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SYNTHESIS AND PHARMACOLOGY OF KAZCAINE AND OTHER 4-ETHYNYL PIPERIDINE DERIVATIVES: A REVIEW

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Abstract. Piperidine derivatives represent a structurally diverse and pharmacologically significant class of nitrogen-containing heterocycles with broad application in medicinal chemistry. This review provides an analysis of recent advances in the synthesis of piperidine-based compounds, with a particular focus on two major approaches: hydrogenation of heterocyclic precursors and intramolecular cyclization strategies. The hydrogenation pathway includes catalytic methods utilizing metal complexes such as Rh, Pd, and Ru, as well as organocatalytic approaches, enabling high stereoselectivity and enantiomeric purity. Intramolecular cyclization is explored across multiple substrate classes, including alkenes, alkynes, and dienes, under the influence of (Pd), gold (Au), iron (Fe), nickel (Ni), and samarium (Sm) catalysts. Notable reactions such as oxidative amination, hydroalkenylation, and cycloisomerization demonstrate the versatility of modern cyclization techniques in building complex piperidine frameworks. Additionally, case studies on novel compounds such as Kazcaine (1-(2-ethoxyethyl)-4-ethynyl-4-benzoyloxypiperidine hydrochloride) emphasize the therapeutic potential and synthetic accessibility of functionally rich piperidine analogues. Due to its defined pharmacophore and ease of functionalization, Kazcaine serves as a valuable template for designing analogues with improved pharmacokinetic or pharmacodynamic profiles. It also provides a platform for testing synthetic methods, such as selective alkylation and acylation. This review highlights the latest key achievements and methodological innovations that facilitate the efficient synthesis of nitrogen-containing heterocyclic

molecules with potential biological activity and emphasizes the importance of implementing modern synthetic approaches grounded in the principles of green chemistry.

Keywords: kazcaine, piperidines, piperidinones, biological activity, pharmacological activity

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ҚАЗКАИН ЖӘНЕ БАСҚА ДА 4-ЭТИНИЛПИПЕРИДИН ТУЫНДЫЛАРЫНЫҢ СИНТЕЗІ МЕН ФАРМАКОЛОГИЯСЫ: ШОЛУ МАҚАЛАСЫ

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Аннотация. Пиперидин туындылары құрылымы әртүрлі және фармакологиялық тұрғыдан маңызды азотты гетероциклдер класына жатады және медициналық химияда кеңінен қолданылады. Бұл шолуда пиперидин негізіндегі қосылыстарды синтездеу саласындағы соңғы жетістіктерге талдау жасалып, екі негізгі бағытқа – гетероциклді прекурсорларды гидрлеу және молекулаішілік циклдену стратегияларына – ерекше назар аударылады. Гидрлеу бағытына родий (Rh), палладий (Pd) және рутений (Ru) секілді металл кешендерін қолданатын каталитикалық әдістер, сондай-ақ жоғары стереоселективтілік пен энантиомерлік тазалықты қамтамасыз ететін органокаталитикалық тәсілдер жатады. Молекулаішілік циклдену алкендер, алкиндер және диендер сияқты әртүрлі субстраттар үшін палладий (Pd), алтын (Au), темір (Fe), никель (Ni) және самарий (Sm) катализаторларының қатысуымен зерттеледі. Тотығу арқылы аминирлеу, гидроалкенилация және циклоизомеризация сияқты реакциялар күрделі пиперидин құрылымдарын құруда қазіргі заманғы циклдену әдістерінің әмбебаптығын көрсетеді. Сонымен қатар, жаңа қосылыстардың, соның ішінде айқын анестезиялық және кардиопротекторлық белсенділікке ие Казкаиннің (1-(2-Этоксиэтил)-4-этинил-4-бензоилоксипиперидин гидрохлориді) синтезі мысал ретінде келтіріліп, функционалдық топтарға бай пиперидин аналогтарының терапевтік әлеуеті мен синтетикалық қолжетімділігін айқындайды. Фармакофорлық құрылымының

айқындығы мен функционализацияға бейімділігінің арқасында Казкаин фармакокинетикалық және фармакодинамикалық қасиеттері жақсартылған аналогтарды әзірлеуге арналған құнды модель болып табылады. Сондай-ақ ол селективті алкилирлеу мен ацилирлеу сияқты синтетикалық әдістерді сынауға арналған платформа ретінде қызмет етеді. Асимметриялық катализді, лигандтық басқаруды, радикалды немесе фотохимиялық активацияны біріктіру синтетикалық әдістер арсеналын кеңейтіп, пиперидин туындыларын фармацевтикалық әзірлеуге қолжетімдірек етеді. Бұл шолу биологиялық белсенділігі бар азотты гетероциклді молекулаларды тиімді синтездеуді қамтамасыз ететін соңғы негізгі жетістіктер мен әдістемелік инновацияларды көрсетіп, жасыл химия қағидаттарына негізделген заманауи синтетикалық тәсілдерді енгізудің маңыздылығын атап көрсетеді.

Түйін сөздер: казкаин, пиперидиндер, пиперидинондар, биологиялық белсенділік, фармакологиялық әсер

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СИНТЕЗ И ФАРМАКОЛОГИЯ КАЗКАИНА И ДРУГИХ ПРОИЗВОДНЫХ 4-ЭТИНИЛПИПЕРИДИНА: ОБЗОРНАЯ СТАТЬЯ

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Аннотация. Производные пиперидина представляют собой структурно разнообразный и фармакологически значимый класс азотсодержащих гетероциклов, находящих широкое применение в медицинской химии. Настоящий обзор предоставляет анализ последних достижений в области синтеза соединений на основе пиперидина с особым акцентом на два основных подхода: гидрирование гетероциклических предшественников и стратегии внутримолекулярной циклизации. Путь гидрирования включает каталитические методы с использованием комплексов металлов, таких как родий (Rh), палладий (Pd) и рутений (Ru), а также органокаталитические подходы, обеспечивающие высокую стереоселективность и энантиомерную чистоту. Внутримолекулярная циклизация рассмотрена для различных классов субстратов — алкенов, алкинов и диенов

