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Total Synthesis of the *Strychnos* Alkaloid (+)-Minfiensine: Tandem Enantioselective Intramolecular Heck–Iminium Ion Cyclization

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Abstract

A 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole (**4**) is a central structural feature of the *Strychnos* alkaloid minfiensine (**1**) and akuammiline alkaloids such as vincorine (**5**) and echitamine (**6**). A cascade catalytic asymmetric Heck-iminium cyclization was developed that rapidly provides 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazoles in high enantiomeric purity. Two sequences were developed for advancing 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole **27** to (+)-minfiensine. In our first-generation approach, a reductive Heck cyclization was employed to form the fifth ring of (+)-minfiensine. In a second more concise total synthesis, an intramolecular palladium-catalyzed ketone enolate vinyl iodide coupling was employed to construct the final ring of (+)-minfiensine. This second-generation total synthesis of enantiopure (+)-minfiensine was accomplished in 6.5% overall yield and 15 steps from 1,2-cyclohexanedione and anisidine **13**. A distinctive feature of this sequence is the use of palladium-catalyzed reactions to form all carbon–carbon bonds in the transformation of these simple precursors to (+)-minfiensine.

Introduction

Minfiensine (**1**), a secoiridoid indole alkaloid, was isolated from the African plant *Strychnos minfiensis* by Massiot and co-workers in 1989.[1] Its structure was assigned using ^{1}H and ^{13}C NMR spectroscopy (C–H and H–H COSY, NOESY), with long-range coupling of the C15 methine hydrogen to the C17 allylic methylene and C19 vinylic hydrogens being particularly diagnostic. Although a variety of *Strychnos* alkaloids having a molecular formula of $C_{19}H_{22}N_2O$ have been isolated (e.g., **1**–**3**, Figure 1), the structure of minfiensine has no precedent.[2] No details of its biosynthesis are known, but its genesis from a corynantheine precursor is likely.

The 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole (**4**) moiety is the defining structural feature of minfiensine (**1**) (Figure 2). Although rare in *Strychnos* alkaloids, this tetracyclic ring system is found in a number of akuammiline alkaloids such as vincorine (**5**) and echitamine (**6**).3 Extracts containing akuammiline alkaloids are used throughout the world in the practice of traditional medicine, with some heightened interest in the medicinal

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data (^{1}H, ^{13}C, and HPLC) for new compounds, and CIF files of crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

potential of pure akuammiline alkaloids being seen in recent years.[4] Dihydro-9a,4a-(iminoethano)-9*H*-carbazoles (**4** having a 1,2- or 2,3-double bond) could serve as versatile platforms for constructing alkaloids of the types illustrated in Figure 2. Stitching an ethylideneethano unit between the pyrrolidine nitrogen and C3 of such a precursor would generate the ring system of minfiensine, whereas inserting such a unit between the pyrrolidine nitrogen and C2 would generate the ring system of vincorine and congeners.

In this article, we report the development of an efficient catalytic enantioselective synthesis of 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazoles by combining a palladium-catalyzed asymmetric Heck cyclization with an intramolecular iminium ion cyclization. We also describe the details of our use of such an intermediate to complete the first total synthesis of minfiensine (**1**)[5] and our development of an improved end play that allows a notably efficient and concise catalytic asymmetric construction of this structurally unique *Strychnos* alkaloid to be realized.

Results and Discussion

Synthesis Plan

We envisaged minfiensine (**1**), as well as alkaloids of the vincorine family, to be accessible from 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole **7** (Scheme 1). The central transformation in our total synthesis plan is catalytic enantioselective formation of tetracyclic intermediate **7** from cyclohexadienyl carbamate **10**. In this pivotal conversion, an intramolecular catalytic asymmetric Heck reaction would generate dihydrocarbazole **9** and form the critical quaternary carbon stereocenter.[6,7] Selective in situ protonation of the enecarbamate double bond of diene product **9** would generate *N*-acyloxyiminium ion **8**, which was expected to be trapped by the tethered amine to form dihydro(iminoethano)carbazole **7**. One attractive feature of this sequence was the expected ready construction of cyclohexadienyl carbamate **10** from aniline **11** and 1,2-cyclohexanedione (**12**).

Enantioselective Formation of the 3,4-Dihydro-9a,4a-(iminoethano)-9*H*-carbazoles by Tandem Enantioselective Intramolecular Heck-Iminium Ion Cyclization

The sequence developed to prepare the cyclohexadienyl aryl triflate cyclization precursor **21** is summarized in Scheme 2. Although acid-catalyzed condensation of 1,2-cyclohexanedione (**12**) with anisidine **13**[8] was low-yielding under all the conditions that we examined, the related condensation with morpholine enamine **14**[9] in the presence of 1 equiv of *p*-toluenesulfonic acid (*p*-TsOH) in warm benzene provided 2-anilino-2-cyclohexenone **15** in high yield.[10] Attempts to protect the nitrogen of this intermediate prior to elaboration to the cyclohexadiene were complicated by competitive reaction of the ketone. For example, deprotonation of intermediate **15** with a strong base (lithium, sodium or potassium bis(trimethylsilyl)amide, or NaH), followed by addition of $ClCO_2Me$, yielded mixtures of carbamate **16** and products resulting from reaction of the ketone enolate on oxygen or carbon.[5] We eventually discovered that the aniline nitrogen could be selectively masked by reaction of the lithium salt of aniline **15** with Mander's reagent.[11] The optimum condition identified involved dropwise addition of 3 equiv of lithium bis(trimethylsilyl)amide (LHMDS) to a THF solution of aminocyclohexenone **15** and excess methyl cyanoformate at −78 °C, in which case crystalline carbamate **16** was formed in 89% yield. When 1.5 or 2.0 equiv of LHMDS was used, significant amounts of cyclohexenone **15** were recovered.[12] Addition of sodium bis(trimethylsilyl)amide (NaHMDS) to a THF solution of carbamate enone **16** and the Comins' triflating reagent **17** (5-chloro-2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]pyridine)[13] at −78 °C provided cyclohexadienyl triflate **18** in 82% yield. A β-aminoethyl side chain was then introduced in 71% yield by Suzuki

cross-coupling of triflate **18** with the alkylborane generated in situ by hydroboration of enecarbamate 19[14] with 9-borabicyclo[3.3.1]nonane (9-BBN).[15] Finally, silyl-protected phenol **20** was transformed in one step and 85–95% yield to dienyl aryl triflate **21** upon reaction at room temperature with triflating reagent **17** in DMF in the presence of CsF and Cs_2CO_3.[16] In order to obtain reproducibly high yields in this transformation, it was critical to use freshly dried cesium salts. Comins' reagent was used rather than *N*-phenyltriflamide ($PhNTf_2$) to ensure a rapid triflation of the cesium phenoxide and to facilitate purification of the aryl triflate product. Without these precautions, the triflation reaction was sluggish and irreproducible, with cyclic carbamate **22** being occasionally formed as a major byproduct. By the sequence summarized in Scheme 2, Heck cyclization precursor **21** was prepared in five steps and 46% overall yield from aniline **13** and 2-morpholino-2-cyclohexenone (**14**).

The asymmetric Heck cyclization of dienyl aryl triflate **21** was initially examined using $Pd(OAc)_2$/BINAP as the precatalyst (Scheme 3). Under these conditions, intramolecular Heck reaction of **21** proceeded readily at 80 °C in acetonitrile (or toluene) in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP) to give dihydrocarbazole **23** (ca. 60% yield).[17] The conjugated cyclohexadiene product is undoubtedly produced by Pd–H-mediated isomerization of the initially formed Heck product (**24** → **23**). Use of a large excess of PMP or the stronger base 1,8-bis(dimethylamino)naphthalene, which has been reported to minimize double-bond migration,[18] did not prevent the formation of the 1,3-cyclohexadiene product.

Chiral (phosphinoaryl)oxazolines have been shown to be effective ligands for asymmetric Heck reactions and to exhibit a low propensity for promoting double-bond migration.[19] The Pd[(phosphinoaryl)oxazoline]-catalyzed Heck cyclization of dienyl aryl triflate **21** was initially explored using the commercially available isopropyl-substituted PHOX ligand **26a** (Scheme 4). The Heck reaction of triflate **21** using $Pd(OAc)_2$ (20 mol %), ligand **26a**, and PMP in toluene provided the cross-conjugated dihydrocarbazole **25** in 79% yield (92% yield based on consumed **21**) and 88% ee after heating at 100 °C for 70 h.[20] The conjugated alkene isomer **23** was not observed under these reaction conditions. Improved enantioselectivity (96% ee) was achieved when the reaction was conducted in acetonitrile at 85 °C; however, alkene isomerization occurred to a limited extent (ca. 10%) in this more polar solvent. Optimal results were obtained using the *tert*-butyl-substituted PHOX ligand **26b**,[19a] in which case dihydrocarbazole **25** was produced in 75–87% yield and 99% ee; dihydrocarbazole **23**, the product of double-bond migration, was not detected. The only disadvantage of the palladium–phosphinooxazoline catalyst is the long reaction time (ca. 70 h). In order to increase the rate of this transformation, we investigated the effects of microwave heating.[21] Larhed, Hallberg, and co-workers reported significant acceleration of intermolecular asymmetric Heck reactions using microwave heating, although enantioselectivities were reduced somewhat.22 Under microwave heating, the Heck reaction of **21** was complete in only 30–45 min at 170 °C, with no erosion of yield or enantiomeric purity of dihydrocarbazole **25** being observed (87% yield, 99% ee). This microwave-promoted Heck cyclization was carried out reproducibly on synthetically useful scales (ca. 500–600 mg). Furthermore, the shorter reaction times allowed the catalyst loading to be reduced to 10 mol % of Pd.

The tandem reaction sequence to form 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole **27** was achieved in 75% overall yield from dienyl aryl triflate **21** by adding excess trifluoroacetic acid (TFA, 10 equiv) to the crude Heck reaction product after the reaction vessel was removed from the microwave reactor and cooled to 0 °C. A large excess of TFA was required in this one-pot sequence because excess PMP and the basic phosphine ligand were both present in the crude Heck reaction product. The 4a*R*,9a*R* absolute configuration of

dihydro(iminoethano)-carbazole **27** was not established at this point, but at a later stage of the synthesis (vide infra).

