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Update for oxidopyridinium cycloadditions and their synthetic applications: advances after Katritzky's pioneering studies

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Since the pioneering studies of the Katritzky group, the cycloaddition of 3-oxidopyridinium betaines has been continuously studied because (1) the multifaceted reactivity of 3-oxidopyridiniums has attracted attention from the viewpoint of physical chemistry, and (2) the production of nitrogen heterocycles with three-dimensional frameworks is crucial for natural product chemistry and pharmaceutical sciences. In this review, the development of oxidopyridinium cycloadditions is discussed. First, the results of the seminal investigations on oxidopyridinium cycloadditions are briefly presented. Subsequently, the follow-up research conducted since the pioneering studies of Katritzky and others is discussed.

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1. Introduction: early discoveries of oxidopyridinium cycloadditions

Nitrogen heterocycles (N-heterocycles) are found in natural products, drug molecules, and functional materials. Although aromatic N-heterocycles are ubiquitous, saturated non-aromatic N-heterocycles have attracted the attention of medicinal chemists because their three-dimensional structures tend to exhibit higher biological activity and target selectivity than aromatic N-heterocycles with planar two-dimensional structures.[1] Therefore, synthetic chemists have focused on the development of efficient methods to construct complex saturated N-heterocycles. The dearomative transformations of aromatic pyridines, quinolines, isoquinolines and their derivatives offer an attractive approach for saturated N-heterocycles.[2] These dearomative transformations can be categorized into two major groups: catalytic hydrogenation and N-activation followed by sequential functionalization (Fig. 1A). In addition to these methods, a different synthetic approach for saturated N-heterocycles from pyridin-3-ols has been developed by the Katritzky group and others. In this approach, pyridin-3-ols are converted into oxidopyridinium betaines, which subsequently

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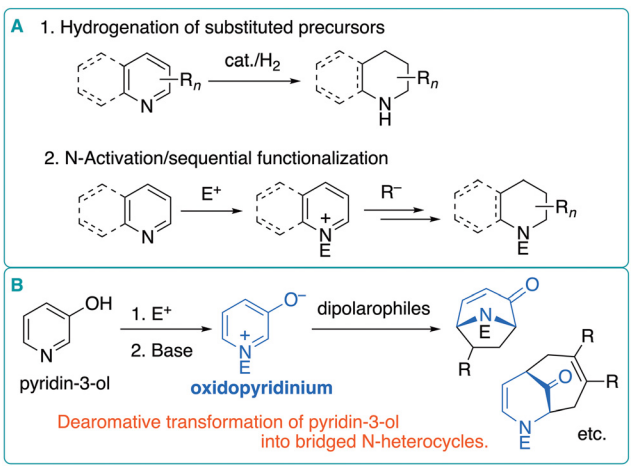

Fig. 1 (A) Dearomative transformations of pyridine and derivatives to saturated N-heterocycles. (B) Dearomative transformation of pyridin-3-ol to bridged N-heterocycles *via* 3-oxidopyridinium.

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undergo cycloaddition with an appropriate dipolarophile (Fig. 1B).[3] Because oxidopyridinium cycloadditions enable the streamlined construction of various bridged N-heterocyclic scaffolds, they have been applied to the synthesis of natural products and biologically relevant molecules. In this review, the development of oxidopyridinium cycloadditions will be discussed. First, pioneering investigations on oxidopyridinium cycloadditions will be briefly outlined and then the research after Katritzky's seminal studies will be discussed in the following sections. To date, in addition to Katritzky's review articles, only a few reviews have discussed oxidopyridinium cycloadditions,[3] and, to our knowledge, no review article has summarized recent advances in this field.[4]

Pyridin-3-ol (**1a**) has a phenol-like structure unlike pyridin-2-ol (**1b**) and pyridin-4-ol (**1c**), which mainly exist as 2-pyridone (**2b**) and 4-pyridone (**2c**), respectively (Fig. 2A).[5] In aqueous solution, **1a** is in equilibrium with its tautomeric form (**3a**). Because **3b**, one of the resonance structures of betaine **3a**, is very similar to azomethine ylides, **3a** exhibits 1,3-dipolar-cycloaddition reactivity similar to that of oxidopyrylium **4**.[6] Actually, Katritzky *et al.* reported that when **1a** was heated under reflux in a large excess of acrylonitrile or methyl acrylate, tropane-like bicyclic compounds **6** were formed regioselectively in high yield *via* (5 + 2) cycloaddition at the 2- and 6-positions of **3a** (Fig. 2B).[7,8] It was proposed that the direct reaction of betaine **3a** with electron-deficient alkenes initially formed *N*–H products **5**, which then underwent aza-Michael reaction with the alkene to afford **6**. However, an alternative pathway starting with the aza-Michael reaction of **1a** cannot be excluded. Other electron-deficient alkenes, such as *N*-phenylmaleimide, diethyl maleate, and phenyl vinyl ketone, failed to afford the corresponding products. Later, El-Abbady *et al.* reported that the reaction of **1a** with 1 equivalent of 4-phenyl-1,2,4-triazoline-3,5-dione proceeded in dioxane even at −10 °C to afford (5 + 2) cycloadduct **7** in 68% yield.[9] On the other hand, increased amounts (2 equiv.) of the triazolinone led to the formation of 1 : 2 adduct **8** in 71% yield. Moreover, the (5 + 2) cycloaddition of pyridoxine with *N*-methylmaleimide proceeded in pH 7.5 aqueous buffer at room temperature, affording the corresponding product in 63% yield.[10]

Although the scope of dipolarophiles in the cycloaddition of **1a** is severely limited, Katritzky *et al.* reported that *N*-substituted oxidopyridinium betaines underwent (5 + 2) cycloadditions with various alkenes. They prepared 1-methyl-3-oxidopyridinium **10** through the deprotonation of *N*-methylated pyridinium **9** with Amberlite IRA-401 (Fig. 3A).[11] Betaine **10** underwent 1,3-dipolar cycloaddition at the 2- and 6-positions with activated alkenes to afford cycloadducts with the tropane scaffold, which is found in diverse bioactive molecules, such as cocaine. Typically, **10** and *N*-phenylmaleimide were heated in THF/dioxane (1 : 3) to stereoselectively afford (5 + 2) cycloadduct *exo*-**11a** in 72% yield. The reaction with a large excess of acrylonitrile stereo- and regioselectively afforded cycloadduct *exo*-**11b**, albeit in low yield (17%). In contrast, the reaction with methyl acrylate produced a mixture of the corresponding *exo*- and *endo*-cycloadducts **11c** in 75% yield. Sasaki *et al.* also reported that betaine **10** underwent (5 + 2) cycloaddition with the strained cycloalkene, oxabenzonorbornadiene (**12**), to afford *exo*-**13** in 80% yield.[12] Notably, 5-methoxy-1-methyl-3-oxidopyridinium (**14**) exhibited high reactivity toward styrene in refluxing acetonitrile, affording *endo*-**15** in 94% yield.[13] The reaction with diethyl azodicarboxylate proceeded within 10 min in THF at room temperature to afford **16** in 71% yield.

