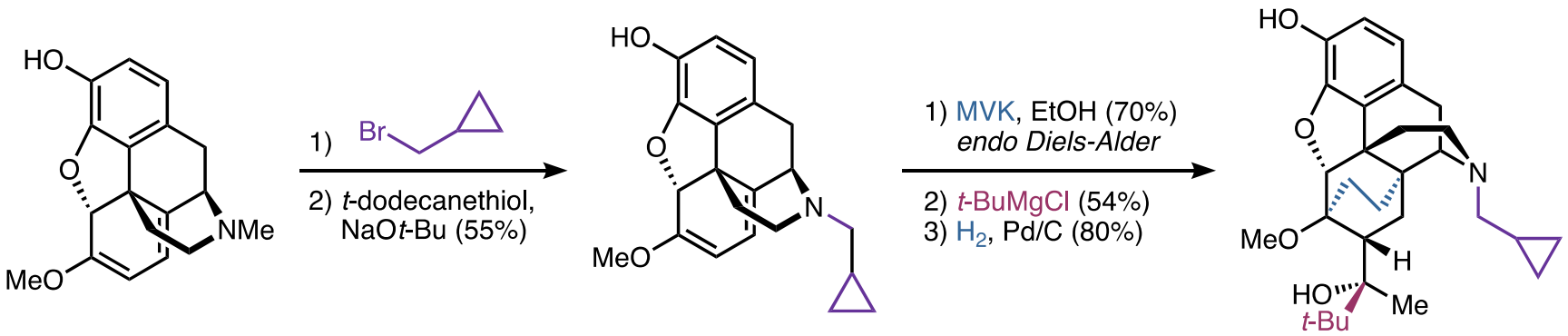
conventional ring notation for
natural and semisynthetic opiates



alkaloid	R^1	R^2	R^3
(-)-morphine	H	H	Me
(-)-codeine	Me	H	Me

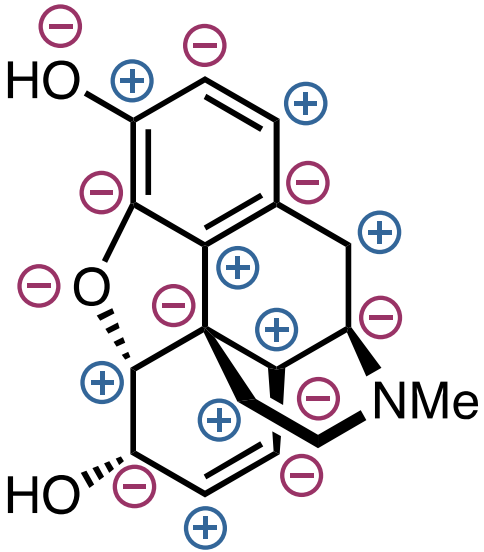
Licit Semisynthetic Opiates

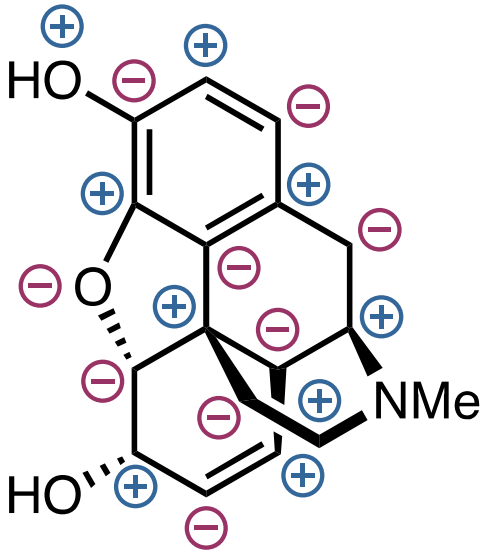


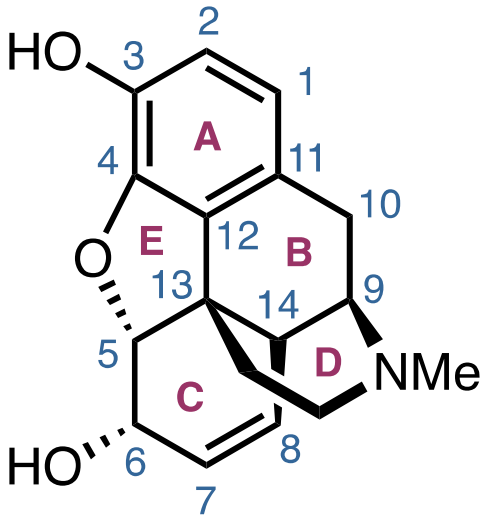


Nature **1965**, 103; *JACS* **1967**, 3267–3273; *JACS* **1967**, 3273–3280; *JACS* **1967**, 3281–3292; *ACS Chem. Neurosci.* **2018**, 2307–2330