Attempts to Construct the Minfiensine Ring System by an Intramolecular Asymmetric Heck Reaction–Carbonylation Sequence

From the outset, we envisaged constructing minfiensine (**1**) from a 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole intermediate such as **27** by the sequence outlined retrosynthetically in Scheme 5. The central step in this elaboration would be the formation of pentacyclic ester **28** from tetracyclic precursor **30** by a Heck cyclization–carbon monoxide insertion sequence.[6d] Assembling the cyclization precursor **30** with the α-orientation of the allylic oxygen substituent was anticipated to favor the desired cascade reaction sequence by avoiding the possibility that pentacyclic palladium alkyl intermediate **29** could decompose by *syn*-β-hydride elimination. Either ketone **31** or α-epoxide **32** were seen as plausible precursors of dienyl iodide intermediate **30**.

If dihydro(iminoethano)carbazole **27** could be epoxidized stereoselectively from the α-face, a concise route to Heck cyclization precursor **30** could likely be developed. For this reason, we examined this possibility even though a preliminary examination of molecular models of tetracyclic alkene **27** did not suggest a significant steric bias for approach of an oxidant from either alkene face. To our delight, standard epoxidation of alkene **27** with *m*-chloroperoxybenzoic acid (*m*-CPBA) proceeded with 10:1 stereoselectivity to give, after separation on silica gel, the α-epoxide **34** in 87% yield; the β-epoxide stereoisomer was also isolated in 9% yield (Scheme 6). The relative configuration of epoxide **34** was assigned on the basis of analogy to the major (8:1) epoxide stereoisomer **35** produced by *m*-CPBA epoxidation of methoxy congener **33**. In this latter case, the epoxide was obtained as single crystals, allowing the relative configuration of epoxide **35** to be secured by X-ray analysis.[23]

To examine what was responsible for the 10:1 selectivity observed in the epoxidation of tetracyclic alkene **27**, this intermediate was modeled computationally. This study showed a 1.2–2.5 kcal/mol preference for the cyclohexene ring of **27** to exist in the half-chair conformation illustrated in Figure 3.[24] Assuming for steric reasons that C–O bond formation is more advanced at alkene carbon *b*, torsional effects would favor epoxidation from the alkene stereoface anti to the indoline bridge, as depicted in Figure 3.[25]

Without success, we explored initially the possibility of converting tetracyclic epoxide **34** to allylic alcohol **36** using lithium amide bases at various temperatures (Scheme 6).[26] For example, reaction of epoxide **34** with lithium diethylamide in THF at −40 °C led to rapid loss of the methyl carbamate group. Cleavage of the methyl carbamate group occurred more slowly when lithium diisopropylamide (LDA) was used as a base; however, an allylic alcohol product was never isolated, even after reactions conducted in THF were heated at 45 °C for several hours.

To avoid base-promoted side reactions, we turned to the organoselenide method developed by Sharpless and Lauer.[27] As expected, epoxide **34** reacted regioselectively with sodium phenylselenide to generate a single β-hydroxy selenide product. Oxidation of this intermediate to the selenoxide, followed by heating at 60 °C, delivered allylic alcohol **36** in 50% yield from epoxide precursor **34**. Protection of alcohol **36** as a benzyl ether proceeded uneventfully under standard conditions to give tetracyclic allylic ether **37**.

To our surprise, attempts to cleave the Boc group of intermediate **37** under standard acidic conditions [trifluoroacetic acid (TFA), CH_2Cl_2, 0 °C] led to the formation of indole **38**. This fragmentation was rapid, occurring instantaneously at 0 °C to provide indole aldehyde **38** in 92% yield. ^{1}H and COSY NMR spectra confirmed the presence of an unsaturated aldehyde,

with a large vinylic coupling constant (15.7 Hz) indicating the *E* geometry for the 4-oxo-2-butenyl side chain. Because of the facility of this rearrangement under acidic conditions, other methods were briefly investigated for removing the Boc group. Attempted thermolytic fragmentation upon conventional heating in dimethylsulfoxide (DMSO, 120–150 °C) or in a microwave reactor did not afford the desired secondary amine product. Likewise, attempted deprotection of **37** with ceric ammonium nitrate (CAN)[28] provided only recovered starting material and indole aldehyde **38**.

A plausible sequence for formation of indole **38** from tetrahydro(iminoethano)carbozle precursor **37** is suggested in Scheme 7. In the presence of acid, aminal **37** should be in equilibrium with tricyclic *N*-acyloxyiminium ion **39**.[29] In a process that undoubtedly would be exothermic, fragmentation of bond *a* of this intermediate would generate indole oxocarbenium ion **40**. This latter intermediate would be expected to be trapped with trifluoroacetate to form allylic trifluoroacetate **41** and its allylic isomers. Upon aqueous workup, **41** and/or its *E* allylic isomer would deliver indole **38**.

The sequence that was ultimately developed for advancing epoxide **34** to Heck cyclization precursor **48** is summarized in Scheme 8. As the alkoxycarbenium ion potentially generated by fragmentation of the cyclohexane ring of epoxide **34** would be less stable than that produced from allylic ether **37** (Scheme 7), exchange of the Boc group of epoxy carbamate **34** for an allyloxycarbonyl (Alloc) protecting group was straightforward. Rearrangement of the epoxide functionality of Alloc product **43** and triethylsilyl (TES) protection of the resultant allylic alcohol provided allylic silyl ether **45** in 68% overall yield from Boc-protected epoxide **34**. Removal of the Alloc group of intermediate **45** using $Pd(PPh_3)_4$ and excess pyrrolidine proceeded cleanly to yield tetracyclic amine **46**. The Heck cyclization precursor **48** was then secured in 96% yield by reaction of secondary amine **46** with 2 equiv of allylic tosylate **47**[30] in hot MeCN in the presence of K_2CO_3.

We explored briefly a second sequence for elaborating dihydro(iminoethano)carbazole **27** to an appropriate precursor for forming the fifth ring of minfiensine (Scheme 9). Toward that end, tetracyclic alkene **27** was allowed to react with borane–methyl sulfide complex at room temperature, followed by oxidation with tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide (TPAP/NMO) to provide a chromatographically separable mixture of ketones **49** (63% yield) and **50** (21% yield). As has been reported several times previously in hydroborations of structurally related alkenes, reaction of tetracyclic alkene **27** with BH_3 placed boron preferentially at the more hindered neopentylic position.[31,32] Although the minor ketone isomer was not of immediate interest (vide infra), it did allow the absolute configuration of the product **27** of tandem asymmetric Heck–iminium ion cyclization to finally be established. Thus, reduction of ketone **50** with sodium borohydride provided a 1:1 mixture of separable alcohol products. Reaction of the lower R_f epimer with *p*-bromobenzoyl chloride yielded crystalline ester **51**. Single-crystal X-ray analysis of this derivative allowed its relative and absolute configuration to be determined,[33] proving the sense of stereoinduction in the asymmetric Heck cyclization of **21** to give (*R*)-dihydrocarbazole **25** (Scheme 4).

In an attempt to process the major ketone isomer to a suitable precursor for forming the final ring of minfiensine, tetracyclic ketone **49** was dehydrogenated by reaction with 2-iodoxybenzoic acid (IBX) (Scheme 9).[34] Subsequent cleavage of the Boc group with TFA provided cyclohexenone **53** in 40% yield for the two steps. To our surprise, attempted N-allylation of secondary amine **53** with allylic tosylate **47**[30] yielded dienone **54** as the major product. The formation of this dihydroindolone likely arises from deprotonation of intermediate **53** at the γ-position to give a dienolate anion, which β-eliminates the aniline carbamate conjugate base.[35] As an alternate route to an appropriate precursor for closing the

final ring of minfiensine had been developed (see Scheme 8), this strategy was pursued no further.

We turned to examine forming the final ring of minfiensine and simultaneously installing the remaining carbon atom by the Heck cyclization–carbonylation sequence posited in Scheme 5. To this end, tetracyclic vinyl iodide **48** was subjected to a number of standard conditions that had been used by others to carry out cascade intramolecular Heck reaction–carbonylation reactions (Scheme 10).[7d] A variety of palladium precatalysts [$Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$], ligands [Ph_3P, 1,3-bis-(diphenylphosphoryl)propane, and 1,4-bis(diphenylphosphoryl)butane], bases (triethylamine, K_2CO_3), cosolvents (DMF, MeCN, toluene), and CO pressures (1 atm to 150 psi) were explored in various combinations. However, under no reaction condition that we examined was the desired pentacyclic ester **55** detected. Besides recovered dienyl iodide **48**, secondary amine **46**,[36] the α,β-unsaturated ester **56** resulting from carbonylation of the vinyl iodide side chain, and a pentacyclic product **57**, whose structure was revealed after additional experimentation (vide infra), were isolated from these experiments.

Reductive Heck Cyclization to Form the Fifth Ring. Completion of the First Total Synthesis of (+)-Minfiensine

Our inability to accomplish a cascade Heck cyclization–carbonylation reaction prompted us to examine the pivotal ring-forming step under reductive conditions.[7d] In this context, the intramolecular Heck reaction of vinyl iodide **48** was carried out in the presence of sodium formate with the expectation that pentacycle **58** would result (Scheme 11). However, reaction of alkenyl iodide **48** with 10 mol % of $Pd(OAc)_2$, 1,4-bis(diphenylphosphoryl) butane (dppb), Et_3N, and NaO_2CH in acetonitrile did not produce pentacyclic product **58**, but rather pentacyclic isomer **57** and the product **46** of N-dealkylation. The presence of sodium formate had no apparent effect on this reaction, with pentacyclic allylic alcohol **57** being isolated in 48% yield in a reaction carried out in the absence of sodium formate and triethylamine. Removal of the TES group from pentacyclic product **57** provided the crystalline alcohol **59**, whose structure was established by single-crystal X-ray analysis. Remarkably, pentacyclic product **57** produced by Pd(0)-catalyzed cyclization of tetracyclic dienyl iodide **48** is the product of formal C–H insertion of the alkenylpalladium side chain at the allylic carbon of the cyclohexene ring.

Insertion of an alkenylpalladium species into a C–H σ-bond is not expected under Heck reaction conditions.[7d,37] We surmised that the formation of product **57** could result from the lability of the aminal functionality of the pyrrolidinoindoline moeity.[30] This lability provides a straightforward pathway for migration of the cyclohexene double bond (Scheme 12). Thus, ring opening of tetracyclic aminal **48** to give iminium ion **60**, likely promoted by some protic or Lewis acidic species (illustrated by H^+ in Scheme 12), could readily lead to the formation of dienamine **61**. Protonation of this intermediate at the terminal carbon would provide conjugated iminium cation **62**, which upon ring closure would deliver isomer **63** of the original Heck cyclization substrate. Standard 5-exo-Heck cyclization of this intemediate would lead directly to the observed tetracyclic product **57**.