The N-substituent of 3-oxidopyridinium betaines affects both the reactivity and stereoselectivity of their (5 + 2) cycloaddition substantially. The reaction of 3-oxido-1-phenylpyridinium **17** with *N*-phenylmaleimide or acrylonitrile produced (5 + 2) cycloadducts **18a** or **18b** in 81% and 76% yields, respectively, with an *exo*/*endo* selectivity of 4 : 5 (Fig. 3B).[14] The latter yield was substantially improved in relation to that of *N*-methyl analog **10** (Fig. 3A). The reaction of **17** with benzyne, derived from anthranilic acid, afforded the corresponding product **19** in 35% yield. The reaction of styrene with **17**, which is generated *in situ* from the reaction of salt **17**·HCl, afforded *endo*-**18c** in 50% yield, whereas a similar reaction with methyl acrylate produced *exo*-**18d** in 31% yield. Later, other groups reinvestigated the (5 + 2) cycloaddition of betaines **10** and **17** with 1,2-disubstituted electron-deficient alkenes.[15]

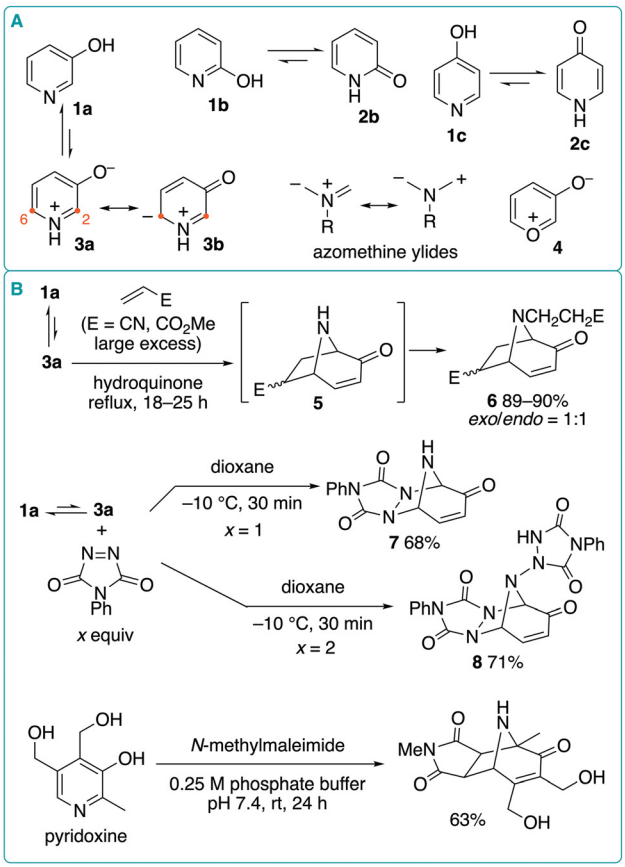

Fig. 2 (A) Structures of pyridinols. (B) (5 + 2) cycloaddition of pyridin-3-ol and pyridoxine.

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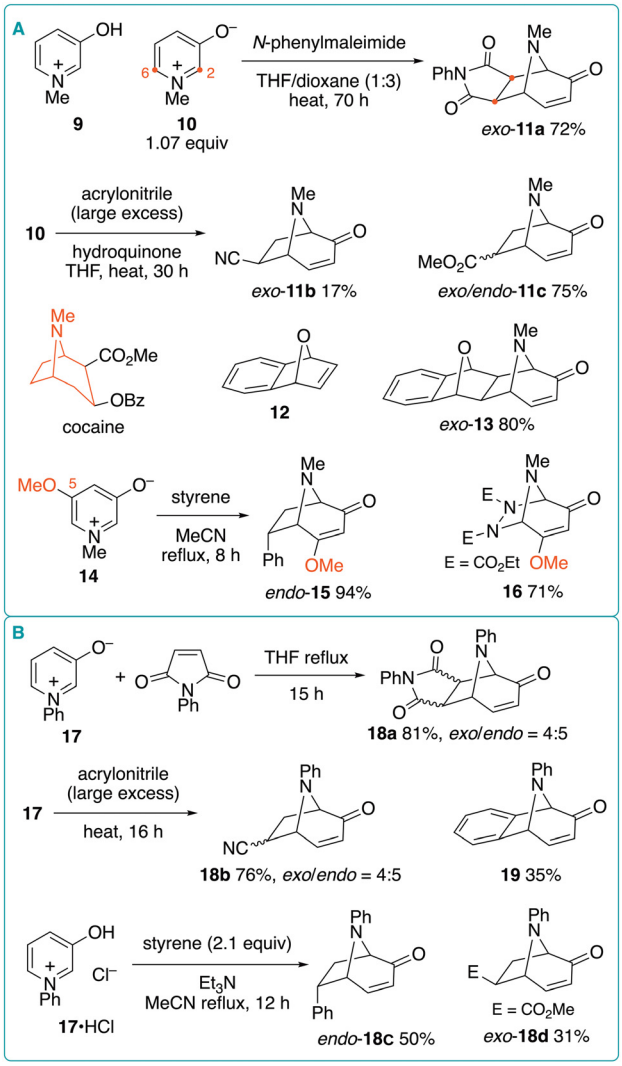

Fig. 3 (A) Preparation of *N*-methylated 3-oxidopyridinium and (5 + 2) cycloaddition of *N*-methylated 3-oxidopyridinium betaines. (B) (5 + 2) Cycloaddition of 3-oxido-1-phenylpyridinium betaine.

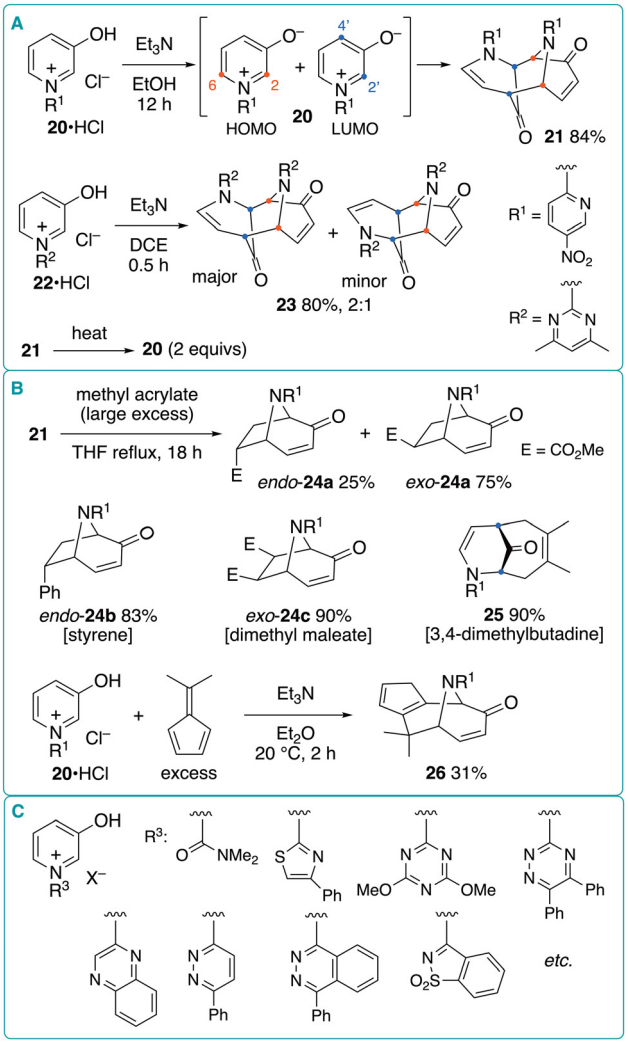

Fig. 4 (A) Dimerization of oxidopyridinium betaines bearing electron-withdrawing heteroaryl groups at the 1-position. (B) (5 + 2), (5 + 4), and (5 + 6) cycloadditions of 1-(5-nitropyridin-2-yl)-3-oxidopyridinium. (C) Oxidopyridinium precursors with diverse electron-withdrawing N-substituents.