Total Synthesis of Morphine

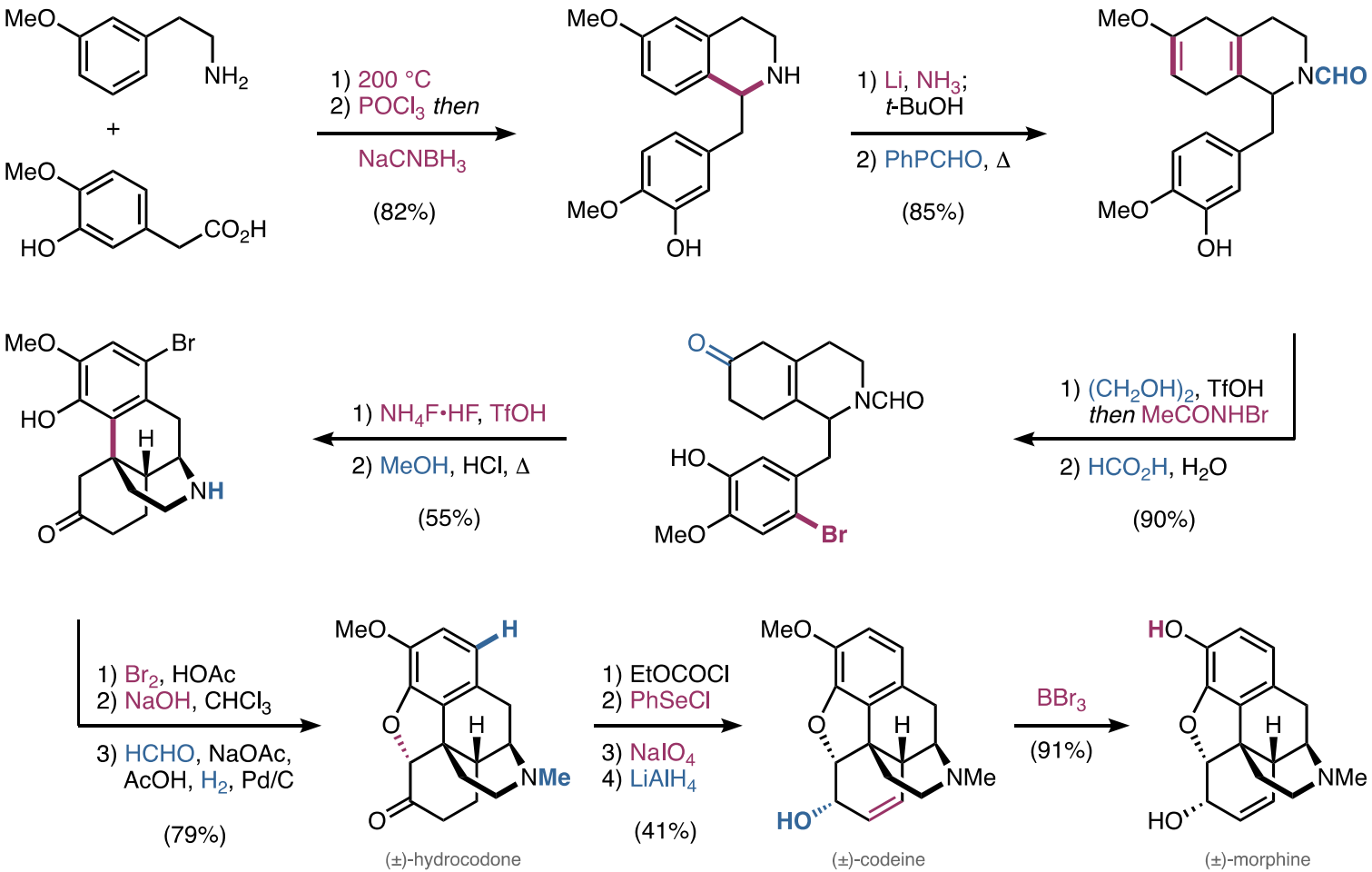






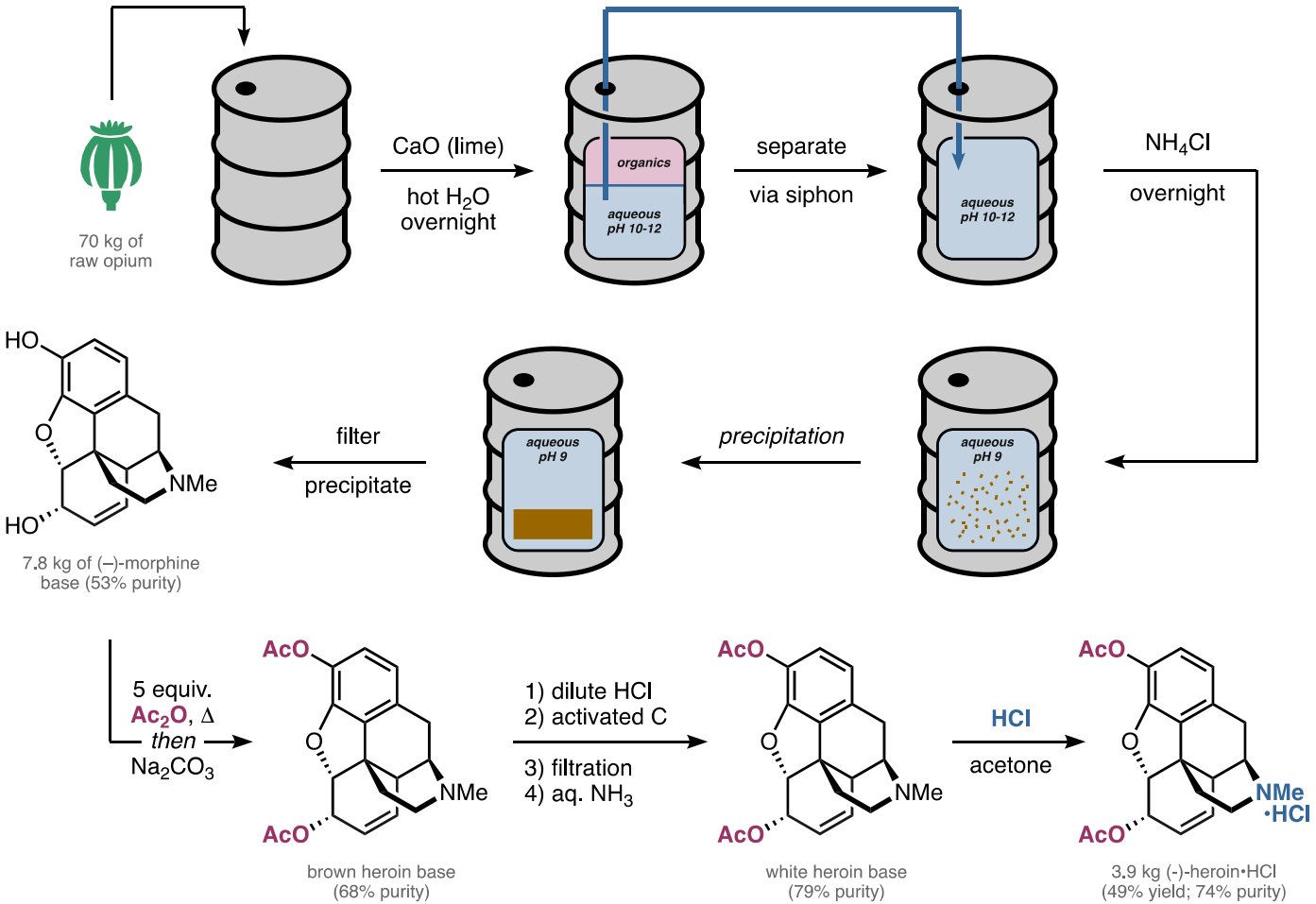
(±)-morphine

Total Synthesis of Morphine

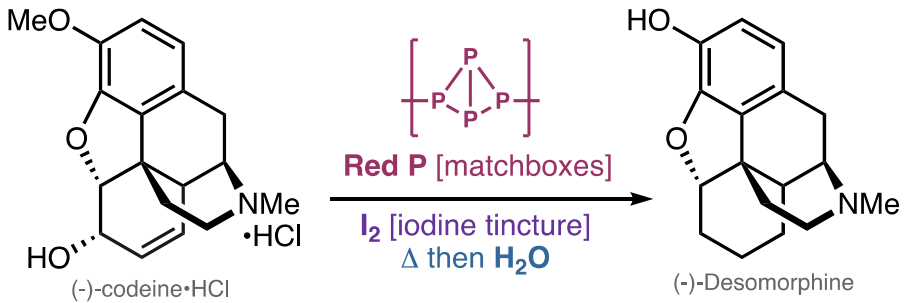


Heterocycles **1977**, 1157–1165; *J. Med. Chem.* **1977**, 164–165; *J. Org. Chem.* **1980**, 592–601; *J. Org. Chem.* **1980**, 3135–3137

Ilicit Semisynthetic Opiates - Diacetylmorphine (Heroin)

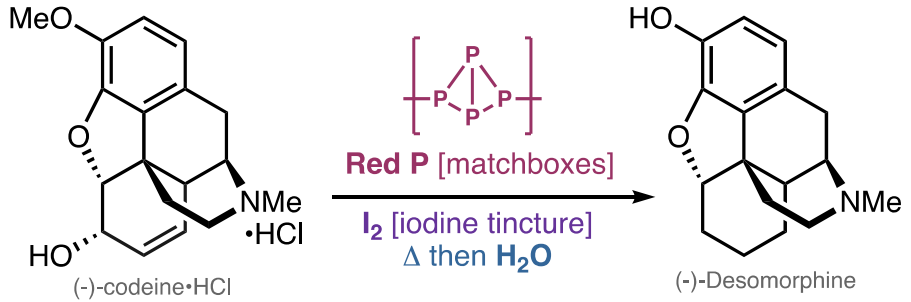


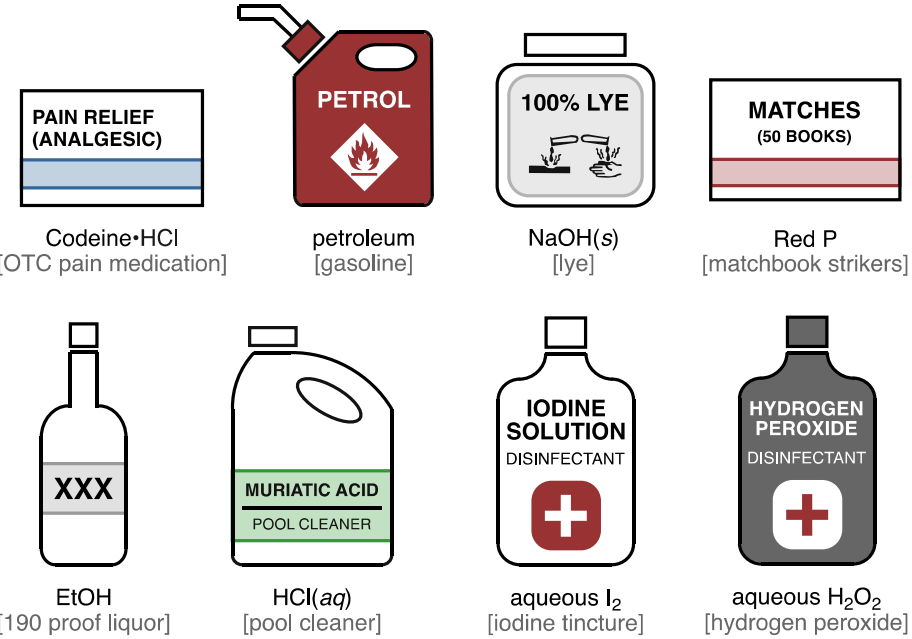
Ilicit Semisynthetic Opiates - Desomorphine (Krokodil)



JAMA Dermatol **2015**, 32; *Forensic Sci. Int.* **2015**, 76–82; *Life Sciences* **2014**, 81–87; *Forensic Sci. Int.* **2015**, 207–213; *Chem. Res. Toxicol.* **2017**, 1609-1621; *ACS Chem. Neurosci.* **2018**, 2307–2330

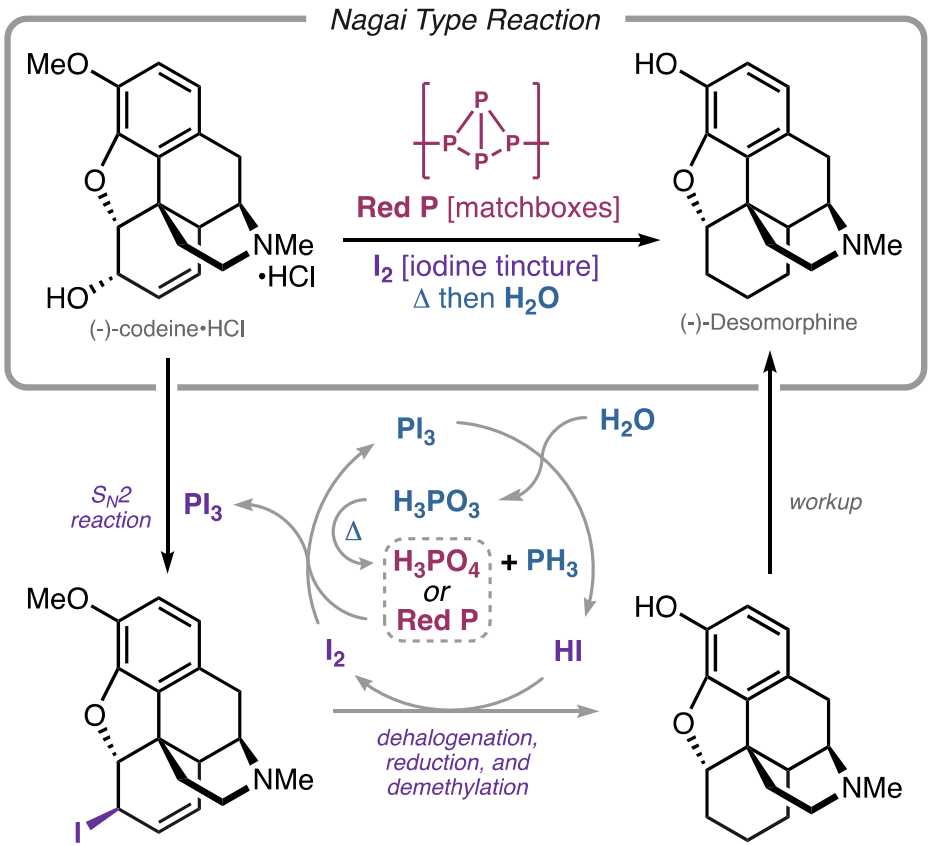
Ilicit Semisynthetic Opiates - Desomorphine (Krokodil)





