

Review: Synthetic Methods for Amphetamine

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Abstract:

This review focuses on synthesis of amphetamine. The chemistry of these methods will be discussed, referenced and precursors highlighted. This review covers the period 1985 to 2009 with emphasis on stereoselective synthesis, classical non-chiral synthesis and bio-enzymatic reactions. The review is directed to the Forensic Community and thus highlights precursors, reagents, stereochemistry, type and name reactions. The article attempts to present, as best as possible, a list of references covering amphetamine synthesis from 1900 -2009. Although this is the same fundamental ground as the recent publication by K. Norman; "Clandestine Laboratory Investigating Chemist Association" 19, 3(2009)2-39, this current review offers another perspective.

Keywords: Review, Stereoselective, Amphetamine, Syntheses, references,

Introduction:

It has been 20 years since our last review of the synthetic literature for the manufacture of amphetamine and methamphetamine. Much has changed in the world of organic transformation in this time period. Chiral (stereoselective) synthetic reactions have moved to the forefront of organic transformations and these stereoselective reactions, as well as regio-reactions and biotransformations will be the focus of this review. Within the synthesis of amphetamine, these stereoselective transformations have taken the form of organometallic reactions, enzymatic reactions, ring openings, α -aminooxylations, alkylations and amination reactions. The earlier review (*J. Forensic Sci. Int.* 42(1989)183-189) addressed for the most part, the "reductive" synthetic methods leading to this drug of abuse. It could be said that the earlier review dealt with "classical organic transformations," roughly covering the period from 1900-1985. This time-line is graphically illustrated below in Figure 1. As illustrated in this figure, certain categories have been historically active. Early synthetic organic transformations such as aldol condensations, the Hofmann rearrangement [105, 116], the Curtius rearrangement [118, 110, 80], the Schmidt rearrangement [80], the Lossen rearrangement [118], the Beckmann rearrangement [111], the Wolff rearrangement [109], the Friedel-Craft alkylation [102, 105] together with catalytic reductions; populated the literature from 1900-1985. Of course, overlap has occurred between these categories as the field of organic chemistry has progressed.

Interestingly, organic synthetic transformations have entered, in the last 20 years, a period of "stereoselective organic transformation". This is graphically illustrated in Figure 1a. The multiplicity of these transformations and their unique starting precursors and reagents may come as a challenge to the forensic community to keep up with the latest organic modifications and "off-precursor-watch-list" circumventions. Herein, we hope to summarize as exhaustively as possible, the chemistry pictorially and compose a

list of precursor chemicals (IUPAC nomenclature, *see supplemental material*) that address these transformations to amphetamine.

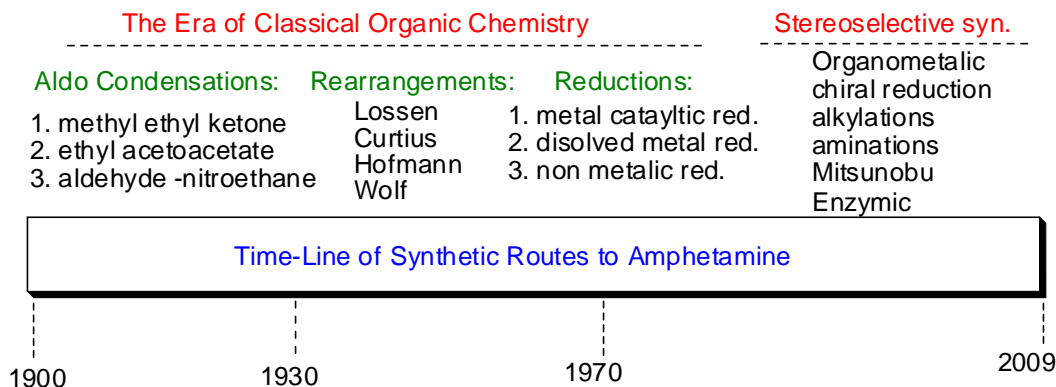


Figure 1

As best as possible, we have attempted to keep the needs of the forensic chemist and law enforcement personnel in mind when creating the categories for retrieving the information on a particular synthetic route. This has added a degree of difficulty to our task since in many cases, the chemist thinks visually (synthetic routes) and the law enforcement investigator works texturally (list of precursors). The categories of this review are listed below and are not without their limitations.

Outline:

Review of amphetamine syntheses **1985 – 2009** (*Schema 2, 3, 4*)

1. Stereoselective syntheses (*Schema 2*)
2. Non-Chiral Syntheses (*Schema 3*)
3. Biotransformation (*Schema 4*)

Review of classical amphetamine syntheses **1900 – 1985** (*Schema 5 and 6*)

1. Classical Organic Transformations (*Schema 5*)
2. Summary Routes to Amphetamine (*Schema 6*)

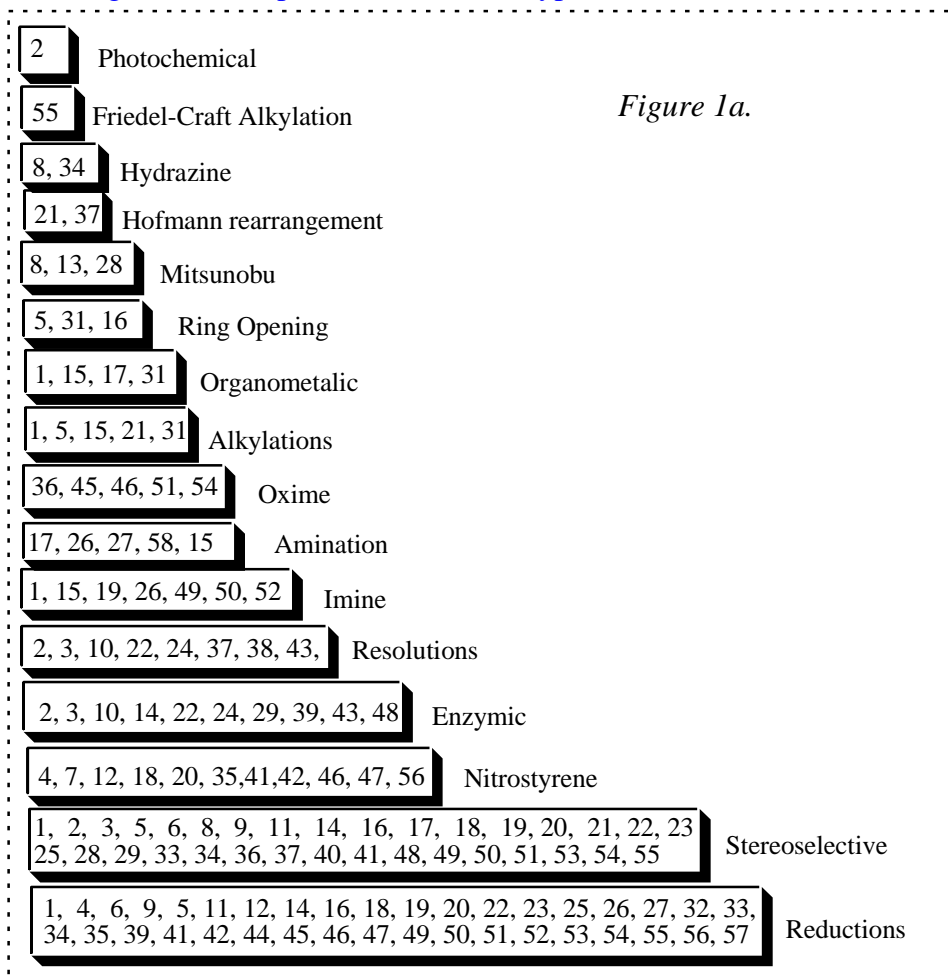
Overview:

In this reviewing period (1985-2009), with progress in stereoselective syntheses and organometallic transformations, academia, along with private industry have been motivated to explore new approaches to the synthesis of amphetamine. These numerous publications have undoubtedly been prompted more by the introduction of a chiral center alpha to a primary amine than the desire to add yet another synthetic approach to the multitude of synthetic routes to amphetamine.

Organometallic chemistry has been used in creative region-constructions of amphetamine, not only with magnesium metal [21, 15], but also with cerium [49], titanium [26], iridium [1] and lithium [1]. Similarly, in the area of organometallic reductions to amphetamine, the field of reagents has expanded to include samarium iodide [4, 6, 9], ruthenium-(chiral-ligands) [18, 20, 36, 41], rhodium-(chiral ligands) [51], titanium-ligands [26], copper [32, 17], magnesium [32] and novelties with borane [33, 42, 56], lithium aluminum hydride [12, 35, 47], L-Selectride [25], Red-Al® [46],

palladium [11, 14, 16, 23, 27, 40, 50, 53] and Raney nickel [33, 49 50]. Creative synthetic routes that do not employ a reductive step have also been published [15, 17, 21, 28, 31, 37, 55, 58]. Ring opening strategies have been developed against phosphorylated aziridines [31] and Sharpless epoxides [5] to yield amphetamine. Mitsunobu transformations [5, 8, 14, 19, 34] have been exploited in a variety of approaches to swap an alcohol precursor to the amine complement toward amphetamine. Hofmann, Curtius [37, 80], Lossen[37] and Schmidt rearrangement [80] continue to be used in synthetic schemes to produce amphetamine. The “classical” Friedel-Craft alkylation [105] of benzene with iron or aluminum trichloride has been improved with the use of *N*-(trifluoroacetyl)- α -amino acid chloride as a chiral F-C reagent to manufacture amphetamine [55]. Intermediates of nitrostyrene have been reduced chirally and non-chirally to amphetamine [4, 12, 18, 20, 35, 41, 42, 56]. Likewise, hydroxylamine via chiral hydrosilylation [51] and hydrazines [8, 52] have been exploited in routes to amphetamine. Reductive aminations via phenyl-2-propanone; P-2-P [19, 40, 51, 54] have appeared in these years, as well as other creative approaches like α -amination [5], alkyne-amination [26], alkene-amination [27], α -aminoxylation [5], electrophilic aminations [15], and sulfinyl-imine amination [17]. Photochemical-induced racemization has been utilized for the transformation of the less pharmacologically active *R* isomer to an equilibrium mix of *R,S*-amphetamine [2]. Improved resolution from racemic mixture of amphetamine to a single isomer has been achieved with “enzymatic transformations” [3, 10, 22, 24, 43] and “classical organic salts resolutions” [37, 47]. Illustrated in Figure 1a and 1b are the histograms and citations for some of the active categories within the transformations to amphetamine between 1985-2009. The activities of stereoselectivity, resolutions and enzymatic transformations are expressly evident.

Histograms for amphetamine reaction types 1985-2009 (#-reference)



Literature Citations for the Synthesis of Amphetamine 1985-2009

Enzymatic (Bio Transformations)

(see Scheme 4)

2. *J. Org. Chem.*, *JOC* 73(2008)364
3. *J. Org. Chem.*, *JOC* 72(2007)6918
10. *Indian J. Chem. Soc. B*, *IJCS* 44B(2005)1312
14. *J. Chemical Research*, *JCR* 10(2004)681
22. *Tetrahedron Asymmetry*, *TA* 13(2002)1315
24. *Synthetic Comm.*, *SC* 31(2001)569
39. *Chem. & Pharm. Bull.*, *CPB* 38(1990)3449
43. US Patent 04950606B1 (1990)

Non-Chiral Organic Synthesis

(see Scheme 3)

4. *Tetrahedron Letter*, *TL* 48(2007)5707
12. *J. Organic Chem.*, *JOC* 70(2005)5519
13. *Organic & Biomol. Chem.*, *OBC* 3(2005)1049
15. *Organic Letters*, *OL* 6(2004)4619
26. *Organic Letters*, *OL* 2(2000)1935
27. *Tetrahedron*, *Tetra* 56(2000)5157
31. *Tetrahedron*, *Tetra* 53(1997)4935
32. *J. Chem. Soc. Perkin I*, *JCSP1* 1(1996)265
37. *J. Labeled Comp. Rad.*, *JLCR* 31(1992)891
38. *J. Medicinal Chem.*, *JMC* 34(1991)1094
40. *J. Chromatographic Sci.*, *JCS* 28(1990)529
41. *Tetrahedron*, *Tetra* 46(1990)7403
42. *Tetrahedron*, *Tetra* 46(1990)7743
45. *Coll. Czech. Chem. Comm.*, 54(1989)1995
48. *Organic Reactions*, Vol 36 (book, 1988)
57. *J. Medicinal Chem.*, *JMC* 31(1988)1558
52. *J. Chem. Soc. Chem. Comm.* 2(1986)176
54. *Khimya Geter. Soed* #12,1648(1985)
56. *Synthetic Comm.*, *SC* 15(1985)843
22. *Tetrahedron Asymmetry*, *TA* 13(2002)1315

Stereoselective Synthesis

(see Scheme 2)

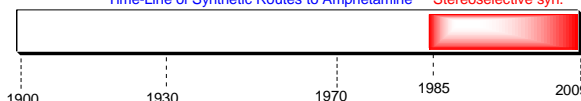
1. *J. American Chem. Soc. JACS* 131(2007)9882
5. *Tetrahedron*, *Tetra* 63(2007)9758
6. *Chemistry A European J.*, *JEC* 12(2006)4197
8. *Biological Med. Chem. Letter*, *BMCL* 15(2005)3039
9. FZSGS patent # 1673210 (2005)
11. *J. Medicinal Chem.*, *JMC* 48(2005)1229
14. *J. Chem. Research*, *JCR* 10(2004)681
16. *Tetrahedron Asymmetry*, *TA* 15(2004)3111
17. *J. Combinatorial Chem.* 5(2003)590
18. *J. Chem. Research*, *JCR* 3(2003)128
19. *Tetrahedron Asymmetry*, *TA* 14(2003)2119
20. *J. Chinese Chem. Soc.* 49(2002)505
21. *J. Chem. Soc. Perkin I*, *JCSP1* 16(2002)1869
22. *Tetrahedron Asymmetry*, *TA* 13(2002)1315
23. US patent #6399828(2002)
25. *J. Organic Chem.*, *JOC* 65(2000)5037
28. *Tetrahedron Letters*, *TL* 41(2000)6537
33. *Tetrahedron Letters*, *TL* 36(1995)1223
34. *Tetrahedron Asymmetry*, *TA* 4(1993)1619
36. *Tetrahedron Asymmetry*, *TA* 3(1992)1283
37. *Acta. Chimica Scan.* 45(1991)431
41. *Tetrahedron*, *Tetra* 46(1990)7403
44. *Angew Chem. Int.* 28(1989)218
49. *J. American Chem. Soc. JACS* 109(1987)2224
51. *Organometallics*, 5(1986)739
53. *Analytical Chem.* 58(1986)1642
54. *Khimya Geter. Soed.* 12(1985)1648
55. *J. Organic Chem.*, *JOC* 50(1985)3481

= Reference

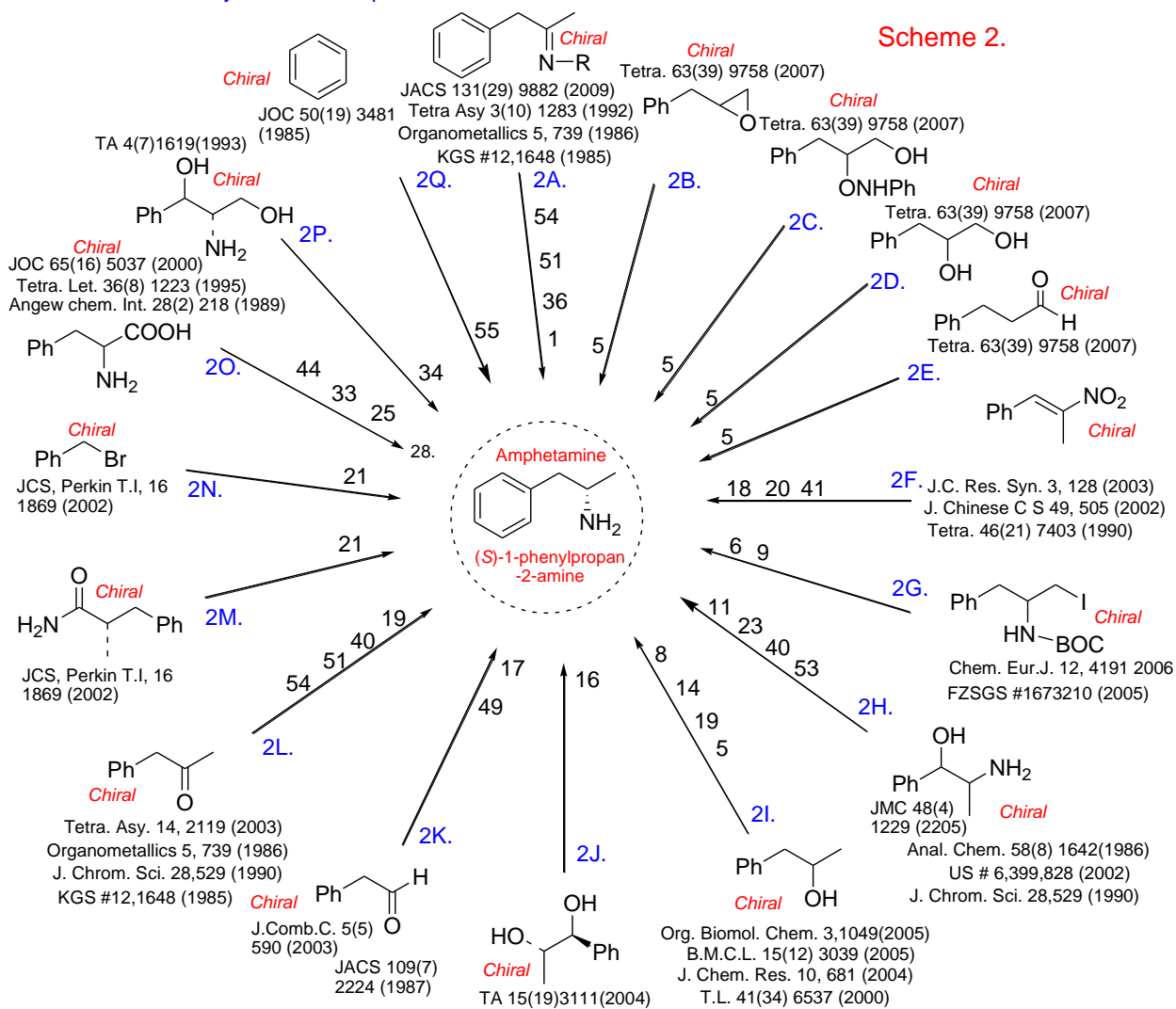
Figure 1b.

Amphetamine Review (1989 – 2009)

Time-Line of Synthetic Routes to Amphetamine Stereoselective syn.



Stereoselective Synthesis of Amphetamine 1985--2009



Discussion of Stereoselective Syntheses of Amphetamine 1985-2009:

Illustrated in Scheme 2, routes 2A-2Q, represent the multitude of stereoselective approaches to amphetamine published between 1985 –2009. Within this illustrated pinwheel of reaction routes, we have arranged references in reverse chronological order – clockwise [#’s]. As a starting point for discussion, take the Schiff base (1-phenylpropan-2-imine, route 2A) as a chiral approach to amphetamine [1, 36, 51, 54]. This approach has been facilitated by the improvements of chiral organometallic ligands with transition metals in order to effect chiral catalytic reductions [1, 36, 51, 54, route 2A]. Similarly, armed with chiral organometallic ligands with ruthenium and rhodium, the reduction of nitrostyrenes [(*E*)-(2-nitroprop-1-enyl)benzene] have been achieved stereoselectively [18, 20, 41; route 2F].

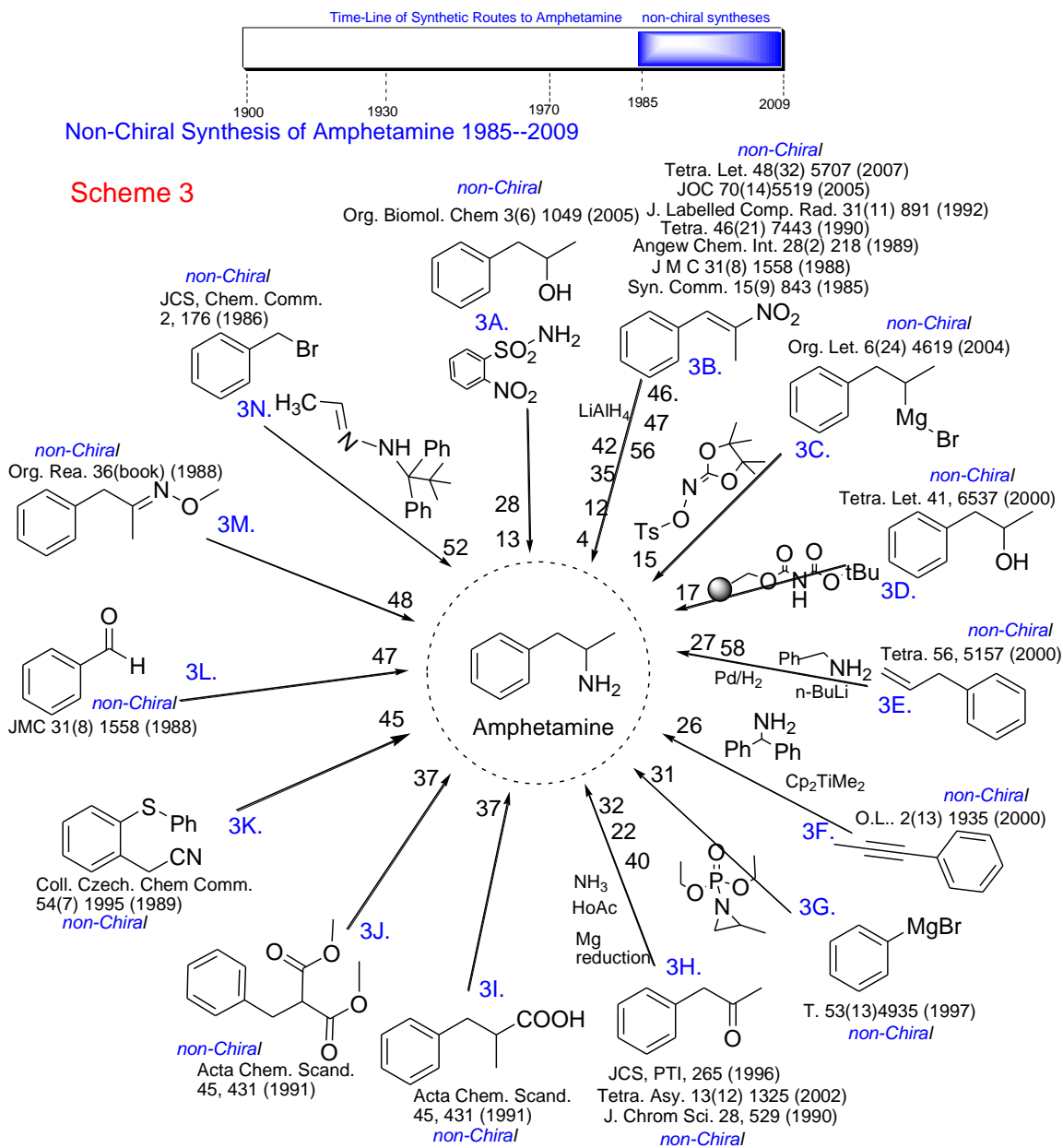
A completely different approach was taken by Talluri, S. et. al.; [routes 2B-E], wherein they initiated the route to amphetamine from 1-phenylpropanal [5, route 2E]. Starting from this one-carbon extended aldehyde as opposed to the typical 2-phenylacetaldehyde [17, 49; route 2K] or benzaldehyde [47, 80, 89, 92, 95, 110; route 5Z, also implicit in 18, 20, 41, 42, 44, 56, 60, 39, 54, 61, 35, 22, 20, 18, 12, 4.57, 85, 84, 75, 74, 70, 67, 62, 94, 87, 86, 113, 114; route 5A] precursor, these workers performed a chiral oxy-alkylation with nitrosobenzene to (*R*)-3-phenylpropan-1,2-diol [5, route 2C-2D]. Tosyl chloride assisted ring closure lead to the epoxide, 2-benzyloxirane [5, route 2B]. Reductive ring opening of the epoxide produced the alcohol, (*S*)-1-phenylpropan-2-ol; [see structure in route 2I]. This was followed by swapping the alcohol moiety for azide. The final step was catalytic (PtO₂) reduction to amphetamine [5]. Although a lengthy process to amphetamine, its potential importance to forensic chemists lies in the fact that each intermediate is a potential starting precursor for a chiral synthesis to amphetamine. Closely allied to the alcohol-azide swap in the previous route are the variations achieved by *Mitsunobu reaction-type* exchanges from (*R*)-1-phenylpropan-2-ol to (*S*)-1-phenylpropan-2-NX, wherein inversion of configuration is complete to the amine complement [8, 14, 19, 5, 34; route 2I and route 2P].