When the N-substituent was an electron-withdrawing 5-nitropyridin-2-yl group, the corresponding betaine **20** underwent facile dimerization in such a way that the 2- and 6-positions of one betaine (HOMO) and the 2′- and 4′-positions of the other betaine (LUMO) are involved, selectively producing **21** in 84% yield (Fig. 4A).[16] Similarly, pyridinium **22**·HCl, with a 4,6-dimethylpyrimidin-2-yl group at the 1-position, afforded the corresponding dimer **23** as a mixture of regioisomers (2 : 1) in 80% yield. Dimer **21** underwent retro-dimerization to generate two equivalents of betaine **20** at a higher temperature; (5 + 2) cycloaddition with dipolarophiles was carried out using **21** as the oxidopyridinium precursor in the absence of a base.

Dimer **21** and excess methyl acrylate were heated in THF to afford *endo*-**24a** and *exo*-**24a** in 25% and 75% yields, respectively (Fig. 4B).[17] Similarly, the reaction with styrene selectively afforded *endo*-**24b** in 83% yield. The reaction with dimethyl maleate exclusively produced *exo*-**24c** in 90% yield, indicating that *cis*/*trans* isomerization of both maleate and cycloadduct was suppressed in the absence of a base. Moreover, the reaction with 2,3-dimethyl-1,3-butadiene afforded (5 + 4) cycloadduct **25** in 90% yield as a result of the cycloaddition at the 2- and 4-positions of betaine **20**. This chemoselectivity can be rationalized as the cycloaddition proceeding *via* the interaction between the LUMO of betaine **20** and the HOMO of butadiene. In the presence of excess 6,6-dimethylfulvene, pyridinium salt **20**·HCl was treated with triethylamine at 20 °C in diethyl ether for 2 h, affording (5 + 6) cycloadduct **26**, albeit in moderate yield. In addition, 1-(4,6-dimethylpyrimidin-2-yl)-3-oxidopyridinium exhibited similar cycloaddition reactivities toward alkenes, 1,3-dienes, and fulvenes. Accordingly, Katritzky *et al.* demonstrated that oxidopyridinium betaines bearing an electron-withdrawing heteroaryl group at the 1-position are highly versatile 1,3-dipolar reagents. Moreover, the cycloaddition reac-

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tivities of 3-oxidopyridinium betaines with diverse electron-withdrawing N-substituents were investigated by the Katritzky group and others (Fig. 4C).[18]

Katritzky *et al.* introduced frontier molecular orbital theory to explain the experimentally observed stereo-, regio-, and peri-selectivities of oxidopyridinium cycloadditions.[19] Later, several groups employed modern theoretical calculations based on density functional theory (DFT).[20] Although the (5 + 2) cycloaddition of 1-methyl-3-oxidopyridinium with C70 fullerene has yet to be realized experimentally, it was theoretically investigated.[21]

Katritzky *et al.* reported the (3 + 2) cycloaddition of 3-oxidopyridinium betaines with haloketenes, in which the oxido moiety and C4 of the betaines were involved (Fig. 5).[22] The reaction of **17**·HCl with dichloroacetyl chloride in the presence of an excess of triethylamine generated oxidopyridinium **17** and dichloroketene **27a**, whose (3 + 2) cycloaddition produced intermediate **28**. Subsequent dehydrochlorination afforded the final product **29** in 57% yield. The yield of *N*-(4,6-dimethylpyrimidin-2-yl)-substituted analog **30** was higher (85%) than that of **29**. Although the reaction with bromoketene **27b** instead of **27a** produced regioisomeric mixtures (*e.g.*, **31** and **32**), the (3 + 2) cycloaddition of 1-(*p*-chlorostyryl)-3-oxidopyridinium with **27b** selectively afforded **33** in 61% yield.

Although less extensively investigated, oxidoisoquinolinium betaines have also been used for (5 + 2) cycloaddition. Katritzky *et al.* reported that the reaction of 2-methyl-4-oxidoisoquinolinium (**34**) with acrylonitrile afforded (5 + 2) cycloadduct *endo*-**35a** in 18% yield (Fig. 6A).[23] Interestingly, the observed stereoselectivity was opposite to that observed for the formation of *exo*-**11b** (Fig. 3A). The reaction with methyl acrylate afforded *exo*- and *endo*-**35b** in 13% and 10% yields, respectively. This loss of stereoselectivity was similar to that observed in the reaction of **10** with methyl acrylate (Fig. 3A). Moreover, the reaction of *N*-(2,4-dinitrophenyl)-substituted oxidoisoquinolinium **36** with *N*-phenylmaleimide exclusively produced *endo*-**37a** in 72% yield.[24] In striking contrast, the reaction with acrylonitrile afforded *endo*-**37b** in a low yield. Katritzky *et al.* transformed oxidopyridinium dimer **23**, with *N*-(4,6-dimethylpyrimidin-2-yl) group, into mixed dimer **38** (Fig. 6B).[25] Upon heating, **38** underwent retrodimerization to generate 4-oxidoisoquinolinium **39**, which could be trapped by *N*-phenylmaleimide; however, the reaction conditions and yield of *exo*-**40** were not reported. The (5 + 4) cycloaddition of 3-hydroxyquinolinium-derived betaine with 1,3-butadienes was also described; however, neither details of the reaction conditions nor product characterization data were provided (Fig. 6C).[26]

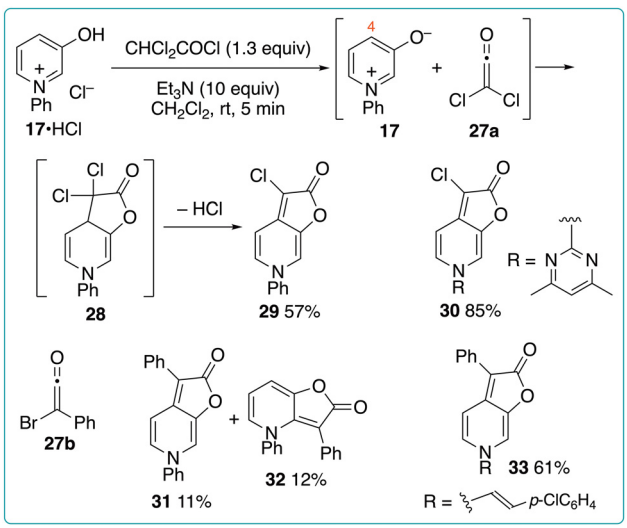

Fig. 5 (3 + 2) cycloaddition of 3-oxidopyridinium betaines with haloketenes.