— с участием катализаторов на основе палладия (Pd), золота (Au), железа (Fe), никеля (Ni) и самария (Sm). Такие реакции, как окислительное аминирование, гидроалкенилирование и циклоизомеризация, демонстрируют универсальность современных методов циклизации в построении сложных пиперидиновых структур. Кроме того, приведены примеры синтеза новых соединений, таких как Казкаин (1-(2-Этоксиэтил)-4-этинил-4-бензоилоксипиперидин гидрохлорид) с выраженной анестезирующей и кардиопротективной активностью, подчеркивающие терапевтический потенциал и синтетическую доступность функционально насыщенных аналогов пиперидина. Благодаря своей четко выраженной фармакофорной структуре и легкости функционализации, казкаин представляет собой ценную модель для разработки аналогов с улучшенными фармакокинетическими и фармакодинамическими свойствами. Он также служит платформой для отработки синтетических методов, таких как селективное алкилирование и ацилирование. Интеграция асимметричного катализа, лигандного управления и радикальной или фотохимической активации расширяет арсенал синтетических методов, делая производные пиперидина более доступными для фармацевтической разработки. Обзор освещает новейшие ключевые достижения и методологические инновации, способствующие эффективному получению азотсодержащих гетероциклических молекул с потенциальной биологической активностью, и подчеркивает важность внедрения современных синтетических подходов, основанных на принципах зелёной химии.

Ключевые слова: казкаин, пиперидины, пиперидиноны, биологическая активность, фармакологическая активность

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Introduction. Piperidine and its analogues form a family of nitrogen-containing heterocycles with impact in synthetic and pharmaceutical chemistry. Piperidines exhibit widespread utility in pharmacy, representing the molecular backbone of numerous bioactive natural products and drugs. With development in synthetic protocols, including transition-metal-catalyzed cyclization, multi-component cascade processes, and enantioselective hydrogenation. Potent 4-ethynyl piperidine derivatives have become accessible for assembly through efficient protocols. Not only 4-ethynyl piperidine derivatives have such breakthroughs as increased piperidine frameworks' chemical diversity but have enriched them with character relevant to drugs through stereochemical fidelity and functional group diversity. In this review, current research in piperidine derivatives synthesis with an emphasis on its 4-ethynyl containing piperidines has been compiled, including state-of-the-art methodologies, mechanisms, and implications in pharmacy.

In the last several years, many reviews and research articles about specific methodologies for the preparation of piperidine, its functionalization and its use

in pharmacy have been published. Herein, we focus on the synthesis of piperidine derivatives shown in Figure 1.

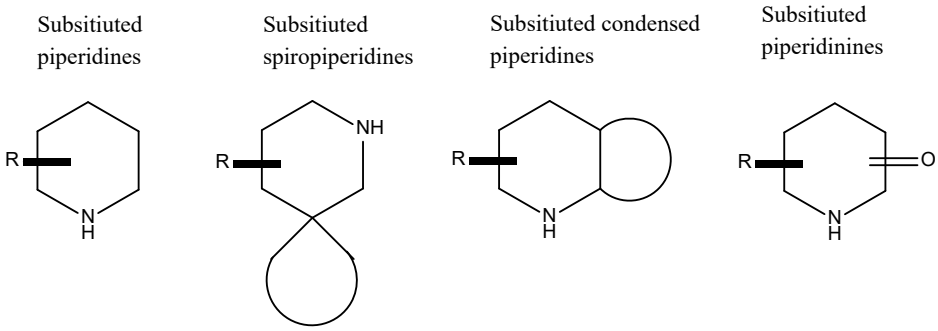


Figure 1. Piperidine derivatives discussed in this review.

Object of the study. The primary objective of this review is to examine and classify modern synthetic approaches for the preparation of piperidine derivatives, with a special focus on 4-ethynyl-substituted analogues due to their pharmacological relevance. The review seeks to identify novel catalytic systems and methodologies employed in the formation of the piperidine core, to analyze stereoselective and enantioselective strategies in the synthesis of bioactive piperidines; to highlight the utility of intramolecular cyclization and hydrogenation as principal routes to structural diversity and illustrate the synthetic accessibility and biological potential of specific compounds, including Kazcaine.

Materials and Methods. This review was conducted through a comprehensive literature search and critical analysis of peer-reviewed scientific publications related to the synthesis and pharmacological evaluation of piperidine derivatives, with a focus on 4-ethynyl-substituted analogues such as Kazcaine. The primary sources were obtained from scientific databases, including Scopus, Web of Science, PubMed and Google Scholar. The search was conducted using combinations of the following keywords: piperidine synthesis, 4-ethynyl piperidine, intramolecular cyclization, hydrogenation, kazcaine, asymmetric catalysis, and bioactive heterocycles. The most recent articles published up to 2024 were prioritized to ensure the inclusion of the most recent developments. Earlier foundational works were also cited where necessary for historical context. Each selected publication was examined for synthetic route (e.g., hydrogenation, cyclization), catalytic system and conditions, reaction scope and yields, enantioselectivity or regioselectivity and reported biological activity (where it was applicable). Comparative tables and mechanistic schemes were constructed based on this data. Notable methodologies were categorized by reaction type and catalyst class. A case study of Kazcaine was highlighted to exemplify the integration of synthesis and pharmacological application.

Results and Discussion. Hydrogenation

Two routes for piperidine preparation have been identified and discussed: hydrogenation of heterocyclic compounds and intramolecular cyclization (Figure 2).

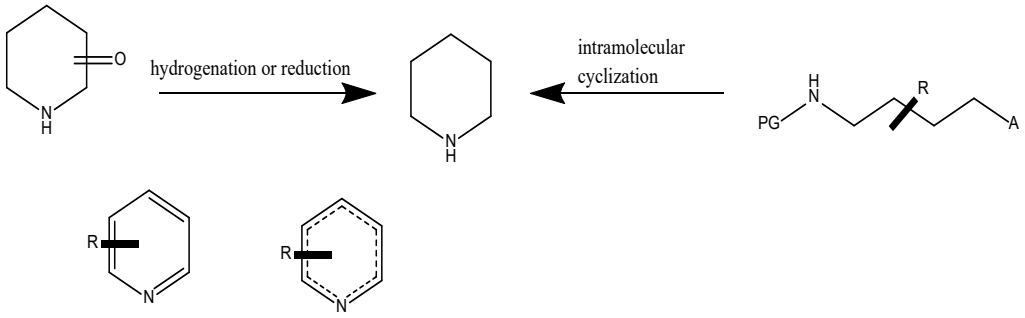


Figure 2. Main routes to the piperidine cycle synthesis.

