GREEN CHEMISTRY

Laurea Magistrale in Scienze Chimiche

Prof. Leucio Rossi

6 CFU – AA 2017-2018

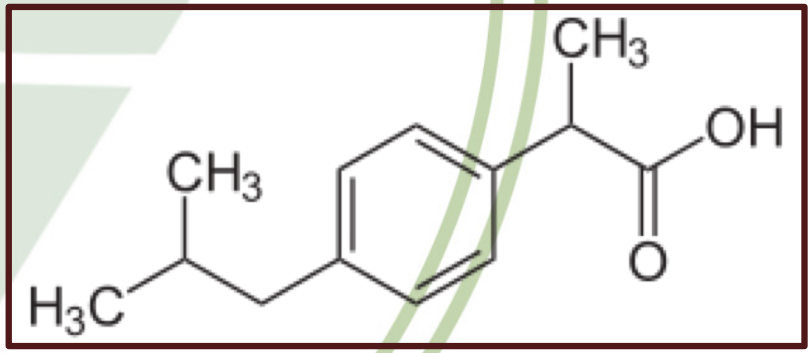
Green Chemistry 05

APPLICATIONS OF GREEN TECHNOLOGIES

Ibuprofene

Ibuprofen is the first pharmaceutical compound that was recognized by the U.S. Environmental Protection Agency Presidential Green Chemistry Challenge Awards in 1997. The Boots-Hoechst-Celanese (BHC) synthesis has been used as a model of green chemistry achievement over the original Boots Drug Company plan.

is a nonsteroidal anti-inflammatory drug (NSAID) used for relieving pain, alleviating fever, and reducing inflammation.

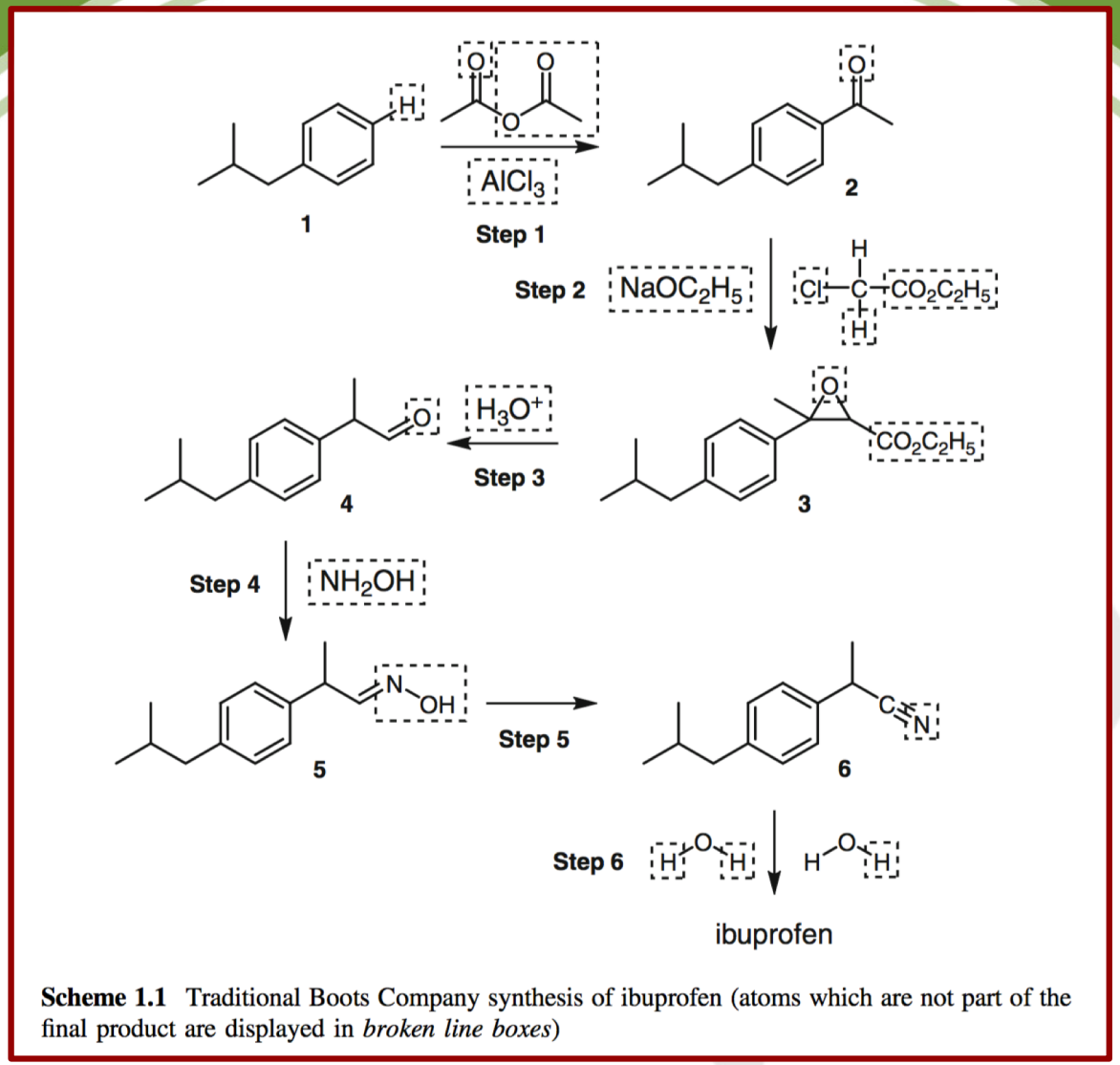


Ibuprofene

TABLE 2.5
Summary of E-Factor Breakdowns for Syntheses of Ibuprofen

Plan	Year	Type	E-Kernel	E-Excess	E-Aux	E-Total	Total Mass of Waste (kg/Mole Ibuprofen)
Upjohn	1977	Linear	4.78	1.03	45.9	51.7	10.7
DD113889	1975	Linear	9.17	15.55	30.47	55.19	11.4
Hoechst-Celanese	1988	Linear	1.72	1.17	111.9	114.79	23.6
Boots	1968	Linear	8.59	15.42	96.52	120.53	24.8
Ruchardt	1991	Linear	12.62	52.06	79.98	144.66	29.8
duPont	1985	Linear	4.67	61.83	150.1	216.61	44.6
Pinhey	1984	Convergent	7.8	152.2	540.3	700.33	144.3
RajanBabu	2009	Linear	3.91	21.81	1,888	1,913.8	394.2
Furstoss	1999	Linear	17.8	12.13	2,286	2,316.2	477.1
McQuade	2009	Linear	7.73	346.6	4,1968	42,322	8,718

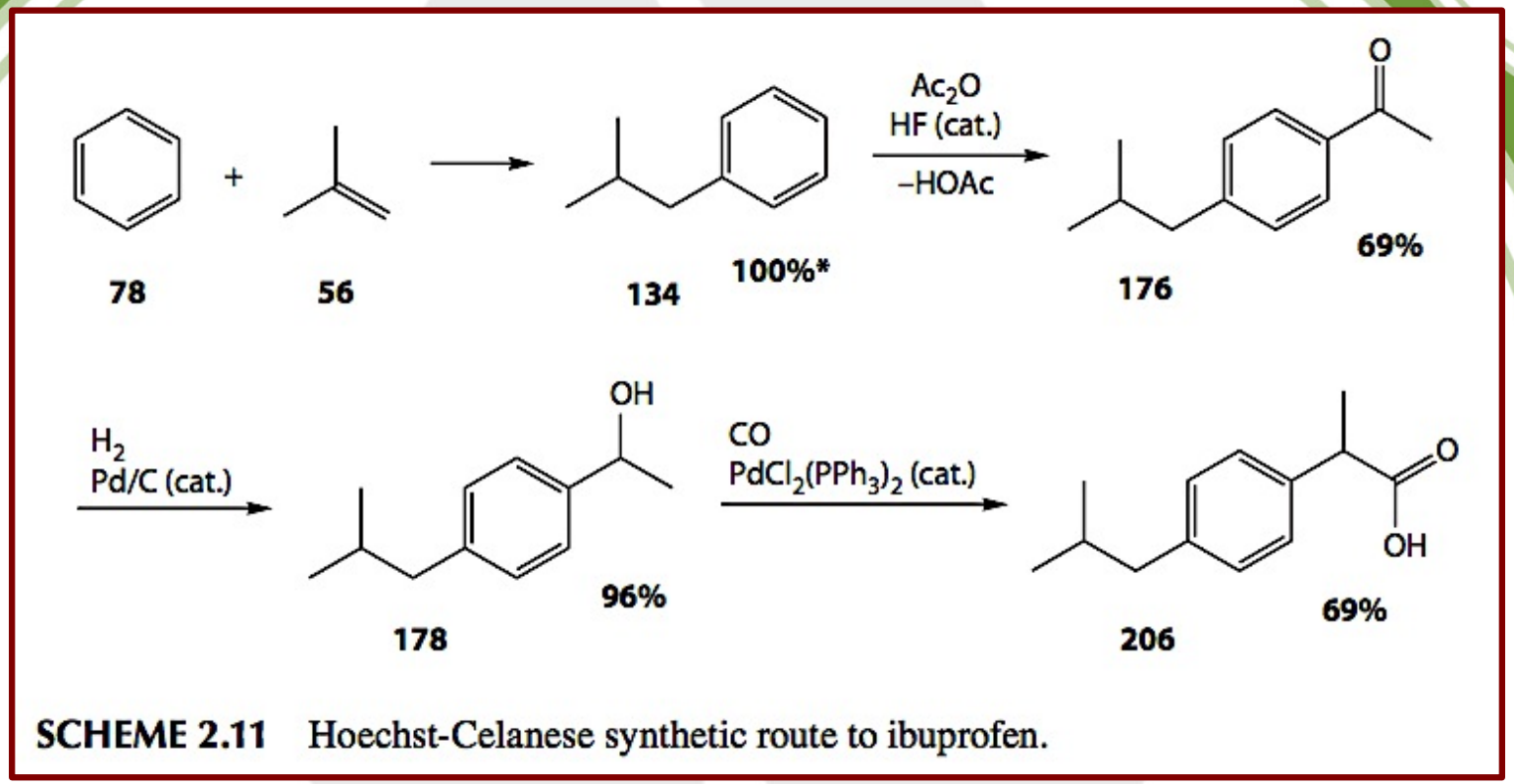
Ibuprofene



Scheme 1.1 Traditional Boots Company synthesis of ibuprofen (atoms which are not part of the final product are displayed in *broken line boxes*)

Ibuprofene

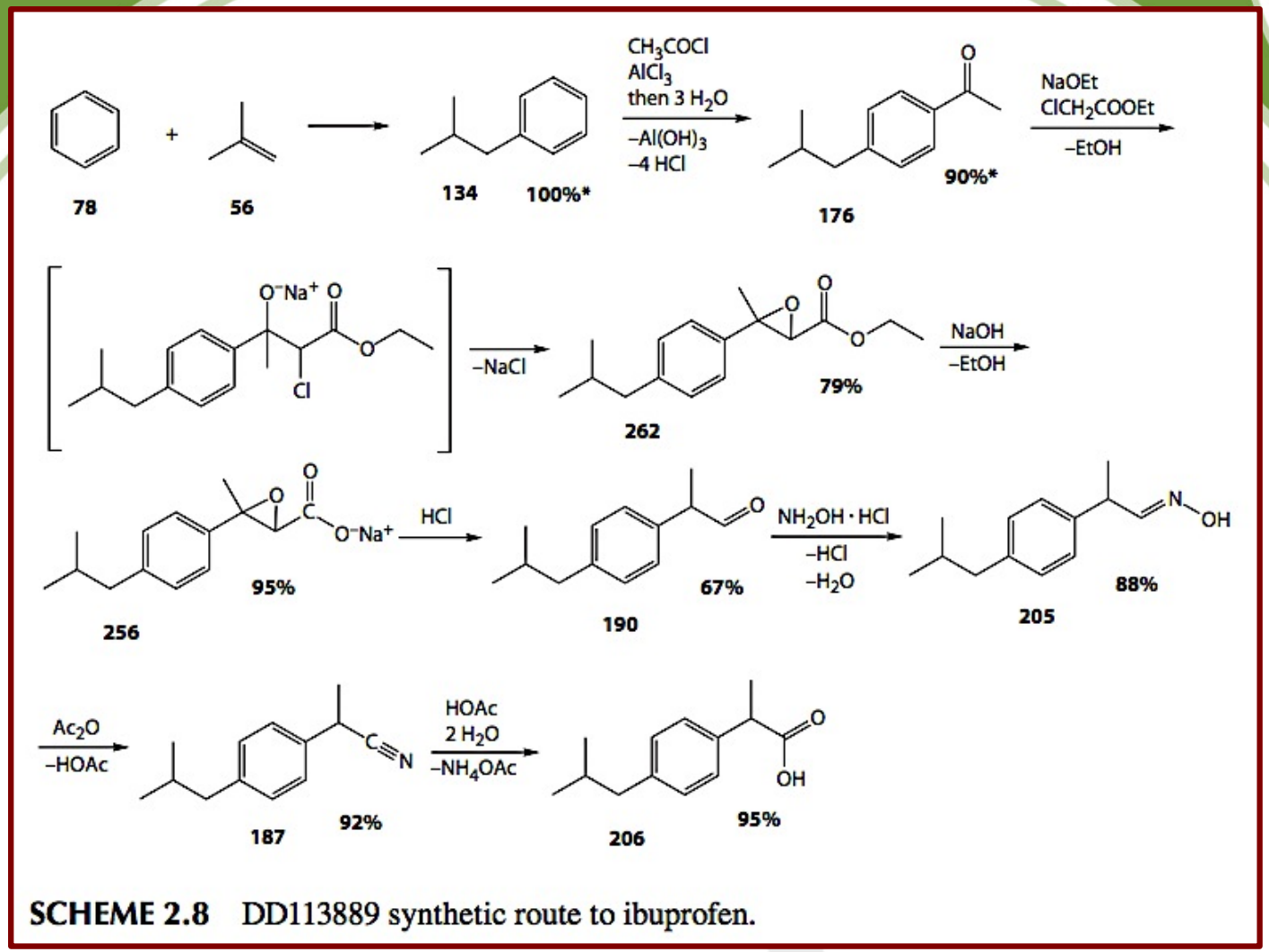
Presidential Green Chemistry Challenge Award in 1997



SCHEME 2.11 Hoechst-Celanese synthetic route to ibuprofen.

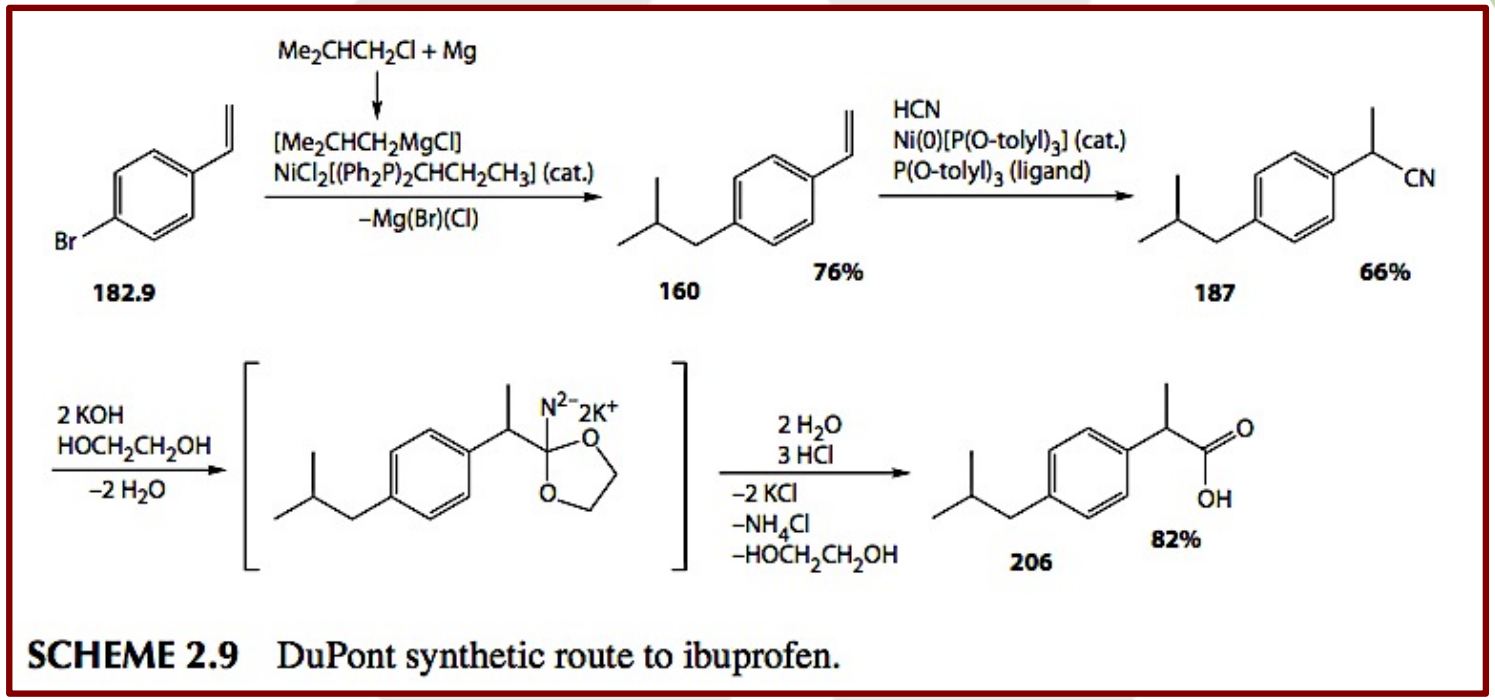
Elango V et al. (1991) U.S. Patent 4981995; Lindley DD et al. (1991) U.S. Patent 5068448

Ibuprofene



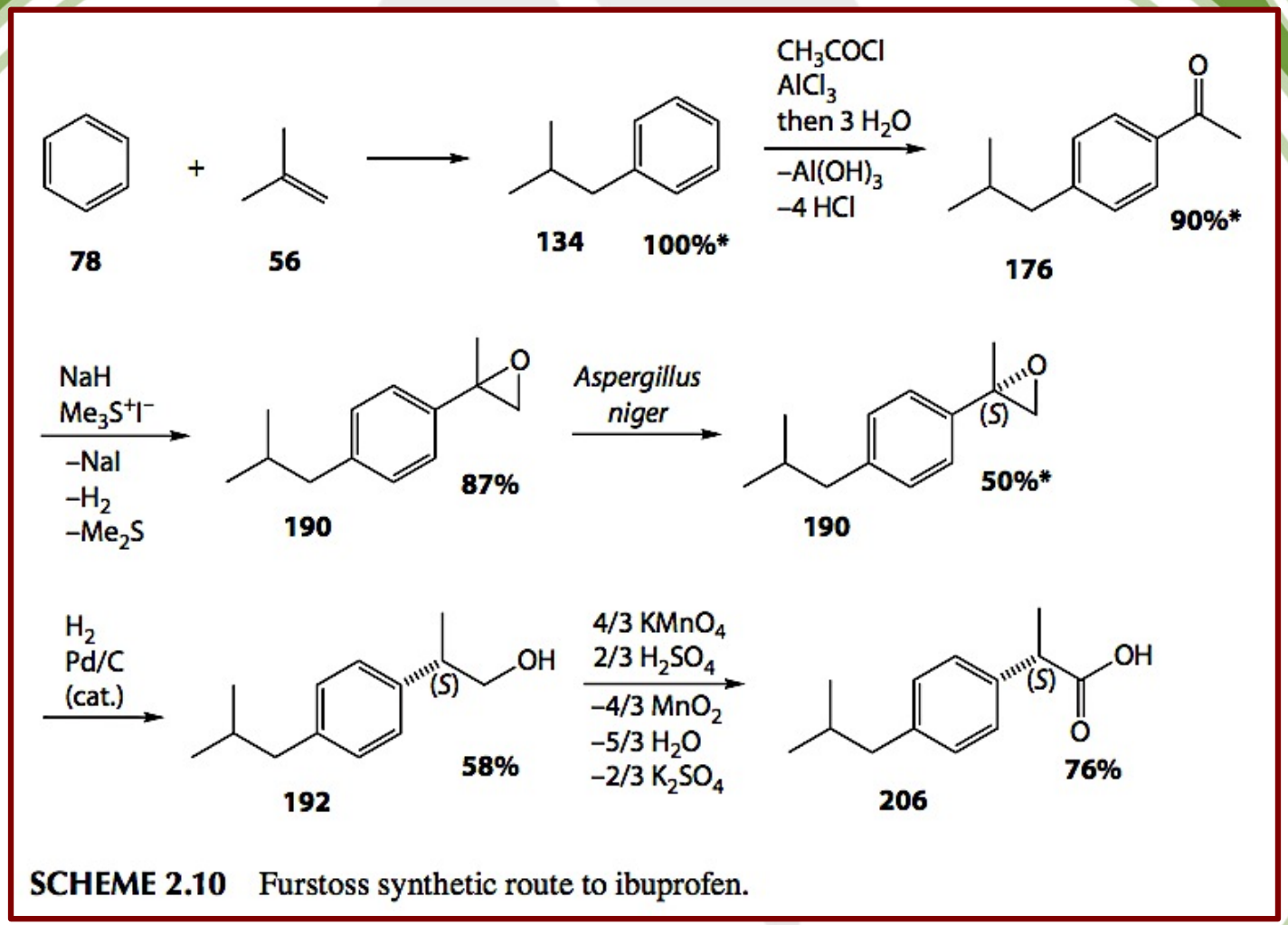
SCHEME 2.8 DD113889 synthetic route to ibuprofen.