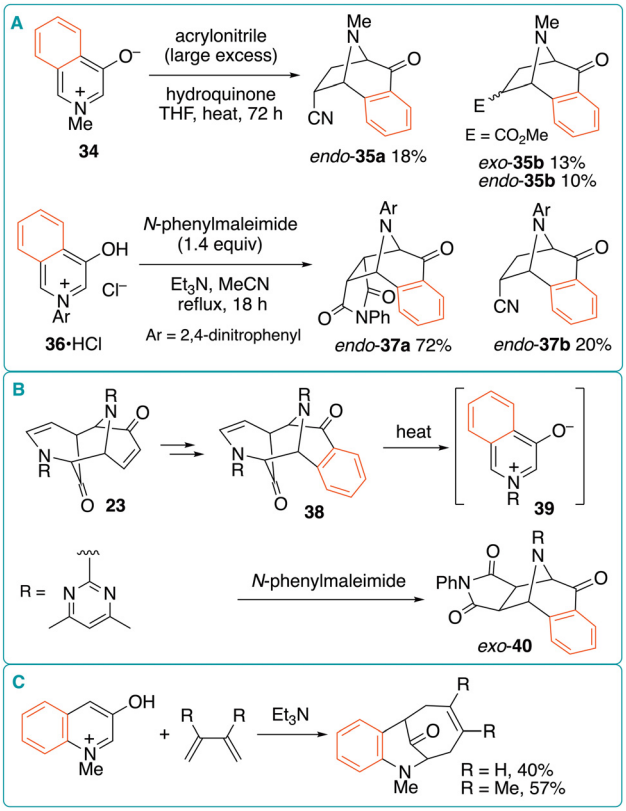

Fig. 6 (A) (5 + 2) cycloaddition of 2-methyl- and 2-(2,4-dinitrophenyl)-4-oxidoisoquinoliniums. (B) Generation of 2-(4,6-dimethylpyrimidin-2-yl)-4-oxidoisoquinolinium and its (5 + 2) cycloaddition with *N*-phenylmaleimide. (C) (5 + 4) cycloaddition of 1-methyl-3-oxidoquinolinium with 1,3-butadienes.

In this section, the early discoveries and development of oxidopyridinium cycloaddition have been briefly reviewed. In seminal studies by the Katritzky group, the divergent 1,3-dipolar-cycloaddition reactivity of oxidopyridinium betaines was disclosed. However, because these studies focused on establishing the reaction profiles of oxidopyridinium betaines, their applications in the synthesis of bioactive compounds and natural products lagged. In the following section, advances in the oxidopyridinium cycloadditions after the pioneering discoveries by Katritzky and others are discussed.

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2. Advances in (5 + 2) cycloaddition

2.1 Methodological developments

2.1.1 Intramolecular (5 + 2) cycloaddition. Connecting an oxidopyridinium betaine with a dipolarophile renders the cycloaddition entropically favorable. Such an intramolecular cycloaddition is an effective strategy for constructing complex polycyclic frameworks in a regio- and stereoselective manner. Sammes *et al.* pioneered the development of intramolecular oxidopyridinium (5 + 2) cycloadditions.[27] They heated 1-(4-pentenyl)-3-oxidopyridinium (**41**) in acetonitrile at 140 °C for 24 h to selectively obtain tricyclic product **42** in a moderate yield of 32% (Fig. 7A). In the presence of *N*-phenylmaleimide, heating **41** at 80 °C exclusively produced intermolecular cycloadduct **43**. In contrast, when 1-methyl-3-oxidopyridinium **44**, bearing a 4-pentenyl group at the 2-position, was heated at 160 °C, **45** was obtained in a considerably higher yield of 91%. Because these intramolecular reactions require high temperatures owing to their slow rates, Sammes *et al.* designed oxidopyridinium **46**, featuring a phenylene-tethered alkene.[28] Heating **46** in benzene at 80 °C for 20 h quantitatively afforded **47**. The two methyl substituents on the phenylene moiety are imperative because no reaction occurred in their absence. Joshi and Ravindranathan reported the reaction of oxidopyridinium betaines with activated alkenes connected by shorter tethers;[29] thus, heating **48** in xylene under reflux afforded **49** in 60% yield. Interestingly, the tetracyclic product **51** was obtained in 48% yield from betaine **50**.

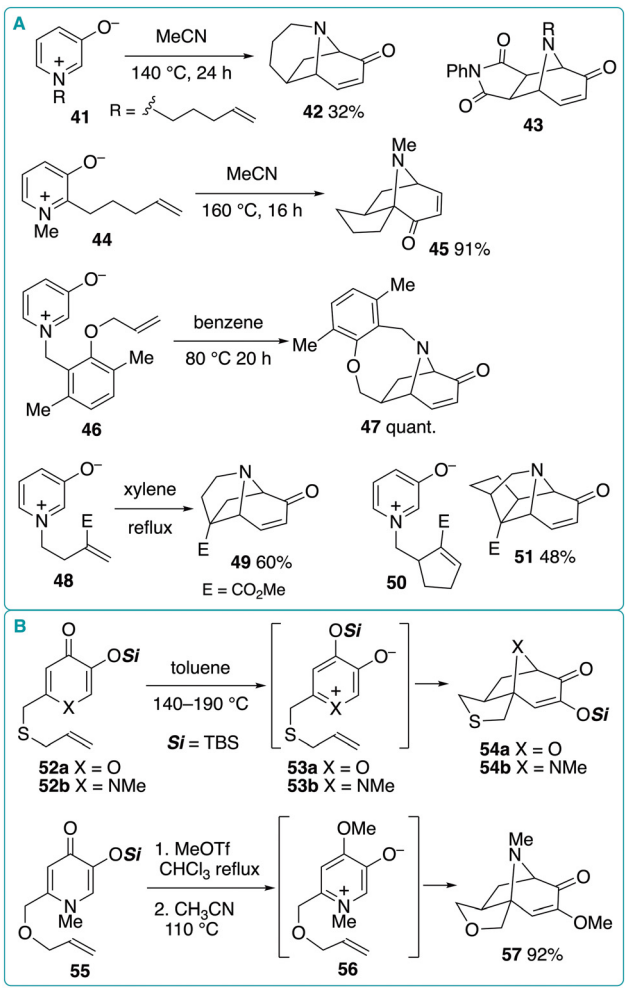

Fig. 7 (A) Intramolecular (5 + 2) cycloaddition of oxidopyridinium betaines with a tethered alkene. (B) Intramolecular (5 + 2) cycloaddition of oxidopyridinium betaine derived from kojic acid.

Mascareñas *et al.* investigated the intramolecular (5 + 2) cycloaddition of precursors **52**, which were prepared from commercially available kojic acid (Fig. 7B).[30] Although 4-pyrone **52a**, with a sulfur-tethered alkene, was heated in toluene at 140 °C to afford the desired product **54a** *via* 4-siloxy-3-oxidopyrylium **53a**, similar 4-pyridone **52b** failed to produce the corresponding product **54b**. After searching for different reaction conditions, it was found that the treatment of **55** with methyl triflate in chloroform under reflux followed by heating in acetonitrile at 110 °C generated 4-silyloxy-3-oxidopyridinium **56**, which underwent the smooth (5 + 2) cycloaddition to afford **57** in 92% yield.