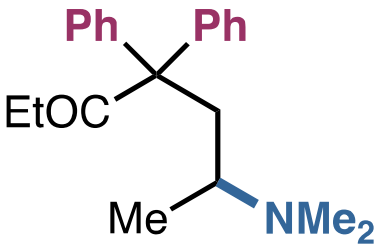
JAMA Dermatol **2015**, 32; *Forensic Sci. Int.* **2015**, 76–82; *Life Sciences* **2014**, 81–87; *Forensic Sci. Int.* **2015**, 207–213; *Chem. Res. Toxicol.* **2017**, 1609-1621; *ACS Chem. Neurosci.* **2018**, 2307–2330

Mechanism of the Reduction of Codeine to Desomorphine

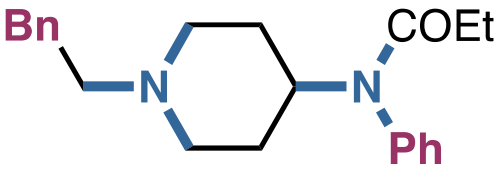


JAMA Dermatol **2015**, 32; *Forensic Sci. Int.* **2015**, 76–82; *Life Sciences* **2014**, 81–87; *Forensic Sci. Int.* **2015**, 207–213; *Chem. Res. Toxicol.* **2017**, 1609-1621; *ACS Chem. Neurosci.* **2018**, 2307–2330

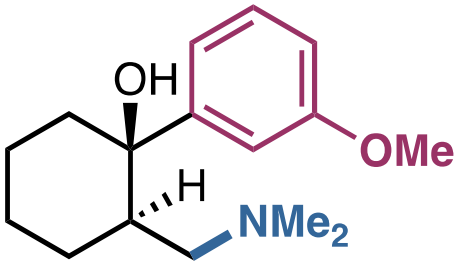
Introduction to Opioids



Methadone

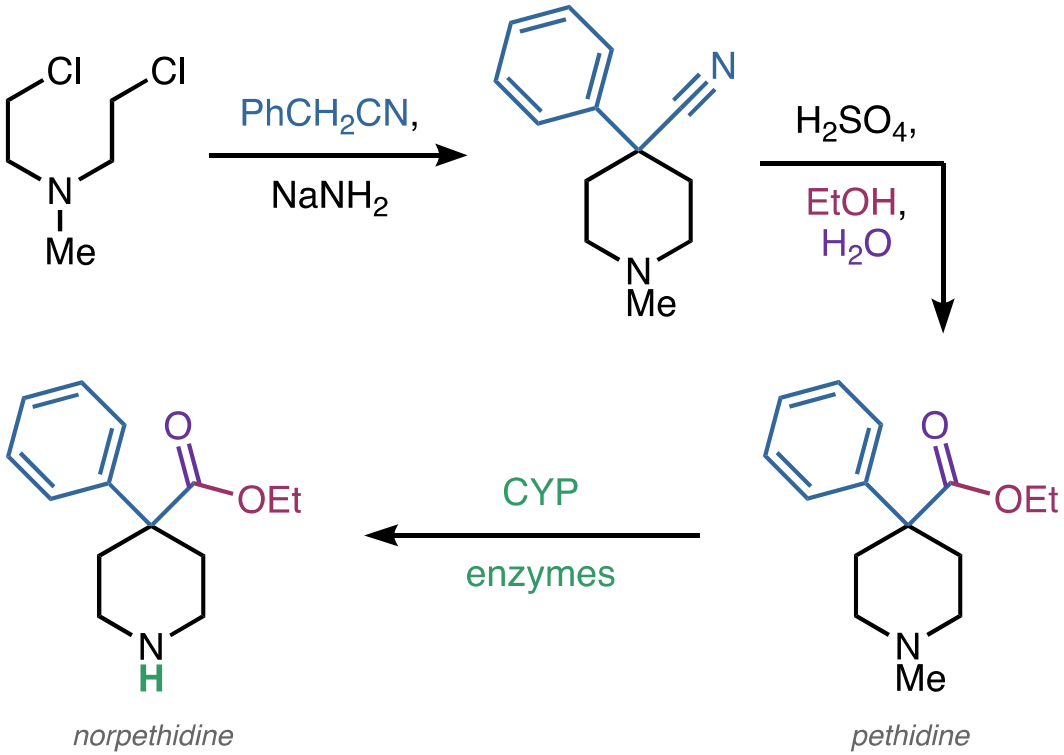


Fentanyl



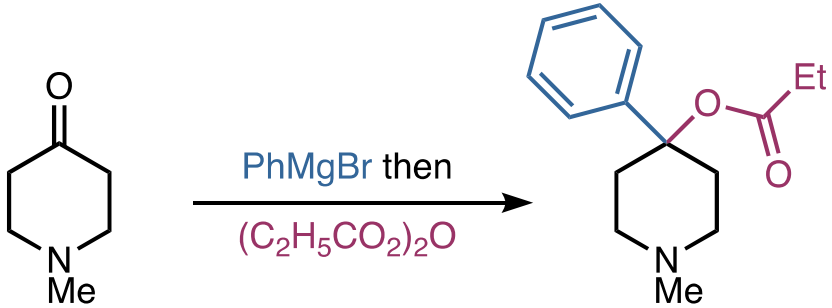
Tramadol

Historical Context - Pethidine (Demerol)



US Patent US 2167351A; *Am. J. Ther.* **2002**, 53–68; *J. Pharm. Pract. Res.* **2008**, 88–89; *Nat. Prod. Rep.* **2014**, 880–904; UNODC, *Crime and instability,* **2010**

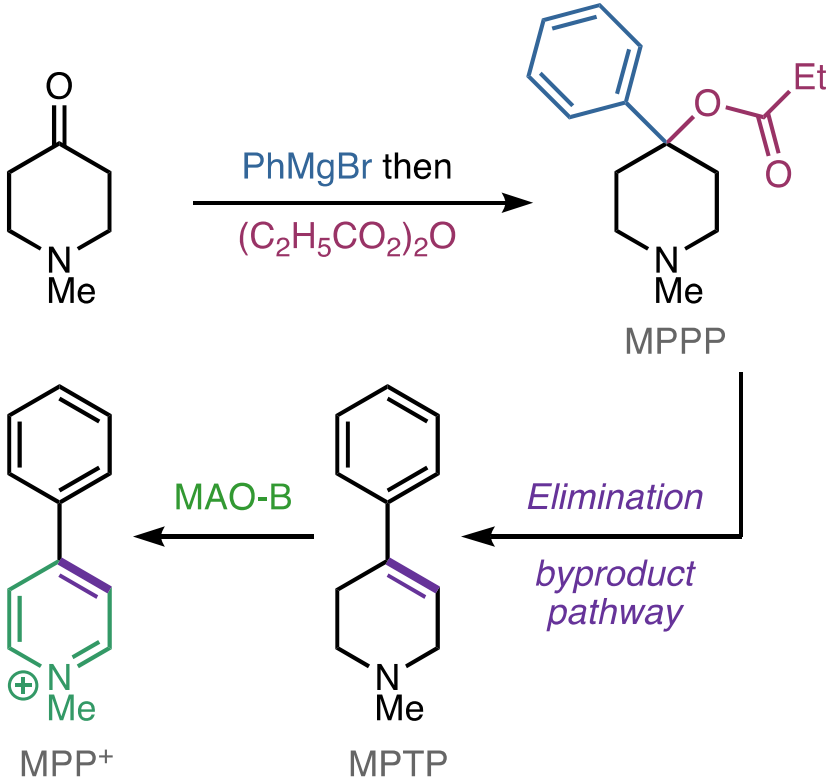
The Advent of Clandestine Synthesis - MPPP (China White)



MPPP

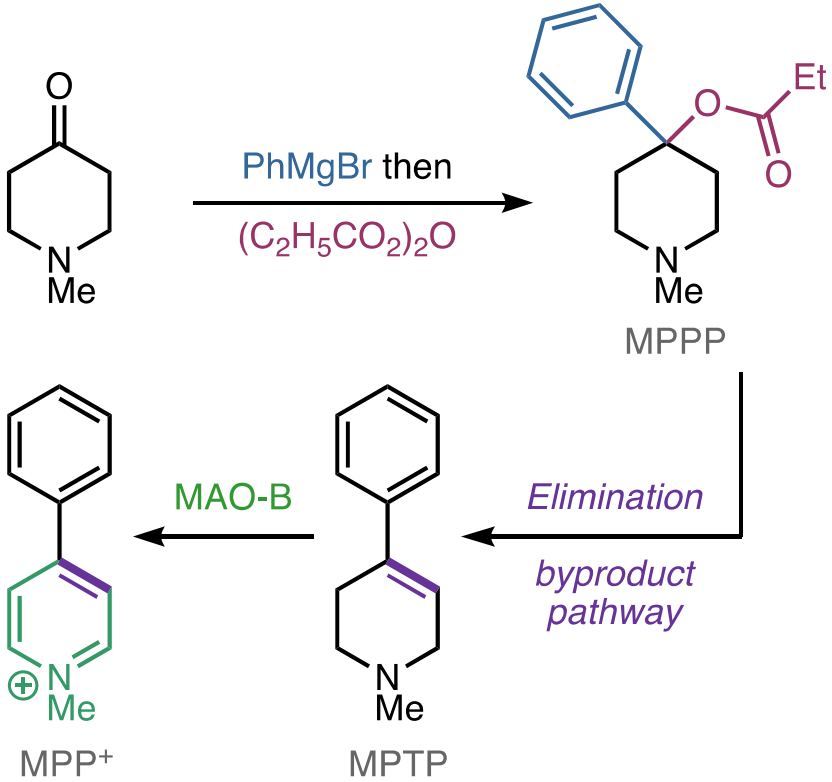
Science **1983**, 979–980; *Proc. Natl. Acad. Sci.* **1983**, 4546–4550; *New Engl. J. Med.* **1996**, 2002–2003; *Chem. Eng. News* **2013**, 11–15

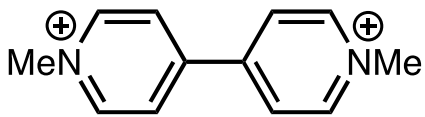
The Advent of Clandestine Synthesis - MPPP (China White)



