C−H FUNCTIONALIZATION OF CYCLIC AMINES MEDIATED BY TEMPO OXOAMMONIUM CATIONS

DOI: http://dx.medra.org/10.17374/targets.2023.26.100

Silvano Cruz-Gregorio, Julio Romero-Ibañez,* Fernando Sartillo-Piscil*

Centro de Investigación de la Facultad de Ciencias Químicas,
Benemérita Universidad Autónoma de Puebla (BUAP), 72570 Puebla, México
(e-mail: julio.romero@alumno.buap.mx; fernando.sartillo@correo.buap.mx)

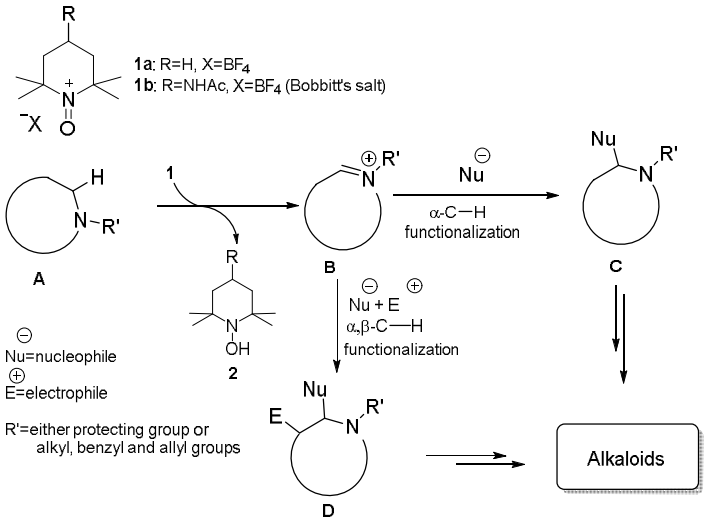
Abstract. *The 2,2,6,6-Tetramethylpiperidine-N-oxoammonium cation, also known as TEMPO oxoammonium cation (TEMPO$^+$), is a stable organic salt which has been widely utilized as a non-metallic reagent for the C−H oxidation of primary and secondary alcohols to their corresponding carbonyl compounds. In contrast, its use for similar C−H functionalization of amines has been modestly explored, particularly for cyclic amines. Moreover, few but remarkable efforts have been conducted, and the straightforward transformation of cyclic amines into advanced alkaloid precursor have been accomplished. In the present book chapter, we reviewed and briefly discussed the use of TEMPO$^+$ and its 4-NHAc analogous (Bobbitt´s salt) for the selective functionalization of the pre-existing N-heterocycle into valuable alkaloid precursors as a convenient synthetic alternative to the cyclization routes.*

Contents

1. Introduction

The direct functionalization of strong and unreactive C−H bonds into weaker C−X bonds (where X≠H), through a transition-metal C−H activation process, is the chemical transformation that is responsible for the accelerated advance of the science of organic synthesis.[1] With this approach, the chemist is able to consider unreactive CH_3, CH_2 or CH groups as potential functional groups, thus expanding the strategic repertory of the retrosynthesis analysis.[2] In this regard, an increasing number, but still insufficient, of environmentally friendly reactions and reagents have been reported.[3] Particularly relevant are those reactions which involves the use of either the 2,2,6,6-tetramethylpiperidine-1-oxoammonium cation (TEMPO$^+$) **1a** or its analogous cation: the 4-acetamido-2,2,6,6-tetramethyl-piperidine-1-oxoammonium tetrafluoroborate (4-AcNH-TEMPO$^+$) **1b**, also known as the Bobbitt's salt.[4] Although these mild and selective oxidizing reagents are widely employed in the C−H oxidation of primary and secondary alcohols into their respective carbonyl compounds,[5] their use in the C−H oxidation of amines, and particularly in cyclic amines, has been practically limited to either benzylic or allylic amines. Accordingly, the C−H functionalization reactions of cyclic amines **A** mediated by either **1a** or **1b** to iminium cation **B** plus TEMP-OH **2**, permits the straightforward conversion of simple *N*-heterocyclic skeleton into advanced alkaloid intermediates **C**, and **D**, in a low economic and ecological cost, which is highly desirable in the chemical industry. Additionally, the dual α,β-C−H functionalization **A**→**B**→**D**, albeit is a much less common process than the α-C−H functionalization

A→B→C it could be more relevant because permits a higher functionalization of the nitrogenated ring which it would be reflected in a more straightforward access to alkaloid precursors (Scheme 1).



Scheme 1. α-C−H And α,β-C−H functionalization of cyclic amines **A** to alkaloid precursors **C** and **D**, respectively, mediated by either $TEMPO^+$ cation **1a** or Bobbitt´s salt **1b**.

Accordingly, in the current book chapter we review the literature which relates the use of both cations (prepared or generated during the chemical or electrochemical process) in the mono, dual and tri-C−H functionalization of *N*-heterocycles with the tentative to provide relevant information which could be used for planning or developing a synthesis route to biologically important cyclic alkaloids.

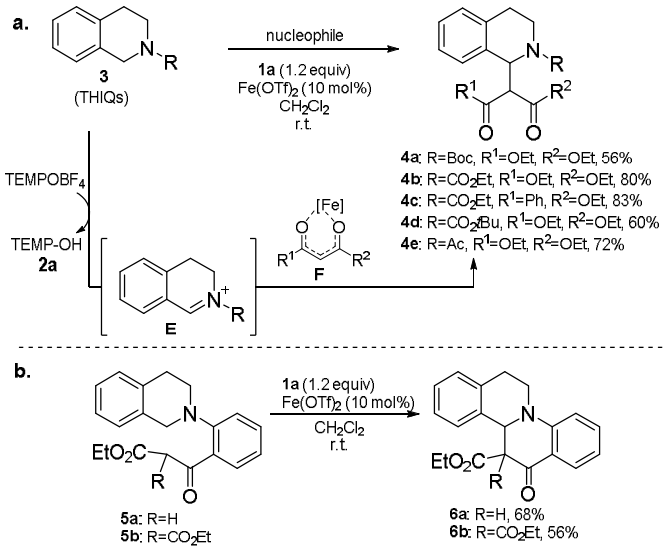
2. α-C−H Functionalizations

2.1. Tetrahydroisoquinolines (THIQs)

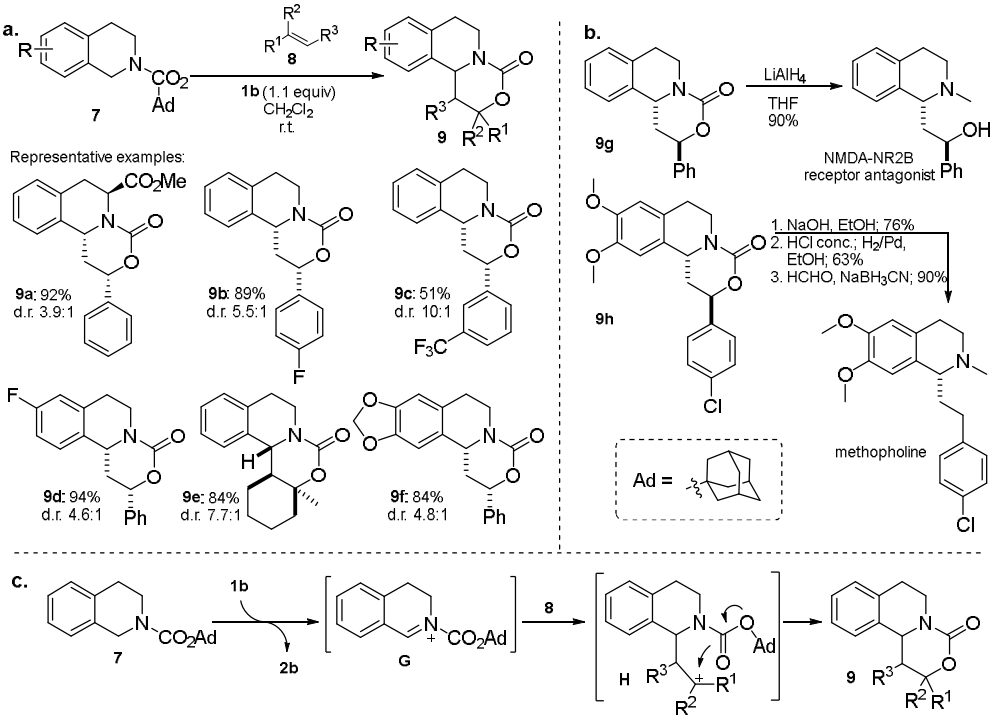
The group of García-Mancheño was one of the first to use oxoammonium cations in the α-C−H functionalization of tetrahydroisoquinolines **3** (THIQs).[6] They reported a dehydrogenative coupling between enolized pronucleophiles and THIQs **3** mediated by **1a** in the presence of $Fe(OTf)_2$ to give α−functionalized THIQs **4** in moderated and good yields (Scheme 2a).[7] The proposed reaction mechanism involves a hydride transfer from THIQ to the oxoammonium cation **1a** generating thus the *N*-acyliminium intermediate **E** plus TEMP-OH **2a**, from which, the former reacts with the iron-activated nucleophile **F** to produces α−functionalized THIQs **4a-e** in moderated to good yields (Scheme 2a). This methodology was extended to intramolecular α-C−H functionalization of *N*-aryltetrahydroisoquinolines **5a** and **5b** to tetracyclic compounds **6a** and **6b** in similar yields (Scheme 2b).

Two years later, the same group reported the construction of oxazinones through an α-alkylation/cyclization of *N*-protected tetrahydroisoquinolines **7** with non-activated olefins **8** mediated by Bobbitt's salt **1b** (Scheme 3a).[8] The oxazinones **9** were prepared in good yields, except when strong electron-withdrawing (EWG) group such as *m*-CF_3 is attached to the olefin **9c**. The mild reaction conditions used for these C−H functionalization reactions do not compromise the integrity of the chiral center at C3 of enantiopure THIQ **7a,** and high yield but modest diastereoselectivity of **9a** was obtained (Scheme 3a). Additionally, this synthetic technology has been used in the synthesis of bioactive compounds. While the oxazinone derivate **9g** was utilized for the concise synthesis of the receptor antagonist (NMDA-NR2B), the analgesic drug methopholine was prepared in three steps from oxazinone **9h** (Scheme 3b). Based on a kinetic isotope study, they proposed that hydrogen abstraction is the limiting step of the formation of *N*-acyl iminium intermediate

G, which reacts with the olefin **8** producing cationic intermediate **H**, which is trapped by the carbamate group leading the departure of the *O*-adamantyl group to thus generate the cyclized product **9** (Scheme 3c).

