Published in final edited form as:
Tetrahedron. 2011 September 23; 67(38): 7195–7210. doi:10.1016/j.tet.2011.06.040.

Indole synthesis: a review and proposed classification

Douglass F. Taber[a,*] and **Pavan K. Tirunahari**[b]

[a]Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716, USA

[b]Accel Synthesis, Inc., Garnet Valley, PA 19060, USA

1. Introduction

The indole alkaloids, ranging from lysergic acid to vincristine, have long inspired organic synthesis chemists. Interest in developing new methods for indole synthesis has burgeoned over the past few years. These new methods have been fragmented across the literature of organic chemistry. In this review, we present a framework for the classification of all indole syntheses.

As we approach the classification of routes for the preparation of indoles, we are mindful that the subject has occupied the minds of organic chemists for more than a century. There have been many reviews of indole synthesis.[1] We were also aware that much more could be said than we have written. We have only briefly covered the conversion of indolines into indoles, and the reduction of oxindoles to indoles. We have not covered the extensive literature on the modification of existing indoles. Throughout, our interest has been to be illustrative, not exhaustively inclusive. It is apparent, however, that every indole synthesis must fit one or the other of the nine strategic approaches adumbrated here. The web of scientific citations unites and organizes the world-wide research effort. It is our intention that the system put forward here for classifying indole syntheses will be universally understood. As authors conceive of new approaches to the indole nucleus, they will be able to classify their approach, and so readily discover both the history and the current state of the art with that strategy for indole construction. In addition to avoiding duplication, it is also our hope that efforts will then be directed toward the very real challenges that remain to be overcome. It is noteworthy that, in the most recent year we have covered, 2009, significant new contributions were reported for each of these nine strategies. We have highlighted these at the end of each section.

There are four bonds in the five-membered indole ring. In classifying methods for synthesis (Fig. 1), we have focused on the last bond formed. We have also differentiated, in distinguishing Type 1 versus Type 2 and Type 3 versus Type 4, between forming a bond to a functionalized aromatic carbon, and forming a bond to an aromatic carbon occupied only by an H. Type 5 has as the last step C–N bond formation, while with Type 6 the last step is C–C bond formation. In Type 7, the benzene ring has been derived from an existing

*Corresponding author. taberdf@udel.edu (D.F. Taber).

cyclohexane, and in Type 8, the benzene ring has been built onto an existing pyrrole. Finally, in Type 9, both rings have been constructed.

There are several name reactions associated with indole synthesis. We have tried to note these in context, and to group examples of a particular name reaction together. For convenience, the 'name reaction' indole syntheses mentioned in this review are:

Bartoli indole synthesis—Type 1

Bischler indole synthesis—Type 5

Fischer indole synthesis—Type 1

Hemetsberger indole synthesis—Type 3

Julia indole synthesis—Type 5

Larock indole synthesis—Type 5

Leimgruber–Batcho indole synthesis—Type 5

Madelung indole synthesis—Type 6

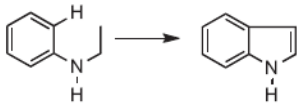
Nenitzescu indole synthesis—Type 7

Reissert indole synthesis—Type 5

Sundberg indole synthesis—Type 5

While it might be sufficient to merely label the nine strategies 1–9, for ease of recollection we have also associated each strategy with the name of an early or well-known practitioner. The division of strategies is strictly operational. Thus, the Fischer indole synthesis is classified as Type 1, Ar–H to C2, since that is the way it is carried out, even though the last bond formed, as the reaction proceeds, is in fact N to C1.

2. Type 1



Fischer strategy

Type 1 synthesis (Scheme 1-17) involves aromatic C–H functionalization. Although C–H activation is thought of as a modern topic, the venerable Fischer indole synthesis (still under active development, Schemes 1-3) falls under this heading. Paul R. Brodfuehrer and Shaopeng Wang of Bristol-Myers Squibb described[2] the convenient (Scheme 1) reaction of an aryl hydrazine **1** with dihydropyran **2** to give the 3-hydroxypropylindole **3**. Stephen L. Buchwald of MIT developed[3] an elegant (Scheme 2) amination of aryl iodides to give Boc-protected aryl hydrazines, such as **4**. Acid-mediated condensation of **4** with the ketone **5** delivered the indole **6**. The condensation of **4** and **5** proceeded with high regioselectivity. Norio Takamura of Musashino University, Tokyo presented[4] a complementary approach (Scheme 3), the addition of an aryllithium **8** to an α-diazo ester **7**, followed by acid-

mediated cyclization. The ester of **9** is easily manipulated, and can also be removed altogether. Several other useful variations on the Fischer indole synthesis have been reported.[5-7]

Indoles can also be formed by acid-mediated cyclization of aldehydes. Richard J. Sundberg of the University of Virginia described[8] the preparation from **10** (Scheme 4) and cyclization of acetals, such as **11** to give the indole **12**. The Bischler indole synthesis[9a,b] is a variation on this approach. Chan Sik Cho and Sang Chul Shim of Kyungpook National University, Taegu devised[9c] a route to indoles (Scheme 5) based on Ru-mediated addition of an aniline **13** to an epoxide **14**. An interesting oxidatione–reduction cascade led to the 2-alkyl indole **15**, probably via a Bischler-like tautomerization.

Other transition-metal-mediated protocols for indole synthesis have been developed. In a variant on the Bartoli indole synthesis, Kenneth M. Nicholas of the University of Oklahoma reported[10] the Ru-catalyzed reductive coupling of a nitrosoaromatic, such as **16** (Scheme 6) with an alkyne **17** to give the indole **18**. Akio Saito and Yuji Hanzawa of Showa Pharmaceutical University described[11] the Rh-catalyzed cyclization of **19** (Scheme 7) to **20**. The reaction was thought to proceed via the allene **21**.

Several other Type 1 indole syntheses have been described. In the examples cited so far, only one regioisomeric aryl H could be substituted. In an *ortho*-metalation approach, Francis Johnson of SUNY Stony Brook showed[12] that (Scheme 8) the anion from cyclization of **22** could be alkyated with an electrophile, such as **23** to give the indole **24**. Darrell Watson and D.R. Dillin at the University of Mary Hardin-Baylor reported[13] a photochemical route (Scheme 9) to indoles. Irradiation of **25** in an oxygen atmosphere led to **26**. When the photolysis was carried out under nitrogen, the product was **27**. Frank Glorius of the Universität Münster devised[14] a related catalytic oxidation of enamines, such as **28** (Scheme 10) to the indole **29**. Just recently, Yan-Guang Wang of Zhejian University, Hangzhou described[15] the coupling (Scheme 11) of a wide range of anilides, such as **30** with ethyl diazoacetate **31** to give the indole **32**.

Indoles, such as **35** (Scheme 12) can also be prepared from oxindoles, such as **34**, prepared from **33**. Wendell Wierenga, then at Upjohn, optimized[16] both the Gassman synthesis of oxindoles from anilines, and the subsequent reduction. This is a net Type 1 synthesis.

Samir Z. Zard of Ecole Polytechnique described[17] the cyclization (Scheme 13) of allyl anilines, such as **36** to the indoline **38** using **37**. As indolines can be converted into indoles by oxidation[18] or by base-mediated elimination of an *N*-sulfonyl group[19] this is also a net Type 1 indole synthesis.

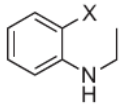
In 2009, four interesting new examples of Type 1 indole synthesis were described. It had been thought that the cyclization of an acetal (Scheme 4) to the indole would only work with electron-rich aromatic rings. Dali Yin of the Institute of Materia Medica, Beijing[20] observed that **39** (Scheme 14), readily prepared by sequential displacement on the corresponding difluorodintrobenzene, smoothly cyclized to **40**.

Following up on the work of Glorius (Scheme 10), Ning Jiao of Peking University found[21] that, under oxidizing conditions, an aniline derivative, such as **41** (Scheme 15) could be condensed with the diester **42** to give the indole **43**. Note that the cyclization proceeded with high regioselectivity. The product was easily hydrolyzed and decarboxylated to give the 2,3-unsubstituted indole.

Akio Saito and Yuji Hanazawa of Showa Pharmaceutical University published[22] a full account of the Rh-mediated cyclization of propargylaniline derivatives, such as **44** (Scheme 16) that they developed. This reaction is apparently proceeding via rearrangement to an intermediate *o*-allenylaniline, that then cyclizes to the product, **45**.

Erik J. Sorensen of Princeton University uncovered[23] a route to indoles (Scheme 17) based on an interrupted Ugi reaction, the combination of **46** and *tert*-butyl isocyanide to give the aminoindole **48**. The acid **47** was particularly effective at mediating this reaction.

3. Type 2



Mori strategy

In a landmark paper in 1977, Miwako Mori, working with Yoshio Ban at Hokkaido University, reported[24] the first intramolecular Heck cyclization, converting the 2-bromoaniline derivative **49** (Scheme 18) into the *N*-acetyl indole **50** with a Pd catalyst. In 1980, Louis S. Hegedus at Colorado State University showed[25] that iodides were superior to bromides for the cyclization, and that free amines, such as **51** (Scheme 19) were compatible with the reaction conditions, forming **52**.

This approach has been extended in several directions. John E. Macor at Pfizer found[26] that cyclization of the dibromide **53** to **54** (Scheme 20) was more efficient than cyclization of the corresponding monobromide. Note that the potentially labile allylic carbamate survived the Pd reaction conditions. Haruhiko Fuwa and Makoto Sasaki of Tohoku University devised[27] the conversion of the *N*-acetyl aniline **55** (Scheme 21) into the enol phosphonate **56**. Consecutive Suzuki coupling followed by Heck cyclization delivered the indole **57**.

Morten Jørgensen of H. Lundbeck A/S, Denmark took advantage[28] of the more facile oxidative addition of aryl iodides compared to aryl bromides to accomplish sequential N-arylation and Heck cyclization, converting **58** (Scheme 22) into the indole **59**. Lutz Ackermann of the Ludwigs-Maxmilian-Universität München effected[29] regioselective Ti-mediated hydroamination of the alkyne **61** (Scheme 23) with the aniline **60**. Pd-mediated cyclization of the nucleophilic enamine so formed gave the indole **62**.

Indoles can also be prepared by free radical cyclization. Athelstan L. J. Beckwith of the University of Adelaide cleverly employed[30] the nitroxide **64** (Scheme 24) to effect first reduction, to facilitate loss of N_2 from the diazonium salt **63**, then radical cyclization, then radical-radical coupling with the nitroxide, followed by loss of the amine to give the indole

aldehyde **65**. Richard P. Hsung, now at the University of Wisconsin, demonstrated[31] that a more conventional reductive cyclization of the allenylaniline **66** to form **67** (Scheme 25) was also effective.

Lanny S. Liebeskind of Emory University showed[32] that *ortho*-bromo allyl anilines, such as **68** (Scheme 26) could, on transmetalation, be induced to cyclize to the indoline anion. The anion could be trapped with a variety of electrophiles. The product indoline was readily oxidized to the indole **69**. Professor Buchwald generated[33] from **70** (Scheme 27) a zirconocene benzyne complex that inserted into the pendent alkene. Iodination delivered the indoline **71**, that via elimination and bromination was carried on to the indole **72**.

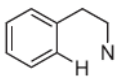
Brian M. Stoltz of Caltech added[34] the anion derived from **74** (Scheme 28) to the benzyne derived from **73** to give the indoline **75**. The authors did not oxidize **75** to the corresponding indole, but this should be straightforward.

As described[35] by Brigitte Jamart-Grégoire of the Université de Nancy, a benzynewas also the intermediate in the cyclization of the anion derived from **76** (Scheme 29) to the indole **77**. Daniel Solé of the Universitat de Barcelona effected[36] the conceptual alternative, the Pd-mediated arylation of the anion derived from **78** (Scheme 30). Depending on the reaction conditions, the dominant product could be either the indoline, or the indole **79**.

Among the several Type 2 indole syntheses reported in 2009, two were particularly interesting. Sandro Cacchi of the Università degli Studi ‘La Sapienza’, Roma, prepared[37] the enaminone **80** (Scheme 31) by condensation of the iodoaniline with the acetylenic ketone. On exposure to a Cu catalyst, **80** cyclized to the indole **81**.

Luc Neuville and JZhu of CNRS Gif-sur-Yvette assembled[38] (Scheme 32) the amide **82** by a four-component coupling. With the proper choice of ligand, **82** could be cyclized to **83**. The conversion of an oxindole into the indole is described in the preceding section.

4. Type 3



Hemetsberger strategy

The lead Type 3 approach is the Hemetsberger[39] indole synthesis, as, for instance, employed[40] by John K. MacLeod of Australia National University in his synthesis (Scheme 33) of *cis*-trikentrin A. The aldehyde **84** was homologated to the azido ester **85**, that was then heated to convert it into the indole **86**.

The thermal conversion of azido styrenes, such as **85** into the indole had been shown[39] to proceed by way of the azirine. We therefore developed[41] a general method for the conversion of an α-aryl ketone, such as **87** (Scheme 34) into the azirine **88**. Thermolysis of the azirine gave the indole **89**. Subsequently, Koichi Narasaka of the University of Tokyo demonstrated[42] that Rh trifluoroacetate catalyzed the conversion of azirines, such as **88** into indoles at room temperature. Tom G. Driver of the University of Illinois, Chicago later

found[43] that the same catalyst converted azido styrenes, such as **85** (Scheme 33) into the indole, also at room temperature.

Kang Zhao of Tianjin University established[44] that PIFA oxidation of an enamine, such as **92** (Scheme 35), prepared from **90** and **91**, offered a convenient route to the *N*-aryl indole **93**. This cyclization may likely also be proceeding by way of the intermediate azirine.

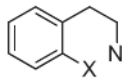
H. Person of the Université de Rennes found[45] that exposure of a β-nitro styrene **94** (Scheme 36) to an isonitrile **95** led to the *N*-hydroxy indole **96**. Glen A. Russell of Iowa State University reported[46] a related reductive cyclization of a β-nitro styrene with triethyl phosphite.

The coupling of a phenol **97** (Scheme 37) with a diazonium salt **98** is a well-known process. Masato Satomura of Fuji Photo Film Co. discovered[47] that exposure of the adduct **99** to mild acid led to cyclization to the indole **100**. The N–N bond was readily cleaved by Raney nickel to give the free amine.

The cyclic heptadepsipeptide HUN-7293 contains the *N*-methoxy tryptophan **104** (Scheme 38). To prepare **104**, Dale L. Boger of Scripps/La Jolla took advantage[48] of the Kikugawa oxindole synthesis to convert **101** into **102**. Reduction followed by acid-catalyzed condensation with the enamide **103** then delivered **104**.

In 2009, Vy M. Dong of the University of Toronto found[49] that CO could serve (Scheme 39) as the reductant for the cyclization of a β-nitro styrene **105** to the indole **106**. Jin-Quan Yu, also of Scripps/La Jolla, developed[50] an oxidant that enabled the Pd-mediated cyclization of **107** (Scheme 40) to the indole **108**.

5. Type 4



Buchwald strategy

The development of transition-metal-mediated aryl halide amination opened the way to Type 4 indole synthesis. In 1998, Stephen L. Buchwald of MIT reported[51] that on exposure to benzylamine in the presence of a Pd catalyst, the dibromide **109** (Scheme 41) smoothly cyclized to the indoline **110**. Ammonium formate in the presence of Pd/C converted **110** into the indole **111**.

In the course of a synthesis of the duocarmycins, Tohru Fukuyama of the University of Tokyo employed[52] a similar approach, cyclizing **112** (Scheme 42) to **113**. By that time, the Cu catalysts for aryl halide amination had been developed.

José Barluenga of the University of Oviedo took advantage[53] of the greater reactivity of an aryl bromide compared to the chloride as he developed the convergent coupling of **114** (Scheme 43) with **115** to give the indole **116**. For this coupling, a Pd catalyst was required.

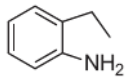
Alexander V. Karchava of Moscow State University devised[54] a route to indoles from *ortho*-bromophenylacetic acid esters, such as **117** (Scheme 44). Formylation followed by condensation with an amine **118** set the stage for the Cu-mediated intramolecular amination to give the indole **119**.

Phenols, under photolysis, can activate *meta*-substituted halides for nucleophilic displacement. Nien-chu C. Yang of the University of Chicago devised[55] an indoline synthesis based on this effect, irradiating **120** (Scheme 45) to give **121**.

Similarly, nitro groups can activate *para*-substituted halides for nucleophilic displacement. Douglas C. Neckers of Bowling Green State University observed[56] that exposure to a primary amine converted the thiadiazole **123** (Scheme 46), prepared from **122**, into the indole-2-thiol **124**. The reaction is thought to be proceeding by way of the alkyne thiol.

In 2009, Qian Cai and Ke Ding of the Institute of Biological Chemistry, Guangzhou described[57] (Scheme 47) the CuI-mediated condensation of the isocyano ester **126** with *o*-halo aromatic ketones and aldehydes, such as **125** to give directly the corresponding indole **127**. Stuart L. Schreiber of Harvard University took[58] a related approach, cyclizing **128** (Scheme 48), prepared via the corresponding aziridine, to the indole **129**.

6. Type 5



Sundberg strategy

In 1969, Richard J. Sundberg of the University of Virginia reported[59] that *ortho*-azido styrenes, such as **130** (Scheme 49) were converted on thermolysis into the corresponding indole **131**. He later found[60] that heating *ortho*-nitro styrenes, such as **132** (Scheme 50) with $P(OEt)_3$ also delivered the indole. Aryl migration dominated over alkyl migration, leading to **133**. Recently, Tom G. Driver of the University of Illinois, Chicago showed[61] that the azide version of the Sundberg indole synthesis could be carried out at lower temperature with a Rh catalyst.

Benzylic methyl groups are acidic enough to be deprotonated, especially when there is an *ortho*-nitro group. This is the basis for the Reissert indole synthesis[62] (**134** to **135**, Scheme 51) and the Leimgruber–Batcho indole synthesis[63] (**136** to **138**, Scheme 52).

Amos B. Smith III of the University of Pennsylvania took advantage[64] of the acidity of **139** (Scheme 53). Double deprotonation followed by condensation with **140** delivered the indole **141**.

Donal F. O'Shea of University College Dublin demonstrated[65] that an alkyllithium first deprotonated **142** (Scheme 54), and then added to the pendent alkene. Benzonitrile **143** was added to the resulting carbanion to give the indole **144**.

It is clear that any synthetic route to *ortho*-amino or *ortho*-nitro α-aryl ketones or aldehydes can be used to prepare indoles. Joseph F. Bunnett of the University of California, Santa Cruz observed[66] that, under $S_{RN}1$ conditions, acetone enolate displaced the bromide of **145** (Scheme 55), leading to the indole **146**. Viresh H. Rawal of the University of Chicago arylated[67] the silyl enol ether **147** (Scheme 56) with an *ortho*-nitrophenyl iodinium salt (NPIF) to give, after reduction, the indole **148**. M. Mahmoun Hossain of the University of Wisconsin, Milwaukee inserted[68] ethyl diazoacetate into the aldehyde **149** (Scheme 57), converting it, via reduction, into the indole **150**.

As demonstrated[69] by Ken-ichi Fujita and Ryohei Yamaguchi of Kyoto University, in situ oxidation of the alcohol **151** (Scheme 58) led to the indole **152**. With added 2-propanol, an alcohol with an *ortho*-nitro group was also converted into the indole.

Hironao Sajiki and Kosaku Hirota of Gifu Pharmaceutical University showed[70] that reduction of an *ortho*-amino nitrile, such as **153** (Scheme 59) delivered the indole **154**, presumably by trapping of the intermediate imine. It may well be that an *ortho*-nitro substituent would work as well, but such a transformation was not included in this report.

K. C. Nicolaou of Scripps/La Jolla prepared[71] the enone **155** (Scheme 60) from the intermediate in the Bischler indole synthesis. Reduction of **155** gave an intermediate that reacted with mild nucleophiles, such as the allylsilane **156** to give the indole **157**.

In 1986, Sylvestre A. Julia of the Ecole Normale Supérieure, Paris reported[72] that sulfinamides, such as **159** (Scheme 61), readily prepared from the aniline **158**, were converted by heating into the indole **161** via **160**. It is striking that the Julia indole synthesis has been little used since it was reported.

The preparation of indoles from *ortho*-haloanilines by condensation with an alkyne goes back at least to 1963, when C. E. Castro of the University of California, Riverside, observed[73] (Scheme 62) that coupling of **162** with **163** led not to the diaryl alkyne, but to the indole **164**.

In 1985, Edward C. Taylor of Princeton University and Alexander McKillop of the University of East Anglia showed[74] that Pd was effective at cyclizing *ortho*-alkynylanilines to the corresponding indole. This led to the 1989 report[75] by J. K. Stille of Colorado State University that the two-step coupling described by Castro (Scheme 62) could be carried out at much lower temperature using Pd catalysis. With this precedent, in 1991 Richard C. Larock of Iowa State University disclosed[76] that, using Pd catalysis (Scheme 63), internal alkynes, such as **166** could be condensed with an *ortho*-iodoaniline **165** under Pd catalysis to give the 2,3-disubstituted indole **167** with high regiocontrol. One of the advantages of the Larock indole synthesis is the malleability of the 2-silyl substituent on the product indole.

More recently, (the late) Keith Fagnou of the University of Ottawa demonstrated[77] that Rh catalysis could effect *ortho* functionalization of acetanilides, such as **168** (Scheme 64). Subsequent coupling with internal alkynes, such as **169** led to the indole **170** with high regiocontrol.

Several other flexible routes to indoles have been developed. Mark Lautens of the University of Toronto established[78] that *ortho* dihaloalkylidene anilines, such as **171** (Scheme 65) could be condensed with alkyl, alkenyl or aryl boranes or boronic acids to give the 2-substituted indole, in this case **172**. Kentaro Okuma of Fukuoka University found[79] that the sulfonium salt **174** (Scheme 66) effected cyclization of an *ortho* alkenyl aniline, such as **173** to the indole **175**. Jeffrey N. Johnston, now at Vanderbilt University, effected[80] free radical reductive cyclization of halides, such as **176** (Scheme 67), to give the indole **177**.

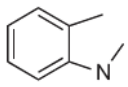
Toyohiko Aoyama of Nagoya City University reacted[81] *ortho*-acylanilines, such as **178** (Scheme 68) with lithio TMS diazomethane **179** to give an alkylidene carbene, that inserted into the adjacent NH to give the indole **180**. Bartolo Gabriele of the Università della Calabria added[82] acetylides, such as **182** (Scheme 69) to *ortho*-acylanilines, such as **181** to give alkynyl alcohols, that underwent carbonylative cyclization with Pd catalysis to give the indole **183**.

In 2009, Hideo Nagashima of Kyushu University reported[83] that an *o*-nitrophenyl acetonitrile **184** could indeed (Scheme 70) be reductively cyclized to the indole **185**. Yanxing Jia of Peking University prepared[84] **188**, a key intermediate in the synthesis of (−)-*cis*-clavicipitic acid, by selective condensation of the aldehyde **187** (Scheme 71) with the iodoaniline **186**.

Sandro Cacchi of the Università ‘La Sapienza’, Rome, extended[85] the Gabriele approach, cyclizing (Scheme 72) the propargylic carbonate **189** to **190**. This transformation may be proceeding by way of the intermediate allene. Two related approaches to indole synthesis[86,87] also appeared.

Tao Pei of Merck Rahway developed[88] a powerful new approach to substituted indoles, based on the addition (Scheme 73) of an organometallic to a chloro ketone **191**. The conversion into **192** proceeded by 1,2-migration of the arene with nucleophilic displacement of chloride.

7. Type 6



Madelung strategy

The Madelung indole synthesis, as exemplified by the cyclization (Scheme 74) of **193** to **194**, was originally carried out at elevated temperature with bases, such as $NaNH_2$. Willam J. Houlihan of Sandoz, Inc. (now Novartis) showed[89] that, with BuLi, the cyclization of **193** to **194** was facile below room temperature. D. N. Reinhoudt of the University of Twente found[90] that phenylacetonitriles, such as **195** (Scheme 75) could be cyclized under even milder conditions, to form **196**.

George A. Kraus of Iowa State University described[91] a conceptually related cyclization (Scheme 76). Condensation of an aldehyde **198** with the aniline **197** gave the imine, that on exposure to strong base gave the indole **199**. Gary A. Sulikowski, now at Vanderbilt University, showed[92] that cyclization of the carbene derived from **200** (Scheme 77) proceeded to give **201** with high regiocontrol.

Bond formation in the opposite direction has also been developed. William D. Jones reported[93] that a Ru complex catalyzed the conversion of the isonitrile **202** (Scheme 78) into the indole **203**. This reaction may be proceeding by way of the Ru vinylidene complex.

Charles D. Jones of Lilly described[94] an anionic cyclization in this direction, converting **204** (Scheme 79) into **205**. Yoshinori Nakamura of the Tanabe Seiyaku Co. contributed[95] the Rh-mediated coupling of the diazophosphonate **207** (Scheme 80) to an *ortho*-acylaniline, such as **206**, to give, after cyclization, the indole **208**. Note that, in the cyclization of **209** (Scheme 81) developed[96] by RodneyW. Stevens of Pfizer Nagoya, re-aromatization to the indole **210** was achieved by elimination of arenesulfinate.

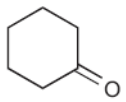
In 1994, Tohru Fukuyama, now at the University of Tokyo, disclosed[97a] the cascade radical cyclization of the isonitrile **211** (Scheme 82) to the indole **212**. Later, he applied[97b] a variant of this cyclization in the total synthesis of a complex indole alkaloid. Jon D. Rainier, now at the University of Utah, has explored[97c] related radical cyclizations.

Alois Fürstner of the Max-Planck-Institute Mülheim developed[98a, b] a reductive coupling of acyl anilides, such as **213** to give **214** (Scheme 83). In the presence of a silyl chloride, the reaction was catalytic in Ti. Bruce C. Lu of Boehringer Ingelheim employed[98c] this reductive coupling in a combinatorial route to indoles.

In 2009, Professor Doyle reported[99] an alternative (Scheme 84) diazo-based approach to indoles, Lewis acid-mediated cyclization of **215** to **216**.

Churl Min Seong of the Korea Research Institute of Chemical Technology described[100] the facile cyclization (Scheme 85) of an *o*-cyano *N*-benzyl aniline **217** to the indole **218**. Andrew D. Hamilton employed[101] a related protocol (Scheme 86), the cyclization of **219** to **220**.

8. Type 7



Nenitzescu strategy

Type 7 includes all routes to indoles from cycloalkane derivatives. The earliest such approach is the Nenitzescu indole synthesis, exemplified (Scheme 87) in a modern manifestation[102] by Daniel M. Ketcha of Wright State University and Lawrence J. Wilson of Procter & Gamble. The combination of the benzoquinone **221** with the resin-bound enamine **222** gave, after release from the resin, the indole **223**.

Michael A. Kerr of the University of Western Ontario developed[103] (Scheme 88) a complementary protocol for the conversion of a benzoquinone into the indole. Diels–Alder cycloaddition of the imine **224** to the diene **225** gave the adduct **226**. Protection followed by oxidative cleavage and condensation delivered the indole **227**.

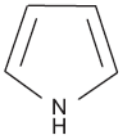
Fused pyrroles, such as **231** (Scheme 89) and **235** (Scheme 90) are readily aromatized. Brian L. Pagenkopf of the University of Western Ontario established[104] a pyrrole synthesis from cyclohexanone, by cyclopropanation of the enol ether **228** followed by condensation with the nitrile **230**. The aromatization of **231** to **232** was accomplished by heating with Pd/C in mesitylene.

Teruhiko Ishikawa and Seiki Saito of Okayama University condensed[105] (Scheme 90) cyclohexane-1,3-dione **233** with the nitroalkene **234**, leading after exchange with benzylamine to the pyrrole **235**. Aromatization gave the 4-oxygenated indole **236**. Chihiro Kibiyashi of the Tokyo College of Pharmacy reported[106] a related approach to 4-oxygenated indoles.

Michel Pfau of ESPCI Paris devised[107] an intriguing protocol for indole construction, starting with the benzyl imine of the monoprotected cyclohexane-1,4-dione **237** (Scheme 91). Metalation of the imine followed by condensation with maleic anhydride **238**, with methanol workup, delivered the lactam **239**. Exposure of **239** to $POCl_3$ effected aromatization to the 5-methoxyindole **240**.

In 2009, Yong-Qiang Tu of Lanzhou University described[108] the ring expansion (Scheme 92) of **241** to **242**. The aromatization of **242** to the indole should be facile. Tsutomu Inokuchi of Okayama University showed[109] that reduction (Scheme 93) of the Michael adduct **243** followed by aromatization delivered the indole **244**.

9. Type 8



van Leusen strategy

Type 8 indole syntheses include all those that proceed by way of the preformed *N*-containing five-membered ring. In 1986, Albert M. van Leusen of Groningen University established[110] a route to highly substituted indoles, based on the condensation of isonitriles, such as **245** (Scheme 94) with unsaturated ketones, such as **246** to give the 2,3-bisalkenylpyrrole **247**. Heating followed by aromatization with DDQ completed the synthesis of the indole **248**.

