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The Chemistry of Bridged Lactams and Related Heterocycles

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1. INTRODUCTION

The amide bond is one of the most important functional groups in chemistry and biology.[1] Due to the strong resonance interaction between n_N and $\pi^*_{C=O}$ orbitals (Figure 1),[2] the vast majority of amides are planar; however, some deviations from planarity have been often observed in peptides[3–14] and small molecules alike.[15–34] Other notable properties of amides resulting from the amide bond resonance[1,2] include (i) relatively short N–C(O) bonds, (ii) high rotational barrier for cis-trans isomerization (typically 15–20 kcal/mol), (iii) resistance of the carbonyl group towards nucleophilic addition and hydrolysis, (iv) minimized ability to engage in coordination at the nitrogen atom, and (v) lower C=O infrared stretching frequencies and more upfield shifts in ^{13}C NMR spectra as compared to other carboxylic acid derivatives. Perhaps because the planar geometry of amides is such an intrinsic part of how we understand amide chemistry, distorted amides that deviate from these norms have attracted the widespread attention of organic chemists.[3–59] To do so, a number of methods to modify the spatial arrangement of substituents around the amide bond have been devised in the last two decades (Figure 2). They include (i) steric repulsion,[11–34] (ii) conformational effects (ring or allylic strain),[35–43] (iii) electronic delocalization (as manifested in amides of XXN–C(O) type where X is an electronegative substituent),[44–54] and (iv) steric restriction[55–59]. Of these four classes, geometrically-restricted amides (bridged, twisted amides)[55–59] are particularly interesting because these amides do not necessarily suffer from excessive steric hindrance around the amide bond[11–43]or the severe electronic influence of neighboring substituents.[44–54] Moreover, bridged amides can be more easily modified and diversified when compared to other classes of distorted amides,[59] and thus represent one of the most straightforward and wide-ranging methods of constraining an amide bond into a non-planar conformation.

In this article, we will provide a comprehensive survey of the synthesis and reactivity of bridged lactams that have been published between 1938 – when Lukeš proposed for the first time[60] that incorporating the amide bond nitrogen atom into a bridgehead position in a bicyclic system would result in a distortion of the resulting bond – until 2012. Owing to the fact that the lone pair of electrons of the nitrogen atom is no longer in conjugation with the adjacent π orbitals of the carbonyl group,[1,2] bridged amides have properties that differ from those of planar amides. These include enhanced reactivity toward amide bond hydrolysis[61–66] and toward nucleophilic attack at the carbonyl atom,[67–69] different

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regiochemistry of amide protonation and alkylation reactions,[70–74] different spectroscopic[16–18,75] and physical properties.[76–83] Besides the insight that such compounds provide into the nature of the amide bond, twisted amides are analogous to the transition state encountered by peptides as they undergo cis-trans isomerisation,[84–87] a critical feature of protein folding.

Bridged lactams have been the subject of previous reviews,[55–59] however a comprehensive review on this topic has not been published prior to this work. In contrast, other strained molecules[88,89] including sterically-hindered amides,[90–94] anomeric amides[95–97] and anti-Bredt olefins,[98–105] have been frequently reviewed in recent years.

The review is arranged by the type of bridged lactams and their method of synthesis. We limited the scope of the review to compounds in which the overall sum of carbon atoms forming the core 1-azabicyclo scaffold is less than or equal to ten. Amides contained in more flexible systems generally have properties analogous to planar amide bonds despite their bridged structures. Some derivatives of bridged lactams (bridged enamines, iminium ions, and sultams) featuring the relevant bond at the bridgehead position in 1-azabicyclo scaffold are also covered. Due to the geometric restriction, these compounds can differ in chemical properties from their planar counterparts in a manner similar to bridged/planar amides.

The general structures of bridged lactams and their derivatives that will be reviewed are presented in Figure 3. Bridged lactams are divided depending on the placement of N–C(O) bond on either one-carbon (**3**) or larger bridge (**2**). Such division is justified by different chemical properties of these two classes of lactams and supported by distinct methods of their synthesis. In general, bridged lactams of the type **3** are more strained and more reactive than their analogs **2**. Furthermore, quinuclidone and admanatanone-derived amides are presented at the beginning of the review because of their historical importance to the advances in the field of bridged lactams, and also because these two classes of compounds provided some of the most strained amide bonds reported to date. The section focusing on the reactivity of bridged lactams emphasizes that the chemical properties of these compounds differ from those of standard amides. In particular, we discuss the hydrolytic behavior, reactivity of the nitrogen atom, reactivity of the carbonyl group, chemical properties of derivatives of bridged lactams. Finally, the specific application of bridged lactams in natural product synthesis and a selection of natural products containing bridged amide bonds are presented.

We hope that this review will serve as a useful reference for chemists involved in probing the effect of amide bond geometry on chemical and biological properties of amides, and those interested in using twisted amides as tools in physical, organic and biological chemistry.

2. GENERAL PROPERTIES OF BRIDGED LACTAMS

2.1. Distortion Parameters of Bridged Lactams

In 1971, Winkler and Dunitz introduced three independent parameters to quantitatively define distortion of amide bonds: twist angle (τ), pyramidalization at nitrogen (χ_N), and pyramidalization at carbon (χ_C) (Figure 4).[106] Twist angle describes the magnitude of rotation around the N–C(O) bond, while χ_N and χ_C define the tetrahedralcharacter of the nitrogen and carbon atom, respectively. A twist angle of 0° corresponds to a planar amide bond and of 90° corresponds to a fully orthogonal bond; χ_N and χ_C are 0° for planar bonds, and 60° for fully pyramidalized amide bonds.

To date, two bridged lactams with perfectly perpendicular amide bonds have been structurally characterized (see **52**,[107] Scheme 7 and **78**,[108] Scheme 16). The remaining bridged lactams display distorted geometries of amide bonds characterized by medium τ and χ_N values. Importantly, for all reported bridged lactams, the χ_C values are close to 0° regardless of the degree of distortion. This tendency reflects the predominant contribution of the amino ketone form to the resonance structure of amides (Figure 1, A and B).[109,110] In this context it is important to note the work by Wiberg and coworkers on the thermochemical stability of amides arising from the third major resonance contributor (Figure 1, C) in which the resonance overlap takes place primarily between carbon and nitrogen with little π electron transfer to oxygen.[76,109,110] Here, we will discuss distortion parameters of specific amides in the section focused on the synthesis of bridged lactams. Moreover, since a large number of bridged lactams with varying Winkler-Dunitz parameters have been characterized, these structurally-defined analogues provide an accurate gauge of the degree of distortion in cases when the X-ray values are not available.

Besides Winkler-Dunitz parameters, distortion of amide bonds can be quantified by the sum of three bond angles at nitrogen (θ).[39] For an ideally sp^3 hybridized atom θ = 328.4°, while for an sp^2 atom θ = 360.0°. In addition, Yamada has proposed a qualitative description of distorted amides based on twist angle and pyramidalization at nitrogen: type A amides with perpendicularly twisted N–C(O) bonds and non-pyramidalized nitrogen atoms, type B amides with planar N–C(O) bonds and sp^3 nitrogen atoms, and type C amides with perpendicular N–C(O) bonds and pyramidalized nitrogen atoms.[91,92]

2.2. Bond Lengths of Bridged Lactams

Upon increased distortion of amide bonds, the length of N–C(O) bond significantly increases, while the C=O bond only slightly shortens.[1,15,111] This tendency reflects significantly larger contribution of the amino ketone resonance form to the resonance structure of non-planar amides (Figure 1), and indicates a gradual pyramidalization of nitrogen occurring with rotation around the N–C(O) bond.[109,110] As a specific example, in a perfectly perpendicular 1-aza-2-adamantanone (**78**)[108] the N–C(O) bond of 1.475 Å is 0.15 Å longer than the corresponding bond in the planar *N*-methyl-δ-valerolactam (1.325 Å),[111] while the C=O bond of 1.196 Å is 0.037 Å shorter the same bond in the *N*-methyl-δ-valerolactam (1.233 Å). In this review, the bond lengths of structurally-characterized bridged amides will be given together with their distortion parameters.

2.3. Spectroscopic Properties of Bridged Lactams

Infrared C=O stretching frequencies of amide bonds are sensitive to changes in the extent of resonance stabilization of the nitrogen lone pair, while carbonyl shifts in ^{13}C NMR spectra of amides respond to changes in the charge density of the carbonyl carbon.[112] Due to the limited resonance contribution of the zwitterionic form **B** (Figure 1), IR and ^{13}C NMR spectra of bridged lactams[16–18] are characterized by increased $\nu_{C=O}$ values and more downfield ^{13}C=O resonances as compared to planar amides. In general, IR and ^{13}C NMR values of amide bonds in bridged lactams appear in the region between those for isolated ketones and planar amides. For example, in the perfectly perpendicular 1-aza-2-adamantanone (**78**), the carbonyl group resonates at 1732 cm^{-1} IR, while the ^{13}C NMR signal appears at 200.0 ppm.[108] In this review, spectroscopic properties of bridged lactams will be discussed only in specific cases and the reader is suggested to consult the primary literature to obtain values of interest.

2.4. Analogy of Bridged Lactams to Bridgehead Olefins

Due to the partial double bond character, bridged amides have been frequently referred to as anti-Bredt lactams.[55–59] In general, bridged lactams are more stable and easier to prepare than the corresponding bridgehead olefins because the amide nitrogen atom can adopt sp^3 geometry in the amino ketone resonance form without violating the octet rule. In contrast, the only alternative resonance structures for anti-Bredt olefins do not possess closed-shell octets and represent high-energy species.[98–105] The importance of the amino ketone resonance form in bridged lactams is manifested by low values of χ_C and the progressive shortening of the C=O bond with increased distortion of the amide bond.[55–59]

To allow prediction of stability and reactivity of bridgehead olefins, in 1981, Schleyer introduced “olefin strain” energy parameter[113] (defined as the difference between the strain energy of the olefin and that of its parent hydrocarbon and directly related to the enthalpy of hydrogenation) as a guide to evaluate accessibility of bridgehead olefins under experimental conditions. Bridged olefins with olefin strain energy lower than 17 kcal/mol were suggested to be isolable, those with olefin strain energy between 17 and 21 kcal/mol classified as observable, and those with olefin strain energy higher than 21 kcal/mol were grouped as unstable.[113] Despite outlined above differences between bridged amides and bridged olefins,[114–116] Schleyer’s olefin strain energy provides a useful predictive tool for evaluating the stability and likelihood of isolation of bridged lactams. Figure 5 presents structures of several of the more common ring systems of bridged lactams, the year of their first synthesis, and the corresponding bridged olefins with their olefin strain energy as calculated by Schleyer.[117–127] From comparison of these values, it is evident that even highly strained bridged lactams are stable enough for isolation (for example, compare bridged olefins **10**, **11**, **17** with bridged lactams **18**, **19**, **25**). Furthermore, in the group of superficially similar bridged lactams **20–24**, the structure **23** is predicted to be the least stable on the basis of the Schleyer's olefin strain energy; indeed, a successful synthesis of this type of bridged lactams has not been reported so far. In contrast, lactams represented by **20** and **24** have been extensively studied in recent years, which led to many insights into the properties of distorted amide bonds,[55–59] in part, because of the stability of the parent lactam scaffolds.

2.5. Chemical and Biological Significance of Distorted Amides

Non-planar amides have been frequently employed to investigate fundamental properties of amide bonds, such as proton exchange,[70–72] bonding,[128–131] rotational barriers,[76–77] chemical reactivity.[67–69] The effect of amide distortion has been leveraged to control chemical transformations[132–140] including hydrolysis,[61–66] acylation,[132–134] desymmetrization[135] and kinetic resolution[136,137] of alcohols. Bridged lactams have been applied as intermediates in the synthesis of bioactive natural products[141–192] and are even present in the structures of several alkaloids.[193–207] Moreover, bridged lactams have been used as model systems[208] for activation of traditionally inert C–N bonds[209–213] in transition metal catalyzed processes.

The study of distorted amides also has important biological consequences. Twisted amides have been invoked in variety of enzymatic transformations including peptide hydrolysis,[61,214–216] protein splicing[217–220] and cis-trans isomerization of peptidyl-proline bonds.[84–86] Inhibition of the latter process is of considerable interest in treatment of drug-resistant cancer cells[221] and neurodegenerative diseases.[222] Furthermore, bridged lactams have been utilized as models for activated peptide units[223–225] in acylation of serine,[226–228] aspartate[229,230] and cysteine proteases,[231] and reported as novel lead structures[232–236] and as constrained analogues[237–246] in medicinal chemistry. Finally, it is worth noting that distorted amide bonds, while not twisted per se, are key structural elements of penicillin and other β-lactam antibiotics.[247,248]

3.SYNTHESIS OF HISTORICALLY IMPORTANT BRIDGED LACTAMS

3.1.Quinuclidone Derivatives

In 1924, Julius Bredt formulated his famous rule, suggesting that bridgehead carbon-carbon double bonds in the camphene and pinene series would be incapable of existence due to the insufficient overlap between their π orbitals.[249] Fourteen years later, in 1938, Rudolf Lukeš applied Bredt's rule to the amide zwitterionic resonance structure, proposing that bicyclic bridged lactams featuring amide nitrogen atom at the bridgehead position would be "sterically impossible" (Scheme 1).[60] Being unsuccessful in preparing bridged amides **27** and **29** by condensation under thermal conditions, Lukeš correctly predicted that if such amides were ever made they would exhibit properties of ketones rather than amides.[60] At about the same time, R. B. Woodward attempted synthesis of related bicyclic 2-quinuclidones **31** (Scheme 1).[250] Although Woodward was unsuccessful in his studies, he also concluded that such compounds would represent a new type of aminoketone (see his comments to this effect in a footnote included in Doering's paper,[251] discussed below).

In 1946, during studies on the autoxidation of quininone, Doering reported the first synthesis (but not isolation) of a bridged lactam (Scheme 2).[251] Treatment of the potassium enolate of quninone **32** with molecular oxygen afforded quinic acid **33** and amino ester **34**. The amino ester **34** was proposed to arise from a rapid alcoholysis of the corresponding bridged lactam **32c** by *tert*-butanol, which was used as a solvent for the reaction. The inability to directly isolate **32c** and its subsequent in situ transformation forecasted the increased reactivity of twisted amides embedded in unsubstituted quinuclidin-2-one scaffolds.

In 1957, Yakhontov reported that the intramolecular condensation of amino acyl chloride **38**, afforded the parent quinuclidin-2-one (Scheme 3).[252] However, the isolation of the bridged lactam **18** as reported by Yakhontov has been questioned in the literature on several occasions[253,254,107] because of the propensity of unsubstituted quinuclidin-2-ones to polymerize, vigorous conditions utilized for the synthesis of lactam **18** and the lack of any characterization data save elemental analysis of nitrogen.[252]

During the same time period, Pracejus found that in contrast to the parent 2-quinuclidone **18**, the dimethyl analogue **44** could be reliably prepared using an intramolecular condensation of the corresponding amino acyl chloride (Scheme 4).[253] Subsequently, the research groups of Pracejus[254,255] and Yakhontov[256–258] studied the synthesis of 2-quinuclidones **46**, in which bridged amide bonds were protected from nucleophilic opening by the presence of methyl substitutents near the amide moieties (Scheme 5). More recently, Greenberg optimized the conditions for preparation of 6,6,7,7-tetramethyl-2-quinuclidone **46c** (Scheme 6).[259] It was found that the previously published method for the synthesis of qunuclidone **46c**[256,257] gives almost exclusively polymeric material. Using high dilution techniques, the highly-strained lactam **46c** was obtained in modest yield.[259]

In 2006, Tani and Stoltz achieved an unambiguous synthesis of the iconic twisted amide, 2-quinuclidone, using an intramolecular Schmidt reaction as the key step (Scheme 7).[107] This method allowed for the rigorously anhydrous conditions required for isolation of the unstable lactam **52** (in water, its $t_{1/2}$ was found to be less than 15 s).[107] The Schmidt reaction produced the parent 2-quinuclidone protected as its trifluoroborate salt, thus preventing the lactam from extensive polymerization. To our knowledge, this was the first example of an *N*-protonated amide bond to be characterized by X-ray crystallography. The initial Schmidt reaction afforded a mixture of lactams **52** and **53** resulting from migration of the two possible alkyl groups to nitrogen (Scheme 8), from which the desired compound was isolated by crystallization. Through careful optimization, it was found that the use of HBF_4 in ether as a solvent provided the best system for this reaction, while other acids resulted in lower regioselectivity. The X-ray structure of the protonated amide **52** indicated a fully orthogonal amide bond ($\tau = 90.9°$; $\chi_N = 59.5°$; $\chi_C = 0.2°$; N–C(O) = 1.526 Å; C=O = 1.192 Å).[107]

Subsequently, Stoltz reported a gas-phase synthesis of the protonated 2-quniclidonium **52** (Scheme 9).[260] Using kinetic proton affinity measurements, the authors determined that lactam **52** is characterized by a much higher basicity (proton affinity = 965 kJ/mol) than typical amides (proton affinity = 880–900 kJ/mol), which is consistent with a low degree of amide resonance in **52**.[260] DFT calculation suggested that *N*-protonation of **52** is favored over *O*-protonation by approximately 90 kJ/mol.[260] These studies are in a good agreement with earlier DFT calculations carried out by Greenberg, which suggested that *N*-protonation of **52** is favored over *O*-protonation by 100 kJ/mol.[70,71]

In comparison with simple 2-quinuclidones, their benzo-substituted analogues are less prone to hydrolysis and polymerization. In 1980, Blackburn reported the synthesis of lactam **60** by intramolecular amide coupling reaction under standard conditions in high yield (Scheme 10).[261] Shortly thereafter, Brown and coworkers reinvestigated the synthesis of this and

related benzoquinuclidones.[223–225] Under their conditions, DCC was applied as a more efficient coupling reagent (Scheme 11).[223] Utilizing a similar protocol, Brown has accomplished the synthesis of related benzo-fused bridged lactams (Scheme 12).[224,225] Notably, these lactams did not require special precautions during synthesis and isolation despite highly-strained structures. X-ray structures of amides **64a–c** indicated a progressive decrease of amide bond distortion in the series **64a** ($\tau = 30.7°$; $\chi_N = 57.2°$; $\chi_C = 9.0°$; N–C(O) = 1.401 Å; C=O = 1.216 Å), **64b** ($\tau = 33.2°$; $\chi_N = 52.8°$; $\chi_C = 11.0°$; N–C(O) = 1.413 Å; C=O = 1.225 Å), and **64c** ($\tau = 15.3°$; $\chi_N = 38.6°$; $\chi_C = 4.3°$; N–C(O) = 1.370 Å; C=O = 1.233 Å).[262] Interestingly, lactams **64a** and **64b** were characterized by almost completely pyramidal nitrogen atoms with only moderate tortional distortion of p-orbitals. Subsequently, a similar divergence between χ_N and τ values has also been found in other types of bridged lactams (see Section 4.3). Infrared stretching frequencies of C=O bonds demonstrated that lactam **60** is the most twisted compound in the series **60** (1755 cm^{-1}), **64a** (1705 cm^{-1}), **64b** (1712 cm^{-1}), and **64c** (1677 cm^{-1}).[223–225]

Additional examples of synthesis of 2-quinuclidones include oxidation of amines to the corresponding lactams under Gif conditions (Scheme 13)[263] and stereoselective rearrangement of modified Cinchona alkaloids to bridged lactams as reported by Hoffmann (Scheme 14).[264,265] Both are reminiscent of the attempted reactions reported by Doering (cf. Scheme 2),[251] but are low yielding and limited to specific cases.

3.2. Adamantanone Derivatives

Due to the enforced proximity in rigid molecular frameworks, derivatives of adamantane are useful templates to study stereoelectronic effects. In 1990, Rebek reported a remarkable rate enhancement in cyclization reactions involving nitrogen atoms of lactam and imide functions prepared from Kemp triacid (Scheme 15).[266] The involvement of bridged imide **71a** and imidinium **72a** was inferred on the basis of racemization of optically active precursors[267] and deuterium labeling studies.

In 1998, Kirby, while studying the reverse anomeric effect,[268,269] achieved the synthesis of 1-aza-2-adamantanone **78** (Scheme 16).[270,108] The amino acid precursor **77** was prepared from the commercially available Kemp triacid **73** in an eight-step sequence.[108] A proximity-induced cyclization carried out by sublimation afforded lactam **78** in quantitative yield. The X-ray structure of amide **78** indicated a perfectly perpendicular amide bond ($\tau = 90.5°$; $\theta = 325.7°$; N–C(O) = 1.475 Å; C=O = 1.196 Å).[108] Moreover, the chemical[271,108] (see Sections 7.1–7.2) and spectroscopic properties[108] (see Section 2.3) of **78** are in full agreement with keto-amine-like character of the amide bond in this system. Like the unstabilized 2-qunuclidone **52** prepared by Stoltz,[107] lactam **78** also undergoes rapid hydrolysis in water ($t_{1/2} < 50s$).[272]

The methyl substituents in 1-aza-2-adamantanone derivatives like **78** help to keep the amino group in close proximity to the carboxylic acid, thus facilitating condensation to the lactam(Figure 6).[273,274] Accordingly, computational studies on the stability of **78** revealed that methyl substituents destabilize the amino acid form and contribute to the overall stability of Kirby's amide.[275]

In 2003, Coe prepared bridged lactam **85**, which is a higher homologue of 1-aza-adamantanone, as an intermediate in the synthesis of nicotinic receptor ligands (Scheme 17).[232] The key reaction involved base-catalyzed condensation of the open-form amino ester to the bridged lactam **85** under thermal conditions. The final precursor **84** was quickly assembled from cyclopentene **81**, using Heck reaction and reductive amination as key transformations. The infrared stretching frequency of the C=O group (1728 cm^{-1}) and instability to the aqueous conditions were consistent with a highly-strained structure of lactam **85**.

4. SYNTHESIS OF BRIDGED LACTAMS WITH N–(CO) BOND ON TWO-CARBON OR LARGER BRIDGE, ([m.(≥ 2).n] Type)

The synthesis of bridged lactams with the N–(CO) bond placed on a bridge having two or more carbons is challenging because of the strain associated with distorted amide bonds and general lack of stabilizing features on the lactam skeleton (cf. alkyl-quinuclidones and adamantine-derived lactams). In some cases, the high reactivity of non-planar amide bonds may be incompatible with the reaction conditions used for their synthesis. In this section, bridged lactams are classified based on the reaction type employed for their preparation. Condensation reactions that directly form the amide bond can be used to prepare this type of lactams. However, alternative approaches with the amide bond already present in the precursor usually lead to more strained and diverse examples.

4.1. Condensation Reactions Forming N–C(O) Bond

The first synthesis of a 1-azabicyclo[3.3.1]nonan-2-one derivative was reported by Walker and coworkers in 1949 (Scheme 18).[276] During studies on hydrogenation reactions catalyzed by copper chromite, these researches performed an intramolecular condensation of the cyano diester **86** to the bridged lactam **87**, which was further reduced under the reaction conditions to 1-azabicyclo[3.3.1]nonane **88** in 39% yield. Concurrently, Albertson reported that the hydrogenation of another cyano ester **89** over Raney nickel catalyst gave two compounds, one of which was originally assigned as bridged lactam **90** (Scheme 19a).[277] However, upon reinvestigation of this transformation, Albertson found that the compound originally proposed as lactam **90** was more consistent with the bicyclic enaminone **93** (Scheme 19b).[278]

In 1980, Hall reported the synthesis of 1-azabicyclo[3.3.1]nonan-2-one **96** applying vacuum pyrolysis conditions (Scheme 20).[279] Although the yield was very low, lactam **96** could be separated from the polymer **97** by sublimation from the reaction mixture. The condensation of the corresponding acid chloride using a protocol developed by Yakhontov and Pracejus for the synthesis of 2-quinuclidones (Schemes 3–5)[252–258] was unsuccessful in this case. Based on its infrared stretching frequency of 1680 cm^{-1}, stability in water, and moderate tendency to undergo polymerization, Hall proposed lactam **96** to be only slightly distorted from planarity.[279] However, subsequent structural characterization of related lactams containing [3.3.1] bridged system[280–283] and mechanistic studies by Greenberg[284,70,71] clearly demonstrate that 1-azabicyclo[3.3.1]nonan-2-ones are sufficiently non-planar to protonate at nitrogen and display other keto-amine-like characteristics.

In 1981, Buchanan improved the synthesis of 1-azabicyclo[3.3.1]nonan-2-ones by using a gem-dialkyl effect to facilitate cyclization to the bridged amides (Scheme 21).[280,281] With substrate **99** containing a phenyl substitutent at C–3 position (cf. the methyl groups in the Kirby's 1-aza-2-adamantanone, Figure 6), both thermal cyclization under high vacuum and condensation from the corresponding acyl chloride afforded the desired lactam **87**, albeit again in low yield. It is worth noting, that in analogy to bridged lactams featuring [2.2.2] ring system (Section 3.1), the classic intramolecular amine-acid chloride condensation approach provides synthetically more useful results when 1-azabicyclo[3.3.1]nonan-2-one scaffolds are stabilized by additional substitutents (cf. Schemes 26 and 27). On the basis of NMR studies, Buchanan concluded that lactam **87** exists in solution in the chair-boat conformation.[280] Related compounds, such as lactam **96** (Scheme 20)[279] and the analogous anti-Bredt olefin, bicyclo[3.3.1]non-1-ene,[285] also favor the chair–boat conformation, which has been explained on the basis of their preference to place the trans double bond in the larger ring.[102] Buchanan reported the X-ray structure of lactam **87** ($\tau = 20.8°$; $\chi_N = 48.8°$; $\chi_C = 5.9°$; N–C(O) = 1.374 Å; C=O = 1.201 Å).[282] These values together with the infrared stretching frequency of 1695 cm^{-1} indicate a moderate distortion of the amide bond in **87**.

The synthesis of 1-azabicyclo[3.3.1]nonan-2-ones was further improved when Steliou introduced Bu_2SnO as an efficient promoter for difficult lactamizations.[286] Under high dilution (0.005 M), the synthesis of lactam **96** was thus achieved in 77% yield (Scheme 22). However, this reagent was ineffective for synthesis of eight-membered and larger lactams. Subsequently, Sim applied Bu_2SnO in the synthesis of the structurally-related 1-azabicyclo[3.3.1]nonane-2,6-dione (Scheme 23).[283] The X-ray structure of lactam **103** ($\tau = 16.3°$; $\chi_N = 49.1°$; $\chi_C = 5.8°$; N–C(O) = 1.377 Å; C=O = 1.217 Å),[283] and the infrared stretching frequency of 1680 cm^{-1} mirror the properties of **87**.[282] This study further confirmed that lactams with the N–C(O) bond placed at one of the larger bridges are characterized by large χ_N values and moderate twist angles (cf. lactams **64a–c** prepared by Brown (Scheme 12)).[262] A tin-mediated lactamization protocol was also employed by Gerlach in a rare example of the synthesis of an enantiomerically-enriched bridged lactam (Scheme 24).[287] Earlier, Pracejus had prepared lactams **44** and **46a–b** in enantiomerically enriched form by resolution of the intermediate amino esters with dibenzoyl-D-tartaric acid.[253–255]

In another study, Najera noticed a significant difference in cyclization rates between diastereoisomeric amino esters to form bridged lactams **107** (Scheme 25).[288] The endo lactam was obtained quantitatively during removal of the benzyl group, whereas amino lactam **106** was more resistant to condensation. However, the corresponding lactam **107-exo** was generated in a separate step after treatment of the amino ester with LDA. Based on NOE analysis, these authors proposed that lactam **107-endo** exists in a twist boat-boat conformation due to steric interactions between the axial methyl group and an axial hydrogen atom, while the lactam **107-exo** adopts the usual chair-boat conformation.

As is the case with benzo-2-quinuclidones (see Schemes 10–12),[223–225,261,262] appendage of a fused aromatic ring improves the stability of 1-azabicyclo[3.3.1]nonan-2-ones. Cuny reported intramolecular lactamization to yield quinolino-substituted 1-azabicyclo[3.3.1]nonan-2-ones using thionyl chloride (Scheme 26).[289] Modification of the

reaction conditions resulted in the concomitant introduction of the chloride in the 2-position of quinoline ring. Lactam **110** was further derivatized via nucleophilic aromatic substitution. Denzer and Ott reported the synthesis of two different ring systems of bridged lactams, while studying new 1,5-benzodiazocine derivatives with potential biological activity (Scheme 27).[290] The amino acid precursors were readily prepared by dearomatization of the corresponding quinazolines. Cyclization using mixed anhydride protocol offered an advantage over the standard conditions with thionyl chloride/triethylamine in terms of yields of isolated products. The highly twisted nature of amide bonds in these lactams was confirmed by infrared stretching frequencies (**112**: 1720 cm^{-1}; **114**: 1780 cm^{-1}), rapid hydrolysis in water, and chemical reactivity (see Schemes 116 and 137). Compound **114** is one of the very few examples of reported bridged lactams bearing a [3.2.1] scaffold.

4.2. Heck Reactions

Grigg has pioneered the use of Heck reaction for the synthesis of bridged lactams featuring the N–(CO) bond on external bridge (Scheme 28).[291,292] With a catalyst system consisting of $Pd(OAc)_2$ and PPh_3, 6-exo-trig and 7-exo-trig cyclizations of enamide substrates occurred in high yields to generate a variety of bridged amide scaffolds. Isomerization of the double bond in products was rarely observed. An attempt to form the bridged lactam with a [3.2.1] ring system was unsuccessful, reflecting a high ring strain present in the transition state (Scheme 29).[292] Subsequently, Grigg extended this method by combining the Heck reaction with ring-closing metathesis (RCM) in a tandem process (Scheme 30).[293,294] In a telescoped sequence, bridged lactams **124a** and **118a** were prepared from simple acyclic starting materials in a one-pot transformation.[294] This methodology was also employed for the synthesis of analogous bridged sulfonamides (see Section 6.5).[291–294] More recently, Paquette reported the synthesis of [4.3.1], [3.3.2] and [4.3.2] bridged lactams via Heck reaction utilizing similar conditions to those reported by Grigg (Scheme 31).[295] The enamide substrates were synthesized by RCM of acyclic dienes, again providing an efficient route to bridged lactams.

Judd and coworkers developed an exceptional tandem reaction sequence for the synthesis of bridged lactams employing the Heck reaction as a key step (Scheme 32).[296] Starting from commercially available reagents, sequential Ugi and RCM reactions rapidly provided advanced intermediates. The subsequent Heck reaction was accomplished under microwave irradiation conditions using $Pd(PPh_3)_2Cl$ or immobilized palladium catalysts to deliver bridged lactams **133** in high yields and short reaction times. The X-ray structures of lactams **133** indicate significant degrees of pyramidalization at nitrogen (**133a**: $\tau = 33.4°$; $\chi_N = 49.1°$; **133b**: $\tau = 7.1°$; $\chi_N = 35.3°$; **133c**: $\tau = 17.6°$; $\chi_N = 26.2°$; **133d**: $\tau = 19.8°$; $\chi_N = 31.1°$; **133e**: $\tau = 19.8°$; $\chi_N = 15.9°$).[296] Impressively, this study provided full structural characterization of four different ring systems of bridged lactams. Currently, the Heck reaction is one of the most reliable methods for the synthesis of bridged lactams with the N–(CO) bond on a larger bridge.

4.3. Diels-Alder Reactions

Shea reported the synthesis of bridged lactams containing bridgehead olefins via thermal type II intramolecular acyl-imino Diels-Alder reaction (Scheme 33).[297,298] Heating the

acetoxy amides under high dilution conditions resulted in elimination of acetic acid and [4+2] cycloaddition of the intermediate *N*-acyl imines. Under the optimized conditions, the reactions were not allowed to reach full conversion because of the thermal instability of the bridged lactams. The synthesis of lactam **142a** required a strictly inert atmosphere because the bridgehead olefin present in **142a** readily formed the corresponding epoxide upon exposure to air (see Scheme 154).[298] On the other hand, the lower yield of lactam **142d** was postulated to result from a competing ene reaction of the *N*-acyl imine intermediate.[298] In all of these Diels-Alder reactions, only one regioisomer was observed due to a short tether between the reactive functionalities (Scheme 34) – products resulting from the exo transition state were not detected.

The X-ray structures of analogues **142a–c** were solved.[298] As expected, they show a progressive decrease of the amide bond distortion in the series **142a** (τ = 16.7°; χ_N = 54.9°; χ_C = 1.4°; N–C(O) = 1.399 Å; C=O = 1.215 Å), **142b** (τ = 7.5°; χ_N = 46.4°; χ_C = 1.2°; N–C(O) = 1.375 Å; C=O = 1.219 Å), and **142c** (τ = 0.9°; χ_N = 38.2°; χ_C = 0.2°; N–C(O) = 1.376 Å; C=O = 1.224 Å). Similar to other lactams with the N–C(O) bond placed on the larger bridge, lactams **142** were found to have pyramidalized nitrogen atoms and small twist angles. Furthermore, infrared and NMR spectroscopy provide a clear indication of the gradual changes in the electronic properties of the amide bonds in these lactams ($\nu_{C=O}$ [cm^{-1}] **a**: 1703; **b**: 1660; **c**: 1645; **d**: 1641; $\delta_{C=O}$ [ppm] **a**: 182.6; **b**: 180.6; **c**: 177.4; **d**: 173.7).[298] Interestingly, in the ^{13}C NMR spectra, all of the carbonyl carbons were observed closer to the region expected for a typical amide rather than ketone, while the IR and NMR values of the least distorted lactam **142d** are in the region expected for a planar amide. Structural properties of non-planar olefins, including those in compounds **142**, have been recently reviewed.[56,104]

4.4. Carbene Insertion Reactions

The synthesis of strained non-planar lactams using carbenes is an attractive strategy due to the high reactivity of these intermediates,[299–301] which are capable to overcome strain associated with the formation of bridged amide bonds. In 1995, Doyle demonstrated the synthesis of 1-azabicyclo[5.2.1]decan-9-one **145** via Rh-catalyzed C–H insertion reactions with excellent enantioselectivity (Table 1, entries 2–4).[302] The less flexible, one-carbon shorter, analogue **144a** afforded exclusively the fused lactam **146** (entry 1). Rh_2(4*S*-MACIM)$_4$ catalyst (entry 4) gave the opposite enantiomer of **145** than Rh_2(4*S*-MEOX)$_4$ or Rh_2(5*S*-MEPY)$_4$ (entries 2–3).

More recently, Aszodi and coworkers reported Rh- and Cu-catalyzed N–H insertion reactions to generate strained lactams containing a [3.2.1] scaffold as a part of their studies on bridged analogues of carbapenem and carbacephem antibiotics (Table 2).[233] A remote alkyl substitutent exerted significant influence on the competing C–H insertion process, leading instead to the fused derivative **149** from precursor **147** where R = Et. Williams has applied a similar N–H insertion reaction to prepare some of the most strained bridged lactams isolated to date (see Section 5.1).[303,304]

4.5. Reactions via Radical Intermediates

Sundberg developed the synthesis of indole-containing bridged lactams featuring a [5.3.1] ring system using Witkop photocyclization (Scheme 35).[305] It was determined that these reactions proceed smoothly in methanol. Sodium carbonate was used as an additive to prevent hydrolysis of the ketal moiety in certain starting materials. An attempt to form a [6.2.2] ring system from the corresponding 4-piperidylmethyl substrate was unsuccessful.[305] The authors observed a new type of atropoisomerism in the resulting bridged lactams, with half-lives for the interconversion of atropoisomers **152** and **153** between 2.5 and 8 h at 170 °C (Figure 7).[305]

Subsequently, Sundberg reported the photocyclization in the 3-piperidylmethyl series to yield bridged lactams with a [6.3.1] ring system (Scheme 36).[306] In this case, yields and diastereoselectivities were slightly improved, while the barrier for interconversion between atropoisomers was lower than in the [5.3.1] ring system ($t_{1/2}$ in the range of hours at 140 °C). The X-ray structure of lactam **155b**[306] revealed that lengths of the N–C(O) bond of 1.356 Å and the C=O bond of 1.235 Å are comparable with those encountered in planar amides.

In the course of studying radical cyclization of allenamides, Hsung reported the synthesis of benzo-fused bridged lactam **157** with a [4.2.1] ring system (Scheme 37).[307] The product was proposed to arise from 7-endo/5-endo alkene/allene cyclization of an aryl radical intermediate. Beckwith found that the fragmentation of methyl xantates **159**, using tributyltin hydride and di-*tert*-butylperoxide in refluxing toluene, afforded the corresponding ethylidene-substituted bridged lactams containing a [5.3.1] ring system (Scheme 38).[308]

4.6. Miscellaneous Examples

During synthetic studies on iso-indolobenzazepine alkaloids, Ruchirawat and coworkers discovered the Friedel-Crafts cyclization of *N*-benzylbenzazepinones **161** to dibenzo-fused bridged lactams **162** (Scheme 39a).[309] In a related work, the same group investigated the use of acyclic amide acetals **163**, which participated in a sequential Friedel-Crafts cyclization to afford bridged lactams **164** (Scheme 39b).[310] As a part of their research on indole alkaloids, Dolby and Sakai reported a tandem fragmentation–transannular cyclization to give bridged lactam **166** with a [6.2.2] ring system (Scheme 40).[311,312] In the context of studies on bis-*nor*-meptazinols as cholinesterase inhibitors,[313] Qiu and co-workers reported the X-ray structure of lactam **167a**[314] (Figure 8; **167a**: $\tau = 14.4°$; $\chi_N = 27.8°$; $\chi_C = 2.5°$; N–C(O) = 1.347 Å; C=O = 1.243 Å). Finally, Wärnmark and coworkers reported[315,316] the synthesis of bridged lactams **167b** and **167c** via direct oxidation of the parent amine (Tröger's base) at the benzylic position with $KMnO_4$ in 25–28% yields (Figure 8). The X-ray structure of the bis-twisted lactam was solved[315] and indicates significant distortion of the amide bond in **167c** ($\tau = 43.7°$; $\chi_N = 57.6°$; $\chi_C = 4.8°$; N–C(O) = 1.437 Å; C=O = 1.209 Å).

5. SYNTHESIS OF BRIDGED LACTAMS WITH N–(CO) BOND ON ONE-CARBON BRIDGE, ([m.1.n] Type)

Bridged lactams featuring the N–(CO) bond on one-carbon bridge are typically more strained than their two-carbon bridged and larger analogues (see Figure 5). Carbene insertion, ring expansion and transannular condensation reactions forming directly the N–(CO) bond are powerful methods for the assembly of this class of compounds. In general, other synthetic methods are less efficient and/or limited to specific structural types. The majority of successful approaches to non-planar one-carbon bridged lactams involve generation of a high-energy intermediate.

5.1. Carbene Insertion Reactions

In 1986, Williams reported the synthesis of highly distorted bridged lactams containing [4.1.1] ring system using Rh-catalyzed carbene N–H insertion chemistry (Scheme 41).[303,304] The reaction of diazo β-keto esters **168** proceeded smoothly in the presence of catalytic $Rh_2(OAc)_4$ in refluxing benzene to afford bridged lactams in 20–70% yields. Lactams **169** with a sterically-undemanding substituent at the C–8 position (such as **169a**) exhibited limited stability at room temperature ($t_{1/2}$ ~ 1 h in $CDCl_3$, IR = 1795 cm^{-1}). This was proposed to be due to the nucleophilic opening of the strained lactam moiety from the unshielded α face (Figure 9a).[304] Higher stability was observed in isopropyl analogues such as **169b–e**, in which the *i*-Pr group hindered the Bürgi-Dunitz trajectory (**169b–c**: stable in $CDCl_3$, IR = 1795 cm^{-1}; **169d–e**: $t_{1/2}$ ~12 h in $CDCl_3$ at −30 °C, IR = 1805–1810 cm^{-1}). Further improvement was achieved by blocking the bridgehead position to prevent abstraction of the bridgehead methine proton and possible fragmentation (Figure 9b).[304] The lactam **169f** proved to be significantly more stable than previous analogues, however it decomposed when stored neat at room temperature. The crystalline analogues **169g–h** were found to be stable in $CDCl_3$ solution over several days. The X-ray structure of **169h**[304] (IR = 1785 cm^{-1}) revealed pyramidalized nitrogen atom (θ = 326.8°, which may be compared with θ = 325.7° for Kirby's amide[108] and θ = 324.0° for trimethylamine)[304] and a long N–C(O) bond of 1.418 Å. Several 1,3-bridged 2-azetidinones and bridged analogues of β-lactam antibiotics inspired by the William's work have been reported.[242–246]

5.2. Schmidt Reactions

The intramolecular Schmidt reaction[317–320] has been applied to the synthesis of one-carbon bridged lactams. To date, this method has been used to prepare [4.3.1], [5.3.1], [3.2.1], [4.2.1], and [5.2.1] ring systems of these heterocycles. While two constitutional isomers can, in principle, be formed from the intramolecular Schmidt reactions of 2-azidoalkylketones (Scheme 42),[317] the latter pathway (path b) requires particular circumstances to compete with the much more commonly observed path a, which leads to fused bicyclic lactams.[318–320] In the last decade, four complementary methods that allow synthesis of bridged lactams via Schmidt reaction have been developed: (1) axial 2-azidoalkyl tethers,[208] (2) cation–π interactions involving diazonium cation intermediates,[321,322] (3) cation–n interactions involving diazonium cation intermediates,[323,324] and (4) two-carbon 2-

azidoalkyl tethers.[325] In addition, Schmidt reaction of 2-azidoalkylacetals affords bridged orthoamides, which can be converted into bridged lactams.[326]

In 2005, Aubé reported the synthesis of tricyclic bridged lactams **177** via a tandem Diels-Alder/Schmidt reaction (Table 3).[208] This class of bridged lactams was first encountered five years earlier in the context of a total synthesis of stenine.[327–329] Mechanistically, an intramolecular Diels-Alder reaction of triene **175** afforded cis-decalone **178**, in which the carbon bearing the azidoalkyl side chain is axial relative to the cyclohexanone ring embedded in the bicyclic intermediate (Scheme 43).[327] The bridged lactams were obtained by subsequent C→N migration and loss of N_2. The intermediate **178-eq** containing the leaving N_2group in a pseudoequatorial position led to the fused lactam **176**, whereas migration of the bond antiperiplanar to the pseudoaxial N_2^+ afforded the lactam **177**. The X-ray structure of lactam **177b** indicated that it contains a half-way rotated amide bond (τ = 51.5°; χ_N = 36.1°; χ_C = 12.8°; N–C(O) = 1.387 Å; C=O = 1.218 Å;[208] see also compound **511b** in Figure 15).

Subsequent work led to an improved sequence in which a cation–π directed Schmidt reaction afforded bicyclic bridged lactams as the major products (Scheme 44).[321,322] In this case, the combination of an axial azidoalkyl tether and an aromatic group positioned in a 1,3-diaxial relationship with the diazonium cation in the key azidohydrin intermediate **179-ax** (Scheme 45) resulted in high selectivity for the rearrangement to bridged lactams. Electron-rich aromatic groups led to high yields, while electron-poor aromatic groups were less effective, providing strong support for the proposed cation–π interactions.[322] The X-ray structure of lactam **181b** (τ = 43.2°; χ_N = 33.8°; χ_C = 16.3°; N–C(O) = 1.363 Å; C=O = 1.234 Å)[330] confirmed that the amide bond in the [4.3.1] bicyclic system is significantly distorted from planarity.

The Aubé group also reported the synthesis of bicyclic bridged lactams using conformationally-flexible 2-azidoalkylketone substrates containing an α-heteroatomic group (Scheme 46).[323] A thiomethyl substitutent in the α-position gave the best results in terms of yields and selectivity. A stabilizing 1,3-diaxial interaction between the diazonium cation and thiomethyl group in the azidohydrin intermediate **182a** (Scheme 47) was proposed to explain the regioselectivity of this transformation.[323] Recently, cation–π and cation–n directed Schmidt reactions have been investigated using density functional theory, confirming the role of non-bonding interactions involving the diazonium cation on the regioselectivity of the rearrangement.[324]

Murphy reported that the intramolecular Schmidt reaction of conformationally-flexible 2-azidoalkylketones containing a two-carbon tether affords predominantly bridged isomers (Table 4).[325] Several five-, six- and seven-membered azidoketone substrates produced one-carbon bridged lactams **186**, which were converted to the corresponding amino esters **187**. The authors observed that the bridged lactam **186a** containing a [3.2.1] ring system was unstable to the aqueous work-up conditions due to the high strain associated with the non-planar amide bond.[325] Moreover, **185b** participated in a competing fragmentation pathway driven by the aryl group.[325] The preference for bridged lactams in these examples was

explained on the basis of strain developing during the C→N migration to the alternative fused four-membered ring lactams (as also observed in another context[331,332]).

Additional examples of bridged lactams prepared by Schmidt reactions have been reported by Aubé[208] and Murphy[325] (Scheme 48). Although yields were moderate, this methodology offers a concise route to these lactams. The X-ray structure of lactam **190c** (τ = 35.9°; χ_N = 43.7°; χ_C = 12.4°; N–C(O) = 1.375 Å; C=O = 1.219 Å)[333] shows a significantly distorted amide bond and is in good agreement with other bridged lactams featuring a [4.3.1] ring system.

In 2010, Aubé reported that 2-azidoalkylketals undergo Schmidt reaction via iminium ion intermediates to give bridged orthoamides (Table 5a).[326] The α-amino ketals **193** could be readily transformed into the parent twisted lactams (Table 5b).[326] The synthesis of bridged orthoamides provided the first examples of any intramolecular Schmidt reaction affording exclusively bridged products.[331,332,326]

5.3. Condensation Reactions Forming N–C(O) and C–C or N–C Bonds

Transannular amidation reactions of medium-size ring amino esters have emerged as a versatile method for the synthesis of one-carbon bridged lactams due to the release of transannular strain during the formation of bicyclic systems.

In 1987, using a transannular cyclization under thermal conditions, Schill developed the synthesis of indole-derived bridged lactams **195** as potential precursors to higher analogues of vinca alkaloids (Scheme 49).[334–339] The condensation between the amine and pentafluorophenyl esters was applied to the successful synthesis of three different ring systems of bridged lactams.[336–338] The presence of an additional substituent (cf. **195b**)[336] was found to be crucial in obtaining bridged products. In contrast, the cyclization of the indole-derived amino acids was less general, affording only a [4.4.1] ring system in modest yield (Scheme 50).[338] Magnus and coworkers reported the synthesis of a related bridged lactam **199** containing a [4.3.1] ring system as a part of their studies towards the synthesis of vinblastine (Scheme 51a).[340,341] The transannular cyclization between the methyl ester and amine proceeded smoothly under thermal conditions.[340] The nine-membered ring precursor was efficiently prepared from the tetracyclic amine **200** via ring fragmentation and nucleophilic trapping of the resulting iminium ion (Scheme 51b).[340]More recently, Dennison and coworkers applied a transannular condensation reaction to prepare a complex bridged lactam **205** from the vincristine metabolite **204** to facilitate the structural assignment of **204** (Scheme 52).[342]

In 2009, Aubé reported the synthesis of six different ring systems of one-carbon bridged lactams via a tandem RCM-transannular amidation sequence (Scheme 53).[343] The medium-size ring precursors were obtained in high yields from simple dienes using Hoveyda-Grubbs II catalyst. The transannular cyclization took place under thermal conditions with Cs_2CO_3 or DBU as a base, affording highly strained bridged lactams in the process.

One-carbon bridged lactams have also been prepared by other condensation reactions forming C–C or C–N bonds (Schemes 54–55, Table 6). However, in contrast to the

transannular amidation reactions,[336–343] these approaches are limited to specific examples. Arata reported the Dieckmann condensation of amido ester **209** to give the corresponding bridged lactam in 30% yield (Scheme 54a).[344] Waly found that a sequential treatment of *N*-acetylaminonitrile **211** with NaH and KO*t*-Bu afforded the bridged trione **212** (Scheme 54b),[345] while Smet reported the synthesis of lactam **214** from 4-bromoisatin (Scheme 54c).[346] Nazarenko proposed the intermediacy of bridged lactam **216** in the intramolecular condensation of 1,4-benzothiazin-3-one derivative **215**, ultimately affording the more stable **217** from the lactam viaintramolecular transacylation (Scheme 55).[347] Chibale reported the synthesis of tetracyclic bridged lactams based on thiolactone-isatin scaffolds (Table 6).[235] The X-ray structures of lactams **220c–220e** indicated moderate distortions from planarity despite flexible ring systems (**220c**: $\tau = 10.4°$; $\chi_N = 5.1°$; $\chi_C = 0.7°$; N–C(O) = 1.357 Å; C=O = 1.227 Å; **220d**: $\tau = 5.3°$; $\chi_N = 1.1°$; $\chi_C = 3.0°$; N–C(O) = 1.355 Å; C=O = 1.223 Å; **220e**: $\tau = 0.6°$; $\chi_N = 8.9°$; $\chi_C = 4.5°$; N–C(O) = 1.361 Å; C=O = 1.223 Å).[235]

5.4. RCM Reactions

Doodeman and Hiemstra carried out an extensive study to probe the synthesis of one-carbon bridged lactams using RCM.[348] In a systematic screening of dienes that could afford bridged lactams with eight different ring systems ranging from [4.3.1] to [8.2.1], only one bridged lactam containing a [6.2.1] ring was formed in low yield (Scheme 56). Since polymeric material was obtained in many cases despite high dilution conditions, it is apparent that the starting planar lactam was unable to achieve a suitable conformation in sufficient amounts to permit cyclization.

5.5. Aziridinium rearrangement

Aziridinium ions are known to undergo regioselective ring opening with a wide range of nucleophiles and this type of rearrangement has been used extensively to make planar nitrogen-containing heterocycles.[349,350] In 1970, Arata reported the synthesis of bridged lactam **225** containing a [4.4.1] ring system via aziridinium rearrangement using a one-pot protocol (Scheme 57).[351,352] The proposed mechanism is outlined in Scheme 58,[352] and involves the following steps: (1) tautomerization of enamine **224** to iminium ion, (2) addition of the trichloromethyl moiety, (3) formation of the aziridinium **224b**, (4) regioselective nucleophilic ring opening to the trichloroderivative **224c**, and (5) hydrolysis to give the bridged lactam **225**. Subsequently, Miyano and coworkers studied a related rearrangement in the 1-azabicyclo[3.3.1]nonane system (Scheme 59).[353,354] In their case, the reaction was carried out step-wise and the trichloromethyl analogue **227** was isolated.[353] This intermediate then underwent rearrangement to 1-azabicyclo[3.3.1]nonane **229** upon heating in pyridine. Hydrolysis to the corresponding bridged lactam has not been reported for this example.[354]

5.5. Fragmentation Reactions

Fragmentation reactions have been used to prepare relatively flexible ring systems of one-carbon bridged lactams. In 1994, Bremner reported a photolysis of vinylogous chloroacetamides in water-acetonitrile for the synthesis of bridged lactams containing [6.2.1] and [6.3.1] scaffolds (Scheme 60).[355] Improved yields were obtained in acidified

aqueous solutions, which could be due to the involvement of iminium **230a** in the photoinduced electron transfer step (Scheme 61). The authors proposed that the addition of water could occur at the stage of iminium aromatic cation **230c**, which then could undergo C–C bond fragmentation to give bridged lactams. The X-ray structures of **231a** and **231b** have been solved (**231a**: θ = 356.4; N–C(O) = 1.322 Å; C=O = 1.236 Å; **231b**: θ = 359°; N–C(O) = 1.333 Å; C=O = 1.235 Å).[355] These values are comparable to those of planar *N*-methyl-δ-valerolactam (see Section 2.2).

Schuman and coworkers reported the photo-oxidation of the tricyclic enamine **232**, yielding bridged lactams with a [7.3.1] ring system (Scheme 62).[356] The authors proposed that the bridged lactam **233** arose from a singlet oxygen reaction with the electron-rich double bond to give the corresponding dioxetane, which then underwent retro [2+2] (Scheme 63a).[356] The trioxygenated lactams **234** and **235** were formed in a sequence starting with the intermolecular redox reaction between the enamine **232** and intermediate **232a**, followed by standard steps of the photosensitized oxygen transfer process (Scheme 63b).[356]

During their studies on reactions of arenesulfonylazides with strained indoles, Bailey and coworkers reported an oxidative rearrangement of pyrrolo[1,2–*a*]indole **236** leading to a benzofused bridged lactam bearing a [6.2.1] ring system (Scheme 64).[357] The formation of lactam **237** was not observed in apolar solvents. The reaction involves (1) nucleophilic addition of **236** to the azide, (2) hydration of the imnium **236c**, and (3) oxidative cleavage of the C–C bond to give bridged lactam **237** (Scheme 65). The X-ray structure of an oxime derivative of bridged lactam **237** has been solved (θ = 356.6; N–C(O) = 1.372 Å; C=O = 1.215 Å),[358] and indicates some differences from the related bridged lactam **231a**.

5.6. Rearrangements of Nitrogen Ylides

Synthesis of bridged lactams in reactions proceeding via ylide intermediates is a promising approach, however such reactions are not well developed. In 1993, Rudler reported the synthesis of one-carbon bridged lactams containing [5.1.2] and [6.1.2] ring systems using nitrogen ylides, obtained by thermolysis of aminocarbene complexes of chromium (Scheme 66).[359] By performing the theromolysis in cyclohexane, the ylides could be isolated in 52–84% yields. Their subsequent thermolysis in toluene afforded bridged lactams **240** in moderate yields. When nitrogen was a part of 6- or 7-membered ring, the rearrangement afforded bridged lactams; however, only fused lactams were obtained from azetidine-and pyrrolidine-containing chromium complexes. The authors proposed that the reaction starts with intramolecular alkyne and carbon monoxide insertion to give **239b** (Scheme 67).[359] Addition of the tertiary amine to the ketene group in the vinylketene generates intermediate **239c**, which then rearranges to the corresponding lactams.

Chuche reported the application of spiro pyrazolium ylides to the synthesis of bridged pyrazolin-5-ones (Scheme 68).[360] Intermediates **242a** could be isolated in good yields by performing flow pyrolysis at 325–350 °C. However, the thermolysis at 400 °C led directly to the bridged pyrazolin-5-ones. The infrared stretching frequencies of 1765 and 1760 cm^{-1} for **243a** and **243c**, respectively, indicated significant distortion of amide bonds.

5.7. Miscellaneous Examples

Kutney reported the synthesis of bis-indole-derived bridged lactams containing [6.3.1] scaffolds via oxidation and Polonovski reaction of the corresponding bridged amines (Scheme 69).[361,362] Williams attempted to prepare bridged lactam **251** with the unprecedented [3.2.1] ring system. Despite obtaining promising spectroscopic properties from a neat sample, this material underwent polymerization upon isolation (Scheme 70).[304] Toshimitsu reported the use of intramolecular amidoselenation reaction towards the synthesis of bridged lactams,[363] however the originally-assigned bridged structure **254** was later found to be incorrect (Scheme 71).[364,365] A similar tendency of amides to cyclize via oxygen rather than nitrogen atom was also described by Smissman and coworkers in the context of their work on bridged barbituric acid derivatives (see Section 6.2.2).[366–371]

6. SYNTHESIS OF BRIDGED LACTAMS WITH COMPLEX RING SYSTEMS AND RELATED HETEROCYCLES

6.1. Bridged Lactams with Complex Ring Systems

In this section, we discuss the synthesis of bridged lactams embedded in more complex ring systems. It is also possible to classifythese compounds by the type of reaction used for their synthesis (condensation reactions forming N–C(O) bond[372–374] or reactions involving radical intermediates).[375–377] Bridged monothioimide **263** (Scheme 73)[375] and bridged imides **269** (Scheme 74)[376,377] can be also classified as heteroatom-containing derivatives of bridged lactams.

In 1992, during synthetic studies toward the alkaloid stemofoline, Thomas reported the synthesis of bridged lactams containing a rigid tropane-type scaffold (Scheme 72).[372–374] Lithium–halogen exchange, followed by intramolecular organolithium addition to carbamates **257** gave tetrahedral intermediates **258**, which collapsed to bridged amides upon warming to room temperature. When the reactionswere quenched at −78 °C, transannular ester migration occurred. The X-ray structure of bridged lactam **259c**[372] (N–C(O) = 1.432 Å) and its infrared stretching frequency of 1746 cm^{-1}indicated non-planar character of the amide bond. However, it should be noted that the synthesis and chemical properties (see Scheme 144)[373] of lactams **259** are strongly influenced by the presence of the tropanone ring system.

In 1990, Sakamoto reported the synthesis of bridged monothioimide via Norrish type I reaction of a thiocarbonyl group (Scheme 73a).[375] The authors suggested that the ring strain in the five-membered ring precursor **262** played an important role in the cleavage of C–C(S) bond. In agreement with this hypothesis, the substrate **264** containing a six-membered ring underwent an alternative [2+2] cycloaddition to give the fused enamide **265** (Scheme 73b).

In 2009, Booker-Milburn reported the synthesis of tetracyclic bridged imides **267** via intramolecular [2+2] photocycloaddition (Scheme 74).[376] This reaction relies on the use of sensitizers to control [2+2][376] over [5+2][377] mode of cycloaddition of *N*-alkenyl maleimide substrates (Scheme 75). In the presence of benzophenone sensitizer, [2+2] cycloaddition occurred with high selectivity, while under direct irradiation conditions the synthesis of

tricyclic azepines **268** was achieved.[376] All bridged imides were isolated as single diastereoisomers. The authors proposed that a sufficiently long lifetime of the triplet excited state allowed the side chain to achieve the lowest energy conformation for the cycloaddition. The X-ray structure of **267f**[377] indicated that the endocyclic imide carbonyl group (N–C(O) = 1.412 Å; C=O = 1.198 Å) is less planar than the exocyclic carbonyl group (N–C(O) = 1.394 Å; C=O = 1.221 Å).

6.2. Heteroatom-Containing Derivatives of Bridged Lactams

A sampling of heteroatom-containing derivatives of bridged lactams is depicted in Figure 10a. In general, heterocycles containing heteroatoms adjacent to amide bonds (such as, bridged ureas and bridged urethanes; see Section 6.2.1) are easier to synthesize than the parent bridged lactams because of the stabilizing resonance interaction involving the amide bond and the additional heteroatom (Figure 10b). Another class of heteroatom-containing derivatives of bridged lactams consists of bridged oxazinolactams and bridged diazines (see Section 6.2.2), in which the bridgehead nitrogen atom is accompanied by an α-heteroatom. Amide bonds in these compounds are subjected to similar strain to those in the parent lactams, however transannular interactions in medium-sized rings often contribute to the distortion of these compounds. Finally, bridged imides (such as, barbiturates, oxazolidinediones and hydantoins; see Figure 11 for structures, Section 6.2.3) exhibit a ring-size dependent inhibition of the amide bond resonance and their synthesis can be problematic.

6.2.1. Bridged Ureas and Urethanes—The first successful synthesis of a bridged urea was reported by Hall in 1972 (Scheme 76).[378] Treatment of an easily accessible diamine **274** with phosgene at 0 °C resulted in the net acylation of both nitrogen atoms to afford bridged urea **275** in moderate yield. In contrast, the reaction at −75 °C gave the corresponding bis-carbamoyl chloride, which was converted into **275** using Ag_2CO_3 in refluxing acetonitrile in lower yield.[378] The infrared frequency of **275** of 1650 cm^{-1} was in the region expected for planar tetraalkylureas, indicating that this compound is not particularly strained. In 1980, Hall reported the synthesis of another bridged urea **278** via depolymerization of a polymeric pre-urea under high vacuum (Scheme 77).[379]

Concurrently, Hall developed the synthesis of bridged urethanes using phosgene as a carbonyl source (Scheme 78).[380,381] The optimum conditions for the synthesis of bridged urethane **281** containing a [3.3.1] ring system proceeded via chloroformate salt **280** (Scheme 78a), while the urethane **284** containing a [3.2.1] ring system was obtained via an alternative route involving an *N*-carbamoyl chloride (Scheme 78b).[380] The first of these reactions proceeds via O→N rearrangement prior to the lactamization step. The infrared frequencies of bridged urethanes (**281**: 1710 cm^{-1}; **284**: 1770 cm^{-1}) were found to be higher than those of the corresponding planar urethanes (1,3-oxazinan-2-one: 1700 cm^{-1}; oxazolidin-2-one: 1730 cm^{-1}). In contrast to these results, treatment of **276** with phosgene resulted in only 5% yield of **278** (Scheme 77), possibly due to competitive formation of a bis phosgene adduct at the free nitrogen atom in the initially formed intermediate.[379]

Recently, Mangion and coworkers reported the synthesis of β-lactamase inhibitor MK-7655 featuring a bridged urea (Scheme 79).[234] A protocol employing triphosgene in the presence of Hünig's base, followed by treatment with dilute phosphoric acid gave the highest yield. Other carbonyl sources than triphosgene proved ineffective in promoting the cyclization to the bridged urea. The authors proposed that phosphoric acid aids in conversion to **286** by hydrolyzing the intermediate trichloromethyl carbamate. The bridged urea **286** proved sufficiently stable to allow synthesis of MK-7655 in three more steps.

6.2.2. Bridged Oxazinolactams, Oxazinourethanes and Diazines—In 2000, Shea reported the synthesis of bridged oxazinolactams and oxazinourethanes using type II intramolecular nitroso Diels-Alder reaction (Scheme 80).[382] This study followed the successful application of acyl-imino Diels-Alder reaction to the synthesis of bridged lactams by the Shea group (see Scheme 33).[297,298] The reactive *N*-acylnitroso dienophiles **290** were generated in situ from the corresponding hydroxamic acids.[382] Oxidation using Et_4NIO_4led to bridged oxazinolactams containing [4.3.1] and [5.3.1] ring systems in high yield. Other oxidants were used for preparation of bridged oxazinourethanes (such as **289c–d**).[382] The synthesis of [6.3.1] ring system required milder conditions due to decomposition of the acylnitroso dienophile.[383] This result was explained on the basis of developing transannular strain in the transition state leading to the 9-membered ring. Ultimately, the desired [6.3.1] oxazinolactam was formed when the *N*-acylnitroso dienophile was generated thermally from the dimethyl-acetylene cycloadduct (Scheme 81).[383] In this case, the more flexible tether led to competitive formation of the regioisomeric bridged oxazinolactam containing [6.2.2] ring system. The X-ray structures of oxazinolactams bearing [4.3.1], [5.3.1] and [6.3.1] ring systems showed that *N*-oxy amide bonds exhibit comparable degree of strain to the analogous bridged lactams[383] (**289a**: $\tau = 3.5°$; $\chi_N = 54.8°$; $\chi_C = 0.4°$; N–C(O) = 1.406 Å; C=O = 1.217 Å; **289b**: $\tau = 10.4°$; $\chi_N = 52.6°$; $\chi_C = 1.5°$; N–C(O) = 1.398 Å; C=O = 1.219 Å; **293**: $\tau = 16.4°$; $\chi_N = 49.0°$; $\chi_C = 4.1°$; N–C(O) = 1.388 Å; C=O = 1.219 Å; see Section 4.3 for data on the corresponding bridged lactams[298]). The authors proposed that the release of transannular interactions in medium-sized rings led to the counterintuitive increase of twist angles with larger ring sizes in this series.

Shea extended this methodology to substituted bridged oxazinolactams (Scheme 82).[384] Interestingly, 2-alkyl and 2-oxy-substituted hydroxamic acid precursors resulted in complementary diastereoisomers of the bridged products. This outcome was explained by dipole minimalization in the transition state. High diastereoselectivity was also observed with 3- and 4-substituted hydroxamic acid substrates.

Following this account, Shea achieved the synthesis of bridged 1,2-diazines via type II intramolecular *N*-acylazo Diels-Alder reaction (Scheme 83).[385] Initially, the required acylazo dienophiles were generated in situ from the corresponding hydrazides using *n*-Bu_4NIO_4 as the oxidant. Subsequently, a two-step protocol involving NBS-promoted synthesis of acylazo precursors and $ZnCl_2$-catalyzed Diels-Alder cycloaddition was developed. This methodology was applied to the synthesis of bridged diazines containing [4.3.1] and [5.3.1] ring systems. The X-ray structures of bridged 1,2-diazines were found to match those of the corresponding bridged oxazinolactams (**298a**: $\tau = 0.8°$; N–C(O) = 1.394

Å; C=O = 1.216 Å; **298b**: τ = 17.6°; N–C(O) = 1.401 Å; C=O = 1.219 Å).[385] An unsuccessful attempt to prepare a related bridged diazine with a [3.2.1] ring system was reported by Hoornaert and coworkers.[386]

In 2005, Shea reported an asymmetric synthesis of bridged oxazinourethane **301** (Scheme 84).[387] Treatment of the hydroxamic acid precursor with *tert*-butyl hydrogenperoxide in the presence of a catalytic amount of ruthenium salen complex **302** at 15 °C under high dilution conditions afforded the desired product with high levels of enantioinduction and in excellent yield. The authors proposed a catalytic cycle, in which the active Ru(IV) catalyst **302b** performs a dual role: (1) dehydrogenation of the *N*-hydroxy formate ester **300** to produce an ion pair **302c**, and (2) catalysis of the Diels-Alder reaction to give the bridged oxazinourethane **301** (Scheme 85).

6.2.3. Bridged Barbiturates, Oxazolinediones and Hydantoins ("Smissmanones")—

In a 1964 report, in analogy to known drugs containing planar imide bonds, Smissman proposed bridged bicyclic imides **307–310** as potential anticonvulsant agents (Figure 11).[237] However, over the next 20 years, Smissman and coworkers found that synthesis of the proposed bridged imides **307–310** was more difficult than initially expected.[366–371] Attempts to prepare bridged barbituric acids, bridged amides or bridged imides via intramolecular alkylation approaches (Scheme 86)[366–370] or via intramolecular condensation methods (Scheme 87)[371] were unsuccessful due to the propensity of the tested precursors to react with electrophiles at the oxygen rather than nitrogen atom. Moreover, Smissman found that structures of bridged imides reported in literature by other groups were incorrect (Scheme 88).[388,389]

Inspired by Smissman's work,[390] in 1984, Brouillette accomplished the synthesis of bridged 2,4-oxazolinediones containing [4.2.1] and [5.2.1] ring systems using acylation of α-hydroxy lactams with aryl chloroformate as a key step (Scheme 89).[391] Thus, the reaction of lactams **330** with 4-nitrophenyl chloroformate in refluxing toluene provided bridged oxazolinediones **331b–c** in 44–90% yields. Under the same experimental conditions, the corresponding oxazolidinedione containing a [3.2.1] scaffold was not formed, likely because of the higher strain present in this ring system.[391] The X-ray structure of oxazolinedione **331b**[391] indicated that the endocyclic amide bond is more distorted than the exocyclic bond (i.e., the endocyclic N–C(O) bond is 0.038 Å longer and the endocyclic C=O bond 0.014 Å shorter than the corresponding N–C(O) and C=O exocyclic bonds). Later, the X-ray structure of bridged oxazolidinedione **331c** was reported by Kubicki (**331c**: endocyclic N–C(O) = 1.368 Å; C=O = 1.211 Å; exocyclic N–C(O) = 1.383 Å; C=O = 1.193 Å).[392]

Subsequently, Brouillette achieved the first synthesis of bridged hydantoins containing [4.2.1][393] and [5.2.1][240] ring systems (Scheme 90). The exposure of carboxyamides **335** to $Pb(OAc)_2$ resulted in the Hoffman rearrangement to the intermediate isocyanates, which underwent intramolecular attack by the lactam nitrogen atom to afford the desired bridged hydantoins in 48–67% yields. The conditions using 2,6-lutidine in the absence of alcohol proved crucial for the efficient intramolecular *N*-alkylation of the intermediate isocyanates. Bridged hydantoins were distinguished from the potential *O*-alkylated products on the basis

of ^{15}N NMR experiments (**336b**: bridgehead nitrogen atom 139.1 ppm; 7-methoxy-3,4,5,6-tetrahydro-2H-azepine: 233.1 ppm).[393]

Finally, Brouillette revised[394] the structure of bridged barbituric acid **338** as originally reported by Smissman[395] (Scheme 91), while Gmünder and Lindenmann reported the attempted synthesis of bridged barbituric acid **341** with an alternative bond connectivity (Scheme 92).[396] These examples underline the difficulty of ring closure using *N*-alkylation and *N*-acylation via amide nitrogen atom to obtain strained lactams. In recognition of Smissman's work, bridged amides with the general structures **307–310** are generally referred to as "smissmanones".[241]

6.3. Bridged Enamines

Enamines in which nitrogen atom is placed at the bridgehead position in a bicyclic ring system are subject to similar geometrical restrictions as bridged lactams.[397] In cases where resonance interaction between the nitrogen lone pair and the π electrons of the double bond is limited, the characteristic nucleophilicity of the carbon atom of enamines decreases with HOMO orbital localized at the nitrogen atom in these systems.

In 1985, Doering published a seminal report on the conjugative interaction of bridged enamines using compound **347** containing a [3.2.2] ring system (Scheme 93).[398] The required enamine was prepared from 1-azabicyclo[2.2.2]octan-3-one **344** in a four-step sequence (Scheme 93a). The final step involved equilibration of the allyl amine **346** to the bridged enamine with $LiNMe_2$–HMPA and subsequent fractional crystallization of the corresponding HI salt. Doering demonstrated that the bridged enamine **347** can be equilibrated to **346** using $LiNMe_2$–HMPA or $RuH(NO)(PPh_3)_3$ (Scheme 93b).[398] The equilibrium constant of 1.0 for both reactions indicates the lack of conjugative interaction between the enamine nitrogen and the olefin double bond in this [3.2.2] ring system. In contrast, planar enamines favor the enamine form by approx. 4 kcal/mol.[397]

In 2006, Crawley and Funk reported the synthesis of bridged enamine containing a [3.3.2] ring system during their approach to communesin B (Scheme 94).[399] The enamine **349** was formed via a gold-catalyzed 7-exo-dig cyclization of a piperidine nitrogen onto a tethered alkyne in **348**. Later, it was found that this cyclization also proceeded spontaneously at room temperature.[399] The X-ray structure of enamine **349** has been reported (θ = 337.6°; N–$C(CH_2)$ = 1.444 Å; $C{=}CH_2$ = 1.329 Å).[399]

In 2008, Ellman reported the synthesis of endocyclic bridged enamines with a [4.3.1] scaffold via a C–H activation/alkenylation/electrocyclization sequence (Scheme 95).[400] A catalyst generated in situ from $[Rh(coe)_2Cl]_2$ and the electron-rich monophosphine ligand $(4\text{-}NMe_2)PhPEt_2$ (used in 1:1 ratio) was identified as optimal for this transformation. The reaction efficiency was highly dependent on the substitution of α,β-unsaturated aldimine moiety and the length of tether connecting the alkyne. The proposed mechanism, shown in Scheme 96,[400] involves generation of the hydrido(vinyl)rhodium intermediate **351a**, its addition to the alkyne in a 2,1-fashion, reductive elimination to give the cyclic aza-triene **351c**, and electrocyclization under the reaction conditions.

Pearson reported the synthesis of bridged enamines via an intramolecular Schmidt reaction[318–320] using azidoalkyl olefins or azidoalkyl alcohols (Scheme 97).[401] Azides tethered to five-membered rings afforded mixtures of regioisomeric bridged enamines with [2.2.2] and [3.2.1] scaffolds, while six-membered ring precursors led exclusively to [3.2.2] bridged systems. The use of alkyl-substituted substrates (cf. aryl as in **356**) resulted in olefin isomerization in the final products. The mechanism of this rearrangement proceeds via (1) generation of the carbocation, (2) its trapping by the tethered azide, (3) 1,2-carbon migration with expulsion of nitrogen to give bridged iminium ion, and (4) deprotonation to give the twisted enamine product (Scheme 98). The enamine is reprotonated at nitrogen under the reaction conditionsbut the basic work-up gives the final neutral product. Other bridged enamines based on the quinuclidine skeleton[402–405] have been reviewed.[406,407]

Bridged enamines have also been prepared from bridged lactams (see Section 7.2.4).[108,408]

6.4. Bridged Iminium Ions

Iminium ions containing nitrogen atom at the bridgehead position cannot achieve full resonance stabilization and are typically considered as carbocations.[409–412,102] Although several bridgehead imines and iminium ions have been reported,[413–419] only a few of these compounds bear nitrogen atom at the bridgehead position in a bicyclic system.[420–424,353,354]

During studies on solvolysis of modified Cinchona alkaloids containing good leaving groups at the C–9 position, Hoffmann discovered their rearrangement to 1-azabicyclo[3.2.2]nonanes via bridged iminium ions (Scheme 99).[420] High yields were obtained in both the quinine (Scheme 99a) and quinidine (Scheme 99b) series.[420] In these systems, 1,2-alkyl shift to give strained non-planar iminium ions is favored by stereoelectronic factors. The participation of the aziridinium ions was ruled out on the basis of control experiments probing the ability of activated Cinchona alkaloids to undergo self-quaternization reactions. This rearrangement was subsequently described as “the first Cinchona rearrangement”.[421,422]

Hoffmann also reported the synthesis of enantiomerically pure 1-azabicyclo[3.2.2]nonanes in quincorine (Table 7) and quincoridine (Table 8) series.[423] Treatment of β-amino iodides **366** and **369** with methanol in the presence of AgOBz resulted in stereoselective rearrangement to α-amino ethers via bridged iminium ions. Other silver salts proved less efficient in promoting the reaction or led to partial epimerization of the desired products. The reaction showed good functional group compatibility, tolerating alkynes, ketones, and esters. Notably, the bridged iminium ions were found to be configurationally stable and no equilibration between the quincorine and quincoridine series was observed.

Applying the same concept, Hoffmann developed the synthesis of functionalized 1-azabicyclo[3.2.2]nonanes from quincorine (Table 9) and quincoridine (Table 10).[424] A wide range of carbon, nitrogen and sufur nucleophiles was used to capture bridged iminium ions **373** and **376** with complete diastereoselectivity.

Miyano reported the formation of bridged iminium ions in 1-azabicyclo[3.3.1]nonane system (Scheme 100).[353,354] Aziridinium rearrangement of pyrrolizidine **227** provided the

bicyclic precursors **229**/**378** (Scheme 100a; see also Section 5.5). The unexpected stability of these products was proposed to arise from the gauche conformation between the lone pair of electrons at nitrogen and the two C–Cl bonds.[353] Both chlorine atoms could be displaced by alkoxides upon heating in alcoholic solvents via bridged cation **379** (Scheme 100b).[354] Extensive NMR studies suggested that introduction of two substituents at the C–9 position in 1-azabicyclo[3.3.1]nonane system forces the ring in a double-chair conformation (cf. Section 4.1).

6.5. Bridged Sultams

In contrast to amide bonds, incorporation of a sulfonamide moiety into a bridged bicylic ring system does not result in its hyperreactivity.[425] Bridged sulfonamides (sultams) are the area of considerable current interest due to their potential application in medicinal chemistry[426,427] and stereoselective synthesis.[428,429] The chemistry of fused sultams has been recently reviewed.[430]

In the last twenty years, three general approaches to the synthesis of bridged sultams have been reported: i) Heck reactions,[292–295,431–436] ii) radical cyclization reactions,[437–439] iii) alkylation reactions.[440,441]

In 1991, Grigg demonstrated that Heck cyclizations of *ortho*-bromoarylsulfonamides onto tethered alkenes proceed in good yields to give the corresponding bridged sultams (Scheme 101).[292] In contrast to the analogous Heck reaction leading to bridged lactams (see Schemes 28 and 29),[291–294] sulfonamide-containing substrates allowed for the preparation of sultams bearing [3.2.1] and [3.2.2] ring systems.[292] This trend was explained by the lower rotational barrier around the $N–S(O)_2$ bond in sulfonamides as compared to the N–C(O) bond in amides. The regioselectivity of the reaction leading to the [3.2.2] ring system was significantly improved by using a catalyst system comprising of $Pd(OAc)_2$, PPh_3, and Tl_2CO_3.[292] Subsequently, Grigg investigated cascade and one-pot RCM-Heck reactions to prepare bridged sultams.[293,294] Recently, a similar Heck reaction protocol was utilized by Paquette to construct bridged sultams containing [4.3.1] and [4.2.1] ring systems (Scheme 102),[295,431] while Evans reported the synthesis of bridged sultams containing [3.2.1] scaffolds via a tandem Heck reaction/hydrogenation process (Scheme 103).[432–436]

In 1999, Paquette reported a seminal study on the synthesis of bridged sultams via intramolecular radical cyclization reactions of cyclic unsaturated halomethylsulfonamides (Scheme 104).[437] This reaction was successfully applied to the synthesis of five different ring systems of unsubstituted bridged sultams, however bridged sultam containing a [2.2.1] scaffold did not form under these reaction conditions. The X-ray structure of **392c** indicated O–S–N–lone pair dihedral angles of −90° and 40°. In contrast, the lone pair of electrons at nitrogen in planar sulfonamides is found in a plane bisecting the O–S–O angle. Despite these structural differences, all bridged sultams **392** were found to be hydrolytically stable. Using radical cyclization reaction, Paquette also reported the synthesis of bridged disulfonimide with a [3.2.2] ring system (Scheme 105),[438] and complex tricyclic bridged sultams.[439] The X-ray structure of **394**[438] showed a large θ value (**394**: θ = 345.8°; **392c**: θ = 325.2°), indicating a relatively flexible sulfonimide bond in this compound.

Subsequently, available ring systems of bridged sulfonamides have been expanded to include bridged sultams bearing sulfur atom at the apex position.[440,441] In 2006, Paquette reported the synthesis of a bridged sultam containing a [4.2.1] ring system via an intramolecular alkylation reaction (Scheme 106a).[440] Attempts to close the bicyclic system via RCM proved unsuccessful (Scheme 106b).[440] More recently, de Meijere and coworkers demonstrated that related bridged sultams can be generated by dialkylation of simple monocyclic precursors (Scheme 107).[441] The X-ray structures of several bridged sultams have been reported (**400a**: θ = 310.2°; **400b**: θ = 325.3°; **400d**: θ = 340.0°; **400e**: θ = 341.6°),[441] and indicate progressive decrease of the pyramidalization at nitrogen in this series.

An alternative approach to bridged sultams was reported by Hanson and coworkers (Scheme 108).[442] As a part of the reaction pairing strategy to access structurally diverse sultams,[443–445] these researchers developed a sequential sulfonylation-S_NAr protocol starting from *ortho*-flurobenzenesulfonyl chloride and cyclic amino alcohols to afford bridged sultams with [4.2.1] and [5.2.1] ring systems in good overall yields.[442] This protocol was recently employed for the synthesis of a 40-member library of bridged sultams bearing [4.2.1] scaffolds.[446]

Finally, Blakey reported the synthesis of heteroatom-derived bridged sultams via rhodium-catalyzed allene sulfonamidation (Scheme 109).[447] The reaction showed good substrate scope, allowing for the synthesis of densly functionalized sulfonamides. The mechanism was proposed to involve (1) sulfonamidation to give 2-amidoallylcations, (2) rearrangement to strained *N*-sulfonylimino-cyclopropanes, and (3) formal [3+3] cycloaddition with acyclic nitrones (Scheme 110).

7. REACTIVITY OF BRIDGED LACTAMS AND RELATED HETEROCYCLES

Due to the limited $n_N \rightarrow \pi^*_{C=O}$ conjugation, distorted amides exhibit reactivity dissimilar to traditional amides.[57–59] In general, the C=O group is more electrophilic than in planar amides, while the nitrogen atom might behave as a basic amine. Both of these properties depend on the degree of twist of the amide bond; in extreme cases, the amide bond reacts as an isolated amino-ketone rather than an amide, however it is also hydrolytically labile. Conversely, bridged lactams in which the amide bond is close to planarity tend to react as traditional amides and are hydrolytically stable.

For the purpose of this review reactions of bridged lactams are classified depending on the reacting center of the amide bond (that is, carbonyl group or nitrogen atom), and the type of reaction. Because of its historical importance, the hydrolysis of distorted amide bonds is addressed separately. Reactions of heteroatom-containing derivatives of bridged lactams, bridged enamines and bridged sultams are also addressed in this section.

7.1. Hydrolysis of Bridged Lactams

Planar amide bonds are remarkably stable to hydrolysis, with half-life for neutral hydrolysis at room temperature counted in hundreds of years.[448] Due to their enhanced electrophilicity, bridged lactams are more susceptible to hydrolysis than planar amides.[61] Bridged lactams

characterized by large twist angles are hydrolytically unstable, which complicates their synthesis, isolation, and examination of physico-chemical properties, especially in nucleophilic solvents including water.

Between 1958 and 1965, Pracejus studied the hydrolysis of 2-quinuclidones and their hydrochloride salts (Scheme 111).[253,254] Near pH = 5, the half-life for methanolysis of the bridged lactam **44** was less than 5 minutes; however, this compound hydrolyzed only very slowly in water at 20 °C (Scheme 111a).[254] Under basic conditions, the lactam **44** underwent solvolysis 10^4 faster than the planar 2-azabicyclo[2.2.2]octan-3-one at 100-times higher alkali concentration.[254] The hydrochloride salt **409** was found to be even more labile towards hydrolysis and alcoholysis than the parent amide (Scheme 111b).[254] Furthermore, methyl-substituted 2-quinuclidones were found to hydrolyze in the order corresponding to the degree of steric shielding of the amide bond by the neighboring methyl substituents (**44** > **46b** (endo) > **46a** (exo); see Figure 12 for structures of **46a–b**).[254]

Pracejus determined the pK_a of methyl-substituted 2-quinuclidones to be 5.33–5.60,[254] while Yakhontov established the pK_a of a tetramethyl-substituted 2-quinuclidone at 6.37 (Figure 12).[256,257] Although these values are consistent with the high basicity of the amide nitrogen in this [2.2.2] ring system, methyl-substituted 2-quinuclidones did not succeed as good models for reactivity of bridged lactams due to steric hindrance around amide bonds.

In the early 1980s, Blackburn[261] and Brown[262] independently studied the rate of hydrolysis of benzo-fused bridged lactams derived from 2-quinuclidones (Scheme 112). Blackburn observed an increase of seven and nine orders of magnitude in the rate of basic and acidic hydrolysis of the 2-quinuclidone **60**, respectively, as compared to the planar 1-phenyl-2-piperidone.[261] Brown measured the rate of hydrolysis of several 2-quinuclidone derivatives characterized by different distortion parameters, finding a good relationship between the rate of hydrolysis and twist angles.[262] However, for two of these lactams the correlation was better when pyramidalizations at nitrogen were also considered (Table 11).[262]

In 1998, Kirby reported the unusual hydrolytic behavior of perpendicularly twisted 1-aza-2-adamantanone (Scheme 113).[272,108] This lactam was rapidly hydrolyzed to the ring-opened amino acid when dissolved in water ($t_{1/2}$ < 50 s). Similarly, the half-life of 0.3 s for acidic hydrolysis at pH = 5 showed that 1-aza-2-adamantanone is significantly more reactive than methyl-substituted 2-quinuclidones (cf. Scheme 111). The pK_a value of 5.2 indicated the expected high basicity of the lactam nitrogen atom.[108] Interestingly, below pH 4 1-aza-2-adamantanone was quantitatively converted into the protonated orthoamide **412**, which at pH = 4.3 existed in equilibrium with the open-form amino acid. Furthermore, the amino acid **411** gave the parent bridged lactam when dissolved in neutral methanol (Scheme 114).[108]

Stolz reported that the perpendicularly twisted 2-quinuclidone **52** is rapidly hydrolyzed in water with $t_{1/2}$ < 15 s (Scheme 115).[107] This compound was also unstable in other nucleophilic solvents, including DMSO, pyridine and MeOH, which led to the nucleophilic cleavage of the amide bond.

Aubé studied the hydrolysis of one-carbon bridged lactams characterized by medium twist angles (Scheme 116).[449] Tricyclic and bicyclic lactams were found to be stable in aqueous

solutions under biologically relevant pH conditions (pH = 4–10), however these compounds rapidly hydrolyzed under more acidic or basic pH conditions. Their stability was proposed to result from incorporation of the amide bond into a one-carbon bridge placed across medium-sized heterocycles, where it benefits from the scaffolding effects of medium-sized rings. The spontaneous re-formation of amide **175b** from the seco-amide form **416** in water is a notable feature of such systems.

Studies on the hydrolytic stability of bridged lactams bearing the amide bond on the external bridge in a bicyclic system have also been reported. Judd and coworkers found that lactam **133a** containing a [3.3.1] ring system was significantly more labile under acidic conditions than the regioisomeric lactams with [4.3.1] ring systems (Figure 13).[296] Denzer and Ott discovered that the hydrolytic behavior of bridged lactams containing an additional nitrogen atom at the bridgehead position in [3.3.1] and [3.2.1] ring systems corresponds to the degree of strain associated with the bridged amide bond (Scheme 117).[290] Hall investigated the hydrolytic stability of a family of unsubstituted bridged lactams,[279] bridged ureas[378,379] and bridged urethanes[380,381] (Table 12 and Figure 14). Derivatives containing a [3.3.1] ring system were relatively stable under the tested reaction conditions, while the bridged urethane containing a [3.2.1] scaffold rapidly hydrolyzed in water.[380]

Wärnmark investigated acid-catalyzed hydrolysis of twisted bis-amide **167c** derived from Tröger's base (see Figure 8 for structure of **167c**).[315] A complete hydrolysis was observed in a 0.58 *N* solution of HCl within 400 min, while kinetic and ^{18}O labeling studies suggested irreversible collapse of the protonated tetrahedral intermediate.[315]

Arata reported an interesting rearrangement of the one-carbon bridged lactam **225** bearing a leaving group at the bridgehead position on treatment with NaOH (Scheme 118).[352] Finally, several theoretical studies addressing the hydrolysis of non-planar lactams have been published.[62–66]

7.2. Reactivity of Nitrogen Atom of Bridged Lactams

Two types of reactions of bridged lactams involving the nitrogen atom have been reported: (1) reactions with electrophiles leading to derivatives with intact bicyclic skeleton, and (2) reactions proceeding with scission of the C–NC(O) bond, following electrophilic activation of the lactam nitrogen atom.

7.2.1. *N*-Protonation and *N*-Methylation—Although oxygen is the protonation site of planar amide bonds, the limited $n_N \rightarrow \pi^*_{C=O}$ donation in bridged lactams leads to the enhanced basicity of nitrogen.[70,71] In general, even moderately distorted bridged lactams favor *N*-protonation over *O*-protonation.[70,71,284]

Pracejus and Yakhontov were the first to show that bridged lactams undergo protonation and methylation reactions at the nitrogen atom (Scheme 119).[253–257] The potential products resulting from the cleavage of C–NC(O) bonds were not observed in these systems.

Kirby demonstrated that 1-aza-2-adamantanone readily forms quaternary ammonium salts upon treatment with Meerwein's reagent or HCl (Scheme 120).[108] The latter product,

isolated as the *N*-protonated hydrate **427**, may be considered as a model for a cationic tetrahedral intermediate in acid-catalyzed acyl transfer reactions.[450] The X-ray structure of **427**[108] was characterized by a long C–N bond of 1.552 Å and significantly shortened C–O bonds of 1.382 Å. The stability of **427** resulted from the torsional restriction imposed by the adamantane scaffold.

In an important study, Brown found that methylation of the bridged lactam containing a [3.2.2] ring system takes place at nitrogen, while the less distorted analogue with a [3.3.2] ring system reacts at the oxygen atom under the same experimental conditions (Scheme 121).[451] Using DFT calculations, Greenberg predicted that related bridged lactams display higher electron density at nitrogen as compared to planar amides.[70,71] Recently, Greenberg reported that protonation of the relatively undistorted 1-azabicyclo[3.3.1]nonan-2-one also proceeds at nitrogen (Scheme 122).[284] This finding is important in the light of the hydrolytic stability of **96** (see Table 12)[279] and its unstrained structure (see lactam **87** for the amide bond distortion parameters in the [3.3.1] ring system: $\tau = 20.8°$, $\chi_N = 48.8°$, $\chi_C = 5.9°$).[282,283]

Aubé reported several examples of *N*-protonated and *N*-methylated lactams bearing a [4.3.1] scaffold (Scheme 123).[330] The structures of three of these analogues were examined by X-ray crystallography and provided the first direct crystallographic comparison between any twisted lactam and its corresponding salt. The distortion parameters and bond lengths of the *N*-protonated lactam **434b**[330] indicated a significant increase of pyramidalization around the C–N amide bond compared to its neutral analogue (**434b**: $\tau = 81.9°$; $\chi_N = 52.1°$; $\chi_C = 1.4°$; N–C(O) = 1.502 Å; C=O = 1.192 Å; the corresponding bridged lactam **177b**: $\tau = 51.5°$; $\chi_N = 36.1°$; $\chi_C = 12.8°$; N–C(O) = 1.387 Å; C=O = 1.218 Å).[330]

7.2.2. Cleavage of C–NC(O) Bond—Electrophilic activation of the nitrogen atom in bridged lactams may result in the scission of the adjacent C–N bond. Thus, Yakhontov reported cleavage reactions of the C–NC(O) bond in the tetramethyl-substituted 2-quinuclidone using PhLi, PCl_5 and acetone cyanohydrin (Scheme 124).[256,257] The nucleophile had a pronounced effect on the reaction outcome (cf. Table 14). This reaction was limited to systems capable of forming tertiary carbocations (Scheme 125).[256,257]

Aubé reported that one-carbon bridged lactams undergo C–NC(O) bond cleavage reactions under very mild conditions (Scheme 126).[208] The mechanism of the MeI-mediated scission was proposed to proceed via the amidinium ion, while the cleavage mediated by DDQ to involve the initial single-electron transfer from the amide bond.[208] In all cases, the σ C–N bond furthest away from co-planarity with the carbonyl group in the neutral lactam was selectively cleaved. Tricyclic and bicyclic bridged lactams were also found to participate in regioselective hydrogenolysis reactions of the C–NC(O) bond using $Pd(OH)_2$ in alcoholic solvents (Scheme 127).[208] The activation of bridged lactams by hydrogen bonding to nitrogen was proposed to play an important role in facilitating these reactions. In another study, medium-bridged bicyclic lactams containing an internal double bond showed increased reactivity towards the C–NC(O) bond hydrogenolysis (Table 13).[343] Recently, Aubé reported the cleavage of a C–NC(S) bond in bridged thioamide containing a [4.3.1] ring system (Scheme 128).[452]

7.3. Reactivity of Carbonyl Group of Bridged Lactams

The geometric constraints of non-planar amides modify the chemistry of the affected carbonyl group and its derivatives. Typically, amide bonds in bridged lactams are more electrophilic than those in planar amides because of the limited amide bond resonance.[67–69] Moreover, torsional restriction imposed by bicyclic scaffolds of bridged lactams often permit isolation of stable tetrahedral intermediates of the amide bond addition reactions.[450]

For the purpose of this review, the reactivity of carbonyl group of bridged lactams has been classified into the following classes: (1) reactions with heteroatom nucleophiles proceeding with cleavage of amide bonds, (2) reactions with heteroatom nucleophiles proceeding without cleavage of amide bonds, (3) reduction reactions, (4) reactions with organometallic and related reagents, and (5) miscellaneous reactions.

7.3.1. Reactions with Heteroatom Nucleophiles with Cleavage of Amide Bonds

—Yakhontov was first to demonstrate the nucleophilic ring opening of bridged lactams with a variety of nucleophiles, such as water, alcohols, amines and hydrazines (Table 14).[256,257] The resulting piperidines were isolated in good yields after the basic workup. Yakhontov also observed an unexpected transacylation of the twisted amide bond during reduction of the sterically-hindered 2-quinuclidone **46c** with $LiAlH_4$ (Scheme 129). The parent bridged lactam reacted in situ with the amino alcohol product to give amino ester product **449**. Concurrently, Pracejus reported a rapid alcoholysis of another 2-quinuclidone under acidic conditions (Scheme 130).[253,254] These reactions confirm that amide bonds in bicyclic 2-quinuclidines exhibit properties of isolated amino-ketones.

The susceptibility of non-planar amides to nucleophiles has been reported to complicate the synthesis and isolation of some bridged lactams.[250] Aszodi and coworkers reported a facile aminolysis of the amide bond in a [3.2.1] bridged lactam **451** during the attempted removal of its *p*-nitrobenzyl group (Scheme 131).[233] Later, this undesired side reaction was minimized by performing the hydrogenolysis in acetone to in situ convert the reactive 4-toluidine into the less nuclophilic *N*-isopropylaniline.[233] Murphy subjected hydrolytically-unstable bridged lactams, prepared by an intramolecular Schmidt reaction, to methanolysis under mild conditions with TfOH and MeOH to facilitate identification of these compounds (Scheme 132).[325]

Hall developed a series of polymerization reactions[453–455,55] of bridged lactams relying on the inherent strain of amide bonds (Table 15a).[279,378–381] Lactam **96** containing a [3.3.1] scaffold[279] was more reactive than the corresponding bridged ureas[378,379] and urethanes.[380,381] The analogous planar lactams, ureas and urethanes did not polymerize under the same reaction conditions (Table 15b).

7.3.2. Reactions with Heteroatom Nucleophiles without Cleavage of Amide Bonds—

Diols,[108,408] hydrazines[232,408] and amines[408] have been used as successful nucleophiles to give bridged derivatives of twisted lactams without cleavage of the amide bond. In all reported examples to date, scaffolding effects of adamantane-type or medium-sized rings stabilize the final products.

Kirby and coworkers reported the synthesis of a bridged hemiaminal from 1-aza-2-adamantanone using standard conditions for ketal formation (Scheme 133).[108] The same research group prepared a bridged tosylhydrazone as a precursor to amino carbene **459** (Scheme 134),[271] which subsequently was shown to react as a singlet carbene.[271]

In their search for novel ligands of nicotinic receptor, Coe and coworkers reported the synthesis and Wolff-Kishner reduction of a bridged amino hydrazone to give the tricyclic amine **463** (Scheme 135).[232] Impressively, the synthesis of **463** could be conducted on 10–95 mmol scale directly from the ring-opened amino ester **84** (see Scheme 17) without isolating the intermediate bridged lactam and amino hydrazone in excellent overall yields (64–85%). During the course of this study, mixed ethanol-hydrazine intermediates were detected by APCI MS analysis (Scheme 136).[232] The bridged hydrazone **462** was obtained upon removal of solvent.

Finally, Aubé reported the synthesis of bridged amino ketals and amidines from moderately distorted tricylic lactams containing [4.3.1] ring system (Scheme 137).[408] These reactions demonstrate that the amide bond does not need to be fully perpendicular to exhibit ketone-like properties.

7.3.3. Reduction of Carbonyl Group—The reduction of bridged lactams occurs under mild conditions to give hemiaminals, which are frequently isolated because of the geometrical constraints prohibiting their further reduction via bridged iminium ions.[450]

Denzer and Ott were among the first to demonstrate the reduction of bridged lactams with $NaBH_4$, which is considered unreactive towards planar amides (Scheme 138).[290] The resulting hemiaminal collapsed to the aldehyde, which underwent further reduction. Interestingly, hydrogenation of **469** over PtO_2 resulted in the cleavage of methylene bridge to afford 1,5-benzodiazocinone **471**. Subsequently, Coe and coworkers used $NaBH_4$ or $LiAlH_4$ to obtain isolable hemiaminal product from an adamantane-derived bridged lactam (Scheme 139).[232] It was proposed that the bis-axially bridged piperidine ring system provided an additional degree of stabilization in this system. Aubé reported that moderately distorted medium-bridged lactams efficiently react with $NaBH_4$, and that the resulting hemiaminals are stable to reaction and isolation conditions (Scheme 140).[408] In some cases, mixtures of hemiaminals and primary alcohols were obtained (Scheme 141).[408] When an electron-withdrawing group was α to the twisted amide bond, an unusual C–C bond cleavage reaction was observed to occur completely exclusive to breakage of the alternative C–N bond (Scheme 141).[408]

Arata studied the reduction of one-carbon bridged lactam containing a leaving group α to the twisted amide bond (Scheme 142a).[352] Thus, lactam **225** was converted to hemiaminal **479** by electron transfer reduction using Na/NH_3,or by the two-stage hydrogenolysis of the C–Cl bond, followed by amide bond reduction with $LiAlH_4$. Notably, the product of this reaction was the hemiaminal instead of fully reduced amine, as would be expected for planar amides under LAH reduction conditions. However, bridged hemiaminal **479** could be readily converted into the parent 1-azabicyclo[4.4.1]undecane (Scheme 142b). In contrast to

the above conversions, the direct reduction of lactam **225** with $LiAlH_4$ afforded quinazoline **478**. The proposed mechanism for this reaction is shown in Scheme 143.

Several examples documenting the reduction of bridged lactams in total synthesis of natural products have been reported. The Thomas group utilized hemiaminal **481**, prepared by $LiAlH_4$ reduction of the bridged lactam **480**, as a precursor to the corresponding tricyclic amine in their approach towards the tropane alkaloid stemofoline (Scheme 144).[372,373] Attempts to deoxygenate the bridged hemiaminal by employing *S*-methyl xanthate or halides under free-radical conditions were unsuccessful.[373] Ultimately, the desired tricyclic amine was prepared in high yield via an intermediate acetate. Several alkaloids from Amaryllidaceae family contain bridged hemiaminals in a [3.2.1] benzofused ring system (Scheme 145).[183,188] The Wildman group investigated the reduction of oxohaemanthidine **484** to the corresponding hemiaminal using $NaBH_4$ in methanol,[183] while Hendrickson and coworkers synthesized 6,11-dihydroxycrinene **487** under similar conditions.[188] Dolby and Sakai studied the reduction of a bridged lactam bearing a relatively flexible [6.2.2] ring system (Scheme 146).[311,312] In this case, standard treatment with $LiAlH_4$ achieved exhaustive reduction to the corresponding amine. This suggests that the properties of the amide bond in the [6.2.2] ring system embodied in **488** are similar to those of planar amides. Finally, Harley-Mason determined that a bridged lactam containing a [5.2.2] ring system gives a stable hemiaminal on treatment with triethyloxonium tetrafluoroborate, followed by reduction with sodium borohydride (Scheme 147).[155] Attempts to prepare the corresponding amine were unsuccessful, leading only to the reduction of the ester group in the starting material. The bridged hemiaminal **490** was subsequently used as a key intermediate in the synthesis of indole alkaloid condylocarpine (see Scheme 178).[155]

7.3.4. Reactions with Organometallic and Related Reagents—Besides hydride, addition of more sterically-demanding organometallic reagents to bridged lactams has been reported to yield stable hemiaminals.[450]

By subjecting bicyclic and tricyclic bridged lactams containing a [4.3.1] ring system to organometallic reagents of increasing steric demand, Aubé has shown that the resulting adducts can range from products having stable tetrahedral carbon to the collapsed amino ketone isomers (Tables 16–17).[408] Bicyclic lactams afforded the corresponding amino ketones (Table 16), but in contrast the parent tricyclic lactams were found to be more effective in stabilizing the hemiaminal products (Table 17). The observed difference in reactivity was explained on the basis of the scaffolding effect provided by the additional six-membered ring in the latter system. In some cases, intermediary products featuring intramolecular N···C=O interactions involving $n_N \rightarrow \pi^*_{C=O}$ transitions in nine-membered amino ketones were observed.[408]

The same group established that bridged lactams can function as effective substrates for the synthesis of bridged α-aminoepoxides using dimethylsulfonium methylide under Corey-Chaykovsky epoxidation conditions (Scheme 148).[456] The success of this reaction relied on both the increased electrophilicity of distorted amide bonds and the stability of these bridged aminoepoxides to the reaction and isolation conditions due to the limited $n_N \rightarrow \sigma^*_{C\text{-}O}$ delocalization.

Olefination of bridged lactams provides facile access to bridged enamines featuring decreased overlap between the lone pair of electrons of nitrogen and the olefin π systems (see Section 6.3).[397–398] Kirby demonstrated that 1-aza-2-adamantanone undergoes the Wittig reaction to give a bridged enamine under standard conditions employed for olefination of ketones (Scheme 149a),[108] Aubé utilized a Petasis olefination to afford exo-cyclic enamine with a [4.3.1] ring system (Scheme 149b),[408] while Wärnmark functionalized Tröger's base-derived bridged lactams using the less reactive carbethoxymethylene-triphenylphosphorane under thermal conditions (Scheme 149c).[316]

During synthetic studies on Aspidosperma alkaloids, Ban demonstrated that under certain conditions cyanide adds to bridged lactam containing a [6.3.1] ring system (Scheme 150).[457] Structure of **499** was confirmed by X-ray crystallography. The proposed mechanism for this rearrangement involves cleavage of the bridged amide bond to give the reactive amino acyl cyanide, which undergoes further transformations (Scheme 151).

7.3.5. Other Reactions Involving Carbonyl Group—Ban has studied[164] the alkylation of bridged lactams with a [6.3.1] ring system at the bridgehead position[458] (Table 18). In this system, the bridgehead enolate was readily formed in the presence of LDA at −78 °C, but only a few electrophiles could be used to install C-electrophiles.[164] For example, when the bridgehead enolate was treated with methyl bromoacetate, the corresponding α-bromo lactam was formed as the major product.

Schill reported a Friedel-Crafts-type α-arylation of bridged lactam featuring [5.4.1] ring system (Scheme 152).[337]Although these authors also accomplished a related α-arylation of [4.4.1] ring system,[339] the reaction of a bridged lactam with [4.3.1] scaffold was unsuccessful due to its instability to the reaction conditions.[336]

Finally, Judd demonstrated that a complex bridged lactam containing an α,β-unsaturated amide bond on the external bridge in a [4.3.1] ring system could be further functionalized by rhodium-catalyzed conjugate addition of boronic acid with complete diastereoselectivity (Scheme 153).[296]

7.4. Miscellaneous Reactions of Bridged Lactams

Shea reported oxidation and hydrolysis reactions of a bridged lactam containing an additional bridgehead olefin in a [3.3.1] ring system (Scheme 154).[298] The authors proposed a complex mechanism involving two molecules of the bridged lactam. The moderate yield of the hydrolysis was proposed to be a result of decomposition of the bridged lactam under the reaction conditions.

Paquette investigated photocyclization reactions of bridged lactams containing diene motifs (Schemes 155–156).[295] The required substrates were prepared from the monounsaturated bridged lactams via a bromination/elimination sequence (Scheme 155).[295] The best results in the elimination step were achieved using TBAF in DMSO as a solvent at high temperature.[459] Upon irradiation with 300 nm light, bridged lactam **508**, containing a [4.3.1] ring system, underwent disrotatory ring closure to cyclobutene, while bridged lactam **509** with a [4.3.2] scaffold was unreactive under the same conditions (Scheme 156).[295] On the

basis of computational studies, the authors proposed that a non-planar arrangement of the diene moiety in lactam **509** contributed to this divergence in reactivity. It is worth noting that under similar irradiation conditions bridged sultams react with a preferential cleavage of the N–SO_2 bond (see Section 7.7.2).[295,431]

The X-ray structures of oxidation products derived from two other bridged lactams have been reported (Figure 15). Lactam **511a** was prepared by epoxidation of the corresponding olefin by Paquette (**511a**: $\tau = 9.6°$; $\chi_N = 28.3°$; $\chi_C = 3.3°$; N–C(O) = 1.363 Å; C=O = 1.231 Å).[460] The observed diastereoselectivity is similar to that observed in the epoxidation of related bridged sultams (see Scheme 166).[434] Aubé reported the X-ray structure of lactam **511b** prepared by Sharpless dihydroxylation/acylation of the corresponding olefin.[208] As indicated by its Winkler-Dunitz parameters ($\tau = 72.4°$; $\chi_N = 49.8°$; $\chi_C = 7.1°$; N–C(O) = 1.418 Å; C=O = 1.212 Å), this lactam contains one of the most distorted amide bonds isolated to date.

7.4. Reactivity of Heteroatom-Containing Derivatives of Bridged Lactams

In contrast to bridged lactams, the reactivity of their heteroatom-containing derivatives has been sparsely studied. Relevant studies on these heterocycles are limited to transformations of bridged oxazinolactams and 1,2-diazines developed by Shea.[383–385]

Bridged oxazinolactams, prepared in the intramolecular *N*-acylnitroso Diels-Alder reaction (see Section 6.2.1),[382–384] have been shown to undergo hydrogenation of the bridgehead olefin over Pd/C, while Na(Hg) chemoselectively cleaved the N–O bond (Scheme 157a).[383,384] Shea has also achieved highly diastereoselective alkylation of bridged oxazinolactams using reactive electrophiles (Scheme 157b).[384] The alkylation occurs from the more accessible exo face, providing complementary stereochemical outcome to the isomers obtained directly from the *N*-acylnitroso Diels-Alder reaction (Scheme 82).[384] This methodology has been applied to the stereocontrolled synthesis of seven- and eight-membered lactams (Scheme 158),[384] and later expanded to include bridged 1,2-diazines (Scheme 159).[385]

In 2007, Shea and coworkers reported the use of bridged oxazinolactams in their approach towards synthesis of stenine (Scheme 160).[461] The intramolecular *N*-acylnitroso Diels-Alder reaction of diene **520** gave the bridged tricyclic lactam **521** in good yield and diastereoselectivity. Reduction with Na(Hg) afforded the azepane **522**, which was elaborated to the key intermediate **523** in four steps.

7.5. Reactivity of Bridged Enamines

Although planar enamines are nucleophilic at carbon, bridged enamines are expected to exhibit properties of isolated amino-olefins as a result of the limited $n_N \rightarrow \pi^*_{C=C}$ overlap.[397,398] (Doering memorably commented “Of the conventional chemistry of enamines not a vestige remains.”[398]) However, reports on the reactivity of bridged enamines are relatively rare compared to bridged lactams.

Kirby showed that the bridged enamine derived from 1-aza-2-adamantane is alkylated at nitrogen using MeI in high yield (Scheme 161a).[108] This finding is in good agreement with

the reactivity of another bridged enamine containing nitrogen at the apex position in a [3.3.1] ring system reported by Kresge (Scheme 161b).[462] The ammonium salt **525** was characterized by the X-ray crystallography (θ = 326.4°; N–CH_3 = 1.503 Å; N–C(=CH_2) = 1.474 Å; C=CH_2 = 1.301 Å).[108]

Ellman examined the reactivity of endocyclic bridged enamines containing a bridgehead double bond (Scheme 162).[400] The alkylation with Me_2SO_4 also proceeded at the nitrogen atom, while the reduction with $NaBH_4$ afforded **529** as the only isolated product. Mechanistic investigation suggested that this reduction proceeds via the corresponding iminium ion. Finally, hydrogenation over Pd/C afforded the fully saturated bicyclic amine as a single diastereoisomer. The X-ray structure of ammonium salt **528** has been reported (θ = 333.6°; N–CH_3 = 1.511 Å; N–CH(=C) = 1.490 Å; CH=C = 1.330 Å).[400]

Pearson studied the reactivity of bridged enamines prepared by the intramolecular Schmidt reaction (Scheme 163).[401] It was found that hydrogenation and bromination reactions of these enamines proceed in high yields to give bicyclic amines bearing a close resemblance to core common to several Cinchona alkaloids.

7.6. Reactivity of Bridged Sultams

While bridged sultams contain non-planar sulfonamide bonds, these compounds do not show any signs of hyperreactivity.[437] It means that their properties can be examined under the conditions which would result in rapid decomposition of the analogous bridged lactams.

7.6.1. General Reactivity—The first reactions of bridged sultams were described in 2001 by Paquette. It was shown that a sultam containing [4.2.1] ring system undergoes smooth deprotonation with *tert*-butyllithium to give, after quenching with allyl or benzyl bromide, the substitution products in good yields (Scheme 164).[438] The same ring system was found to be stable to highly oxidizing conditions with chromyl acetate, providing the α-amino acetate and the bridged keto-sultam in good selectivity (Scheme 164).[438,431] Paquette also reported the synthesis of bridged sultams containing diene motifs via bromination/ olefination of the corresponding olefins under relatively harsh conditions (Scheme 165).[295,440,431,459] The diene products were later used in the photocyclization studies.[295,440,431]

More recently, Evans studied reactions of unsaturated benzofused bridged sultams with bromine and *m*-CPBA (Scheme 166).[434] In all cases, complete diastereoselectivity was observed, which was ascribed to the steric effect of the aryl group. Interestingly, the bridged sultam bearing an electron-rich aromatic ring participated in a cationic rearrangement upon treatment with bromine in $CHCl_3$.[434] Proposed mechanism for this transformation is outlined in Scheme 167.

The groups of Paquette[463] and Evans[434] further extended the ability to functionalize bridged sultams by developing a set of cross-coupling reactions (Table 19). Halogen-lithium exchange followed by quenching with diverse electrophiles or palladium-catalyzed cross-coupling with aryl boronic acids proceeded efficiently, delivering a variety of functionalized bridged sultams.[463] Evans also demonstrated that hydrogenation of unsaturated bridged

sultams bearing [3.2.1] ring system proceeds with high diastereoselectivity (Scheme 168).[434] In contrast to hydrogenolysis of bridged lactams (see Section 7.2.2),[208] the cleavage of N–SO_2 bond was not observed.