2.1.2 Asymmetric (5 + 2) cycloaddition. Koizumi *et al.* reported that tolyl vinyl sulfone is an effective dipolarophile for the (5 + 2) cycloaddition with oxidopyridinium **10**.[31] Accordingly, they investigated optically active sulfoxide (*R*)-**58** (Fig. 8A).[32] The reaction of **10** with (*R*)-**58** was performed in THF at 90 °C for 4 days, affording the expected (5 + 2) cycloadduct as three diastereomers (*exo*-**59a**, 36%; *exo*-**59b**, 7%; *endo*-**59b**, 29%). It was proposed that the cycloaddition proceeded from the less-hindered lone pair side of (*R*)-**58** in the *s*-trans form. However, **10** underwent cycloaddition in both *exo*- and *endo*-transition states to produce *exo*-**59a** and *endo*-**59b**, respectively. In a related study, Aggarwal *et al.* investigated the (5 + 2) cycloaddition of 1-benzyl-3-oxidopyridinium betaines with racemic 2-methylene-1,3-dithiolane 1,3-dioxide **61** (Fig. 8B).[33] *N*-Benzylated pyridinium salt **60**·HCl and **61** were treated with triethylamine in CH_2Cl_2 at room temperature for 18 h, affording **62** in 79% yield with 2.3 : 1 regioselectivity. Among the four possible transition states, TS2 and TS4 are disfavored because of the steric repulsion between one sulfoxide moiety and the C5–H or oxido moiety, whereas TS1 and TS2 are comparably favored, leading to the formation of the major and minor regioisomers of **62**, respectively. Similarly, the use of 2-methylated precursor **63a**·HCl resulted in the formation of regioisomers of **64a** with an improved selectivity of 8 : 1, albeit in low yield (25%). In contrast, three isomers of **64b** were obtained in a 5.5 : 4.4 : 1 ratio from 6-methylated precursor **63b**·HCl. In addition, the diastereoselective (5 + 2) cycloaddition was studied using an optically active acrylate derived from (*S*)-methyl lactate (see Section 2.2.1).

Oxidopyridinium betaine **66**, bearing a chiral auxiliary, was prepared by the Curtis group (Fig. 9).[34] Starting from 2-furyl phenyl ketone, titanium-mediated condensation with (*S*)-phenethylamine was followed by the reduction of the resultant imine to afford amine **65** in high yield. The subsequent treatment of **65** with Br_2 in aqueous THF produced the desired oxi-

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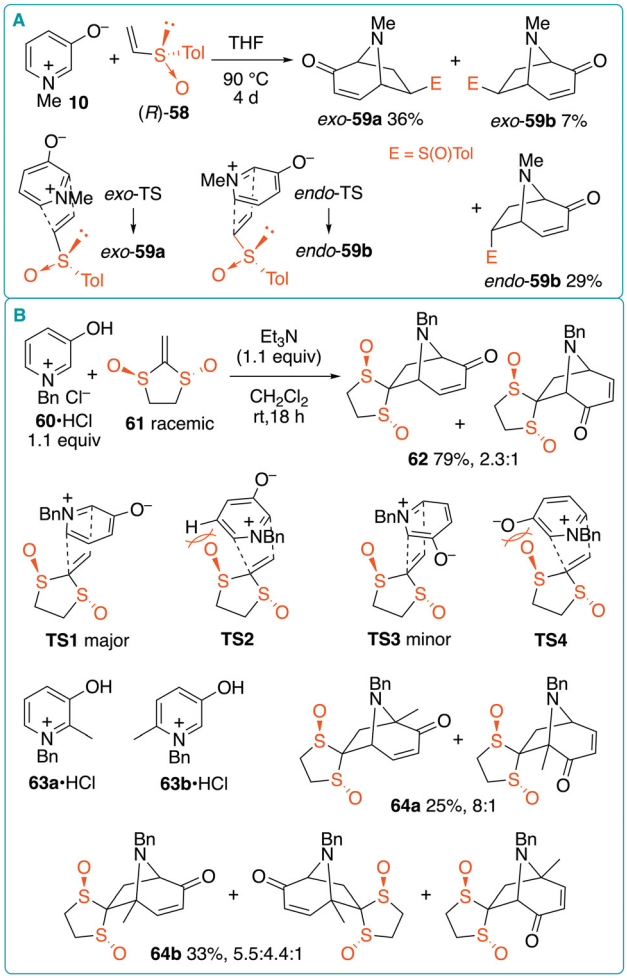

Fig. 8 (A) (5 + 2) Cycloaddition of 1-methyl-3-oxidopyridinium with optically active vinyl sulfone. (B) (5 + 2) cycloaddition of 1-benzyl-3-oxidopyridiniums with racemic 2-methylene-1,3-dithiolane 1,3-dioxide.

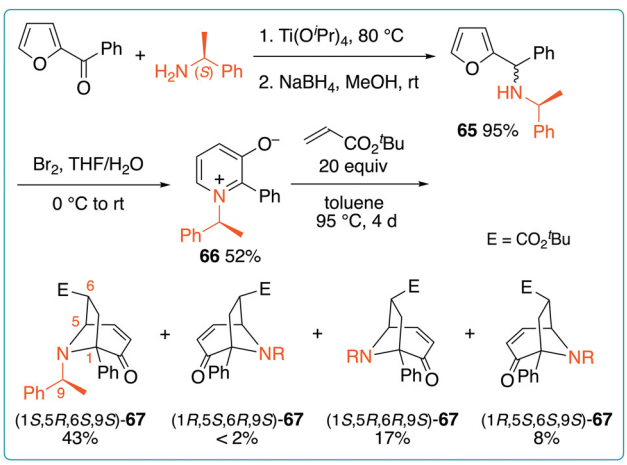

Fig. 9 Preparation of an oxidopyridinium betaine, bearing a chiral auxiliary, and its (5 + 2) cycloaddition with *tert*-butyl acrylate.

dopyridinium **66** in 52% yield. Its (5 + 2) cycloaddition with *tert*-butyl acrylate was conducted in toluene at 95 °C for 4 days, affording four diastereomers of the expected cycloadduct **67**. Among these, (1*S*,5*R*,6*S*,9*S*)-**67** was obtained as the major diastereomer in 43% yield.

Jørgensen *et al.* developed the catalytic enantioselective (5 + 2) cycloaddition using a proline-derived organocatalyst (Fig. 10).[35] A challenge with this method is that oxidopyridinium and chiral dienamine should be simultaneously generated *in situ*. To this end, the authors used dimer **23** as the oxidopyridinium precursor in the presence of catalytic amounts (20 mol%) of organocatalyst **69**, pyridinium salt **22**·HCl, and diphenyl phosphate (DPP). The reaction with crotonaldehyde **68** quantitatively afforded *endo*-**70** with 96% enatiomeric excess (ee) and high *endo*/*exo*- and regioisomeric ratios (Fig. 10A). This method has a broad scope for α,β-unsaturated aldehydes and oxidopyridinium betaines; however, the yield and selectivity altered depending on the substrates (Fig. 10B).