Hiroyuki Ishibashi of Kyoto Pharmaceutical University demonstrated[111] (Scheme 95) a route to 4-substituted indoles from pyrrole itself. Condensation of **249** with the chlorosulfide followed by saponification and intramolecular Friedel–Crafts acylation delivered the

versatile intermediate **250**. Oxidation gave the indole **251**. The addition of nucleophiles to **250** followed by dehydration gave the 4-alkylindole (not illustrated).

Pedro Mancini of the Universidad Nacional de Litoral showed[112] that nitropyrroles, such as **252** (Scheme 96) were effective Diels–Alder dienophiles. Regiocontrol was poor with isoprene, whereas addition to the more activated diene **253** proceeded to give the 5-hydroxyindole **254** with complete regiocontrol.

Edwin Vedejs of the University of Michigan optimized[113] the acetic anhydride-mediated cyclization of the Stobbe condensation product **255** (Scheme 97) to the indole **256**. Although this cyclization had been reported earlier, Vedejs found that the conditions originally described also delivered substantial quantities of an indolizidine by-product.

Masanobu Hidai of the University of Tokyo developed[114] the Pd-catalyzed cyclocarbonylation of the allylic acetate **257** (Scheme 98) to the 4-acetoxyindole **258**. It seems likely that a more highly substituted version of **257** would cyclize with equal facility.

Alan R. Katrizky of the University of Florida devised[115] an approach to indoles with more highly substituted benzene rings. Addition of the benzotriazolyl anion **259** (Scheme 99) to an enone, such as **260** followed by acid-catalyzed dehydrative cyclization delivered the indole **261**.

Naoki Asao of Tohoku University found[116] that $AuBr^3$ was an effective catalyst for the cyclocondensation (Scheme 100) of **262** with **263** to give the indole **264**. F. Dean Toste of the University of California, Berkeley uncovered[117] a related Au-catalyzed cyclization leading to indoles.

In 2009, Chi-Meng Che of the University of Hong Kong[118] described (Scheme 101) the Pt-mediated intramolecular hydroamination of the alkyne **265**. Condensation of the cyclic enamine **266** so prepared with a β-diketone **267** proceeded with high regioselectivity to give the indoline **268**. For the aromatization of a similar *N*-benzyl indoline, see Scheme 41.

10. Type 9

Kanematsu strategy

The least developed approach to indoles is Type 9, the simultaneous construction of both rings of the indole. This route was pioneered in 1986[119] by Ken Kanematsu of Kyushu University. Homologation of **269** (Scheme 102) to the allene led to the intramolecular Diels–Alder cyclization product, that was readily aromatized to the indole **270**.

Three related approaches have been put forward since that time. Michael J. Martinelli, then at Lilly, established[120] that acetic anhydride-mediated decarboxylation of **271** (Scheme 103) led to a 1,3-dipole, that added in an intramolecular fashion to the alkyne, delivering the

dihydro indole **272**. In a complementary approach, A. Stephen K. Hashmi of Ruprecht-Karls-Universität Heidelberg found[121] that with catalytic $AuBr_3$, **273** (Scheme 104) cyclized efficiently to **274**. As outlined earlier in this review, both **272** and **274** would be readily aromatized to the corresponding indoles.

In 2009, Peter Wipf of the University of Pittsburgh described[122] the intramolecular Diels—Alder cyclization (Scheme 105) of the allylic alcohol **275**. Microwave heating led directly to the doubly aromatized product **276**.

11. Conclusions

In this review, we have tried to be inclusive, but certainly not comprehensive. We hope that the scheme outlined here for the classification of synthetic routes to indoles will be useful to future practitioners of the art, and will stimulate new thinking in the field.

Acknowledgments

The authors thank Professor Gordon W. Gribble for his advice and encouragement. PKT thanks Randy W. Jackson for his understanding and support.

References and notes

1. For recent reviews of indole synthesis, see Patil SA, Patil R, Miller DD. Curr Med Chem. 2011; 18:615–637. [PubMed: 21143107] ; Cacchi S, Fabrizi G, Goggiamani A. Org Biomol Chem. 2011; 9:641–652. [PubMed: 21125122] ; Song JJ, Reeves JT, Fandrick DR, Tan Z, Yee NK, Senanayake CH. ARKIVOC. 2010:390–449.; Palmisano G, Penoni A, Sisti M, Tibiletti F, Tollari S, Nicholas KM. Curr Org Chem. 2010; 14:2409–2441.; Patil SA, Patil R, Miller DD. Curr Med Chem. 2009; 16:2531–2565. [PubMed: 19601797] ; Barluenga J, Rodriguez F, Fananas FJ. Chem—Asian J. 2009; 4:1036–1048. [PubMed: 19360759] ; Russel JS, Pelkey ET. Prog Heterocycl Chem. 2009; 20:122–151.; Krüger K, Tillack A, Beller M. Adv Synth Catal. 2008; 350:2153–2167.; Humphrey GR, Kuethe JT. Chem Rev. 2006; 106:2875–2911. [PubMed: 16836303] ; Gribble GW. Pure Appl Chem. 2003; 75:1417–1432.; Gribble GW. J Chem Soc Perkin Trans. 2000; 1:1045–1075.
2. Brodfuehrer PR, Chen B-C, Sattelberg TR Sr, Smith PR, Reddy JP, Stark DR, Quinlan SL, Reid JG, Thottathil JK, Wang S. J Org Chem. 1997; 62:9192–9202.
3. Chae J, Buchwald SL. J Org Chem. 2004; 69:3336–3339. [PubMed: 15132539]
4. Yasui E, Wada M, Takamura N. Tetrahedron Lett. 2006; 47:743–746.
5. Maruoka K, Oishi M, Yamamoto H. J Org Chem. 1993; 58:7638–7639.
6. Cao C, Shi Y, Odom AL. Org Lett. 2002; 4:2853–2856. [PubMed: 12182572]
7. Wagaw S, Yang BH, Buchwald SL. J Am Chem Soc. 1999; 121:10251–10263.
8. Sundberg RJ, Laurino JP. J Org Chem. 1984; 49:249–254.
9. For a modern procedure for the Bischler synthesis, see Sridharan V, Perumal S, Avendaño C, Menéndez JC. Synlett. 2006:91–95.; For a variant leading to 3-substituted indoles, see Pchalek K, Jones AW, Wekking MMT, Black DSC. Tetrahedron. 2005; 61:77–82.Cho CS, Kim JH, Choi H-J, Kim T-J, Shim SC. Tetrahedron Lett. 2003; 44:2975–2977.
10. Penoni A, Volkmann J, Nicholas KM. Org Lett. 2002; 4:699–701. [PubMed: 11869105]
11. Saito A, Kanno A, Hanzawa Y. Angew Chem Int Ed. 2007; 46:3931–3933.
12. Johnson F, Subramanian R. J Org Chem. 1986; 51:5040–5041.
13. Watson D, Dillin DR. Tetrahedron Lett. 1980; 21:3969–3970.
14. Würtz S, Rakshit S, Neumann JJ, Dröge T, Glorius F. Angew Chem Int Ed. 2008; 47:7230–7233.
15. Cui S-L, Wang J, Wang Y-G. J Am Chem Soc. 2008; 130:13526–13527. [PubMed: 18798615]
16. Wierenga W, Griffin J, Warpehoski MA. Tetrahedron Lett. 1983; 24:2437–2440.

17. Quiclet-Sire B, Zard SZ. Org Lett. 2008; 10:3279–3282. [PubMed: 18582076]
18. Chandra T, Zou S, Brown KL. Tetrahedron Lett. 2004; 45:7783–7786.
19. Samet AV, Zakharov EP, Semenov VV, Buchanan AC III, Gakh AA. Synth Commun. 2001; 31:1441–1445.
20. Liu K, Yin D. Org Lett. 2009; 11:637–639. [PubMed: 19108672]
21. Shi Z, Zhang C, Li S, Pan D, Ding S, Cui Y, Jiao N. Angew Chem Int Ed. 2009; 48:4572–4576.
22. Saito A, Oa S, Fukaya H, Hanzawa Y. J Org Chem. 2009; 74:1517–1524. [PubMed: 19159263]
23. Schneekloth JS Jr, Kim J, Sorensen EJ. Tetrahedron. 2009; 65:3096–3101. [PubMed: 22163373]
24. Mori M, Chiba K, Ban Y. Tetrahedron Lett. 1977:1037–1040.
25. Odle R, Blevins B, Ratcliff M, Hegedus LS. J Org Chem. 1980; 45:2709–2710.
26. Macor JE, Ogilvie RJ, Wythes MJ. Tetrahedron Lett. 1996; 37:4289–4292.
27. Fuwa H, Sasaki M. Org Lett. 2007; 9:3347–3350. [PubMed: 17658837]
28. Jensen T, Pedersen H, Bang-Andersen B, Madsen R, Jørgensen M. Angew Chem Int Ed. 2008; 47:888–890.
29. Ackermann L, Kaspar LT, Gschrei CJ. Chem Commun. 2004:2824–2825.
30. Beckwith ALJ, Meijs GFJCS. Chem Commun. 1981:595–597.
31. Shen L, Hsung RP. Org Lett. 2005; 7:775–778. [PubMed: 15727438]
32. Zhang D, Liebeskind LS. J Org Chem. 1996; 61:2594–2595. [PubMed: 11667083]
33. Tidwell JH, Peat AJ, Buchwald SL. J Org Chem. 1994; 59:7164–7168.
34. Gilmore CD, Allan KM, Stoltz BM. J Am Chem Soc. 2008; 130:1558–1559. [PubMed: 18193875]
35. Caubère C, Caubère P, Renard P, Bizot-Espiart J-G, Jamart-Grégoire B. Tetrahedron Lett. 1993; 34:6889–6892.
36. Solé D, Serrano O. J Org Chem. 2008; 73:2476–2479. [PubMed: 18284256]
37. Bernini R, Cacchi S, Fabrizi G, Filisti E, Sferrazza A. Synlett. 2009:1480–1484.
38. Erb W, Neuville L, Zhu J. J Org Chem. 2009; 74:3109–3115. [PubMed: 19284772]
39. Hemetsberger H, Knittel D, Weidmann H. Monatsh Chem. 1970; 101:161–165.
40. MacLeod JK, Monahan LC. Tetrahedron Lett. 1988; 29:391–392.
41. Taber DF, Tian W. J Am Chem Soc. 2006; 128:1058–1059. [PubMed: 16433505]
42. Chiba S, Hattori G, Narasaka K. Chem Lett. 2007; 36:52–53.
43. Stokes BJ, Dong H, Leslie BE, Pumphrey AL, Driver TG. J Am Chem Soc. 2007; 129:7500–7501. [PubMed: 17523647]
44. Du Y, Liu R, Linn G, Zhao K. Org Lett. 2006; 8:5919–5922. [PubMed: 17165894]
45. Person H, Del Aguila Pardo M, Foucaud A. Tetrahedron Lett. 1980; 21:281–284.
46. Russell GA, Yao C-F, Tashtoush HI, Russell JE, Dedolph DE. J Org Chem. 1991; 56:663–669.
47. Satomura M. J Org Chem. 1993; 58:3757–3760.
48. Boger DL, Keim H, Oberhauser B, Schreiner EP, Foster CA. J Am Chem Soc. 1999; 121:6197–6205.
49. Hsieh THH, Dong VM. Tetrahedron. 2009; 65:3062–3068.
50. Mei T-S, Wang X, Yu J-Q. J Am Chem Soc. 2009; 131:10806–10807. [PubMed: 19606861]
51. Aoki K, Peat AJ, Buchwald SL. J Am Chem Soc. 1998; 120:3068–3073.
52. Yamada K, Kurokawa T, Tokuyama H, Fukuyama T. J Am Chem Soc. 2003; 125:6630–6631. [PubMed: 12769562]
53. Barluenga J, Jiménez-Aquino A, Valdés C, Aznar F. Angew Chem Int Ed. 2007; 46:1529–1532.
54. Melkonyan FS, Karchava AV, Yurovskaya MA. J Org Chem. 2008; 73:4275–4278. [PubMed: 18471015]
55. Zhang B, Zhang J, Yang D-DH, Yang N-cC. J Org Chem. 1996; 61:3236–3237.
56. Androsov DA, Neckers DC. J Org Chem. 2007; 72:5368–5373. [PubMed: 17552569]
57. Cai Q, Li Z, Wei J, Ha C, Pei D, Ding K. Chem Commun. 2009:7581–7583.
58. Taylor AM, Schreiber SL. Tetrahedron Lett. 2009; 50:3230–3233. [PubMed: 20046991]
59. Sundberg RJ, Lin L-S, Blackburn DE. J Heterocycl Chem. 1969; 6:441–441.

60. Sundberg RJ, Yamazaki T. J Org Chem. 1967; 32:290–294.
61. Shen M, Leslie BE, Driver TG. Angew Chem Int Ed. 2008; 47:5056–5059.
62. Katayama S, Ae N, Nagata R. J Org Chem. 2001; 66:3474–3483. [PubMed: 11348132]
63. Siu J, Baxendale IR, Ley SV. Org Biomol Chem. 2004; 2:160–167. [PubMed: 14737637]
64. Smith AB III, Visnick M. Tetrahedron Lett. 1985; 26:3757–3760.
65. Coleman CM, O'Shea DF. J Am Chem Soc. 2003; 125:4054–4055. [PubMed: 12670219]
66. Bard RN, Bunnett JF. J Org Chem. 1980; 45:1547–1548.
67. Kozmin SA, Rawal VH. J Am Chem Soc. 1998; 120:13523–13524.
68. Islam MS, Brennan C, Wang Q, Hossain MM. J Org Chem. 2006; 71:4675–4677. [PubMed: 16749805]
69. Fujita, K-i; Yamamoto, K.; Yamaguchi, R. Org Lett. 2002; 4:2691–2694. [PubMed: 12153211]
70. Sajiki H, Ikawa T, Hirota K. Org Lett. 2004; 6:4977–4980. [PubMed: 15606114]
71. Nicolaou KC, Estrada AA, Lee SH, Freestone GC. Angew Chem Int Ed. 2006; 45:5364–5368.
72. Baudin J-B, Julia SA. Tetrahedron Lett. 1986; 27:837–840.
73. (a) Castro CE, Stevens RD. J Org Chem. 1963; 28:2163–2163.(b) Castro CE, Gaughan EJ, Owsley DC. J Org Chem. 1966; 31:4071–4078.
74. Taylor EC, Katz AH, Salgado-Zamora H. Tetrahedron Lett. 1985; 26:5963–5966.
75. Rudisill DE, Stille JK. J Org Chem. 1989; 54:5856–5866.
76. (a) Larock RC, Yum EK. J Am Chem Soc. 1991; 113:6689–6690.(b) Larock RC, Yum EK, Refvik MD. J Org Chem. 1998; 63:7652–7662.
77. Stuart DR, Bertrandf-Laperle M, Burgess KMN, Fagnou K. J Am Chem Soc. 2008; 130:16474–16475. [PubMed: 19554684]
78. Fang Y-Q, Lautens M. J Org Chem. 2008; 73:538–549. [PubMed: 18154302]
79. Okuma K, Takeshita I, Yasuda T, Shioji K. Chem Lett. 2006; 35:1122–1123.
80. Prabhakaran EN, Nugent BM, Williams AL, Nailor KE, Johnston JN. Org Lett. 2002; 4:4197–4200. [PubMed: 12443057]
81. Miyagi T, Hari Y, Aoyama T. Tetrahedron Lett. 2004; 45:6303–6305.
82. Gabriele B, Mancuso R, Salerno G, Lupinacci E, Ruffolo G, Costa M. J Org Chem. 2008; 73:4971–4977. [PubMed: 18540650]
83. Motoyama Y, Kamo K, Nagashima H. Org Lett. 2009; 11:1345–1348. [PubMed: 19236012]
84. Xu Z, Li Q, Zhang L, Jia Y. J Org Chem. 2009; 74:6859–6862. [PubMed: 19711998]
85. Cacchi S, Fabrizi G, Filisti E. Synlett. 2009:1817–1821.
86. Ohta Y, Chiba H, Oishi S, Fujii N, Ohno H. J Org Chem. 2009; 74:7052–7058. [PubMed: 19673483]
87. Mitra T, Das S, Basak A. Tetrahedron Lett. 2009; 50:5846–5849.
88. Pei T, Tellers DM, Streckfuss EC, Chen C-y, Davies IW. Tetrahedron. 2009; 65:3285–3291.
89. Houlihan WJ, Parrino VA, Uike Y. J Org Chem. 1981; 46:4511–4515.
90. Orlemans EOM, Schreuder AH, Conti PGM, Verboom W, Reinhoudt DN. Tetrahedron. 1987; 43:3817–3826.
91. Kraus GA, Guo H. Org Lett. 2008; 10:3061–3063. [PubMed: 18572918]
92. Le S, Lee W-M, Sulikowski GA. J Org Chem. 1999; 64:4224–4225.
93. Jones WD, Kosar WP. J Am Chem Soc. 1986; 108:5640–5641.
94. (a) Jones CD, Suárez T. J Org Chem. 1972; 37:3622–3623.(b) Jones CD. J Org Chem. 1972; 37:3624–3625.
95. Nakamura Y, Ukita T. Org Lett. 2002; 4:2317–2320. [PubMed: 12098236]
96. Nakao K, Murata Y, Koike H, Uchida C, Kawamura K, Mihara S, Hayashi S, Stevens RW. Tetrahedron Lett. 2003; 44:7269–7271.
97. (a) Fukuyama T, Chen X, Peng G. J Am Chem Soc. 1994; 116:3127–3128.(b) Reding MT, Fukuyama T. Org Lett. 1999; 1:973–976.(c) Ranier JD, Kennedy AR. J Org Chem. 2000; 65:6213–6216. [PubMed: 10987962]

98. (a) Fürstner A, Hupperts A, Ptock A, Janssen E. J Org Chem. 1994; 59:5215–5229.(b) Fürstner A, Hupperts A. J Am Chem Soc. 1995; 117:4468–4475.(c) Ding F, Zhang Y, Qu B, Li G, Farina V, Lu BZ, Senanayake CH. Org Lett. 2008; 10:1067–1070. [PubMed: 18275207]
99. Zhou L, Doyle MP. J Org Chem. 2009; 74:9222–9224. [PubMed: 19904905]
100. Seong CM, Park CM, Choi J, Park NS. Tetrahedron Lett. 2009; 50:1029–1031.
101. Wyrembak PN, Hamilton AD. J Am Chem Soc. 2009; 131:4566–4567. [PubMed: 19284758]
102. Ketcha DM, Wilson LJ, Portlock DE. Tetrahedron Lett. 2000; 41:6253–6257.
103. Lebold TP, Kerr MA. Org Lett. 2008; 10:997–1000. [PubMed: 18232706]
104. Morales CL, Pagenkopf BL. Org Lett. 2008; 10:157–159. [PubMed: 18085785]
105. Arai M, Miyauchi Y, Miyahara T, Ishikawa T, Saito S. Synlett. 2008:122–126.
106. Iida H, Yuasa Y, Kibayashi C. Tetrahedron Lett. 1982; 23:3591–3594.
107. Revial G, Jabin I, Lim S, Pfau M. J Org Chem. 2002; 67:2252–2256. [PubMed: 11925236]
108. Zhao X, Zhang E, Tu Y-Q, Zhang Y-Q, Yuan D-Y, Cao K, Fan C-A, Zhang F-M. Org Lett. 2009; 11:4002–4004. [PubMed: 19655804]
109. Ma J-L, Li X-X, Kusuyama T, El-Tantawy El-Sayed I, Inokuchi T. J Org Chem. 2009; 74:9218–9221. [PubMed: 19894747]
110. Moskal J, van Leusen AM. J Org Chem. 1986; 51:4131–4139.
111. Ishibashi H, Tabata T, Hanaoka K, Iriyama H, Akamatsu S, Ikeda M. Tetrahedron Lett. 1993; 34:489–492.
112. Della Rossa C, Kneeteman M, Mancini P. Tetrahedron Lett. 2007; 48:1435–1438.
113. Kim M, Vedejs E. J Org Chem. 2004; 69:6945–6948. [PubMed: 15387633]
114. Iwasaki M, Kobayashi Y, Li J-P, Matsuzaka H, Ishii Y, Hidai M. J Org Chem. 1991; 56:1922–1927.
115. Katritzky AR, Ledoux S, Nair SK. J Org Chem. 2003; 68:5728–5730. [PubMed: 12839470]
116. Asao N, Aikawa H. J Org Chem. 2006; 71:5249–5253. [PubMed: 16808512]
117. Zhao J, Hughes CO, Toste FD. J Am Chem Soc. 2006; 128:7436–7437. [PubMed: 16756286]
118. Liu X-Y, Che C-M. Angew Chem Int Ed. 2009; 48:2367–2371.
119. (a) Hayakawa K, Yasukouchi T, Kanematsu K. Tetrahedron Lett. 1986; 27:1837–1840.(b) Hayakawa K, Yasukouchi T, Kanematsu K. Tetrahedron Lett. 1987; 28:5895–5898.
120. Hutchison DR, Nayyar NK, Martinelli MJ. Tetrahedron Lett. 1996; 37:2887–2890.
121. Hashmi ASK, Rudolph M, Bats JW, Frey W, Rominger F, Oeser T. Chem —Eur J. 2008; 14:6672–6678. [PubMed: 18576410]
122. Petronijevic F, Timmons C, Cuzzupe A, Wipf P. Chem Commun. 2009:104–106.

Biographies

Douglass F. Taber was born in 1948 in Berkeley, California. He earned a B.S. in Chemistry with Honors from Stanford University in 1970, and a Ph.D. in Organic Chemistry from Columbia University in 1974 (G. Stork). After a postdoctoral year at the University of Wisconsin (B.M. Trost), Taber accepted a faculty position at Vanderbilt University. He moved to the University of Delaware of Delaware in 1982, where he is currently Professor

of Chemistry. Taber is the author of more than 200 research papers on organic synthesis and organometallic chemistry. He is also the author of the weekly Organic Highlights published at http://www.organic-chemistry.org/

Pavan K. Tirunahari was born inWarangal, A.P, India in 1968. He received his Bachelor of Science and Master of Science degrees from Osmania University, Hyderabad. He then joined the group of Dr. B. G. Hazra at National Chemical Laboratory, Pune, Maharastra. He received his Ph.D degree in Organic Chemistry from the University of Pune. He did his postdoctoral studies in the group of Professor James. P. Morken at the University of North Carolina. Currently he is working at Accel Synthesis, Inc., Garnet Valley, PA. His research interests include process research, synthetic methodologies, medicinal chemistry, and pharmacology.

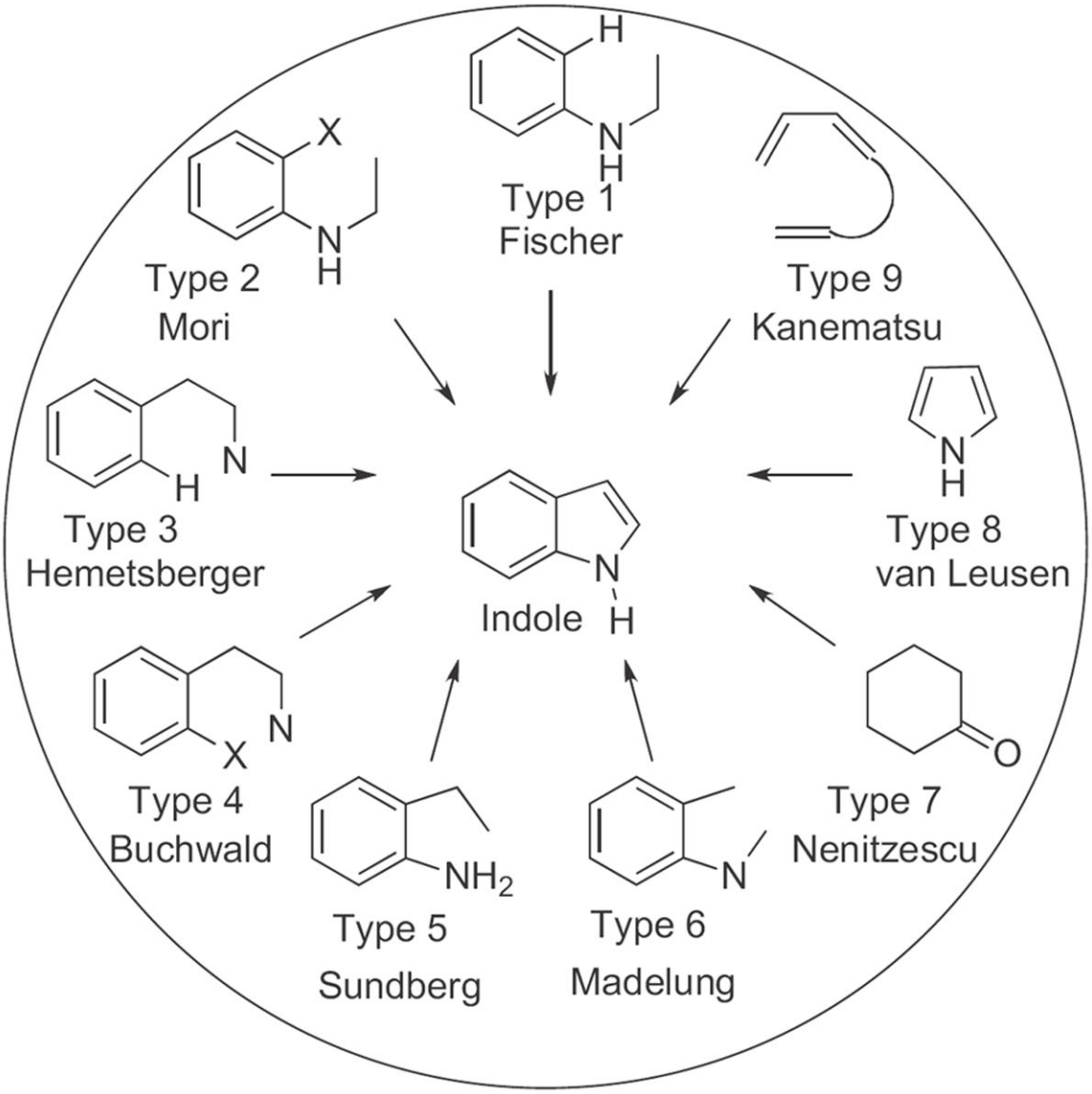
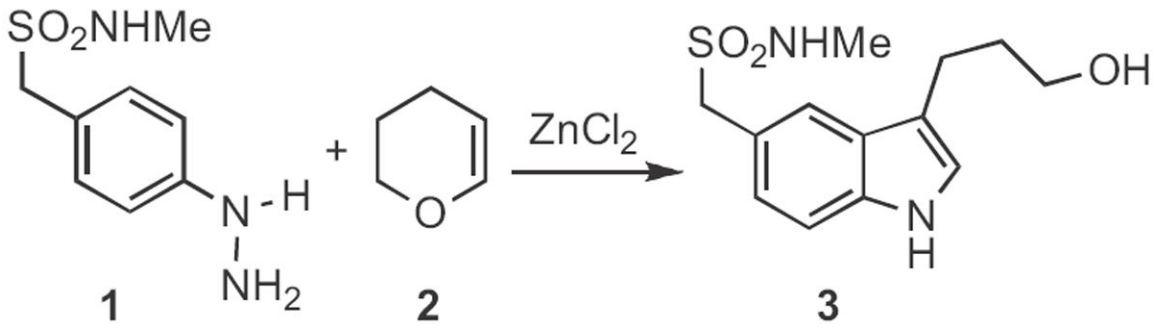
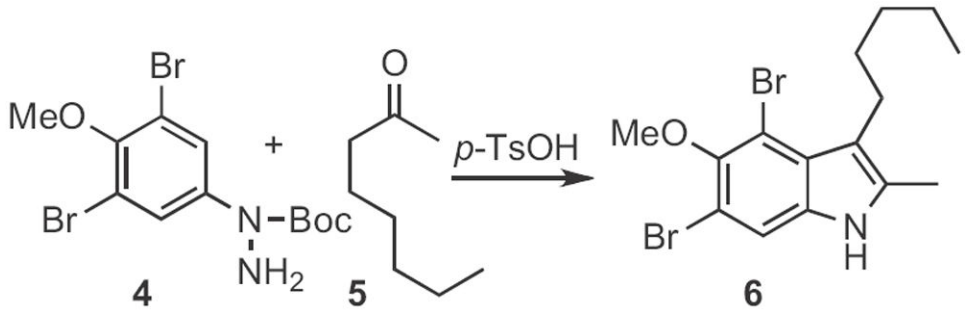


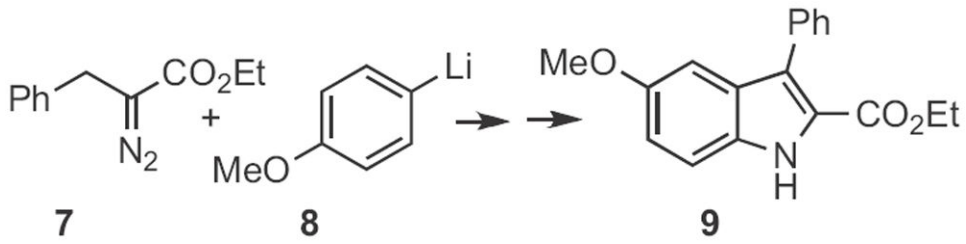
Fig 1.
The nine types of indole synthesis.