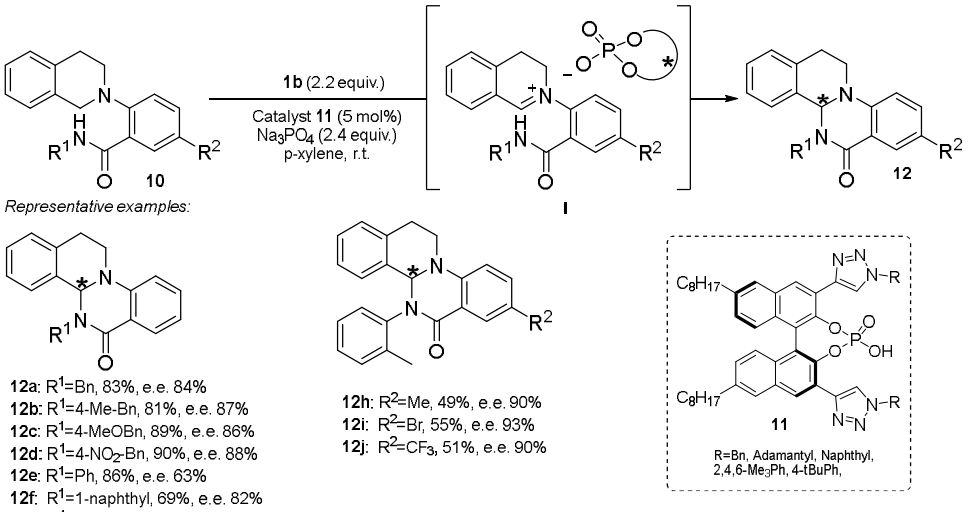


Scheme 2. α-C−H Functionalization (dehydrogenative coupling) of tetrahydroisoquinolines.



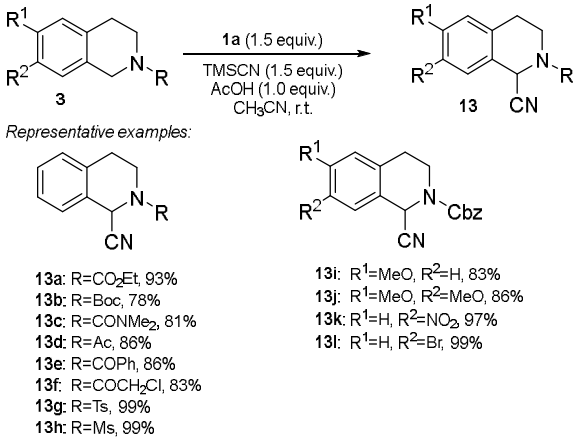
Scheme 3. α-C−H Functionalization of THIQs **7** mediated by the Bobbitt´s salt **1b** and synthetic applications to bioactive products.

Seminal work on the chemistry of oxoammonium cation was reported by Toste *et al* in 2013.[9] They developed a highly enantioselective α-C−H functionalization of *N*-(2-amide)aryl-THIQ derivates **10** to optical enriched cyclic aminals **12** mediated by the Bobbitt's salt **1b**, and catalyzed with 3,3'-triazolyl-BINOL-phosphate derived Bronsted acid **11** (Scheme 4). Likewise, this asymmetric dehydrogenative coupling conversion of **10** to **12** is promoted by the cation salt **1b** from which, the chiral counter ion derived from BINOL-phosphate acid **I** is the responsible for the stereo-induction during the cyclization step. Additionally, the chemical yield and enantiomeric excess were not affected by either electronic or steric factors of the functional groups placed in the aromatic ring and amide group (Scheme 4).



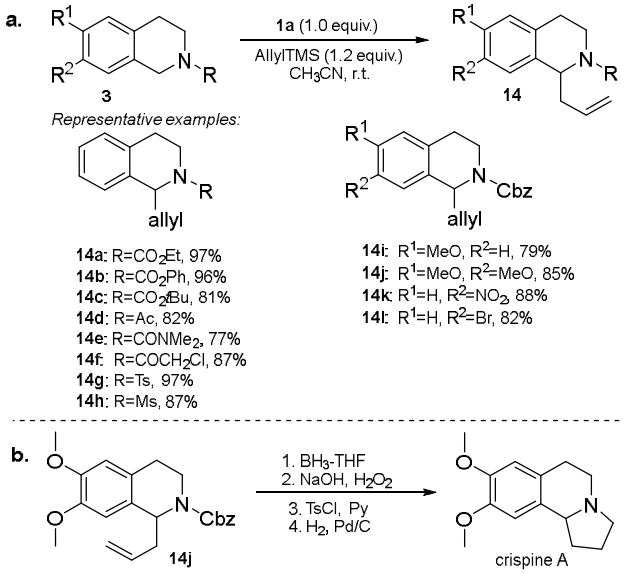
Scheme 4. Enantioselective α-C−H functionalization of THIQs **10** mediated by **1b** and catalyzed by BINOL-derivative phosphate **11**.

Later in 2014, Wang *et al*. reported an oxoammonium catalyzed α-C−H cyanation of *N*-protected-THIQs **3** to their respective nitrile derivatives **13**.[10a] They used trimethylsilyl cyanide (TMSCN) as the cyanide source in the presence of acetic acid to obtain product **13** in good yields (Scheme 5).



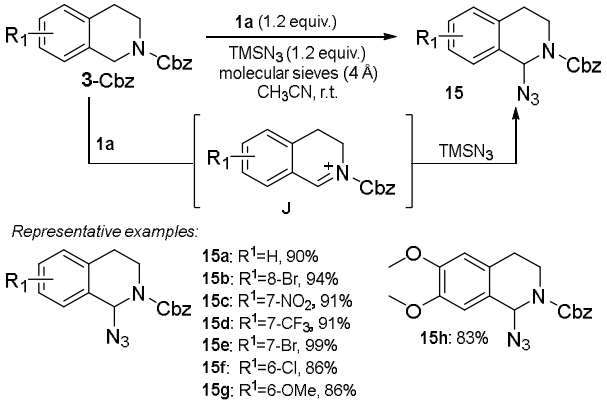
Scheme 5. α-C−H Cyanation of *N*-acyl/sulfonyl THIQs **3** with TMSCN mediated by **1a**.

Following this methodology, they also reported the α-C–H allylation version of **3**, but now using allyltrimethylsilane (AllylTMS) as the nucleophile.[10b] Thus, various allylated THIQs **14** were obtained in good to excellent yields when either electron-donating or electron-withdrawing group is placed at the aromatic ring (Scheme 6a). Subsequently, they took advantages from this methodology to achieve the racemic synthesis of crispine A from allyl-*N*-Cbz THIQ **14j** in 71% overall yield (Scheme 6b).



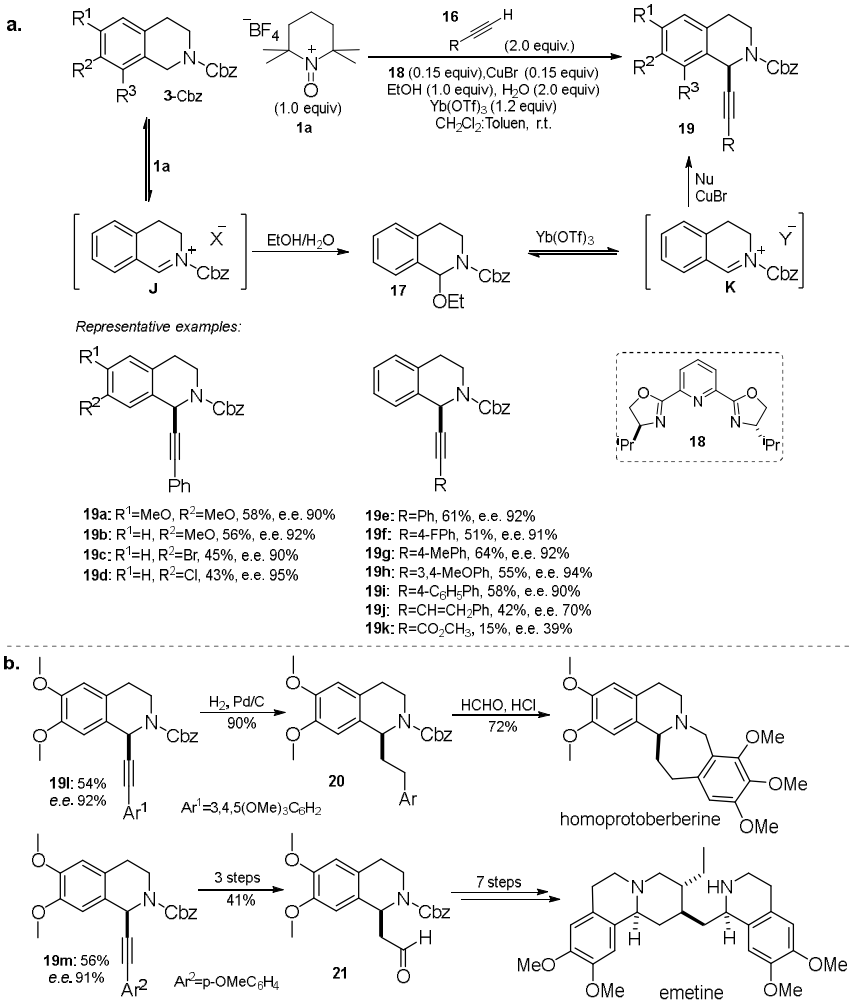
Scheme 6. α-C–H Allylation of *N*-acyl/sulfonyl THIQs **13** with AllylTMS and **1a** and synthetic application to a bioactive product.

In a similar context, Wang *et al*. developed the α-C–H azidation of THIQs **3**-CBz to α-azide-THIQs **15**[11] by using trimethylsilyl azide ($TMSN_3$) as nucleophile. Interestingly, the use of molecular sieves improved the yield up to 99% yield, even on a gram scale (Scheme 7). Like in the other α-C–H functionalization reactions, the proposed mechanism suggests the nucleophilic attack of the azido group to iminium intermediate **J**, which is formed through a hydride transfer process of **3**-Cbz to **1a** (Scheme 7).



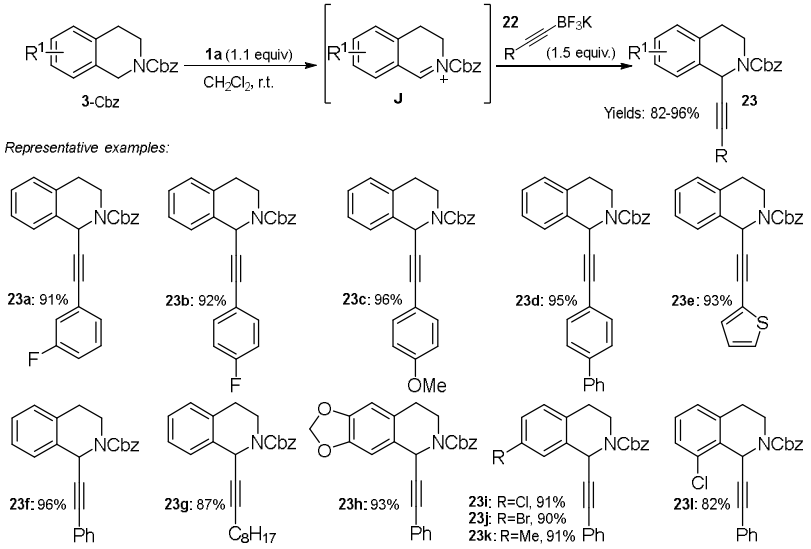
Scheme 7. α-C–H Azidation of *N*-CBz-THIQs (**3**-Cbz) with $TMSN_3$ and mediated by **1a**.