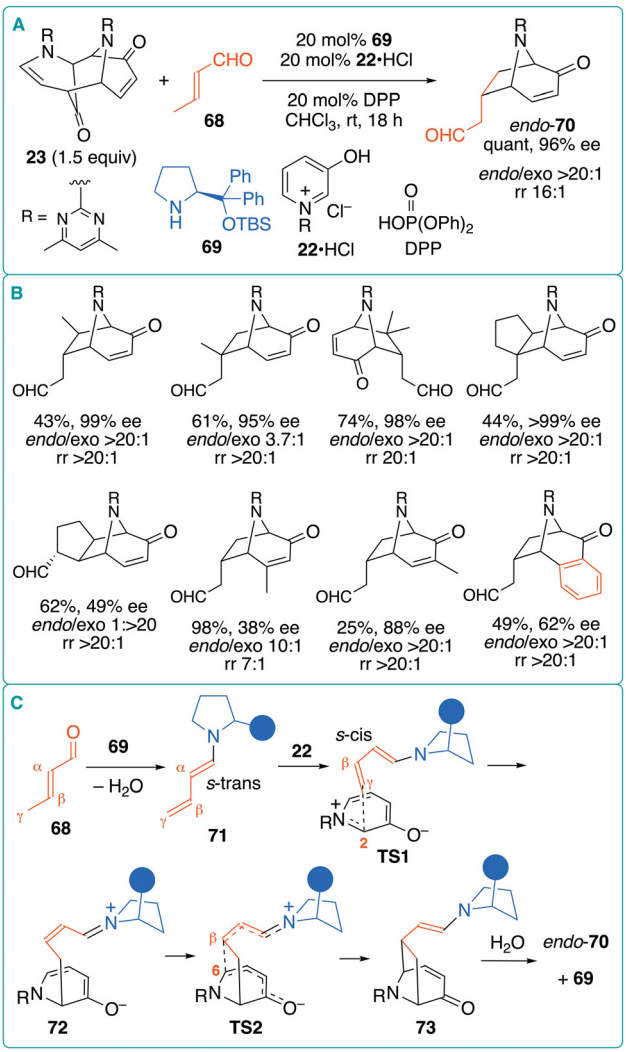

Fig. 10 (A) Catalytic enantioselective (5 + 2) cycloaddition with enals using proline-based organocatalyst. (B) Reaction scope. (C) Proposed mechanism.

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Based on the observed stereoselectivity and the results of DFT calculations, a stepwise mechanism was proposed, as outlined in Fig. 10C. The condensation of enal **68** with catalyst **69** generates dienamine **71**. The *s-cis* form of nucleophilic dienamine **71** attacks **22** such that the C(2)–C(γ) bond is formed *via* TS1. The resultant intermediate **72** undergoes ring closure *via* TS2, where a second C–C bond is formed between C(6) and C(β) to produce **73**. The subsequent hydrolysis of **73** affords *endo*-**70** with the restoration of **69**.

2.1.3 Other methods. After the pioneering studies of the Katritzky group, researchers conducted investigations to improve the oxidopyridinium (5 + 2) cycloadditions. Katritzky *et al.* reported that neither pyridine *N*-oxide **74** nor 1-amino-3-hydroxypyridinium **75** could be used for the (5 + 2) cycloaddition (Fig. 11A).[18a] In contrast, oxidopyridinium **76**, bearing an *N*-imino group, reacted with *N*-phenylmaleimide to afford *exo*/*endo*-**77**. Later, Chen and Yang reported that 3-hydroxy-5-methoxypyridinium *N*-imine **79** underwent (5 + 2) cycloaddition with ethyl propiolate.[36] The treatment of 5-methoxypyridin-3-ol with *O*-mesitylsulfonylhydroxylamine afforded 1-amino-5-methoxypyridin-3-ol (**78**), which was quantitatively converted into **79** using Amberlite IRA-410. The reaction of **79** with ethyl propiolate in chloroform under reflux afforded **80** in 30% yield.

Chavignon *et al.* reported that the reaction of 1-benzyl-3-oxidopyridinium (**60**) with allyl alcohol produced tricyclic product **82** in 70% yield, *via* the intramolecular oxy-Michael addition of (5 + 2) cycloadduct **81** (Fig. 11B).[37] The authors also established a three-component reaction of **60**, ethanol, and acrolein, which diastereoselectively afforded similar tricyclic product **83**, albeit in moderate yield (35%).

Katritzky *et al.* achieved the (5 + 2) cycloaddition of 1-phenyl-3-oxidopyridinium with benzyne, albeit in moderate yield (Fig. 3B).[14a] Moreover, the reaction of 1-methyl-3-oxidopyridinium with benzyne produced a 1 : 2 product. In this study, anthranilic acid was used as the benzyne precursor. Shi *et al.* reported that the use of Kobayashi reagent **84** as the benzyne precursor improved the yield of the (5 + 2) cycloadducts (Fig. 12A).[38] In the presence of CsF (2.6 equiv.), 1-benzyl-3-oxidopyridinium (**60**) and **84** were stirred in acetonitrile at 17 °C for 18 h, affording the desired (5 + 2) cycloadduct **85** in 78% yield. This method allowed the use of various 1-benzylated oxidopyridinium betaines substituted with methyl, chloro, and hydroxymethyl groups. Moreover, aryl and pyridyl groups as well as various alkyl groups were tolerated as N-substituents. Symmetrically substituted benzyne could be used; however, unsymmetrical benzynes produced regioisomers.

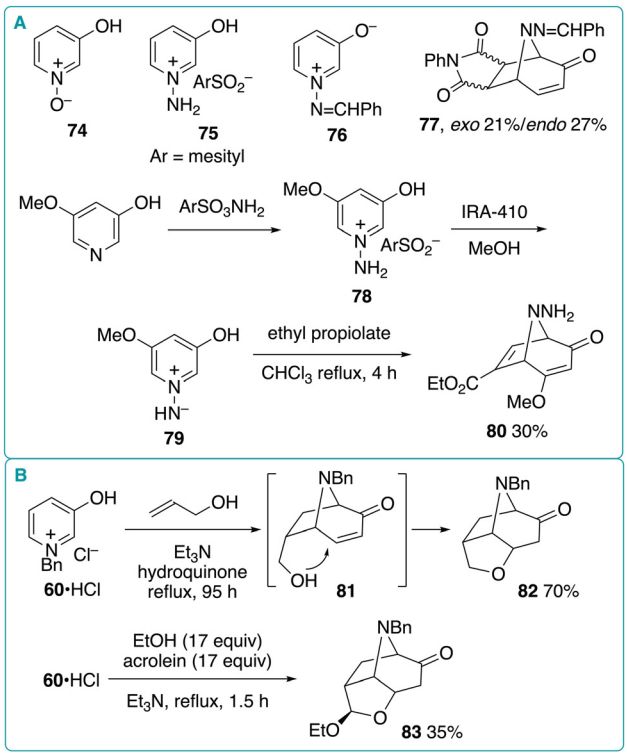

Fig. 11 (A) (5 + 2) cycloaddition of 3-hydroxy-5-methoxypyridinium *N*-imine with *N*-phenylmaleimide. (B) Sequential (5 + 2) cycloaddition and intramolecular oxy-Michael addition.