A single example of an unusual desulfonylative indolization of a bridged sultam was reported by Paquette.[464]

7.6.2. Photochemical Reactions—Photochemical reactions of bridged sultams have been used to probe the effect of non-planar geometry of sulfonamide bonds on their reactivity.[431,295]

In 2004, Paquette reported the rearrangement of a bridged sultam with a [4.2.1] bis-unsaturated scaffold to a complex heterocycle containing cyclobutene, thietane dioxide and pyrrolidine rings (Scheme 169).[431] The proposed mechanism involves (1) homolytic cleavage of the N–SO_2 bond, (2) rebonding to give the bicyclic isomer, (3) thermally-induced [1,5]-hydrogen shift, and (4) photo-induced disrotatory closure to the cyclobutene ring. This reaction constituted the first example of a σ N–SO_2 bond cleavage in a bridged sulfonamide.

In line with the previous report, Paquette observed the photochemical rearrangement of a related benzofused-bridged sultam to a dihydroazepine heterocycle via N–SO_2 bond cleavage and [1,5]-sulfonyl migration (Scheme 170a).[295] In this case, minor quantities of the alternative cyclobutene product were formed via a photo-induced disrotatory closure. Later, Paquette attempted photochemical reactions of a bridged sultam featuring the sulfur atom at the apex position (Scheme 170b).[440] However, under a variety of conditions, polymerization was found to be the predominant reaction pathway. In one case only, a cyclobutene product was isolated in low yield.[440]

Paquette also reported photoinduced di-π-methane rearrangement of benzofused bridged sultams bearing a [3.2.1] ring system (Table 20).[463] Upon irradiation with 300 nm light, a series of functionalized substrates gave formal contraction products **554**. Despite a potential to give two regioisomeric outcomes, in all examples the rebonding step occurred distal to the sulfonamide bond.

7.6.3. Double Reduction—Bridged sultams have been shown to simultaneously undergo the reduction of both N–SO_2 and SO_2–C bonds to give planar nitrogen-containing heterocycles.[432–435]

Evans applied the double reduction of aromatic bridged sultams to the synthesis of pyrrolidines bearing various functional groups (Scheme 171).[432–434] The reaction can be conducted by treatment of the bridged sultams with lithium or sodium metal in ammonia.[432] The use of lithium/ethylenediamine (Benkeser reduction) afforded partially dearomatized products, while sodium naphthalenide led to extensive decomposition.[432]

Evans utilized the double reduction methodology to establish all-carbon quaternary stereocenter in the total synthesis of mesembrane (Scheme 172).[434] The required bridged sultam was prepared in high yield via Heck reaction; however, the double reduction was

achieved in modest yield due to the competing removal of one of the methoxy groups. The reaction was sensitive to the conditions used; for example sodium and lithium naphthalenide afforded the final product with higher selectivity, however in lower yields.

8. APPLICATION OF BRIDGED LACTAMS IN TOTAL SYNTHESIS

Bridged lactams have been used on several occasions in total synthesis of natural products.[141–192] The ability to provide a rigid molecular framework and to attenuate the basicity of a nitrogen atom are among strategic advantages of applying bridged lactams in target-oriented synthesis. Moreover, in recent years a number of natural products containing bridged amide bonds have been isolated,[193–207] suggesting that bridged lactams may be more prevalent in nature than had been previously considered. In the final section of this review, we will cover representative examples of bridged lactams used in total synthesis, with discussion focused on the role of bridged amide bonds.

8.1. Lycopodium Alkaloids

In 2008, Dake reported the total synthesis of Lycopodium alkaloid, (+)-fawcettidine (Scheme 173).[141] The congested tetracyclic framework of this alkaloid was introduced by conjugate addition of the thiolate anion to give a complex bridged lactam **564** in 76% yield. Sequential functional group manipulations transformed **564** into the sulfone **565**, which was subjected to the Ramberg-Bäcklung ring contraction to afford another bridged lactam containing a [4.3.1] ring system. This intermediate was rapidly converted into (+)-fawcettidine in three steps, including an LAH reduction that suggests that this particular lactam, while in a bridged framework, is not unusually twisted.

8.2. Communesins

Communesins are indole alkaloids containing a 1-azabicyclo[3.2.2]nonane moiety.[142] In 2010, Ma reported the first total synthesis of the potently cytotoxic (−)-communesin F using bridged lactam **569** to construct the 1-azabicyclo[3.2.2]nonane core of this molecule (Scheme 174a).[143] Treatment of the allylic alcohol **568** with MsCl and Et_3N provided the required lactam **569** in 63% yield. After mesylate displacement with sodium azide, the intermediate **570** was subjected to an unprecedented Staudinger reaction with the bridged amide, using PPh_3 at 80 °C, to give the amidine **571** in 83% yield. Subsequent reduction and acetylation afforded the natural product. In this case, the inherent strain of the amide bond in the bridged lactam **570** enabled the rapid synthesis of (−)-communesin F.

In 2011, Ma reported another elegant use of bridged lactams during the total synthesis of (−)-communesins A and B (Scheme 174b).[144] Oxidative cross-coupling of the dianion derived from **573** afforded the bridged lactam **574** as a single diastereoisomer in a respectable 73% yield. The obtained stereochemical outcome was proposed to arise from a favorable π-stacking interaction between nitrophenyl and indole rings. The lactam **574** was advanced to the cyanide **575**, which was subjected to the sequential reduction/reductive amination to afford the aminal **576** in 92% yield. This reaction most likely proceeds via the intermediate amino aldehyde, however the mechanism involving a bridged iminium ion

cannot not be excluded. The aminal **576** required only four more steps to complete the synthesis of (−)-communesins A and B.

Biogenetically, communesins have been proposed to originate from two oxidized molecules of tryptamine.[142] In 2003, Stoltz put forward a biomimetic hypothesis for the origin of communesins A and B, in which the key step was a Diels-Alder reaction between the quinine methide imine **579** and aurantioclavine derivative **578** to give the highly twisted bridged lactam **580** (Scheme 175a).[145,146] It was postulated that the amide bond in **580** would then undergo transamination by the tethered primary amine to afford **581**, another key intermediate in the biosynthesis.

In 2004, Funk proposed a similar biomimetic pathway for the synthesis of communesin B (Scheme 175b).[147] Funk validated this biomimetic proposal during the total synthesis of a related natural product perophoramidine (Scheme 175c).[147] The coupling of indole **586** and 3-bromo-3-alkylindolin-2-one **587** afforded the intermediate **589** in 89% yield and ≥20:1 diastereoselectivity. The mechanism for this transformation may involve hetero Diels-Alder reaction to give bridged lactam **588**, as proposed in the biomimetic hypothesis, or a conjugate addition pathway. The subsequent transamidation of **589** provided the pentacycle **590**, which required only 9 steps to furnish the natural product. Recently, the Funk group synthesized communesin F utilizing a similar indol-2-one cycloaddition to rapidly generate the tetracyclic core of this natural product.[148] These studies also featured a bridged lactam (analogous to **569**, Scheme 174a) and prepared via trimethylaluminum-mediated condensation of the corresponding amino ester.

8.3. Cripowellins

The aglycon of cripowellins contains an intriguing 1-azabicyclo[5.3.2]dodecan-2-one ring system, in which the amide bond is placed on the larger external bridge. In 2005, Moon and coworkers reported a rapid synthesis of the skeleton of cripowellins by employing ring expansion reaction under reductive conditions (Scheme 176a).[149] The precursor **594** was efficiently prepared via oxidative cyclization of the acylic amine **592**. The key step proceeded in 51% yield using sodium naphthalenide to afford the bridged keto amide **595** in the following sequence of events: (i) nitrogen deprotection, (ii) nucleophilic addition to the tetrahedral intermediate **595**, and (iii) C–C bond fragmentation.

In the same year, Enders reported asymmetric synthesis of the 1-*epi* aglycon of cripowellins (Scheme 176b).[150,151] In this approach, the bridged ring system was constructed via the intramolecular Heck reaction of the 9-membered precursor **601**, which in turn was easily prepared by the ring-closing metathesis of the appropriately rigidified diene. The asymmetry was introduced by a rare Sharpless asymmetric dihydroxylation of a skipped diene (Scheme 176b, box). The conditions used for the Heck reactions had a significant effect on the outcome of the pivotal cyclization; the neutral conditions employing PPh_3 and Et_3N in DMF led to the disibstituted *Z*-olefin **602**, while under cationic conditions (dppp, Ag_2CO_3, toluene) the anti-Bredt olefin **603** was formed as a mixture of *E* and *Z* isomers. From intermediate **603**, the completion of the synthesis required only four additional steps.

8.4. Quinine Derivatives

The 1946 oxidative degradation of quininone (via 5-vinylquinuclidin-2-one) by Doering and Chanley marks the first synthesis and the first reaction of any bridged lactam (see Scheme 2).[251] Subsequently, this process has been applied to the synthesis of piperidines[152] and isoquinolinones[153] from Cinchona alkaloids.

Recently, Doris and coworkers reported the total synthesis of (+)-mequitazine using oxidative degradation of quinine via an unisolated bridged lactam, 5-vinylquinuclidin-2-one, as the key step (Scheme 177).[154] Oxidation of quinine under Swern conditions provided the required quininone. This intermediate was reacted with potassium *tert*-butoxide in the presence of oxygen to deliver, after alcoholysis of the transient bridged amide bond, the vinyl piperidine in 60% yield. Transannular closure and coupling with phenothiazine completed the synthesis of (+)-mequitazine.

8.5. Aspidosperma and Strychnos Alkaloids

In classic studies on Strychnos-type alkaloids, Harley-Mason investigated the use of bridged lactams (Scheme 178).[155] In particular, his group developed efficient synthesis of bridged lactam **611** containing a [5.2.2] ring system,[155] which then served as a key intermediate in the synthesis of tubifoline,[156] condyfoline[156] and geissoschizoline[157] (Schemes 178a and b). A similar strategy relying on bridged lactams bearing the same bicyclic scaffold[158] was utilized in the rapid syntheses of several other alkaloids, including fluorocurarine[159] (Scheme 178c), condylocarpine[155] (Scheme 178d), tubotaiwine,[160] dihydronorfluorocurarine,[161] and tubifolidine.[156] Interestingly, as early as in 1975, Harley-Mason explicitly proposed that lactams in which the amide bond is non-planar might be useful in the synthesis of complex alkaloids.[155]

In 1981, Ban and coworkers reported the total synthesis of quebrachamine using the bridged lactam **621** containing a [6.3.1] ring system (Scheme 179).[162] The requisite lactam was prepared via an intramolecular *N*-alkylation of **620** using NaH in the presence of KI/18-crown-6, followed by alkylation at the bridgehead position in very good overall yield (see also Table 18). Reduction of **621** followed divergent pathways depending on the conditions used for this step: with $LiAlH_4$ in refluxing dioxane, quebrachamine was formed, whereas in THF, 1,2-dehydroaspidospermidine was obtained via the bridged hemiaminal **623**. Using similar strategy, Ban prepared other aspidosperma alkaloids,[162–164] including 1-acetylaspidoalbidine,[164] deoxyaspidodispermine[164] and 1-acetylaspidospermidine.[163] Recently, Movassaghi[165] reported the use of structurally-related bridged lactams featuring a [6.3.1] ring system[166] in the synthesis of complex dimeric aspidosperma alkaloids.

The groups of Ziegler[167,168] and Bosch[169] utilized bridged lactam **626** bearing the amide bond on the larger external bridge in a [6.3.1] scaffold in an alternative approach to quebrachamine (Scheme 180a). The lactam **626** was prepared from the carboxylic acid **625** by treatment with PPA at 90 °C. This reaction is thought to proceed via the highly reactive acylated intermediate **627**.[168] Subsequent reduction of the bridged lactam with $LiAlH_4$ provided the final alkaloid. Similar synthetic approaches have been reported in the total synthesis of dihydrocleavamine,[170–172] tabersonine[173] and cleavamine[174] by the research

groups of Bosch,[170,171] Lesma,[172] Ziegler,[173] and Hanaoka[174] (Scheme 180b–d). In general, only modest yields have been obtained in the reduction of these bridged lactams.

Another elegant example of the use of bridged lactams was reported by Bosch in the total synthesis of (−)-tubifoline (Scheme 181a).[175,176] Witkop photocyclization of chloroacetamide **637** gave the late stage intermediate **638** containing bridged amide bond in a [5.2.2] ring system as an inconsequential mixture of the double bond isomers. Tandem lactam/olefin reduction and oxidative cyclization using PtO_2/O_2 transformed the lactam **638** into the natural product. Similar Witkop photocyclizations to give bridged lactams in the synthesis of Strychnos alkaloids have been reported independently by Snieckus[177] and Ishikura.[178]

Magnus utilized the bridged lactam **641** featuring the amide bond on the shorter external bridge in a [5.2.2] ring system as an early stage intermediate in the total synthesis of strychnine (Scheme 181b).[179] Conjugate addition of the enolate **640** afforded the bridged lactam **641** in 65–98% yield, forming the F ring of strychnine. It was found that the yield of the conjugate addition was significantly improved when the sulfoxide precursor was used. The next step involved oxidation to the α-keto amide via Pummerer rearrangement.

Büchi[180,181] and Narisada[182] independently reported the total synthesis of velbamine, a degradation product of oncolytic vinblastine and vincristine alkaloids, using bridged lactams as key intermediates (Scheme 182). The approach by Büchi relied on retroaldol cleavage of the β-hydroxyketone **644** to reveal the bridged lactam **645** embedded in a [6.3.1] ring system (Scheme 182a).[180,181] This intermediate was converted into velbamine in five more steps. In contrast, Narisada showed that the analogous bridged lactam **650** could be obtained via fragmentation of **649** under oxidative conditions using $Pb(OAc)_4$ in comparable yield (Scheme 182b).[182] The methoxy group was eliminated under acidic conditions to give bridged enamide **651**, which was converted into velbamine using standard functional group manipulations.

8.6. Amaryllidaceae Alkaloids

Wildman reported the synthesis of bridged lactams from several Amaryllidaceae alkaloids, such as haemanthidine, oxohaemanthidine and apohaemanthidine, using oxidation with MnO_2 (Scheme 183a).[183] When oxohaemanthidine was treated with NaOAc/HOAc, the conjugated lactone was formed via hydrolysis of the bridged amide bond and lactonization.[184,185] After methylation to **652**, this product was used to correlate two common Amaryllidaceae alkaloids, heamanthidine and pretazettine (Scheme 183a).[184,185]

Irie and coworkers reported the use of a related bridged lactam **659** to install the tricyclic core of dihydrocrinine (Scheme 183b).[186,187] Transannular conjugate addition of the precursor **658** under ketalization conditions stereoselectively afforded the required lactam. Lower yields of lactam **659** were observed with NaH, NaO*t*Bu and $NaNH_2$.[187] Interestingly, the minor product isolated in this reaction was the bridged ethylene orthoamide resulting from the reaction of the twisted amide bond with ethylene glycol (not shown; cf. Table 5 and Scheme 133).[187] Similarly, the formation of stable hemiaminals on treatment with $LiAlH_4$

(**659**→**660**) that required additional steps to effect full reduction to the amine indicates that bridged amide bonds in these systems possess a significant ketonic character.

Finally, Hendrickson reported the total synthesis of dioxocrinene **486** featuring the bridged amide bond (Scheme 183c)[188] and haemanthidine using the bridged lactam **664** as the key intermediate (Scheme 183d).[189] Both lactams were constructed from the corresponding esters **662–663** via a sequence involving hydrolysis, homologation with diazomethane, and treatment with dry HCl to effect the cyclization (Scheme 183c–d).[188,189] The ester precursors **662–663** were easily prepared via Curtuis rearrangement followed by Friedel–Crafts cyclization, highlighting the efficiency of this strategy. Hendrickson studied the quasi-amide bond properties of some of the prepared bridged lactams, finding these compounds to be sensitive towards hydrolysis/methanolysis and able to be reduced with the mild reducing agent $NaBH_4$.[188]

8.7. Kopsia Alkaloids

In 2001, Magnus reported the total synthesis of kopsijasminilam, a complex Kopsia alkaloid containing a bridged amide in a pentacyclic ring system (Scheme 184a).[190,191] The transannular cyclization of eleven-membered precursor **665** set the stage for the key Diels-Alder reaction. The Diels-Alder adduct was obtained on treatment of the cyanide **666** with acryloyl chloride. Substituents other than cyanide at the hemiaminal carbon, including OH, OMe or SPh, resulted in decomposition during the Diels-Alder step. Polonovski fragmentation of the *N*-oxide **668** gave the spirocyclic bridged lactam **670** in 90% yield. The synthesis was completed by conjugate reduction/oxidation using catalytic $Mn(dpm)_3/PhSiH_3$ under oxygen atmosphere. Magnus utilized a similar concept based on the peroxyaminal fragmentation of the intermediate **672** in the total synthesis of pauciflorine B (Scheme 184b).[190,191]

At about the same time, Kuehne applied an alternative fragmentation strategy in the total synthesis of kopsijasminilam (Scheme 184c).[192] The key precursor **676** was prepared from alkaloid minovincine. Treatment of **676** with NaCN in refluxing ethanol-water resulted in the nitrogen-assisted fragmentation to give the pentacyclic cyanide **677** in 89% yield. The bridged lactam **678** was obtained after oxidation with potassium *tert*-butoxide in the presence of oxygen. This intermediate was converted to kopsijasminilam in five more steps.

8.8. Natural Products Containing Bridged Amide Bonds

Several natural products containing bridged amide bonds have been isolated from *Stemona*,[193–196] *Daphnum*,[197–202] *Kopsia*,[203] *Strychnos*,[204] *Iboga*,[205] *Amaryllidaceae*[465] and *Lycopodium* species[206,207] (Schemes 185–189).

Representative bridged lactams in the the structural class of *Stemona* alkaloids are tuberostemoninols (**680–682**),[193] neotuberostemoninol (**683**),[194] sessilifoliamide I (**684**),[195] and maireistemoninol (**685**),[196] in which the amide bond is placed on a one-carbon bridge in a [4.3.1] ring system, and the biogenetically-related neotuberostemonone (**686**)[196] and epoxytuberostemonone (**687**)[196] containing [6.4.1] bridged systems (Scheme 185). The X-ray structures and spectroscopic properties of neotuberostemoninol (**683**)[194] and

sessilifoliamide I (**684**)[195] indicate that amide bonds in these compounds aresignificantly distorted from planarity (**683**: $\tau = 49.6°$; $\chi_N = 30.8°$; $\chi_C = 12.7°$; N–C(O) = 1.402 Å; C=O = 1.215 Å; $\nu_{C=O}$ 1682 cm^{-1}; $^{13}C_{C=O}$ 184.7 ppm; **684**: $\tau = 43.9°$; $\chi_N = 35.3°$; $\chi_C = 11.0°$; N–C(O) = 1.390 Å; C=O = 1.232 Å; $\nu_{C=O}$ 1656 cm^{-1}; $^{13}C_{C=O}$ 182.4 ppm).

Daphnum alkaloids containing bridged amide bonds include daphmanidins B–D (**688–690**),[197,198] daphnezomines F, G, and U (**691–693**),[199,200] daphhimalenine A (**694**),[201] and daphnicyclidine J (**695**),[202] which feature 1-azabicyclo[5.2.2]undecane, 1-azabicyclo[5.2.1]decane and 1-azabicyclo[6.2.2]dodecane ring systems (Scheme 186). Infrared stretching frequencies and ^{13}C NMR shifts of daphhimalenine A (**694**)[201] confirm that the amide bond in this alkaloid is non-planar ($\nu_{C=O}$ 1687 cm^{-1}; $^{13}C_{C=O}$ 183.8 ppm).

Pericidine (**696**)[203] and henningsamides (**697–699**)[204] are *Kopsia* and *Strychnos* alkaloids, respectively, which contain the amide bond in a [5.2.2] ring system, while 3-oxocoronaridine (**700**)[205] and 3-oxovoacangine (**701**)[205] are oxygenated *Iboga* alkaloids with bridged amide bonds embedded in complex caged tricyclic structures (Scheme 187). Kopsijasminilam (**671**) and pauciflorine B (**674**) (Scheme 187) have been mentioned in the previous section in the context of their synthesis (see Section 8.7);[190–192] two other *Kopsia* alkaloids, deoxykopsijasminilam (**702**) and pauciflorine A (**703**)[190–192] share their unprecedented skeleton (Scheme 187). The *Amaryllidaceae* alkaloids containing bridged amide bonds, cripowellins A and B (**598–599**) (Scheme 188),[465] have been already discussed in this review (see Section 8.3).[149–151]

Finally, several *Lycopodium* alkaloids, such as phlegmariurines A–C (**704–706**)[206] and lycoposerramine E (**707**)[206] feature bridged amide bonds placed in a [5.3.4] ring system. These compounds belong to the fawcettimine class of *Lycopodium* alkaloids[207] and can be regarded as degradation products of fawcettidine (see Scheme 173).

9. CONCLUSIONS AND OUTLOOK

In the course of 75 years of inquiry, the chemistry of bridged lactams has provided numerous examples of fascinating molecules. Due to the restricted conformation, these lactams cannot benefit from the full resonance stabilization typical to planar amides. The initial interest in bridged lactams was fuelled by the imagination of organic chemists to test the stability of anti-Bredt amides. Over the years, it has been demonstrated that non-planar amides are highly susceptible to hydrolysis, and in general difficult to prepare or isolate. In the last decade, improved mechanistic understanding and the emergence of new synthetic methods have allowed the synthesis of bridged lactams containing perfectly orthogonal amide bonds. Remarkably, many of these perpendicularly twisted amides have been structurally characterized. Furthermore, new structural classes of bridged lactams have been invented and applied to probe the effect of amide bond distortion on its reactivity. The *N*-activation of amide bonds, detailed studies on amide bond hydrolysis, structural characterization of *N*-protonated lactams, and the synthesis of hydrolytically-robust bridged lactams have been described. A large number of bridged lactams have been characterized by X-ray crystallography, which in combination with IR, and ^{13}C NMR spectroscopic data, makes it possible to estimate the relationship between twist angle and chemical reactivity of

these compounds. The importance of bridged lactams is further underlined by their successful application to access complex building blocks in target-oriented synthesis and their tantalizing potential as lead structures in medicinal chemistry.

While progress has been considerable, many areas remain to be explored. Expanding the family of highly-strained bridged lactams, systematic examination of their follow-up chemistry, additional insight into the quantitative evaluation of amide bonds, and application of the new reactivity manifolds of non-planar lactams to simple amides are among the challenges that need to be addressed. Finally, as mechanical distortion plays a key role in the enzymatic activation of amide bonds, non-planar lactams will continue to give us a glimpse into the molecular level of enzymatic catalysis.

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References

1. Greenberg, A.; Breneman, CM.; Liebman, JF., editors. The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science. Wiley; 2000.
2. Pauling, L. The Nature of the Chemical Bond. London: Oxford University Press; 1940.
3. Chalupsky J, Vondrasek J, Spirko V. J. Phys. Chem. A. 2008; 112:693. [PubMed: 18177024]
4. Mannfors BE, Mirkin NG, Palmo K, Krimm S. J. Phys. Chem. A. 2003; 107:1825.
5. Shin SBY, Yoo B, Todaro LJ, Kirshenbaum K. J. Am. Chem. Soc. 2007; 129:3218. [PubMed: 17323948]
6. Poteau R, Trinquier G. J. Am. Chem. Soc. 2005; 127:13875. [PubMed: 16201809]
7. Ramachandran GN. Biopolymers. 1968; 6:1494. [PubMed: 5685106]
8. MacArthur MW, Thornton JM. J. Mol. Biol. 1996; 264:1180. [PubMed: 9000639]
9. Bednarova L, Malon P, Bour P. Chirality. 2007; 19:775. [PubMed: 17687760]
10. Edison AS. Nat. Struct. Biol. 2001; 8:201. [PubMed: 11224559]
11. Beausoleil E, Lubell WD. J. Am. Chem. Soc. 1996; 118:12902.
12. Halab L, Lubell WD. J. Org. Chem. 1999; 64:3312. [PubMed: 11674436]
13. Halab L, Lubell WD. J. Am. Chem. Soc. 2002; 124:2474. [PubMed: 11890796]
14. Wipf P, Miller CP, Grant CM. Tetrahedron. 2000; 56:9143.
15. Yamada S. Angew. Chem., Int. Ed. 1993; 32:1083.
16. Yamada S. Angew. Chem., Int. Ed. 1995; 34:1113.
17. Yamada S. J. Org. Chem. 1996; 61:941.
18. Yamada S, Nakamura M, Kawauchi I. Chem. Commun. 1997:885.
19. Yamada S, Matsuda K. Chem. Lett. 2001:750.
20. Pedone C, Benedetti E, Immirzi A, Allegra G. J. Am. Chem. Soc. 1970; 92:3549.
21. Bennet AJ, Somayaji V, Brown RS, Santarsiero BD. J. Am. Chem. Soc. 1991; 113:7563.
22. Yamada S, Nunami N, Hori K. Chem. Lett. 1998:451.
23. Evans PA, Holmes AB, Collins I, Raithby PR, Russell K. J. Chem. Soc., Chem. Commun. 1995:2325.
24. Yamada S, Homma A. Chem. Commun. 2002:2656.
25. Cow CN, Britten JF, Harrison PHM. Chem. Commun. 1998:1147.
26. Matta CF, Cow CC, Sun S, Britten JF, Harrison PHM. J. Mol. Struc. 2000; 523:241.
27. Duspara PA, Matta CF, Jenkins SI, Harrison PHM. Org. Lett. 2001; 3:495. [PubMed: 11178808]

28. Matta CF, Cow CN, Harrison PHM. J. Mol. Struc. 2003; 660:81.
29. Bain AD, Chen H, Harrison PHM. Can. J. Chem. 2006; 84:421.
30. Yamamoto G, Murakami H, Tsubai N, Mazaki Y. Chem. Lett. 1997:605.
31. Yamamoto G, Tsubai N, Murakami H, Mazaki Y. Chem. Lett. 1997:1295.
32. Yamamoto G, Nakajo F, Tsubai N, Murakami H, Mazaki Y. Bull. Chem. Soc. Jpn. 1999; 72:2315.
33. Saeed A, Erben MF, Bolte M. J. Org. Chem. 2012; 77:4688. [PubMed: 22540173]
34. Hutchby M, Houlden CE, Haddow MF, Tyler SN, Lloyd-Jones GC, Booker-Milburn KI. Angew. Chem., Int. Ed. 2012; 51:548.
35. Alcorta I, Cativiela C, Elguero J, Gil AM, Jiménez AI. New. J. Chem. 2005; 29:1450.
36. Rauk A, Allen LC, Mislow K. Angew. Chem., Int. Ed. 1970; 9:400.
37. Korn A, Rudolph-Böhner S, Moroder L. Tetrahedron. 1994; 50:1717.
38. Shao H, Jiang X, Gantzel P, Goodman M. Chem. Biol. 1994; 1:231. [PubMed: 9383395]
39. Otani Y, Nagae O, Naruse Y, Inagaki S, Ohno M, Yamaguchi K, Yamamoto G, Uchiyama M, Ohwada T. J. Am. Chem. Soc. 2003; 125:15191. [PubMed: 14653754]
40. Ohwada T, Achiwa T, Okamoto I, Shudo K, Yamaguchi K. Tetrahedron Lett. 1998; 39:865.
41. Hori T, Otani Y, Kawahata M, Yamaguchi K, Ohwada T. J. Org. Chem. 2008; 73:9102. [PubMed: 18947252]
42. Hosoya M, Otani Y, Kawahata M, Yamaguchi K, Ohwada T. J. Am. Chem. Soc. 2010; 132:14780. [PubMed: 20882981]
43. Aleman C, Jiménez AI, Cativiela C, Perez JJ, Casanovas. J. Phys. Chem. B. 2005; 109:11836. [PubMed: 16852453]
44. Gerdes RG, Glover SA, ten Have JF, Rowbottom CA. Tetrahedron Lett. 1989; 30:2649.
45. Rauk A, Glover SA. J. Org. Chem. 1996; 61:2337.
46. Glover SA, Rauk A. J. Org. Chem. 1999; 64:2340.
47. Glover SA, Mo G, Rauk A, Tucker DJ, Turner P. J. Chem. Soc., Perkin Trans. 1999; 2:2053.
48. Glover SA, Mo GN. J. Chem. Soc. Perkin Trans. 2002; 2:1728.
49. Glover SA, Rauk A. J. Chem. Soc., Perkin Trans. 2002; 2:1740.
50. Gillson AME, Glover SA, Tucker DJ, Turner P. Org. Biomol. Chem. 2003; 1:3430. [PubMed: 14584807]
51. Banks TM, Bonin AM, Glover SA, Prakash AS. Org. Biomol. Chem. 2003; 1:2238. [PubMed: 12945693]
52. Andrews LE, Banks TM, Bonin AM, Clay SF, Gillson AME, Glover SA. Aust. J. Chem. 2004; 57:377.
53. Glover SA, White JM, Rosser AA, Digianantonio KM. J. Org. Chem. 2011; 76:9757. [PubMed: 22017195]
54. Digianantonio KM, Glover SA, Johns JP, Rosser AA. Org. Biomol. Chem. 2011; 9:4116. [PubMed: 21499599]
55. Hall HK Jr, El-Shekeil A. Chem. Rev. 1983; 83:549.
56. Lease, TG.; Shea, KJA. Advances in Theoretically Interesting Molecules. Vol. Vol. 2. JAI Press Inc.; 1992. Compilation and Analysis of Structural Data of Distorted Bridgehead Olefins and Amides.
57. Greenberg, A. The Amide Linkage as a Ligand-Its Properties and the Role of Distortion. In: Greenberg, A.; Breneman, CM.; Liebman, JF., editors. The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science. Wiley; 2000.
58. Clayden J, Moran WJ. Angew. Chem., Int. Ed. 2006; 45:7118.
59. Szostak M, Aubé J. Org. Biomol. Chem. 2011; 9:27. [PubMed: 21069232]
60. Lukeš R. Collect. Czech., Chem. Commun. 1938; 10:148.
61. Brown, R. Studies in Amide Hydrolysis: The Acid, Base, and Water Reactions. In: Greenberg, A.; Breneman, CM.; Liebman, JF., editors. The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science. Wiley; 2000.
62. Lopez X, Mujika JI, Blackburn GM, Karplus M. J. Phys. Chem. A. 2003; 107:2304.

63. Mujika JI, Mercero JM, Lopez X. J. Phys. Chem. A. 2003; 107:6099.
64. Mujika JI, Mercero JM, Lopez X. J. Am. Chem. Soc. 2005; 127:4445. [PubMed: 15783227]
65. Mujika JI, Formoso E, Mercero JM, Lopez X. J. Phys. Chem. B. 2006; 110:15000. [PubMed: 16869615]
66. Wang B, Cao Z. Chem. Eur. J. 2011; 17:11919. [PubMed: 21901771]
67. Mucsi Z, Tsai A, Szori M, Chass GA, Viskolcz B, Csizmadia IG. J. Phys. Chem. A. 2007; 111:13245. [PubMed: 18041826] For studies on determination of energy changes during the rotation of the amino group in amides, see: Glover SA, Rosser AA. J. Org. Chem. 2012; 77:5492. [PubMed: 22646836] Wiberg KB, Breneman CM. J. Am. Chem. Soc. 1992; 114:831.
68. Mucsi Z, Chass GA, Viskolcz B, Csizmadia IG. J. Phys. Chem. A. 2008; 112:9153. [PubMed: 18763749]
69. Mucsi Z, Chass GA, Csizmadia IG. J. Phys. Chem. B. 2008; 112:7885. [PubMed: 18533695]
70. Greenberg A, Venanzi CA. J. Am. Chem. Soc. 1993; 115:6951.
71. Greenberg A, Moore DT, DuBois TD. J. Am. Chem. Soc. 1996; 118:8658.
72. Cho SJ, Cui C, Lee JY, Park JK, Suh SB, Park J, Kim BH, Kim KS. J. Org. Chem. 1997; 62:4068.
73. Cox C, Wack H, Lectka T. Angew. Chem., Int. Ed. 1999; 38:798.
74. Morgan J, Greenberg A, Liebman JF. Struct. Chem. 2012; 23:9851. Morgan J, Greenberg A. J. Phys. Org. Chem. 2012; 25:1422. Morgan J, Greenberg A, Liebman JF. Struct. Chem. 2012; 23:197.
75. Bednarova L, Malon P, Bour P. Chirality. 2007; 19:775. [PubMed: 17687760]
76. Kemnitz CR, Loewen MJ. J. Am. Chem. Soc. 2007; 129:2521. [PubMed: 17295481]
77. Mujika JI, Matxain JM, Eriksson LA, Lopez X. Chem. Eur. J. 2006; 12:7215. [PubMed: 16807968]
78. Jean Y, Demachy I, Lledos A, Maseras F. J. Mol. Struc. (Theochem). 2003; 632:131.
79. Greenberg A, Moore DT. J. Mol. Struc. 1997; 413:477.
80. Greenberg A, Thomas TD, Bevilacqua CR, Coville M, Ji D, Tsai JC, Wu G. J. Org. Chem. 1992; 57:7093.
81. Greenberg A, Hsing HJ, Liebman JF. J. Mol. Struc. (Theochem). 1995; 338:83.
82. Greenberg A, DuBois TD. J. Mol. Struc. 2001; 567:303.
83. Kesharwani MK, Ganguly B. J. Comput. Chem. 2011; 32:2170.
84. Liu J, Albers MW, Chen CM, Schreiber SL, Walsh CT. Proc. Natl. Acad. Sci. U. S. A. 1990; 87:2304. [PubMed: 2179953]
85. Fischer G. Chem. Soc. Rev. 2000; 29:119.
86. Fischer, G.; Schmid, FX. Peptidyl-prolyl cis/trans isomerases. In: Bakau, B., editor. Molecular Chaperones and Folding Catalysts: Regulation, Cellular Functions and Mechanisms. CRC; 1999.
87. Cox C, Lectka T. Acc. Chem. Res. 2000; 33:849. [PubMed: 11123884]
88. Liebman JF, Greenberg A. Chem. Rev. 1976; 76:311.
89. Hoffmann R, Hopf H. Angew. Chem., Int. Ed. 2008; 47:4474.
90. Yamada S. J. Synth. Org. Chem. Jpn. 1998; 56:303.
91. Yamada S. Rev. Heteroat. Chem. 1999; 19:203.
92. Yamada, S. Sterically Hindered Twisted Amides. In: Greenberg, A.; Breneman, CM.; Liebman, JF., editors. The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science. Wiley; 2000.
93. Aubé J. Angew. Chem., Int. Ed. 2012; 51:3063.
94. Clayden J. Nature. 2012; 481:274. [PubMed: 22258603]
95. Glover SA. Tetrahedron. 1998; 54:7229.
96. Glover SA, Rauk A, Buccigross JM, Campbell JJ, Hammond GP, Mo GN, Andrews LE, Gillson AME. Can. J. Chem. 2005; 83:1492.
97. Glover SA. Adv. Phys. Org. Chem. 2007; 42:35.
98. Fawcett FS. Chem. Rev. 1950; 47:219. [PubMed: 24538877]
99. Köbrich G. Angew. Chem., Int. Ed. 1973; 12:464.

100. Buchanan GL. Chem. Soc. Rev. 1974; 3:41.
101. Keese R. Angew. Chem., Int. Ed. 1975; 14:528.
102. Warner PM. Chem. Rev. 1989; 89:1067.
103. Shea KJ. Tetrahedron. 1980; 36:1683.
104. Bear BR, Sparks SM, Shea KJ. Angew. Chem., Int. Ed. 2001; 40:821.
105. Vazquez S, Camps P. Tetrahedron. 2005; 61:5147.
106. Winkler FK, Dunitz JD. J. Mol. Biol. 1971; 59:169. [PubMed: 5283751]
107. Tani K, Stoltz BM. Nature. 2006; 441:731. [PubMed: 16760973]
108. Kirby AJ, Komarov IV, Feeder N. J. Chem. Soc., Perkin Trans. 2001; 2:522.
109. Wiberg, K. Origin of the Amide Rotational Barrier. In: Greenberg, A.; Breneman, CM.; Liebman, JF., editors. The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science. Wiley; 2000.
110. Wiberg KB. Acc. Chem. Res. 1999; 32:922.
111. Kirby AJ, Komarov IV, Kowski K, Rademacher P. J. Chem. Soc., Perkin Trans. 1999; 2:1313.
112. Silverstein, RM.; Bassler, GC.; Morrill, TC. Spectroscopic Identification of Organic Compounds. New York: John Wiley and Sons; 1991.
113. Maier WF, Schleyer PV. J. Am. Chem. Soc. 1981; 103:1891.
114. Kim JS. Bull. Korean Chem. Soc. 1997; 18:488.
115. van Eis MJ, Wijsman GW, de Wolf WH, Bickelhaupt F, Rogers DW, Kooijman H, Spek AL. Chem. Eur. J. 2000; 6:1537. [PubMed: 10839170]
116. Novak I. J. Chem. Inf. Model. 2005; 45:334. [PubMed: 15807496]
117. Wiseman JR. J. Am. Chem. Soc. 1967; 89:5966.
118. Wiseman JR, Chan HF, Ahola CJ. J. Am. Chem. Soc. 1969; 91:2812.
119. Wiseman JR, Chong JA. J. Am. Chem. Soc. 1969; 91:7775.
120. Wiseman RJ, Pletcher WA. J. Am. Chem. Soc. 1970; 92:956.
121. Marshall JA, Faubl H. J. Am. Chem. Soc. 1970; 92:948.
122. Chong JA, Wiseman JR. J. Am. Chem. Soc. 1972; 94:8627.
123. Kim MG, White JD. J. Am. Chem. Soc. 1977; 99:1172.
124. Gudipati MS, Radziszewski JG, Kaszynski P, Michl J. J. Org. Chem. 1993; 58:3668.
125. Ohno M, Itoh M, Umeda M, Furuta R, Kondo K, Eguchi S. J. Am. Chem. Soc. 1996; 118:7075.
126. Tae EL, Zhu Z, Platz M. J. Phys. Chem. A. 2001; 105:3803.
127. Roach P, Warmuth R. Angew. Chem., Int. Ed. 2003; 42:3039.
128. Hudnall TW, Bielawski CW. J. Am. Chem. Soc. 2009; 131:16039. [PubMed: 19842700]
129. Neilson BM, Lynch VM, Bielawski CW. Angew. Chem., Int. Ed. 2011; 50:10326.
130. Borowiak T, Dutkiewicz G, Sosnicki JG, Jagodzinski TS, Hansen PE. J. Mol. Struct. 2008; 892:438.
131. Nanubolu JB, Sridhar B, Ravikumar K. CrystEngComm. 2012; 14:2571.
132. Yamada S. J. Org. Chem. 1992; 57:1591.
133. Yamada S, Sugaki T, Matsuzaki K. J. Org. Chem. 1996; 61:5932.
134. Yamada S, Misono T, Iwai Y, Masumizu A, Akiyama Y. J. Org. Chem. 2006; 71:6872. [PubMed: 16930040]
135. Yamada S, Katsumata H. Chem. Lett. 1998:995.
136. Yamada S, Ohe T. Tetrahedron Lett. 1996; 37:6777.
137. Yamada S, Katsumata H. J. Org. Chem. 1999; 64:9365.
138. Yamada S, Ichikawa M. Tetrahedron Lett. 1999; 40:4231.
139. Yamada S, Noguchi E. Tetrahedron Lett. 2001; 42:3621.
140. Yamada S, Misono T, Ichikawa M, Morita C. Tetrahedron. 2001; 57:8939.
141. Kozak JA, Dake GR. Angew. Chem., Int. Ed. 2008; 47:4221.
142. Siengalewicz P, Gaich T, Mulzer J. Angew. Chem., Int. Ed. 2008; 47:8170.
143. Zuo Z, Xie W, Ma D. J. Am. Chem. Soc. 2010; 132:13226. [PubMed: 20812683]

144. Zuo Z, Ma D. Angew. Chem., Int. Ed. 2011; 50:12008.
145. May JA, Zeidan RK, Stoltz BM. Tetrahedron Lett. 2003; 44:1203.
146. May JA, Stoltz BM. Tetrahedron. 2006; 62:5262.
147. Fuchs JR, Funk RL. J. Am. Chem. Soc. 2004; 126:5068. [PubMed: 15099080]
148. Belmar J, Funk RL. J. Am. Chem. Soc. 2012; 134:16941. [PubMed: 22978807]
149. Moon B, Han S, Yoon Y, Kwon H. Org. Lett. 2005; 7:1031. [PubMed: 15760131]
150. Enders D, Lenzen A, Raabe G. Angew. Chem., Int. Ed. 2005; 44:3766.
151. Enders D, Lenzen A, Backes M, Janeck C, Catlin K, Lannou MI, Runsink J, Raabe G. J. Org. Chem. 2005; 70:10538. [PubMed: 16323869]
152. Martinelli MJ, Peterson BC, Khau VV, Hutchison DR, Sullivan KA. Tetrahedron Lett. 1993; 34:5413.
153. Hutchison DR, Khau VV, Martinelli MJ, Nayyar NK, Peterson BC, Sullivan KA. Org. Synth. 1998; Vol. 75:223. Org. Synth. 2004, Coll. Vol. 10, 35.
154. Leroux S, Larquetoux L, Nicolas M, Doris E. Org. Lett. 2011; 13:3549. [PubMed: 21657243]
155. Harley-Mason J. Pure Appl. Chem. 1975; 41:167.
156. Dadson BA, Harley-Mason J, Foster GH. Chem. Commun. 1968:1233.
157. Dadson BA, Harley-Mason J. Chem. Commun. 1969:665. (*Communication* 583).
158. Harley-Mason J, Taylor CG. Chem. Commun. 1969:1384.
159. Crawley GC, Harley-Mason J. Chem. Commun. 1971:685.
160. Dadson BA, Harley-Mason J. Chem. Commun. 1969:665. (*Communication* 584).
161. Harley-Mason J, Taylor CG. Chem. Commun. 1970:812.
162. Ban Y, Yoshida K, Goto J, Oishi T. J. Am. Chem. Soc. 1981; 103:6990.
163. Ban Y, Yoshida K, Goto J, Oishi T, Takeda E. Tetrahedron. 1983; 39:3657.
164. Yoshida K, Sakuma Y, Ban Y. Heterocycles. 1987; 25:47.
165. Medley JW, Movassaghi M. Angew. Chem., Int. Ed. 2012; 51:4572.
166. Yates P, MacLachlan FN, Rae ID. Can. J. Chem. 1978; 56:1052.
167. Ziegler FE, Zoretic PA. Tetrahedron Lett. 1968; 22:2639.
168. Ziegler FE, Kloek JA, Zoretic PA. J. Am. Chem. Soc. 1969; 91:2342.
169. Amat M, Lozano O, Escolano C, Molins E, Bosch J. J. Org. Chem. 2007; 72:4431. [PubMed: 17488127]
170. Amat M, Escolano C, Lozano O, Llor N, Bosch J. Org. Lett. 2003; 5:3139. [PubMed: 12917001]
171. Amat M, Escolano C, Lozano O, Gómez-Esqué A, Griera R, Molins E, Bosch J. J. Org. Chem. 2006; 71:3804. [PubMed: 16674053]
172. Danieli B, Lesma G, Passarella D, Silvani A. Tetrahedron Lett. 2000; 41:3489.
173. Ziegler FE, Bennett GB. J. Am. Chem. Soc. 1973; 95:7458. [PubMed: 4747879]
174. Imanishi T, Nakai A, Yagi N, Hanaoka M. Chem. Pharm. Bull. 1981; 29:901.
175. Amat M, Coll MD, Passarella D, Bosch J. Tetrahedron: Asymmetry. 1996; 7:2775.
176. Amat M, Coll MD, Bosch J, Espinosa E, Molins E. Tetrahedron: Asymmetry. 1997; 8:935.
177. Wu A, Snieckus V. Tetrahedron Lett. 1975; 25:2057.
178. Ishikura M, Takahashi N, Yamada K, Abe T. Heterocycles. 2008; 75:107.
179. Magnus P, Giles M, Bonnert R, Johnson G, McQuire L, Deluca M, Merritt A, Kim CS, Vicker N. J. Am. Chem. Soc. 1993; 115:8116.
180. Büchi G, Kulsa P, Rosati RL. J. Am. Chem. Soc. 1968; 90:2448. [PubMed: 5642075]
181. Büchi G, Kulsa P, Ogasawara K, Rosati RL. J. Am. Chem. Soc. 1970; 92:999. [PubMed: 5451014]
182. Narisada M, Watanabe F, Nagata W. Tetrahedron Lett. 1971; 39:3681.
183. Uyeo S, Fales HM, Highet RJ, Wildman WC. J. Am. Chem. Soc. 1958; 80:2590.
184. Wildman WC, Bailey DT. J. Am. Chem. Soc. 1967; 89:5514.
185. Wildman WC, Bailey DT. J. Org. Chem. 1968; 33:3749.
186. Irie H, Uyeo S, Yoshitake A. Chem. Commun. 1966:635.

187. Irie H, Uyeo S, Yoshitake A. J. Chem. Soc. (C). 1968:1802.
188. Hendrickson JB, Foote C, Yoshimura N. Chem. Commun. 1965:165.
189. Hendrickson JB, Bogard TL, Fisch ME, Grossert S, Yoshimura N. J. Am. Chem. Soc. 1974; 96:7781.
190. Magnus P, Hobson LA, Westlund N, Lynch V. Tetrahedron Lett. 2001; 42:993.
191. Magnus P, Gazzard L, Hobson L, Payne AH, Rainey TJ, Westlund N, Lynch V. Tetrahedron. 2002; 58:3423.
192. Kuehne ME, Li YL, Wei CQ. J. Org. Chem. 2000; 65:6434. [PubMed: 11052086]
193. Zhong Y, Gao Y, Guo QP, Li WM. Helv. Chim. Acta. 2010; 93:133.
194. Jiang RW, Hon PM, But PPH, Chung HS, Lin G, Ye WC, Mak TCW. Tetrahedron. 2002; 58:6705.
195. Hitotsuyanagi Y, Hikita M, Nakada K, Fukuya H. Heterocycles. 2007; 71:2035.
196. Cai XG, Luo XD. Planta Med. 2007; 73:170. [PubMed: 17415878]
197. Kobayashi J, Ueno S, Morita H. J. Org. Chem. 2002; 67:6546. [PubMed: 12201780]
198. Morita H, Ishioka N, Takatsu H, Shinzato T, Obara Y, Nakahata N, Kobayashi J. Org. Lett. 2005; 7:459. [PubMed: 15673264]
199. Morita H, Yoshida N, Kobayashi J. J. Org. Chem. 2000; 65:3558. [PubMed: 10843649]
200. Kubota T, Suzuki T, Ishiuchi K, Kuhara T, Kobayashi J. Chem. Pharm. Bull. 2009; 57:504. [PubMed: 19420783]
201. Zhang Y, Di YT, Zhang Q, Mu SZ, Tan CJ, Fang X, He HP, Li SL, Hao XJ. Org. Lett. 2009; 11:5414. [PubMed: 19904981]
202. Morita H, Yoshida N, Kobayashi J. J. Org. Chem. 2002; 67:2278. [PubMed: 11925241]
203. Lim KH, Kam TS. Helv. Chim. Acta. 2007; 90:31.
204. Massiot G, Thepenier P, Jacquier MJ, Henin J, Men-Olivier L, Delaude C. Phytochem. 1991; 30:3449.
205. Nielsen HB, Hazell A, Hazell R, Ghia F, Torssell KBG. Phytochem. 1994; 37:1729.
206. Takayama H, Katakawa K, Kitajima M, Yamaguchi K, Aimi N. Tetrahedron Lett. 2002; 43:8307.
207. Ma X, Gang DR. Nat. Prod. Rep. 2004; 21:752. [PubMed: 15565253]
208. Lei Y, Wrobleski AD, Golden JE, Powell DR, Aubé J. J. Am. Chem. Soc. 2005; 127:4552. [PubMed: 15796502]
209. Ito M, Sakaguchi A, Kobayashi C, Ikariya T. J. Am. Chem. Soc. 2007; 129:290. [PubMed: 17212405]
210. Kajita Y, Matsubara S, Kurahashi T. J. Am. Chem. Soc. 2008; 130:6058–6059. [PubMed: 18412348]
211. Yoshino Y, Kurahashi T, Matsubara S. J. Am. Chem. Soc. 2009; 131:7494. [PubMed: 19435347]
212. Miura T, Yarnauchi M, Murakami M. Org. Lett. 2008; 10:3085. [PubMed: 18558759]
213. Ueno S, Chatani N, Kakiuchi F. J. Am. Chem. Soc. 2007; 129:6098. [PubMed: 17444647]
214. Williams A. J. Am. Chem. Soc. 1976; 98:5645.
215. Perrin CL. Acc. Chem. Res. 1989; 22:268.
216. Brown RS, Bennet AJ, Slebocka-Tilk H. Acc. Chem. Res. 1992; 25:481.
217. Poland BW, Xu MQ, Quiocho FA. J. Biol. Chem. 2000; 275:16408. [PubMed: 10828056]
218. Romanelli A, Shekhtman A, Cowburn D, Muir TW. Proc. Natl. Acad. Sci. U.S.A. 2004; 101:6397. [PubMed: 15087498]
219. Shemella P, Pereira B, Zhang YM, van Roey P, Belfort G, Garde S, Nayak SK. Biophys. J. 2007; 92:847. [PubMed: 17085503]
220. Johansson DGA, Wallin G, Sandberg A, Macao B, Aqvist J, Hard T. J. Am. Chem. Soc. 2009; 131:9475. [PubMed: 19534521]
221. Schiene-Fischer C, Aumüller T, Fischer G. Top. Curr. Chem. 2013; 328:35. [PubMed: 21598101]
222. Rudrabhatla P, Pant HC. J. Alzheimers Dis. 2010; 19:389. [PubMed: 20110589]
223. Somayaji V, Brown RS. J. Org. Chem. 1986; 51:2676.
224. Wang QP, Bennet AJ, Brown RS, Santarsiero BD. Can. J. Chem. 1990; 68:1732.

225. Wang QP, Bennet AJ, Brown RS, Santarsiero BD. J. Am. Chem. Soc. 1991; 113:5757.
226. Somayaji V, Skorey KI, Brown RS, Ball RG. J. Org. Chem. 1986; 51:4866.
227. Skorey KI, Somayaji V, Brown RS. J. Am. Chem. Soc. 1988; 110:5205.
228. Skorey KI, Somayaji V, Brown RS. J. Am. Chem. Soc. 1989; 111:1445.
229. Somayaji V, Brown RS. J. Am. Chem. Soc. 1987; 109:4738.
230. Somayaji V, Keillor J, Brown RS. J. Am. Chem. Soc. 1988; 110:2625.
231. Keillor JW, Brown RS. J. Am. Chem. Soc. 1991; 113:5114.
232. Bashore CG, Samardjiev IJ, Bordner J, Coe JW. J. Am. Chem. Soc. 2003; 125:3268. [PubMed: 12630882]
233. Aszodi J, Rowlands DA, Mauvais P, Collette P, Bonnefoy A, Lampilas M. Bioorg. Med. Chem. Lett. 2004; 14:2489. [PubMed: 15109638]
234. Mangion IK, Ruck RT, Rivera N, Huffman MA, Shevlin M. Org. Lett. 2011; 13:5480. [PubMed: 21916523]
235. Hans RH, Su H, Chibale K. Beilstein J. Org. Chem. 2010; 6
236. Hans RH, Wiid IJF, van Helden PD, Wan B, Franzblau SG, Gut J, Rosenthal PJ, Chibale K. Bioorg. Med. Chem. Lett. 2011; 21:2055. [PubMed: 21376591]
237. Smissman EE, Matuszak AJ, Corder CN. J. Pharm. Sci. 1964; 53:1541. [PubMed: 14255144]
238. Brouillette WJ, Brown GB, DeLorey TM, Shirali SS, Grunewald GL. J. Med. Chem. 1988; 31:2218. [PubMed: 2846842]
239. Brouillette WJ, Grunewald GL, Brown GB, DeLorey TM, Akhtar MS, Liang G. J. Med. Chem. 1989; 32:1577. [PubMed: 2544727]
240. Brouillette WJ, Jestkov VP, Brown ML, Akhtar MS, DeLorey TM, Brown GB. J. Med. Chem. 1994; 37:3289. [PubMed: 7932556]
241. Grimm JB, Stables JP, Brown ML. Bioorg. Med. Chem. 2003; 11:4133. [PubMed: 12927875]
242. Murakami M, Aoki T, Nagata W. Synlett. 1990:684.
243. Buynak JD, Rao AS, Adam G, Nidamarthy SD, Zhang H. J. Am. Chem. Soc. 1998; 120:6846.
244. Sierra MA, Rodriguez-Fernandez M, Mancheno MJ, Casarrubios L, Gomez-Gallego M. Tetrahedron. 2008; 64:9592.
245. Urbach A, Dive G, Marchand-Brynaert J. Eur. J. Org. Chem. 2009:1757.
246. Urbach A, Dive G, Tinant B, Duval V, Marchand-Brynaert J. Eur. J. Med. Chem. 2009; 44:2071. [PubMed: 19038477]
247. Georg, GI. The Organic Chemistry of Beta-Lactams. Wiley-VCH; 1992.
248. Bose, AK.; Manhas, MS.; Banik, BK.; Srirajan, V. β-Lactams: Cyclic Amides of Distinction. In: Greenberg, A.; Breneman, CM.; Liebman, JF., editors. The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science. Wiley; 2000.
249. Bredt J, Thouet H, Schmitz J. Liebigs Ann. Chem. 1924; 437:1.
250. Wasserman HH. Nature. 2006; 441:699. [PubMed: 16760961]
251. Doering WE, Chanley JD. J. Am. Chem. Soc. 1946; 68:586. [PubMed: 21022243]
252. Yakhontov LN, Rubtsov MV. J. Gen. Chem. USSR. 1957; 27:83.
253. Pracejus H. Ber. 1959; 92:988.
254. Pracejus H, Kehlen M, Kehlen H, Matschiner H. Tetrahedron. 1965; 21:2257.
255. Pracejus H. Ber. 1965; 98:2897.
256. Levkoeva EI, Nikitskaya ES, Yakhontov LN. Dokl. Akad. Nauk. 1970; 192:342.
257. Levkoeva EI, Nikitskaya ES, Yakhontov LN. Khim. Geterotsikl. Soedin. 1971:378.
258. Kostyanovsky RG, Mikhlina EE, Levkoeva EI, Yakhontov LN. Org. Mass Spectrom. 1970; 3:1023.
259. Greenberg A, Wu GL, Tsai JC, Chiu YY. Struct. Chem. 1993; 4:127.
260. Ly T, Krout M, Pham DK, Tani K, Stoltz BM, Julian RR. J. Am. Chem. Soc. 2007; 129:1864. [PubMed: 17256939]
261. Blackburn GM, Skaife CJ, Kay IT. J. Chem. Res. Synop. 1980:294.

262. Bennet AJ, Wang QP, Slebocka-Tilk H, Somayaji V, Brown RS, Santarsiero BD. J. Am. Chem. Soc. 1990; 112:6383.
263. Boivin J, Gaudin D, Labrecque D, Jankowski K. Tetrahedron Lett. 1990; 31:2281.
264. Frackenpohl J, Langer P, Hoffmann HMR. Helv. Chim. Acta. 1998; 81:1429.
265. Hoffmann, HMR.; Frackenpohl, J. Organic Chemistry of Cinchona Alkaloids. In: Song, CE., editor. Cinchona Alkaloids in Synthesis and Catalysis. Wiley; 2009.
266. Ballester P, Tadayoni BM, Branda N, Rebek J Jr. J. Am. Chem. Soc. 1990; 112:3685.
267. Jeong KS, Parris K, Ballester P, Rebek J Jr. Angew. Chem., Int. Ed. 1990; 29:555.
268. Jones PG, Kirby AJ, Komarov IV, Wothers PD. Chem. Commun. 1998:1695.
269. Kirby AJ, Komarov IV, Wothers PD, Feeder N, Jones PG. Pure Appl. Chem. 1999; 71:385.
270. Kirby AJ, Komarov IV, Wothers PD, Feeder N. Angew. Chem., Int. Ed. 1998; 37:785.
271. Ye Q, Komarov IV, Kirby AJ, Jones M Jr. J. Org. Chem. 2002; 67:9288. [PubMed: 12492330]
272. Kirby AJ, Komarov IV, Feeder N. J. Am. Chem. Soc. 1998; 120:7101.
273. Davies JE, Kirby AJ, Komarov IV. Helv. Chim. Acta. 2003; 86:1222.
274. Kirby AJ, Komarov IV, Bilenko VA, Davies JE, Rawson JM. Chem. Commun. 2002:2106.
275. Morgan KM, Rawlins ML, Montgomery MN. J. Phys. Org. Chem. 2005; 18:310.
276. Badger GM, Cook JW, Walker T. Chem. Commun. 1949:1141.
277. Albertson NF. J. Am. Chem. Soc. 1950; 72:2594.
278. Albertson NF. J. Am. Chem. Soc. 1952; 74:249.
279. Hall HK Jr, Shaw RG, Deutschmann A. J. Org. Chem. 1980; 45:3722.
280. Buchanan GL. J. Chem. Soc. Chem. Commun. 1981:814.
281. Buchanan GL. J. Chem. Soc. Perkin Trans. 1984; 1:2669.
282. Buchanan GL, Kitson DH, Mallinson PR, Sim GA, White DNJ, Cox PJ. J. Chem. Soc. Perkin Trans. 1983; 2:1709.
283. McCabe PH, Milne NJ, Sim GA. J. Chem. Soc. Perkin Trans. 1989; 2:1459.
284. Sliter B, Morgan J, Greenberg A. J. Org. Chem. 2011; 76:2770. [PubMed: 21391617]
285. Wiseman JR, Kipp JE. J. Am. Chem. Soc. 1982; 104:4688.
286. Steliou K, Poupart MA. J. Am. Chem. Soc. 1983; 105:7130.
287. Brehm R, Ohnhäuser D, Gerlach H. Helv. Chim. Acta. 1987; 70:1981.
288. Alonso DA, Costa A, Mancheno B, Najera C. Tetrahedron. 1997; 53:4791.
289. Hellal M, Cuny GD. J. Org. Chem. 2010; 75:3465. [PubMed: 20394404]
290. Denzer M, Ott H. J. Org. Chem. 1969; 34:183.
291. Grigg R, Sridharan V, Stevenson P, Worakun T. J. Chem. Soc. Chem. Commun. 1986:1697.
292. Grigg R, Santhakumar V, Sridharan V, Stevenson P, Teasdale A, Thorntonpett M, Worakun T. Tetrahedron. 1991; 47:9703.
293. Grigg R, Sridharan V, York M. Tetrahedron Lett. 1998; 39:4139.
294. Grigg R, York M. Tetrahedron Lett. 2000; 41:7255.
295. Paquette LA, Dura RD, Fosnaugh N, Stepanian M. J. Org. Chem. 2006; 71:8438. [PubMed: 17064017]
296. Ribelin TP, Judd AS, Akritopoulou-Zanze I, Henry RF, Cross JL, Whittern DN, Djuric SW. Org. Lett. 2007; 9:5119. [PubMed: 17973488]
297. Shea KJ, Lease TG, Ziller JW. J. Am. Chem. Soc. 1990; 112:8627.
298. Lease TG, Shea KJ. J. Am. Chem. Soc. 1993; 115:2248.
299. Doyle MP. Chem. Rev. 1986; 86:919.
300. Davies HML, Beckwith REJ. Chem. Rev. 2003; 103:2861. [PubMed: 12914484]
301. Doyle MP, Duffy R, Ratnikov M, Zhou L. Chem. Rev. 2010; 110:70.
302. Doyle MP, Kalinin AV. Synlett. 1995:1075.
303. Williams RM, Lee BH. J. Am. Chem. Soc. 1986; 108:6431.
304. Williams RM, Lee BH, Miller MM, Anderson OP. J. Am. Chem. Soc. 1989; 111:1073.
305. Sundberg RJ, Smith FX. J. Org. Chem. 1975; 40:2613.

306. Sundberg RJ, Luis JG, Parton RL, Schreiber S, Srinivasan PC, Lamb P, Forcier P, Bryan RF. J. Org. Chem. 1978; 43:4859.
307. Shen L, Hsung RP. Org. Lett. 2005; 7:775. [PubMed: 15727438]
308. Adamson G, Beckwith ALJ, Kaufmann M, Willis AC. J. Chem. Soc. Chem. Commun. 1995:1783.
309. Phakhodee W, Ploypradith P, Sahakitpichan P, Ruchirawat S. Tetrahedron. 2009; 65:351.
310. Phakhodee W, Sahakitpichan P, Deechongkit S, Ruchirawat S. Heterocycles. 2008; 75:1963.
311. Dolby LJ, Sakai SI. J. Am. Chem. Soc. 1964; 86:1890.
312. Dolby LJ, Sakai SI. Tetrahedron. 1967; 23:1. [PubMed: 6037282]
313. Xie Q, Wang H, Xia Z, Lu M, Zhang W, Wang X, Fu W, Tang Y, Sheng W, Li W, Zhou W, Zhu X, Qiu Z, Chen H. J. Med. Chem. 2008; 51:2027. [PubMed: 18333606]
314. Zheng W, Xie Q, Li F, Qui ZB. Acta Cryst. 2009; E65:3008.
315. Artacho J, Ascic E, Rantanen T, Karlsson J, Wallentin CJ, Wang R, Wendt OF, Harmata M, Snieckus V, Wärnmark K. Chem. Eur. J. 2012; 18:1038. [PubMed: 22234879]
316. Artacho J, Ascic E, Rantanen T, Wallentin CJ, Dawaigher S, Bergquist KE, Harmata M, Snieckus V, Wärnmark K. Org. Lett. 2012; 14:4706. [PubMed: 22958089]
317. Milligan GL, Mossman CJ, Aubé J. J. Am. Chem. Soc. 1995; 117:10449.
318. Lang S, Murphy JA. Chem. Soc. Rev. 2006; 35:146. [PubMed: 16444296]
319. Nyfeler E, Renaud P. Chimia. 2006; 60:276.
320. Grecian, S.; Aubé, J. Schmidt Rearrangement Reactions with Alkyl Azides. In: Bräse, S.; Banert, K., editors. Organic Azides: Synthesis and Applications. Chichester, U.K: Wiley and Sons; 2009.
321. Yao L, Aubé J. J. Am. Chem. Soc. 2007; 129:2766. [PubMed: 17302421]
322. Szostak M, Yao L, Aubé J. J. Org. Chem. 2010; 75:1235. [PubMed: 20095596]
323. Szostak M, Yao L, Aubé J. Org. Lett. 2009; 11:4386. [PubMed: 19722508]
324. Gutierrrez O, Aubé J, Tantillo DJ. J. Org. Chem. 2012; 77:640. [PubMed: 22126337]
325. Macleod F, Lang S, Murphy JA. Synlett. 2010:529.
326. Szostak M, Aubé J. J. Am. Chem. Soc. 2010; 132:2530. [PubMed: 20128606]
327. Golden JE, Aubé J. Angew. Chem., Int. Ed. 2002; 41:4316.
328. Zeng YB, Aubé J. J. Am. Chem. Soc. 2005; 125:15712. [PubMed: 16277507]
329. Frankowski KJ, Golden JE, Zeng YB, Lei Y, Aubé J. J. Am. Chem. Soc. 2008; 130:6018. [PubMed: 18396881]
330. Szostak M, Yao L, Day VW, Powell DR, Aubé J. J. Am. Chem. Soc. 2010; 132:8336.
331. Iyengar R, Schildknegt K, Aubé J. Org. Lett. 2000; 2:1625. [PubMed: 10841495]
332. Iyengar R, Schildknegt K, Morton M, Aubé J. J. Org. Chem. 2005; 70:10645. [PubMed: 16355981]
333. Wrobleski, AD. Ph.D. Thesis. University of Kansas; 2003.
334. Schill G, Priester CU, Windhövel UF, Fritz H. Helv. Chim. Acta. 1986; 69:438.
335. Schill G, Löwer H, Priester CU, Windhövel UF, Fritz H. Tetrahedron. 1987; 43:3729.
336. Schill G, Priester CU, Windhövel UF, Fritz H. Tetrahedron. 1987; 43:3747.
337. Schill G, Priester CU, Windhövel UF, Fritz H. Tetrahedron. 1987; 43:3765.
338. Schill G, Priester CU, Windhövel UF, Fritz H. Tetrahedron. 1990; 46:1211.
339. Schill G, Priester CU, Windhovel UF, Fritz H. Tetrahedron. 1990; 46:1221.
340. Magnus P, Ladlow M, Elliott J, Kim CS. J. Chem. Soc. Chem. Commun. 1989:518.
341. Magnus P, Mendoza JS, Stamford A, Ladlow M, Willis P. J. Am. Chem. Soc. 1992; 114:10232.
342. Dennison JB, Kulanthaivel P, Barbuch RJ, Renbarger JL, Ehlhardt WJ, Hall SD. Drug Metab. Dispos. 2006; 34:1317. [PubMed: 16679390]
343. Szostak M, Aubé J. Org. Lett. 2009; 11:3878. [PubMed: 19708701]
344. Arata Y, Tanaka KI, Yoshifuji S, Kanatomo S. Chem. Pharm. Bull. 1979; 27:981.
345. Waly MA, Kodier MN, Hossini MS. Chin. Pharm. J. 1994; 46:135.

346. Smet M, Van Oosterwijck C, Van Hecke K, Van Meervelt L, Vandendriessche A, Dehaen W. Synlett. 2004:2388.
347. Nazarenko KG, Shtil NA, Buth SA, Chernega AN, Lozinskii MO, Tolmachev AA. Tetrahedron. 2008; 64:4478.
348. Doodeman, R. Ph.D. Thesis. University of Amsterdam; 2002.
349. Cossy J, Pardo DG. Chemtracts. 2002; 15:579.
350. Metro TX, Duthion B, Pardo DG, Cossy J. Chem. Soc. Rev. 2010; 39:89. [PubMed: 20023840]
351. Arata Y, Kobayashi T. Chem. Pharm. Bull. 1970; 18:2361.
352. Arata Y, Kobayashi T. Chem. Pharm. Bull. 1972; 20:325.
353. Miyano S, Mibu N, Irie M, Fujii S, Fujisaki F, Abe N, Sumoto K. J. Chem. Soc. Perkin Trans. 1987; 1:313.
354. Miyano S, Irie M, Mibu N, Miyamoto Y, Nagata K, Sumoto K. J. Chem. Soc. Perkin Trans. 1988; 1:1057.
355. Bremner JB, Eschler BM, Skelton BW, White AH. Aust. J. Chem. 1994; 47:1935.
356. Schumann D, Geirsson J, Naumann A. Chem. Ber. 1985; 118:1927.
357. Bahadur GA, Bailey AS, Scott PW, Vandrevala MH. J. Chem. Soc. Perkin Trans. 1980; 1:2870.
358. Prout K, Sims M, Watkin D, Couldwell C, Vandrevala M, Bailey AS. Acta Cryst. 1980; B36:1846.
359. Chelain E, Parlier A, Audouin M, Rudler H, Daran JC, Vaissermann J. J. Am. Chem. Soc. 1993; 115:10568.
360. Coqueret X, Bourelle-Wargnier F, Chuche J. J. Org. Chem. 1985; 50:909.
361. Kutney JP, Balsevich J, Bokelman GH. Heterocycles. 1976; 4:1377.
362. Kutney JP, Balsevich J, Bokelman GH, Hibino T, Honda T, Itoh I, Ratcliffe AH, Worth BR. Can. J. Chem. 1978; 56:62.
363. Toshimitsu A, Terao K, Uemura S. Tetrahedron Lett. 1984; 25:5917.
364. Toshimitsu A, Terao K, Uemura S. J. Chem. Soc. Chem. Commun. 1986:530.
365. Toshimitsu A, Terao K, Uemura S. J. Org. Chem. 1987; 52:2018.
366. Smissman EE, Robinson RA. J. Org. Chem. 1970; 35:3532.
367. Smissman EE, Robinson RA, Matuszak AJ. J. Org. Chem. 1970; 35:3823. [PubMed: 5474329]
368. Smissman EE, Ayres JW. J. Org. Chem. 1971; 36:2407. [PubMed: 5156462]
369. Smissman EE, Ayres JW, Wirth PJ, Abernethy DR. J. Org. Chem. 1972; 37:3486. [PubMed: 5077644]
370. Smissman EE, Wirth PJ. J. Org. Chem. 1975; 40:1576. [PubMed: 1142039]
371. Smissman EE, Wirth PJ, Glynn DR. J. Org. Chem. 1975; 40:281.
372. Beddoes RL, Davies MPH, Thomas EJ. J. Chem. Soc. Chem. Commun. 1992:538.
373. Baylis AM, Davies MPH, Thomas EJ. Org. Biomol. Chem. 2007; 5:3139. [PubMed: 17878973]
374. Baylis AM, Thomas EJ. Tetrahedron. 2007; 63:11666.
375. Sakamoto M, Watanabe S, Fujita T, Yanase T. J. Org. Chem. 1990; 55:2986.
376. Roscini C, Cubbage KL, Berry M, Orr-Ewing AJ, Booker-Milburn KI. Angew. Chem., Int. Ed. 2009; 48:8716.
377. Booker-Milburn KI, Anson CE, Clissold C, Costin NJ, Dainty RF, Murray M, Patel D, Sharpe A. Eur. J. Org. Chem. 2001:1473.
378. Hall HK Jr, Johnson RC. J. Org. Chem. 1972; 37:697.
379. Hall HK Jr, Ekechukwu OE, Deutschmann A, Rose C. Polym. Bull. 1980; 3:375.
380. Hall HK Jr, El-Shekeil A. J. Org. Chem. 1980; 45:5325.
381. Hall HK Jr, El-Shekeil A. Polym. Bull. 1980; 2:829.
382. Sparks SM, Vargas JD, Shea KJ. Org. Lett. 2000; 2:1473. [PubMed: 10814476]
383. Sparks SM, Chow CP, Zhu L, Shea KJ. J. Org. Chem. 2004; 69:3025. [PubMed: 15104440]
384. Chow CP, Shea KJ, Sparks SM. Org. Lett. 2002; 4:2637. [PubMed: 12153197]
385. Molina CL, Chow CP, Shea KJ. J. Org. Chem. 2007; 72:6816. [PubMed: 17676912]

386. Lahousse H, Martens HJ, Toppet S, Hoornaert GJ. J. Org. Chem. 1982; 47:2001.
387. Chow CP, Shea KJ. J. Am. Chem. Soc. 2005; 127:3678. [PubMed: 15771485]
388. Meltzer RI, Lewis AD. J. Org. Chem. 1956; 21:256.
389. Baumler J, Sorkin E, Erlenmeyer H. Helv. Chim. Acta. 1951; 34:459.
390. Brouillette WJ, Smissman EE, Grunewald GL. J. Org. Chem. 1979; 44:839.
391. Brouillette WJ, Einspahr HM. J. Org. Chem. 1984; 49:5113.
392. Kubicki M, Codding PW. Acta Cryst. 2001; E57:o406.
393. Akhtar MS, Brouillette WJ, Waterhous DV. J. Org. Chem. 1990; 55:5222.
394. Brouillette WJ, Friedrich JD, Muccio DD. J. Org. Chem. 1984; 49:3227.
395. Smissman EE, Robinson RA, Carr JB, Matuszak AJ. J. Org. Chem. 1970; 35:3821. [PubMed: 5474328]
396. Gmünder J, Lindenmann A. Helv. Chim. Acta. 1964; 47:66.
397. Rappoport, Z. The Chemistry of Enamines. John Wiley & Sons; 1994.
398. Doering WV, Birladeanu L, Andrews DW, Pagnotta M. J. Am. Chem. Soc. 1985; 107:428.
399. Crawley SL, Funk RL. Org. Lett. 2006; 8:3995. [PubMed: 16928057]
400. Yotphan S, Bergman RG, Ellman JA. J. Am. Chem. Soc. 2008; 130:2452. [PubMed: 18247623]
401. Pearson WH, Walavalkar R, Schkeryantz JM, Fang WK, Blickensdorf JD. J. Am. Chem. Soc. 1993; 115:10183.
402. Nielsen AT. J. Org. Chem. 1966; 31:1053.
403. Bender DR, Coffen DL. J. Org. Chem. 1968; 33:2504.
404. Warawa EJ, Campbell JR. J. Org. Chem. 1974; 39:3511.
405. O'Neil IA, Wynn D, Lai JYQ. Tetrahedron Lett. 2000; 41:271.
406. Yakhontov L. Heterocycles. 1977; 7:1033.
407. Hamama WS, El-Magid OMA, Zoorob HH. J. Heterocycl. Chem. 2006; 43:1397.
408. Szostak M, Yao L, Aubé J. J. Am. Chem. Soc. 2010; 132:2078. [PubMed: 20095610]
409. Sheridan RS, Ganzer GA. J. Am. Chem. Soc. 1983; 105:6158.
410. Radziszewski JG, Downing JW, Wentrup C, Kaszynski P, Jawdosiuk M, Kovacic P, Michl J. J. Am. Chem. Soc. 1985; 107:2799.
411. Wayne GS, Snyder GJ. J. Am. Chem. Soc. 1993; 115:9860.
412. Eguchi S, Okano T, Takeuchi H. Heterocycles. 1987; 26:3265.
413. Brummond KM, Lu JL. Org. Lett. 2001; 3:1347. [PubMed: 11348231]
414. Brummond KM, Hong SP. J. Org. Chem. 2005; 70:907. [PubMed: 15675848]
415. Yamazaki N, Suzuki H, Kibayashi C. J. Org. Chem. 1997; 62:8280. [PubMed: 11671957]
416. Suzuki H, Yamazaki N, Kibayashi C. Tetrahedron Lett. 2001; 42:3013.
417. Yoshimura Y, Kusanagi T, Kibayashi C, Yamazaki N, Aoyagi S. Heterocycles. 2007; 75:1329.
418. Rodriguez-Escrich S, Sola L, Jimeno C, Rodriguez-Escrich C, Pericas MA. Adv. Synth. Catal. 2008; 350:2250.
419. Wang YF, Toh KK, Ng EPJ, Chiba S. J. Am. Chem. Soc. 2011; 133:6411. [PubMed: 21449592]
420. Braje W, Wartchow R, Hoffmann HMR. Angew. Chem., Int. Ed. 1999; 38:2540.
421. Franz MH, Röper S, Wartchow R, Hoffmann HMR. J. Org. Chem. 2004; 69:2983. [PubMed: 15104435]
422. Hoffmann HMR, Frackenpohl J. Eur. J. Org. Chem. 2004:4293.
423. Röper S, Frackenpohl J, Schrake O, Wartchow R, Hoffmann HMR. Org. Lett. 2000; 2:1661. [PubMed: 10880195]
424. Röper S, Wartchow R, Hoffmann HMR. Org. Lett. 2002; 4:3179. [PubMed: 12227743]
425. Katritzky, AR.; Rees, CW.; Scriven, EFC. Comprehensive Heterocyclic Chemistry II. Vol. Vol. 3. Elsevier; 1996. p. 4
426. Drews J. Science. 2000; 287:1960. [PubMed: 10720314]
427. Sneader, W. Drug Discovery: A History. Wiley; 2005.
428. Davies FA, Chen BC. Chem. Rev. 1992; 92:919.

429. Oppolzer W. Pure Appl. Chem. 1990; 62:1241.
430. Majumdar KC, Mondal S. Chem. Rev. 2011; 111:7749. [PubMed: 21894896]
431. Paquette LA, Barton WRS, Gallucci JC. Org. Lett. 2004; 6:1313. [PubMed: 15070325]
432. Evans P, McCabe T, Morgan BS, Reau S. Org. Lett. 2005; 7:43. [PubMed: 15624973]
433. Evans P. J. Org. Chem. 2007; 72:1830. [PubMed: 17256907]
434. Kelleher S, Quesne PY, Evans P. Beilstein J. Org. Chem. 2009; 5
435. Klein JEMN, Geoghegan K, Méral N, Evans P. Chem. Commun. 2010; 46:937.
436. Geoghegan K, Kelleher S, Evans P. J. Org. Chem. 2011; 76:2187. [PubMed: 21381780] For a recent study on regioselectivity in the Heck reaction forming bridged sultams, see: Geoghegan K, Evans P, Rozas I, Alkorta I. Chem. Eur. J. 2012; 18:13379. [PubMed: 22969008]
437. Paquette LA, Leit SM. J. Am. Chem. Soc. 1999; 121:8126.
438. Paquette LA, Ra CS, Schloss JD, Leit SM, Gallucci JC. J. Org. Chem. 2001; 66:3564. [PubMed: 11348146]
439. Schloss JD, Leit SM, Paquette LA. J. Org. Chem. 2000; 65:7119. [PubMed: 11031038]
440. Preston AJ, Gallucci JC, Paquette LA. J. Org. Chem. 2006; 71:6573. [PubMed: 16901145]
441. Rassadin VA, Grosheva DS, Tomashevskiy AA, Sokolov VV, Yufit DS, Kozhushkov SI, de Meijere A. Eur. J. Org. Chem. 2010:3481.
442. Samarakoon TB, Loh JK, Rolfe A, Le LS, Yoon SY, Lushington GH, Hanson PR. Org. Lett. 2011; 13:5148. [PubMed: 21899284]
443. Zhou A, Rayabarapu D, Hanson PR. Org. Lett. 2009; 11:531. [PubMed: 19115841]
444. Rolfe A, Samarakoon TB, Hanson PR. Org. Lett. 2010; 12:1216. [PubMed: 20178346]
445. Samarakoon TB, Hur MY, Kurtz RD, Hanson PR. Org. Lett. 2010; 12:2182. [PubMed: 20394415]
446. Loh JK, Yoon SY, Samarakoon TB, Rolfe A, Porubsky P, Neuenswander B, Lushington GH, Hanson PR. Beilstein J. Org. Chem. 2012; 8:1293. [PubMed: 23019462]
447. Stoll AH, Blakey SB. Chem. Sci. 2011; 2:112.
448. Radziecka A, Wolfenden R. J. Am. Chem. Soc. 1996; 118:6105.
449. Szostak M, Yao L, Aubé J. J. Org. Chem. 2009; 74:1869. [PubMed: 19178141]
450. Adler M, Alder S, Boche G. J. Phys. Org. Chem. 2005; 18:193.
451. Werstiuk NH, Brown RS, Wang Q. Can. J. Chem. 1996; 74:524.
452. Szostak M, Aubé J. Chem. Commun. 2009:7122.
453. Hall HK Jr, Schneider AK. J. Am. Chem. Soc. 1958; 80:6409.
454. Hall HK Jr. J. Am. Chem. Soc. 1958; 80:6412.
455. Hall HK Jr. J. Am. Chem. Soc. 1960; 82:1209.
456. Szostak M, Aubé J. J. Am. Chem. Soc. 2009; 131:13246. [PubMed: 19715274]
457. Yoshida K, Nomura S, Nishibata Y, Ban Y. Heterocycles. 1986; 24:2239.
458. Hayes CJ, Simpkins NS, Kirk DT, Mitchell L, Baudoux J, Blake AJ, Wilson C. J. Am. Chem. Soc. 2009; 131:8196. [PubMed: 19507906]
459. Dura RD, Paquette LA. Synthesis. 2006:2837.
460. Gallucci JC, Dura RD, Paquette LA. Acta Cryst. 2007; E63:3417.
461. Zhu L, Lauchli R, Loo M, Shea KJ. Org. Lett. 2007; 9:2269. [PubMed: 17489596]
462. Chiang Y, Kresge AJ, Walsh PA. J. Org. Chem. 1990; 55:1309.
463. Dura RD, Paquette LA. J. Org. Chem. 2006; 71:2456. [PubMed: 16526797]
464. Preston AJ, Paquette LA. Heterocycles. 2006; 70:41.
465. Velten R, Erdelen C, Gehling M, Göhrt A, Gondol D, Lenz J, Lockhoff O, Wachendorff U, Wendisch D. Tetrahedron Lett. 1998; 39:1737.

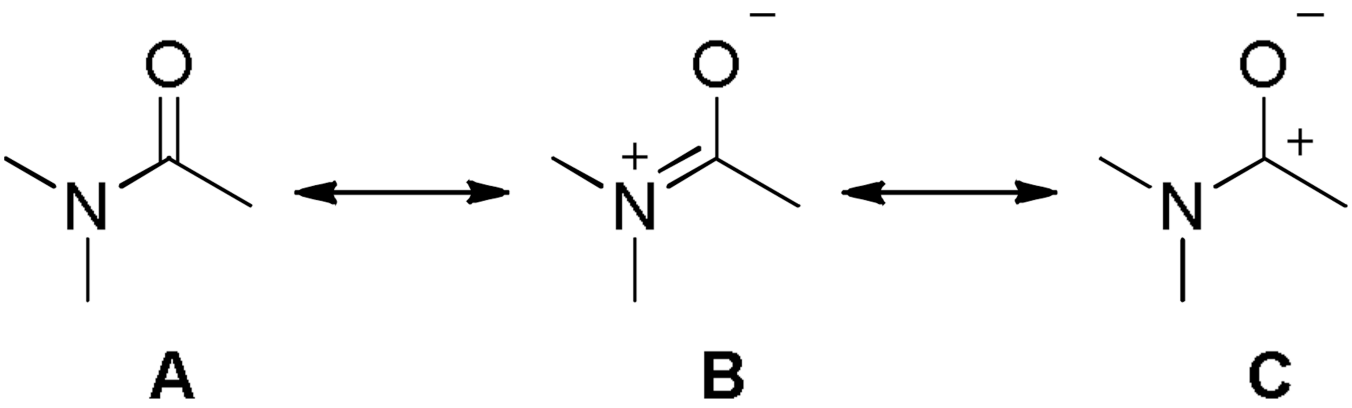


Figure 1.
Resonance descriptions of the amide bond.

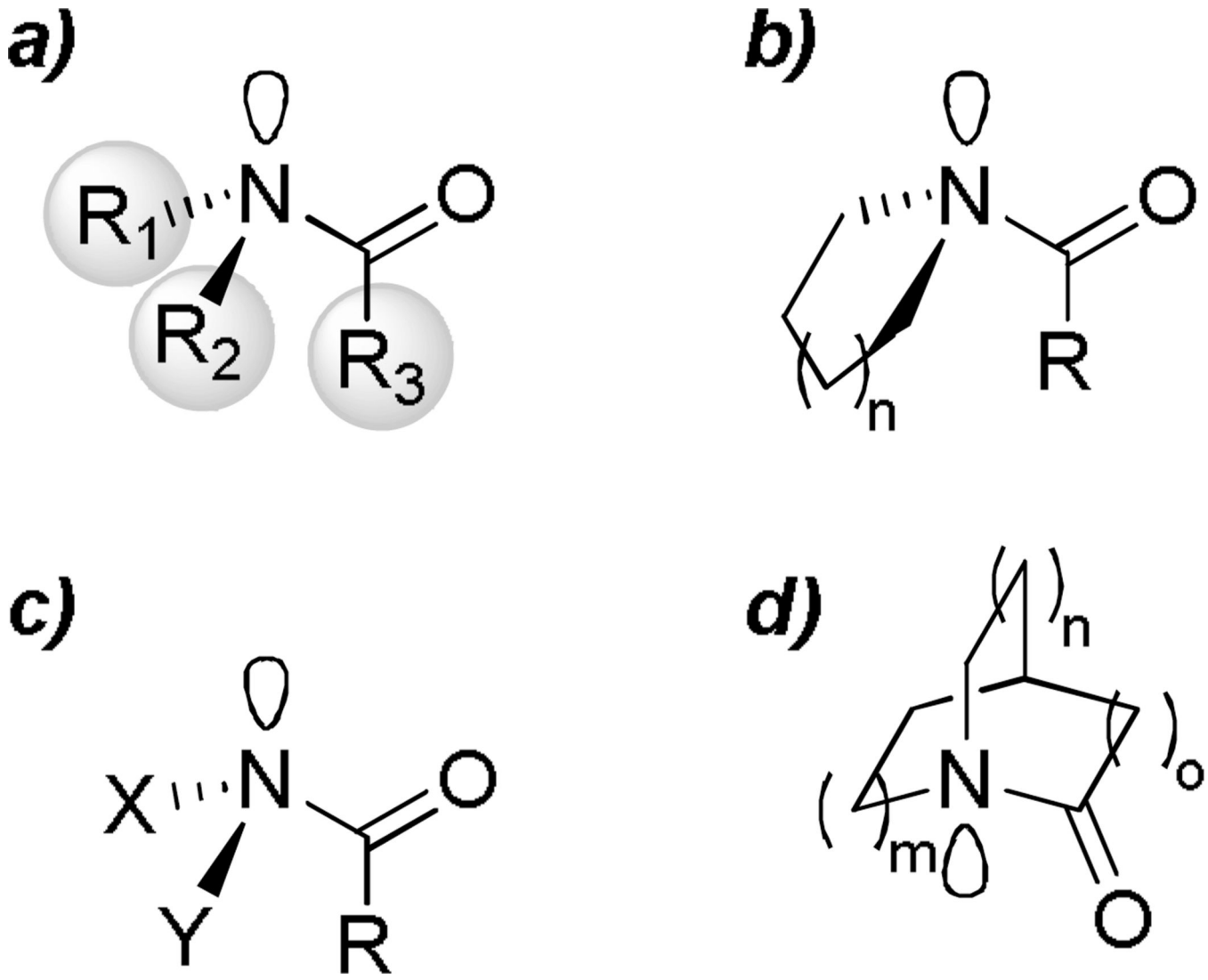


Figure 2.
Types of distorted amide bonds: a) steric repulsion; b) conformational effects; c) anomeric amides; d) steric restriction.

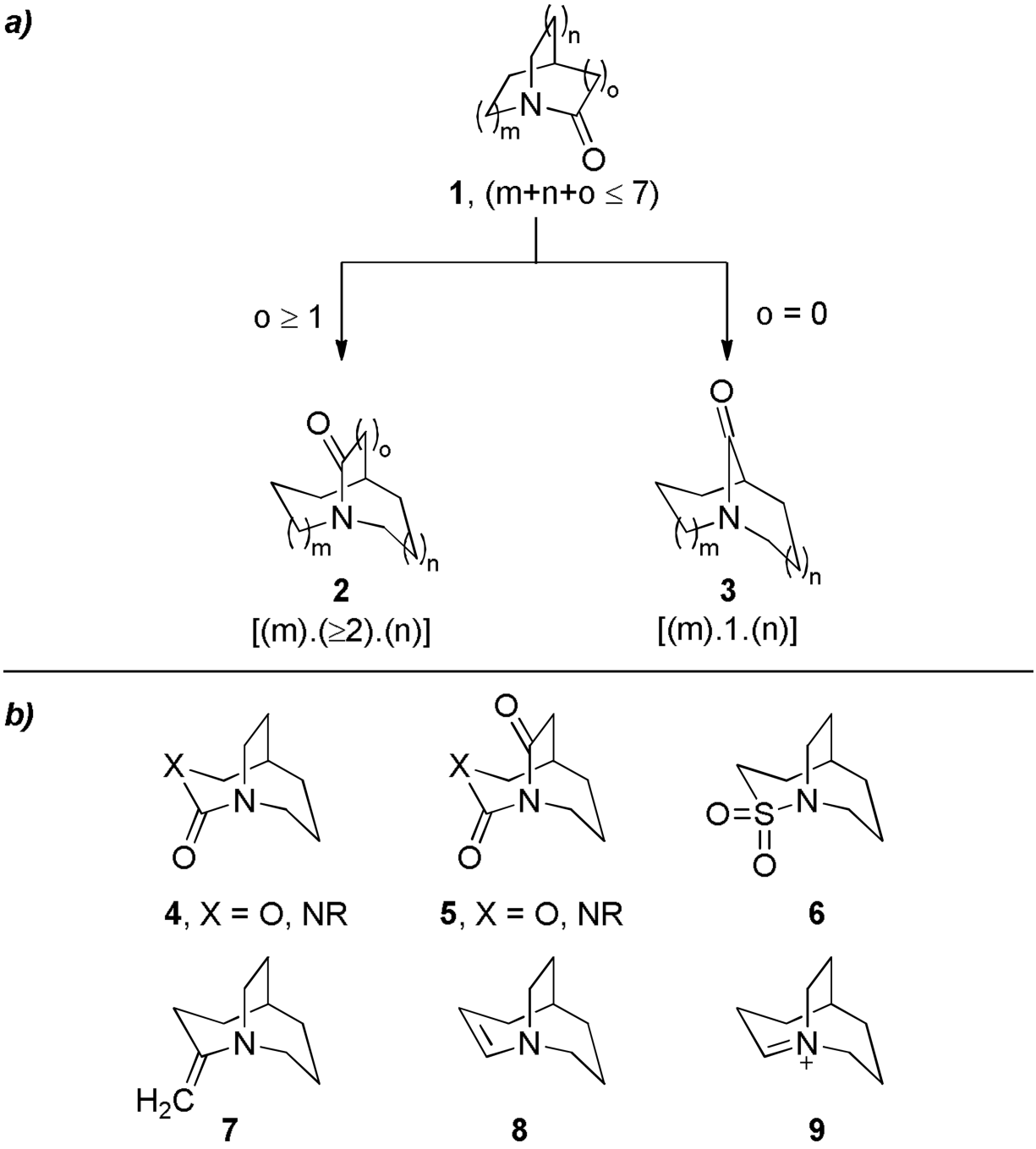
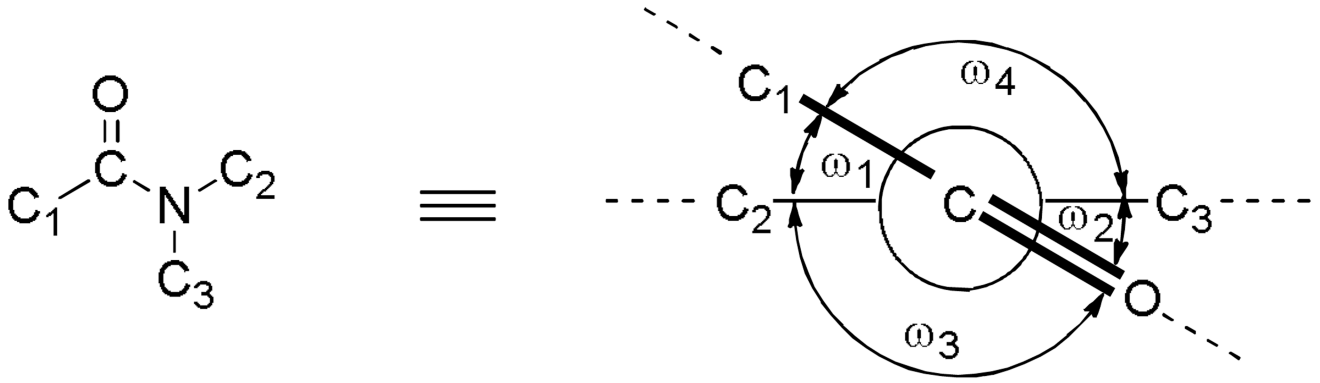


Figure 3.
Scope of the review: a) types of bridged lactams; b) heterocycles with 1-aza-bridged scaffold.



$$\omega_1 = \omega(C_1\text{-}C\text{-}N\text{-}C_2)$$
$$\omega_2 = \omega(O\text{-}C\text{-}N\text{-}C_3)$$
$$\omega_3 = \omega(O\text{-}C\text{-}N\text{-}C_2)$$
$$\omega_4 = \omega(C_1\text{-}C\text{-}N\text{-}C_3)$$

$$\tau = 1/2(\omega_1 + \omega_2),\ |\omega_1 - \omega_2| < \pi$$
$$\chi_C = (\omega_1 - \omega_3 + \pi) = (\omega_4 - \omega_2 + \pi)$$
$$\chi_N = (\omega_2 - \omega_3 + \pi) = (\omega_4 - \omega_1 + \pi)$$

Figure 4.
Winkler-Dunitz distortion parameters of amide bonds.

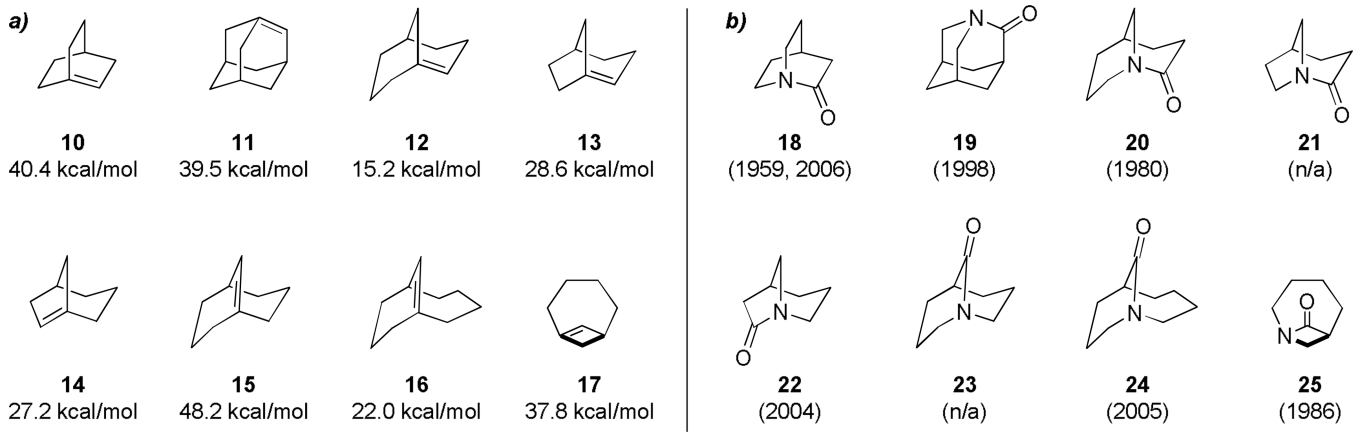


Figure 5.

Comparison of anti-Bredt olefins and lactams: a) calculated olefin strain energy of bridged olefins by Schleyer; b) year of synthesis of the corresponding bridged lactam. (please use double-column format for Figure 5)

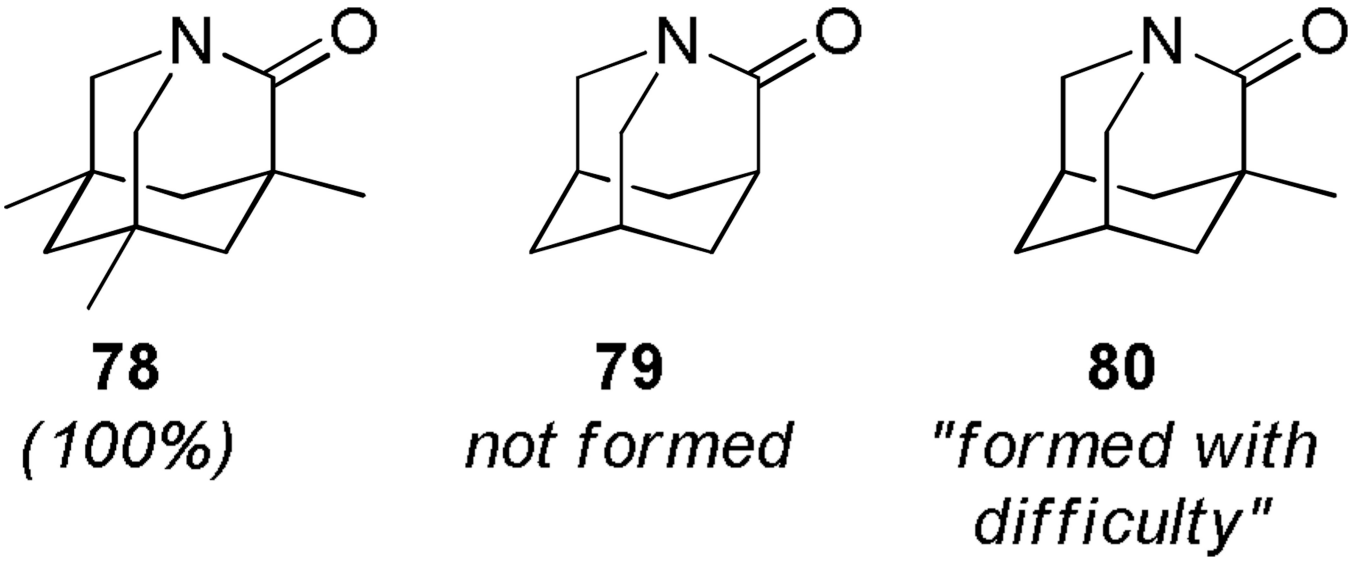


Figure 6.
Role of methyl substituents in synthesisof 1-aza-2-adamantanones from the corresponding amino acids.

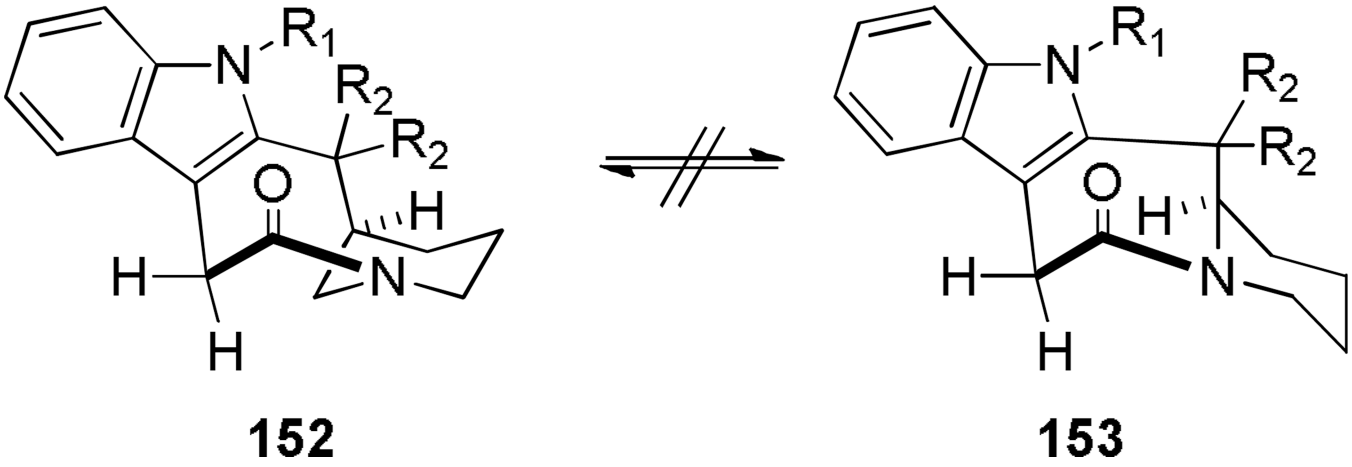


Figure 7.
Atropoisomers formed in Witkop photocyclization of (*N*-chloroacetylpiperidyl)indole **150**.

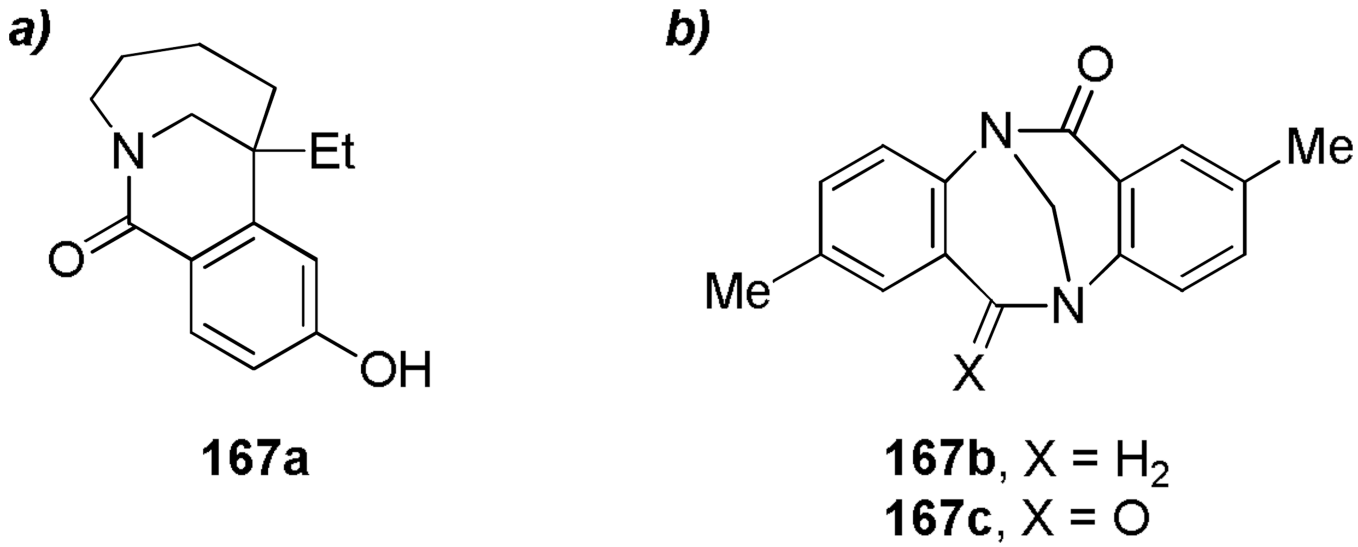


Figure 8.
Benzofused bridged lactams: a) Benzo-1-azabicyclo[4.3.1]decan-9-one by Qiu; b) Bridged lactams derived from Tröger's base by Wärnmark.

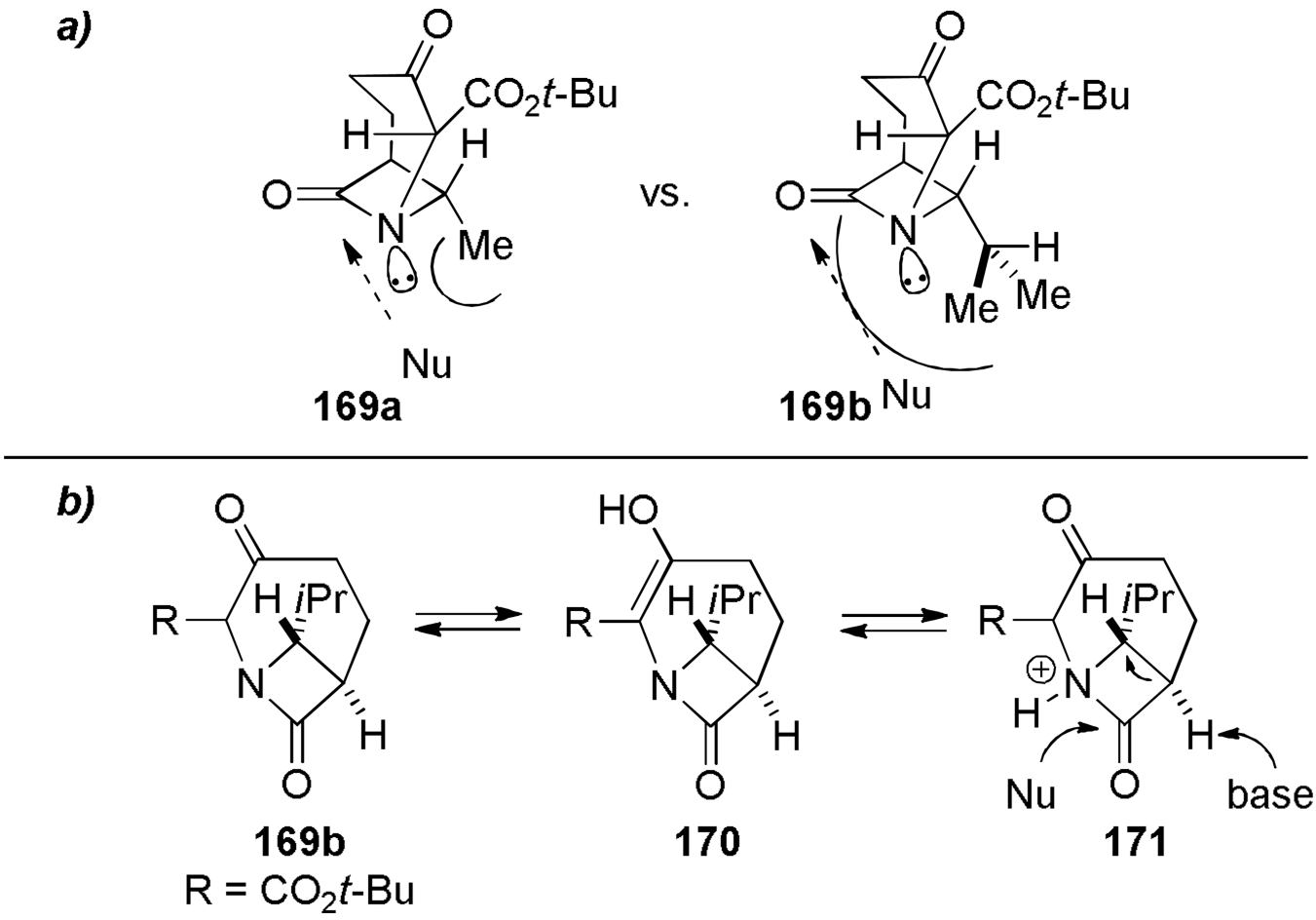


Figure 9.

Design of 1-azabicyclo[4.1.1]octan-7-ones with increased stability: a) nucleophilic attack on lactam carbonyl group; b) deprotonation of bridgehead methine proton.

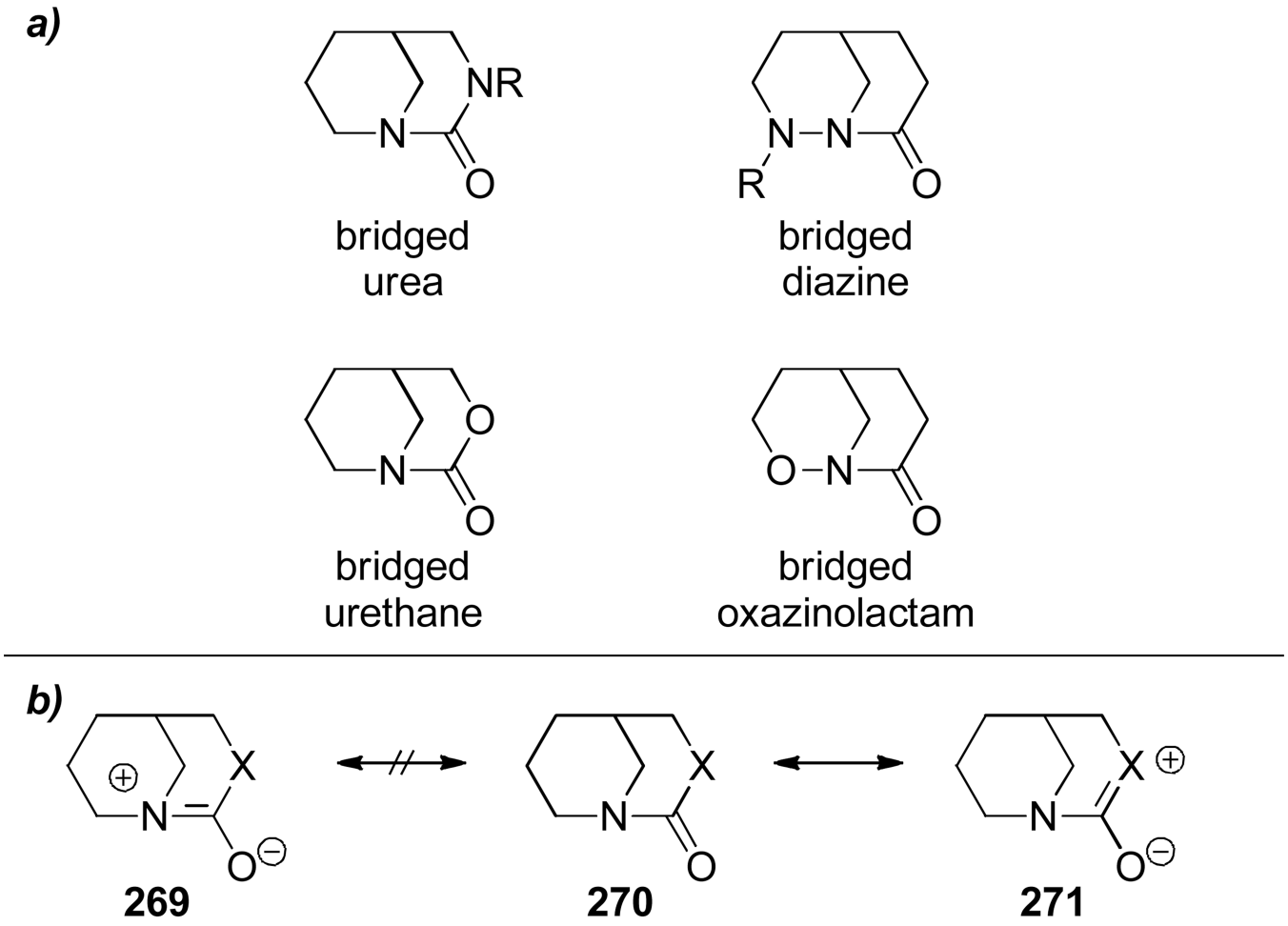


Figure 10.

a) Heteroatom-containing derivatives of bridged lactams; b) Stabilizing resonance interaction in bridged ureas and urethanes.