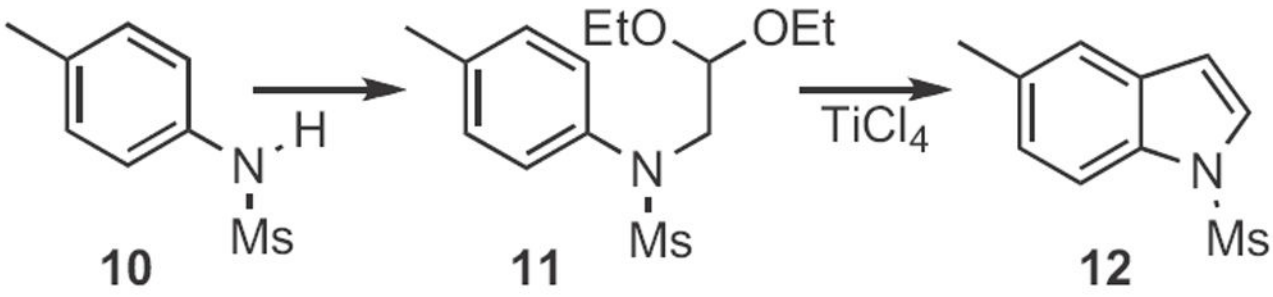
Scheme 1.



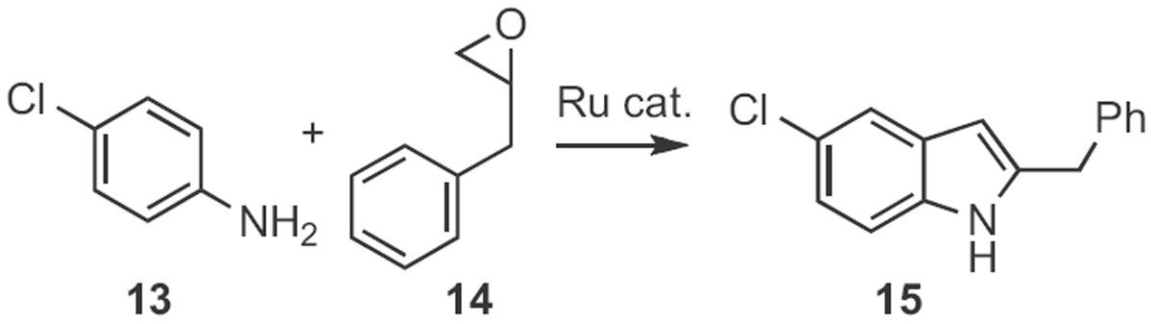
Scheme 2.



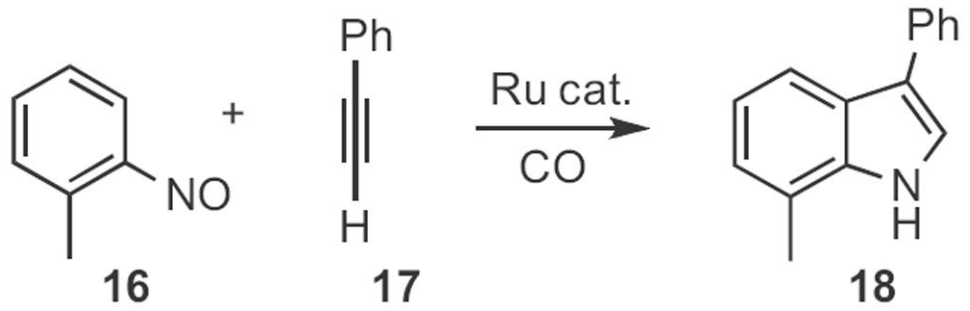
Scheme 3.



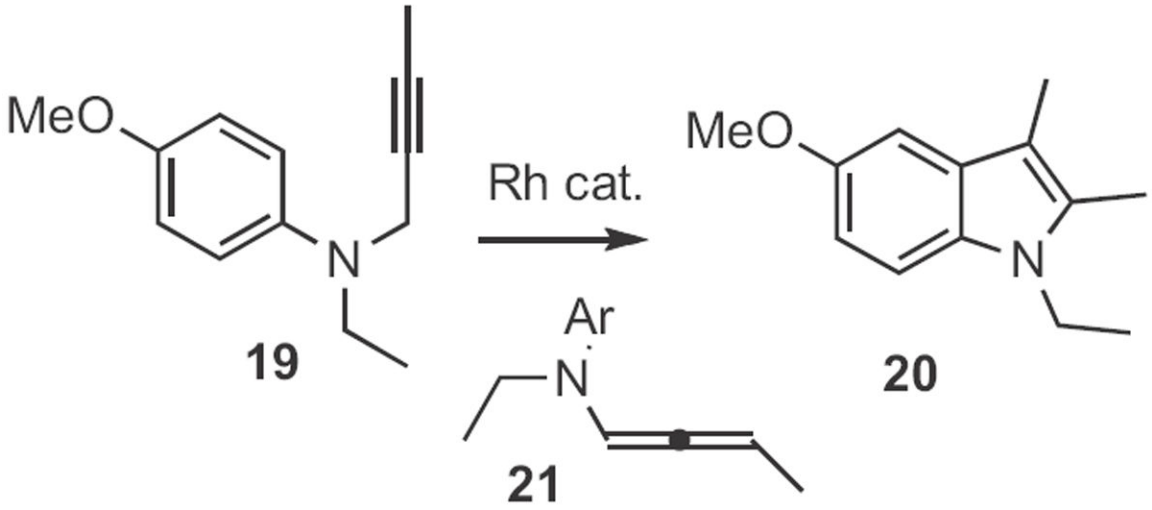
Scheme 4.



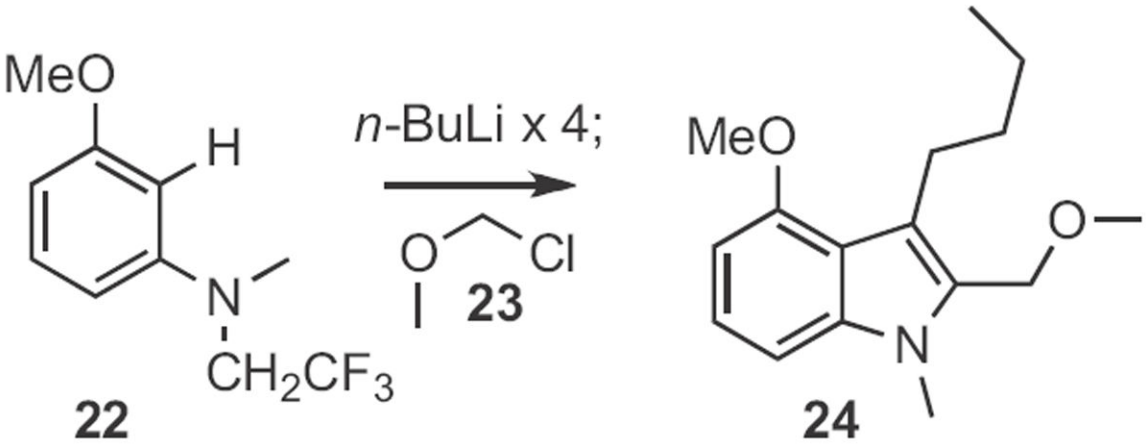
Scheme 5.



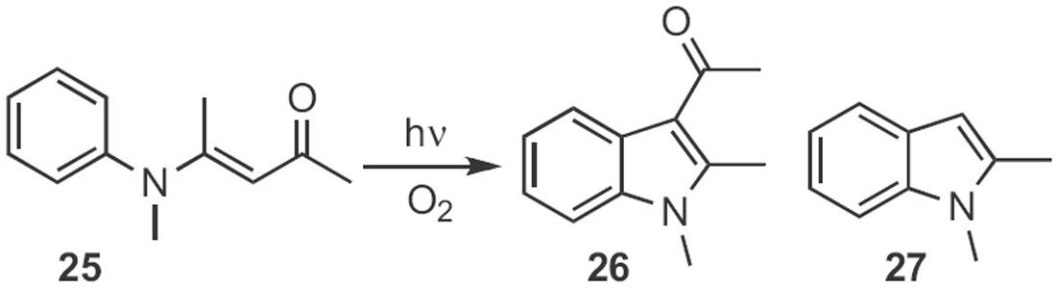
Scheme 6.



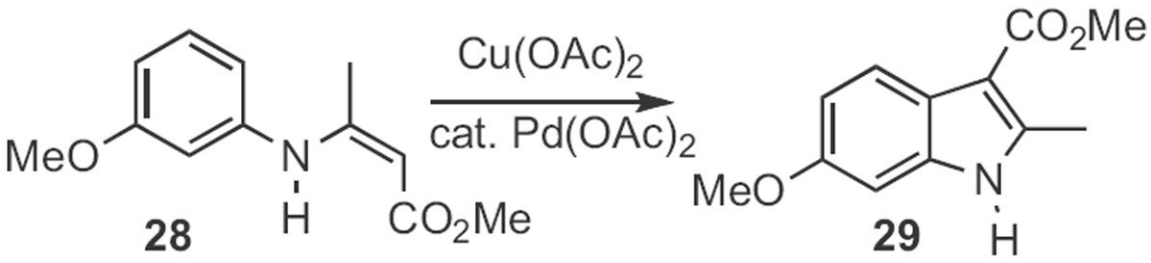
Scheme 7.



Scheme 8.

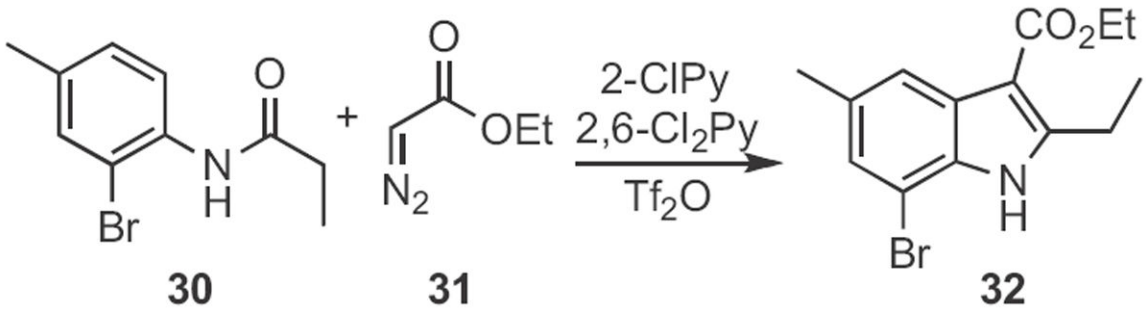


Scheme 9.

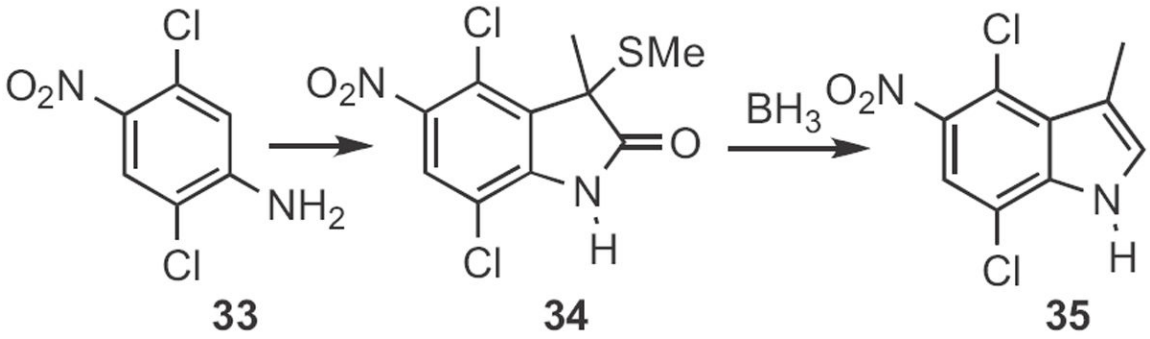


28 29

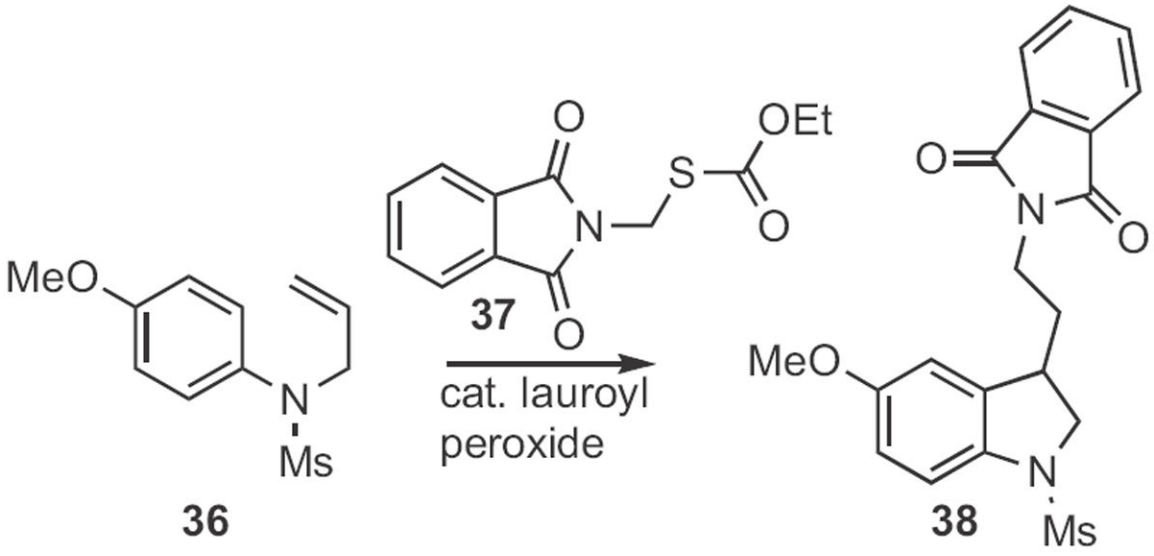
Scheme 10.



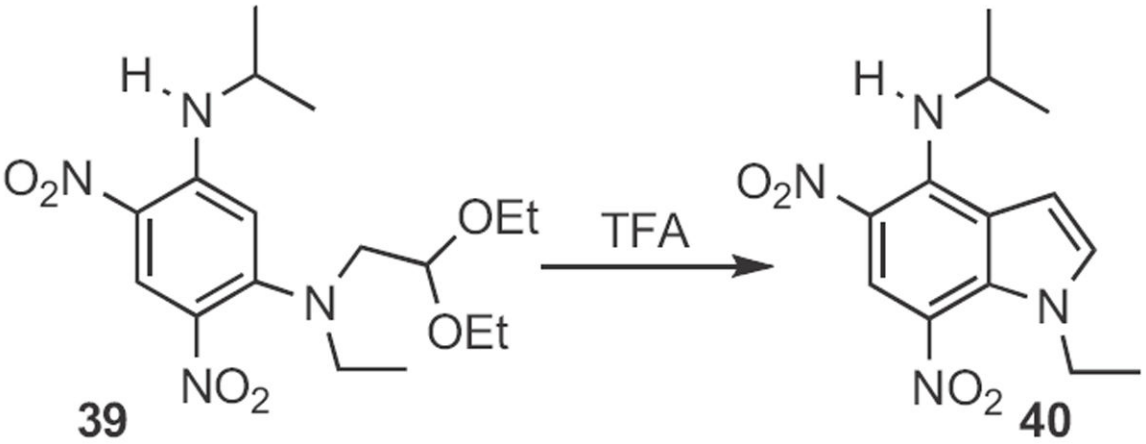
Scheme 11.



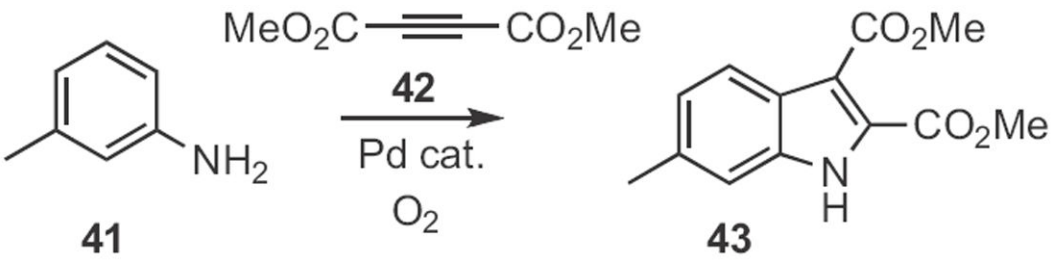
Scheme 12.



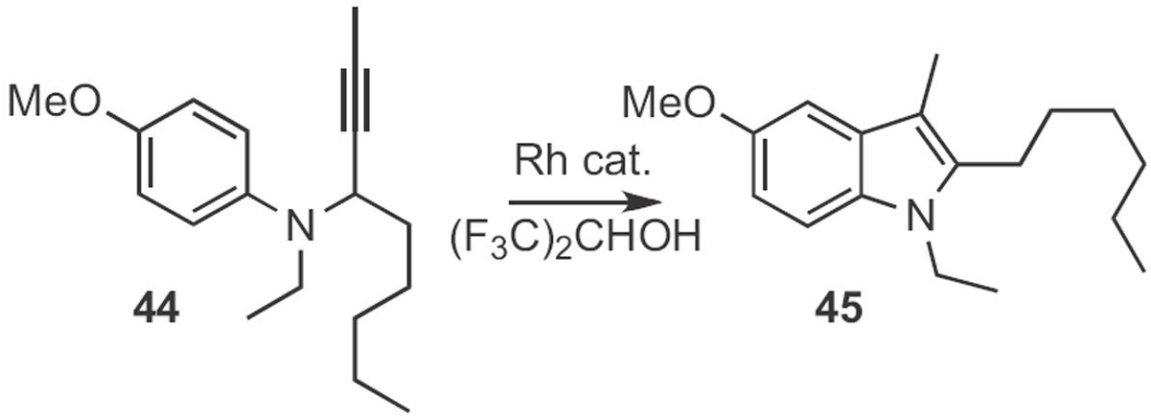
Scheme 13.



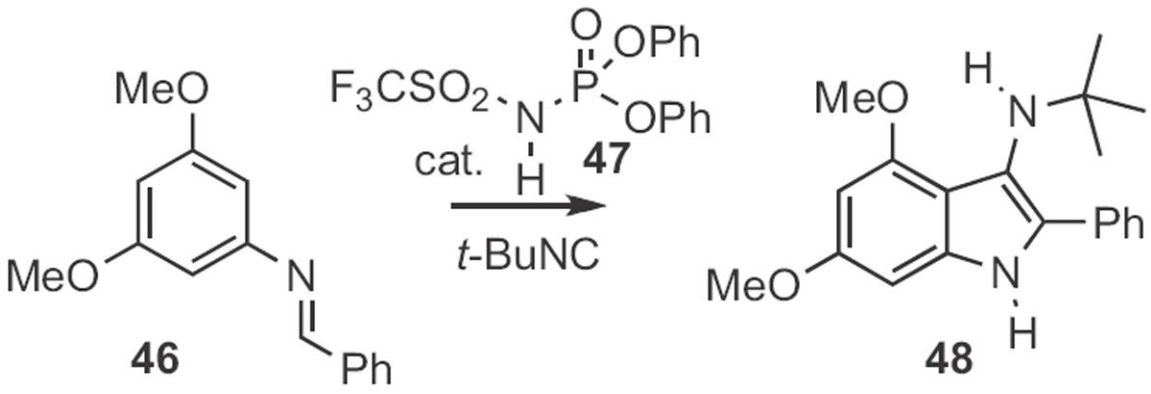
Scheme 14.



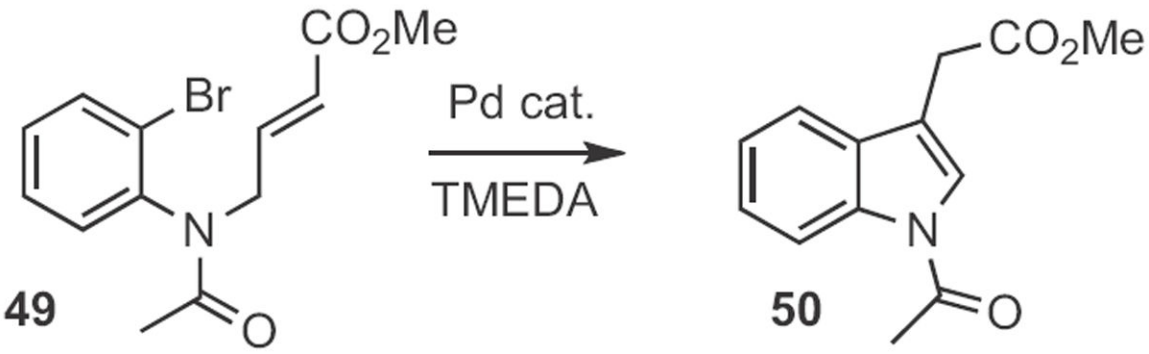
Scheme 15.



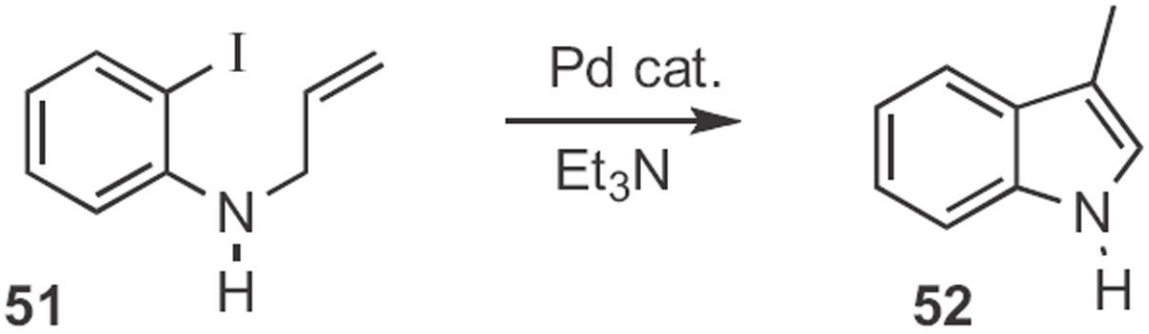
Scheme 16.



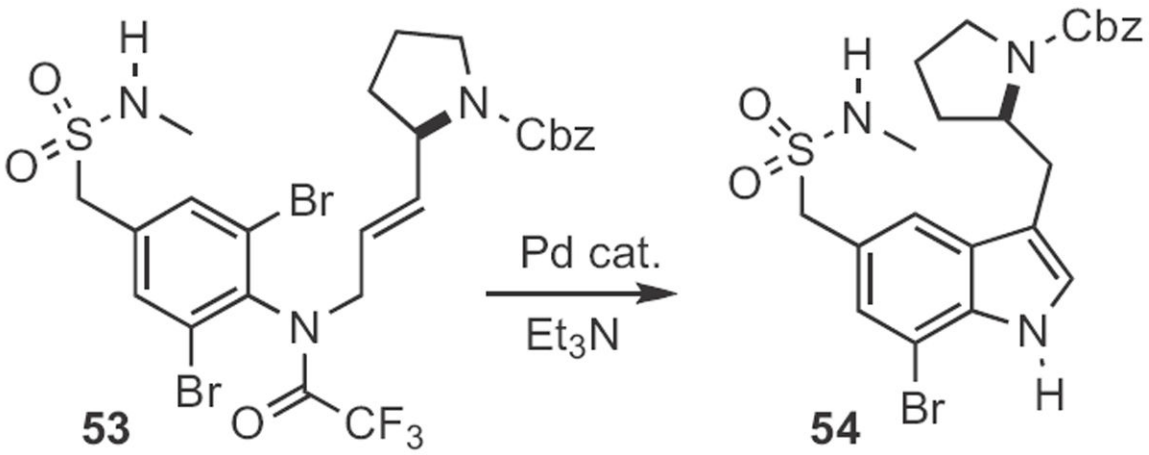
Scheme 17.



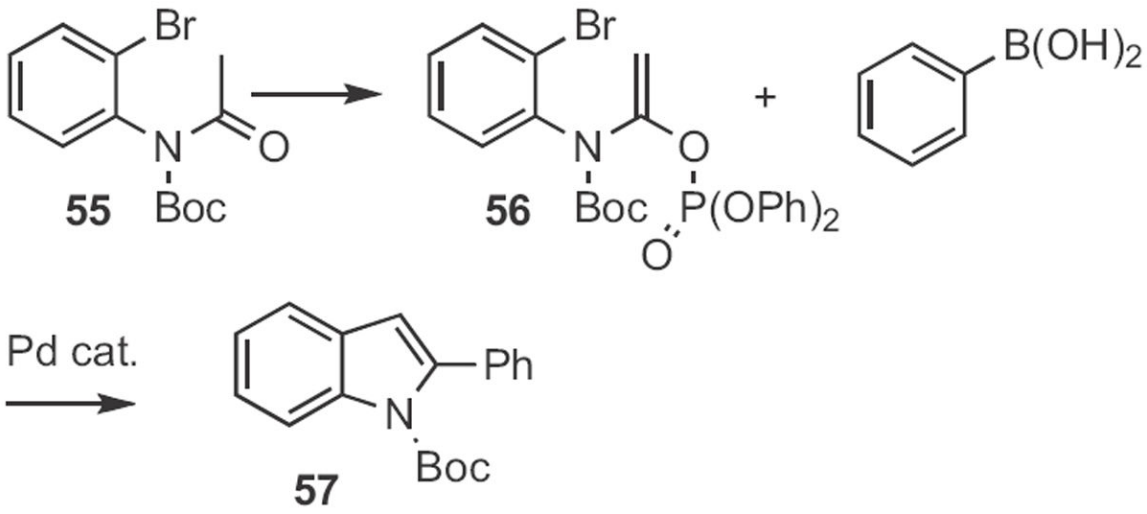
Scheme 18.



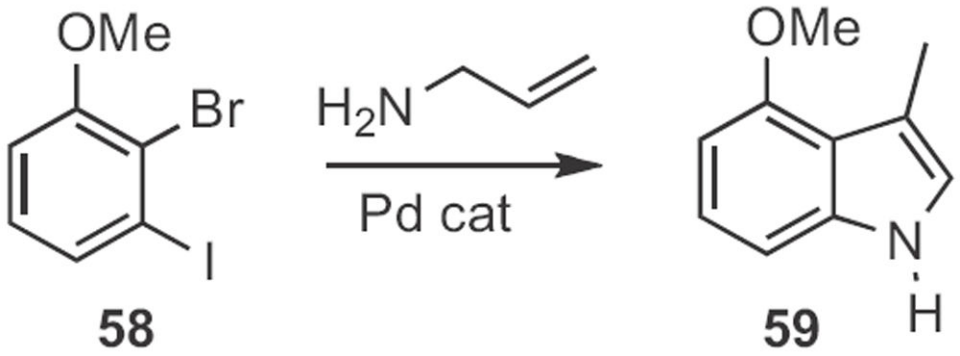
Scheme 19.



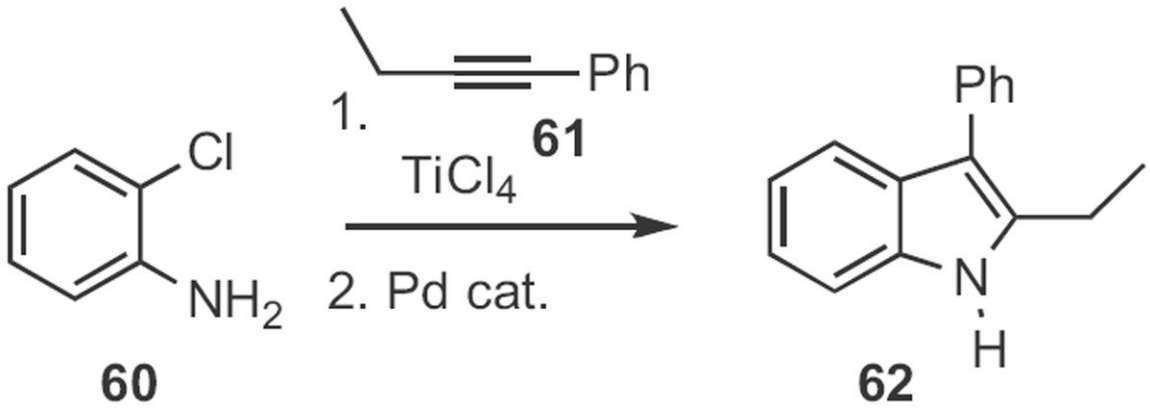
Scheme 20.