Chiral starting materials like phenylpropanolamine [11, 23, 29, 40, 53; route 2H] and phenylalanine [33, 25, 6, 9, 44; route 2O and route 2G] have been easy targets for precursors to the stereoselective synthesis of amphetamine. The routes from phenylalanine are variations on J.W. Wilson’s original article from 1977 [84; route 6BB] utilizing alternative reagents for the reduction of the carboxylic acid, alcohol to halide swap, reduction of the alkyl halide and BOC deprotection.

In the case of phenylpropanolamine as precursor, earlier literature [40,53, route 6P] make use of the chloro-pseudonorephedrine intermediate, as most typically seen in clandestine laboratories, however more recent literature [11, 23, route 6P] makes use of

acetic anhydride to yield the ester for catalytic reductive removal of the OH moiety to amphetamine.

Creative chiral scaffolding has been used to introduce stereoselectivity early in the amphetamine synthesis [17, 49, 21; routes 2M, 2N and 2K]. These unique approaches start with the achiral, off-listed precursors, benzylbromide [21, route 1N] or 2-phenylacetaldehyde [17, 49, route 2K]. The stereoselectivity is introduced and controlled by simpler commercially available chiral directors. Interestingly, the Hofmann rearrangement, which retains stereoselectivity, was utilized at the end of route 2M [21] with the modern uses of hypervalent iodine [21]. Another older “classical synthesis” improvement was profiled in the Friedel-Crafts alkylation of benzene through the use of chiral (s)-2-(2,2,2-trifluoroacetamido)propanoyl chloride [55, route 2Q].



Discussion of Non-Chiral Syntheses of Amphetamine 1985-2009:

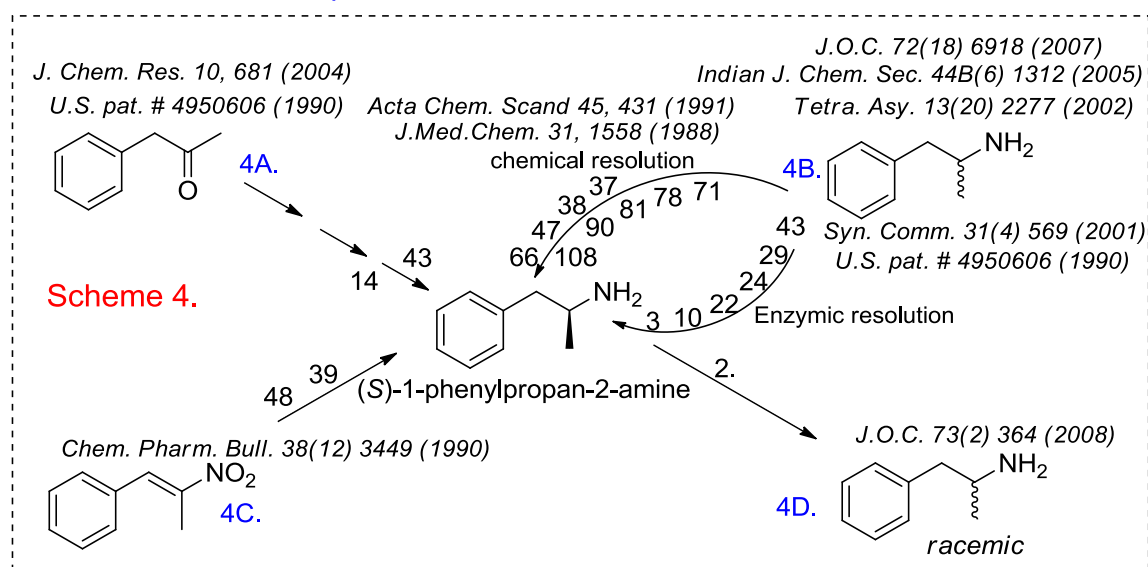
Non-chiral syntheses of amphetamine (Scheme 3, routes 3A-N) have also appeared in the literature; **1985-2009**. These variations are graphically illustrated in Scheme 3 and represent 25 individual citations. As described above with regards to chiral routes, the *Mitsunobu type reaction* chemistry has been exploited in 3 different non-chiral routes, each starting from racemic 1-phenylpropan-2-ol [13, 17, 28; route 3A and 3D]. Achiral reductions of nitrostryene to amphetamine were the most popular approaches in this time period [4, 12, 35, 42, 46, 47, 56; route 3B]. These citations are

primarily in the course of building pharmaceutical analogs / research. Organo-metallic (Grignard or lithium alkylation) reactions were used in a variety of alkylation reactions to amphetamine [15, 31, 52; route 3C, 3G and 3N]. These variations include Grignard ring opening of a phosphorylated-aziridine (nucleophilic ring-opening of *N*-phosphorylated aziridines) [31; route 3G], reaction with an electron deficient oxime (electrophilic amination of Grignard reagent) [15; route 3C], and lithium alkylation of an α -amino carbanion equivalent reaction [52; route 3N].

The amination of allylbenzene was affected in a base-catalyzed hydroamination reaction [27; route 3E]. This reaction is similar in precursor and product, however different in mechanism to the 1982 phosphoramidomercuration-demercuration of allylbenzene to amphetamine [58; route 6U]. Amination with a commercially available α -aminodiphenylmethane, which serves as an ammonia equivalent, was used for the hydroamination of 1-phenyl-1-propyne to amphetamine [26; route 3F].

Several citations occurred in the literature for the reductive amination of P-2-P to amphetamine [32, 22, 40; route 3H]. The classical malonic ester synthesis was used to construct 2-methyl-3-phenyl propanoic acid [37, route 3I] which was then converted to amphetamine via a Curtius rearrangement / hydrolysis [37]. A similar classical reaction, that of a Claisen / Dieckmann condensation, utilizing a benzylnitrile analog was used to construct a P-2-P complement [45; route 3K]. This analog was converted to the oxime, followed by reduction and de-sulfuration with sodium / ethanol to amphetamine [45; route 3K]. Finally, O-methoxy-oxime of P-2-P was reduced with Red-Al® to yield amphetamine with marginal success [48; route 3M].

Enzymic, Photo-induced and Chemical Manipulation of Amphetamine Isomers 1985 - 2009



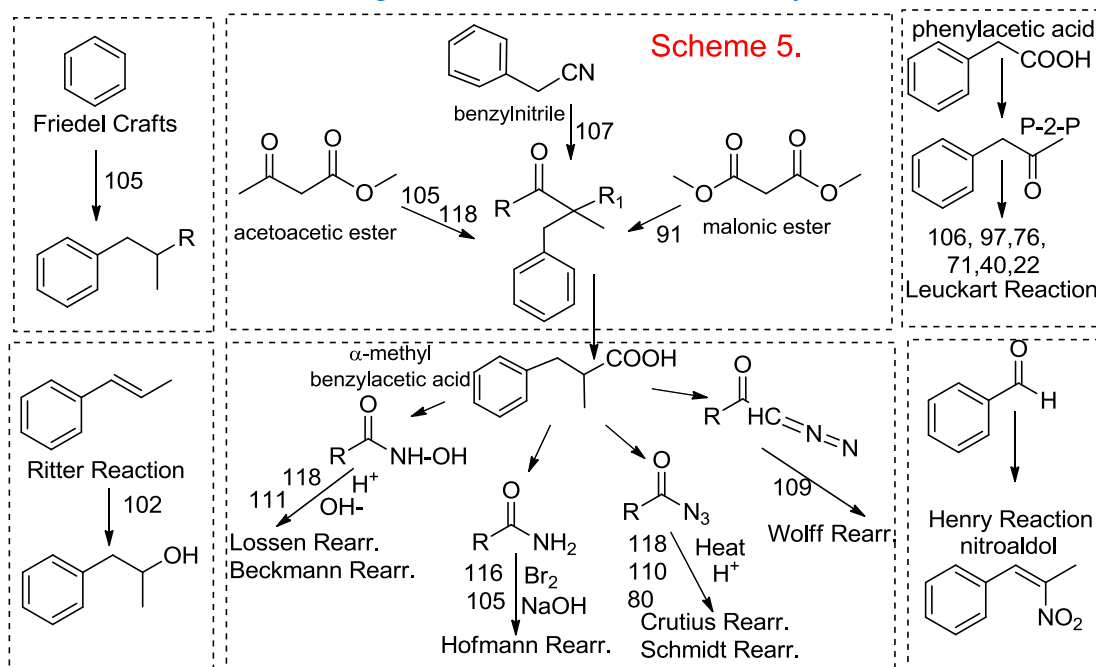
Scheme 4.

Discussion of Enzymatic, Photo-induced and Chemical Manipulation of Amphetamine Isomers: 1985-2009

Biotransformations have increased in interest, proof of concept and patent applications from **1985-2009**. Illustrated in Scheme 4 are the citations within this topic regarding amphetamine isomers. Both phenyl-2-propanone [14, 43; route 4A] and the nitrostyrene, (*E*)-1-(2-nitroprop-1-enyl)benzene [39,48; route 4C] have been used as starting points to the enzymatic synthesis to amphetamine. Alternatively, biotransformations of *racemic* amphetamine leading to the exclusion or enhancement of one isomer (enhanced ee) have been published or patented [3, 10, 22, 24, 29, 43; route 4B]. Conversely, one citation [2; route 4D] describes the photochemically induced-radical mediated racemization of the single amphetamine isomer to the racemic mixture. Classical methods of chiral resolution based upon chiral organic salts have been reported in the time frame of 1900-2009, with the use of D-(-)-tartaric acid [30, 47, 38, 71, 81a, 88, 90, 108], benzoyl-d-tartaric acid [38], di-p-toluoyl-d-tartaric acid [38], (S)-2-naphthylglycolic acid [66], α -amino acids [78] and optical-10-camphorsulfonyl chloride [37].

Organic Transformation from 1900 -2009:

Classical Organic Transformation in the Early 1900-1950's:



Scheme 5.

Classical Organic Transformation in the Early 1900-1950's:

The early literature regarding amphetamine synthesis of the 1900's was dominated by classical organic transformations (Scheme 5). These reactions like the Friedel-Crafts reaction [105,], Ritter Reaction [102], Leuckart reductive amination reaction [106, 97, 76, 71], nitro-aldol dehydration reaction, also called the Henry Reaction [116, 96, 94, 89, 87, 86, 85, 82, 70, 67] and rearrangement reactions that came to be known as the Hofmann rearrangement [105, 116], Curtius rearrangement [118, 110, 80], Schmidt rearrangement [80], Lossen rearrangement [118], Beckmann rearrangement [111] and the Wolff rearrangement [109], were productive routes to the synthesis of amphetamine. The non-amine component, α-methylbenzylacetic acid, was constructed with carbon-carbon bond formation via a carbo-anion enolate condensed with a suitable alkylhalide. These condensations, that were classically referred to as acetoacetic ester synthesis [105, 118] and malonic ester synthesis [91], later came to be referred to as cases of the Claisen condensation. In the case of phenylacetonitrile (benzyl nitrile) [107], the acidity of the central methylene hydrogens between the nitrile and aromatic ring, are used for abstraction and carbo-anion production before alkylhalide reaction.

Organic Transformation in the Early 1950-1985s:

Moving forward in time, from the period dominated by “classical organic transformations” (1900-1950), we enter a period for amphetamine synthesis that saw expanded interest in dissolved metal reductions and early chiral constructions. This time frame (1950-1985) was the focus of our previous review (*J. Forensic Sci. Int.* 42, (1989) 183-189) and highlighted catalytic reductions, dissolving metal reductions and metal

hydride reduction leading to amphetamine. It was during this period that chiral complement to the Friedel-Crafts reaction was introduced for the synthesis of amphetamine [55]. Amination of a double bond was improved with the use of diethyl phosphoramidate [58], as well as acetonitrile mercuration [69] each leading to amphetamine. Reductive amination with (R)-1-phenylethylamine on the Schiff-base of phenyl-2-propanone followed by diastereoisomeric separation allowed for a chiral synthesis of amphetamine [64]. Later (1977, 1978), two chiral syntheses to amphetamine were published starting from D-phenylalanine [84a, 84b].

Summary:

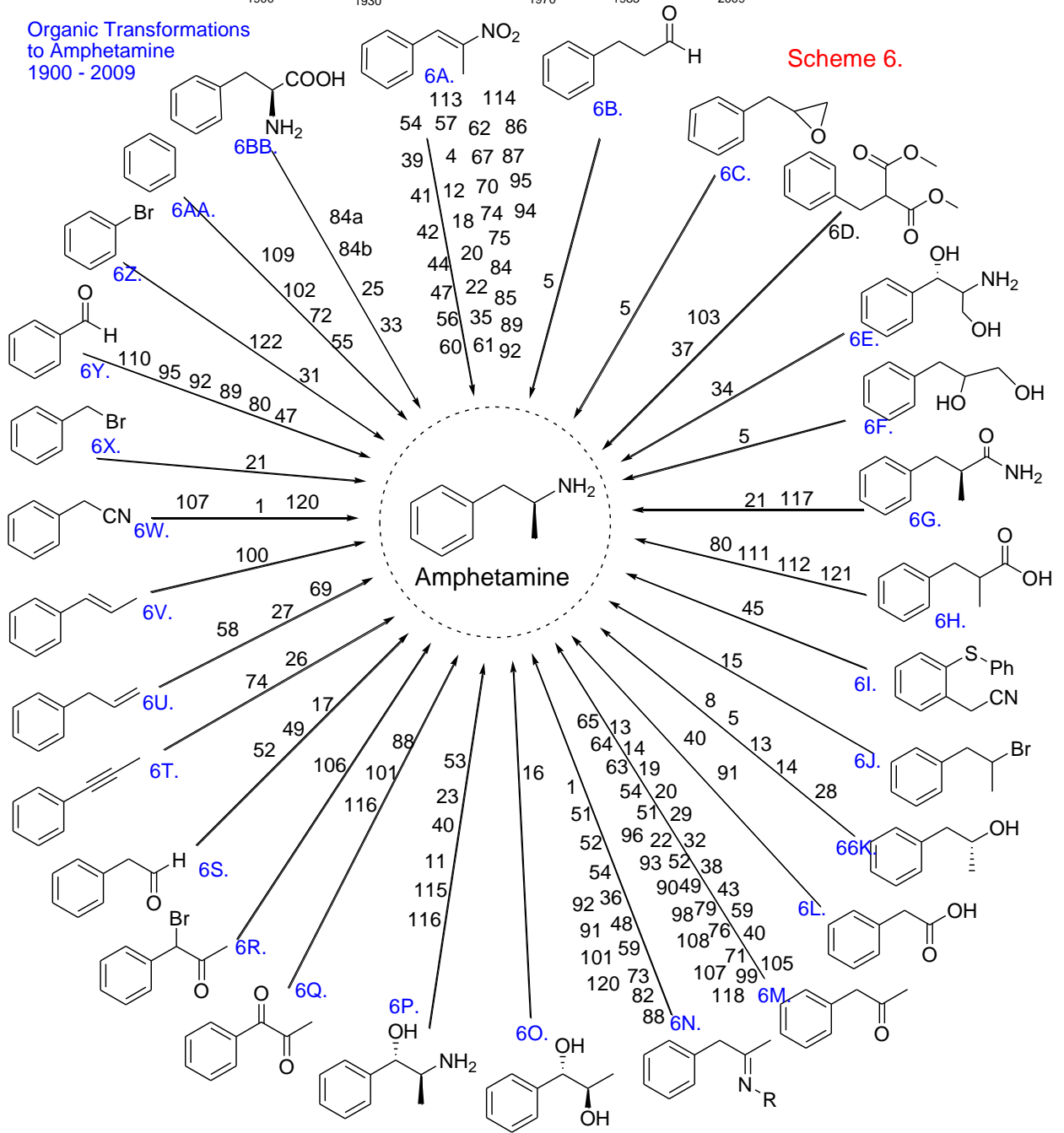
As best as possible the authors have attempted to summarize the synthetic transformations published within the period **1900-2009**, with emphasis upon **1985-2009**. The complete visual precursor / references to amphetamine pin-wheel is illustrated in Scheme 6 and is intended for the forensic chemist as a complete map of amphetamine routes / literature. These individual reactions are broken out, expanded and illustrated with added nomenclature in the supplemental material. Furthermore, precursor names via IUPAC (ChemDraw, Cambridge Software) are tabulated for the non-chemist with cross reference to literature citations.

Time-Line of Synthetic Routes to Amphetamine non-chiral syntheses



Organic Transformations to Amphetamine 1900 - 2009

Scheme 6.