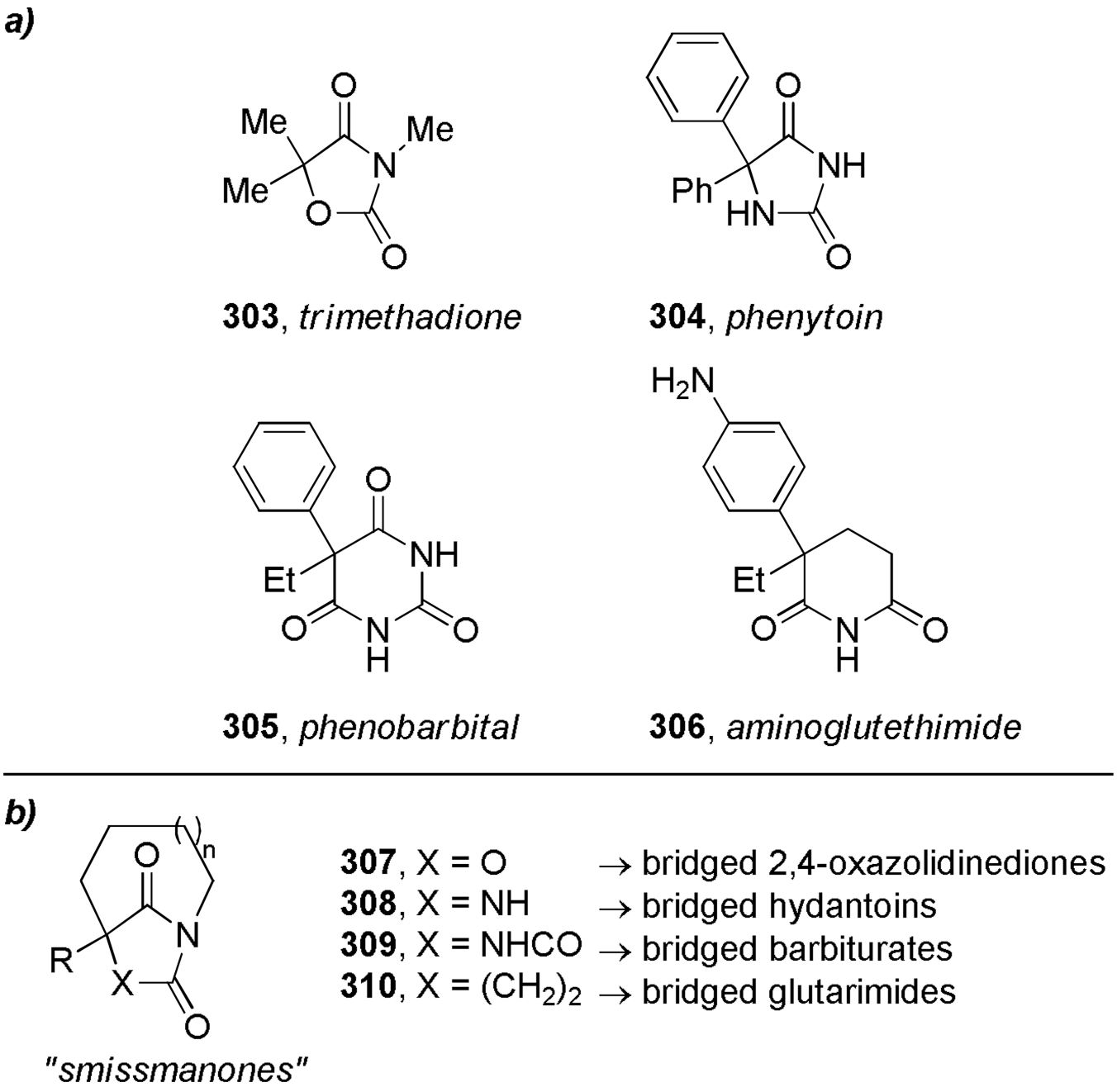


Figure 11.

Design of conformationally-constrained analogues by Smissman: a) anticonvulsant and anti-steroid drugs containing planar amide bonds; b) potential analogues containing bridged amide bonds (“smissmanones”).

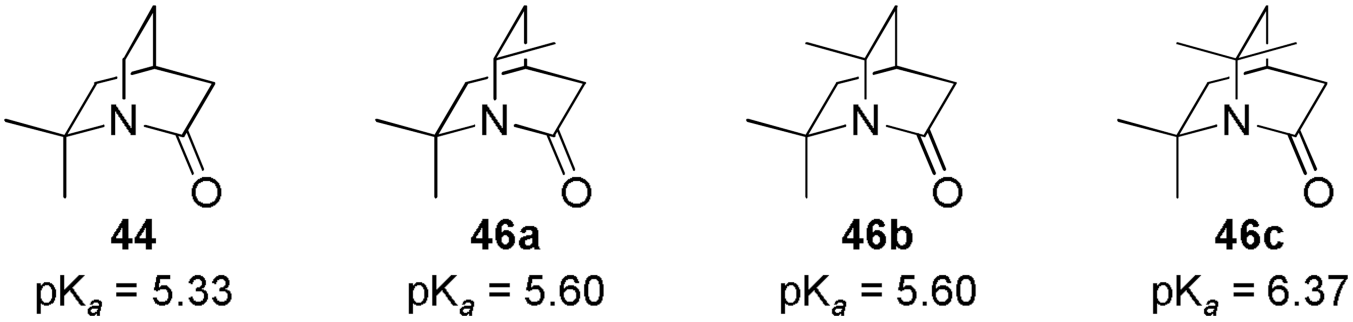


Figure 12.
Determination of pK$_a$ of 2-quinuclidones by Pracejus (**44**, **46a–b**) and Yakhontov (**46c**)

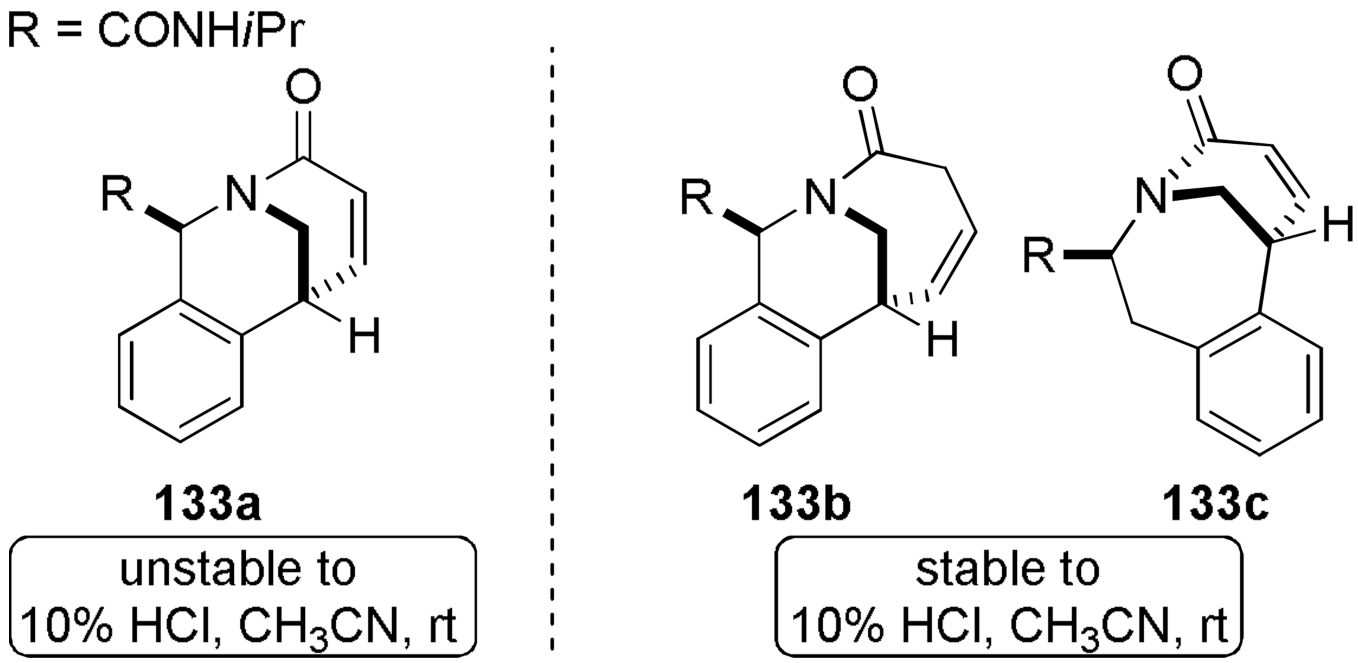


Figure 13.
Hydrolysis of Bridged Homologues of1-Azabicyclo[3.3.1]nonan-2-oneby Judd

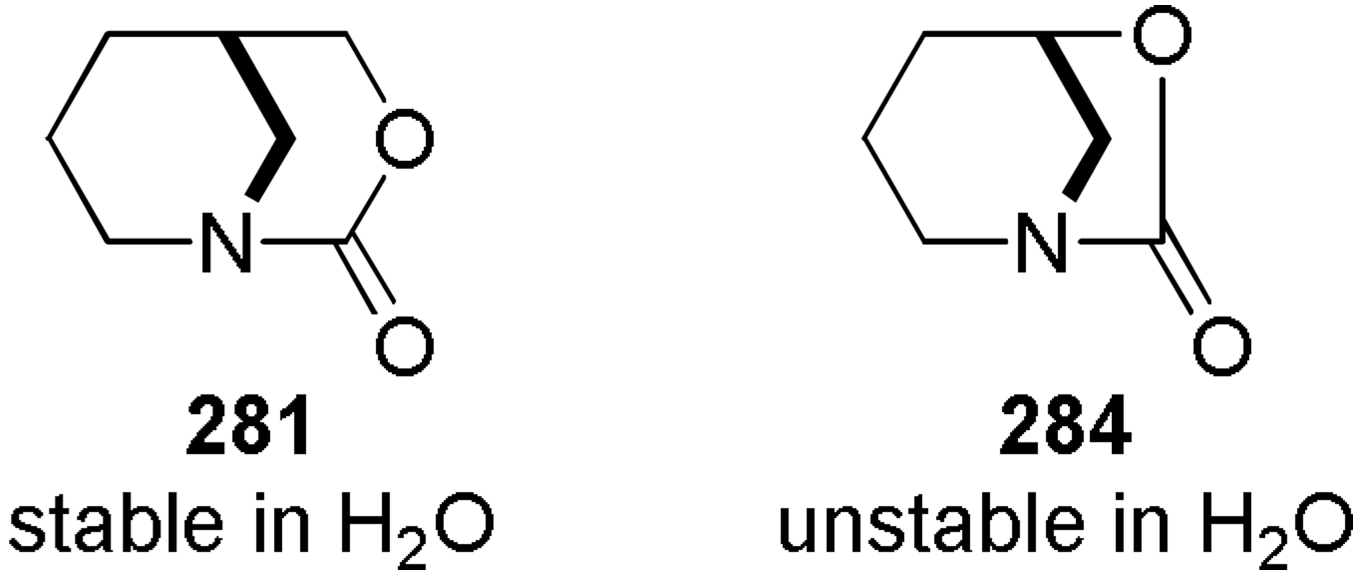
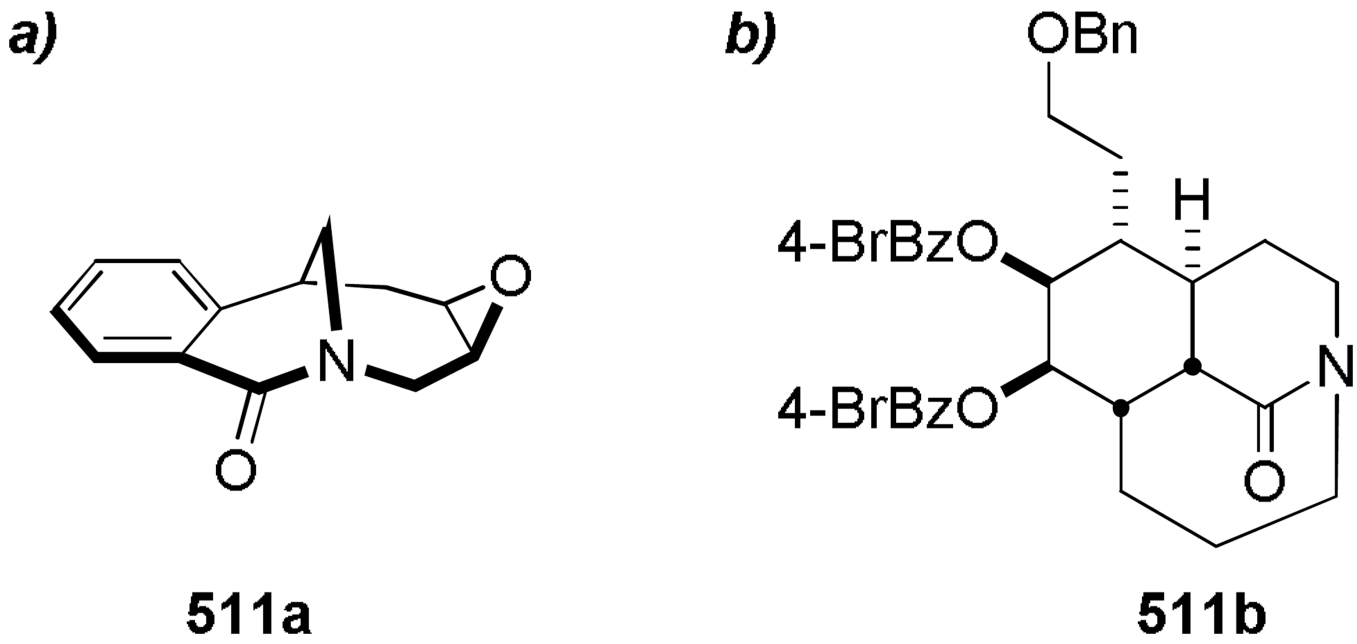
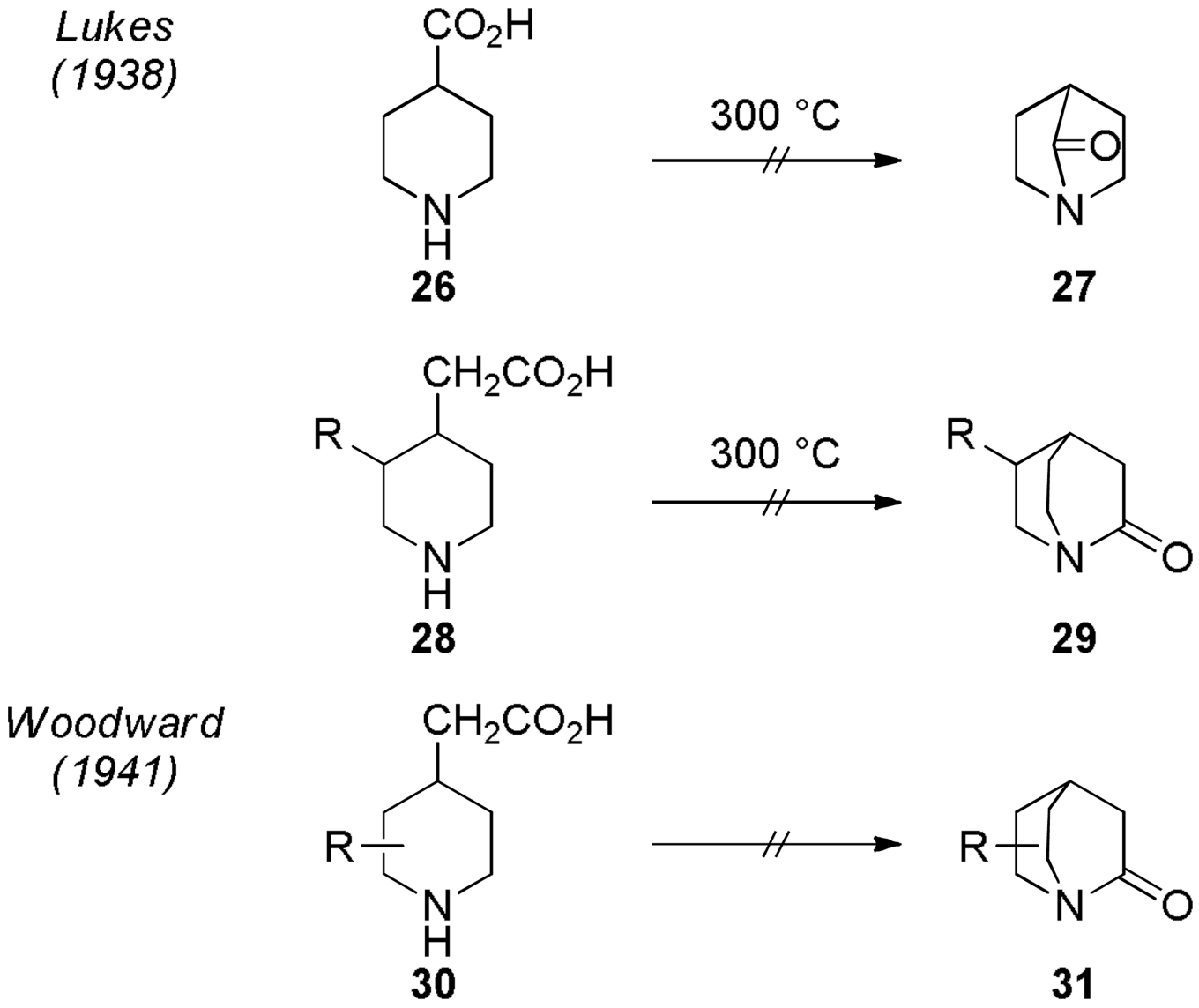


Figure 14.
Hydrolysis of bridged urethanes by Hall.

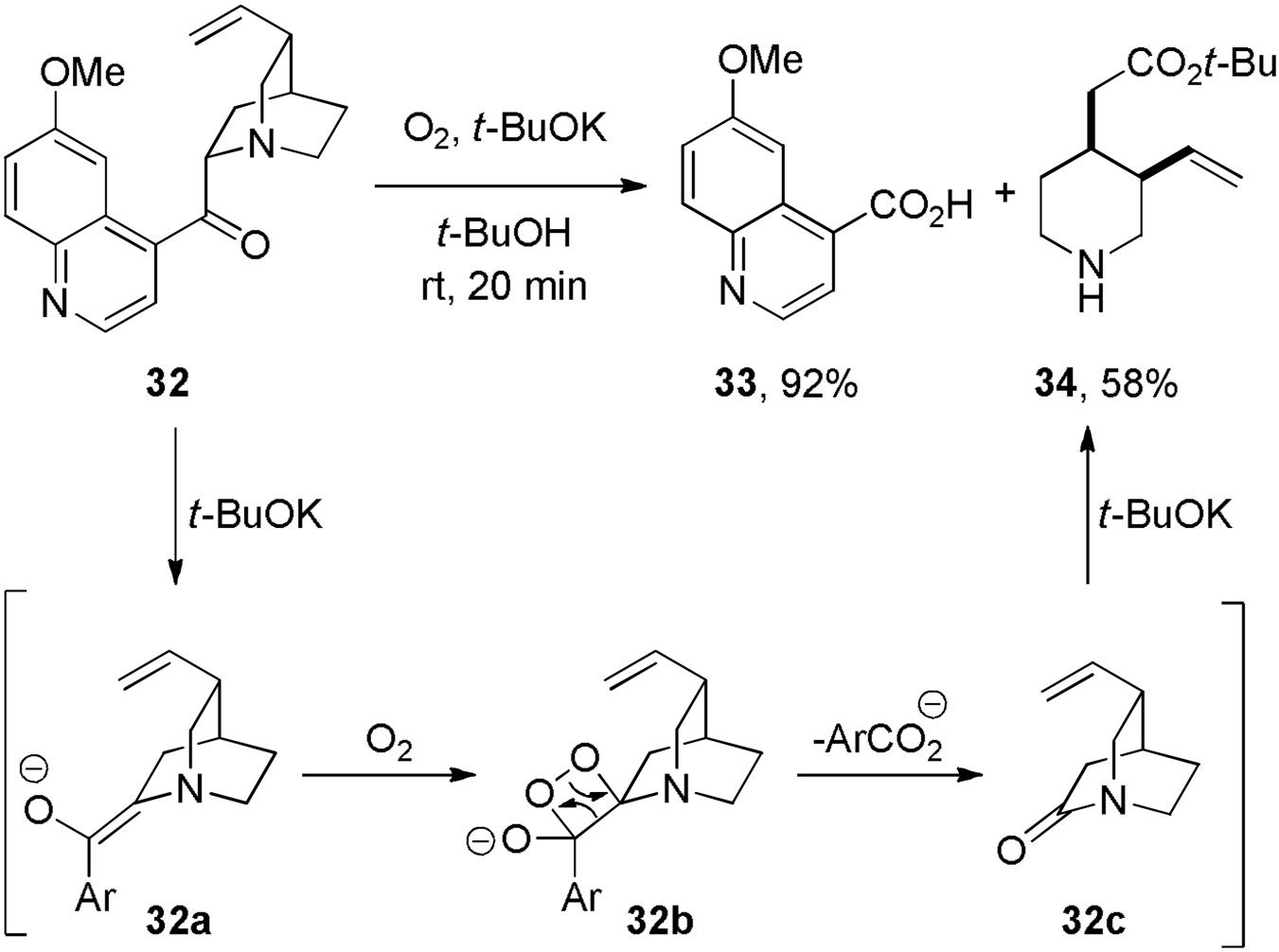


511a **511b**

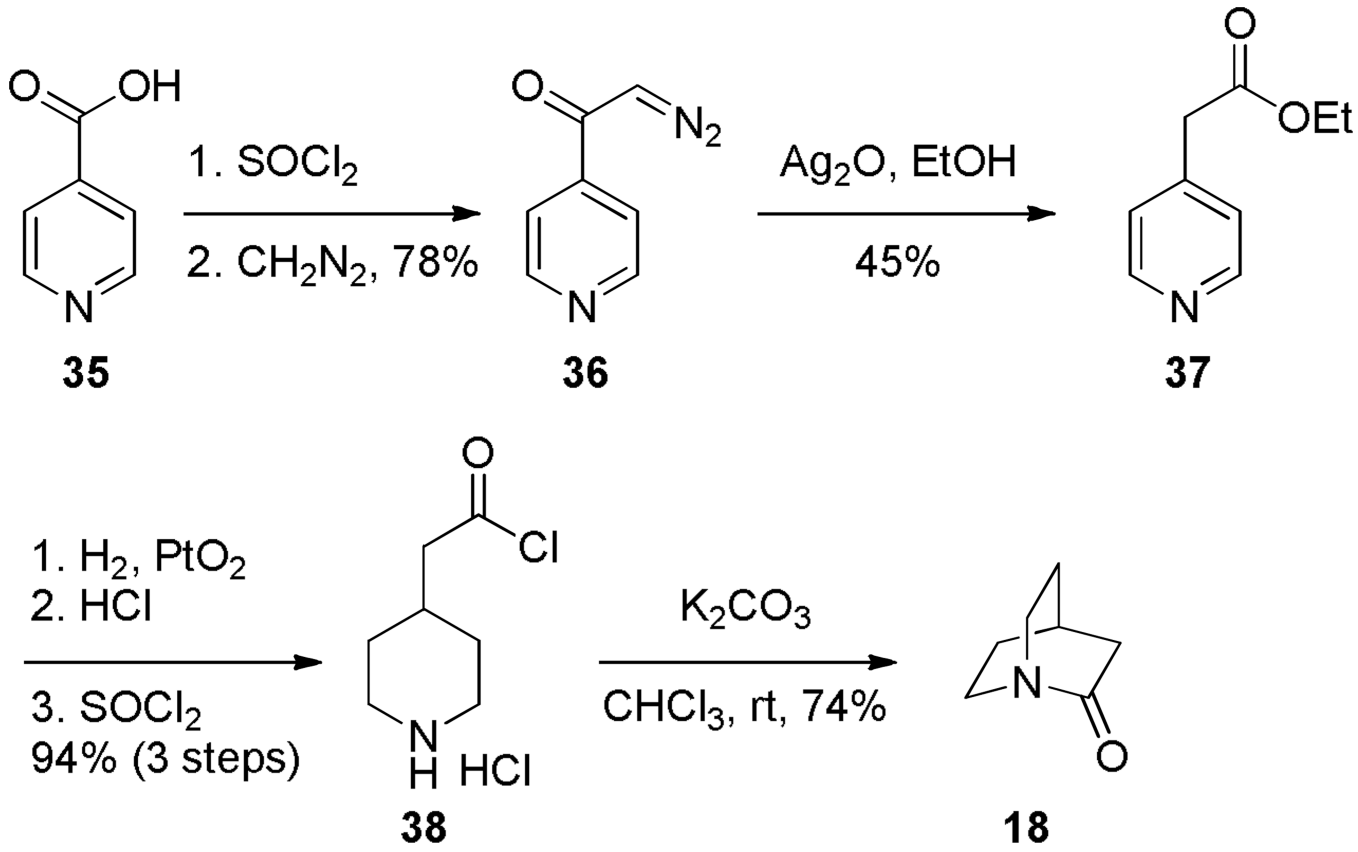
Figure 15.
a) Bridged Lactam Bearing Epoxide by Paquette; b) Tricyclic Bridged Lactam by Aubé



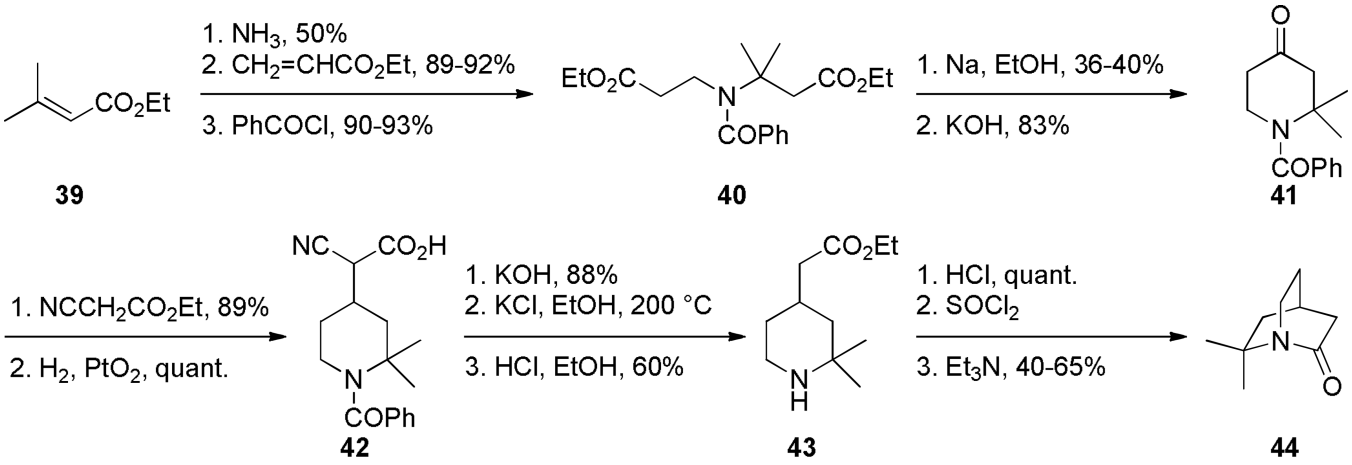
Scheme 1.
Early Attempts of Synthesis of Bridged Lactams



Scheme 2.
Synthesis of 2-Quinuclidone during Autoxidation of Quininone by Doering and Chanley

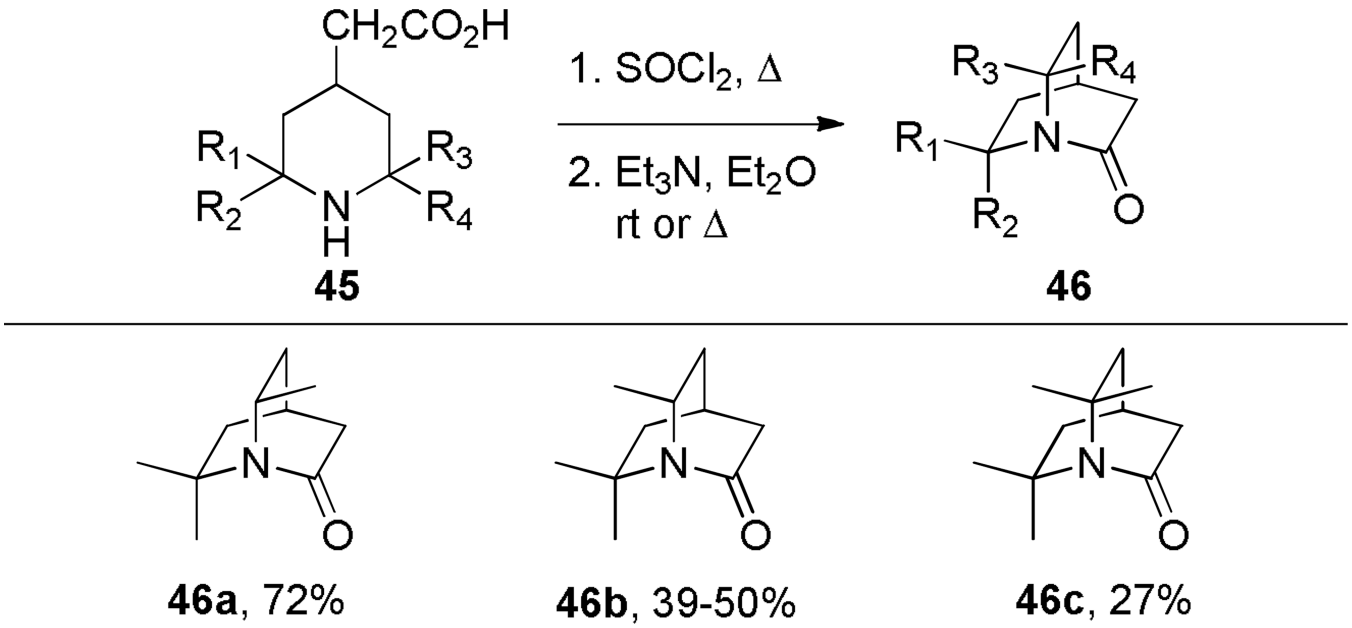


Scheme 3.
Synthesis of Unsubstituted 2-Quinuclidone by Yakhontov

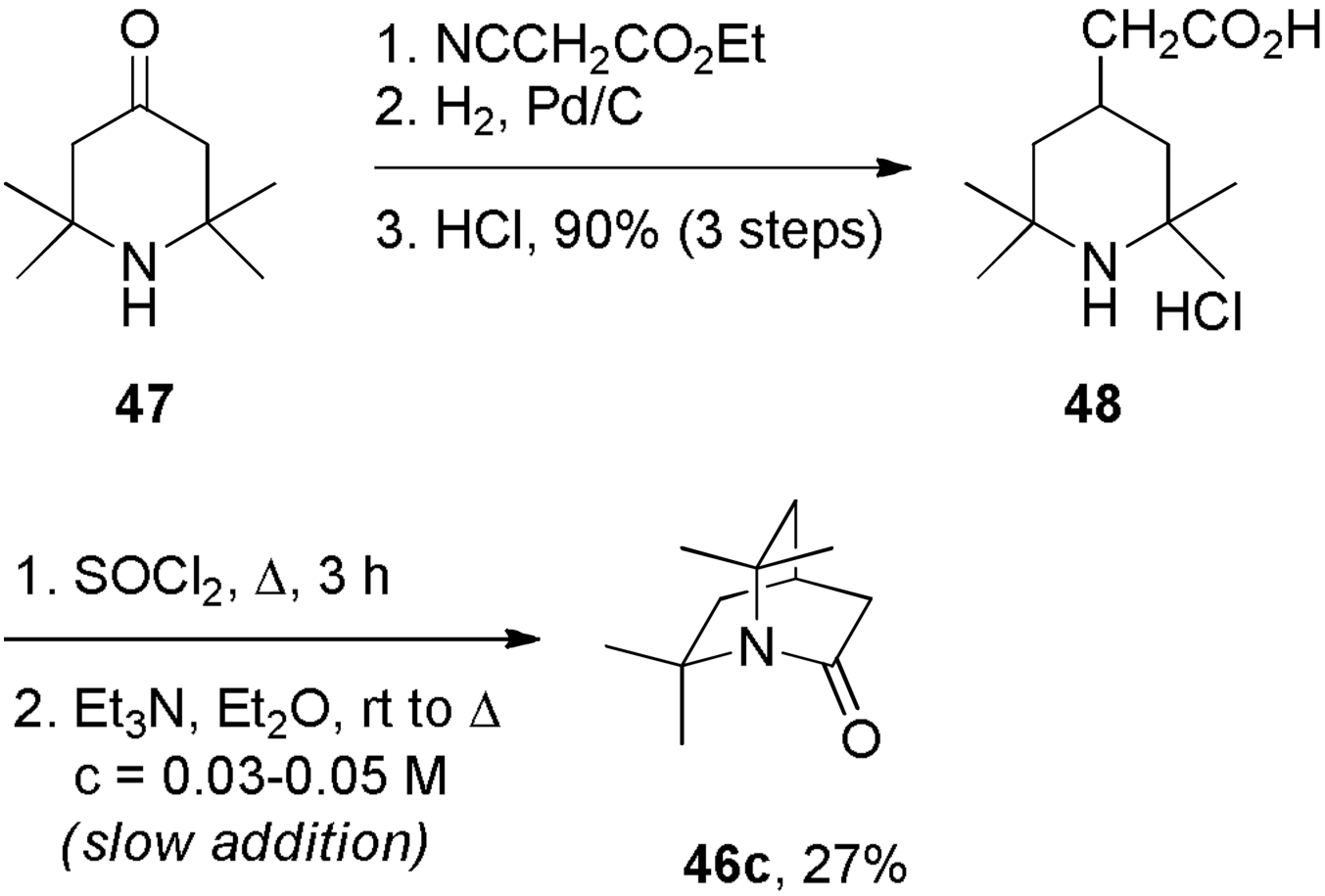


Scheme 4.

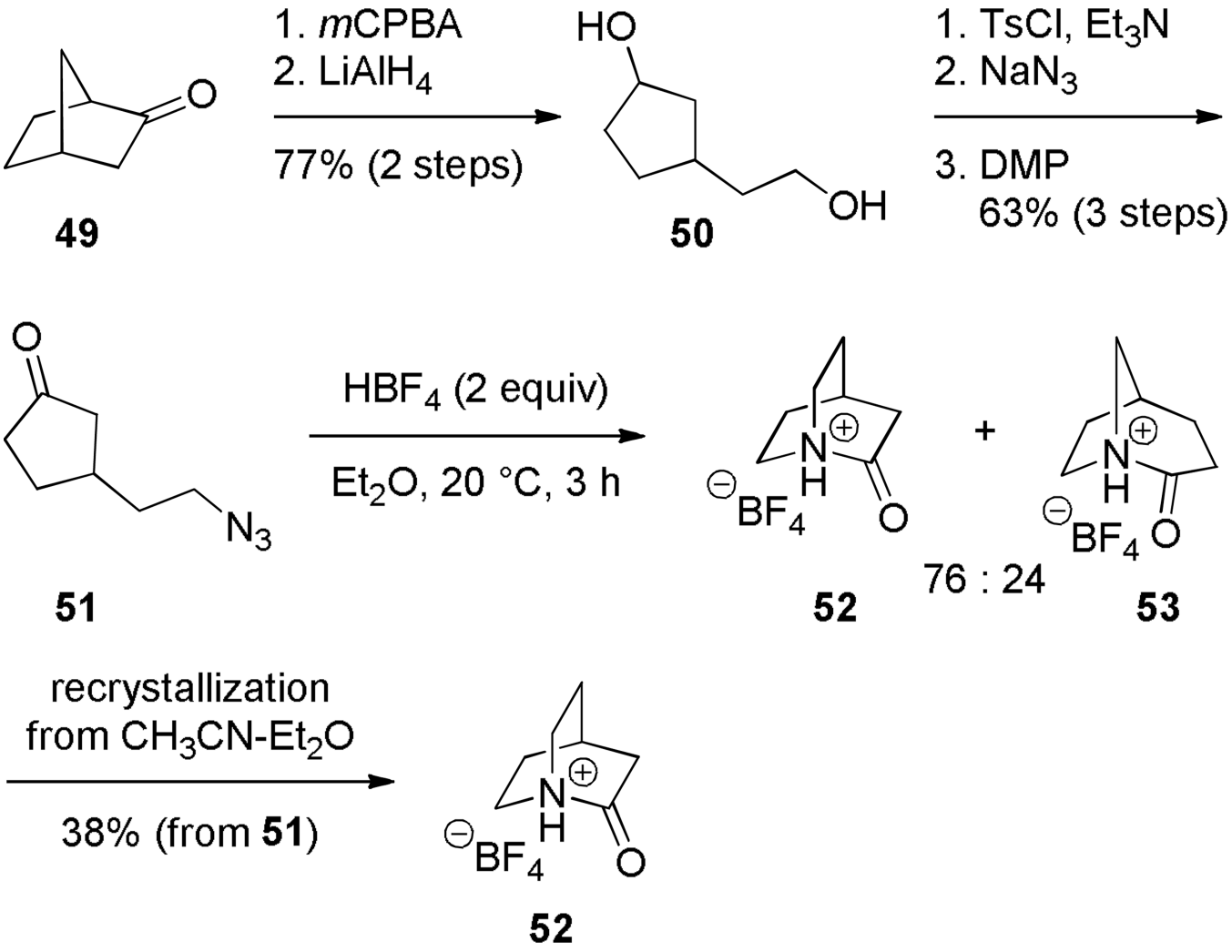
Synthesis of 6,6-Dimethyl-2-Quinuclidone by Pracejus (please use double-column format for Scheme 4)



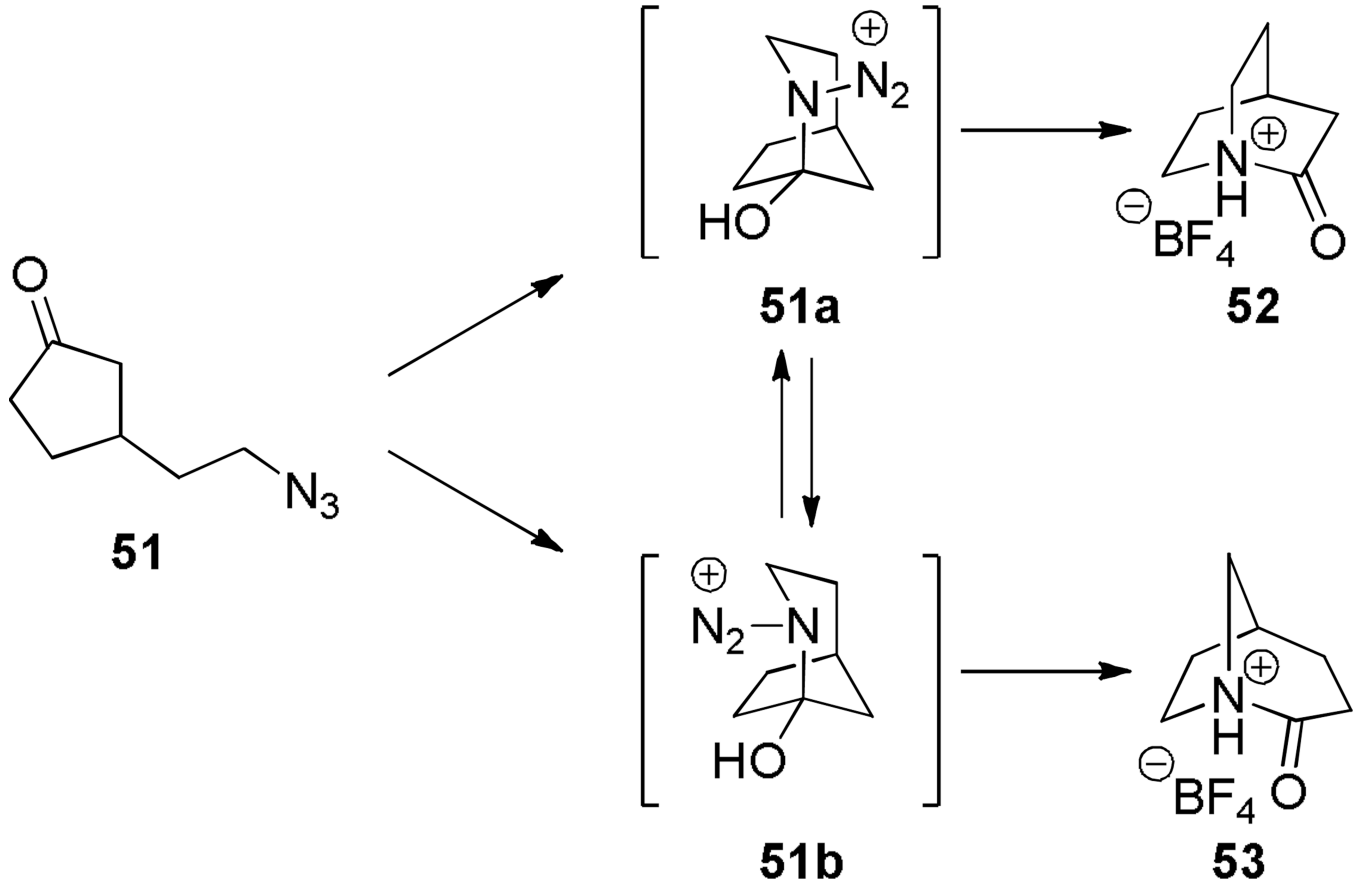
Scheme 5.
Synthesis of Substituted 2-Quinuclidones by Pracejus and Yakhontov



Scheme 6.
Improved Synthesis of 6,6,7,7-Tetramethyl-2-Quinuclidone by Greenberg

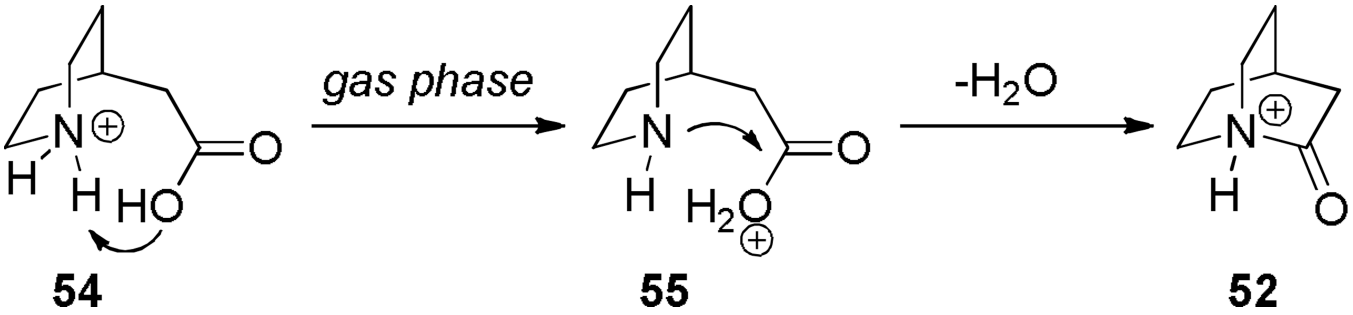


Scheme 7.
Synthesis of 2-Quinuclidonium Tetrafluoroborate by Tani and Stoltz

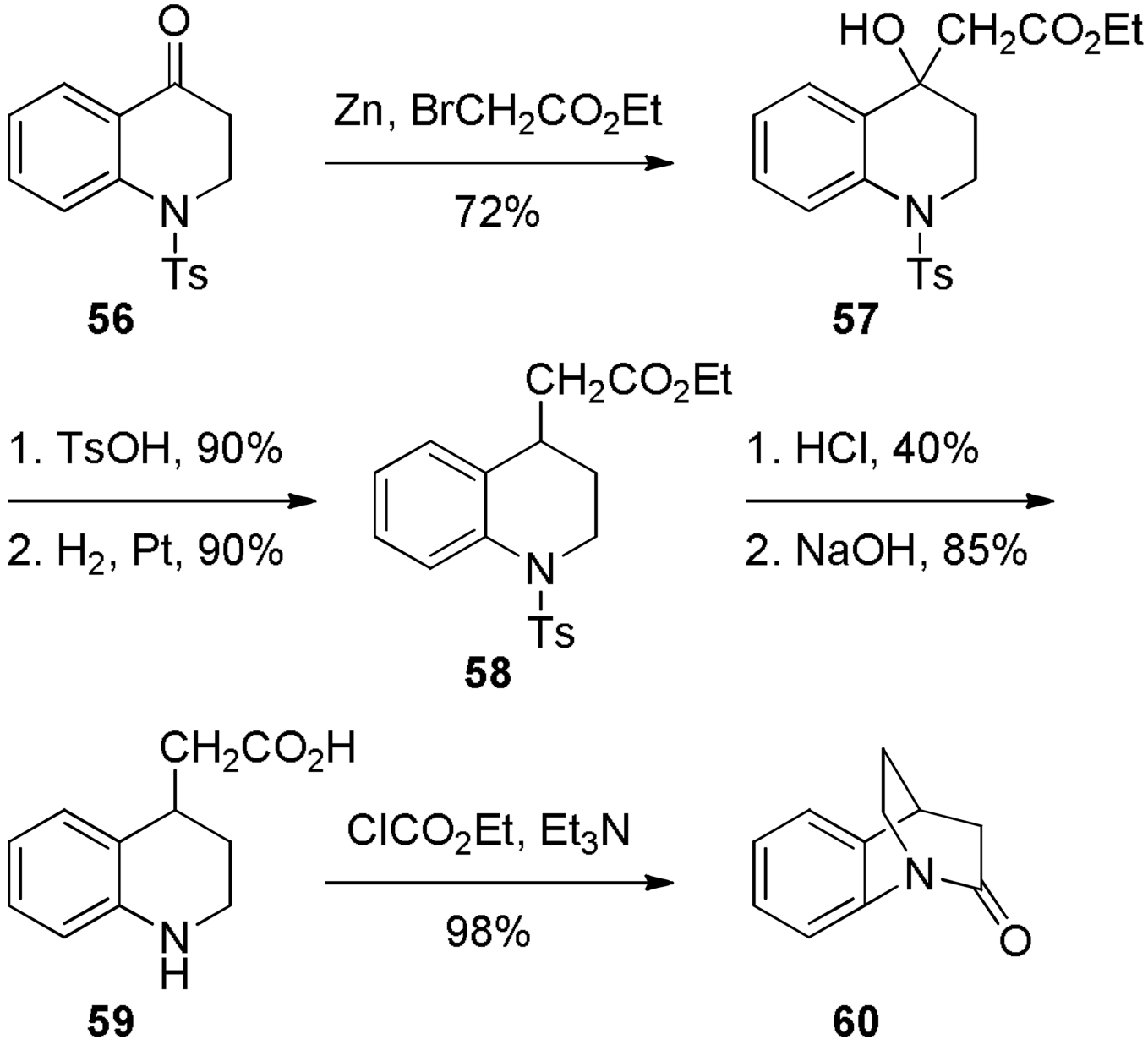


Scheme 8.

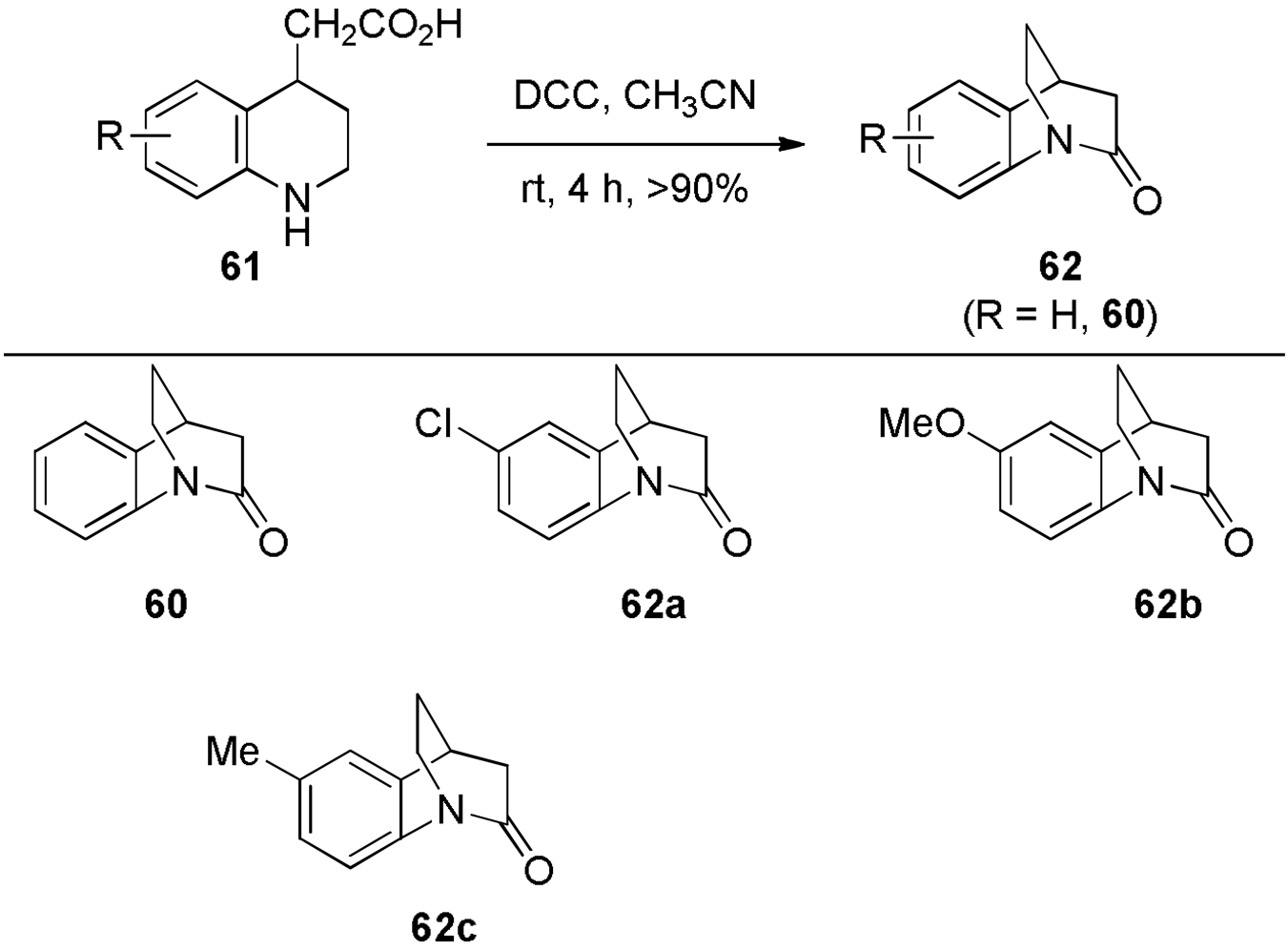
Proposed Mechanism for Schmidt Reaction of 3-Azidoalkyl Ketone **51**



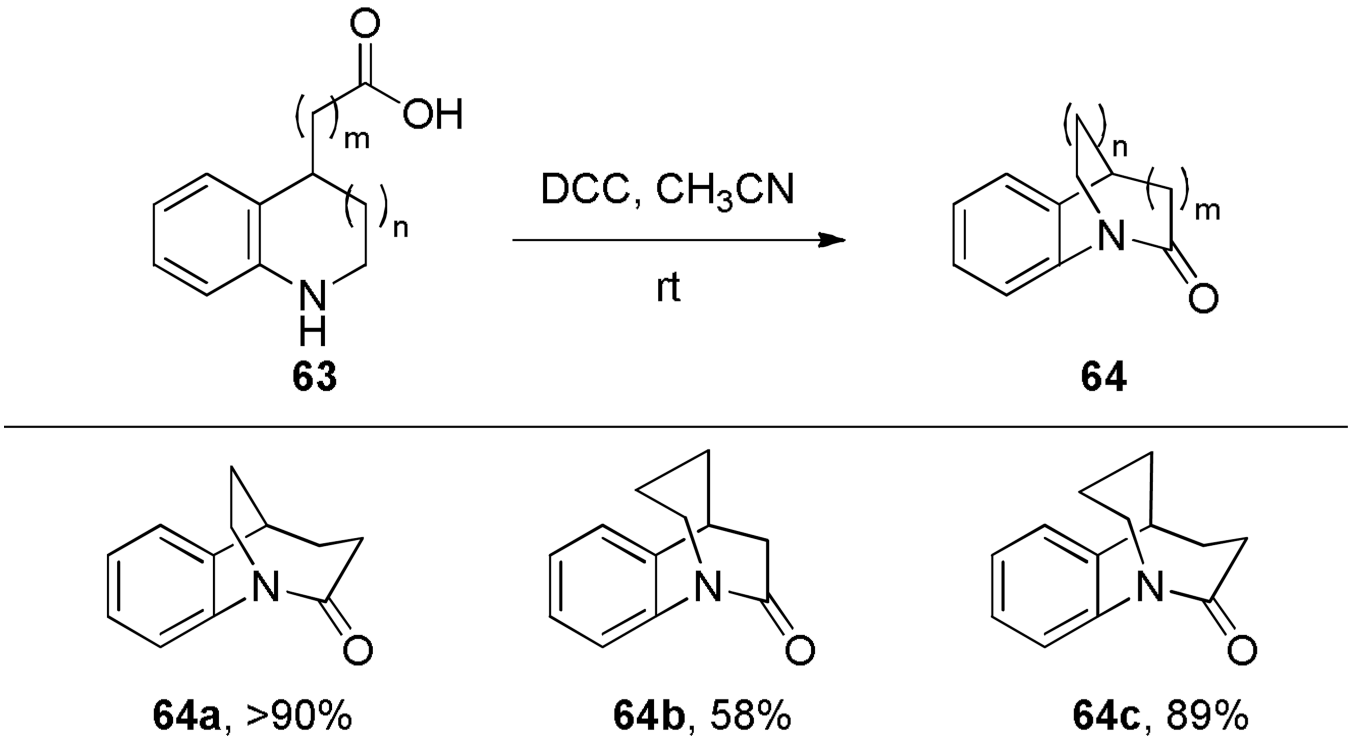
Scheme 9.
Synthesis of Unsubstituted 2-Quinuclidone in a Gas Phase by Stoltz



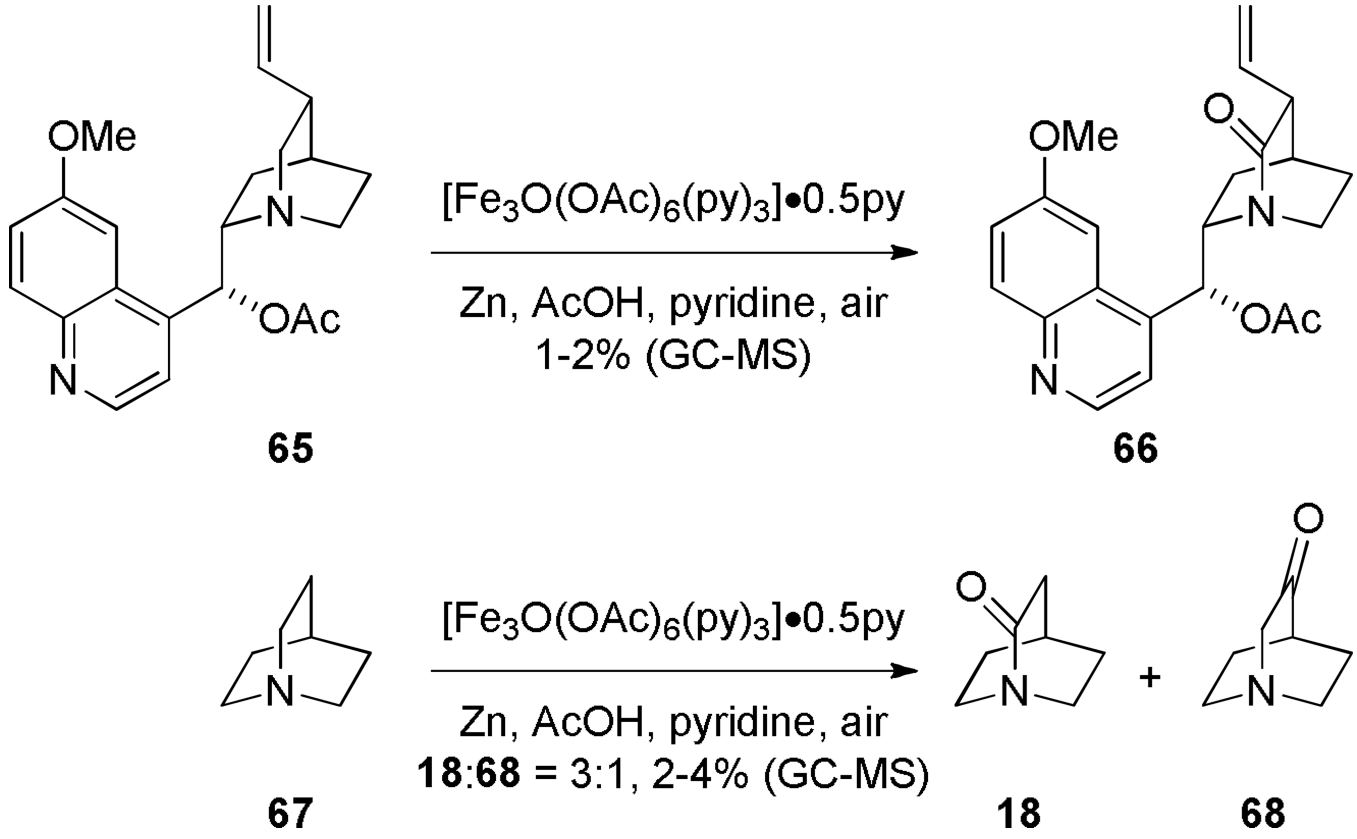
Scheme 10.
Synthesis of Benzo-2-Quinuclidone by Blackburn



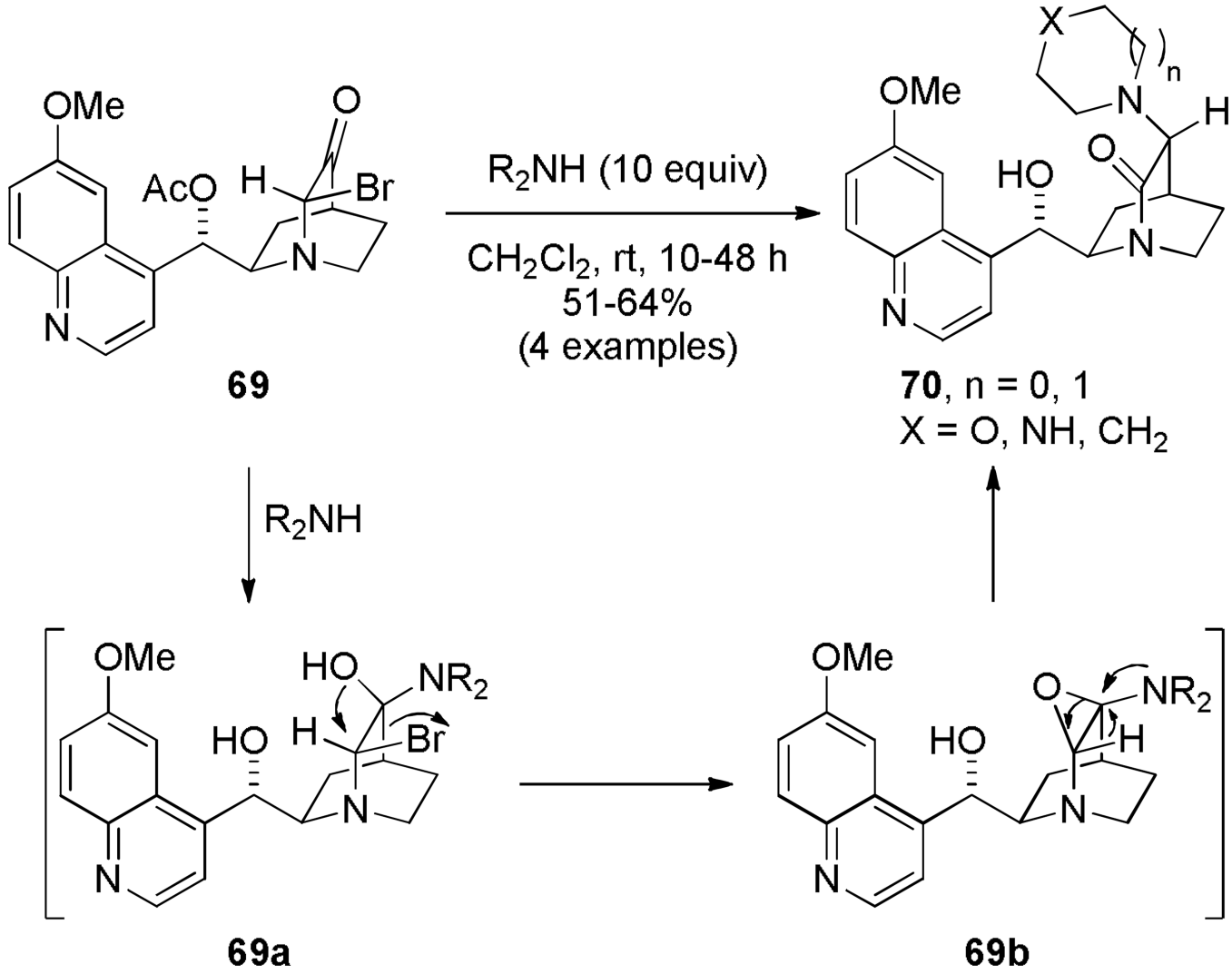
Scheme 11.
Synthesis of Benzo-2-Quinuclidones by Brown



Scheme 12.
Synthesis of Expanded Ring Systems of Benzo-2-Quinuclidones by Brown

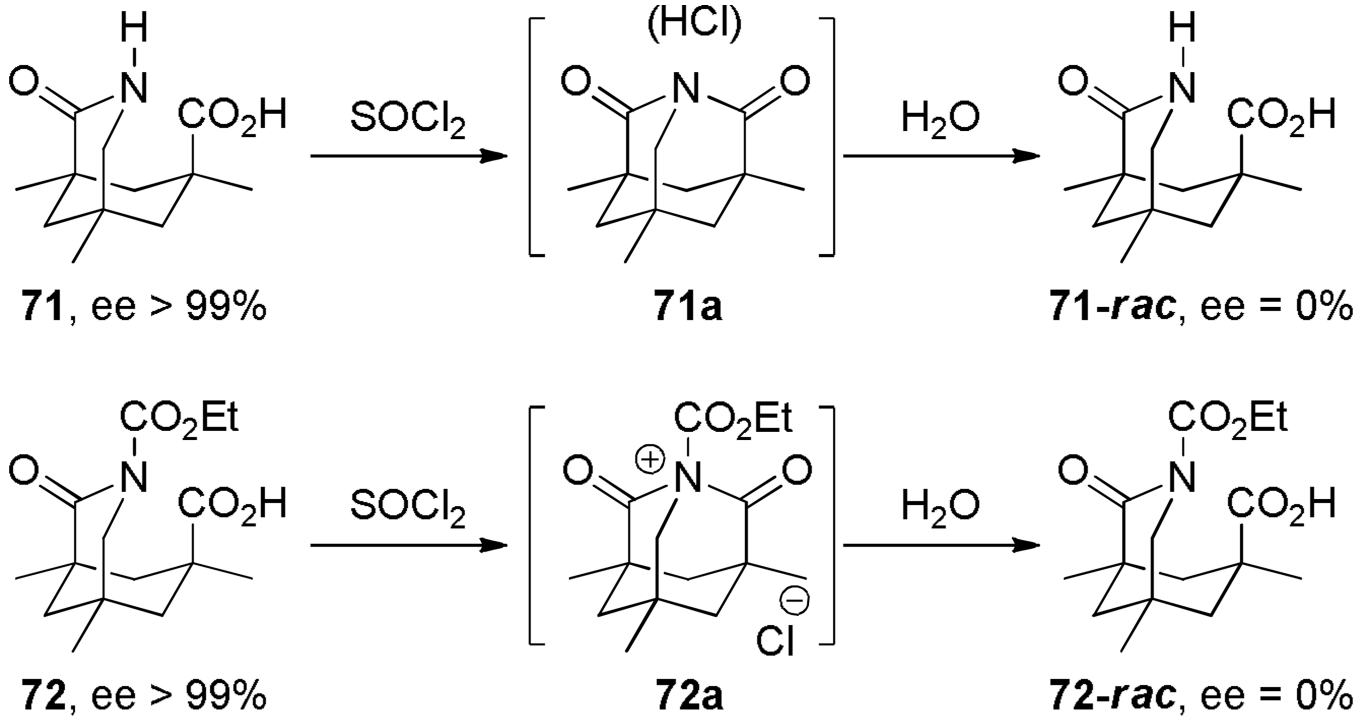


Scheme 13.
Synthesis of 2-Quinuclidones under Gif Conditions by Jankowski

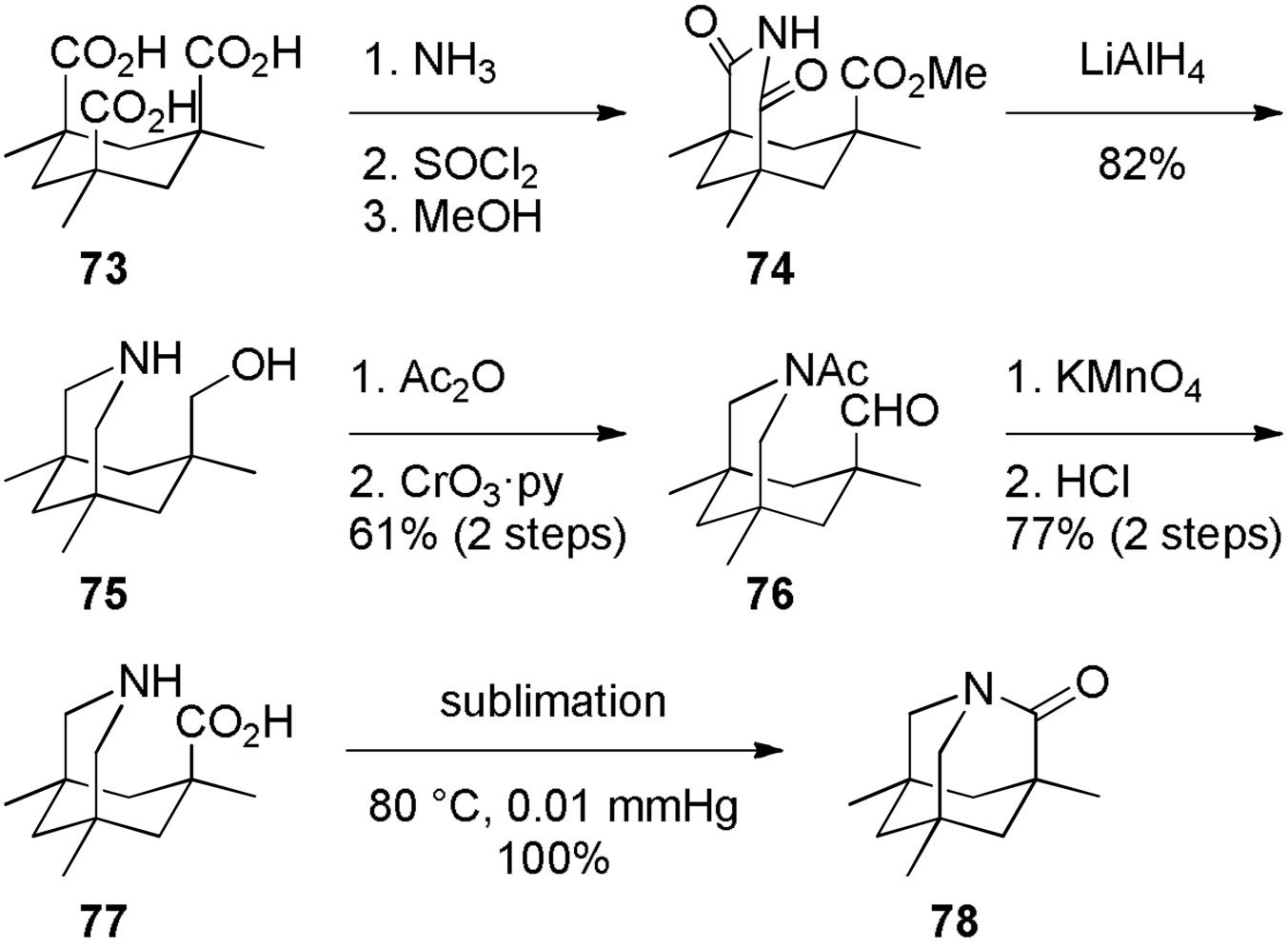


Scheme 14.

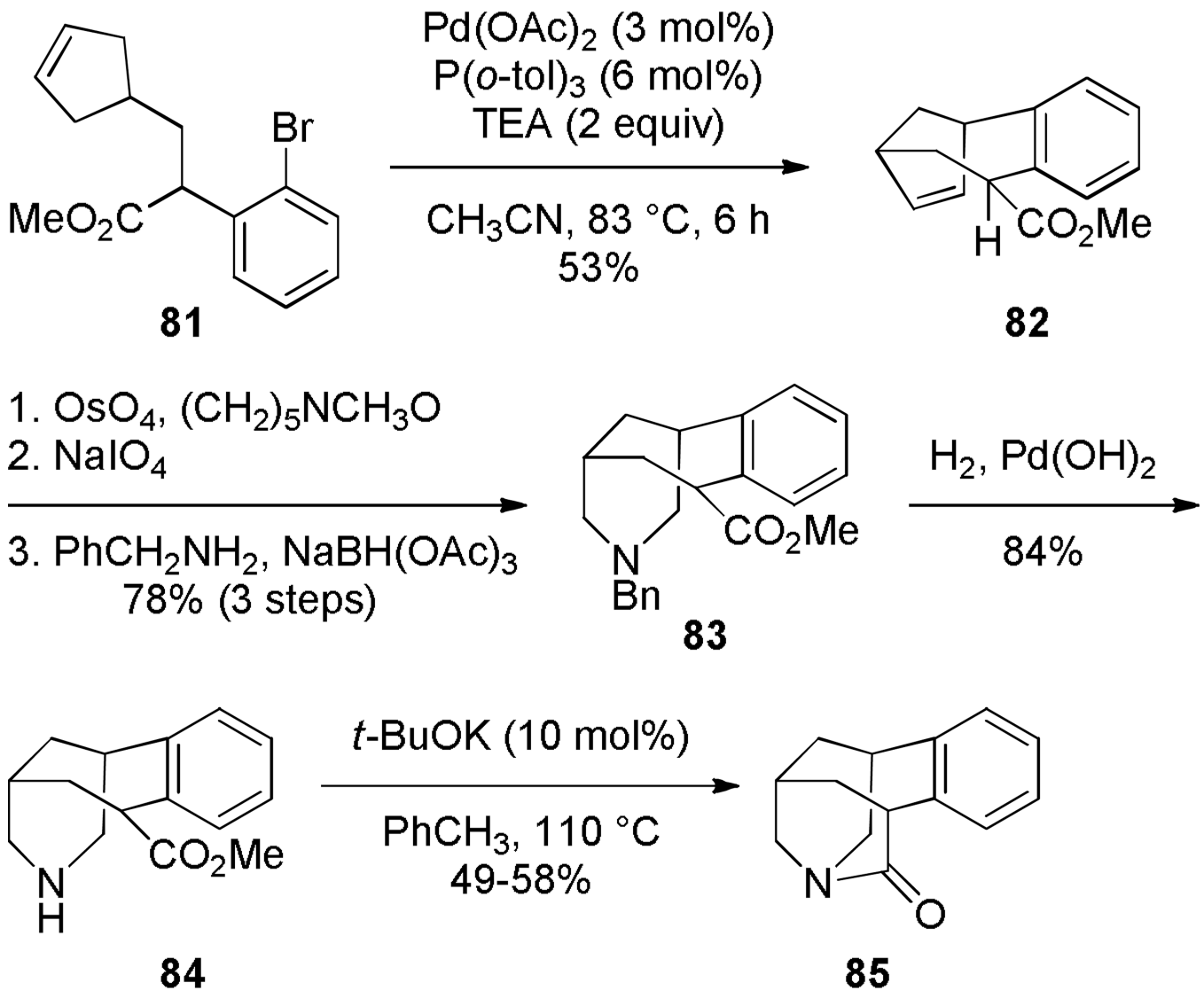
Synthesis of 2-Quinuclidones from Modified Cinchona Alkaloids by Hoffmann



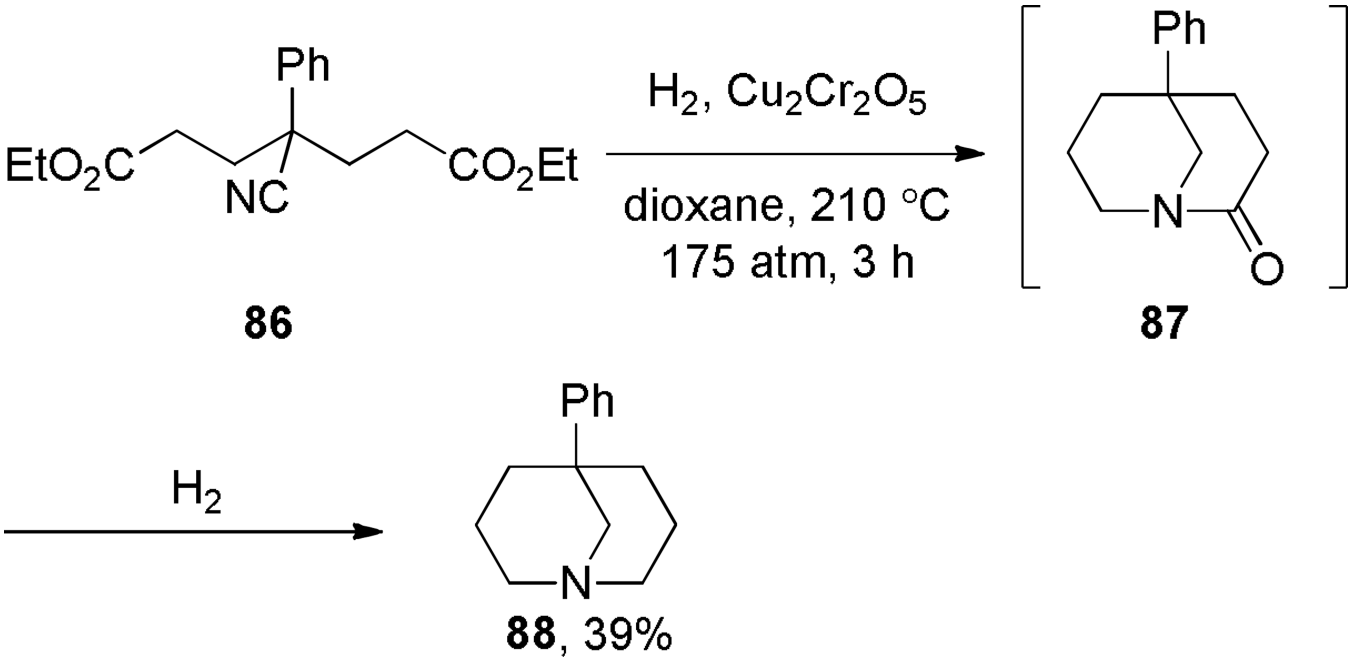
Scheme 15.
Synthesis of Bridged Imides from Kemp Triacid by Rebek



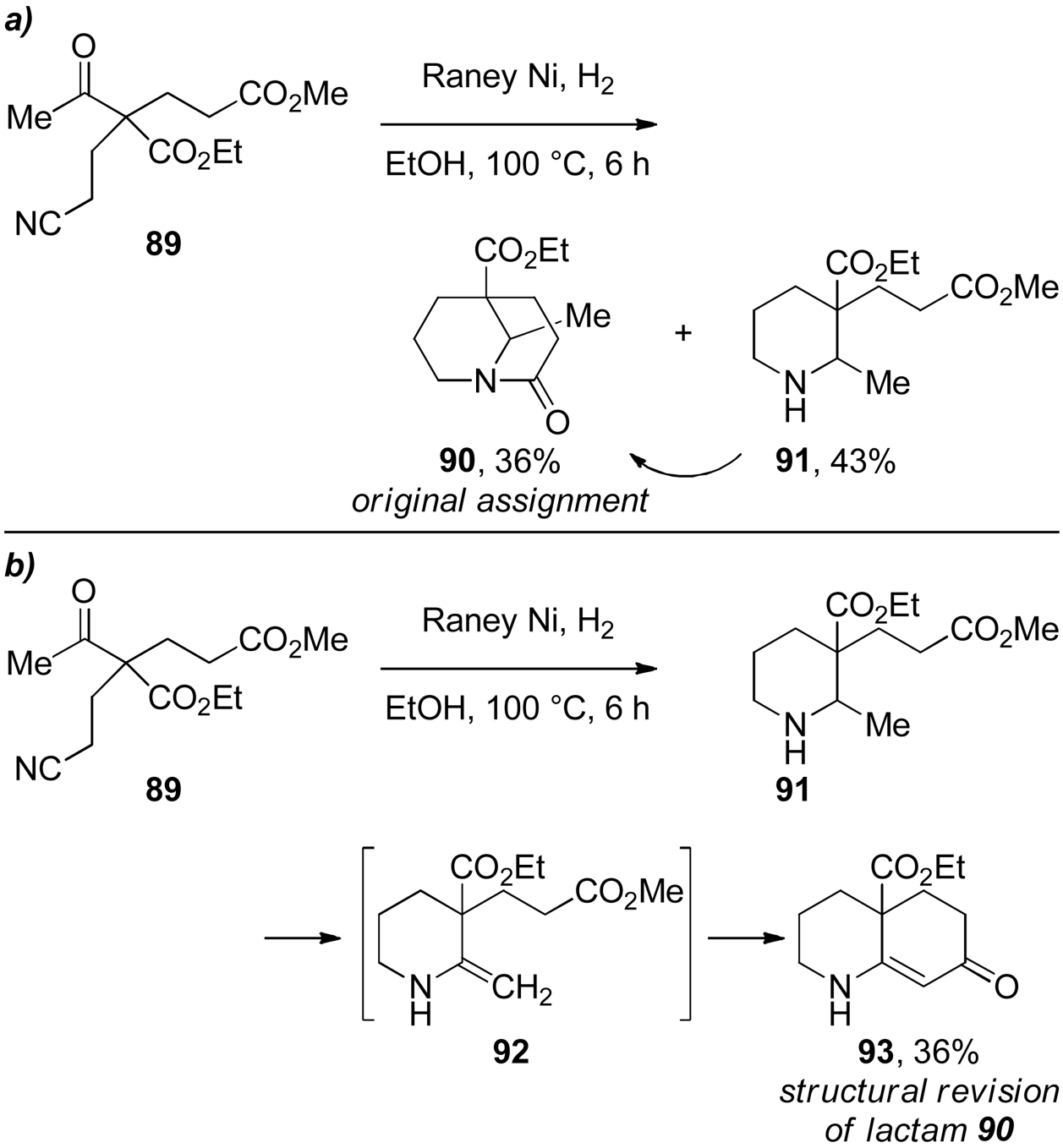
Scheme 16.
Synthesis of 1-Aza-2-adamantanone (“the Most Twisted Amide”) by Kirby



Scheme 17.
Synthesis of Benzo-1-aza-2-adamantanone by Coe

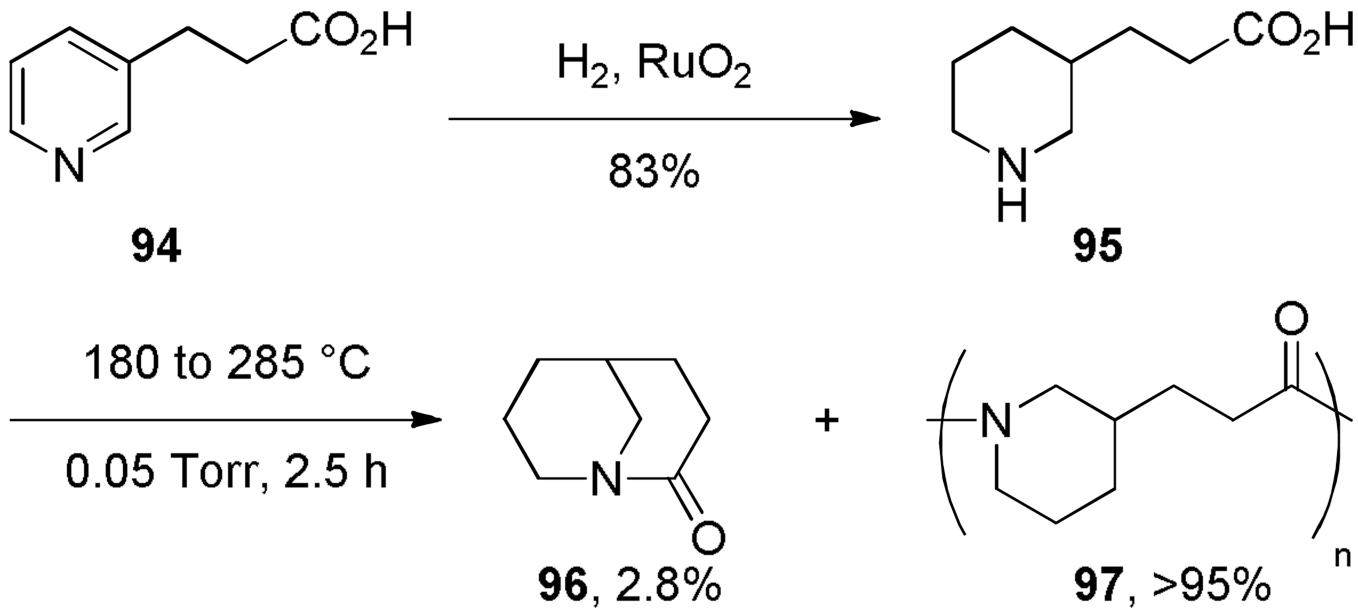


Scheme 18.
Synthesis of 1-Azabicyclo[3.3.1]nonan-2-one **87** by Walker

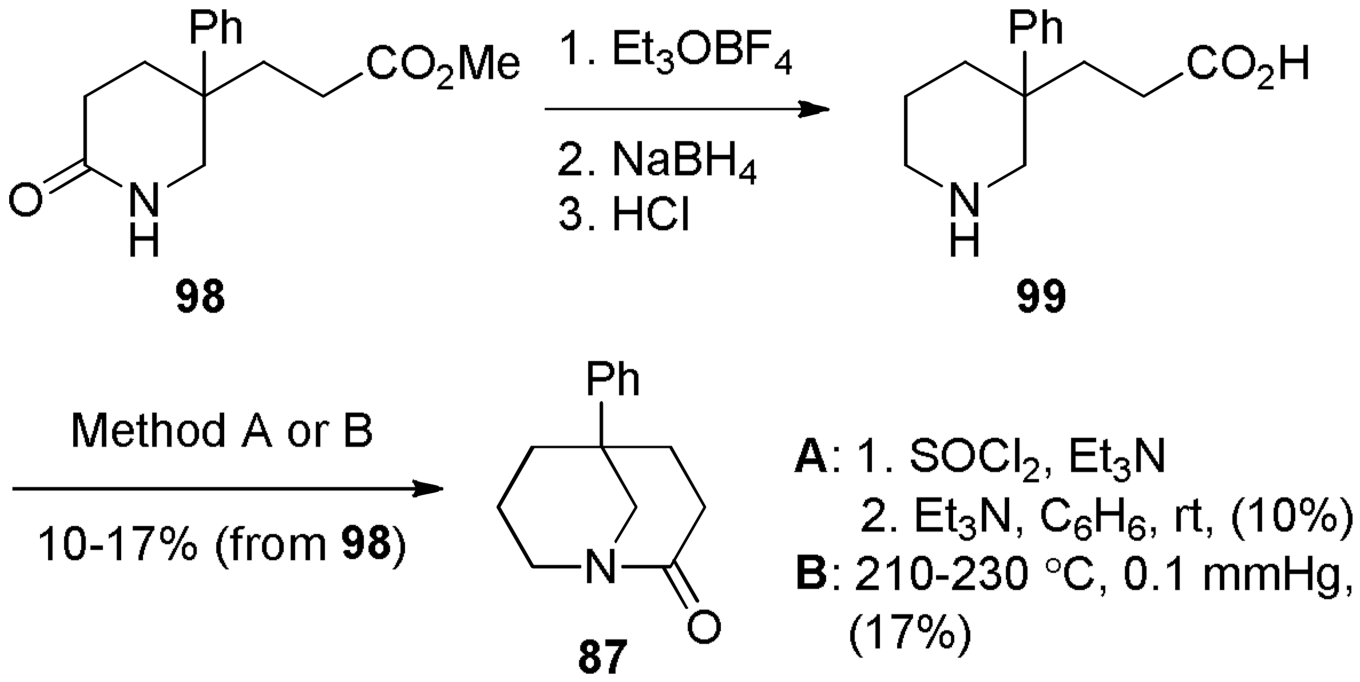


Scheme 19.

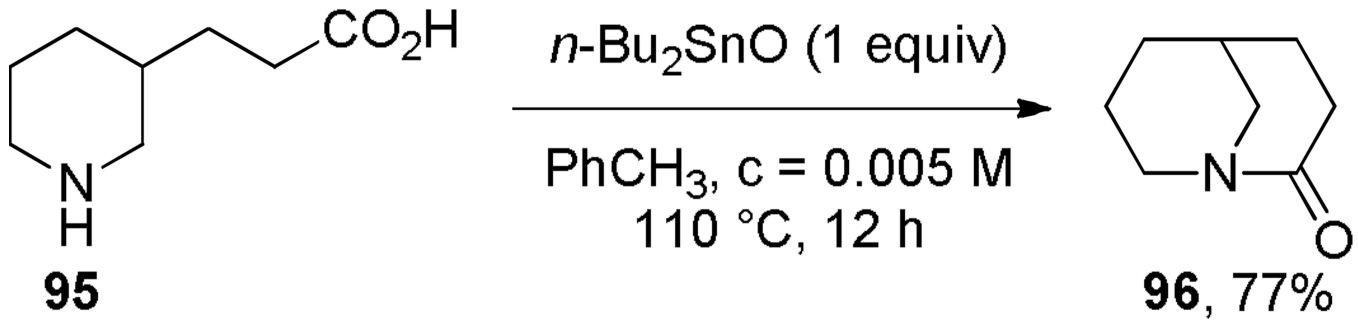
a) Condensation to 1-Azabicyclo[3.3.1]nonan-2-one by Albertson; b) Revision of Proposed Structure of **90**



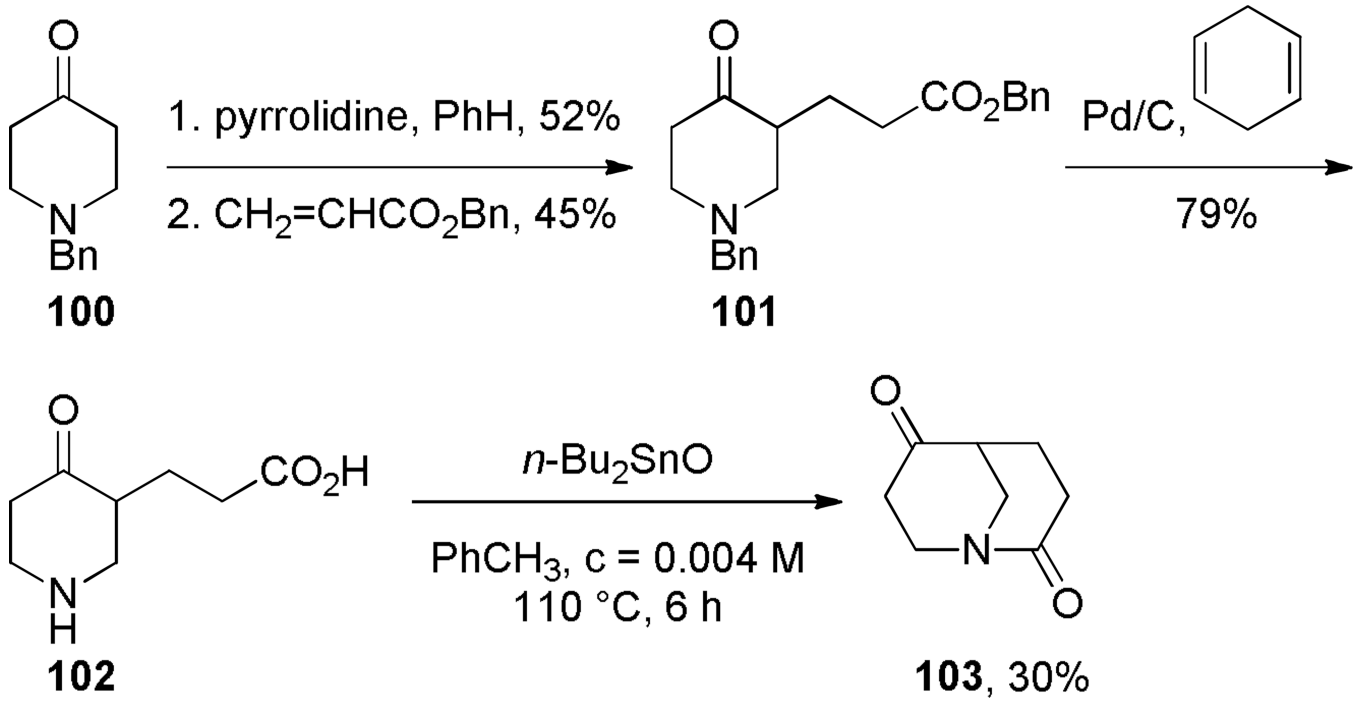
Scheme 20.
Synthesis of 1-Azabicyclo[3.3.1]nonan-2-one by Hall



Scheme 21.
Synthesis of 5-Phenyl-1-Azabicyclo[3.3.1]nonan-2-one by Buchanan

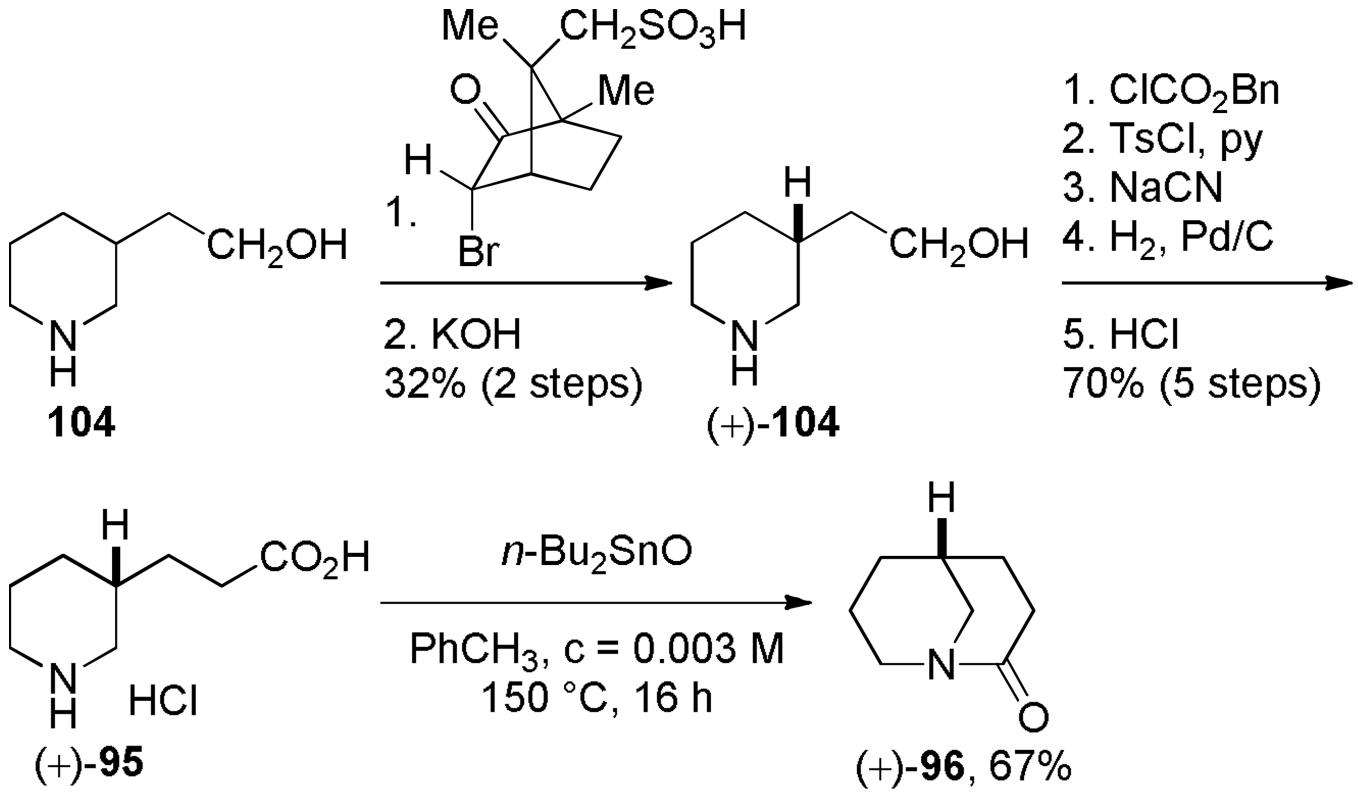


Scheme 22.
Improved Synthesis of 1-Azabicyclo[3.3.1]nonan-2-one by Steliou



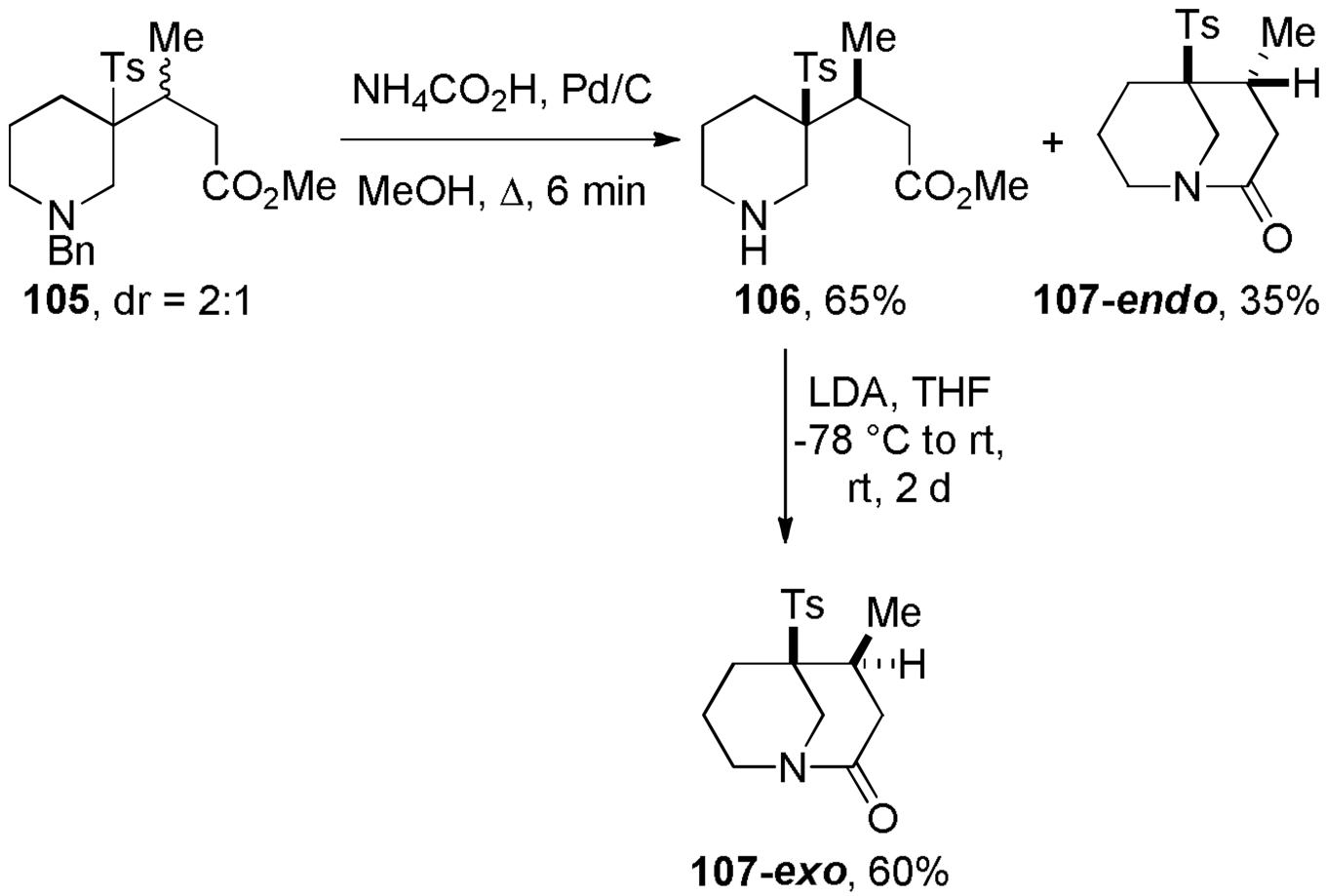
Scheme 23.

Application of Bu_2SnO in Synthesis of 1-Azabicyclo[3.3.1]nonane-2,6-dione by Sim

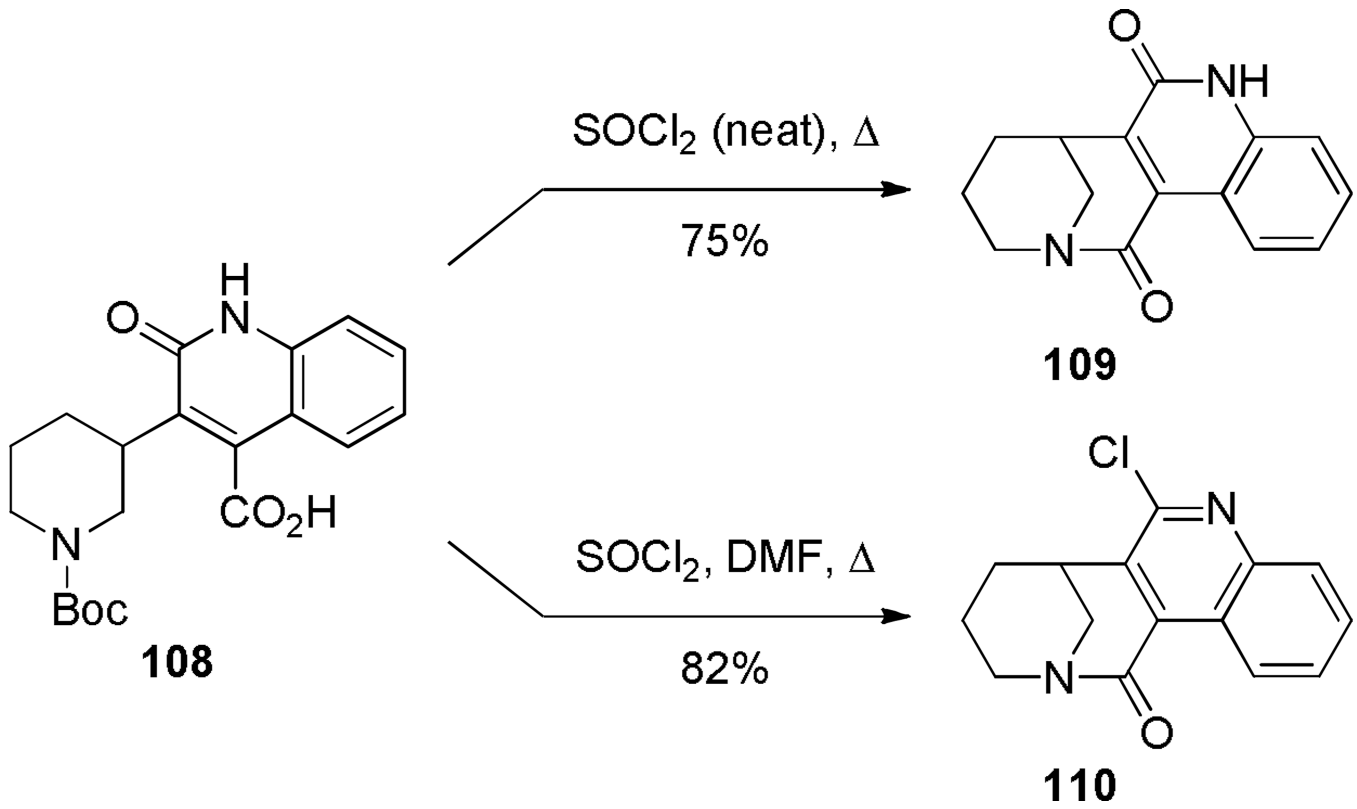


Scheme 24.

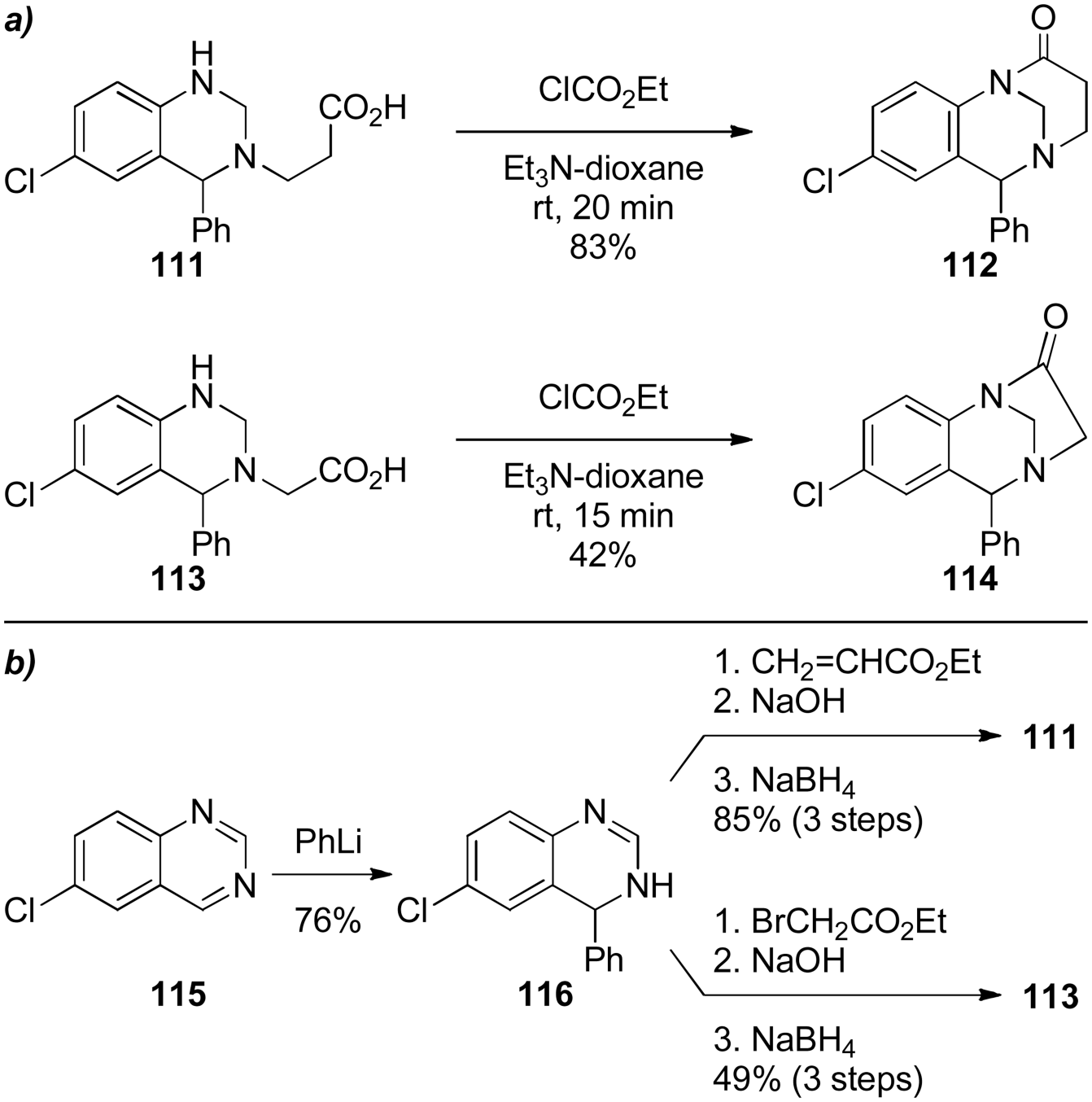
Application of Bu_2SnO in Synthesis of (+)-(*R*)-1-Azabicyclo[3.3.1]nonan-2-oneby Gerlach



Scheme 25.
Synthesis of 4-Methyl-5-tosyl-1-azabicyclo[3.3.1]nonan-2-ones by Najera

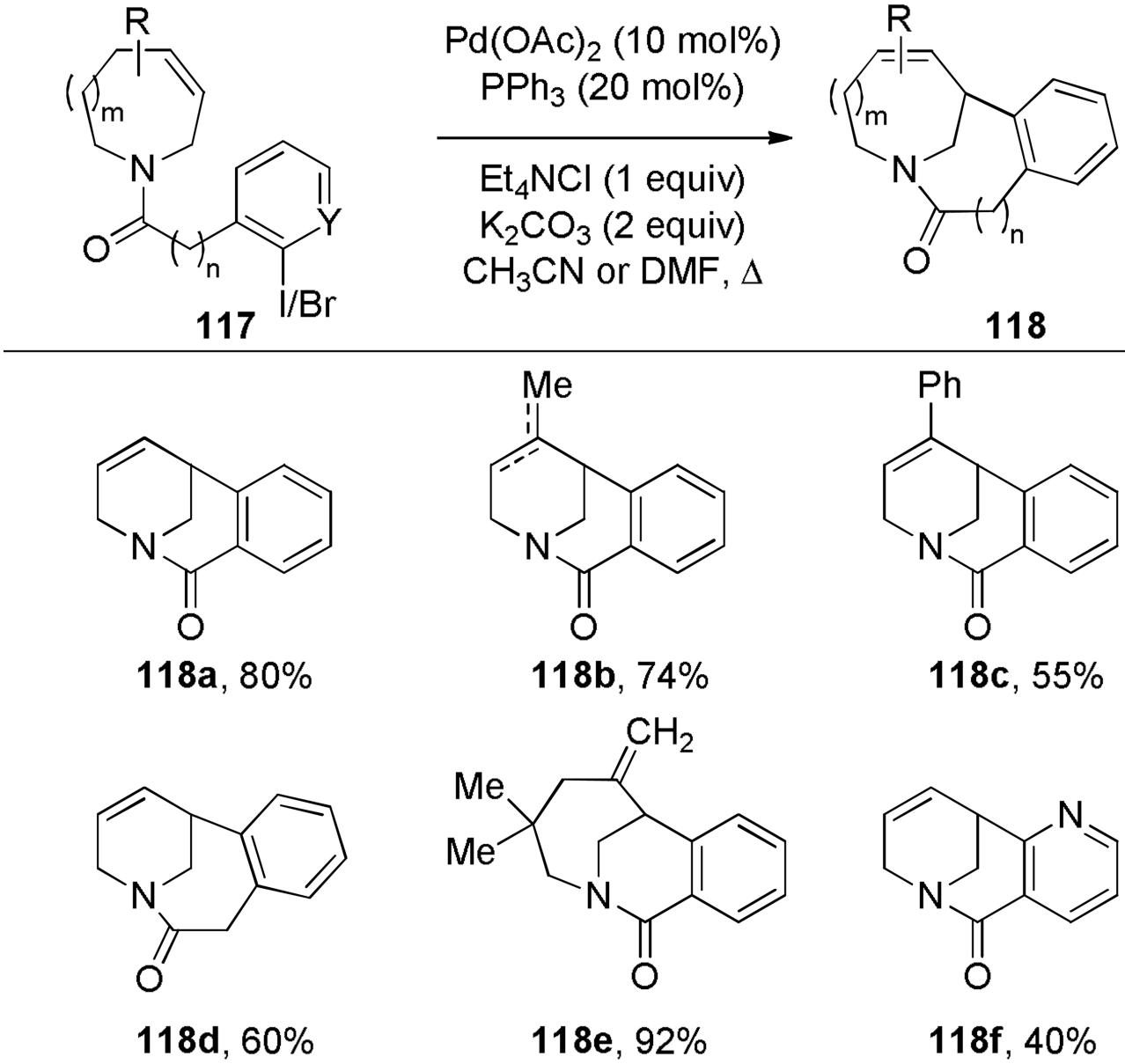


Scheme 26.
Synthesis of Quinolino-1-Azabicyclo[3.3.1]nonan-2-ones by Cuny

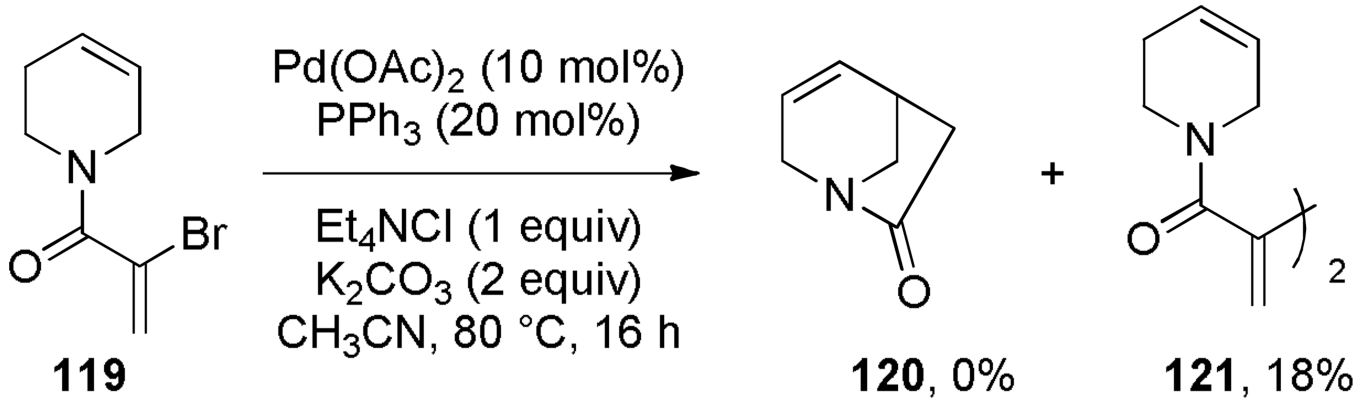


Scheme 27.