A substitued pyridine, with an unprotected or a protected nitrogen atom, is a general starting compound. Often, a substrate in most cases already bears all substituents for a target compound in its initial form in advance. In such a case the synthesis has become shorter and less expensive under one of the newest protocols in contrast to the cases when both hydrogenation and functionalization have been incorporated in one reaction in one pot.

It is appreciative to mention the work of (Sandmeier, et.al.,2020) for careful reporting of catalysts used in piperidine synthesis. The chapter by (Sandmeier, et.al.,2020) presents new catalytic methodologies towards piperidine construction with high enantioselectivity, an important reaction in pharmaceutical development. Features include chiral hydrogenation with chiral catalysts such as $[Rh(NBD)_2]BF_4$ (Bis(norbornadiene) rhodium(I) tetrafluoroborate) and BINAP (2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl), generating high-enantiomeric excesses, and organocatalysis, in terms of Mannich and Michael reaction processes with catalysts such as derivatives of proline. Additionally, metal-catalysis cyclization with gold(I) and palladium(II) catalysts in combination with chiral phosphoramidite ligands plays a key role. Examples include constructions of complex structures such as (-)-sedamine, presenting useful methodologies for accessing chiral piperidines effectively in drug development.

(Yu, et.al., 2015) presents a straightforward one-pot method for synthesizing N-substituted 4-methyl-1-oxa-8-azaspiro [4,5] deca-3-en-3-carboxylic acids. This synthesis involves reacting 1-(2-ethoxyethyl)-4-acetyl-4-hydroxypiperidine or 1-(2-phenylethyl)-4-acetyl-4-hydroxypiperidine with acrylonitrile at room temperature using an alkaline catalyst, leading to the formation of spirocyclic compounds. Subsequent hydrolysis yields the desired carboxylic acids. The proposed mechanism suggests that an initial cyanoethylation is followed by aldol condensation to form the spirocyclic structure.

(Pitna, et al.,2021) developed a one-pot reaction with a Pd/C catalyst combining hydrogenation with Suzuki-Miyaura cross-coupling in the modification of derivatives of pyridine and thus presented an efficient and convenient path for complex heterocycle preparation (Figure 4).

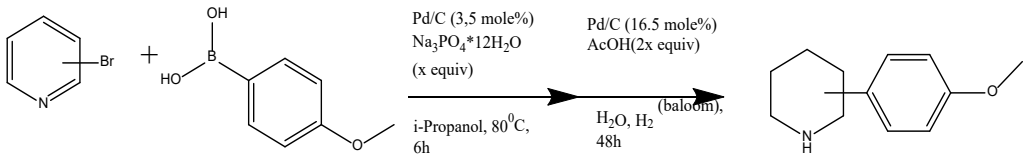


Figure 4. Suzuki-Miyaura cross-coupling with a Pd/C catalyst.

(Tanaka, et.al., 2020) have documented hydrogenation of heteroarenes and arenes with Pd/C under atmospheric pressure and have discovered a remarkably mild and efficient catalytic reaction (Figure 5). The reaction is incredibly useful in terms of ease of operation and application in bulk chemical processes. The authors pointed out the utmost importance of maintaining the optimal starting material concentration for the successful hydrogenation process. The mild hydrogenation method was studied in detail on a broad spectrum of substrates. The authors concluded that the HOMO/LUMO states and the bulkiness of the substituents majorly influenced the reaction rate.

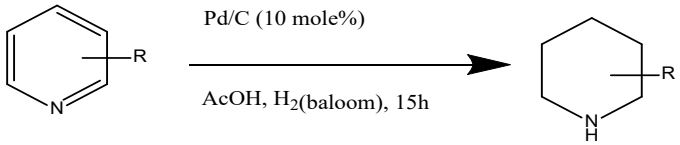


Figure 5. hydrogenation of heteroarenes and arenes with Pd/C.

Further developments in pyridine reduction proceeded with (Clarke, et.al., 2021). The authors reported a borenium-catalyzed hydrogenation and hydrogen or hydrosilane mixed reductants protocol (Figure 6). The newness in the mechanism in the strategy presented an effective route from the documented protocols for the hydrogenation of pyridines to derivatives. In a documented article, (Yang et.al.,2021) developed a borane-catalyzed cascade of hydrogenation and hydroboration. It presented an effective mechanism for transforming pyridines to more saturated derivatives, opening more avenues for functionalization of pyridines.

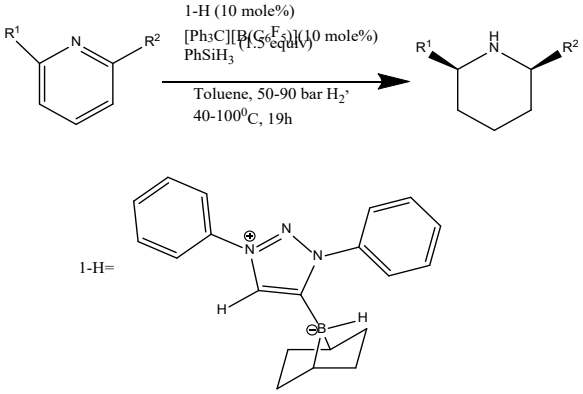


Figure 6. Borenium-catalyzed hydrogenation of 2,5-pyridine.

Intramolecular Cyclization. In intramolecular cyclization the initiation of cyclization originates from the starting reactant in its full form. A variety of functional groups and bond activation processes contribute to the reaction, with cyclization exhibiting an intramolecular nature in its direction. The primary pathway of intramolecular cyclization is presented in Figure 7.