In 2015, Liu *et al*. reported a catalytic enantioselective α-C−H functionalization of *N*-Cbz-THIQs **3**-Cbz mediated by oxoammonium cation **1a** and using terminal alkynes as carbon-based nucleophiles **16**.[12] Initial experiments failed to produce the iminium intermediate **J**, which was presumably attributed to poor stability of the iminium **J** (Scheme 8a). To solve this problem, the authors mixed protic additive and a Lewis acid to promote the formation of iminium cation **K** from transient hemiaminal **17** (Scheme 8a). Then, with the use of CuBr and pyridine derivative ligand **18** in combination with KOH, H_2O, and $Yb(OTf)_3$, they found optimal reaction conditions for the asymmetric α-C−H alkynylation (Scheme 8a). Moderate yields, and high enantioselectivities were obtained for aryl acetylenes bearing either electron-withdrawing or electron-donating groups, except for the case of **16k**, which produced **19k** in low yield and enantiomeric excess (Scheme 8a). They also showed the synthetic relevance of this methodology in the total synthesis and configurational assignment of homoprotoberberine, and the preparation of an advanced intermediate of emetine (Scheme 8b).[13] The former bioactive compound was obtained from **19i**, which is reduced to **20** with H_2 and Pd. And the latter from **19m**, which is transformed to **21** in three steps.



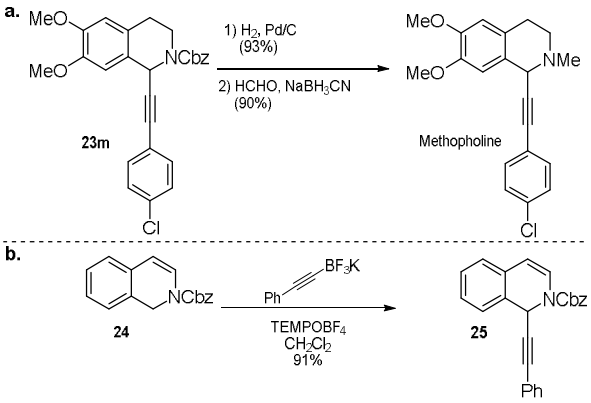
Scheme 8. Asymmetric α-C−H alkynylation of N-Cbz THIQs, and its use in the synthesis of homoprotoberberine and emetine.

Later, Wan, Zhao and co-workers[14] published an α-C−H alkynylation of *N*-Cbz-THIQs (**3**-Cbz) mediated by **1a**. In this work, they tested various oxoammonium cations such as TEMPOTfO, $TEMPOPF_6$, $TEMPOSbCl_6$, $TEMPOClO_4$; however, they found that **1a** was the one that showed good compatibility with alkyne potassium trifluoroborates. Like in the previously mentioned α-C−H functionalization reactions, the iminium cation **J** was proposed as the key intermediate, which is attacked by potassium trifluoroborate derivate **22** to give α-alkynylated compounds **23** in high yields (Scheme 9). The yield was not affected either by substituents in **3**-Cbz or in alkynes **22** (Scheme 9).



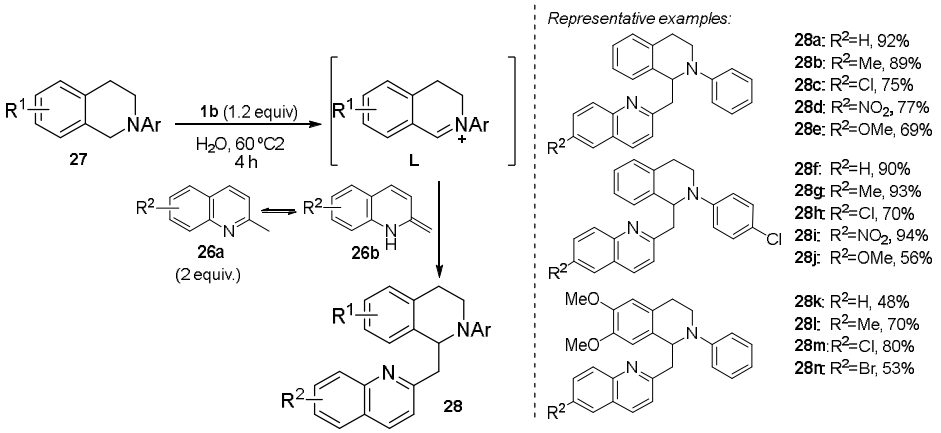
Scheme 9. α-C−H Alkynylation of N-Cbz-THIQs with R-BF_3K and **1a**.

Additionally, this methodology was applied to the formal synthesis of methopholine from a α-alkynyl-THIQ intermediate **23m**. Hydrogenation of THIQ **23m** with H_2, Pd/C followed by *N*-methylation[8] with HCHO and $NaBH_3CN$ afforded the methopholine in 84% overall yield (Scheme 10a). Another interesting result was the α-C−H-alkynylation of an *N*-Cbz-dihydroisoquinoline **24** under the established conditions. Despite of the high reactivity of the enamine moiety toward oxoammonium cations,[15] the expected α-alkynylated dihydroisoquinoline product **25** was obtained in good yield (Scheme 10b).



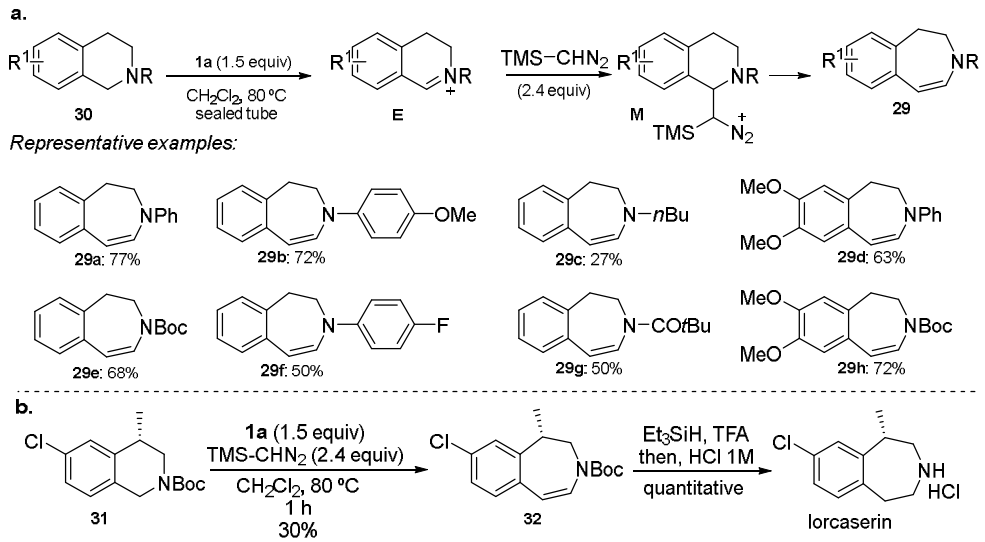
Scheme 10. a. Formal synthesis of methopholine. **b**. C−H Alkynylation of a *N*-Cbz-dihydroisoquinoline **24**.

In 2016, Li, Xie, and collaborators reported the α-C−H functionalization of *N*-aryl-THIQs mediated by the Bobbitt´s salt **1b** and using 2-methylquinoline derivates **26** as nucleophiles.[16] According to the reaction mechanism, iminium intermediate **L** is attacked by nucleophilic tautomeric dienamine **26b** derived from 2-methylquinoline **26a**. In general, the substituent effect in the THIQ moiety of **27** or 2-methylquinoline scaffold **26** was moderated, except for substrates containing OMe groups **28e**, **28j**, **28k**, **28n** (Scheme 11).



Scheme 11. α-C−H Functionalization *N*-aryl-THIQs with 2-methylquinoline derivates mediated by the Bobbitt´s salt **1b.**

Taking advantage of these C−H functionalization of THIQs mediated by oxoammonium salts with various nucleophiles, Alemán and García-Mancheño envisioned a cleaver strategy to access to 3-benzazepines **29** from THIQs **30**.[17] The C−H oxidation of a THIQs **30** to transient iminium cation **E** followed by the addition of a diazomethane derivative at 80 ºC produced **M** which underwent a ring expansion to the corresponding 3-benzazepines **29** and N_2. Diverse *N*-acyl/aryl-THIQs were tested giving moderate to good yields, except *N*-alkyl-THIQ **30c**, which provided low yield of **29c** (Scheme 12a).

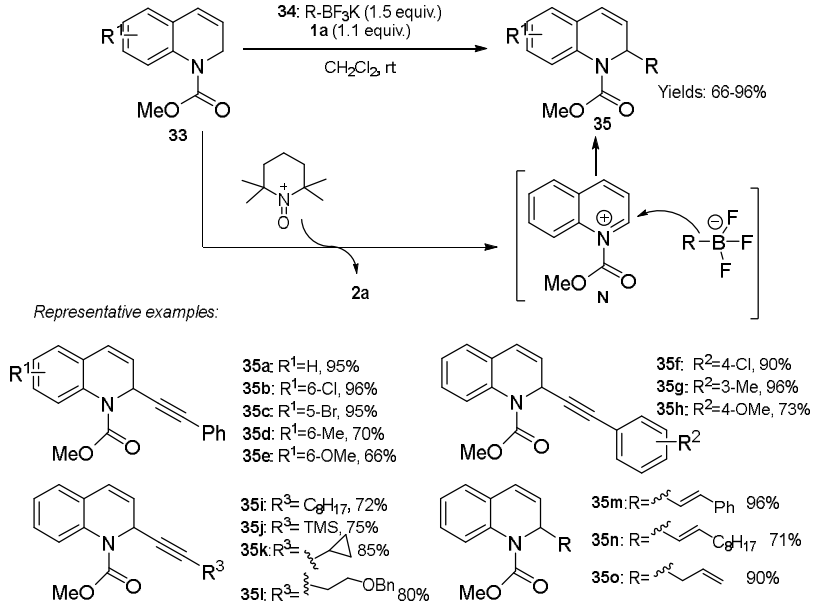


Scheme 12. α-C−H Alkylation/ring-expansion of THIQs to 3-benzazepines and synthetic application.

Additionally, this methodology was applied to the asymmetric total synthesis of the anorectic drug lorcaserin from chiral THIQ **31** in three steps: α-C−H alkylation/ring-expansion of **31** to **32** followed by double bond reduction and Boc-deprotection (Scheme 12b).