Ibuprofene



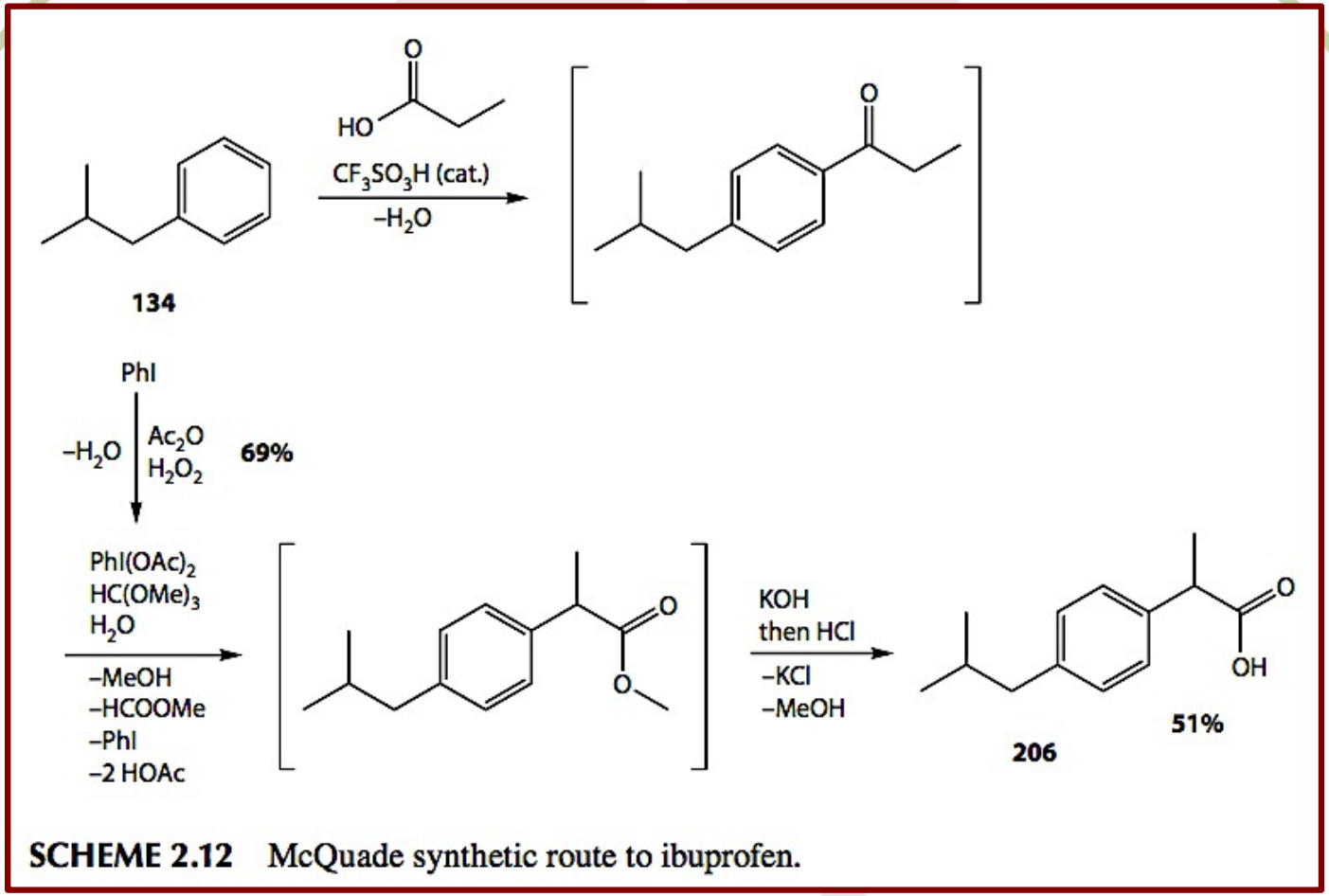
SCHEME 2.9 DuPont synthetic route to ibuprofen.

Ibuprofene



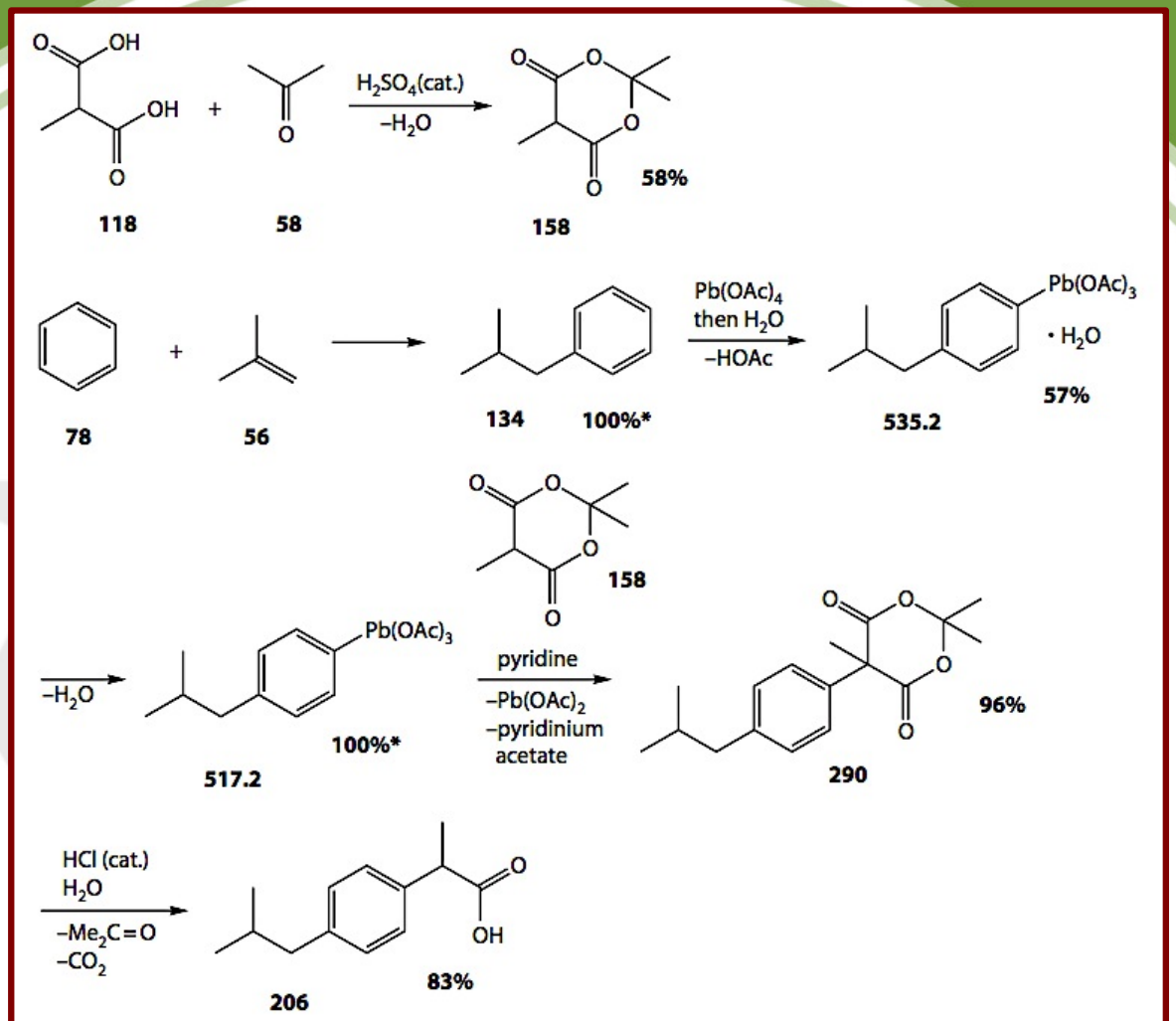
SCHEME 2.10 Furstoss synthetic route to ibuprofen.

Ibuprofene



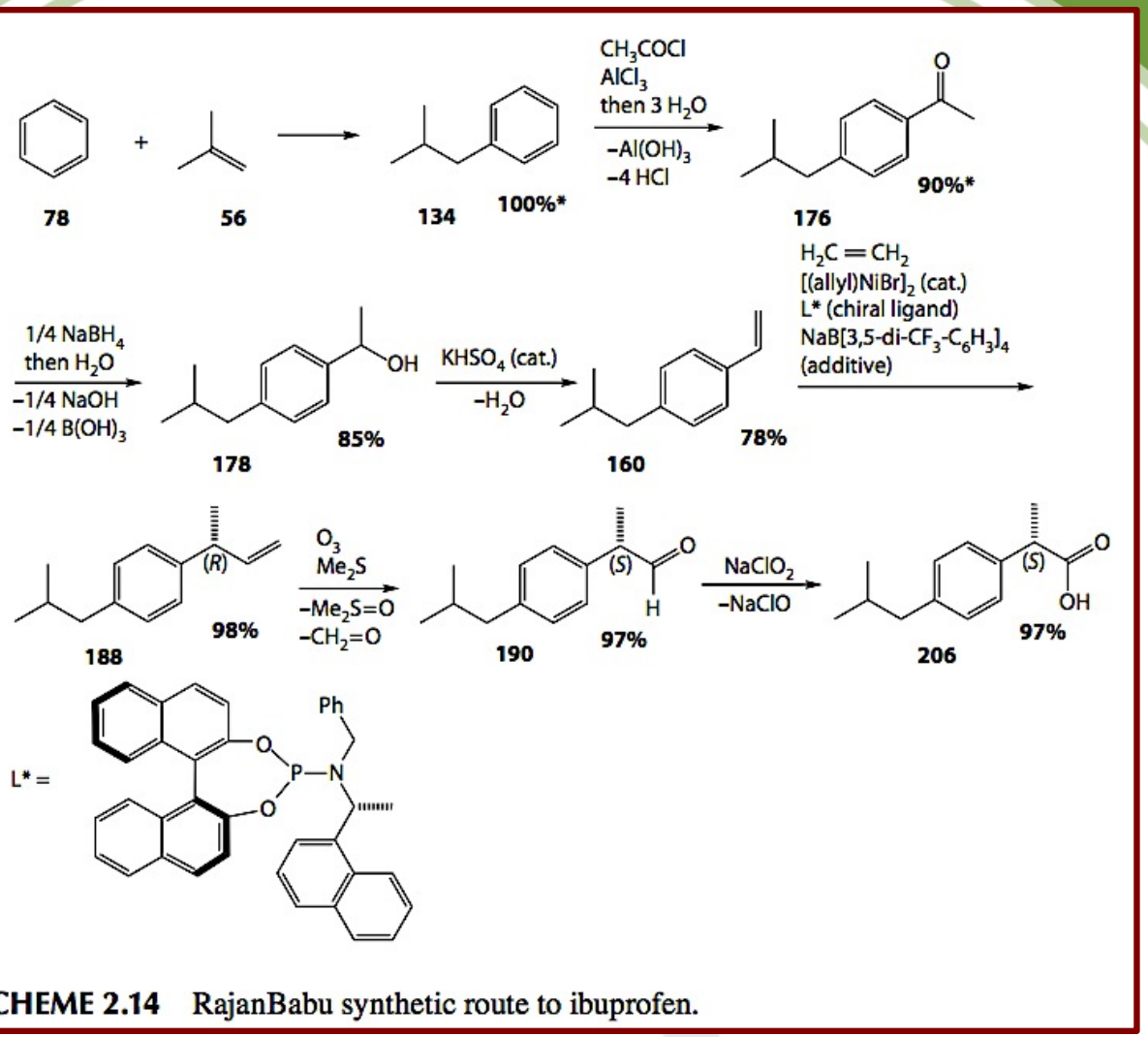
SCHEME 2.12 McQuade synthetic route to ibuprofen.

Ibuprofene



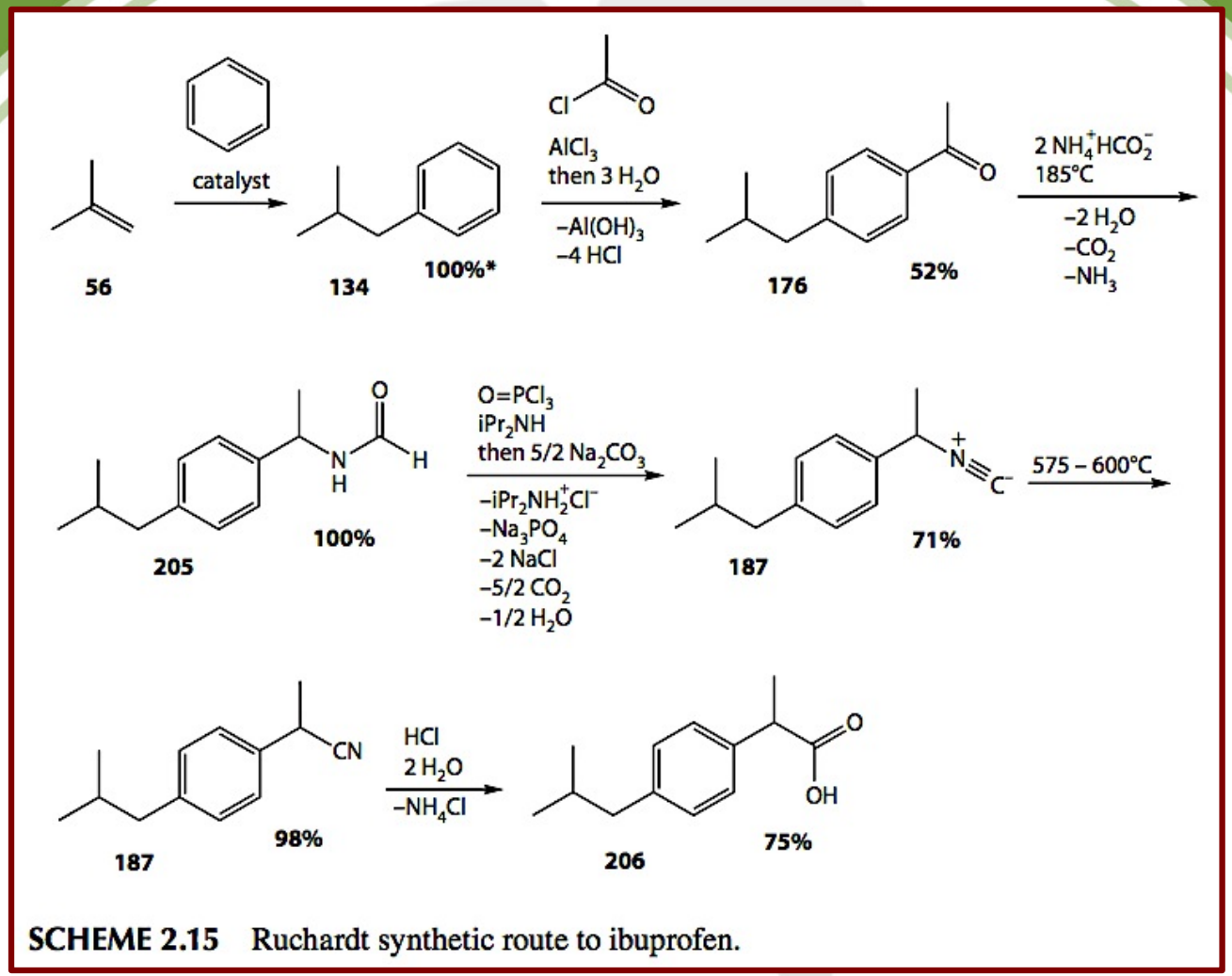
SCHEME 2.13 Pinhey synthetic route to ibuprofen.

Ibuprofene



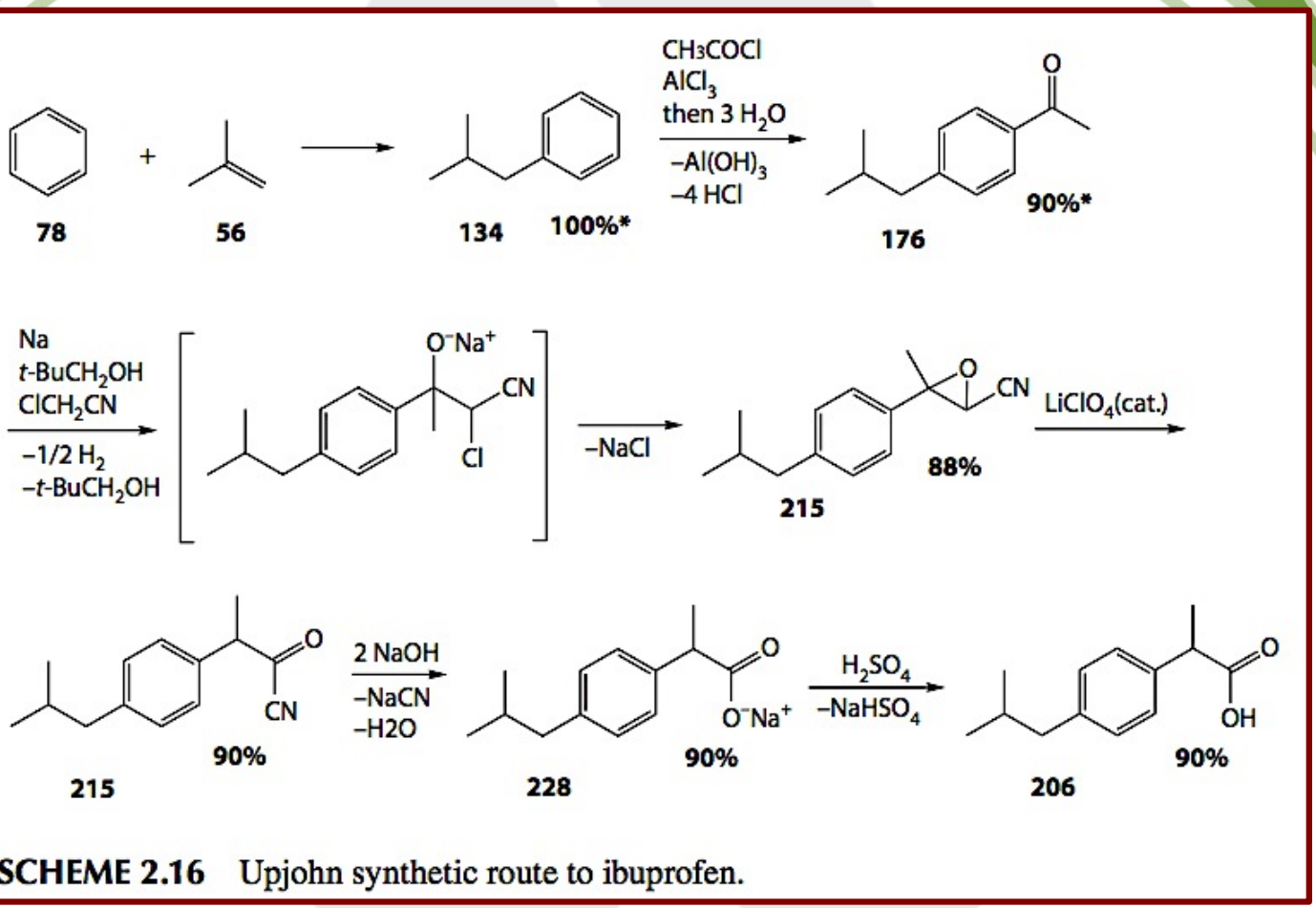
SCHEME 2.14 RajanBabu synthetic route to ibuprofen.

Ibuprofene



SCHEME 2.15 Ruchardt synthetic route to ibuprofen.

Ibuprofene



SCHEME 2.16 Upjohn synthetic route to ibuprofen.

Ibuprofene

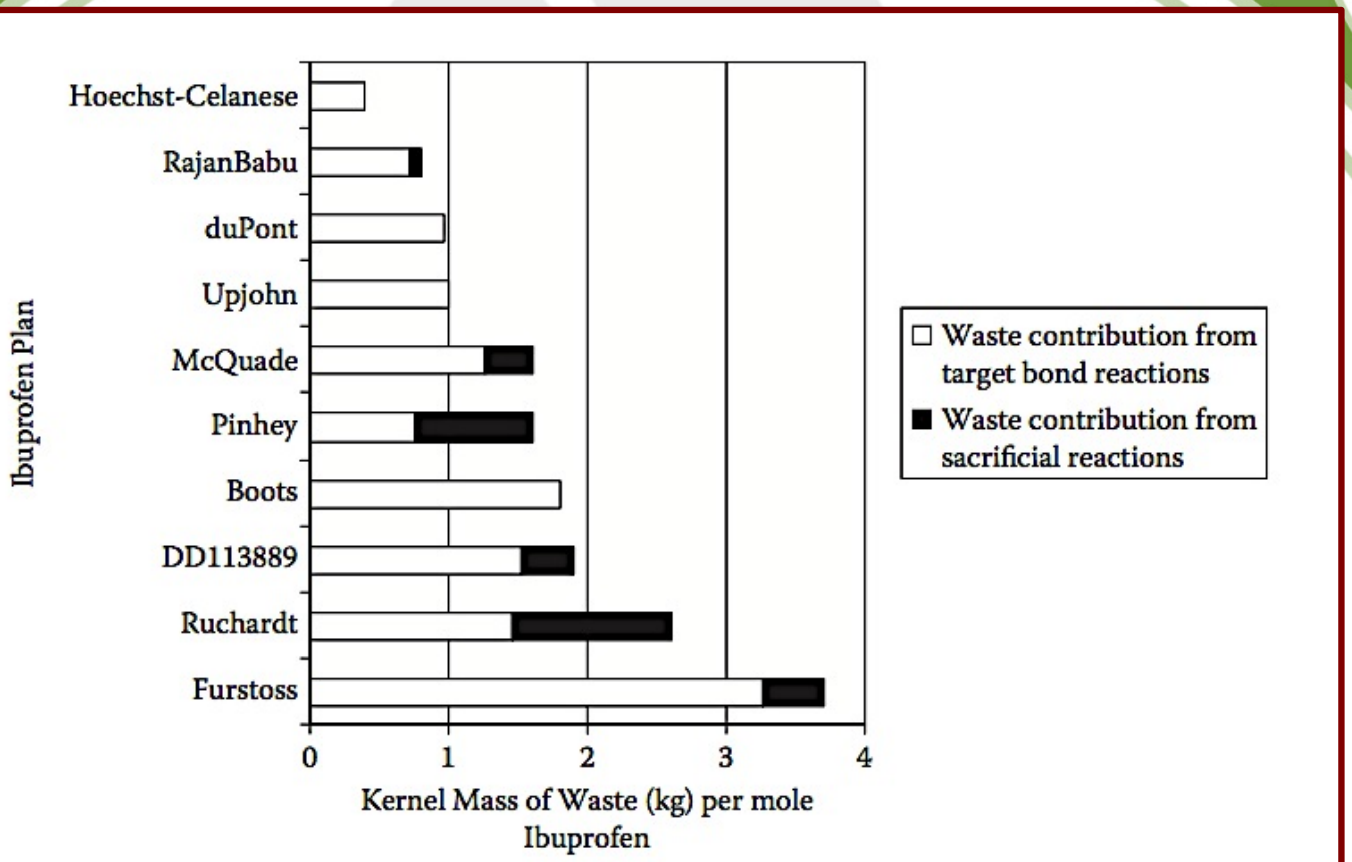
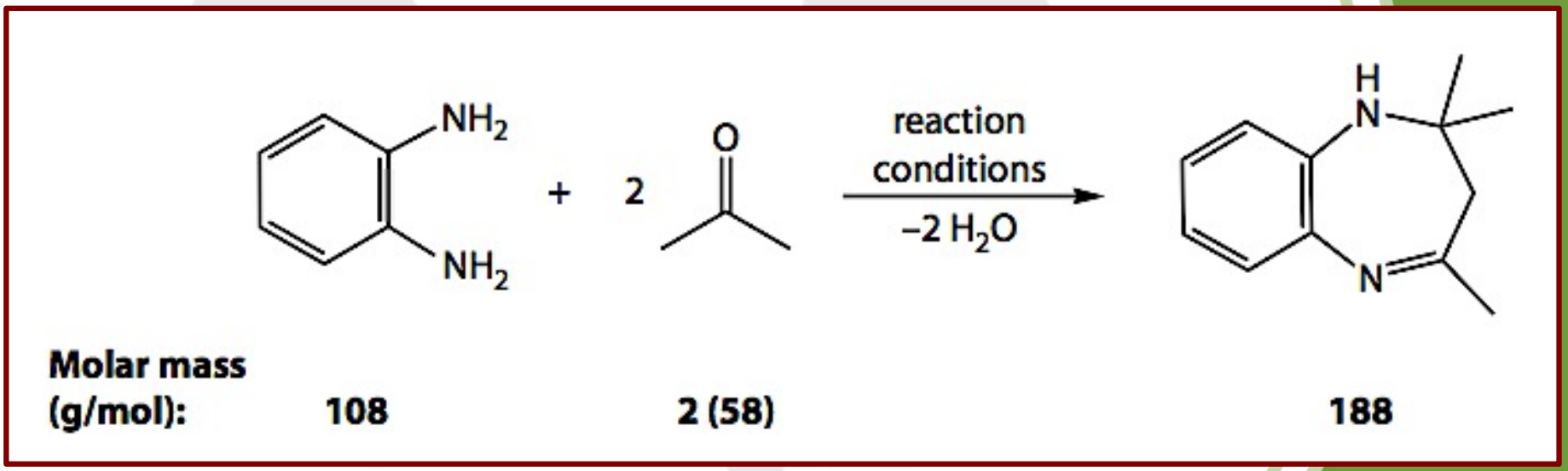


FIGURE 2.4 Bar graph showing ranking by overall kernel waste production and waste contributions from target bond and sacrificial reactions for synthesis plans of ibuprofen.