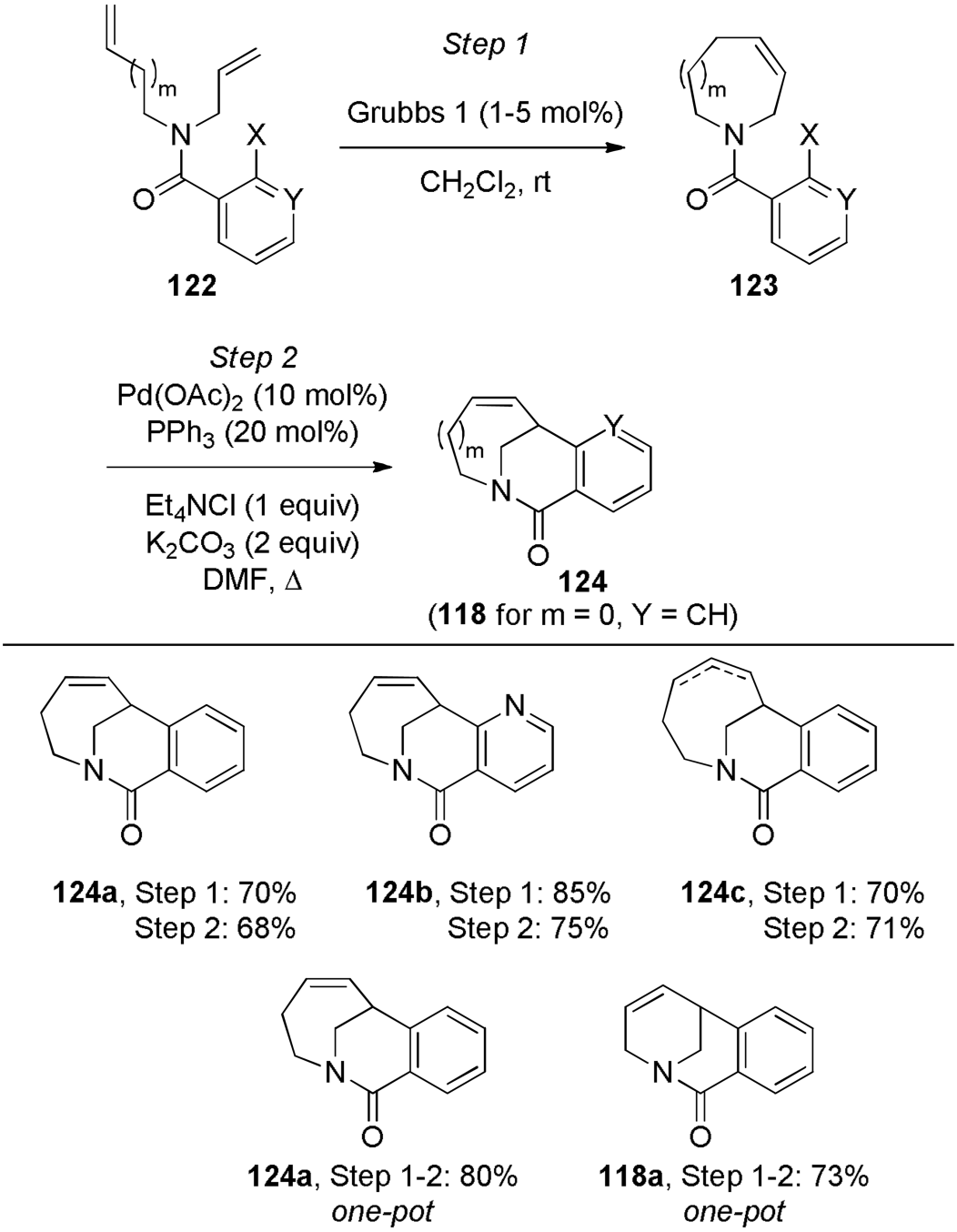
a) Synthesis of Aza-Bridged Lactams by Denzer and Ott; b) Synthesis of Bridged Lactam Precursors via Dearomatization of Quinazolines



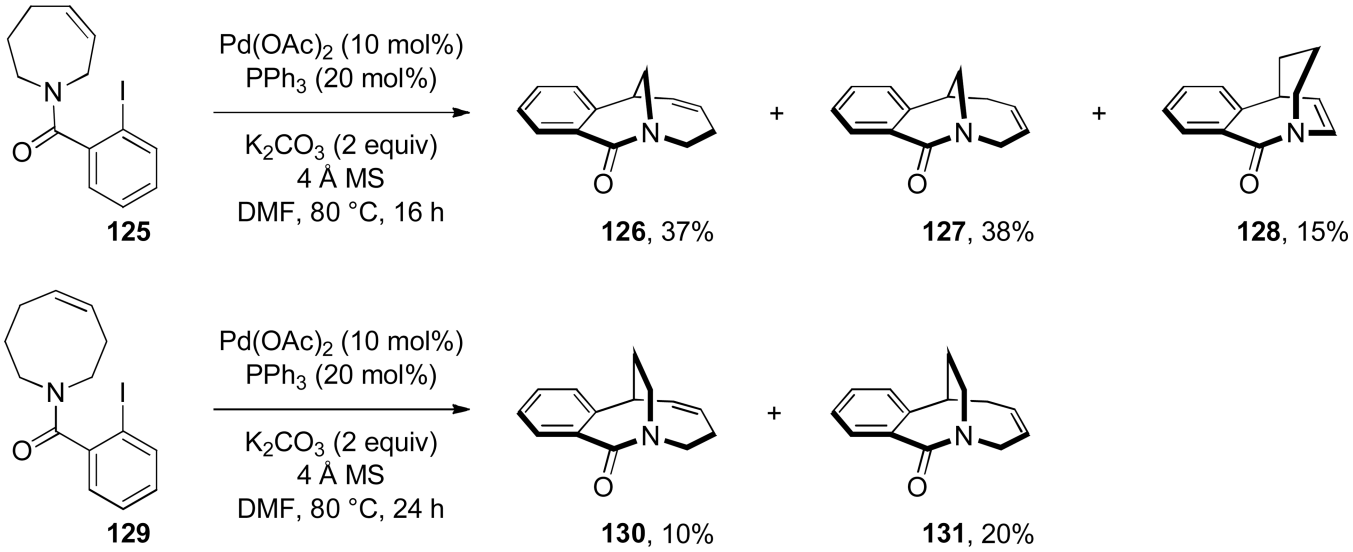
Scheme 28.
Synthesis of Bridged Lactams via Heck Reaction by Grigg



Scheme 29.
Unsuccessful Synthesis of 1-Azabicyclo[3.2.1]oct-3-en-7-one via Heck Reaction by Grigg

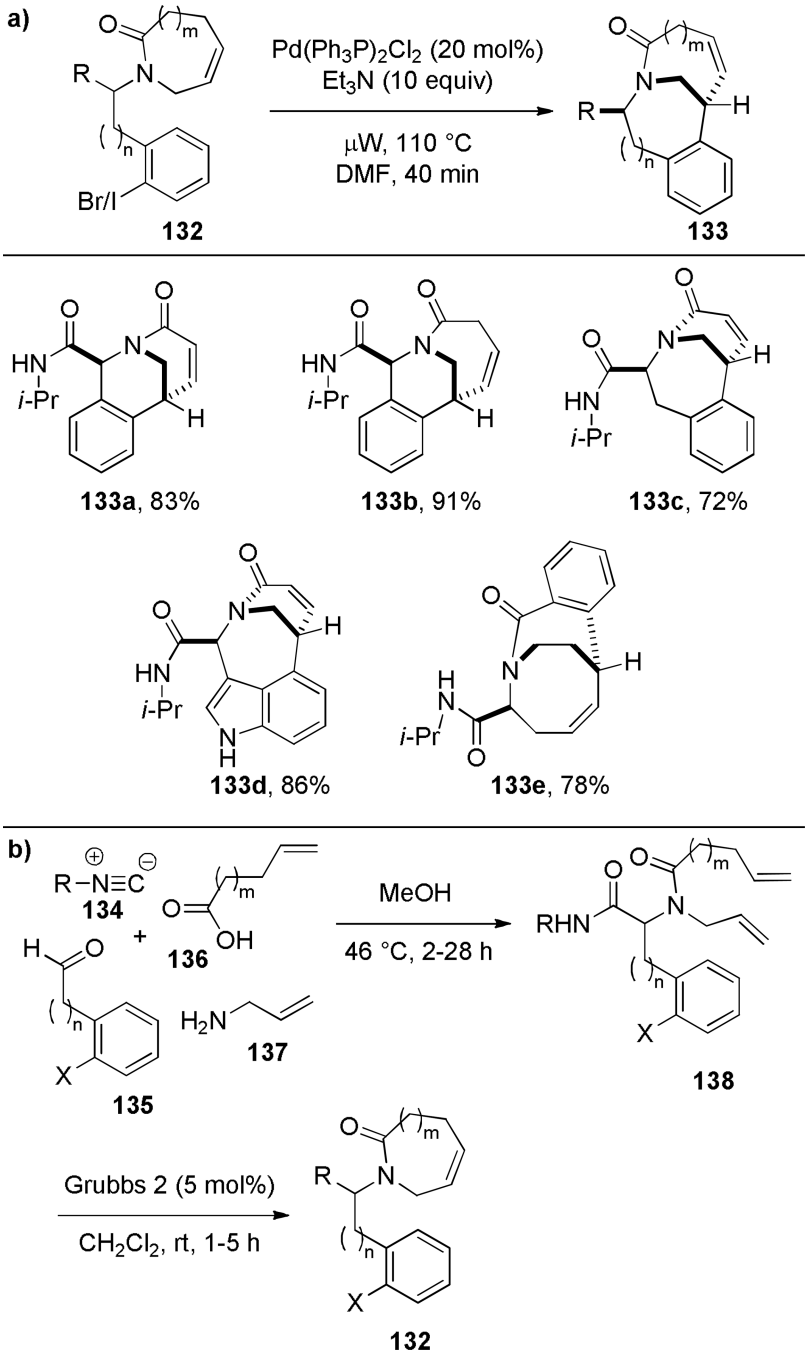


Scheme 30.
Synthesis of Bridged Lactams via Tandem RCM-Heck Reaction by Grigg



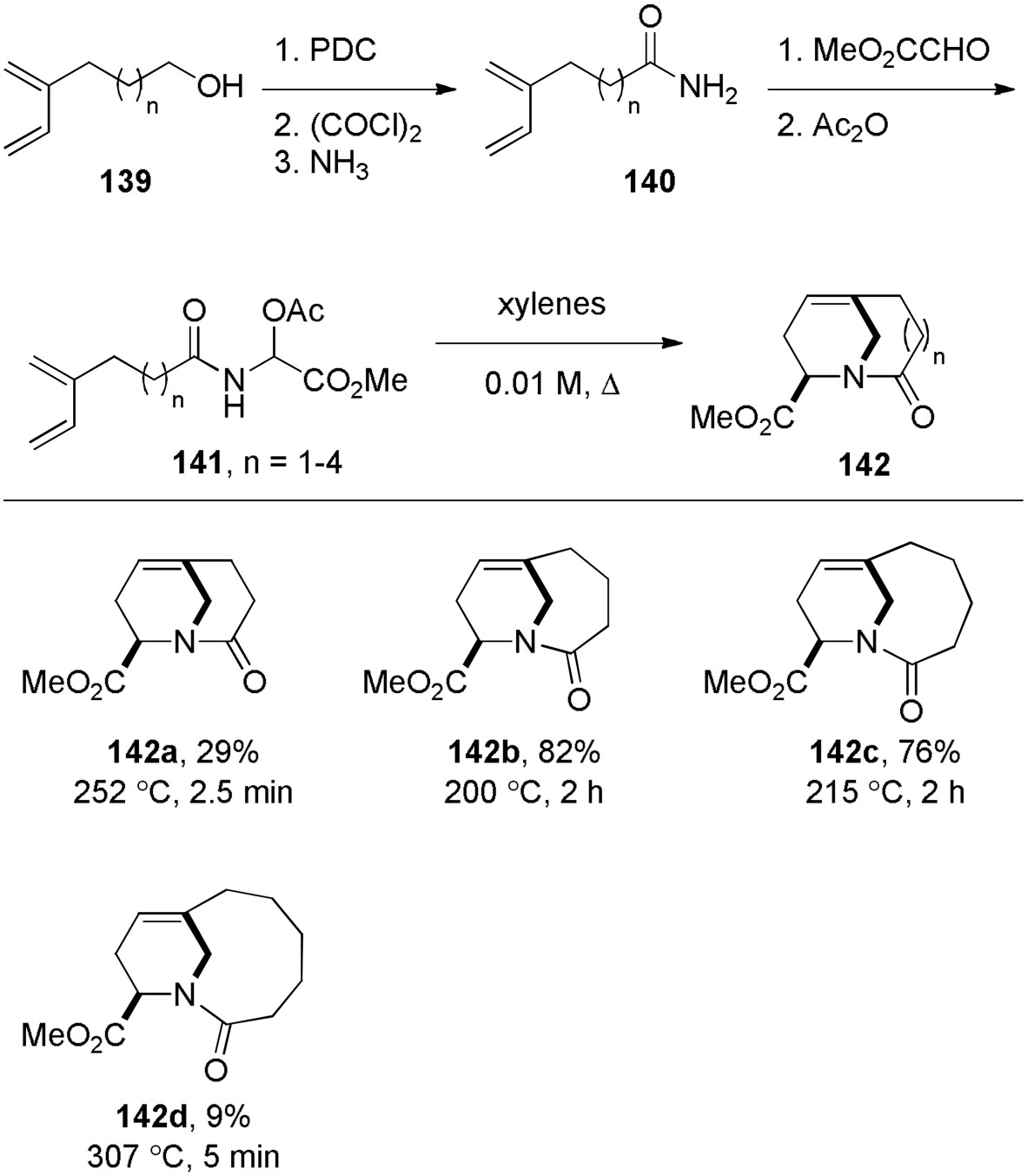
Scheme 31.

Synthesis of Bridged Lactams via Heck Reaction by Paquette (please use double-column format for Scheme 31)



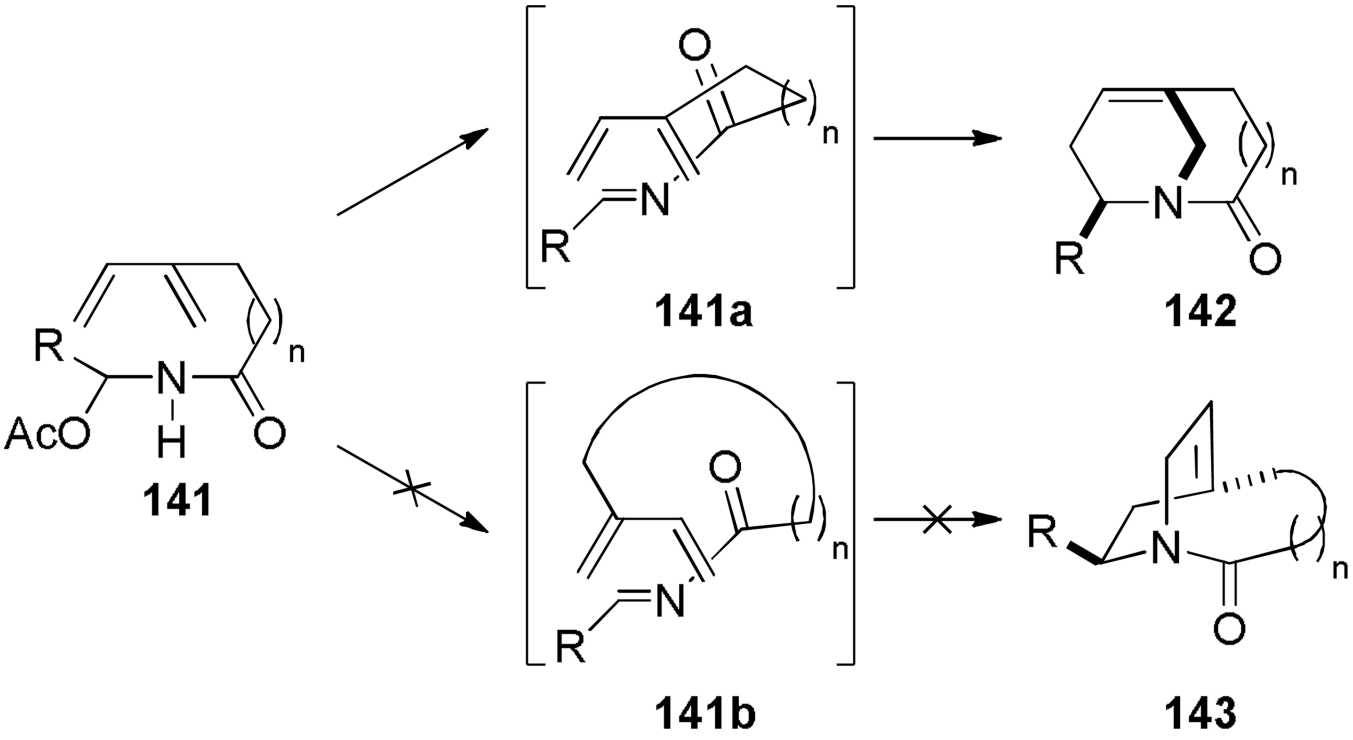
Scheme 32.

a) Synthesis of Bridged Lactams via Heck Reactionby Ribelin; b) Synthesis of Bridged Lactam Precursors via Tandem Ugi-RCM Reaction

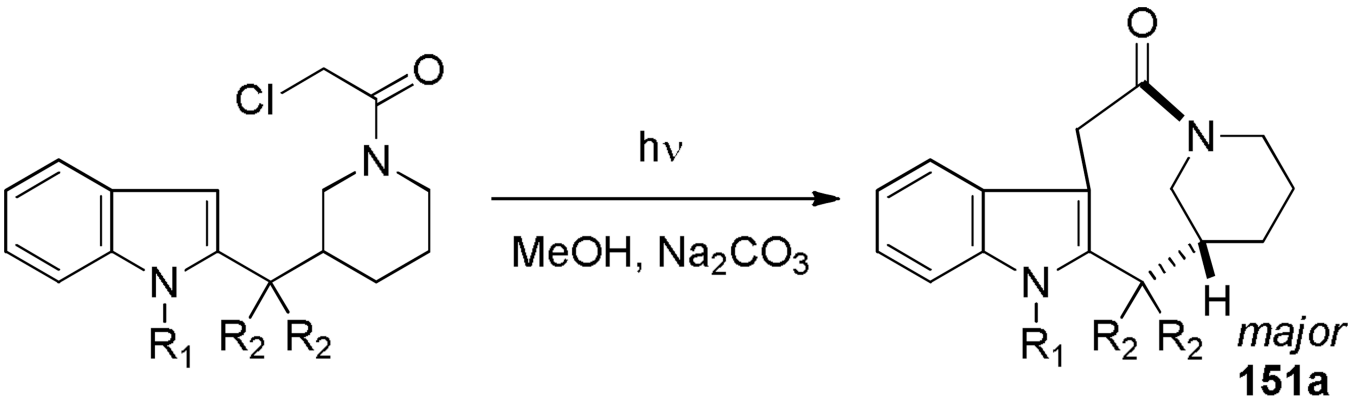


Scheme 33.

Synthesis of Bridged Lactams via Type II Acyl Imino Diels-Alder Reaction by Shea



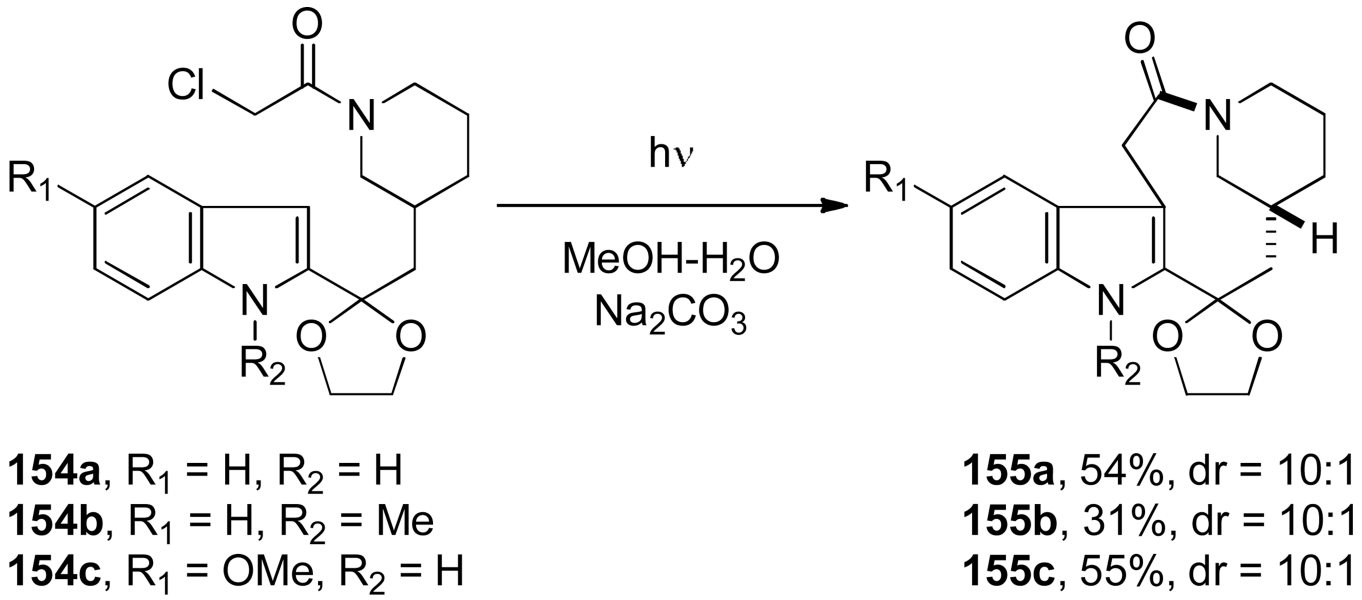
Scheme 34.
Proposed Mechanism for Diels-Alder Reaction of Acetoxyamides **141**



150a, R_1 = H, R_2 = -O(CH$_2$)$_2$O-
150b, R_1 = Me, R_2 = -O(CH$_2$)$_2$O-
150c, R_1 = H, R_2 = H
150d, R_1 = Me, R_2 = H

151a, 44%, dr = 4:1
151b, 28%, dr = 1:5
151c, 30%, dr = 1:2
151d, 22%, dr = 1:2

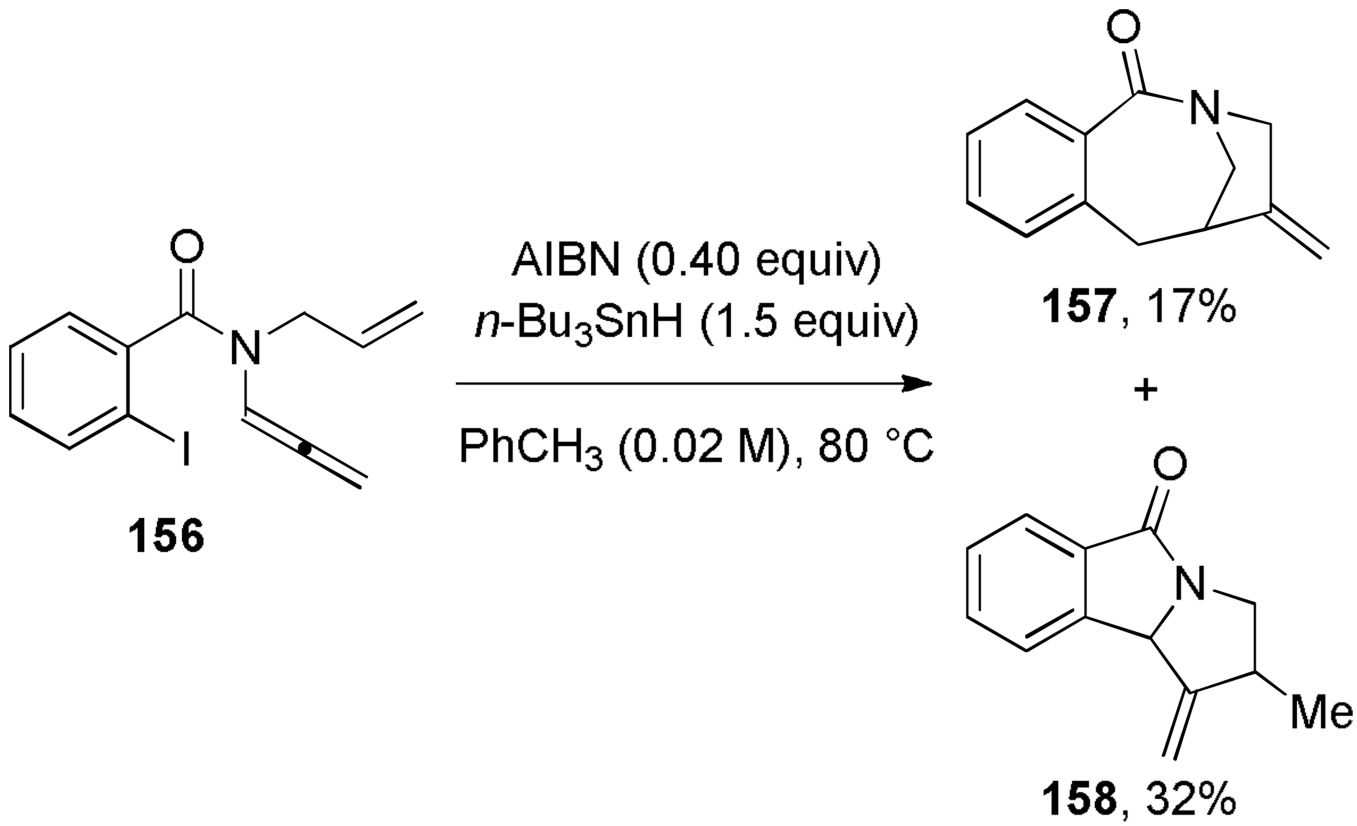
Scheme 35.
Synthesis of Indole-1-azabicyclo[5.3.1]undecan-2-onesvia Witkop Photocyclization by Sundberg



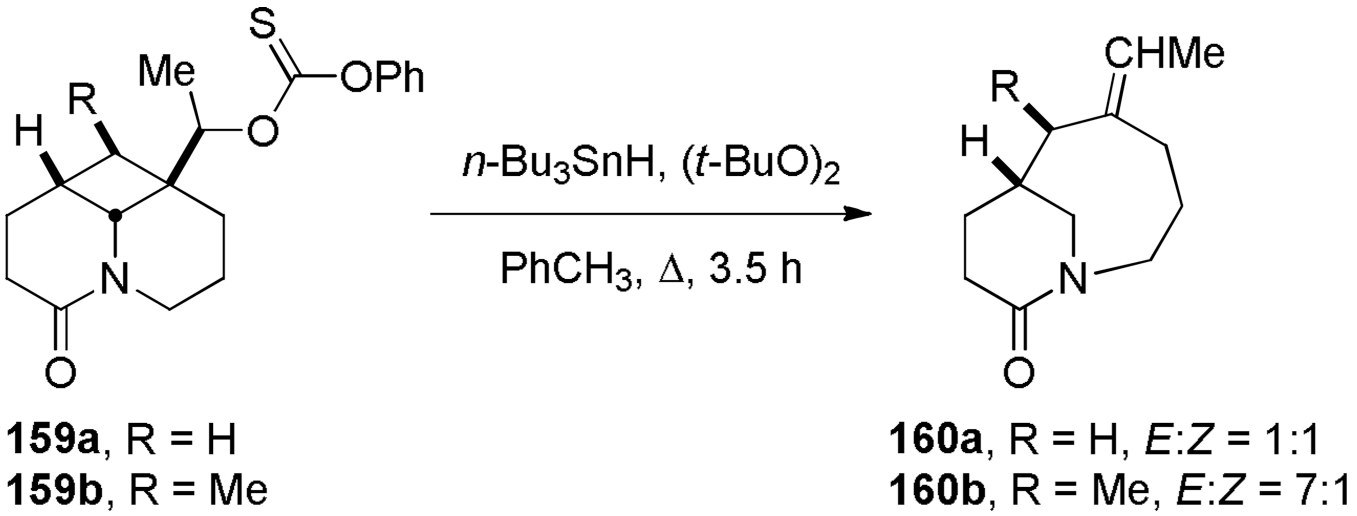
154a, R_1 = H, R_2 = H
154b, R_1 = H, R_2 = Me
154c, R_1 = OMe, R_2 = H

155a, 54%, dr = 10:1
155b, 31%, dr = 10:1
155c, 55%, dr = 10:1

Scheme 36.
Synthesis of Indole-1-azabicyclo[6.3.1]dodecan-2-ones via Witkop Photocyclization by Sundberg



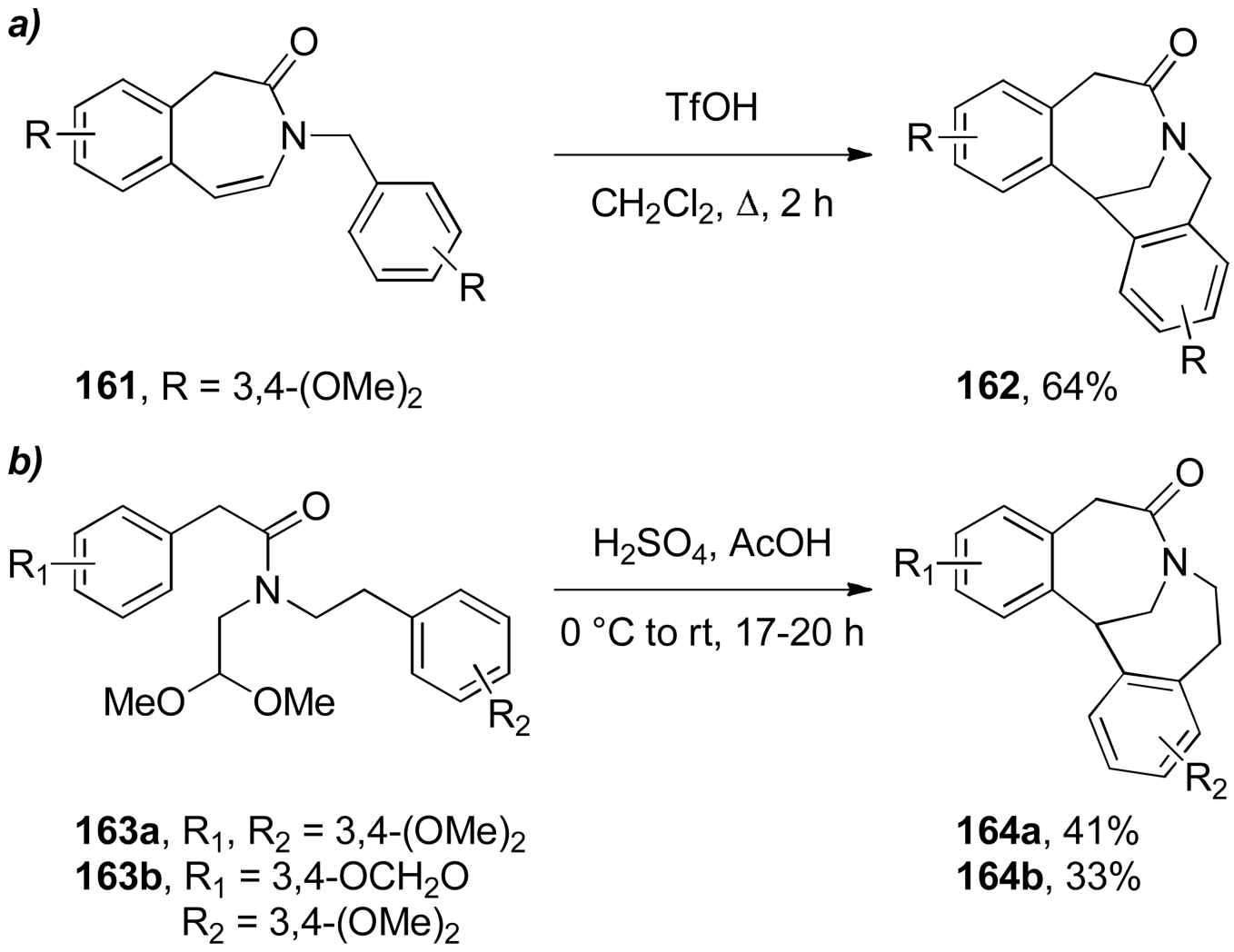
Scheme 37.
Synthesis of Benzo-1-azabicyclo[4.2.1]nonan-2-one via Radical Cyclization by Hsung



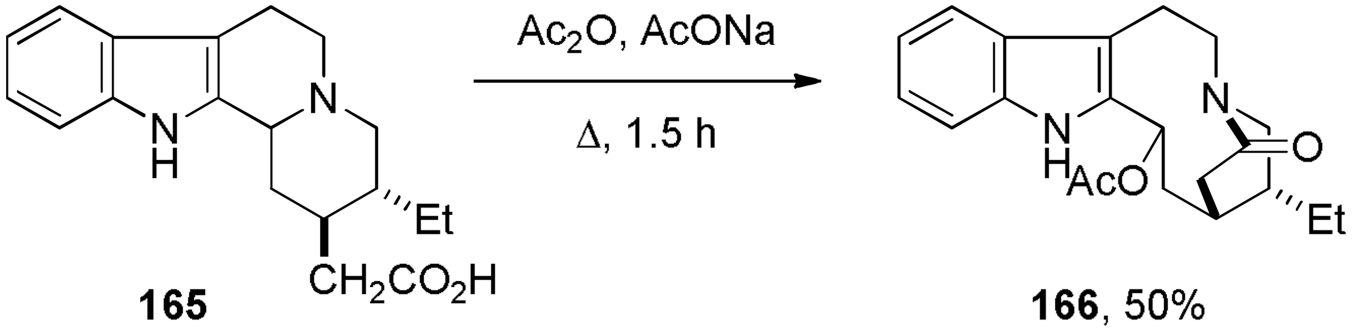
159a, R = H
159b, R = Me

160a, R = H, *E*:*Z* = 1:1
160b, R = Me, *E*:*Z* = 7:1

Scheme 38.
Synthesis of 1-Azabicyclo[5.3.1]undecan-10-ones via Radical Fragmentation by Beckwith

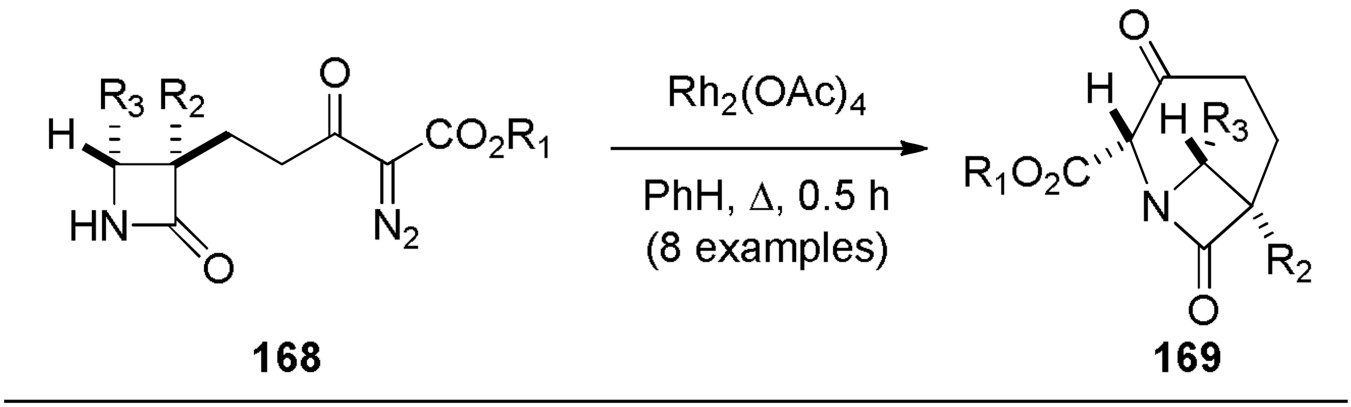


Scheme 39.
Synthesis of Bridged Lactams via Friedel-Crafts Reaction by Ruchirawat

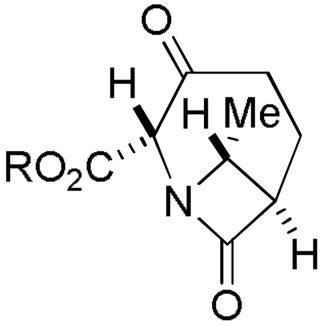


Scheme 40.

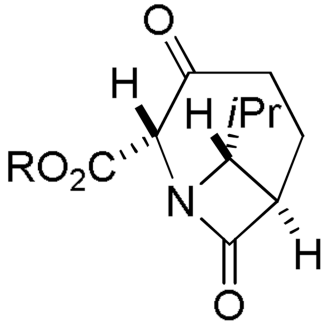
Synthesis of Indole-1-azabicyclo[6.2.2]dodecan-10-one via Fragmentation/Transannular Condensationby Dolby



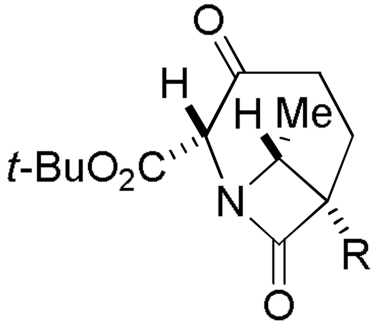
168 **169**



169a, R = *t*-Bu, 50%

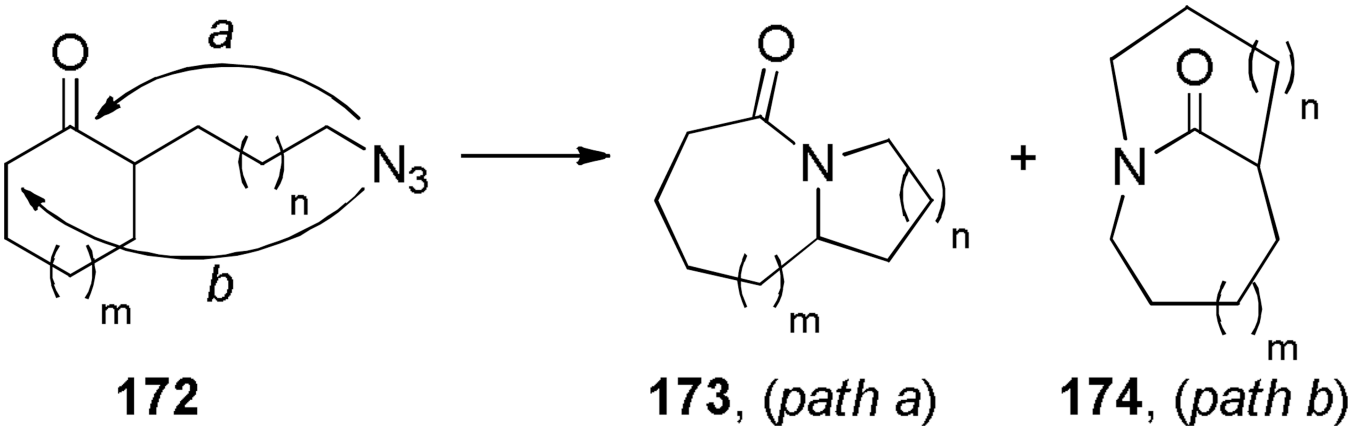


169b, R = *t*-Bu, 20-35%
169c, R = $(CH_2)_2TMS$
169d, R = *p*-NO_2Bn
169e, R = $CH(Ph)_2$

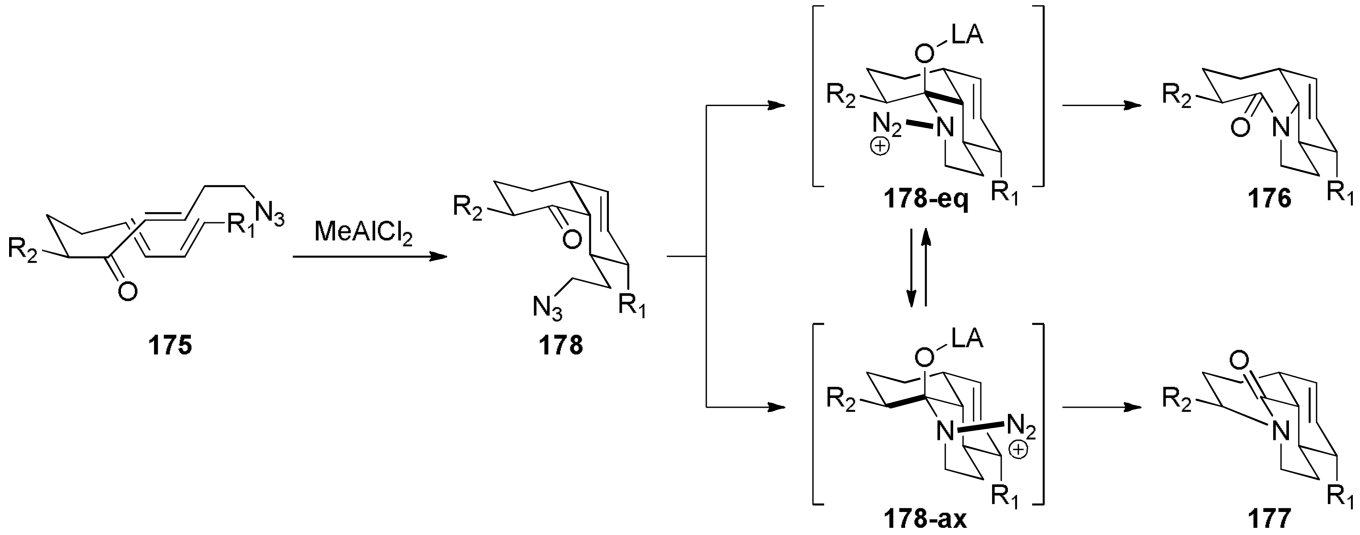


169f, R = Me, 70%
169g, R = $(CH_2)_2O$-4-Ph-C_6H_4, 50%
169h, R = $(CH_2)_2O$-2-(1,6-Br_2-$C_{10}H_5$), 70%

Scheme 41.
Synthesis of 1-Azabicyclo[4.1.1]octan-7-onesvia Rh-Catalyzed N–H Insertion by Williams

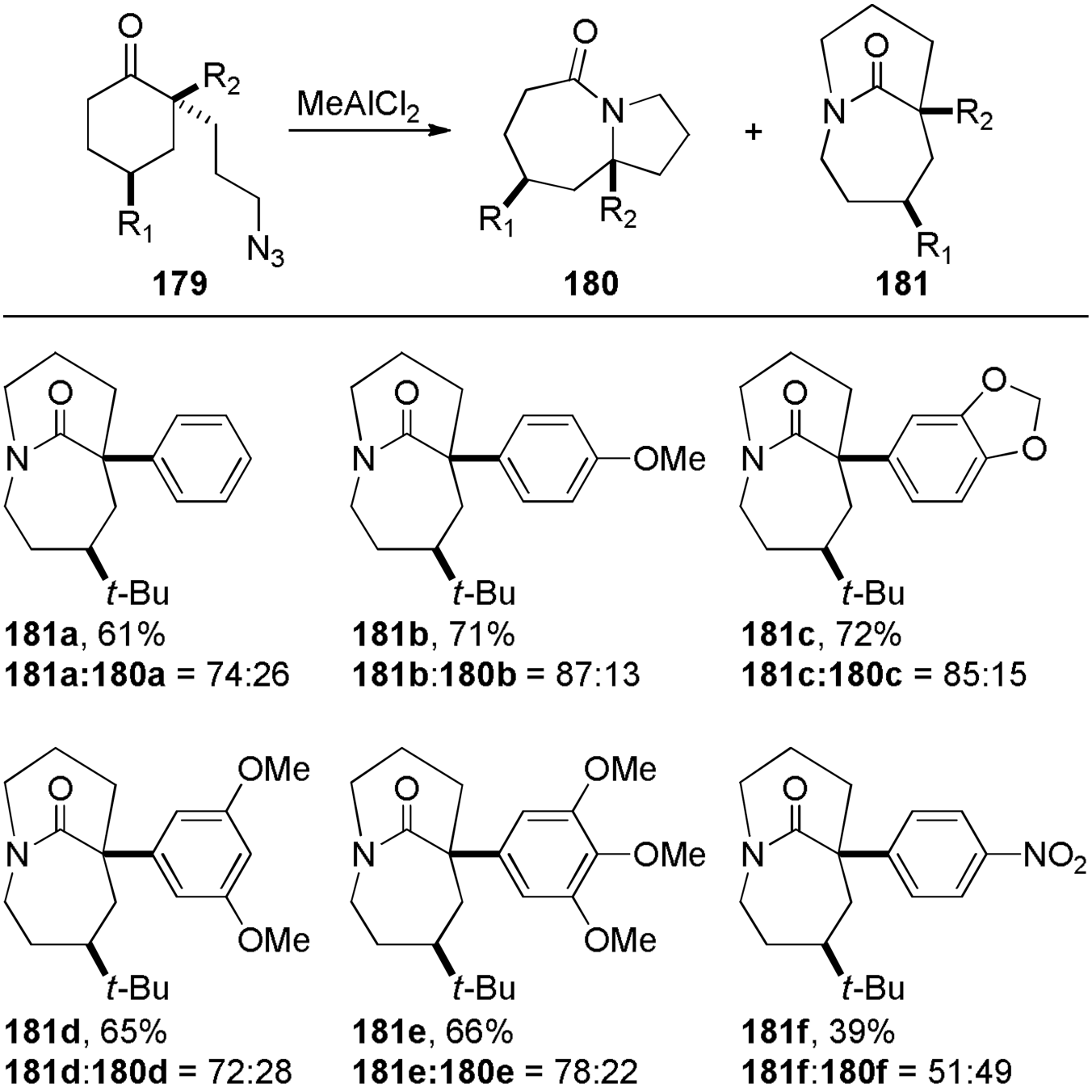


Scheme 42.
Regiochemical Options in the Intramolecular Schmidt Reaction of 2-Alkylazido Ketones

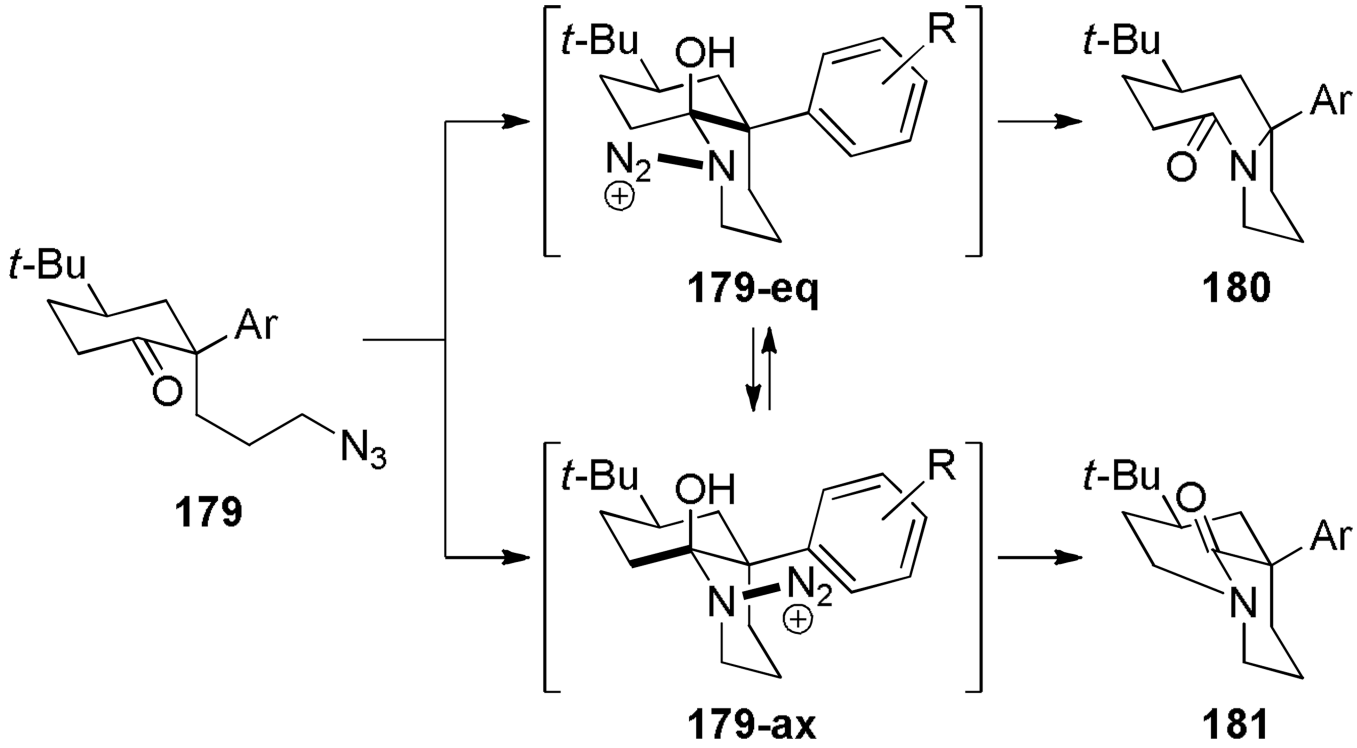


Scheme 43.

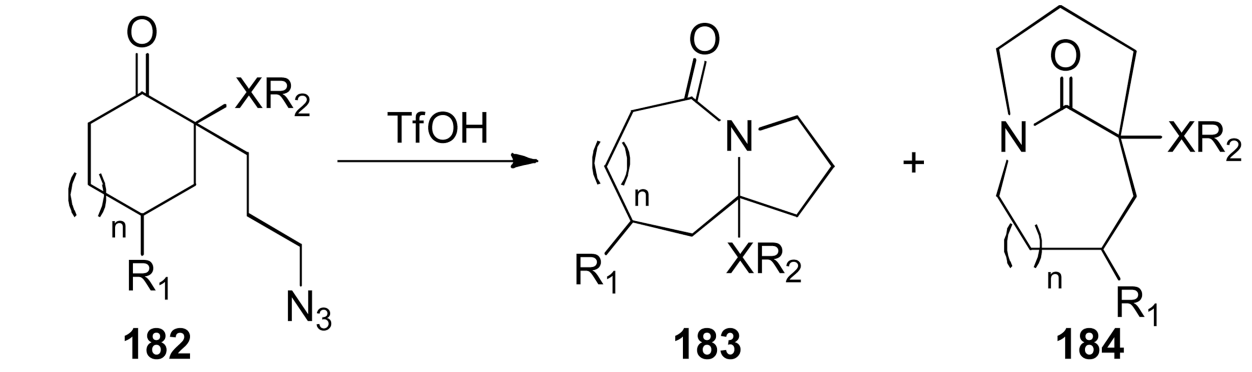
Proposed Mechanism for Domino Diels-Alder/Schmidt Reaction of Keto-Azidotrienes **175** (please use double-column format for Scheme 43)



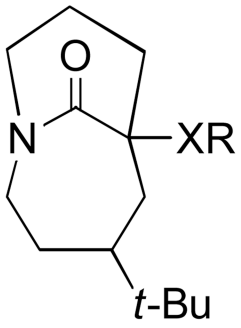
Scheme 44.
Synthesis of Bridged Lactams via Cation-π-Directed Schmidt Reaction by Aubé



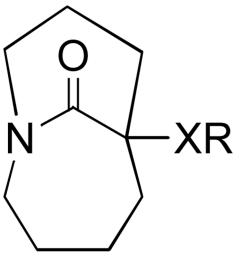
Scheme 45.
Proposed Mechanism for Schmidt Reaction of 2-Aryl-2-Alkylazido Ketones **179**



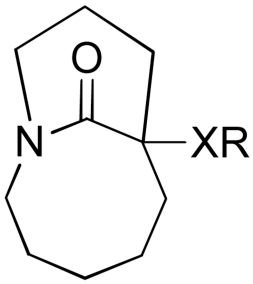
182 **183** **184**



184a, XR = SMe, cis, 64%
184b, XR = SMe, trans, 0%

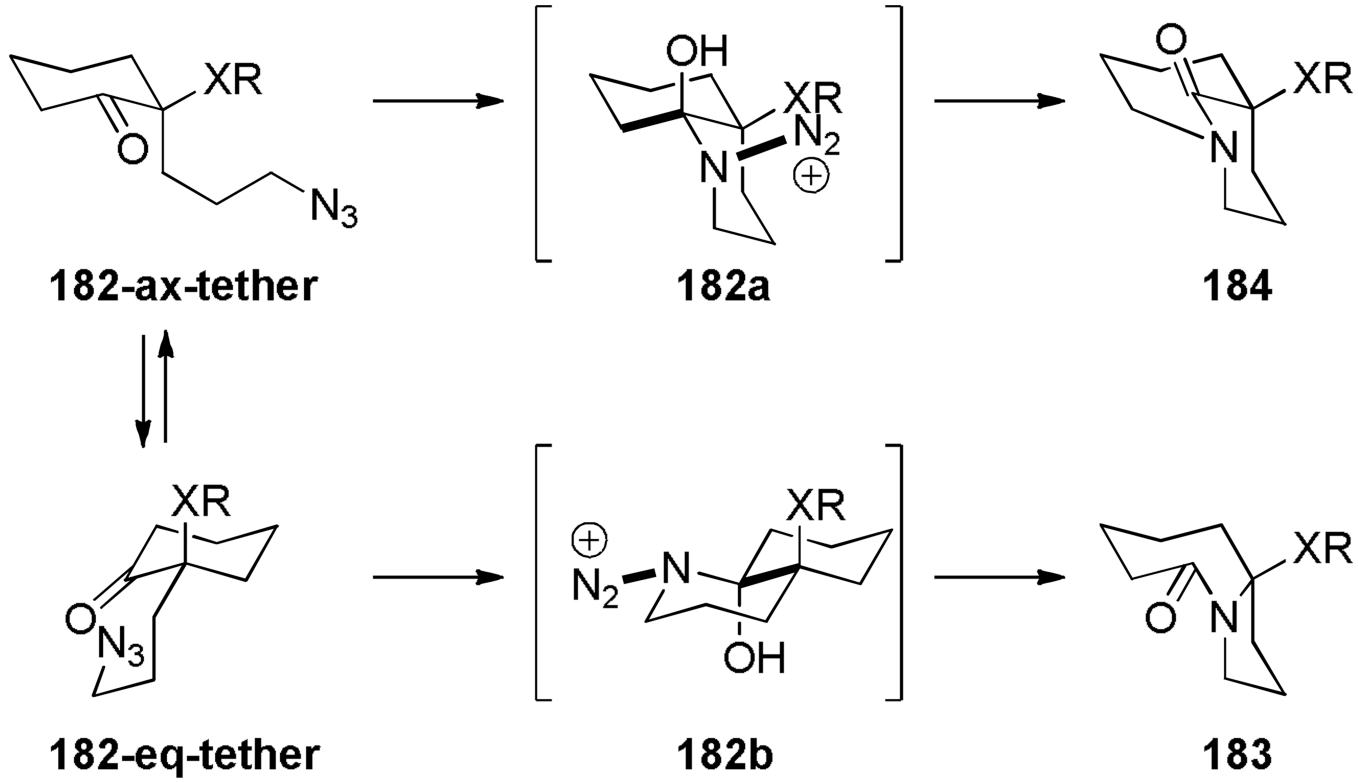


184c, XR = SMe, 65%
184d, XR = SPh, 35%
184e, XR = OMe, 23%
184f, XR = SO_2Me, 48%

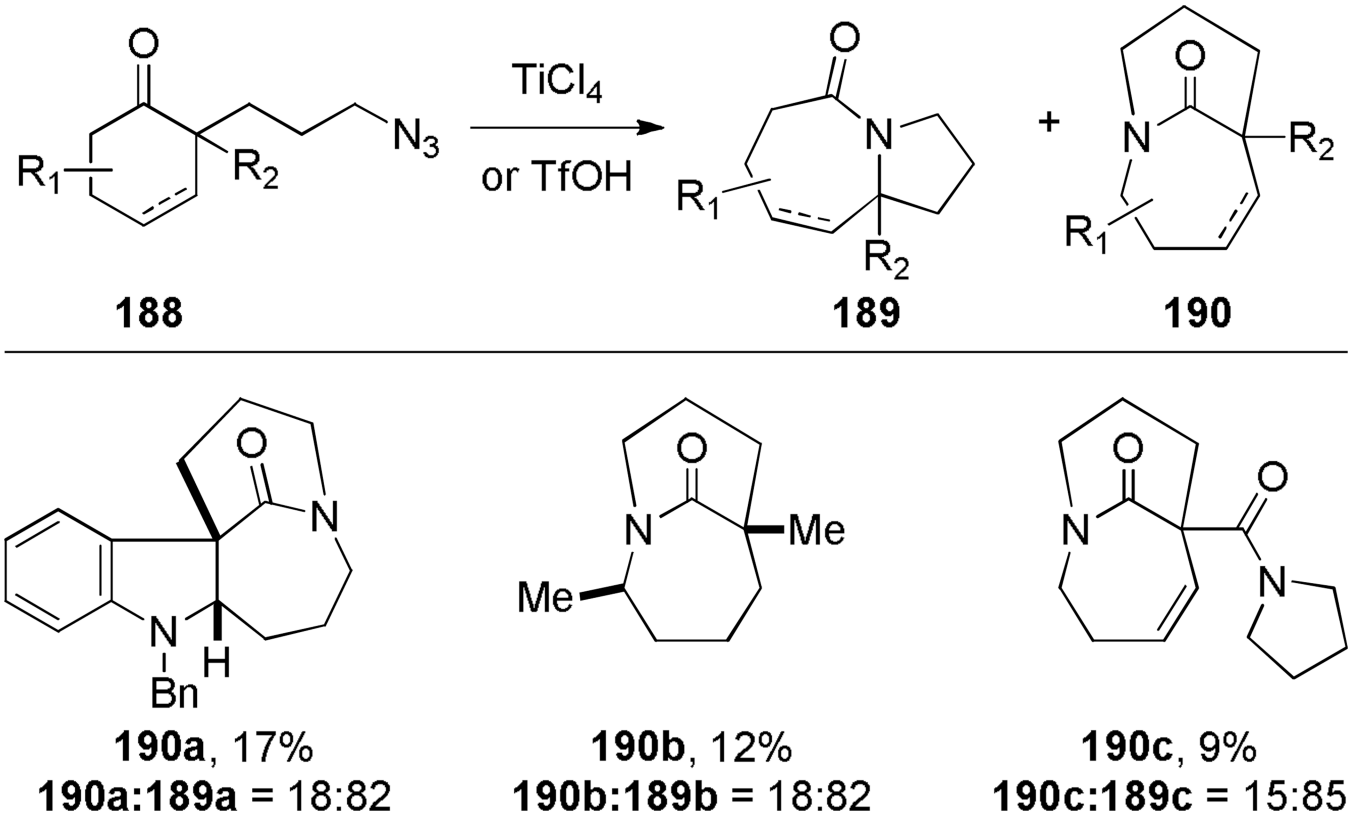


184g, XR = SMe, 62%

Scheme 46.
Synthesis of Bridged Lactams via Cation–*n* Directed Schmidt Reaction by Aubé

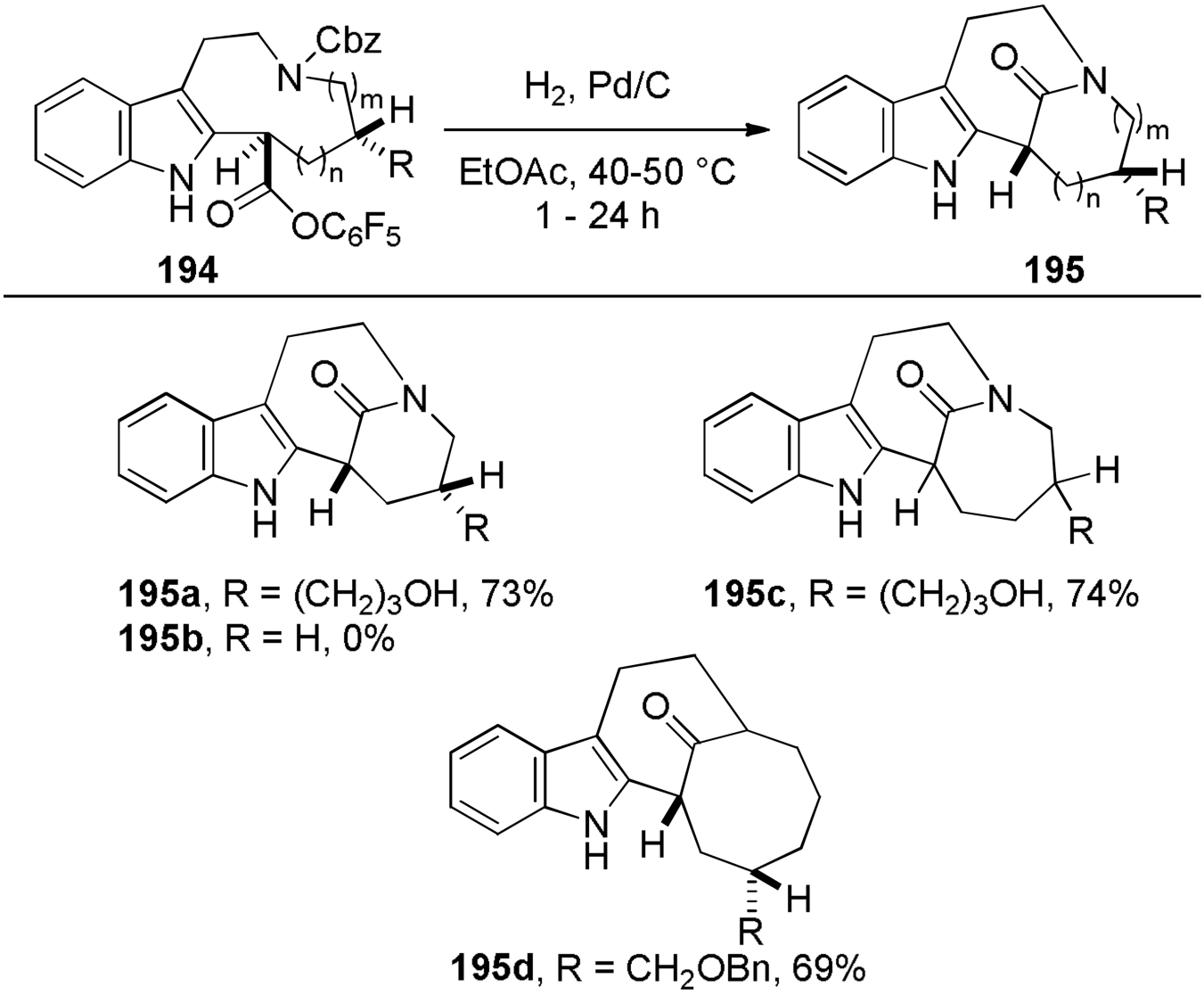


Scheme 47.
Proposed Mechanism for Schmidt Reaction of 2-Alkylazido Ketones **182**



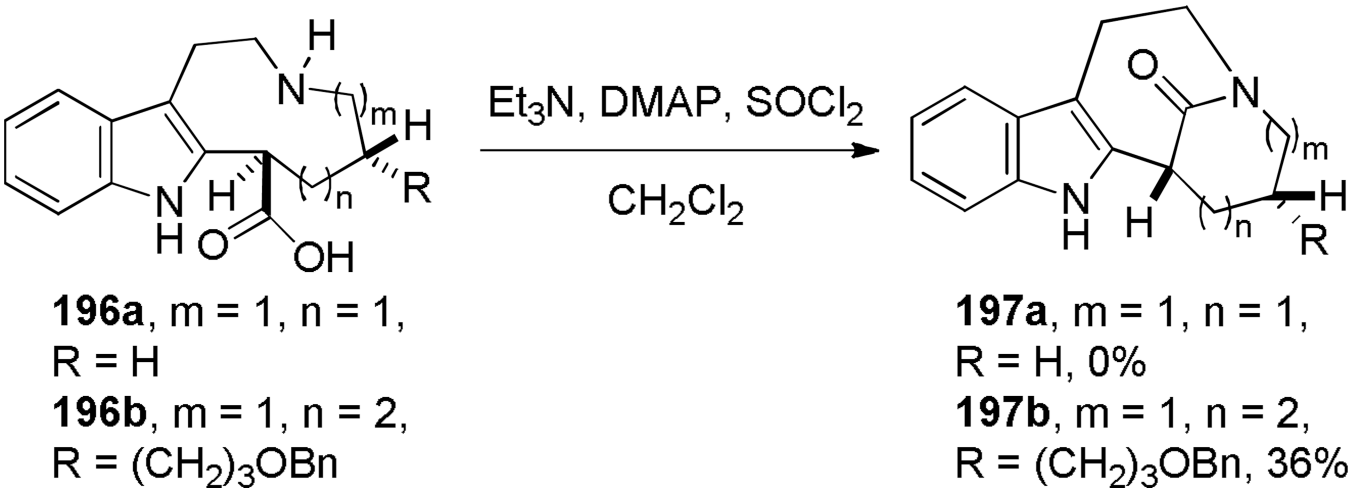
Scheme 48.

Other Examples of Bridged Lactams Synthesized via Intramolecular Schmidt Reaction

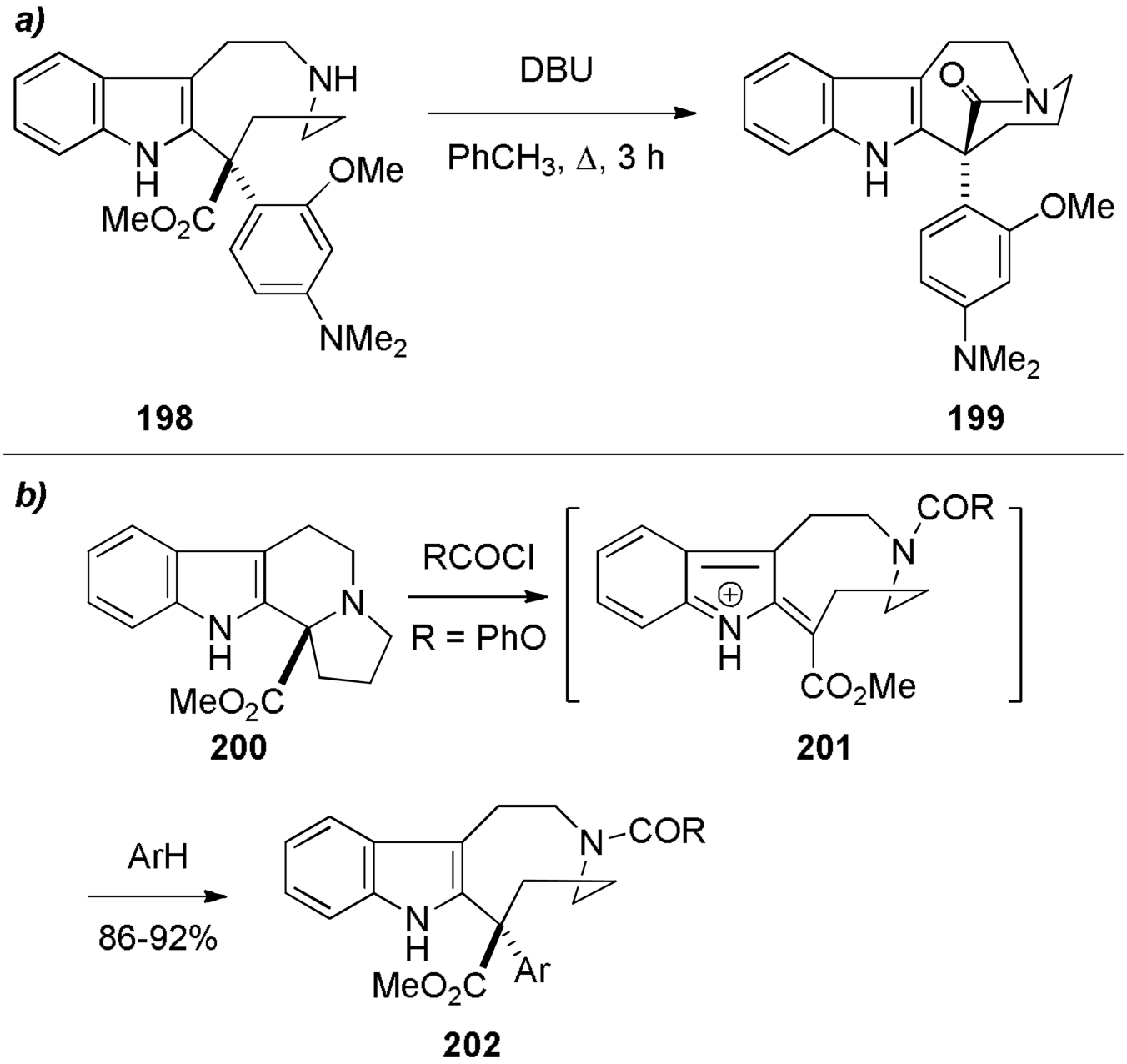


Scheme 49.

Synthesis of Indole-Derived Bridged Lactams via Transannular Amidation by Schill

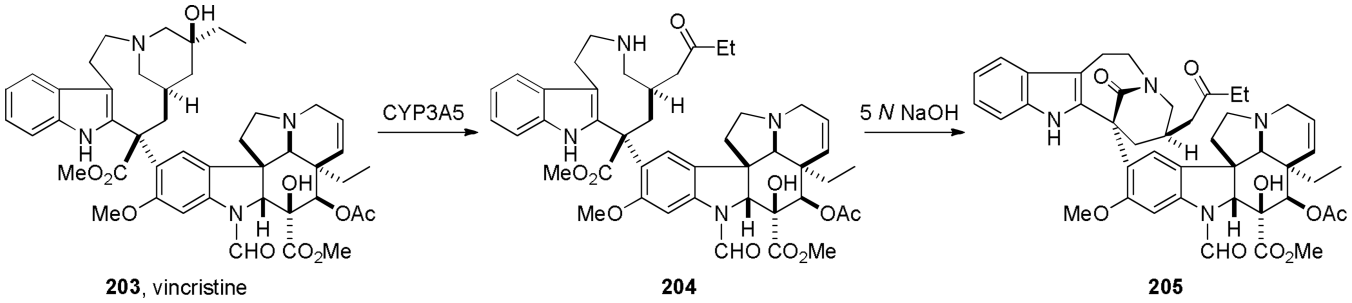


Scheme 50.
Synthesis of Indole-Derived Bridged Lactams via Transannular Amide Coupling by Schill



Scheme 51.

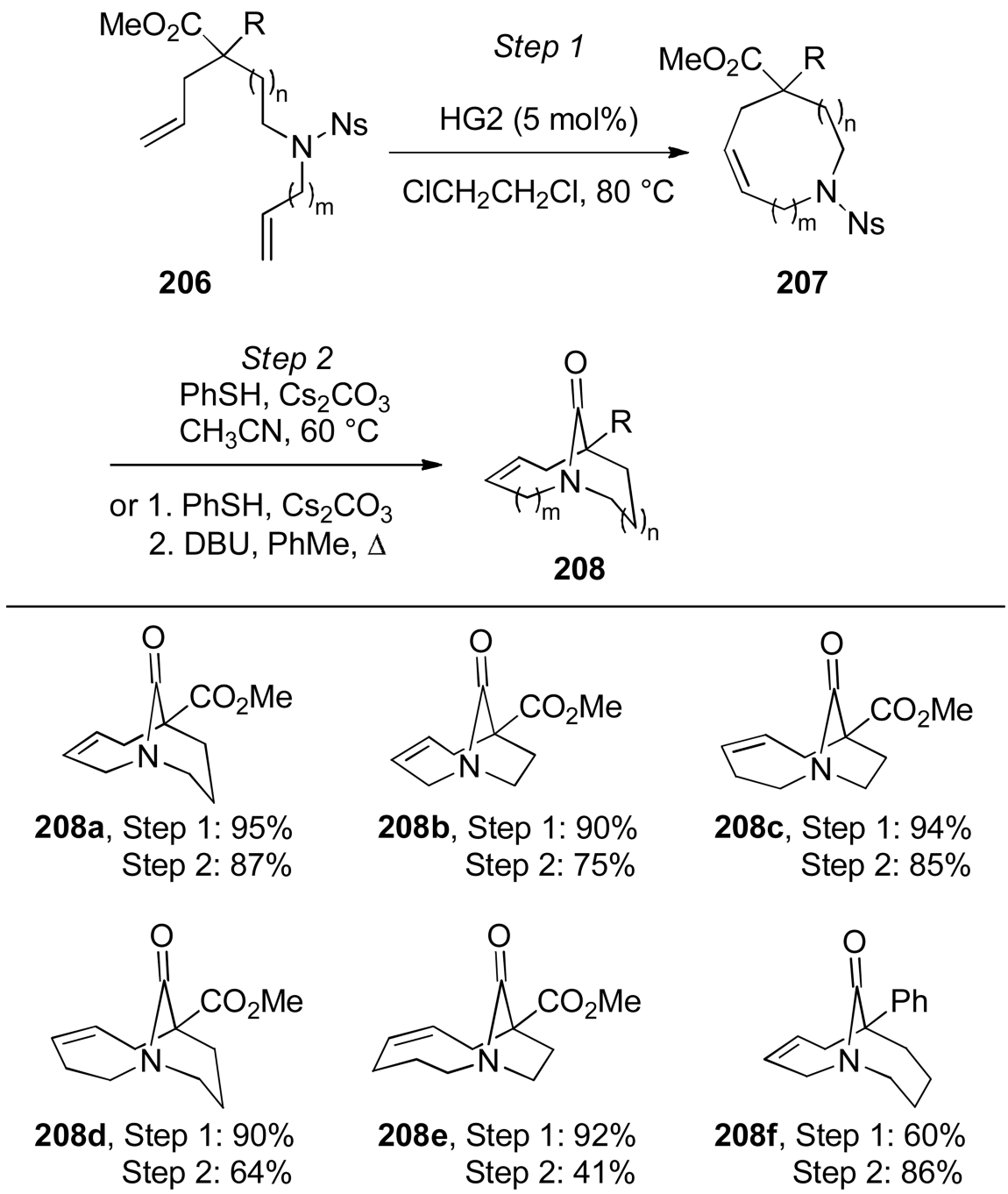
a) Synthesis of 6-Phenyl-1-azabicyclo[4.3.1]decan-10-one by Magnus; b) Synthesis of Nine-Membered Ring Precursor



203, vincristine **204** **205**

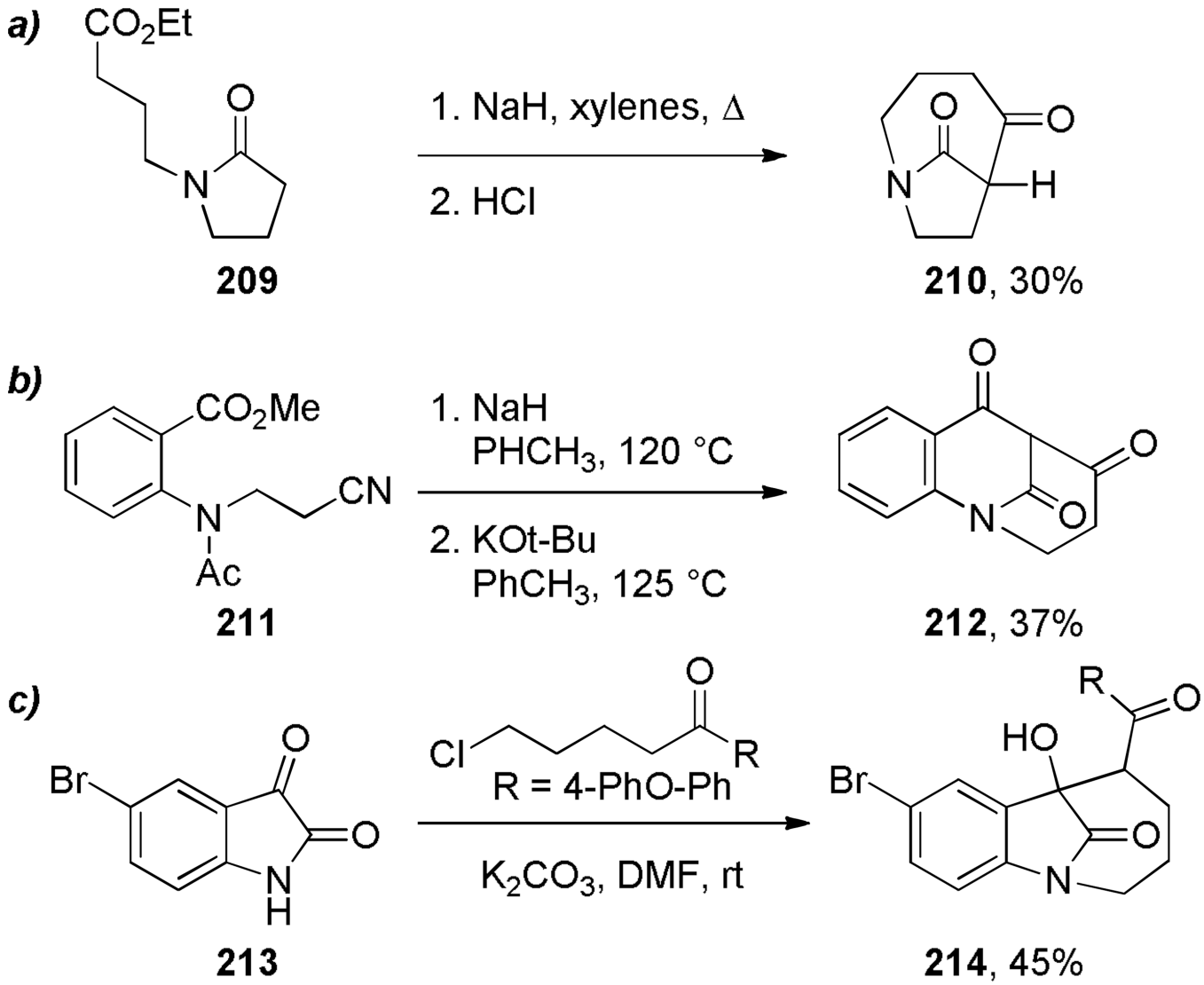
Scheme 52.

Synthesis of Bridged Lactam from Vincristine Metabolite by Dennison (please use double-column format for Scheme 52)



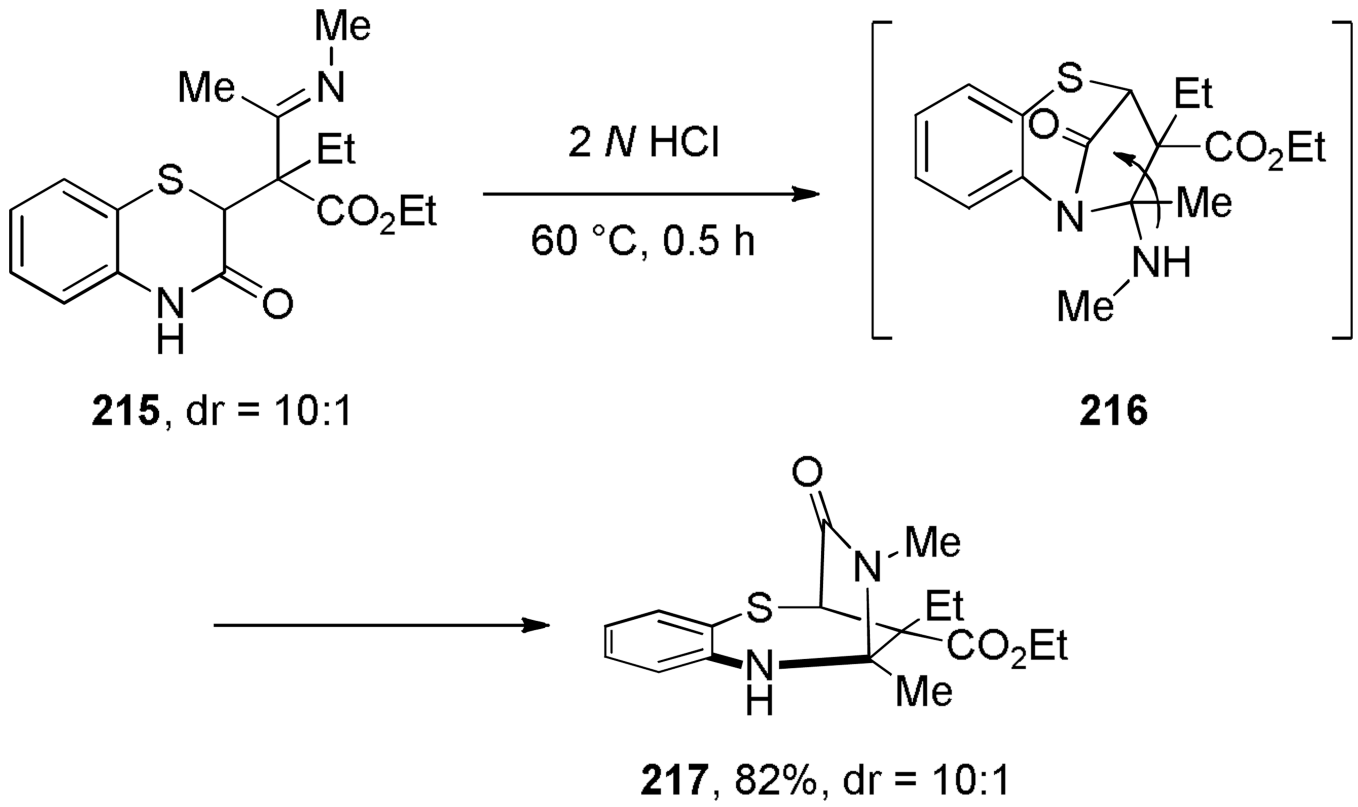
Scheme 53.

Synthesis of One-Carbon Bridged Lactamsvia Tandem RCM/Transannular Amidation by Aubé

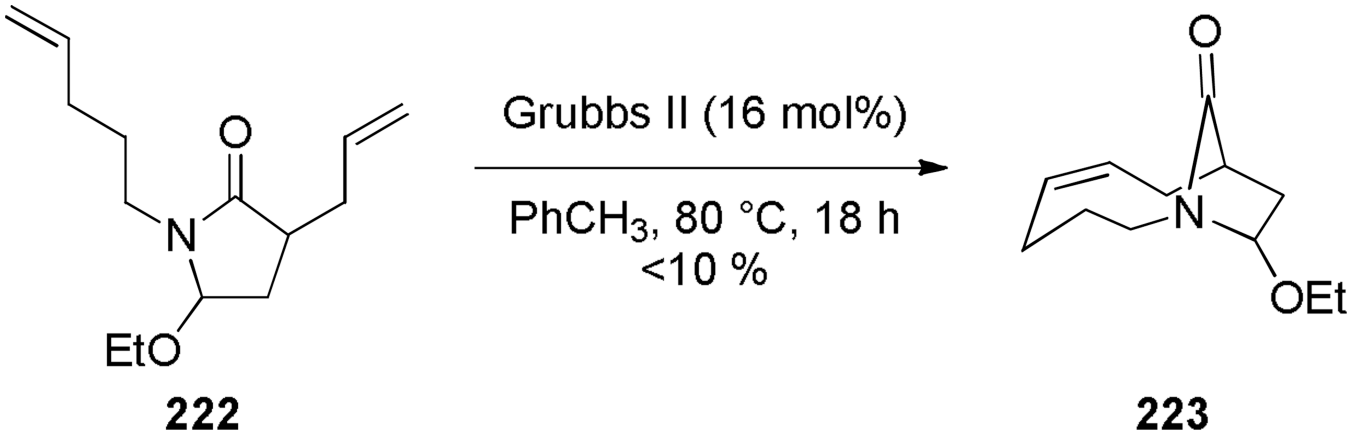


Scheme 54.

Other Examples of Synthesis of One-Carbon Bridged Lactams via Condensation Reactions: a) 1-Azabicyclo[4.2.1]nonane-5,9-dione by Arata; b) 1-Azabicyclo[3.3.1]nonane-4,6,9-trione by Waly; c) 1-Azabicyclo[4.2.1]nonan-9-one by Smet

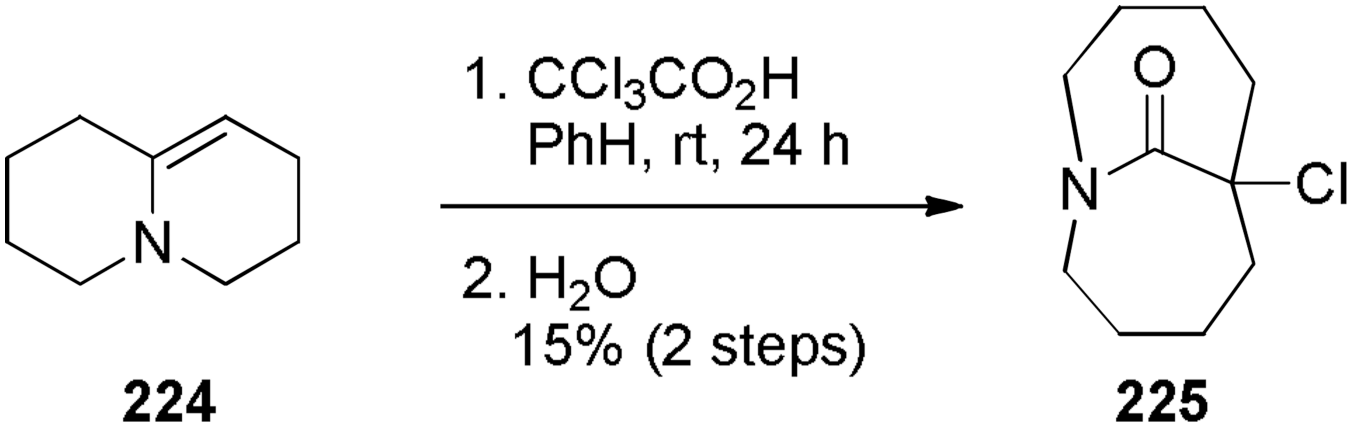


Scheme 55.
Synthesis of Benzo-4-thia-1-azabicyclo[3.2.1]octan-8-one **216** by Nazarenko



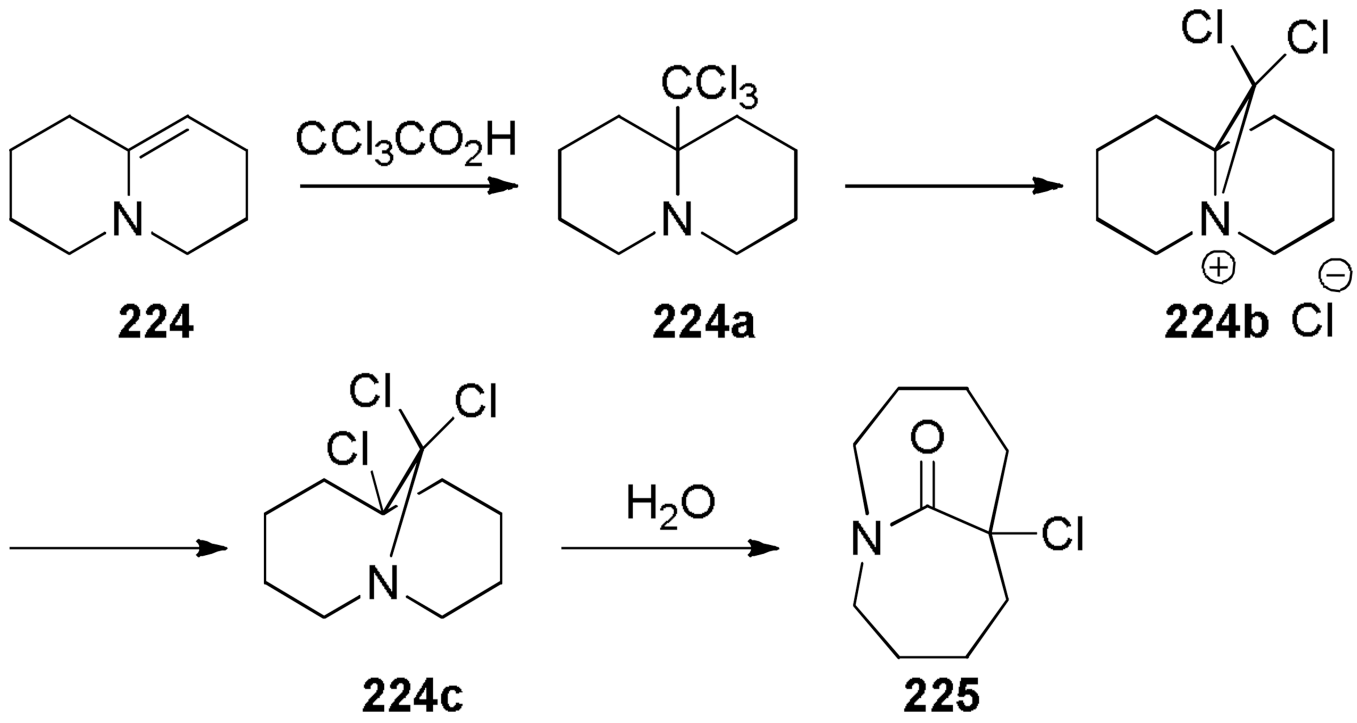
222 223

Scheme 56.
Synthesis of 1-Azabicyclo[6.2.1]undecan-11-one via RCM by Doodeman and Hiemstra

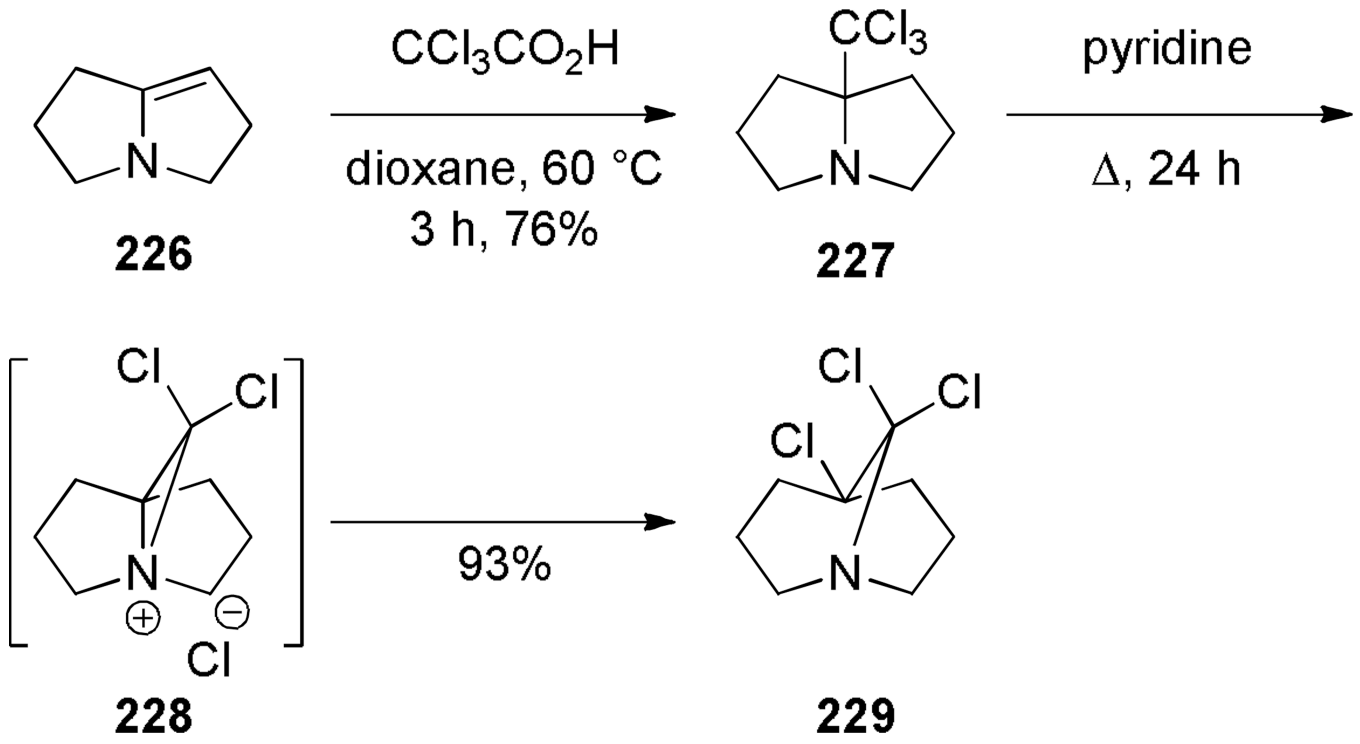


224 **225**

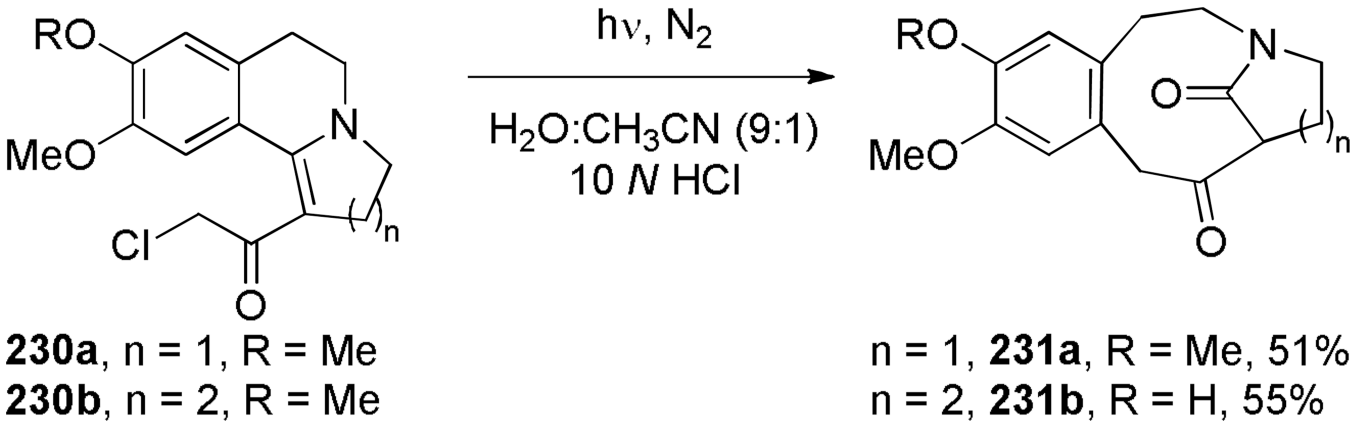
Scheme 57.
Synthesis of Chloro-Substituted Bridged Lactam via Aziridinium Rearrangement by Arata



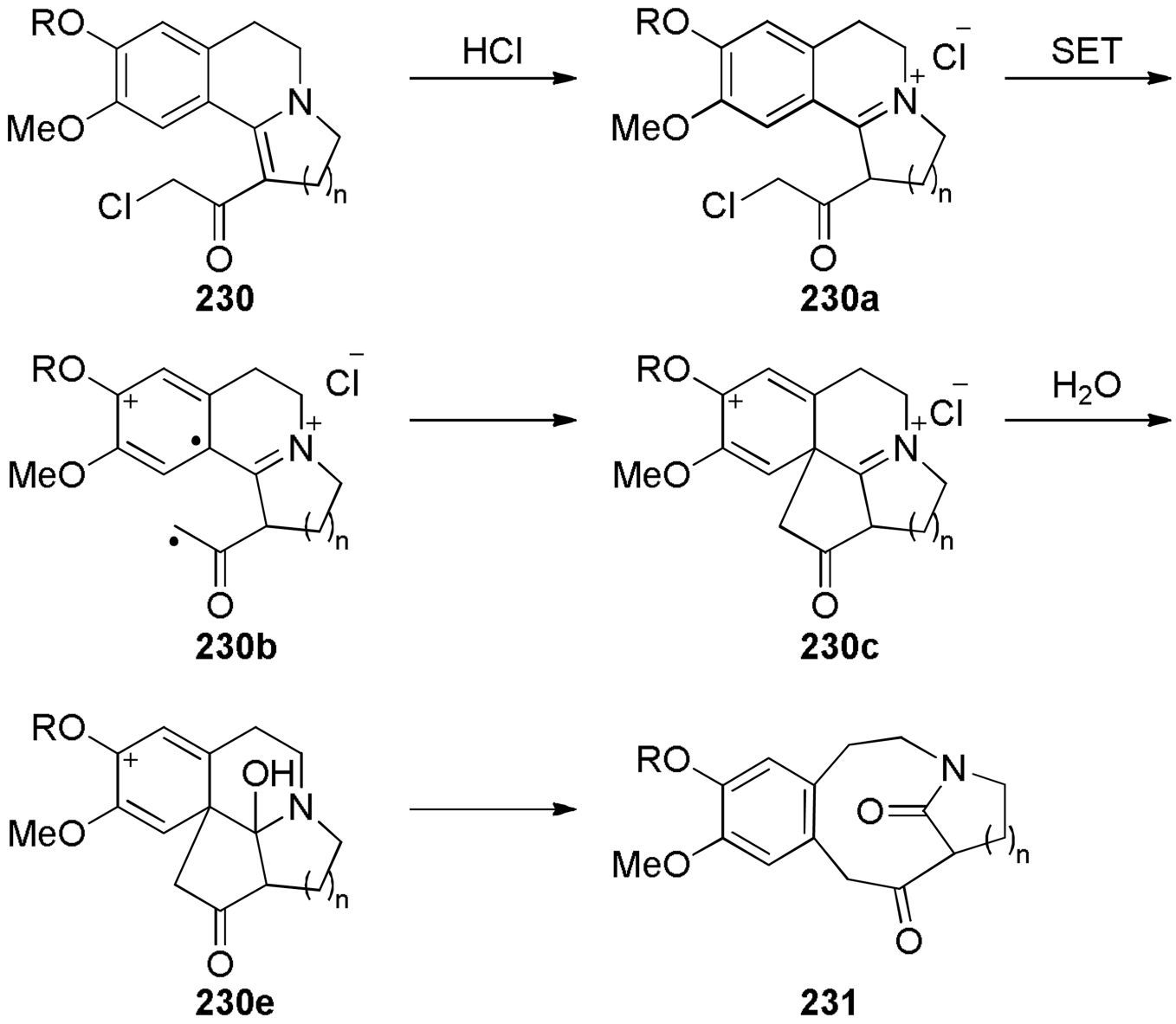
Scheme 58.
Proposed Mechanism for Rearrangement of **224**



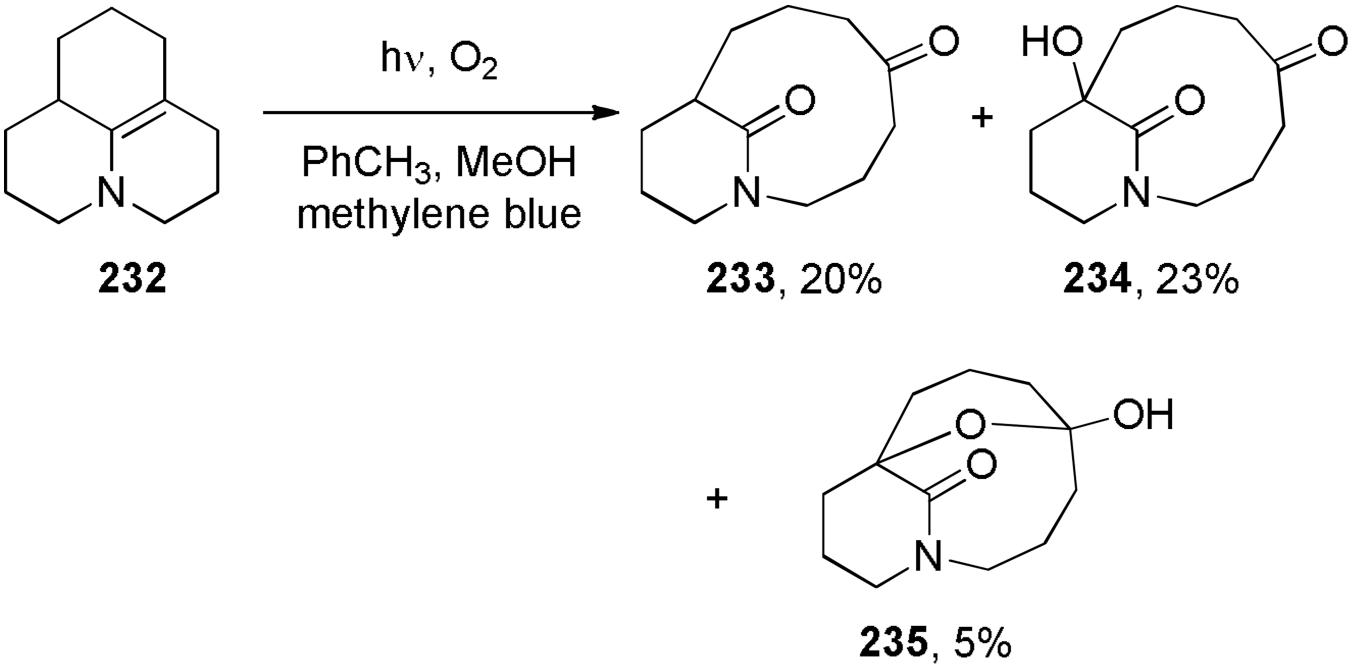
Scheme 59.
Synthesis of 5,9,9-Trichloro-1-azabicyclo[3.3.1]nonane by Miyano



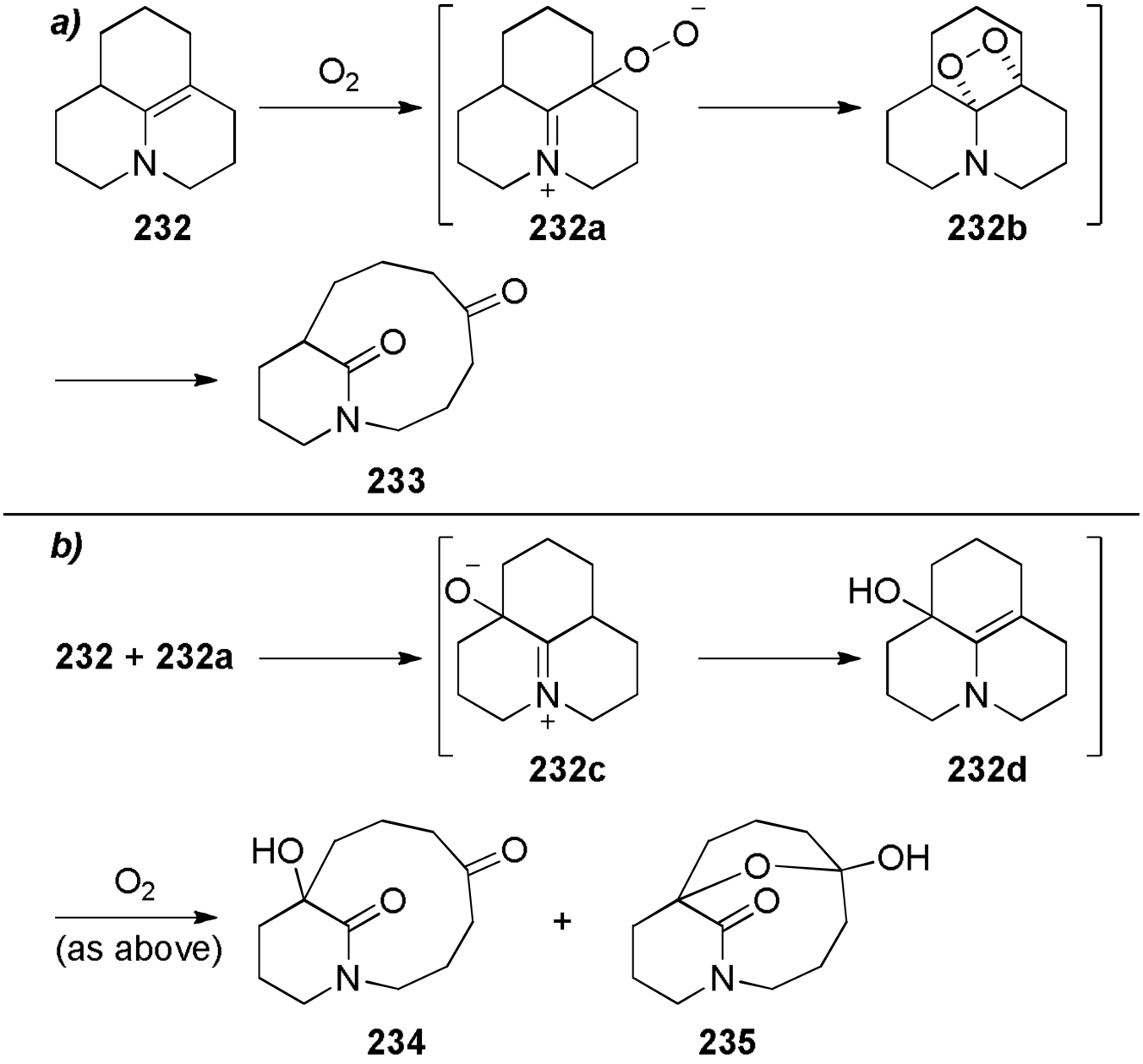
Scheme 60.
Synthesis of Bridged Lactams viaPhotolysis of Chloroacetamides by Bremner



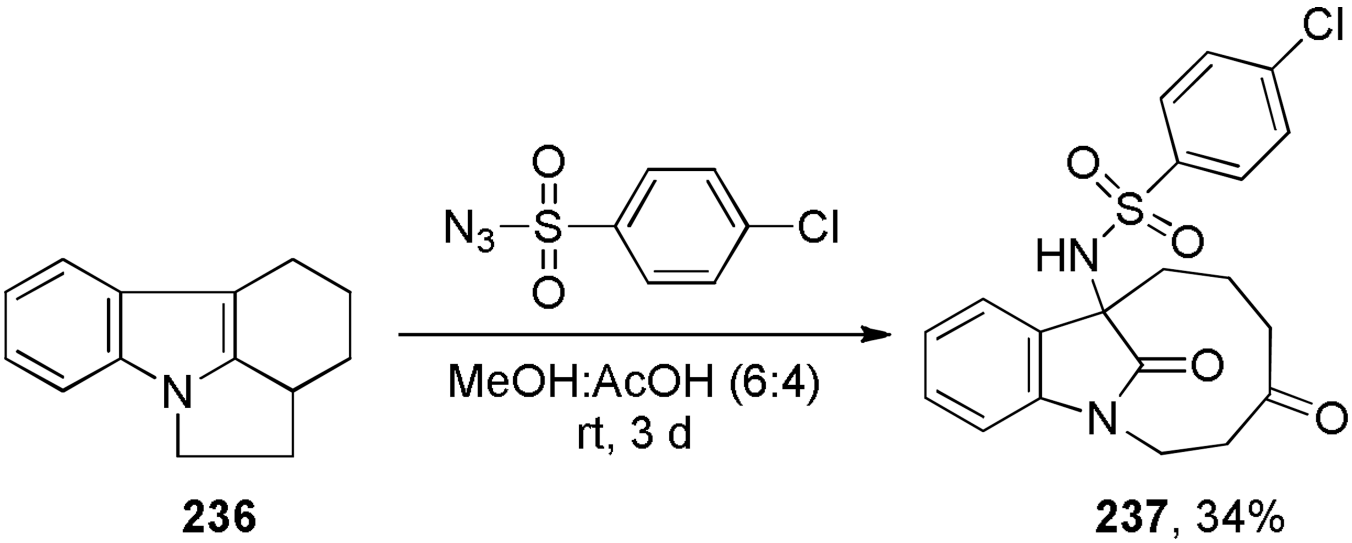
Scheme 61.
Proposed Mechanism for Cyclization/Fragmentation of **230**