To gain experimental evidence for the proposed double-bond migration, a series of NMR studies were carried out with cyclization substrate **48**. First, we examined whether the alkene isomerization would take place in the absence of a palladium species. Accordingly, dienyl iodide **48** and dppb (20 mol %) were heated in d_3-acetonitrile at 75 °C. After 12 h, ca. 25% of diene **48** had isomerized to isomer **63**.[38] This experiment showed that double-bond migration could take place in the absence of palladium. However, the rate of this isomerization was slower than the rate at which pentacyclic product **57** was formed during the Heck reaction. Accordingly, it was reasoned that the double-bond migration was

proceeding by an additional pathway. As a Pd(II) species could be present and these are well-known to promote alkene isomerization,[39] dienyl iodide **48** was exposed to 12 mol % of $PdCl_2(MeCN)_2$ in d_3-acetonitrile at 75 °C. After 40 min, isomerization to diene isomer **63** was ca. 80% complete. As the enoxysilane double-bond isomer was not observed, we believe that a Pd(II) species formed in situ is functioning as a Lewis acid to activate the aminal functionality toward ring cleavage and facilitate double-bond migration in the conversion of **48** → **57** (Scheme 11).

High catalysis rates are often observed with the phosphine-free Heck reaction conditions initially reported by Jeffery (inorganic bases and tetraalkylammonium halides).[40,41] In the hope that Heck cyclization might be faster than double-bond isomerization, we turned to examine the reaction of dienyl iodide **48** under these conditions.[42] After some optimization, we found that reductive Heck cyclization of dienyl iodide **48** to form pentacyclic product **58** (80% yield) took place in DMF within 30 min at 80 °C in the presence of 1 mol % of $Pd(OAc)_2$, K_2CO_3 (5 equiv), $(n\text{-}Bu)_4NCl$ (2.5 equiv), and NaO_2CH (1.2 equiv). Under these conditions, pentacyclic isomer **57** was not detected, and the secondary amine **46** resulting from deallylation was produced to only a limited extent (ca. 10% yield). After removal of the TES group from Heck product **58**, single-crystal X-ray analysis of alcohol **64** confirmed that the minfiensine ring system had been assembled (Scheme 13).

To advance tetracyclic alcohol **64** to minfiensine (**1**) required that a double bond and a one-carbon side chain be installed in the cyclohexane ring. These elaborations were accomplished as follows (Scheme 14). Oxidation of alcohol **64** with Dess–Martin periodinane[43] provided ketone **65**. The lithium enolate of this ketone upon reaction with methyl cyanoformate[11] gave β-keto ester **66**, which existed nearly exclusively as the enol tautomer, in 70% yield over the two steps. Upon reaction with excess $NaBH_4$ in THF/MeOH at 0 °C, β-keto ester **66** was converted to largely one β-hydroxy ester product **67**; the relative configuration of the alcohol and ester substituents of this intermediate was not determined, as these stereocenters are cleared in the subsequent step. After more traditional methods to dehydrate β-hydroxy ester **67** to α,β-unsaturated ester **68**, such as reaction with methanesulfonyl chloride or triflic anhydride and triethylamine, met with failure, this conversion was accomplished by a two-step sequence. The sterically hindered secondary alcohol was first activated by reaction with benzoyl triflate[44] and pyridine in CH_2Cl_2 at 60 °C (sealed tube). Exposure of the resulting benzoate to 2 equiv of potassium bis(trimethylsilyl)amide (KHMDS) in THF at −78 °C then delivered enoate **68** in 83% yield for the two steps. Lithium aluminum hydride reduction of α,β-unsaturated ester **68** provided allylic alcohol derivative **69**, which upon reaction with NaOH in $MeOH/H_2O$ at 100 °C gave (+)-minfiensine (**1**) in 85% yield for the two steps. Synthetic (+)-minfiensine (**1**) displayed ^1H and ^{13}C NMR spectral data identical to that reported for the natural product.[1] The optical rotation of synthetic (+)-minfiensine (**1**) was $[\alpha]_D$ +125 (*c* 0.82, $CHCl_3$), which compared well to the rotation of +134 reported under identical conditions for the natural isolate.[1]

Second-Generation Total Synthesis of (+)-Minfiensine: A Much Improved End Play

In our first-generation total synthesis, facile ring opening of the aminal linkage of the pyrrolidinoindoline fragment (see Scheme 6) significantly hindered elaboration of (iminoethano)carbazole **37** to (+)-minfiensine. To side step these obstacles, a second-generation approach should obviate the possibility of double-bond migration during formation of the final ring and minimize the likelihood of fragmentation of the 3,4-dihydro-9a,4a-(iminoethano)-9*H*-carbazole ring system by avoiding intermediates having an electron-donating heteroatom substituent adjacent to the quaternary benzylic carbon. Constructing the final ring by an intramolecular Pd(0)-catalyzed coupling of a ketone enolate and a vinyl iodide side chain, as posited in Scheme 15 (**70** → **71**→ **72**), should

accomplish these objectives. To our knowledge, this ring-forming tactic was first used by Piers in the total synthesis of triquinanes.[45] In recent years, the use of palladium-catalyzed intramolecular α-vinylation of ketone enolates to assemble complex alkaloid ring systems has been demonstrated by insightful studies from the Cook[46] and Bonjoch[47] laboratories.[48] An additional attractive feature of this strategy was the anticipated ease with which ketone **72** could be elaborated to (+)-minfiensine because this ketone can enolize in only one direction; enolization at the allylic α-carbon would generate a high-energy, anti-Bredt enolate.

Elaboration of the cascade asymmetric Heck/iminium ion cyclization product **27** to tetracyclic ketone vinyl iodide **70** is summarized in Scheme 16. As discussed earlier, hydroboration/oxidation of the double bond of tetracyclic intermediate **27** with BH_3 preferentially functionalizes the neopentylic carbon to provide ketone **49** after oxidation (see Scheme 9). Accordingly, we examined hydroboration of this alkene with the sterically larger reagents catecholborane, thexylborane, and 9-borabicyclo-3.3.1]nonane (9-BBN) (Scheme 16). Neither catecholborane nor thexylborane proved sufficiently reactive, returning only unchanged starting material. Similar results were obtained with 9-BBN in refluxing THF. However, hydroboration with 9-BBN did take place rapidly in THF at 100 °C in a microwave reactor. After oxidation of the crude product with TPAP/NMO, ketones **50** and **49** were isolated in a 2.5:1 ratio and a combined yield of 88%. Although regioselection of this hydroboration was only modest, ketone **50** was obtained in 63% yield by this two-step sequence. The Boc-protecting group was readily removed by allowing ketone **50** to react with excess TFA at room temperature. Alkylation of the resulting secondary amine with allylic bromide **73**[43] then provided the ketone vinyl iodide cyclization substrate **70** in 65% yield for the two steps.

With tetracyclic iodoketone **70** in hand, we turned to forming the final ring of (+)-minfiensine by palladium-catalyzed intramolecular enolate/vinyl iodide coupling (Scheme 17). Exposure of this iodoketone to catalytic $Pd(PPh_3)_4$ and KO*t*-Bu (1.5–4 equiv) in various solvents (THF, DMF, DMF/*t*-BuOH)[46] gave none of the pentacyclic product **72**. Elimination of HI to form the corresponding tetracyclic propargylic amine was the major reaction under these conditions, a competing pathway identified by Piers in his seminal report.[45a] Cook employed weaker bases, typically K_2CO_3, to realize palladium-catalyzed enolate α-vinylation reactions in the total synthesis of a number of alkaloids.[47] In our initial examination of these conditions, ketone **70** was exposed to 10 mol % of $PdCl_2(dppf)_2 \bullet CH_2Cl_2$ and excess K_2CO_3 in either DMF or MeCN [dppf = 1,1′-bis(diphenylphosphino)ferrocene]. Alkyne formation was suppressed; however, the only product detected, **74**, under these conditions arose from loss of the (*Z*)-2-iodo-2-butenyl side chain.[46c] Deallylation was also the major pathway when the identical reaction was carried out in 9:1 DMF/water; nonetheless, in this case, pentacyclic ketone **72** was formed in 30–35% yield. A similar low yield of pentacyclic product **72** was realized using $Pd(OAc)_2/Ph_3P$ instead of $PdCl_2(dppf)$. Increasing the percentage of water in the solvent from 10 to 50% (using either DMF or THF as the cosolvent) had no noticeable effect on the outcome of the reaction; competitive formation of secondary amine **74** remained problematic. When performing the reaction in 1:1 MeOH/water using $PdCl_2(dppf)$ and K_2CO_3, the yield of pentacyclic ketone **72** increased to 45–50%, and the formation of the deallylation byproduct **74** decreased to trace levels.[49] The most significant improvement in yield was registered when the reaction was conducted in MeOH using 10 mol % of $PdCl_2(dppf)$ and 4 equiv of K_2CO_3 at 70 °C. Under these conditions, starting material was consumed within 1 h and tetracyclic ketone **72** was isolated in 74% yield.

Tetracyclic ketone **72** is ideally constituted for direct elaboration to (+)-minfiensine (Scheme 17). Straightforward conversion of ketone **72** to the corresponding enol triflate **75**, followed

by palladium-catalyzed carbonylation of this intermediate in MeOH, provided α,β-unsaturated ester **68** in 77% yield for the two steps. This product, $[\alpha]_D$ − 124 (*c* 1.05, $CHCl_3$), displayed spectroscopic properties identical to those of tetracyclic enoate **68** prepared during our first-generation synthesis. As described in more detail in Scheme 14, α,β-unsaturated ester **68** can be converted in two steps and 85% overall yield to (+)-minfiensine, $[\alpha]_D$ +125 (*c* 0.82, $CHCl_3$).

Conclusion

A catalytic asymmetric Heck–iminium ion cyclization sequence was developed that provides either enantiomer of differentially protected 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole **27** in six steps from 1,2-cyclohexanedione (32% overall yield). Notable in this sequence is the use of microwave heating to accelerate the catalytic asymmetric Heck cyclization of dienyl aryl triflate **21**, which even though the reaction temperature is 170 °C provides dihydrocarbazole **25** in 99% ee (Scheme 4).