2,2,4-Trimethyl-2,3-Dihydro-1H-Benzo[B][1,4]Diazepine

Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), euphoric, anticonvulsant, and muscle relaxant properties; also seen in the applied pharmacology of high doses of many shorter-acting benzodiazepines are amnesic-dissociative actions.



2,2,4-Trimethyl-2,3-Dihydro-1H-Benzo[B][1,4]Diazepine

TABLE 2.3
Summary of E-Factor Breakdowns for Various Syntheses of 2,2,4-Trimethyl-2,3-Dihydro-1H-Benzo[b][1,4]Diazepine

E-Kernel	E-Excess	E-Aux	E-Total	Green Technology Used (reference)
0.22	0.032	0	0.26	Solvent-free, microwaves (18)
0.28	0.066	15.34	15.68	Solid-supported catalyst, microwaves (19)
0.27	0	15.9	16.16	Solvent-free (20)
0.21	0.032	22.68	22.92	Zeolite catalyst (21)
0.32	0.17	25.03	25.52	Solvent-free (22)
8.4	9.08	17.26	34.74	None—benzene solvent used (23)
0.4	0.073	41.75	42.22	Ultrasound (24)
0.28	0.034	65.89	66.2	No catalyst, [bbim]BF_4 solvent (25)
0.2	0.031	71.55	71.78	Solvent-free (26)
0.21	0.16	72.25	72.62	Solid-supported catalyst, microwaves (27)
0.21	0.16	74.97	75.34	Solid-supported catalyst, microwaves (28)
0.25	0.065	78.09	78.41	Solvent-free (29)
0.23	0.098	91.56	91.89	Solvent-free, ball milling (30)
0.28	0.083	104.92	105.29	Water solvent, nanoparticle catalyst (31)
0.29	0.17	109.71	110.17	Solvent-free (32)
0.23	0.16	120.94	121.33	Solid-supported catalyst (33)
0.25	0.16	136.48	136.89	Solid-supported catalyst, [bmim]BF_4 solvent (34)
0.28	0.033	155.54	155.86	Solid-supported catalyst, microwaves (35)
0.4	0	169.13	169.53	Solvent-free, microwaves (36)
0.23	0	307.26	307.49	Water solvent (37)
0.32	0.068	532.28	532.66	Water solvent (38)
0.27	0.033	570.93	571.23	Solvent-free (39)
0.28	0.17	678.64	679.09	Solvent-free (40)

contributions from by-products and unreacted starting materials (E-kernel), excess reagent consumption (E-excess), and auxiliary material consumption, such as reaction solvent, workup extraction solvents, and solvents used in purification procedures (E-aux).

2,2,4-Trimethyl-2,3-Dihydro-1H-Benzo[B][1,4]Diazepine

18. Pozarentzi, M., Stephanidou-Stephanatou, J., Tsoleridis, C. A. *Tetrahedron Lett.* 2002, 43, 1755–1758.
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2,2,4-Trimethyl-2,3-Dihydro-1H-Benzo[B][1,4]Diazepine

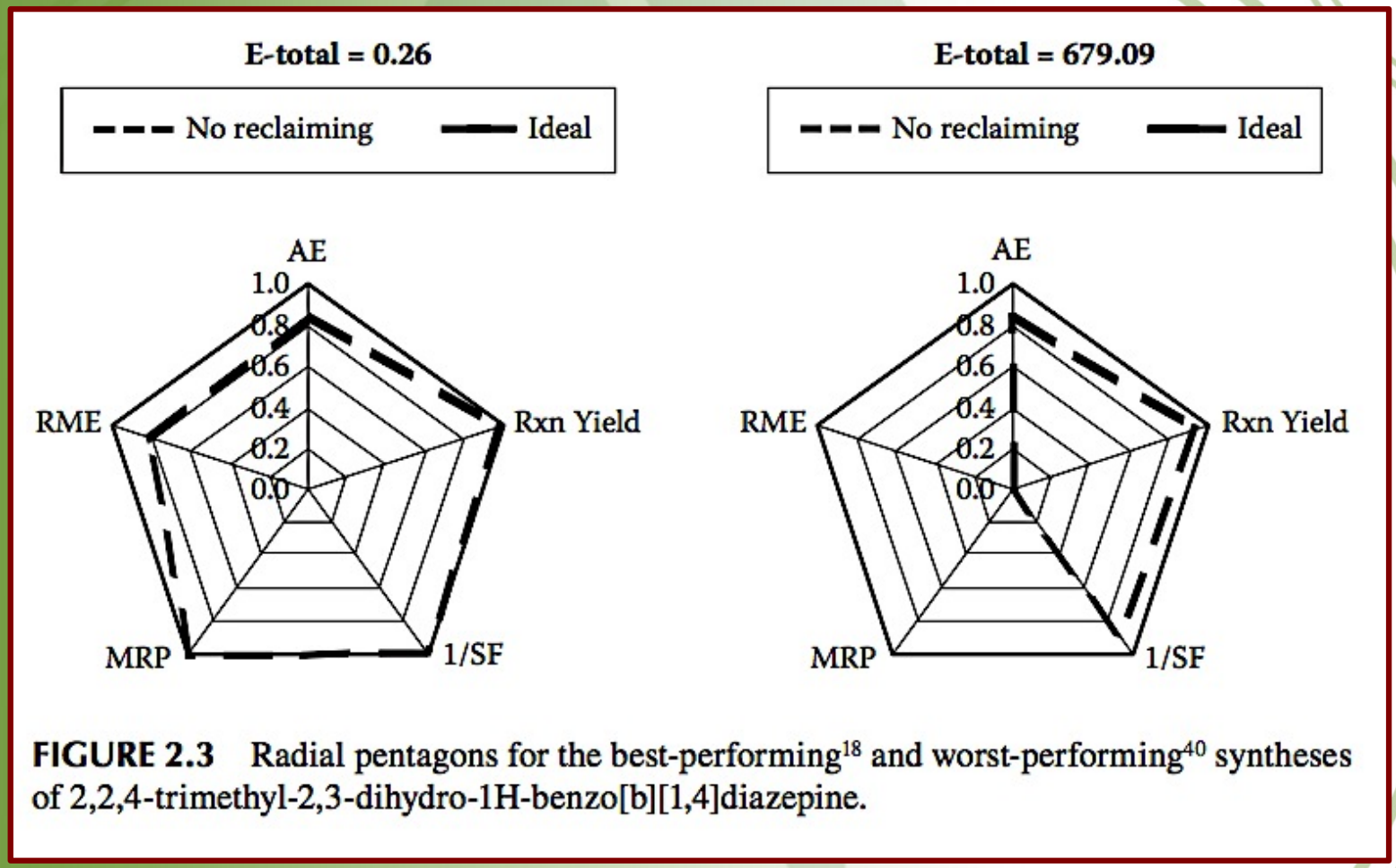


FIGURE 2.3 Radial pentagons for the best-performing[18] and worst-performing[40] syntheses of 2,2,4-trimethyl-2,3-dihydro-1H-benzo[b][1,4]diazepine.

Pravadoline

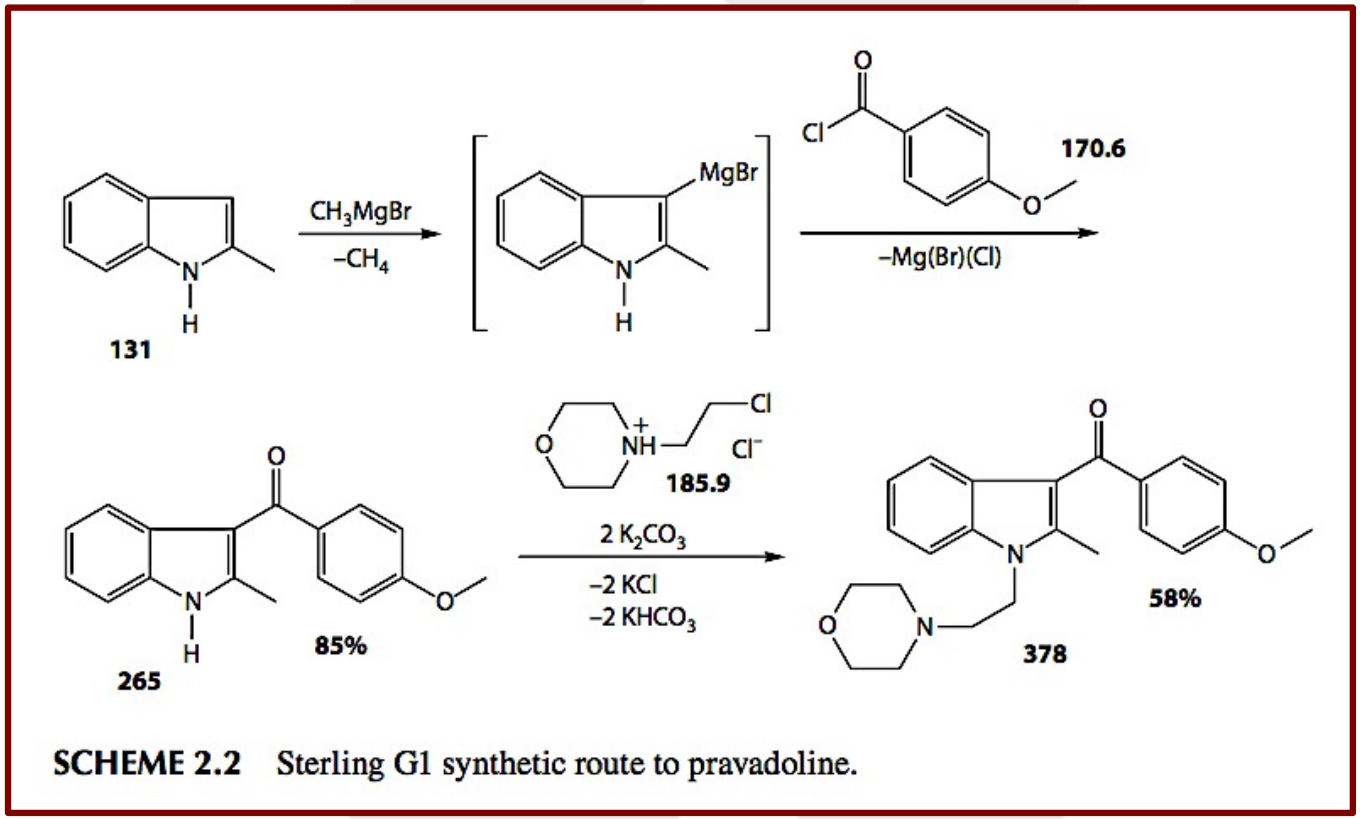
Pravadoline is a nonsteroidal anti-inflammatory drug (NSAID) whose synthesis was the first pharmaceutical to be "greened up" using an ionic liquid as a reaction solvent.

TABLE 2.4
Summary of E-Factor Breakdowns for Various Syntheses of Pravadoline

Plan	Year	Type	E-Kernel	E-Excess	E-Aux	E-Total	Total Mass of Waste (kg/Mole Pravadoline)
Sterling G1	1991	Linear	3.36	1.96	58.89	64.21	24.3
Sterling G2	1990	Linear	1.95	0.63	196.5	199.05	75.2
Cacchi	1994	Linear	6.79	30.4	415.3	452.53	171.1
Seddon[a]	2000	Linear	1.12	?	?	?	?
[bmim]BF_4	2002	Linear	0.56	0.15	6.88	7.58	1.7

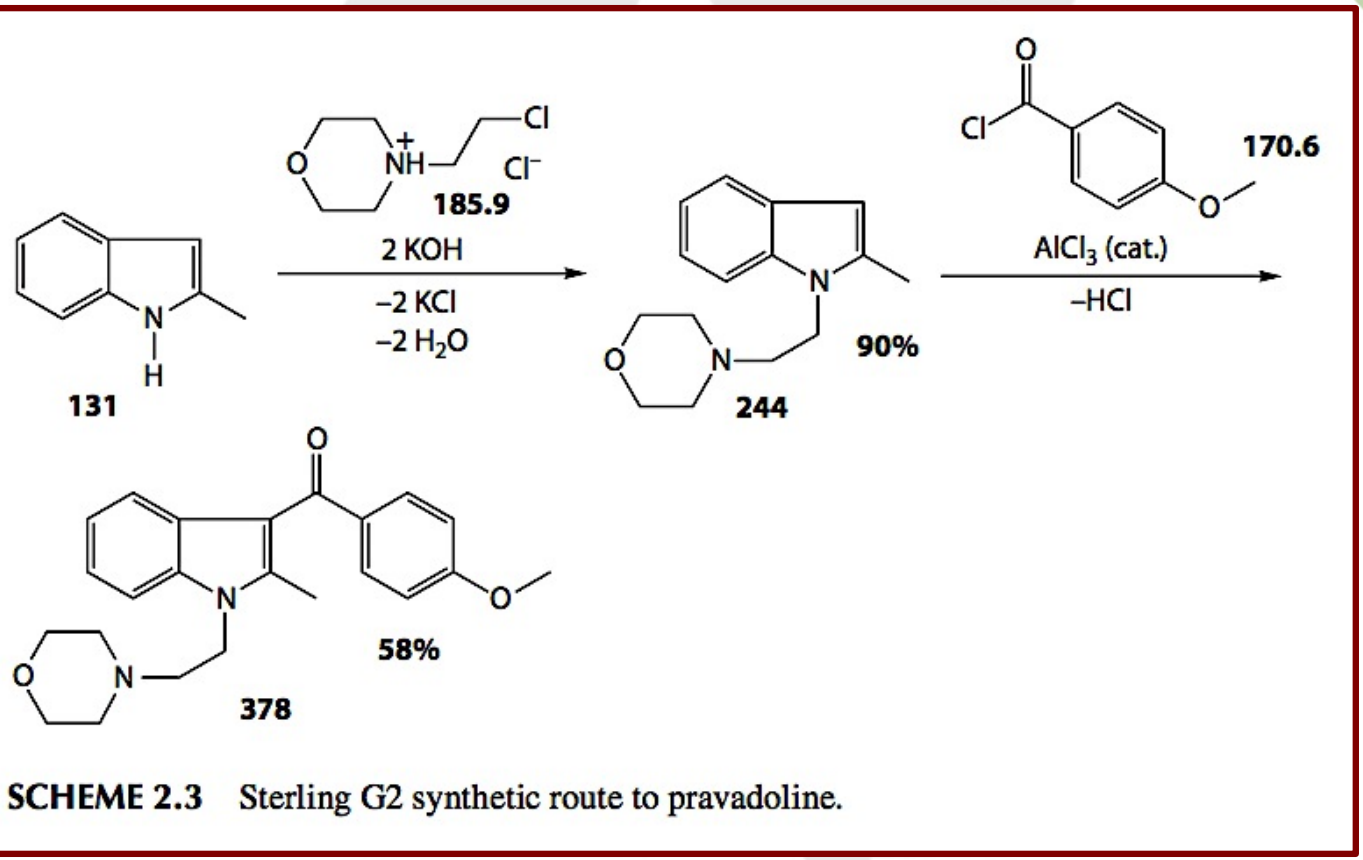
[a] Analysis does not include synthesis of [bmim]BF_4 ionic liquid reaction solvent.

Pravadoline



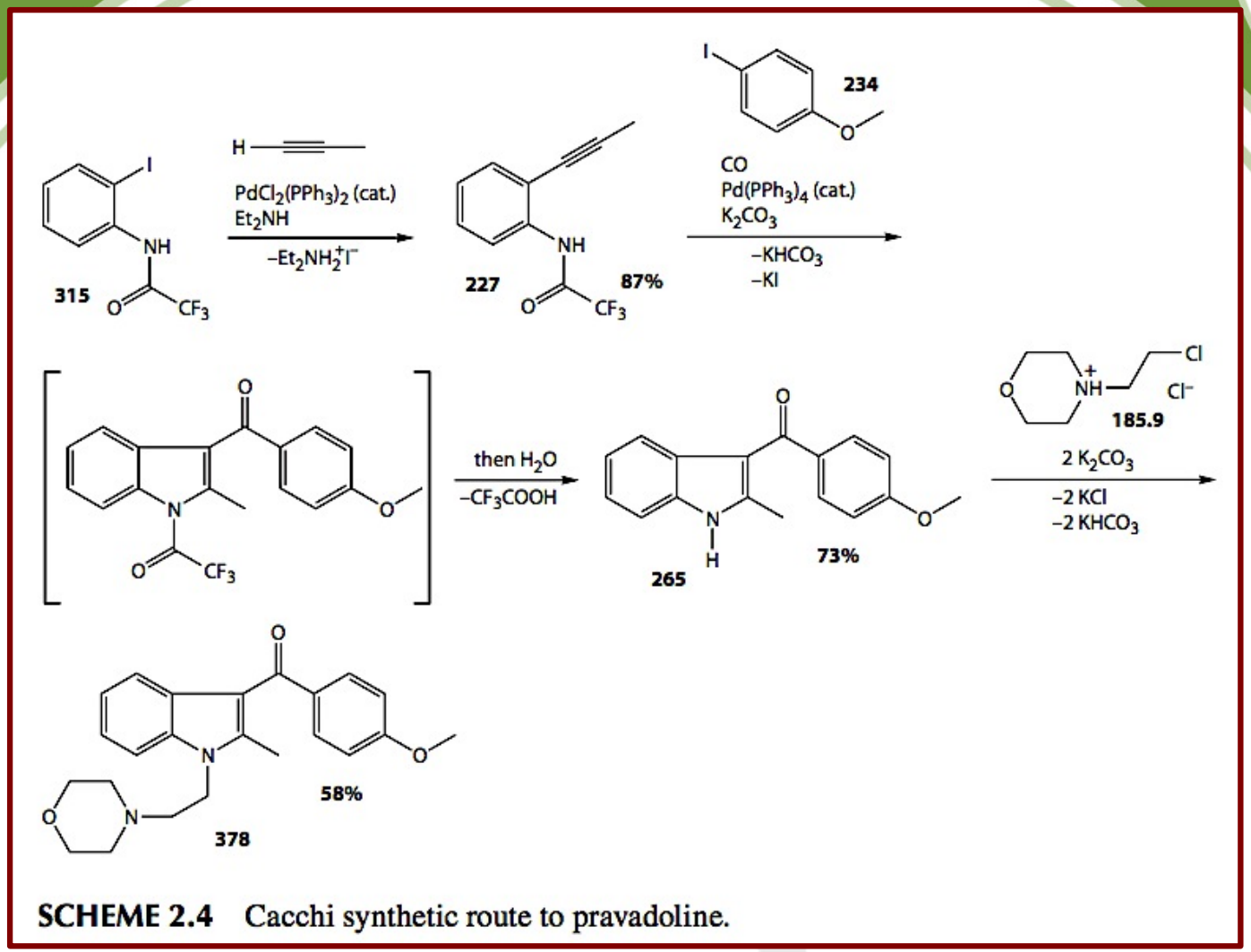
SCHEME 2.2 Sterling G1 synthetic route to pravadoline.