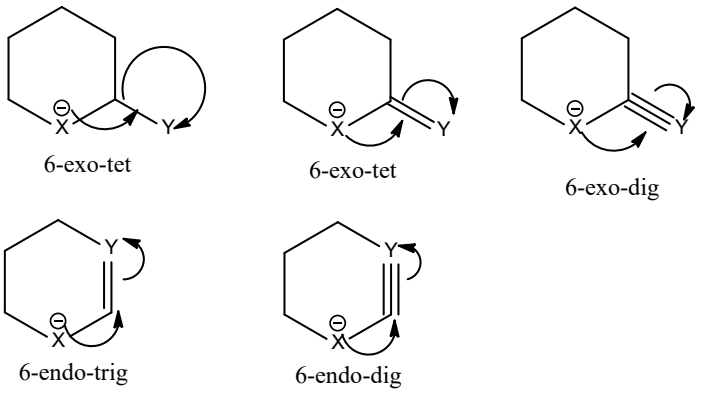


Figure 7. Main route of intramolecular cyclization.

For easier understanding, the chapter was divided by substrate classes.

Alkene cyclization. (Nevado et.al., 2009) have developed a synthetic route for oxidative amination of unactivated alkenes for the preparation of piperidinyl-substituted compounds (Figure 8). This reaction is facilitated through a gold(I) catalyst and involves an iodine(III) oxidant in a one-step incorporation of an N-heterocycle and an O-substituted group onto a double bond.

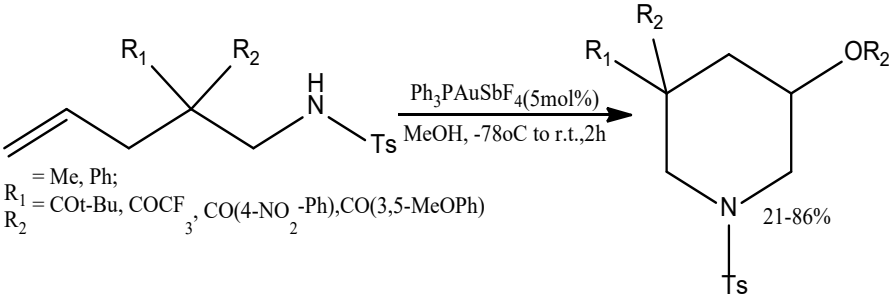


Figure 8. Intramolecular aminations of N-tethered alkenes: gold(I)-catalyzed oxidative amines-terification.

Their studies (Nevado, et.al., 2009)) revealed that substituted in C6 position with a bulk group pyridine-oxazoline ligand modulates the contact between pyridine-nitrogen donor site and Pd(II), and its increased electrophilicity promotes olefin activation. Ligand engineering in azidation reaction was also effective (Figure 9).

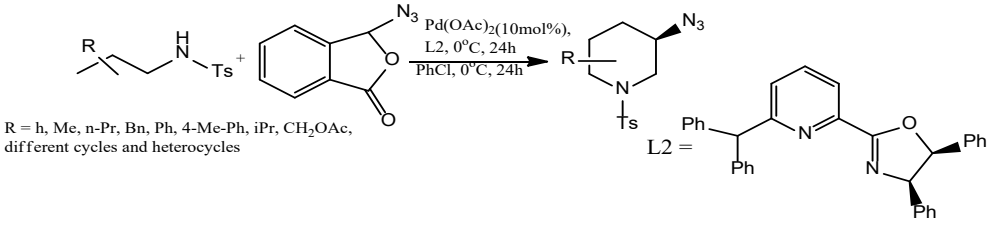


Figure 9. Intramolecular aminations of N-tethered alkenes: palladium(II) catalyzed azidation.

Expanding on ligand-controllable regioselectivity, regioselective diamination of alkenes (Figure 10) was studied by (Li, et.al., 2013). Their work confirmed reaction pathways to be determined via steric hinderance with a bulk ligand, controlling for pyrrolidone formation. Regioselectivity was observed to occur via the steric influence of the nucleophilic reagent, N-Fluorobenzenesulfonimide (NFSI), and its role in controlling direction in transformation.

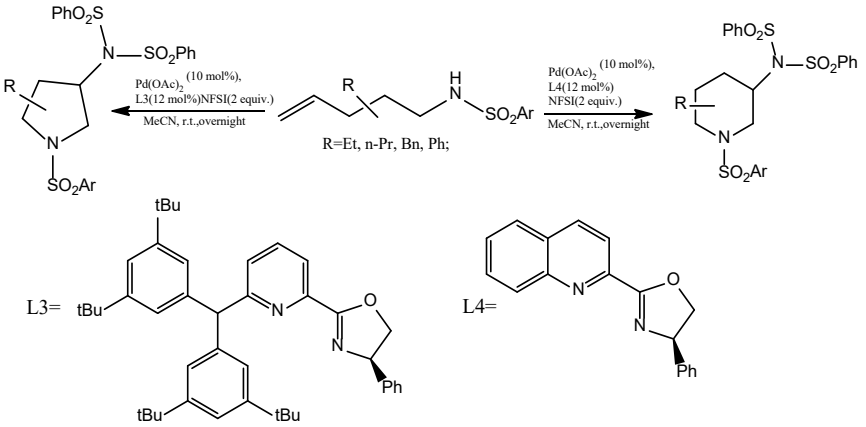


Figure 10. Intramolecular aminations of N-tethered alkenes: palladium(II)catalyzed 6-endo diamination

(Shibata,et.al.,2019)exploredintramolecularaminotrifluoromethanesulfinyloxylation (an amine group and a trifluoromethanesulfinyl (–$SOCHF_3$) of alkenes using palladium catalysis (Figure 11). Their work generated 6-endocyclized piperidines with satisfactory diastereoselectivity and efficiency and underscores the utility of complexed Pd catalysts in cyclization processes for heterocycle construction.