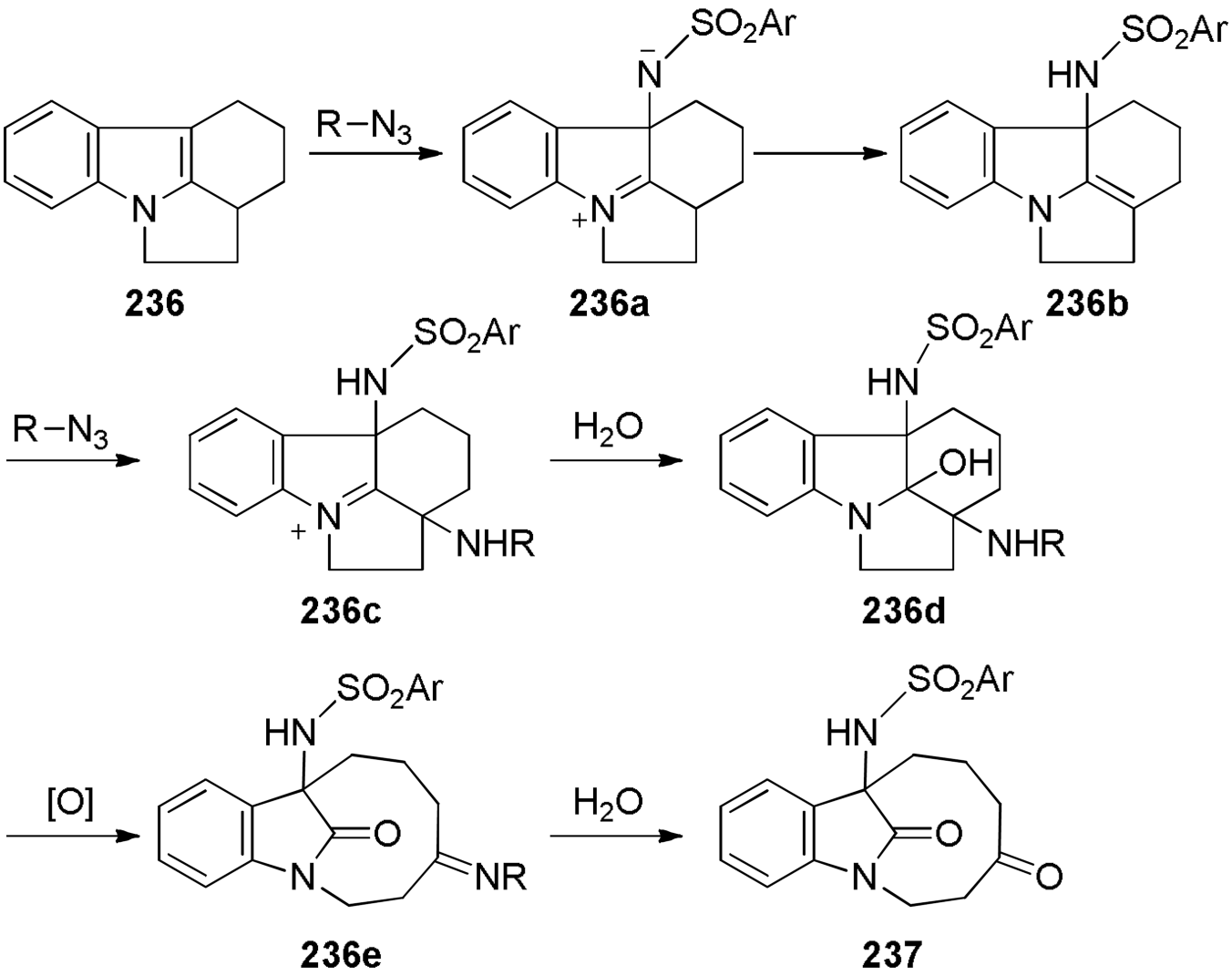
Scheme 62.
Synthesis of 1-Azabicyclo[7.3.1]tridecan-13-onesvia Oxidation of Enamines by Schumann



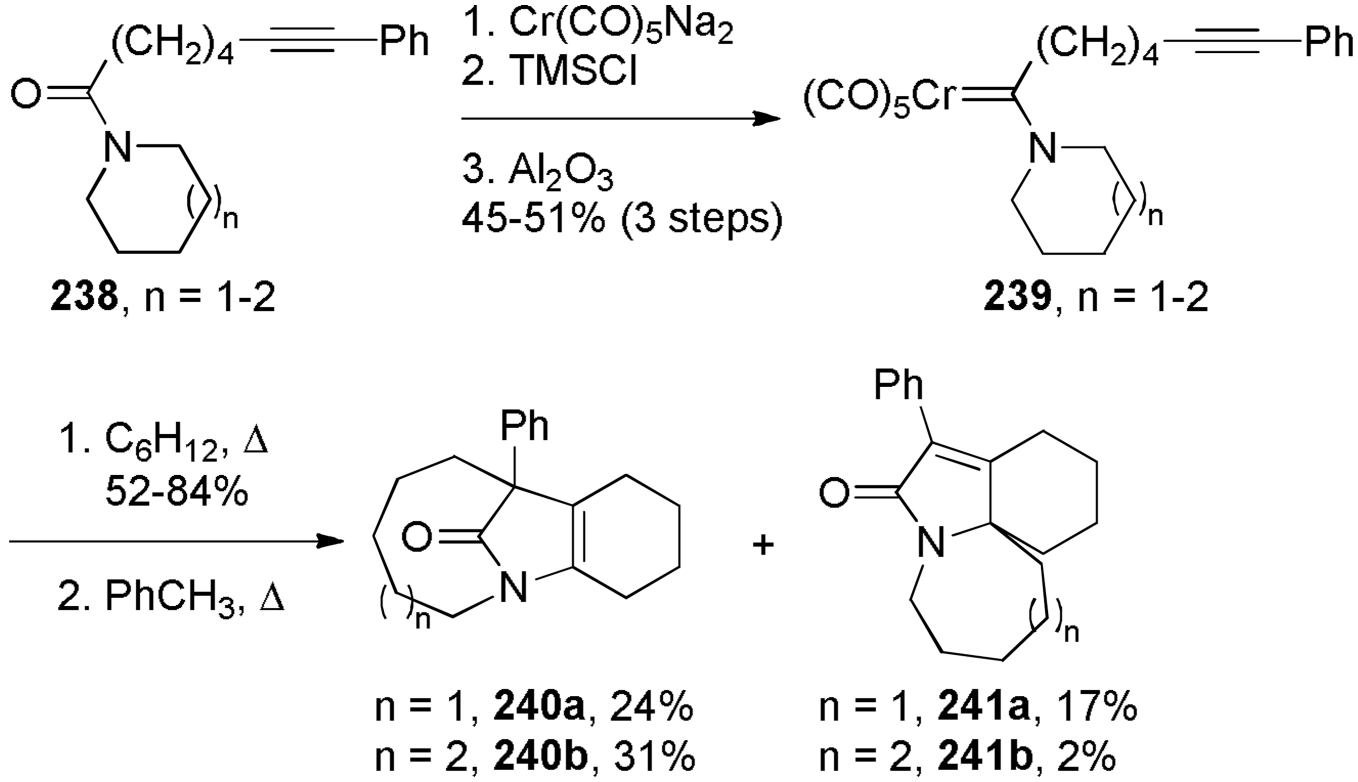
Scheme 63.
Proposed Mechanism for Oxidation/Fragmentation of Enamines **232** and **232a**



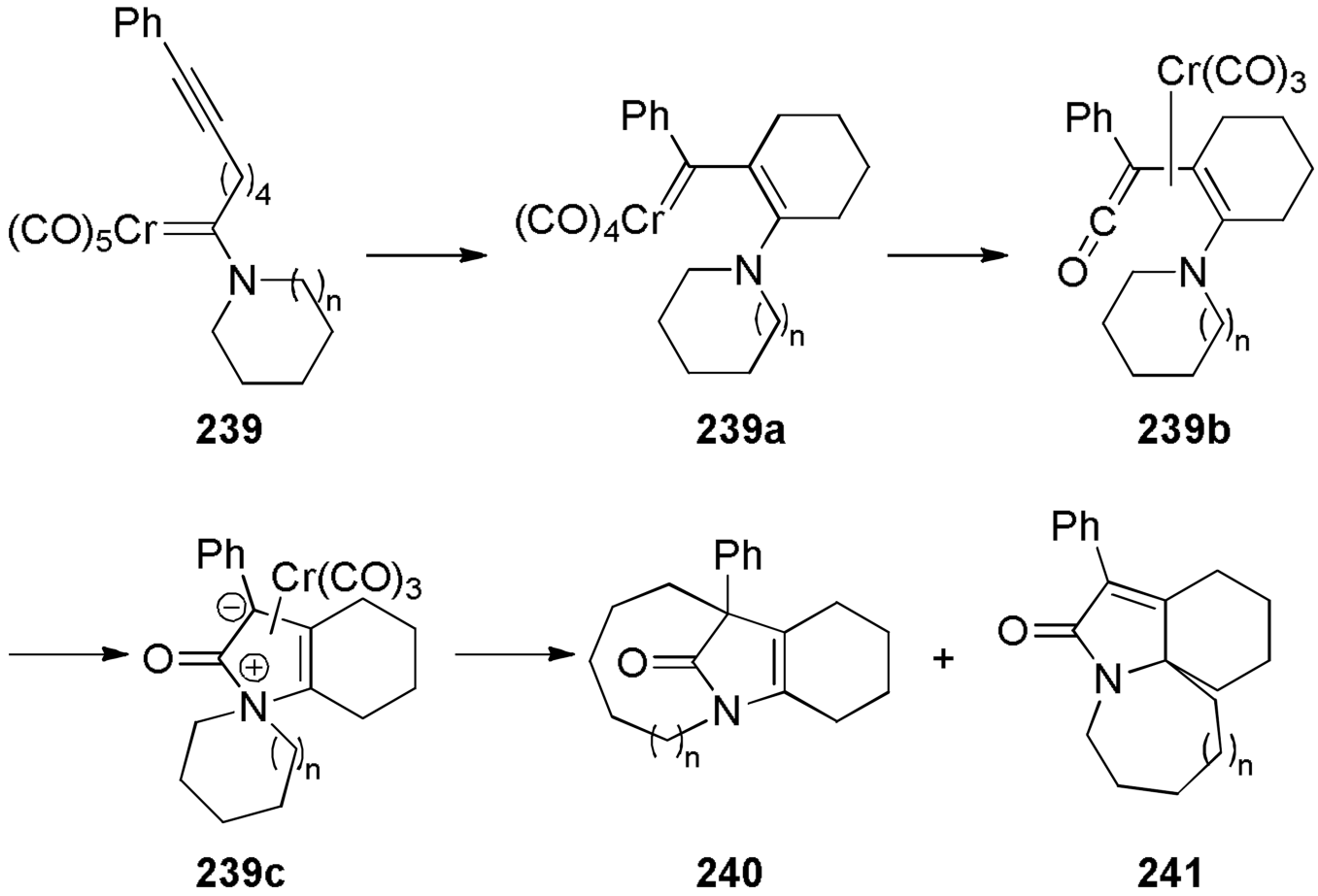
Scheme 64.
Synthesis of 1-Azabicyclo[6.2.1]undecan-11-one by Bailey



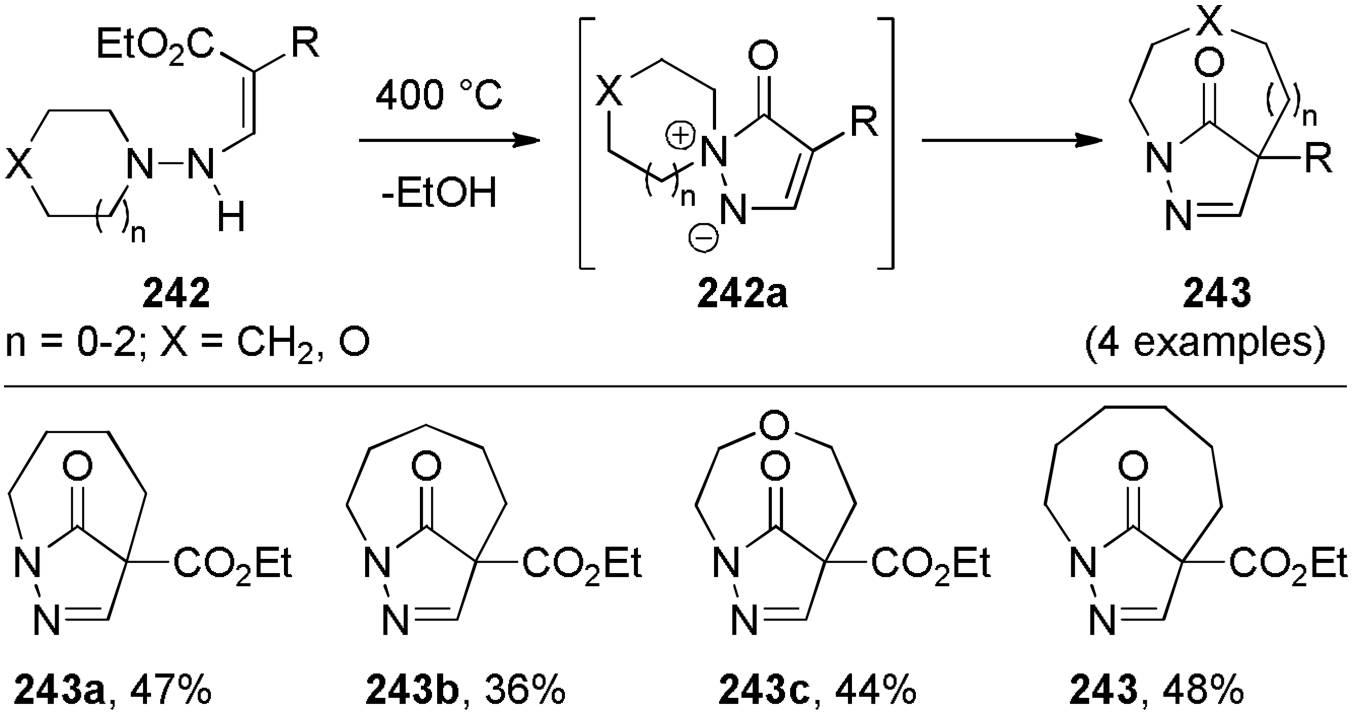
Scheme 65.
Proposed Mechanism for Oxidative Fragmentation of **236**



Scheme 66.
Synthesis of Bridged Lactams via Rearrangement of Nitrogen Ylides by Rudler

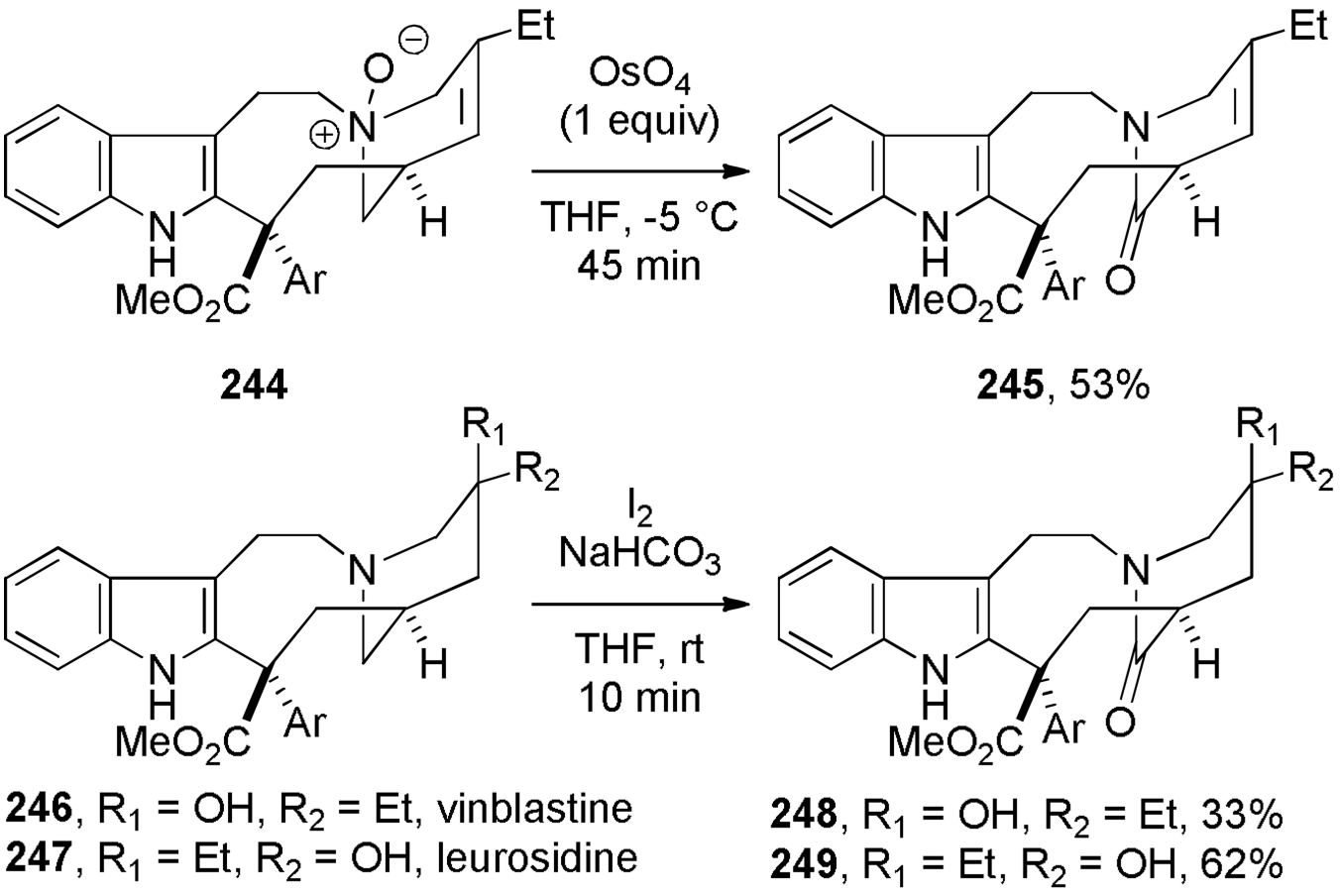


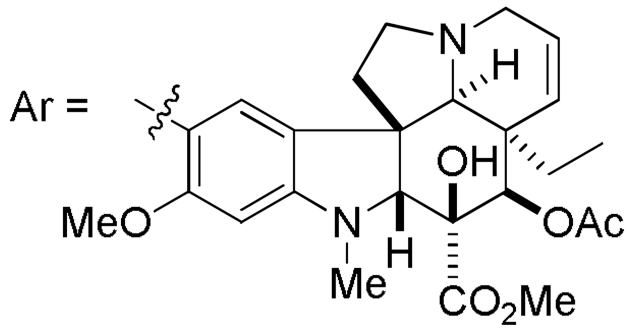
Scheme 67.
Proposed Mechanism for Rearrangement of **239**



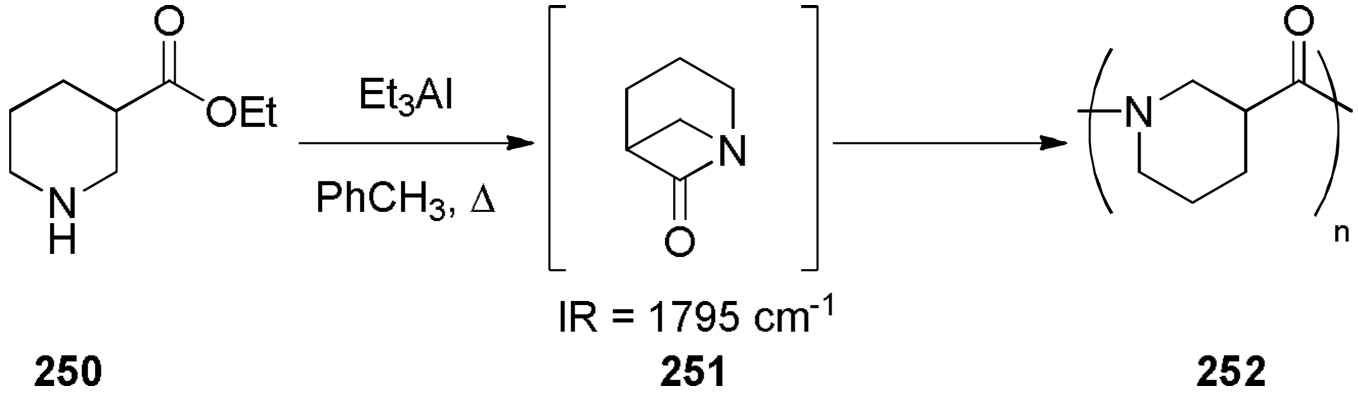
Scheme 68.

Synthesis of 1,4-Bridged Pyrazolin-5-ones via Rearrangement of Spiro Pyrazolium Ylides by Chuche

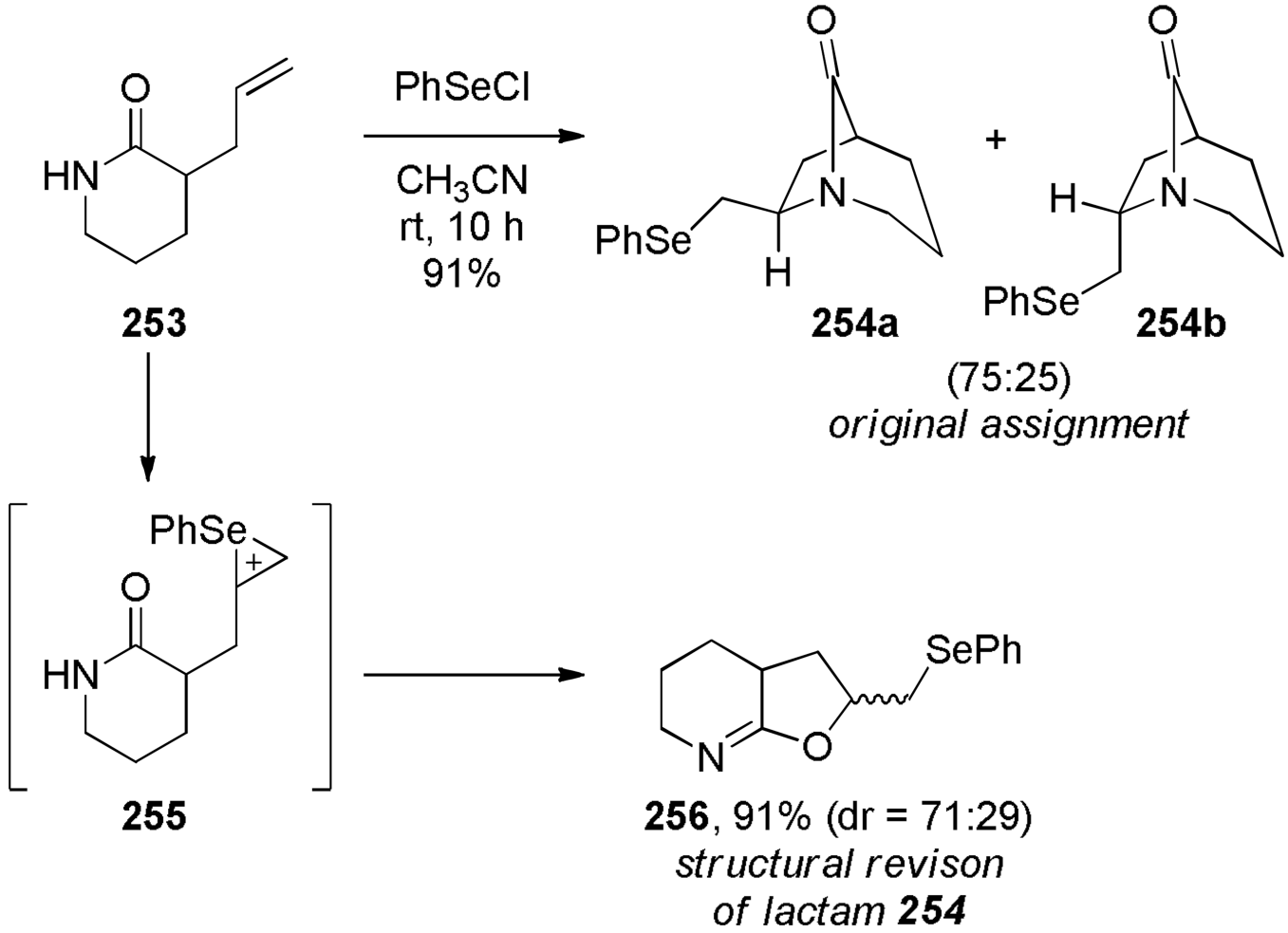




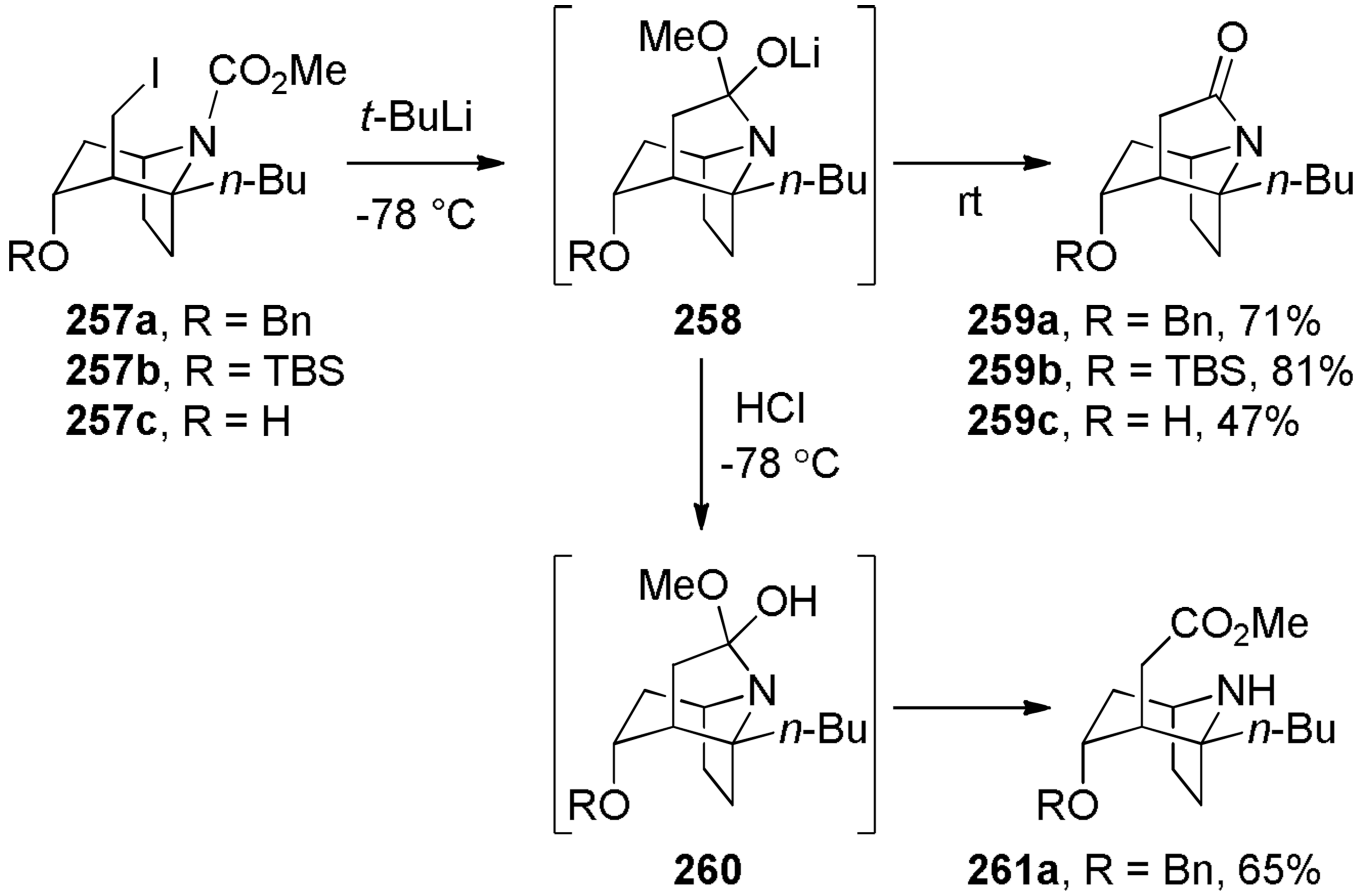
Scheme 69.
Synthesis of Vinblastine-Derived Bridged Lactams by Kutney



Scheme 70.
Attempted Synthesis of 1-Azabicyclo[3.1.1]heptan-6-one by Williams

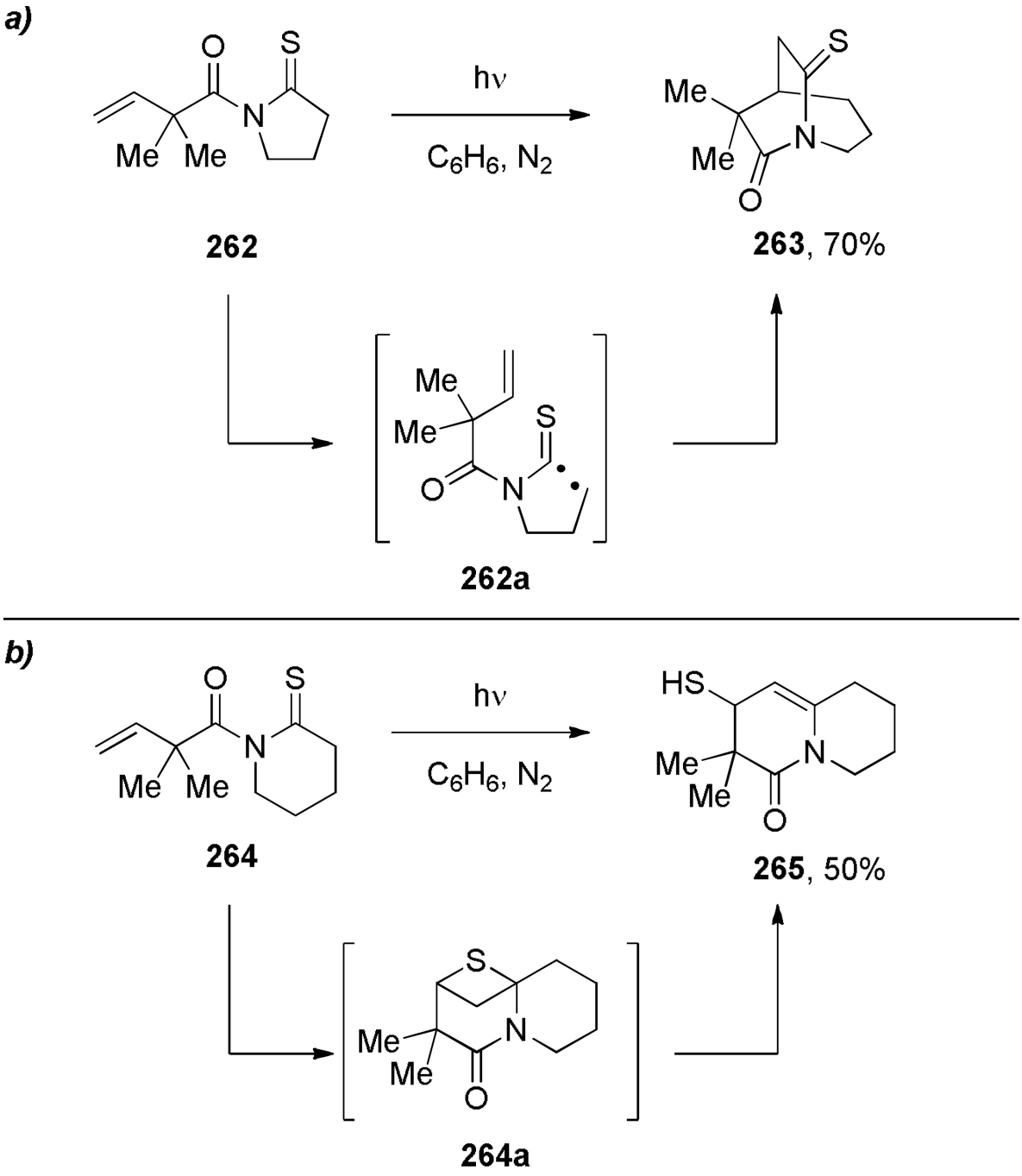


Scheme 71.
Attempted Synthesis of 1-Azabicyclo[3.2.1]octan-8-onesvia Amidoselenation by Toshimitsu



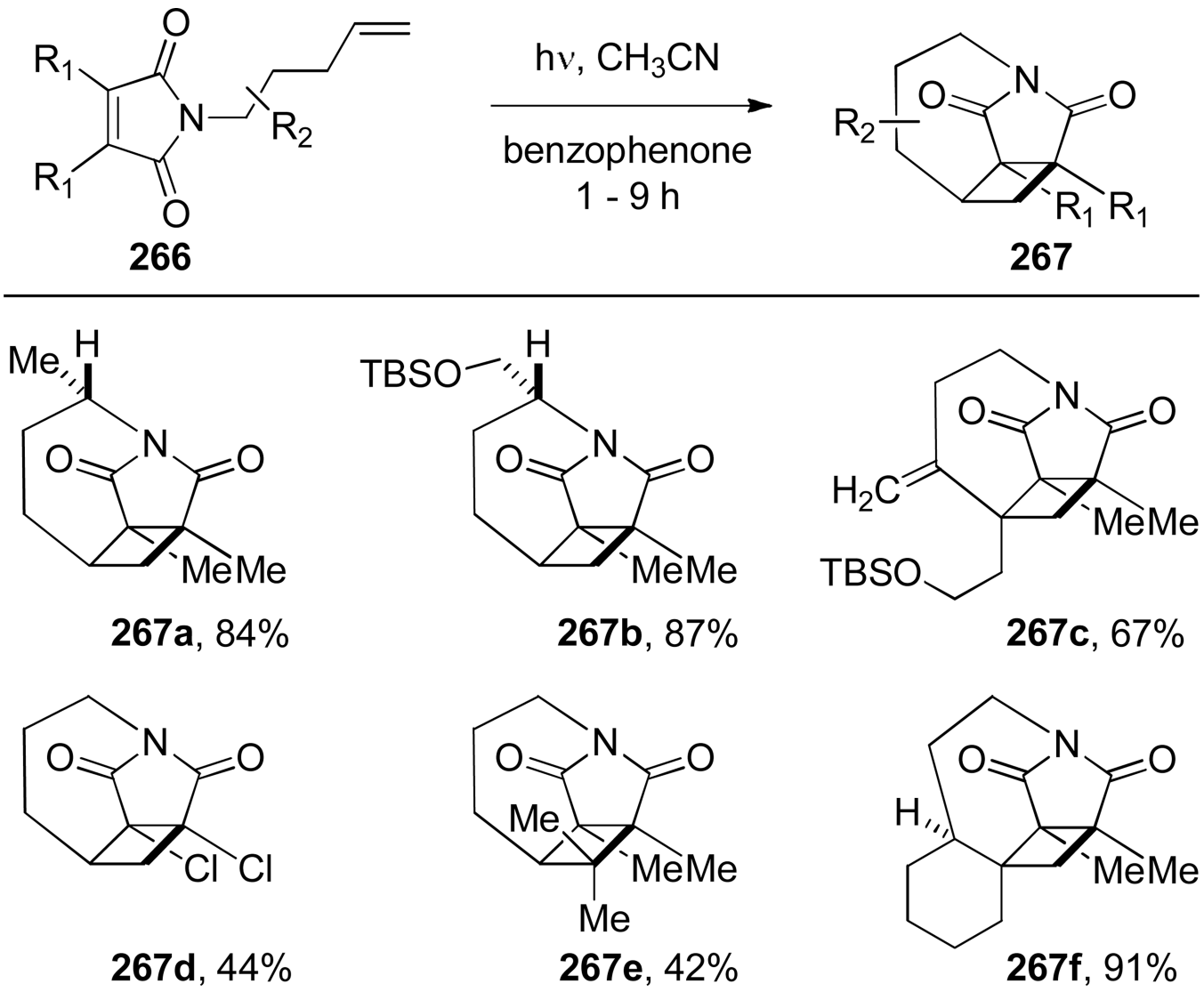
Scheme 72.

Synthesis of Tropane-Derived Bridged Lactams in Synthetic Studies towards Stemofoline by Thomas

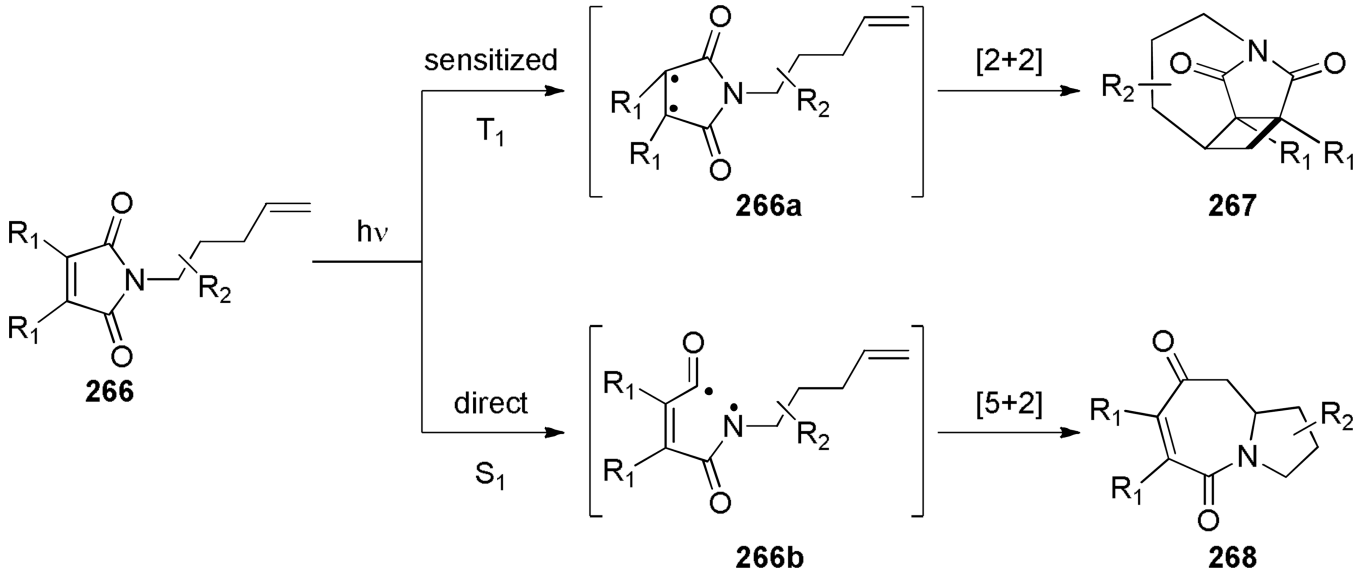


Scheme 73.

a) Synthesis of Bridged Monothioimidevia Photochemical Fragmentation/Photocyclization by Sakamoto; b) Rearrangement of One-Carbon Higher Analog

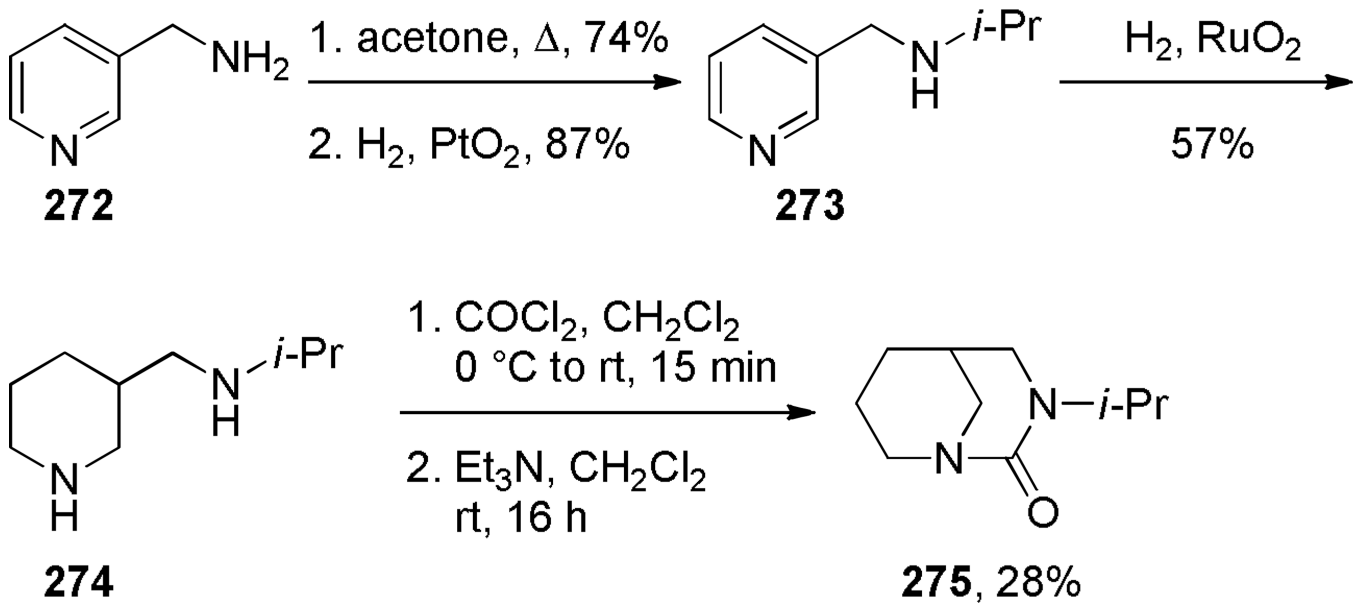


Scheme 74.
Synthesis of Complex Bridged Imides via [2+2] Photocycloaddition by Booker-Milburn

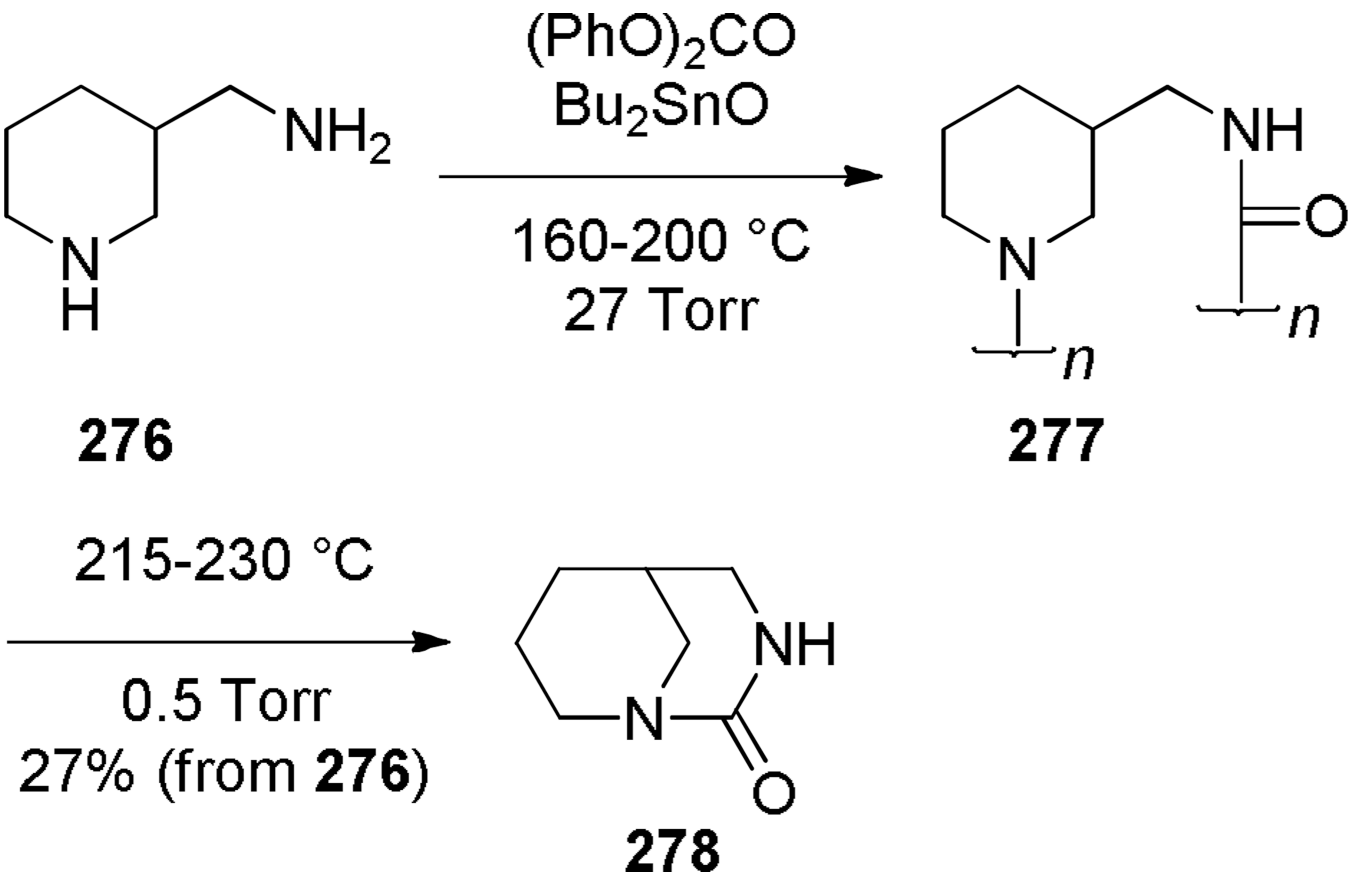


Scheme 75.

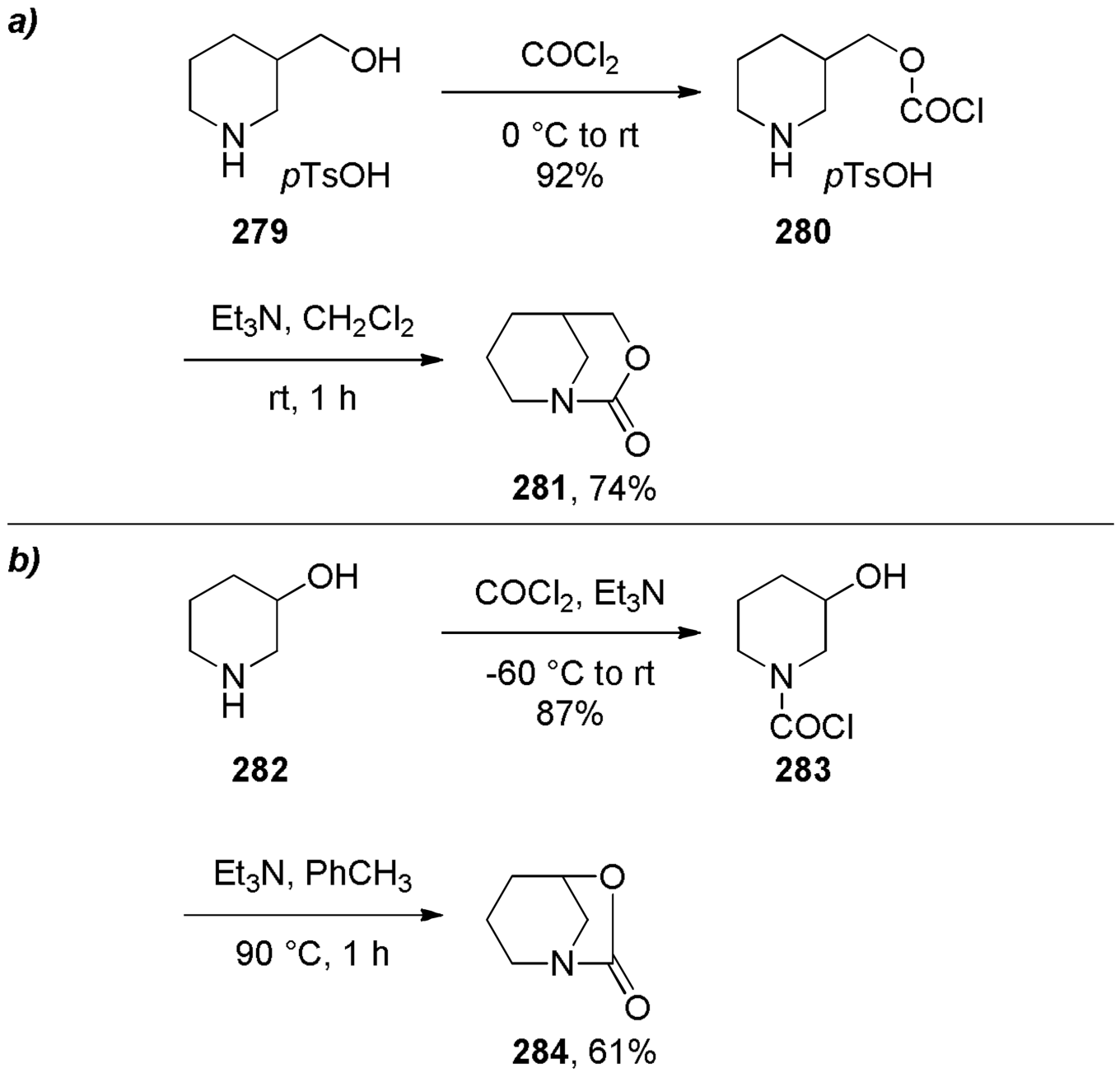
Proposed Mechanism for Photocycloaddition of Imides **266** (please use double-column format for Scheme 75)



Scheme 76.
Synthesis of 3-Alkyl-1,3-diazabicyclo[3.3.1]nonan-2-ones by Hall

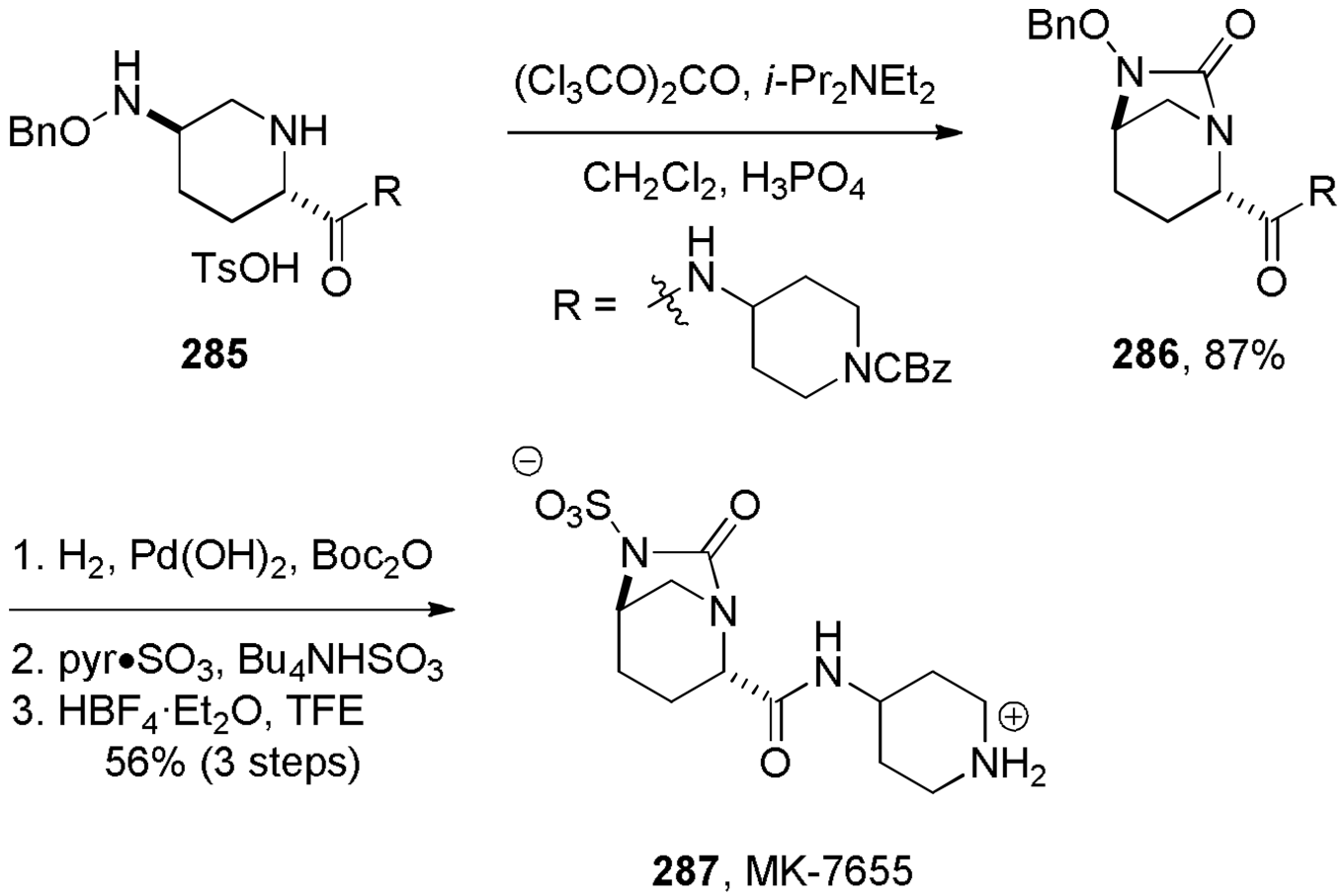


Scheme 77.
Synthesis of 1,3-diazabicyclo[3.3.1]nonan-2-ones by Hall



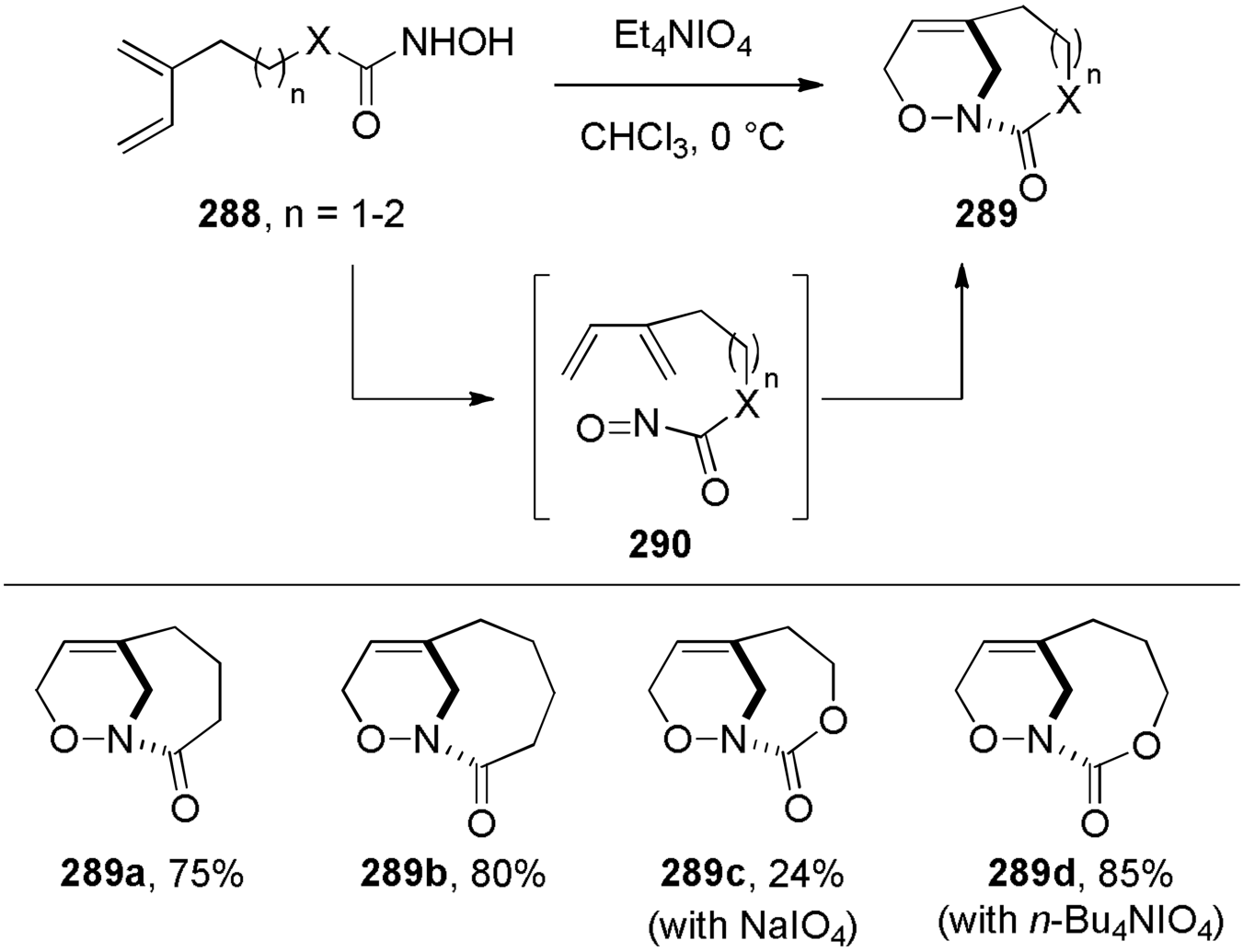
Scheme 78.

Synthesis of Bridged Urethanes by Hall: a) 3-Oxa-1-azabicyclo[3.3.1]nonan-2-one; b) 6-oxa-1-azabicyclo[3.2.1]octan-7-one



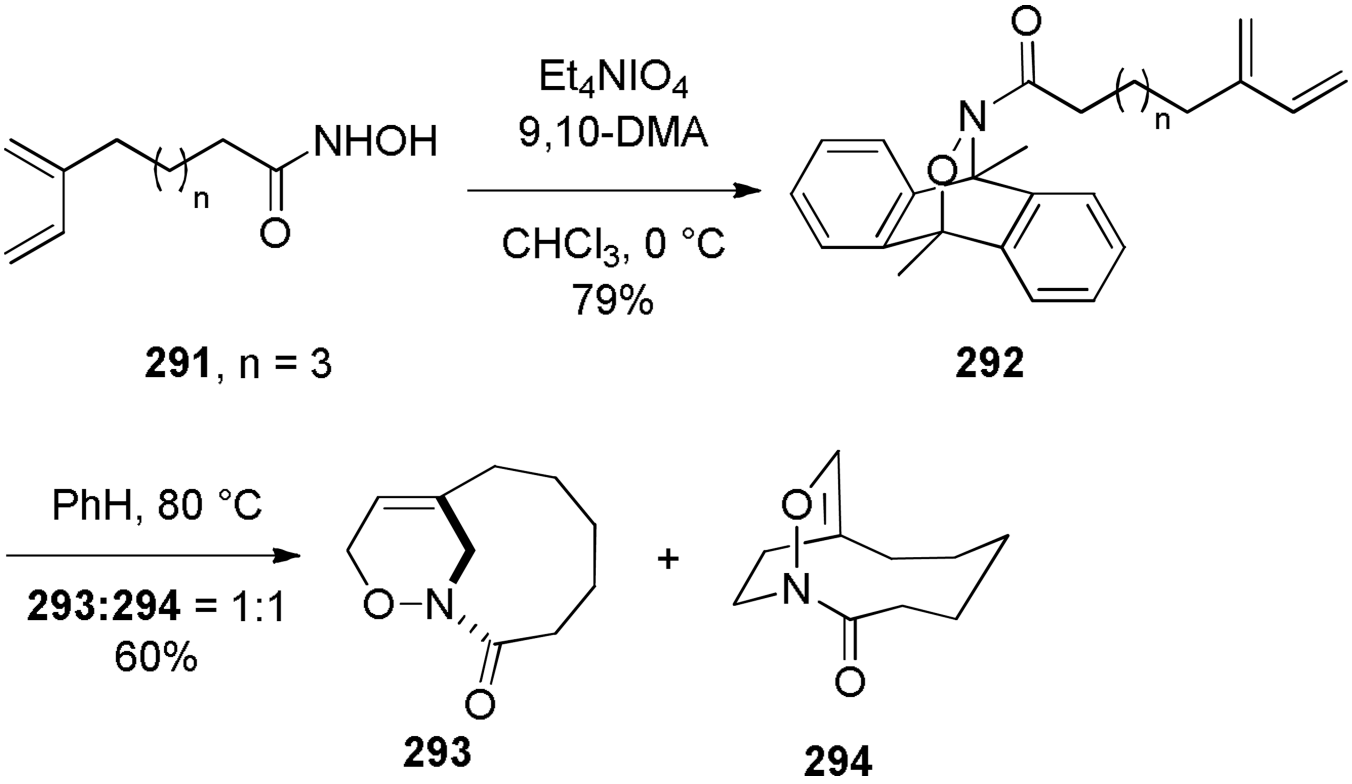
Scheme 79.

Synthesis of β-Lactamase Inhibitor Containing 1,6-Diazabicyclo[3.2.1]octan-7-one Scaffold by Mangion



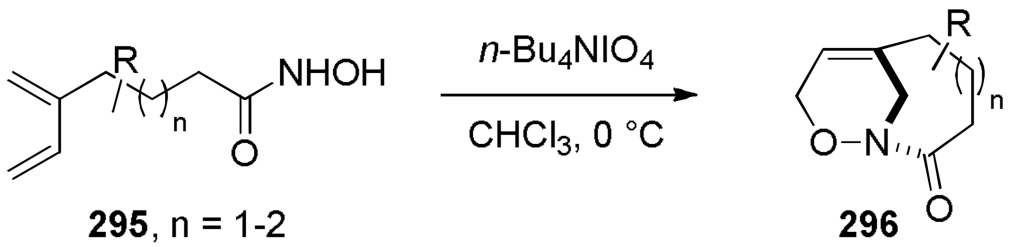
Scheme 80.

Synthesis of Unsubstituted Bridged Oxazinolactams via Type II *N*-Acylnitroso Diels-Alder Reaction by Shea

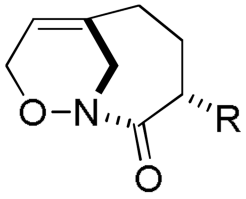


Scheme 81.

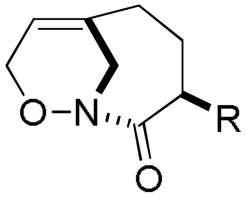
Synthesis of Unsubstituted [6.2.1] Bridged Oxazinolactamvia Type II *N*-Acylnitroso Diels-Alder Reaction by Shea



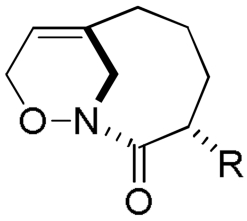
295, n = 1-2 **296**



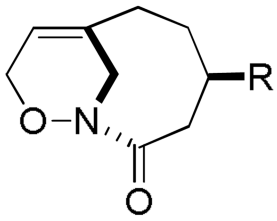
296a, R = Bn, 83%, dr > 95:5
296b, R = allyl, 70%, dr > 95:5



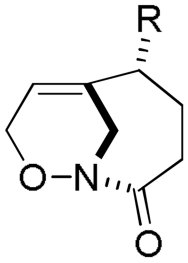
296g, R = OBn, 62%, dr > 95:5
296h, R = OTBDPS, 70%, dr = 84:16



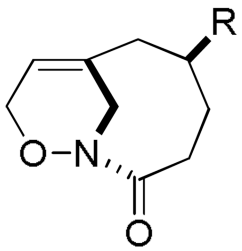
296c, R = Bn, 85%, dr > 95:5
296d, R = allyl, 87%, dr > 95:5
296e, R = OBn, 76%, dr > 95:5



296i, R = OTBS, 84%, dr = 80:20 (from 9,10-DMA adduct)

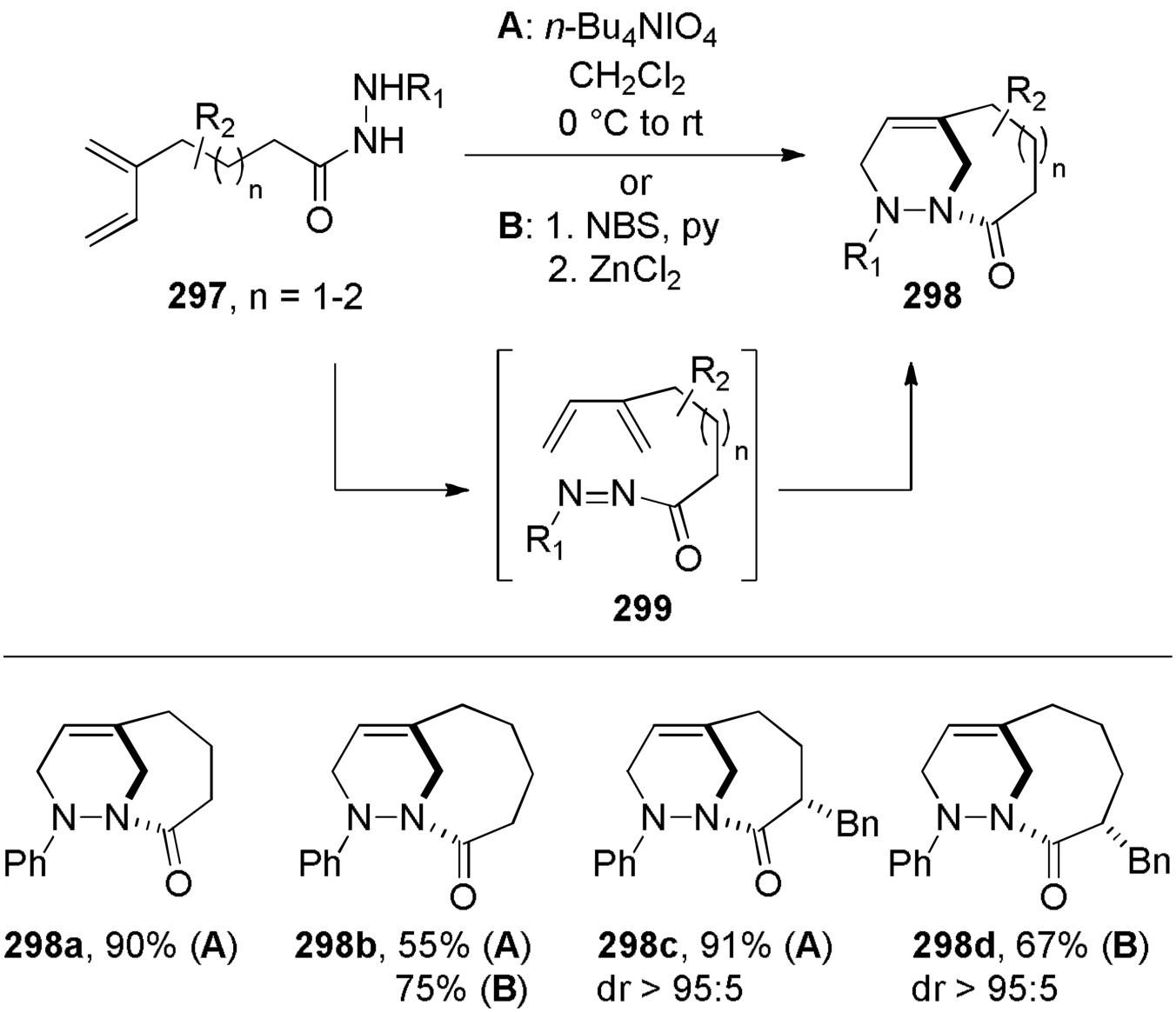


296f, R = $(CH_2)_2$OTBDPS, 50%, dr = 75:25



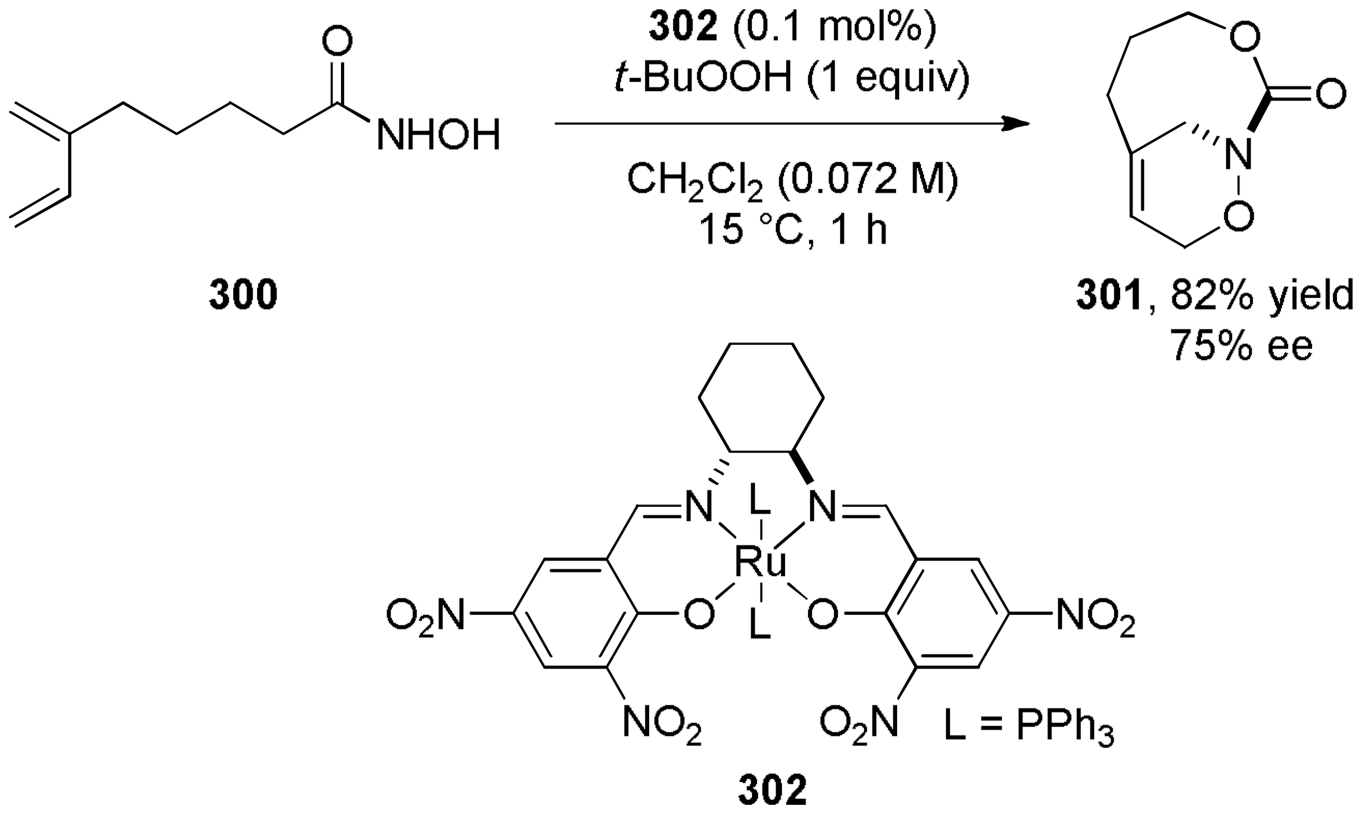
296j, R = OBn, 84%, dr = 79:21

Scheme 82.
Synthesis of Substituted Bridged Oxazinolactams via Type II *N*-Acylnitroso Diels-Alder Reaction by Shea

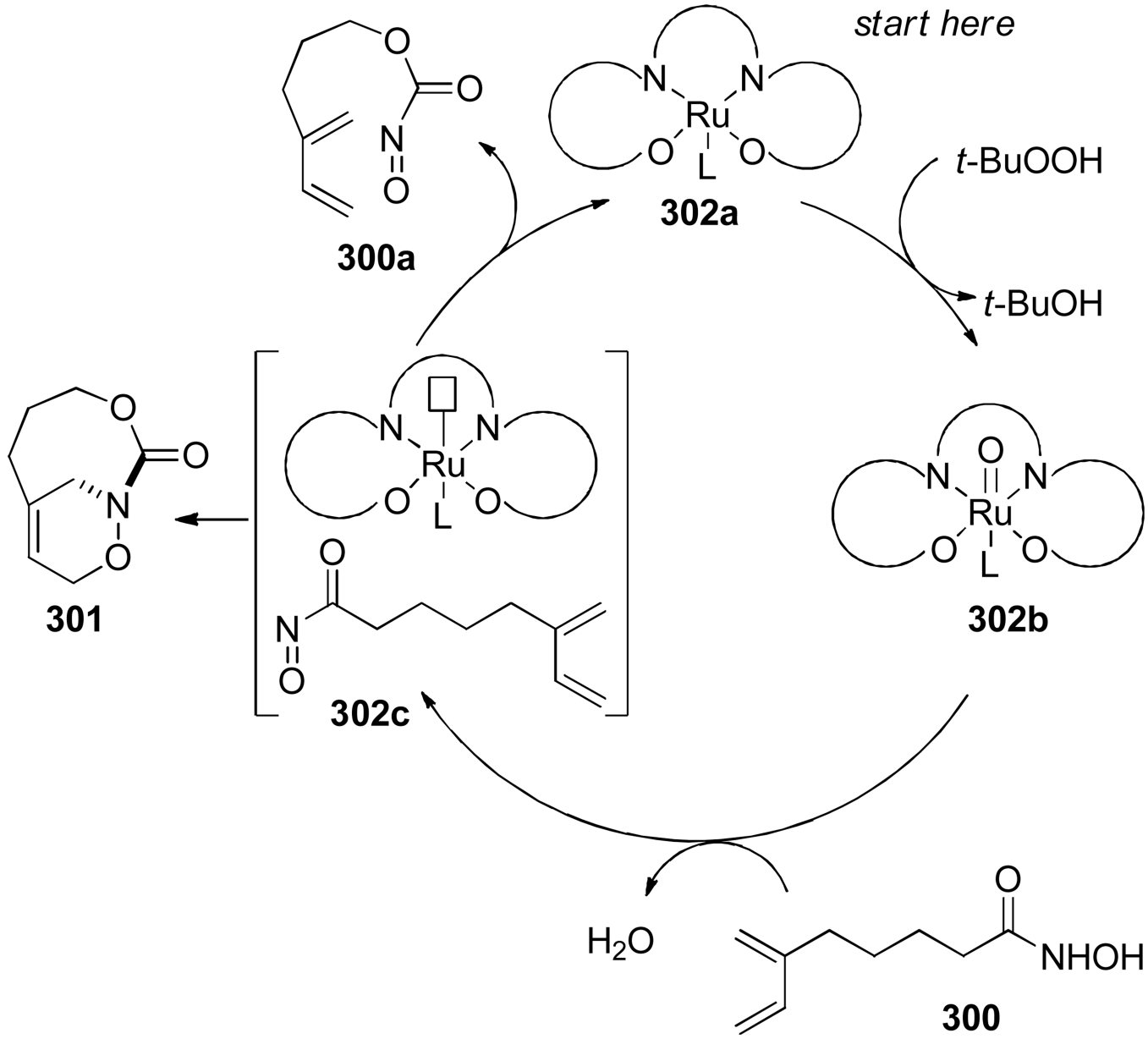


Scheme 83.

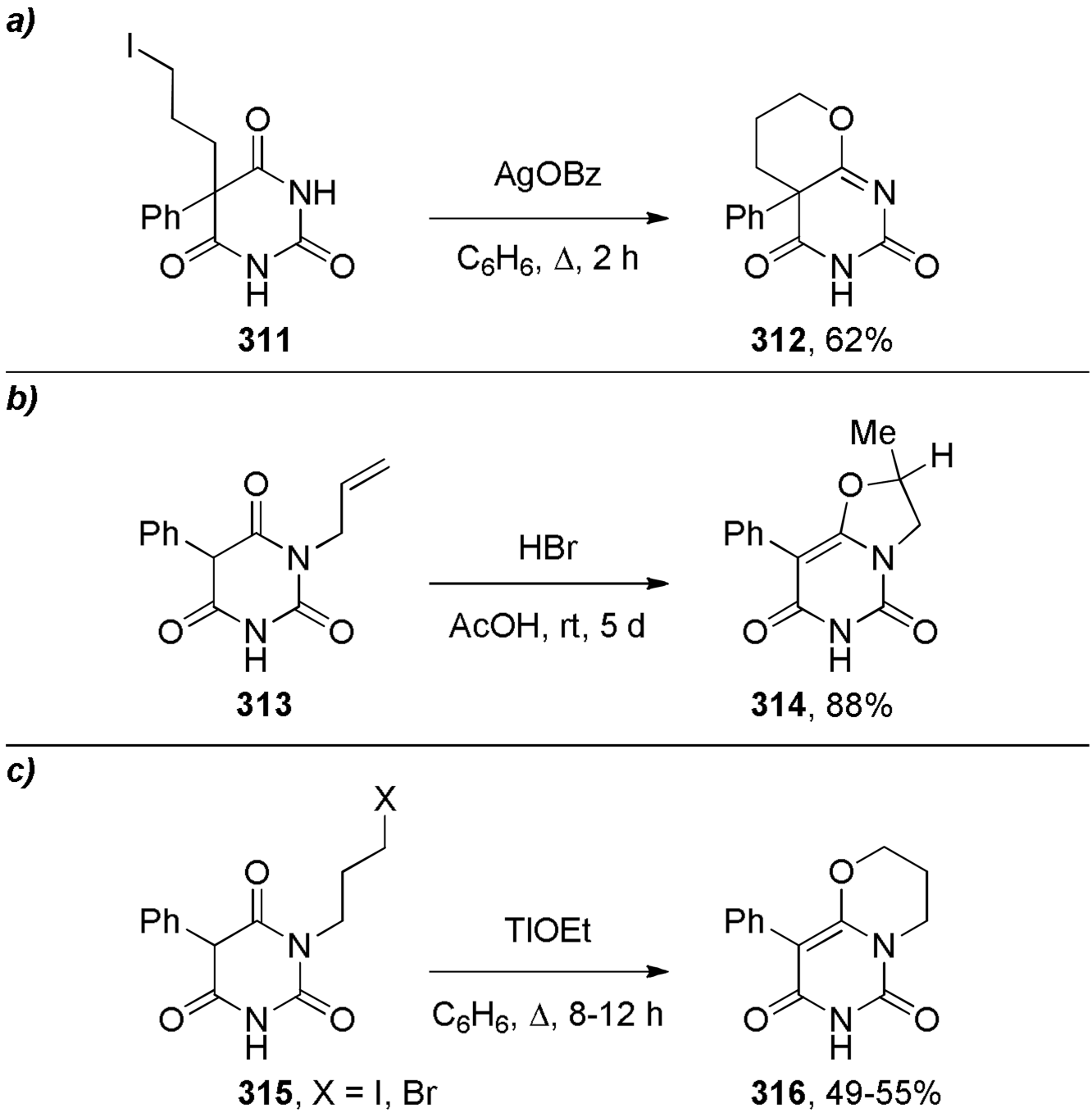
Synthesis of Bridged 1,2-Diazines via Type II *N*-Acylazo Diels-Alder Reaction by Shea



Scheme 84.
Asymmetric Synthesis Bridged Oxazinolactams via Dual Function Catalysis by Shea

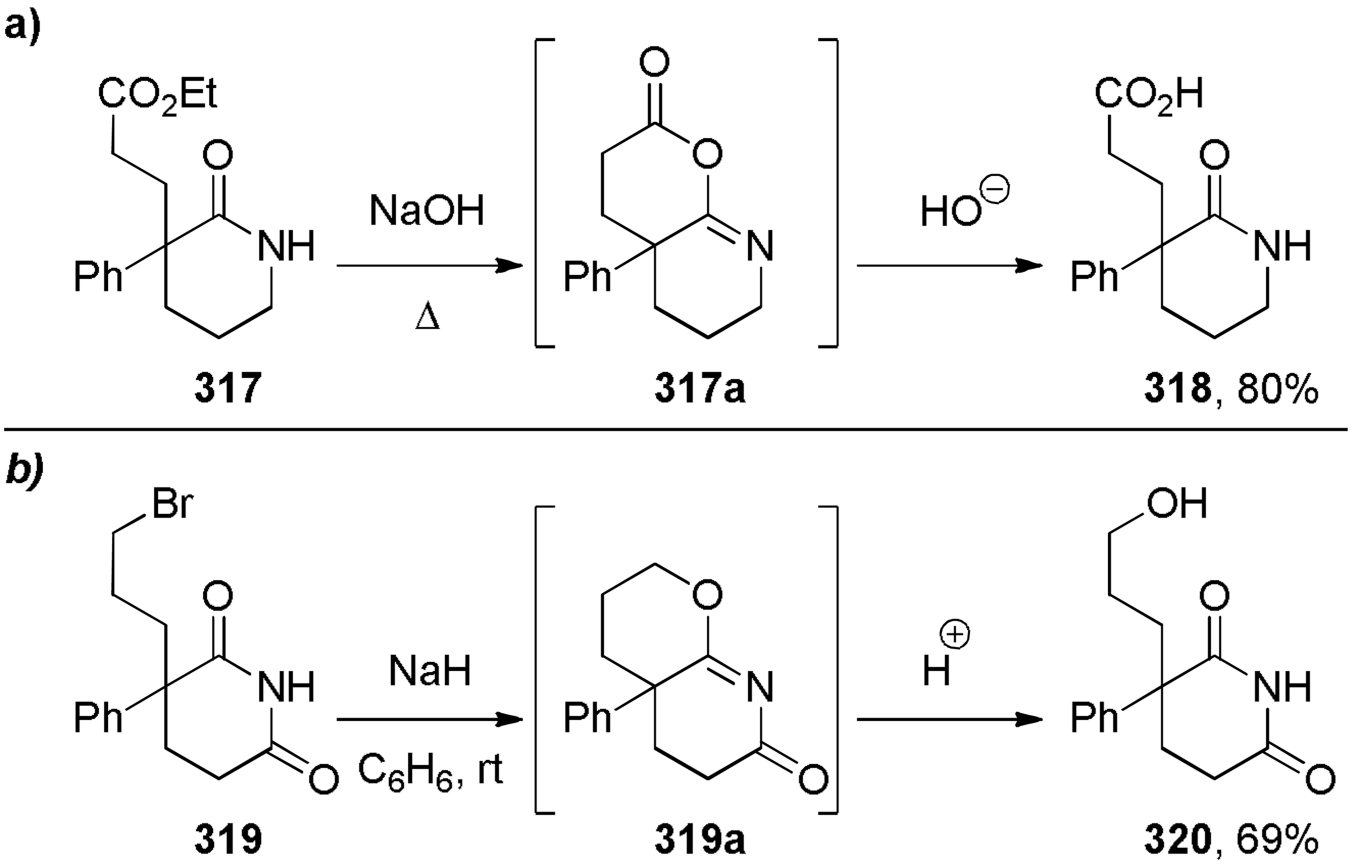


Scheme 85.
Proposed Mechanism for Diels-Alder Reaction of Substrate **300**



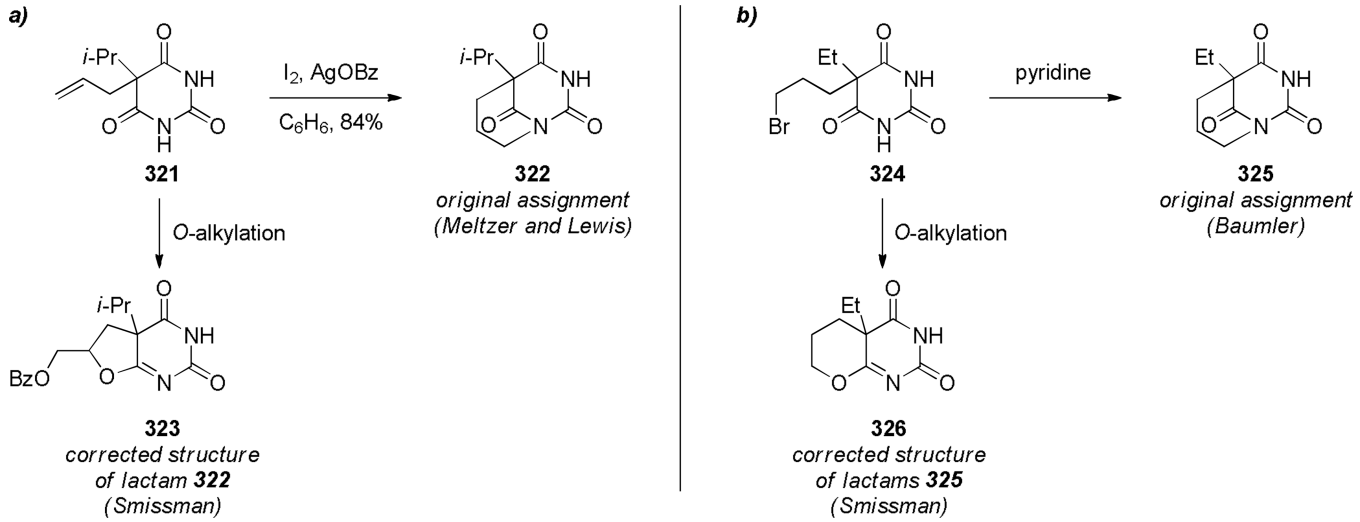
Scheme 86.

Early Attempts to Synthesize Bridged Lactams from Barbituric Acids by Smissman: a) Alkylation of 5-Iodoalkylbarbituric Acid; b) Electrophilic Activation of *N*-Allylbarbituric Acid; c) Alkylation of *N*-Haloalkylbarbituric Acid



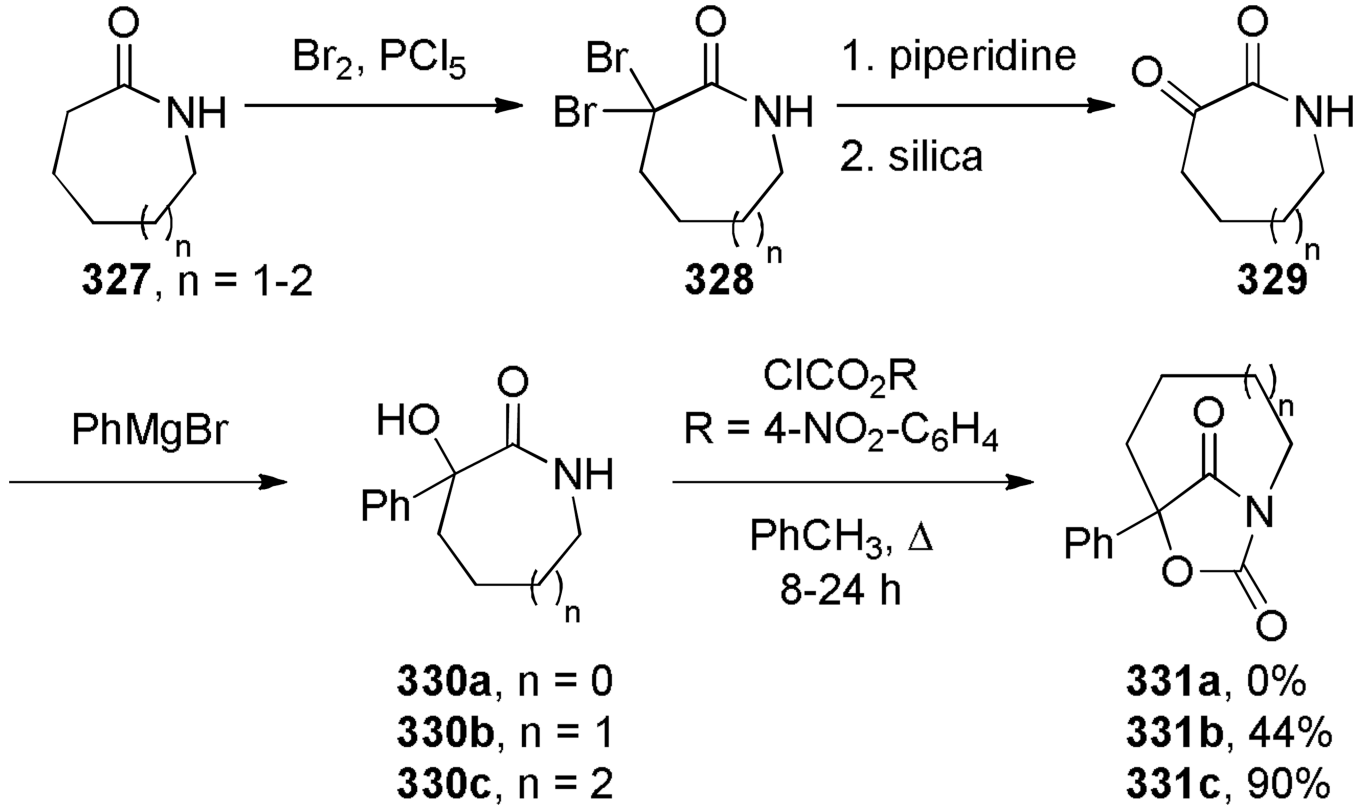
Scheme 87.

Early Attempts to Synthesize Bridged Lactams from Amides and Imides by Smissman: a) Intramolecular Condensation; b) Intramolecular *N*-Alkylation

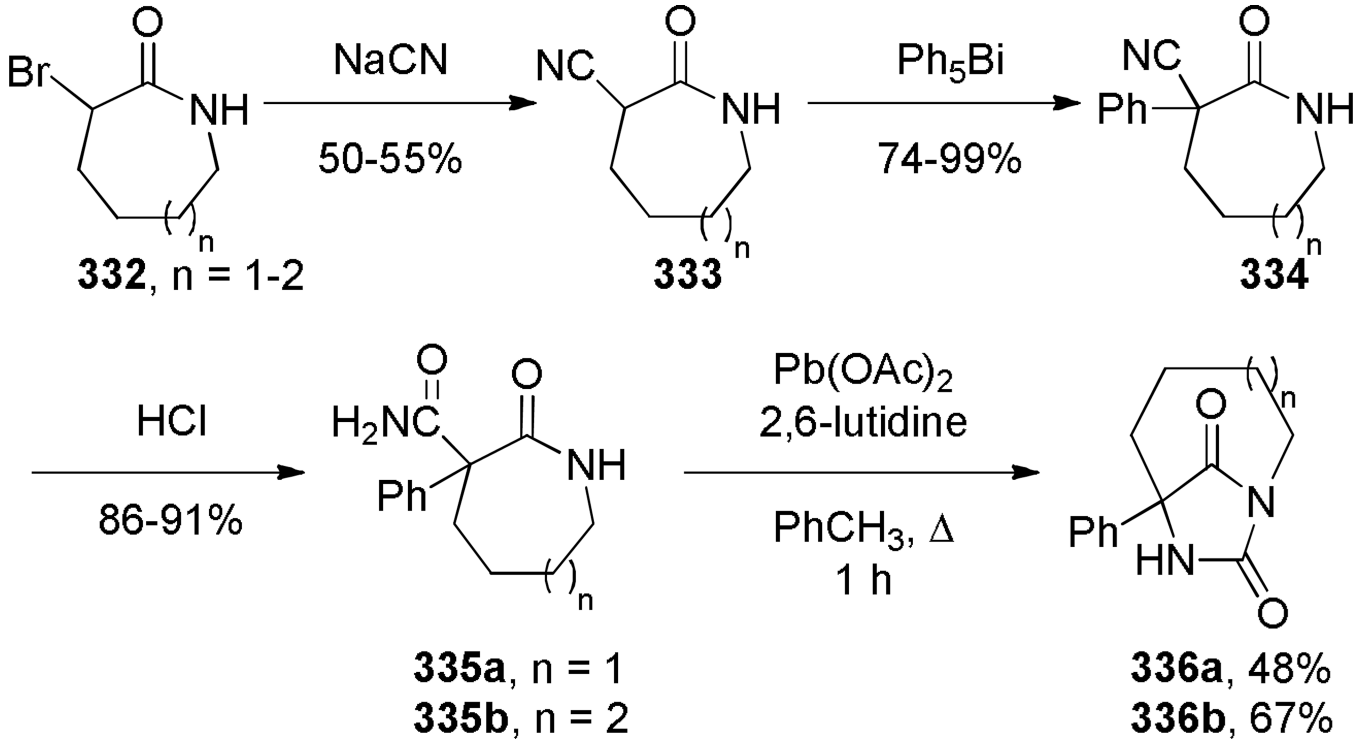


Scheme 88.

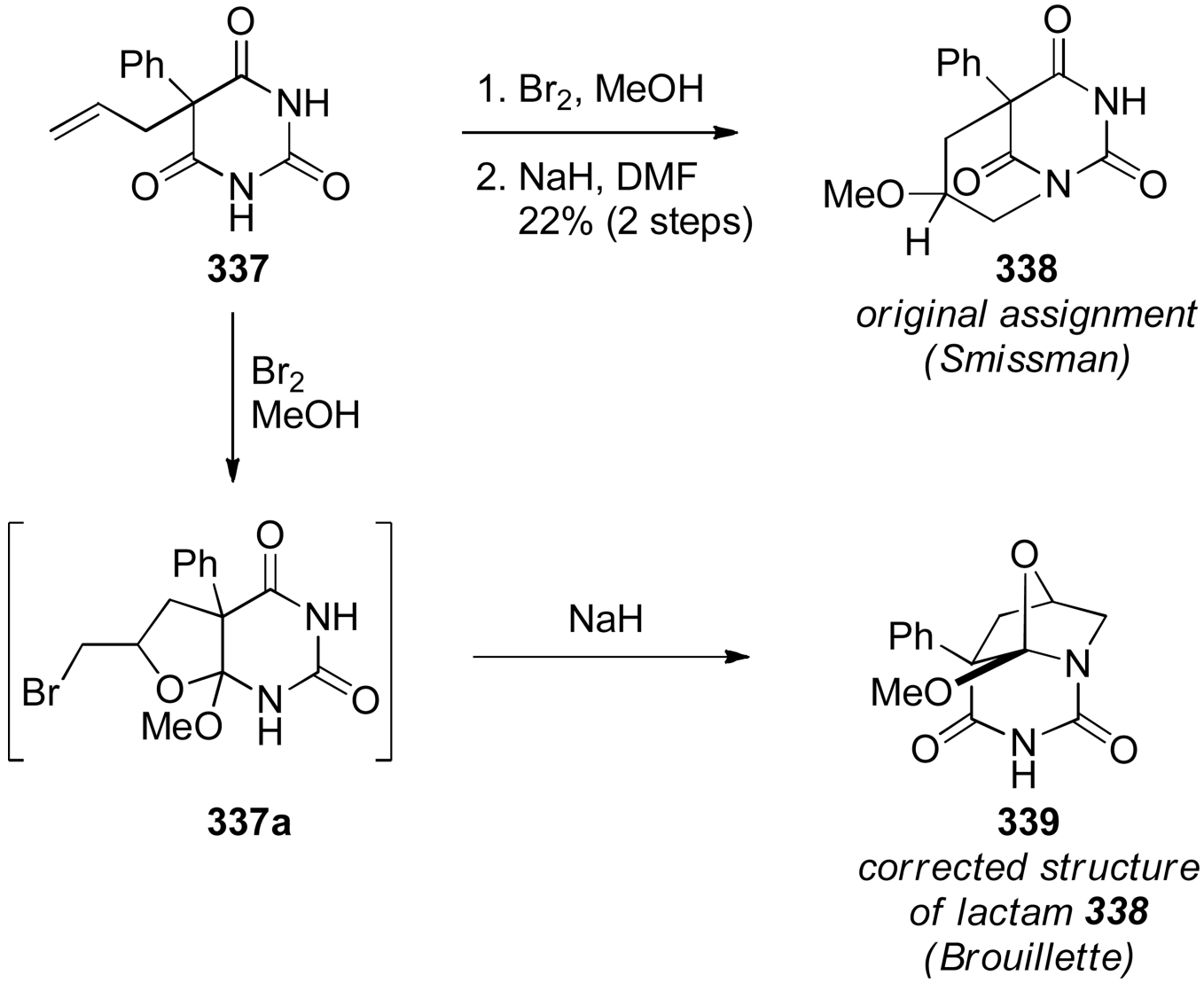
Revision of Initially Reported Structures of Bridged Barbituric Acids: a) Barbituric Acid **322** Reported by Meltzer and Lewis; b) Barbituric Acid **325** Reported by Baumler (please use double-column format for Scheme 88)



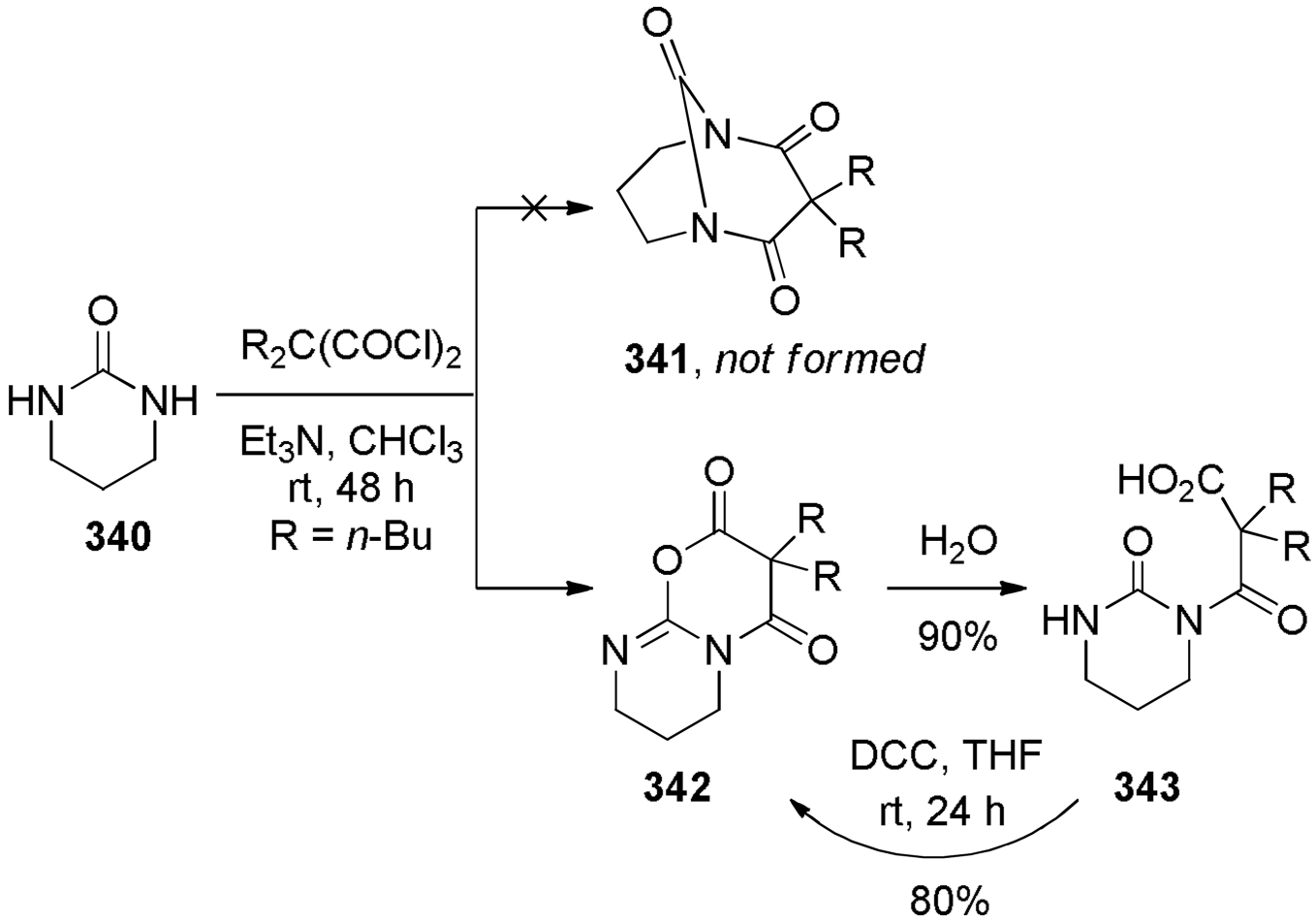
Scheme 89.
Synthesis of Bridged 2,4-Oxazolinediones by Brouillette



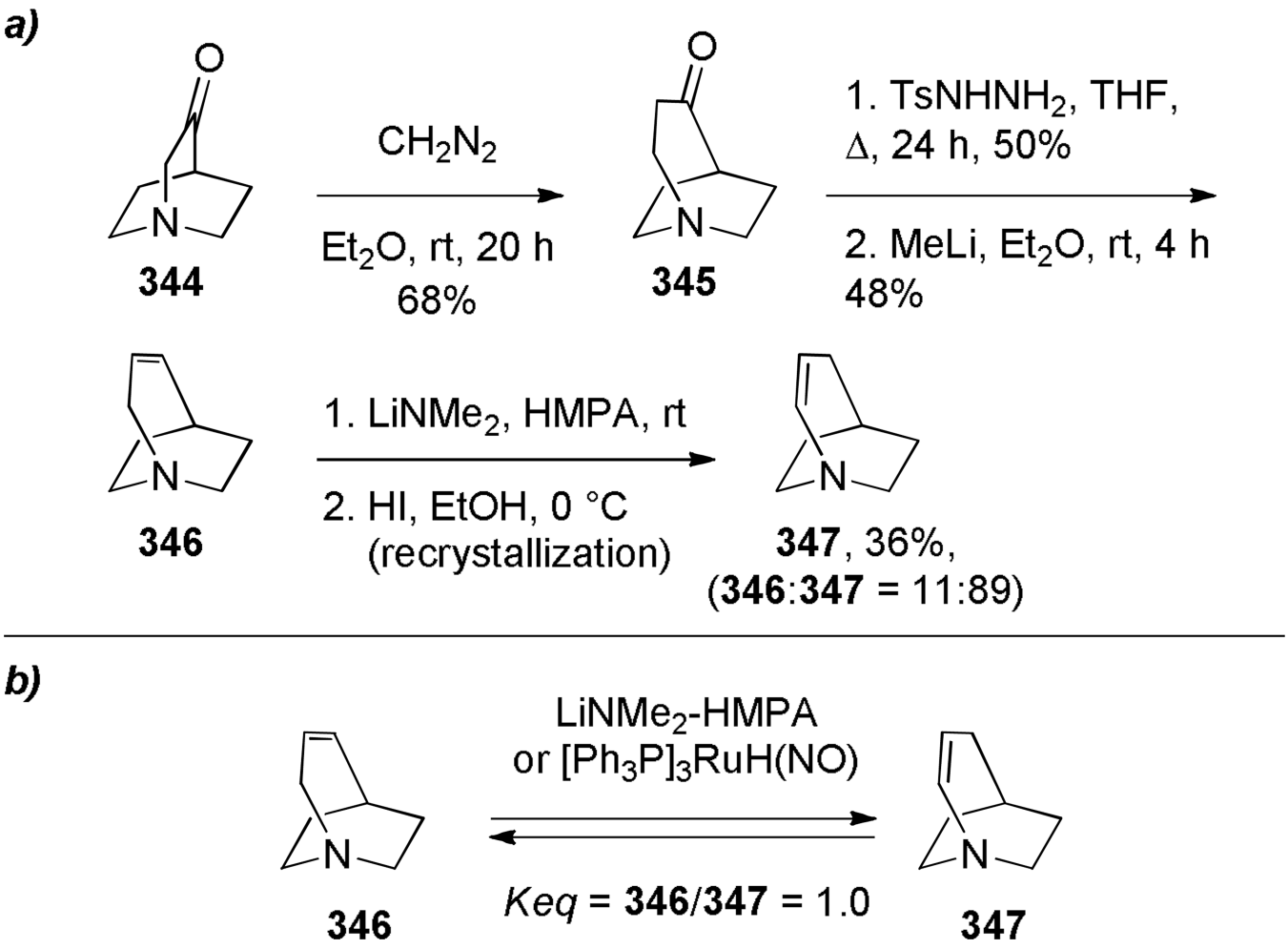
Scheme 90.
Synthesis of Bridged Hydantoines by Brouillette



Scheme 91.
Revision of Structure of Bridged Barbituric Acid Initially Reported by Smissman

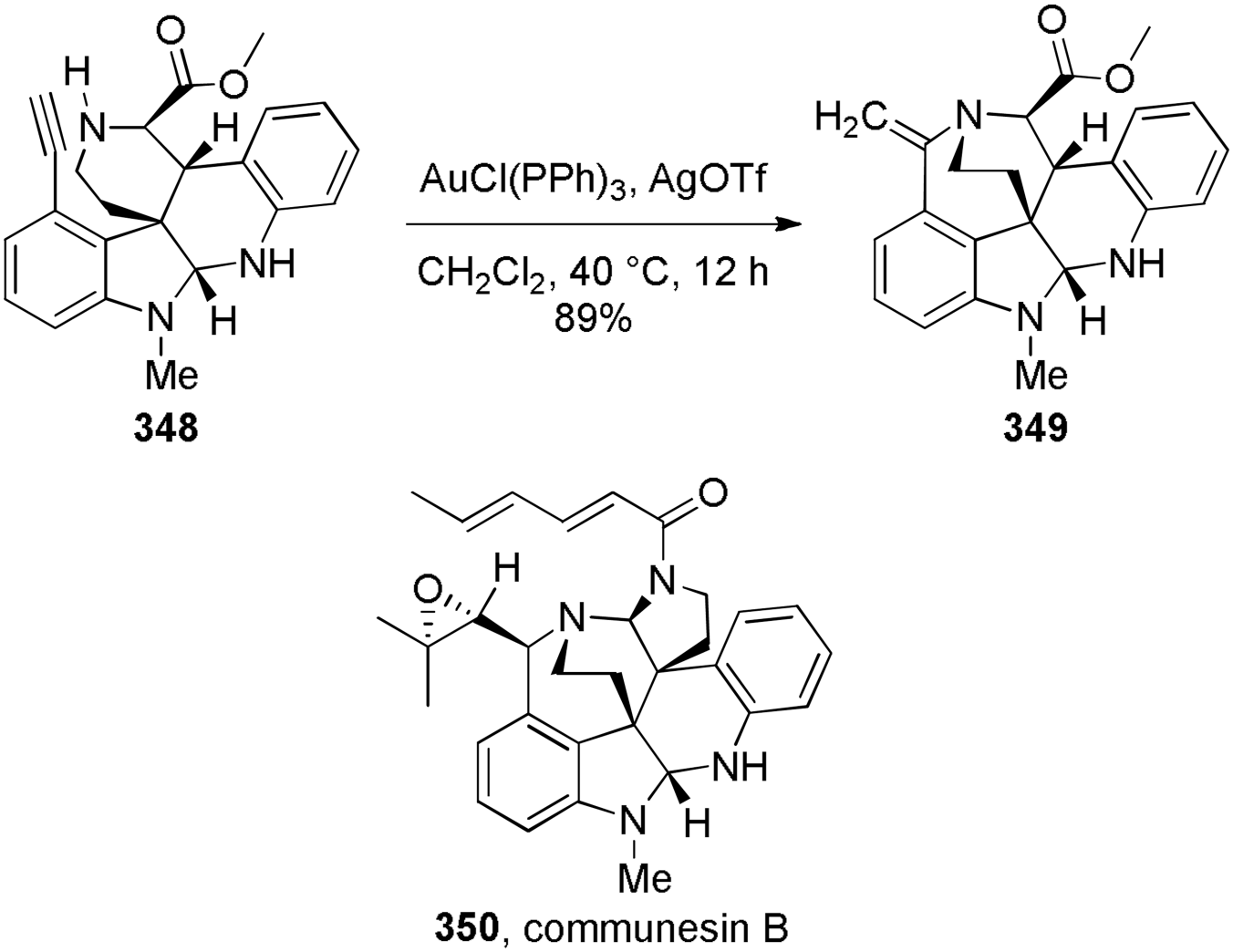


Scheme 92.
Attempted Synthesis of Bridged Barbituric Acid by Gmünder and Lindenmann

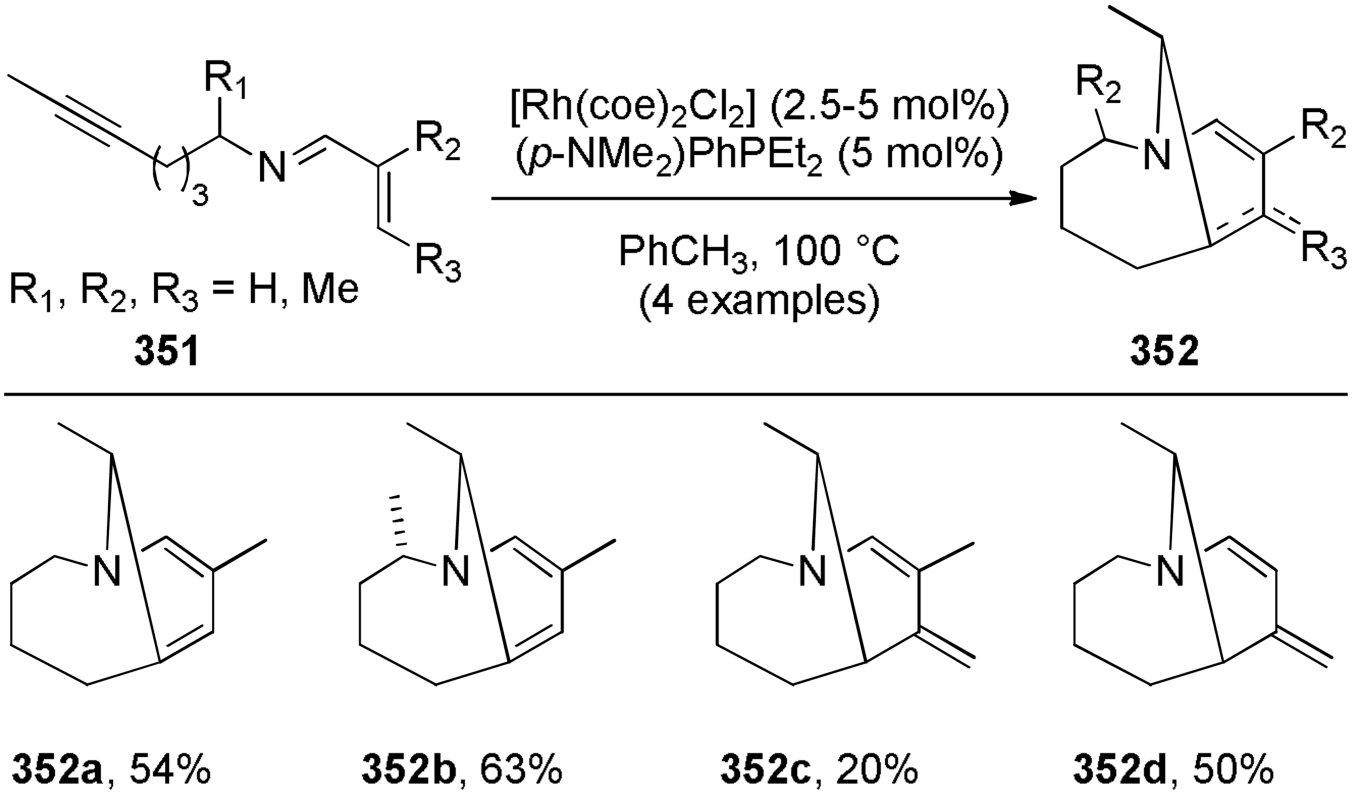


Scheme 93.

a) Synthesis of 1-Azabicyclo[3.2.2]non-2-ene by Doering; b) Equilibrium between Bridged Allylic Amine and Enamine

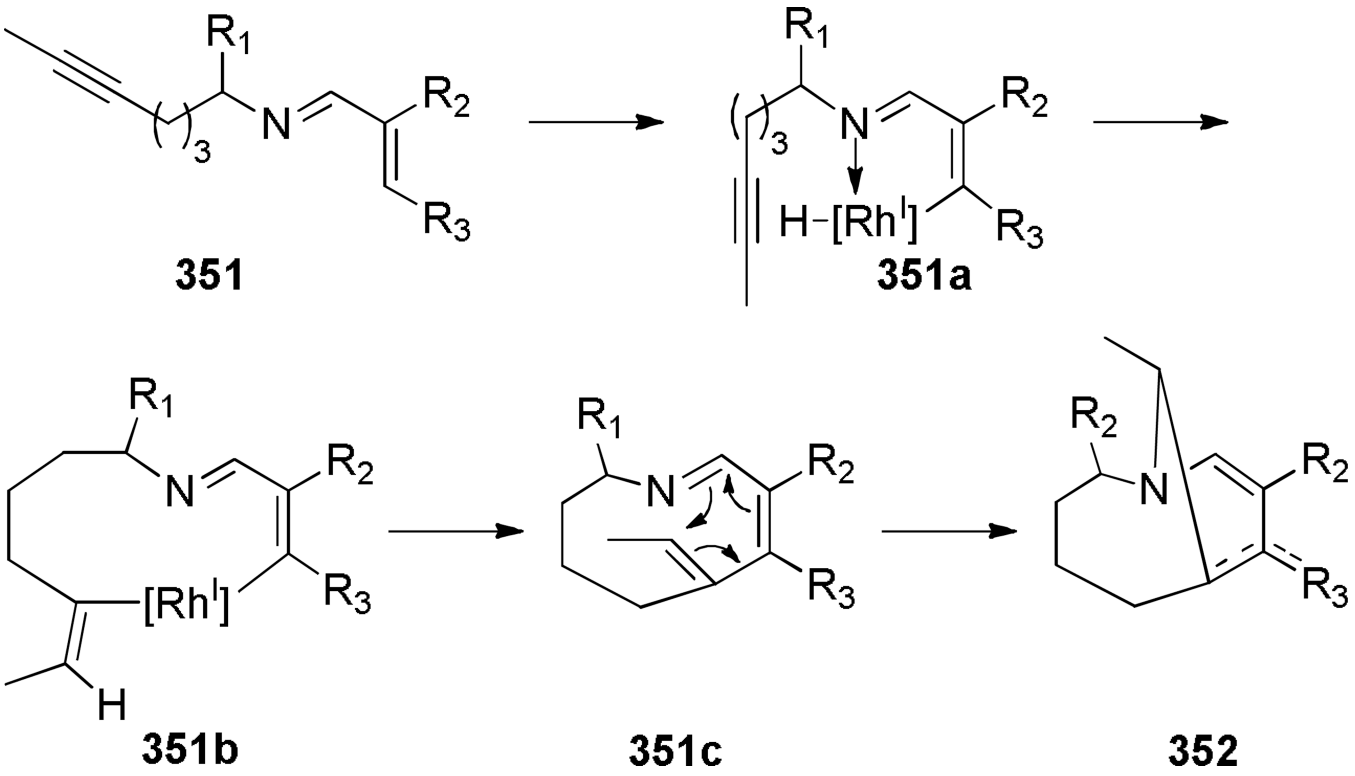


Scheme 94.
Synthesis of Bridged Enamine via Au-Catalyzed Hydroamination by Funk

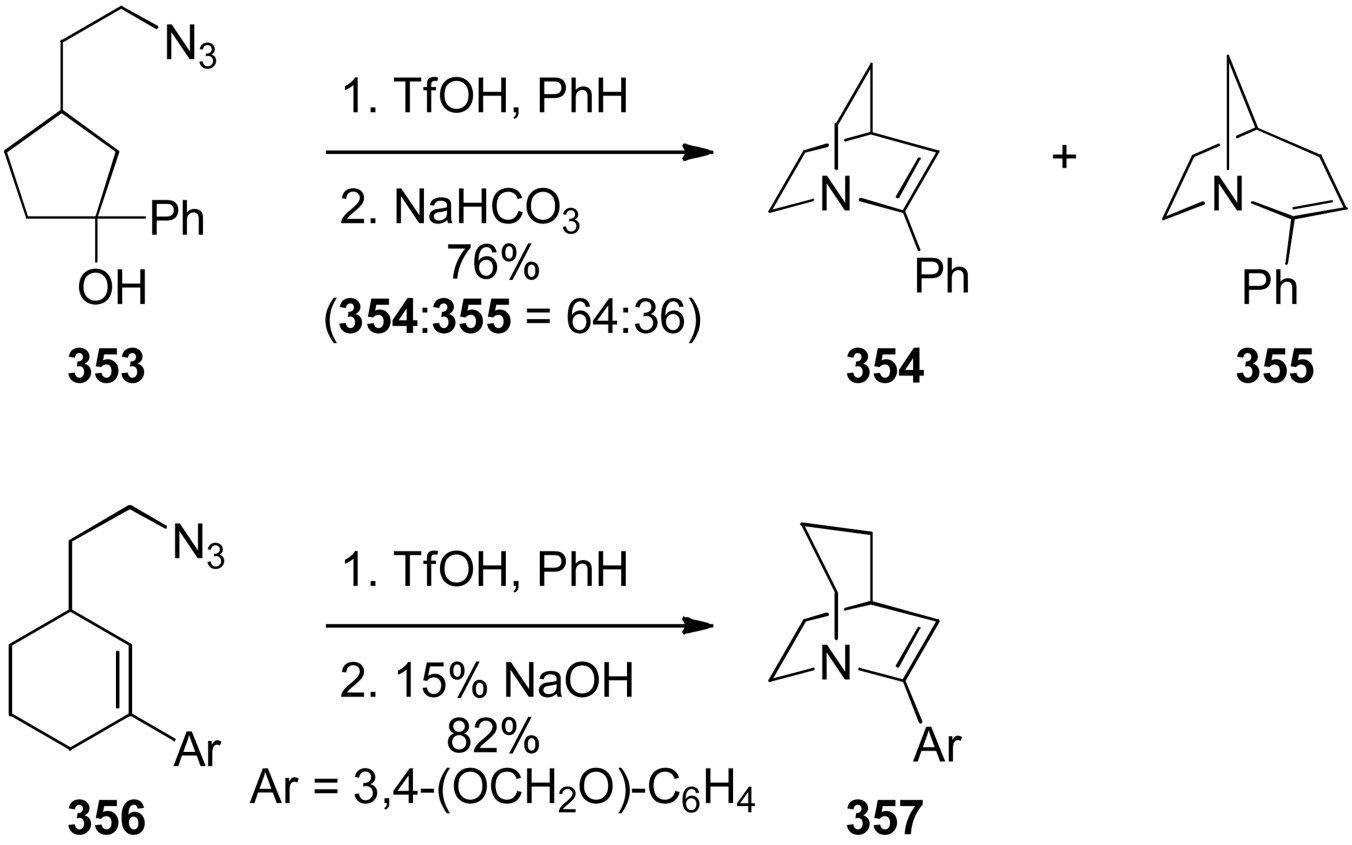


Scheme 95.