Two sequences were developed for advancing (iminoethano)-9*H*-carbazole **27** to (+)-minfiensine. In a first-generation approach, a reductive Heck cyclization was employed to form the fifth ring of (+)-minfiensine. Side reactions resulting from facile ring opening of the pyrrolidinoindoline subunit and our inability to carry out a cascade Heck cyclization–carbonylation sequence combined to compromise the efficiency of this inaugural sequence. A second-generation synthesis side stepped these issues by employing an intramolecular palladium-catalyzed ketone enolate vinyl iodide coupling (**70** → **72**, Scheme 17) to construct the final ring of (+)-minfiensine. Using this approach, the cyclization precursor **70** was assembled from the product **27** of cascade asymmetric Heck–iminium ion cyclization in four steps rather than the seven steps required to prepare the related intermediate **48** in our first-generation synthesis. In addition, the functionality present in pentacyclic product **72** produced by enolate α-vinylation allowed the final elaboration to (+)- minfiensine to be shortened to four transformations. This secondgeneration total synthesis of enantiopure (+)-minfiensine was accomplished in 6.5% overall yield and 15 steps from 1,2-cyclohexanedione (**12**) and aniline **13**. A distinctive feature of this concise sequence is the use of palladium-catalyzed reactions to form all the carbon–carbon bonds in the transformation of these simple precursors to (+)-minfiensine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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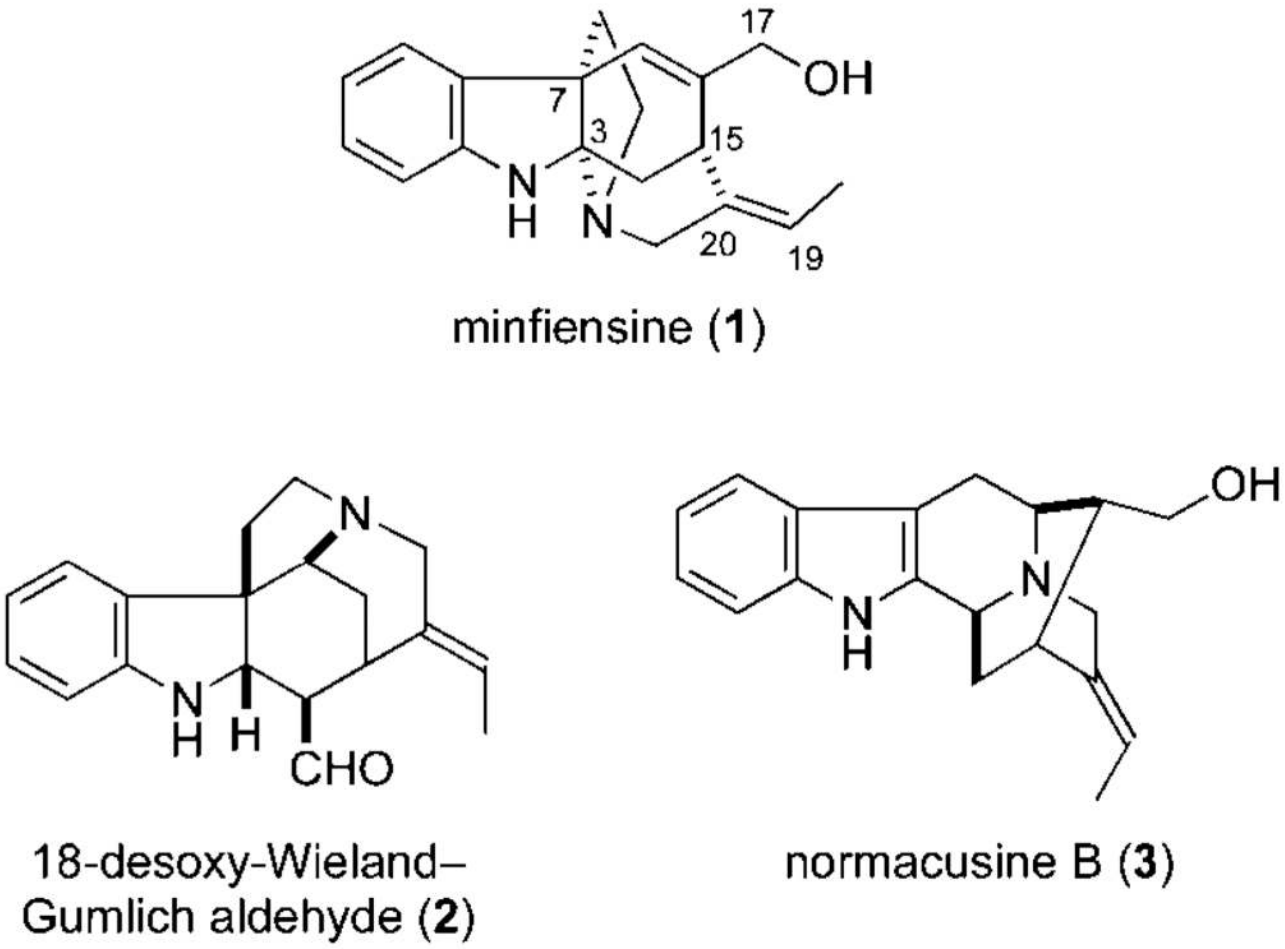


Figure 1.
Minfiensine (**1**) and two additional $C_{19}H_{22}N_2O$ *Strychnos* alkaloids.

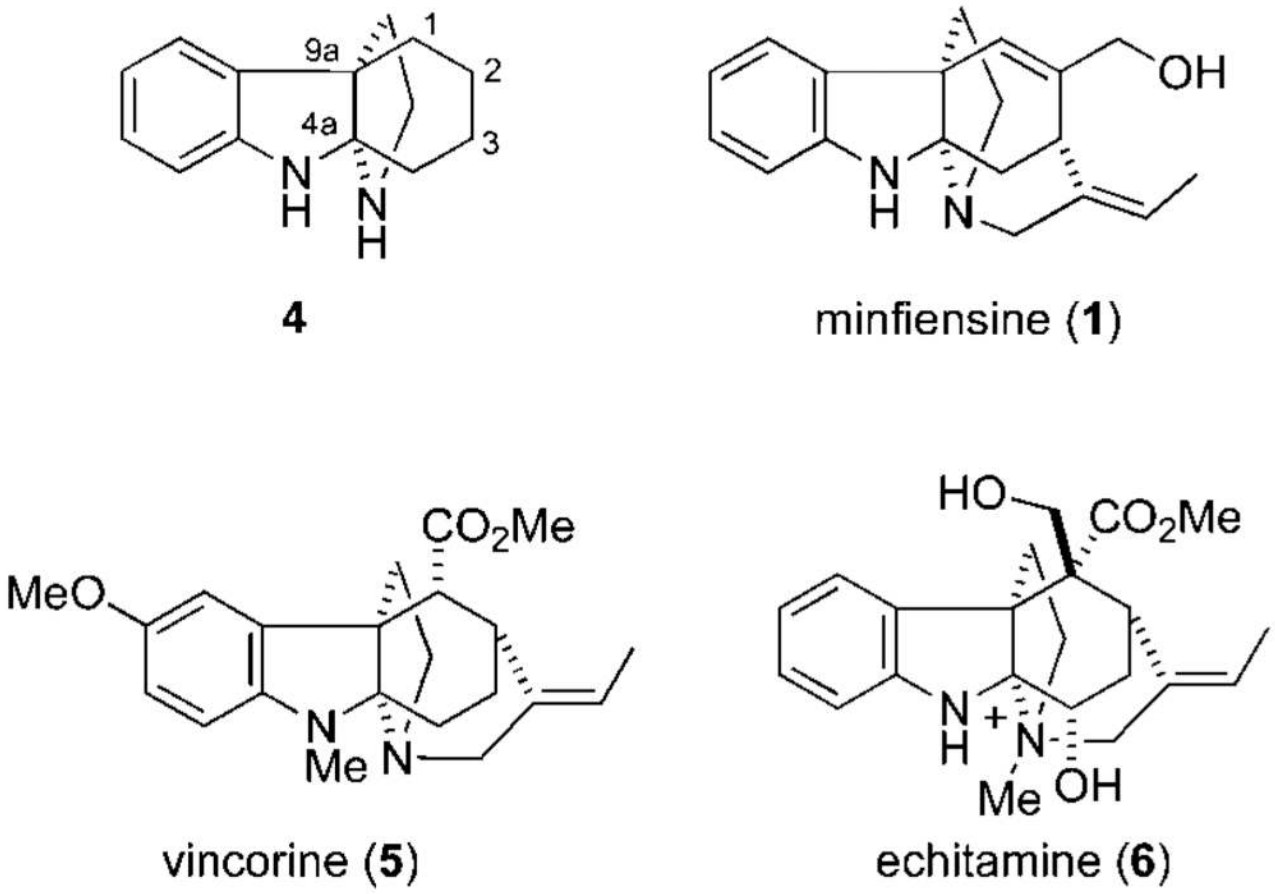


Figure 2.
Representative alkaloids containing a 1,2,3,4-tetrahydro-9a,4a-(iminoethano)-9*H*-carbazole.