2.2. Dihydroquinolines (DHQs)

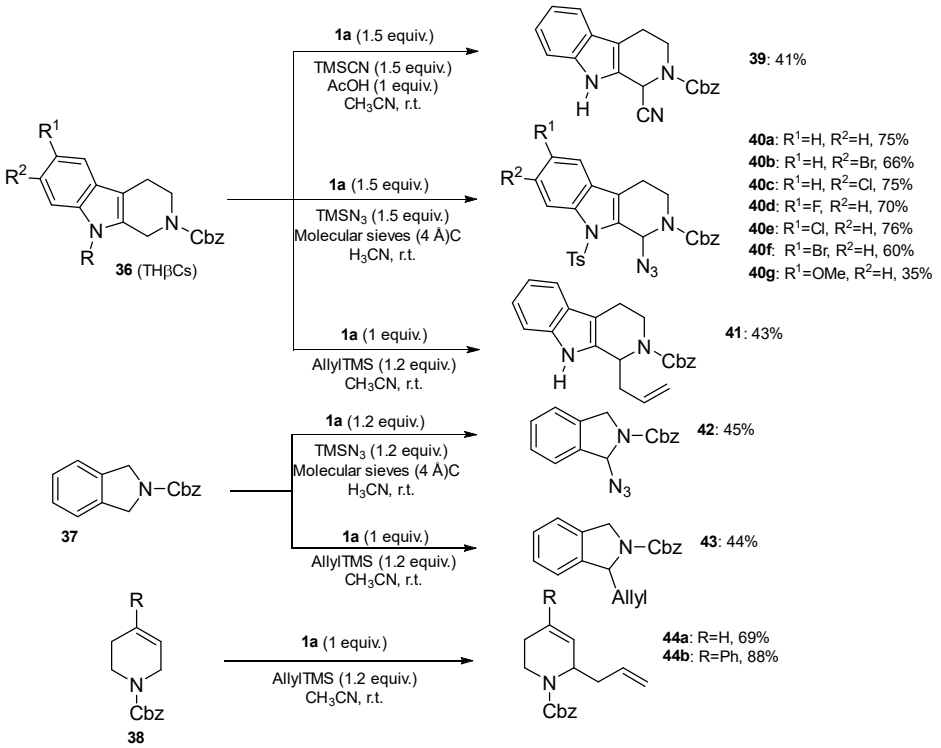
In 2017, Wan, Li, Liu and co-workers described a method for the α-C−H functionalization of dihydroquinolines (DHQs) **33** to α-substituted-1,2-dihydroquinolines **35** mediated by TEMPO$^+$ cation **1a** in the presence of potassium trifluoroborates **34** as nucleophiles (Scheme 13).[18] The authors also suggested that **1a** promotes a direct α-C−H hydride abstraction of 1,2-dihydroquinolines leading to *N*-acyliminium intermediate **N** plus TEMP-OH **2a**, which is attacked by alkynyl potassium trifluoroborates. Although vinyl and allyl potassium trifluoroborates gave good yields of α-vinyl/allyl-dihydroquinolines **35m-o**, due to the low nucleophilicity of aryl trifluoroborate salts, the C−H arylation was not accomplished. It is worth to mention the notable functional group tolerance of highly sensitive functional groups like cyclopropyl **35k** or electronically enriched aryl groups like OMe **35e**. Thus, this transition-metal-free C−C bond coupling represents a useful and simple methodology for the synthesis of 1,2-dihydroquinolines-α-substituted.



Scheme 13. α-C−H Functionalization of DHQs **33** to α-substituted-DHQs **35** with R-BF_3K and mediated by **1a**.

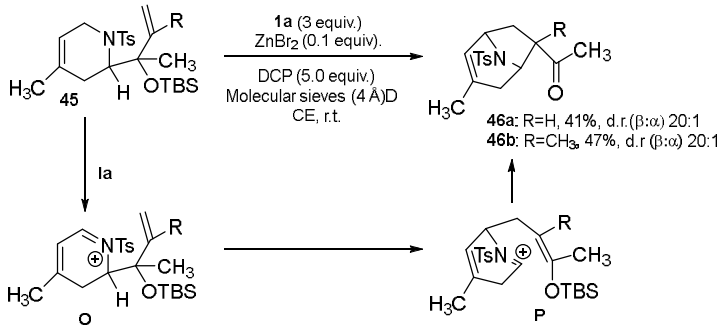
2.3. Tetrahydro-β-carbolines (THβCs), isoindolines, and dehydropiperidines

In a similar approach, the group of Wang studied the α-C−H cyanation/allylation/azidation of protected tetrahydro-β-carbolines (THβCs) **36** with silyl reagents as nucleophiles and mediated by **1a** (Scheme 14).[10,11] Although the α-C−H functionalization of the THβCs **36** to **39, 40, 41** proceeds in moderated to good yields, the better chemical yields were obtained when $TMSN_3$ was the nucleophile in the presence of molecular sieves **40a-g**. While this methodology was applied to the α-C−H functionalization of isoindoline **37** to α-azide isoindoline **42** and α-allyl isoindoline **43** in moderated yields, the respective α-C−H functionalization of dehydropiperidine **38** to α-allyl dehydropiperidines **44a,b** gave good yields.



Scheme 14. α-C−H Functionalization of tetrahydro-β-carbolines **36**, isoindoline **37** and dehydropiperidine **38** mediated by **1a** and silyl reagents.

Another exciting α-C−H functionalization of *N*-heterocycles mediated by **1a** was reported by Shao-Hua and co-workers. They were able to transform 3,4-dehydropiperidines **45** to 3,4-dehydropiperidine-8-azabicyclo[3.2.1]octanes **46** in a tandem fashion. According to them, **45** is functionalized to allylic iminium ion **O** which undergoes an aza-[3,3]-Cope rearrangement to **P** and to **46a-b** after an intramolecular aldol cyclization (Scheme 15).[19]

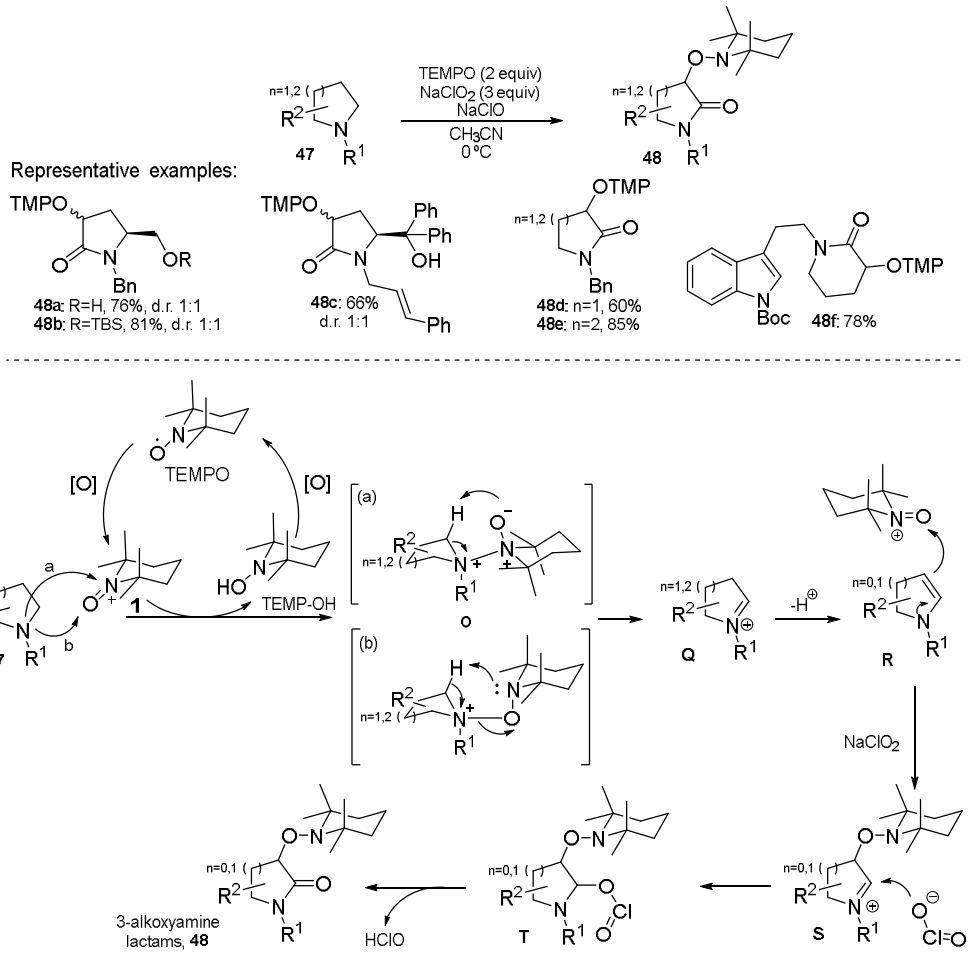


Scheme 15. α-C−H Functionalization of 3,4-dehydropiperidines **45** to 8-azabicylco[3.2.1]octanes **46** mediated by **1a**.

3. α,β-C−H Functionalizations

3.1. Pyrrolidines, piperidines, and piperazines

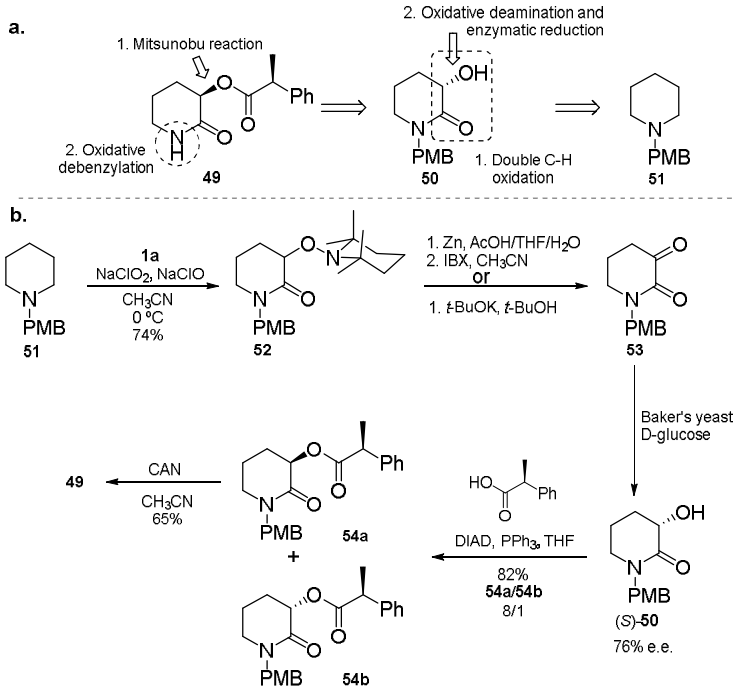
It is well known that oxoammonium cation **1** can be prepared *in situ* from 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) under oxidizing conditions. In this regard, the group of Sartillo-Piscil in 2016 reported the first dual α,β-C−H functionalization of pyrrolidines and piperidines to their corresponding 2-alkoxyamine lactams mediated by **1** (formed *in situ* by TEMPO oxidation with oxychloride reagents).[20] Thus, cyclic amines **47** were transformed into their corresponding 3-alkoxyamine lactams **48** in good chemical yields by employing $NaClO_2$, NaClO, and TEMPO (Scheme 16a). The proposed reaction mechanism suggests that **1** reacts with cyclic amine to produce an iminium intermediate **Q**. Then, the ion iminium **Q** evolves to enamine **R** which attacks to **1** forming another iminium intermediate **S**. Finally, the nucleophilic insertion of the chlorite ion to **S** leads to 3-alkoxyamine lactam **48** from **T** (Scheme 16b).