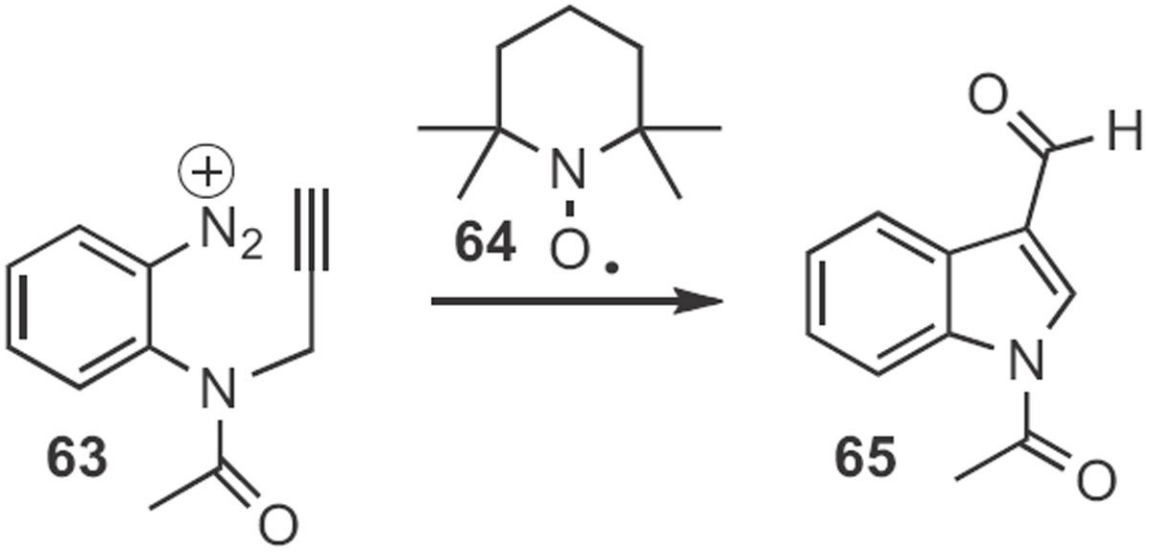
Scheme 21.



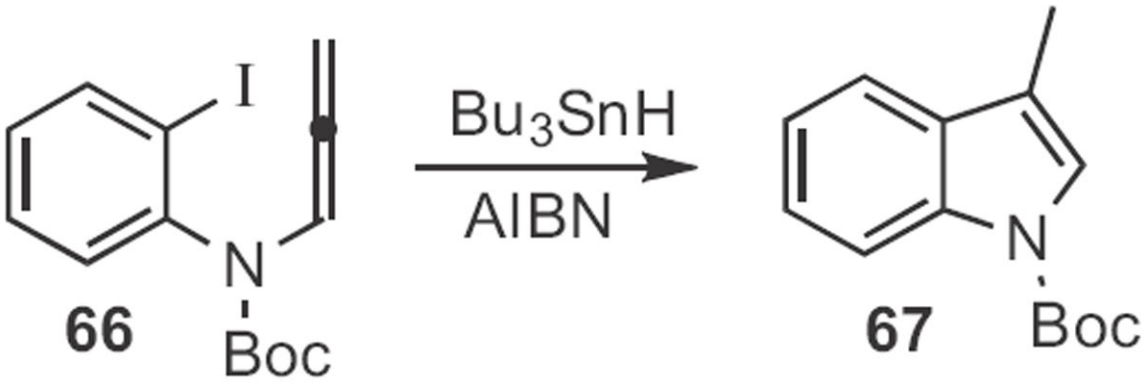
Scheme 22.



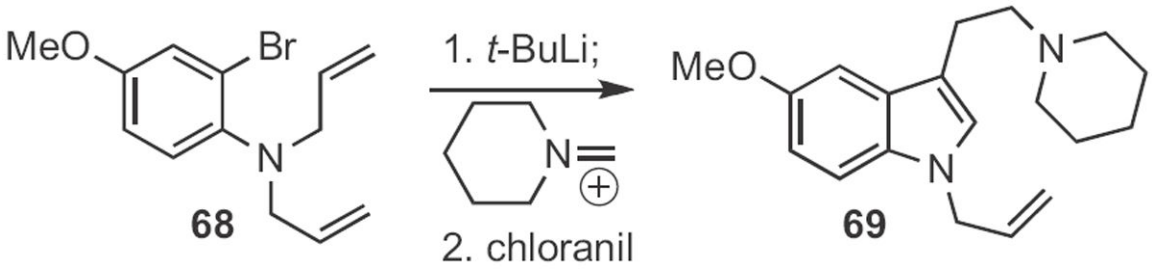
Scheme 23.



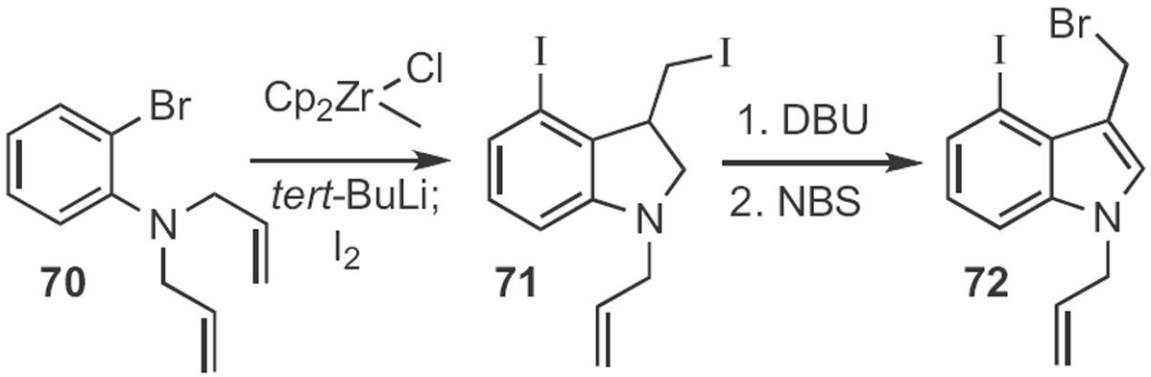
Scheme 24.



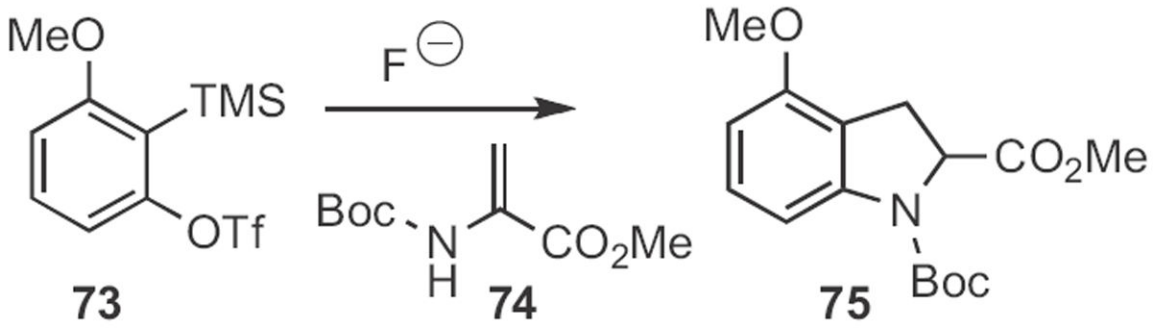
Scheme 25.



Scheme 26.

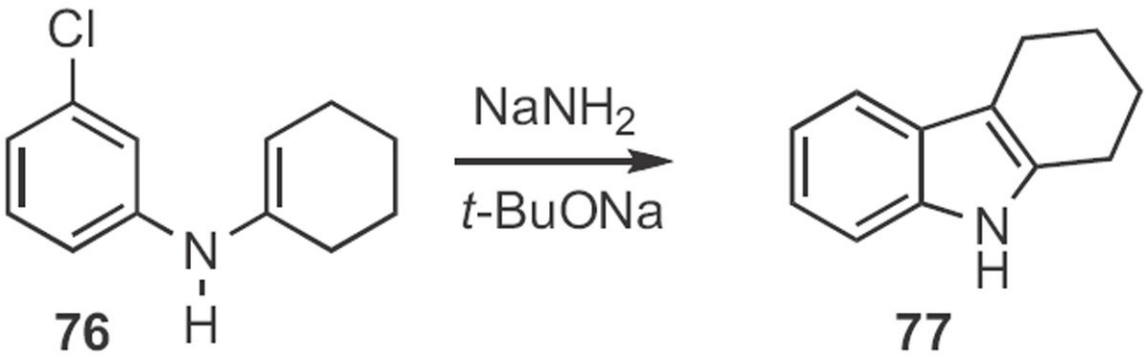


Scheme 27.

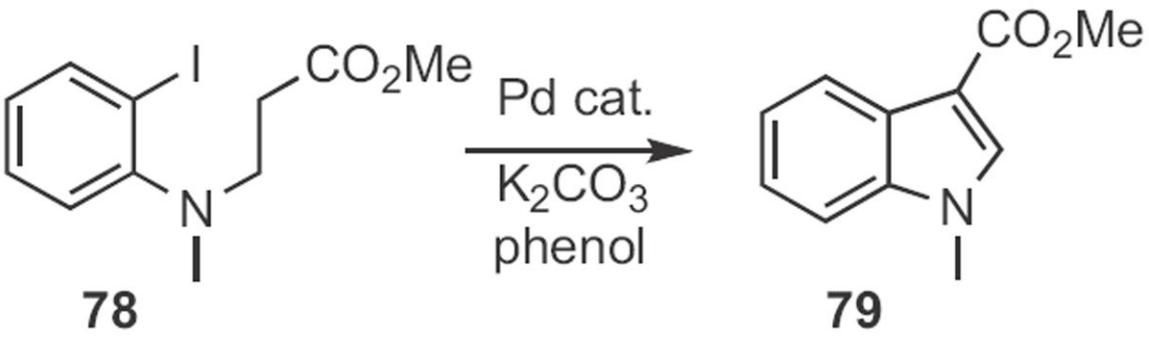


73 74 75

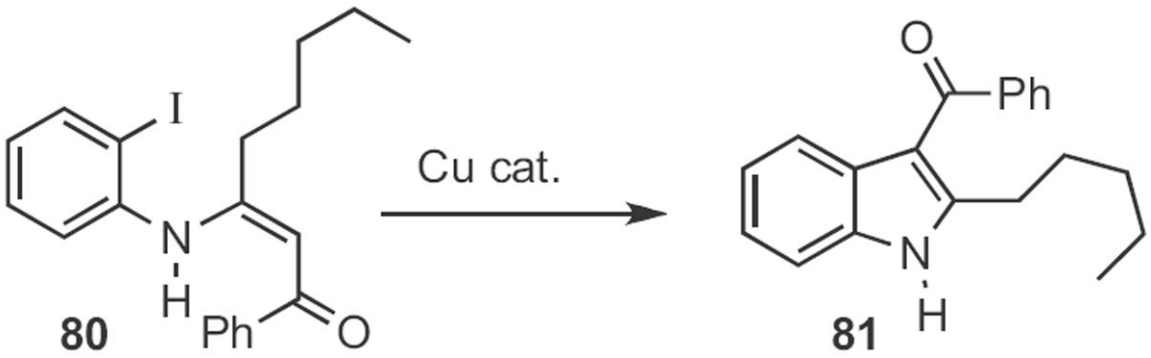
Scheme 28.



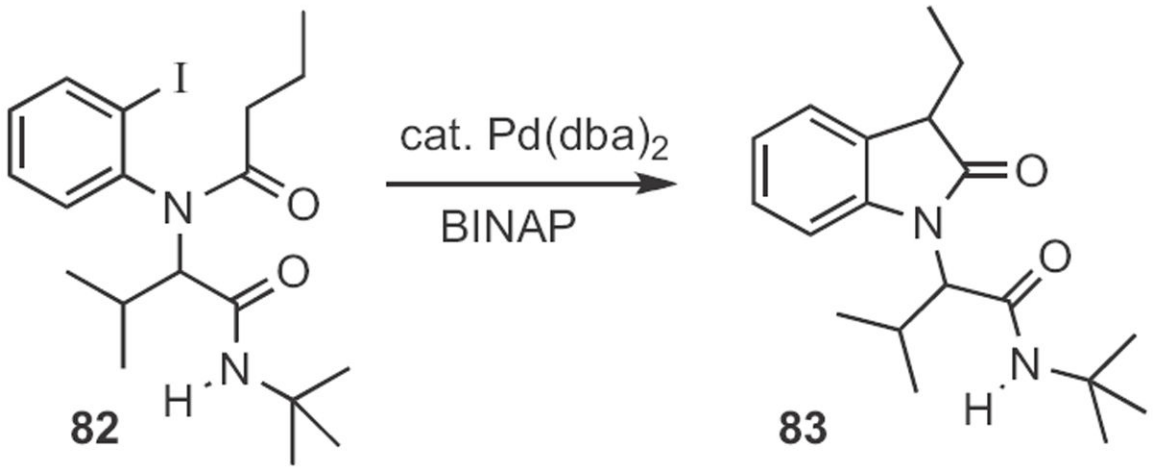
Scheme 29.



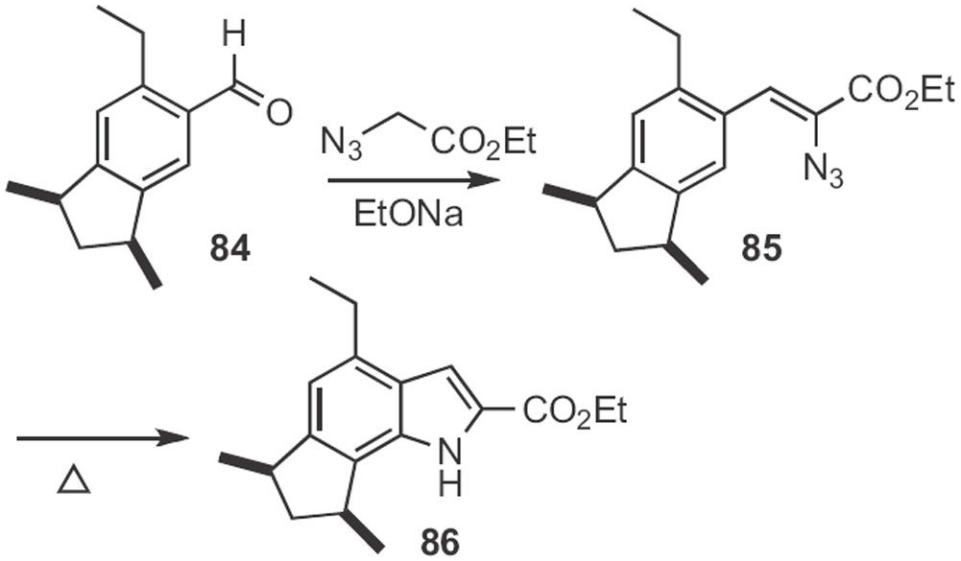
Scheme 30.



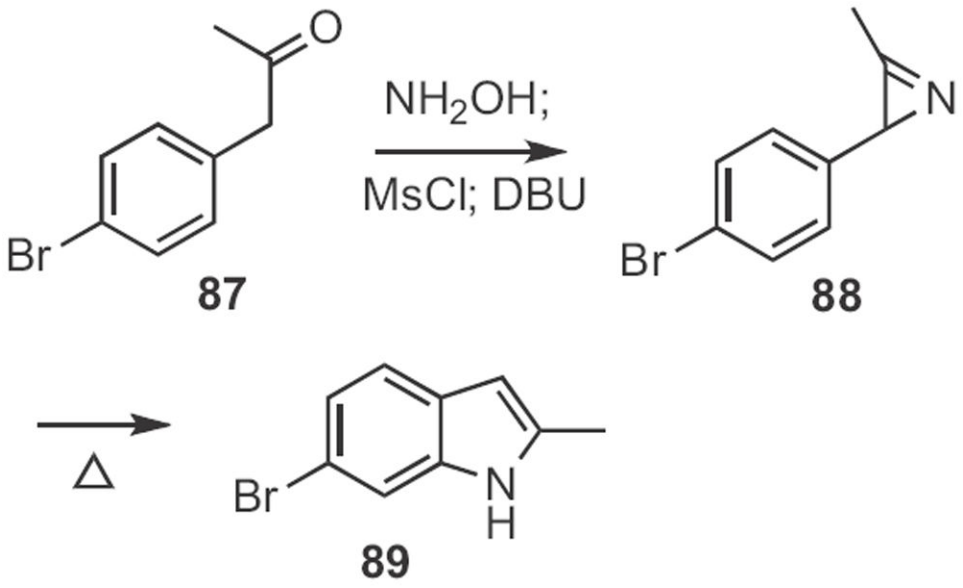
Scheme 31.



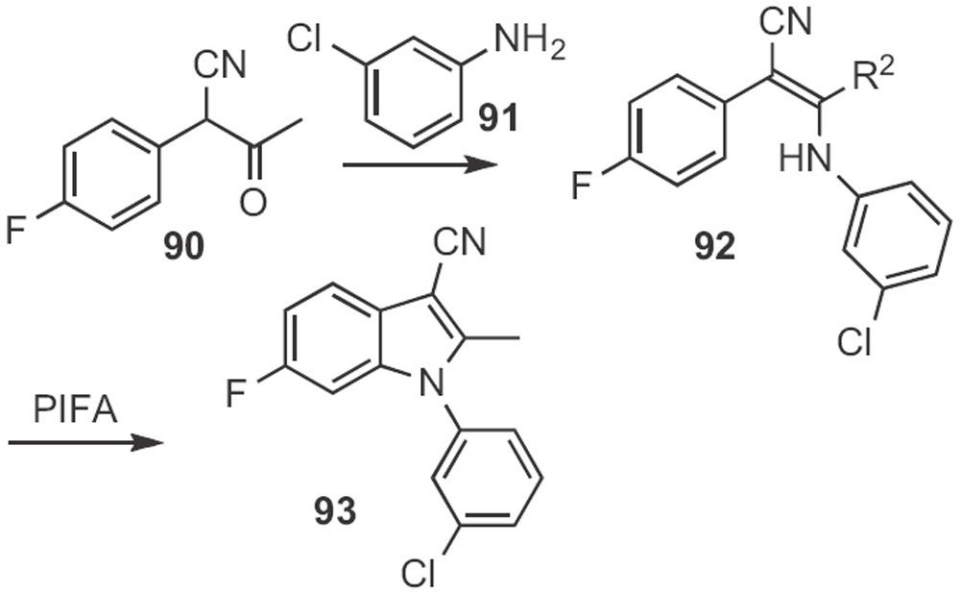
Scheme 32.



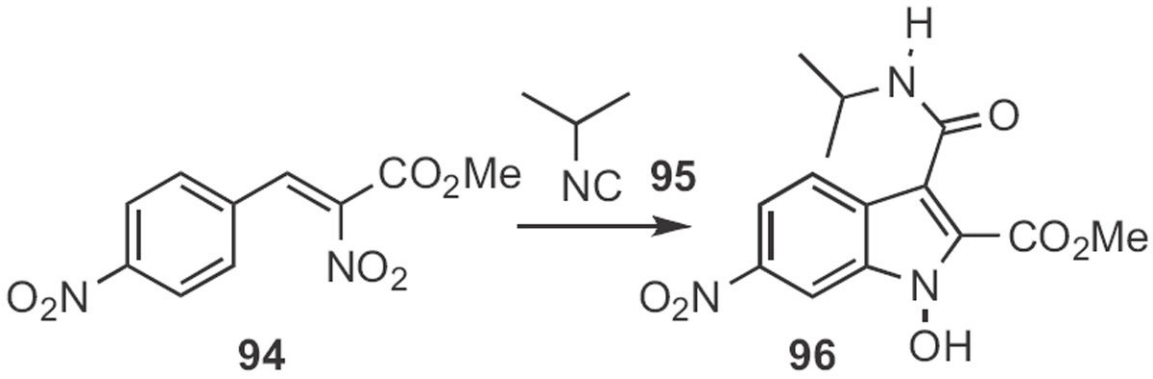
Scheme 33.



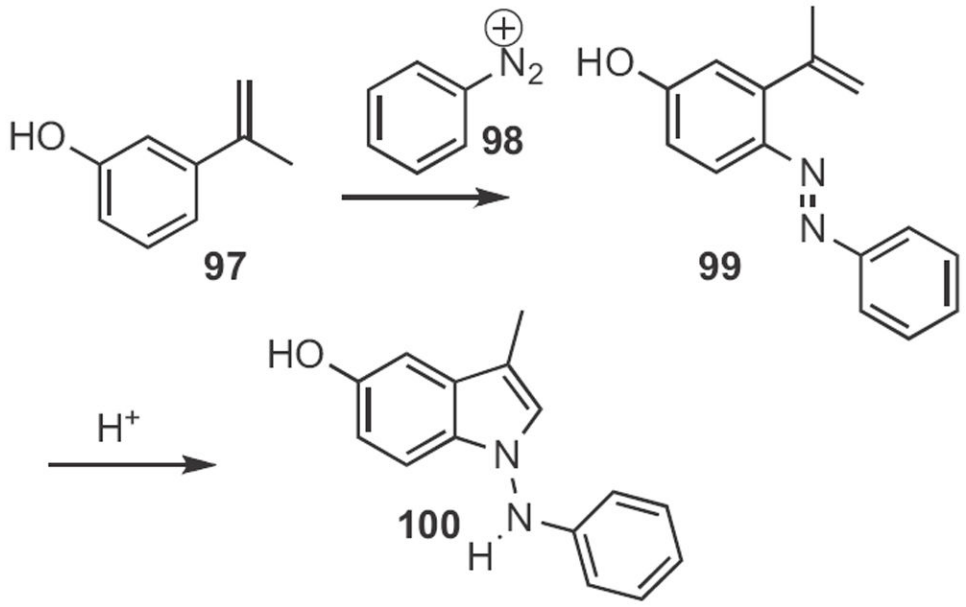
Scheme 34.



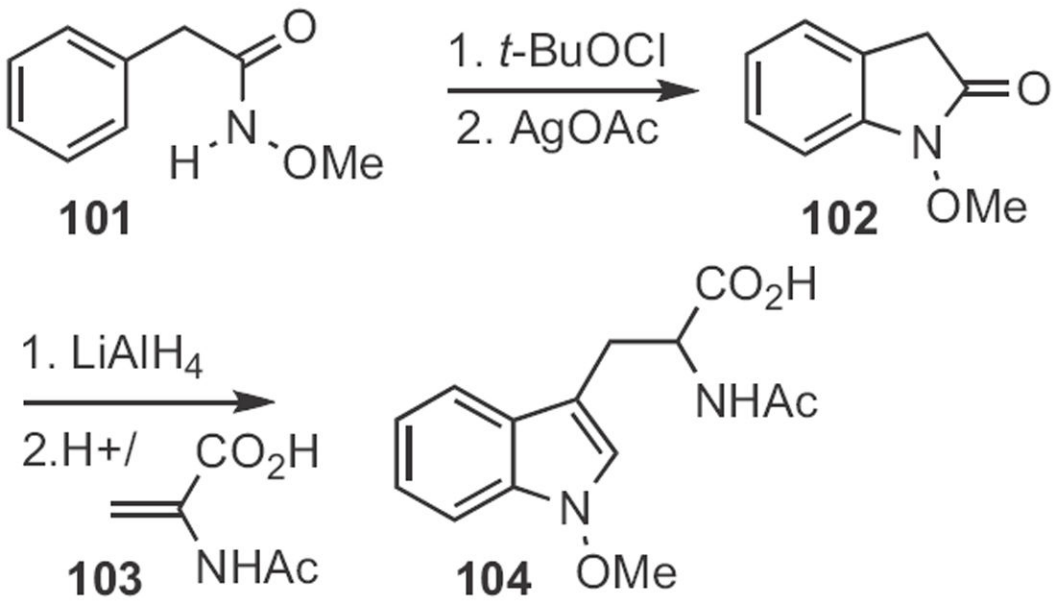
Scheme 35.



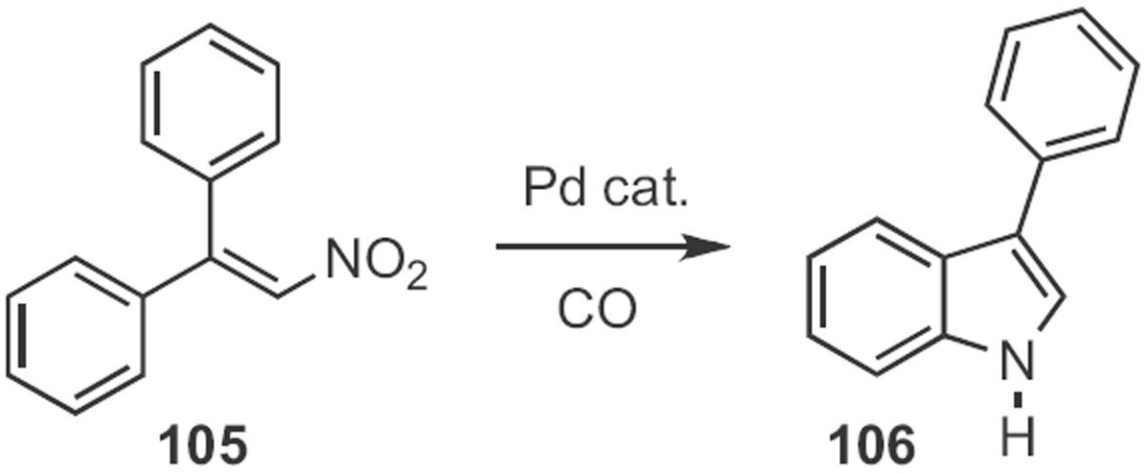
Scheme 36.



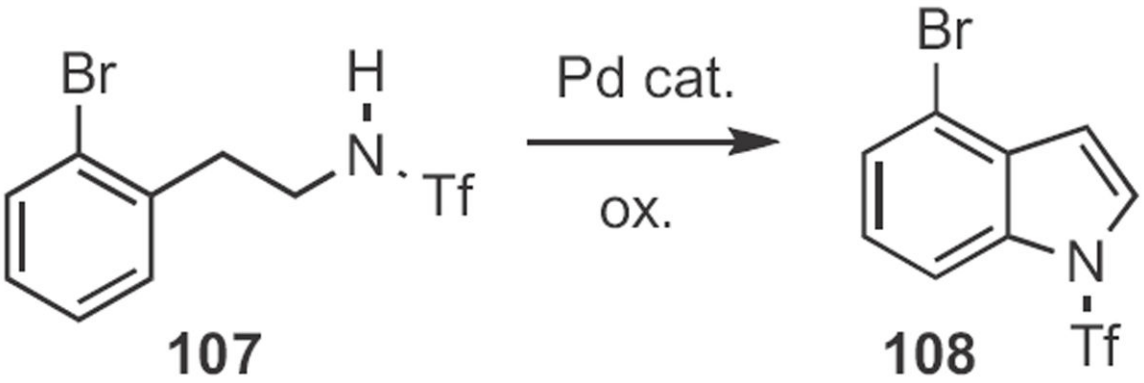
Scheme 37.



Scheme 38.

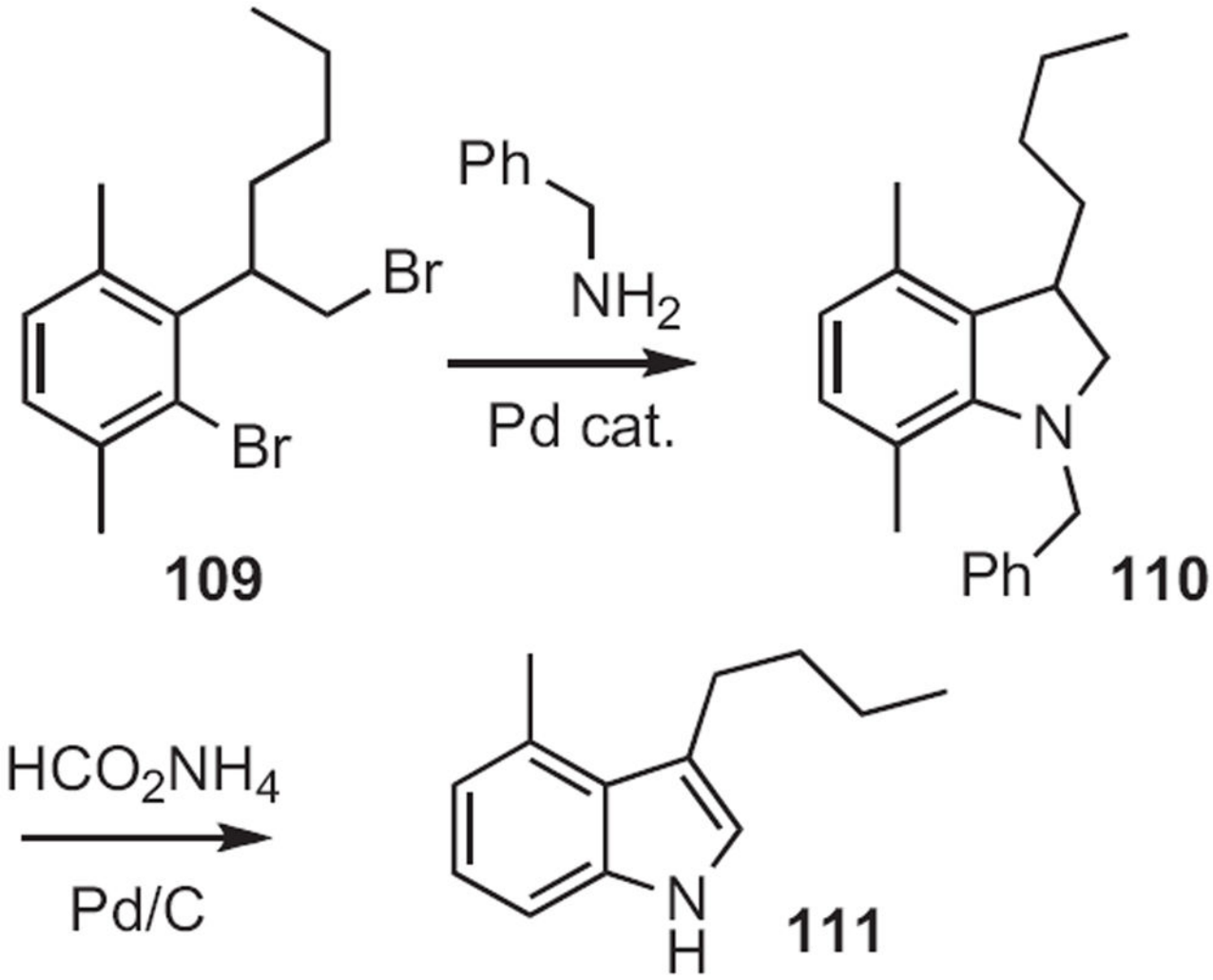


Scheme 39.