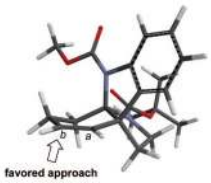
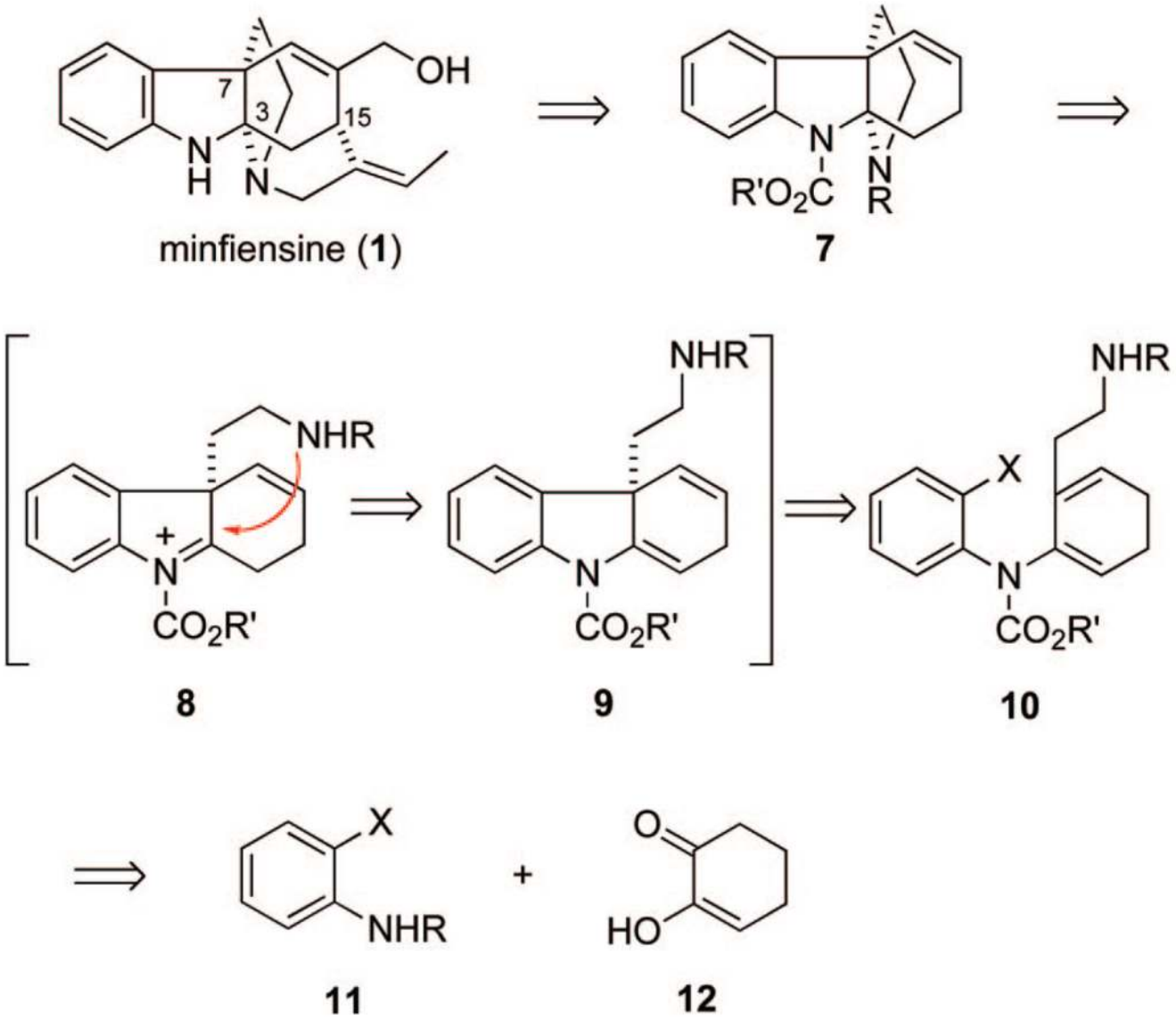
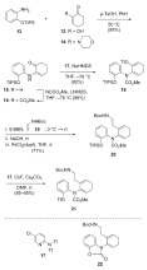


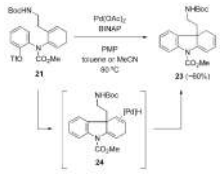
Figure 3.
Proposed rationale for stereoselection in the epoxidation of alkene **27**. Model (6-31G*) of the most stable conformation of alkene **27** showing the favored approach of an oxidant to alkene carbon *b*.



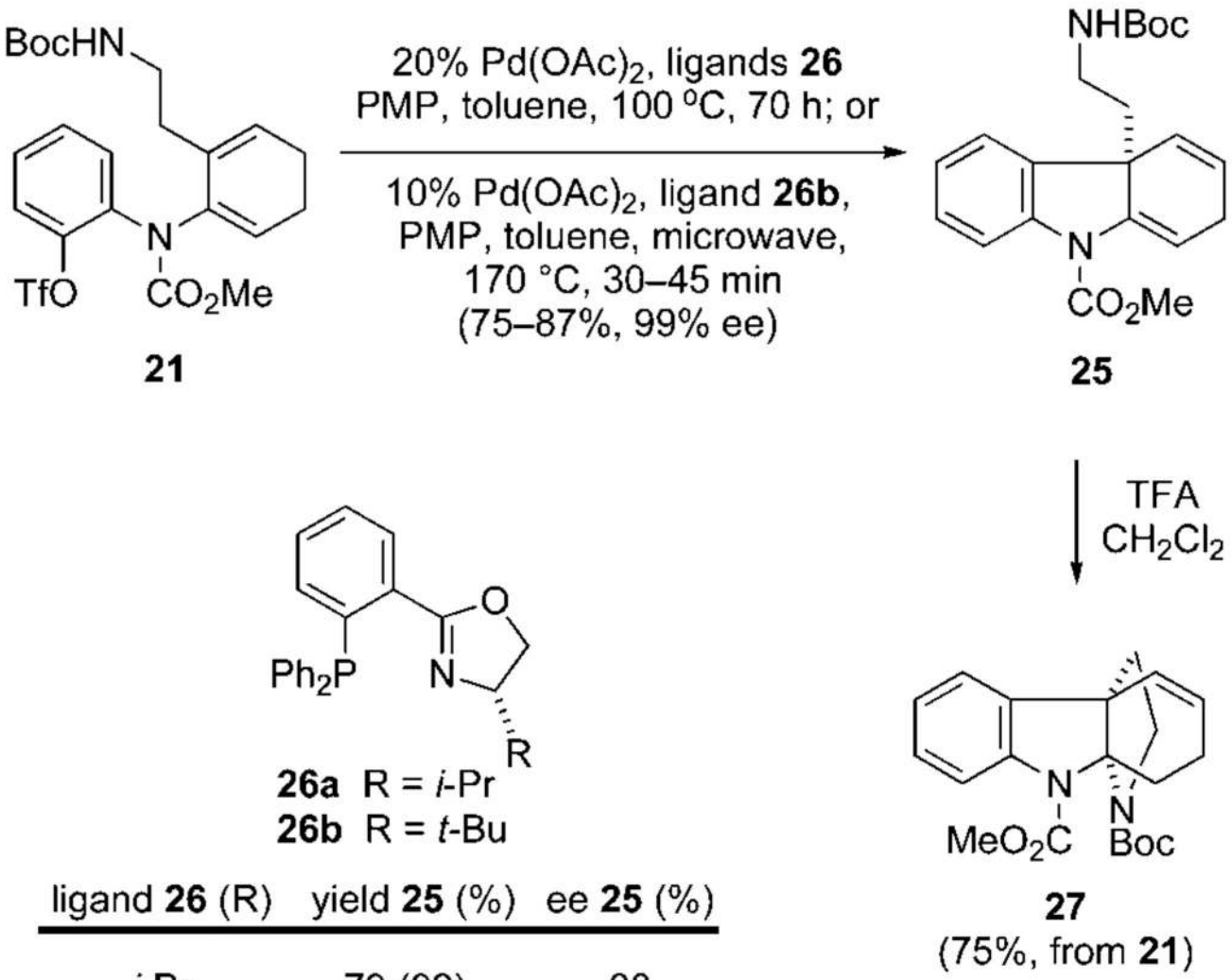
Scheme 1.



Scheme 2.

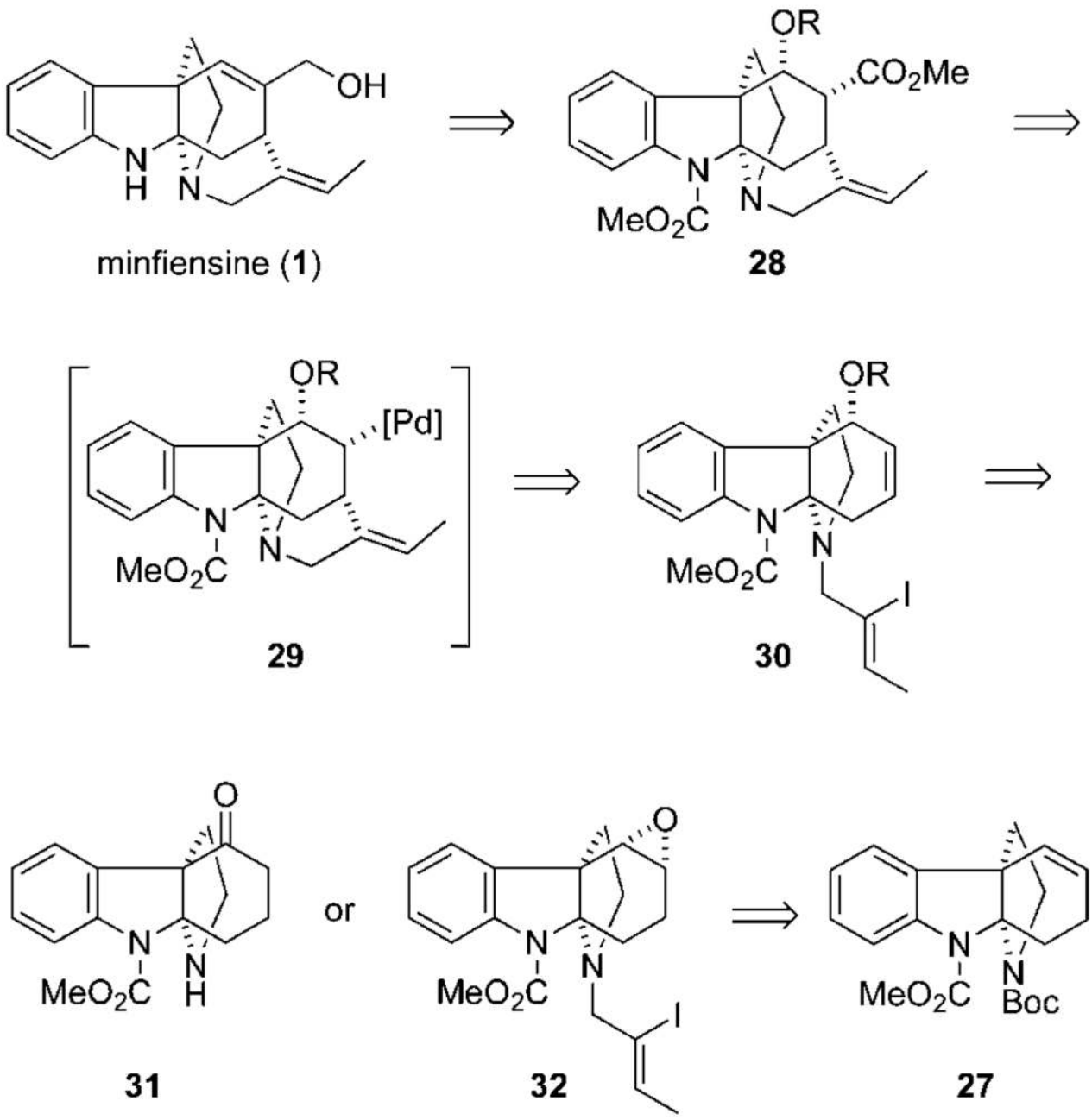


Scheme 3.