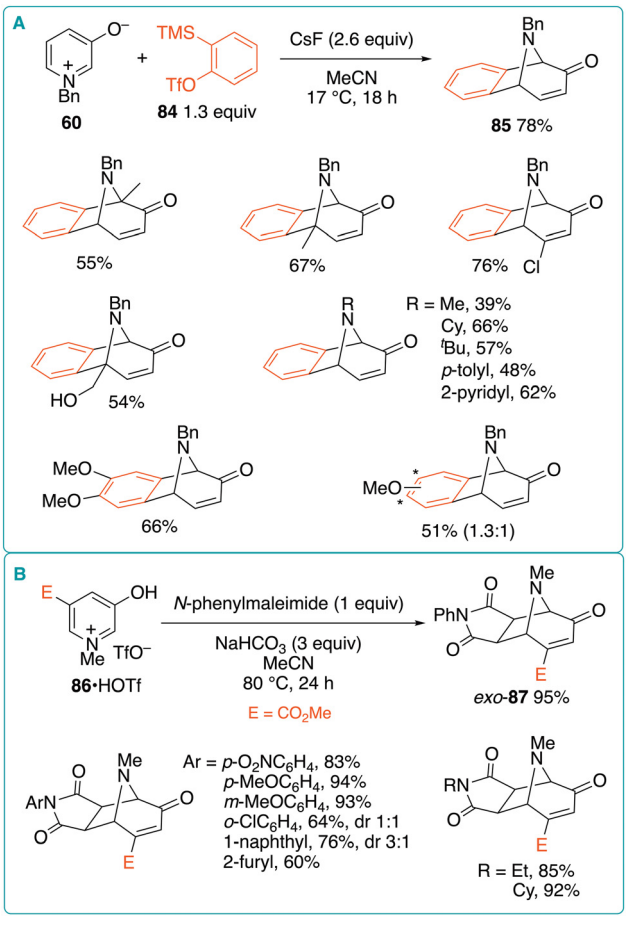

Fig. 12 (A) (5 + 2) cycloaddition of 1-benzyl-3-oxidopyridinium with benzyne generated using the Kobayashi reagent. (B) (5 + 2) cycloaddition of 1-methyl-4-methoxycarbonyl-3-oxidopyridinium with maleimides.

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Because the use of 5-methoxycarbonyl-1-methyl-3-oxidopyridinium significantly improved the (5 + 4) cycloaddition efficiency (see Section 3.1), Wang *et al.* optimized the reaction of pyridinium salt **86**·HOTf, derived from methyl 5-hydroxynicotinate, with *N*-phenylmaleimide to improve the reaction conditions (Fig. 12B).[39] They established the optimal conditions involved the use of $NaHCO_3$ as the base in acetonitrile at 80 °C. A 1 : 1 stoichiometric reaction exclusively afforded the desired product *exo*-**87** in excellent yield (95%). Various *N*-arylmaleimides and *N*-alkylmaleimides were used as dipolarophiles; however, the reaction with *ortho*-substituted phenyl and 1-naphthyl derivatives produced diastereoisomers owing to their axial chirality. Several *N*-alkyl and ester alkyl groups of the oxidopyridinium betaines were also well tolerated.

Hanna *et al.* developed a solid-phase (5 + 2) cycloaddition using resin-supported acrylate or oxidopyridinium betaine (Fig. 13).[40] The reaction of resin-supported acrylate **88** with 1-benzyl-3-oxidopyridinium (**60**, 6 equiv.) produced **89**. The acidic cleavage from the resin support and subsequent methylation using diazomethane afforded the final product **90** as a mixture of regio- and stereoisomers in 45% overall yield. In contrast, the reaction of resin-supported oxidopyridinium **91** with phenyl vinyl sulfone and the cleavage from the resin support of the resultant cycloadduct **92** exclusively afforded the final product **93** after the benzoylation of the bridged nitrogen atom. However, although **92** is the common intermediate, methylation and vinylation, rather than benzoylation, produced regioisomeric mixtures.

The (5 + 2) cycloaddition using ultrasound irradiation conditions was reported by Hagar *et al.* (Fig. 14A).[41] They investigated the reaction of *N*-propargylpyridinium chloride **94**·HCl and ethyl propiolate in the presence of hydroquinone and triethylamine at 40 °C with ultrasonic irradiation for 6 h, which afforded regioisomeric (5 + 2) cycloadducts **95a** and **95b** in 32% and 27% yields, respectively. Additionally, (3 + 2) cycloaddition product **96** was obtained in 11% yield. By substituting diphenylacetylene for ethyl propiolate, (5 + 2) cycloadduct **97** was obtained in 60% yield along with (3 + 2) cycloadduct **98** (14% yield). However, because no results from conventional heating experiments were reported, the efficacy of the ultrasound irradiation conditions is unclear. No comment was made regarding the role played by the *N*-propargyl group.

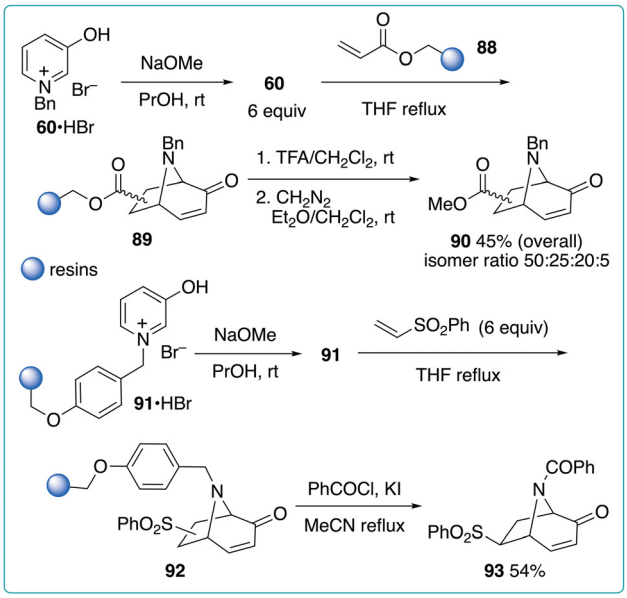

Fig. 13 Solid-phase (5 + 2) cycloaddition using resin-supported substrates.

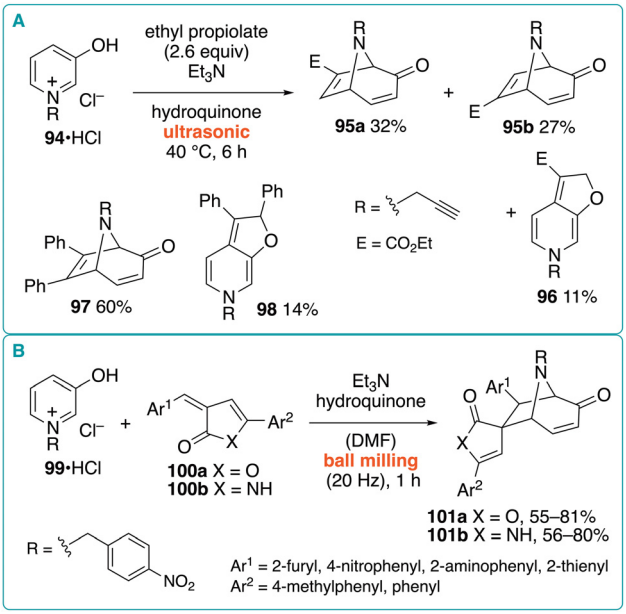

Fig. 14 (A) (5 + 2) cycloaddition upon ultrasonic irradiation. (B) (5 + 2) cycloaddition using the ball-milling method.