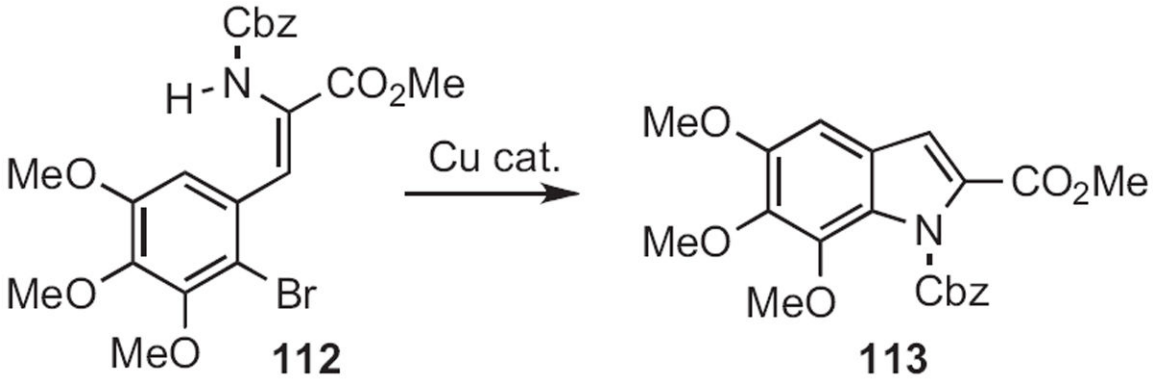


107 108

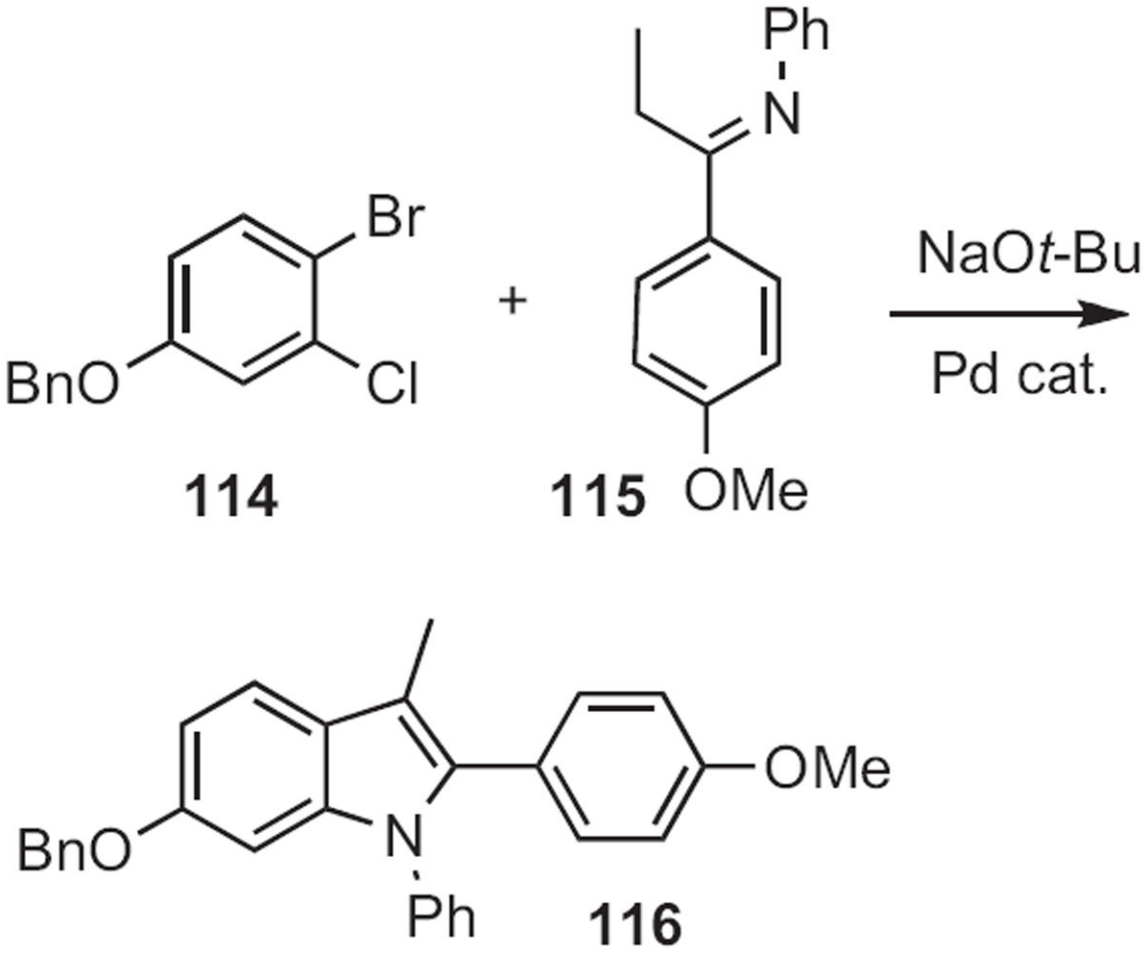
Scheme 40.



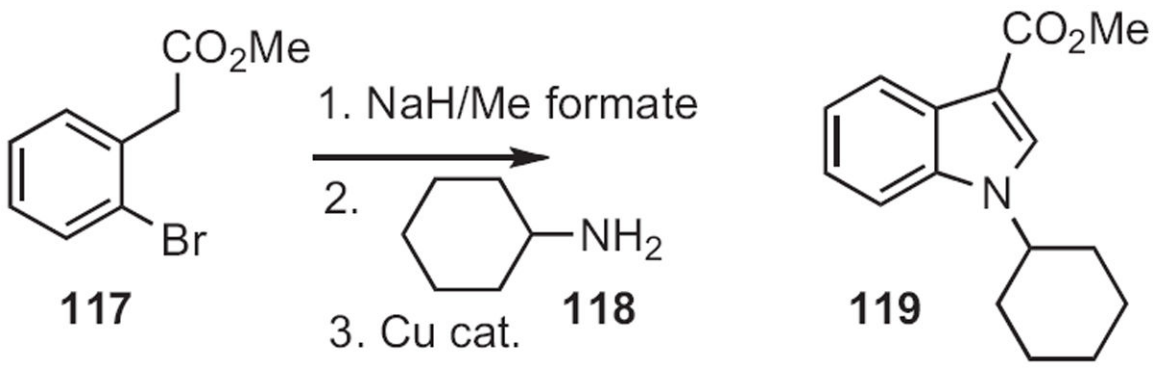
Scheme 41.



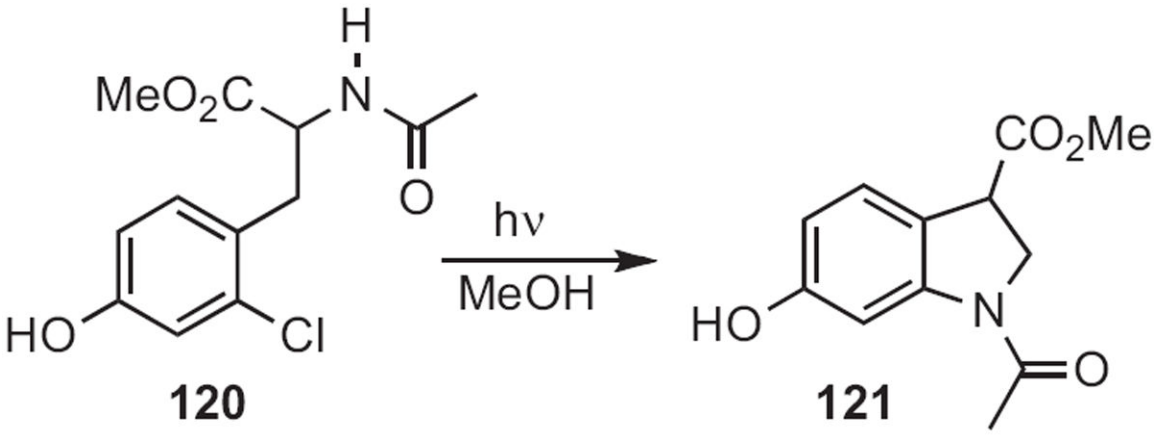
Scheme 42.



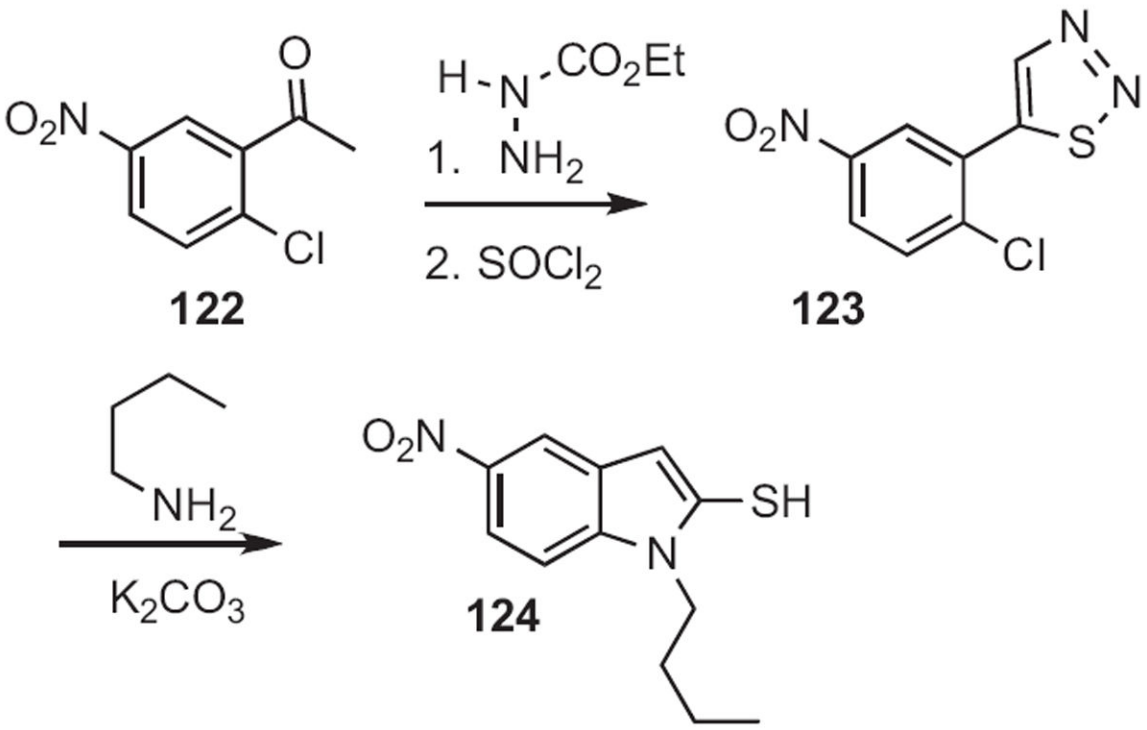
Scheme 43.



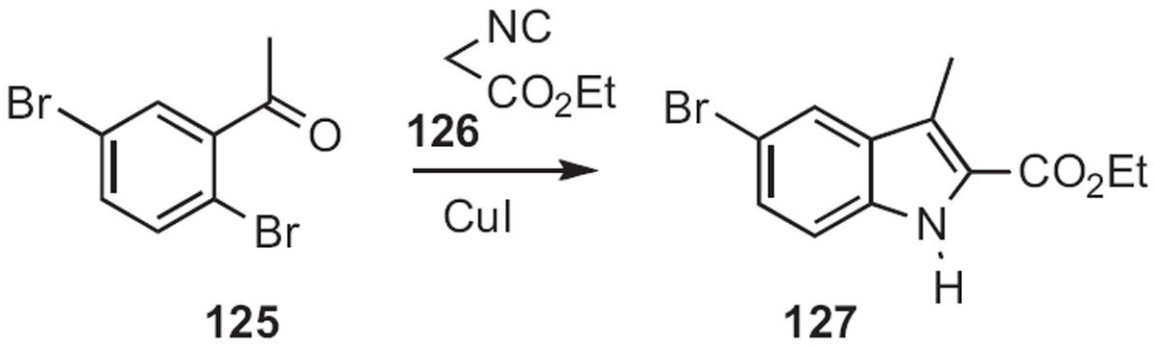
Scheme 44.



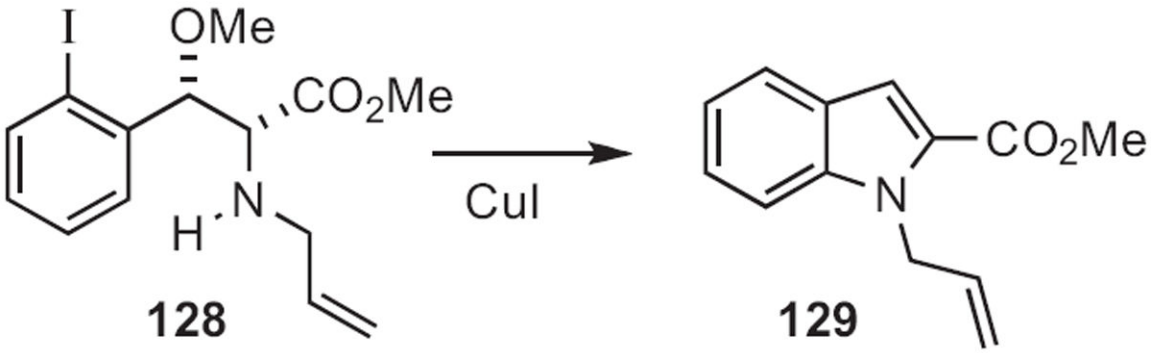
Scheme 45.



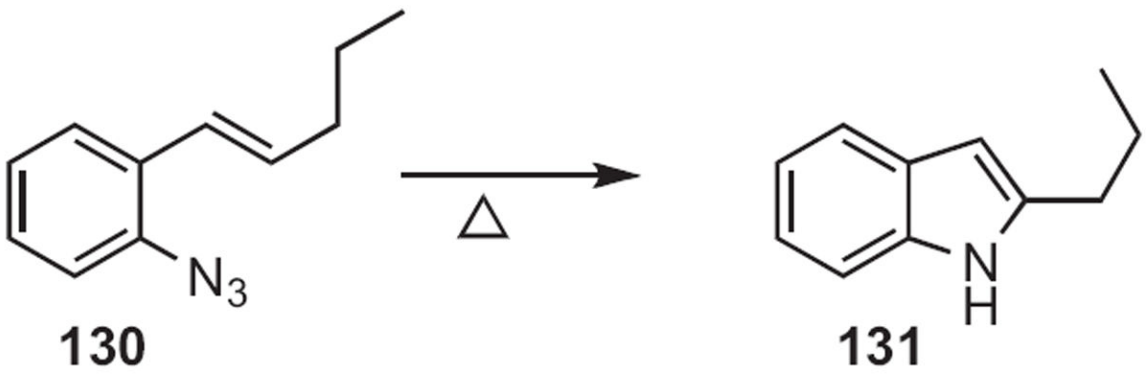
Scheme 46.



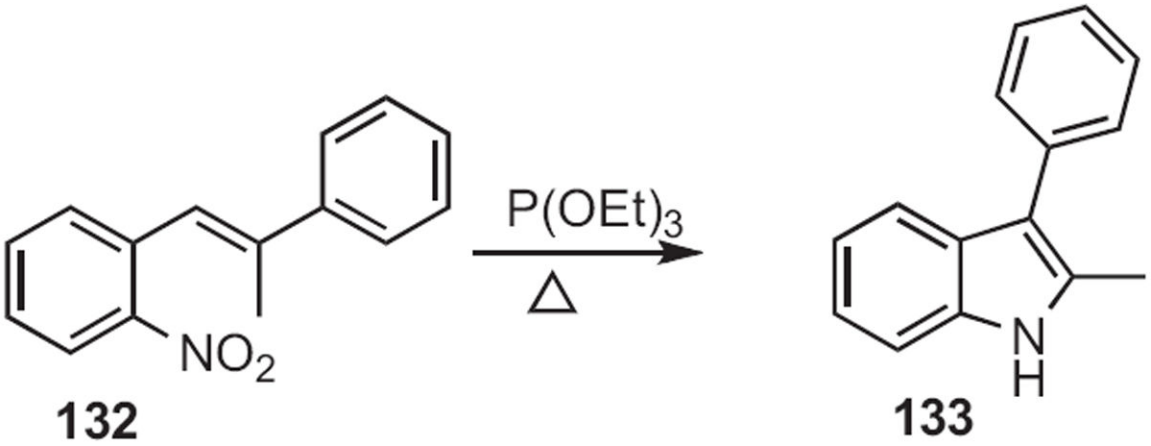
Scheme 47.



Scheme 48.

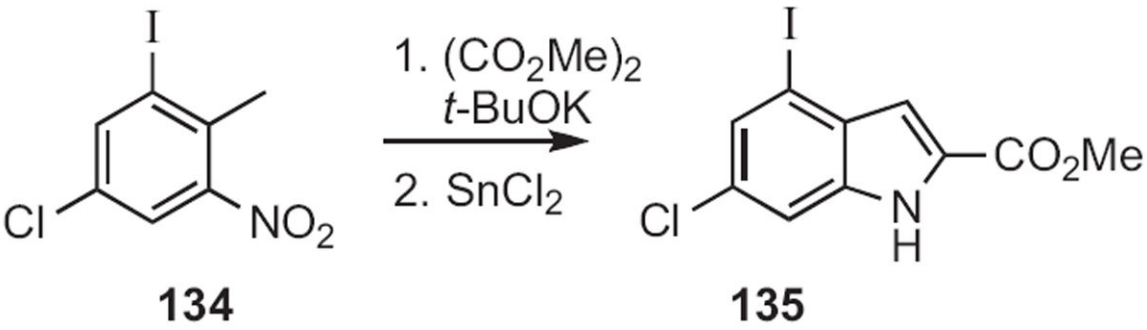


Scheme 49.



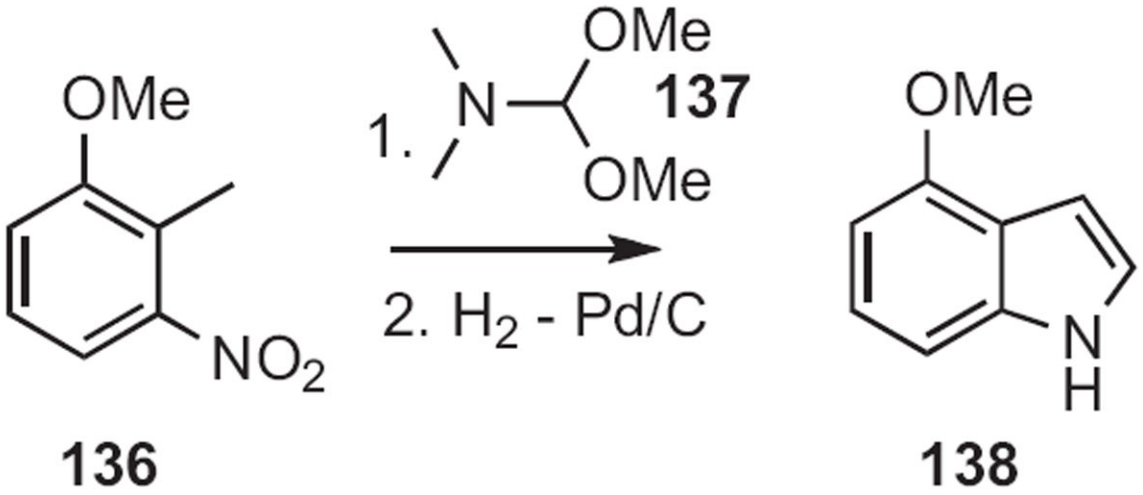
132 133

Scheme 50.



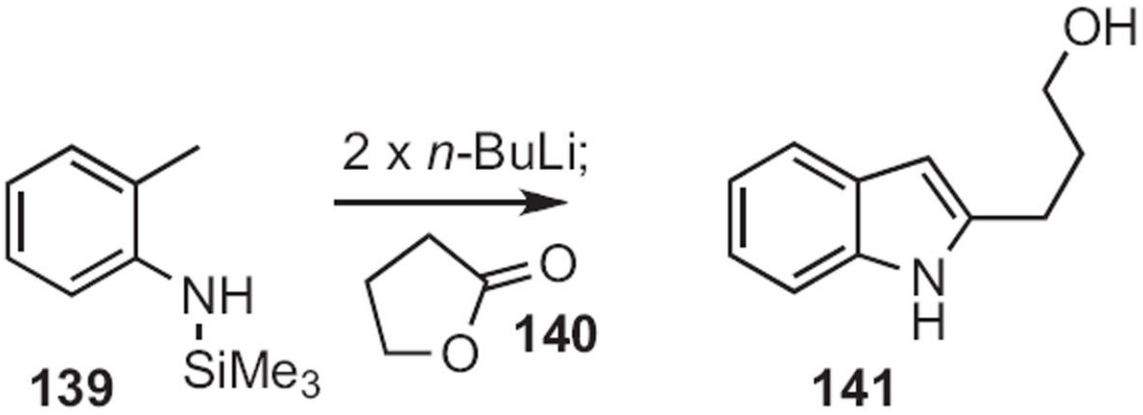
134 135

Scheme 51.

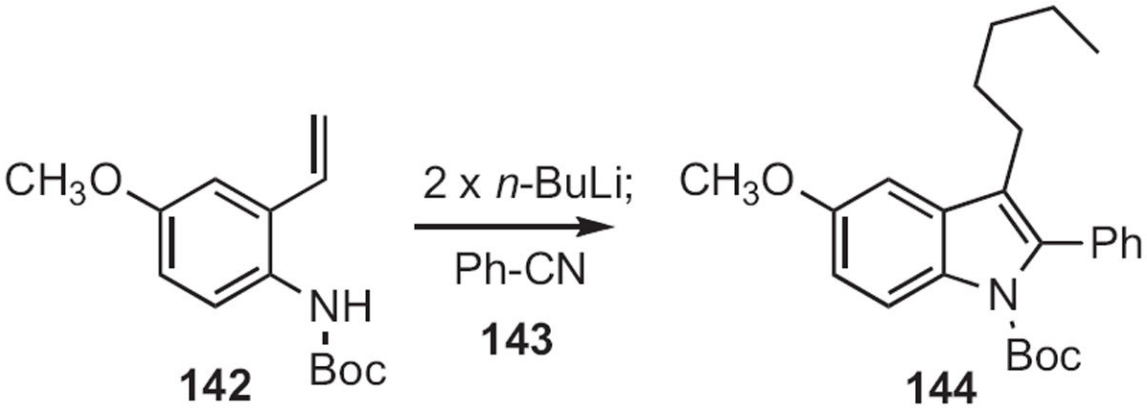


136 138

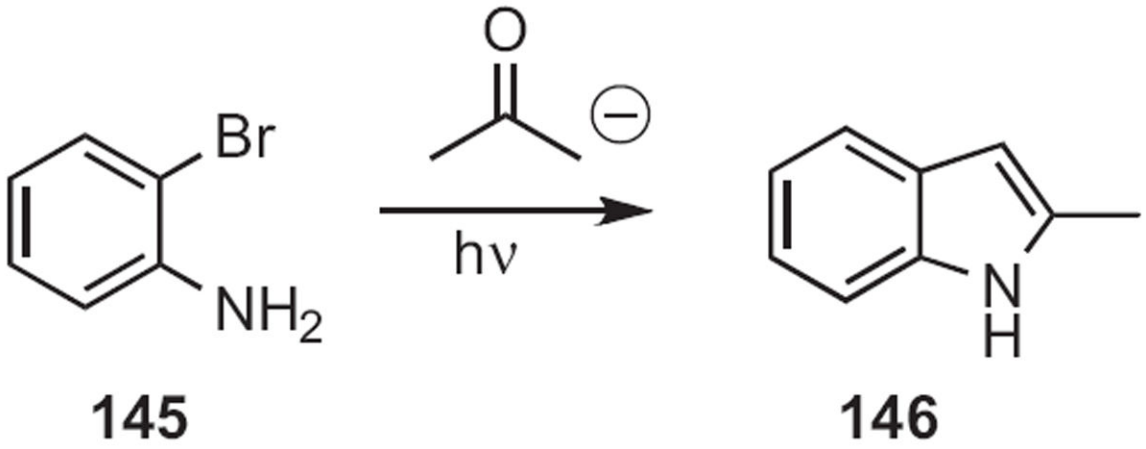
Scheme 52.



Scheme 53.

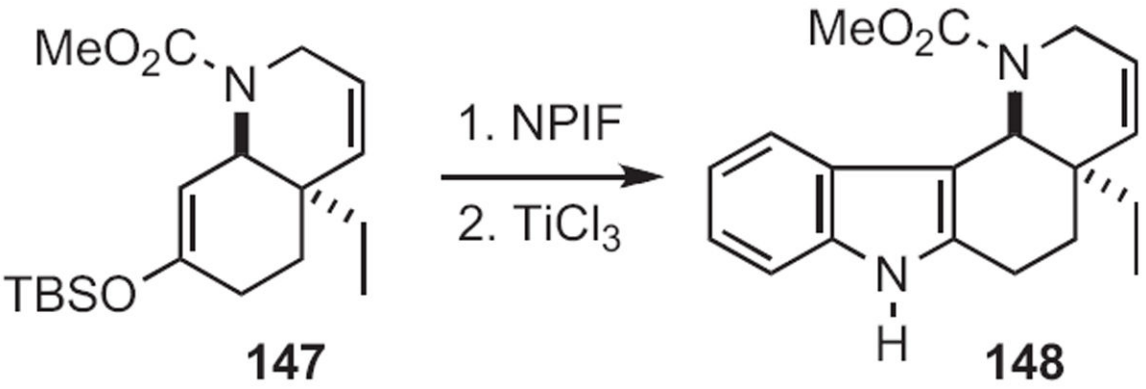


Scheme 54.

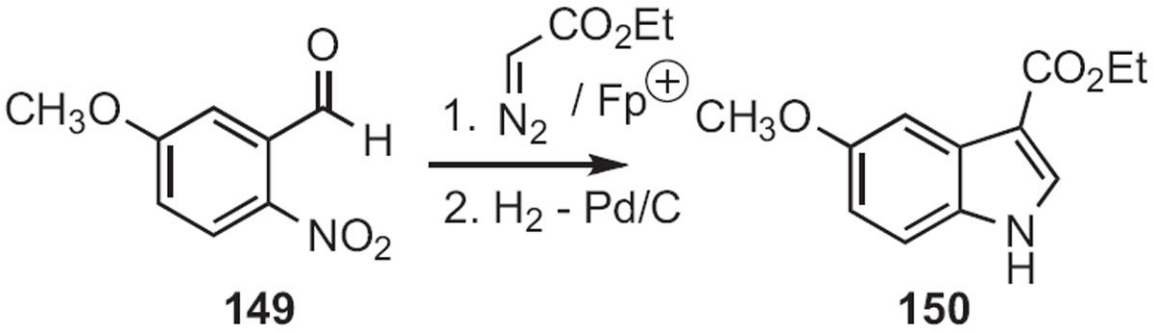


145 146

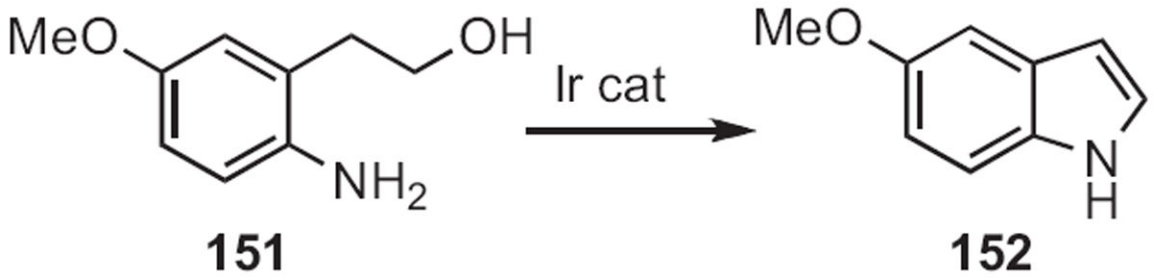
Scheme 55.