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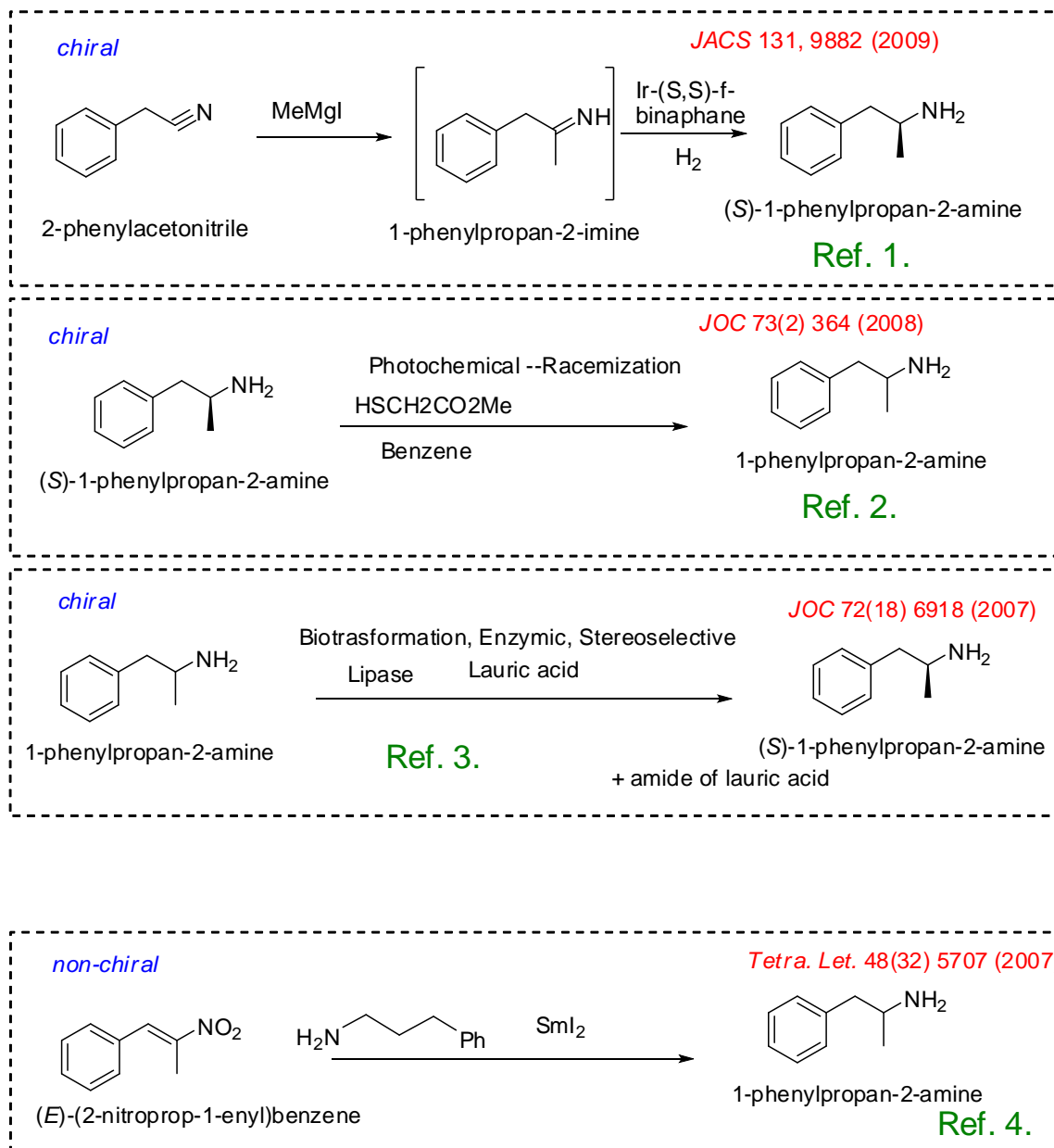
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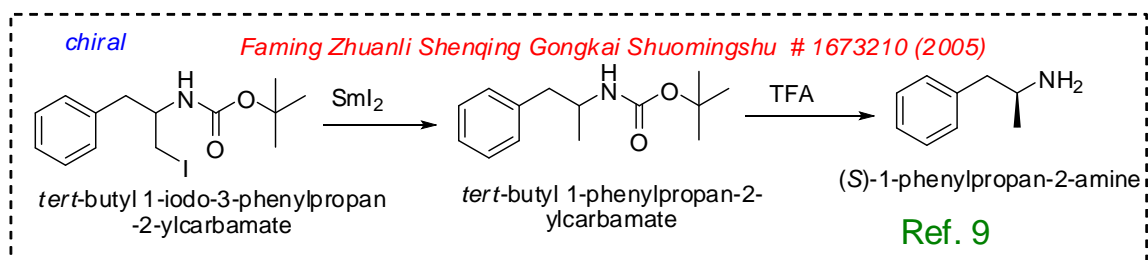
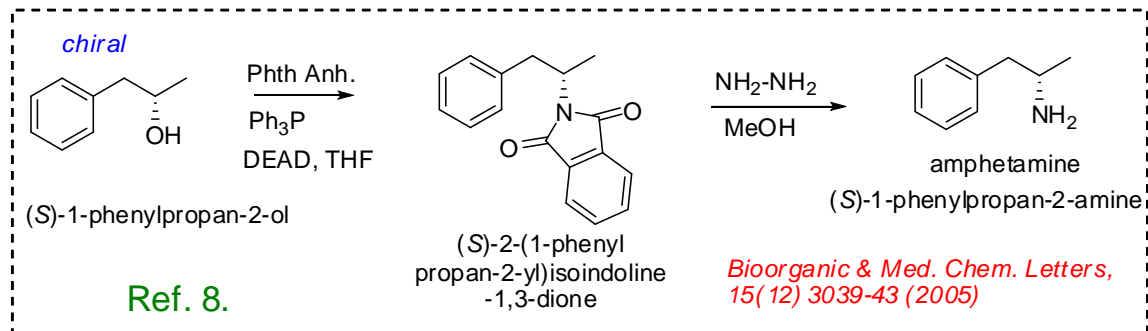
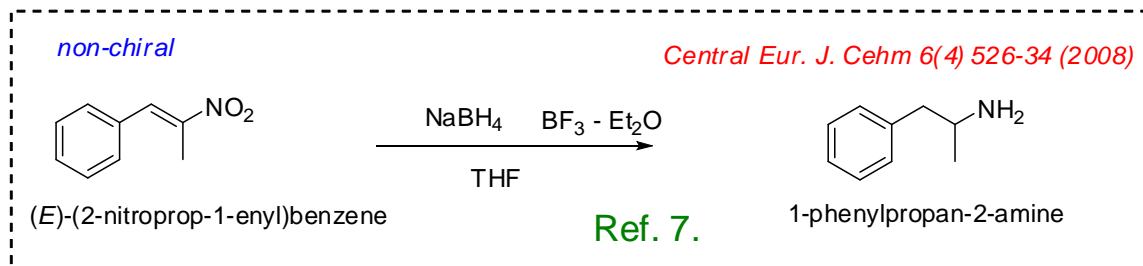
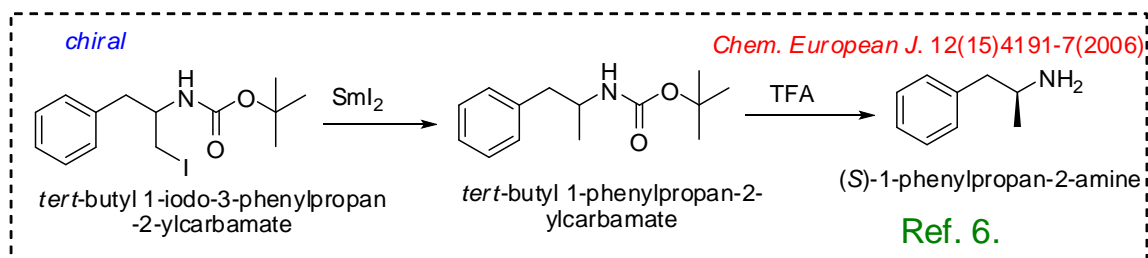
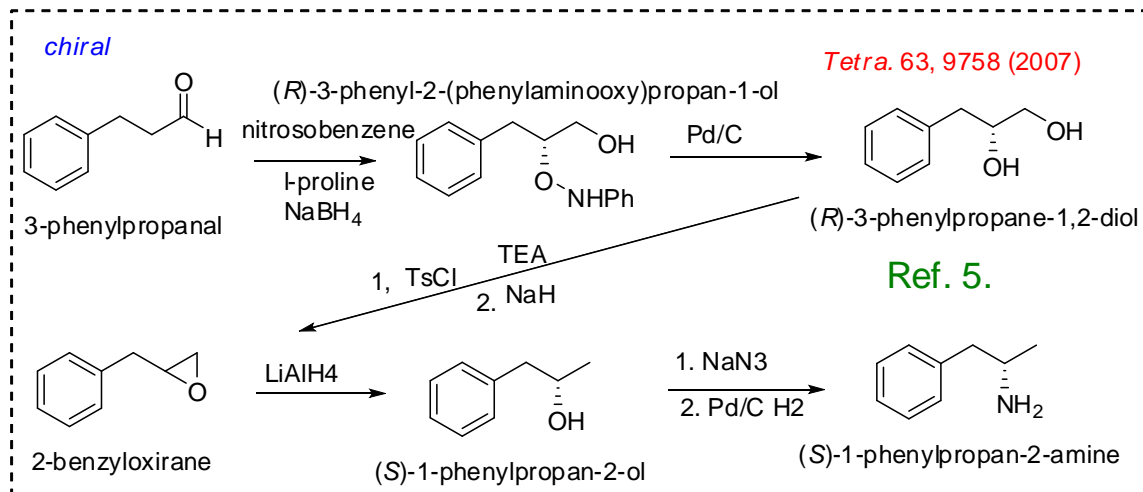
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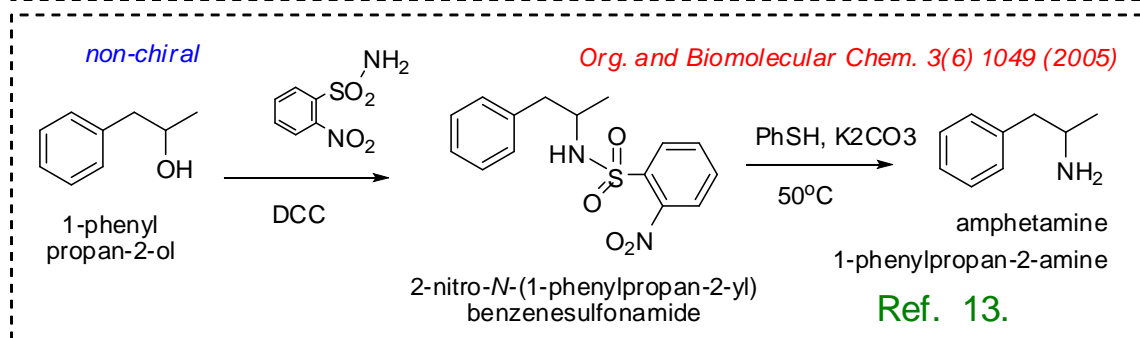
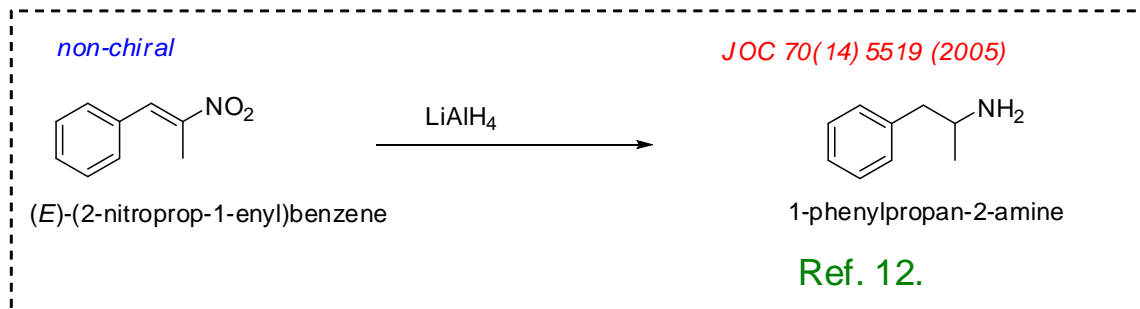
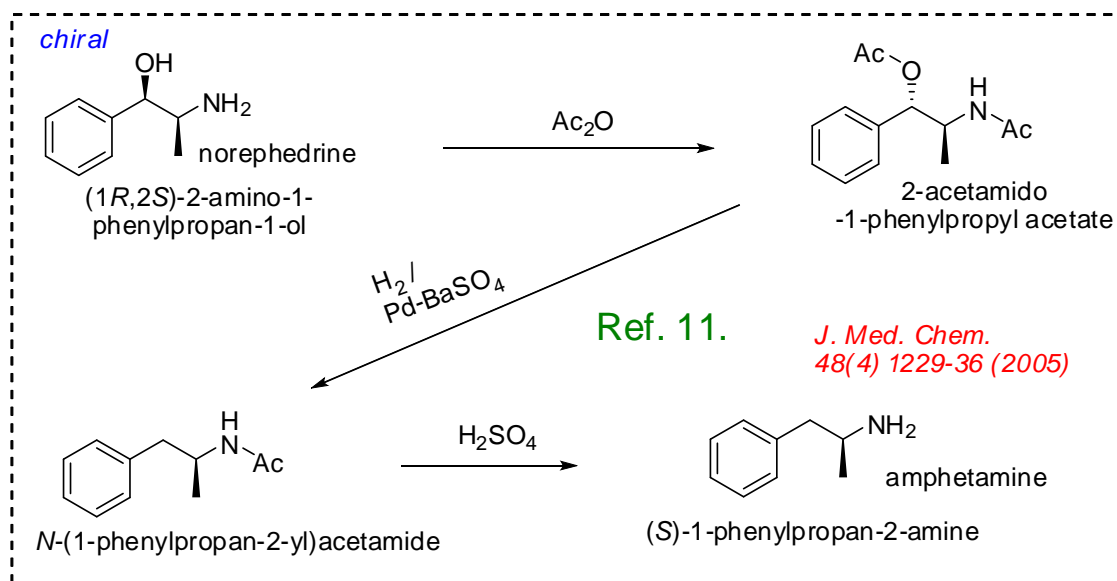
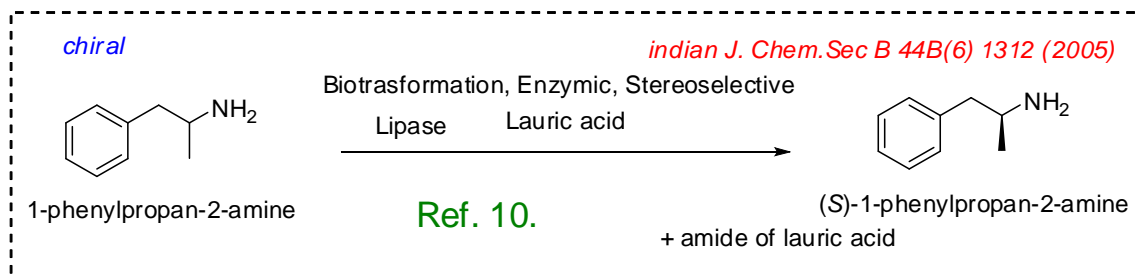
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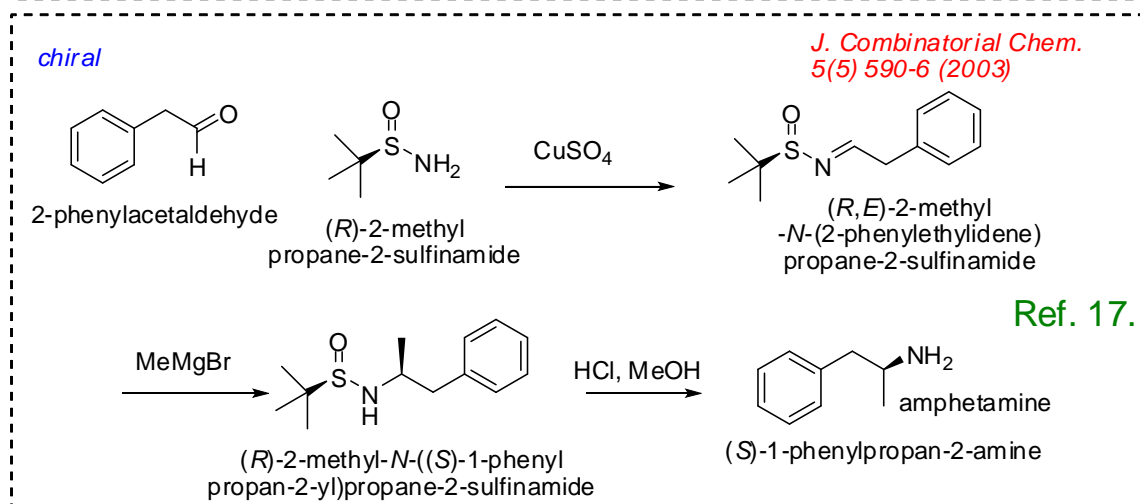
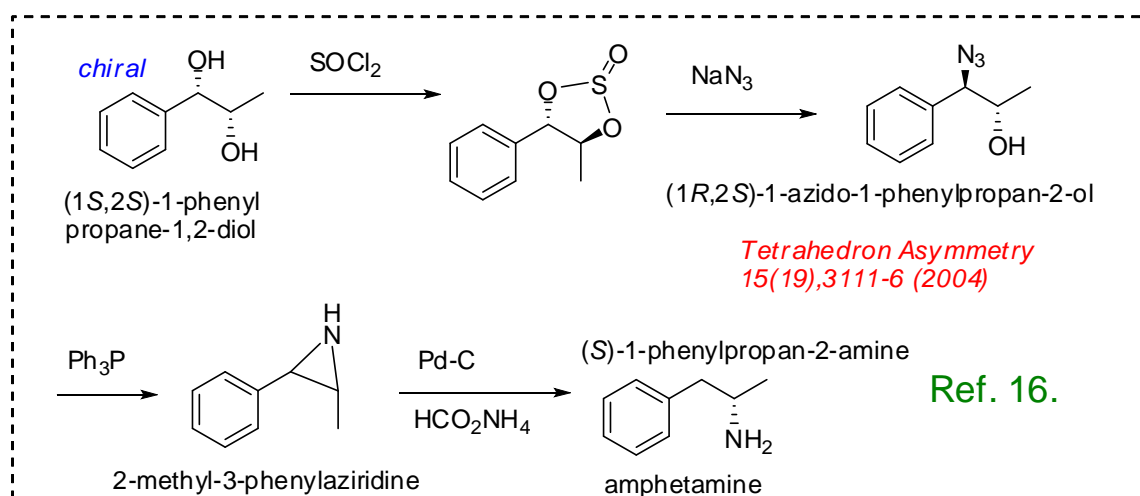
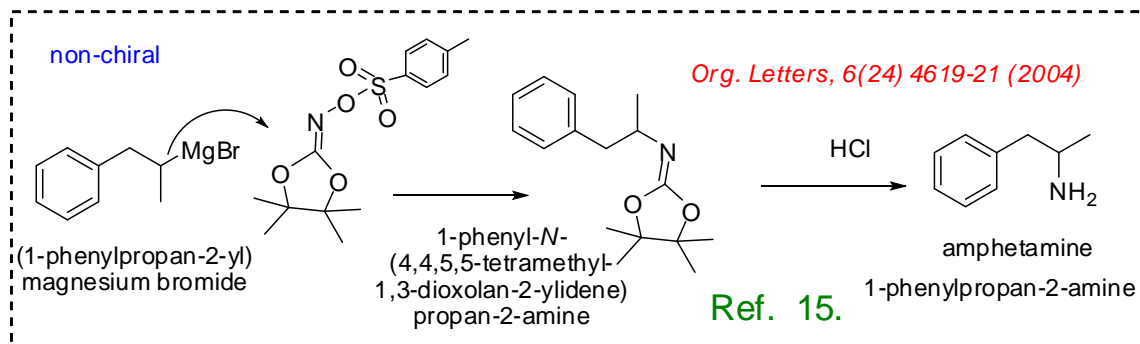
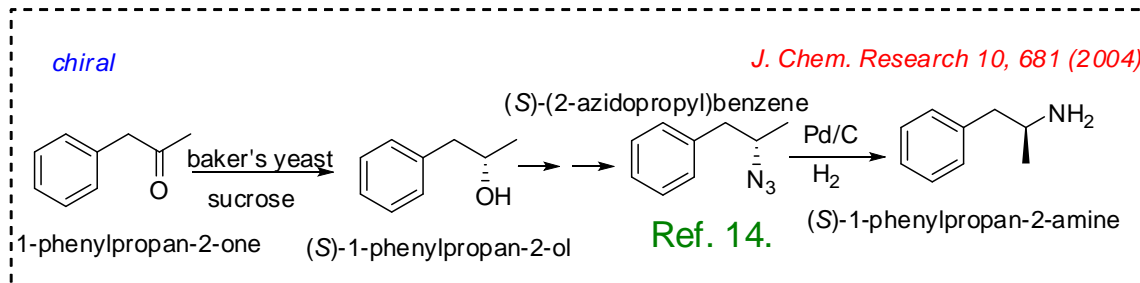
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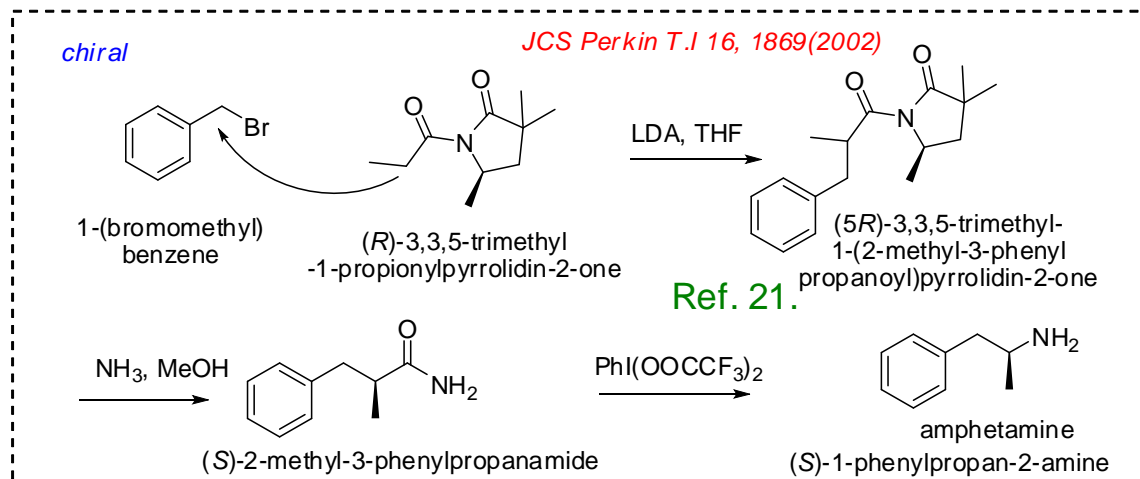
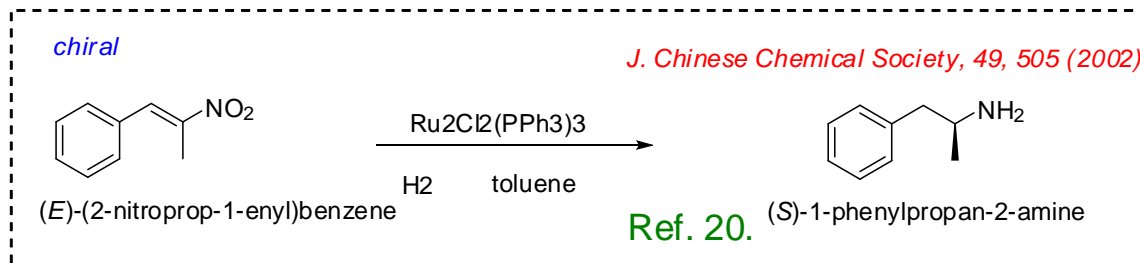
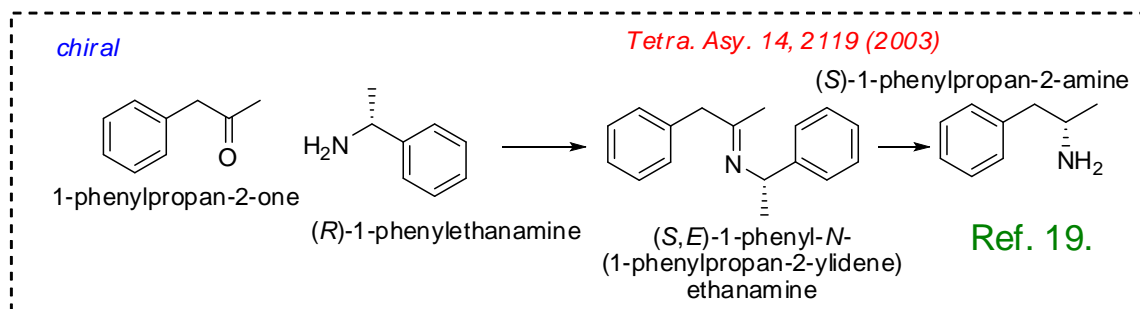
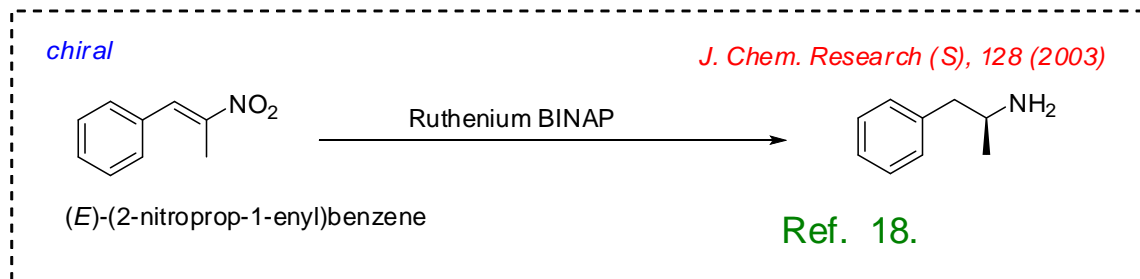
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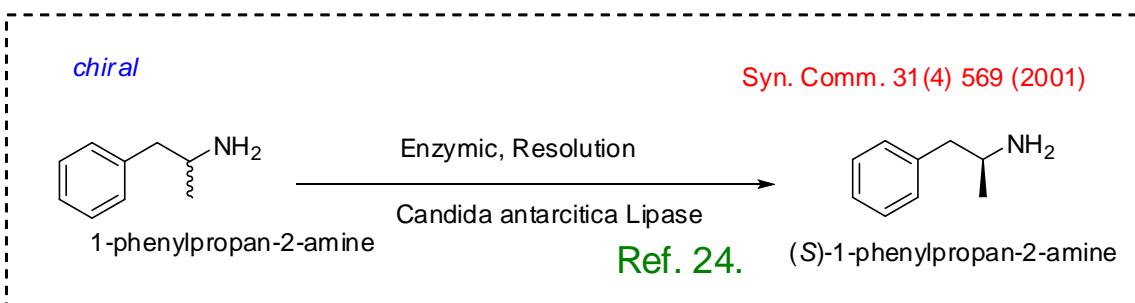
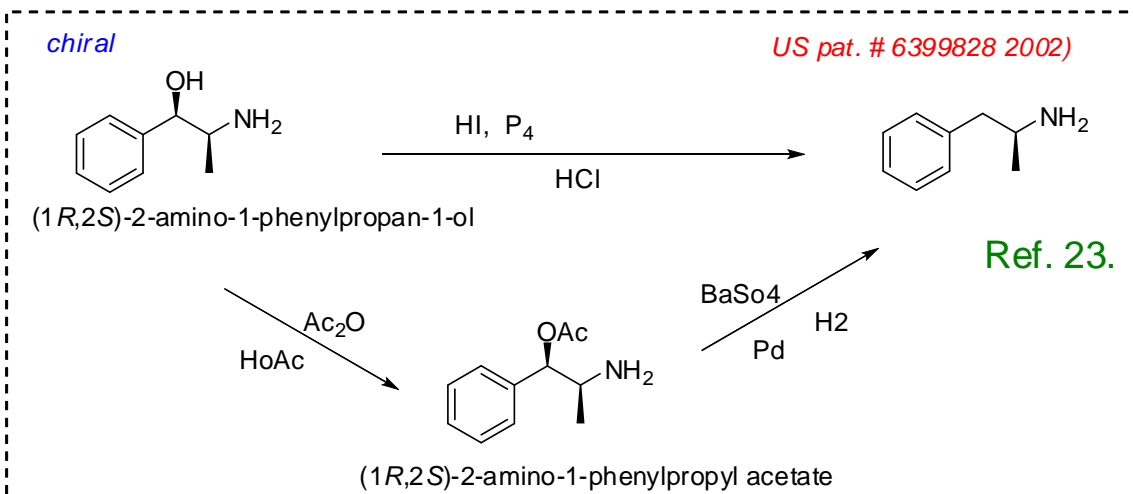
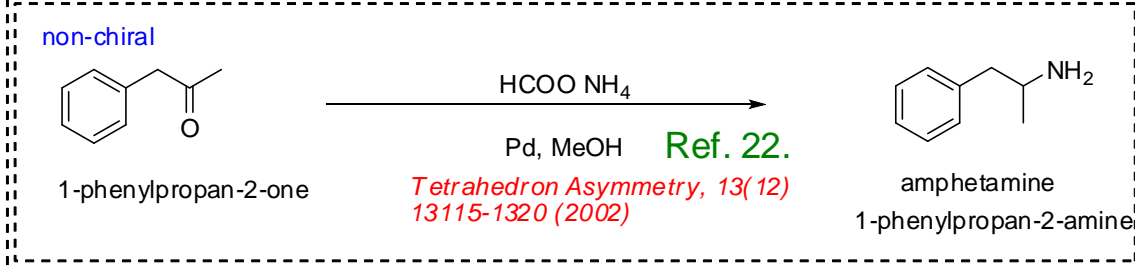
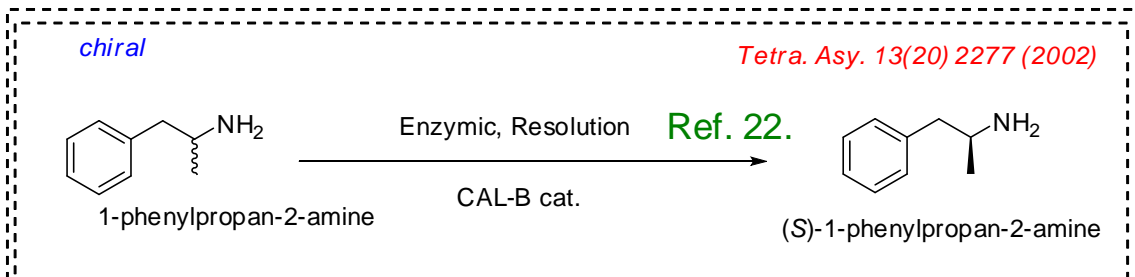