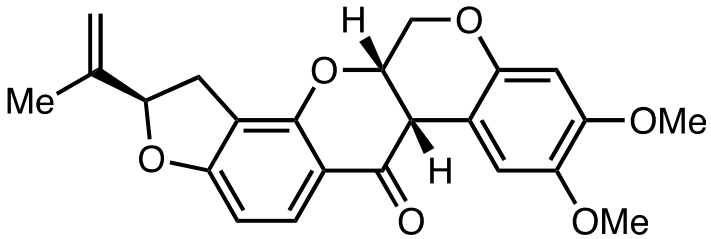
Science **1983**, 979–980; *Proc. Natl. Acad. Sci.* **1983**, 4546–4550; *New Engl. J. Med.* **1996**, 2002–2003; *Chem. Eng. News* **2013**, 11–15

The Advent of Clandestine Synthesis - MPPP (China White)





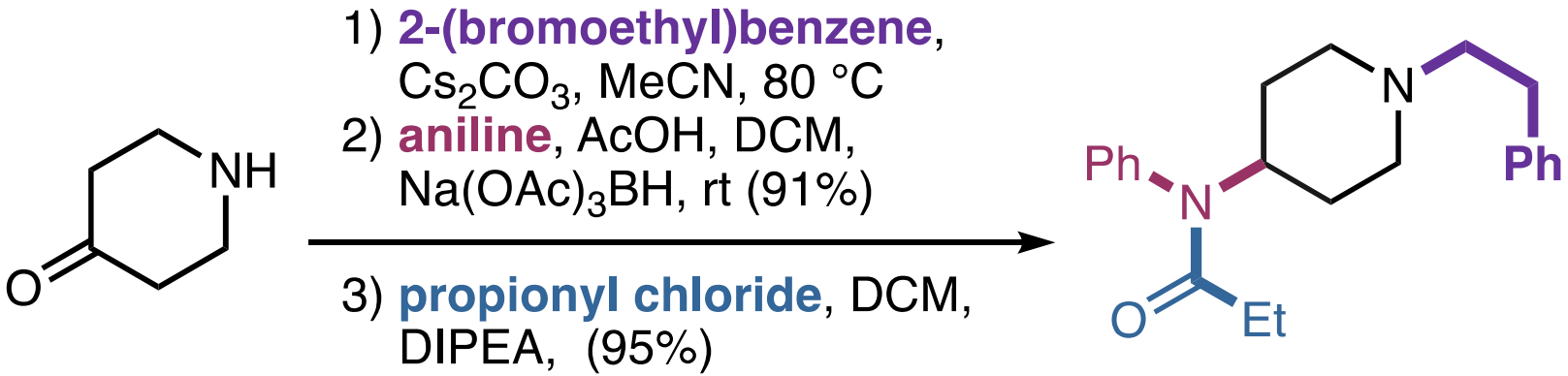
paraquat



rotenone

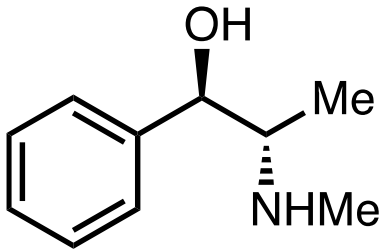
Science **1983**, 979–980; *Proc. Natl. Acad. Sci.* **1983**, 4546–4550; *New Engl. J. Med.* **1996**, 2002–2003; *Chem. Eng. News* **2013**, 11–15

The Current Opioid Epidemic in the United States

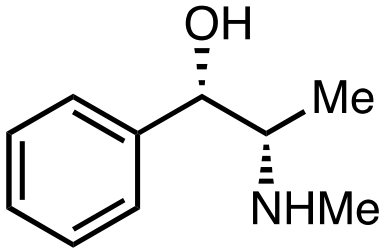


J. Am. Chem. Soc. **2019**, 1798-1806; *ACS Chem. Neurosci.* **2018**, 2428−2437; *J. Anal. Toxicol.* **2012**, 647−656

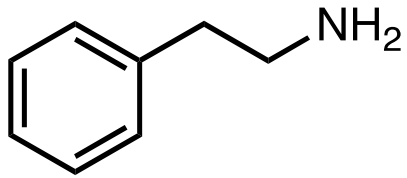
Introduction to Substituted Phenethylamines



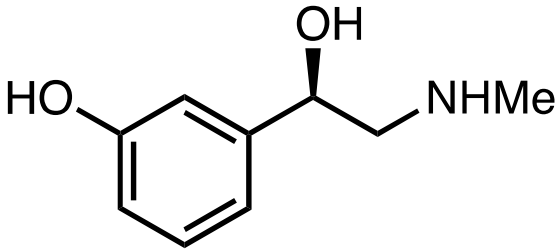
ephedrine
[Bronkaid]



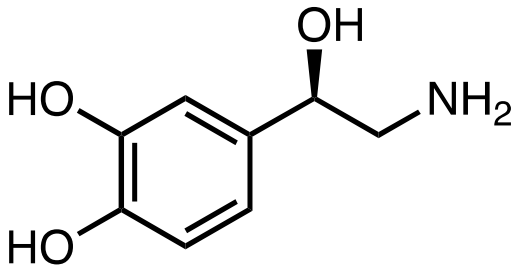
pseudoephedrine
[Sudafed]



phenethylamine
[PEA]



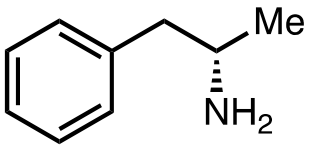
phenylephrine
[Preparation H]



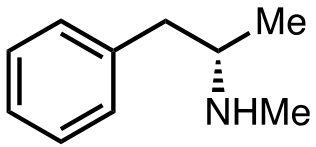
norepinephrine
[Adrenaline]

Front. Neurosci. **2016**, *10*, 148; *Nat. Prod. Rep.* **2014**, 880–904; *J. Anesth.* **2012**, 137–140; *Phytother. Res.* **2003**, 703–712; *Allergy Clin. Immunol.* **2006**, 279–280; *J. Am. Med. Ass.* **1930**, 790–791

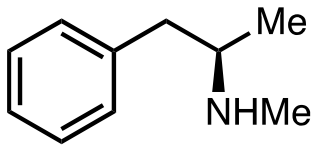
Introduction to Substituted Phenethylamines



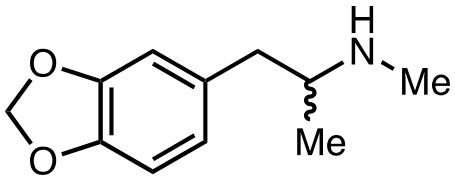
dextroamphetamine
[Dexedrine]



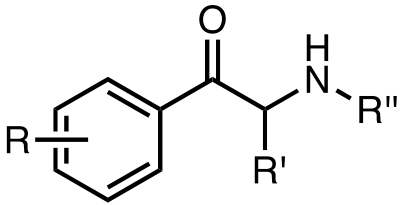
dextromethamphetamine
[Desoxyn]



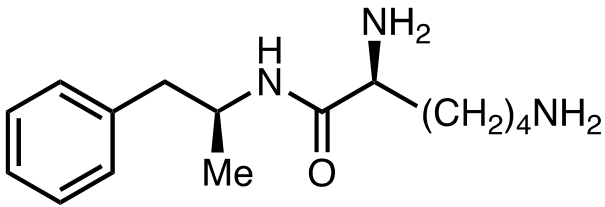
levomethamphetamine
[Vicks Vaporub]



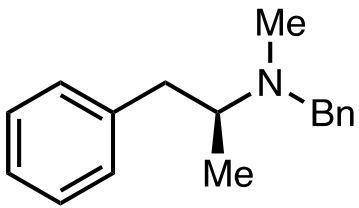
methylenedioxymethamphetamine
[MDMA]



substituted cathinones
[MDPV, mephedrone, etc.]



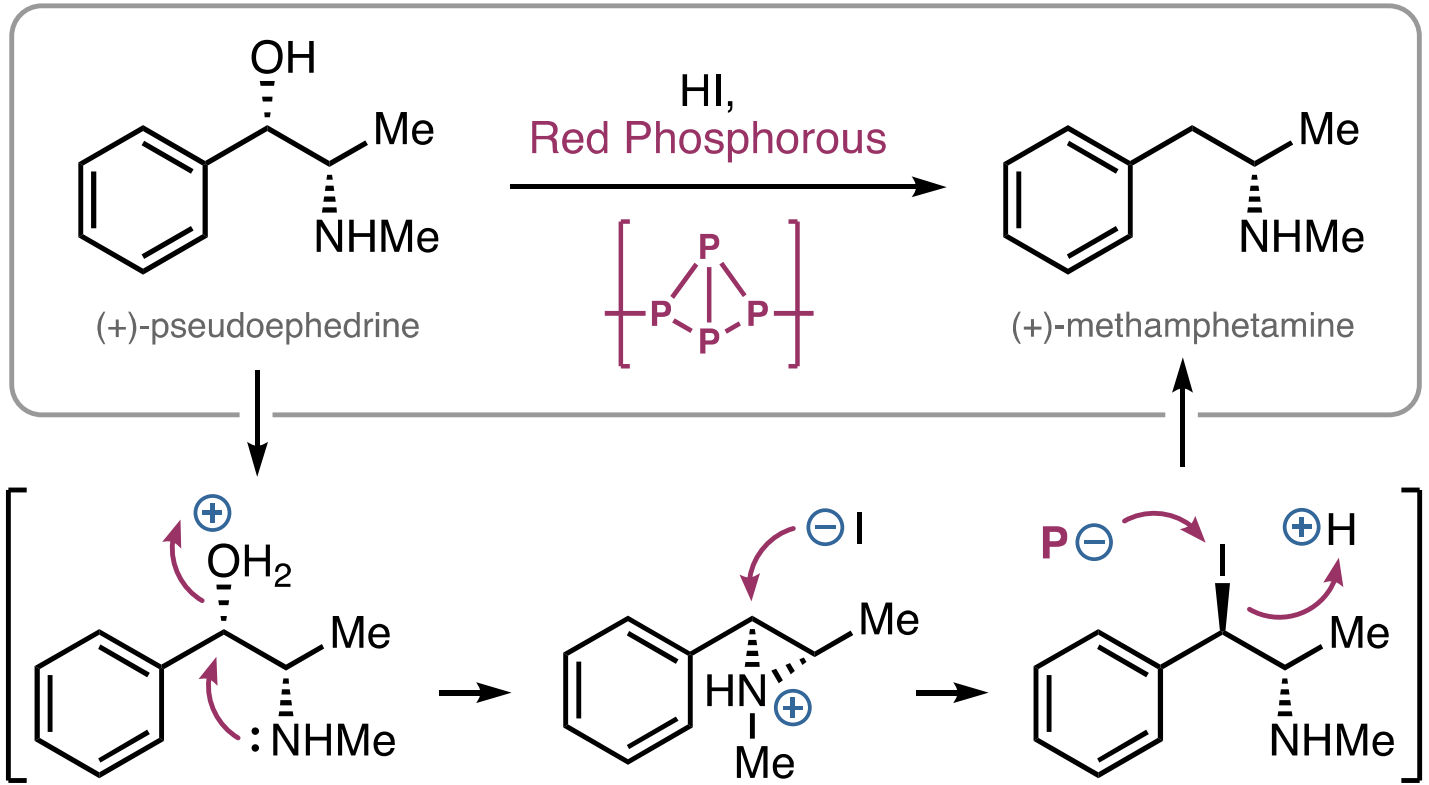
lisdexamfetamine
[Vyvanse]