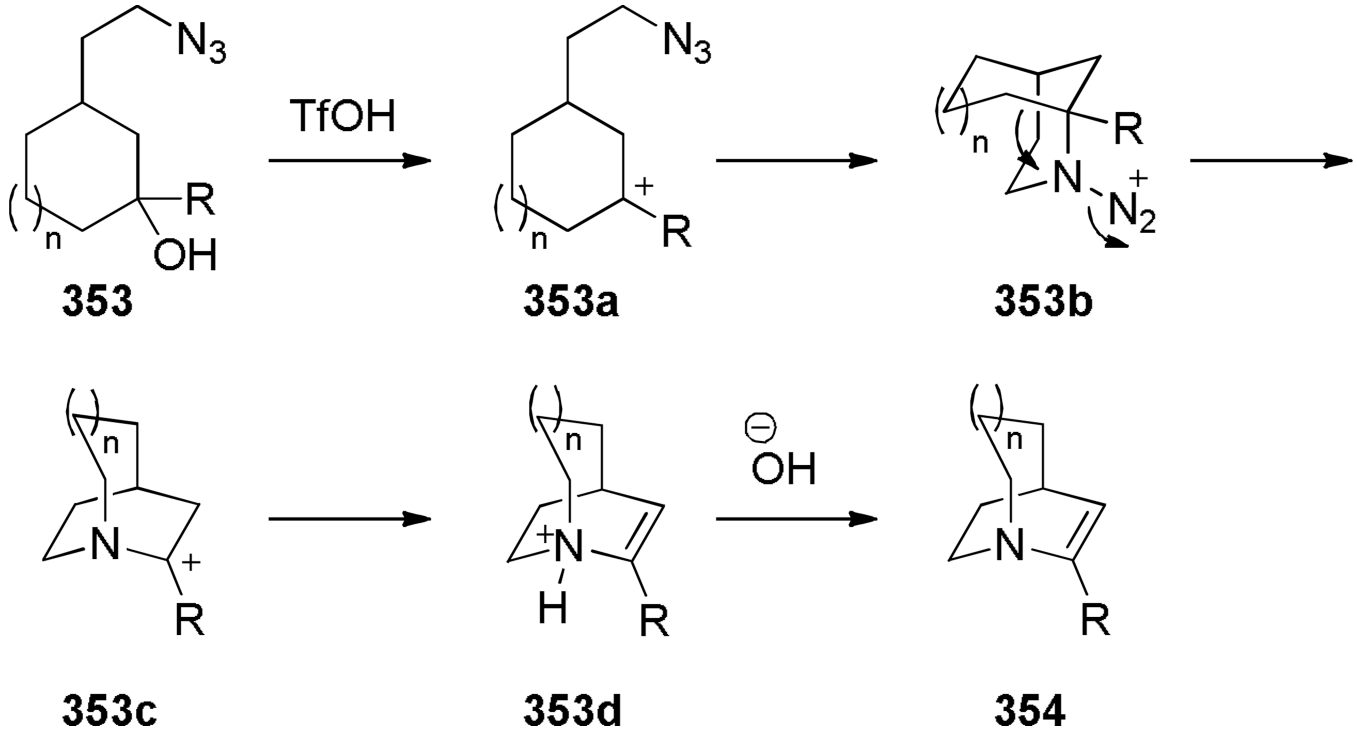
Synthesis of Bridged Bicyclic Enamines by Tandem Rh-Catalyzed C–H Activation/ Alkenylation/Electrocyclization by Ellman



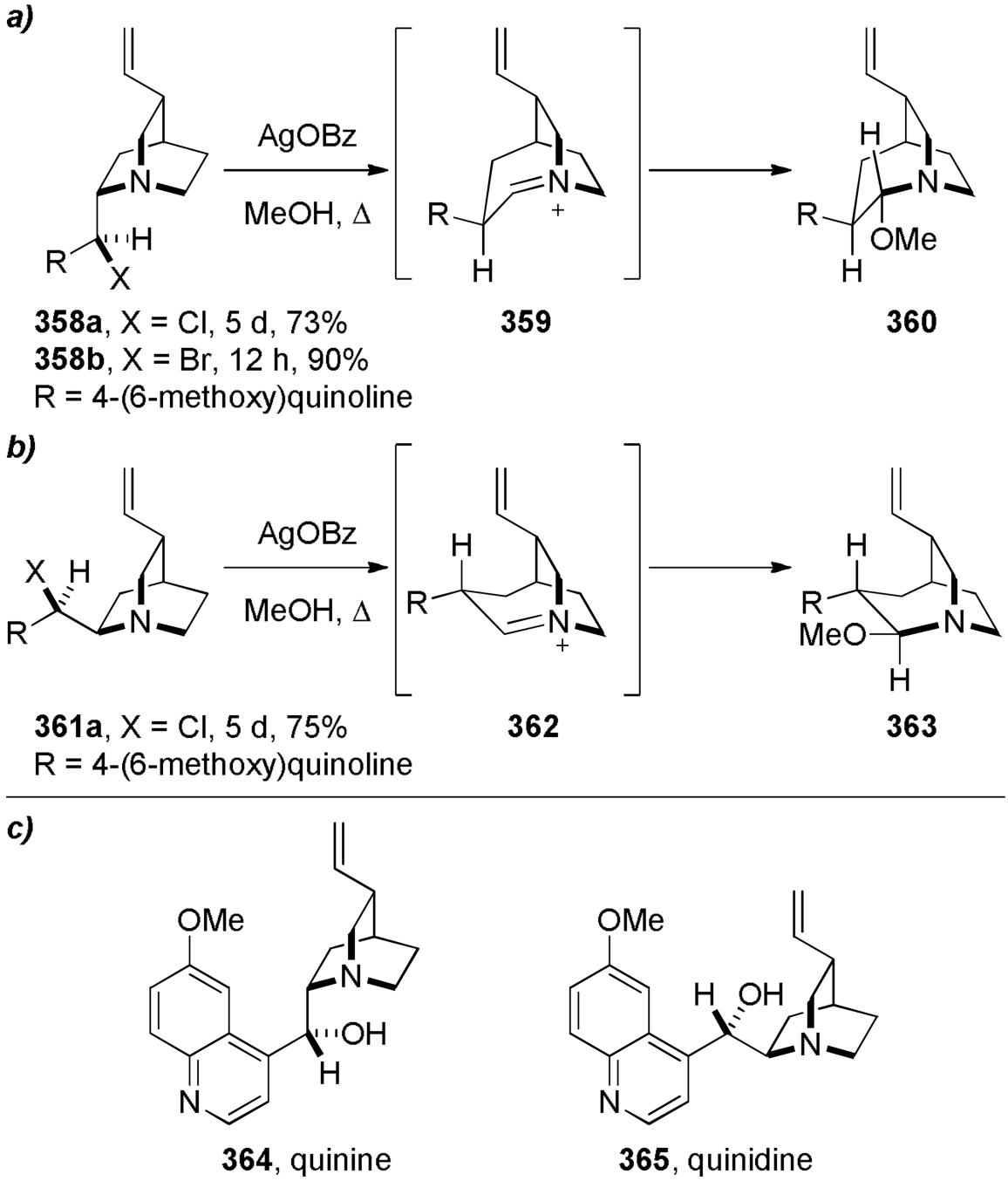
Scheme 96.
Proposed Mechanism for Synthesis of **352**



Scheme 97.
Synthesis of Bridged Enamines viaIntramolecular Schmidt Reaction by Pearson

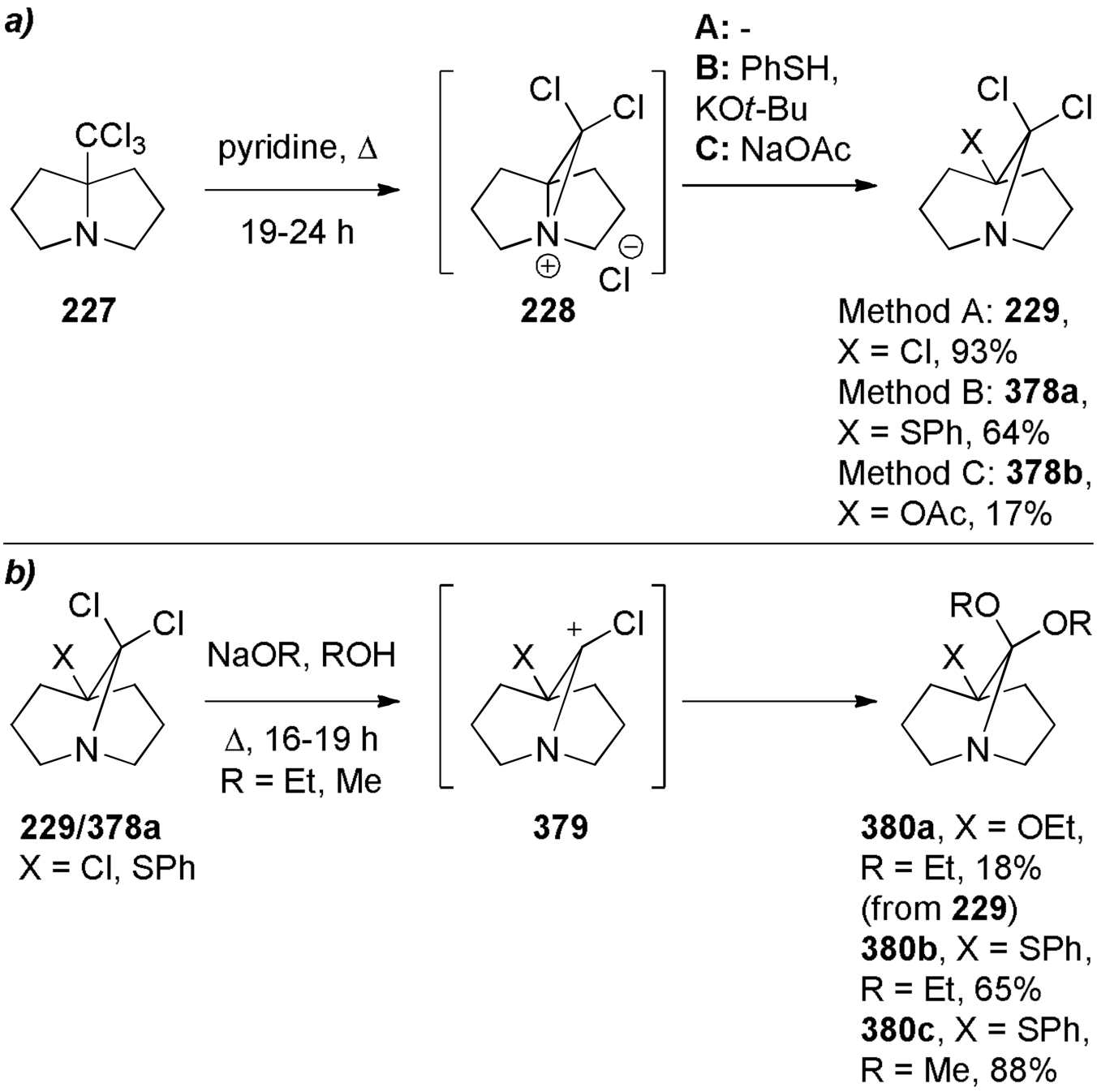


Scheme 98.
Proposed Mechanism for Schmidt Reaction of Azidoalkyl Alcohols



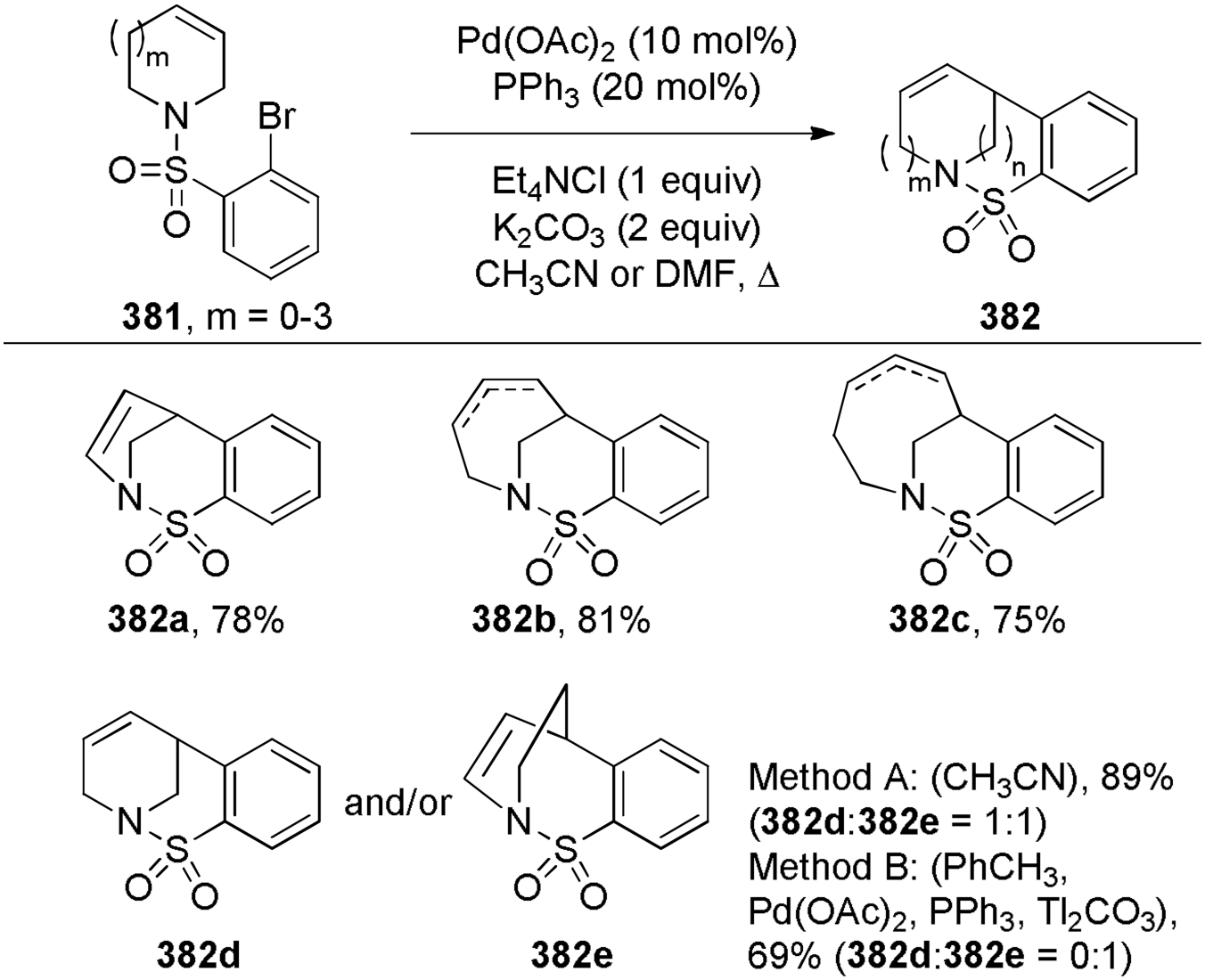
Scheme 99.

Generation of Bridged 1-Aza Iminium Ions by Hoffmann: a) Quinine Series; b) Quinidine Seires; c) Structures of Quinine and Quinidine

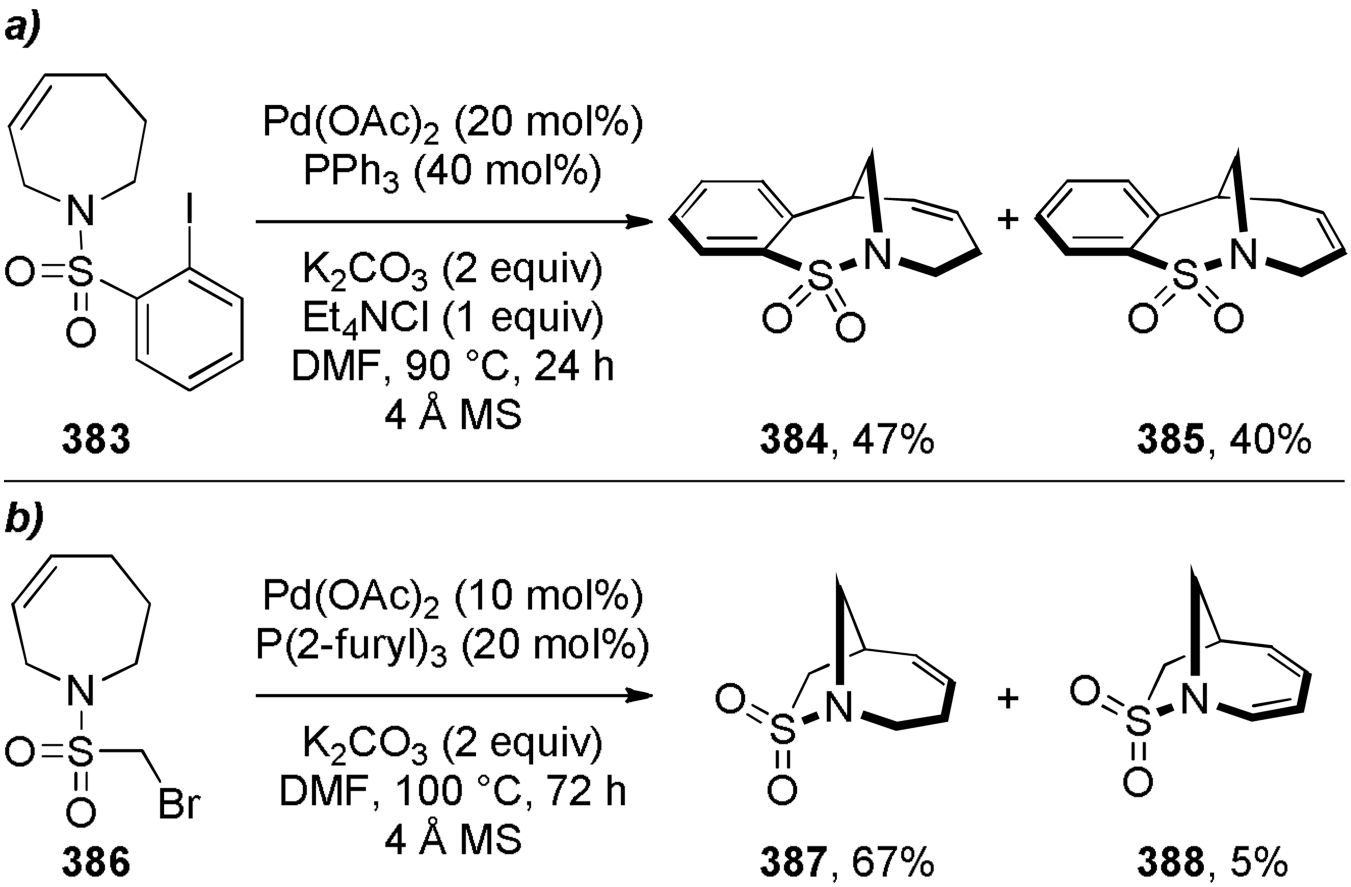


Scheme100.

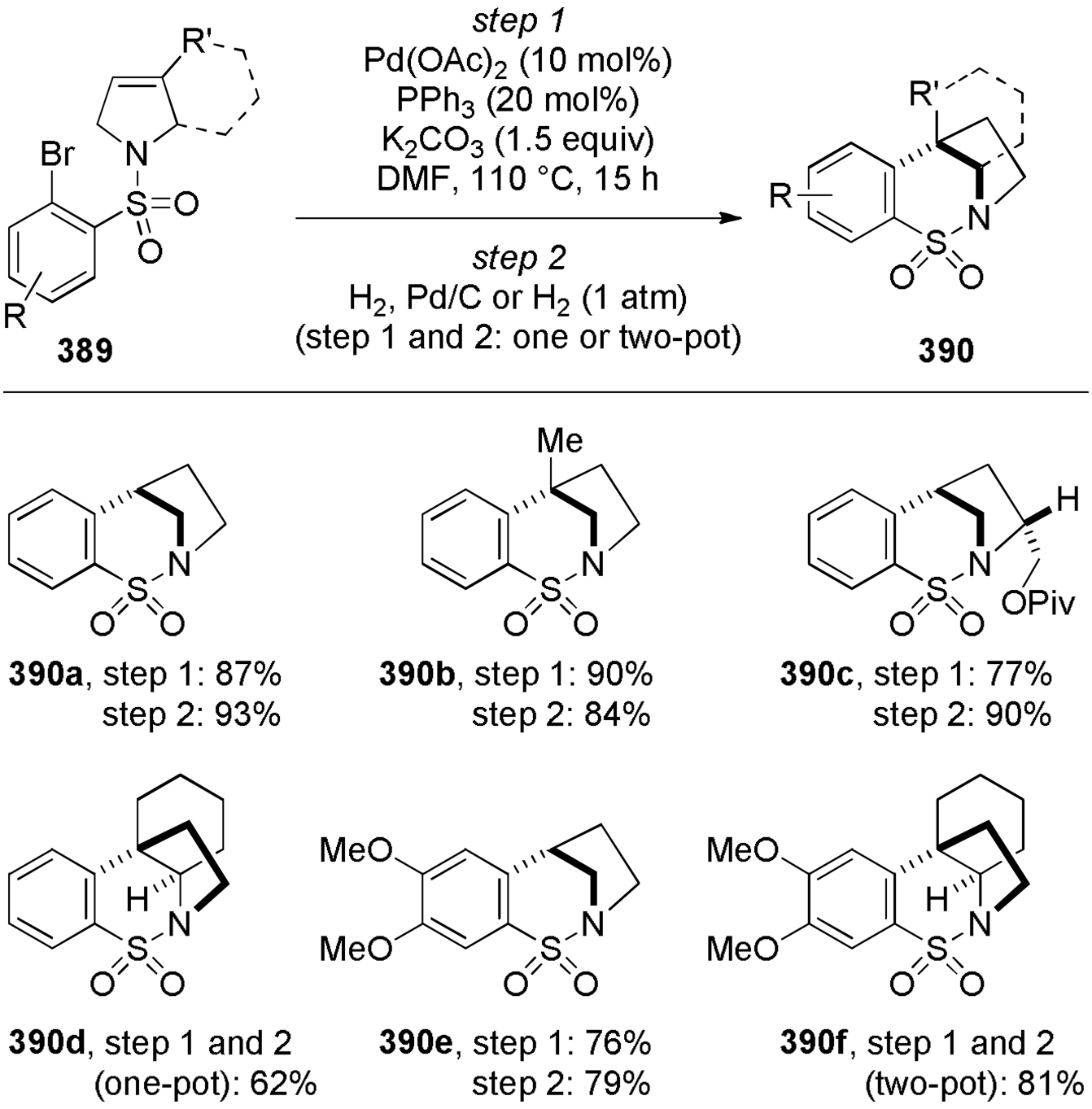
a) Synthesis of 1-Azabicyclo[3.3.1]nonanes by Miyano; b) Generation of Bridged Iminium Ions from 1-Azabicyclo[3.3.1]nonanes



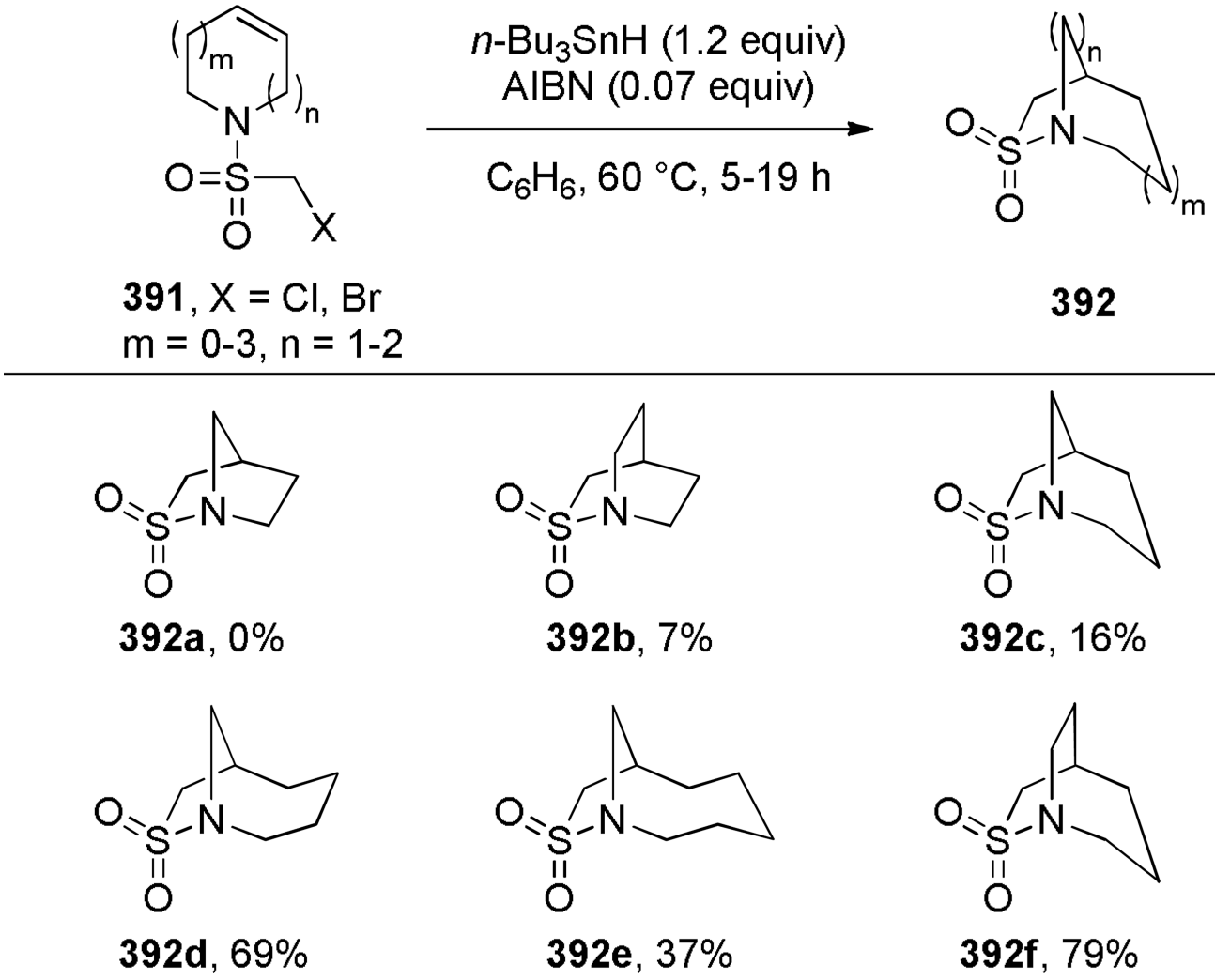
Scheme 101.
Synthesis of Bridged Sultams via Heck Reaction by Grigg



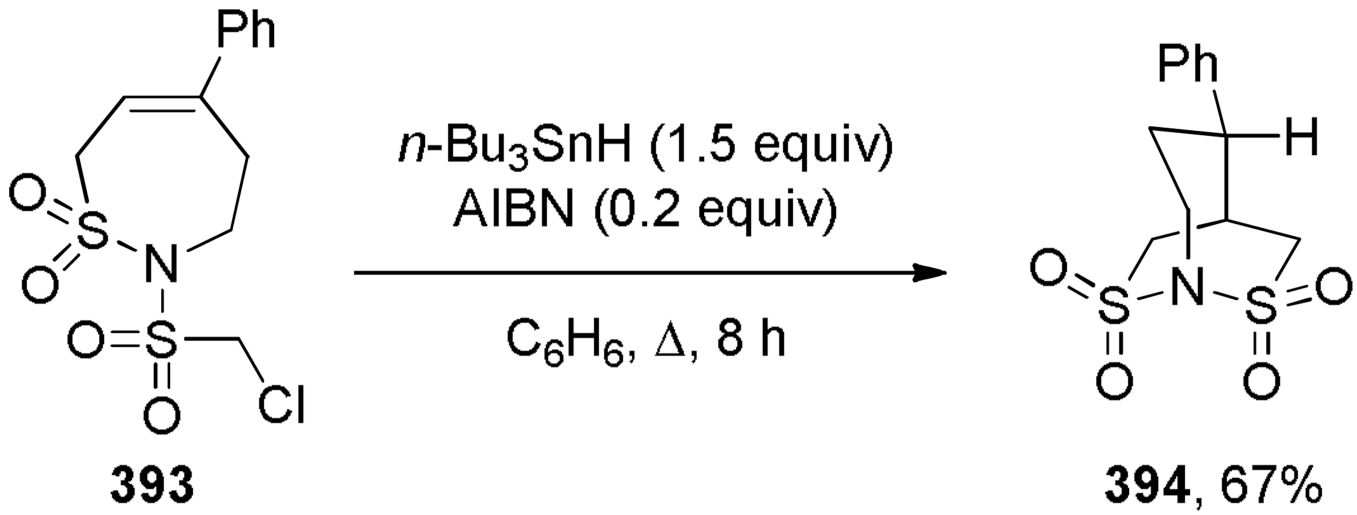
Scheme 102.
Synthesis of Bridged Sultams via Heck Reaction by Paquette



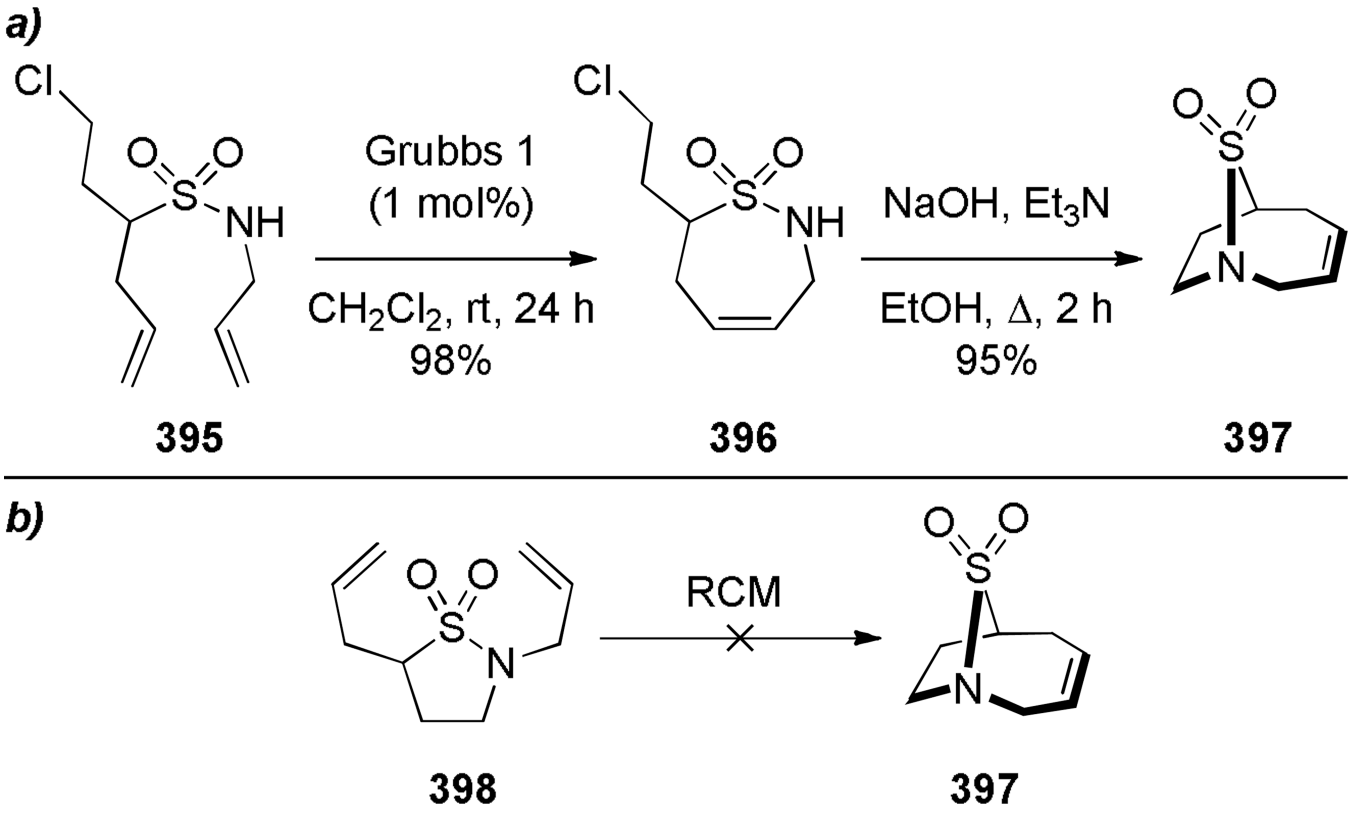
Scheme 103.
Synthesis of Bridged Sultams via Tandem Heck Reaction/Hydrogenation by Evans



Scheme 104.
Synthesis of Bridged Sultams via Radical Cyclization by Paquette

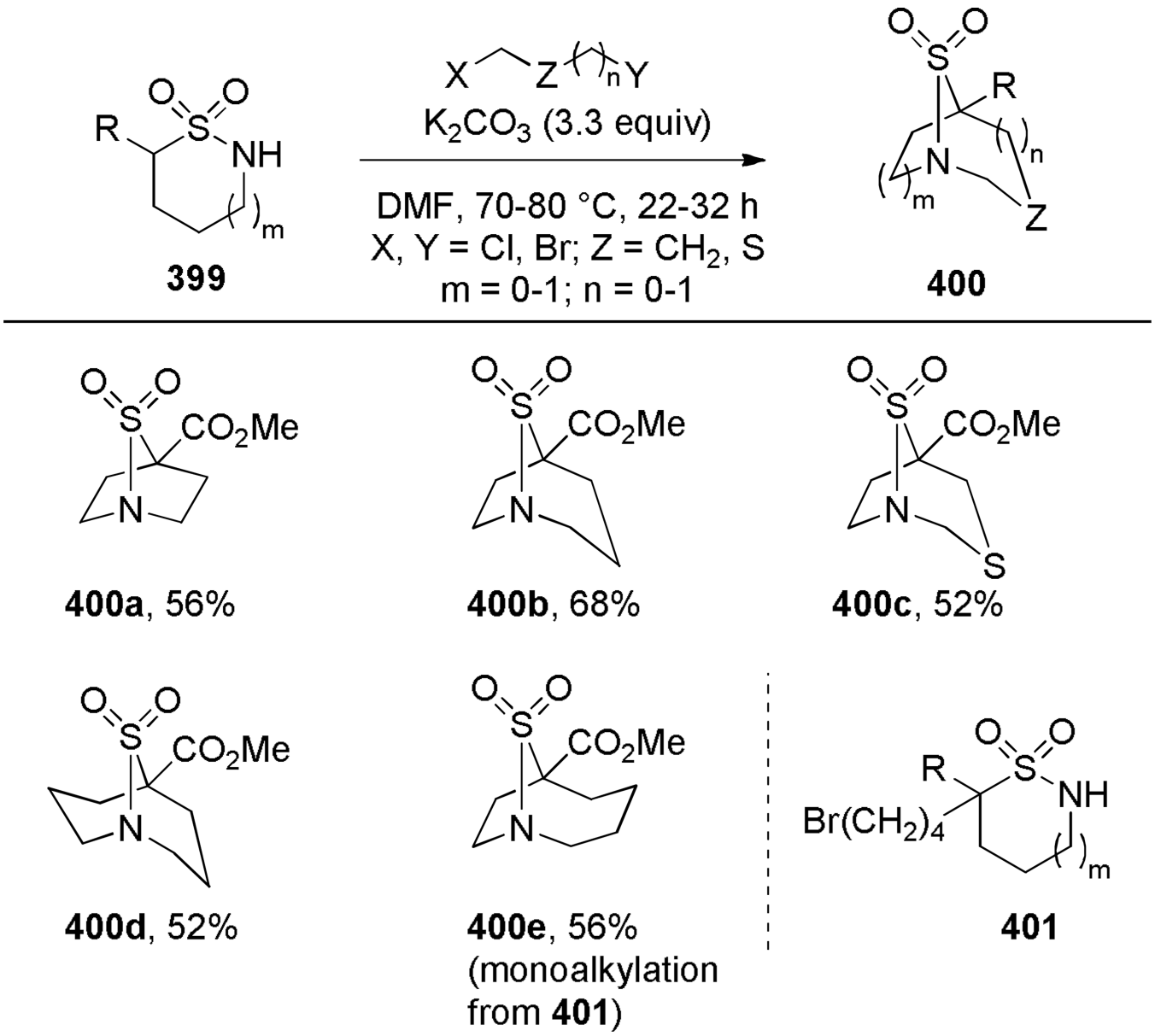


Scheme 105.
Synthesis of Bridged Disulfonimide via Radical Cyclization by Paquette

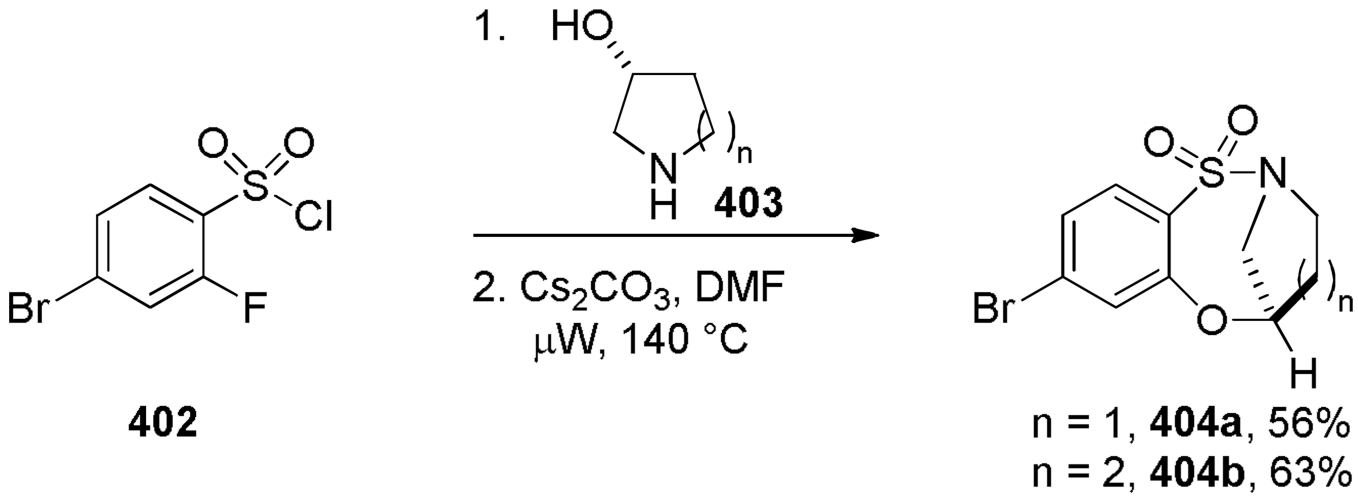


Scheme 106.

a) Synthesis of “Apex” Bridged Sultam by Paquette; b) Unsuccessful Approach via RCM

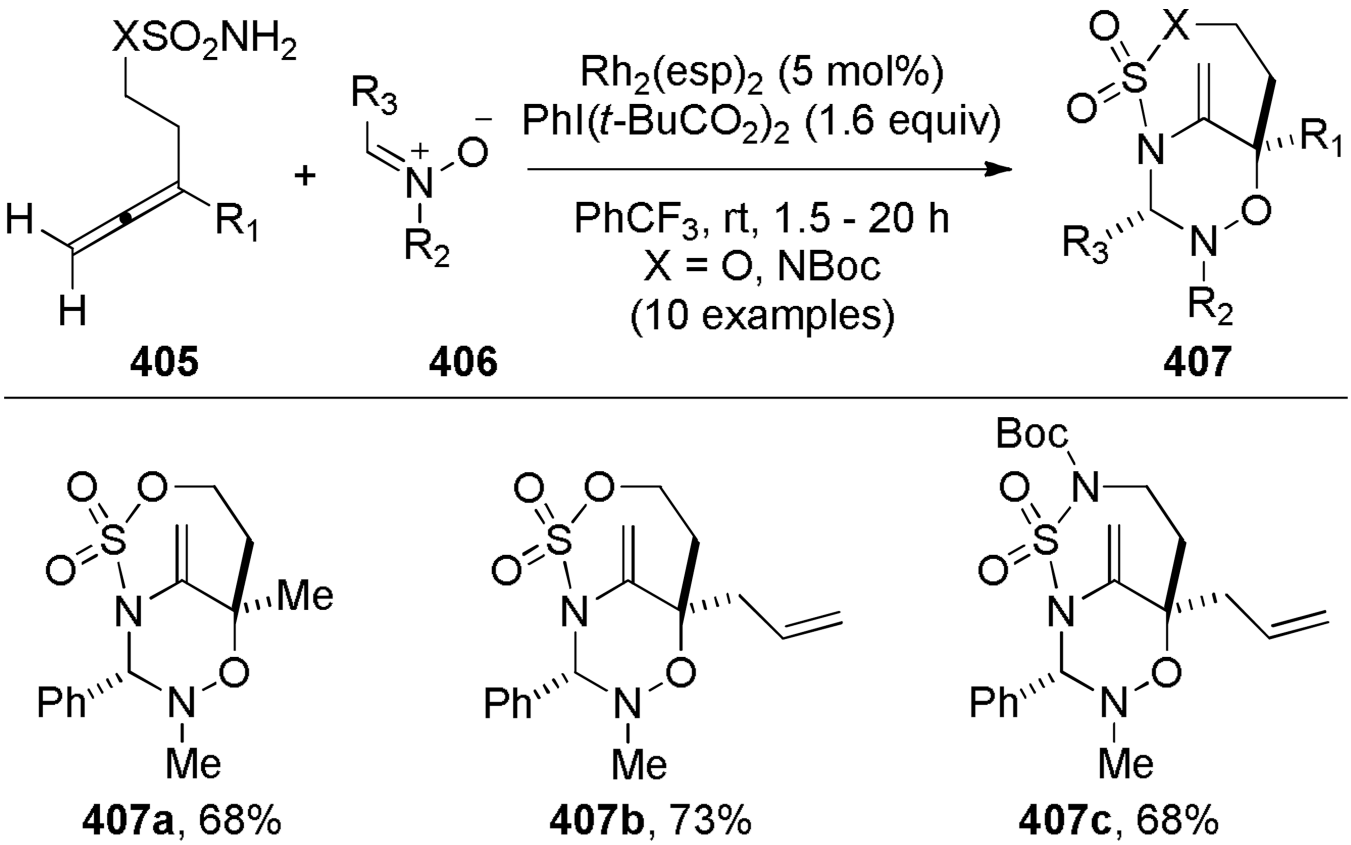


Scheme 107.
Synthesis of Bridged Sultams via Double Alkylation by de Meijere



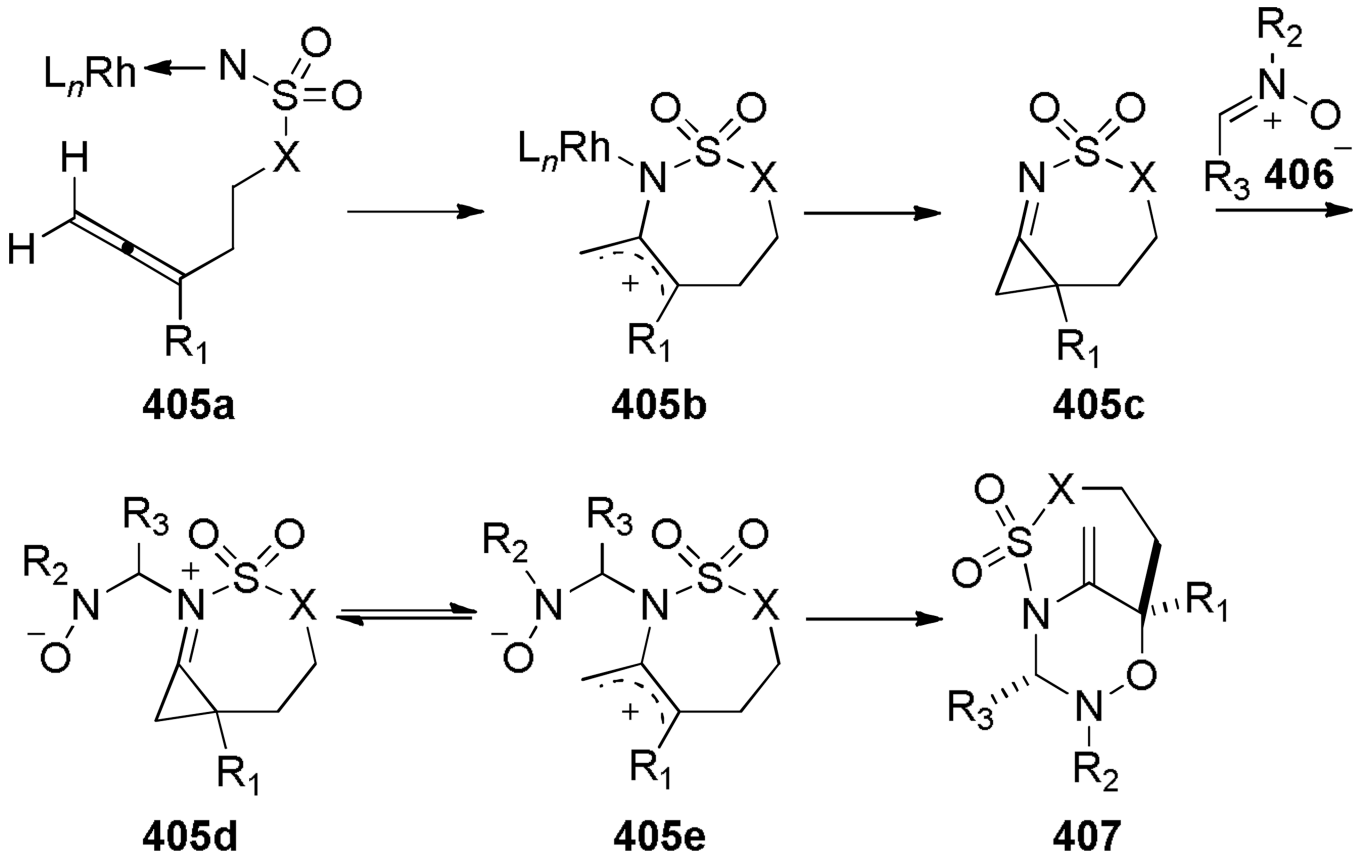
Scheme 108.

Synthesis of Benzofused Bridged Sultams via Sulfonylation/S_NAr of Amino Alcohols by Hanson

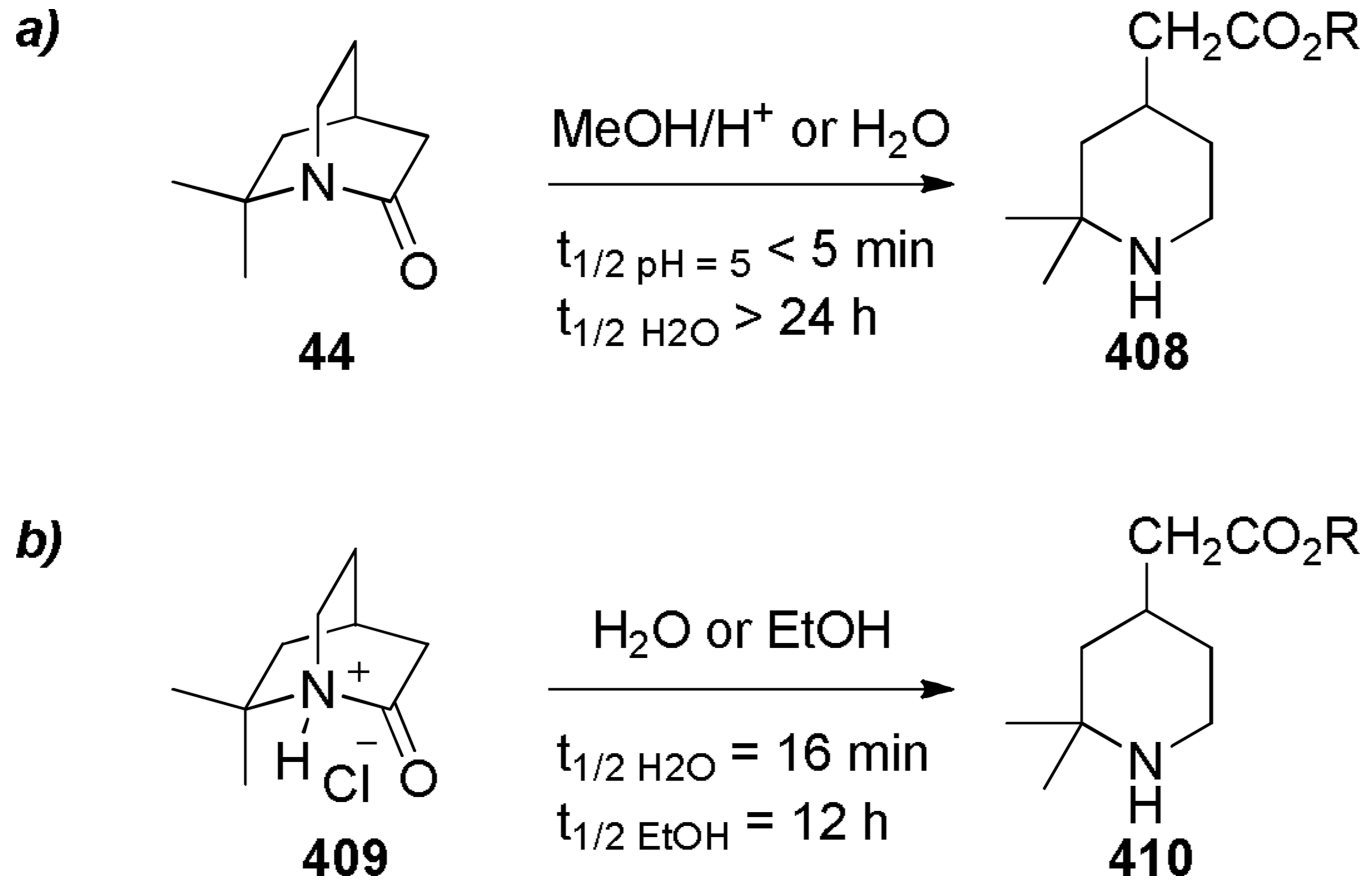


Scheme 109.

Synthesis of Heteroatom-Derived Bridged Sultams via Rh-Catalyzed Allene Sulfamidation by Blakey

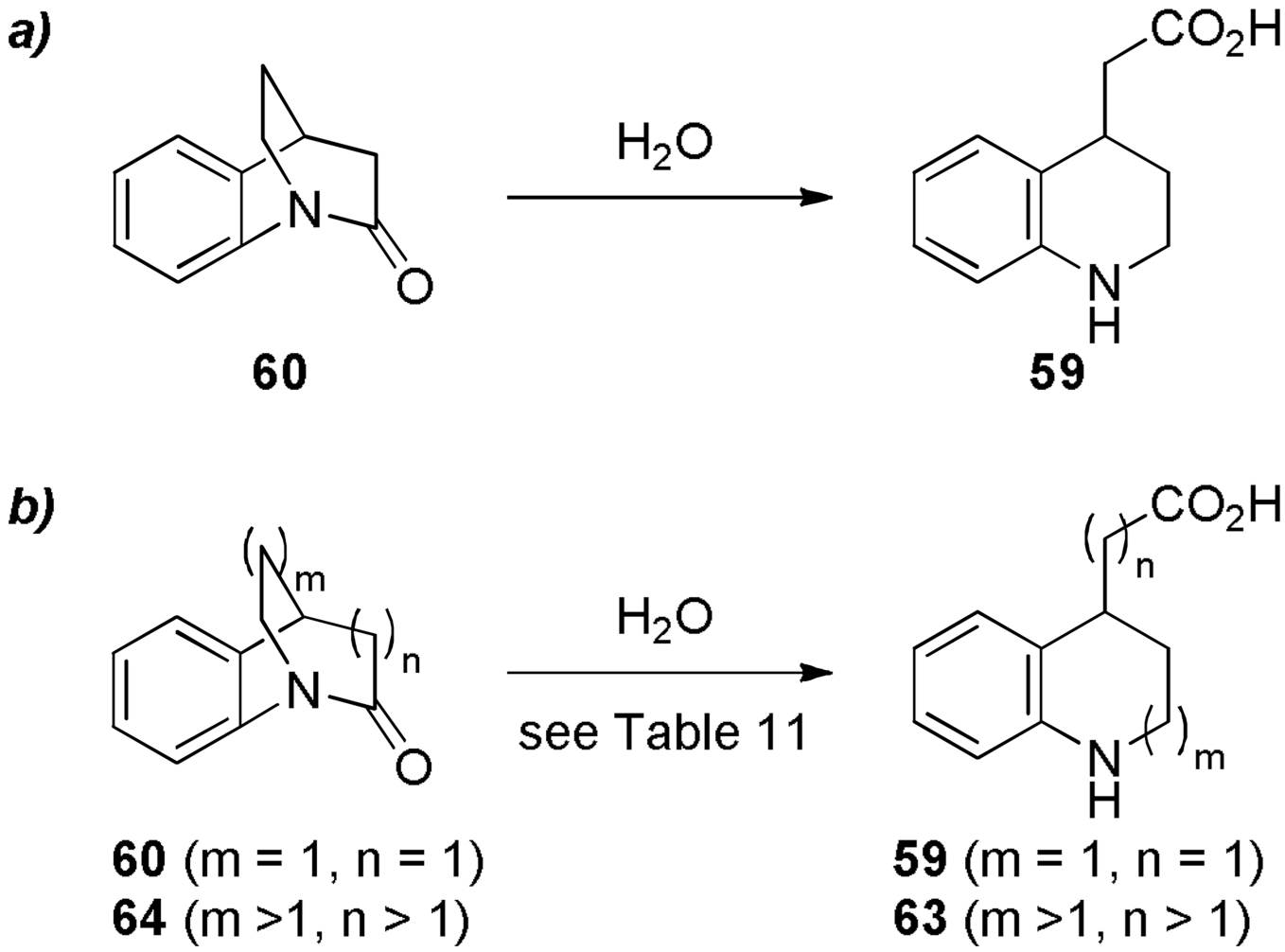


Scheme 110.
Proposed Mechanism for Synthesis of **407**



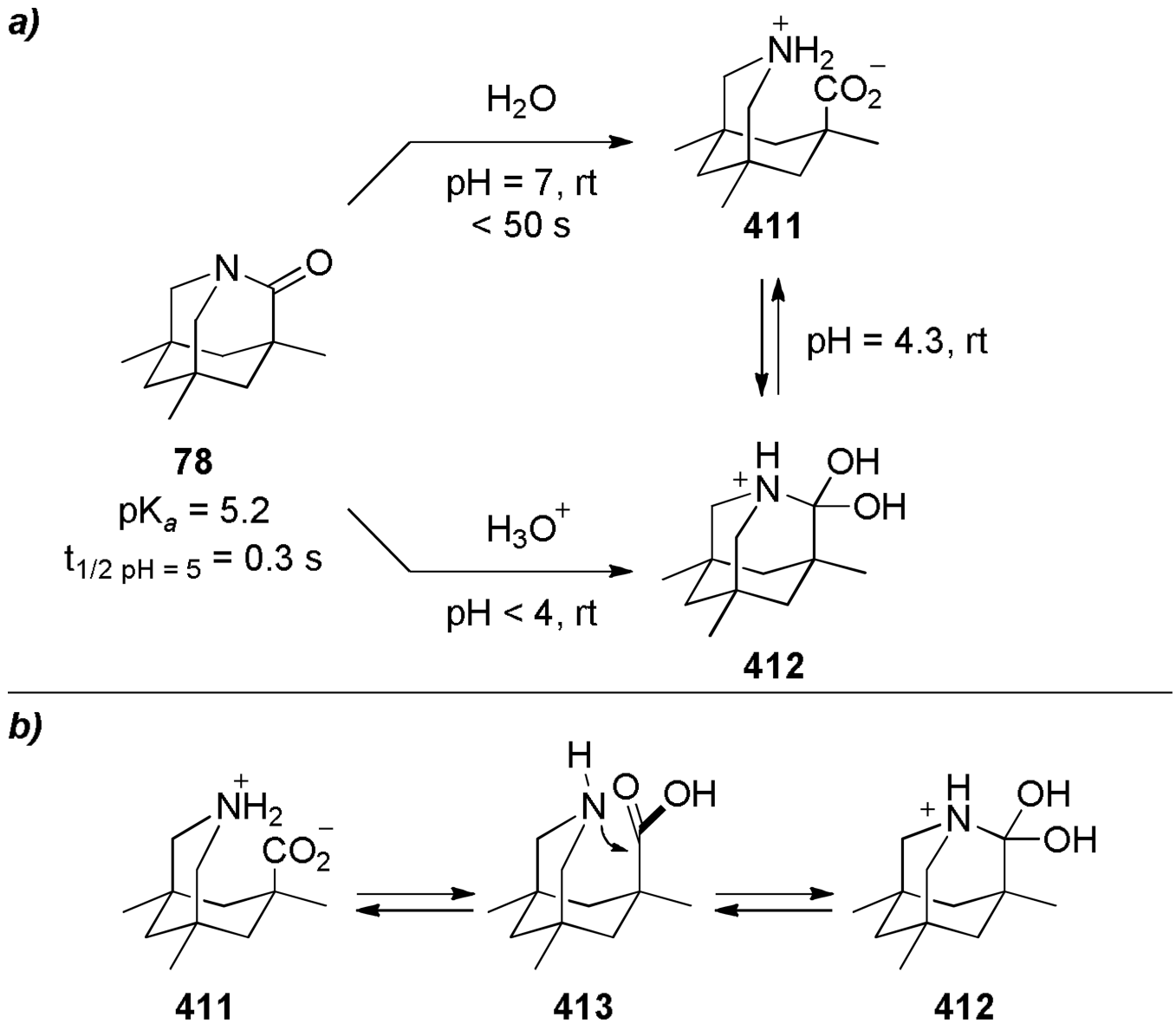
Scheme 111.

a) Hydrolysisof 6,6-Dimethylquinuclidin-2-one; b) Hydrolysis of 6,6-Dimethyl-2-quinuclidinium Chloride by Pracejus



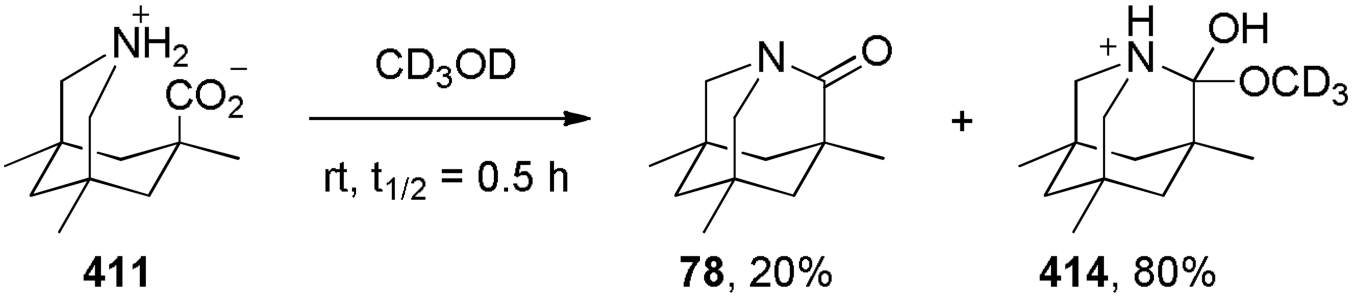
Scheme 112.

a) Hydrolysis of Benzo-2-quinuclidone by Blackburn; b) Hydrolysis of Extended Ring Systems of Benzo-2-quinuclidones by Brown



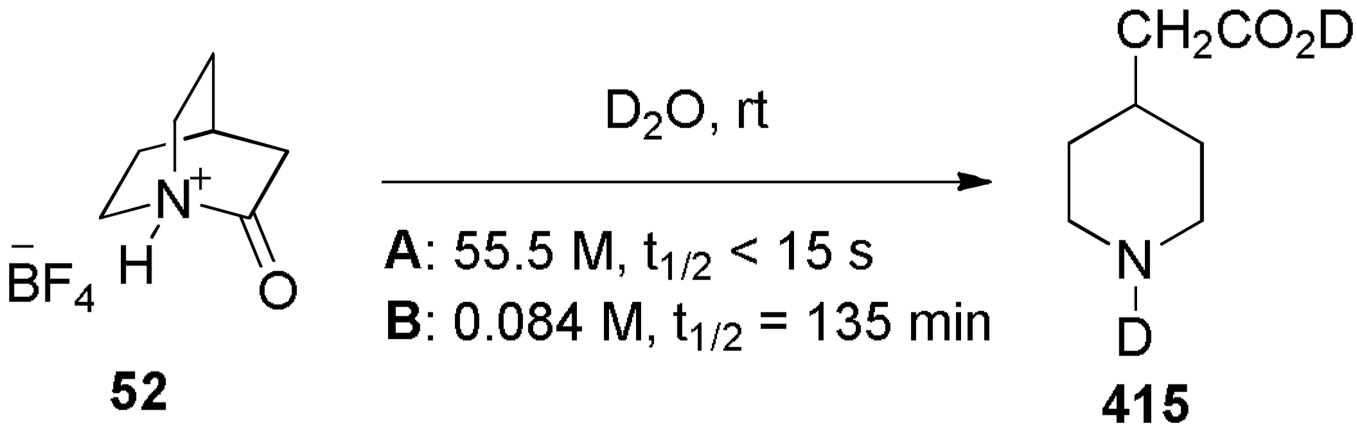
Scheme 113.

a) Hydrolysis of 1-Aza-2-adamantanone; b) Proposed Mechanismfor Hydrolysis by Kirby



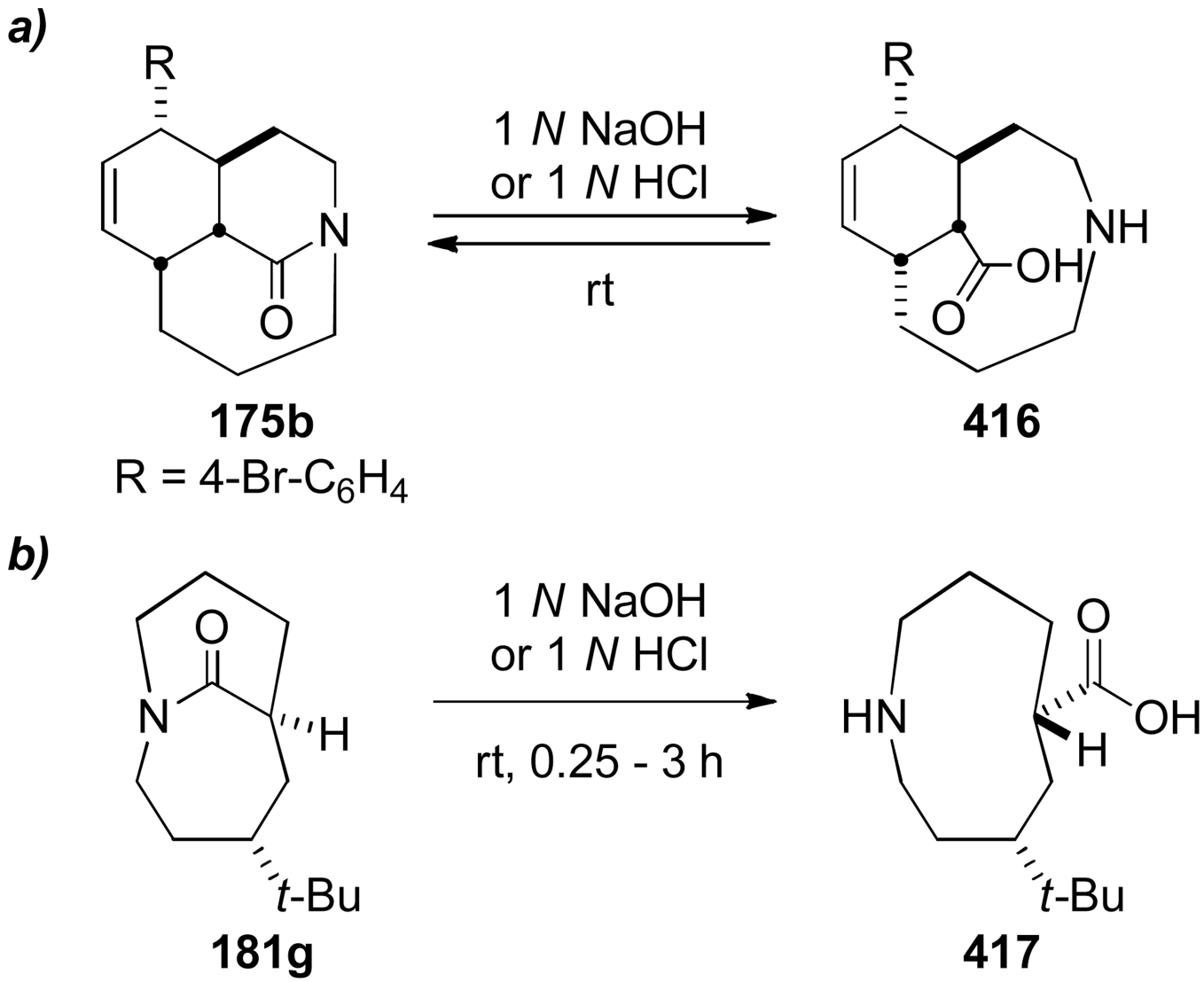
411 **78**, 20% **414**, 80%

Scheme 114.
Synthesis of 1-Aza-2-adamantanone from the Corresponding Amino Acid by Kirby

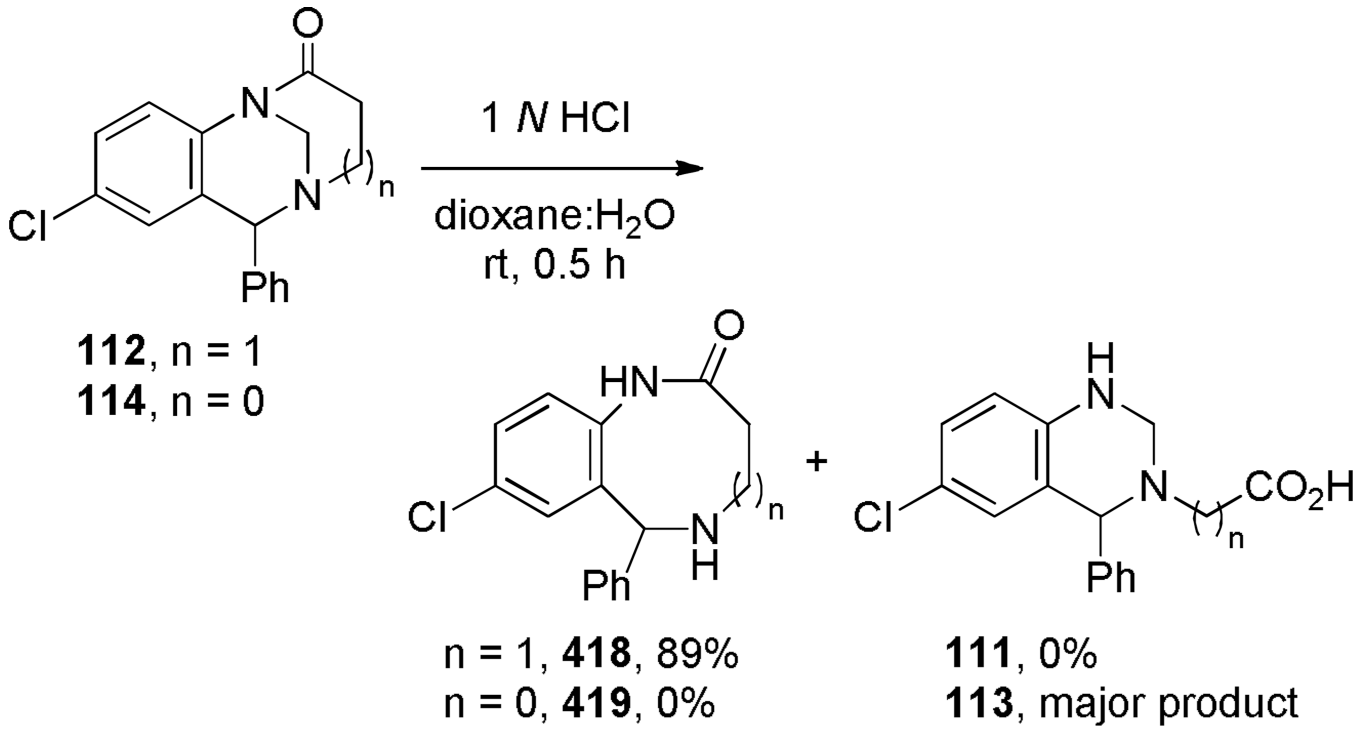


52 415

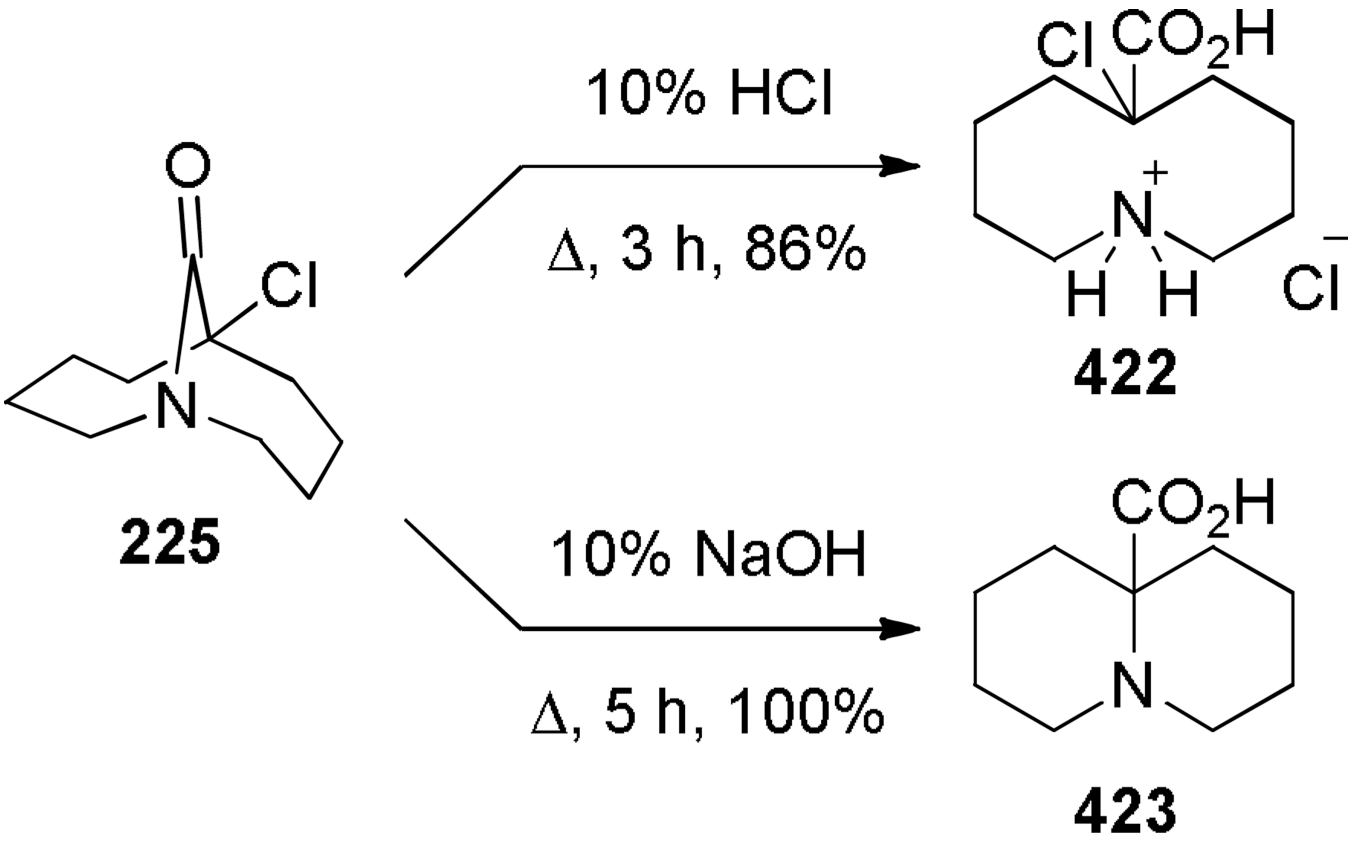
Scheme 115.
Hydrolysis of 2-Quinuclidonium Tetrafluoroborate by Stoltz



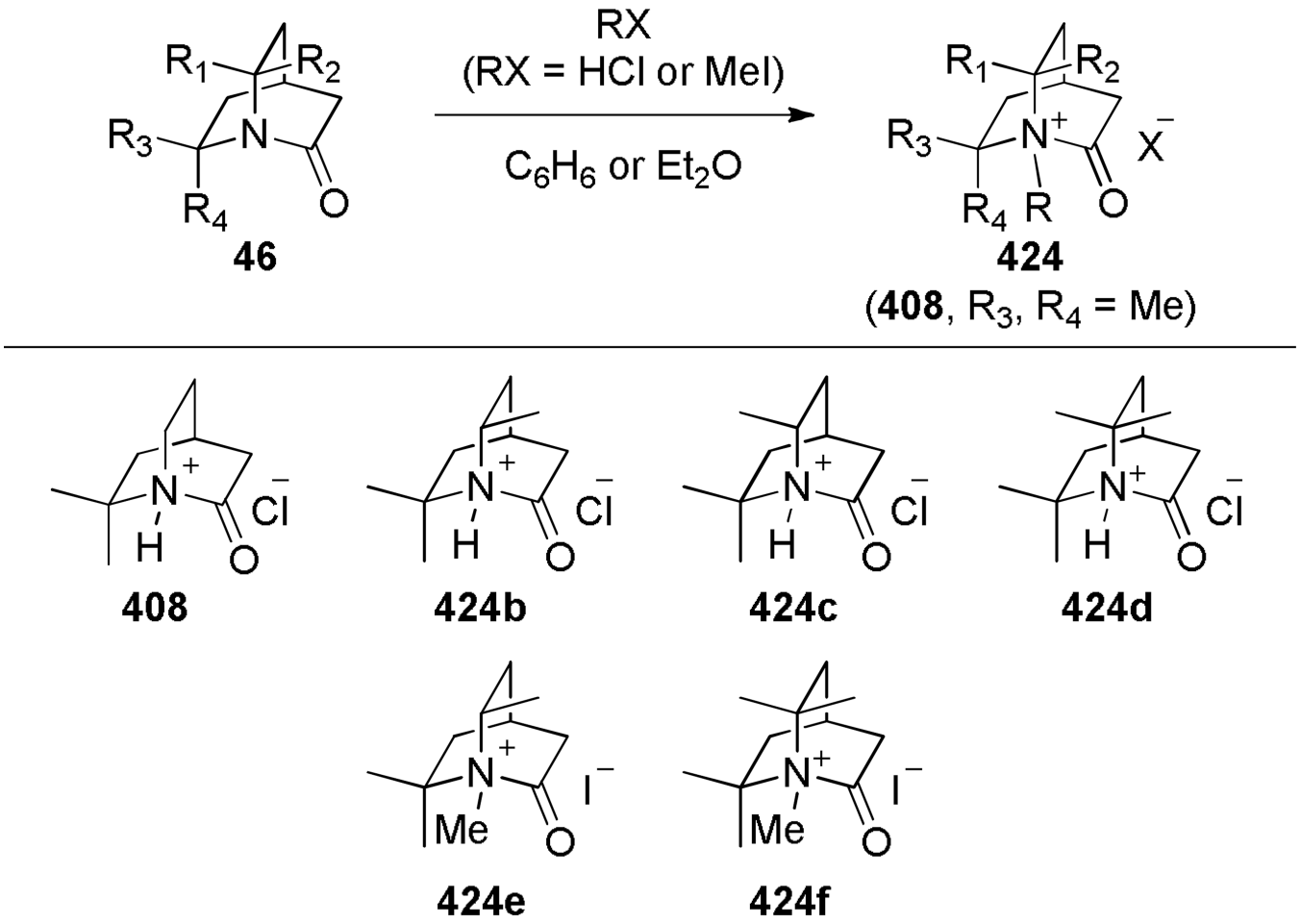
Scheme 116.
Hydrolysis of Medium Bridged Twisted Lactams by Aubé



Scheme 117.
Hydrolysis of Aza-Bridged Lactams by Denzer and Ott

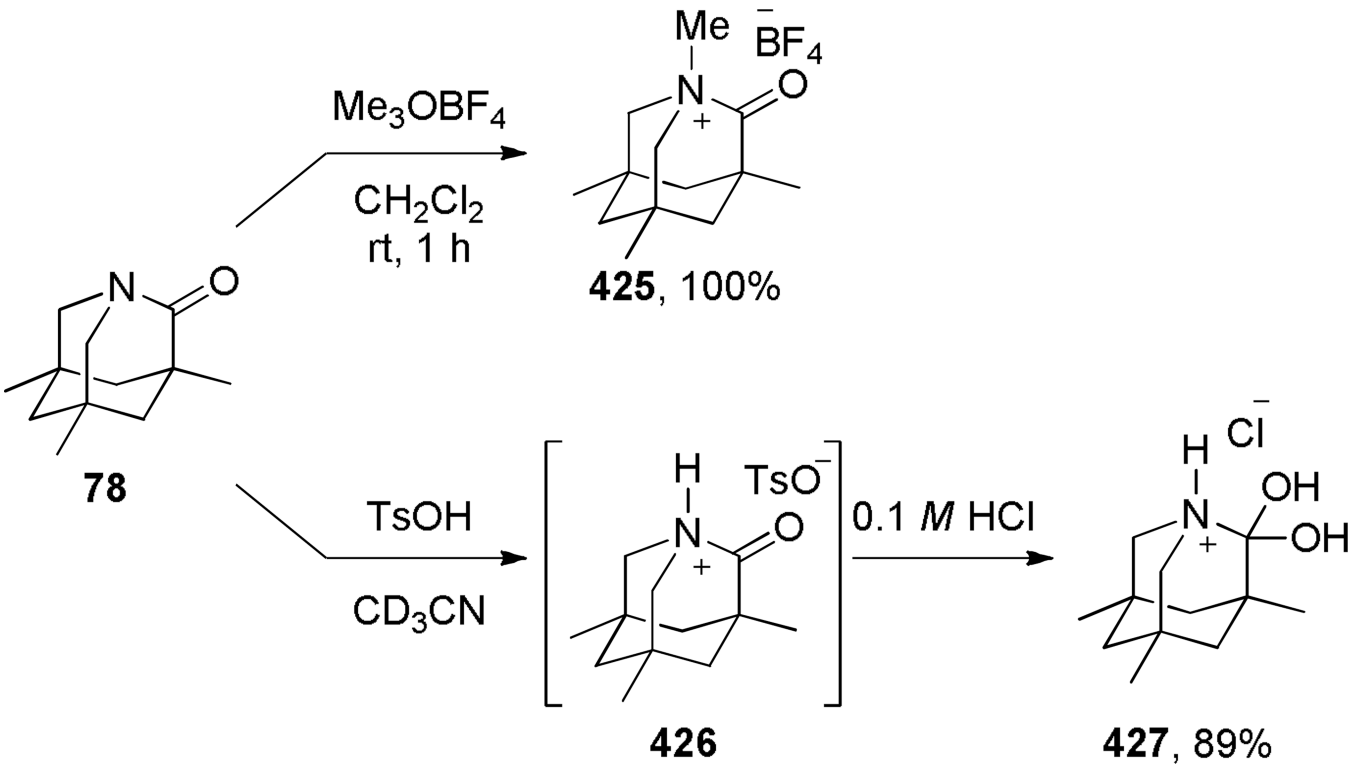


Scheme 118.
Hydrolysis of 6-Chloro-1-Azabicyclo[4.4.1]undecan-11-one by Arata



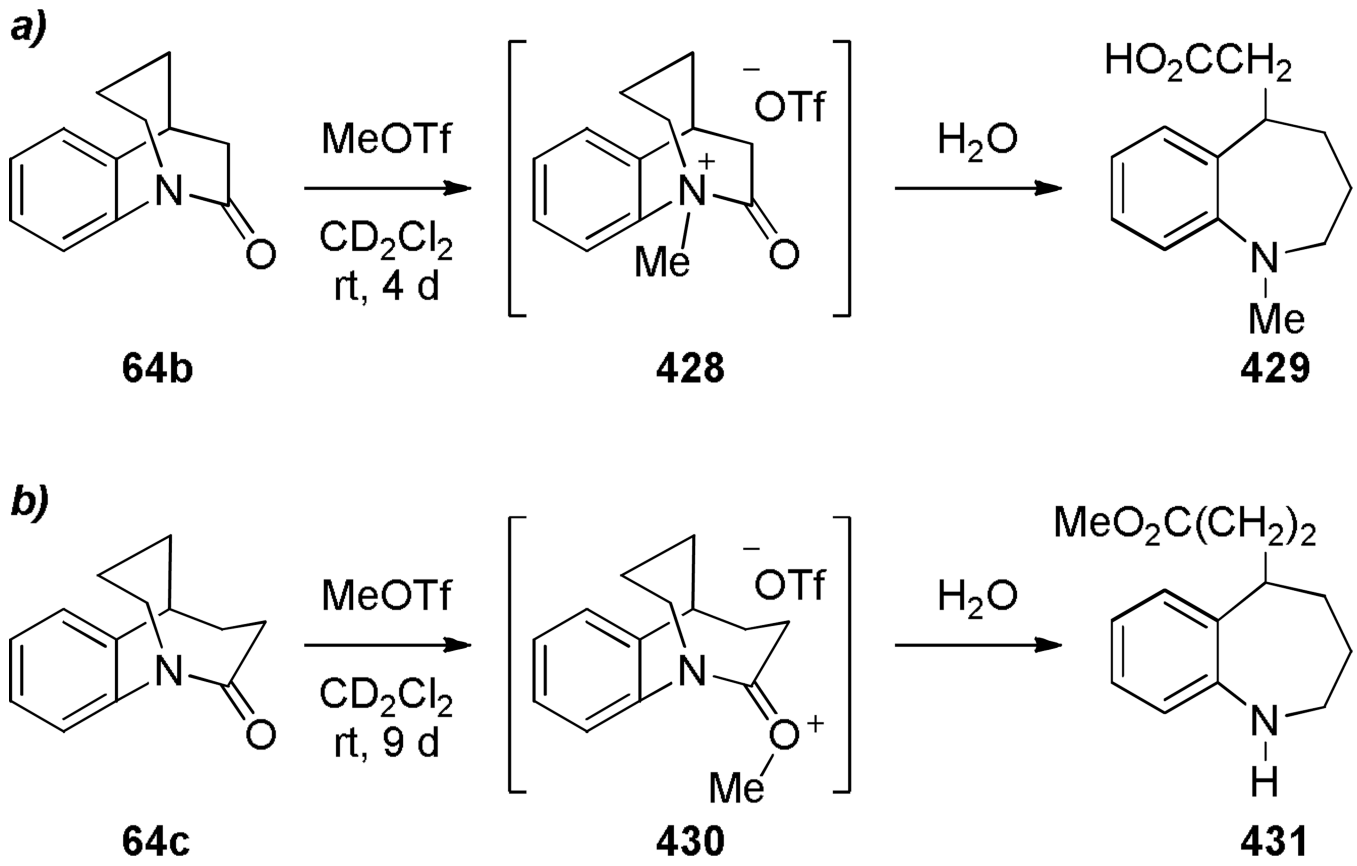
Scheme 119.

N-Protonation and *N*-Methylation of 2-Quinuclidones by Pracejus and Yakhontov

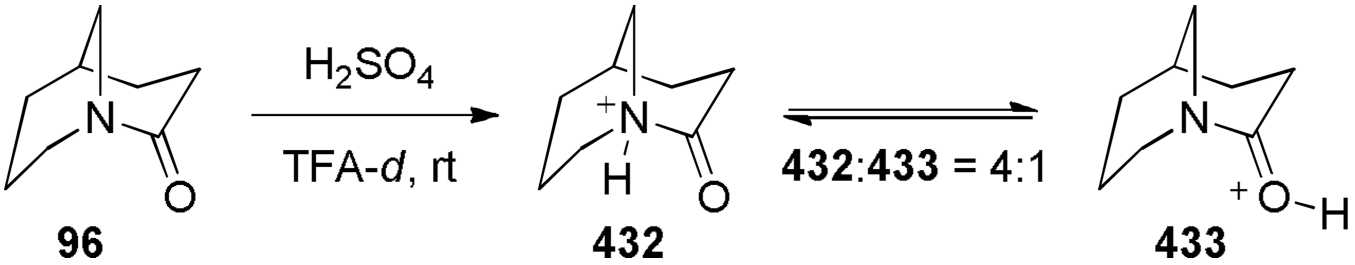


Scheme 120.

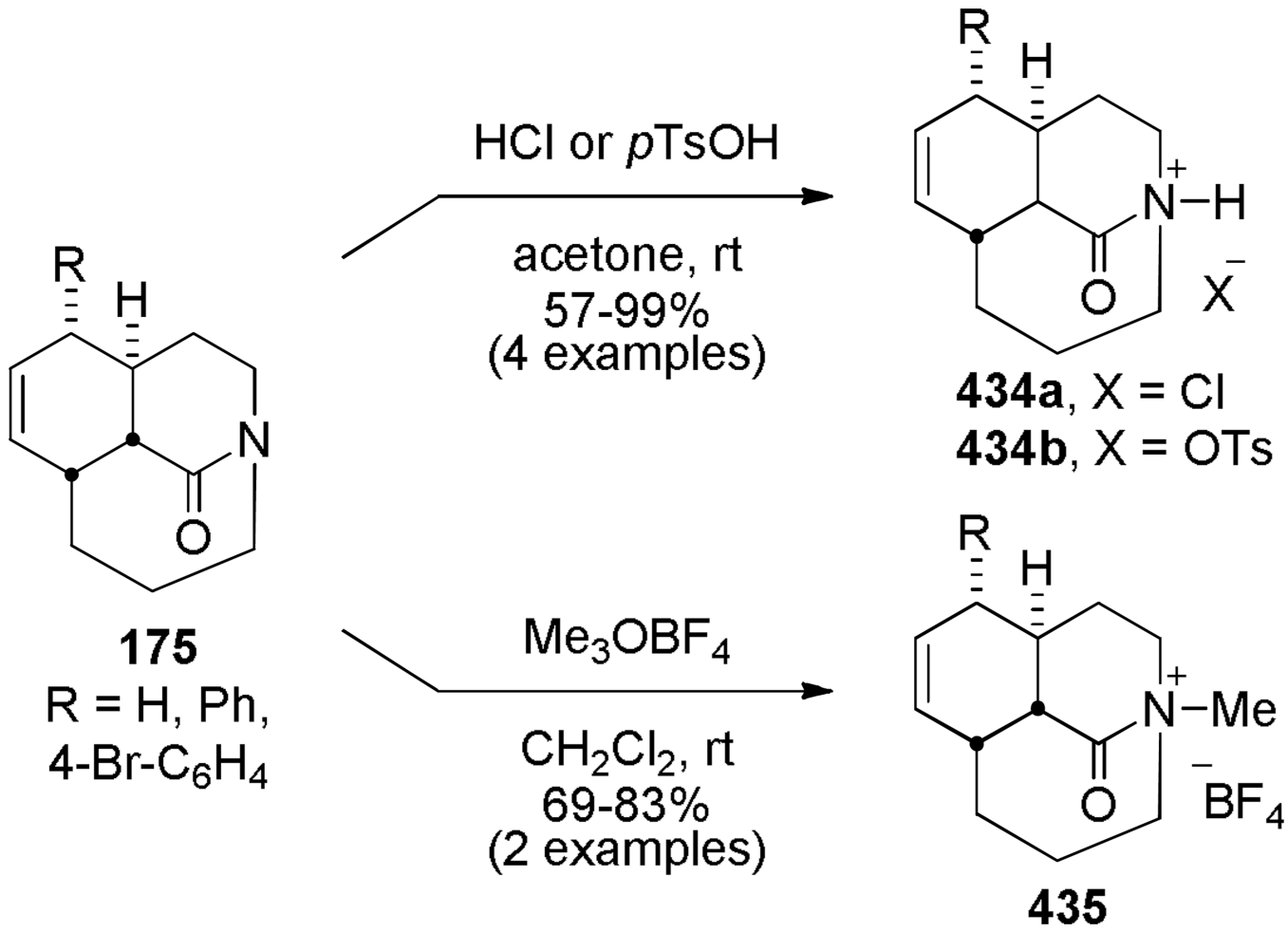
N-Methylation and *N*-Protonation of 1-Aza-2-adamantanone by Kirby



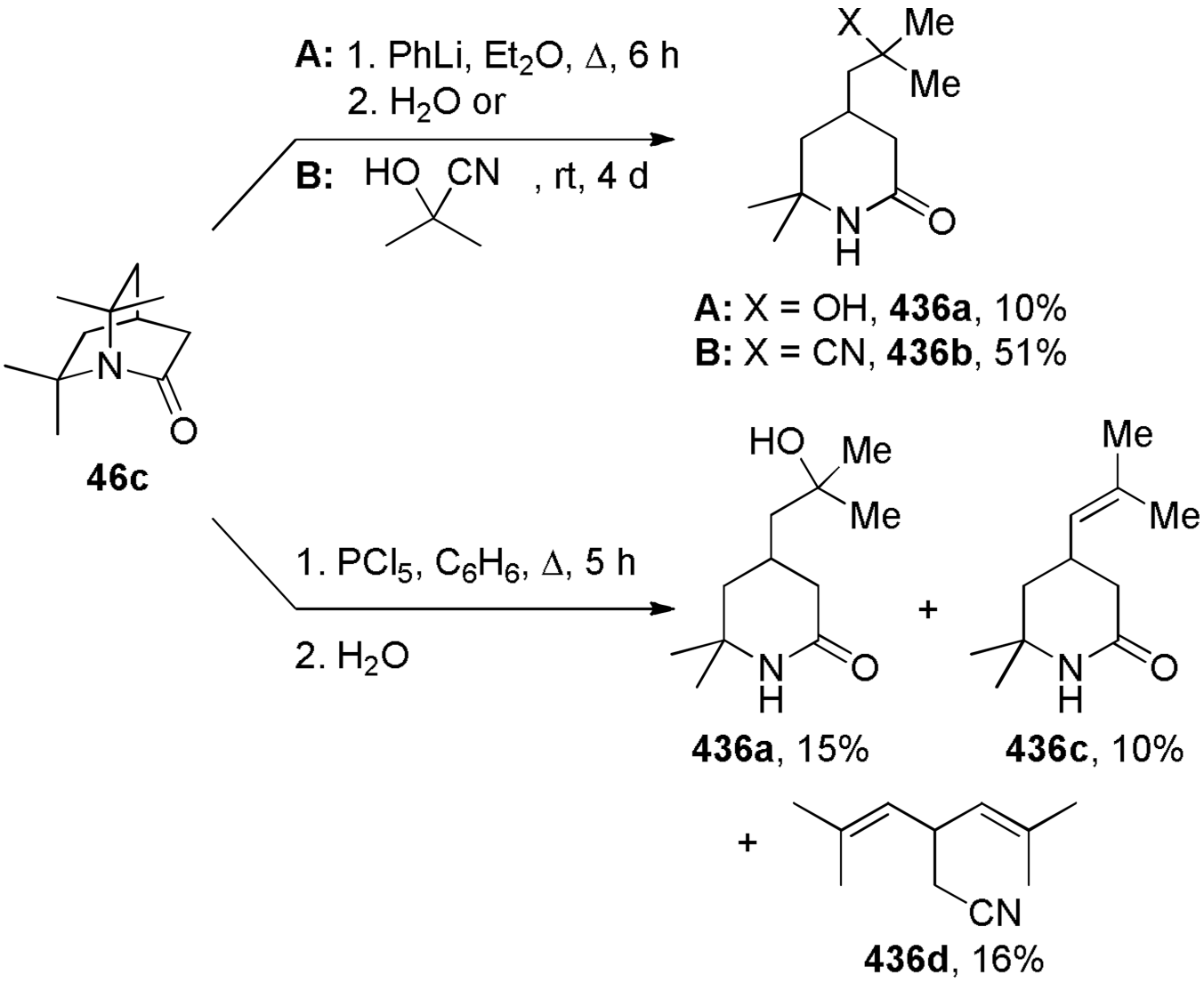
Scheme 121.
N-Methylation vs. *O*-Methylation of Benzo-2-quinuclidones by Brown



Scheme 122.
N-Protonation vs. *O*-Protonation of 1-Azabicyclo[3.3.1]nonan-2-one by Greenberg

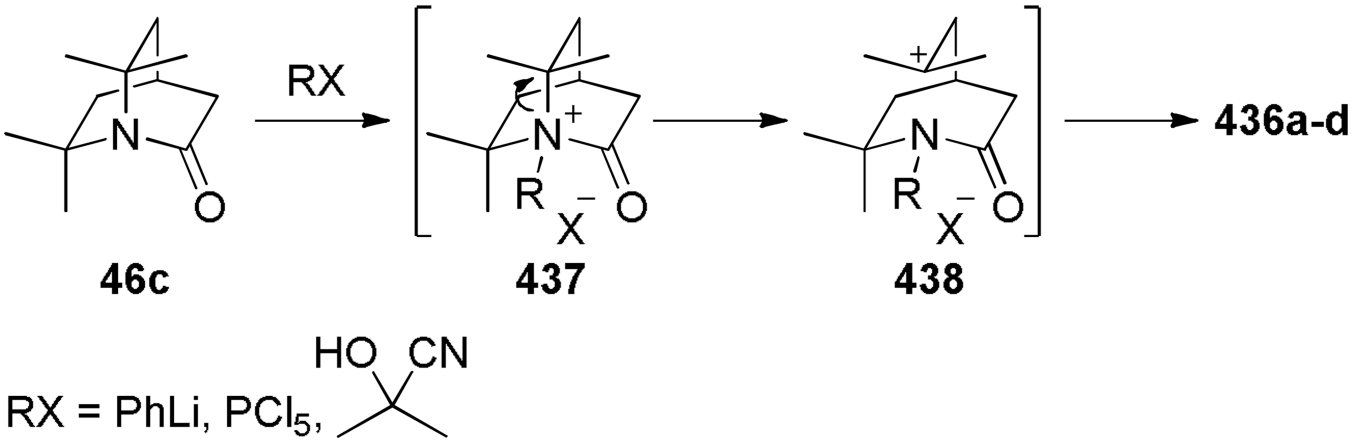


Scheme 123.
N-Protonation and *N*-Methylation of Medium Bridged Twisted Lactams by Aubé

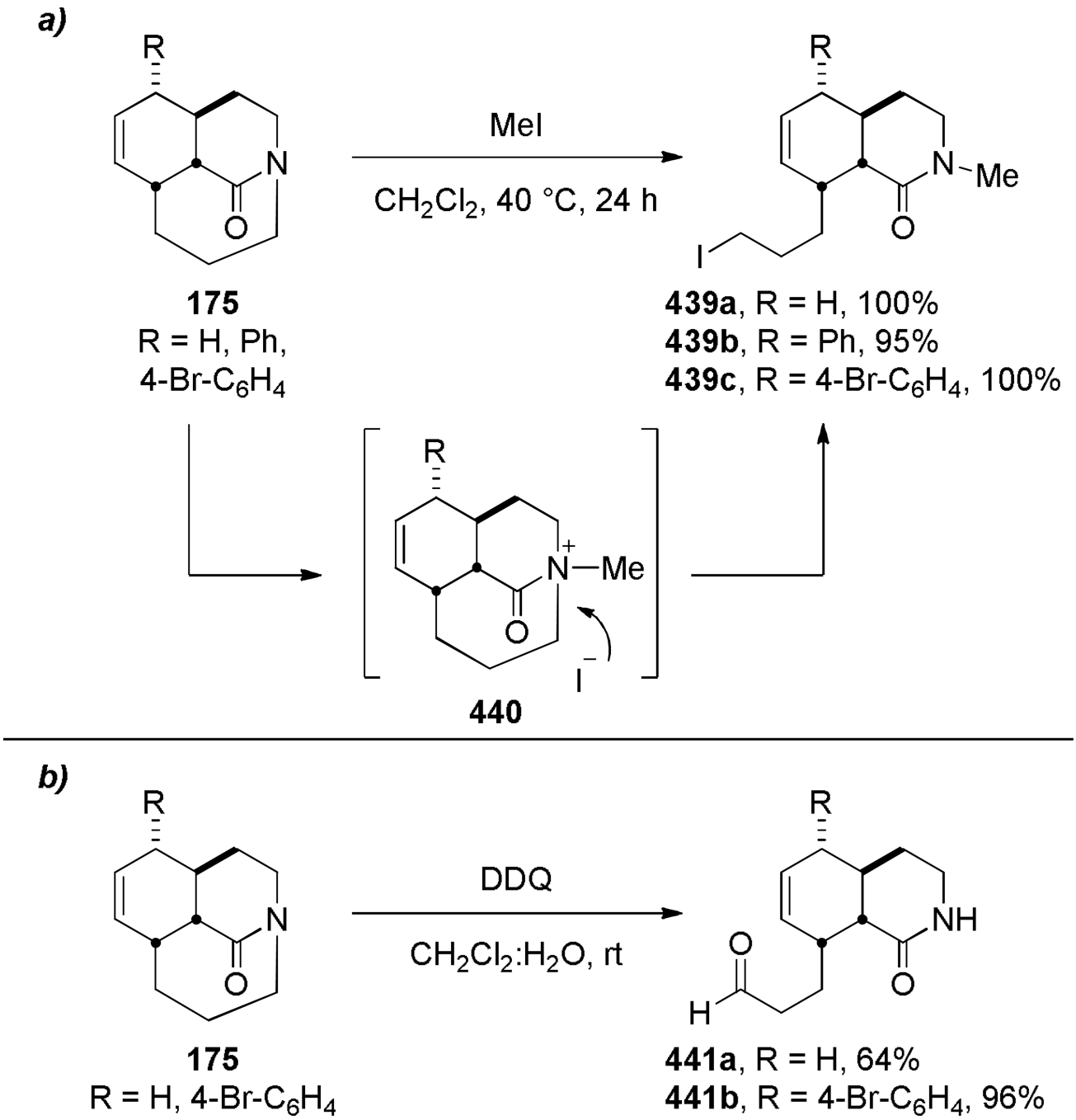


Scheme 124.

Reactions of 6,6,7,7-Tetramethylquinuclidin-2-one with Cleavage of C–NC(O) Bond by Yakhontov

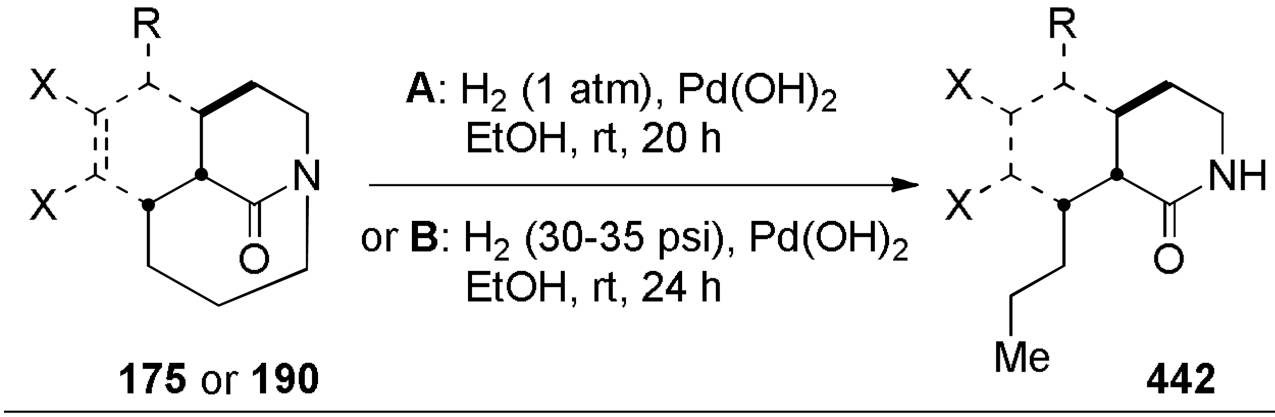


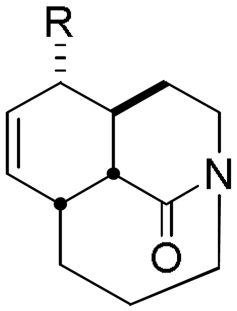
Scheme 125.
Proposed Mechanism for Synthesis of **436**



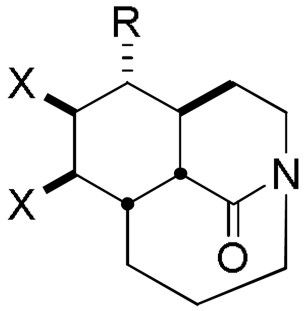
Scheme 126.