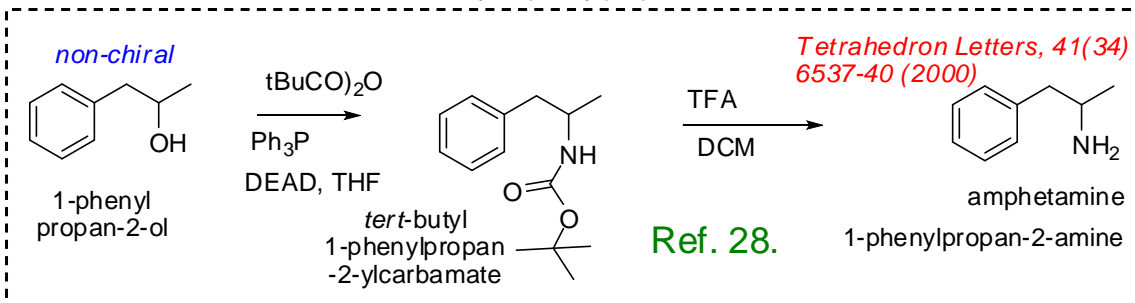
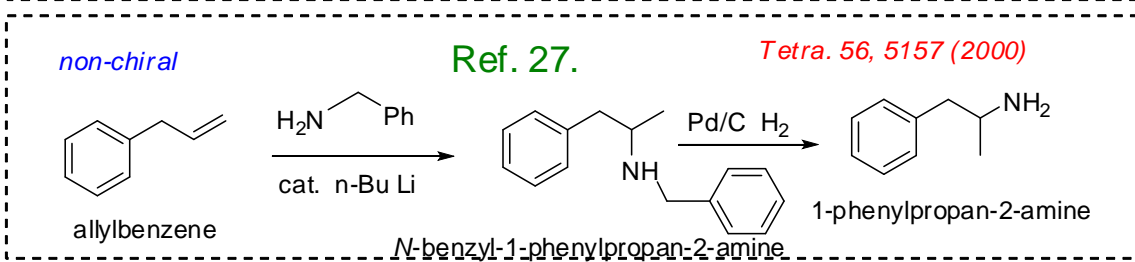
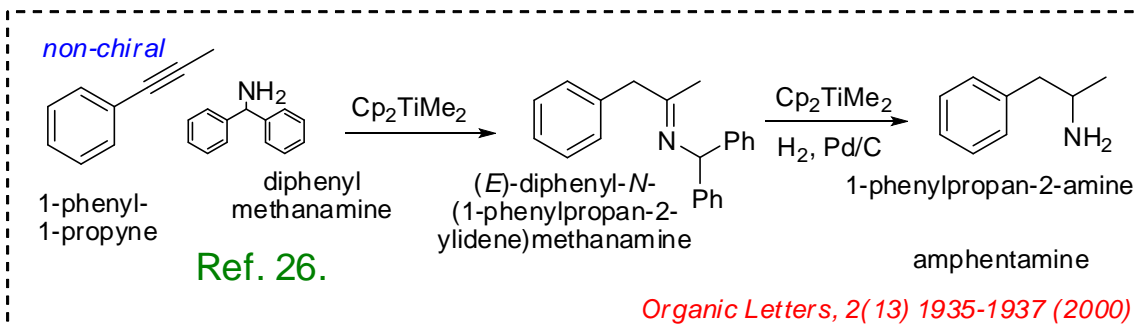
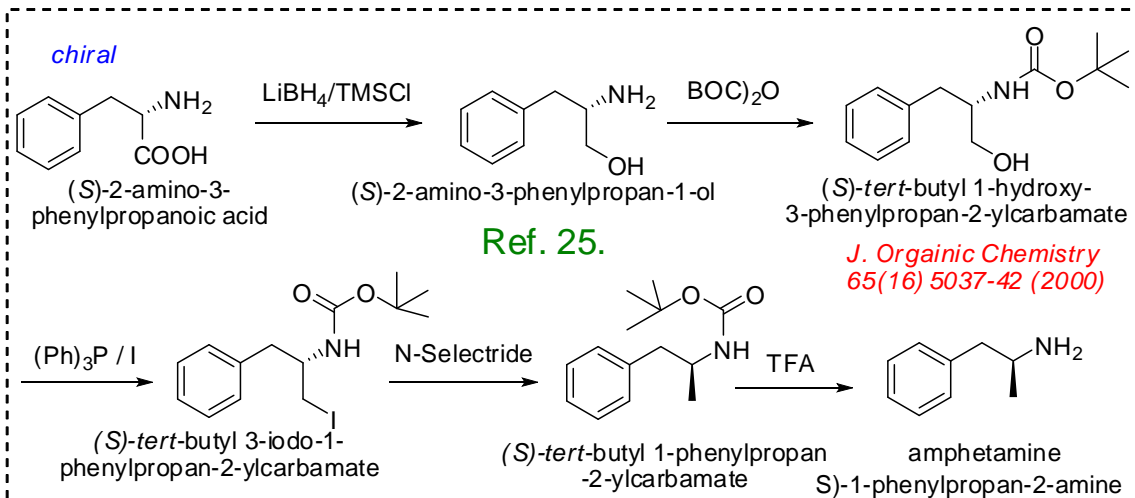


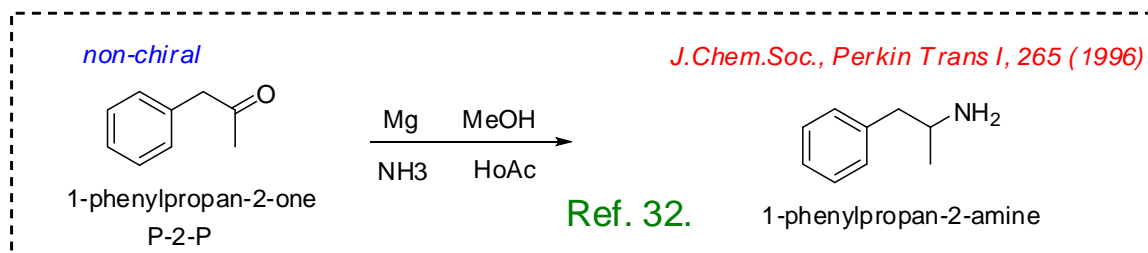
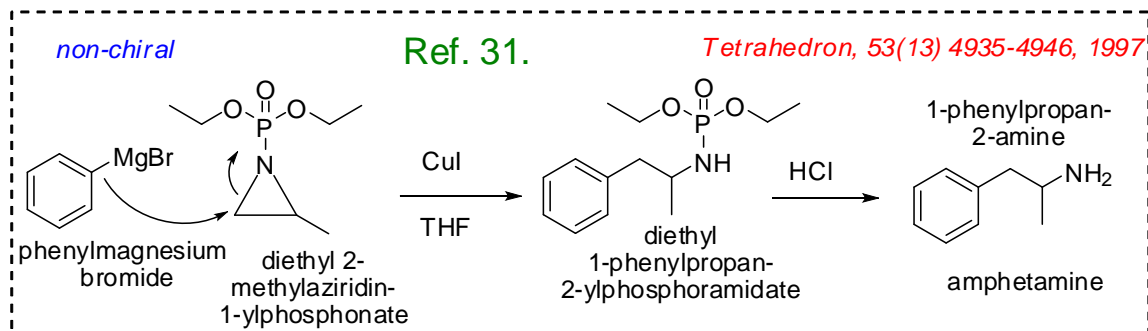
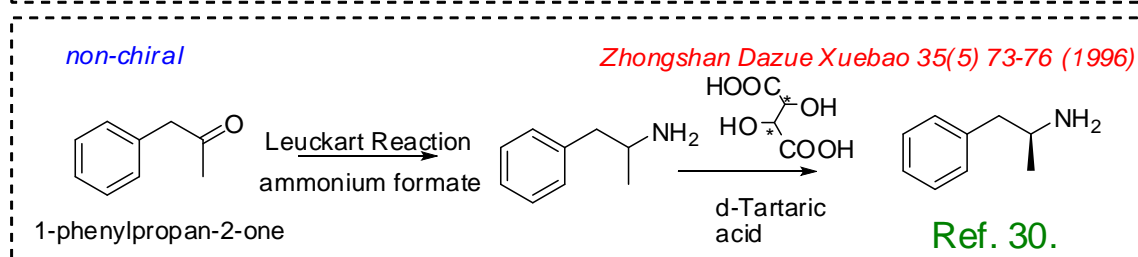
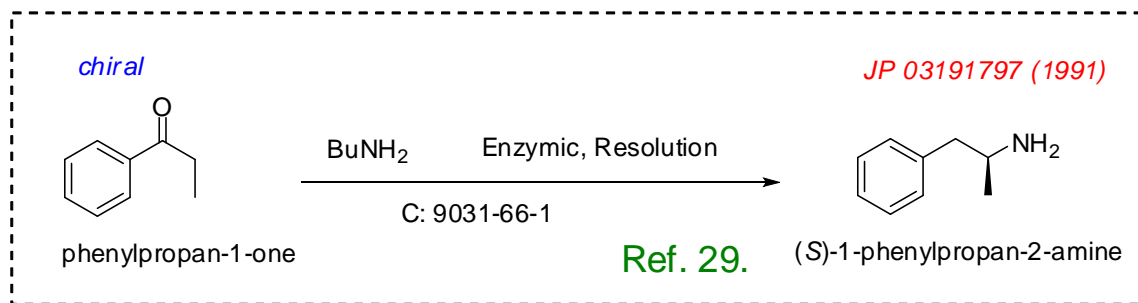


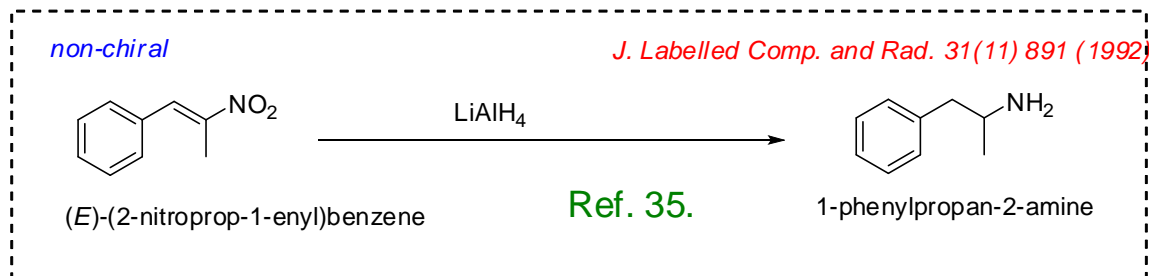
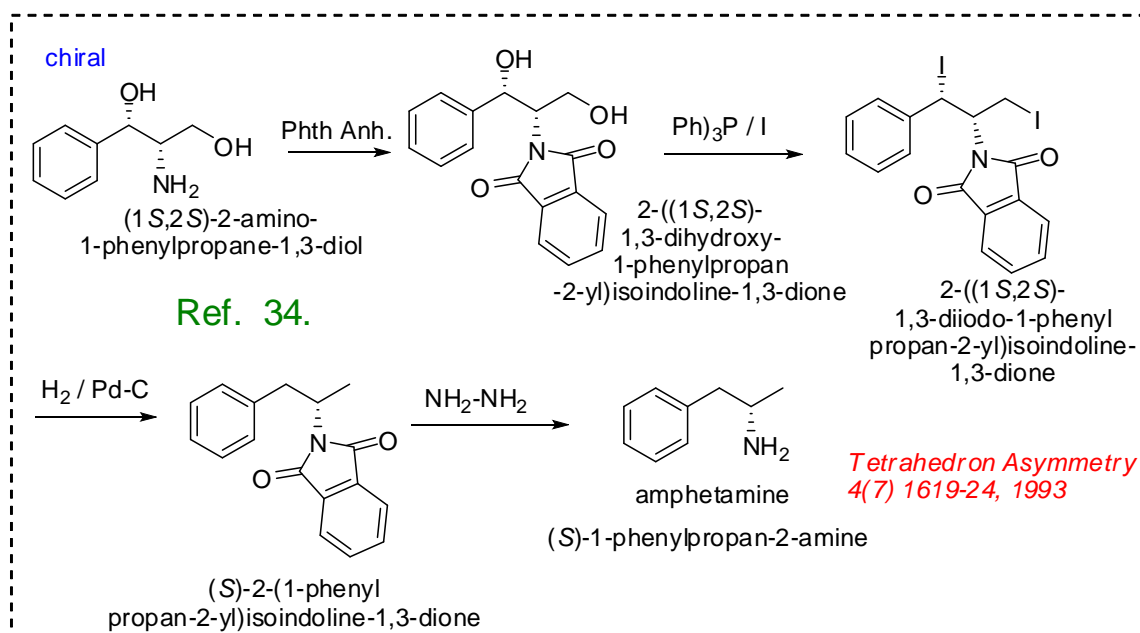
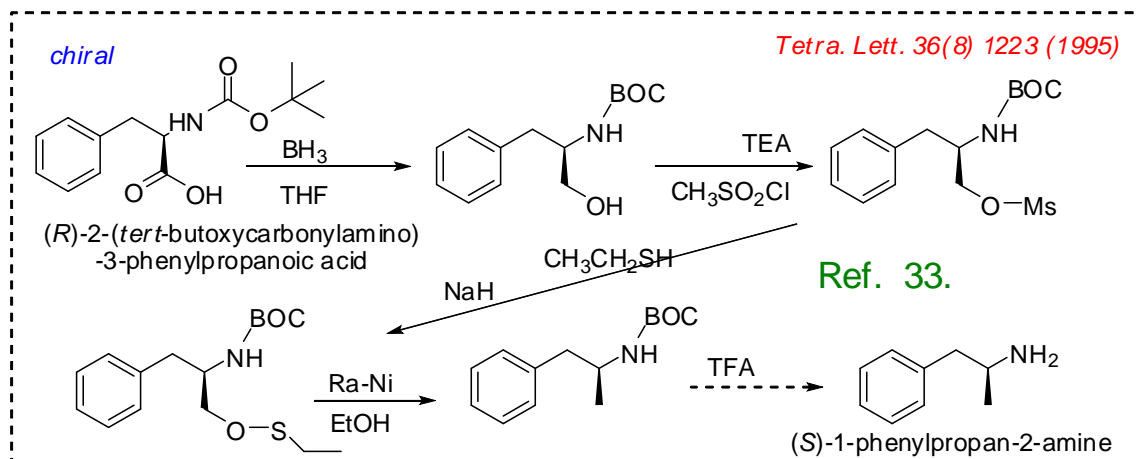


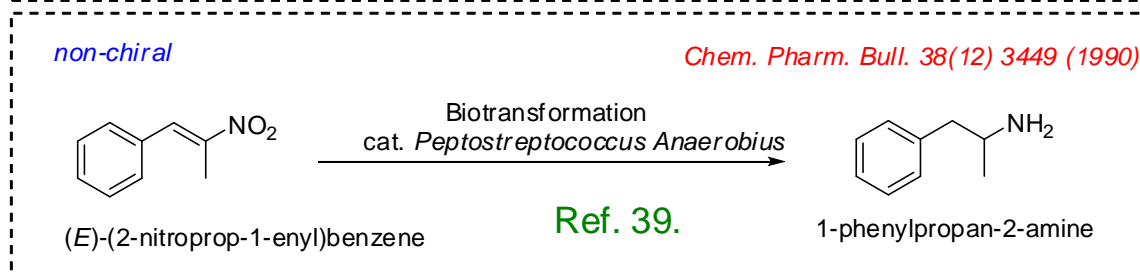
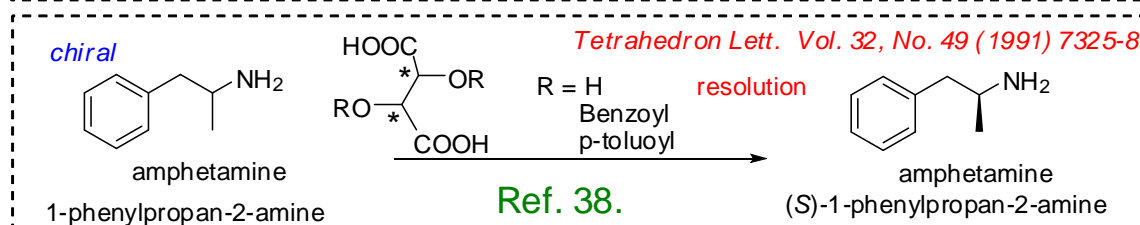
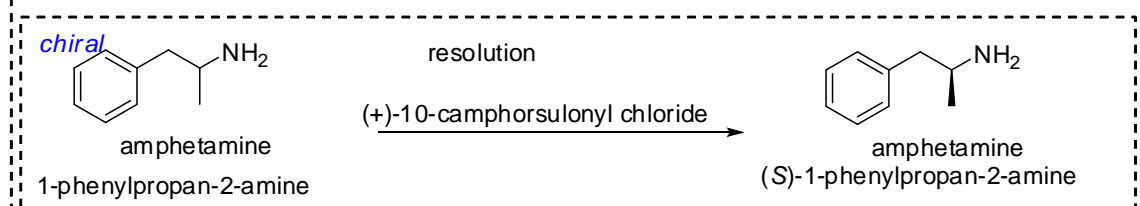
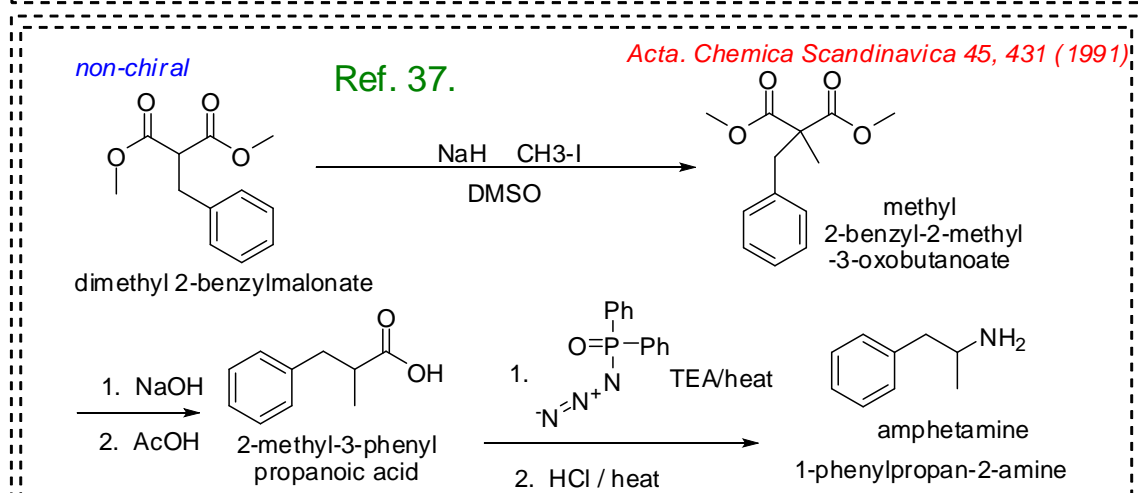
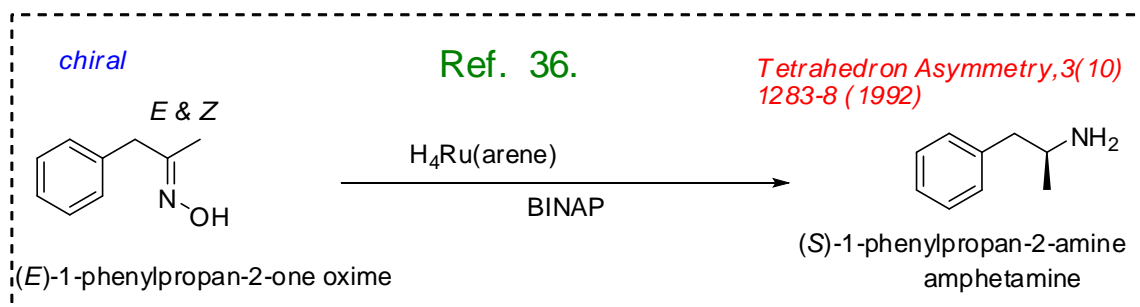