benzphetamine
[Didrex]

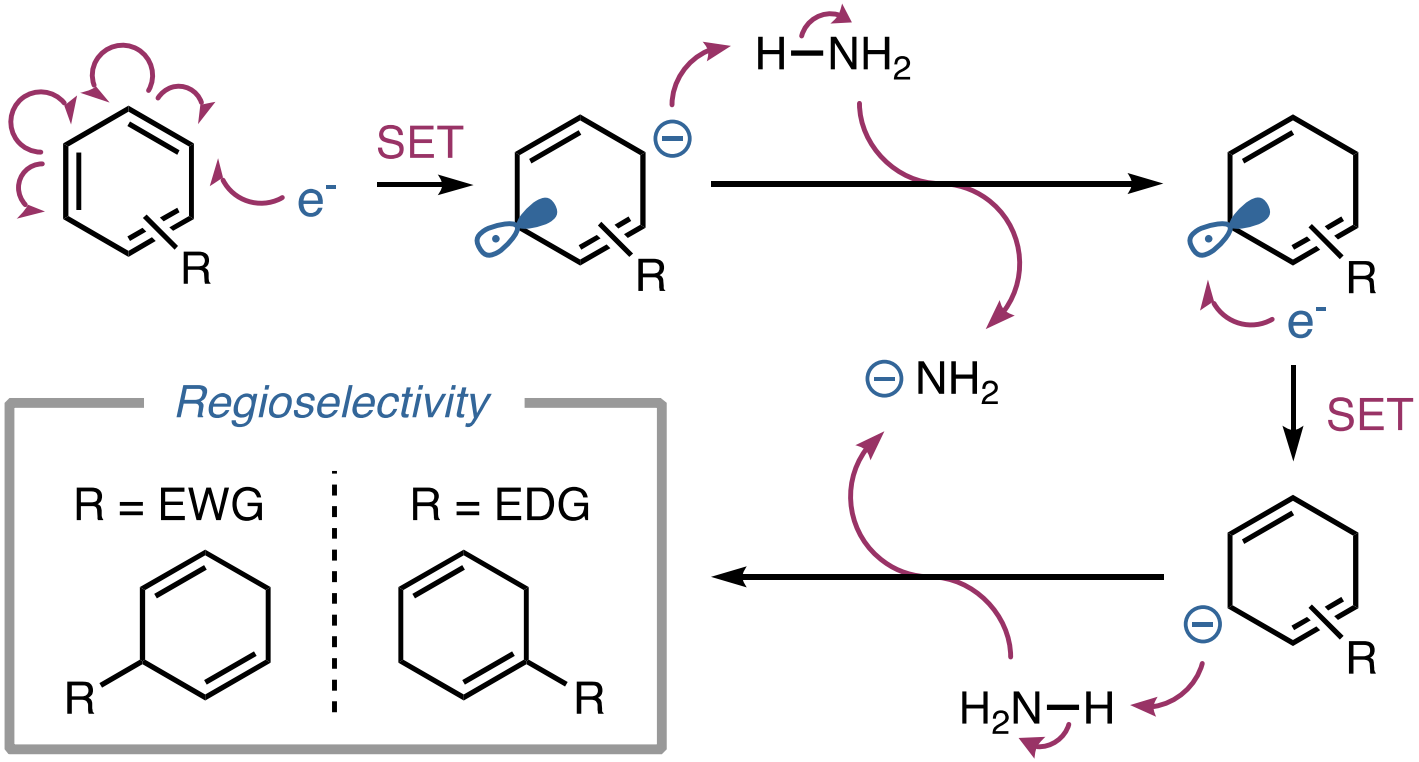
Dis. Mon. **2012**, 38–89; *J. Interdiscip. Hist.* **2011**, 205–233; *J. Psychopharmacol.* **2013**, 479–496; *J. Anal. Toxicol.* **1998**, 299–309; *ACS Chem. Neurosci.* **2018**, 2379–2394

Nagai's Original Synthesis of Methamphetamine (1893)



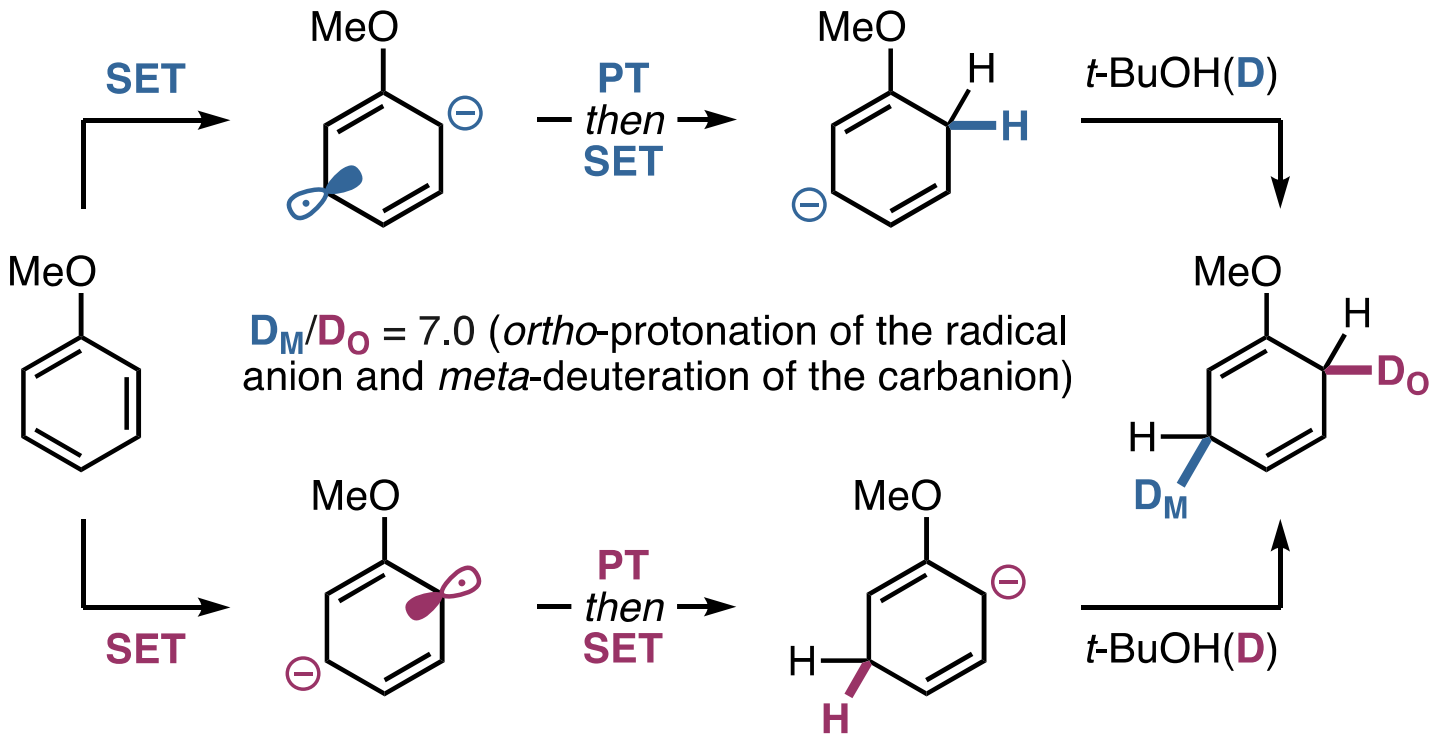
Dis. Mon. **2012**, 38–89; *J. Interdiscip. Hist.* **2011**, 205–233; *J. Psychopharmacol.* **2013**, 479–496; *J. Anal. Toxicol.* **1998**, 299–309; *ACS Chem. Neurosci.* **2018**, 2379–2394