Scheme 56.

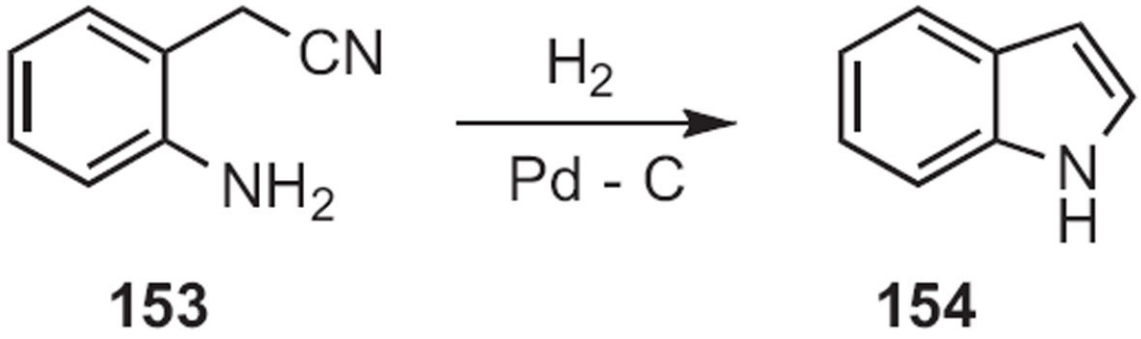


Scheme 57.



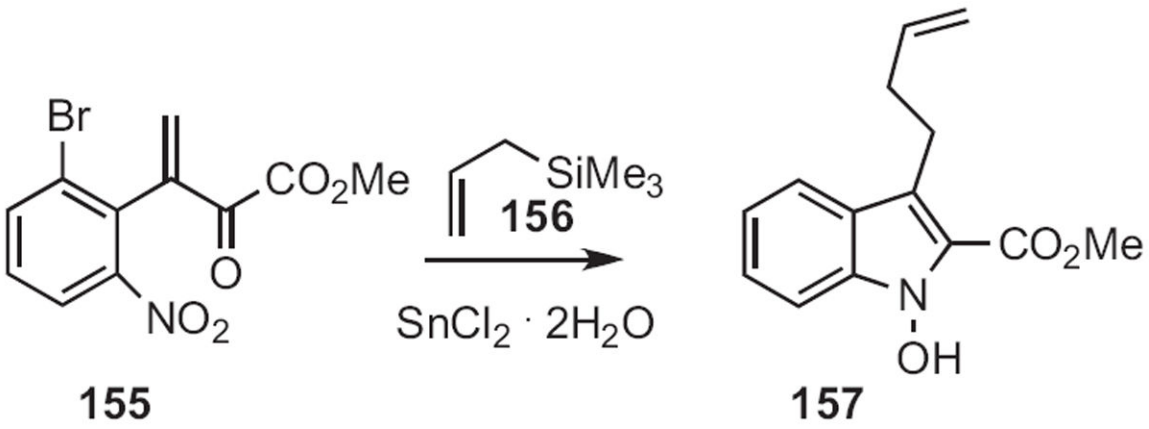
151 152

Scheme 58.



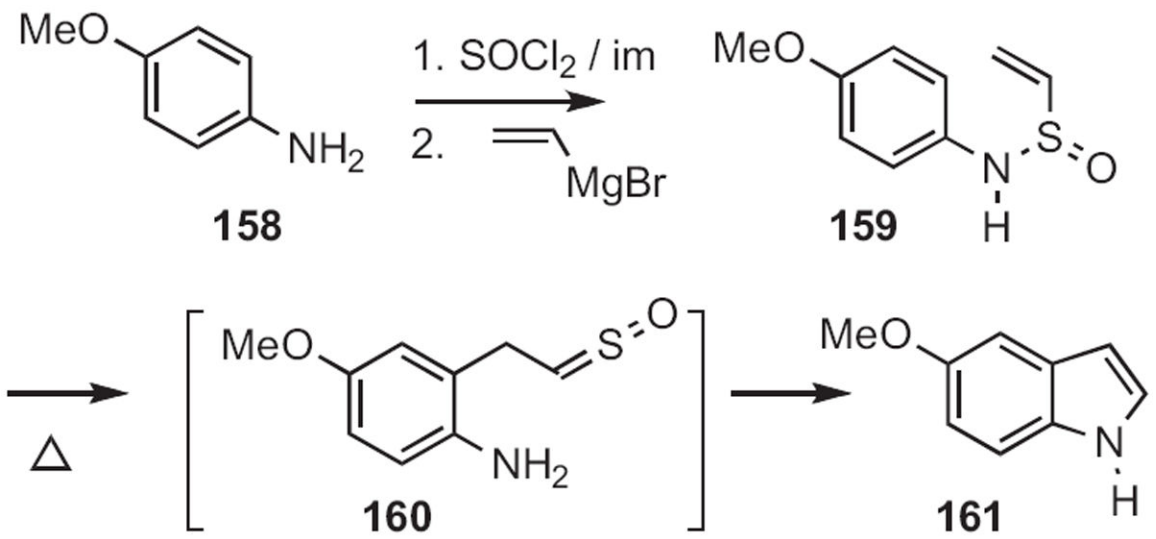
153 154

Scheme 59.

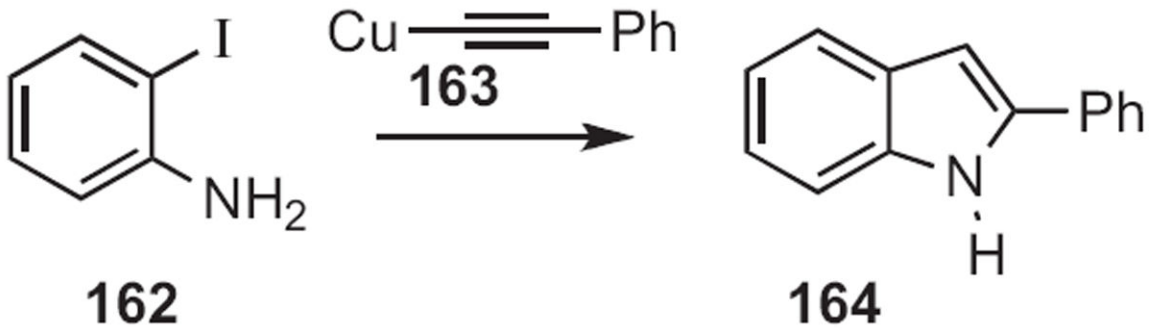


155 157

Scheme 60.

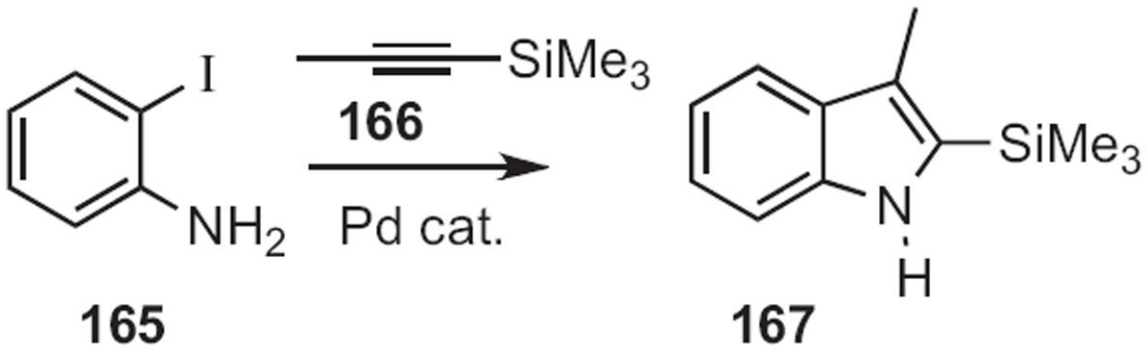


Scheme 61.



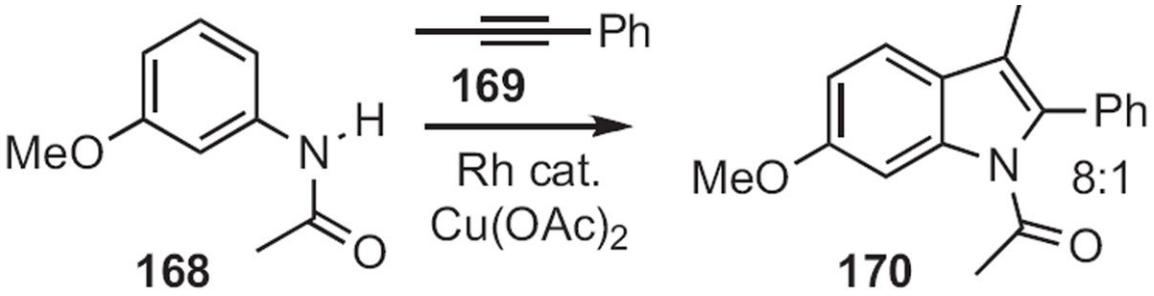
162 164

Scheme 62.

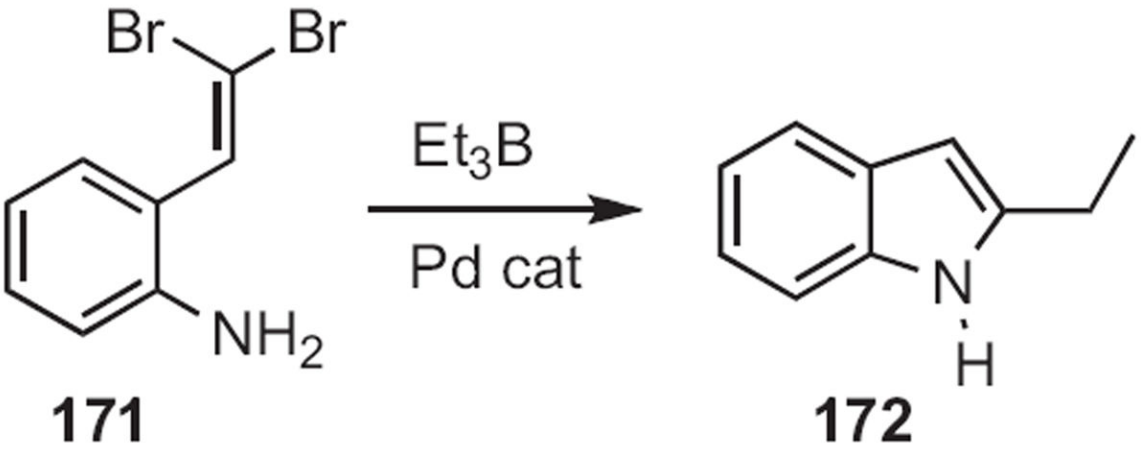


165 167

Scheme 63.

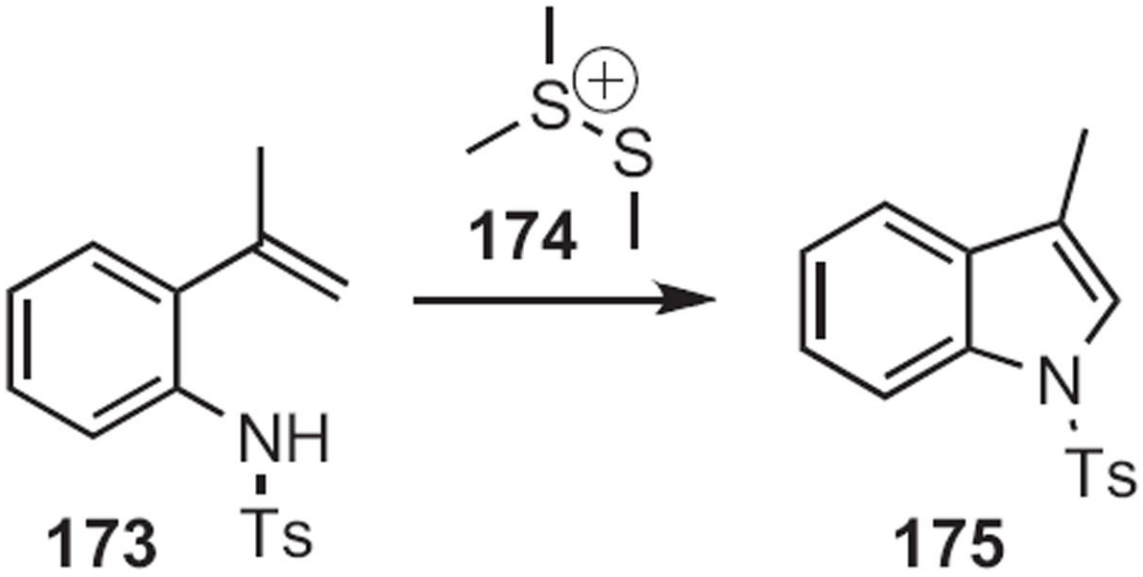


Scheme 64.

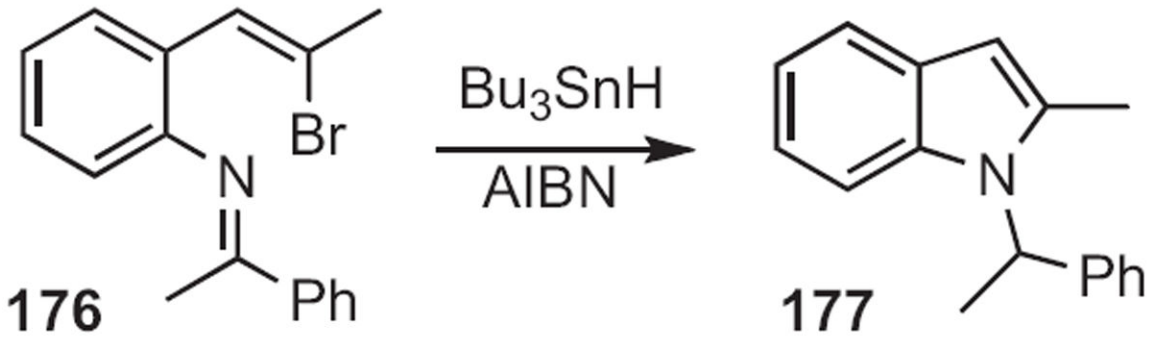


171 172

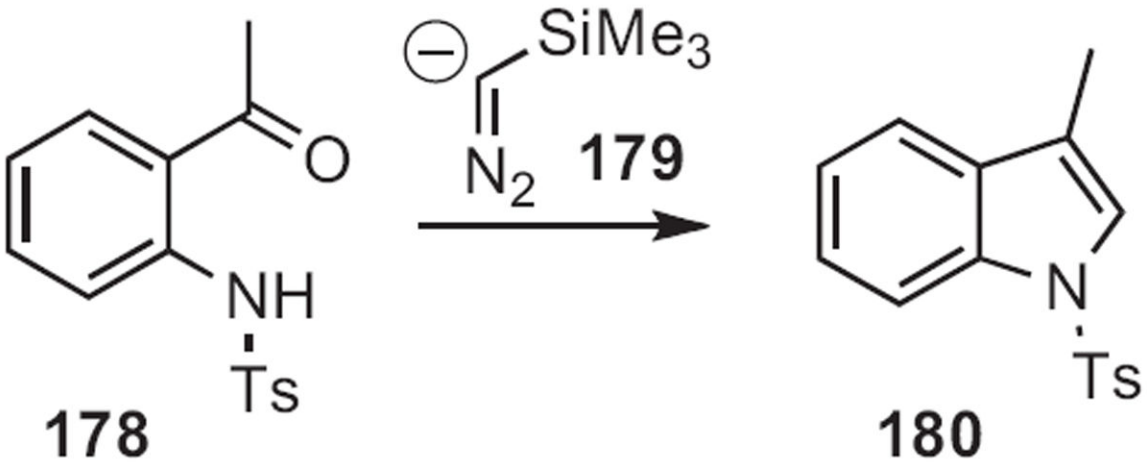
Scheme 65.



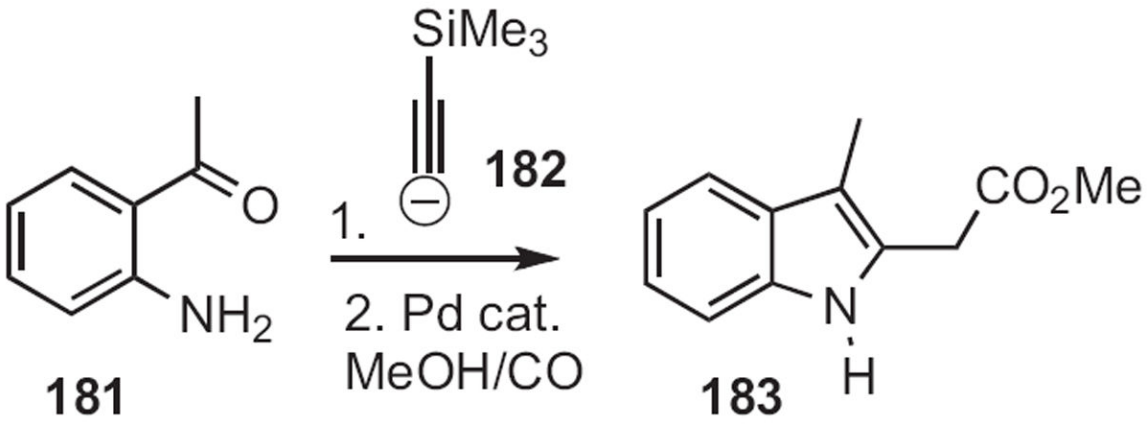
Scheme 66.



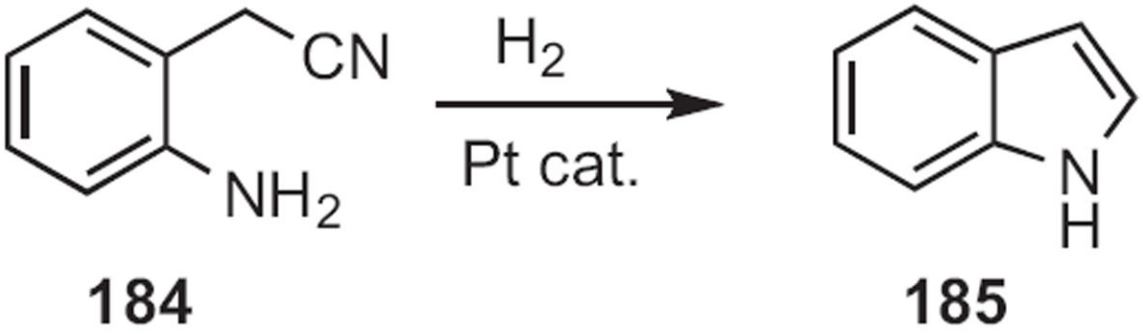
Scheme 67.



Scheme 68.

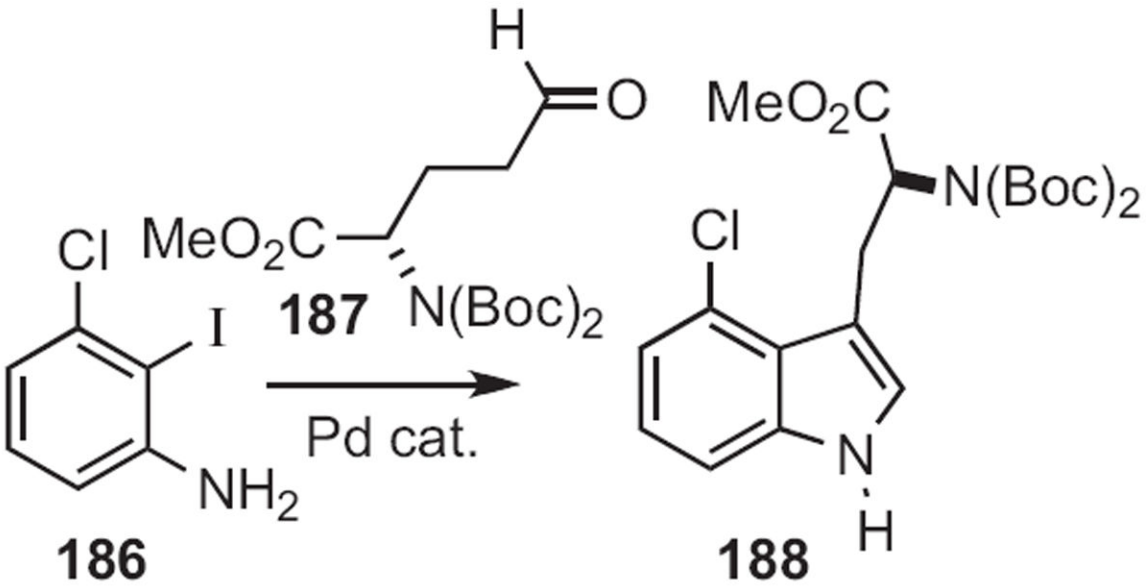


Scheme 69.

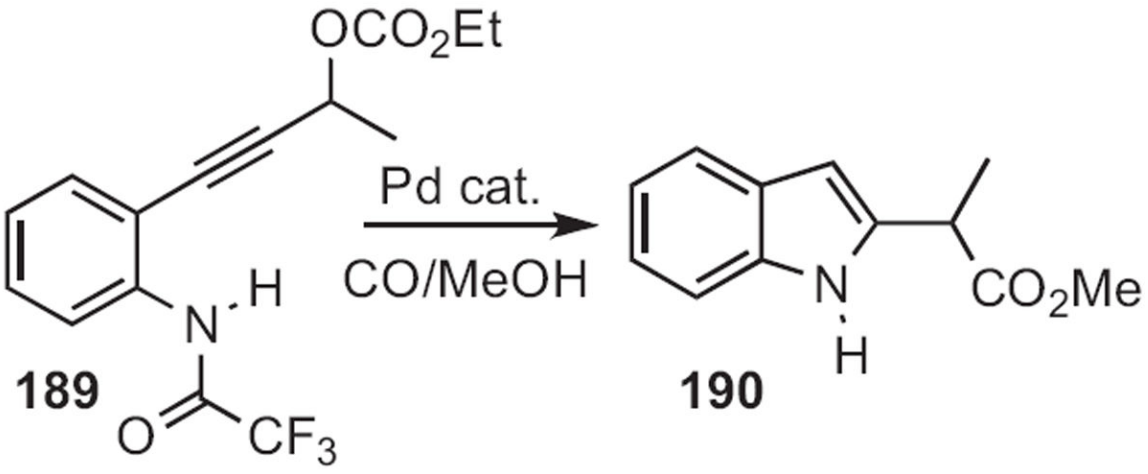


184 185

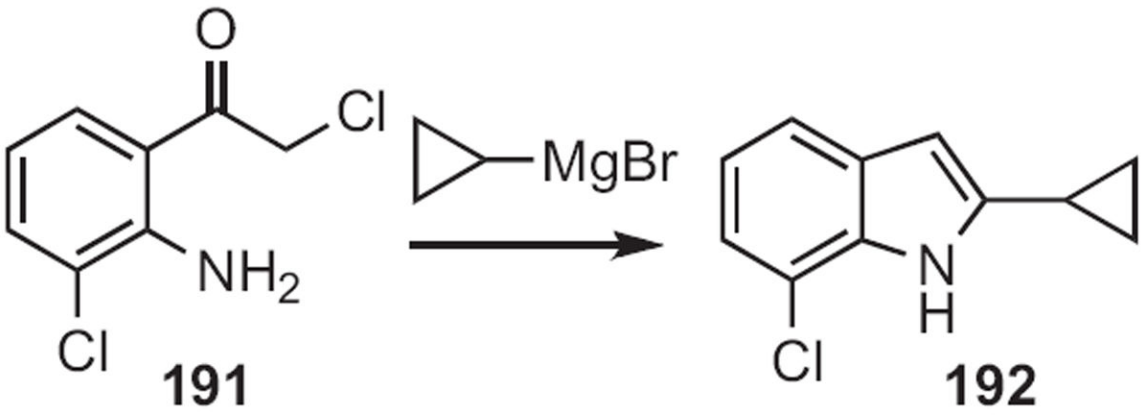
Scheme 70.



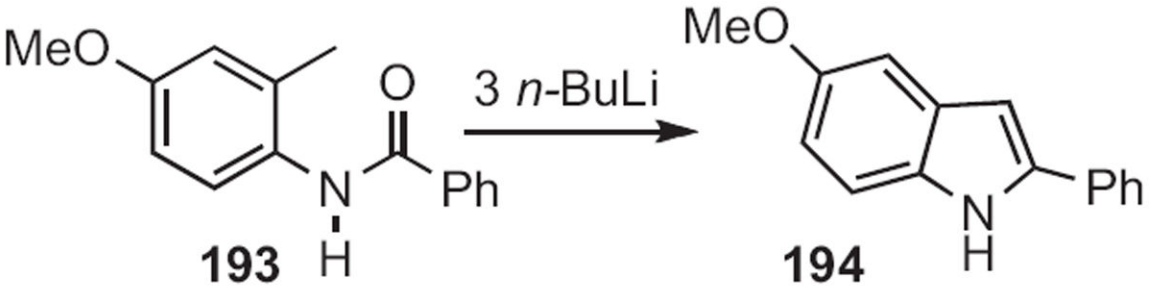
Scheme 71.



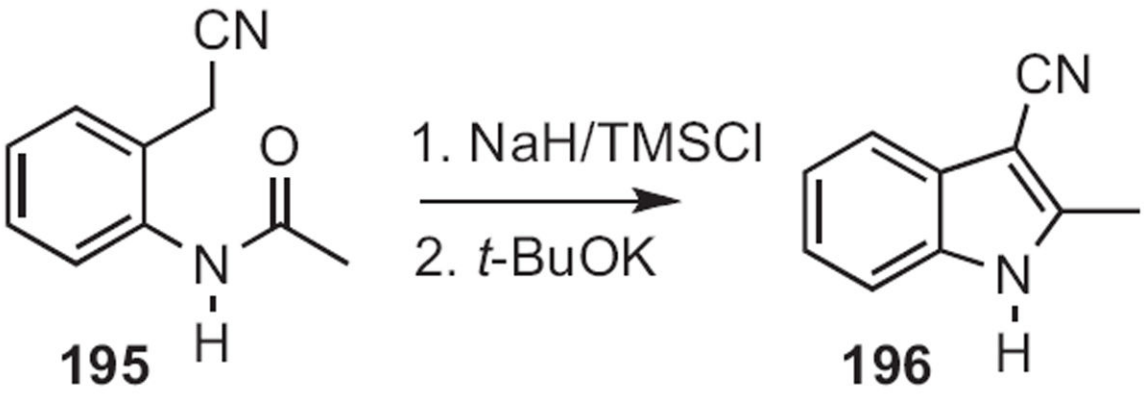
Scheme 72.



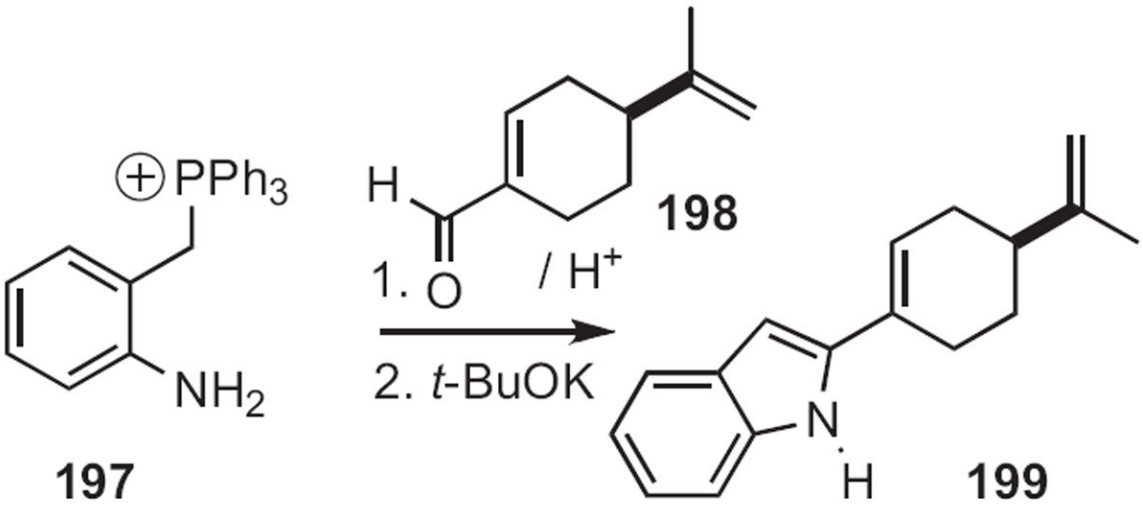
Scheme 73.