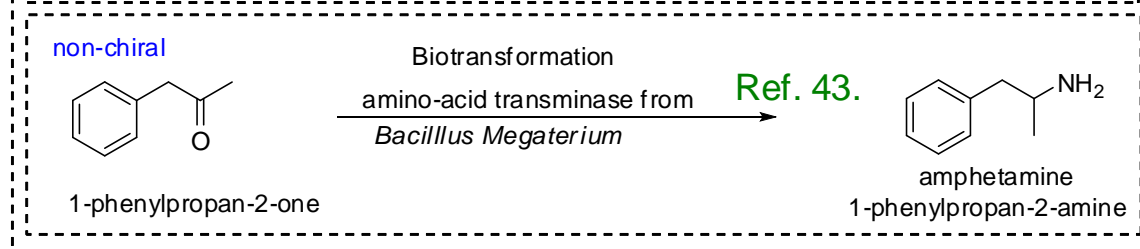
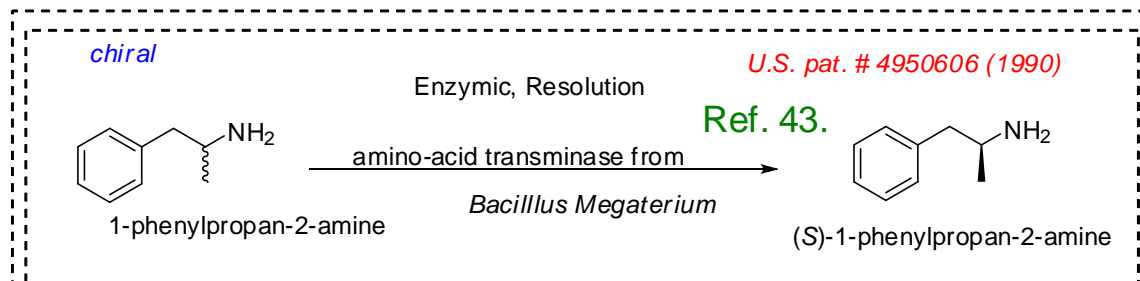
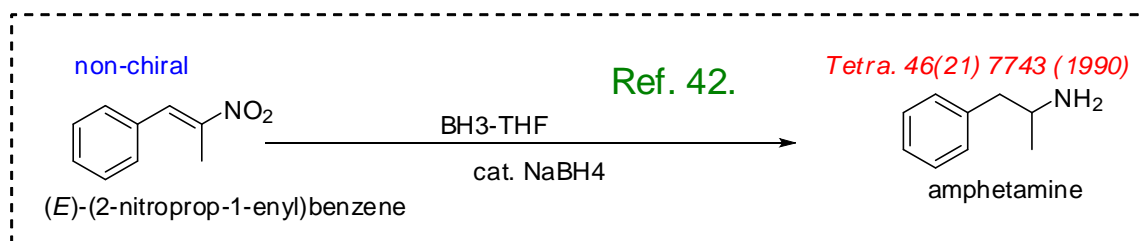
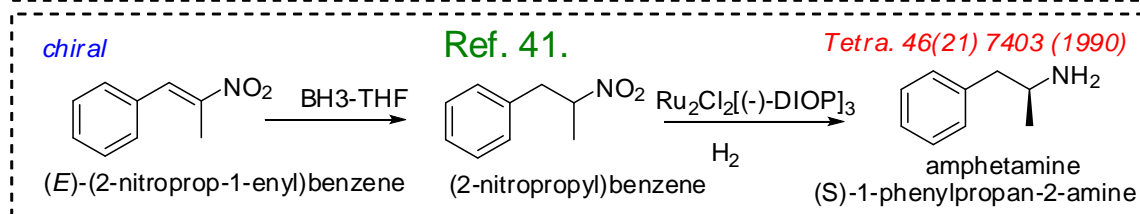
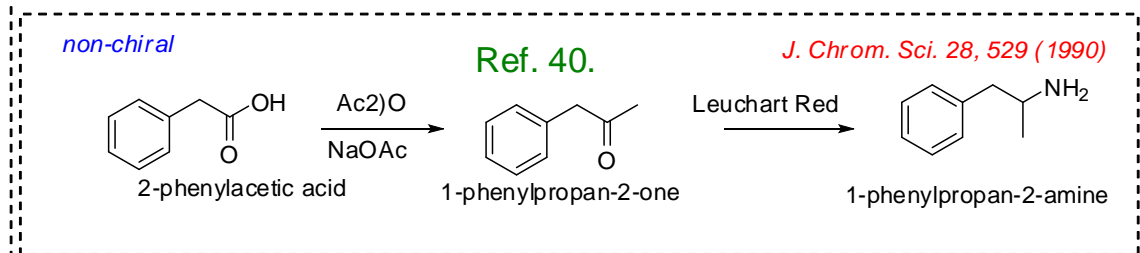
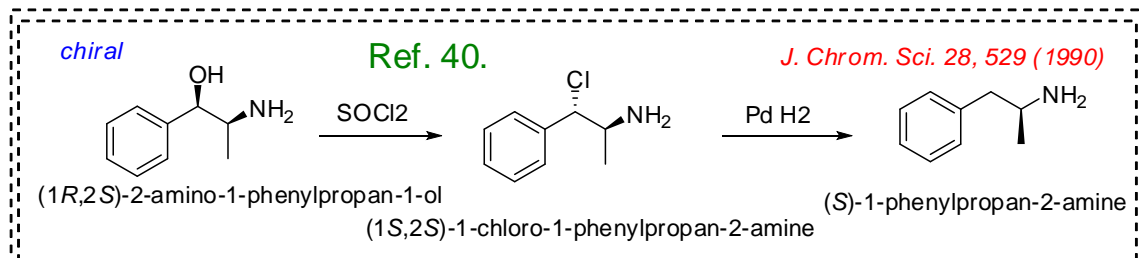


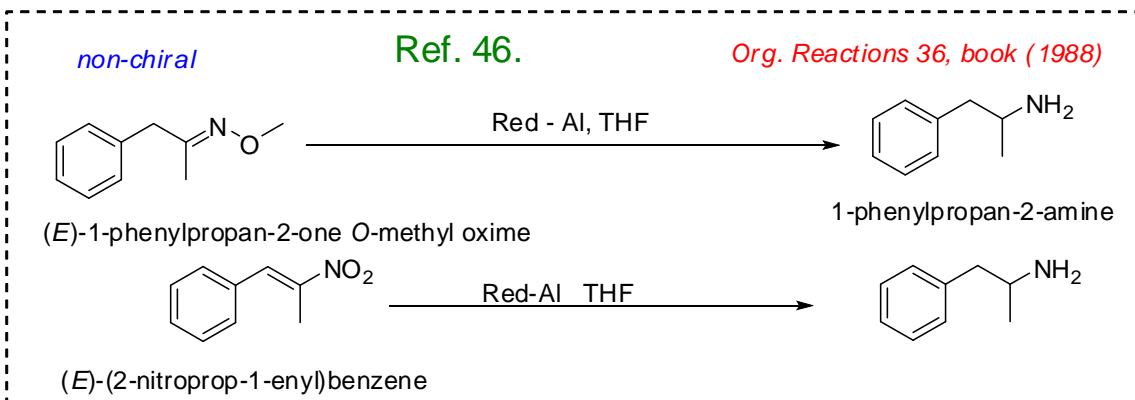
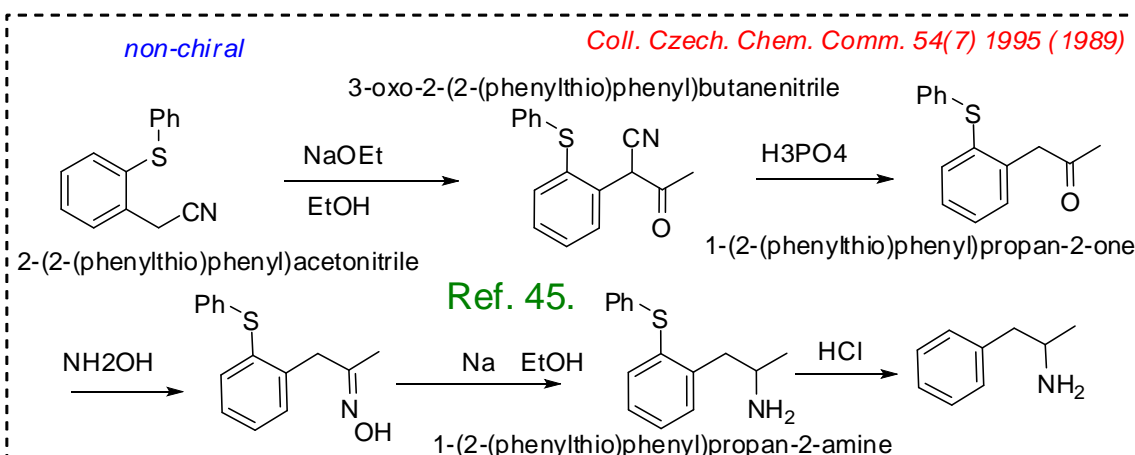
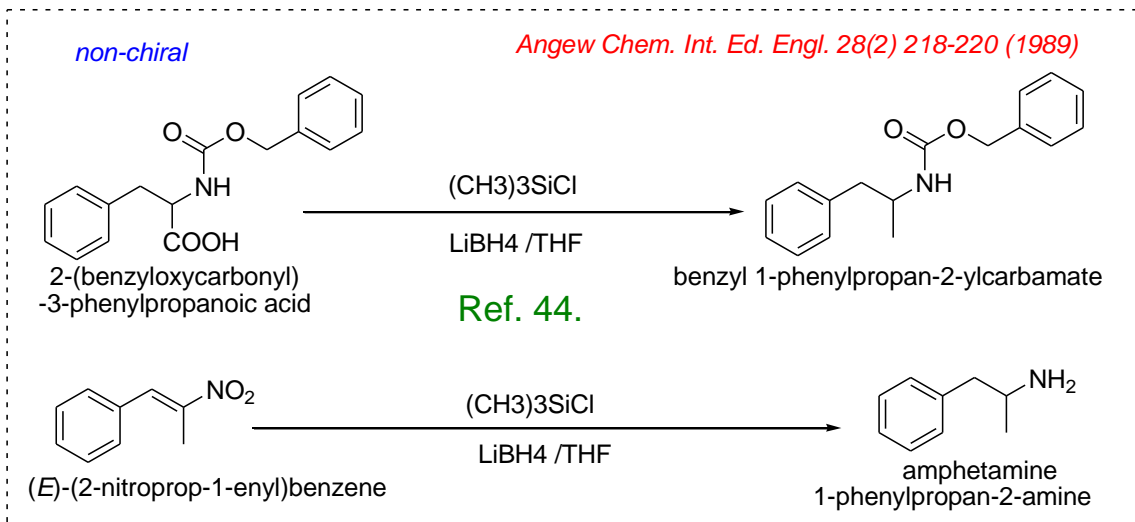


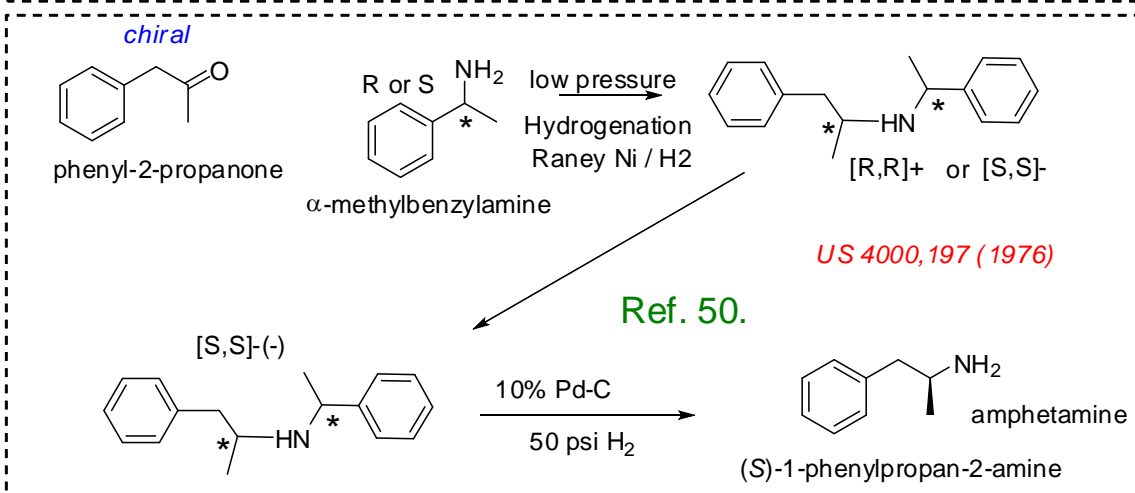
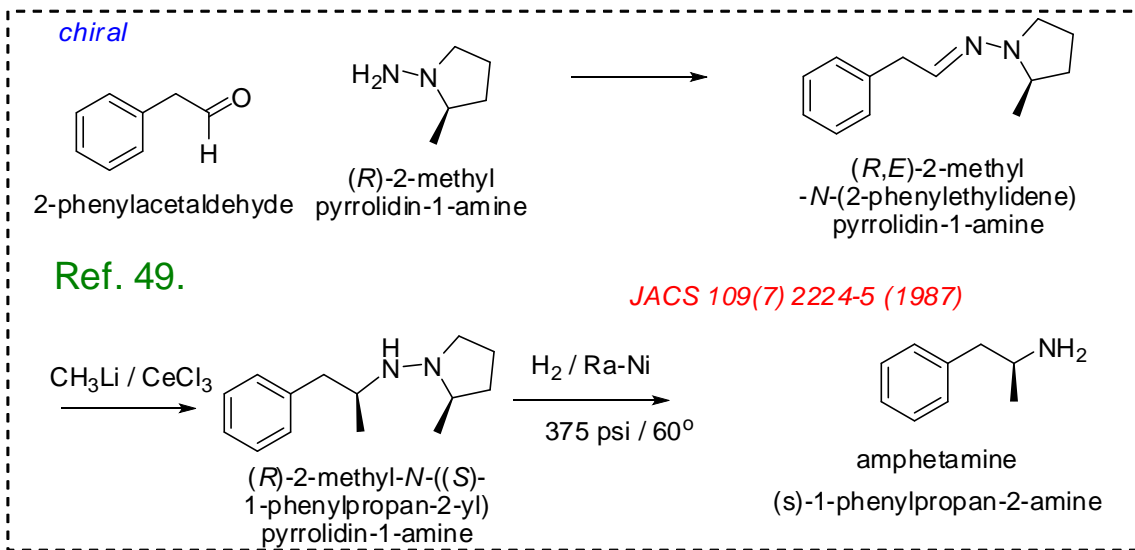
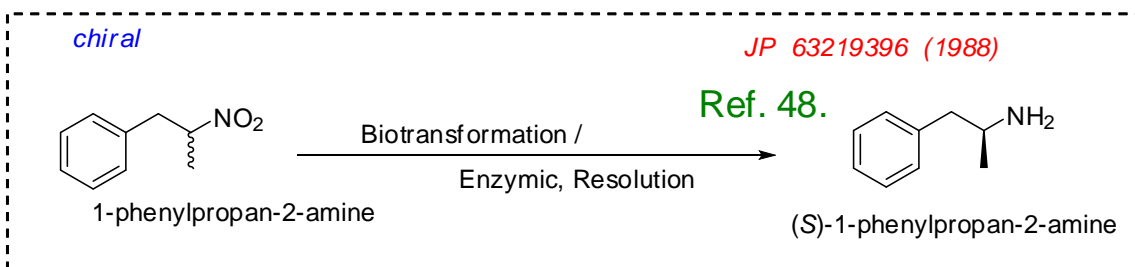
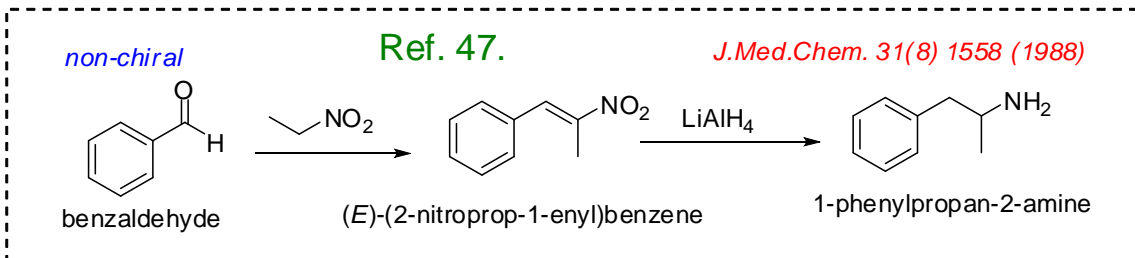


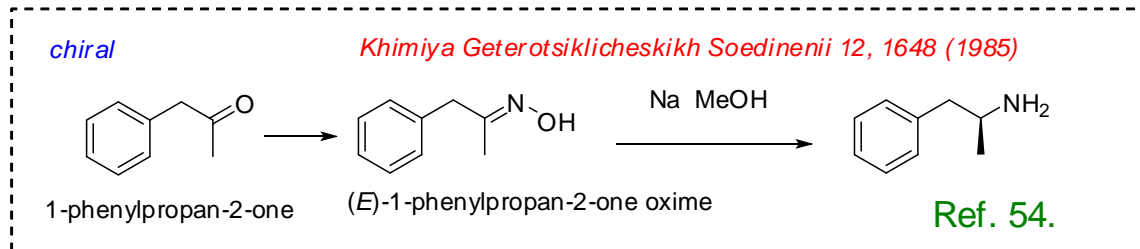
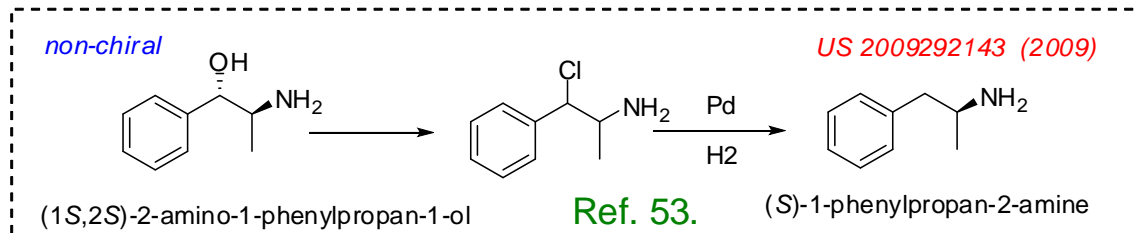
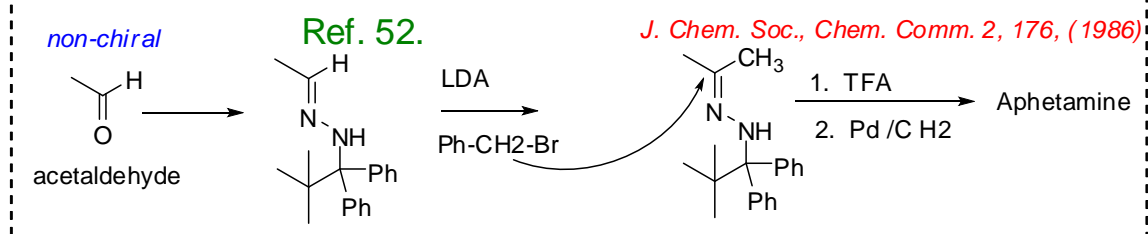
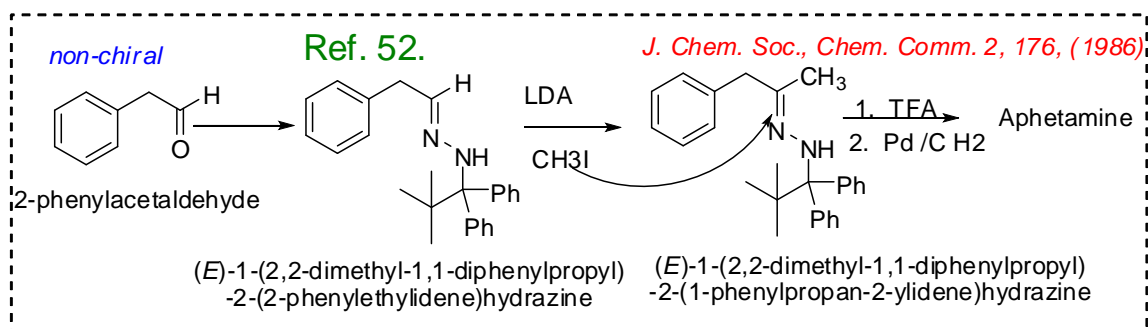
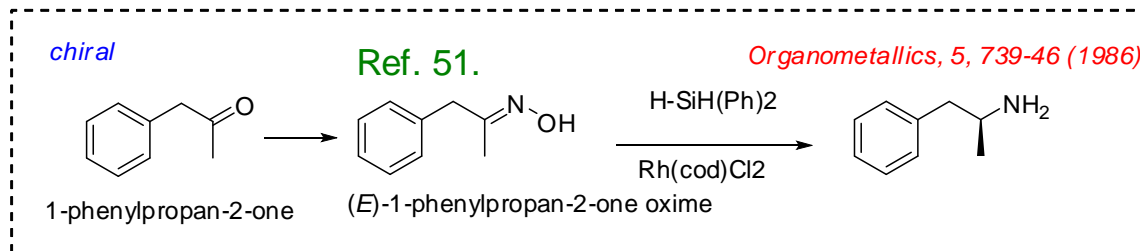