The Birch Reduction

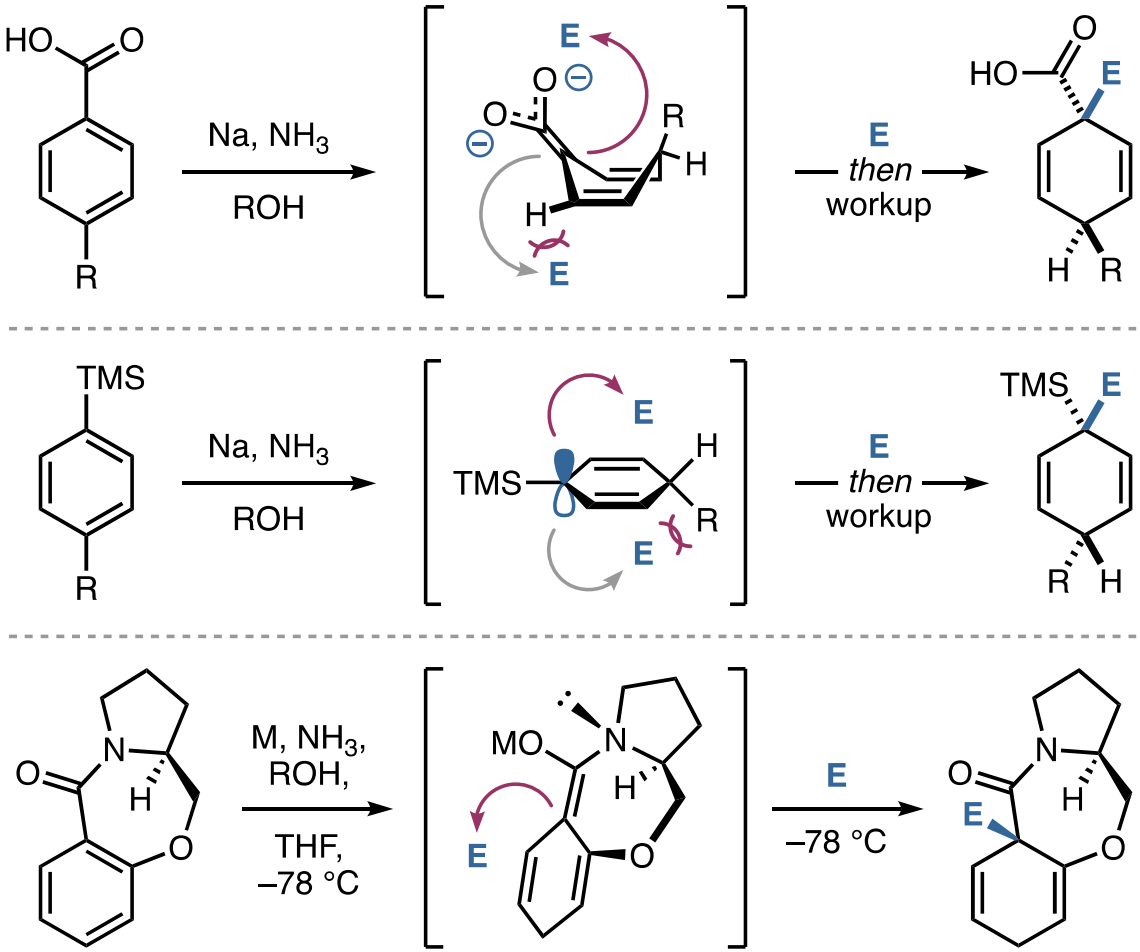


J. Chem. Soc. **1944**, 430–436; *J. Chem. Soc.* **1945**, 809–813; *J. Chem. Soc.* **1946**, 593–597; J. *Chem. Soc.* **1947**, 102–105; *Nat. Protoc.* **2007**, 1888–1895

Dispute Over Mechanism (Birch vs. Zimmerman)

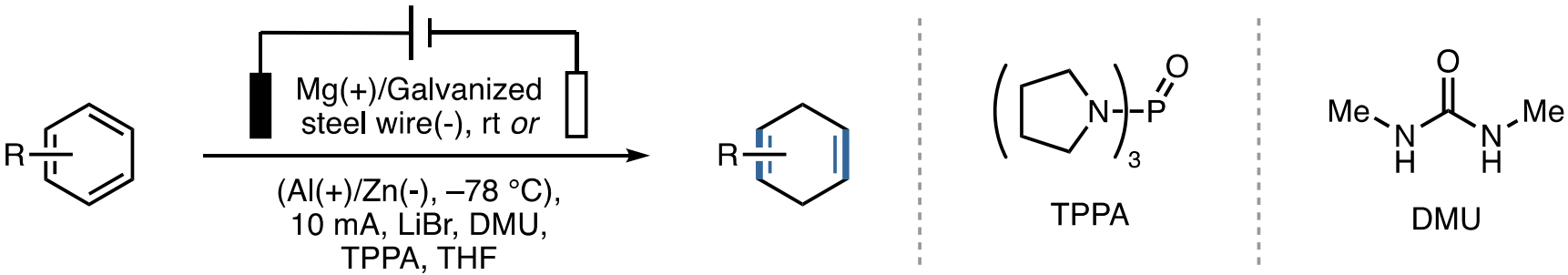


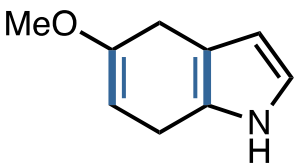
Stereoselectivity in protonation/alkylation



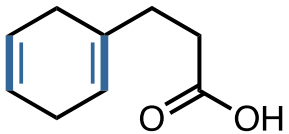
Org. React. **1992**, 1–334; *Acc. Chem. Res.* **1990**, 207–213; *Org. Lett.* **2004**, 3055-3058