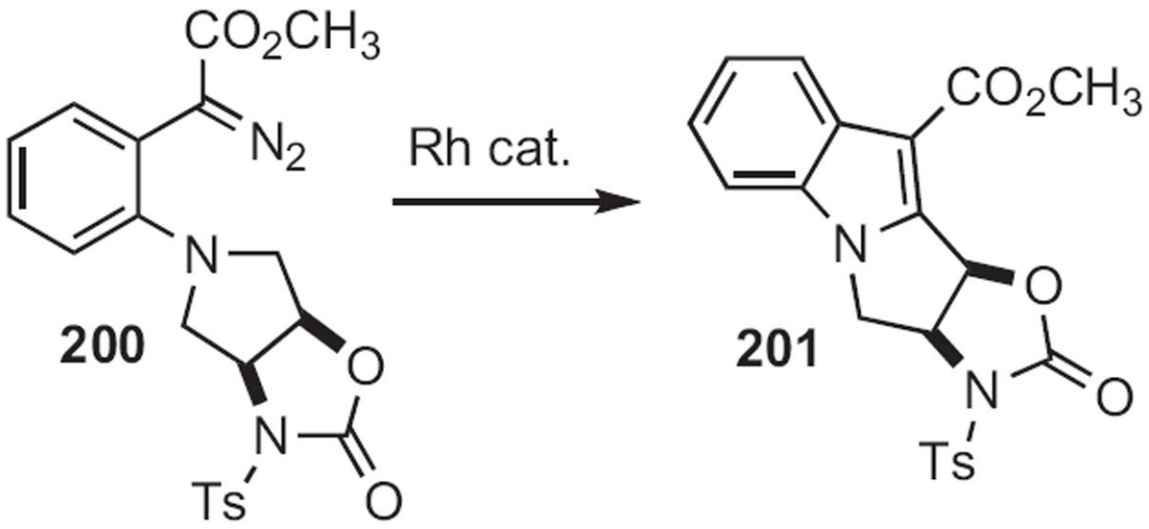
Scheme 74.



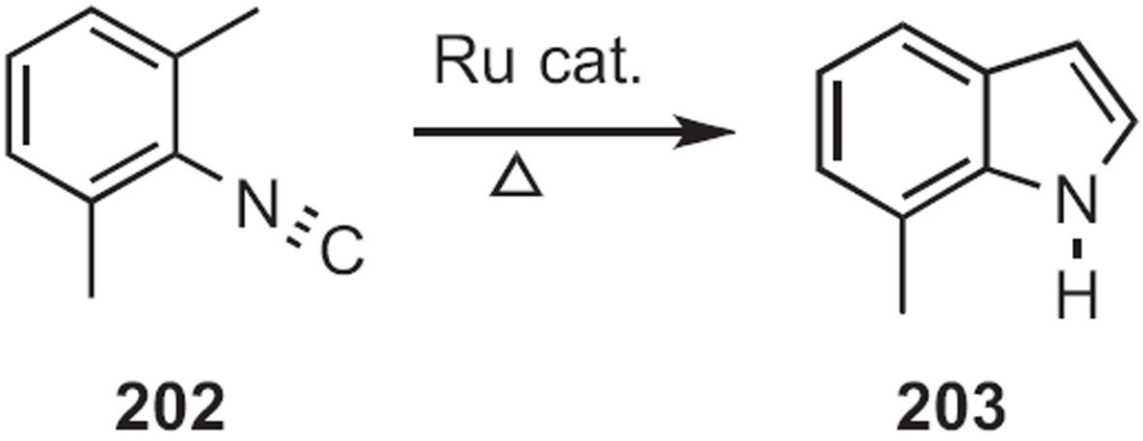
Scheme 75.



Scheme 76.

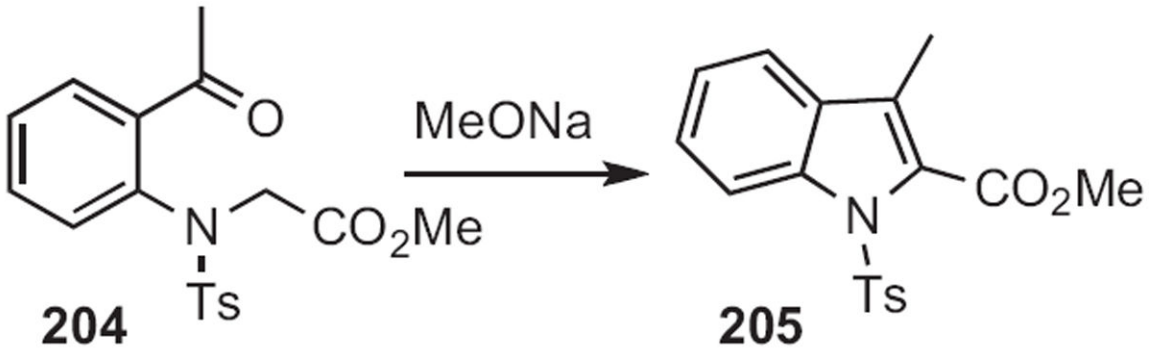


Scheme 77.

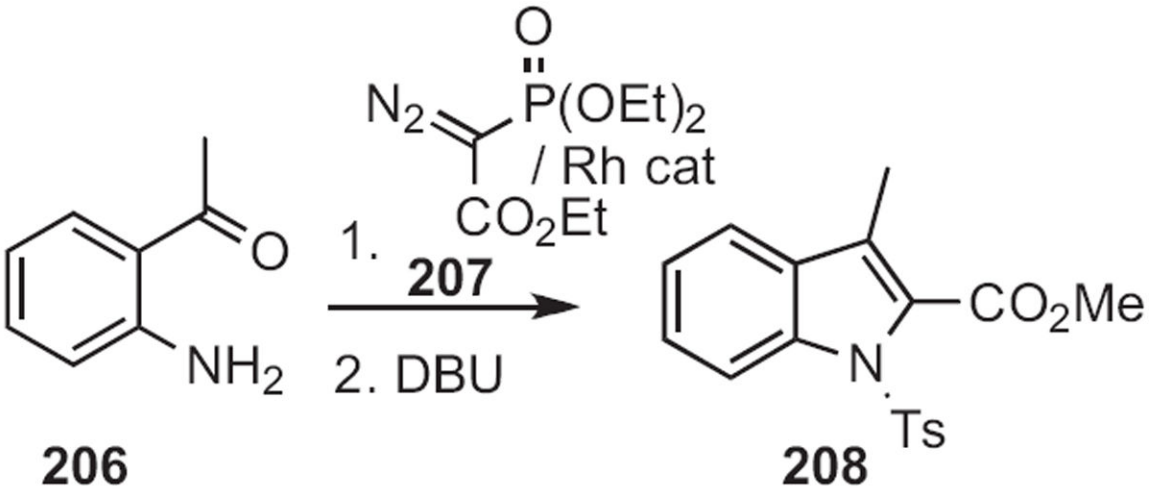


202 **203**

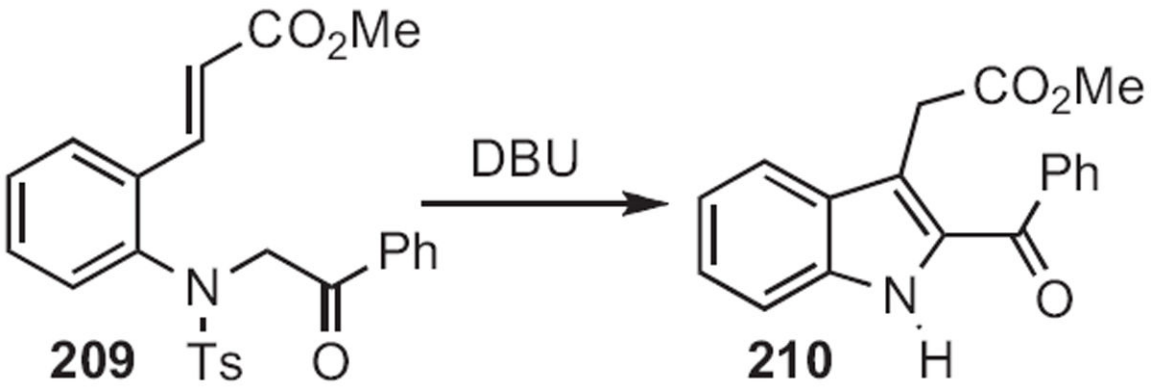
Scheme 78.



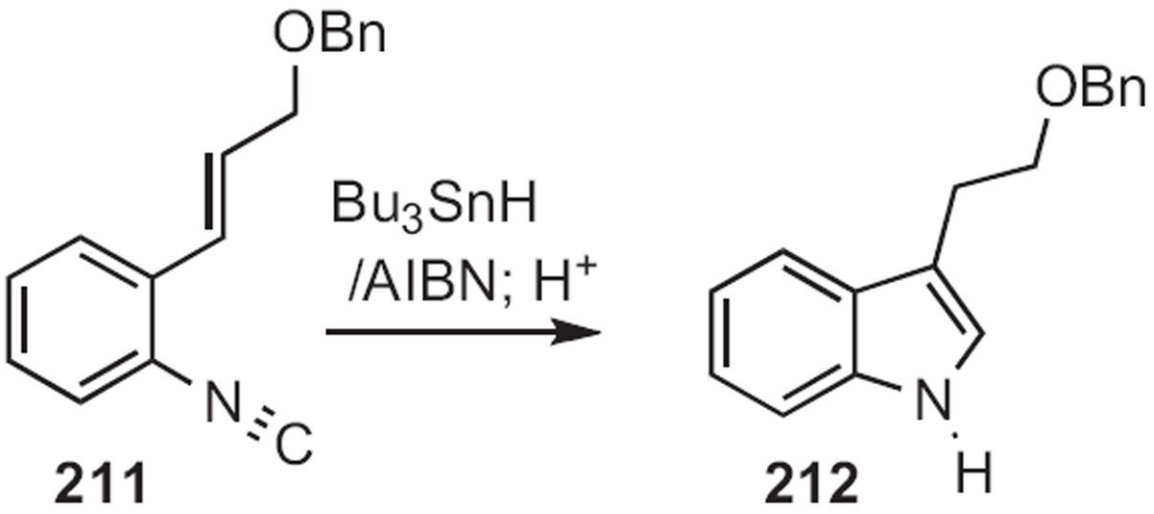
Scheme 79.



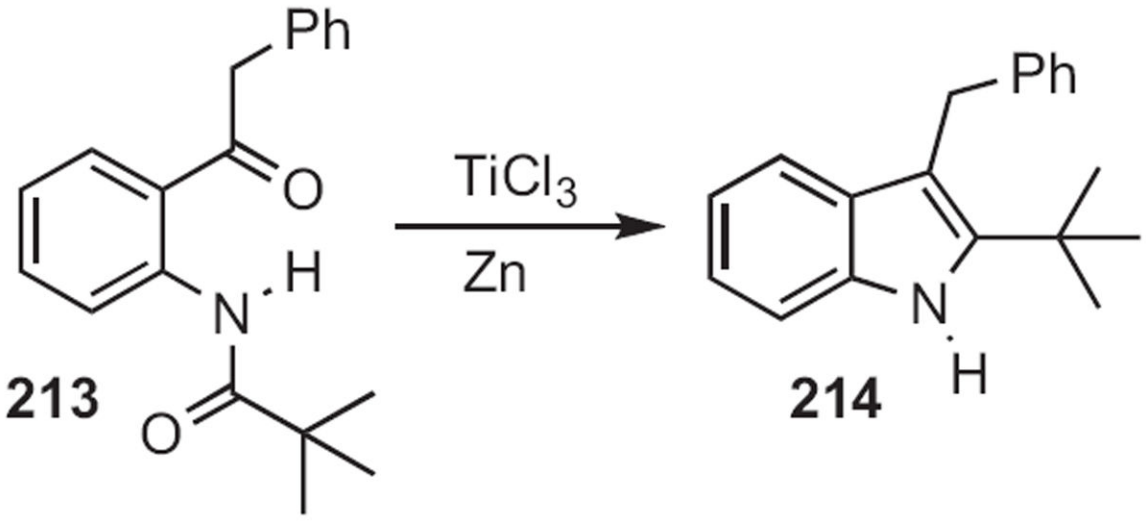
Scheme 80.



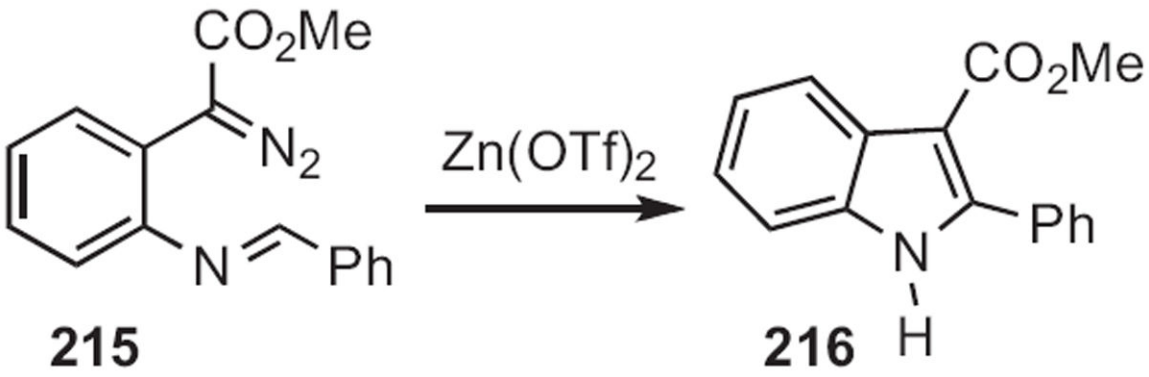
Scheme 81.



Scheme 82.

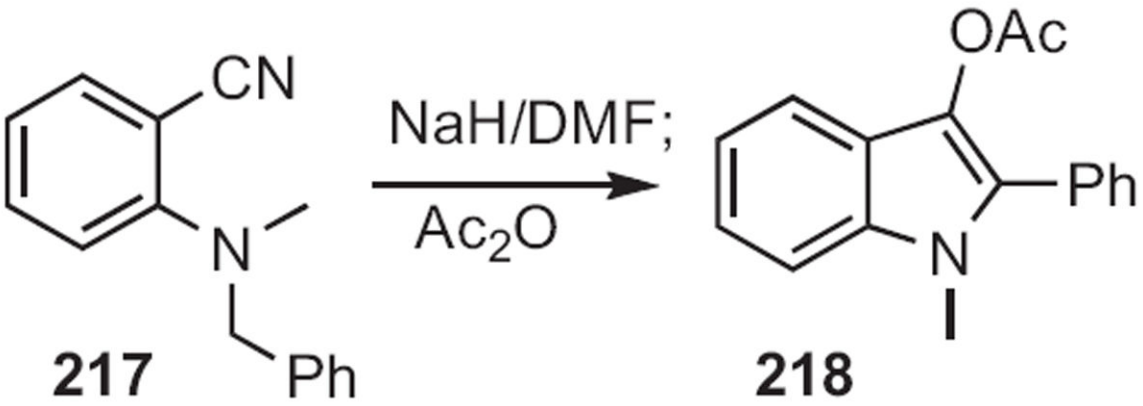


Scheme 83.

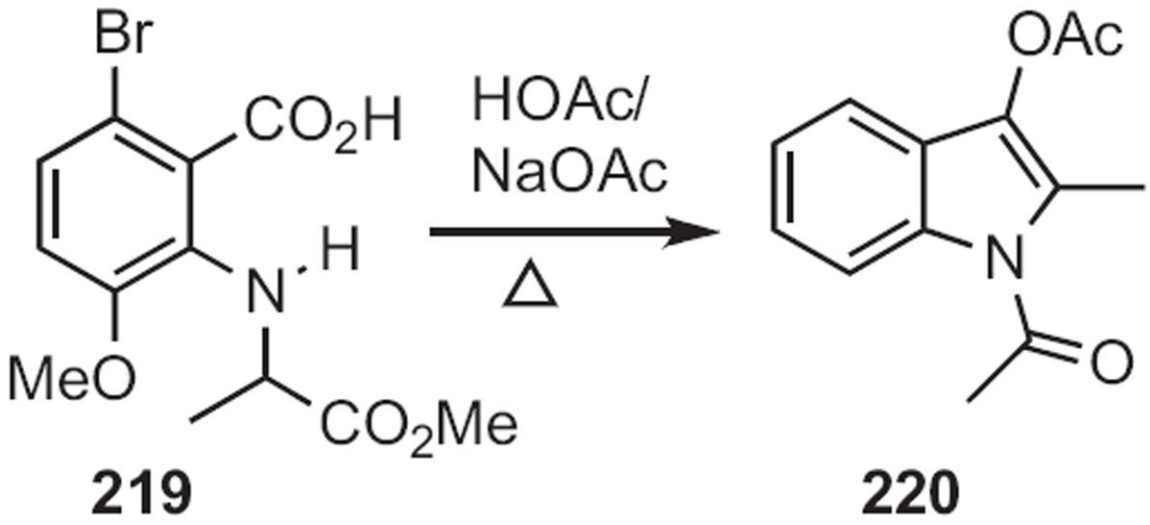


215 216

Scheme 84.

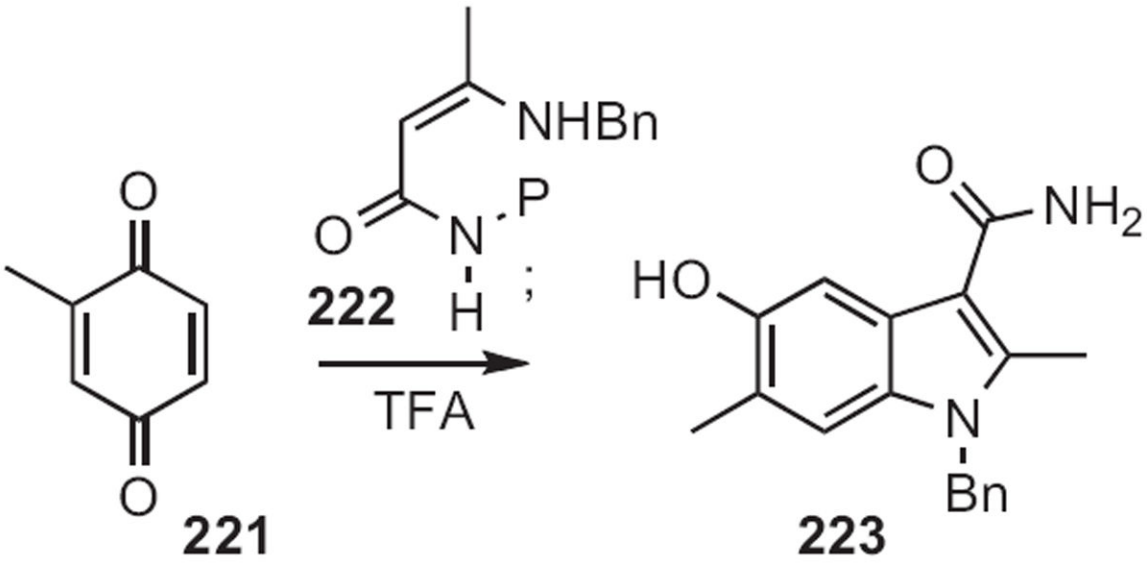


Scheme 85.

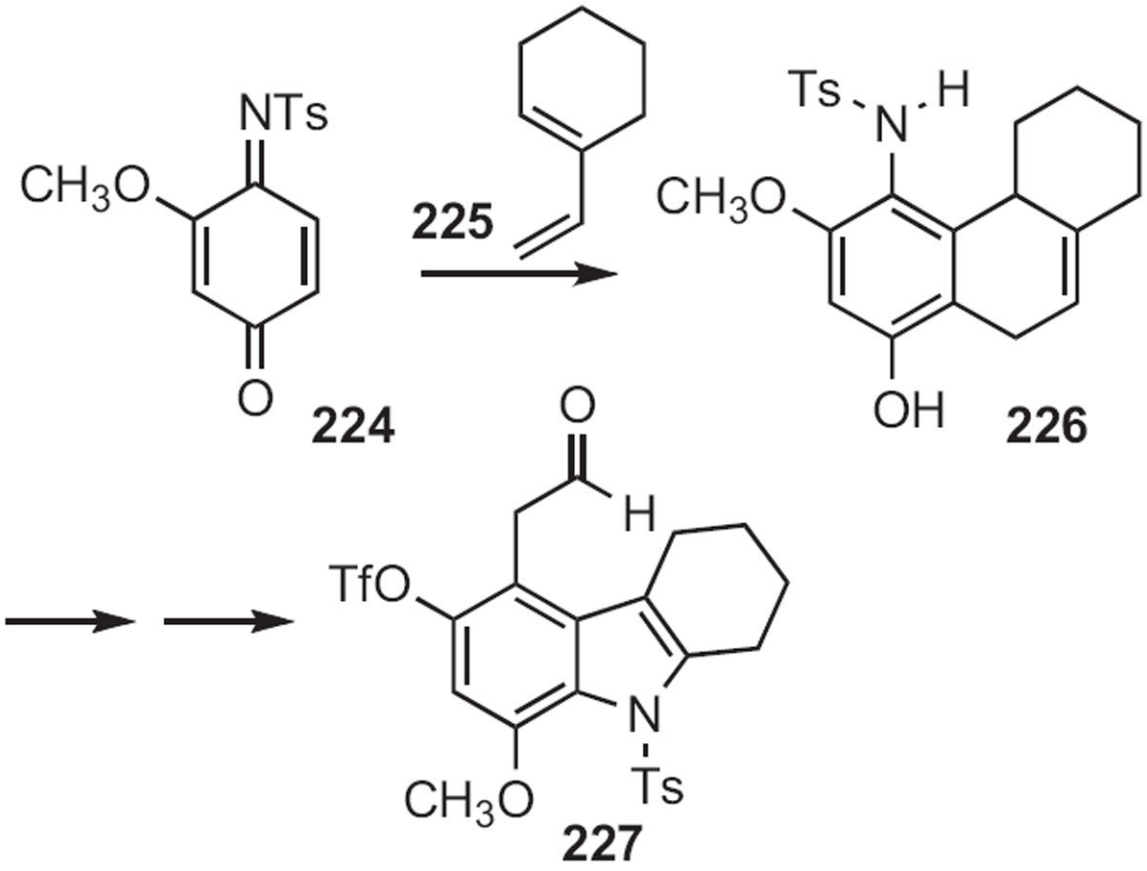


219 **220**

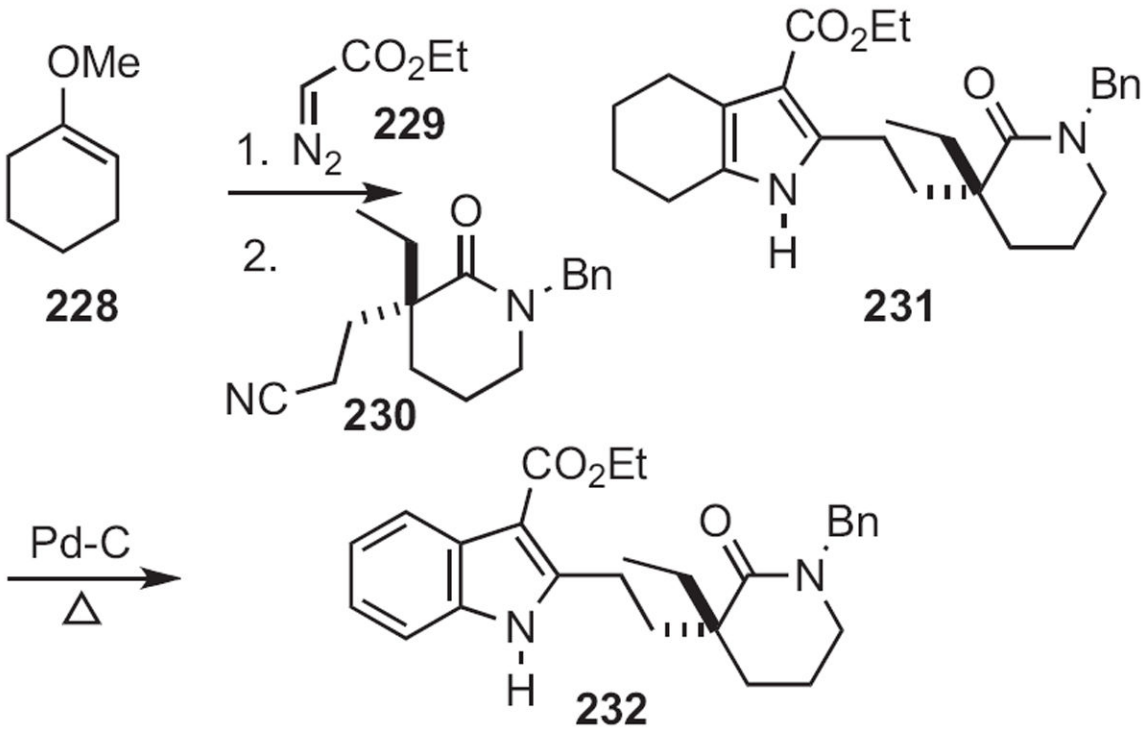
Scheme 86.



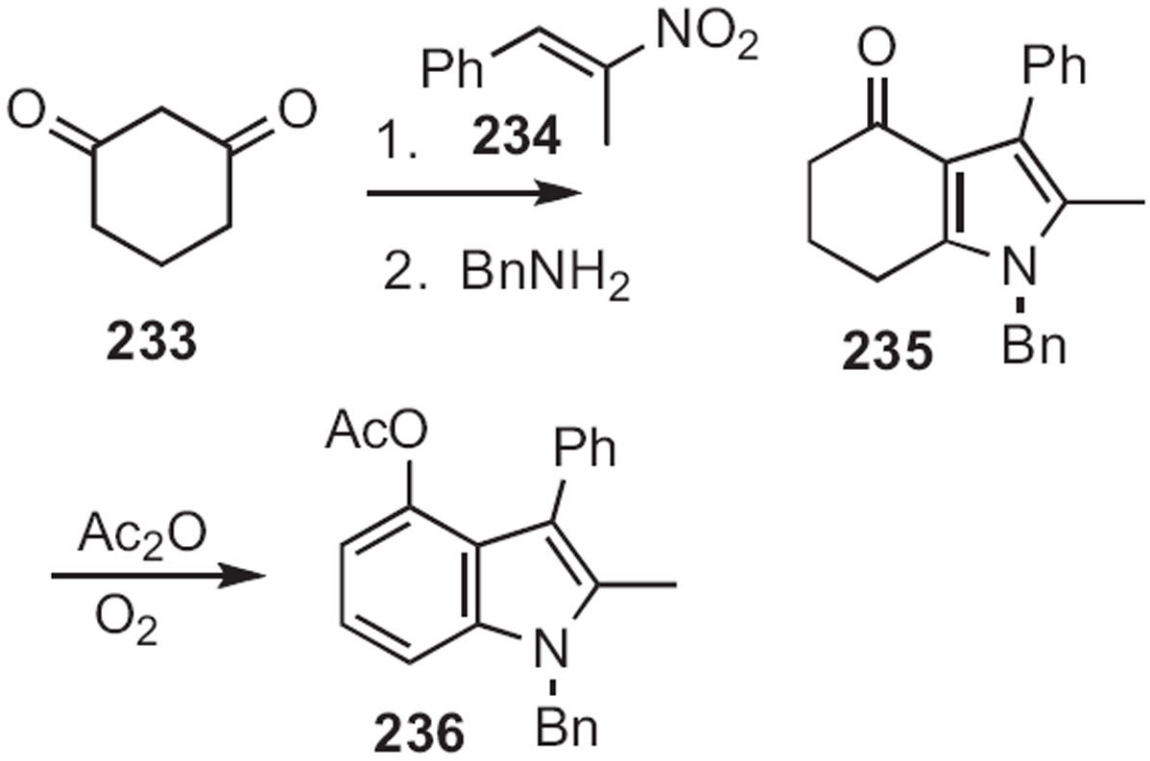
Scheme 87.



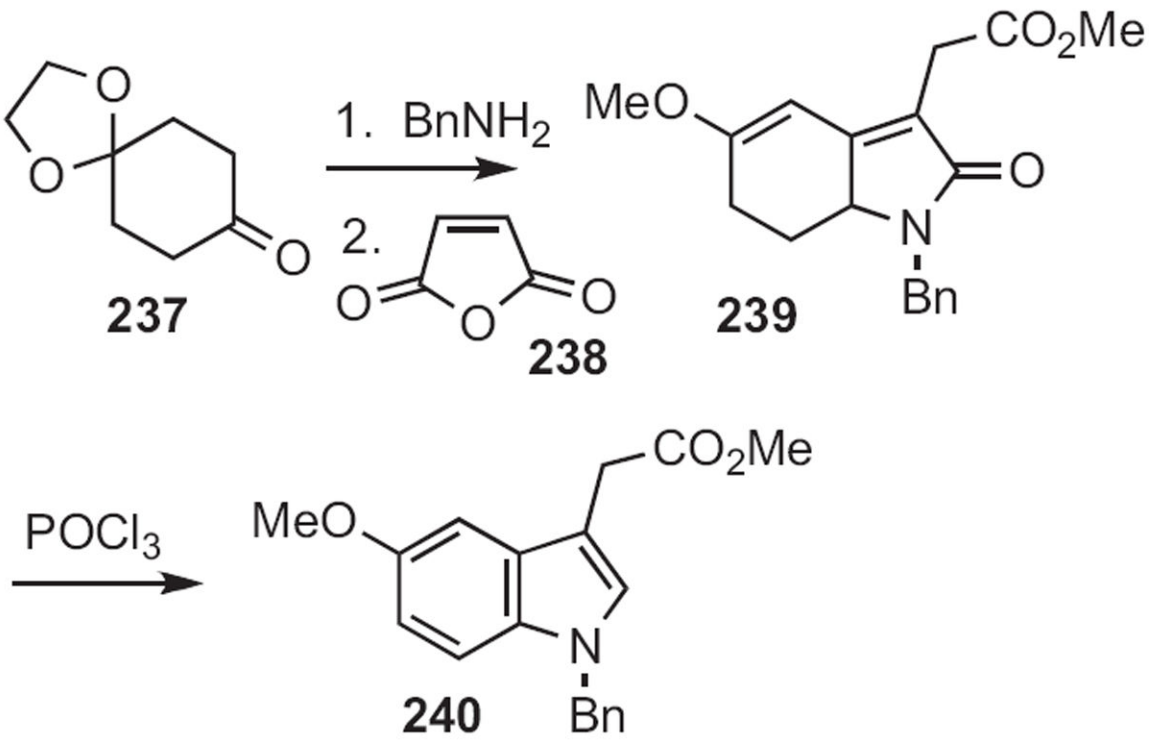
Scheme 88.