Cleavage of C–NC(O) Bond in Medium-Bridged Twisted Lactams by Aubé: a) Amidinium Salts; b) Oxidative Cleavage

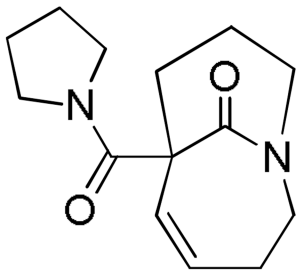




175d, R = H, 92%
175c, R = Ph, 80%
175b, R = 4-Br-C_6H_4, 87%
175a, R = $(CH_2)_2OBn$, 68%

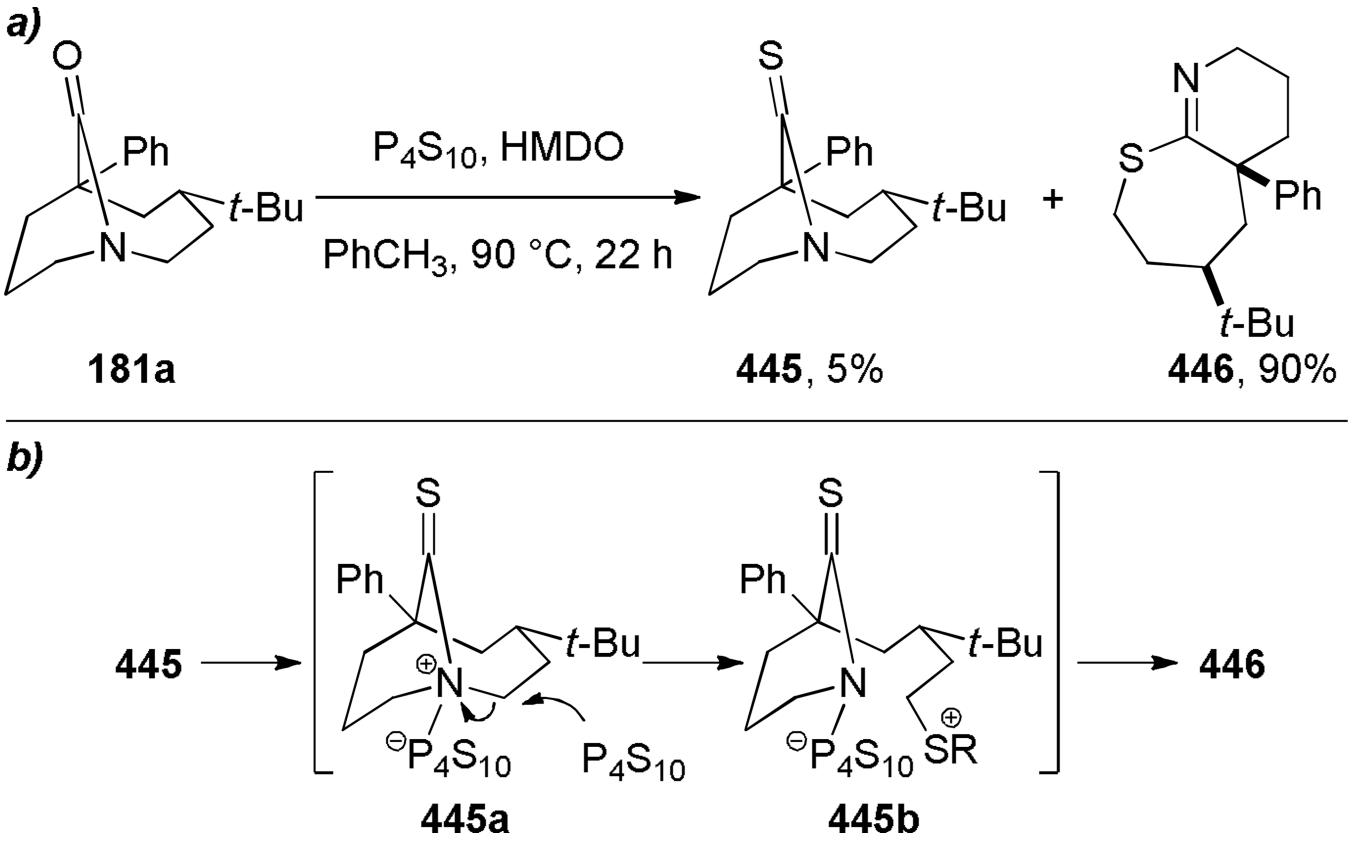


175g, R = H,
X = H, 55%
175h, R = 4-Br-C_6H_4,
X = OH, 90%



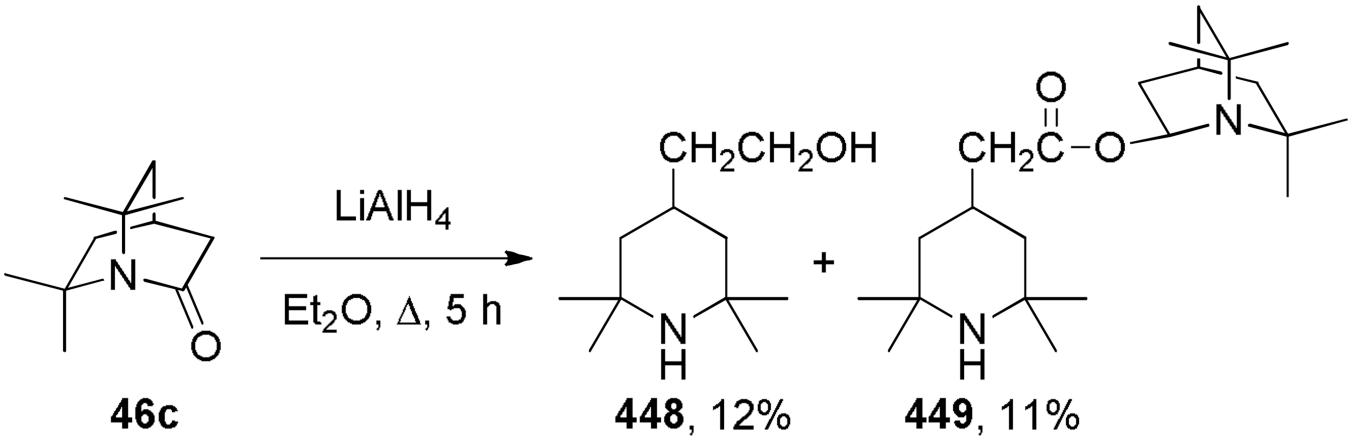
190c, 66%

Scheme 127.
Hydrogenolysis of C–NC(O) Bond in Medium-Bridged Twisted Lactams by Aubé

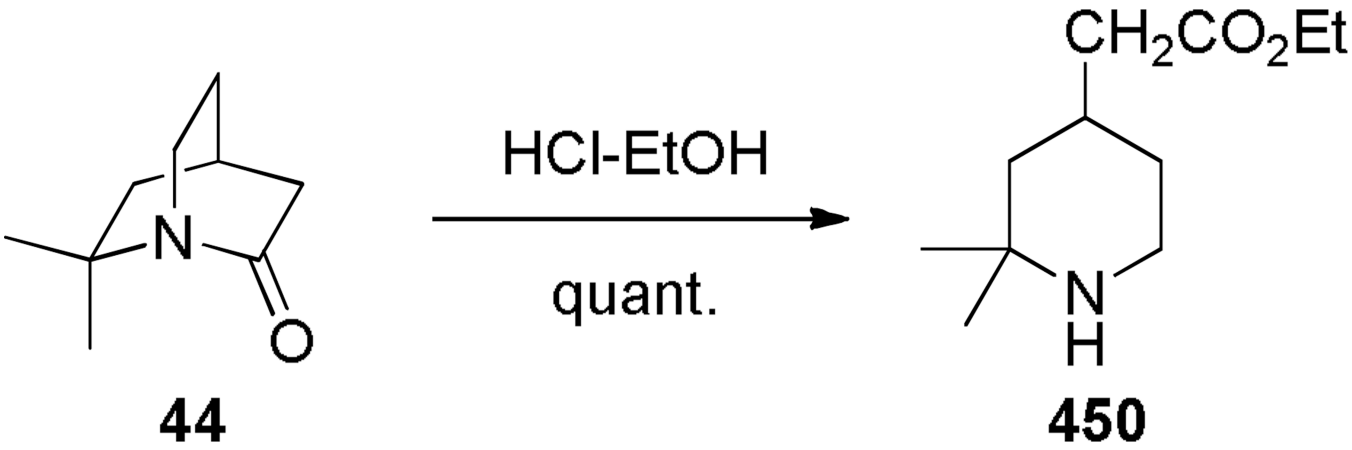


Scheme 128.

a) Synthesis of Bridged Thioamide by Aubé; b) Proposed Mechanism Involving Cleavage of C–NC(S) Bond

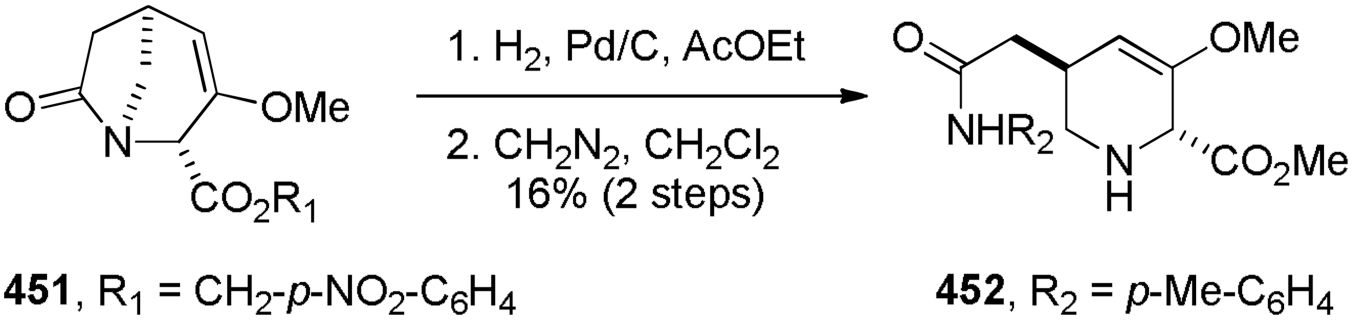


Scheme 129.
Reduction of 6,6,7,7-Tetramethylquinuclidin-2-one by Yakhontov



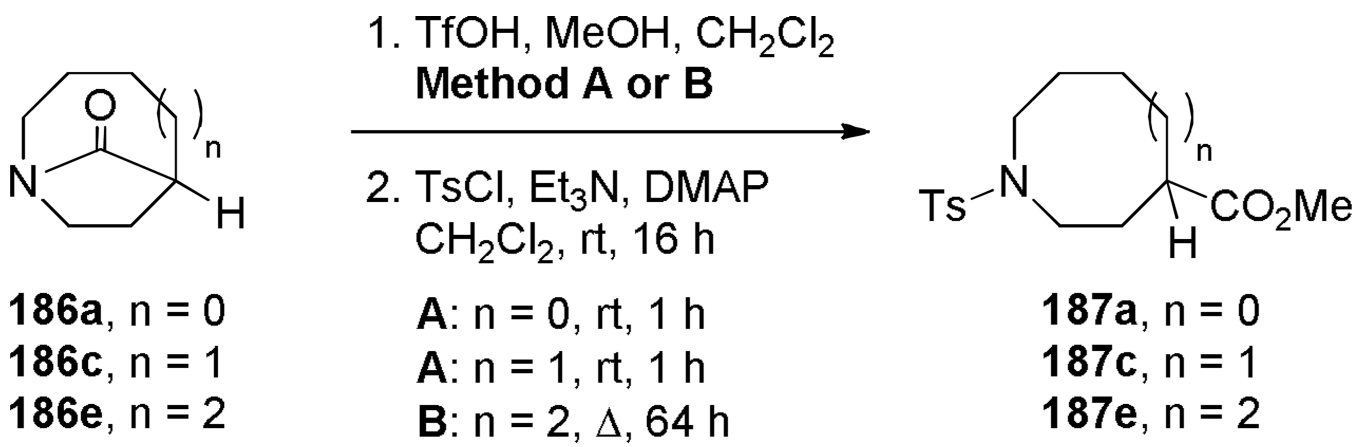
44 **450**

Scheme 130.
Alcoholysis of 6,6-Dimethylquinuclidin-2-one by Pracejus

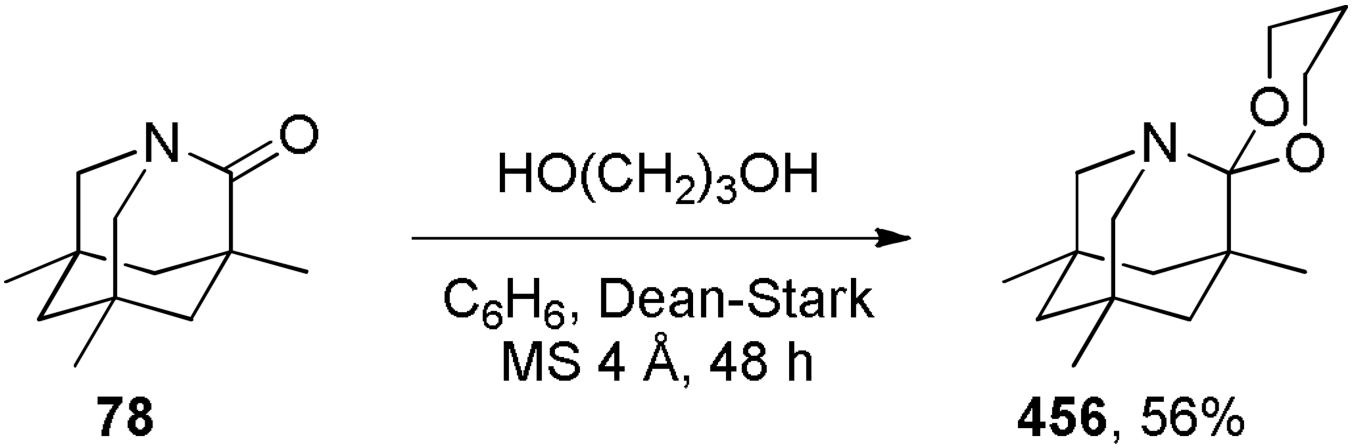


451, $R_1 = CH_2$-*p*-NO_2-C_6H_4 **452**, R_2 = *p*-Me-C_6H_4

Scheme 131.
Aminolysis of [3.2.1] Bridged Lactam by Aszodi

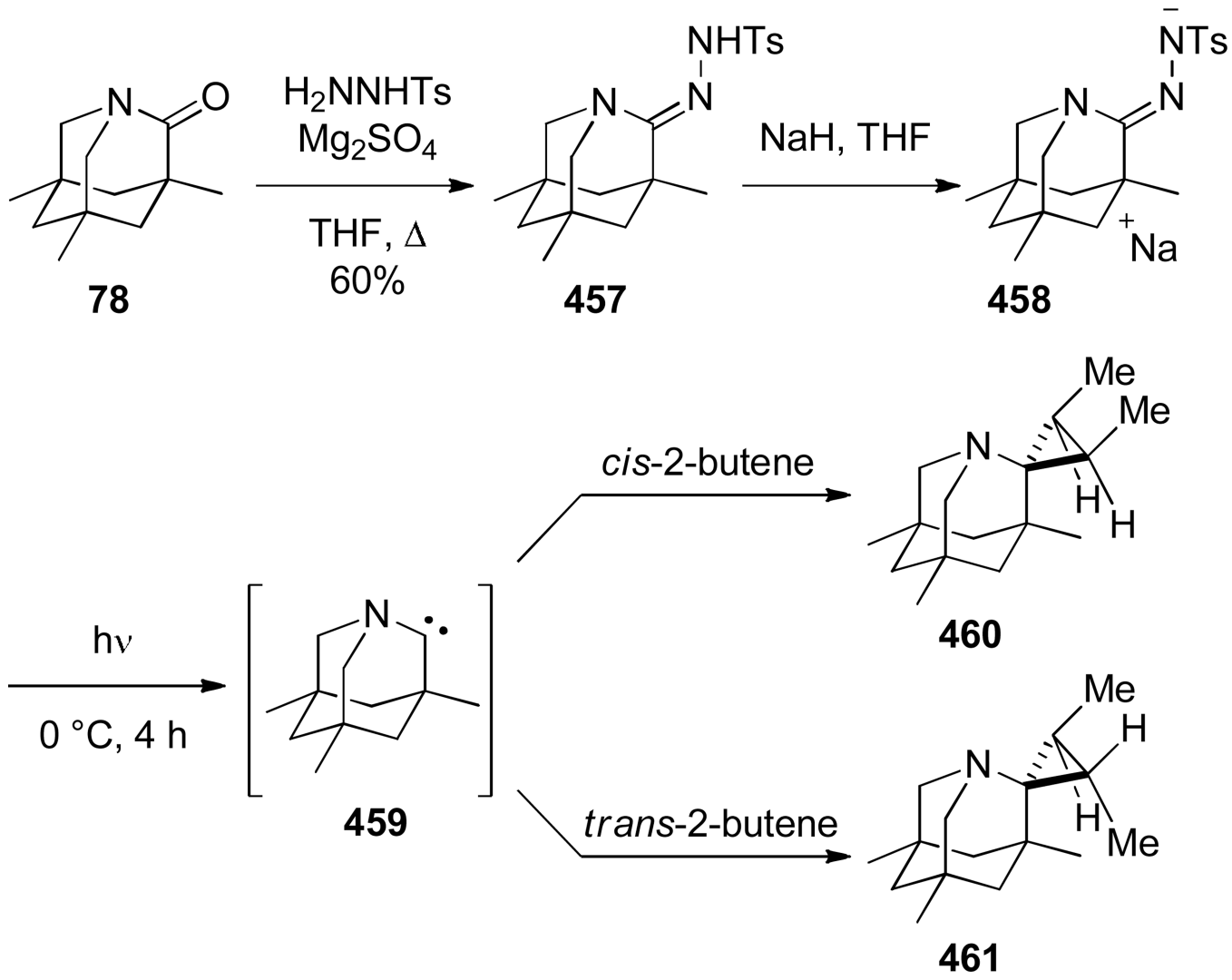


Scheme 132.
Alcoholysis of One-Carbon Bridged Lactams by Murphy

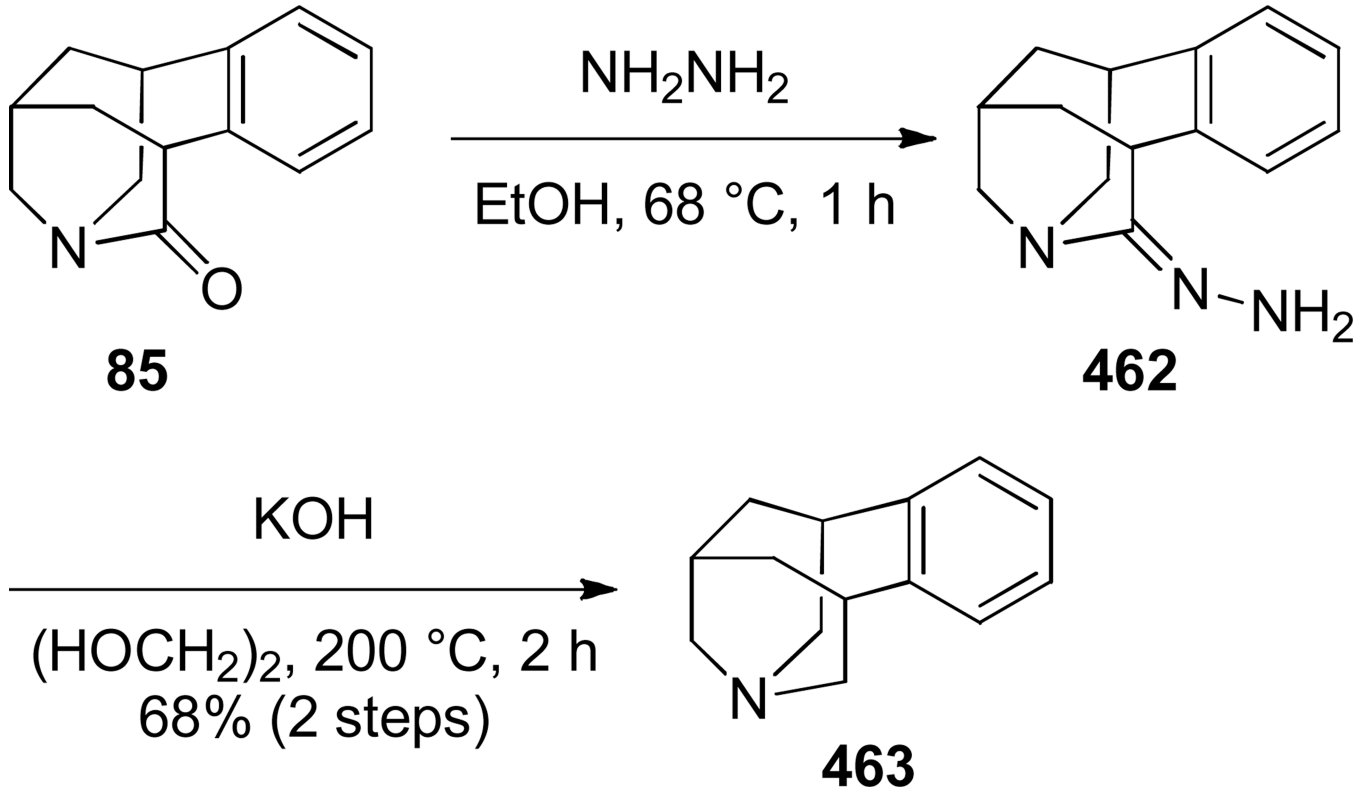


78 **456**, 56%

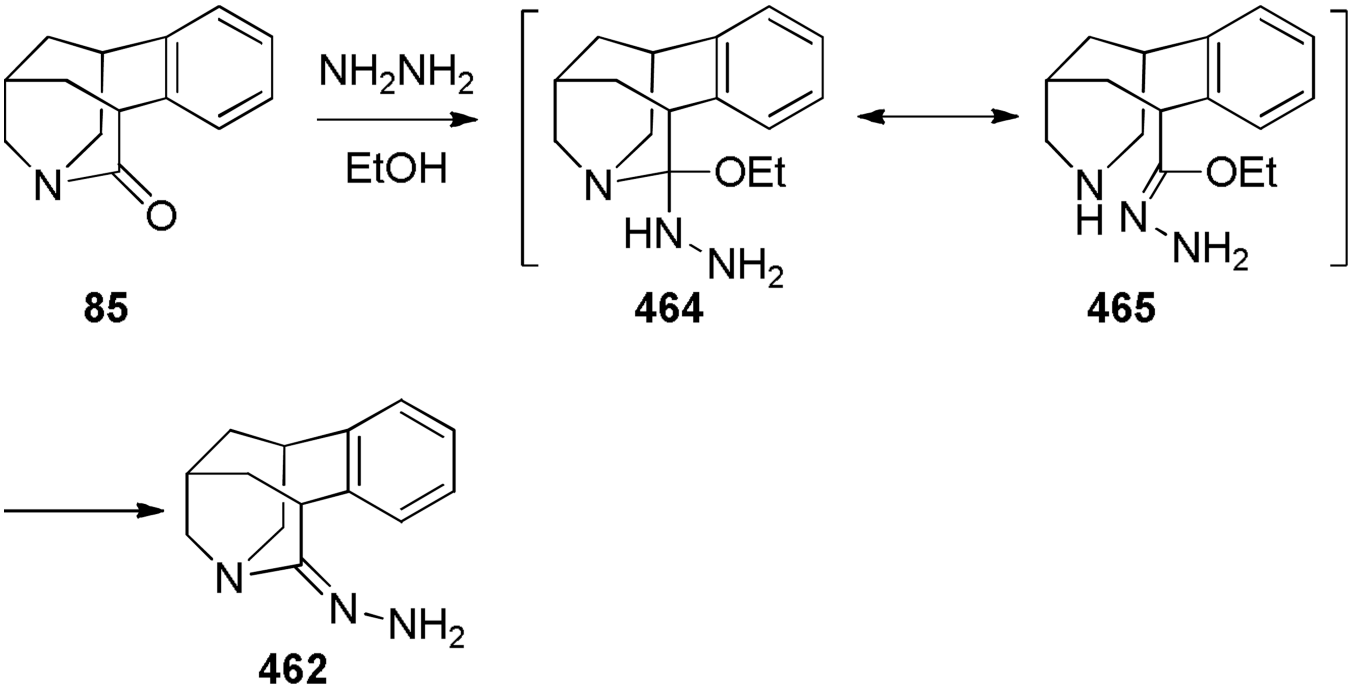
Scheme 133.
Synthesis of Bridged Amino-Ketal from 1-Aza-2-adamantanone by Kirby



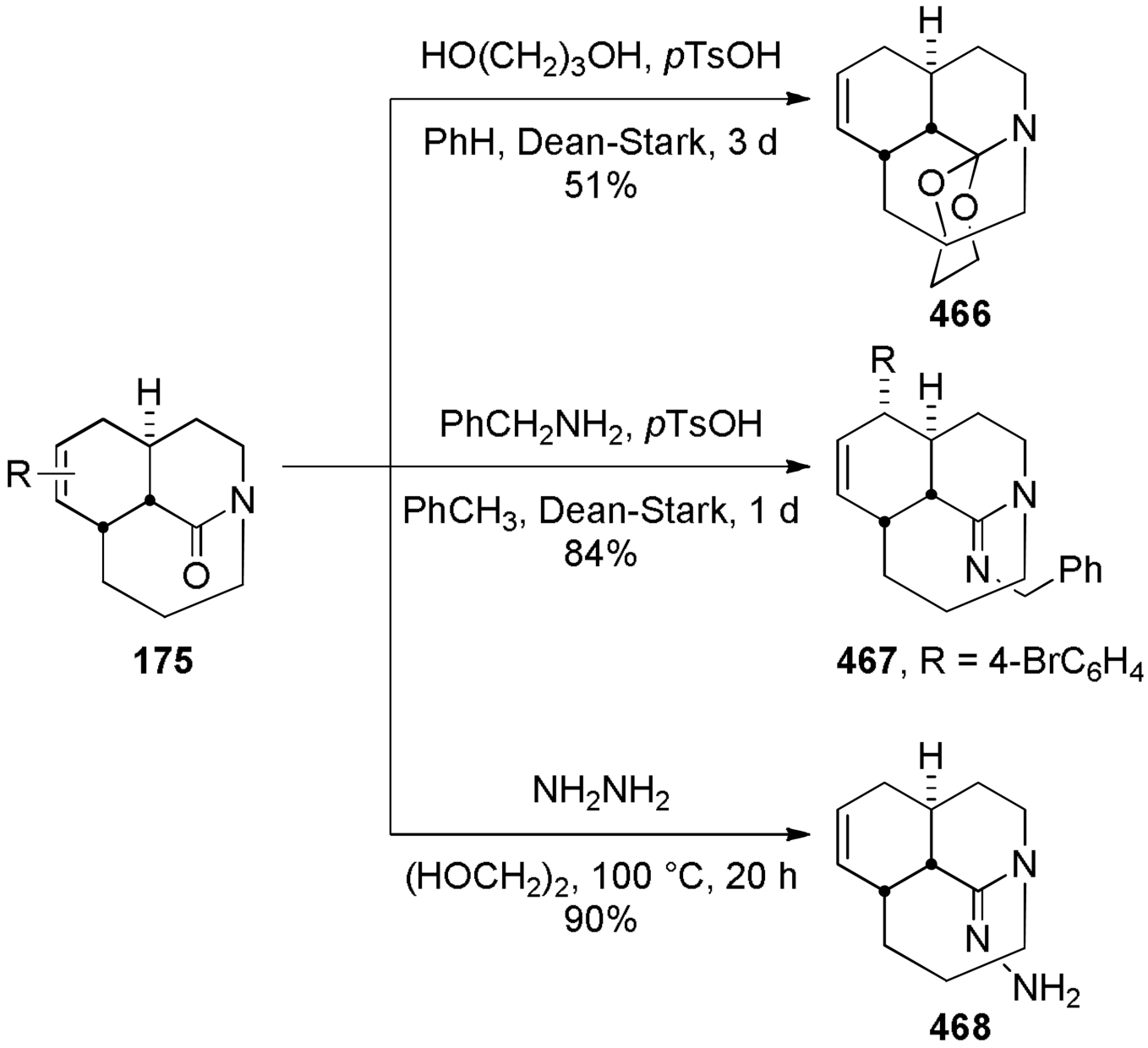
Scheme 134.
Synthesis and Reactions of Aminocarbene from 1-Aza-2-adamantanone by Kirby



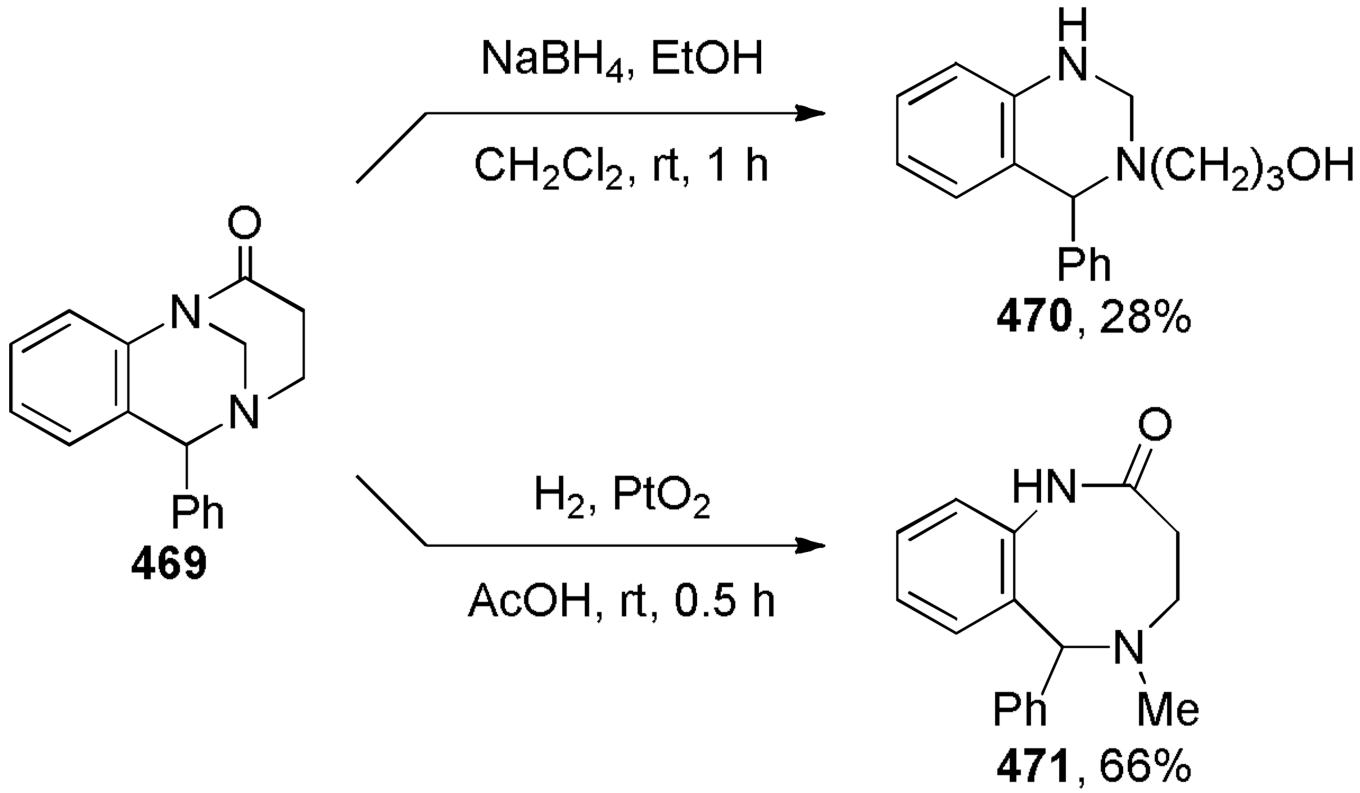
Scheme 135.
Wolff-Kishner Reduction of Bridged Lactam by Coe



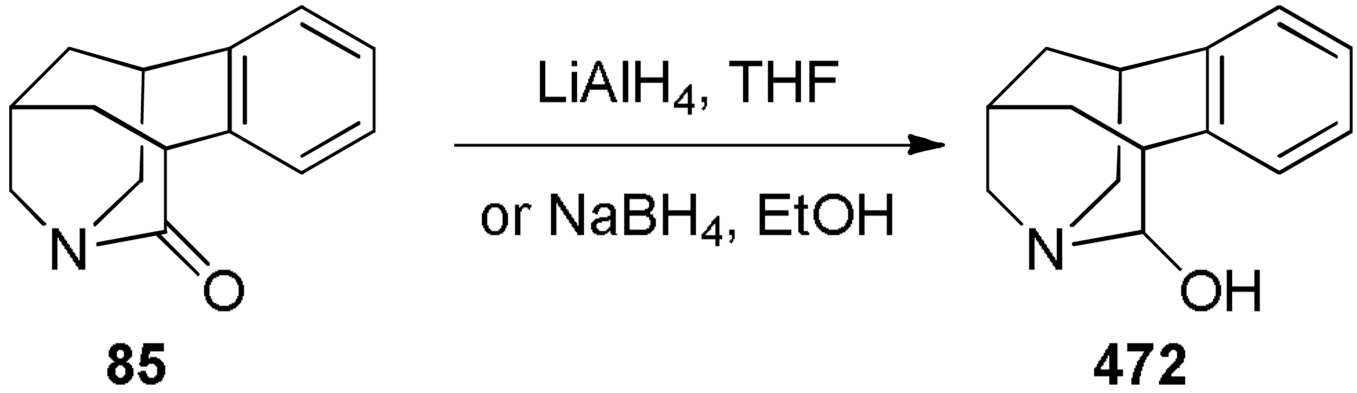
Scheme 136.
Proposed Mechanism for Synthesis of Bridged Amidine **462**



Scheme 137.
Reactions of Medium-Bridged Twisted Lactams with Heteroatom Nucleophiles by Aubé

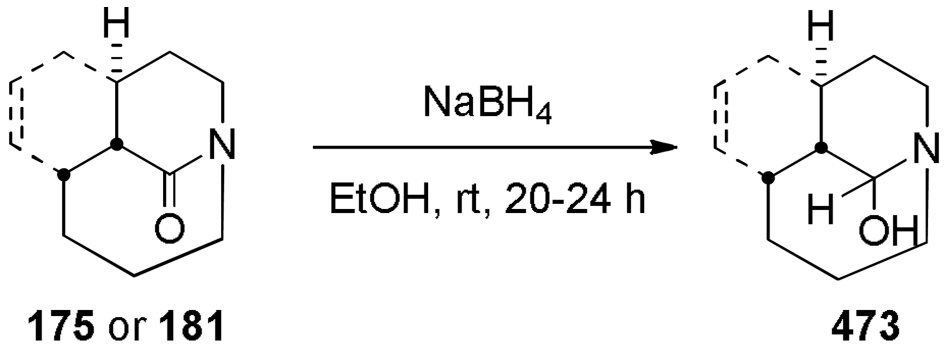


Scheme 138.
Reduction of 1,5-Diazabicyclo[3.3.1]nonan-2-one by Denzer and Ott

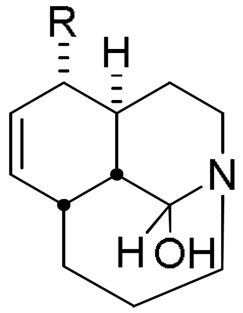


85 472

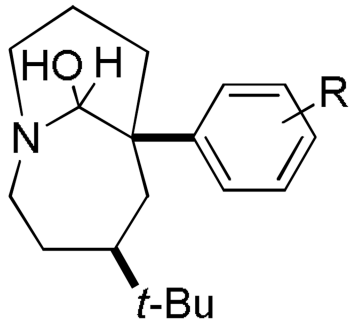
Scheme 139.
Reduction of Adamantane-Derived Bridged Lactam by Coe



175 or **181** **473**

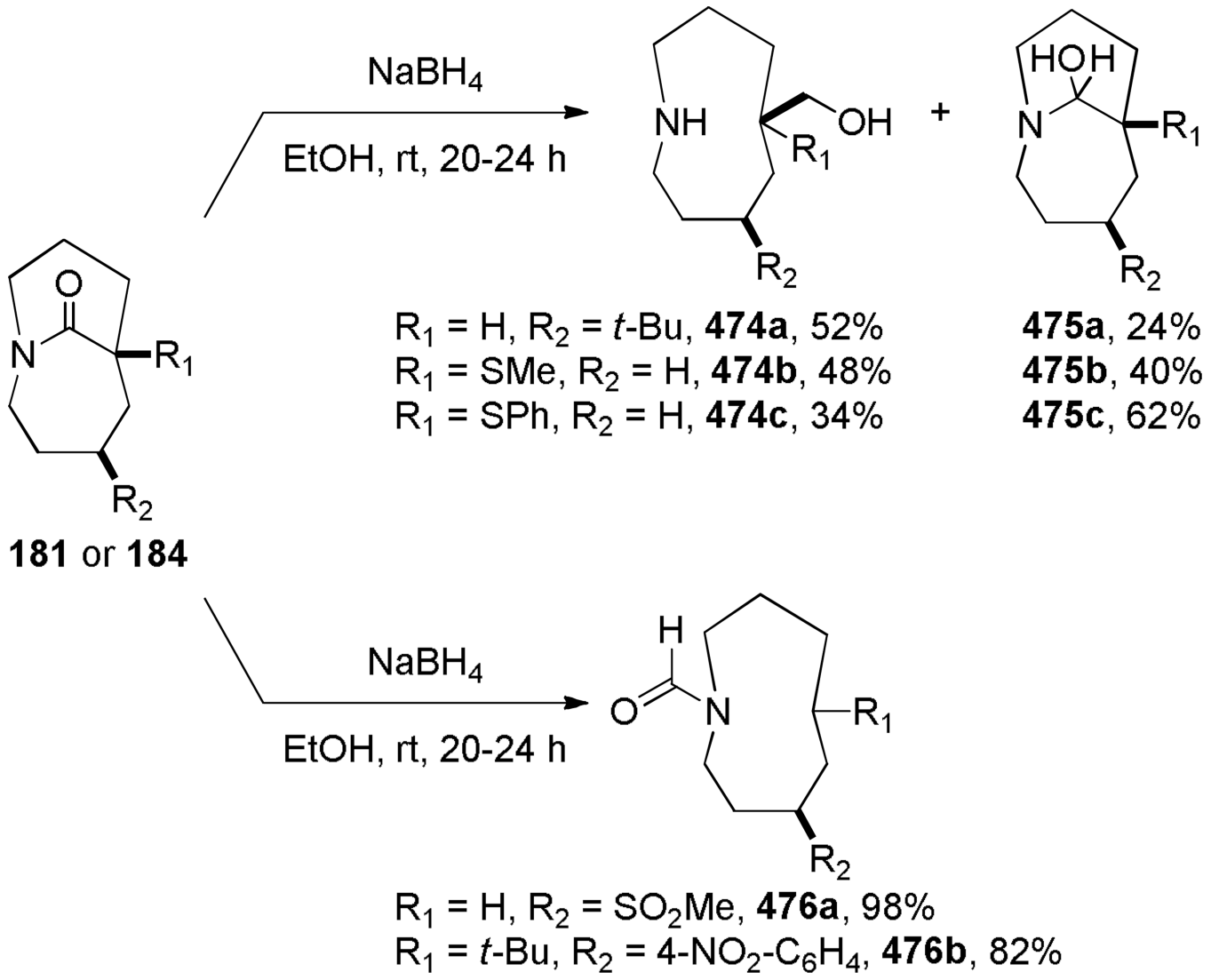


473a, R = H, 91%
473b, R = 4-Br-C_6H_4, 88%

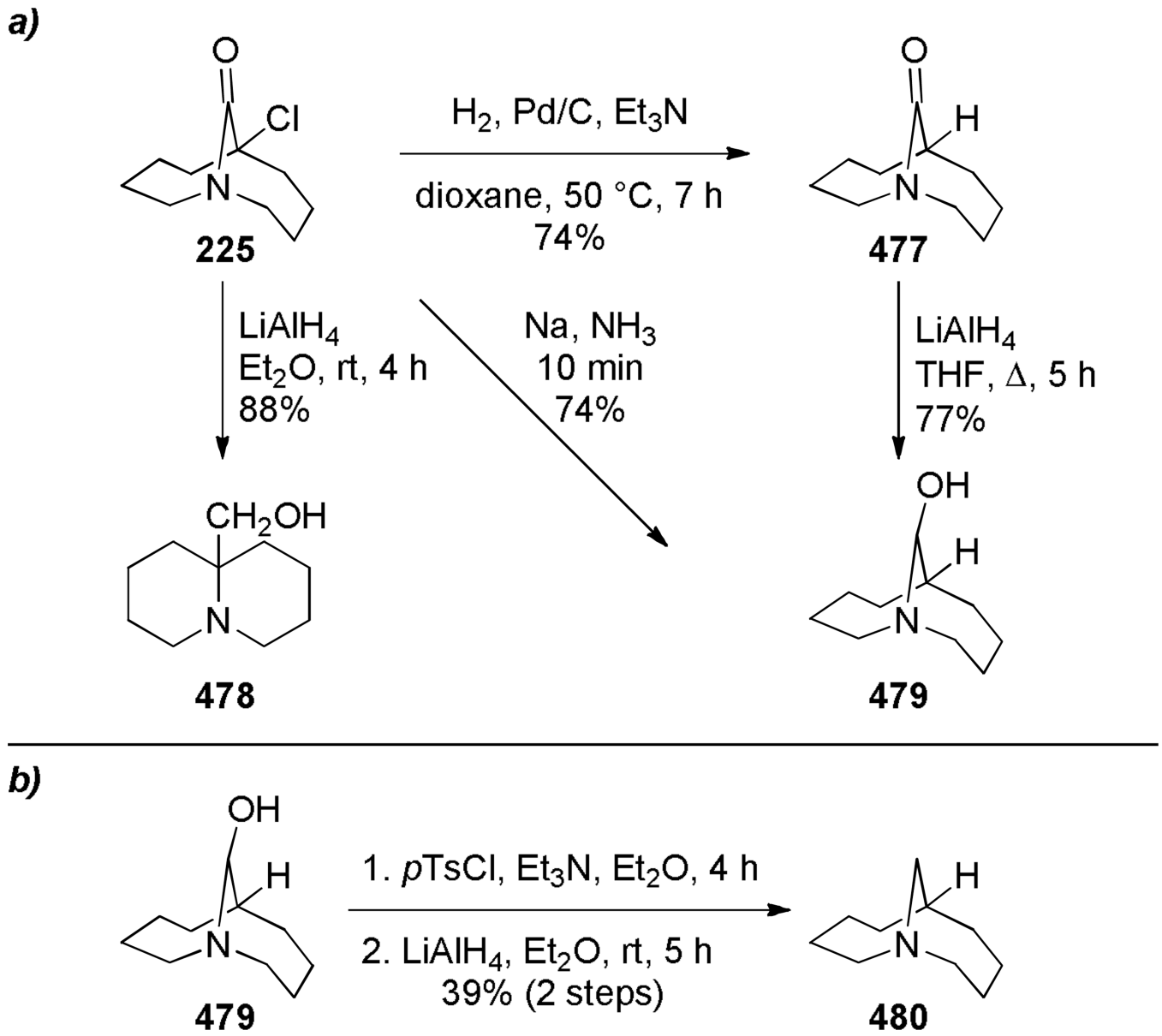


473c, R = H, 90%
473d, R = 4-MeO, 91%
473e, R = 3,5-$(MeO)_2$, 94%
473f, R = 3,4-(OCH_2O), 95%

Scheme 140.
Reduction of Medium-Bridged Twisted Lactams with Formation of Isolable Hemiaminals by Aubé

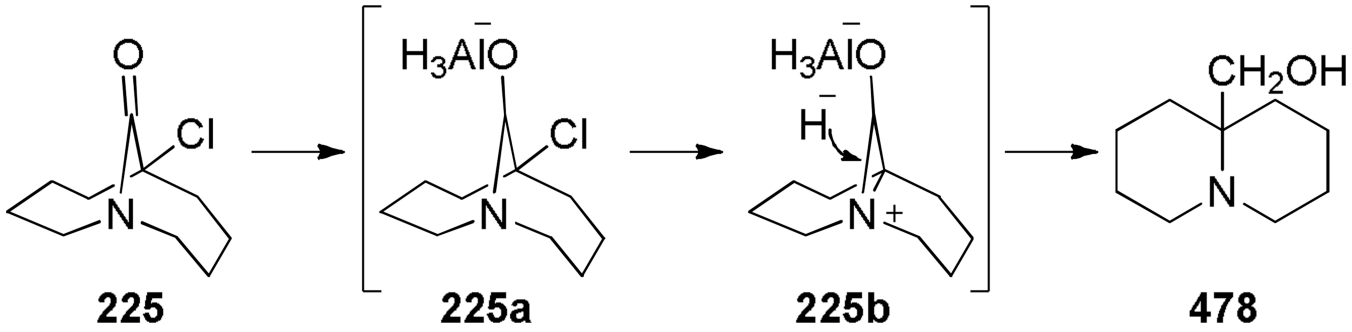


Scheme 141.
Reduction of Medium-Bridged Twisted Lactams with Collapse of Hemiaminals by Aubé

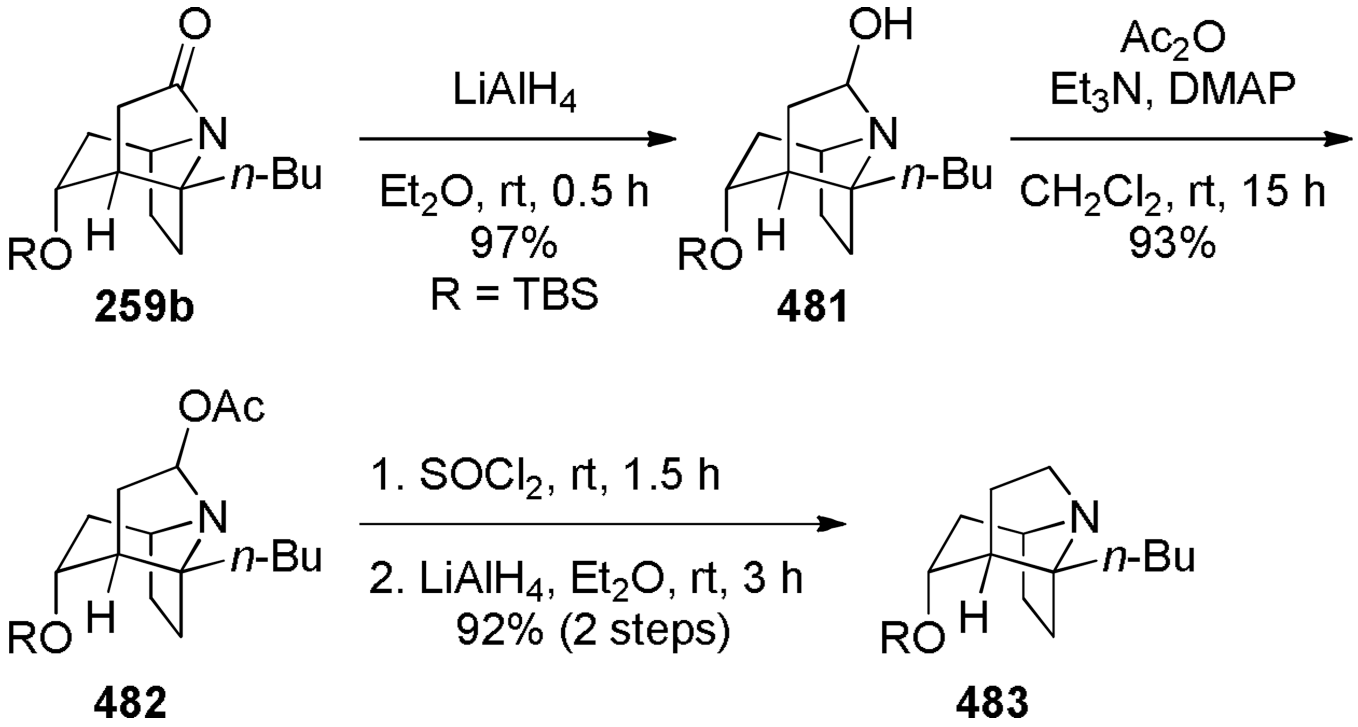


Scheme 142.

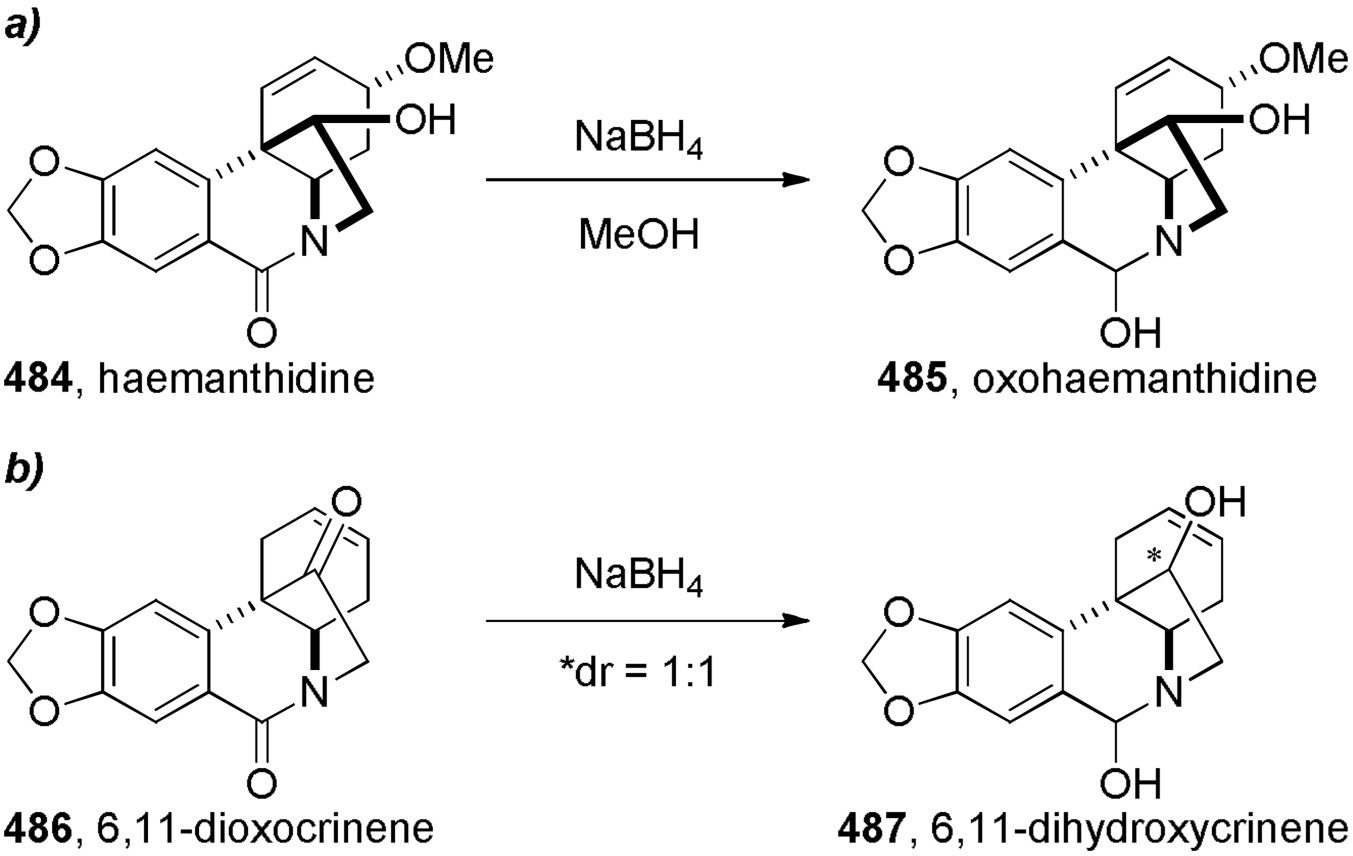
a) Reduction of Chloro-Substituted Bridged Lactam by Arata; b) Synthesis of 1-Azabicyclo[4.4.1]undecane



Scheme 143.
Proposed Mechanism for Rearrangement of **225**

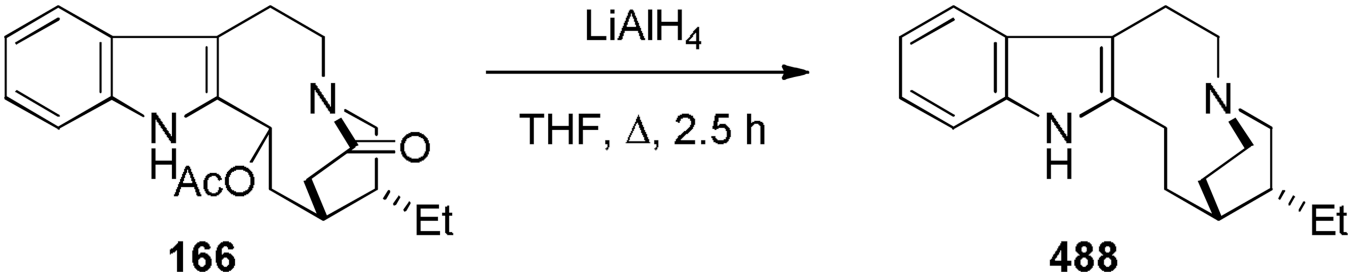


Scheme 144.
Reduction of Tropane-Derived Bridged Lactam by Thomas

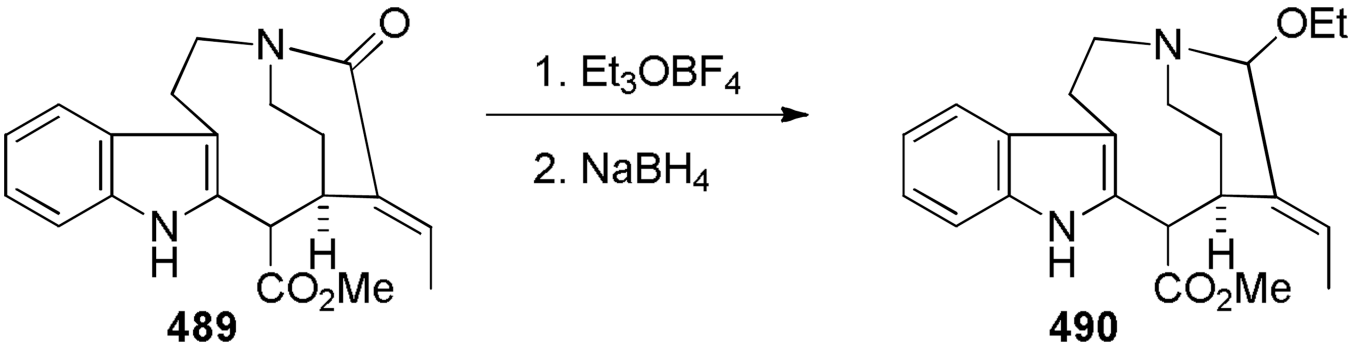


Scheme 145.

Reduction of Bridged Lactams Derived from Amaryllidaceae Alkaloids by: a) Wildman; b) Hendrickson

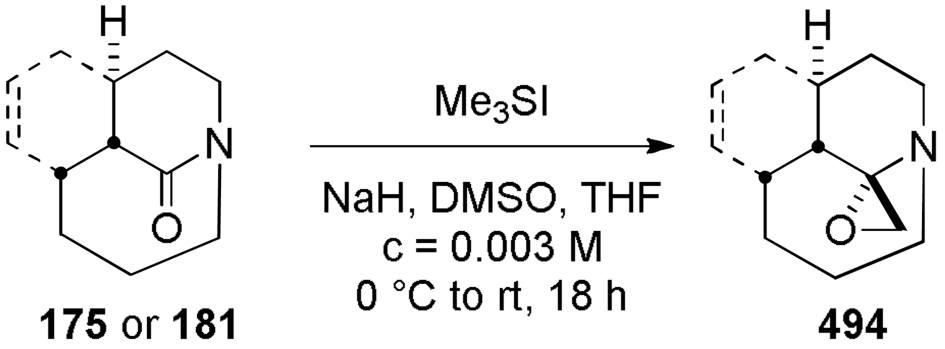


Scheme 146.
Reduction of Indole-1-azabicyclo[6.2.2]dodecan-10-one by Dolby

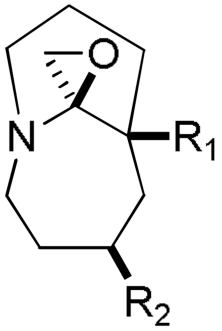


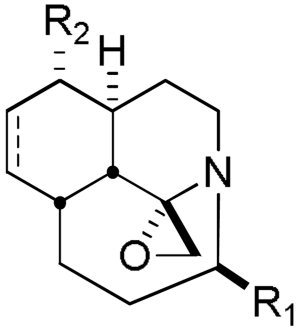
489 490

Scheme 147.
Synthesis of Bridged Hemiaminal from Bridged Lactam by Harley-Mason



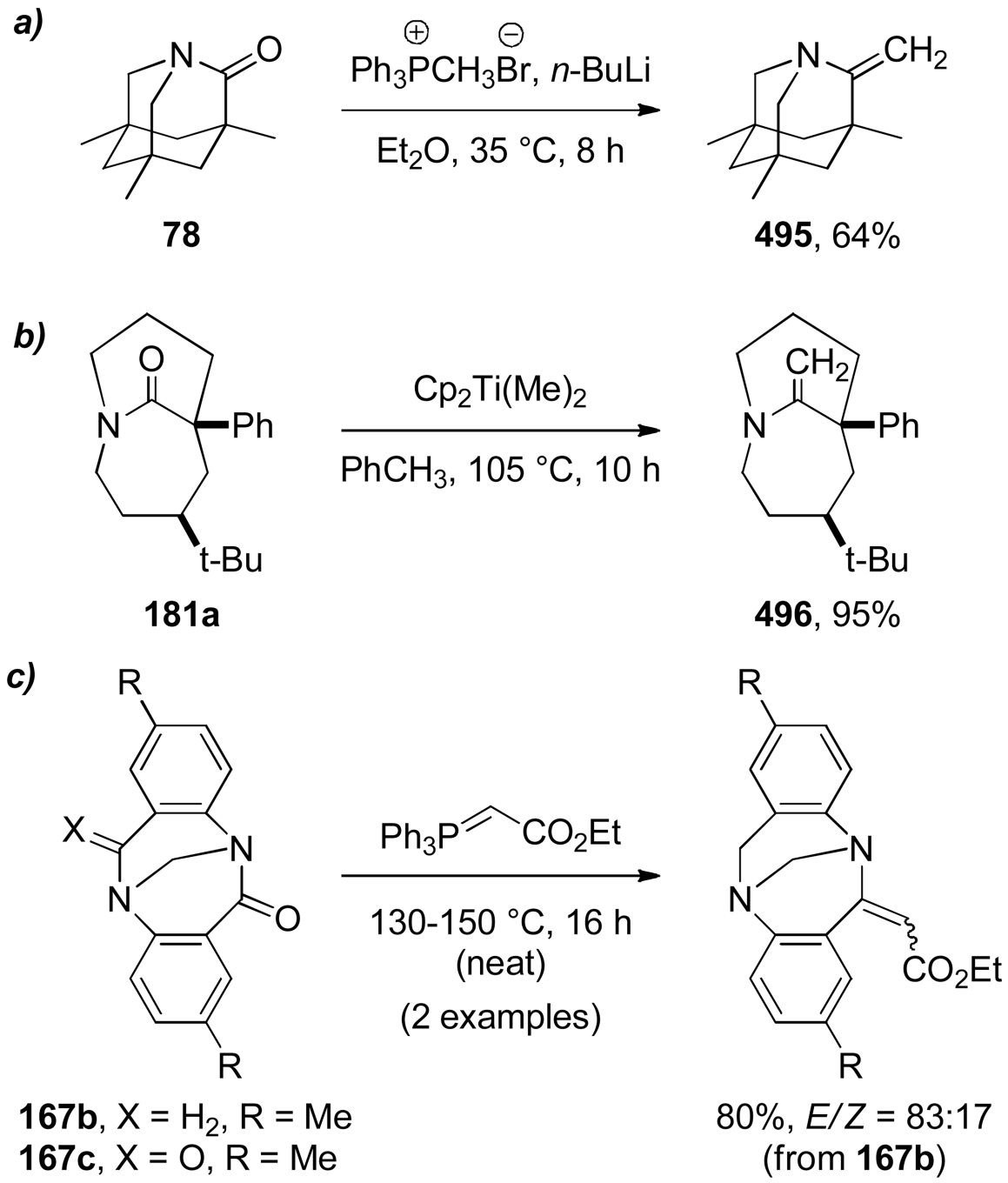
175 or **181** **494**





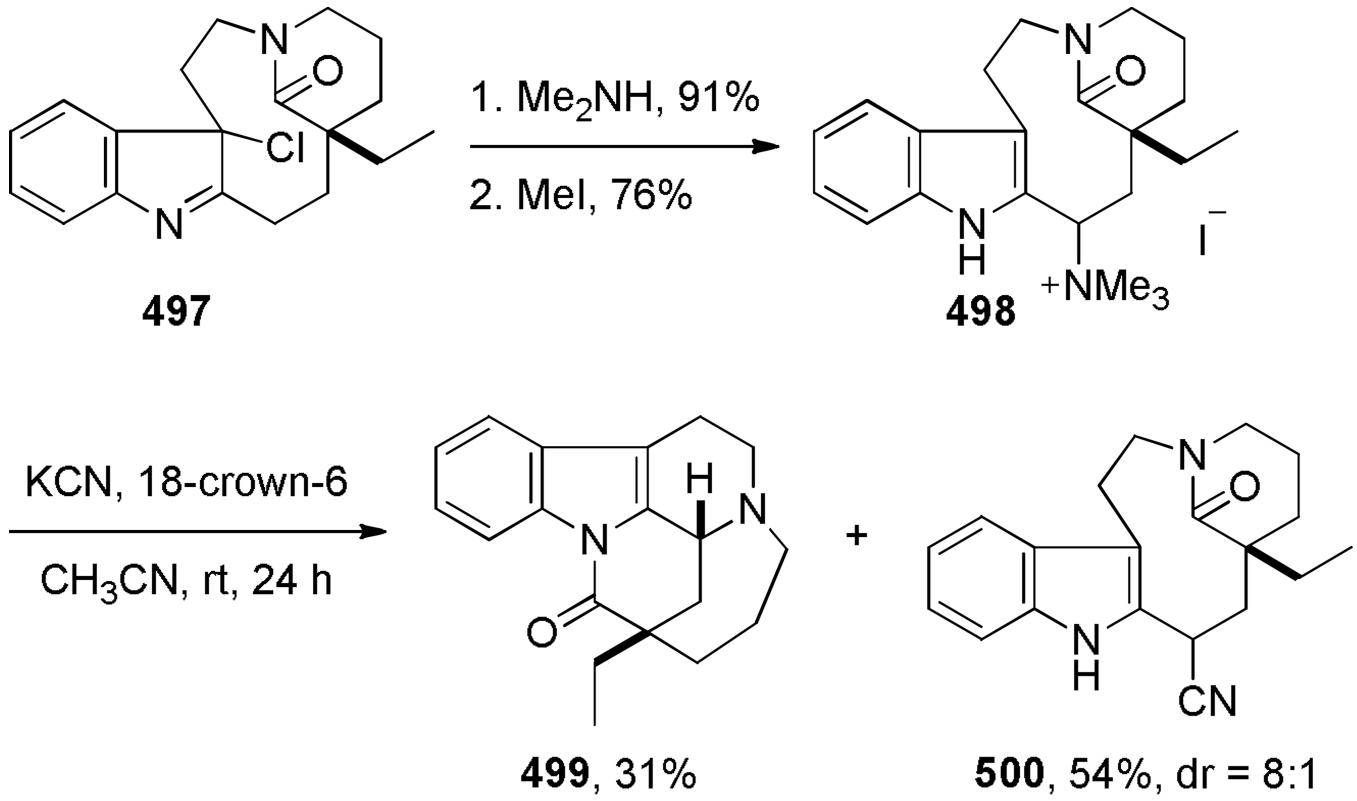
494a, R_1 = Ph, R_2 = *t*-Bu, 88%
494b, R_1 = H, R_2 = *t*-Bu, 41%
494c, R_1 = SMe, R_2 = H, 89%
494d, R_1 = SPh, R_2 = H, 81%
494e, R_1 = H, R_2 = H, 77%
494f, R_1 = H, R_2 = $(CH_2)_2OBn$, 73%
494g, R_1 = H, R_2 = 4-Br-C_6H_4, 70%
494h, R_1 = *i*-Pr, R_2 = H, 70%

Scheme 148.
Corey-Chaykovsky Epoxidation of Bridged Lactams by Aubé



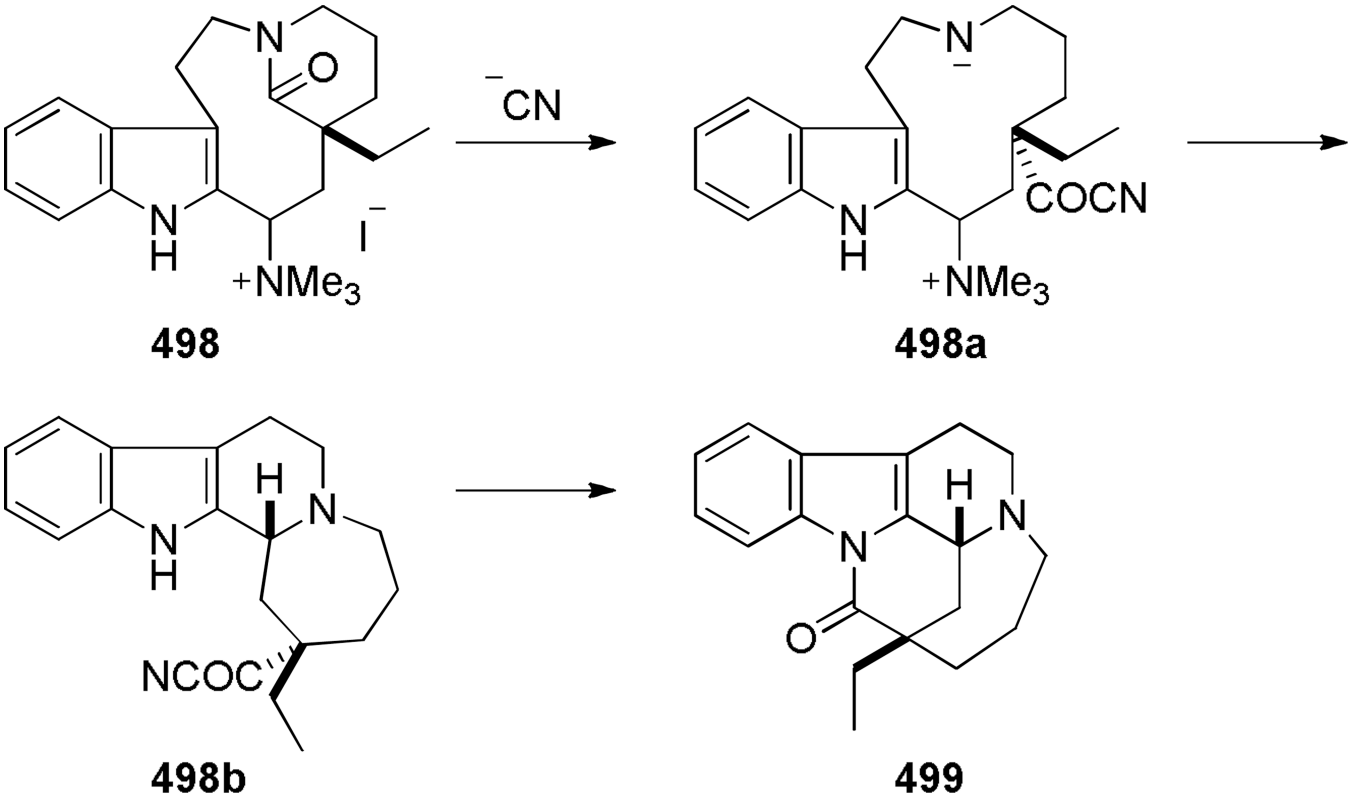
Scheme 149.

a) Wittig Olefination of 1-Aza-2-adamantanone by Kirby; b) Petasis Olefination of Medium Bridged Twisted Lactams by Aubé; c) Wittig Olefination of Tröger's Base-Derived Twisted Lactams by Wärnmark

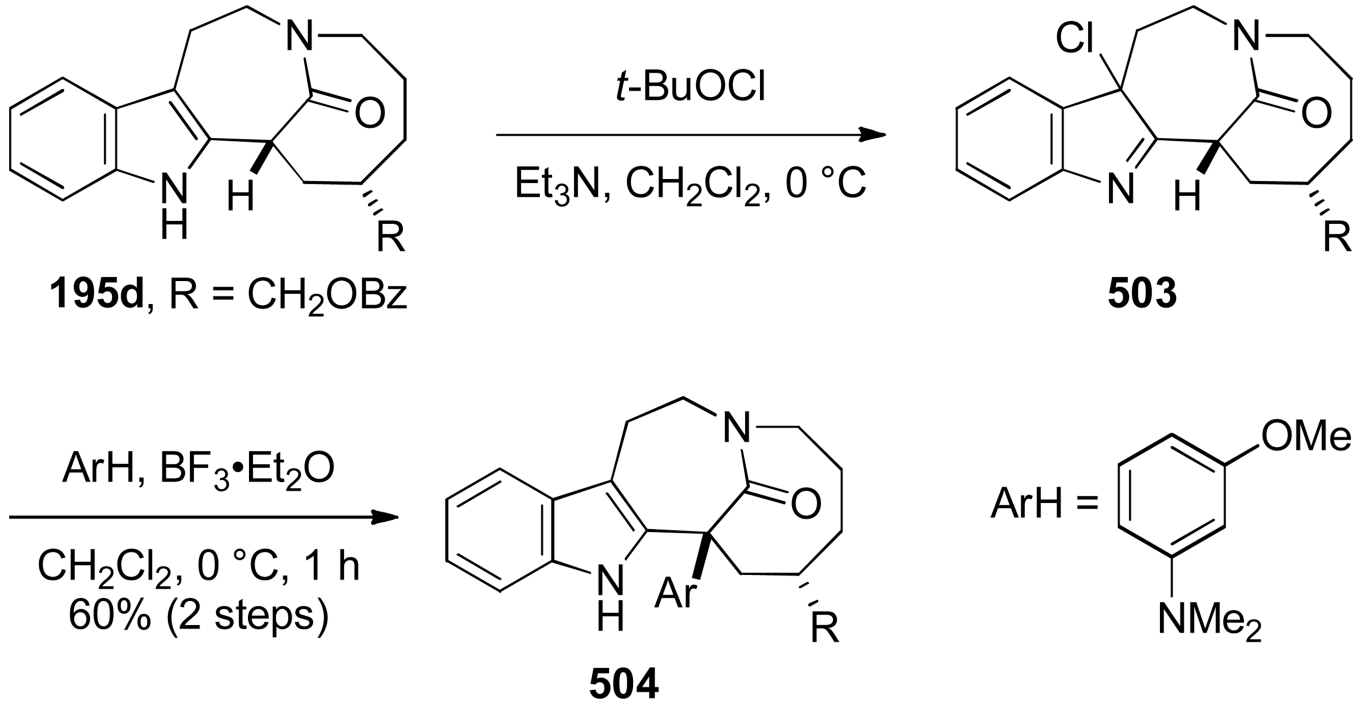


497 498 499, 31% 500, 54%, dr = 8:1

Scheme 150.
Cyanide-Induced Rearrangement of Indole-1-azabicyclo[6.3.1]dodecan-12-one by Ban

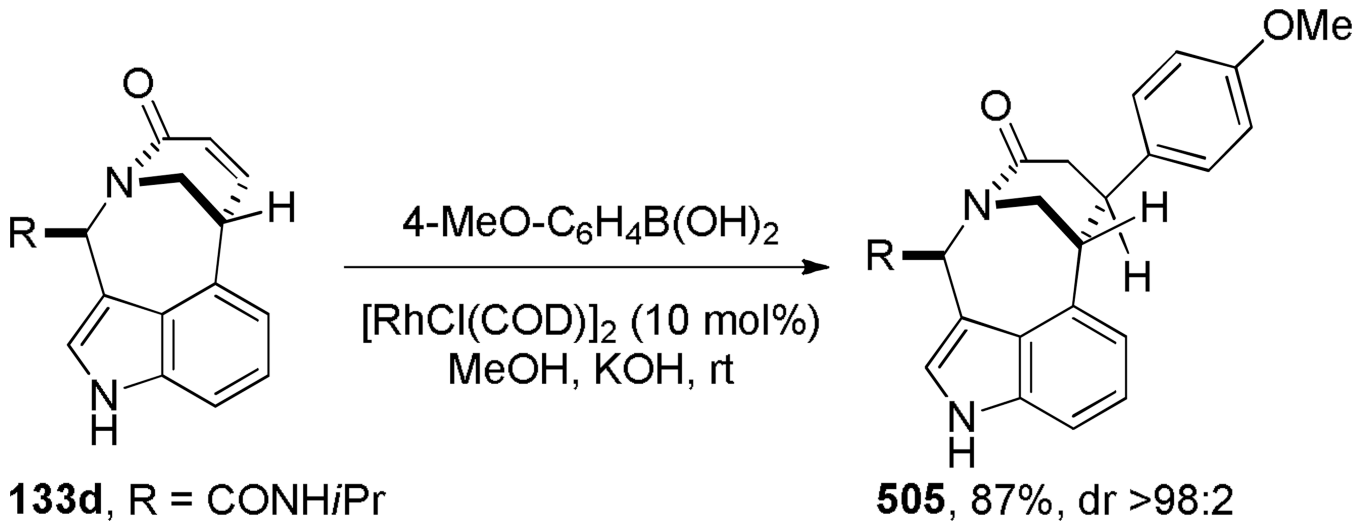


Scheme 151.
Proposed Mechanism for Cyanide-Induced Rearrangement of Lactam **498**



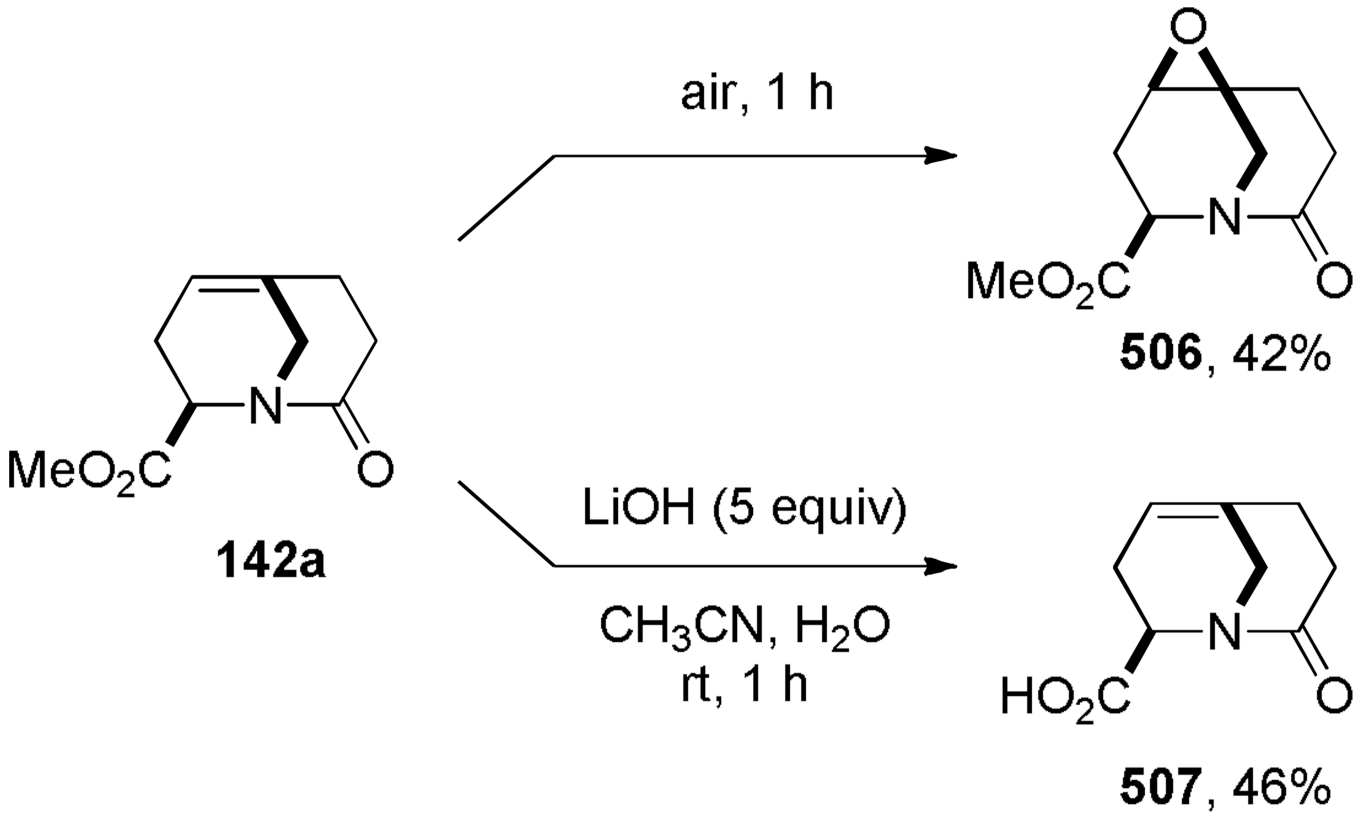
Scheme 152.

α-Arylation of Indole-1-azabicyclo[5.4.1]dodecan-12-one by Schill

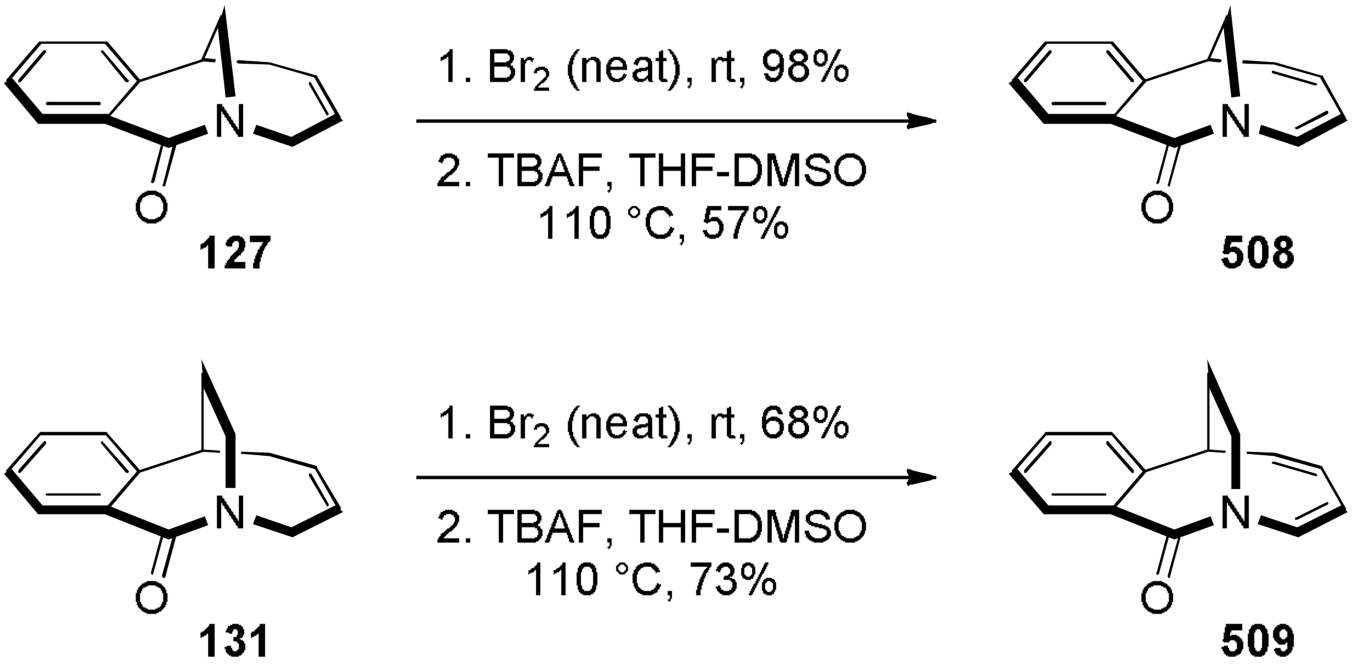


Scheme 153.

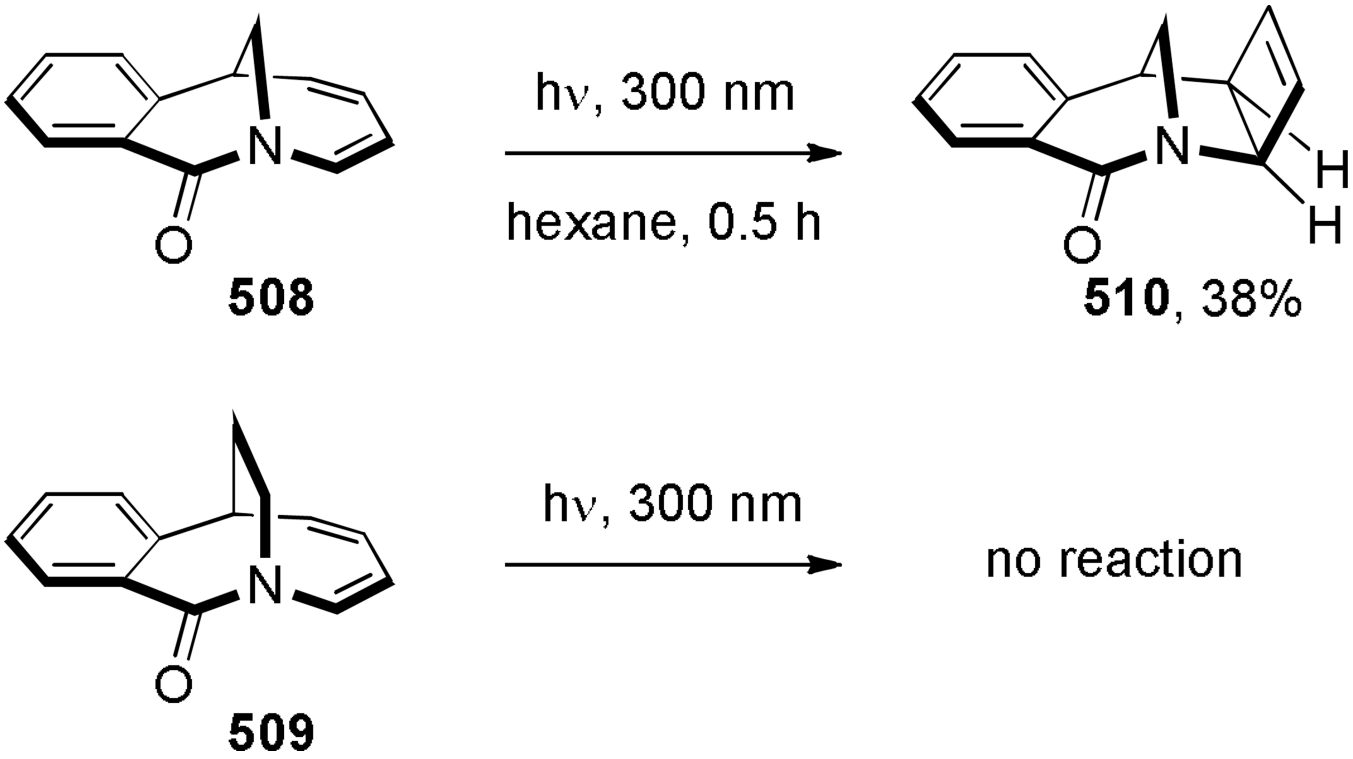
Rh-Catalyzed Conjugate Addition of Boronic Acid to 1-Azabicyclo[4.3.1]dec-7-en-9-one by Judd



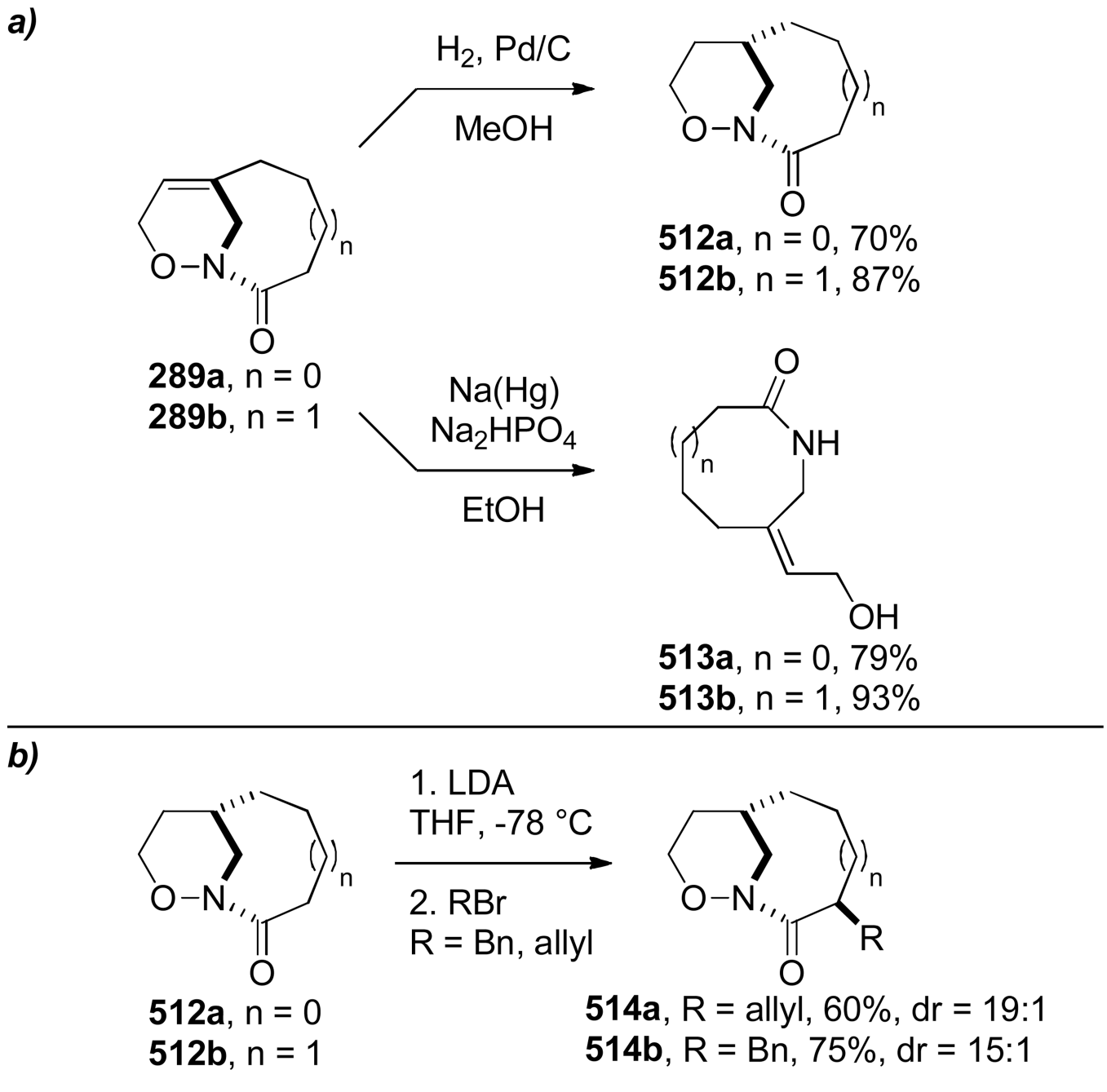
Scheme 154.
Reactivity of 1-Azabicyclo[3.3.1]non-5-en-2-one Bearing Anti-Bredt Olefin by Shea



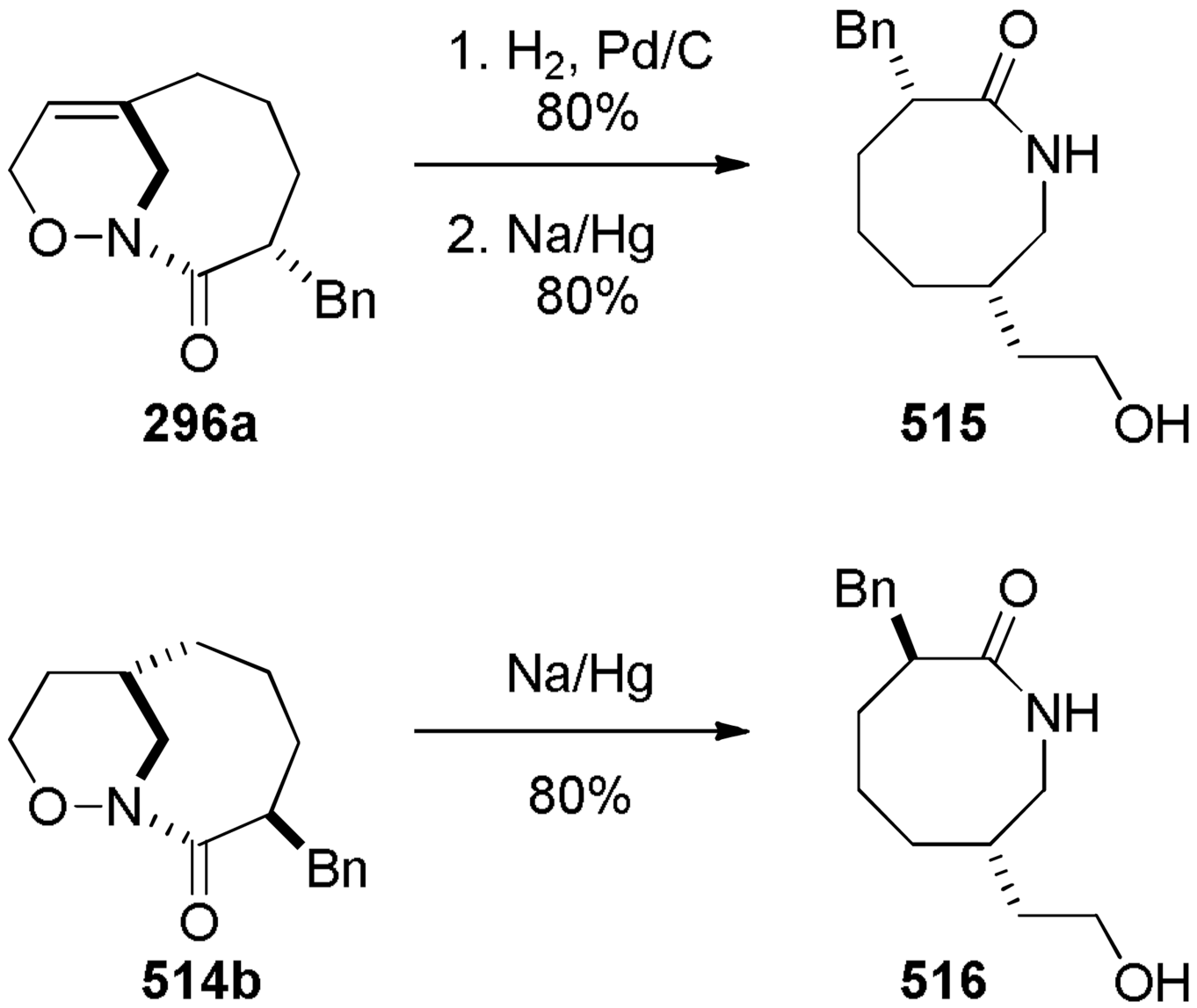
Scheme 155.
Synthesis of Bridged Lactams with Endocyclic Diene Motifs by Paquette



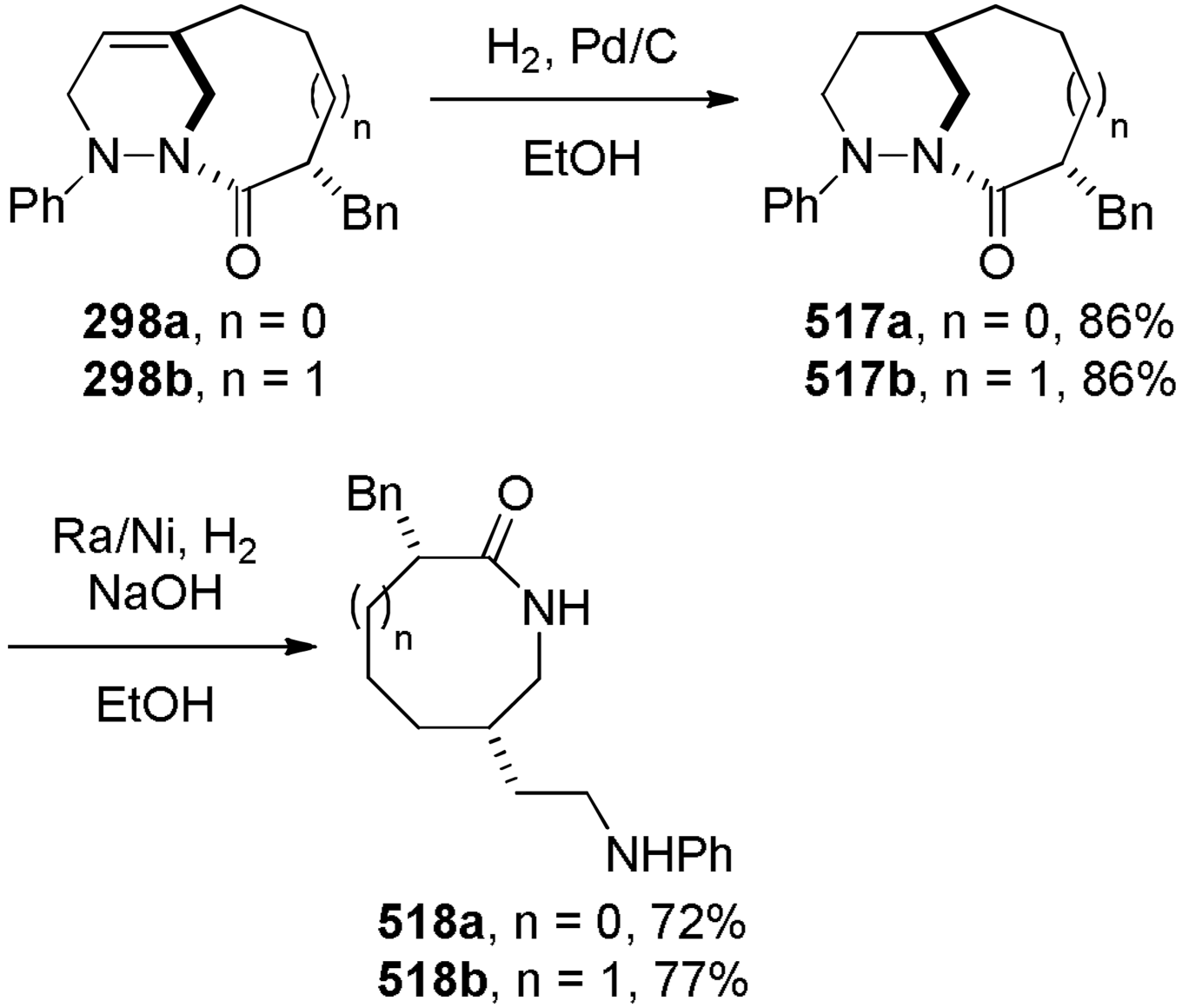
Scheme 156.
Photochemical Reactions of Bridged Lactams Bearing Endocyclic Dienes by Paquette



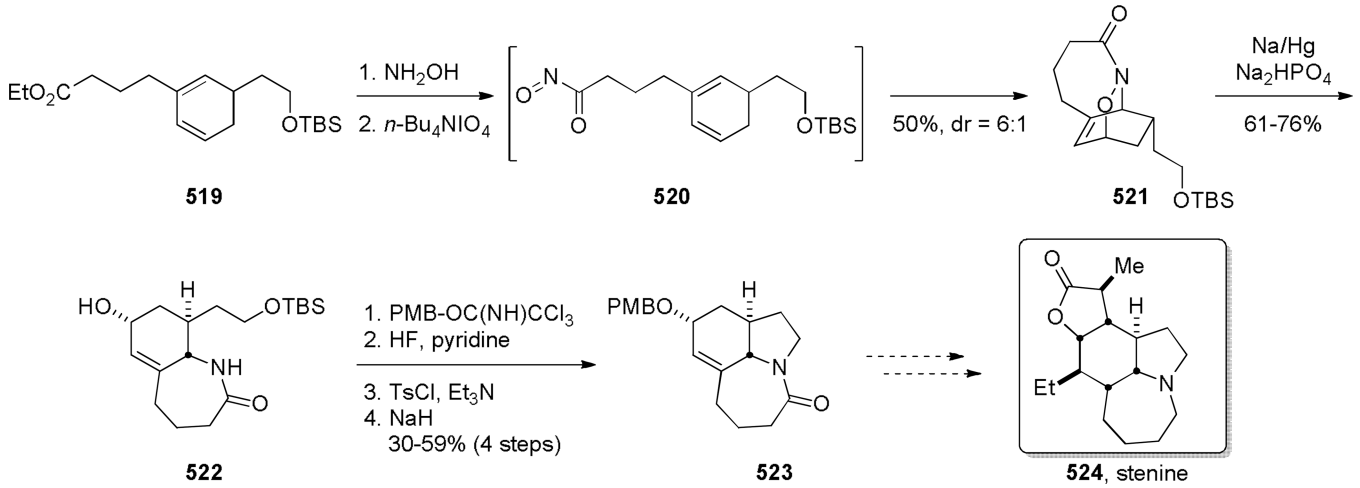
Scheme 157.
Reactivity of Bridged Oxazinolactamsby Shea: a) Reduction; b) Alkylation



Scheme 158.
Stereoselective Synthesis of Medium Ring Lactams from Oxazinolactams by Shea



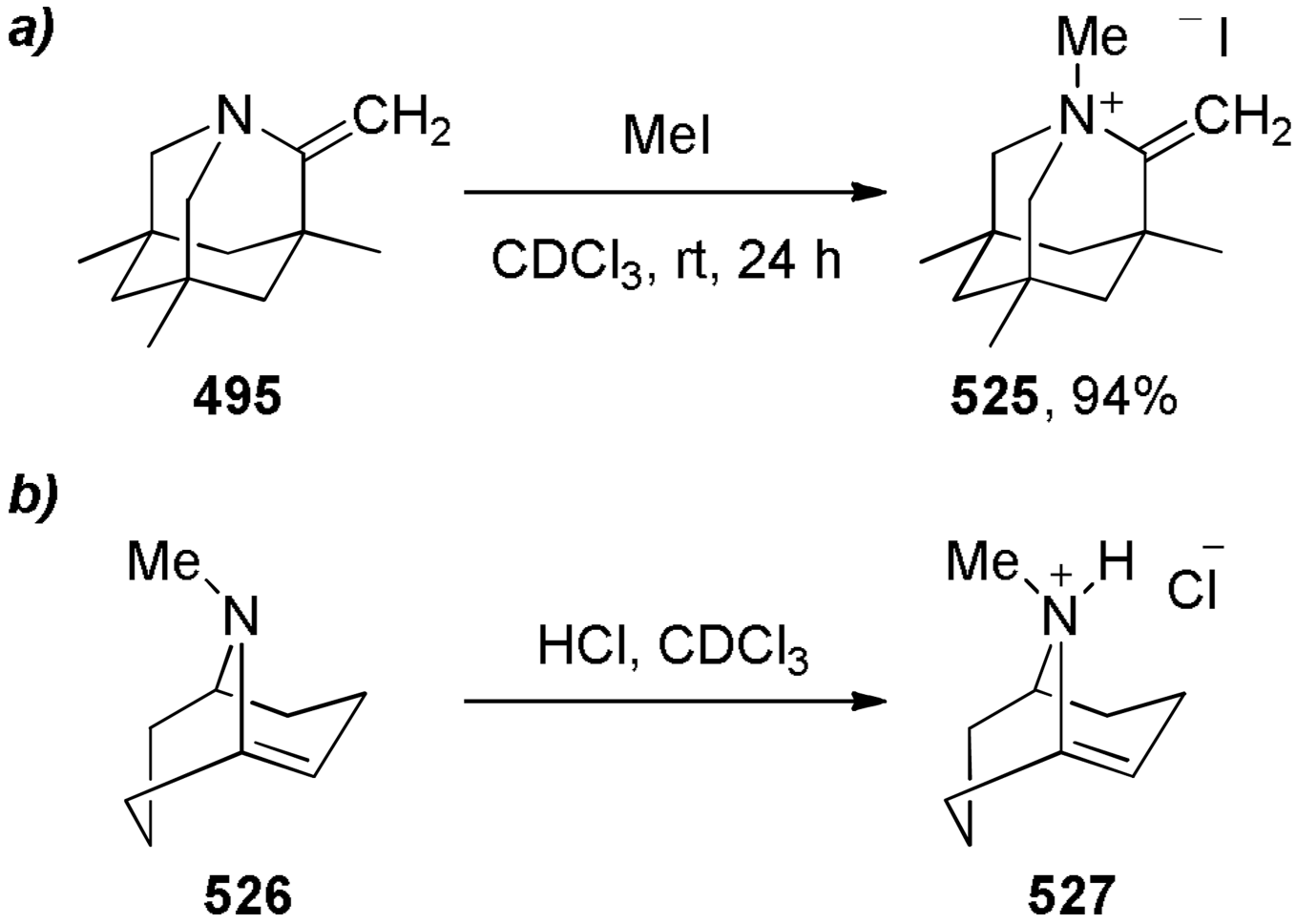
Scheme 159.
Reactivity of Bridged 1,2-Diazines by Shea



Scheme 160.

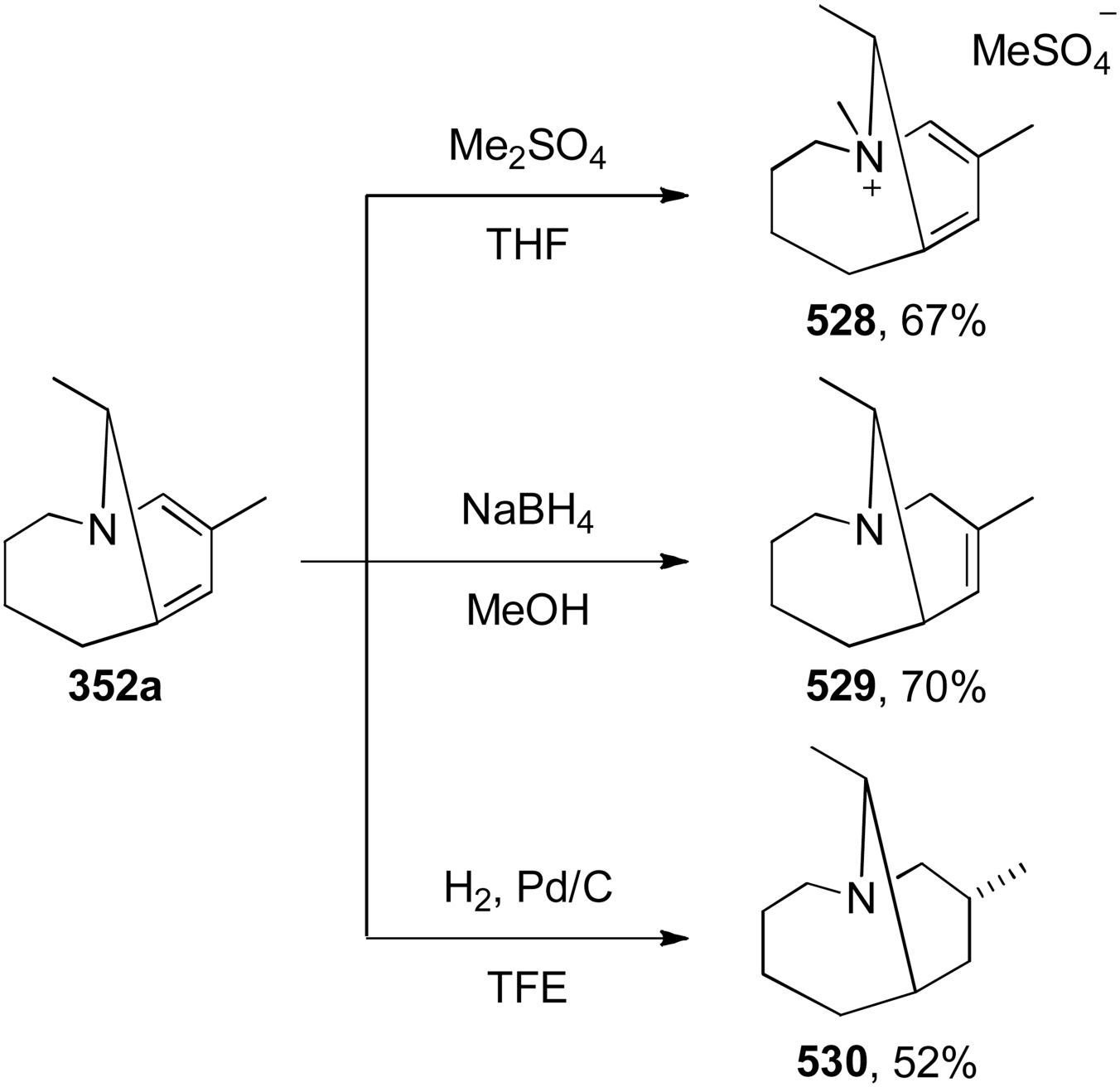
Application of Bridged Oxazinolactams in Synthetic Studies towards Stenine by Shea

(please use double-column format for Scheme 160)

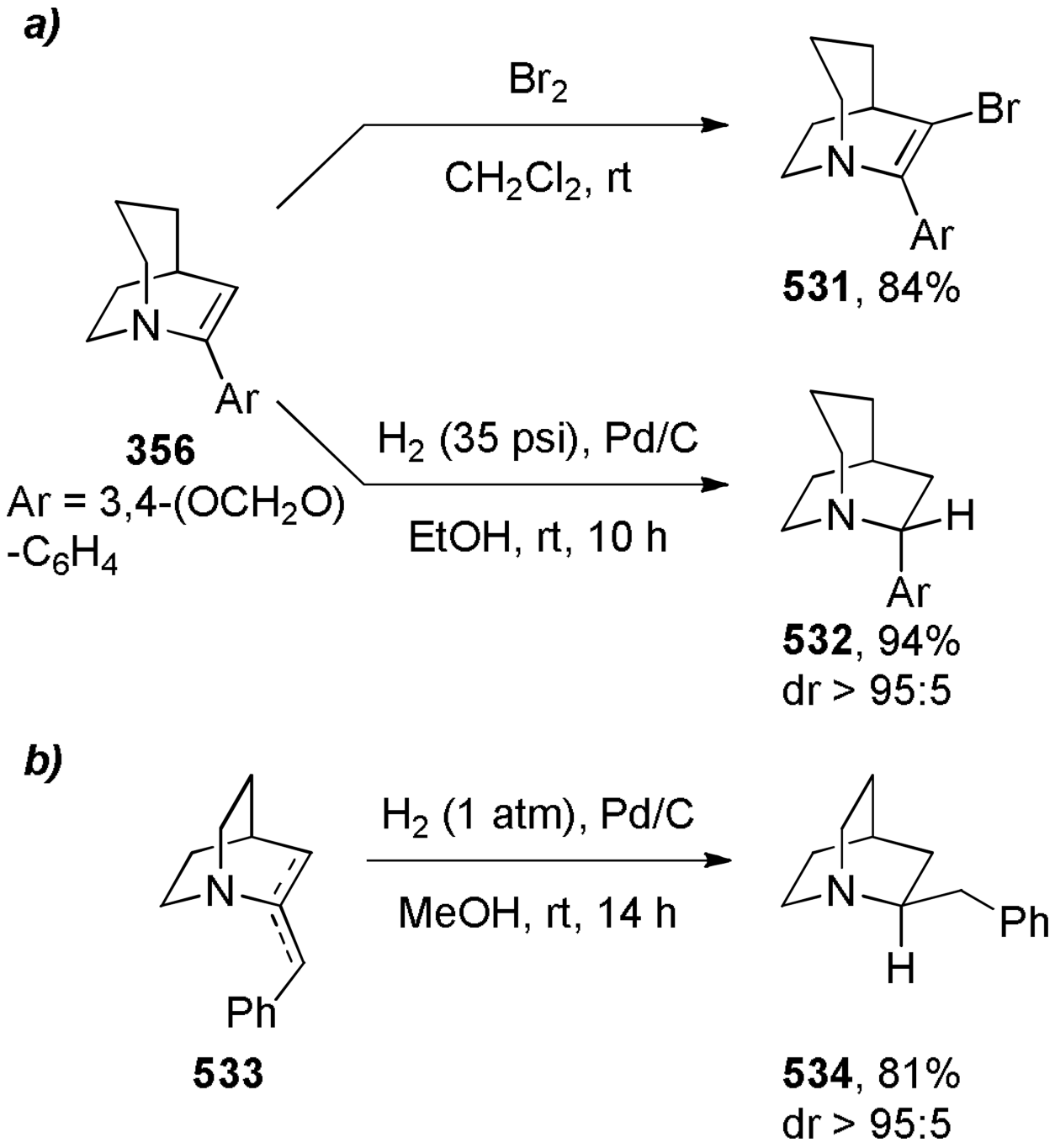


Scheme 161.

a) *N*-Methylation of 3,5,7-Trimethyl-2-methylene-1-azaadamantane by Kirby; b) *N*-Protonation of 9-Methyl-9-Azabicyclo[3.3.1]non-1-ene by Kresge

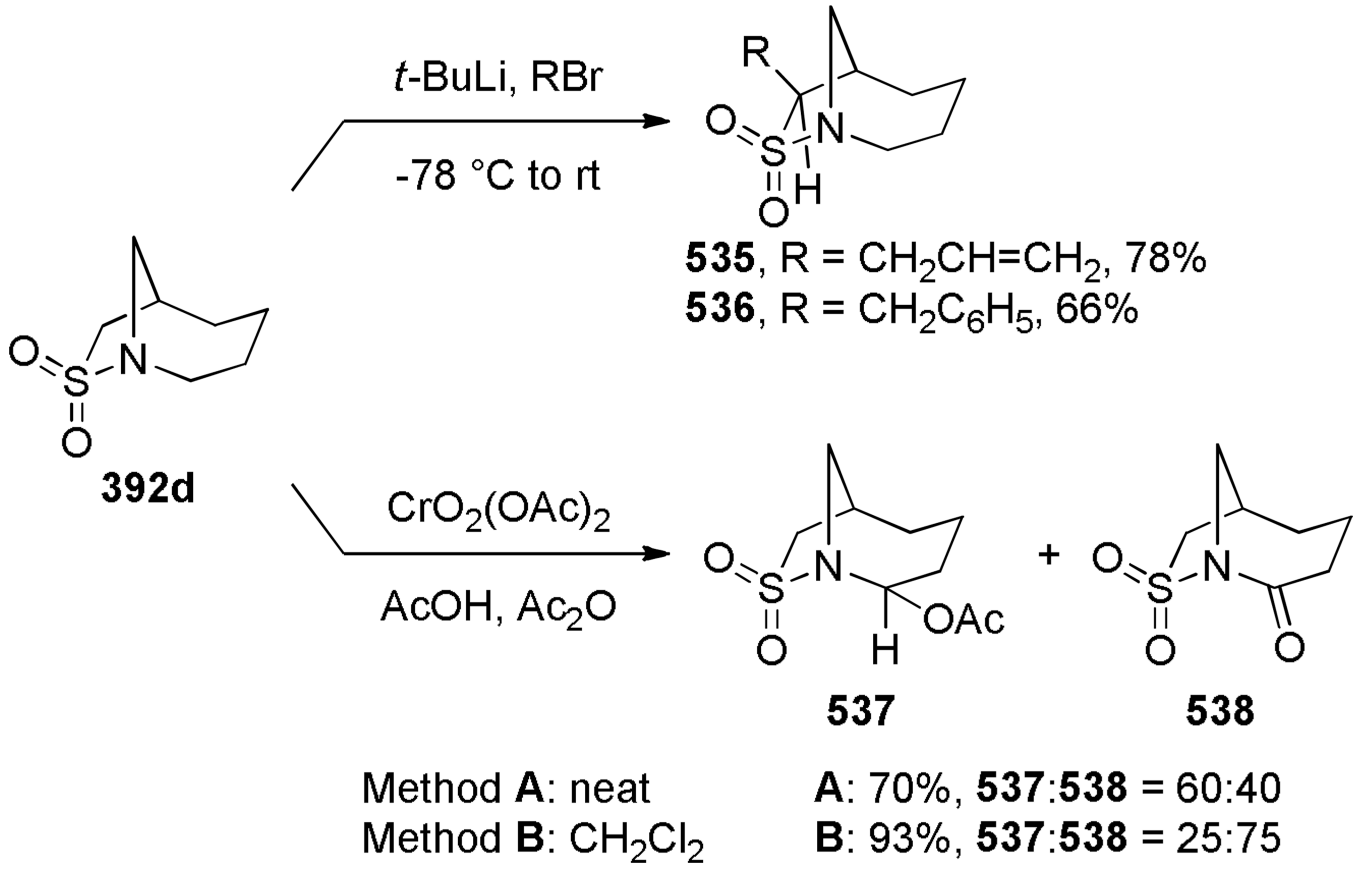


Scheme 162.
Reactivity of Endocyclic [4.3.1] Bridged Enamines by Ellman

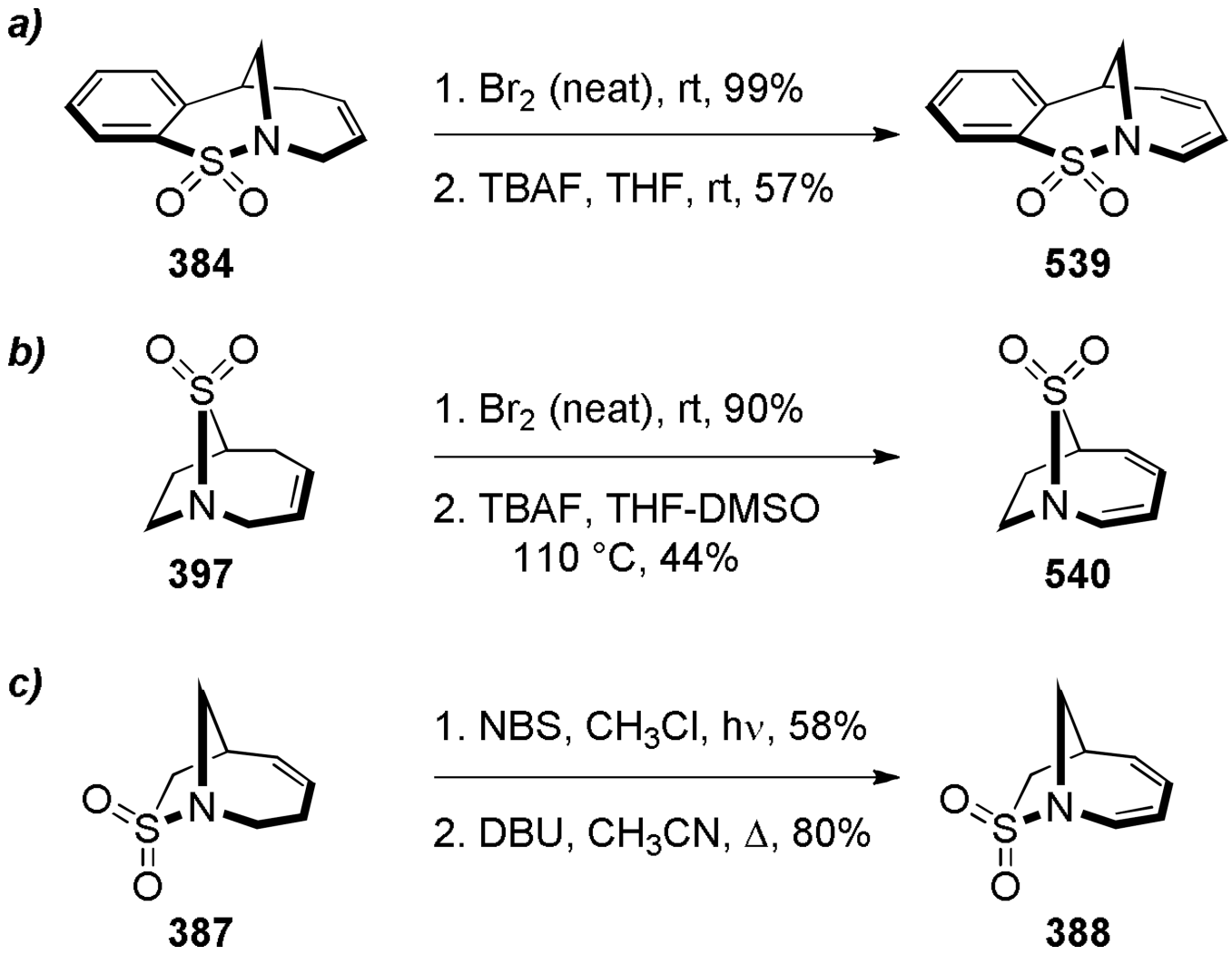


Scheme 163.