Pravadoline



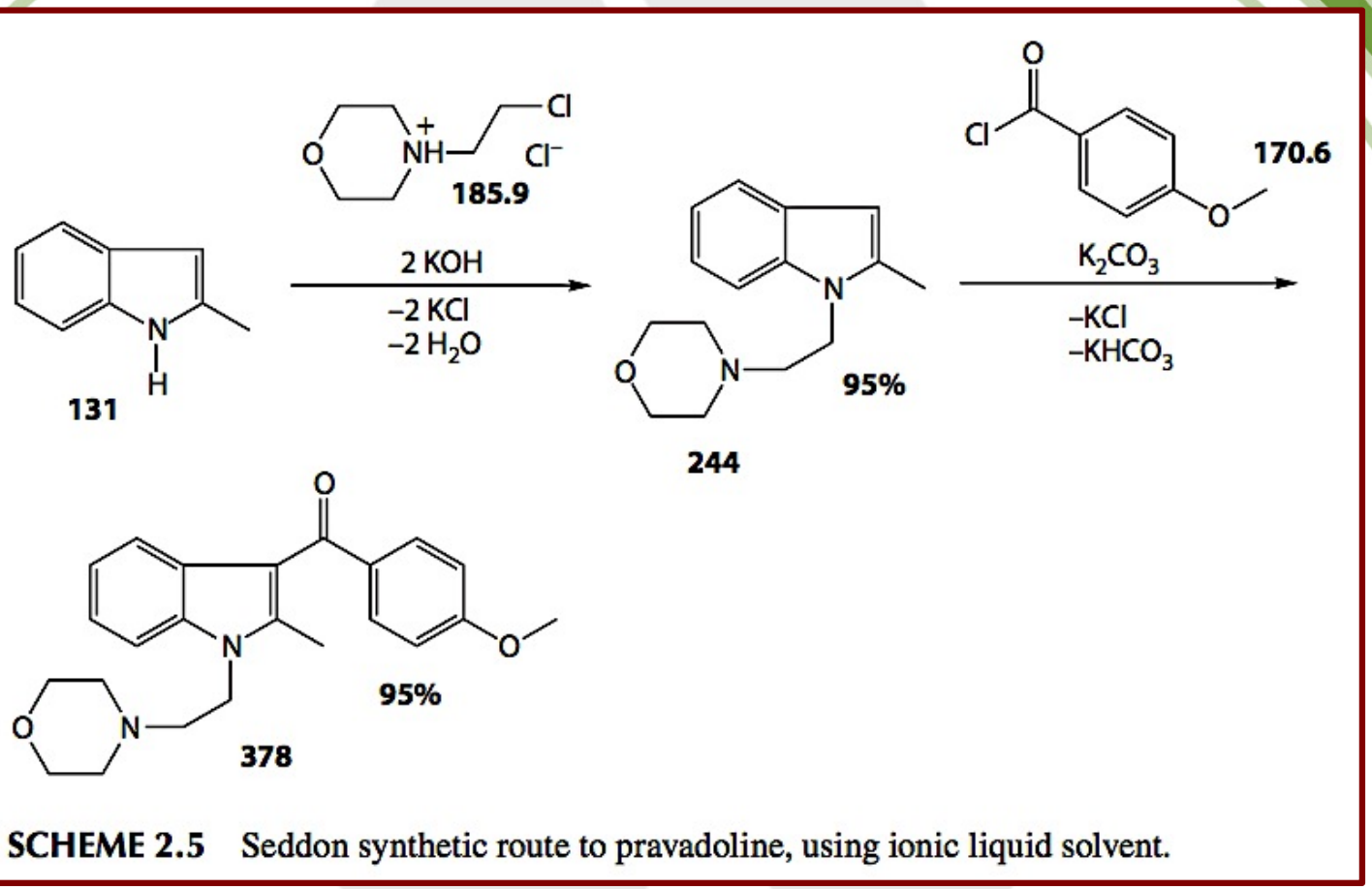
SCHEME 2.3 Sterling G2 synthetic route to pravadoline.

Pravadoline



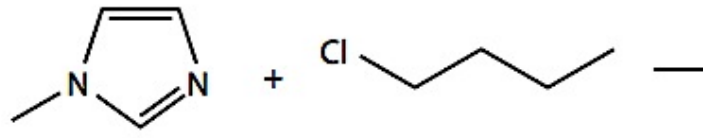
SCHEME 2.4 Cacchi synthetic route to pravadoline.

Pravadoline

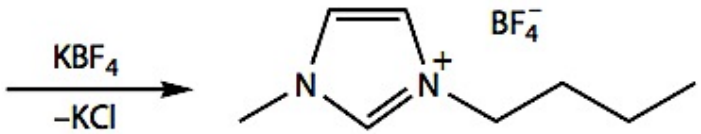


SCHEME 2.5 Seddon synthetic route to pravadoline, using ionic liquid solvent.

Pravadoline



82 92.57 174.67



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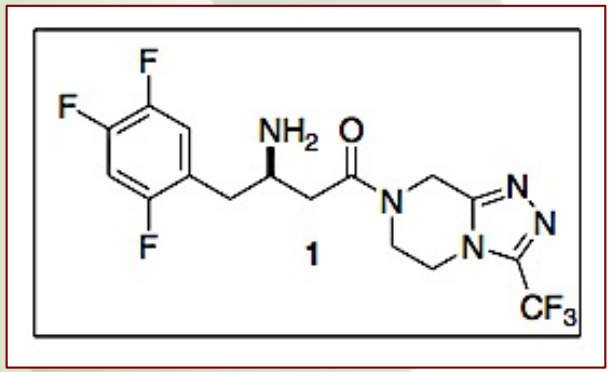
SCHEME 2.6 Synthesis of 1-*n*-butyl-3-methylimidazolium tetrafluoroborate.

Sitagliptin

From Green to Greener; from a Catalytic Reaction to a Metal-Free Enzymatic Process

Sitagliptin is a new treatment for type two diabetes via inhibition of the DPP-IV enzyme



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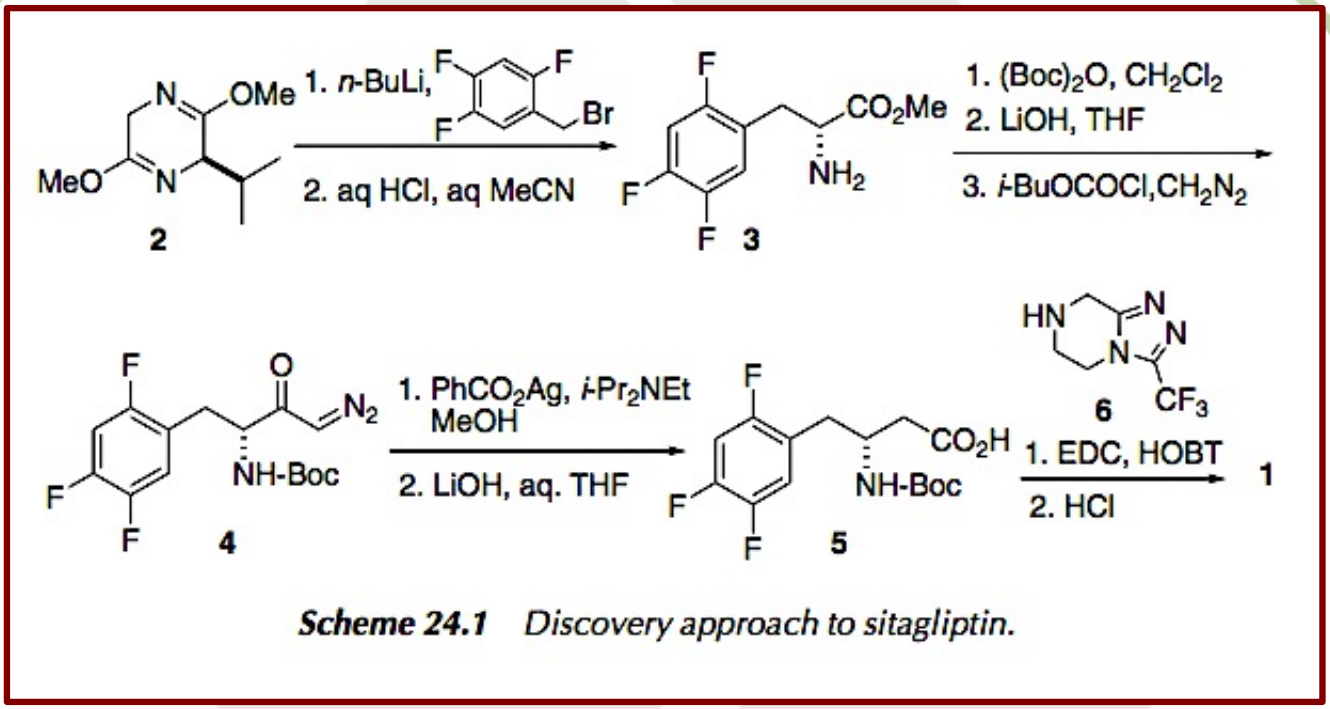
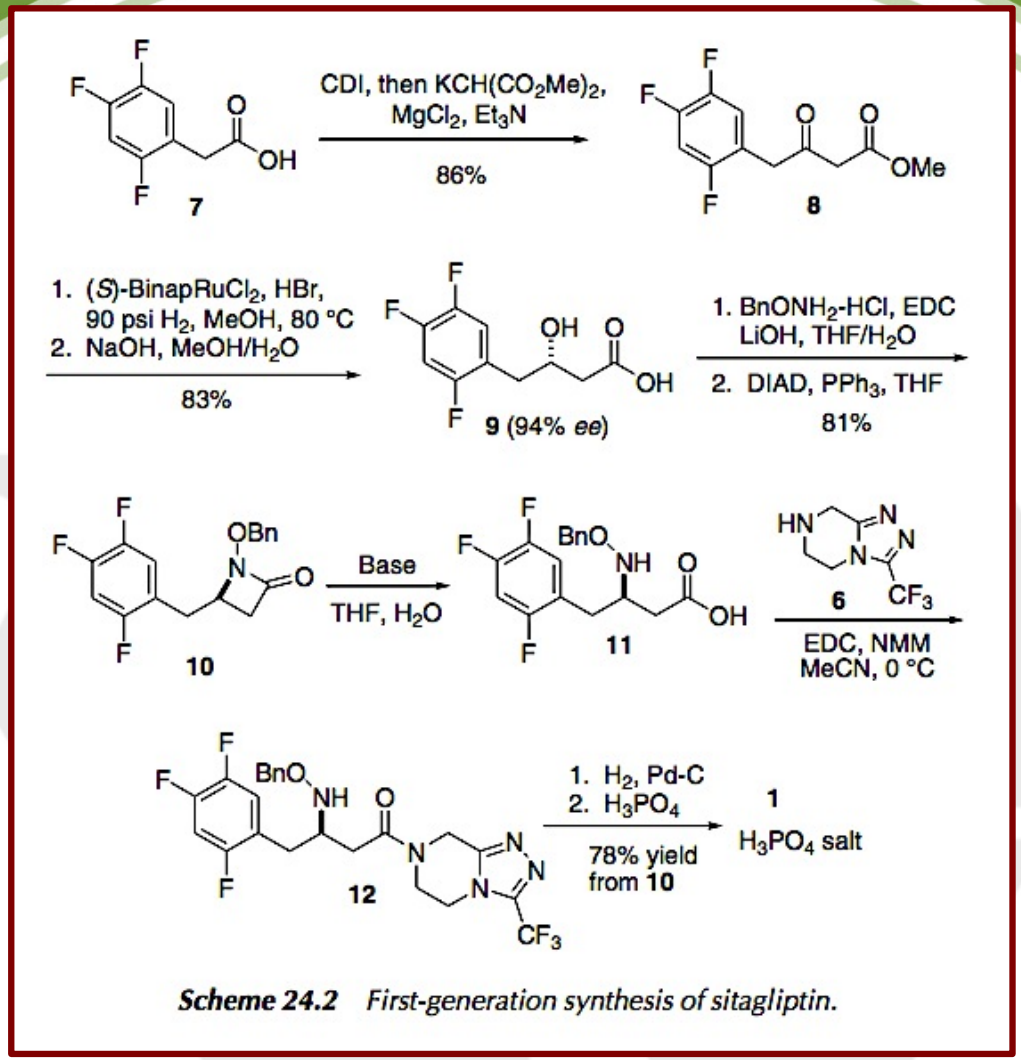
Sitagliptin



Scheme 24.1 *Discovery approach to sitagliptin.*

[Kim, D , Wang, L , Beconi, M et al *J Med Chem* , 2005, *48*, 141–151]

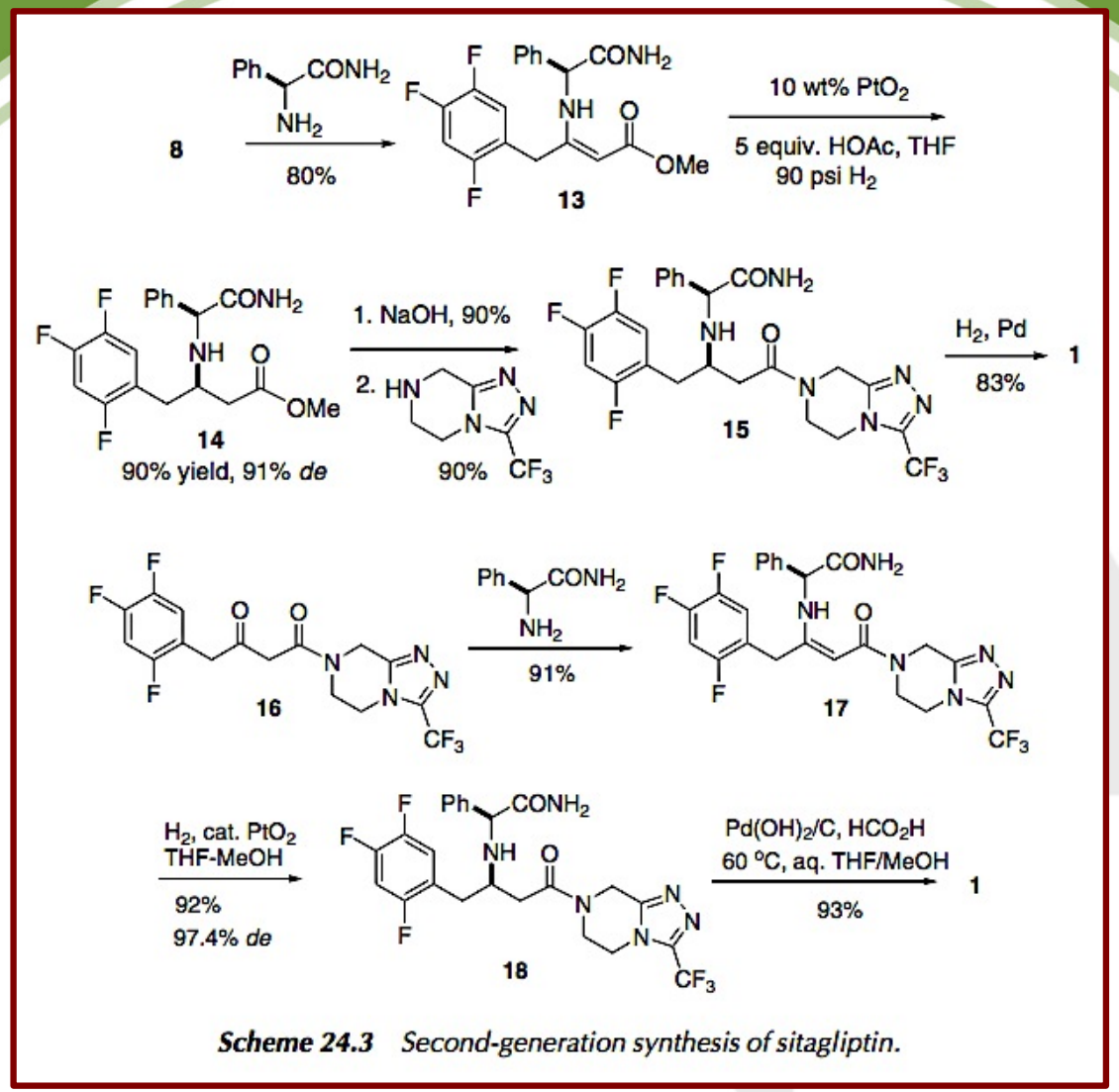
Sitagliptin



Scheme 24.2 *First-generation synthesis of sitagliptin.*

[Hansen, K B , Balsells, J , Dreher, S et al *Org Process Res Dev* , 2005, *9*, 634–639]

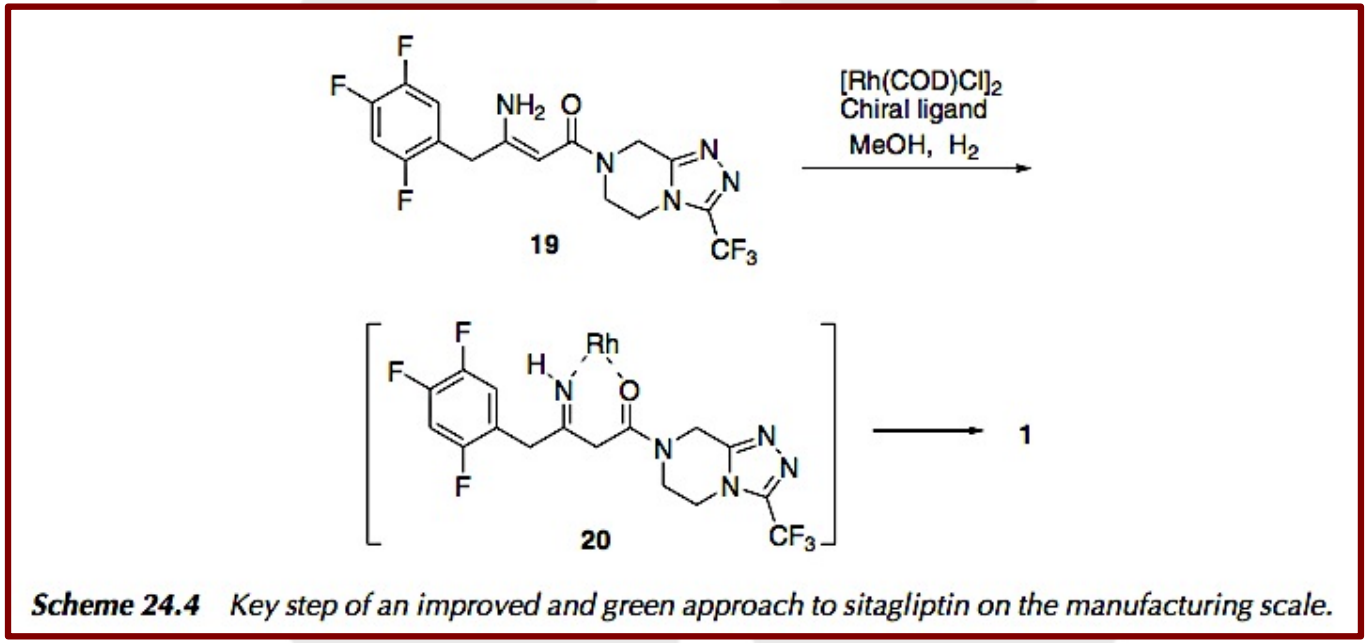
Sitagliptin



Scheme 24.3 *Second-generation synthesis of sitagliptin.*

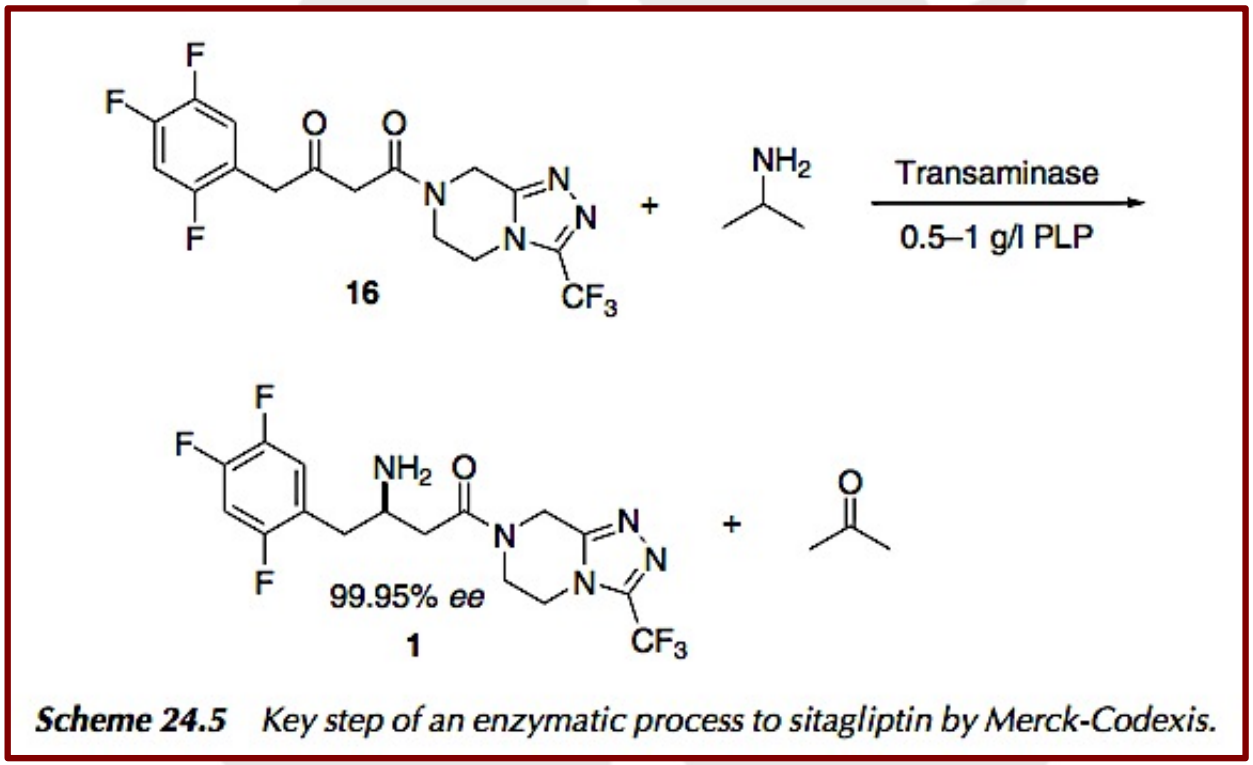
2006 Presidential Green Chemistry Challenge Award for Greener Synthetic Pathways

Sitagliptin



Scheme 24.4 *Key step of an improved and green approach to sitagliptin on the manufacturing scale.*