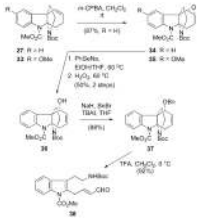


ligand **26** (R)	yield **25** (%)	ee **25** (%)
i-Pr	79 (92)	88
t-Bu	75–85	99

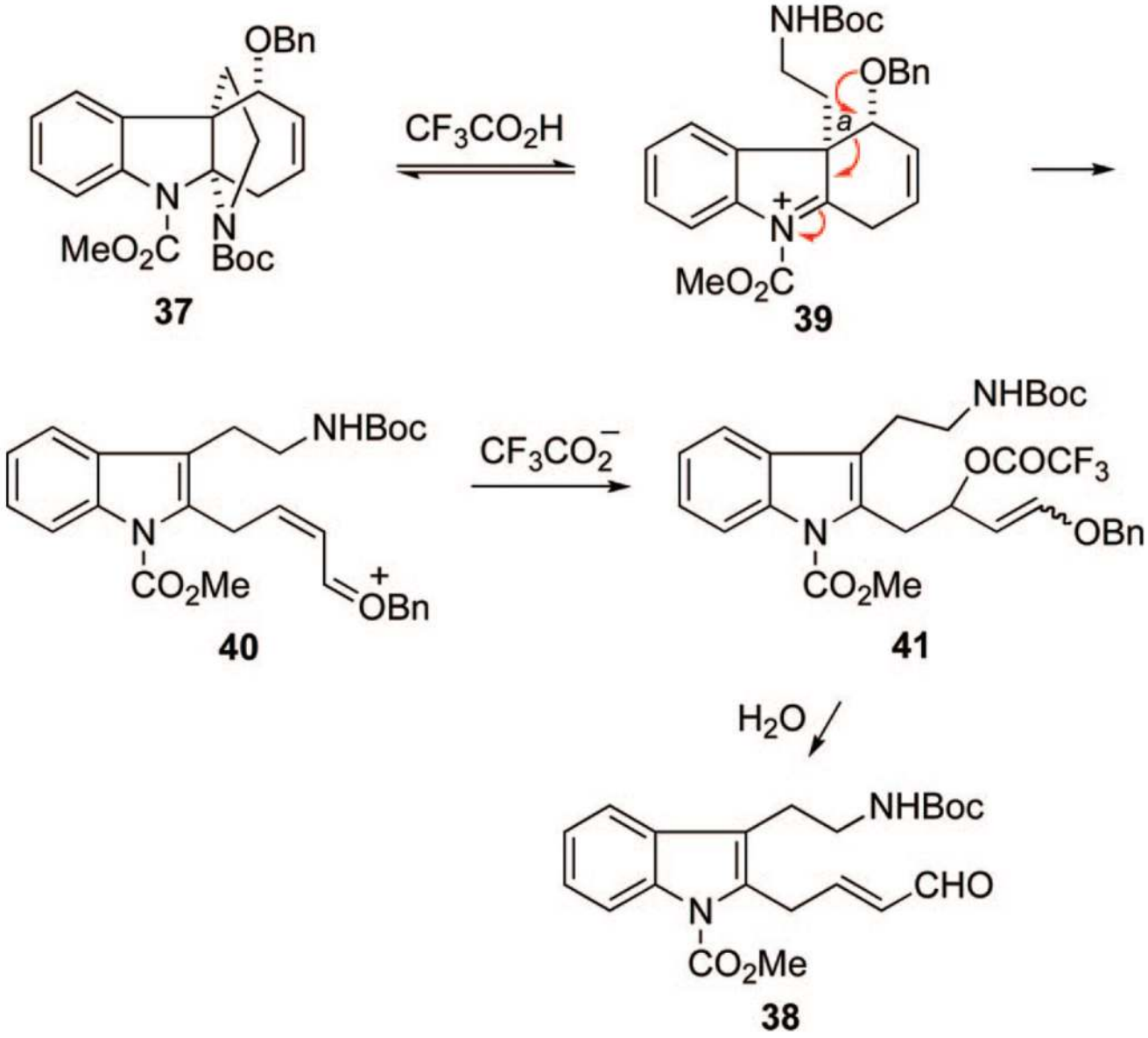
Scheme 4.



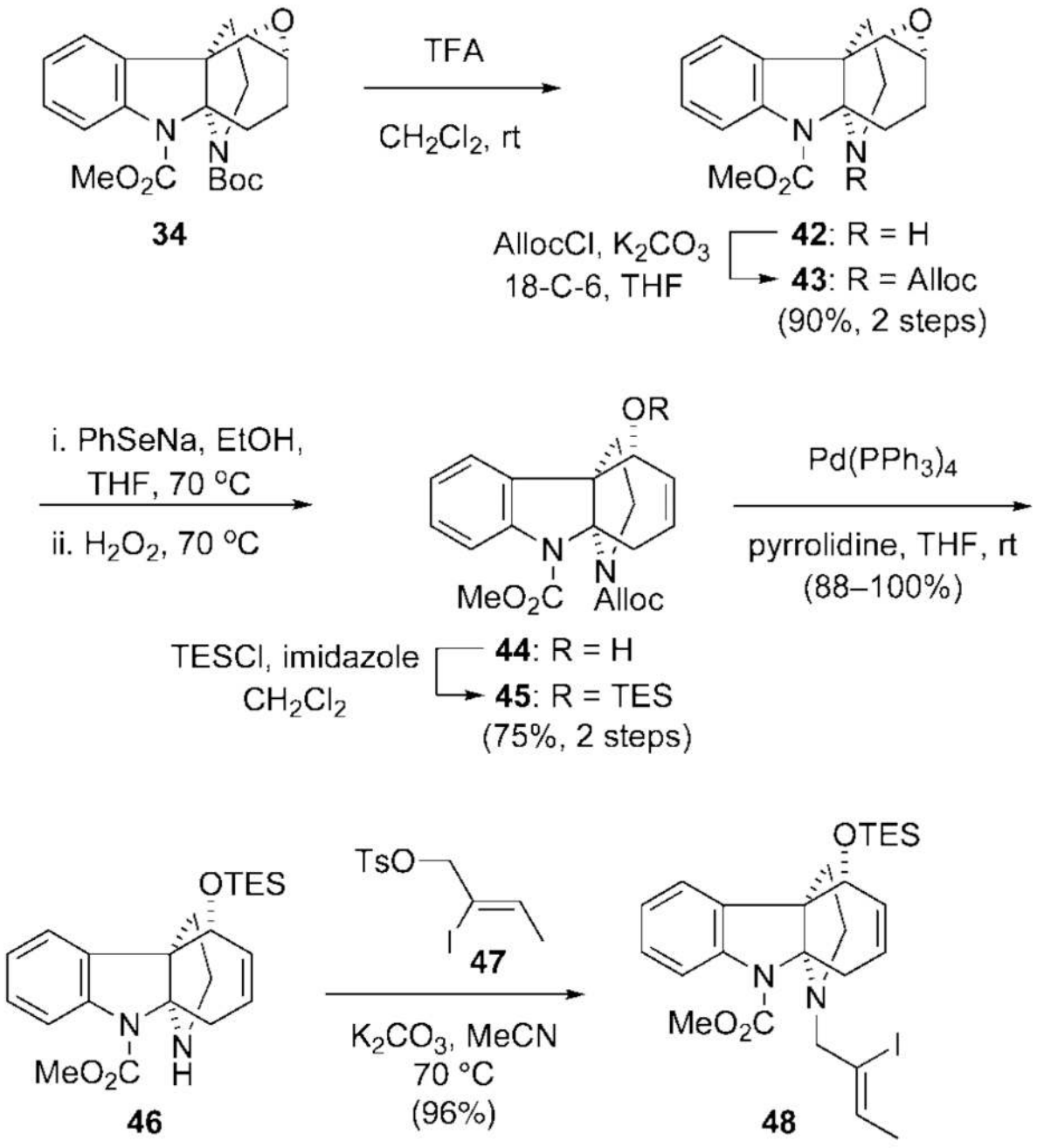
Scheme 5.



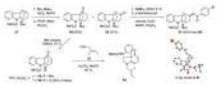
Scheme 6.



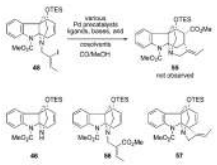
Scheme 7.



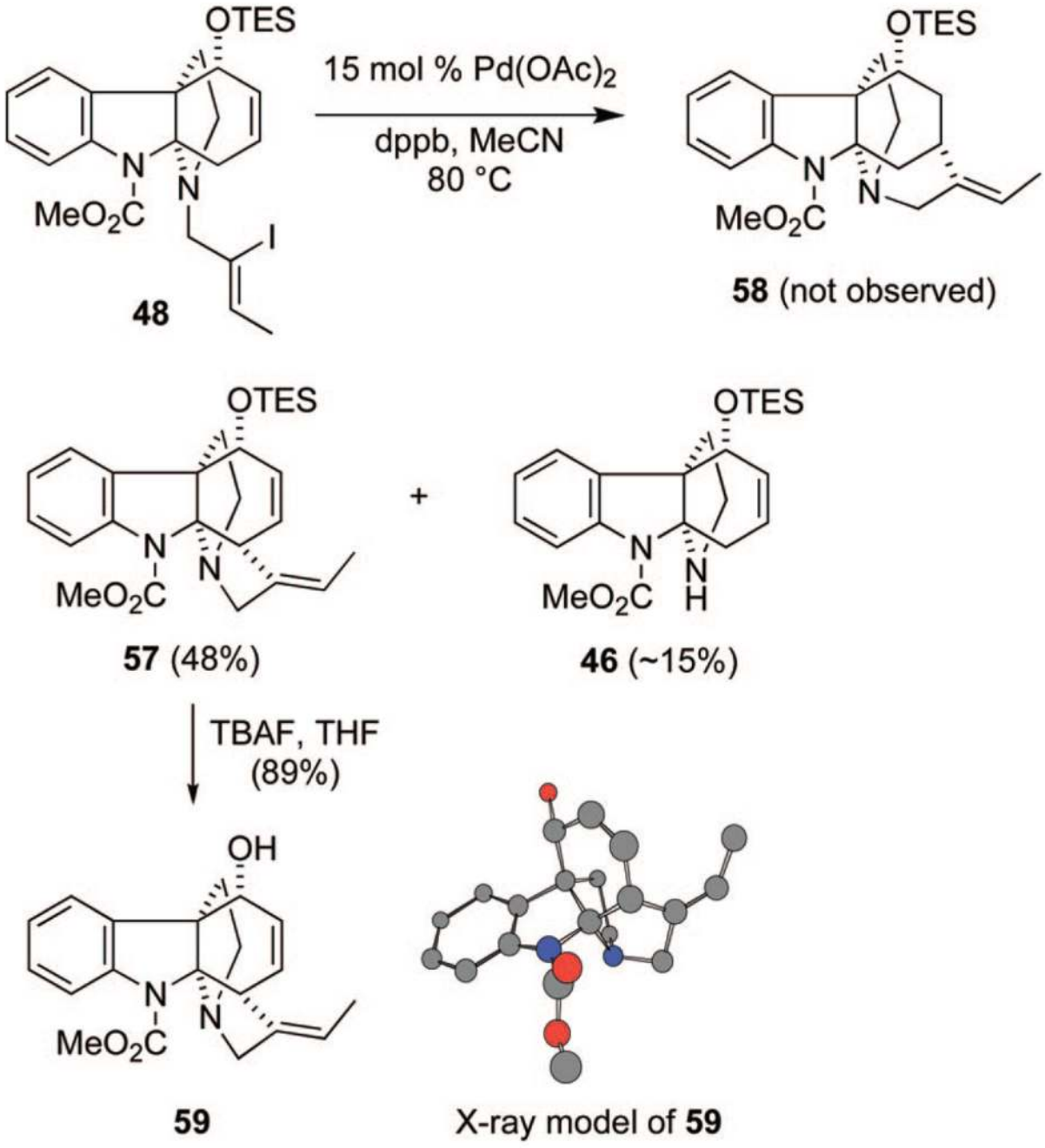
Scheme 8.