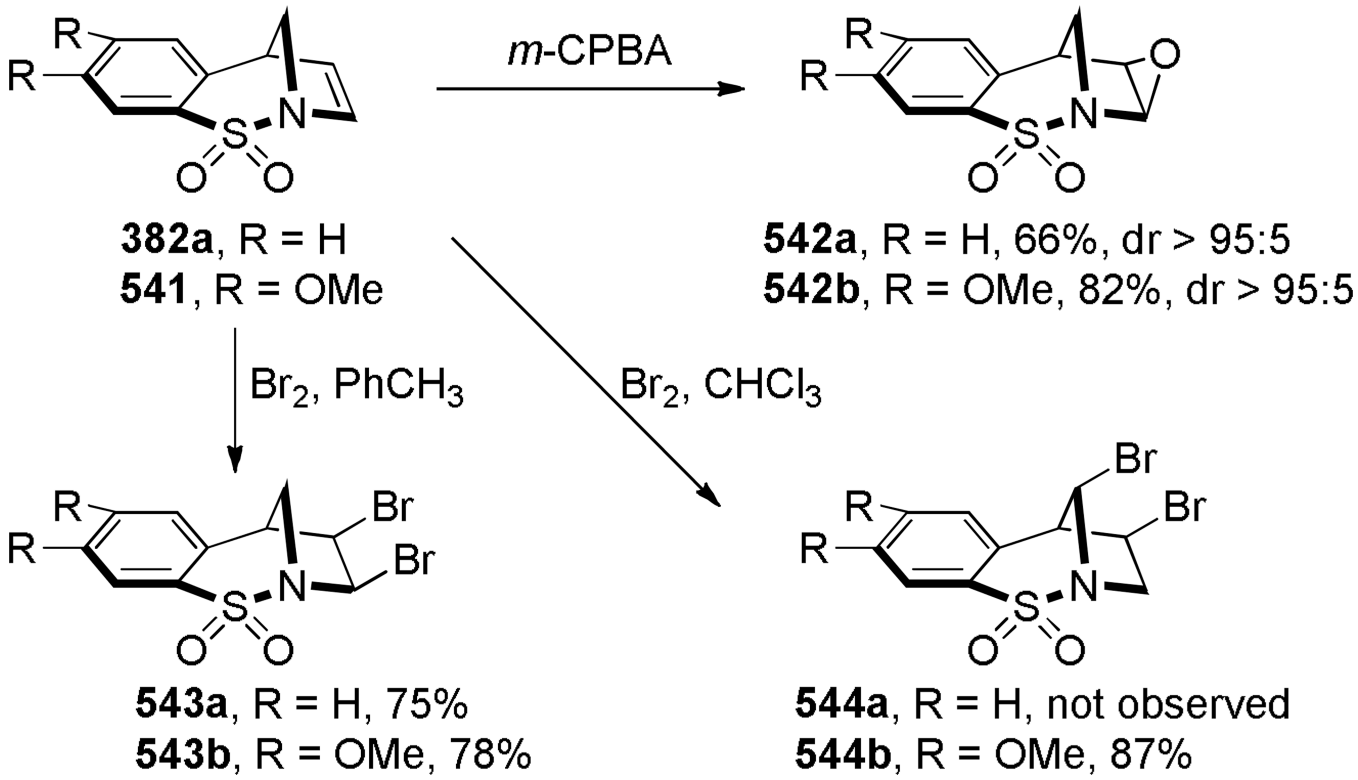
Reactivity of Bridged Enamines Prepared by Schmidt Reaction by Pearson: a) [3.2.2] Scaffold; b) [2.2.2] Scaffold



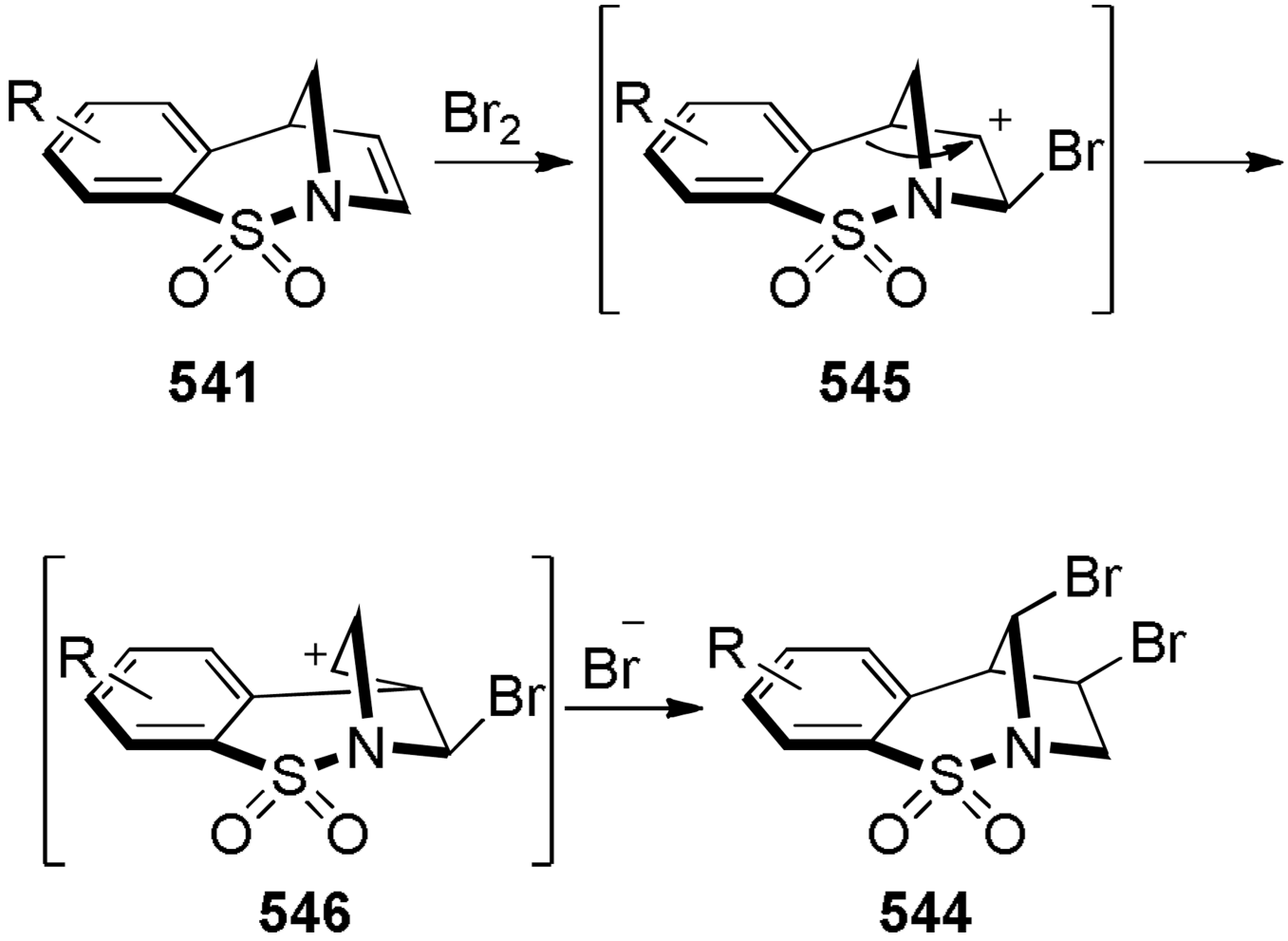
Scheme 164.
Alkylation and Oxidation of Bridged Sultams by Paquette



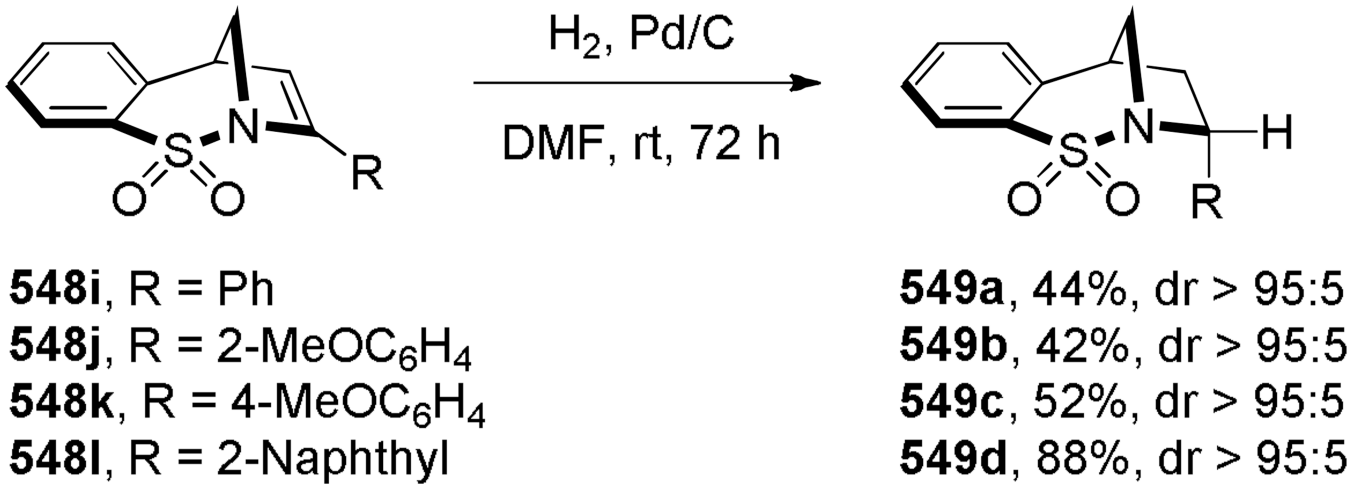
Scheme 165.
Bromination/Elimination of Bridged Sultams by Paquette



Scheme 166.
Bromination and Epoxidation of Benzo-Bridged Sultams by Evans



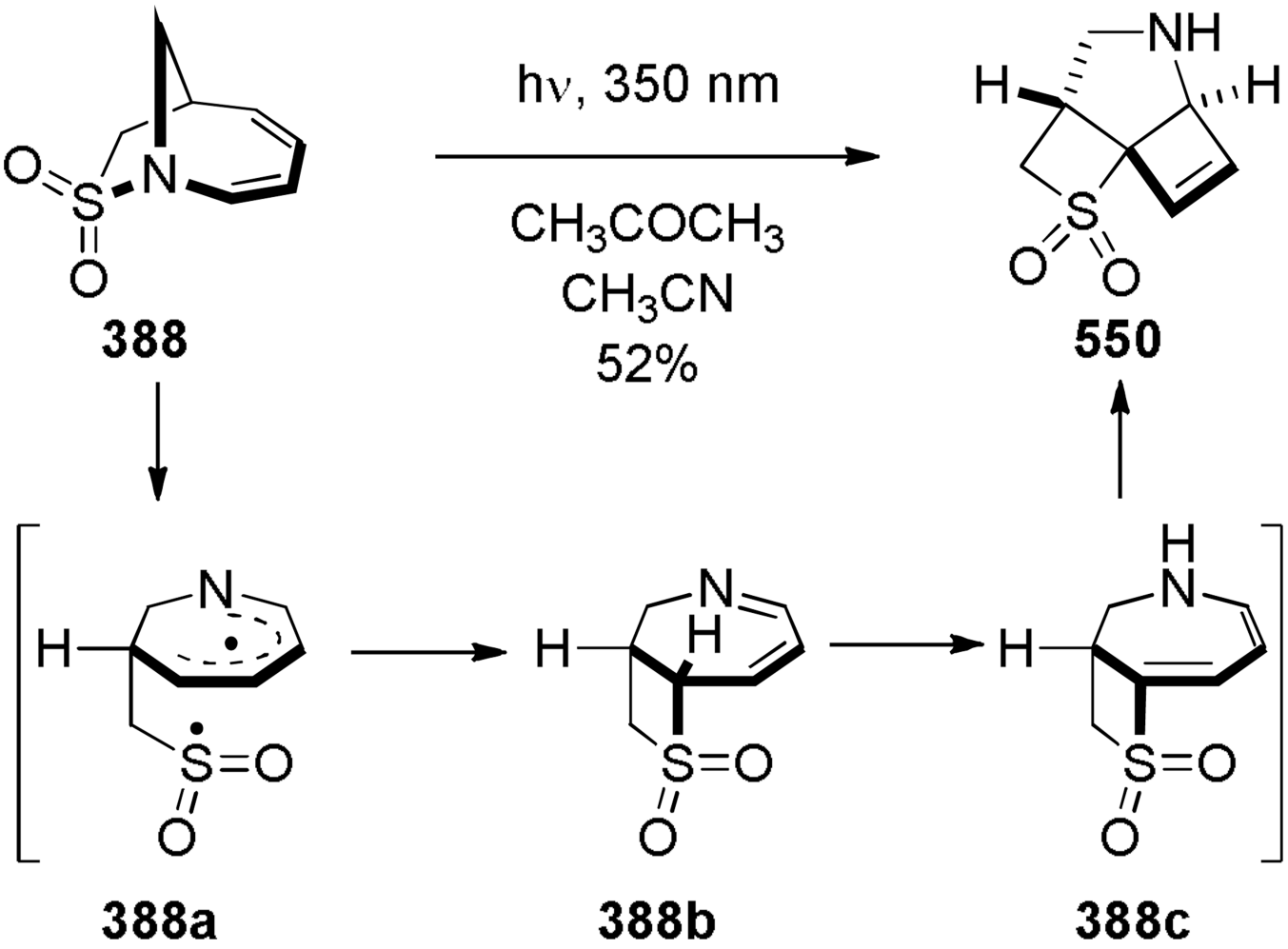
Scheme 167.
Proposed Mechanism for Synthesis of **544**



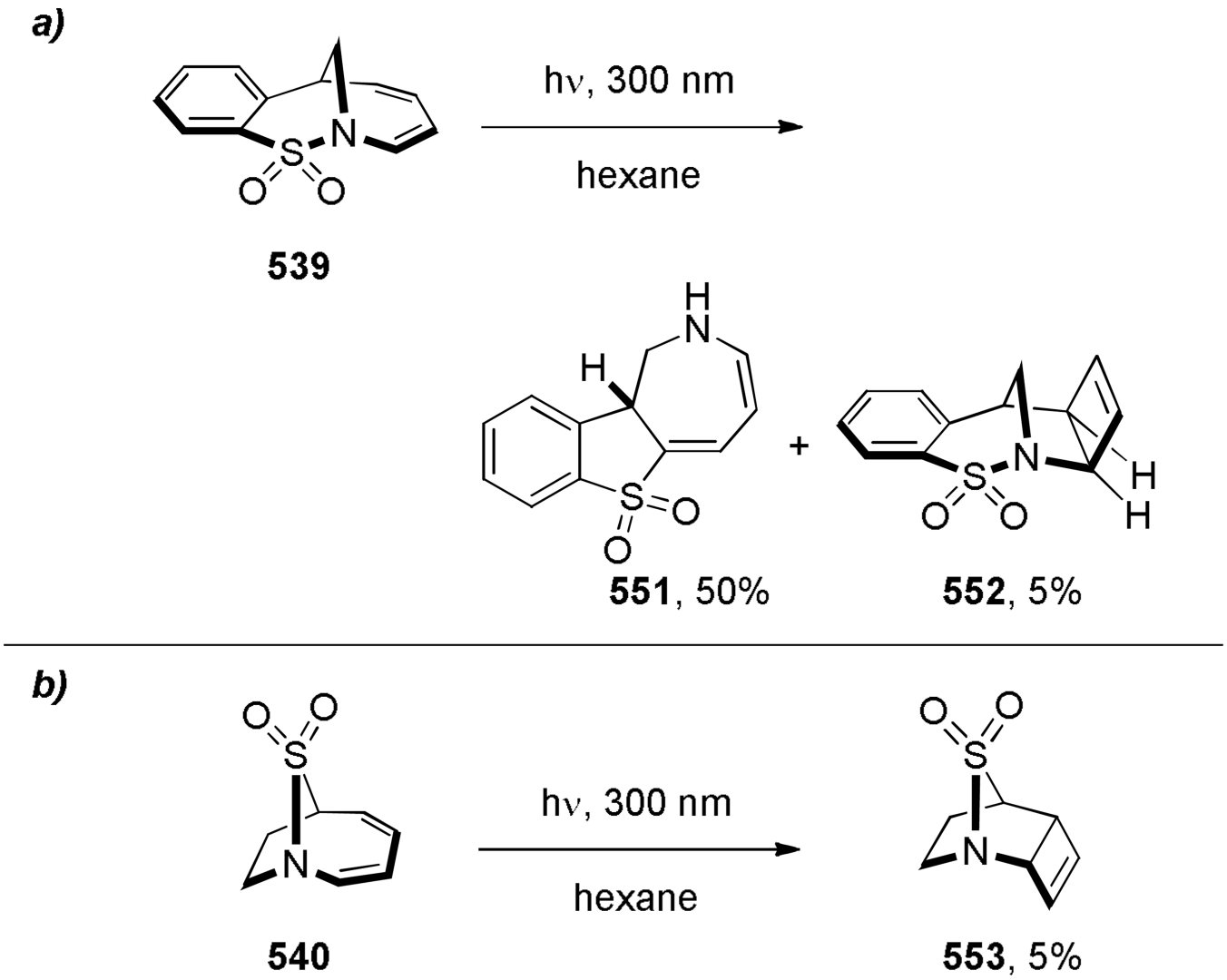
548i, R = Ph
548j, R = 2-MeOC$_6$H$_4$
548k, R = 4-MeOC$_6$H$_4$
548l, R = 2-Naphthyl

549a, 44%, dr > 95:5
549b, 42%, dr > 95:5
549c, 52%, dr > 95:5
549d, 88%, dr > 95:5

Scheme 168.
Hydrogenation of Bridged Sultams by Evans

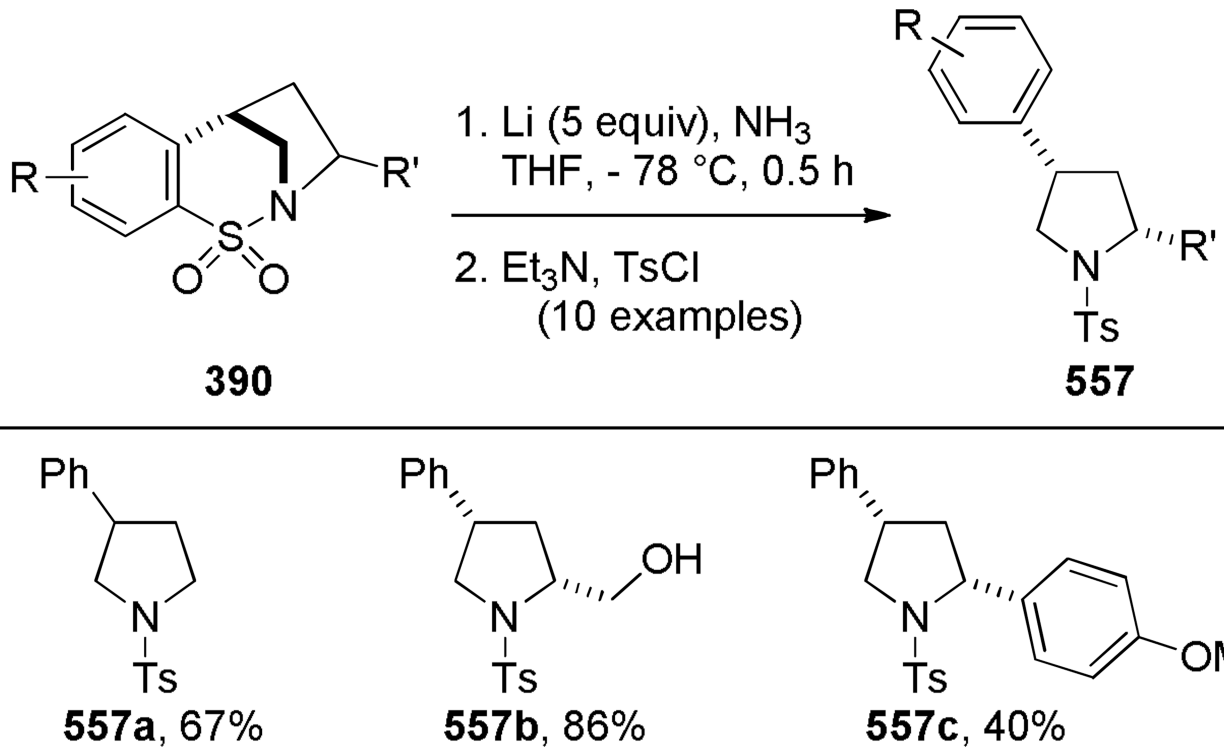


Scheme 169.
Photoinduced Cleavage of SO_2–N Bond of Bridged Sultams by Paquette

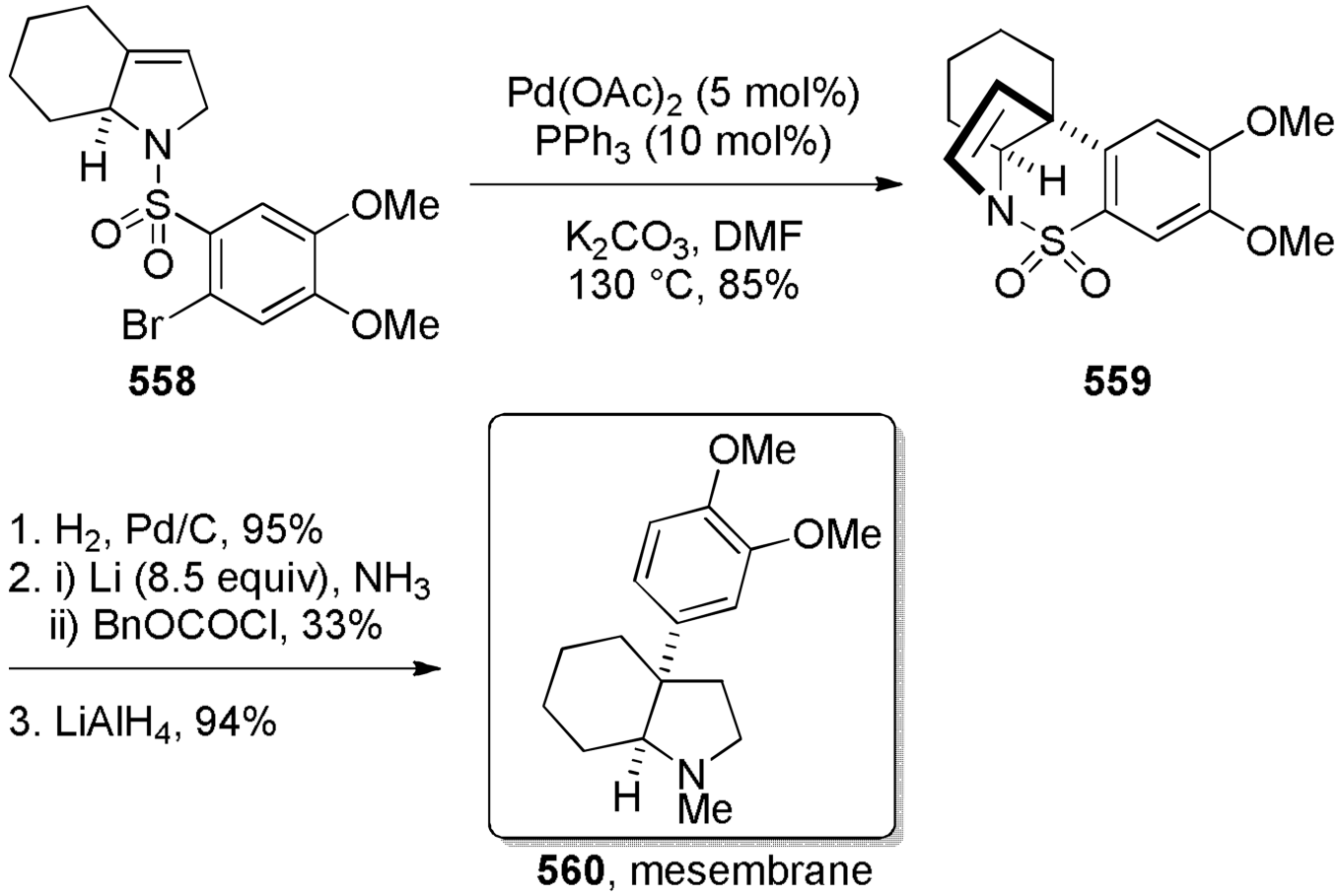


Scheme 170.

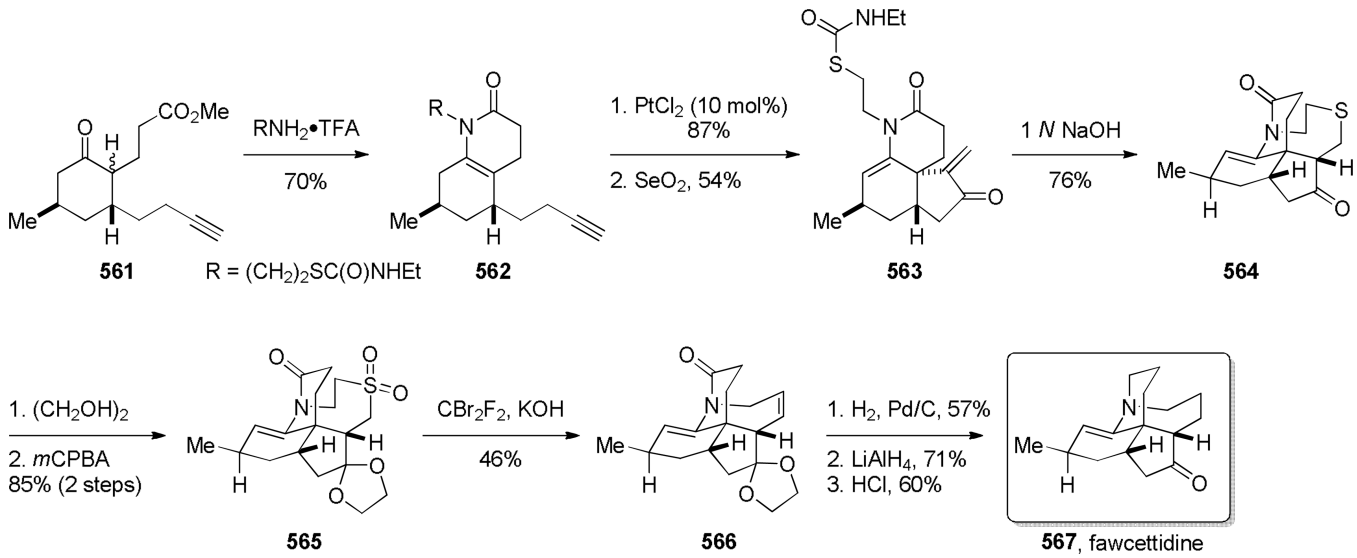
Photoisomerization and Cycloaddition of Bridged Sultams by Paquette: a) Benzo[4.3.1] Ring System; b) [4.2.1] Ring System



Scheme 171.
Synthesis of Pyrrolidines via Double Reduction of Bridged Sultams by Evans

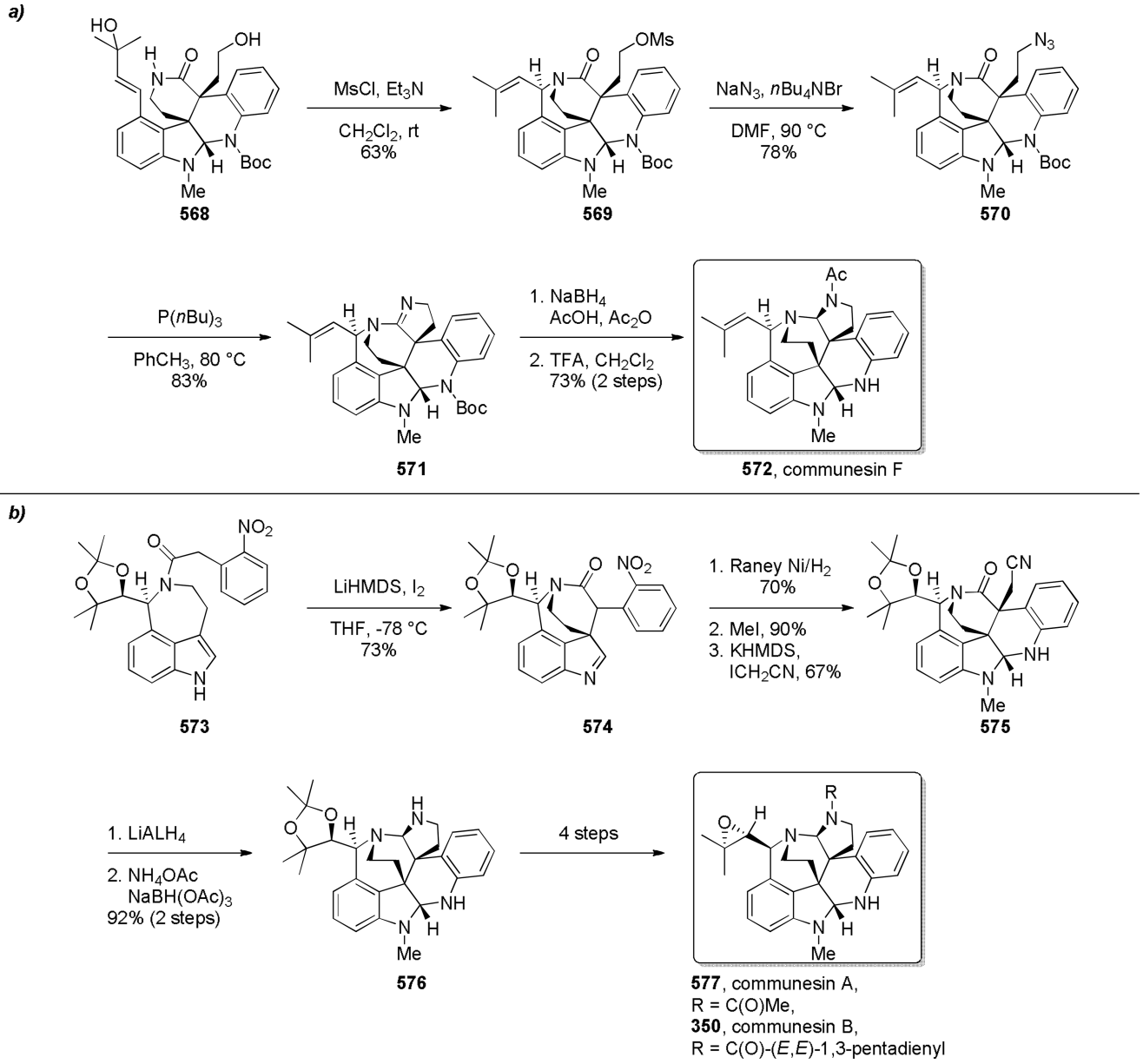


Scheme 172.
Total Synthesis of Mesembrane via Double Reduction of Bridged Sultams by Evans



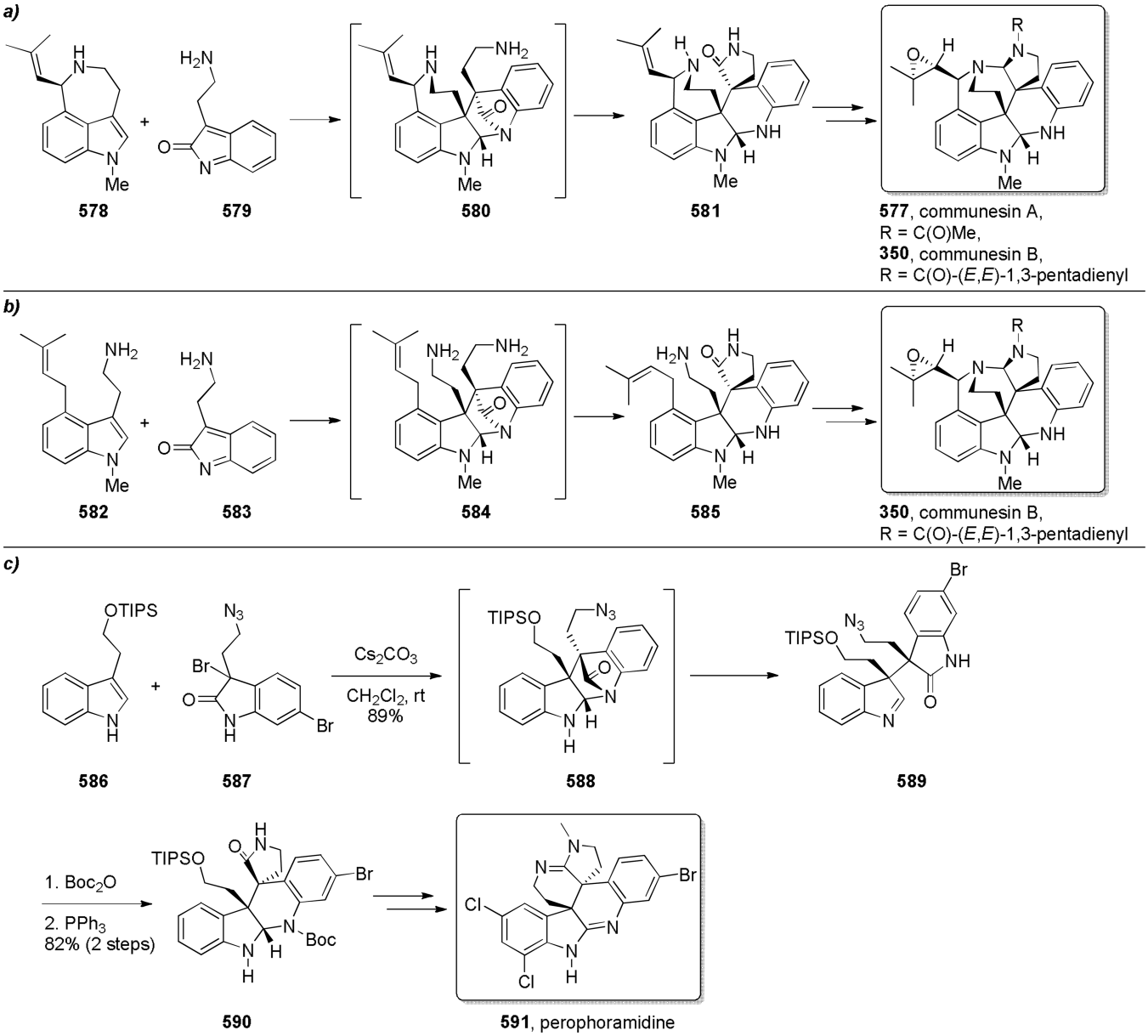
Scheme 173.

Total Synthesis of Fawcettidine by Dake (please use double-column format for Scheme 173)



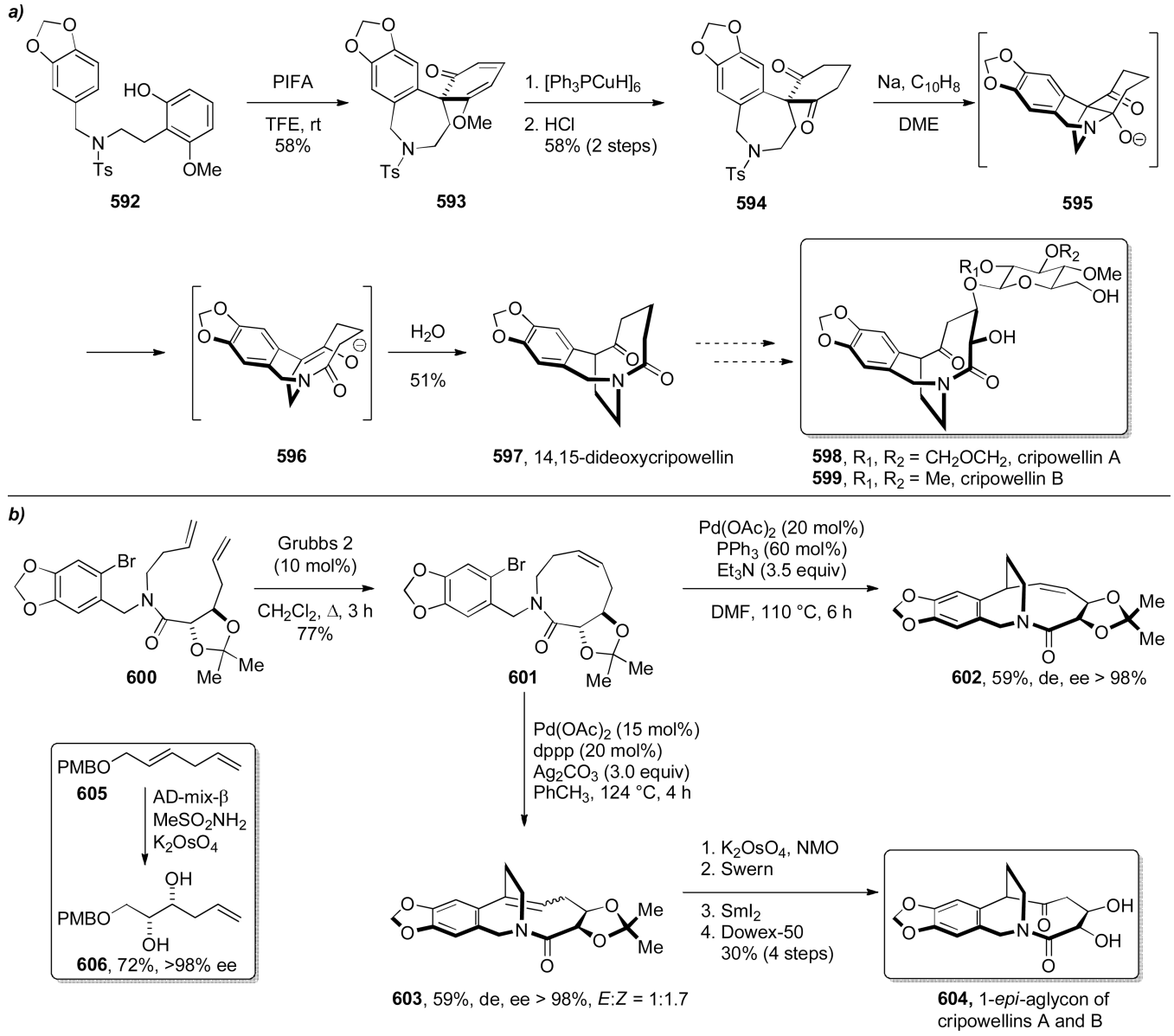
Scheme 174.

a) Total Synthesis of Communesin F by Ma; a) Total Synthesis of Communesins A and B by Ma (please use double-column format for Scheme 174)



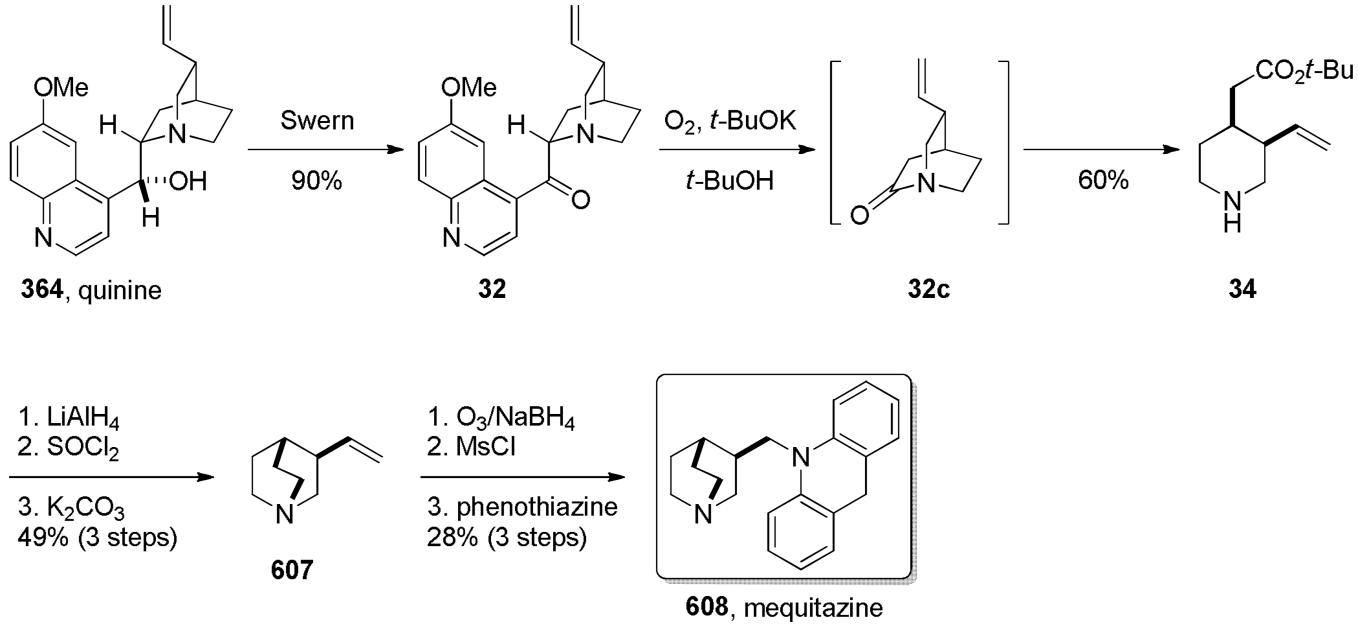
Scheme 175.

a) Biomimetic Proposal for Synthesis of Communesins A and B by Stoltz; b) Biomimetic Proposal for Synthesis of Communesin B by Funk; c) Total Synthesis of Perophoramidine by Funk (please use double-column format for Scheme 175)



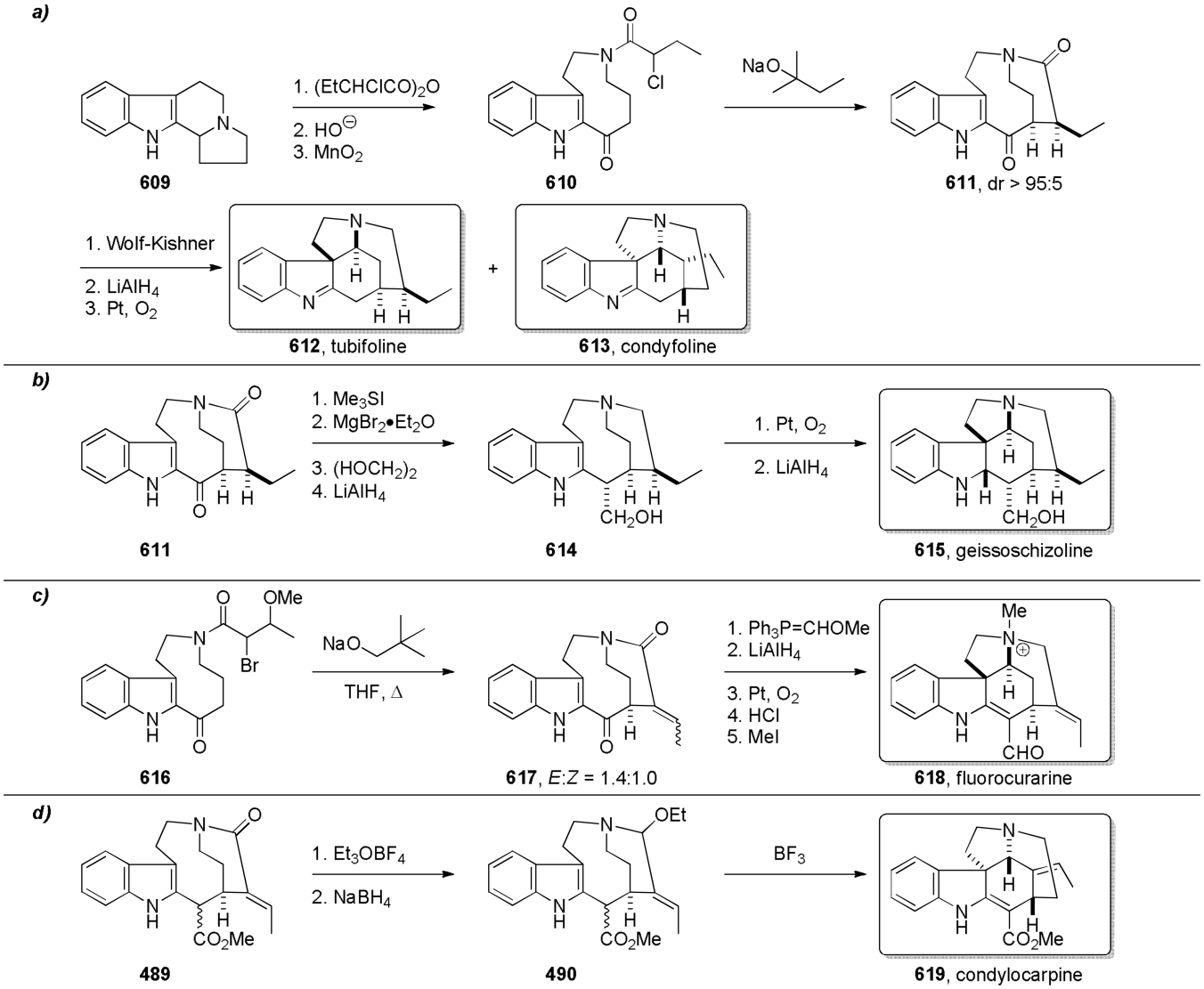
Scheme 176.

a) Approach to Cripowellin Aglycon by Moon; b) Synthesis of 1-*epi*-Aglycon of Cripowellins A nd B by Enders (please use double-column format for Scheme 176)



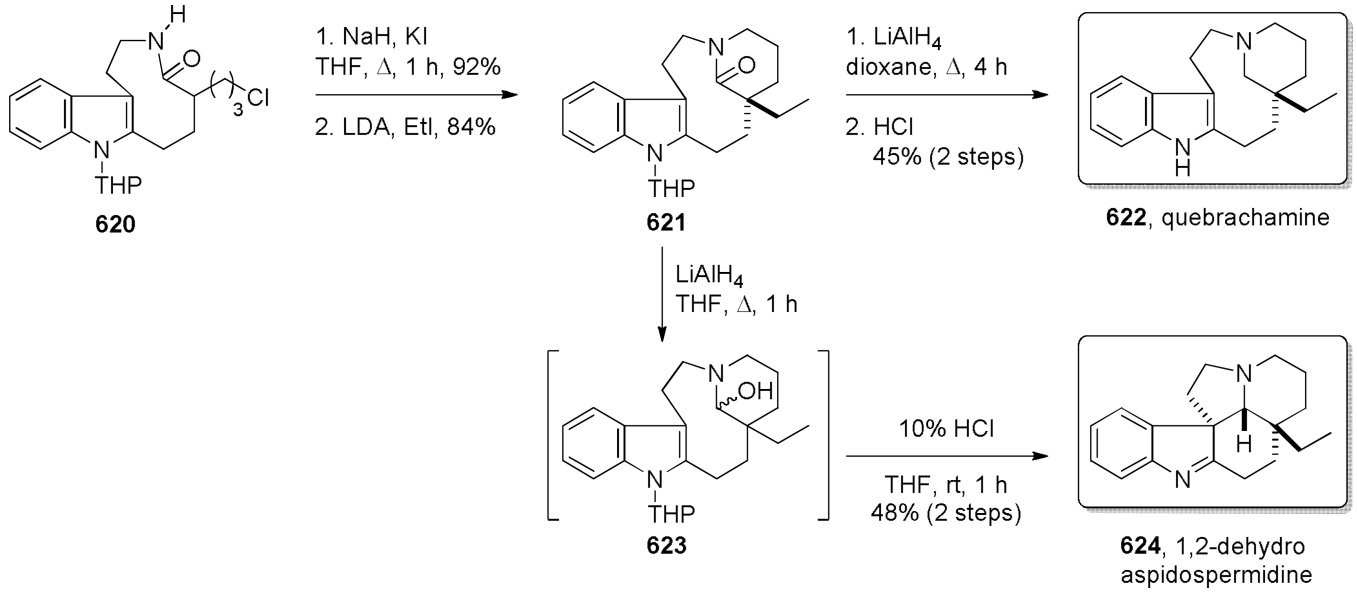
Scheme 177.

Synthesis of Mequitazine by Doris (please use double-column format for Scheme 177)



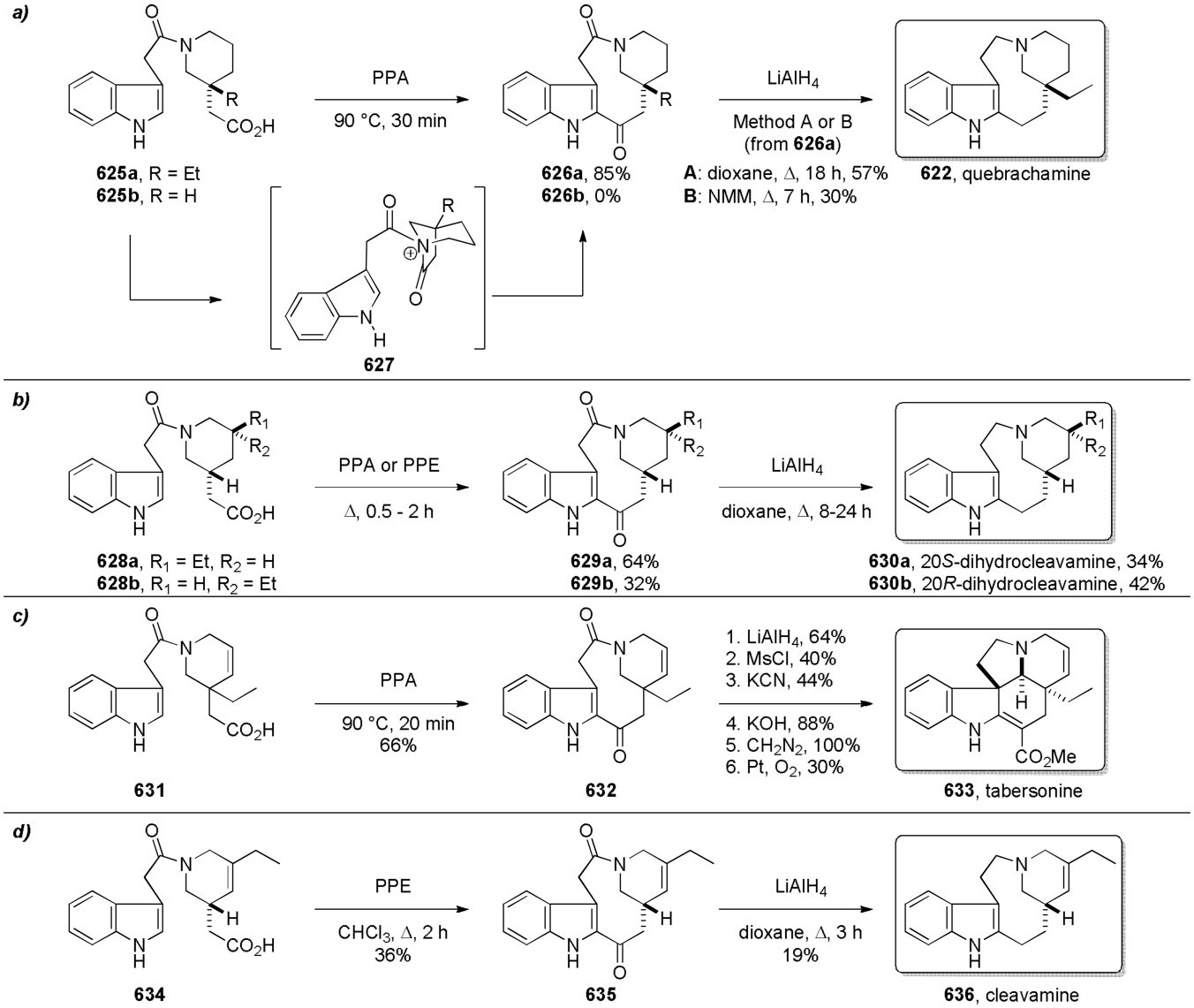
Scheme 178.

Synthesis of Indole Alkaloids by Harley-Mason: a) Tubifoline and Condyfoline; b) Geissoschizoline; c) Fluorocurarine; d) Condylocarpine (please use double-column format for Scheme 178)



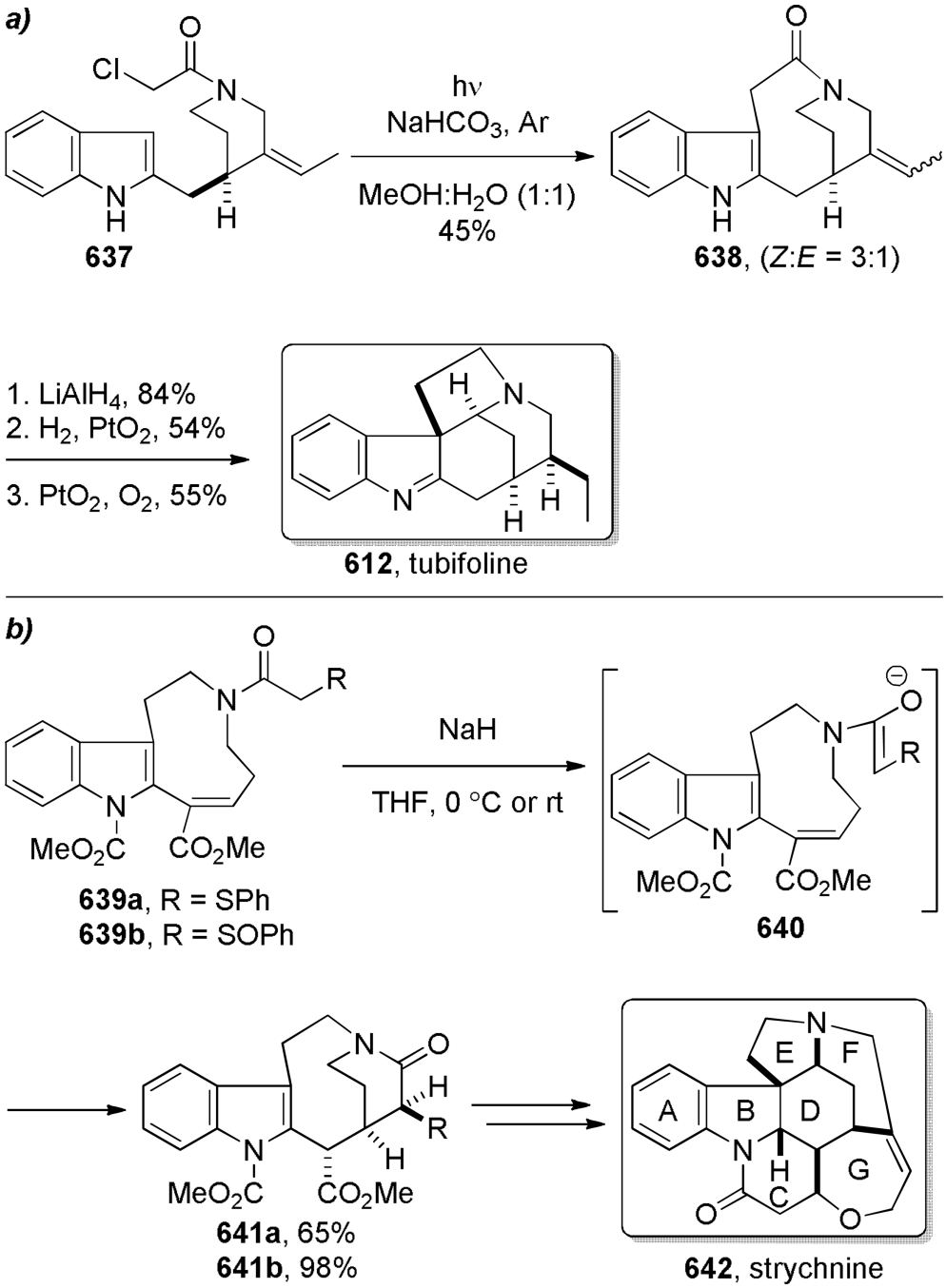
Scheme 179.

Synthesis of Quebrachamine and 1,2-Dehydroaspidospermidine by Ban (please use double-column format for Scheme 179)



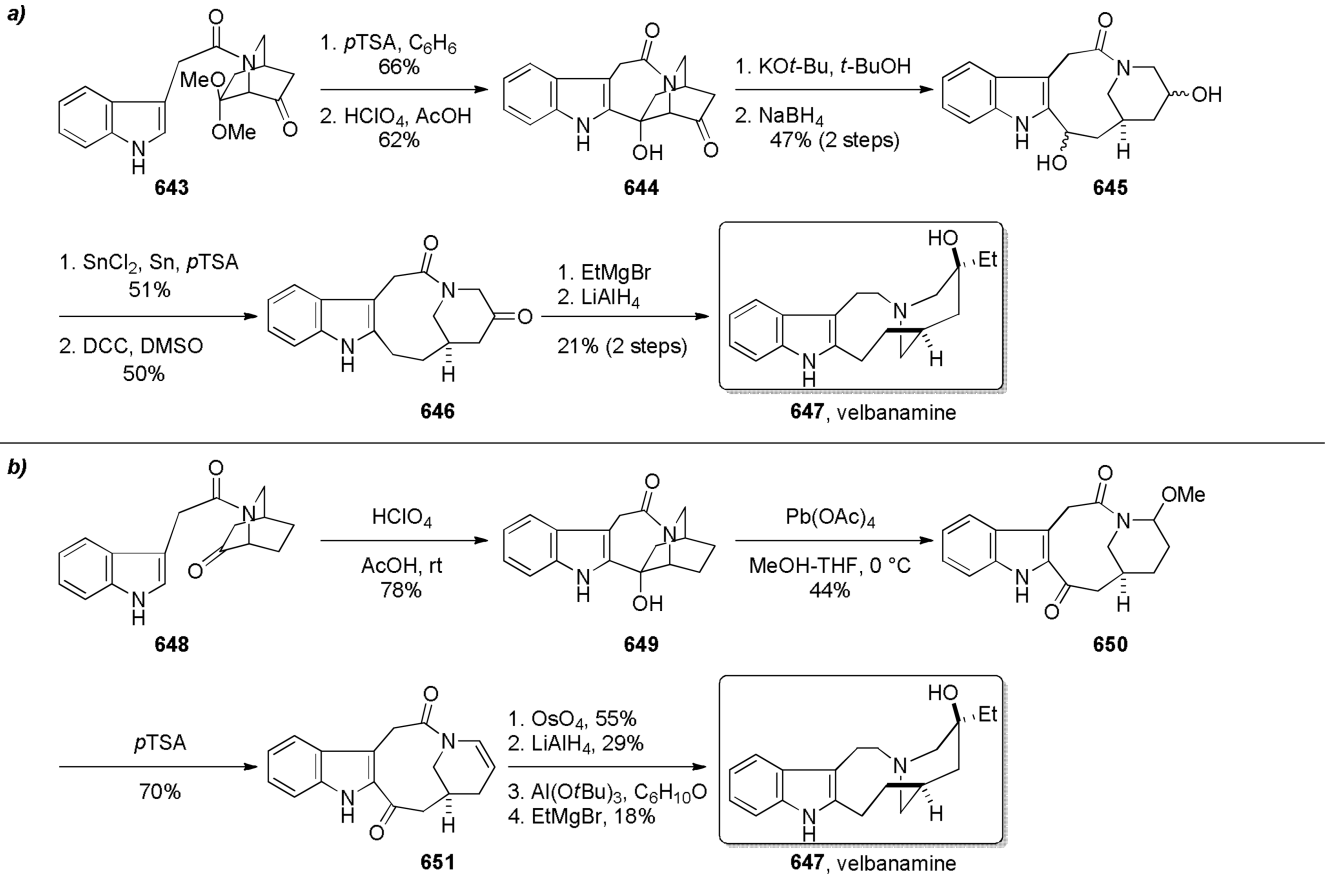
Scheme 180.

Synthesis of Indole Alkaloids via Friedel-Crafts Acylation of Bridged Amides: a) Quebrachamine by Ziegler and Bosch; b) Dihydrocleavamine by Bosch and Lesma; c) Tabersonine by Ziegler; d) Cleavamine by Hanaoka (please use double-column format for Scheme 180)



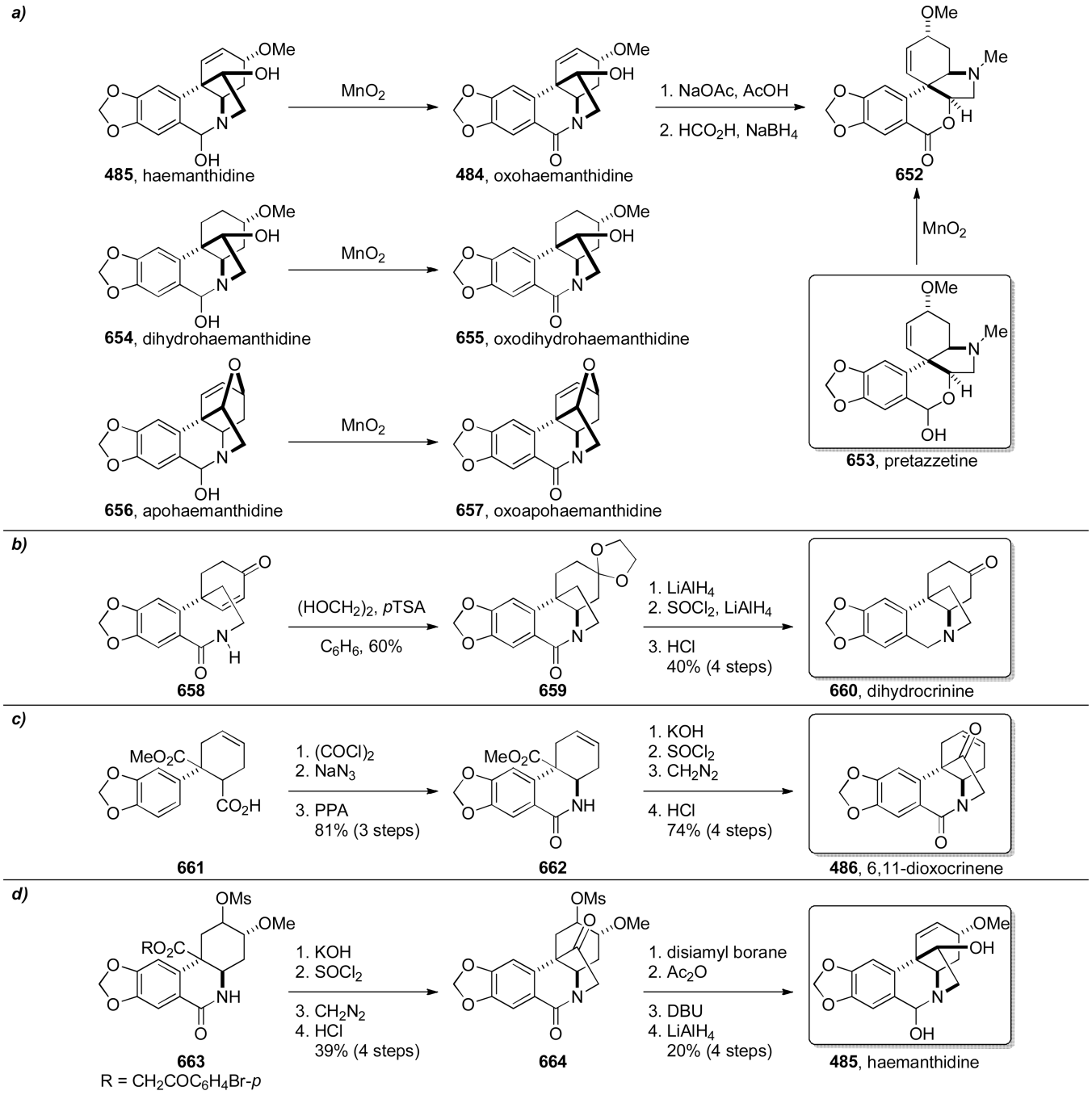
Scheme 181.

a) Application of Bridged Amide in Total Synthesis of Tubifoline by Bosch; b) Application in Bridged Amide in Total Synthesis of Strychnine by Magnus



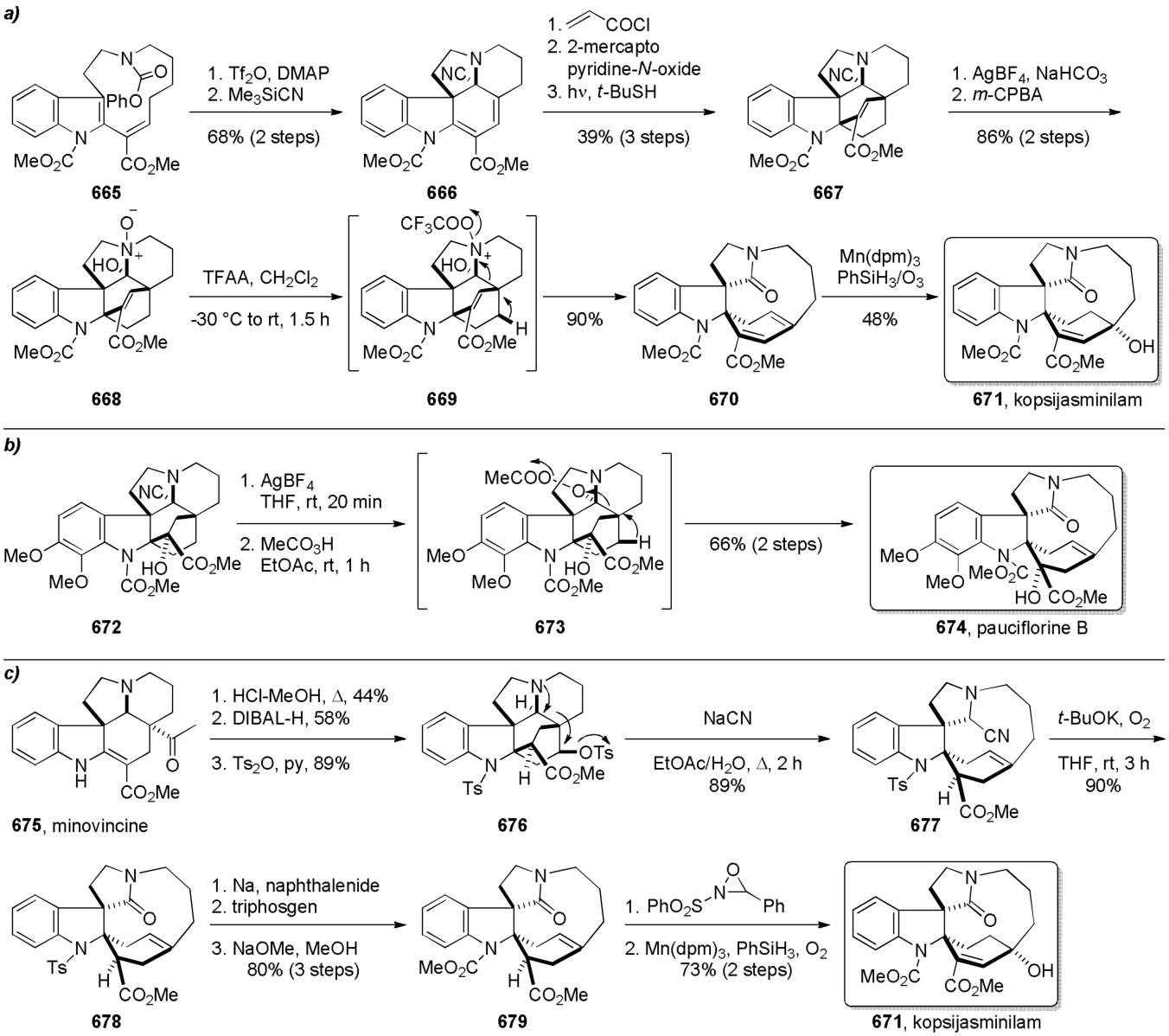
Scheme 182.

Total Synthesis of Velbanamine: a) Büchi; b) Narisada (please use double-column format for Scheme 182)



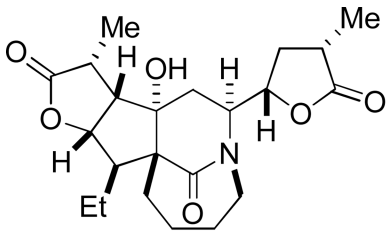
Scheme 183.

Bridged Lactams in Total Synthesis of Amaryllidaceae Alkaloids: a) Oxohaemanthidine, Oxodihydrohaemanthidine, Oxoapohaemanthidine and Pretazzetine; b) Dihydrocrinine; c) 6,11-Dioxocrinene; d) Haemanthidine (please use double-column format for Scheme 183)

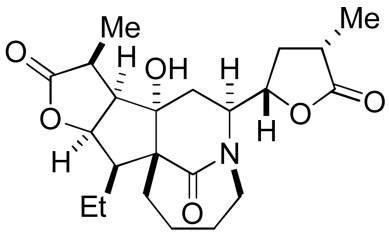


Scheme 184.

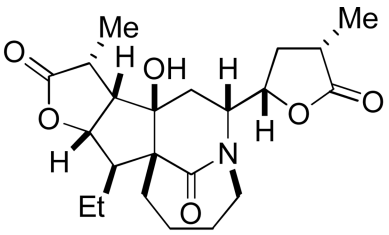
Total Synthesis of Kopsijasminilam by Magnus; b) Total Synthesis of and Pauciflorine B by Magnus; c) Total Synthesis of Kopsijasminilam by Kuehne (please use double-column format for Scheme 184)



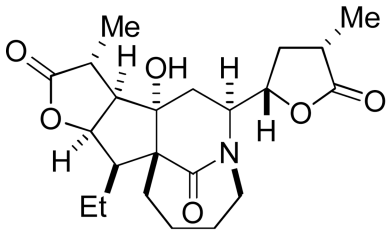
680, tuberostemoninol



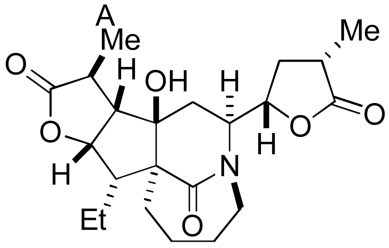
681, tuberostemoninol A



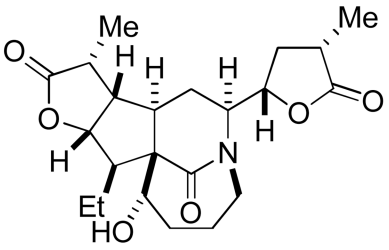
682, tuberostemoninol B



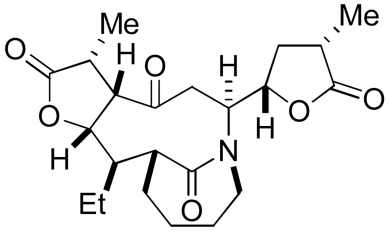
683, neotuberostemoninol



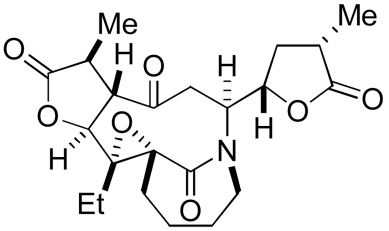
684, sessilifoliamide I



685, maireistemoninol



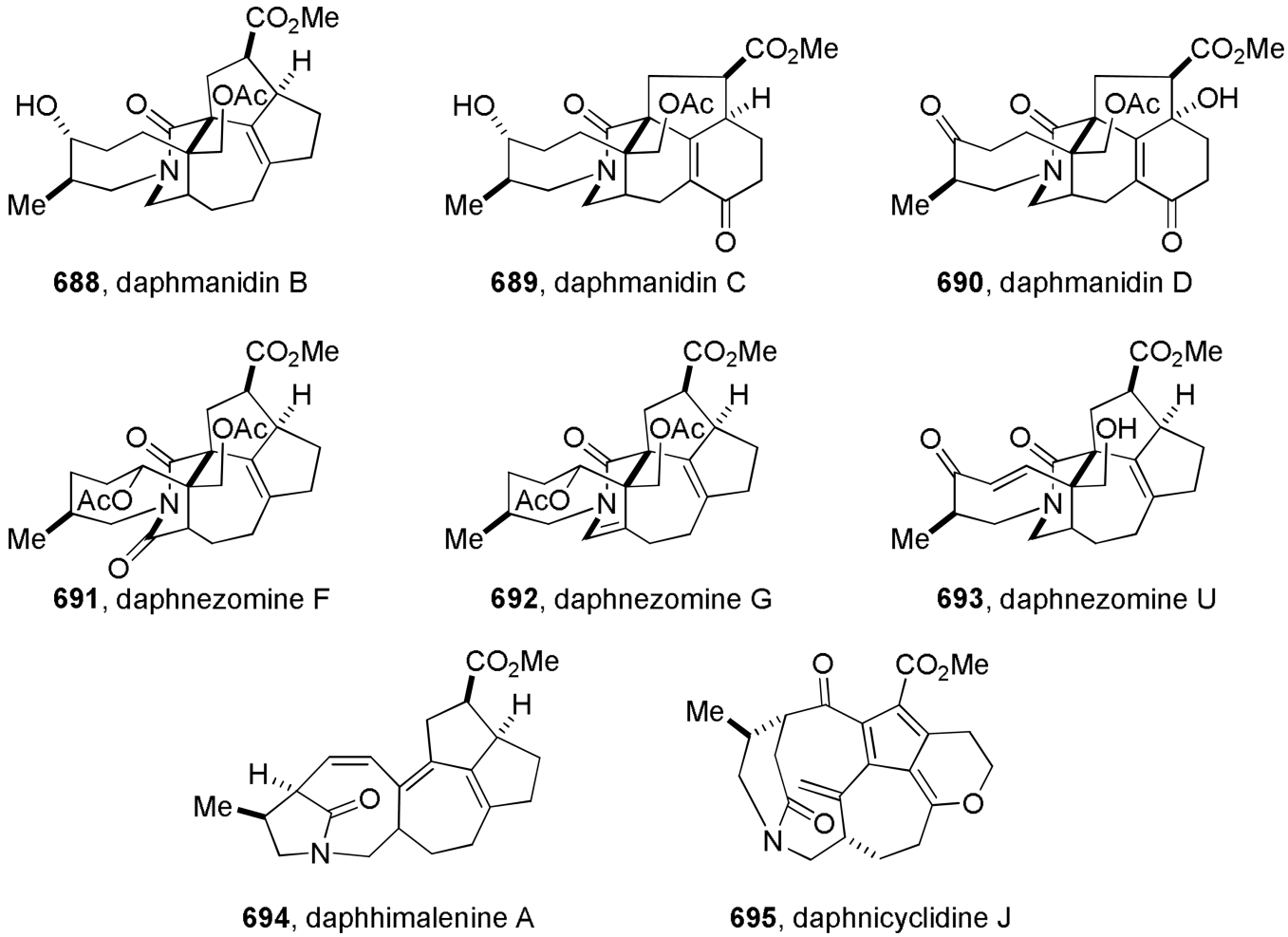
686, neotuberostemonone



687, epoxytuberostemonone

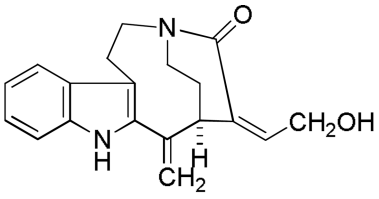
Scheme 185.

Stemona Alkaloids Containing Bridged Amide Bonds (please use double-column format for Scheme 185)

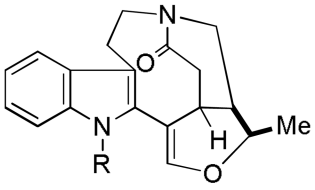


Scheme 186.

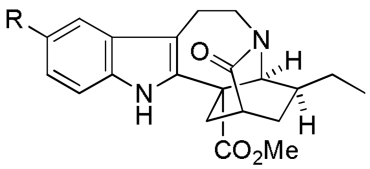
Daphnum Alkaloids Containing Bridged Amide Bonds (please use double-column format for Scheme 186)



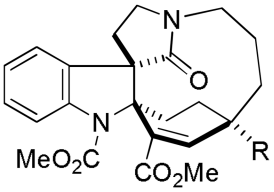
696, pericidine



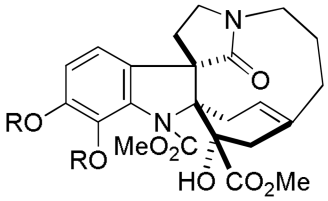
697, R = $COCH_2OH$, henningsamide
698, R = $COCH_2OAc$, *O*-acetylhenningsamide
699, R = H, deshydroxyacetylhenningsamide



700, R = H, 3-oxocoronaridine
701, R = OMe, 3-oxovoacangine



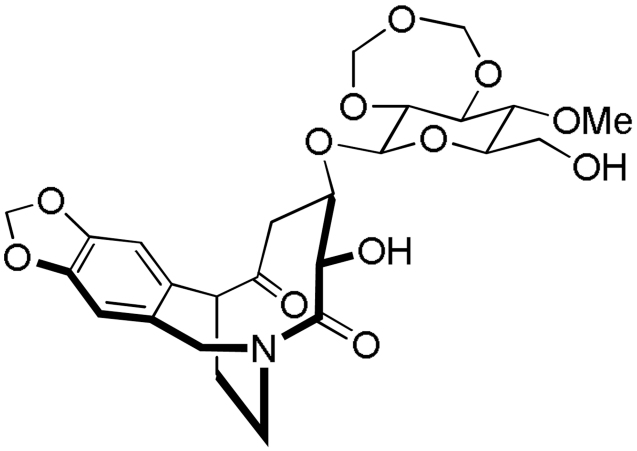
671, R = OH, kopsijasminilam
702, R = H, deoxykopsijasminilam



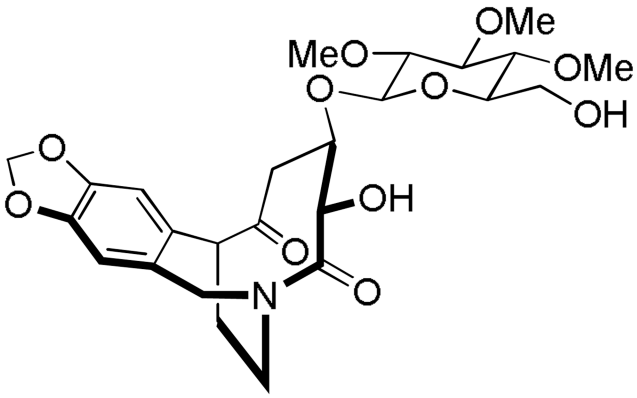
703, R = -CH_2-, pauciflorine A
674, R = Me, pauciflorine B

Scheme 187.

Indole Alkaloids Containing Bridged Amide Bonds (please use double-column format for Scheme 187)



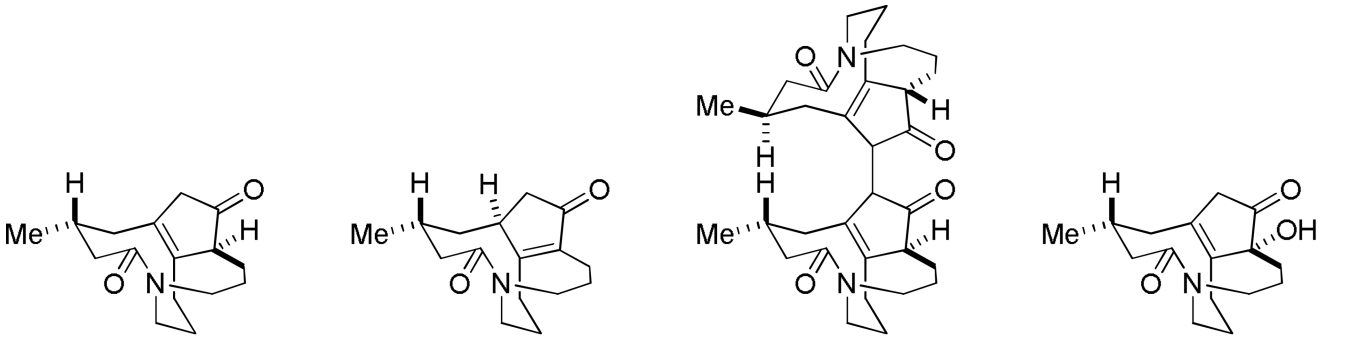
598, cripowellin A



599, cripowellin B

Scheme 188.

Cripowellins Containing Bridged Amide Bonds (please use double-column format for Scheme 188)



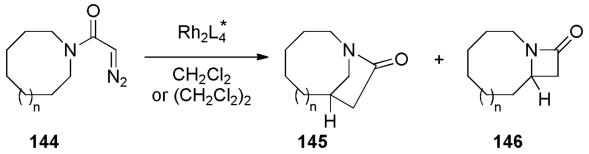
704, phlegmariurine A **705**, phlegmariurine B **706**, phlegmariurine C **707**, lycoposerramine E

Scheme 189.

Lycopodium Alkaloids Containing Bridged Amide Bonds (please use double-column format for Scheme 189)

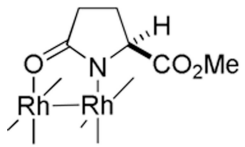
Table 1

Synthesis of 1-Azabicyclo[5.2.1]decan-9-one via Rh-Catalyzed C–H Insertion by Doyle

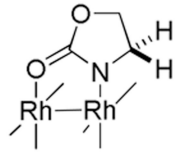


144 **145** **146**

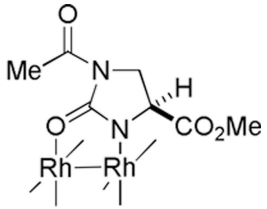
entry	n	144	Rh_2L_4	ratio of 145:146	combined yield (%)	ee of 145 (%)	ee of 146 (%)
1	0	**144a**	Rh_2(5*S*-MEPY)$_4$	1:99	67	n/a	97
2	1	**144b**	Rh_2(4*S*-MEOX)$_4$	74:26	95	98	15
3	1	**144b**	Rh_2(5*S*-MEPY)$_4$	33:67	67	97	30
4	1	**144b**	Rh_2(4*S*-MACIM)$_4$	61:39	81	96	66



Rh_2(5*S*-MEPY)$_4$



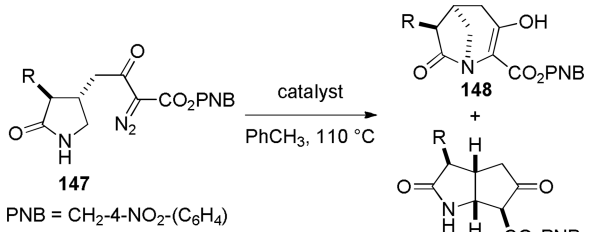
Rh_2(4*S*-MEOX)$_4$



Rh_2(4*S*-MACIM)$_4$

Table 2

Synthesis of 1-Azabicyclo[3.2.1]octan-7-onesvia N–H Insertion by Aszodi

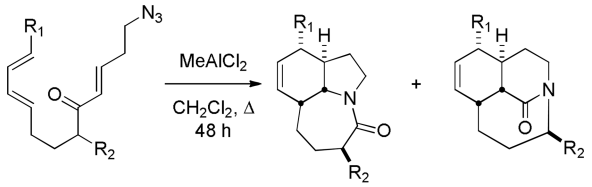


PNB = CH_2-4-NO_2-(C_6H_4)

entry	R	147	catalyst	yield of 148 (%)	yield of 149 (%)
1	H	**147a**	$Rh_2(OAc)_4$	40	42
2	Et	**147b**	$Rh_2(OAc)_4$	5	80
3	Et	**147b**	$Cu(acac)_2$	30	n/a

Table 3

Synthesis of Tricyclic Bridged Lactams via Domino Diels-Alder/Schmidt Reaction by Aubé

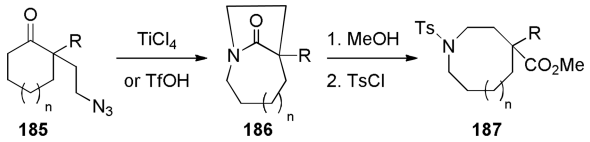


175 **176** **177**

entry	ketoazide 175	R_1	R_2	yield of 176 (%)	yield of 177 (%)
1	**175a**	$(CH_2)_2OBn$	H	43	24
2	**175b**	4-Br-C_6H_4	H	43	23
3	**175c**	C_6H_5	H	46	23
4	**175d**	H	H	41	22
5	**175e**	H	*i*-Pr	43	28
6	**175f**	H	Ph	85	0

Table 4

Synthesis of Bridged Lactams via Schmidt Reaction of 2-(2-Azidoethyl) Ketones by Murphy



185 186 187

entry	n	185	R	acid	yield of 186 (%)	yield of 187 (%)
1	0	**185a**	H	TfOH	n/a	89[a]
2	0	**185b**	4-MeO-C_6H_4	TfOH	n/a	22[a,b]
3	1	**185c**	H	TfOH	n/a	94[a]
4	1	**185d**	4-MeO-C_6H_4	$TiCl_4$	97	n/a
5	2	**185e**	H	TfOH	41	83

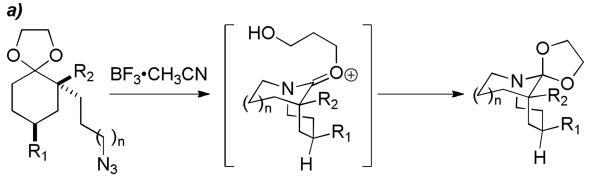
[a] Yield from **185**.

[b] MsCl instead of TsCl.

Table 5

a) Synthesis of Bridged Orthoamides via Schmidt Reaction of 2-Azidoalkyl Ketals by Aubé; b) Conversion of Bridged Orthoamides to Bridged Lactams

a)

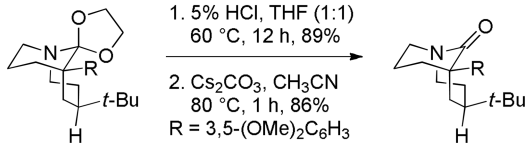


191 **192** **193**

entry	191	n	R_1	R_2	yield of 193 (%)
1	**191a**	1	*t*-Bu	C_6H_5	88
2	**191b**	1	*t*-Bu	4-MeO-C_6H_4	92
3	**191c**	1	*t*-Bu	4-NO_2-C_6H_4	94
4	**191d**	1	H	C_6H_5	59
5	**191e**	1	H	SPh	78[a]
6	**191f**	0	H	C_6H_5	91

b)

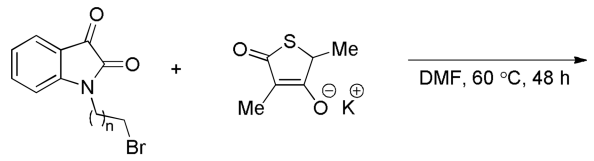
b)



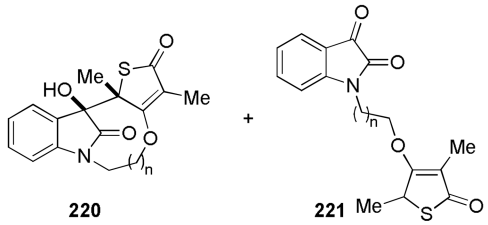
[a] TMSOTf.

Table 6

Synthesis of Tetracyclic Bridged Lactams from Thiolactone-Isatin Hybrids by Chibale



218 **219**

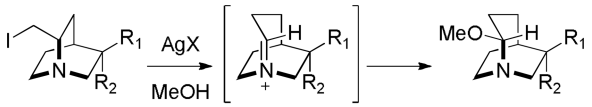


220 **221**

entry	n	218	ratio of 220 221	combined yield (%)	ring system of 220
1	1	**218a**	0:100	36	[5.2.1]
2	2	**218b**	0:100	18	[6.2.1]
3	3	**218c**	78:22	45	[7.2.1]
4	4	**218d**	16:84	31	[8.2.1]
5	5	**218e**	29:71	21	[9.2.1]

Table 7

Rearrangement of Quincorine-Derived 2-Iodomethyl-2-Azabicyclo[2.2.2]octanes via Bridged Iminium Ions by Hoffmann

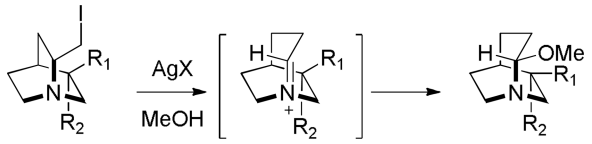


366 **367** **368**

entry	366	R_1	R_2	AgX	yield of 368 (%)
1	**366a**	$CH=CH_2$	H	AgOAc	10
2	**366a**	$CH=CH_2$	H	AgOTf	30
3	**366a**	$CH=CH_2$	H	AgOBz	86
4	**366b**	Et	H	AgOBz	66
5	**366c**	CO_2Me	H	AgOBz	75
6	**366d**	O=		AgOBz	76
7	**366e**	C≡C-Ph	H	AgOBz	82
8	**366f**	C≡CH	H	$AgNO_3$	61

Table 8

Rearrangement of Quincoridine-Derived 2-Iodomethyl-2-Azabicyclo[2.2.2]octanes via Bridged Iminium by Hoffmann

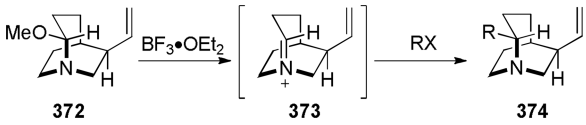


369 **370** **371**

entry	369	R_1	R_2	AgX	yield of 371 (%)
1	**369a**	$CH=CH_2$	H	AgOBz	74
2	**369b**	Et	H	AgOBz	62
3	**369c**	O=		AgOBz	72
4	**369e**	C≡C-Ph	H	AgOBz	70

Table 9

Reactions of Quincorine-Derived Bridged α-Amino Ether **372** with Nucleophiles via Bridged Iminium Ion **373** by Hoffmann

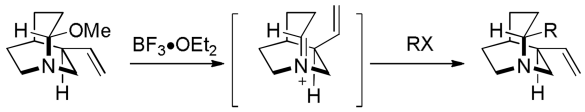


372 **373** **374**

entry	RX	R	yield of 374 (%)
1	Me_3SiCN	-CN	83
2	Me_3SiN_3	$-N_3$	81
3	$Bu_3SnC{\equiv}CH$	$-C{\equiv}CH$	39
4	$Me_2C{=}C(OMe)OSiMe_3$	$-C(CO_2Me)Me_2$	66

Table 10

Reactions of Quincoridine-Derived Bridged α-Amino Ether **375** with Nucleophiles via Bridged Iminium Ion **376** by Hoffmann



375 **376** **377**

entry	RX	R	yield of 377 (%)
1	Me_3SiCN	-CN	68
2	Me_3SiN_3	$-N_3$	75
3	$Bu_3SnC{\equiv}CH$	$-C{\equiv}CH$	70
4	allylMgBr	$-CH_2CH{=}CH_2$	48
5	$Me_3SiCH_2C{\equiv}CH$	$-CH{=}C{=}CH_2$	24
6	$Me_2C{=}C(OMe)OSiMe_3$	$-C(CO_2Me)Me_2$	70
7	$Me_3SiSC_6H_5$	$-SC_6H_5$	59

Table 11

Winkler-Dunitz Distortion Parameters and Hydrolysis Rate Constants of Benzo-2-quinuclidones by Brown

entry	ring system	τ^a [deg]	$\chi_N{}^a$ [deg]	$\chi_C{}^a$ [deg]	$k_3{}^b$ [$M^{-1}s^{-1}$]	$k_3/K_3{}^c$ [$M^{-1}s^{-1}$]
1	[2.2.2]	90.0[d]	63.4[d]	0.0[d]	2.6×10^2	2.3×10^4
2	[3.2.2]	30.7	57.2	9.0	6.0×10^1	5.6×10^1
3	[2.3.2]	33.2	52.8	11.0	1.7×10^1	3.0×10^1
4	[3.3.2]	15.3	38.6	6.7	5.1×10^{-4}	1.2×10^{-4}
5	planar acetanilide[e]	1.5	3.7	−1.5	2.2×10^{-5}	2.2×10^{-7}

[a] Determined by X-ray crystallography.

[b] Rate constant for base hydrolysis.

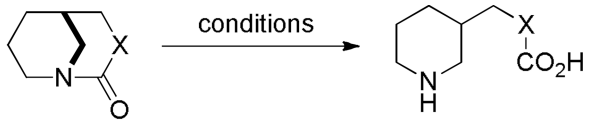
[c] Rate constant for acid hydrolysis.

[d] Calculated values.

[e] *N*-(4-bromo-2-methylphenyl)-*N*-methylacetamide.

Table 12

Hydrolysis of Bridged Lactams and Ureas by Hall



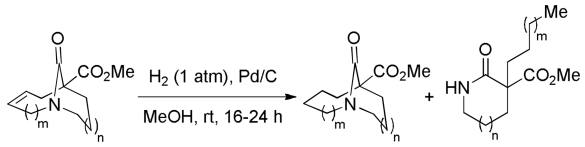
96 (X = CH_2)
278 (X = NH)
275 (X = N-*i*Pr)

95 (X = CH_2)
420 (X = NH)
421 (X = N-*i*Pr)

entry	X	lactam	conditions	result
1	CH_2	**96**	D_2O, 28 °C, 7 d	**96**
2	CH_2	**96**	D_2O, 100 °C, 6 h	**96**
3	CH_2	**96**	D_2O, HCl (g), 28 °C	**95** HCl (quant)
4	*N*-H	**278**	D_2O, 70 °C, 2 h	**278**
5	*N*-H	**278**	D_2O, HCl (g), 28 °C	**420** HCl (quant)
6	*N*-H	**278**	D_2O, KOH, 70 °C, 2 h	**278**
7	*N*-*i*Pr	**275**	D_2O, 100 °C, 20 h	**275**
8	*N*-*i*Pr	**275**	3 M NaOH, 100 °C, 6 h	**420** (quant)

Table 13

Hydrogenolysis of C–NC(O) Bond in Medium-Bridged Twisted Lactams by Aubé

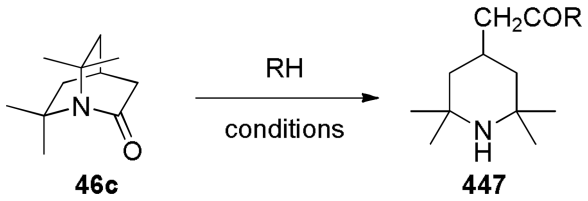


208 **443** **444**

entry	208	m	n	ring system	ratio of 443:444	combined yield (%)
1	**208b**	1	0	[4.2.1]	100:0	74
2	**208a**	1	1	[4.3.1]	25:75	95
3	**208f**	1	2	[4.4.1]	50:50	54
4	**208c**	2	0	[5.2.1]	100:0	72
5	**208d**	2	1	[5.3.1]	100:0	79
6	**208e**	3	0	[6.2.1]	100:0	89

Table 14

Reactions of 6,6,7,7-Tetramethylquinuclidin-2-one with Cleavage of Amide Bond by Yakhontov



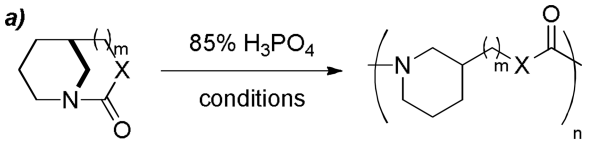
46c **447**

entry	RH	conditions	447	yield (%)
1	H_2O	100 °C, 0.5 h	**447a**	94
2	MeOH	65°C, 5 h	**447b**	76
3	morpholine	Δ, 12 h	**447c**	97
4	NH_2OH	EtOH, 78 °C, 2 h	**447d**	62
5	NH_2NH_2	xylenes, Δ Dean-Stark, 5 h	**447e**	63
6	NH_2NHPh	xylenes, Δ Dean-Stark, 12 h	**447f**	64

Table 15

a) Polymerization of 1-Azabicyclo[3.3.1]nonan-2-one and Related Compounds by Hall; b) Planar Derivatives Inert to Polymerization

a)

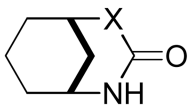


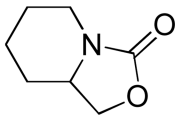
453

entry	X	m	lactam	T [°C]	t (h)	polymerization
1	CH_2	1	**96**	100	0.3	+
2	O	0	**281**	105	20	+
3	O	1	**284**	105	27	+
4	*N*-H	1	**278**	98	2	+
5	*N*-*i*Pr	1	**275**	200	17	–

b)

b)



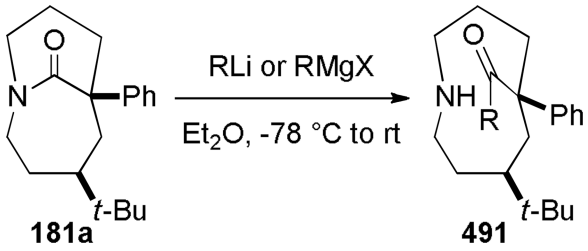


454, X = CH_2, NH, O

455

Table 16

Addition of Organometallic Reagents to Medium-Bridged Bicyclic Lactams by Aubé

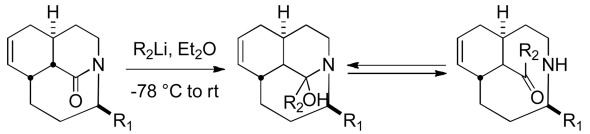


181a **491**

entry	RLi/RMgX	R	491	yield (%)
1	MeLi	Me	**491a**	89
2	MeMgI	Me	**491a**	73
3	*n*-BuLi	*n*-Bu	**491b**	83
4	*sec*-BuLi	*sec*-Bu	**491c**	93
5	*tert*-BuLi	*tert*-Bu	**491d**	80

Table 17

Addition of Organometallic Reagent to Medium-Bridged Tricyclic Lactams by Aubé



175d, R_1 = H
175e, R_1 = *i*-Pr

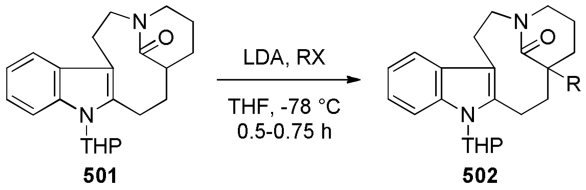
492
favored when
R_2 = *Me, sec-Bu*

493
favored when
R_2 = *t-Bu*

entry	177	RLi	R	487/488	yield (%)
1	**177d**	MeLi	Me	**487a**	95
2	**177d**	*sec*-BuLi	*sec*-Bu	**487b**	80
3	**177d**	*tert*-BuLi	*tert*-Bu	**488a**	90
4	**177e**	MeLi	Me	**487c**	92
5	**177e**	*sec*-BuLi	*sec*-Bu	**487d**	88
6	**177e**	*tert*-BuLi	*tert*-Bu	**488b**	90

Table 18

Alkylation of Indole-1-azabicyclo[6.3.1]dodecan-12-one at Bridgehead Position by Ban

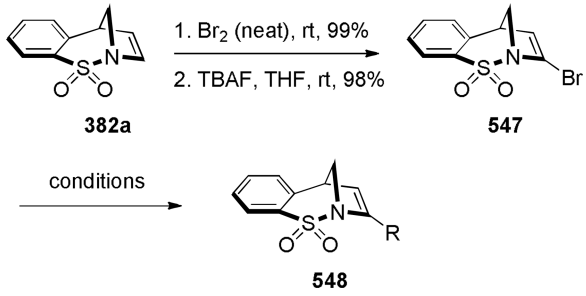


501 **502**

entry	RX	R	502	yield (%)
1	EtI	Et	**502a**	84
2	allylBr	allyl	**502b**	71
3	ICH_2CO_2Me	I	**502c**	42
4	$BrCH_2CO_2Me$	Br	**502d**	34
5	$ClCH_2CO_2Me$	$COCH_2Cl$	**502e**	66
6	$(CO_2Me)_2$	$COCO_2Me$	**502f**	90

Table 19

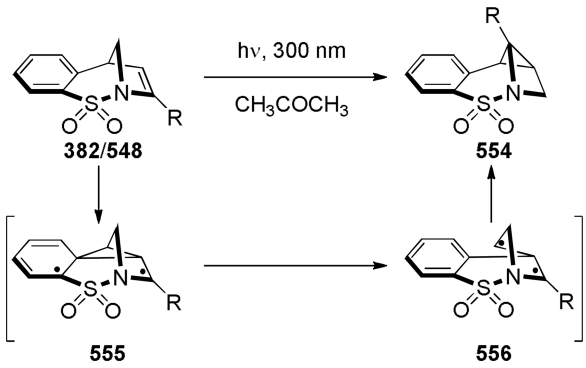
Cross-coupling Reactions of Bridged Sultams by Paquette and Evans



entry	conditions	R	548	yield (%)
1	MeLi/Me_2SO_4	-CH_3	**548a**	70
2	MeLi/$BrCH_2Ph$	-CH_2Ph	**548b**	58
3	*t*BuLi/ClCO*t*Bu	-C(O)*t*Bu	**548c**	44
4	*t*BuLi/ClCOOBn	-C(O)OBn	**548d**	33
5	MeLi/TMSCl	-$SiMe_3$	**548e**	40
6	*t*BuLi/Bu_3SnCl	-$SnBu_3$	**548f**	57
7	*t*BuLi/PhSeCl	-SePh	**548g**	55
8	$Pd(PPh_3)_4$, CuI, $HC{\equiv}CC_4H_9$	-$C{\equiv}CC_4H_9$	**548h**	10
9	PPh_3, $Pd(OAc)_2$ Cs_2CO_3, $ArB(OH)_2$	C_6H_5	**548i**	63
10	as above	2-MeO-C_6H_4	**548j**	76
11	as above	4-MeO-C_6H_4	**548k**	84
12	as above	2-Naphthyl	**548l**	84

Table 20

Di-π-methane Rearrangement of Bridged Sultams by Paquette



entry	382/548	R	554	yield (%)
1	**382a**	H	**554a**	48
2	**548a**	CH_3	**554b**	40
3	**548b**	CH_2Ph	**554c**	50
4	**548c**	C(O)*t*Bu	**554d**	40
5	**548d**	C(O)OBn	**554e**	55
6	**548e**	$SiMe_3$	**554f**	64
7	**548f**	$SnBu_3$	**554g**	49
8	**548g**	SePh	**554h**	23
9	**548h**	$C{\equiv}CC_4H_9$	**554i**	50