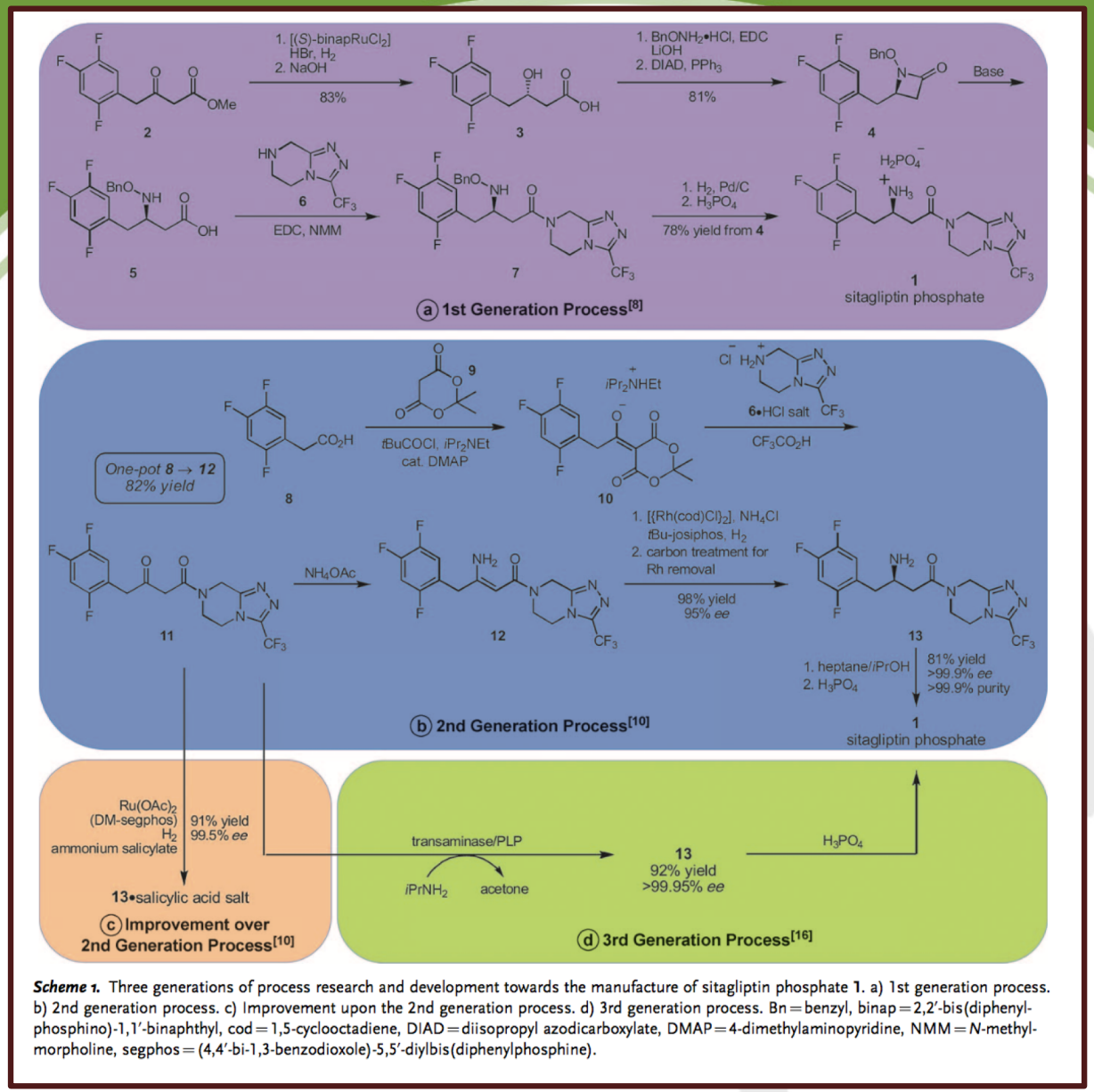
Sitagliptin



Scheme 24.5 *Key step of an enzymatic process to sitagliptin by Merck-Codexis.*

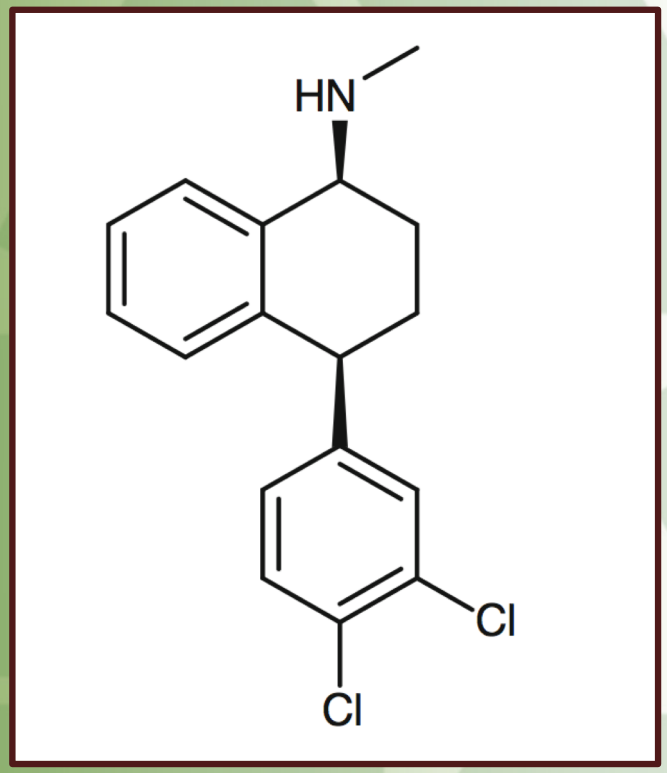
2010 Presidential Green Chemistry Challenge Award for Greener Reaction Conditions

Sitagliptin

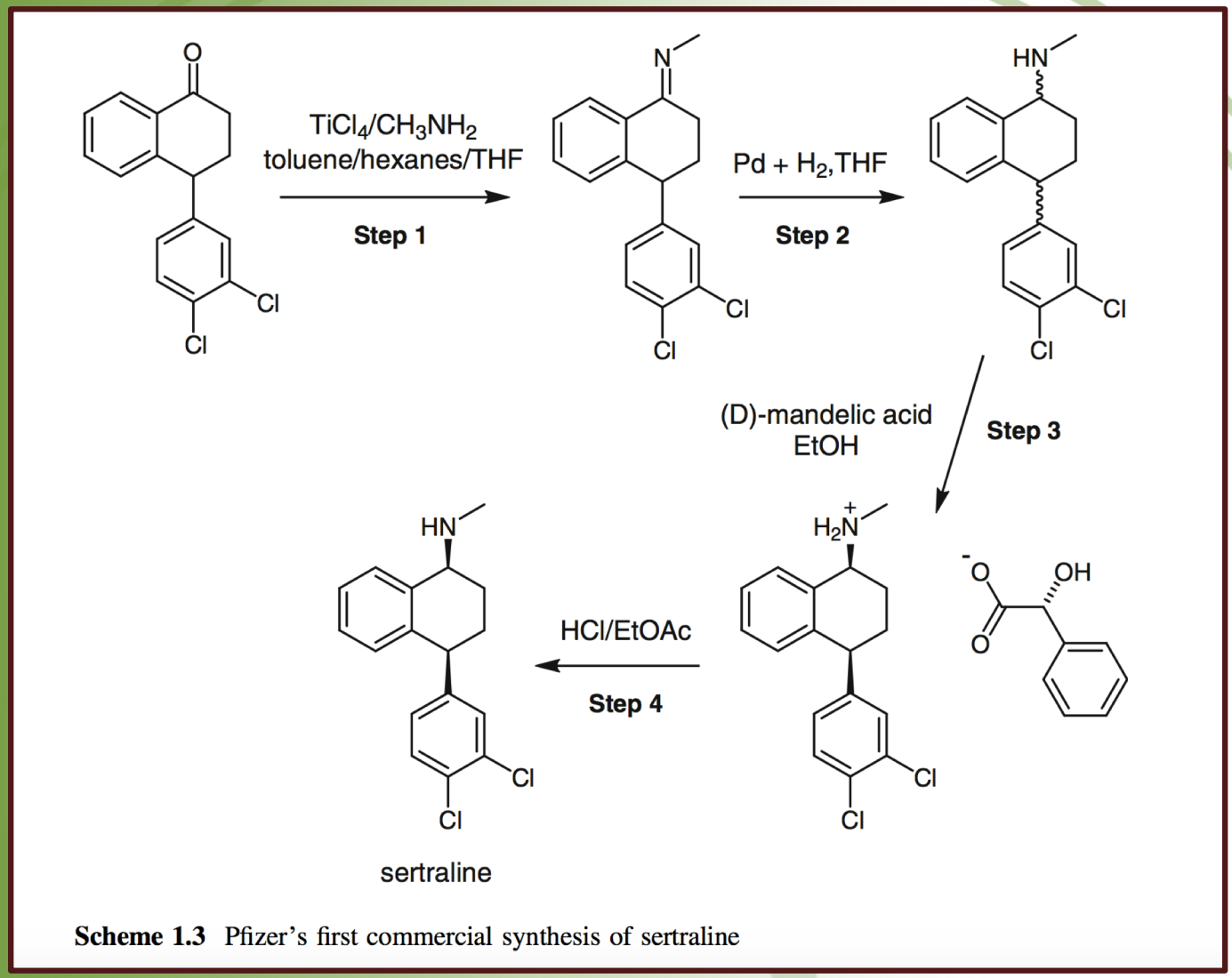


Scheme 1. Three generations of process research and development towards the manufacture of sitagliptin phosphate **1**. a) 1st generation process. b) 2nd generation process. c) Improvement upon the 2nd generation process. d) 3rd generation process. Bn = benzyl, binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, cod = 1,5-cyclooctadiene, DIAD = diisopropyl azodicarboxylate, DMAP = 4-dimethylaminopyridine, NMM = *N*-methylmorpholine, segphos = (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine).

Sertraline



Sertraline

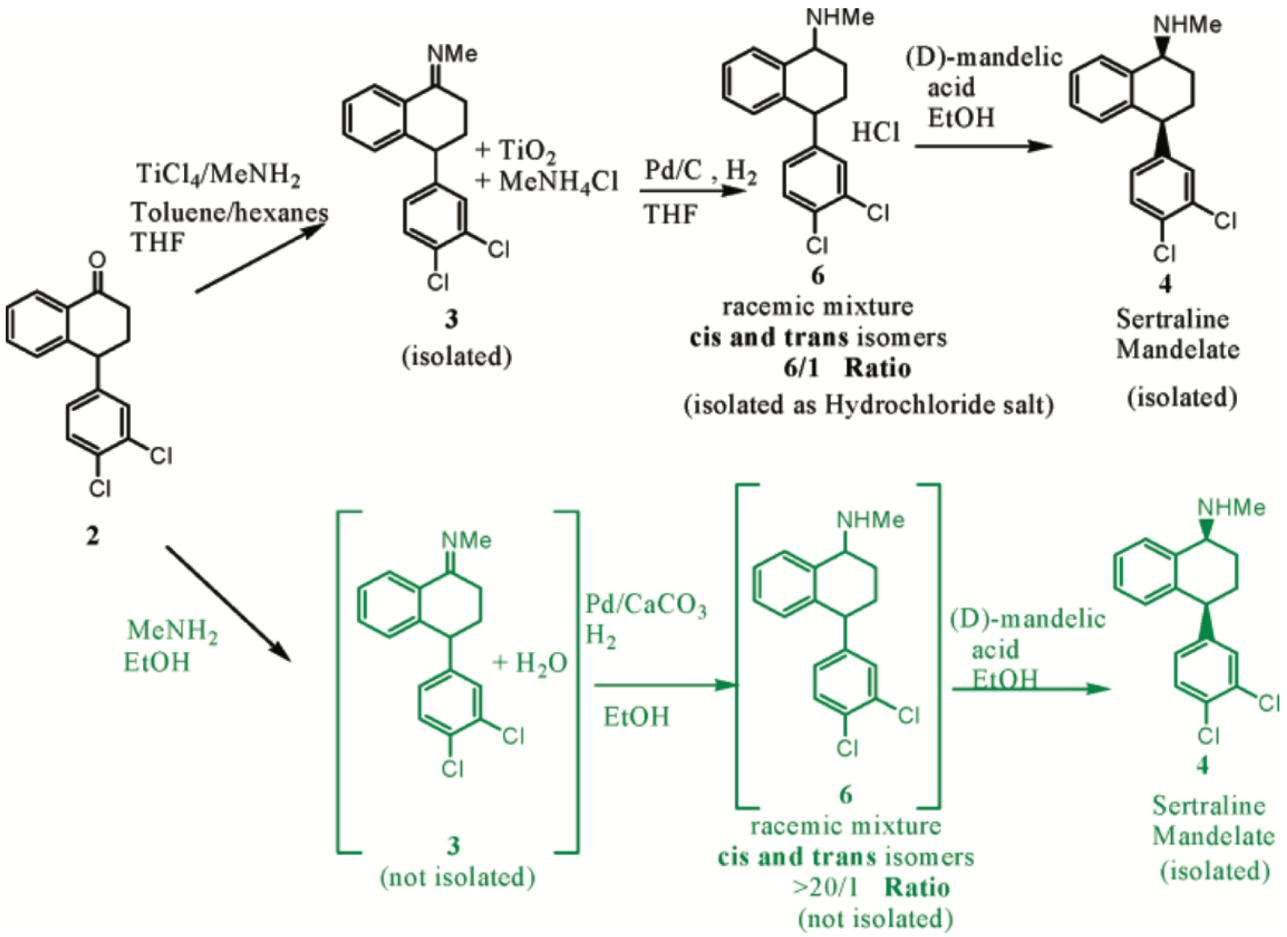


Scheme 1.3 Pfizer's first commercial synthesis of sertraline

34 L of ethanol,
12 L of hexane,
8 L of toluene,
19 L of THF,
28 L of ethyl acetate
per kilogram of
sertraline product

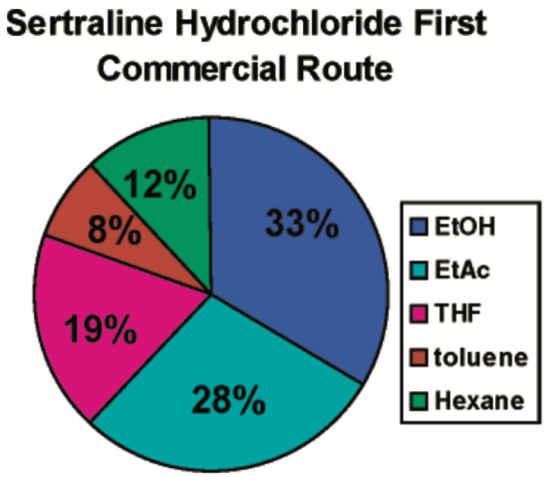
Sertraline

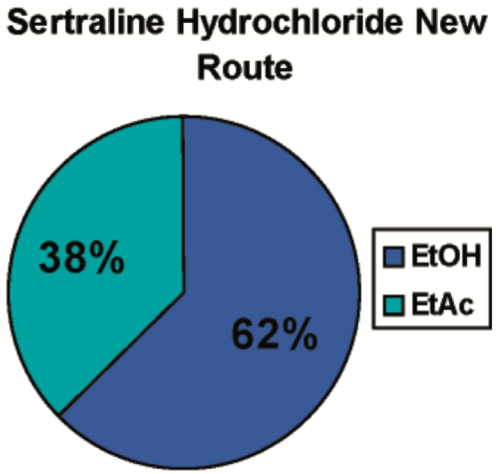
Scheme 1. **Route comparison between the old and new commercial synthesis of Zoloft**



2002 Presidential Green Chemistry Challenge Award for Greener Synthetic Pathways

Sertraline





•EtOH	34,000 L
•EtAc	28,400 L
•THF	19,000 L
•Toluene	8,000 L
•Hexane	12,000 L
Total	101,400 L

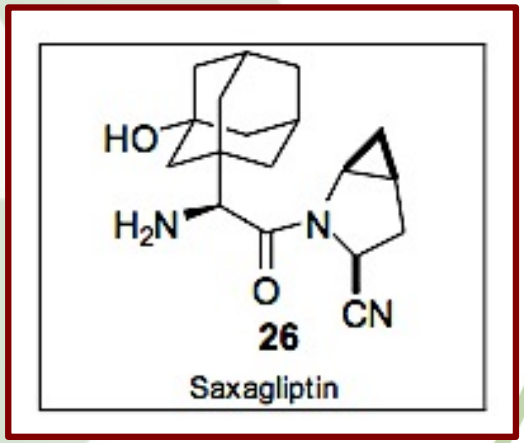
•EtOH	15,000 L
•EtAc	9,000 L
Total	24,000 L

Figure 4. **Comparison of solvent utilization (solvents L/1000 kg of sertraline hydrochloride) between the first commercial route and the new route for Zoloft.**

Saxagliptin

Elimination of Toxic Chemicals and the Use of a Biocatalytic Approach

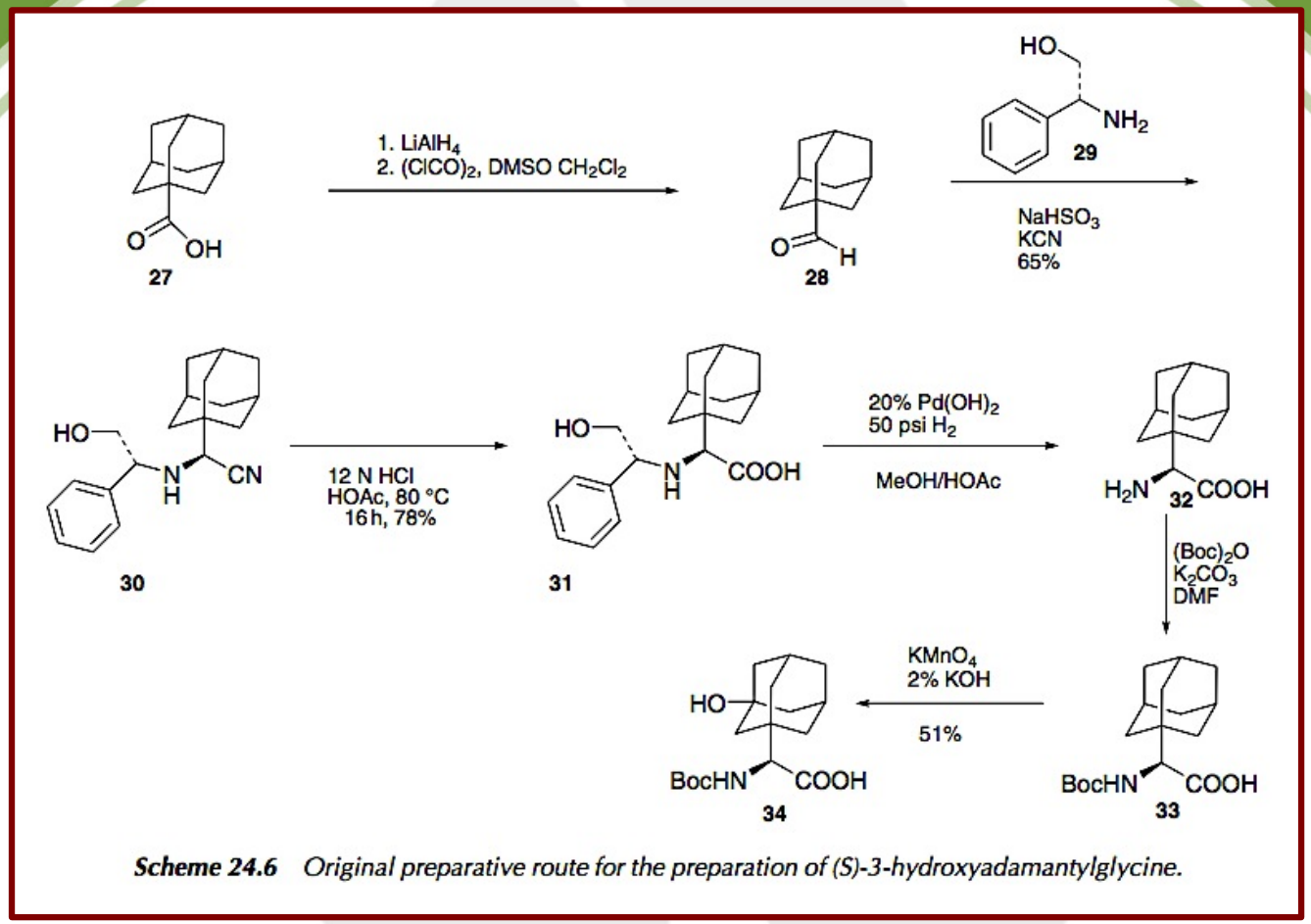
DPP-IV inhibitor developed by Bristol-Myers Squibb



26

Saxagliptin

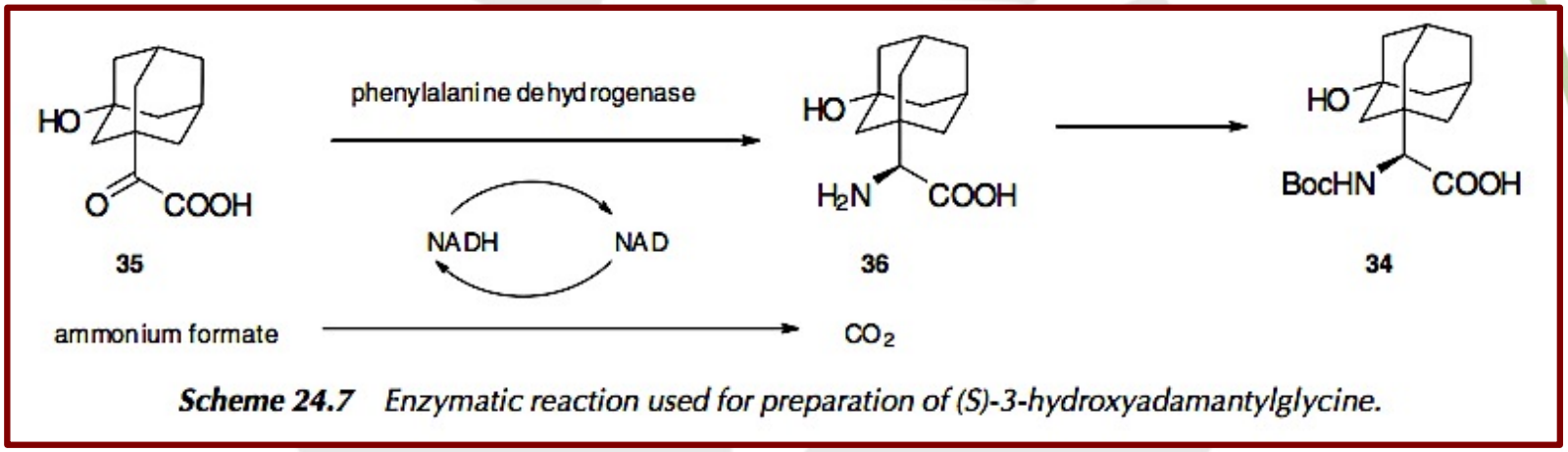
Saxagliptin



Scheme 24.6 *Original preparative route for the preparation of (S)-3-hydroxyadamantylglycine.*