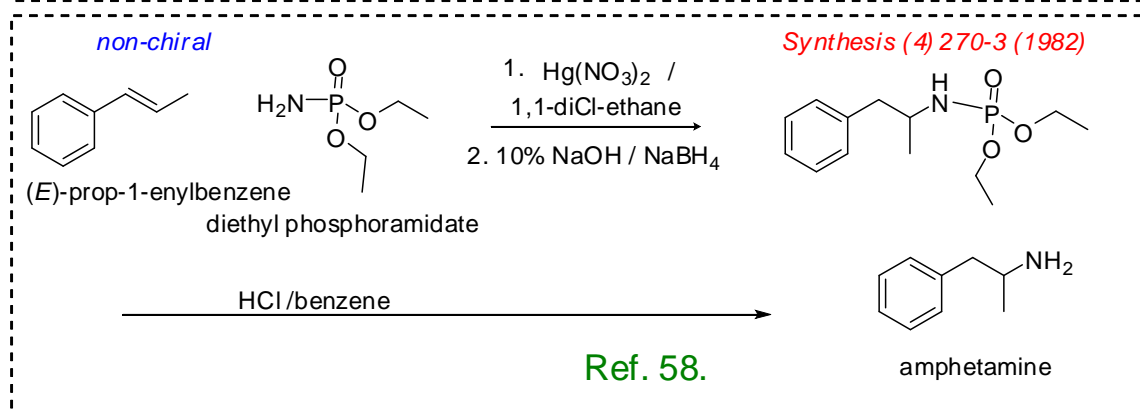
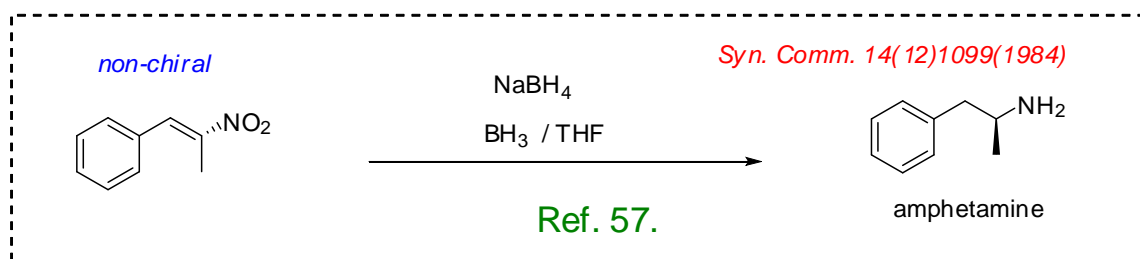
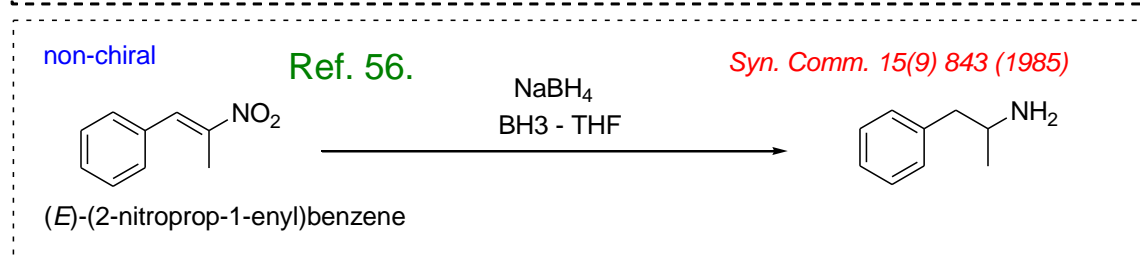
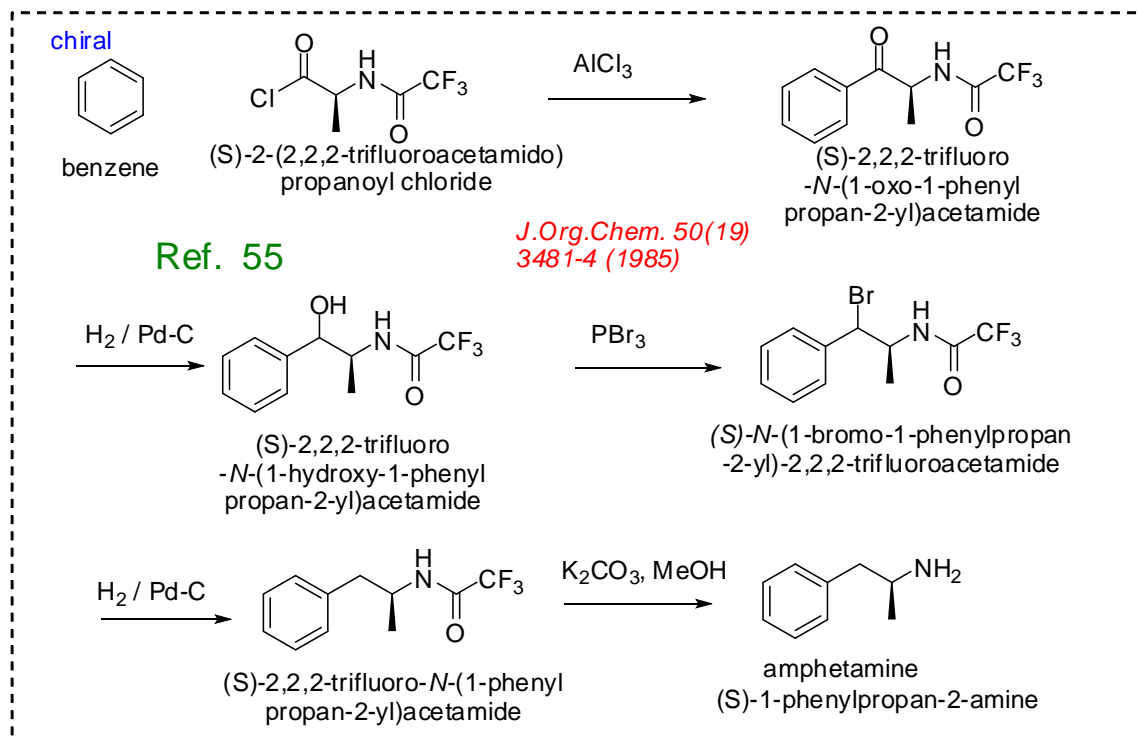


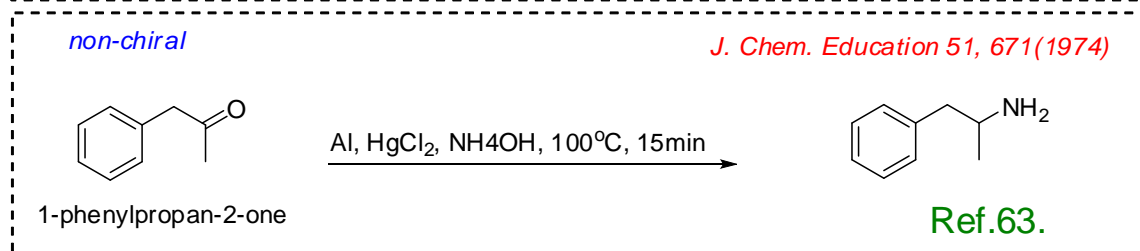
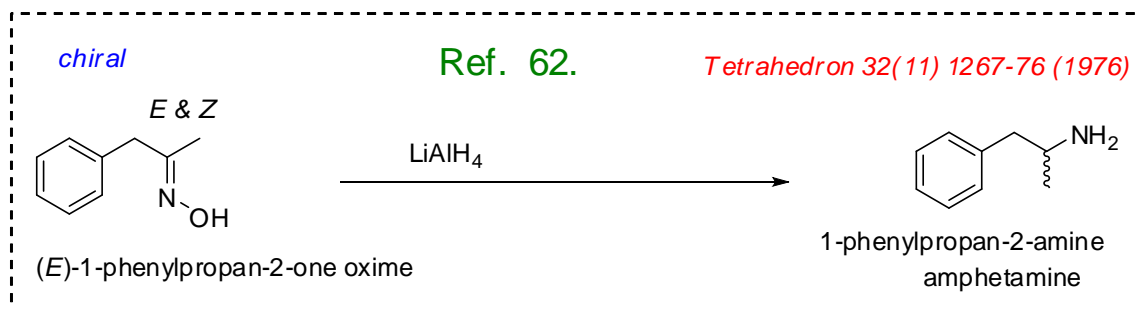
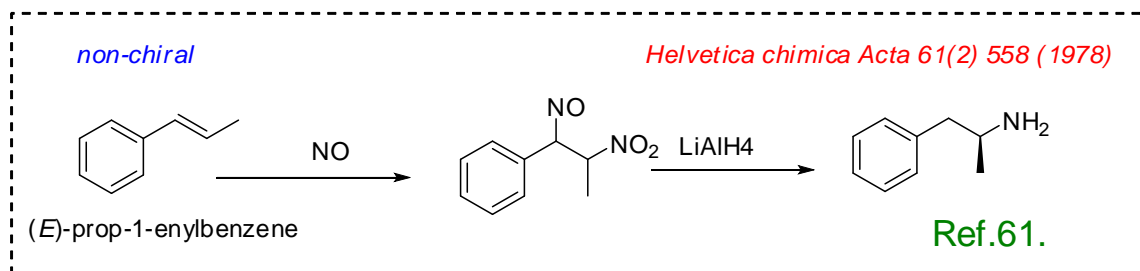
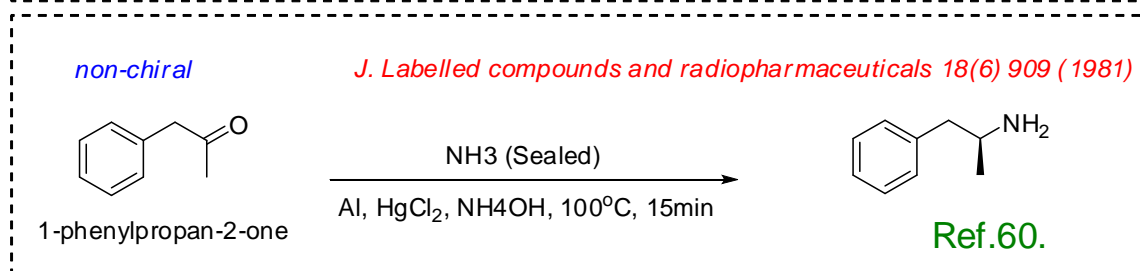
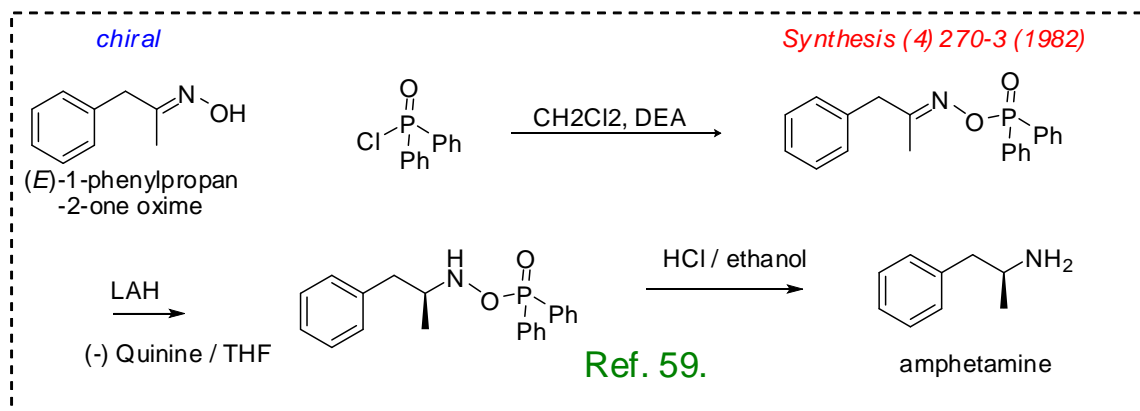


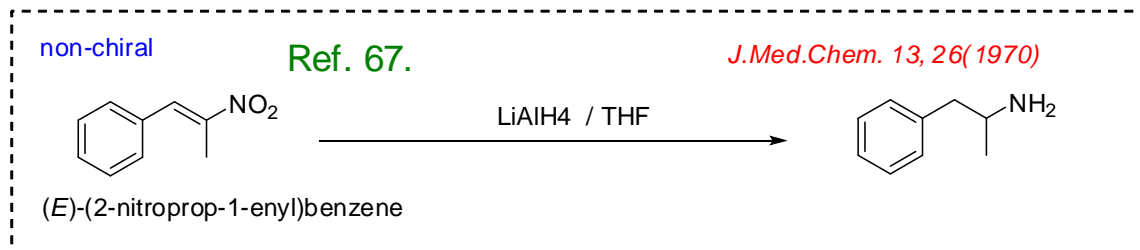
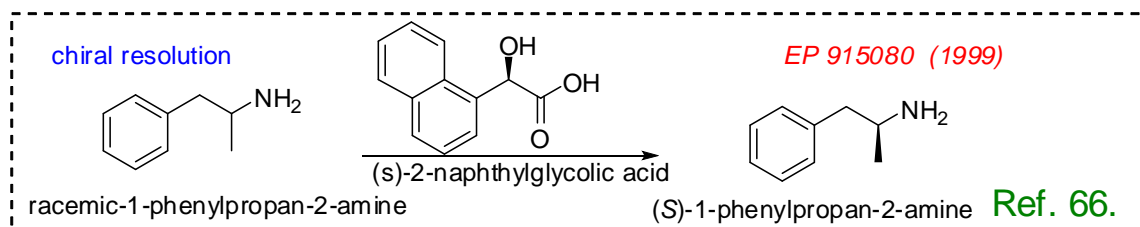
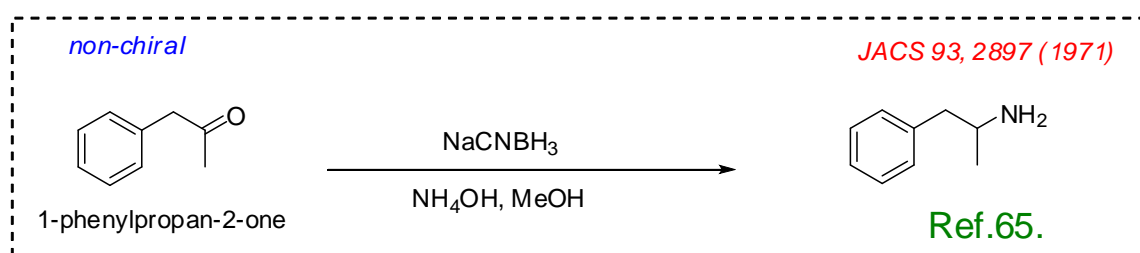
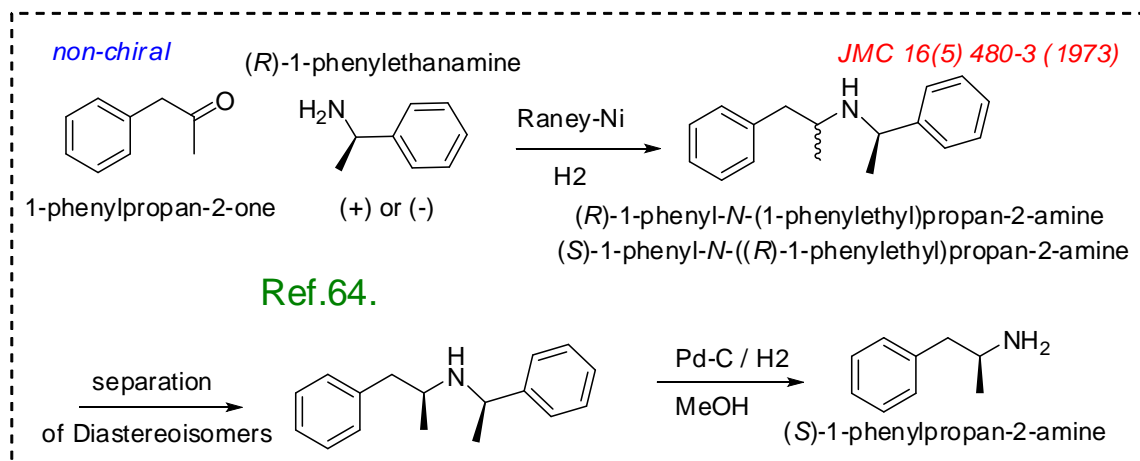


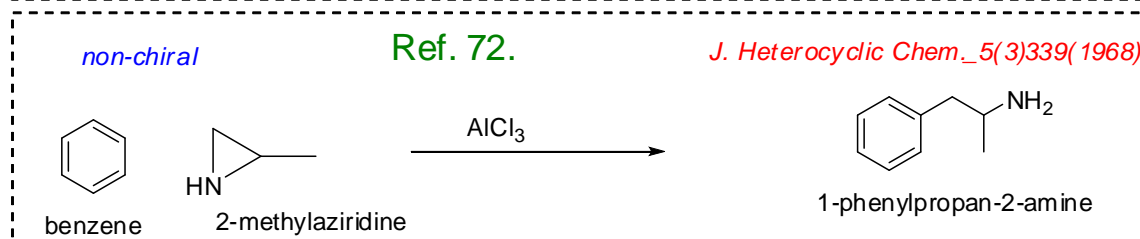
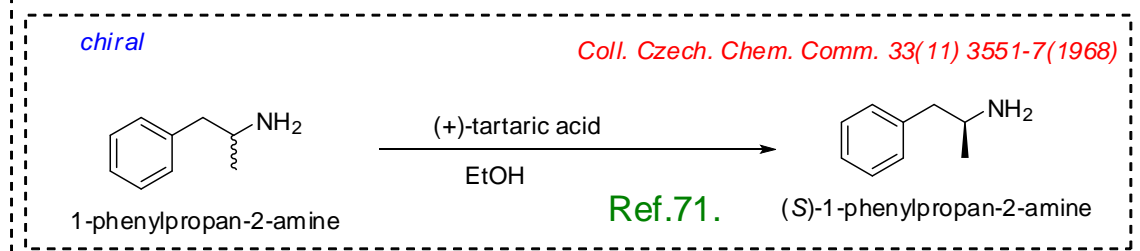
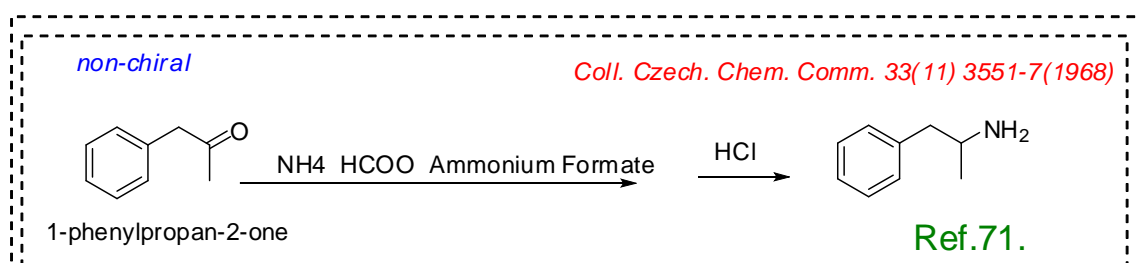
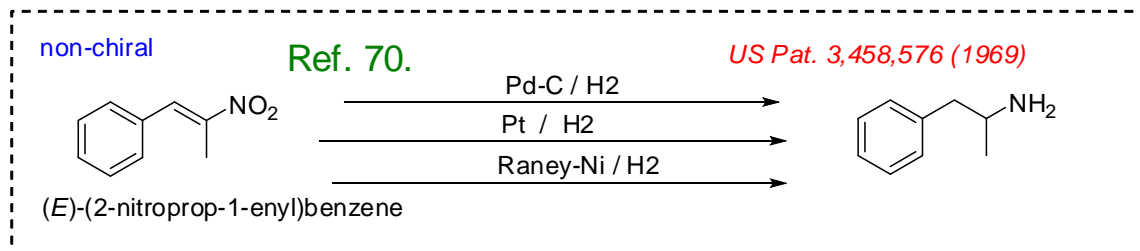
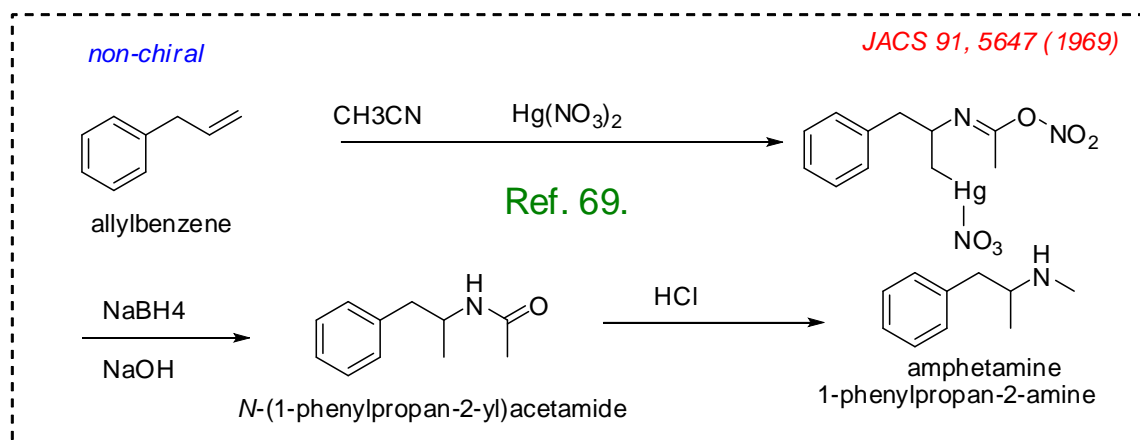