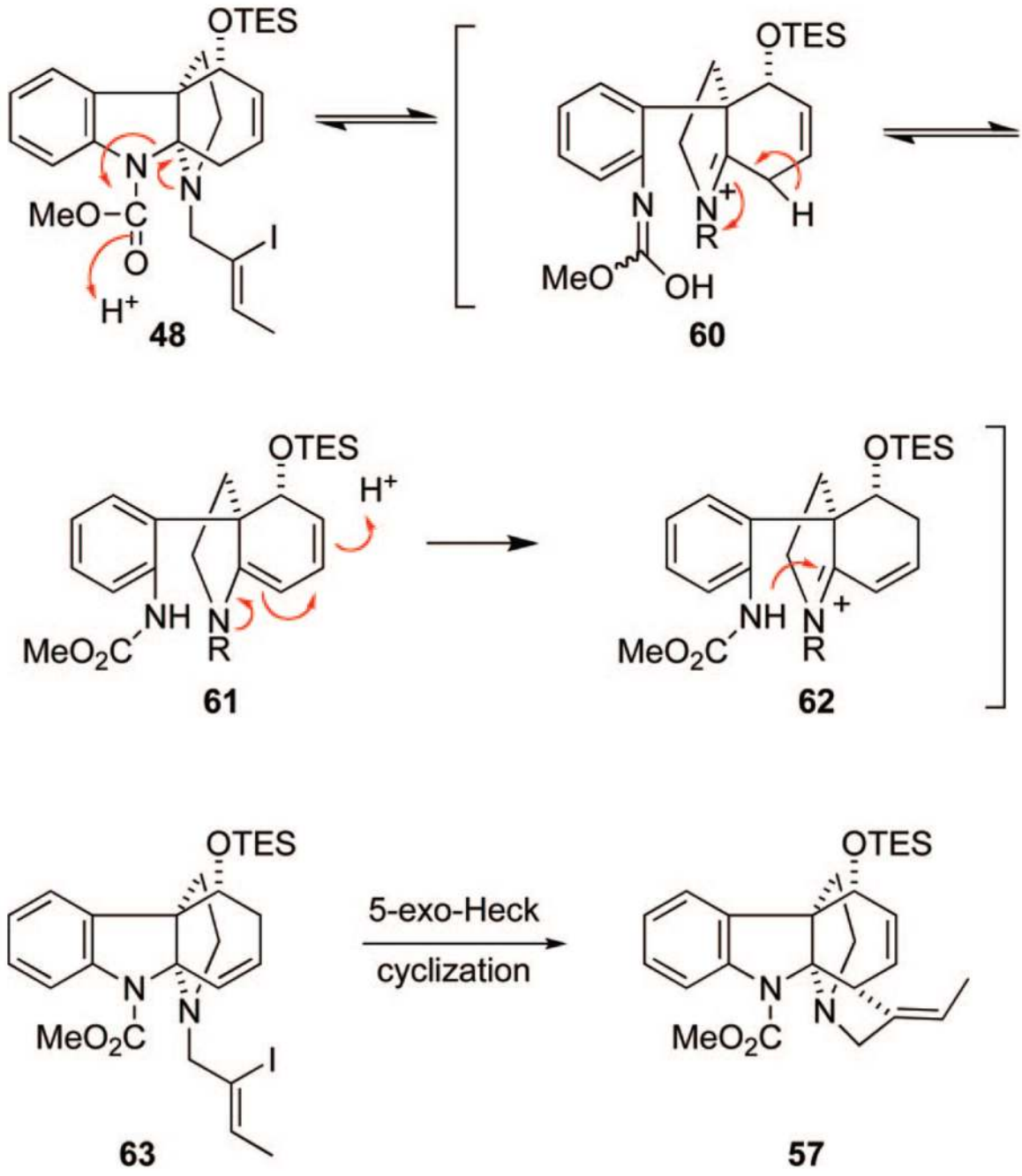
Scheme 9.



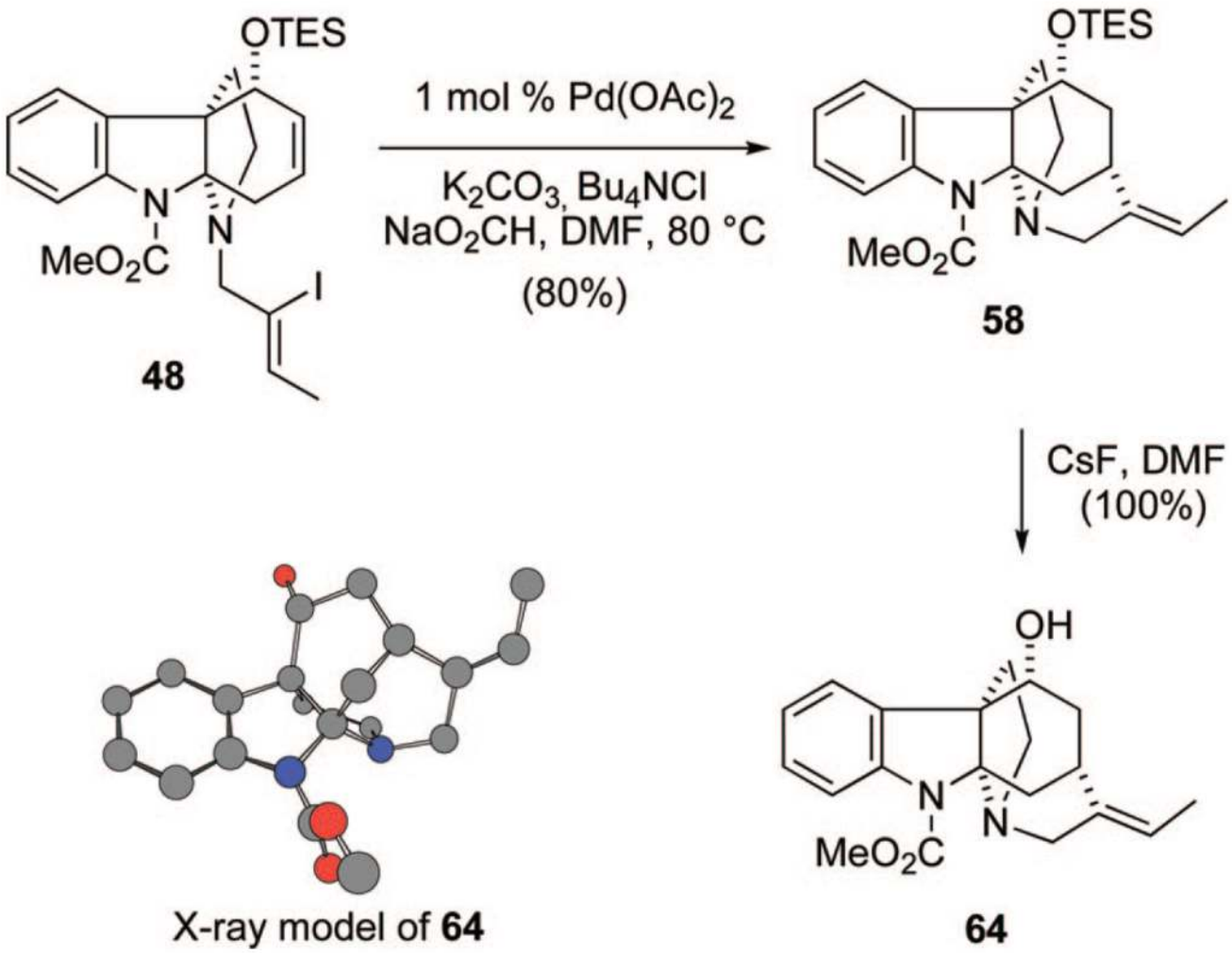
Scheme 10.