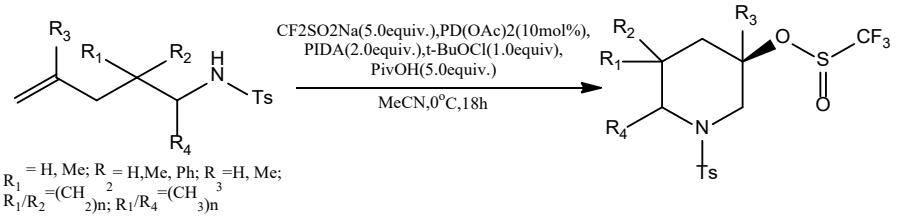


Figure 11. Intramolecular aminations of N-tethered alkenes: palladium (II)-catalyzed aminotrifluoromethanesulfinyloxylation.

Meanwhile, (Zawisza et.al., 2020) presented a diastereoselective, ligand-free palladium-catalyzed intramolecular allylic amination (Figure 12). A stereochemically defined protecting group participated in controlling product stereochemistry, behaving in a similar manner to a chiral auxiliary in mechanism.

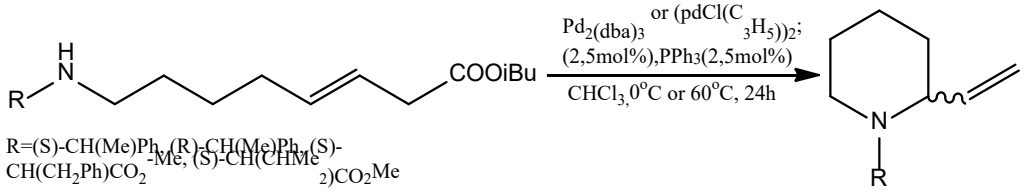


Figure 12. Intramolecular aminations of N-tethered alkenes: palladium(0)-catalyzed allylic amination.

Further expanding the reaction range of palladium-catalysis, (Engle, et.al.,2013) have utilized 8-aminoquinoline as a guiding group for intramolecular alkene hydroamination (Figure 13). This reaction enables five- and six-membered heterocycle preparation through a mechanism of syn-addition and subsequently, proto-depalladation.

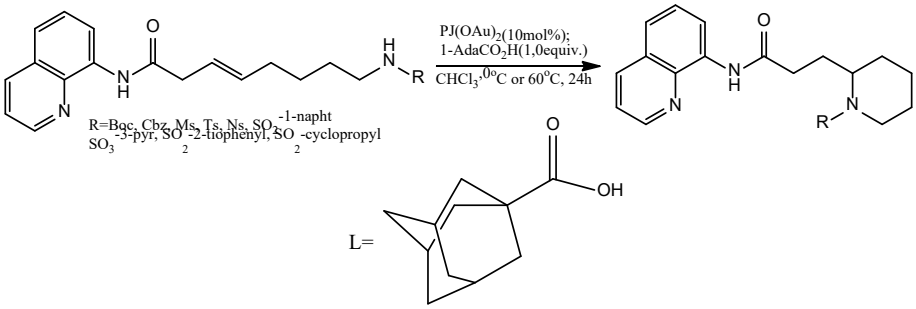
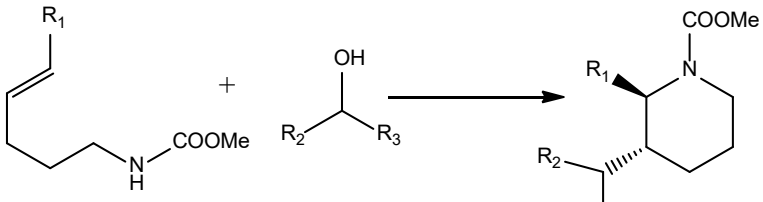


Figure 13. Intramolecular aminations of N-tethered alkenes: palladium(II)-catalyzed hydrofunctionalization.

Lastly, (Cox, et.al., 2022) have revealed a carboamination of alkenes with stereocontrol, in which cyclization is initiated via an in situ-formed carbocation derived from an alcohol precursor (Figure 14).



R1=PMP, CHCHPMP, Ph;
R2= H, Ph, Me, PMP,
R3=H,Ph,Me, PMP, CHCHPMP, CHCHPh, CHCHMe
R2/23=CH2CH, CH2CH(Ph);
HFIP = hexafluoroisopropanol

Figure 14. Intramolecular aminations of N-tethered alkenes:cation-induced alkylation/amination.

This reaction enables both C–N (carboamination) and C–C (alkylation) bond constructions in a single reaction.

Diene cyclization. (Li, et.al., 2018) published a highly enantioselective nickel-catalyzed intramolecular hydroalkenylation reaction of N and O-tethered 1,6-dienes (Figure 15). This enables the construction of six-membered heterocyclic skeletons. According to this routine, chiral piperidines and also tetrahydropyrans were efficiently gained in a fully enantioselective matter. Mechanistically, it involves nucleation of terminal alkyne with nickel(0), thereby resulting in selective intramolecular cyclization. It can be considered further to illustrate strategies developed in reaching nickel catalysis of the title transformation with the emphasis on complexity and enantiomeric purity targets.

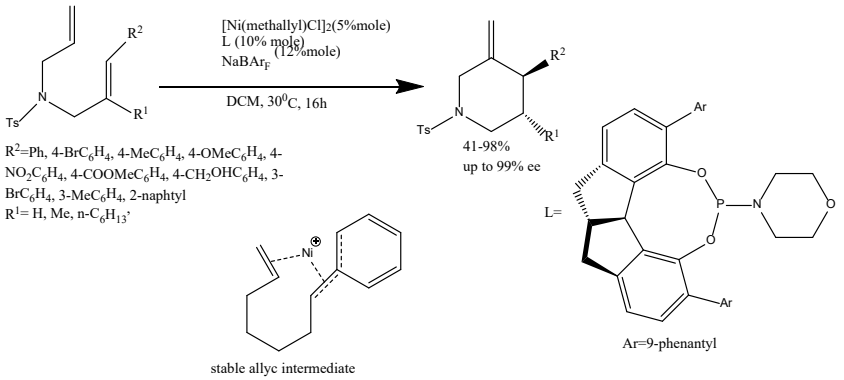


Figure 15. Highly enantioselective nickel-catalyzed intramolecular hydroalkenylation of 1,6-ene-dienes.