Scheme 16. a. Dual α,β-C−H functionalization of cyclic amines mediated by **1a**. **b** Mechanistic proposal.

This synthetic methodology was employed for the asymmetric synthesis of proposed structure of a natural alkaloid **49**[21] from a simple piperidine **51** (Scheme 17a).[22] α,β-C−H Functionalization of *N*-heterocycle **51** with **1a** provided the 2-piperidone **52** in good yield. This key intermediate was transformed into ketolactam **53** through two different approaches (either reductive deamination with Zn followed by oxidation of hydroxyl

group with IBX or by direct deamination with *t*-BuOK). The reaction of **53** with baker's yeast and D-glucose afforded the 3-hydroxylactam (*S*)-**50** in 76% of enantiomeric excess to finally obtain the proposed structure of alkaloid **49** in two further steps: coupling (*S*)-**50** with 2-phenylpropionic acid and under Mitsunobu conditions to **54a** and **54b** followed by removing PMB group of **54a** with CAN gave proposed alkaloid **49** (Scheme 17b).

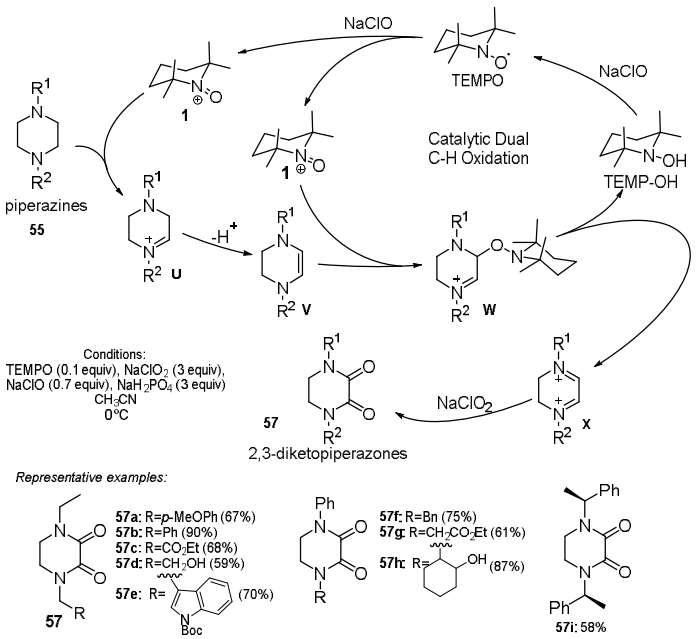


Scheme 17. Application of the dual α,β-C−H functionalization of piperidines to the total synthesis of putative alkaloid **49**.

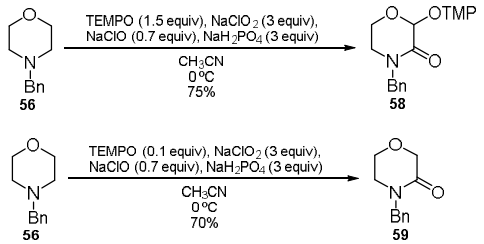
Two years later, this dual α,β-C−H functionalization of piperidines was extended to the dual α,β-C−H functionalization of piperazines **55** and morpholines **56** to their corresponding 2,3-diketopiperazines **57** and alkoxyamine morpholinones **58**, respectively.[23] By taking advantage of the easy elimination of TEMP-OH **2a**, promoted by the nitrogen atom of **W**, diiminium ion **X** is formed. Thus, this chemical transformation was accomplished under catalytic conditions of $TEMPO^+$ **1** (Scheme 18). Symmetrical and unsymmetrical piperazines were transformed into 2,3-diketopiperazines **57** in good yields by using catalytic amount of TEMPO in the presence of oxychloride reagents (Scheme 18). Mechanistic studies revealed that optically pure piperazine **55i** was transformed into **57i** without erosion of the optical purity; thus, complete preservation of the chiral center is observed during the formation of iminium intermediate **U**. Accordingly, when morpholines **56** was subjected under equimolar conditions, the dual α-C−H functionalization produced 3-morpholinones **58** in good yield (Scheme 19). Nevertheless, when a catalytic amount of TEMPO was employed, only the α-C−H oxidation occurred and 3-morpholinone **59** was obtained in good yield (Scheme 19).

In 2019, the groups of He and Fan achieved structural modifications of diverse *N*-heterocycles by means of α,β-C−H functionalization of piperidines and piperazines mediated by oxoammonium cation **1a** and other nonmetallic reagents. They reported a selective synthesis of β-nitrated tetrahydropyridines **61** from *N*-aryl piperidines **60** (X=C) mediated by **1a** and *t*BuONO as a nitrite source. This dual α,β-functionalization showed good yields when molecular sieves and BF_3•Et_2O were used (Scheme 20).[24] Based on previous reports, they suggested that **1a** promoted the α-C−H functionalization and formation of an iminium ion **Y** from *N*-aryl piperidine **60**, which evolved to enamine **Z** through a β-hydrogen elimination. Then, radical NO_2 is added to

Z to form a radical intermediate **A′** which generates the β-nitrated tetrahydropyridine **61** (Scheme 20). The incorporation of a radical scavenger proved that the reaction occurs through a radical fashion. Accordingly, diverse *N*-aryl piperidines containing halides or CN **61a-d** showed better yields than aryl bearing electron-donating groups such as the methyl group **61e**. Additionally, the β-nitrated piperazine **61g** and diazepane **61h** were obtained in low yield when BF_3-Et_2O was omitted (Scheme 20).



Scheme 18. Catalytic dual α,β-C−H oxidation of piperazines to 2,3-diketopiperazones.

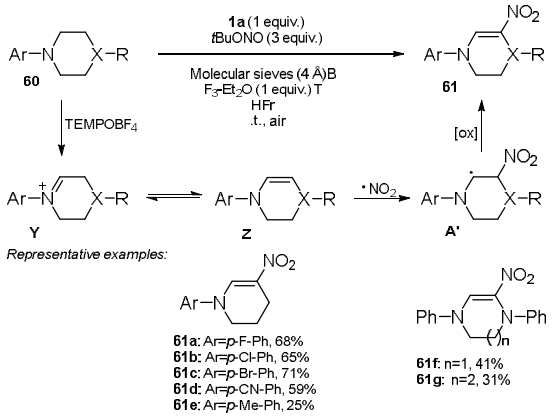


Scheme 19. α,β-C−H And α-C−H functionalization of morpholine mediated by **1a** to 2-alkoxyamine morpholinone **58** and 3-morpholinone **59**, respectively.

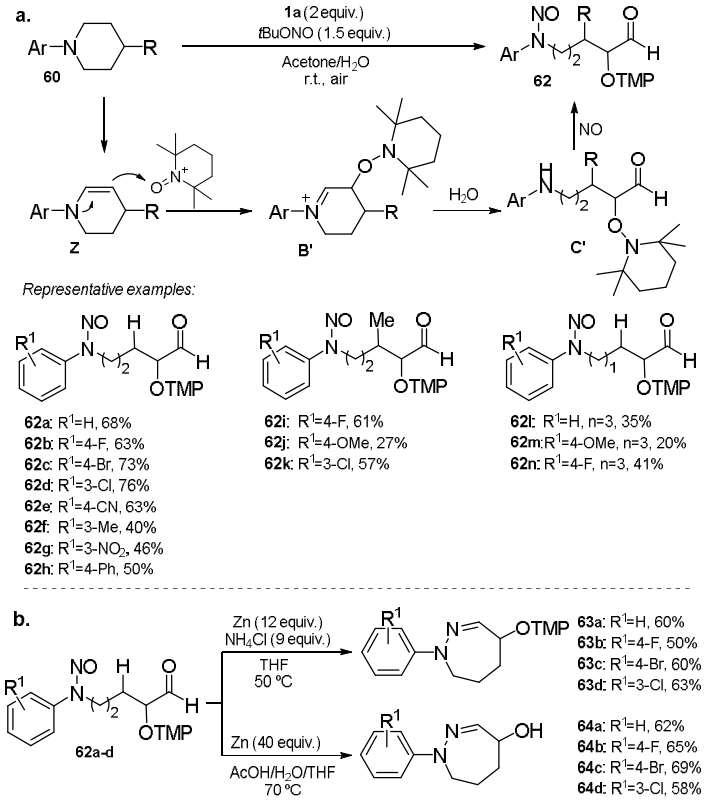
3.1.1. Deconstructive C−C bond functionalizations

Continuing with the investigations of dual α,β-C−H functionalization of piperidines mediated by oxoammonium cation **1a,** Fan and Xe observed that by using a mixture of acetone/H_2O solvents, the C−N bond of *N*-aryl piperidines **60** cleavages to their corresponding *N*-nitroso-2-alkoxyamine aldehydes **62** (Scheme 21a).[24] Accordingly, the formation of imine intermediate **B′** from enamine intermediate **Z** was proposed. Then, the presence of water led to acyclic δ-amine aldehyde **C′** which reacts with NO to afford **62** (Scheme 21a). Diverse *N*-aryl piperidines **60** were deconstructed into acyclic nitro amines in low to moderated chemical yield; except when electron donating group is present: low yields where obtained (**62j** and **62m**). Further functionalization of these *N*-nitro amino aldehydes **62a-d** was showcased in Scheme 21b.

N-aryl-4-alcoxyamine-1,2-diazepines **63** were obtained from **62a-d** by using Zn/NH_4Cl in THF/H_2O. On the other hand, *N*-aryl-4-hydroxy-1,2-diazepines **64** were prepared with Zn in AcOH/H_2O/THF (Scheme 21b).

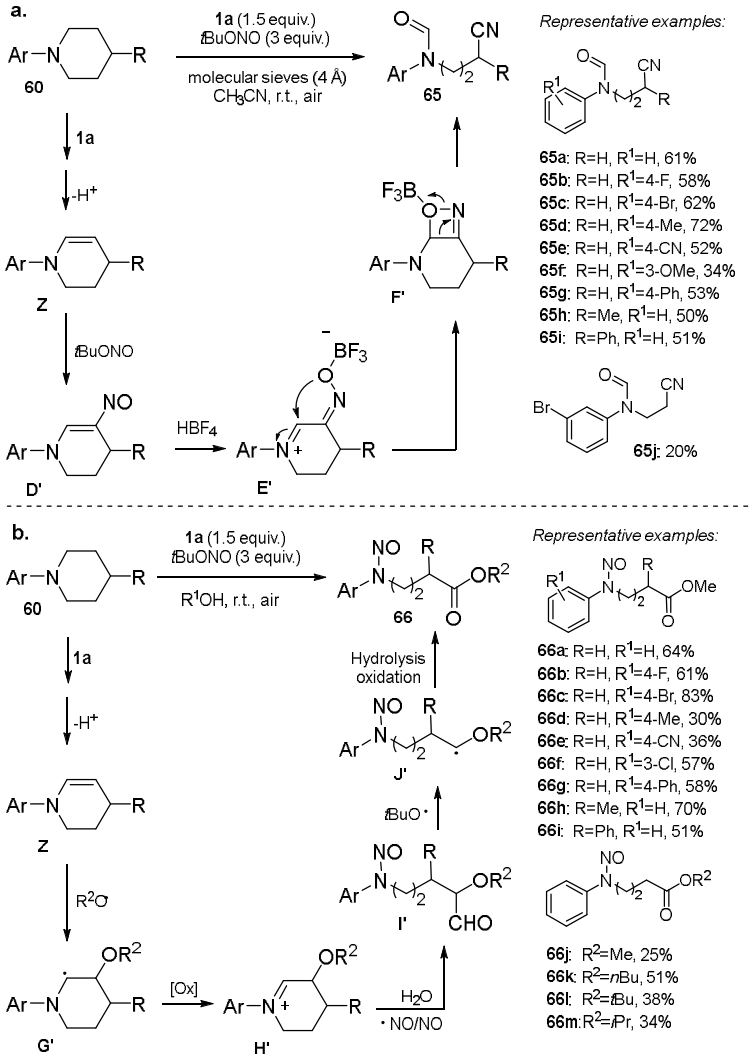


Scheme 20. Dual α,β-C−H functionalization of *N*-aryl piperidines **60** to β-nitrated tetrahydropyridines **61** mediated by **1a**.