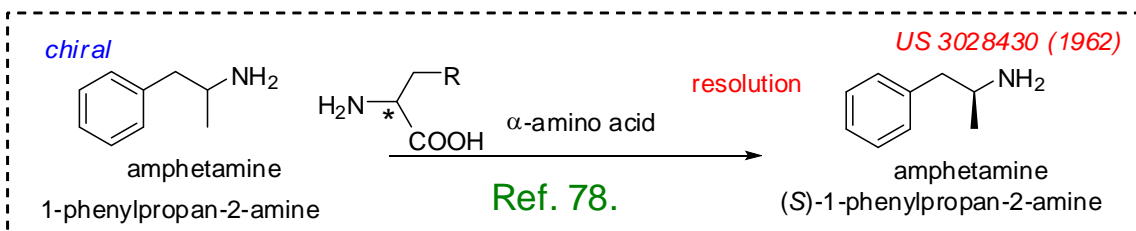
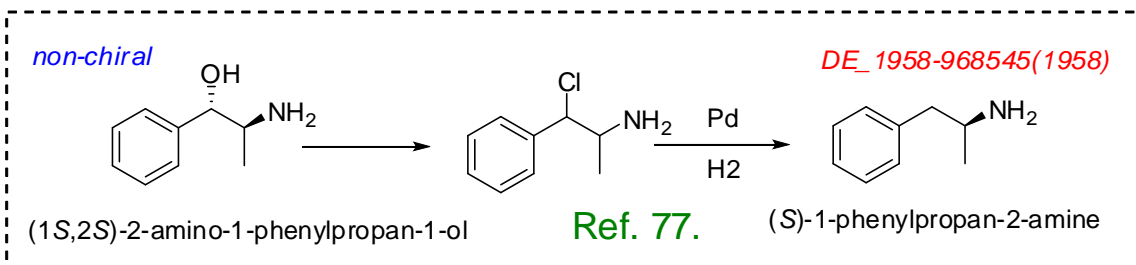
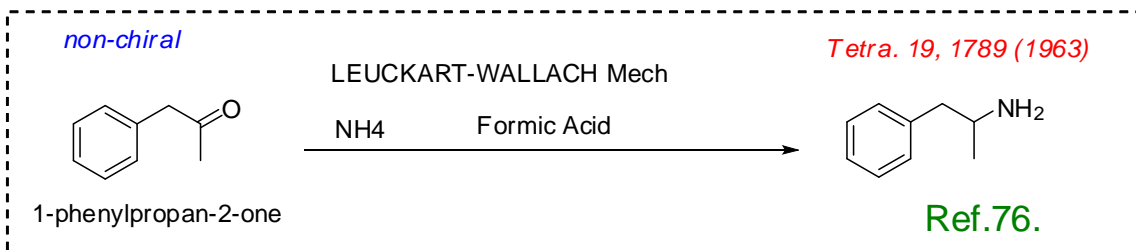
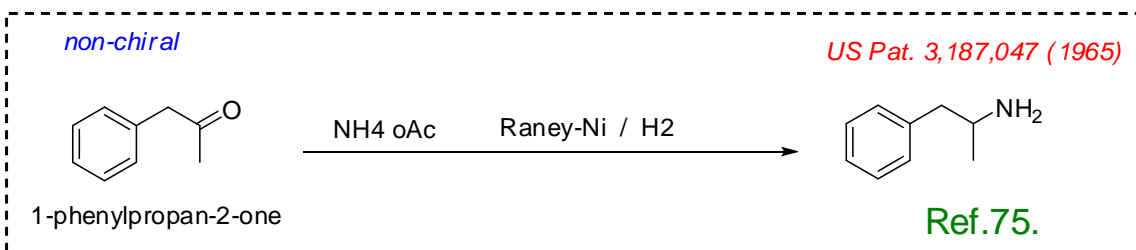
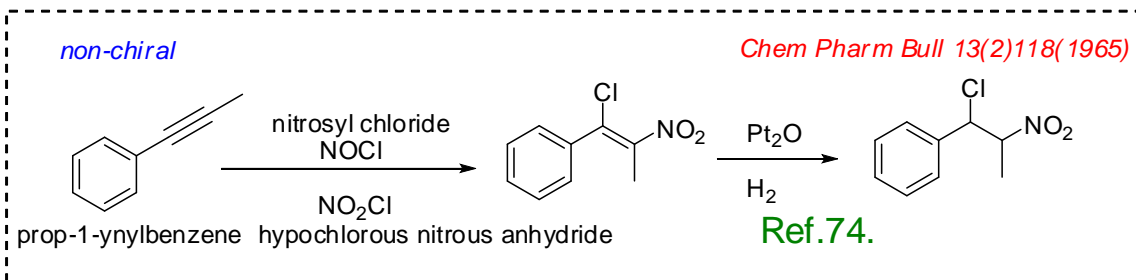
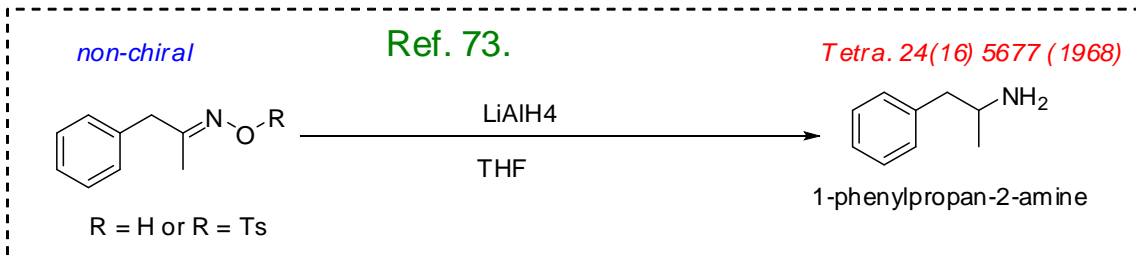


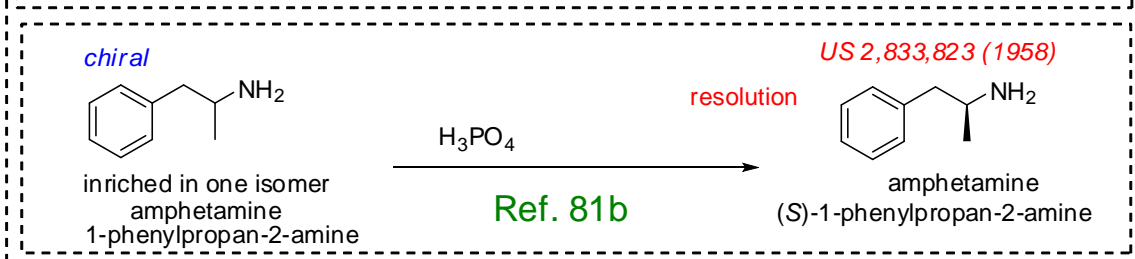
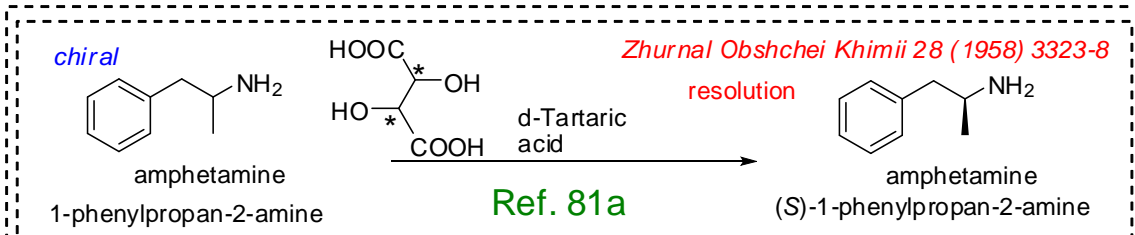
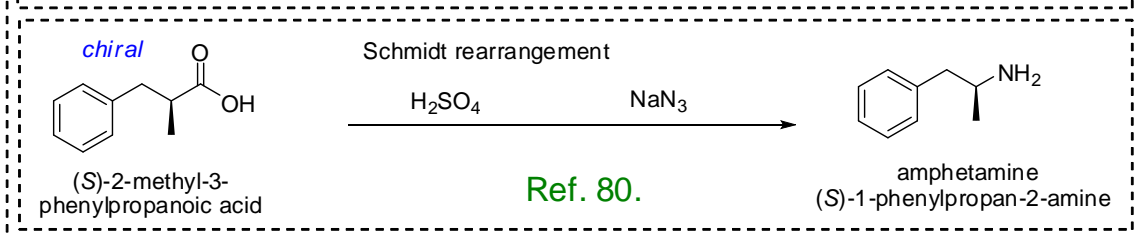
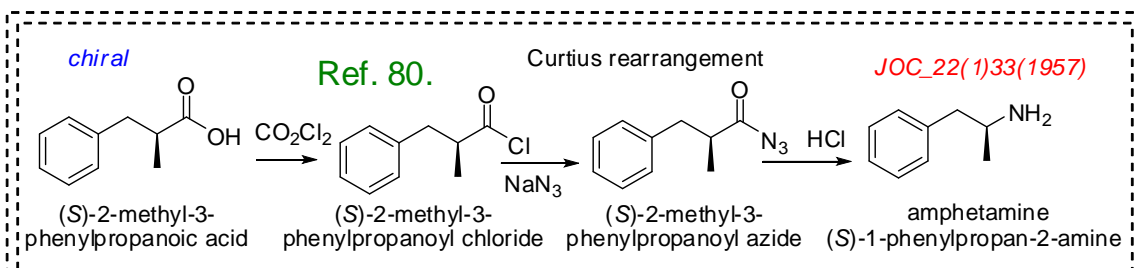
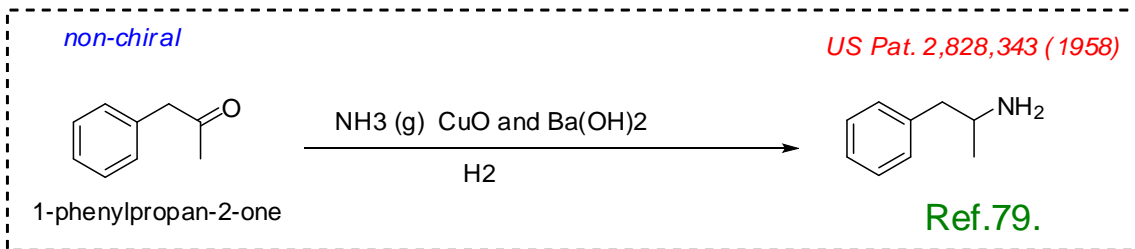


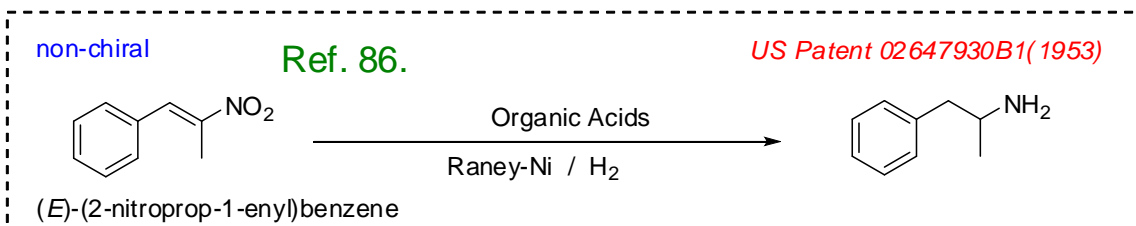
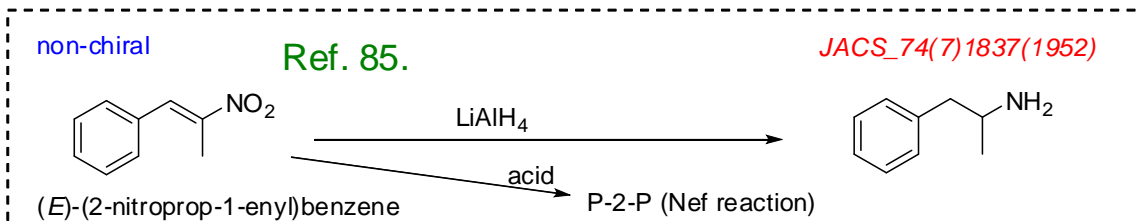
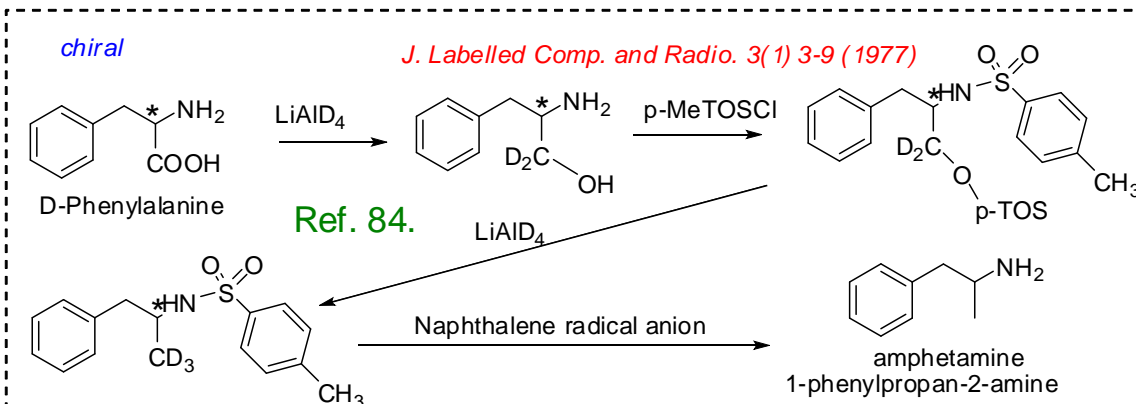
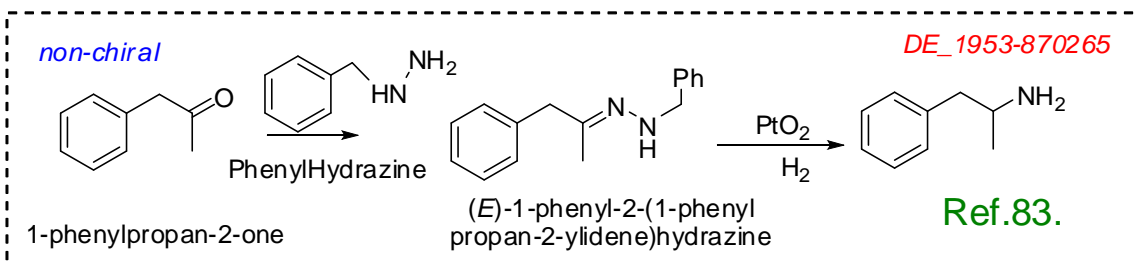
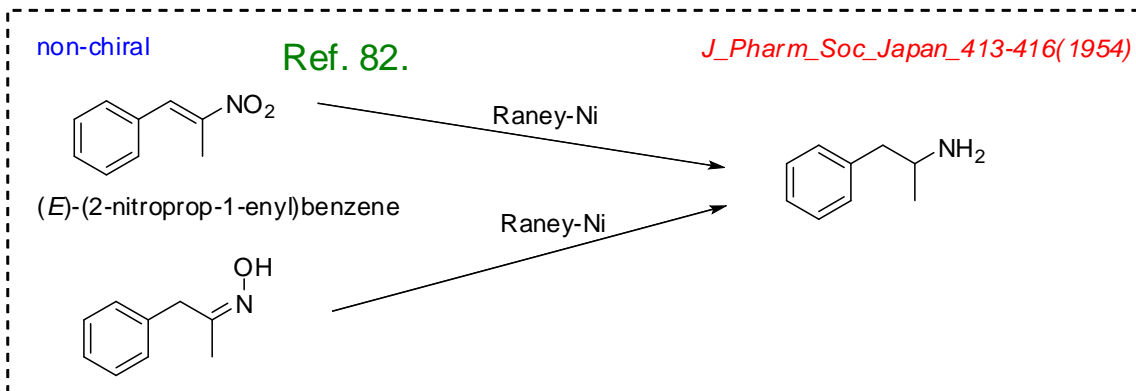


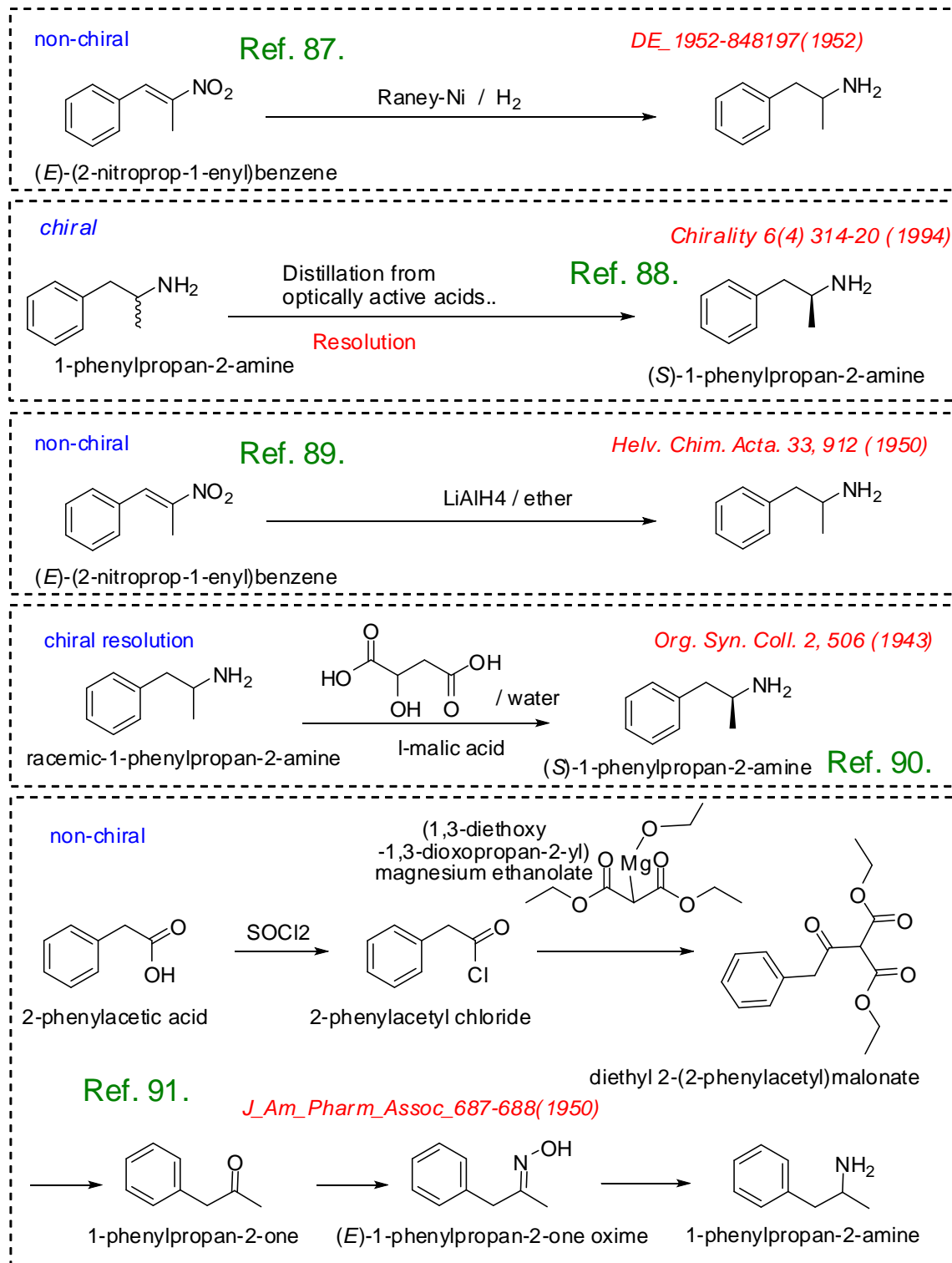


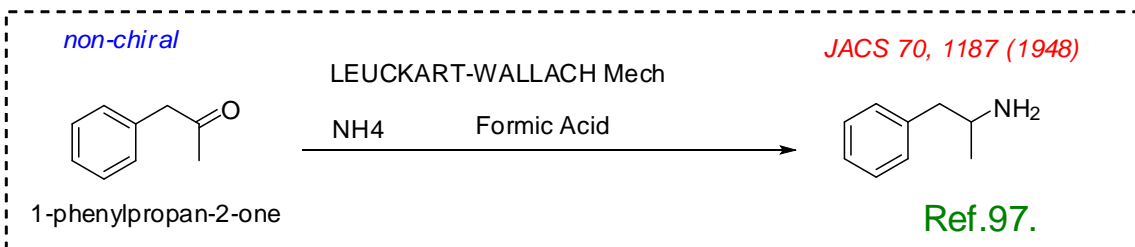
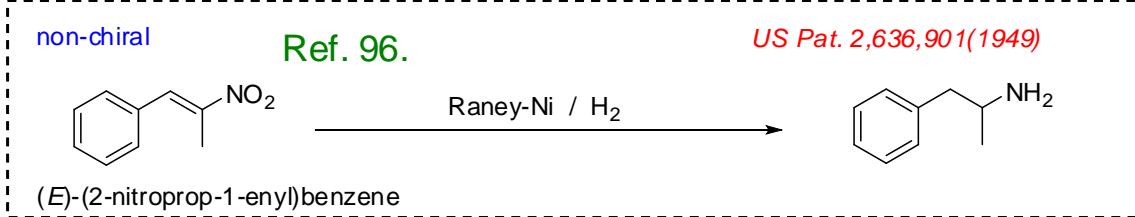
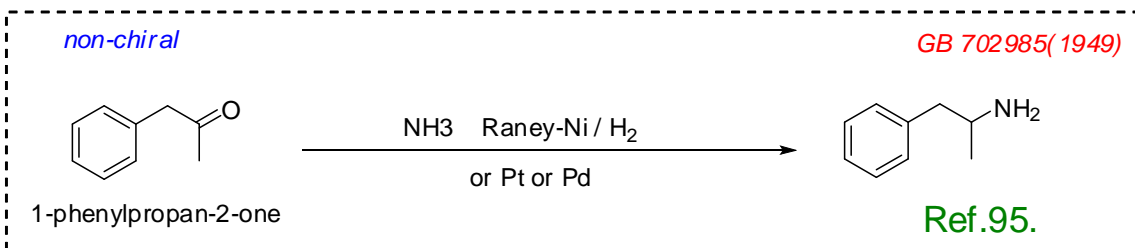
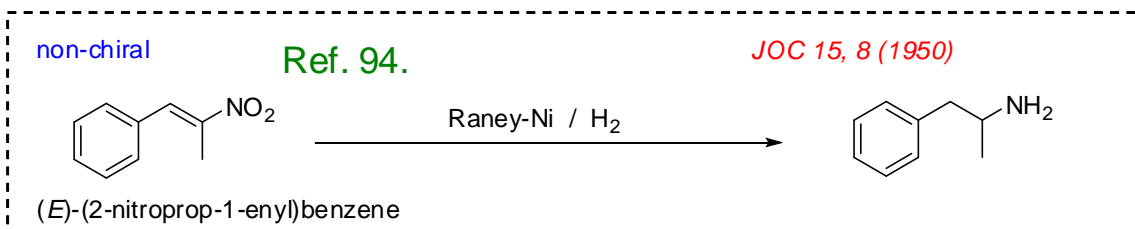
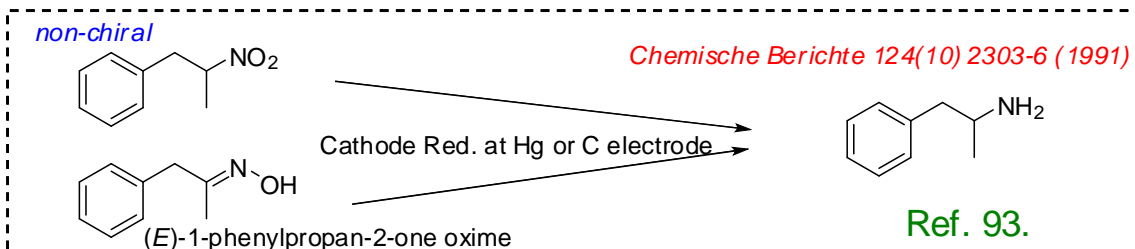
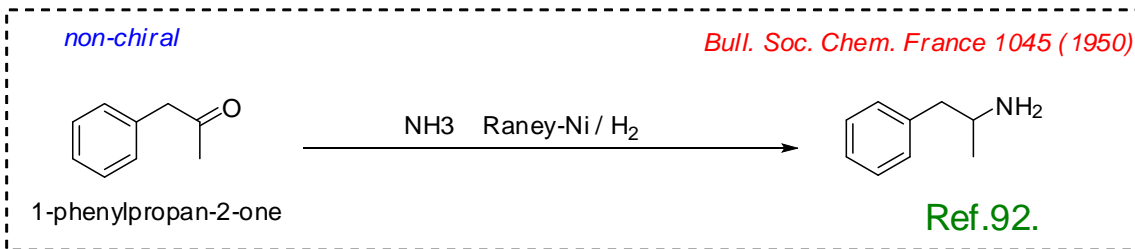