(Cui, et.al.,2019) described a rhodium-catalyzed cycloisomerization of 1,7-ene-dienes directed toward the synthesis of trans-divinylpiperidines (Figure 16). The process involves a formal intramolecular addition reaction, wherein an allylic C-H bond adds across a diene system. The process gives rise to the high selectivity toward the formation of trans-divinylpiperidine derivatives and has proved the great capability of rhodium catalysis in controlling regioselectivity and stereochemistry for the construction of complex piperidine structures.

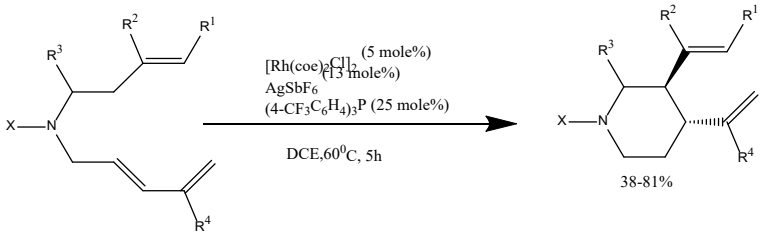
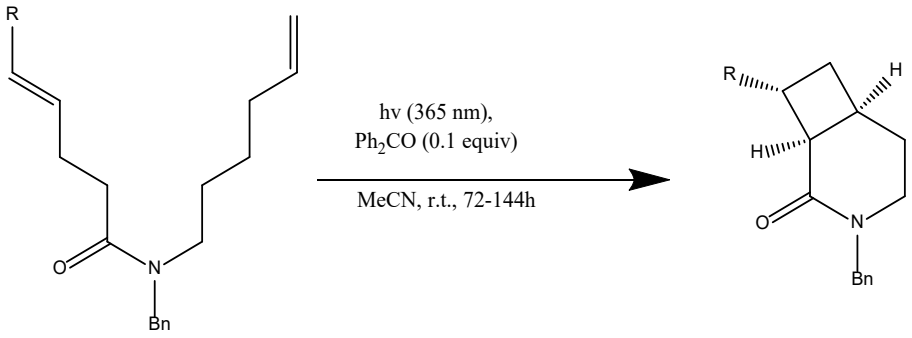


Figure 16. Rhodium(I)-catalyzed cycloisomerization of 1,7-ene-dienes.

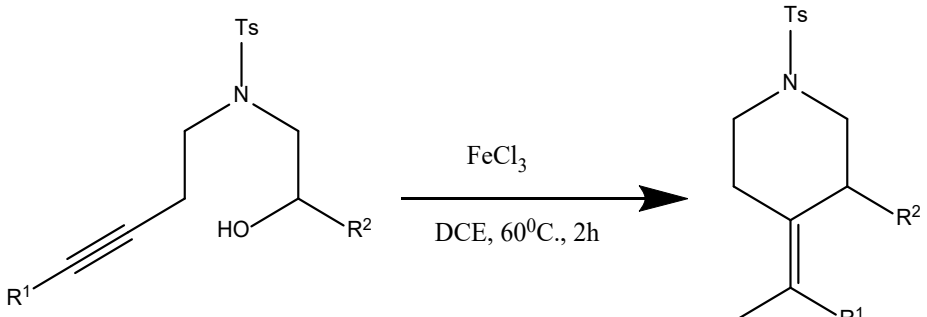
(Shcherbakova, et.al., 2021) have analyzed bicyclic piperidines prepared through a [2+2] photocycloaddition path (Figure 17). In a photochemical reaction of such a kind, piperidine derivatives produce bicyclic structures through a high-strain bicyclic arrangement via a reaction of cycloaddition. What is exciting about such a reaction is that bicyclic frameworks, not accessible with conventional thermal routes, can be prepared through such a reaction. underlines the utility of photochemistry in accessing new and complex molecular architectures.



R= Ph, 4-FC_6H_4, 4-MeC_6H_4, 4-Pyr, 3-Pyr, 2-Pyr, difference heterocycles

Figure 17. Bicyclic piperidines obtained via [2+2] intramolecular cycloaddition.

Alkyne Cyclization. Alkyne cyclization involves the transformation of alkynes into nitrogen-containing heterocycles. An intramolecular cyclization reaction with N-tethered alkyne benzyl alcohols, prompted by $FeCl_3$, has been documented by (Borah, et.al., 2018) (Figure 18). Through a path via early carbenium ion development, it induces its subsequent cyclization towards complex N-heterocycle frameworks. Remarkably, such a tool introduces an alternative for rapid assembling cyclonic rings under mild reaction conditions for use in supporting nitrogen-enriched product fabrication.



R^1=Ph, 4-ClC_6H_4;
R^2=Ph, 4-ClC_6H_4, 4-BrC_6H_4;

Figure 18. Intramolecular cyclization reaction with N-tethered alkyne benzyl alcohols prompted by $FeCl_3$

(Takahashi, et.al., 2018) have discussed Samarium(II) iodide-promoted intramolecular cyclization of haloalkynals to yield five- and six-membered nitrogen-containing heterocycles with an exo-olefin terminus (an alkene functional group positioned outside a ring system) (Figure 19). SmI_2-promoted reaction is particularly useful in assembling heterocycles with high stereocontrol.

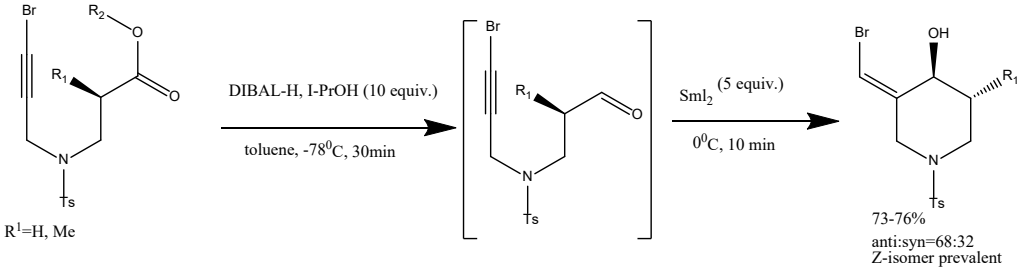


Figure 19. Samarium-catalyzed intramolecular radical cyclization of haloalkynals.