[Augeri, D J , Robl, J A , Betebenner, D A et al , *J Med Chem* 2005, *48*, 5025–5037]

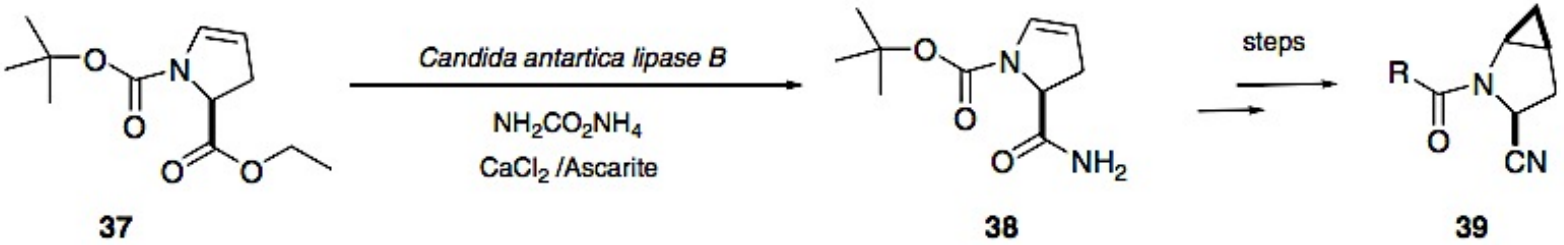
Saxagliptin



Scheme 24.7 *Enzymatic reaction used for preparation of (S)-3-hydroxyadamantylglycine.*

[Godfrey, J D Jr, Fox, R T , Buono, F G et al *J Org Chem* 2006, *71*, 8647–8650]

Saxagliptin

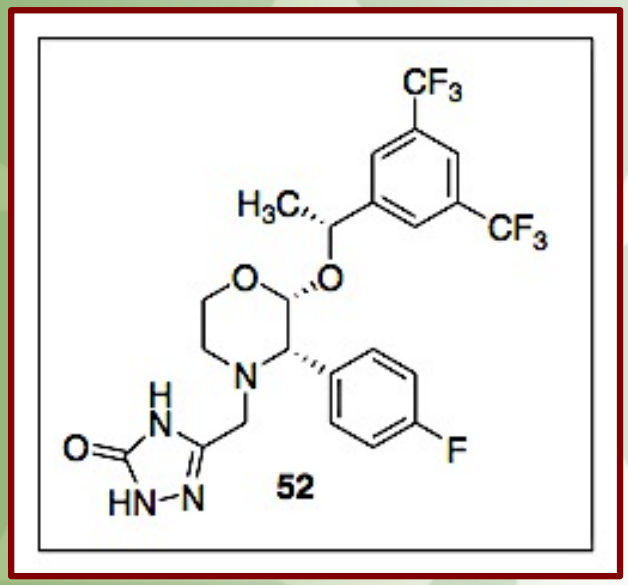


Scheme 24.8 *Saxagliptin revised process for pyrrole ring amidation.*

[Gill, I and Patel, R *Bioorg Med Chem Lett* 2006, *16*, 705–709]

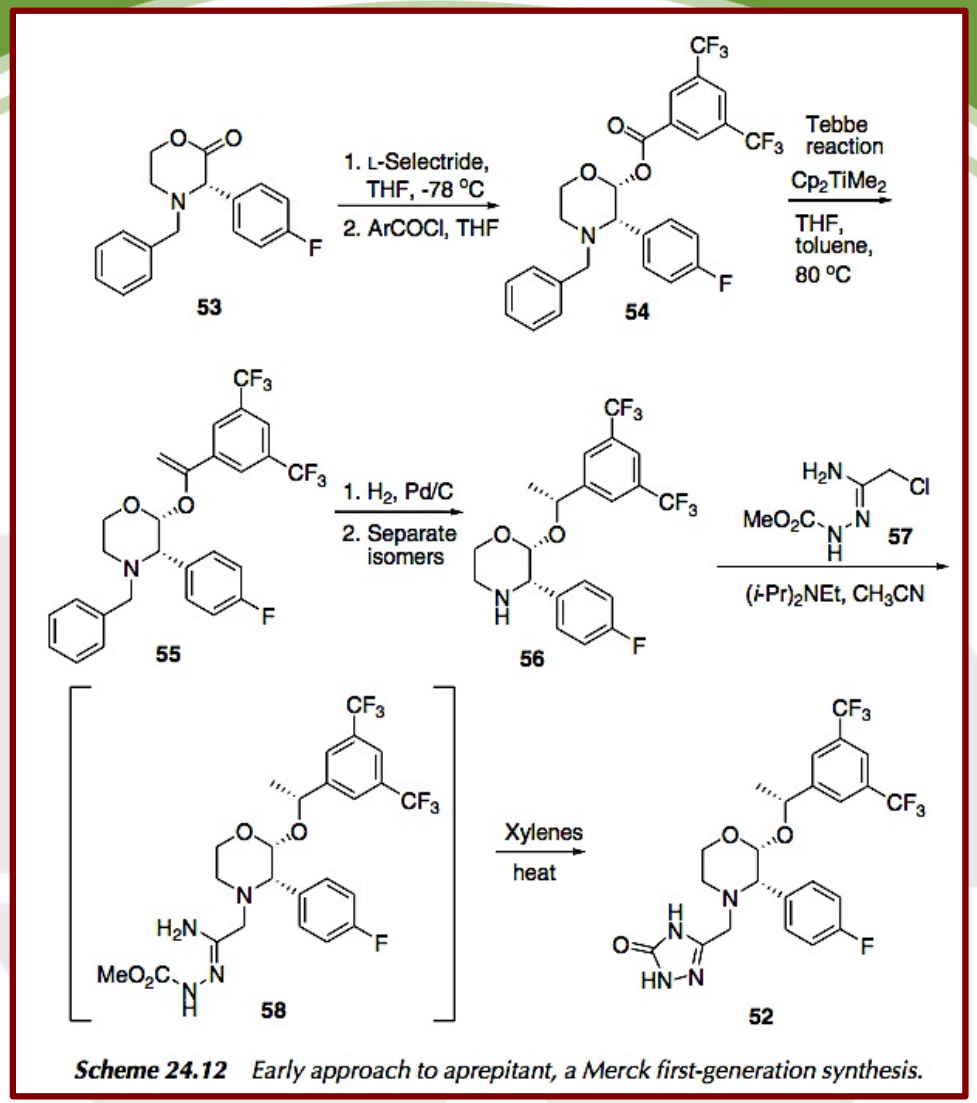
Emend

Emend™ is a new therapy for chemotherapy-induced nausea and vomiting



Aprepitant is the API

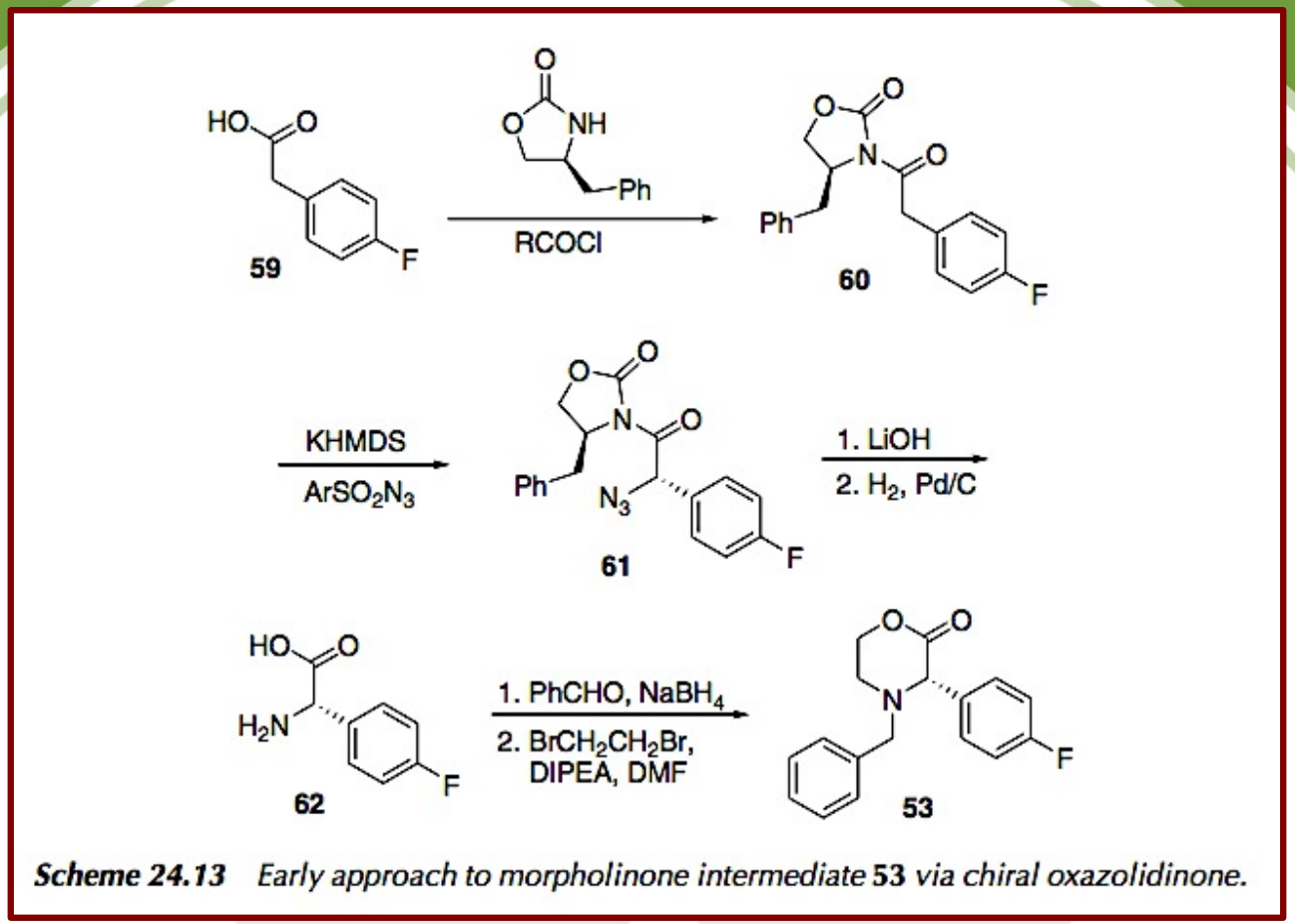
Emend



Scheme 24.12 *Early approach to aprepitant, a Merck first-generation synthesis.*

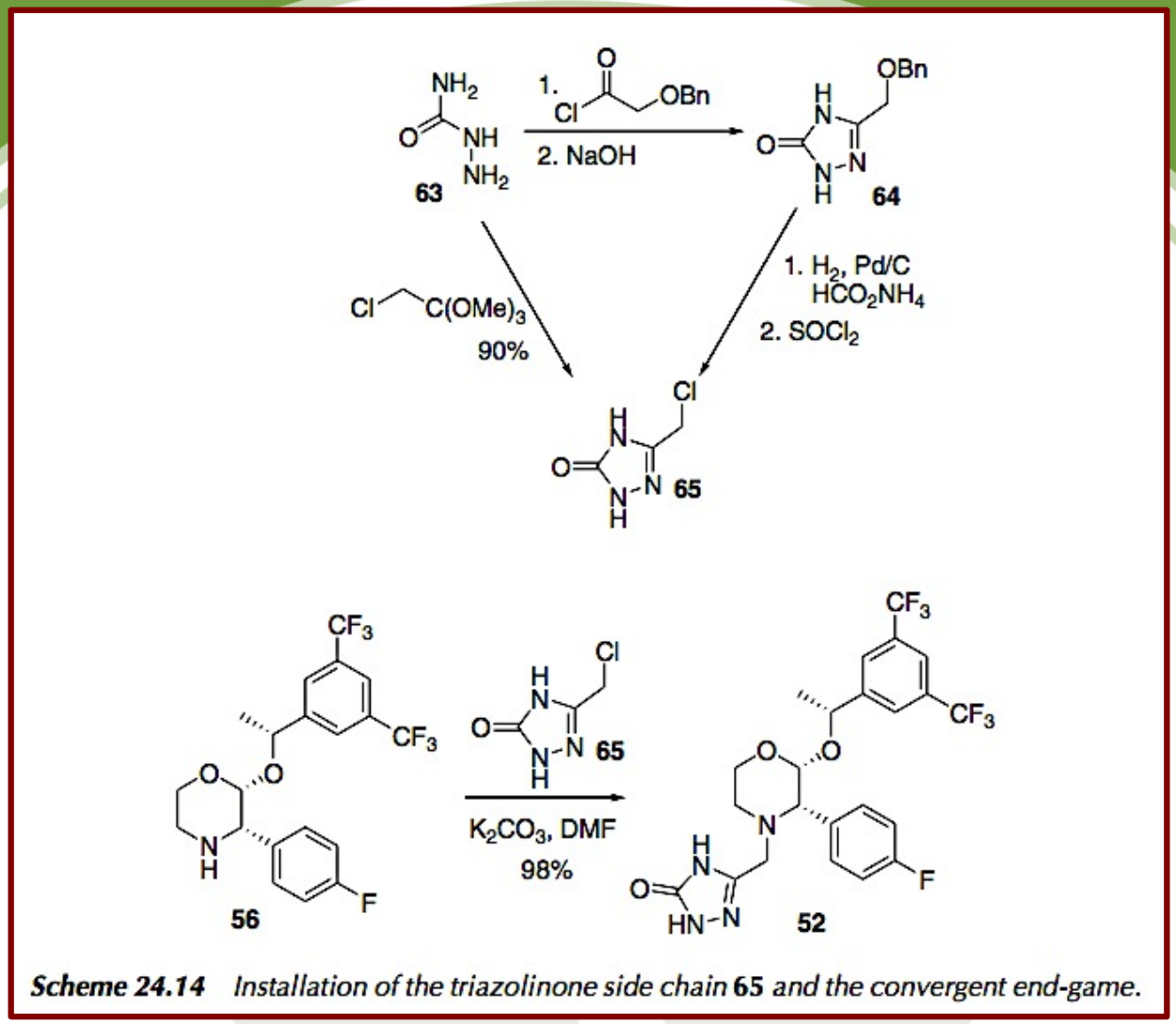
[Hale, J J , Mills, S G , MacCoss, M et al *J Med Chem* , 1998, *41*, 4607–4614]

Emend



Scheme 24.13 *Early approach to morpholinone intermediate* **53** *via chiral oxazolidinone.*

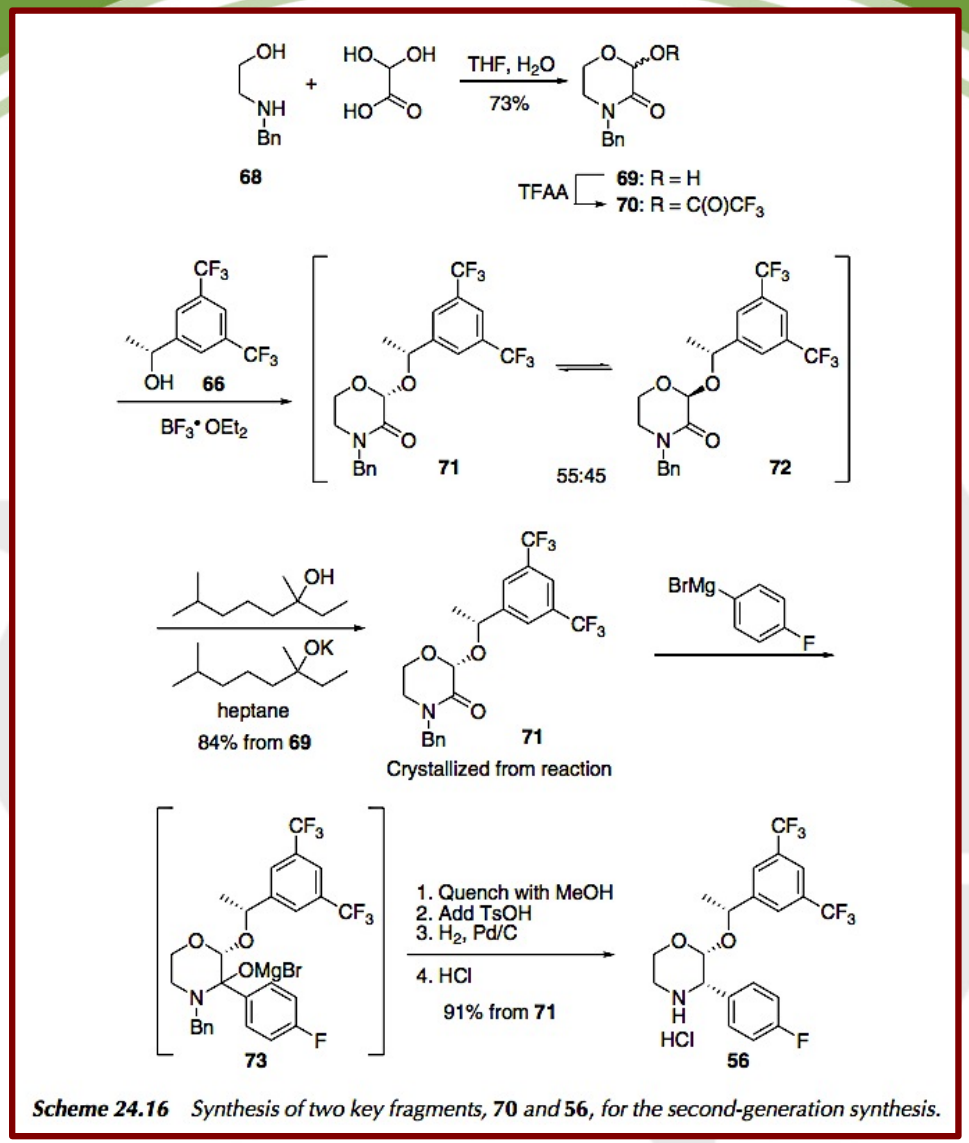
Emend



Scheme 24.14 *Installation of the triazolinone side chain* **65** *and the convergent end-game.*

[Cowden, C J , Wilson, R D , Bishop, B C et al *Tetrahedron Lett* 2000, *41*, 8661–8664]

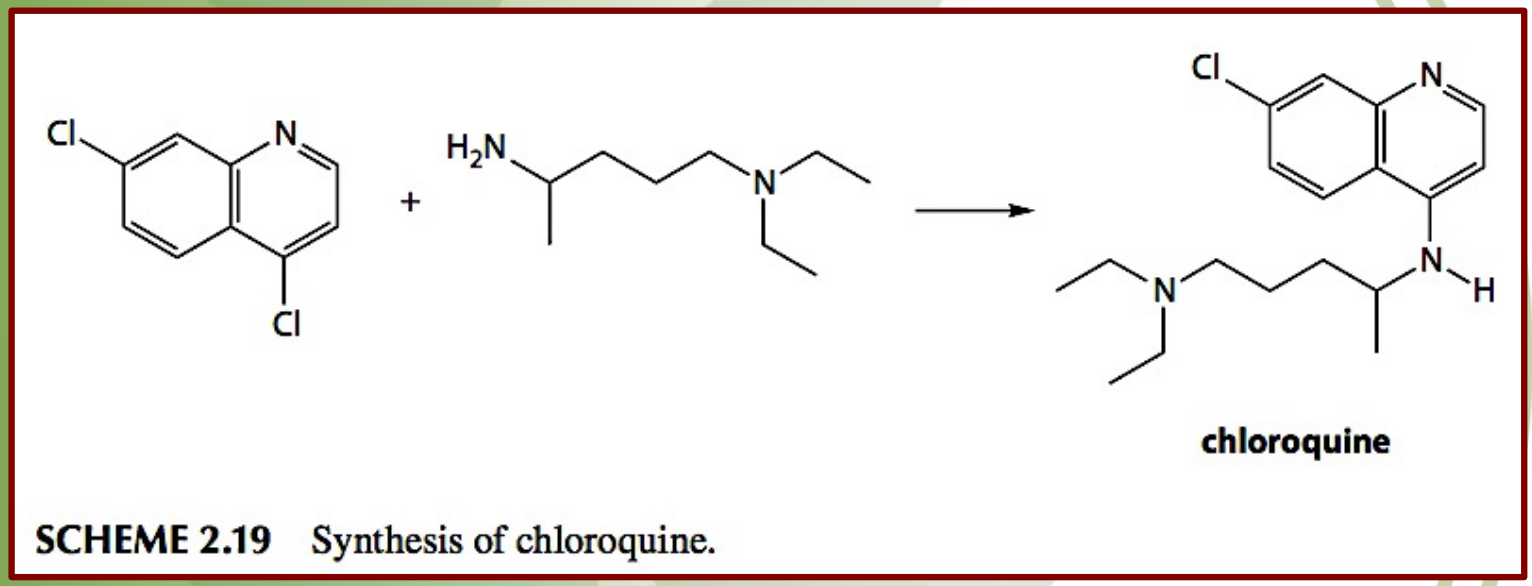
Emend



Scheme 24.16 *Synthesis of two key fragments,* **70** *and* **56**, *for the second-generation synthesis.*

Problem

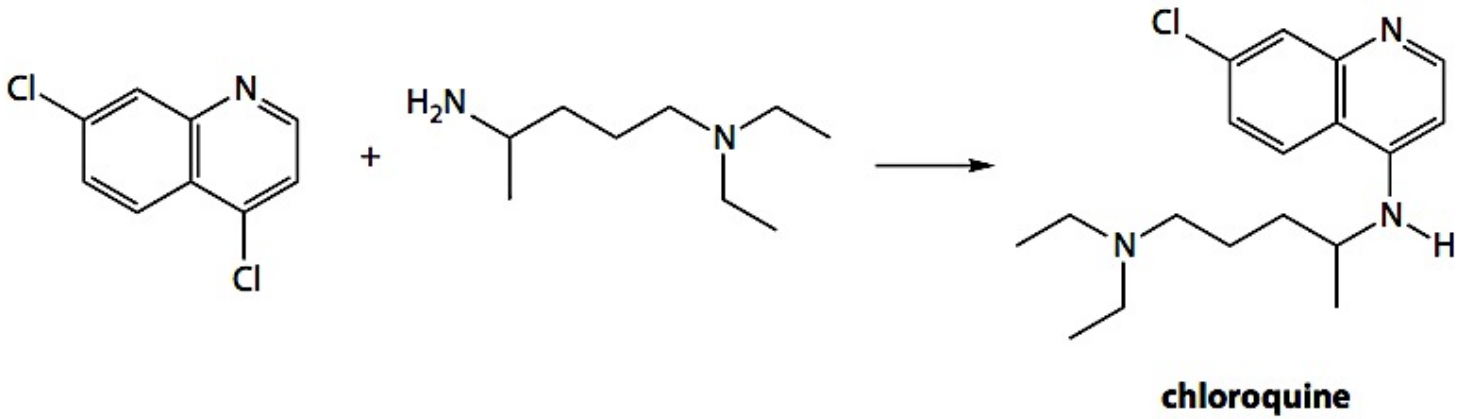
Three routes to 4,7-dichloroquine (Scheme 2.17) and two routes to *N*,*N*'-diethyl-1,4-diaminopentane (Scheme 2.18) are considered for the synthesis of the antirheumatic chloroquine (Scheme 2.19). Find the most atom-economical route to this target compound.