Baran's Electrochemical Birch

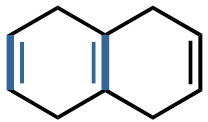




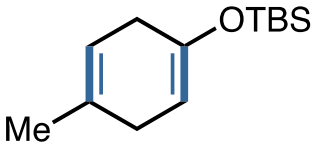
48% (78%)
[Li] = 82%
Na-disp. = 28%



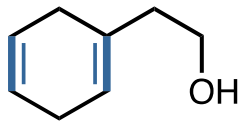
40% (68%)
[Li] = 90%
Na-disp. = 14%



71% (75%)
[Li] = 98%
Na-disp. = 6%

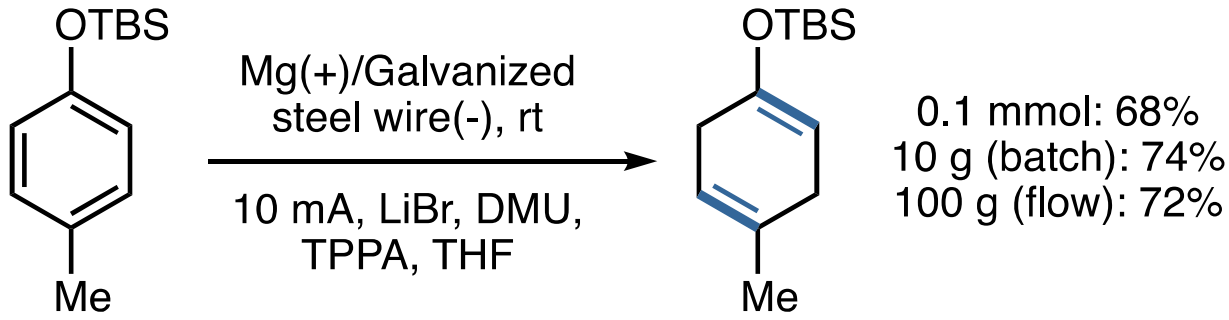


68% (72%)
[Li] = 90%
Na-disp. = 7%

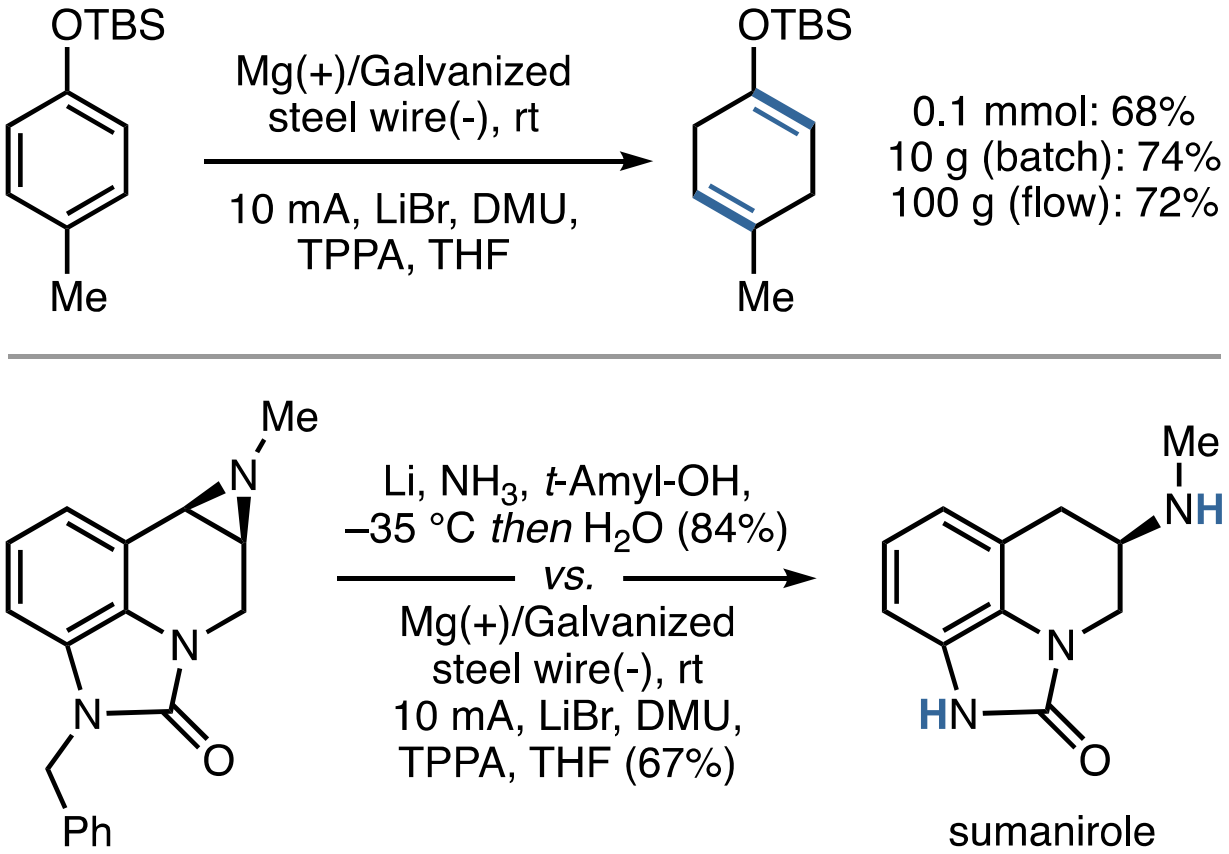


70%
[Li] = 62%
Na-disp. = 10%

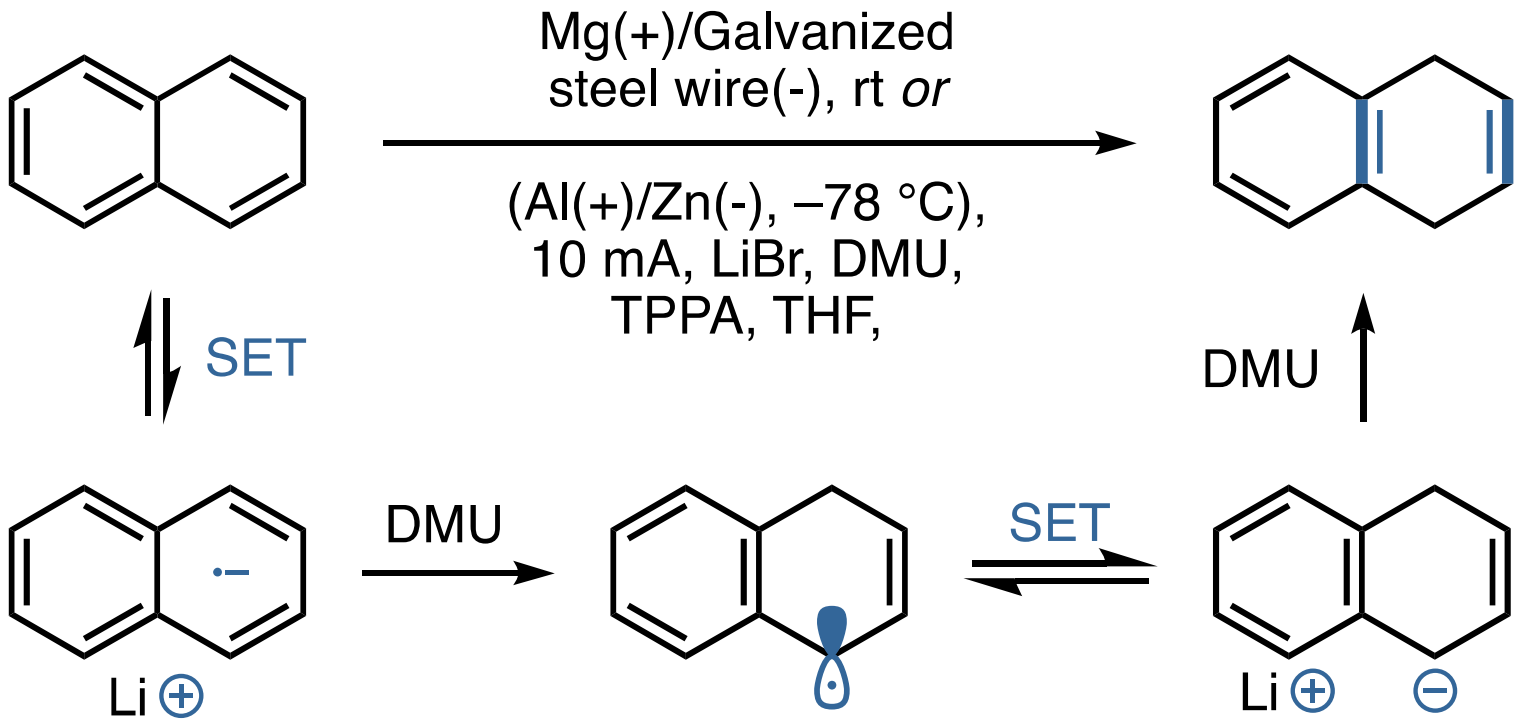
Reaction Scalability and Practical Application