(Ding, et.al.,2020) have accomplished a gold-catalyzed intramolecular dearomatization reaction for spironaphthalenone preparation starting with β-naphthol derivatives (Figure 20). With β-naphthol activation with a gold catalyst, cyclization creates a spirocyclic compound. The reaction is important in terms of incorporation of structural diversity and spirocyclic frameworks preparation, in general, via traditional routes, proving to be challenging in most cases.

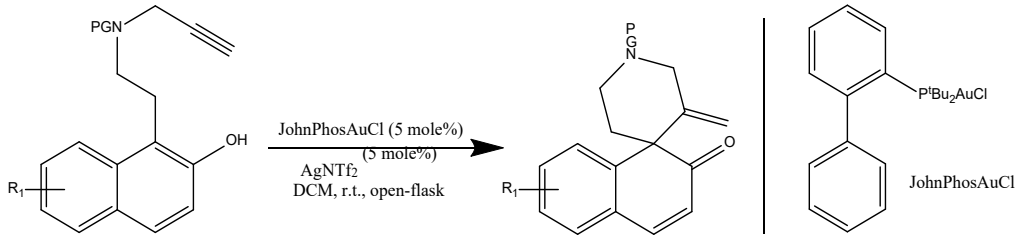


Figure 20**.** General procedure for gold-catalyzed intramolecular dearomatization reaction of β-naphthol derivatives.

(Kamimura, et.al.,2020) disclosed a cumulated radical cascade reaction of aza-1,6-enynes for stereoconvergent preparation of exo-methylene piperidines (Figure 21). It consists of a sequence of radical processes that form piperidine with high stereocontrol. The reaction highlights the efficacy of radical processes in assembling stereostructurally complex N-containing heterocycles.

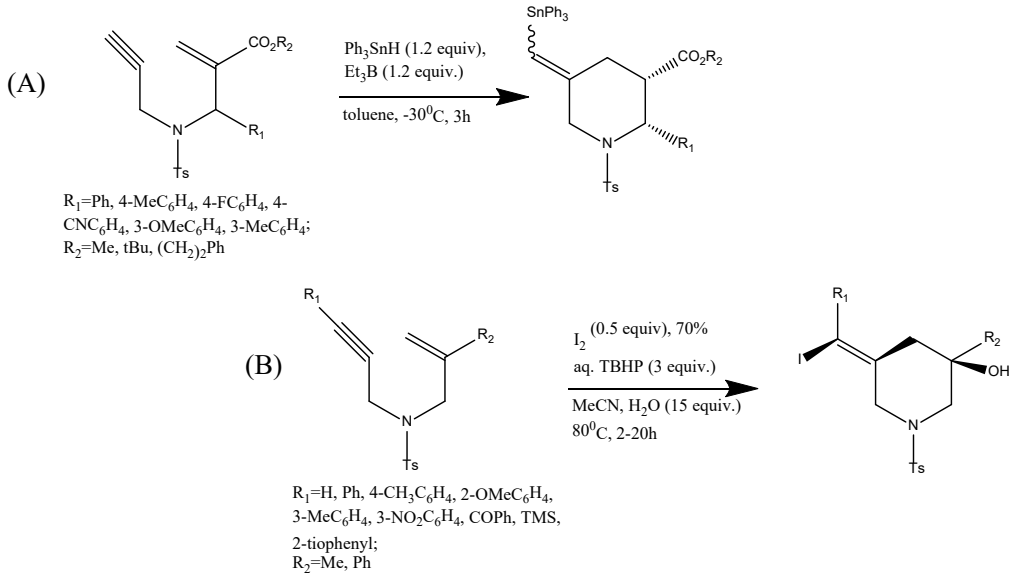


Figure 21. Radical stereoselective cyclization of 1,6-enynes initiated through borane addition.

Other Cyclization. (Anderson, et.al., 2021) have also employed the use of the nitro Mannich reaction in asymmetries in piperidines' synthesis (Figure 22). The most significant reaction processes involve the addition of amines with nitroalkanes and cyclization that forms a piperidine ring.

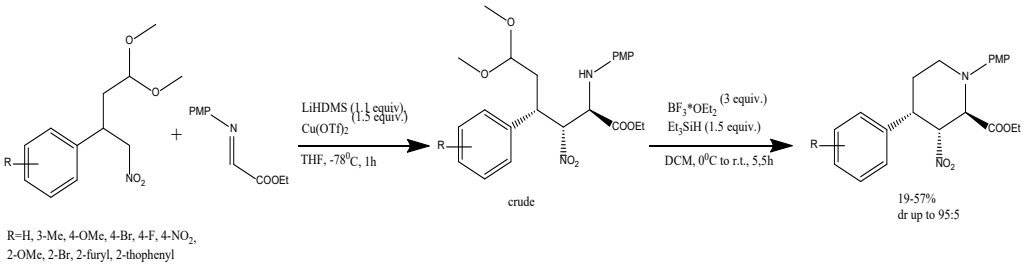


Figure 22. Asymmetric synthesis of piperidines by nitro-Mannich/reduction cyclization.

(Cheng, et.al., 2021) performed a desymmetrization strategy for preparation of piperidinyl acetic acid derivatives (Figure 23). Piperidinyl acetic acid derivatives represent a group of γ-secretase modulators, drugs with therapeutic value for application in Alzheimer's disease therapy. The synthetic sequence features the use of N-tert-butanesulfinyl imine reduction and a diastereoselective lactam formation to set up the chiral centers.