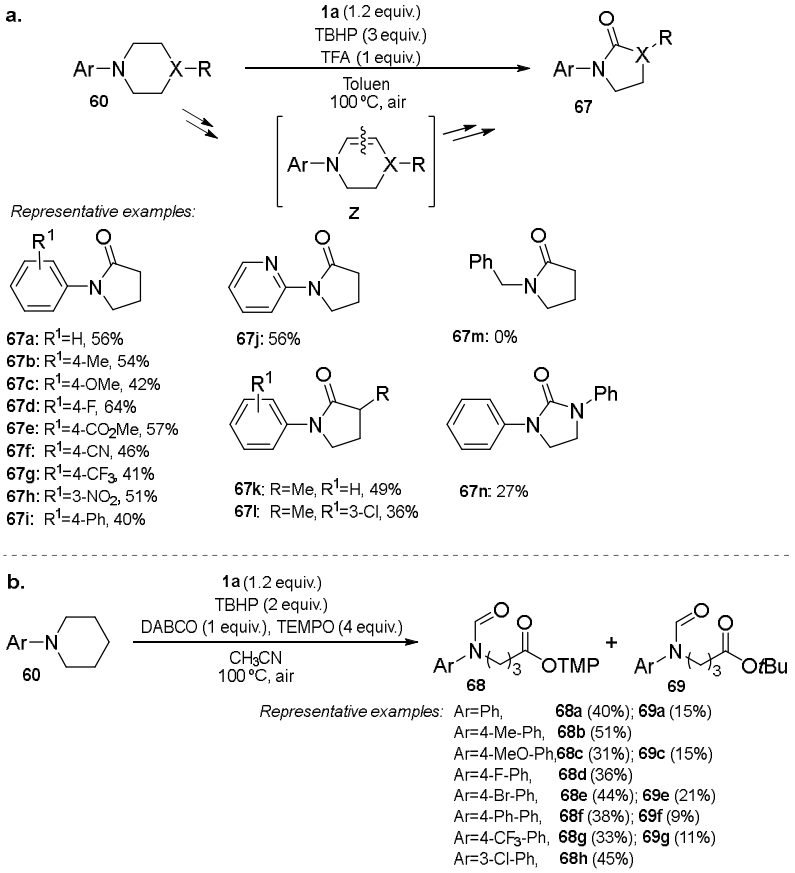
Scheme 21. a. Synthesis of *N*-nitroso-2-alkoxyamine aldehydes **62** from *N*-aryl piperidines **60** mediated by **1a** in the presence of *t*BuONO, and H_2O. **b**. Synthesis of *N*-aryl diazepines.

Another diversification of *N*-aryl piperidines was reported by the same group. They prepared a series of *N*-formyl nitriles **65** and *N*-nitroso chain esters **66** from 4-substituted piperidines **60** by changing the reaction media (Scheme 22).[25] According to the proposed reaction mechanism, intermediate **D′** is deconstructed into **65** through the activation of nitrite group with HBF_4 to iminium ion **E′** followed by a rearrangement to bicyclic intermediate **F′**, which is spontaneously transformed to **65** (Scheme 22a). In other hand, the ester series **66** was obtained by following a free radical/polar pathway: addition of RO• radical to enamine **Z** furnishes the iminium **H′**, which is hydrolyzed and nitrosated with water and either NO or NO• radical to afford the intermediate **I′**. Then, due to the presence of *t*BuO• radical, decarbonylation of **I′** to stabilized **J′** radical followed by radical oxidation afforded the *N*-nitroso esters **66** (Scheme 22b). This piperidine deconstruction showed to be compatible with different electron-donating and electro-withdrawing groups attached to the aryl group giving low to moderated yields (Scheme 22).



Scheme 22. Synthesis of acyclic *N*-formyl nitriles and *N*-nitro chain esters from *N*-aryl piperidines mediated by **1a**.

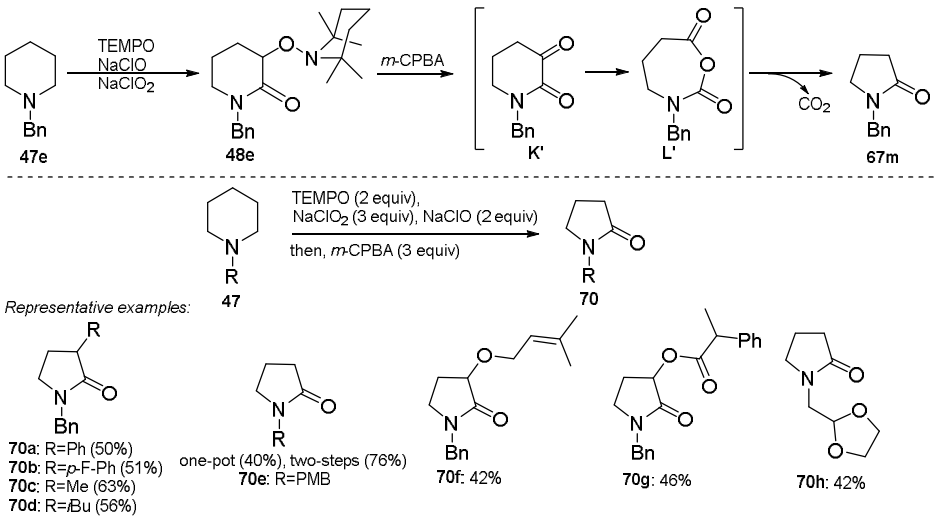
More recently, in 2021, the same group reported a selective cleavage and reconstruction of C−N/C−C bonds in cyclic amines **60** to lactams **67** and *N*-formyl aminoesters **68** and **69**.[26] They explored several TEMPO salts, and found that the reagent system of **1a**/TBHP/TFA in toluene at 100 °C under air conditions gave the best results, albeit in low and moderated yield (Scheme 23a). The case of the 0% yield of *N*-benzyl-pyrrolidinone **67m** is interesting, because we believe that the benzylic C−H oxidation is more favorable than the α,β-C−H functionalization, thus, the expected formation of 2-pyrrolidinone **67m** is suppressed by the formation of further oxidized products (not reported). Also, when *N,N*-diarylpiperazine **60n** was used, imidazolidin-2-one **67n** was obtained in low yield (Scheme 23a). In similar context, when DABCO and TEMPO were incorporated into the reaction conditions, C−C bond oxidative cleavage followed by incorporation of either TEMPO or *t*BuO occurred and **68** and **69** were formed, respectively (Scheme 23b).



Scheme 23. Deconstruction of *N*-aryl piperidines to *N*-aryl 2-pyrrolidinones mediated by **1a.**

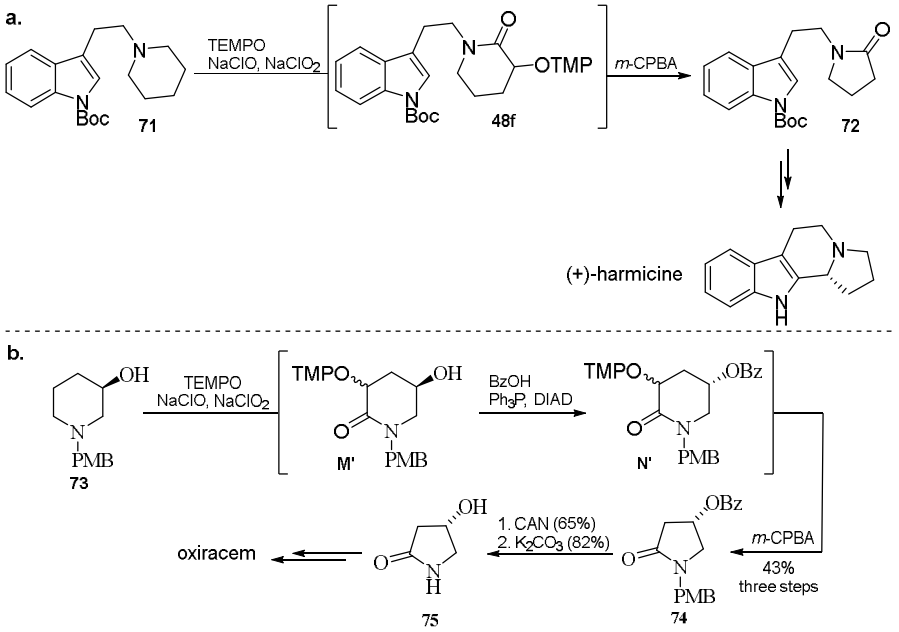
In a similar approach, Sartillo-Piscil and co-workers took advantages from the dual α,β-C−H functionalization of piperidines to 3-alkoxyamine lactams to deconstruct the piperidine ring into γ-lactams. This transition-metal-free deconstructive lactamization of piperidines is performed in two steps: first the α,β-C−H oxidation of piperidine **47e** into 3-alkoxyamine piperidone **48e** mediated by **1** and $NaClO_2$, and then, ring contraction from the transient keto lactam **K′** through a regioselective Baeyer-Villiger oxidation to *N*-carboxyanhydride intermediate **L′** followed by intramolecular translactamization to **67m** with CO_2

elimination (Scheme 24).[27] Thus, this deconstruction of piperidines **47** to lactams **70** can be conducted in either one-pot protocol or two-step sequence.



Scheme 24. Dual α,β-C−H functionalization in the deconstructive lactamization of piperidines.