SCHEME 2.19 Synthesis of chloroquine.

Problem

Three routes to 4,7-dichloroquine (Scheme 2.17) and two routes to *N,N'*-diethyl-1,4-diaminopentane (Scheme 2.18) are considered for the synthesis of the antirheumatic chloroquine (Scheme 2.19). Find the most atom-economical route to this target compound.

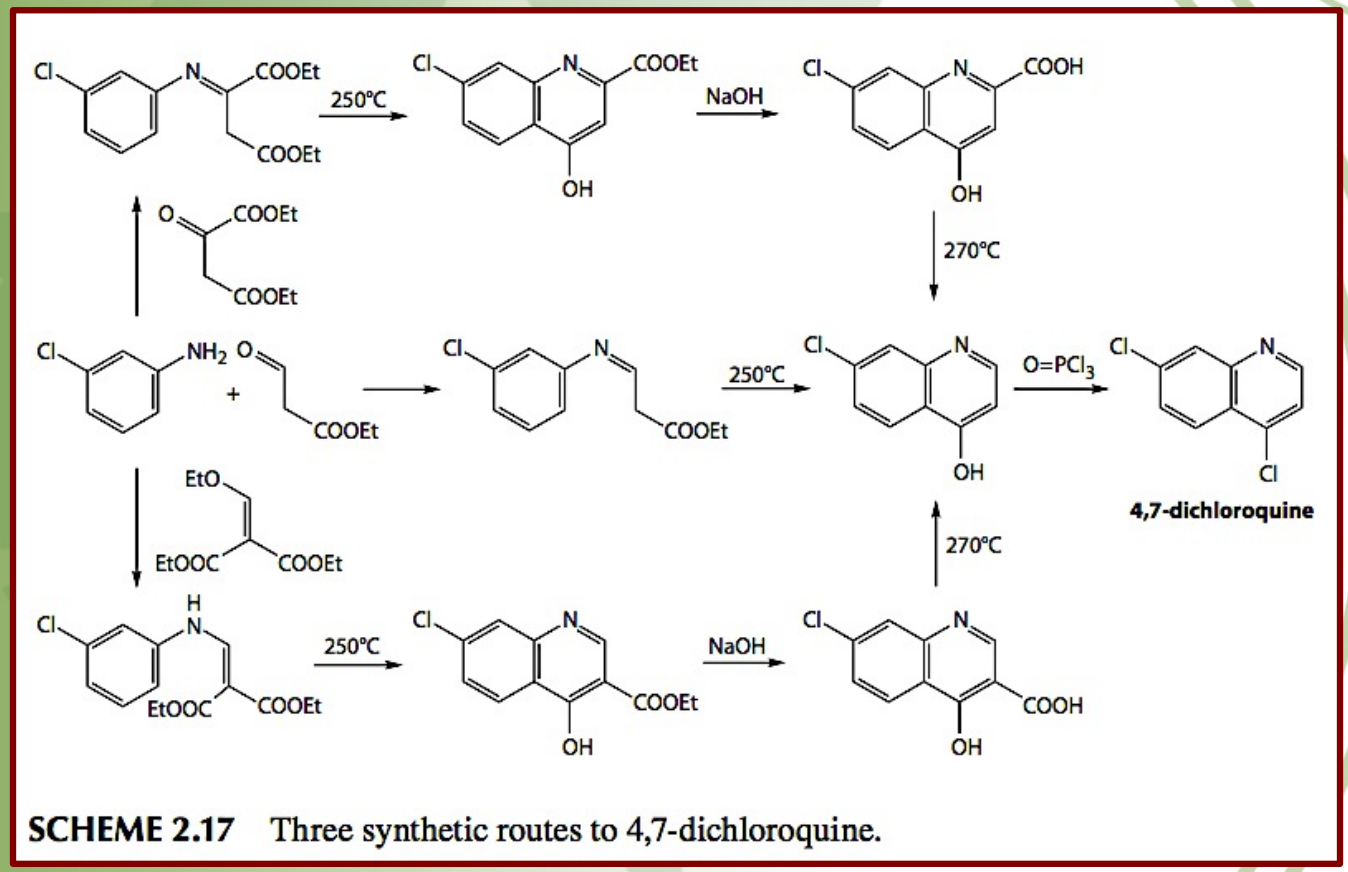


SCHEME 2.19 Synthesis of chloroquine.

Determination of best route based on overall atom economy for each plan

Problem

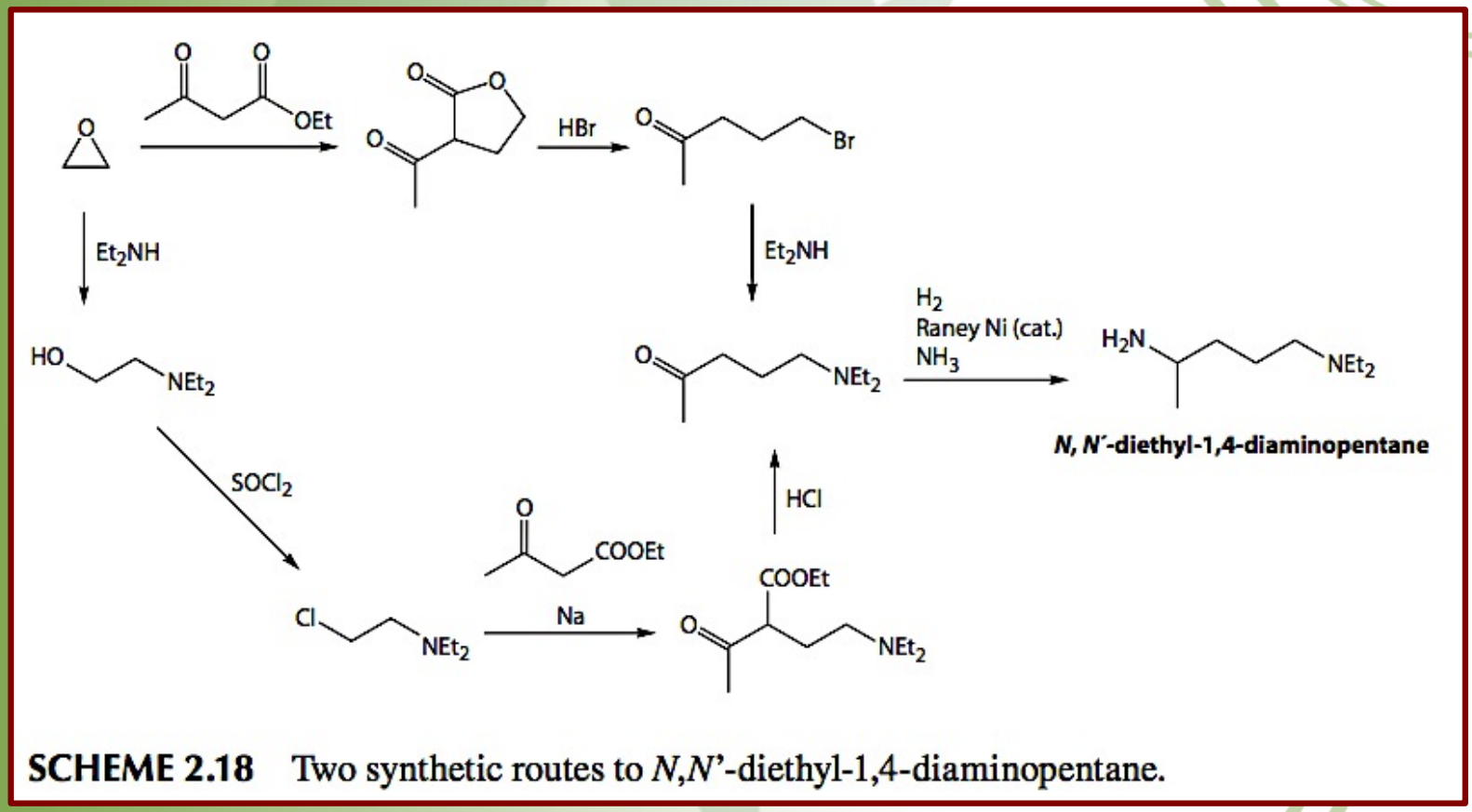
Three routes to 4,7-dichloroquine (Scheme 2.17) and two routes to *N,N'*-diethyl-1,4-diaminopentane (Scheme 2.18) are considered for the synthesis of the antirheumatic chloroquine (Scheme 2.19). Find the most atom-economical route to this target compound.



SCHEME 2.17 Three synthetic routes to 4,7-dichloroquine.

Problem

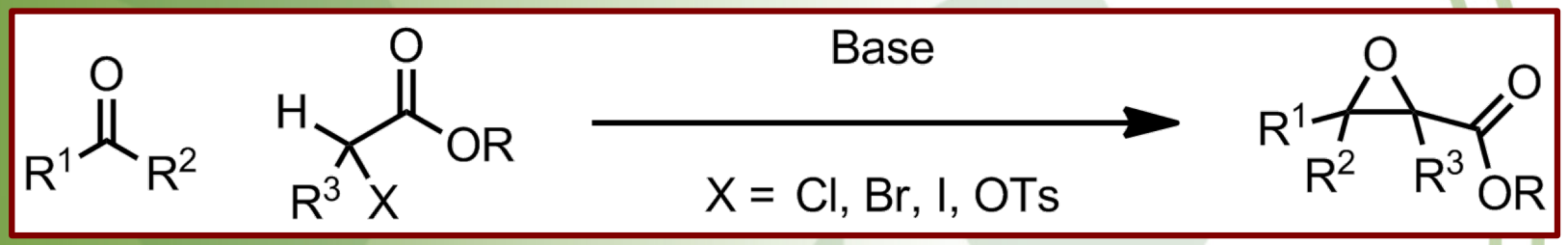
Three routes to 4,7-dichloroquine (Scheme 2.17) and two routes to *N,N'*-diethyl-1,4-diaminopentane (Scheme 2.18) are considered for the synthesis of the antirheumatic chloroquine (Scheme 2.19). Find the most atom-economical route to this target compound.



SCHEME 2.18 Two synthetic routes to *N,N'*-diethyl-1,4-diaminopentane.

Darzens Condensation

The Darzens Reaction is the condensation of a carbonyl compound with an α-halo ester in the presence of a base to form an α,β-epoxy ester.



G. Darzens, *Compt. Rend.* 1904, *13*, *9*, 1214.

Darzens Condensation

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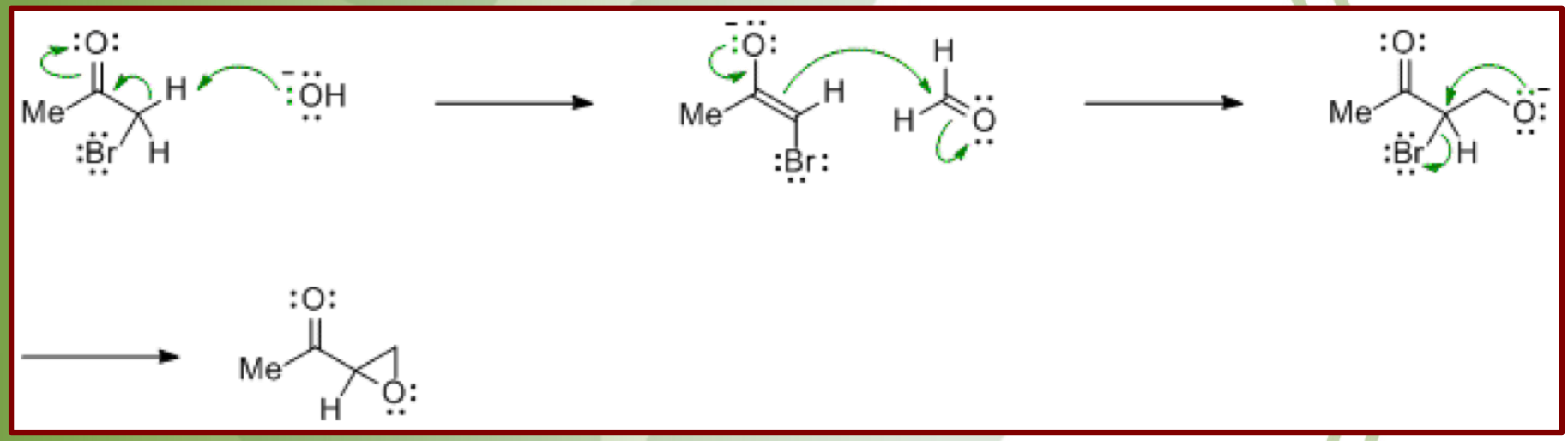
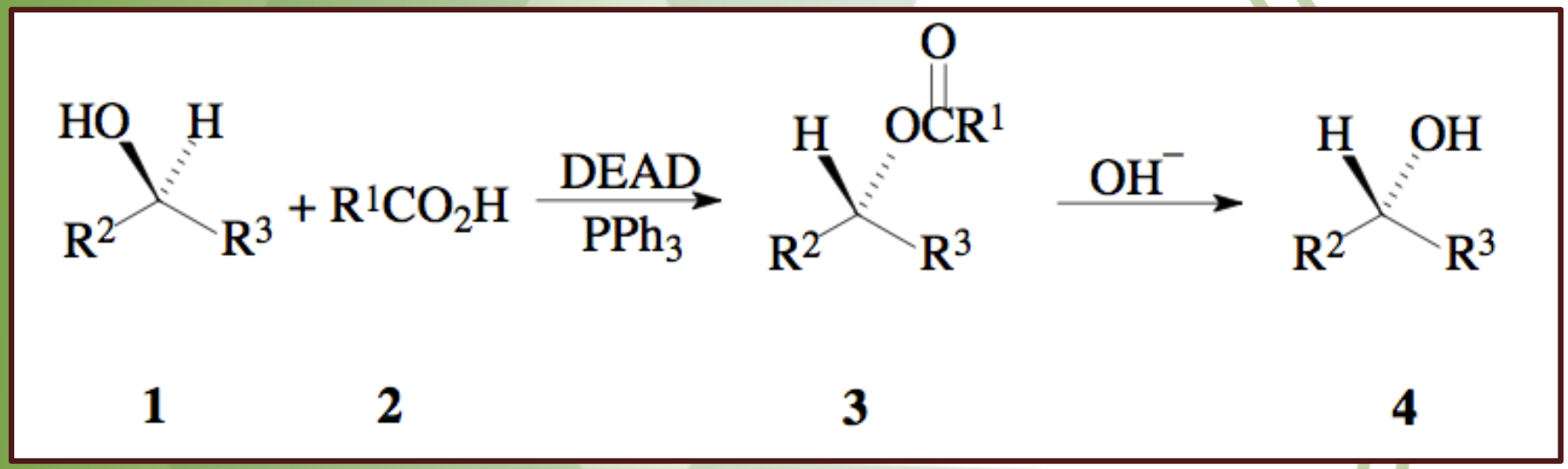


G. Darzens, *Compt. Rend.* 1904, *13*, *9*, 1214.

Mitsunobu Reaction

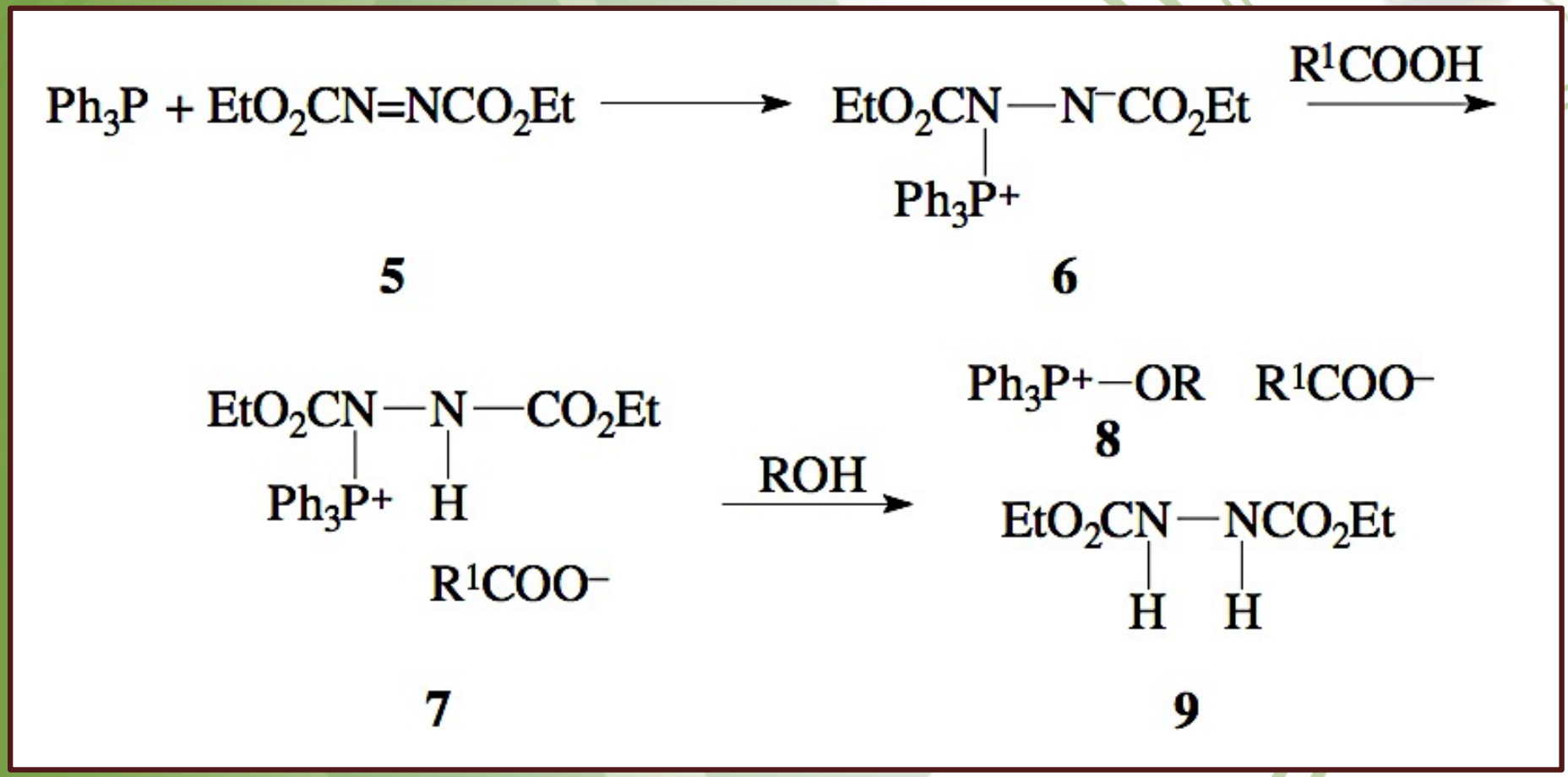
Esterification of an alcohol with carboxylic acid in the presence of dialkyl azodicarboxylate and triphenylphosphine



O. Mitsunobu, *Bull. Chem. Soc. Jpn*. 1967, *40*, 4235–4238.

Mitsunobu Reaction

Mechanism



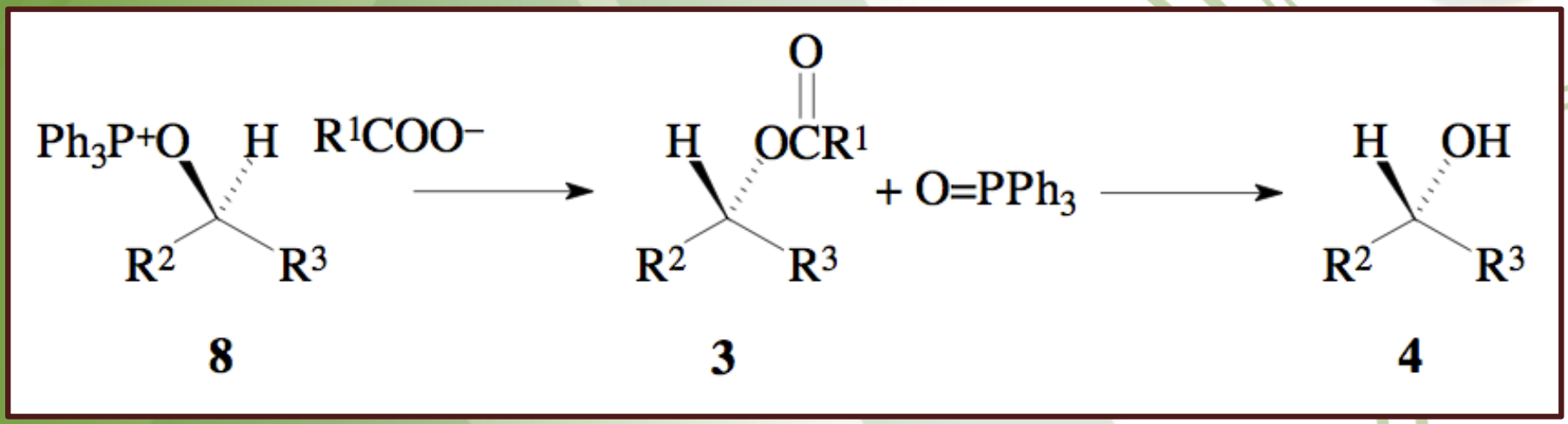
Mitsunobu Reaction

Mechanism

1. formation of the activating agent from triphenylphosphine and diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD);
2. activation of the substrate alcohol 1;
3. a bimolecular nucleophilic substitution (S_N2) at the activated carbon center.