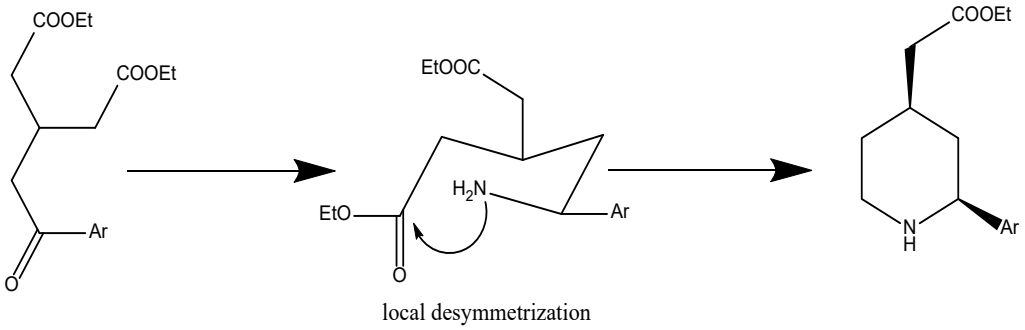


Figure 23. A desymmetrization-based approach for the synthesis of piperidinyl acetic acid γ-secretase modulators.

Kazcaine (Kemelbekov et.al.,2010), chemically 1-(2-ethoxyethyl)-4-ethynyl-4-benzoyloxypiperidine, is a piperidine analogue prepared for its anesthetic and antiarrhythmic activity. It possesses a 4-ethynyl piperidine backbone, whose physicochemical and pharmacologic profiles, such as its lipophilicity, its receptor binding capacity, and its metabolical stability, are specifically determined. Possession of an ethynyl group at position 4 in its piperidine backbone profoundly modulates its electronic character and its target bio-molecular interaction capacity towards sodium and potassium ion channels.

The synthesis is initiated with 1-(2-ethoxyethyl)-4-oxopiperidine and acetylene in liquid ammonia, with potassium hydroxide (KOH) acting as a catalyst for insertion of an ethynyl (-C≡CH) substituent at position 4 of the piperidine ring through regioselective addition, with the intermediate anionic species stabilized in a liquid ammonia environment (Figure 24).

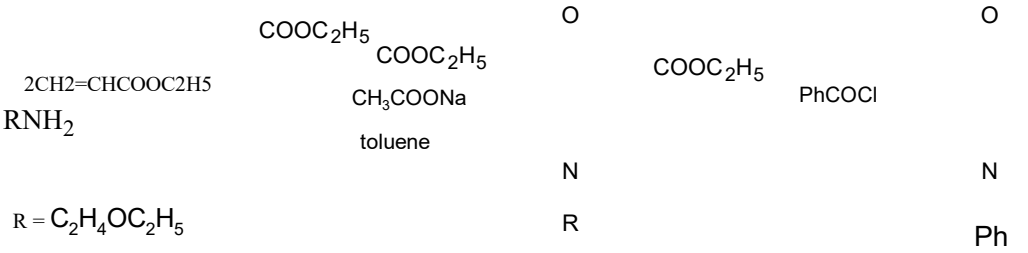


Figure 24. Insertion of an ethynyl (-C≡CH) substituent at position 4 of the piperidine ring.

The intermediate 1-(2-ethoxyethyl)-4-ethynylpiperidine then acylated with benzoyl chloride (C_6H_5COCl) to produce the target compound 1-(2-ethoxyethyl)-4-ethynyl-4-benzoyloxypiperidine hydrochloride (Figure 25).

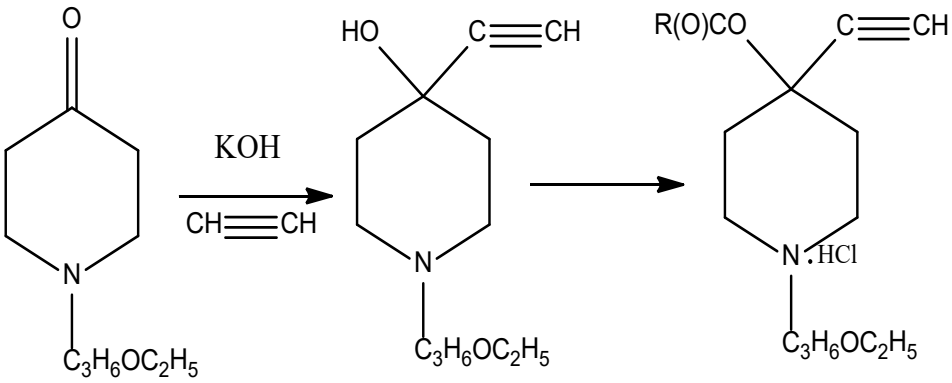


Figure 25. 1-(2-ethoxyethyl)-4-ethynyl-4-benzoyloxypiperidine hydrochloride synthesis.

The addition of a benzoyl ester group strengthens the compound's stability and modulates its lipophilicity. The crude compound is then crystallized with isopropanol (i-PrOH) for purification.

Kazcaine represents a synthetically new piperidine analogue with considerable anesthetic and cardioprotective activity. Its availability through synthetic preparation, together with its novel pharmacologic profiles, warrants further investigation into its therapeutic potential. Innovation in synthetic manipulation, computer simulation, and clinic evaluation will become paramount in shaping its position in present-day pharmaceutical applications.

Conclusion. This review discussed 4-ethynyl piperidine derivatives' preparation, diversity in structure, and pharmaceutical value, with a specific consideration for compound Kazcaine. Transition-metal catalysts, intramolecular cyclization, radical conversions, and hydrogenation routes have amplified piperidine skeletons' availability, and piperidine skeletons can become increasingly functionalized and stereochemically regulated. Kazcaine, as an example, mirrors the value of piperidine-containing compounds in anesthetic and antiarrhythmic activity. Preparation, via efficient condensation and acetylene coupling methodologies, is a model for minimizing synthetic routes towards new bioactivities.

Latest development in the field of synthesis of 4-ethynyl piperidine derivatives were studied and analyzed. Future research will have to focus towards improvement in environmentally friendly and sustainable processes, search for new catalysts, and ongoing studies of new piperidine derivatives' bioapplications. A wider application of computational modelling and high-throughput screening will necessarily boost piperidine drugs' discovery at an even rapid pace, enhancing its role in drug development.

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