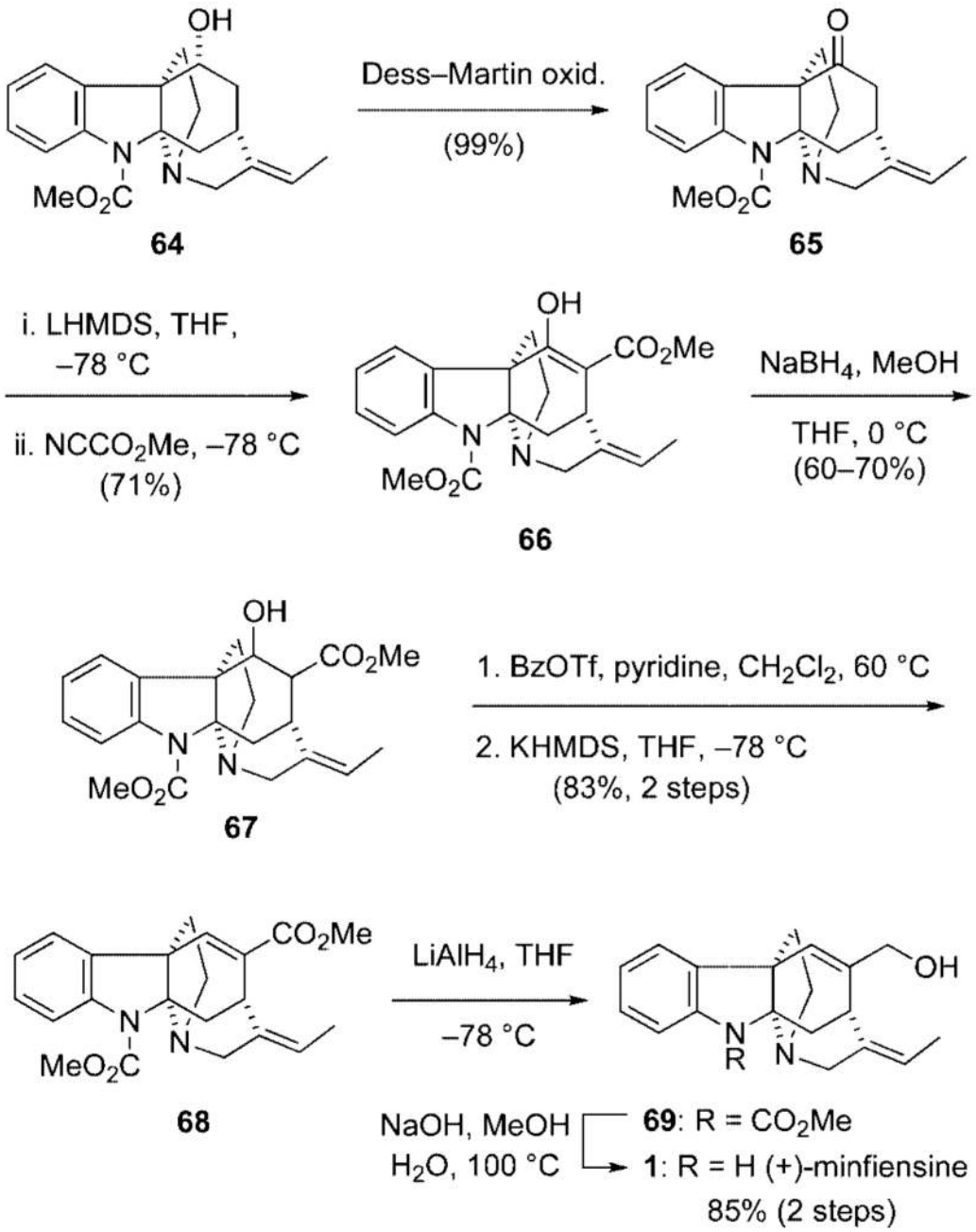
Scheme 11.



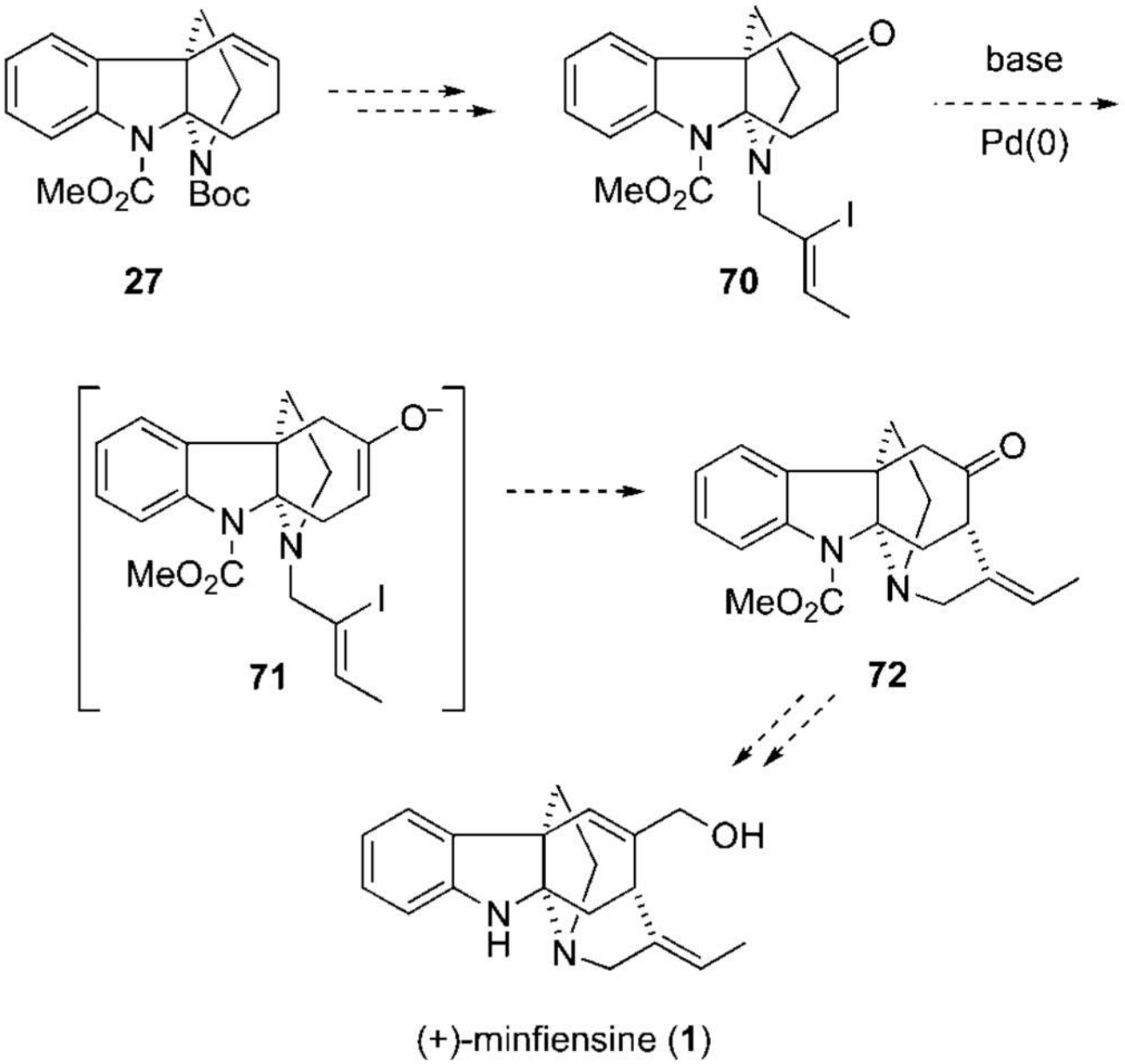
Scheme 12.



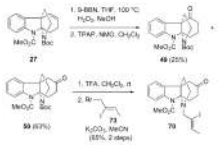
Scheme 13.



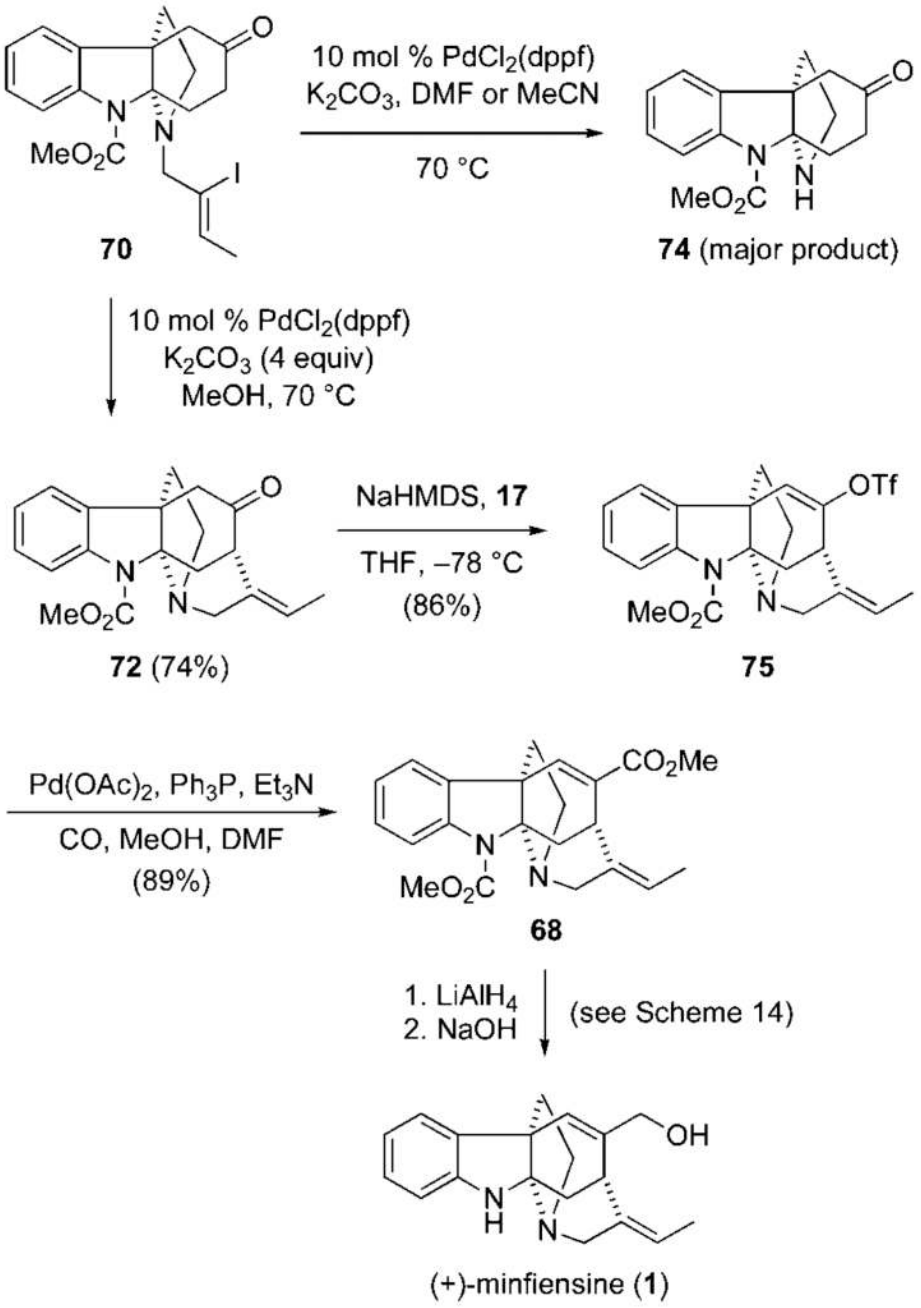
Scheme 14.



Scheme 15.



Scheme 16.



Scheme 17.