Reaction Scalability and Practical Application

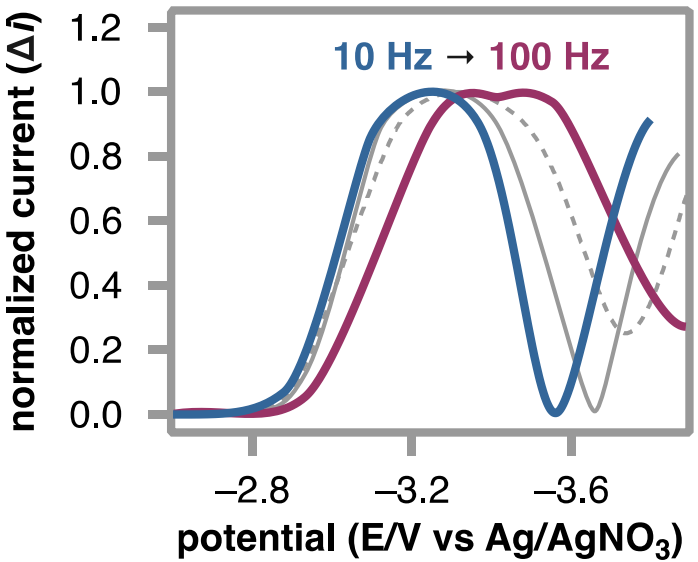


Reaction Mechanism

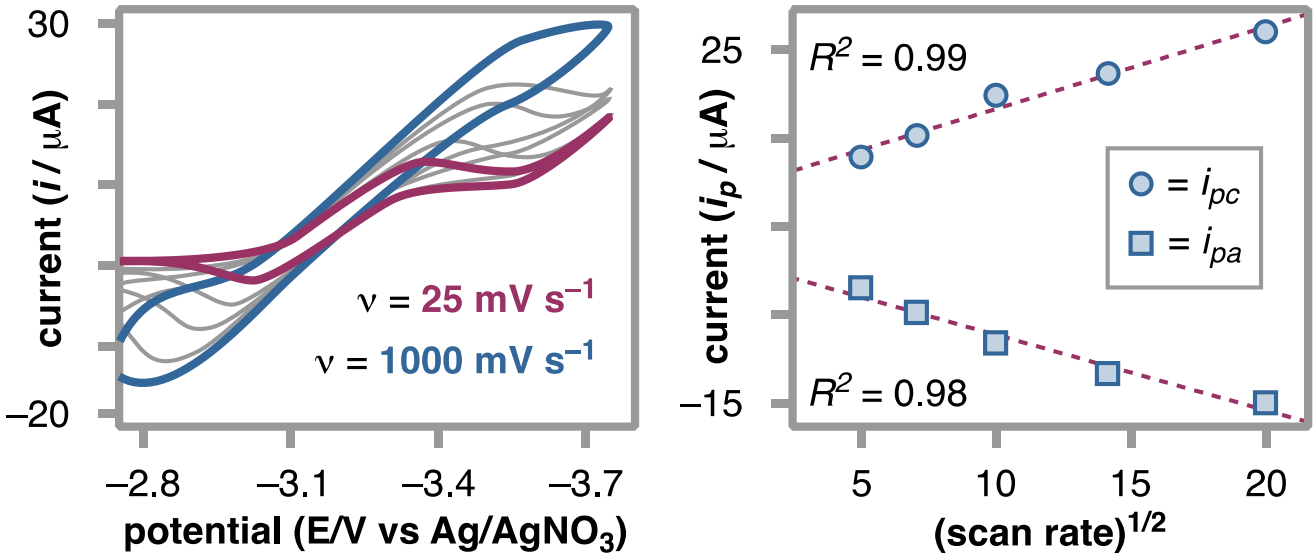


Science, **2019**, 838–845; *Org. Process Res. Dev.* **2005**, 997–1002

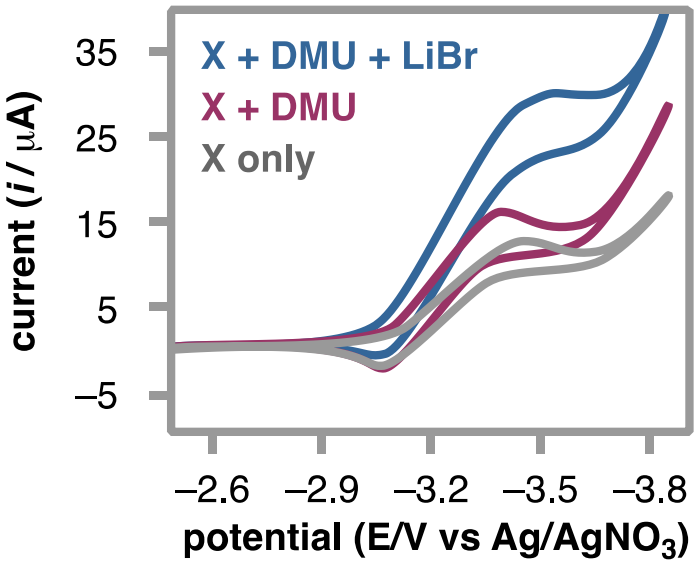
Square Wave Voltammetry (SWV) Analysis



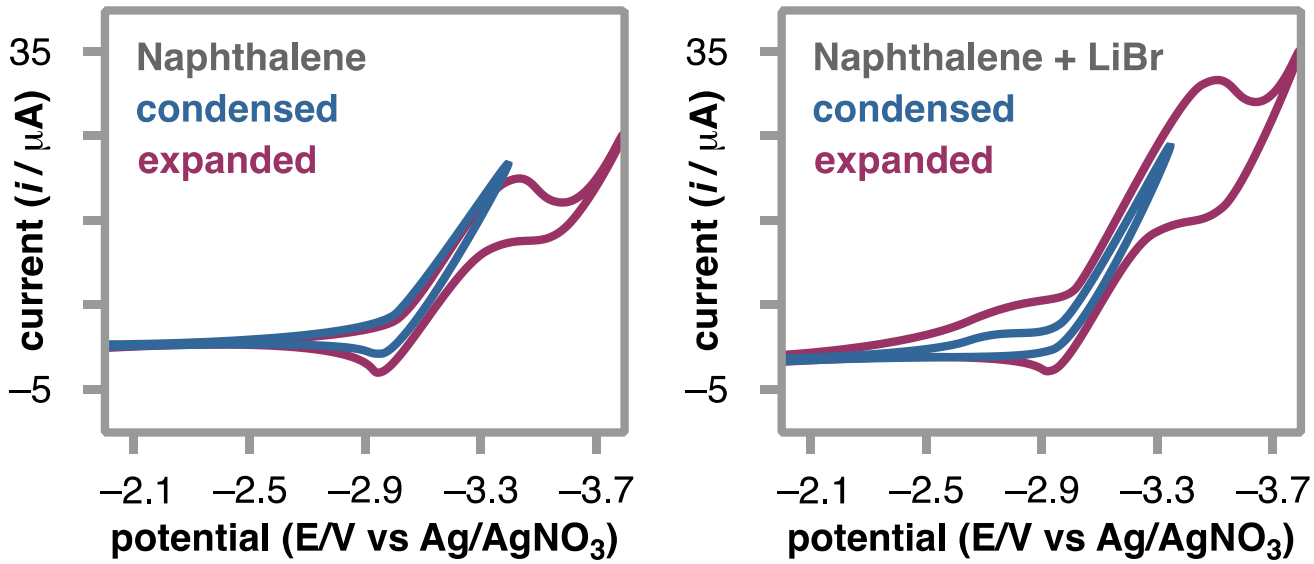
Cyclic Voltammetry (CV) Analysis



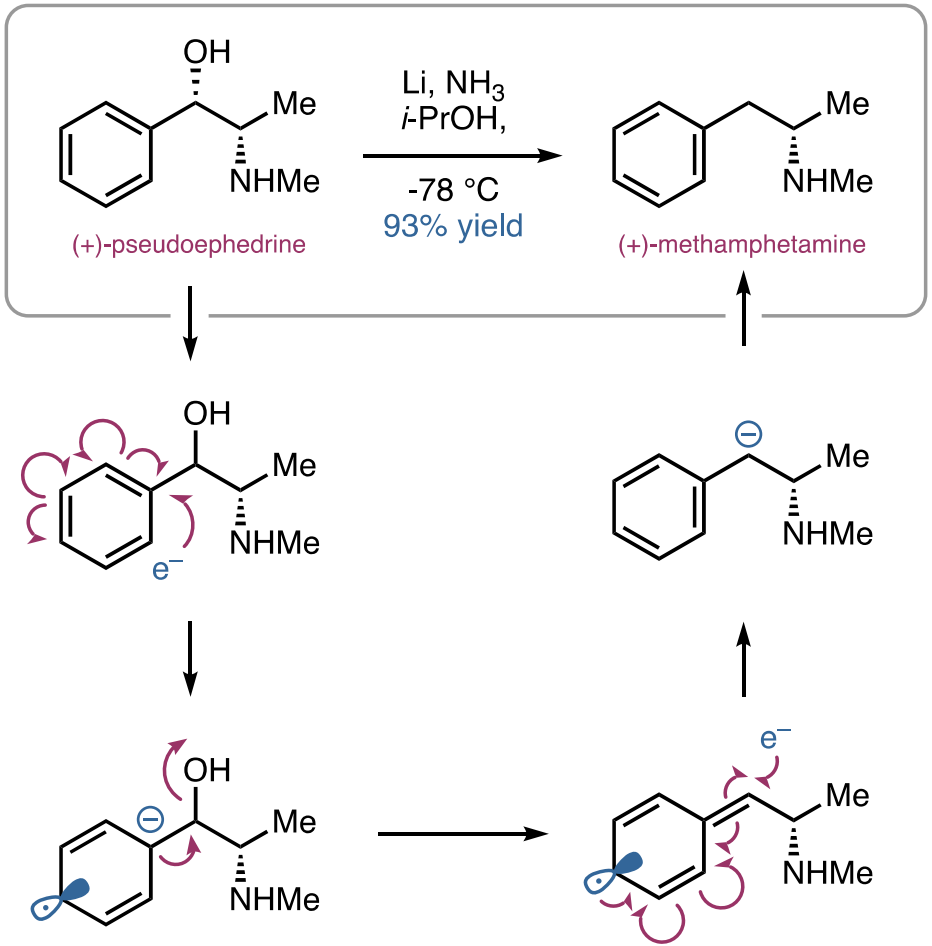
Cyclic Voltammetry (CV) Analysis



Cyclic Voltammetry (CV) Analysis

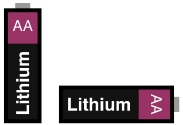


Birch Reduction of Pseudoephedrine

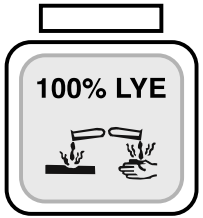


“Shake and Bake” Synthesis of Methamphetamine

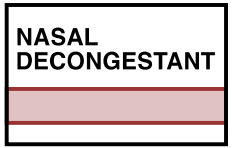
NH_4NO_3
[cold compress]



Li metal
[batteries]



NaOH(*s*)
[lye]

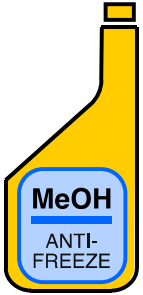


(+)-pseudoephedrine•HCl
[nasal decongestant]

xylenes/toluene
[paint thinner]

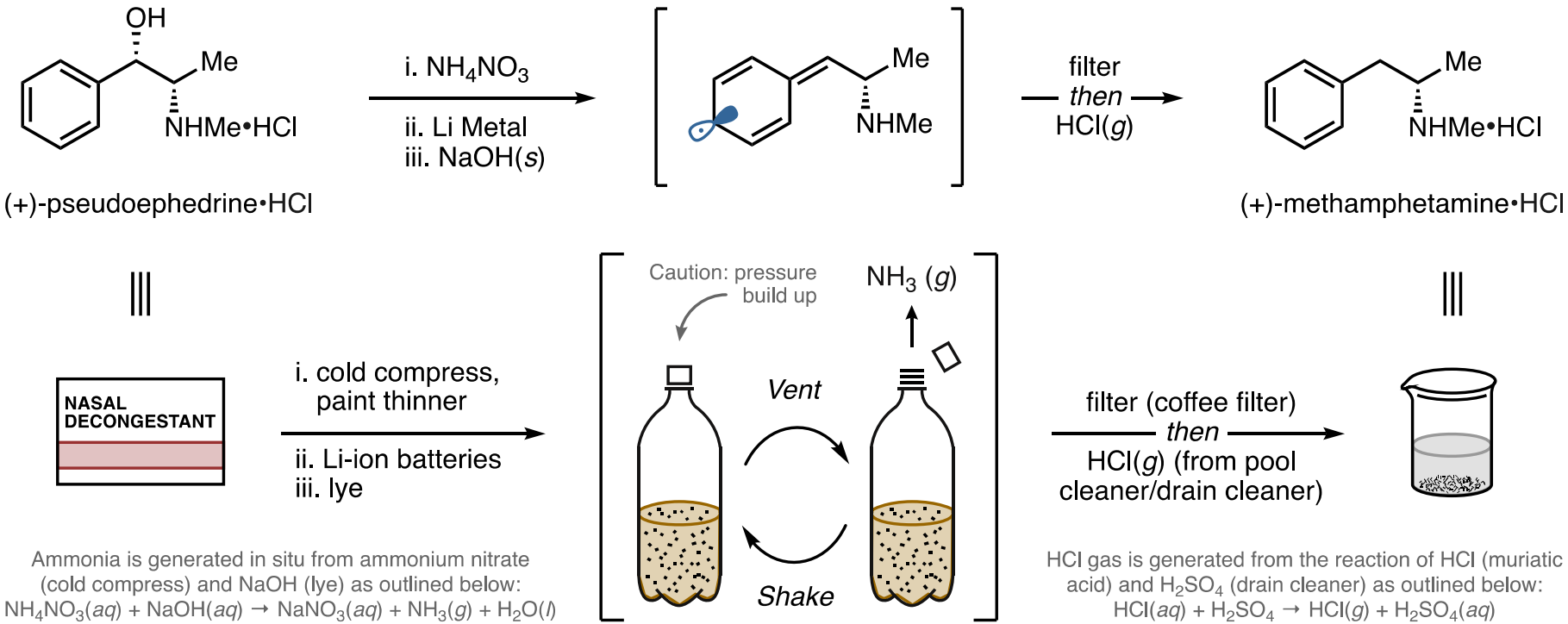
H_2SO_4
[drain cleaner]

HCl(*aq*)
[pool cleaner]



MeOH
[gasline antifreeze]

“Shake and Bake” Synthesis of Methamphetamine



Ammonia is generated in situ from ammonium nitrate (cold compress) and NaOH (lye) as outlined below:
$NH_4NO_3(aq) + NaOH(aq) \rightarrow NaNO_3(aq) + NH_3(g) + H_2O(l)$

HCl gas is generated from the reaction of HCl (muriatic acid) and H_2SO_4 (drain cleaner) as outlined below:
$HCl(aq) + H_2SO_4 \rightarrow HCl(g) + H_2SO_4(aq)$

Secrets of methamphetamine manufacture: including recipes for MDA, ecstasy, and other psychedelic amphetamines, **2009**.