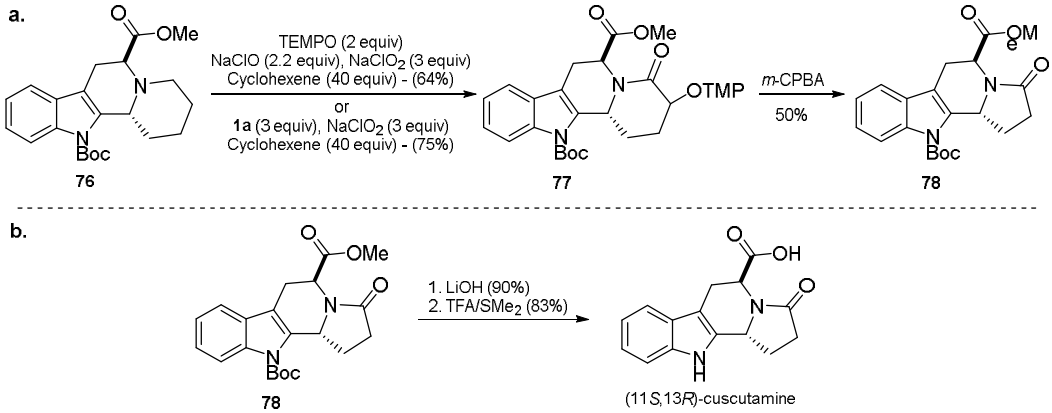
This transition-metal-free deconstruction protocol of piperidines was applied to the formal synthesis of: **a**) (+)-harmicine from indole piperidine derivative **71** *via* alkoxyamine lactam **48f** to pyrrolidinone **72**; **b**) oxiracetam intermediate **75** from chiral 3-hydroxy piperidine **73** through the transient formation of intermediates **M'**, **N'**, **74** and **75** (Scheme 25).



Scheme 25. Synthetic application of the deconstructive lactamization of piperidines.

3.2. Indolo[2,3-*a*]quinolizines

Very recently, the same group extended this synthesis tactic to a more complex molecular structure. The tetracyclic compound **76,** which possesses various C−H bonds prone to be oxidized by **1a,** was exclusively transformed into 3-alkoxyamine lactam **77**. It was also established that using **1a** previously prepared gives better results than when is formed *in situ* from TEMPO oxidation with NaOCl. Accordingly, the reaction between alkoxyamine lactam **77** and *m*-CPBA produced the indolizino[8,7-*b*]indole **78** in moderated yield (Scheme 26a). The total synthesis of the natural product (11*S*,13*R*)-cuscutamine was accomplished after the protecting group removal (Scheme 26b).[28]



Scheme 26. Dual α,β-C−H functionalization of quinolizines in the total synthesis of (11*S*,13*R*)-cuscutamine.

4. Triple α,β,γ-C−H functionalization of piperidines

The same research group went further toward the tandem multi-C−H functionalization of piperidines. The *in-situ* generation of oxoammonium cation **1** by using the dual C−H oxidizing conditions, coupled with a thermal hemolysis of the alkoxyamine lactam intermediate, allowed the α,β,γ-functionalization of saturated piperidines to α,β-unsaturated-2-pirrolidinones(Scheme 27). Consequently, various synthetic bioactive alkaloids were synthesized from simple *N*-substituted piperidines. For instance, paroxetine from **47e** to **79** followed by tandem conjugated Grignard addition/electrophilic quenching (formaldehyde) to **79** and then to **80**; femoxetine from unsaturated piperidone **81** to **82** following the same protocol as the paroxetine; and vesamicol was obtained from **83**→**84**→**85** following a similar sequence (Scheme 27).[29]

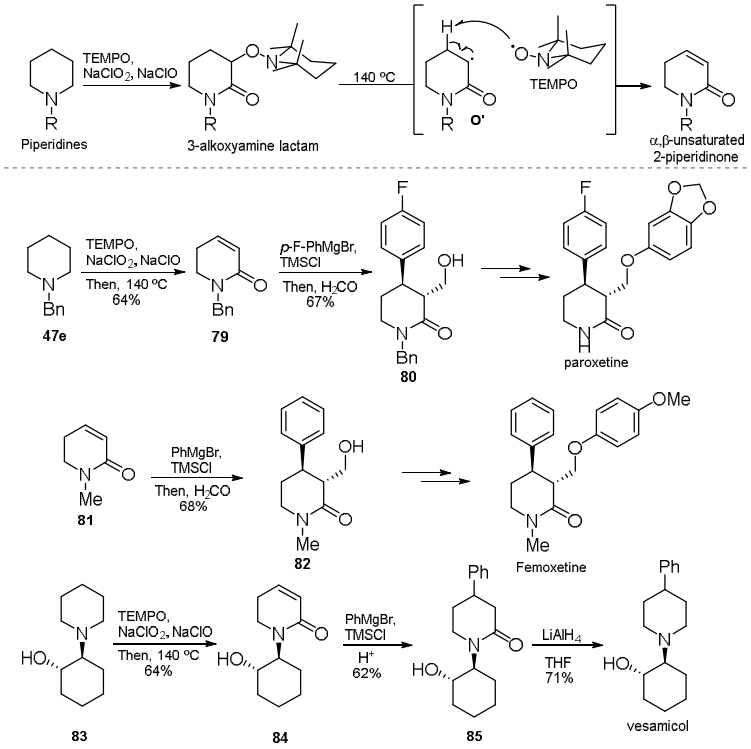
Additionally, this triple α,β,γ-C−H functionalization was also applied in the total synthesis and revision of the absolute configuration of the natural occurring alkaloid (−)-pipermethystine from piperidine **73**. The acetylation of **86** with acetic anhydride followed by an oxidative debenzylation with CAN and acylation with 3-phenylpropionyl chloride gave the (−)-pipermethystine in only 4 steps (Scheme 28).[30]

5. *In-situ* generation of oxoammonium cation by electricity

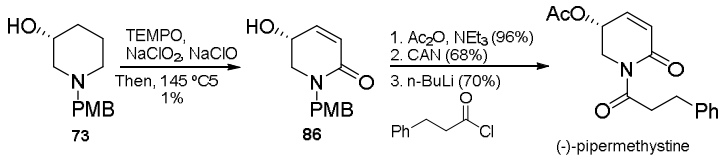
As above-mentioned, oxoammonium cation **1** has been used as a versatile oxidant of alcohols, carbohydrates, naphthols, and amines. However, the chemical oxidation commonly requires equimolar quantities of this reagent. In this regard, Little and co-workers reported a catalytic electrochemical TEMPO α-C−H oxidation of tetrahydroisoquinolines (THIQs) **3** to dihydro-isoquinolinones **87** (Scheme 29).[31] First, TEMPO is electrochemical oxidized in the anode to oxoammonium cation **1**, then the latter chemically oxidizes to isoquinoline **3** to radical cation **P′**, which is transformed to iminium ion **Q′**. The hydrolysis of iminium cation **Q′** produces the α-hydroxylamine **R′** which is electrochemically oxidized to isoquinolinones **87**. Interestingly, cation **1** selectively oxidizes the endocyclic hydrogens rather the benzylic C−H hydrogens in **87a-c**, and **87g-i**.

Later, the group of Ye reported the α-C−H arylation of tertiary cyclic amines with benzonitrile derivatives **89**.[32] They took advantage of a paired electrolysis in which the intermediate **S′** is formed in the

cathode, while TEMPO$^+$ **1** in the anode to thus reacts with *N*-aryl pyrrolidines **88** and afford the cationic radical **T′**. Then, a deprotonation of **T′** gave the radical **U′** which reacts with **S′** to generate **V′** and the latter to **90** after cyanide expulsion. They reported several examples of α-C−H arylation of *N*-aryl cyclic amines bearing different groups at the aromatic ring **90a-n** (Scheme 30).

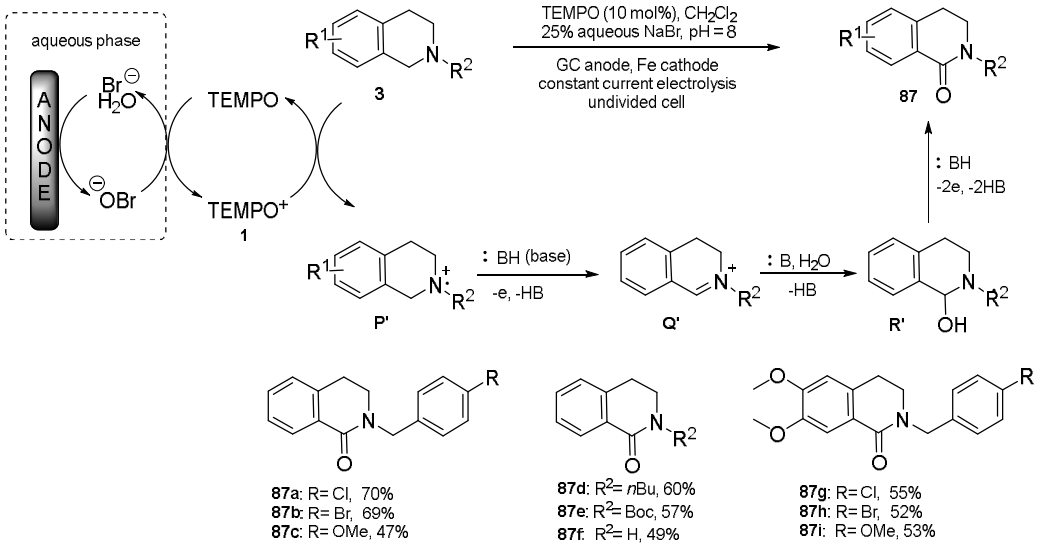


Scheme 27. Triple α,β,γ-C−H functionalization of *N*-substituted piperidines to bioactive alkaloids mediated by TEMPO.

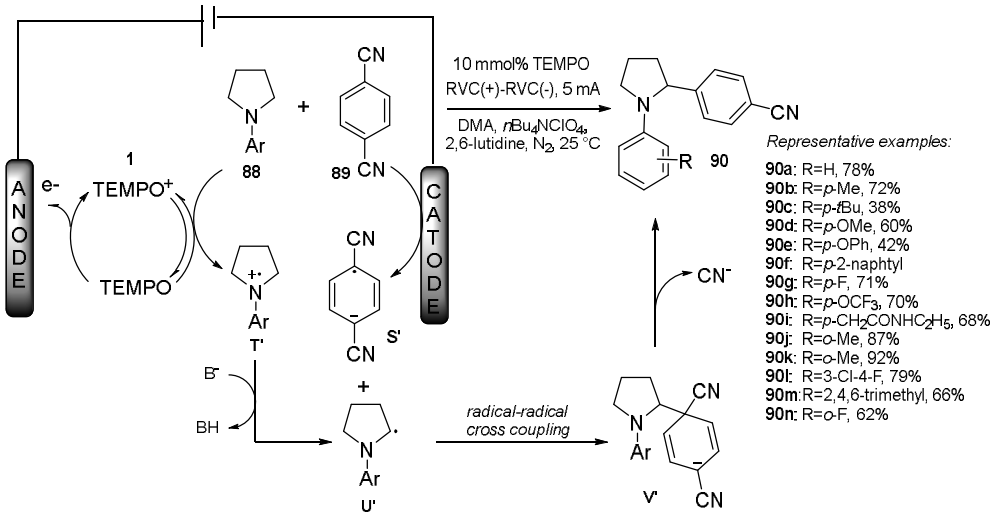


Scheme 28. Triple α,β,γ-C−H functionalization of chiral hydroxyl-piperidine **73** to the total synthesis of (-)-pipermethystine.