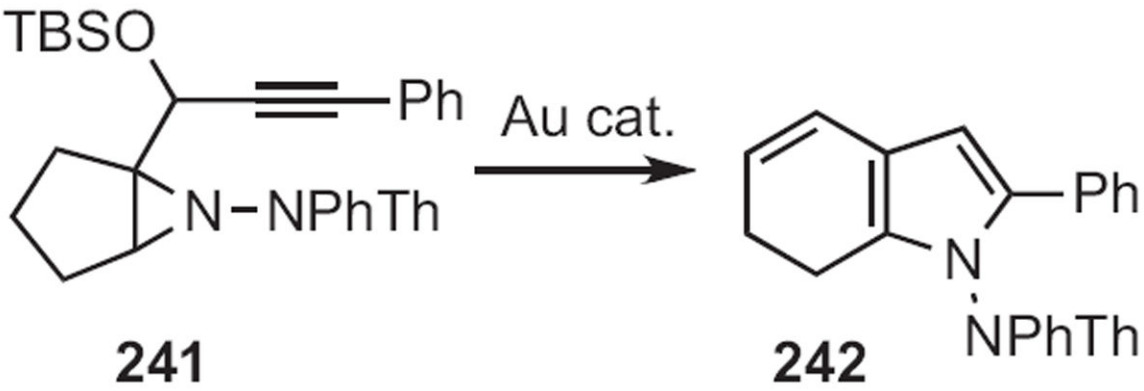
Scheme 89.



Scheme 90.

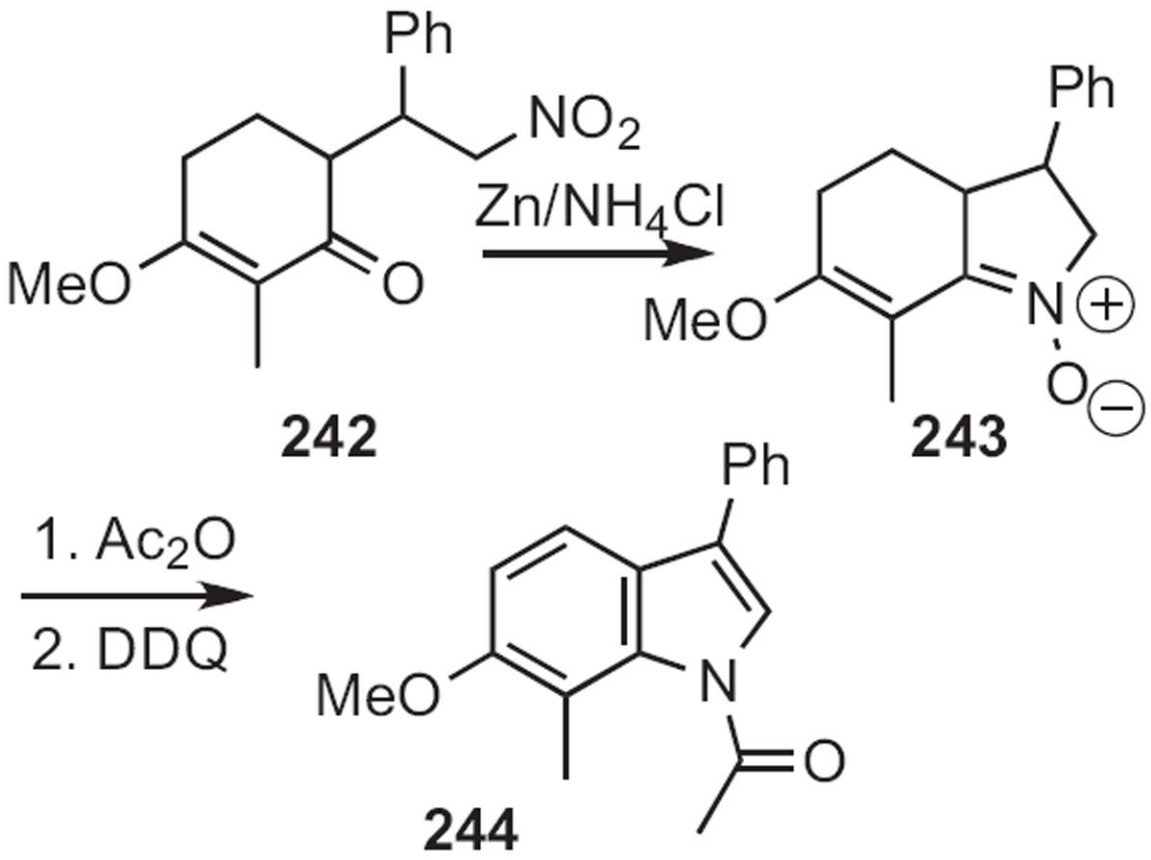


Scheme 91.

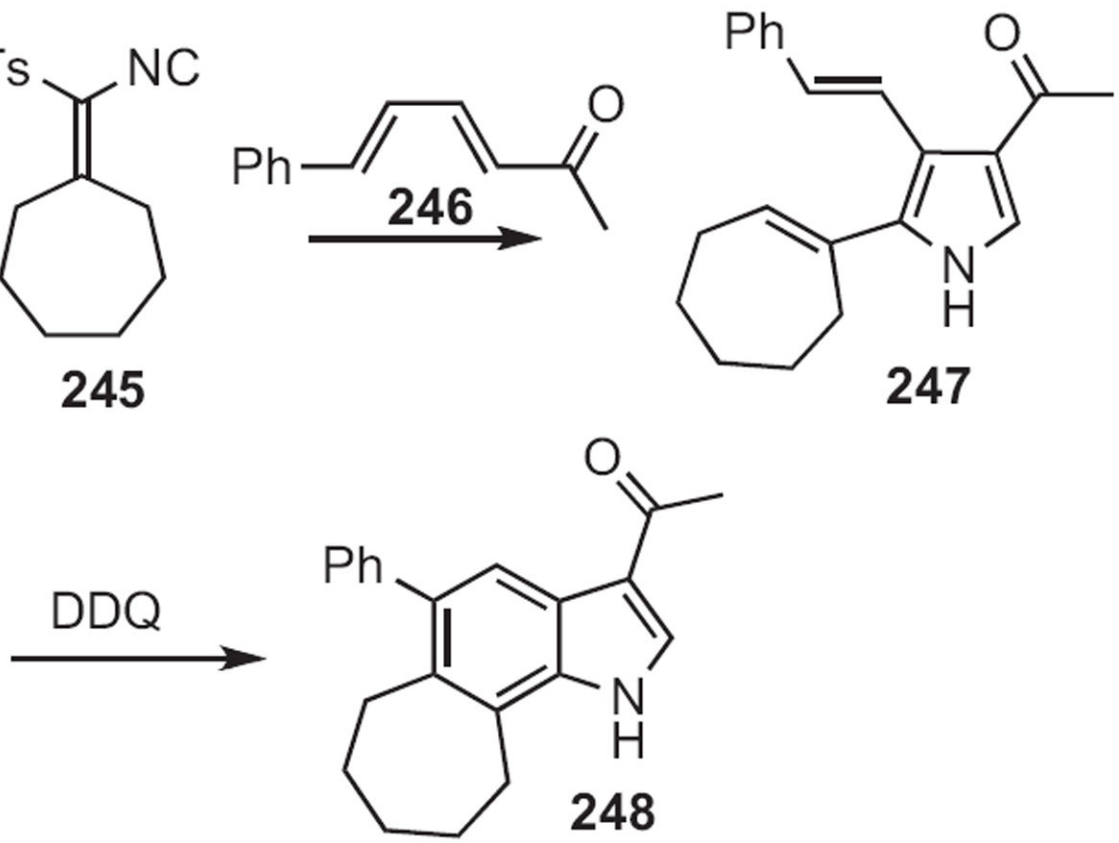


241 242

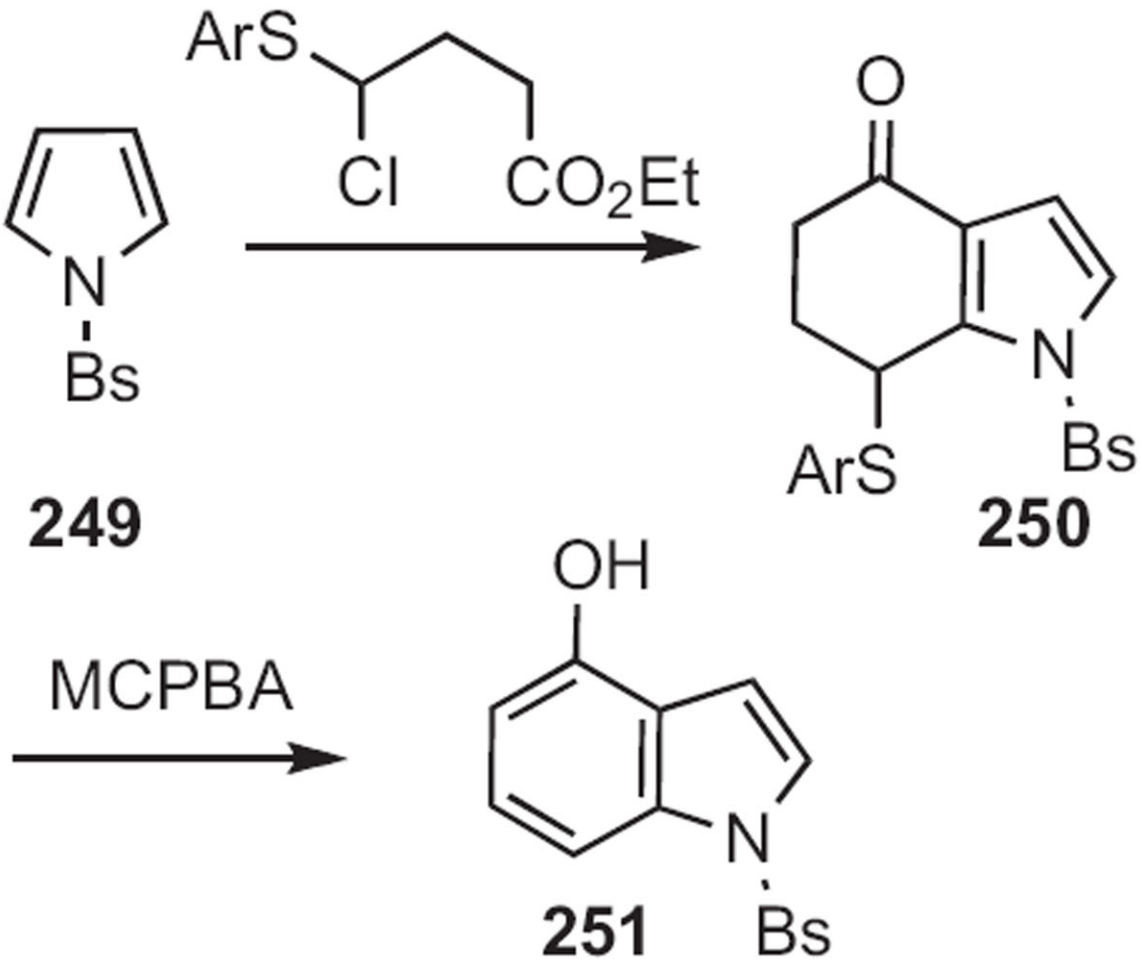
Scheme 92.



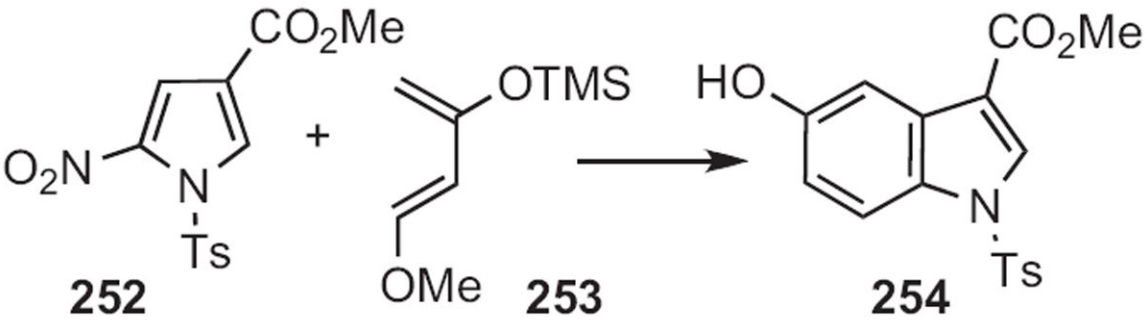
Scheme 93.



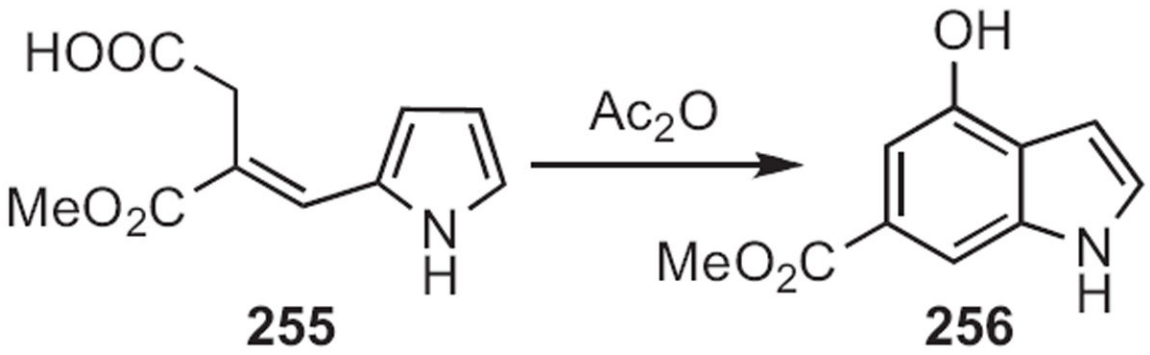
Scheme 94.



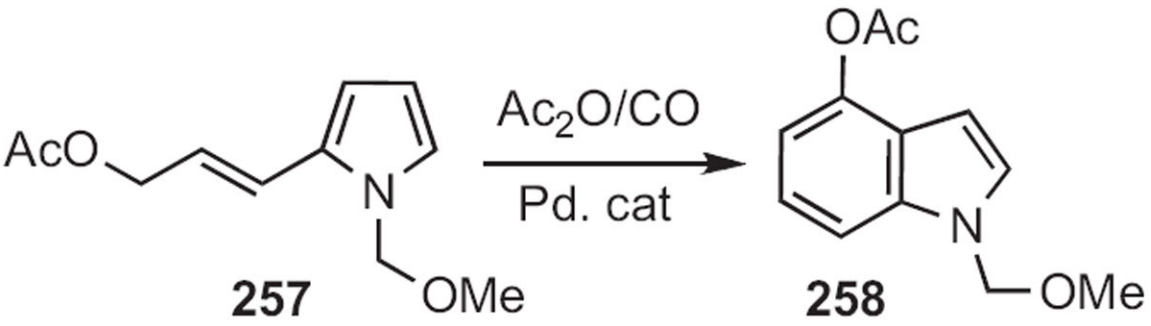
Scheme 95.



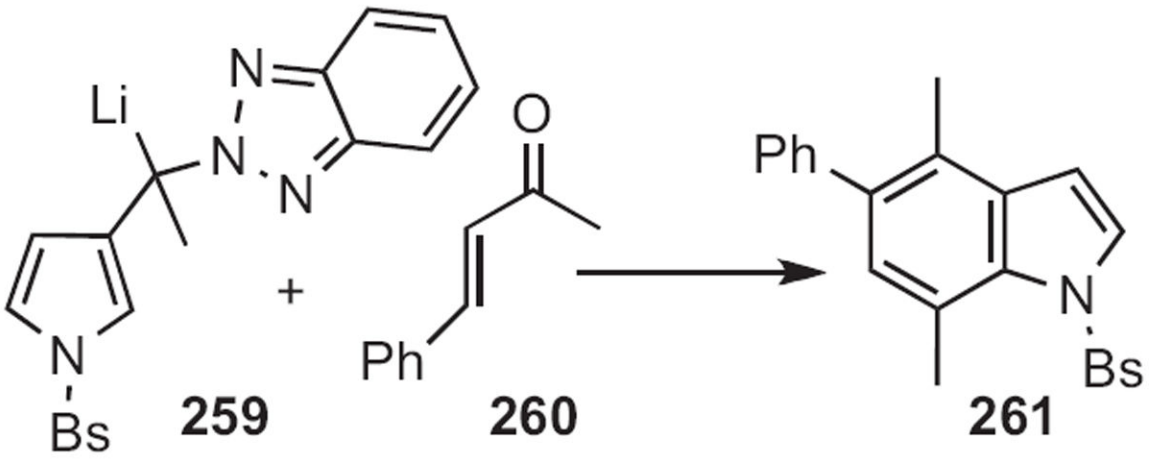
Scheme 96.



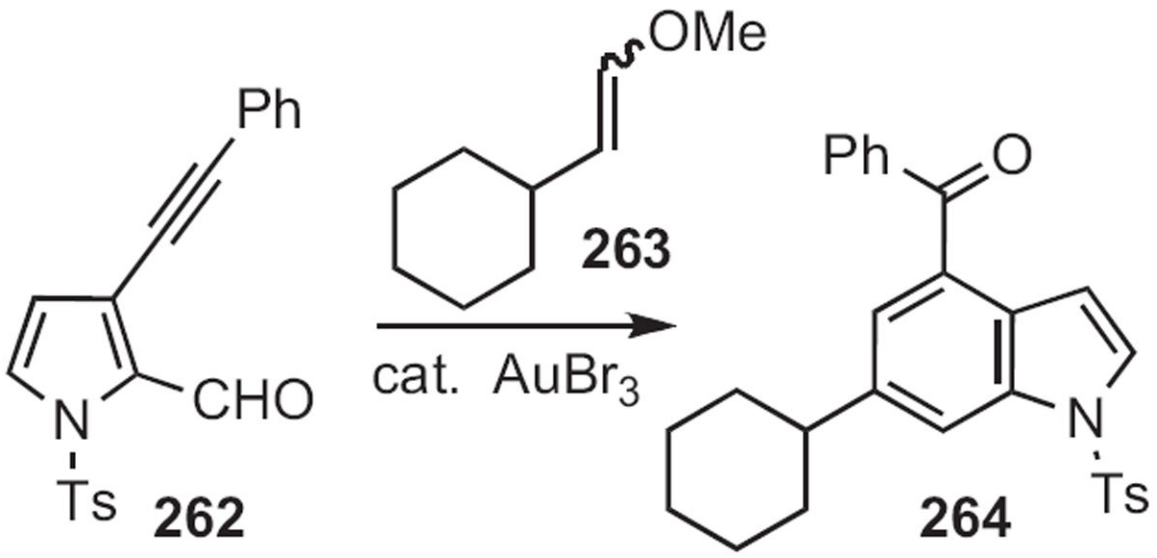
Scheme 97.



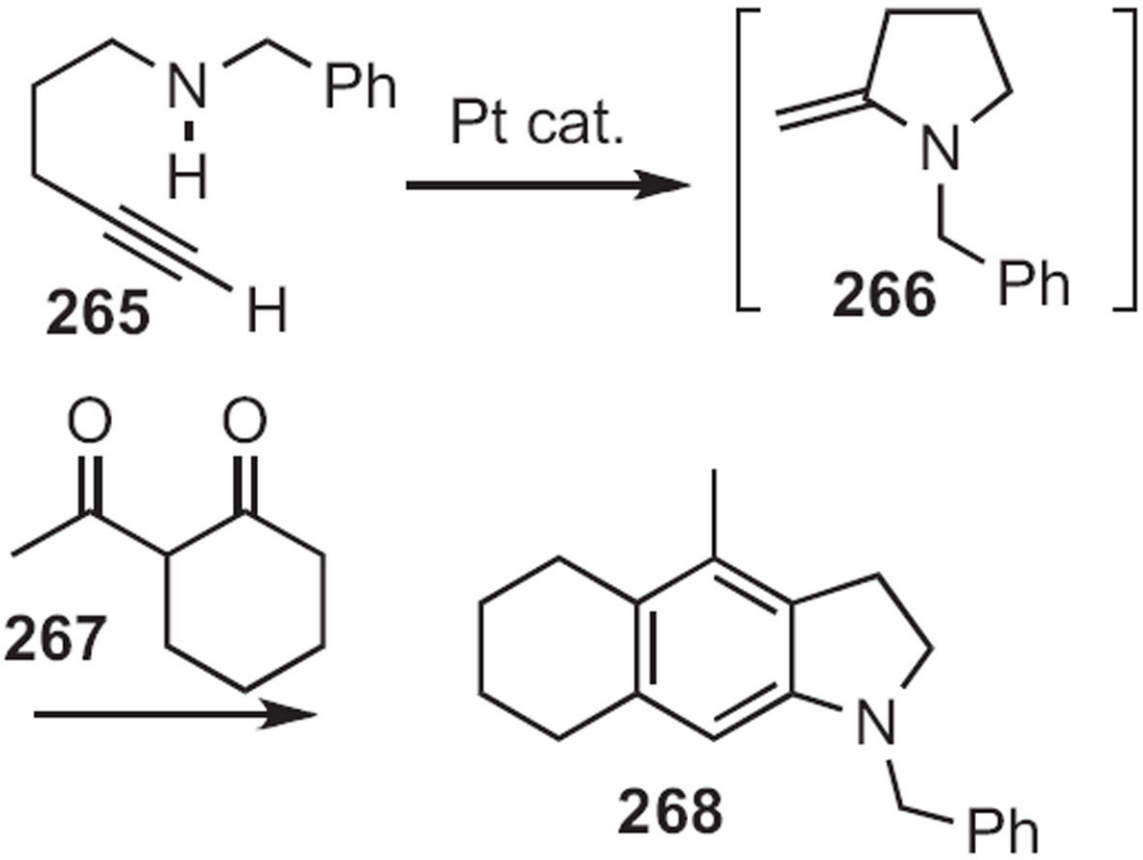
Scheme 98.



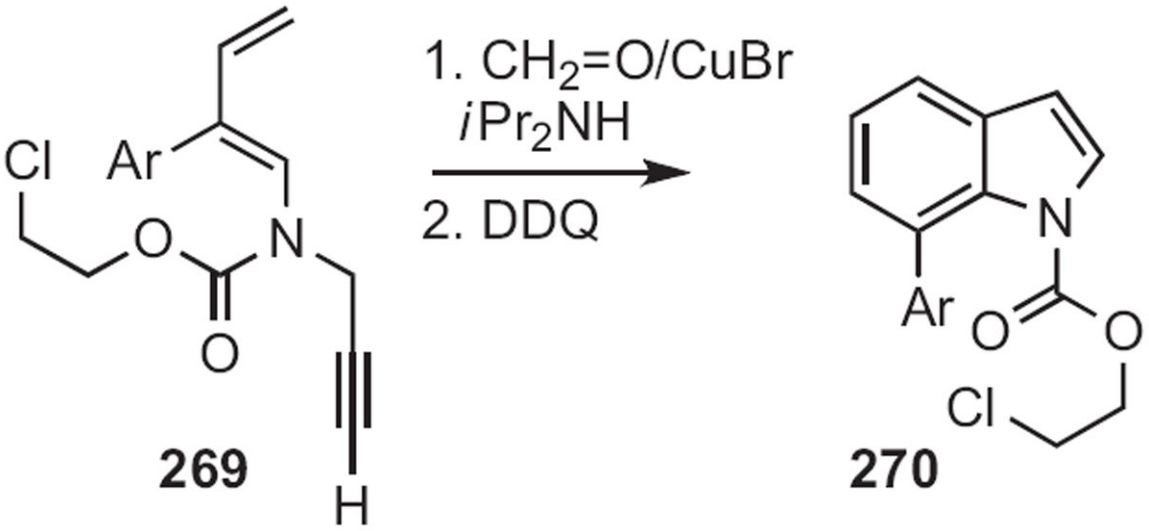
Scheme 99.



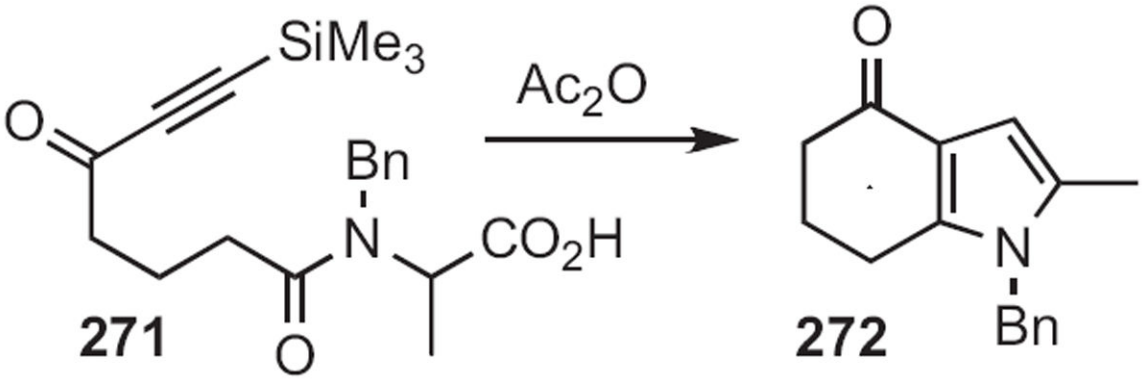
Scheme 100.



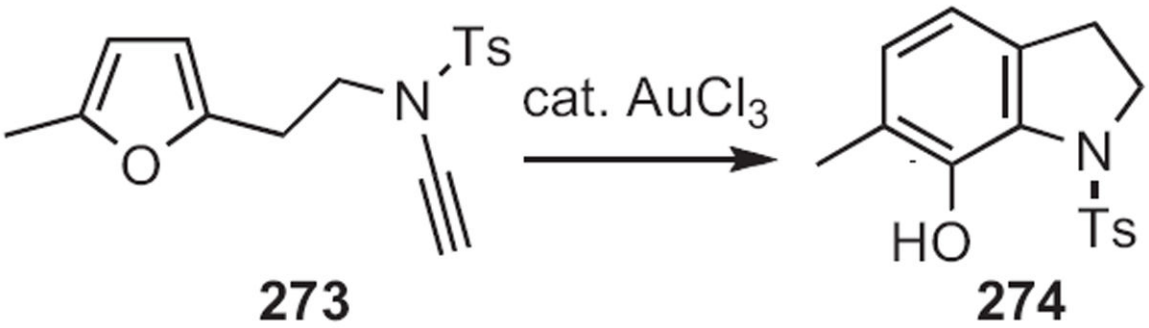
Scheme 101.



Scheme 102.

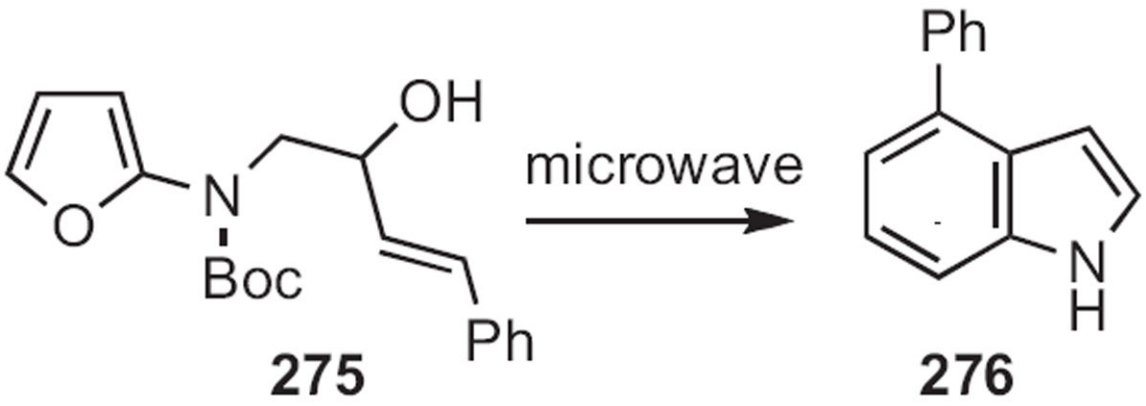


Scheme 103.



273 274

Scheme 104.



275 **276**

Scheme 105.