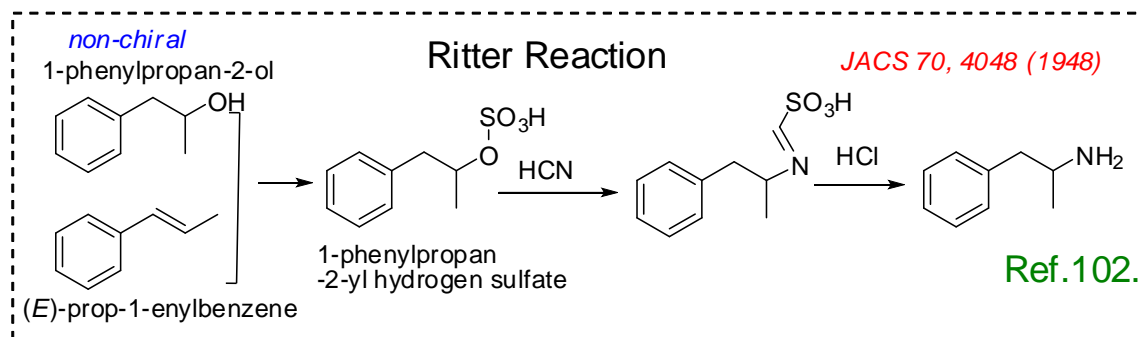
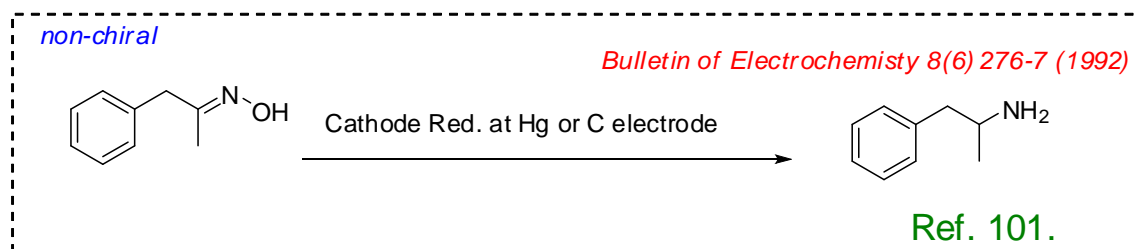
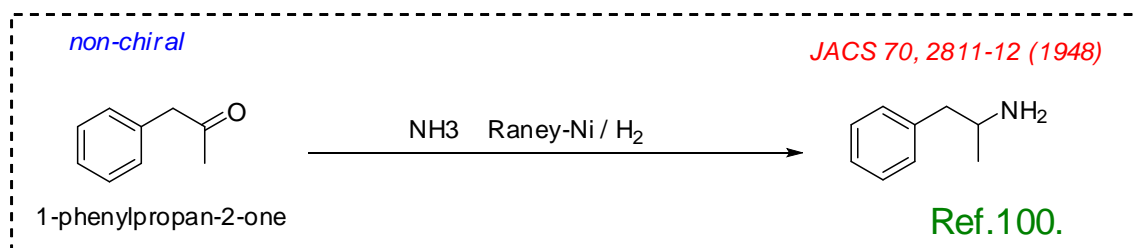
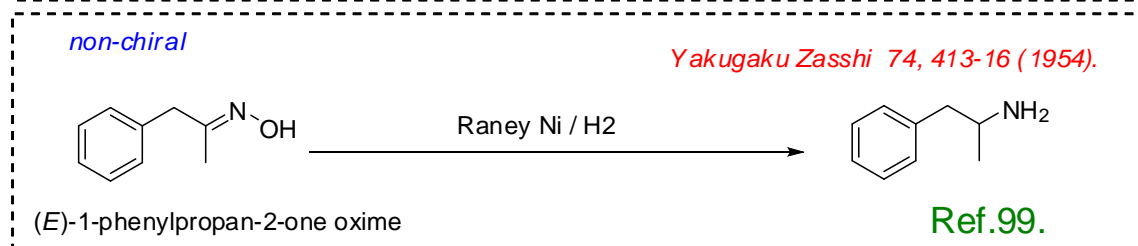
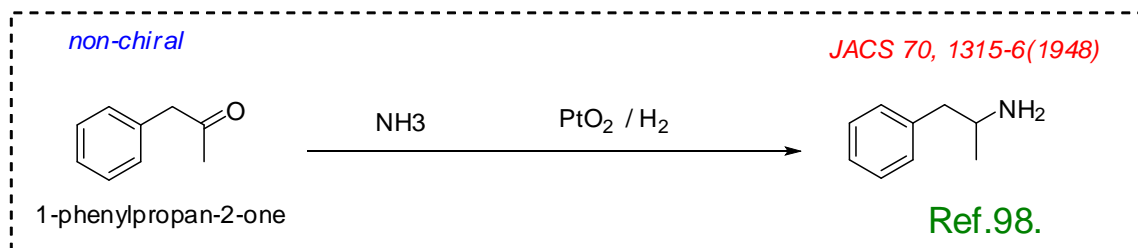


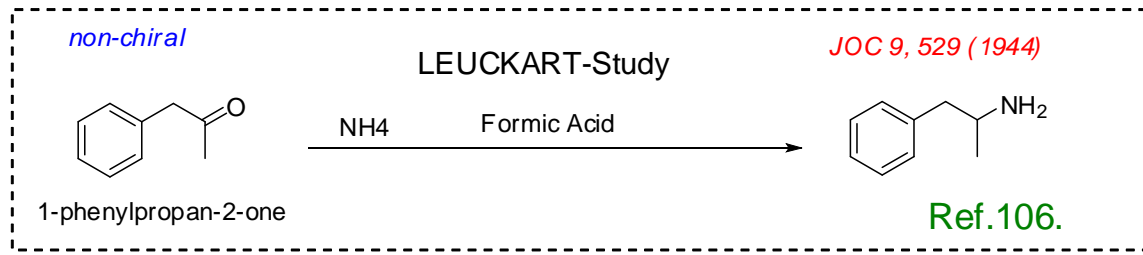
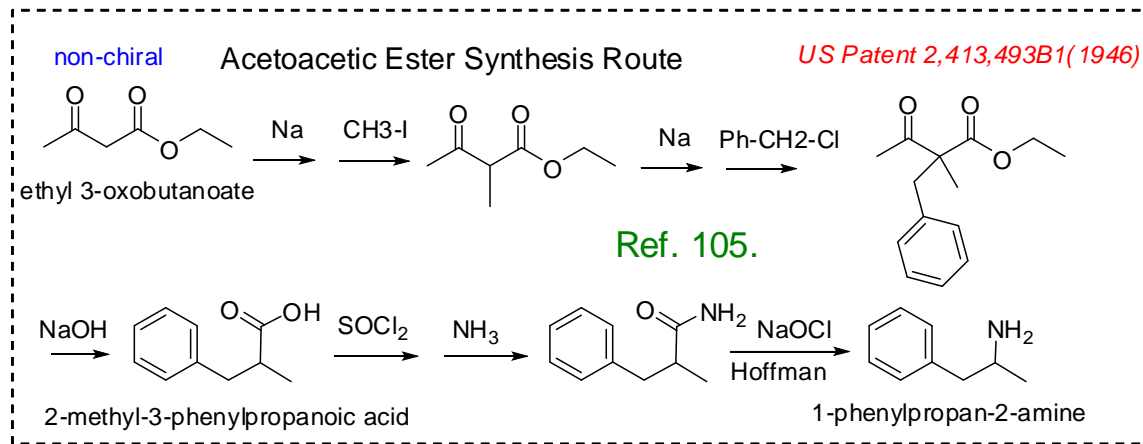
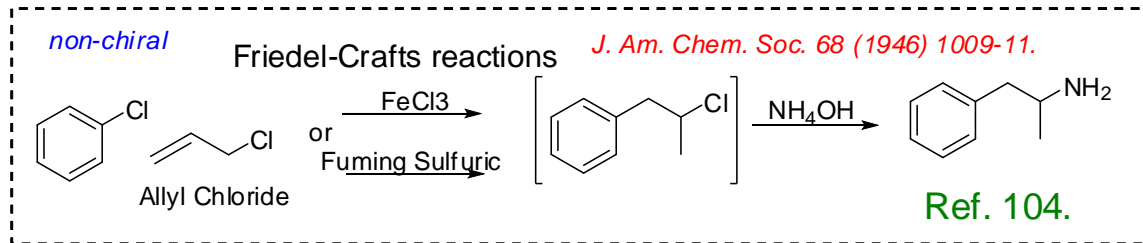
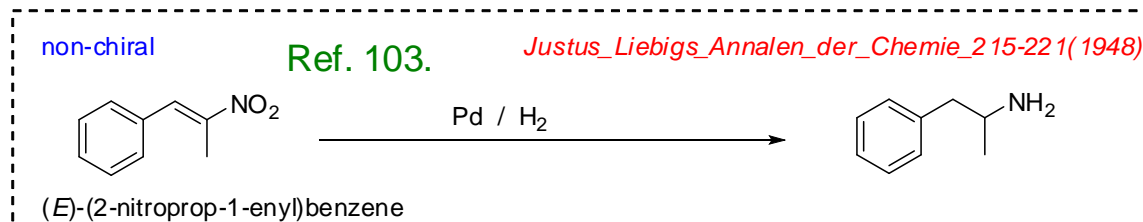








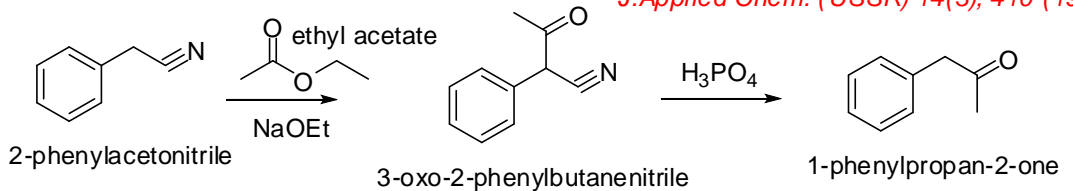




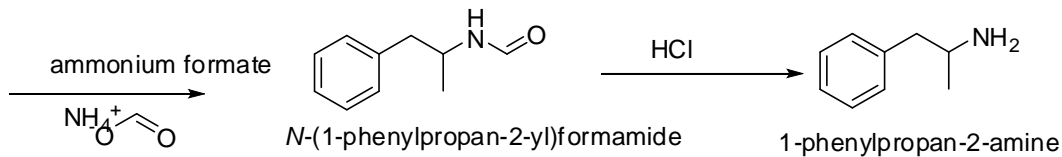
Acetylbenzylcyanide Reaction Route

non-chiral

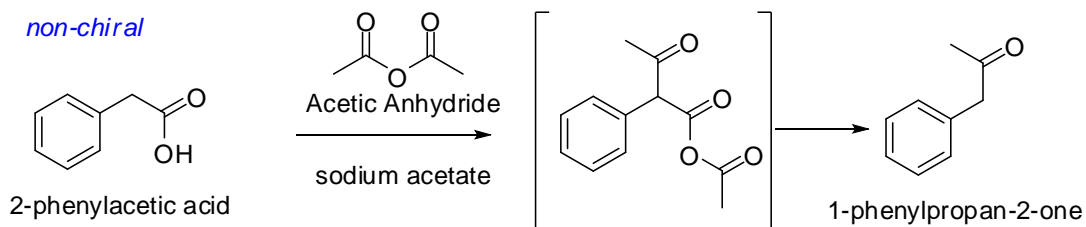
J. Applied Chem. (USSR) 14(3), 410 (1941)



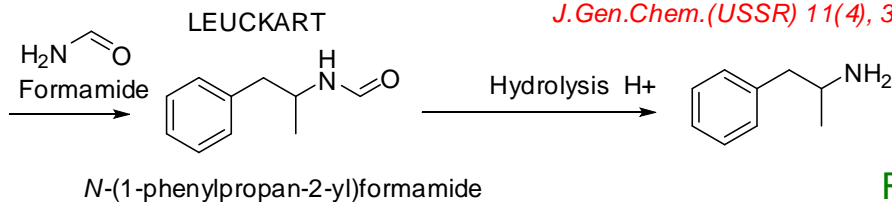
Ref. 107.



non-chiral



J. Gen. Chem. (USSR) 11(4), 339 (1941)

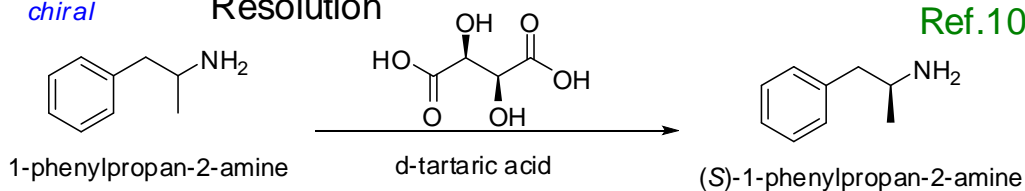


Ref. 108.

chiral

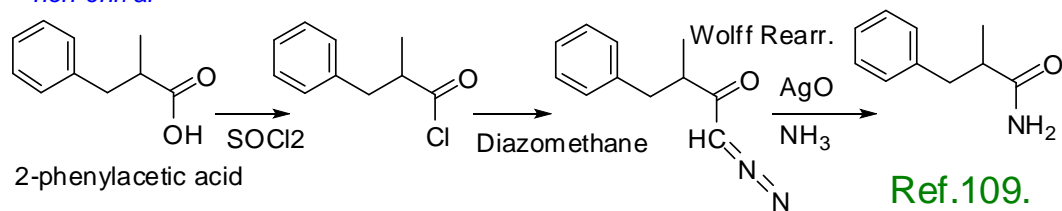
Resolution

Ref. 108.

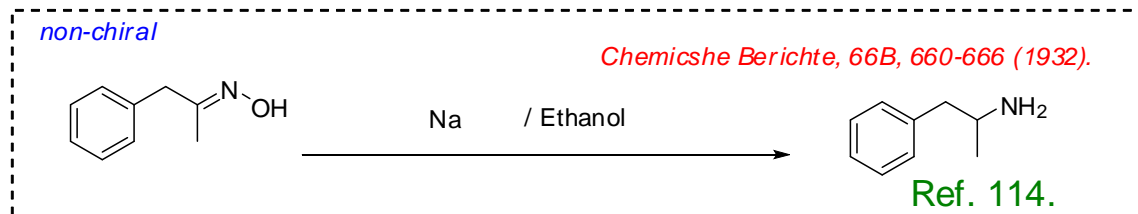
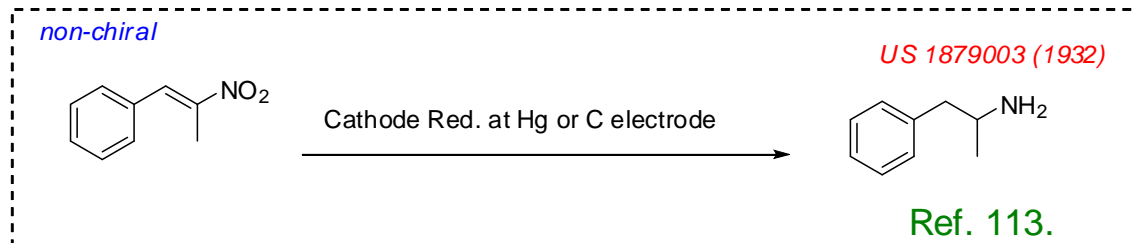
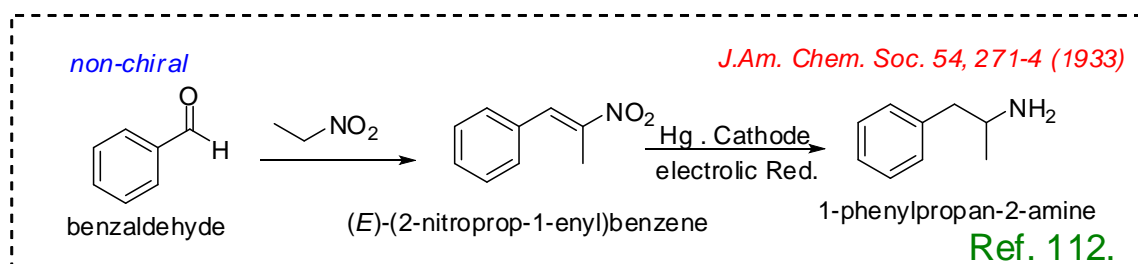
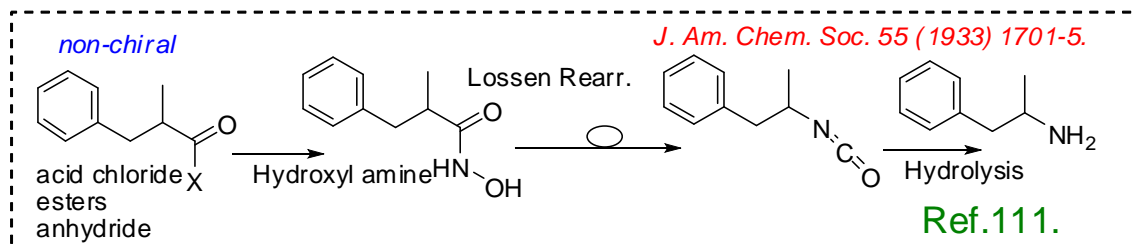
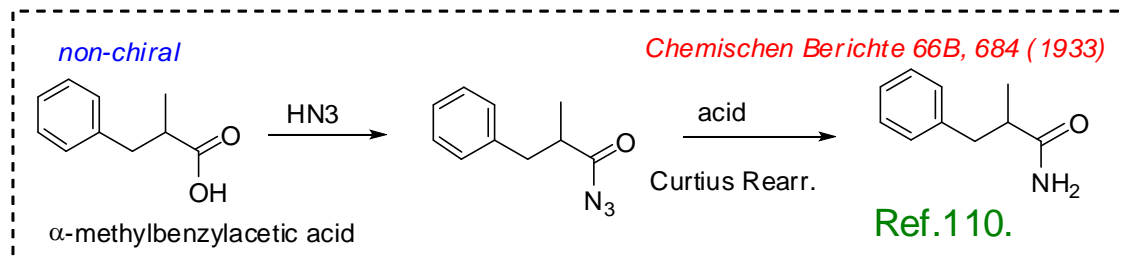


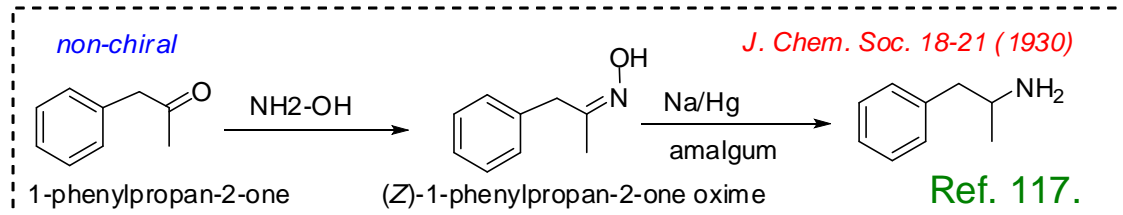
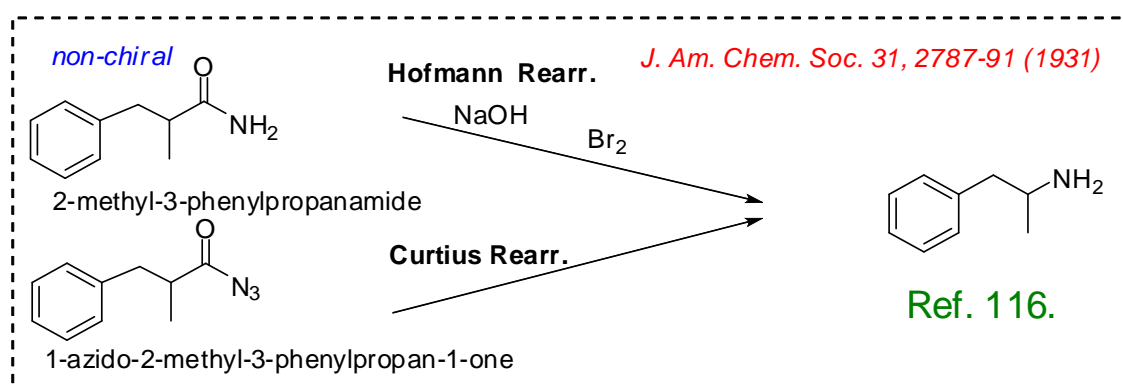
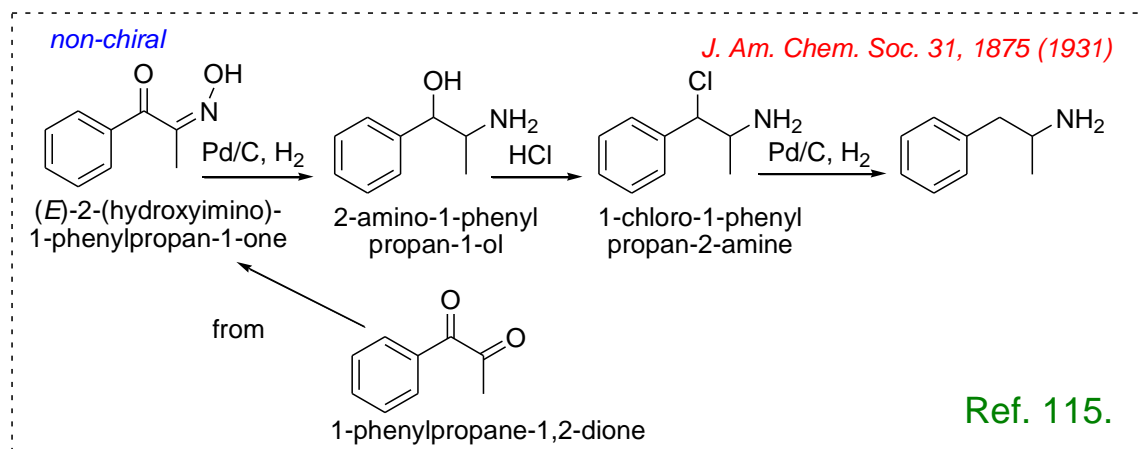
non-chiral

J. Am. Chem. Soc. 5 (1940) 267-85



Ref. 109.





Precursor list to amphetamine 1985 -2009

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