Mitsunobu Reaction

Mechanism



nucleophilic displacement of the oxyphosphonium group by the carboxylate anion *via* a S_N2-mechanism, yielding ester 3 with inverted configuration at the stereogenic center

Mitsunobu Reaction

Summary

condensation of an alcohol 1 and a nucleophile—NuH—11, where the reagent triphenylphosphine is oxidized to triphenylphosphine oxide and the azodicarboxylate reagent 12 is reduced to a hydrazine derivative 13

$$PPh_3 + RO_2C\text{-}N{=}N\text{-}CO_2R + R'OH + NuH \rightarrow$$

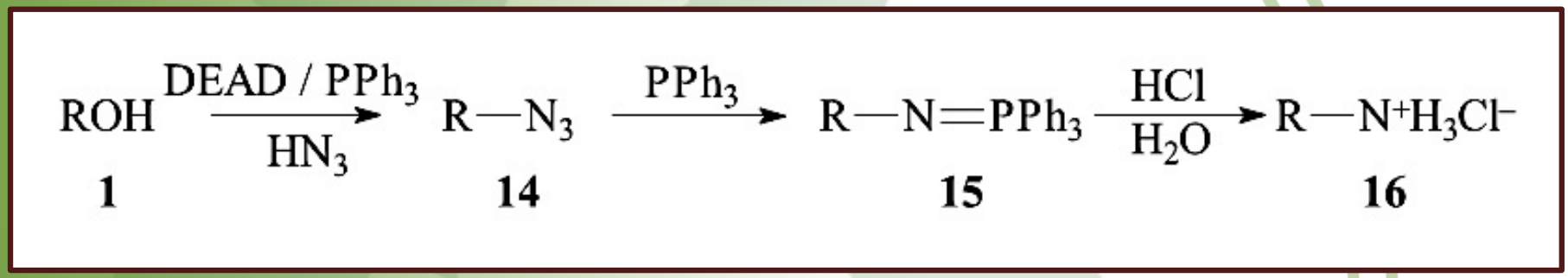
12 **1** **11**

$$\rightarrow RNu + PPh_3O + RO_2C\text{-}NH\text{-}NH\text{-}CO_2R$$

13

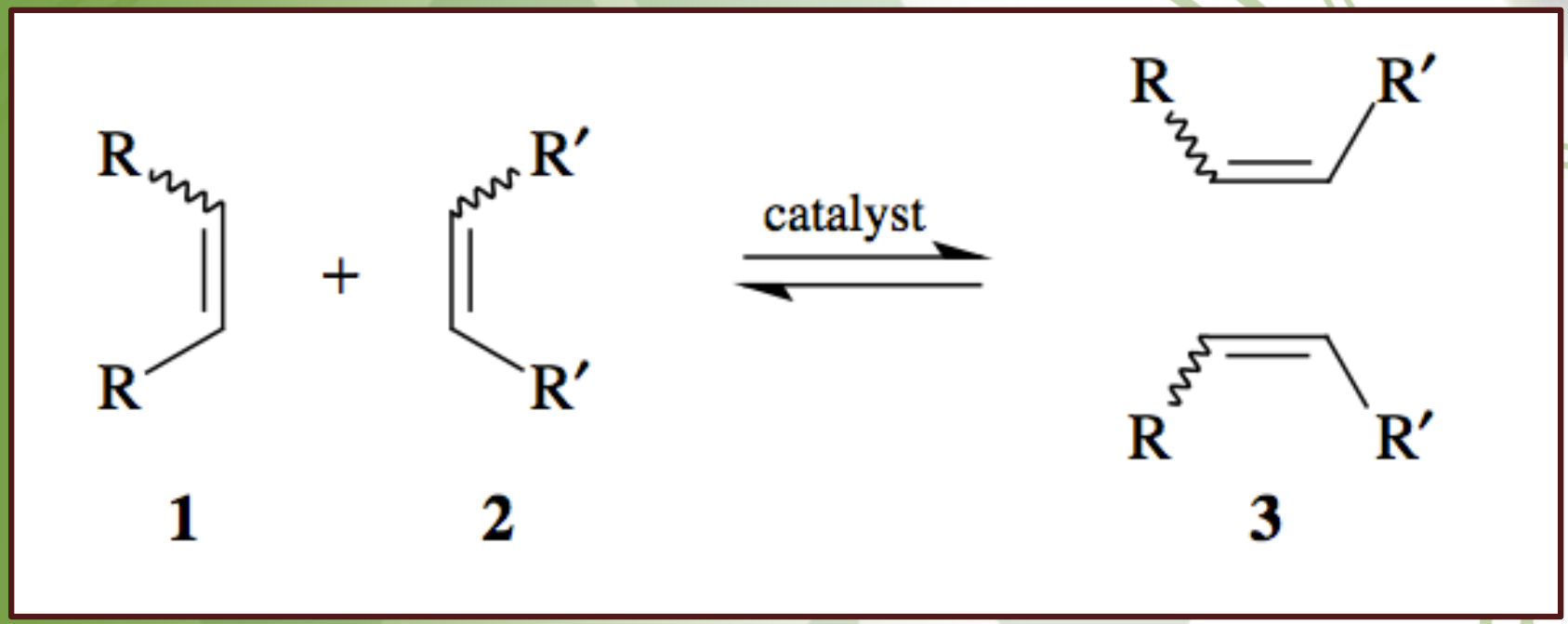
Mitsunobu Reaction

Variation



Alkene Metathesis

Exchange of alkylidene groups of alkenes- metathesis of olefins

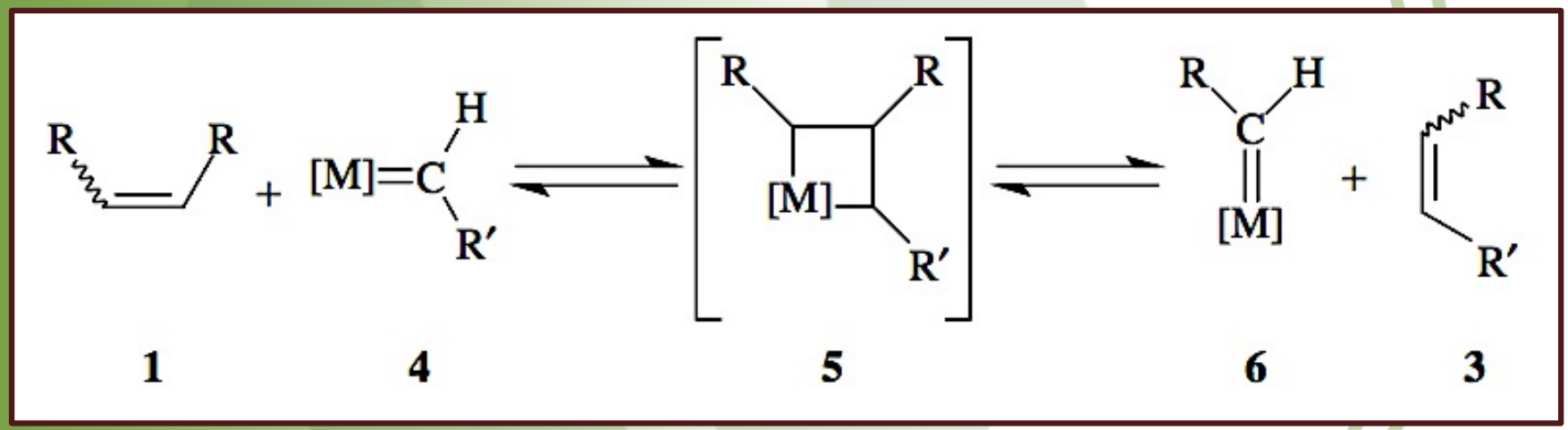


In synthetic organic chemistry, alkene metathesis has become a valuable method for the construction of ring systems. This reaction has also gained industrial importance.

Alkene Metathesis

Mechanism

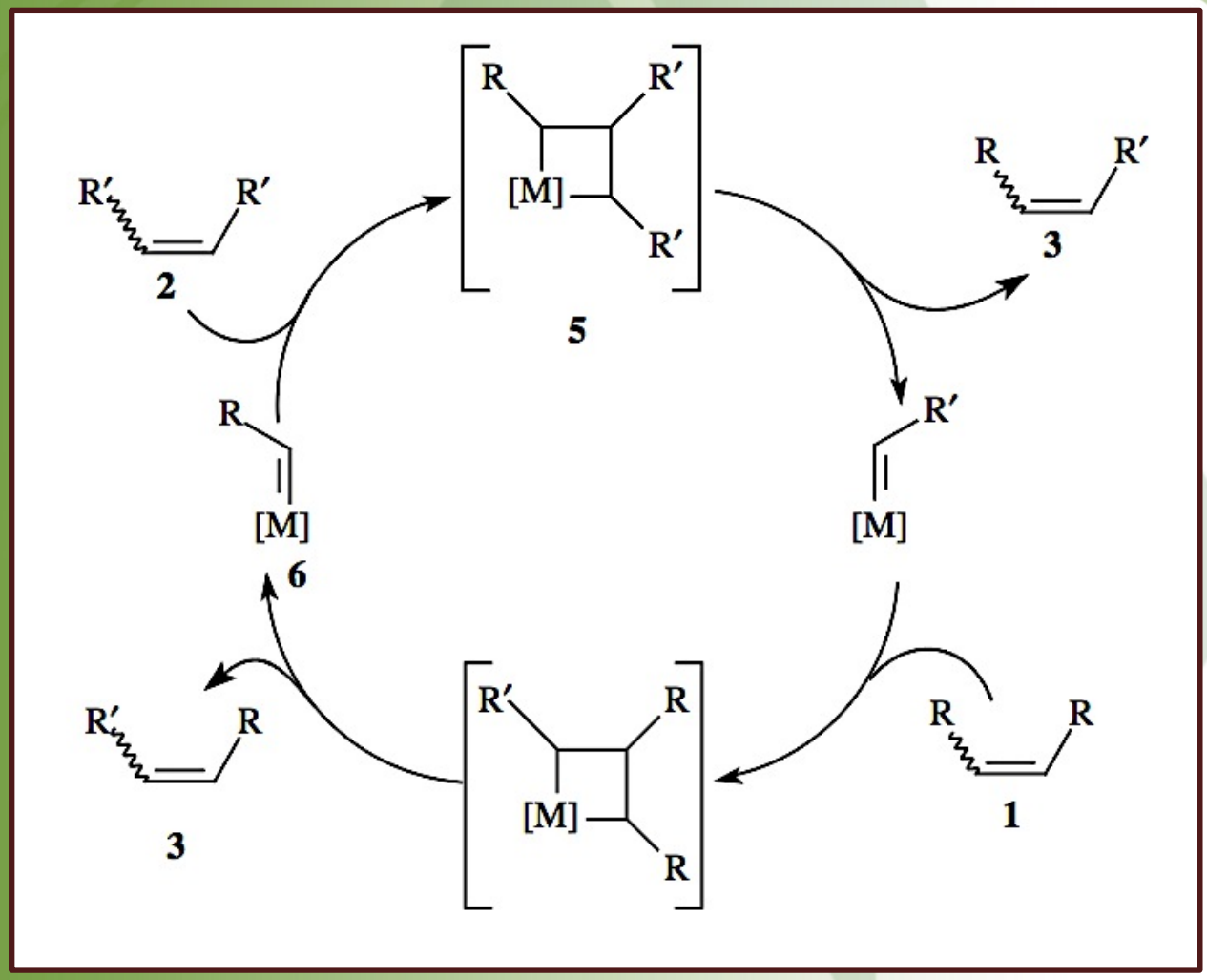
The reaction proceeds by a catalytic cycle mechanism

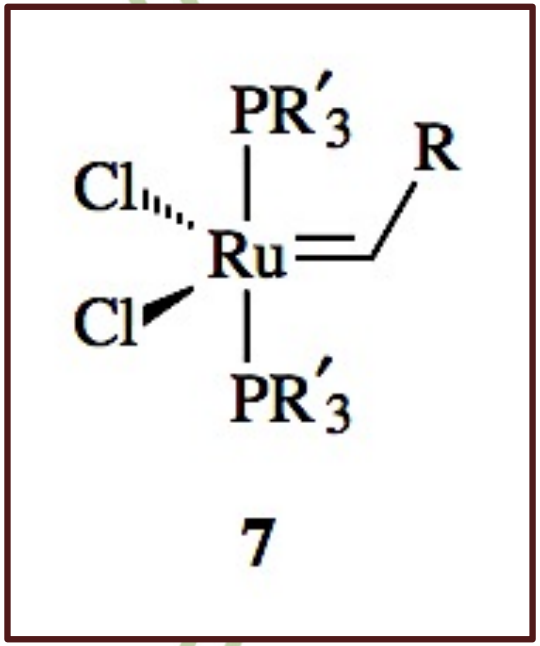


Alkene Metathesis

Mechanism

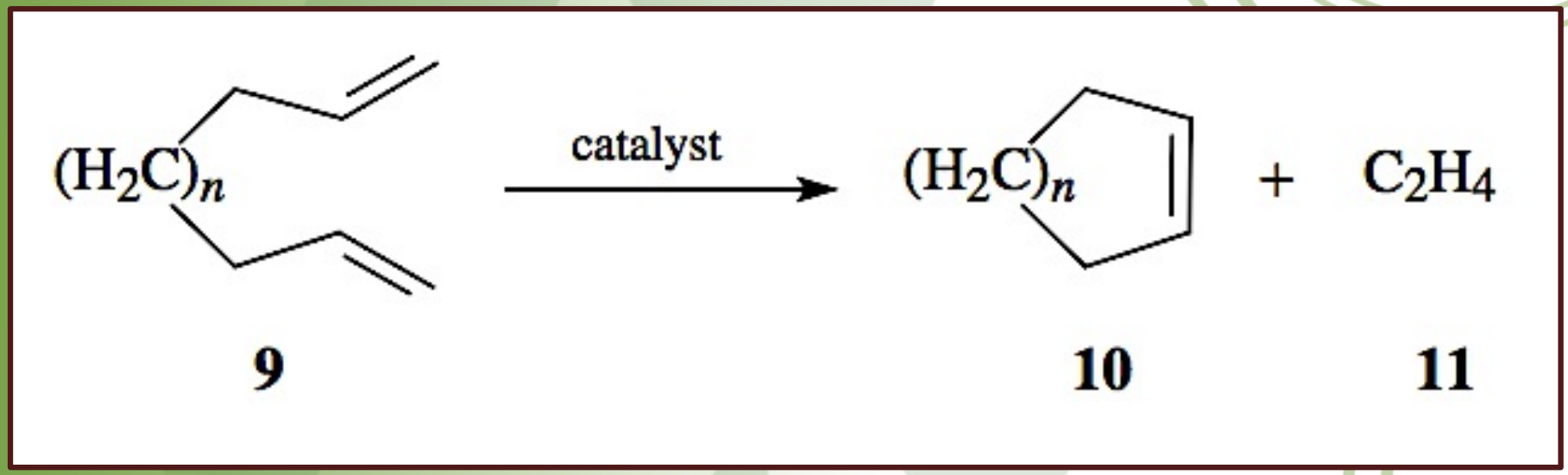
The reaction proceeds by a catalytic cycle mechanism





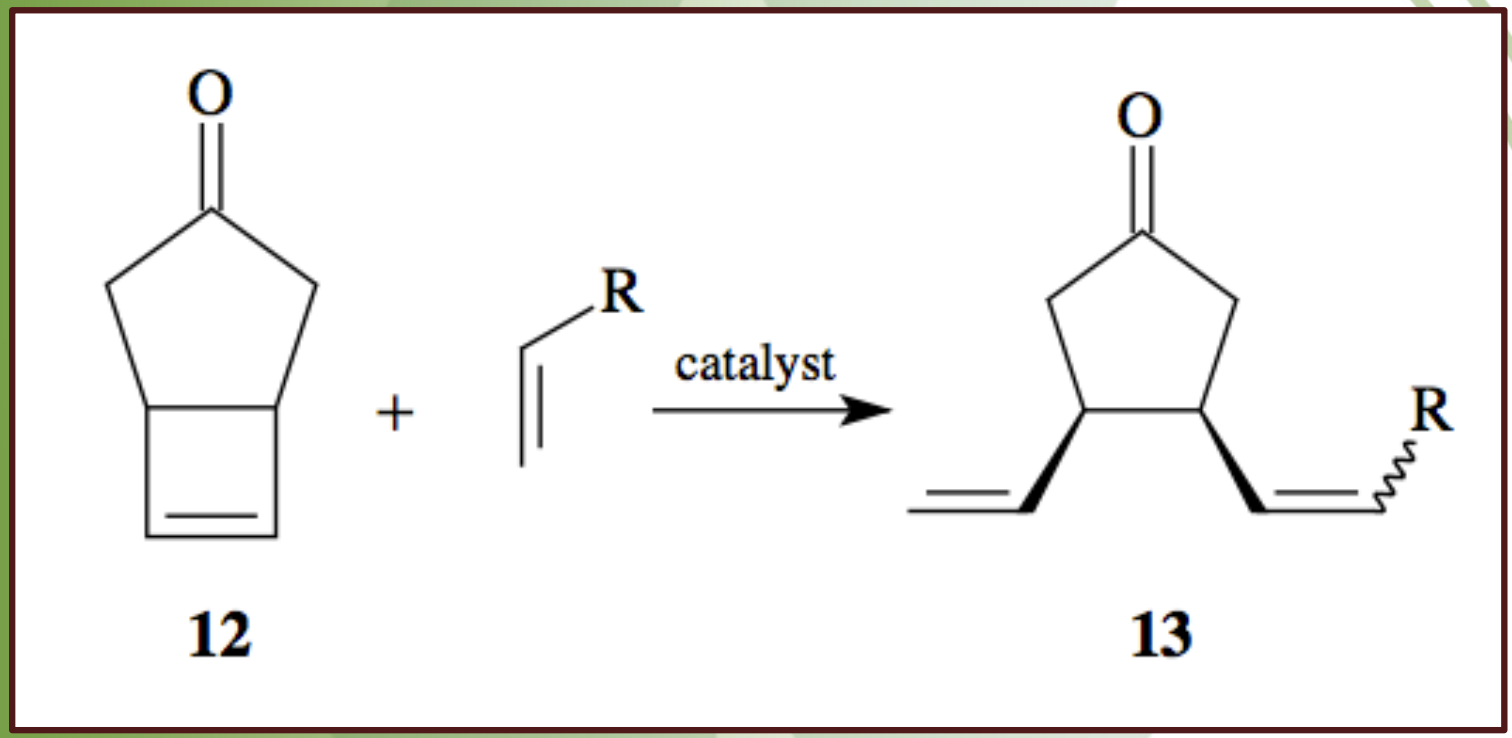
Alkene Metathesis

Ring-Closing Metathesis



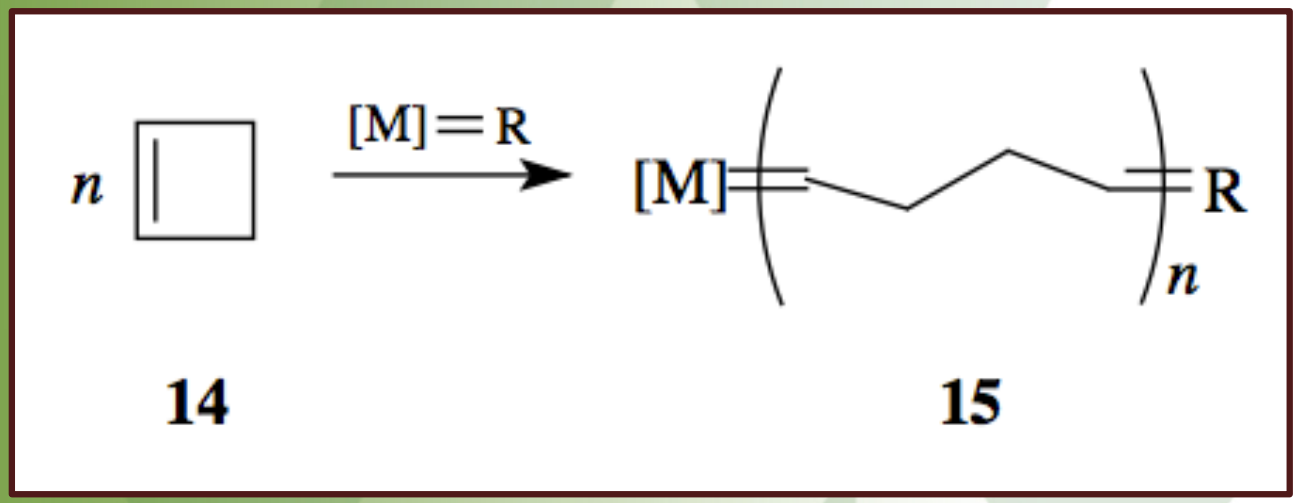
Alkene Metathesis

Ring-Opening Metathesis



Alkene Metathesis

Ring-Opening Metathesis Polymerizations (ROMPS)



14 **15**