In 2020, the group of Mei reported an asymmetric electrochemical Shono-type oxidative cross-coupling of THIQs **91** and THβCs by using TEMPO in the presence of Cu(II) and chiral bisoxazoline ligand **92** (Scheme 31).[33] According to proposed reaction mechanism, TEMPO radical is electrochemically oxidized to TEMPO$^+$, then, hydride transfer from THIQ to TEMPO$^+$ and iminium intermediate **W′** is formed. On the other hand, alkyne **93** is metalated with Cu(I) by the action of nBu$_4$NPF$_6$, and ligand **92** to afford a chiral acetylide, which reacts with iminium ion **W′** giving THIQs and -THβCs **94** in good yields and high enantiomeric excess (except in THQs bearing ester groups at the N-atom, which **91r-v** gave low yield of **94r-v** but the enantiomeric excess remains high) (Scheme 31).



Scheme 29. Electrochemical α-C–H oxidation of THIQs to dihydro-isoquinolinones **87**.

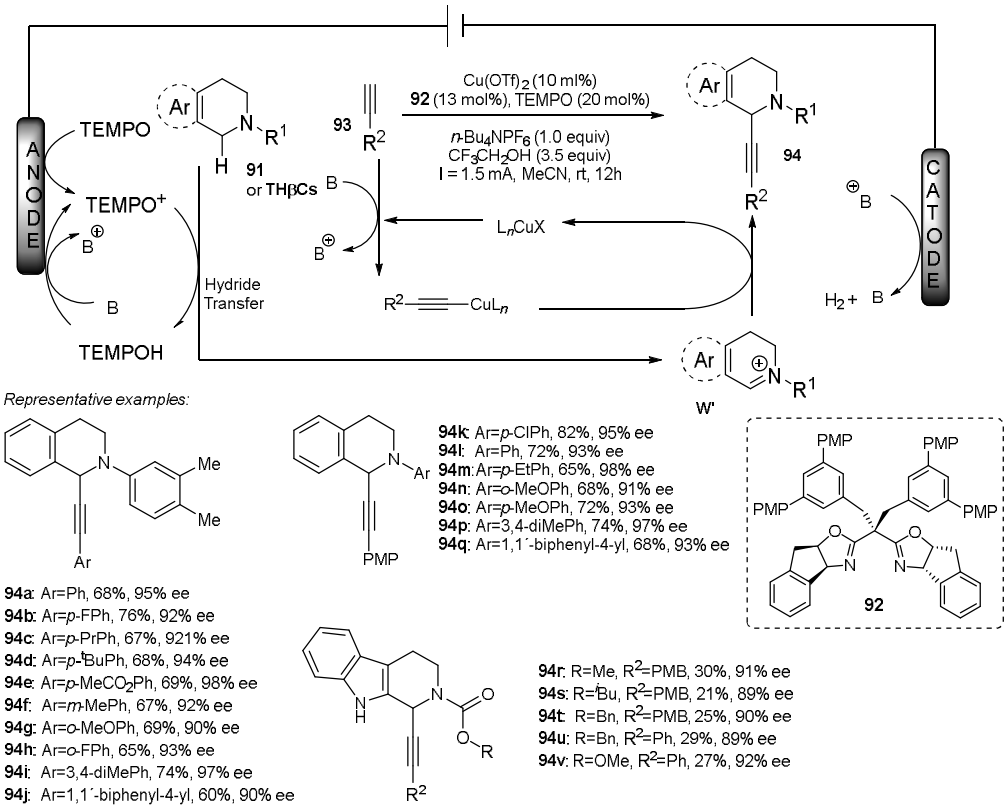


Scheme 30. Electrochemical α-arylation of *N*-aryl pyrrolidines with TEMPO.

6. Conclusions

The genuine task of making molecules by following, as much as possible, the principles of the green chemistry, should be the primary commitment for any synthetic organic chemist. Consequently, it must be highly desirable that chemists try to perform chemical reactions by keeping in consideration the low economic cost and minimal ecological impact. In this regard, the remarkably compatibility of the sp^3-nitrogen atom with oxoammonium cations derived from TEMPO permits that the selective C–H functionalization occurs before the premature oxidation of the nitrogen atom, which is not common with other non-metallic oxidizing reagents, and even, in some cases is not necessary to deactivate the nitrogen atom with a protecting group.

In summary, we expect that the current book-chapter illustrate that exist an exciting and promising chemistry of TEMPO cations **1a** and **1b** beyond the chemical oxidizing of alcohols to their respective aldehydes and ketone compounds.



Scheme 31. Asymmetric electrochemical α-C−H acetylination of THIQs and THβCs with **1**.

Acknowledgements

The authors thankfully acknowledge CONACYT (Grant # A1-S-21450, and A1-S-24140). Partial support BUAP-VIEP.

References

1. Altus, K.M.; Love, J. A. *Commun. Chem.* **2021**, *4*, 173.
2. Börgel, J.; Ritter, T. *Chem.* **2020**, *6*, 1877-1887.
3. Sun, C.-L.; Shi, Z.-J. *Chem. Rev*. **2014**, *114*, 9219-9280.
4. Merbouh, N.; Bobbitt, J. M.; Brückner, C. *Org. Prep. Proced. Int*. **2004**, *36*, 1-31.
5. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem*. **1987**, *52*, 2559-2562.
6. Gini, A.; Brandhofer, T.; García-Mancheño, O. *Org. Biomol. Chem.* **2017**, *15*, 1294-1312.
7. Richter, H.; García-Mancheño, O. *Eur. J. Org. Chem.* **2010**, 4460-4467.
8. Richter, H.; Fröhlich, R.; Daniliuc, C.-G.; García-Mancheño, O. *Angew. Chem. Int. Ed*. **2012**, *51*, 8656-8660.
9. a) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc*. **2013**, *135*, 14044-14047. b) Milo, A.; Nee, A. J.; Toste, F. D.; Sigman, M. S. *Science* **2015**, *347*, 737-743.

10. a) Yan, C.; Liu, Y.; Wang, Q. *RSC Adv*. **2014**, *4*, 60075-60078. b) Yan, C.; Liu, Y.; Wang, Q. *Org. Lett*. **2015**, *17*, 5714-5717.
11. Dong, J.; Xia, Q.; Yan, C.; Song, H.; Liu, Y.; Wang, Q. *J. Org. Chem*. **2018**, *83*, 4516-4524.
12. Sun, S.; Li, C.; Floreancig, P. E.; Lou, H.; Liu, L. *Org. Lett*. **2015**, *17*, 1684-1687.
13. Tietze, L. F.; Rackelmann, N.; Müller, I. *Chem. Eur. J*. **2004**, *10*, 2722-2731.
14. Chen, L.; Sun, C.; Feng, G.; Cao, M.; Zhao, S.-l.; Yan, J.; Wan, R.-z.; Liu, L. *Org. Biomol. Chem*. **2018**, *16*, 2792-2799.
15. Romero-Ibañez, J.; Fuentes, L.; Sartillo-Piscil, F. *Synlett* **2021**, *32*, 1385-1396.
16. Fang, L.; Li, Z.; Jiang, Z.; Tan, Z.; Xie, Y. *Eur. J. Org. Chem*. **2016**, *2016*, 3559-3567.
17. Gini, A.; Bamberger, J.; Luis-Barrera, J.; Zurro, M.; Mas-Ballesté, R.; Alemán, J.; García Mancheño, O. *Adv. Synth. Catal*. **2016**, *358*, 4049-4056.
18. Liu, Z.; Chen, L.; Li, J.; Liu, K.; Zhao, J.; Xu, M.; Feng, L.; Wan, R.-z.; Li, W.; Liu, L. *Org. Biomol. Chem*. **2017**, *16*, 7600-7606.
19. Liu, L.; Cheng, H.-L.; Ma, W.-Q.; Hou, S.-H.; Tu, Y.-Q.; Zhang, F.-M.; Zhang, X.-M.; Wang, S.-H. *Chem. Commun*. **2018**, *54*, 196-199.
20. Osorio-Nieto, U.; Chamorro-Arenas, D.; Quintero, L.; Höpfl, H.; Sartillo-Piscil, F. *J. Org. Chem*. **2016**, *81*, 8625-8632.
21. a) Wang, Q.-X.; Li, S.-F.; Zhao, F.; Dai, H.-Q.; Bao, L.; Ding, R.; Gao, H.; Zhang, L.-X.; Wen, H.-A.; Liu, H.-W. *Fitoterapia* **2011**, *82*, 777. b) Krishna, P. R.; Kumar, P. V. A.; Mallula, V. S.; Ramakrishna, K. V. S. *Tetrahedron* **2013**, *69*, 2319-2326.
22. Romero-Ibañez, J.; Cruz-Gregorio, S.; Quintero, L.; Sartillo-Piscil, F. *Synthesis* **2018**, *50*, 2878-2886.
23. Chamorro-Arenas, D.; Osorio-Nieto, U.; Quintero, L.; Hernández-García, L.; Sartillo-Piscil, F. *J. Org. Chem*. **2018**, *83*, 15333-15346.
24. He, Y.; Zheng, Z.; Liu, Y.; Qiao, J.; Zhang, X.; Fan, X. *Chem. Commun*. **2019**, *55*, 12372-12375.
25. He, Y.; Zheng, Z.; Liu, Y.; Qiao, J.; Zhang, X.; Fan, X. *Org. Lett.* **2019**, *21*, 1676-1680.
26. He, Y.; Yang, J.; Zhang, X.; Fan, X. *Org. Chem. Front*. **2021**, *8*, 5118-5123.
27. Romero-Ibañez, J.; Cruz-Gregorio, S.; Sandoval-Lira, J.; Hernández-Pérez, J. M.; Quintero, L.; Sartillo Piscil, F. *Angew. Chem. Int. Ed*. **2019**, *58*, 8867-8871.
28. Recoba-Torres, A.; Cruz-Gregorio, S.; Quintero, L.; Sandoval-Lira, J.; Romero-Ibañez, J.; Sartillo-Piscil, F. *Eur. J. Org. Chem*. **2022**. DOI: 10.1002/ejoc.202200292.
29. Chamorro-Arenas, D.; Nolasco-Hernández, A. A.; Fuentes, L.; Quintero, L.; Sartillo-Piscil, F. *Chem. Eur. J*. **2020**, *26*, 4671-4676.
30. Vázquez-Amaya, L. Y.; Quintero, L.; Rodríguez-Molina, B.; Sartillo-Piscil, F. *J. Org. Chem*. **2020**, *85*, 3949-3953.
31. Li, C.; Zeng, C.-C.; Hu, L.-M.; Yang, F.-L.; Yoo, S. J.; Little, R. D. *Electrochim. Acta*. **2013**, *114*, 560-566.
32. Ma, Y.; Yao, X.; Zhang, L.; Ni, P.; Cheng, R.; Ye, J. *Angew. Chem. Int. Ed*. **2019**, *58*, 16548-16552.
33. Gao, P.-S.; Weng, X.-J.; Wang, Z.-H.; Zheng, C.; Sun, B.; Chen, Z.-H.; You, S.-L.; Mei, T.-S. *Angew. Chem. Int. Ed*. **2020**, *59*, 15254-15259.