Aboelnaga and Abbady reported the (5 + 2) cycloaddition of oxidopyridinium betaine **99** with benzylidenefuranones **100a** or benzylidenepyrrolinones **100b** using the ball-milling method (Fig. 14B).[42] In the presence of triethylamine and hydroquinone, *N*-(*p*-nitrobenzyl)pyridinium salt **99**·HCl and furanones **100a** (1 : 1) were allowed to react under ball-milling conditions (20 Hz, stainless-steel vial) for 1 h to afford (5 + 2) cycloadducts **101a** as single isomers in 55–81% yield. Notably, chromatographic purification was not required. Although *N*,*N*-dimethylformamide (DMF) was used as the solvent, a similar ball-milling reaction using pyrrolinones **100b** afforded the corresponding products **101b** in 56–80% yield. Because these results were not compared with those of conventional methods, the efficacy of the ball-milling conditions has not been clarified.

2.1.4 Transition-metal-mediated annulations. Transition-metal-mediated annulations involving carbenoid intermediates are efficient methods to generate 4-oxidoisoquinolinium intermediates from acyclic starting materials. In the pioneering study by Padwa *et al.*, the Rh-catalyzed reaction of α-diazo ester **102**, bearing an imine moiety, with *N*-phenylmaleimide

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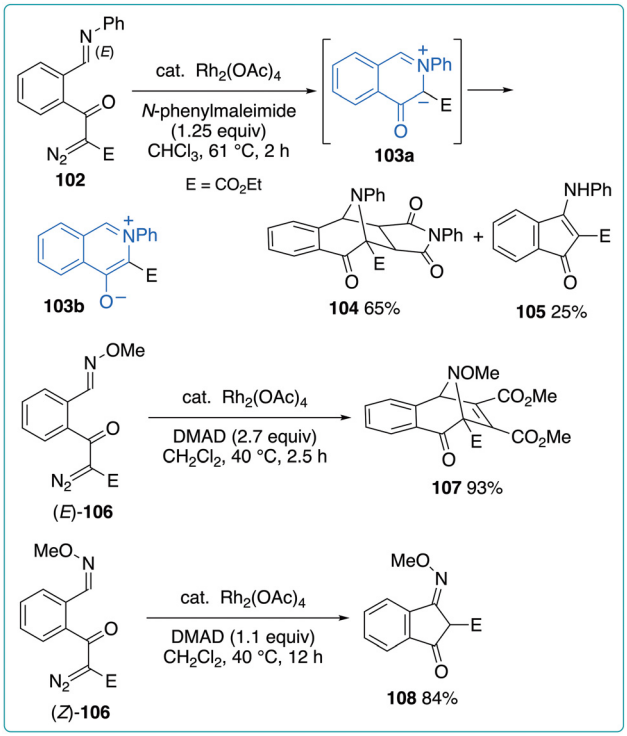

Fig. 15 Rh-catalyzed reaction of α-diazo esters bearing a pendant imine with *N*-phenylmaleimide and DMAD.

afforded cycloadduct **104** and indenone **105** in 65% and 25% yields, respectively (Fig. 15).[43] The authors proposed that rhodium-catalyzed decomposition of **102** generated azomethine ylide **103a**, which is a resonance form of 4-oxidoisoquinolinium **103b**. The subsequent (5 + 2) cycloaddition produced **104**; however, neither the catalyst loading nor the stereoselectivity for the formation of **104** was described. In addition to *N*-phenylimine **102**, the corresponding (*E*)- and (*Z*)-oximes **106** were separately used as the carbenoid precursors. The reaction of (*E*)-**106** with dimethyl acetylenedicarboxylate (DMAD) afforded (5 + 2) cycloadduct **107** in 93% yield, whereas indane-1,3-dione oxime **108** was obtained from (*Z*)-**106**, even in the presence of DMAD.

Shin *et al.* reported that when *o*-alkynylphenyl nitrone **109**, with a pendant alkene, was heated in the presence of 2 mol% $AuCl_3$ at 70 °C in nitromethane for 1 h, tetracyclic product **113** was obtained in 82% yield (Fig. 16).[44] It was proposed that the 6-*exo*-cyclization of the nitrone oxygen to the Au-activated alkyne moiety generates vinyl gold intermediate **110**, which undergoes internal redox isomerization to generate α-oxo gold carbene complex **111**. The subsequent attack of the imine nitrogen on the gold carbene moiety in **111** generates an Au complex of a 4-oxidoisoquinolinium (**112**). The final intramolecular (5 + 2) cycloaddition of **112** affords **113**. This reaction tolerated both the internal and terminal substituents on the pendant alkene moiety. Alkynes could also be used as dipolarophiles, with **114** being obtained in high yield. A tosylamide was compatible as a tether between the alkyne and

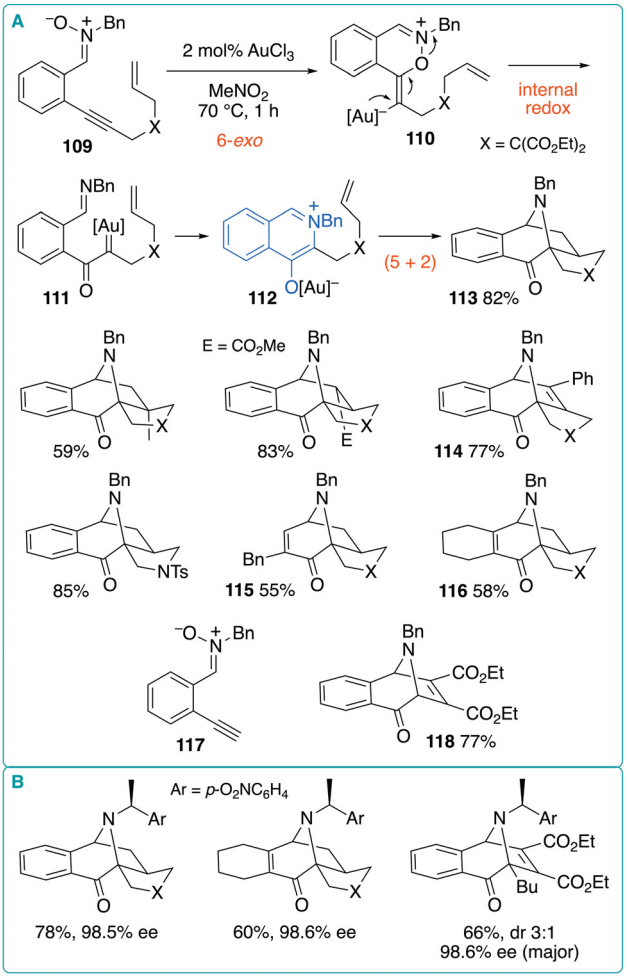

Fig. 16 (A) Au-catalyzed cycloisomerization of *o*-alkynylphenyl nitrones bearing a pendant alkene. (B) Diastereoselective cycloisomerization using a chiral auxiliary.

alkene moieties; however, the ether-tethered substrate underwent decomposition. The phenylene moiety between the nitrone and alkyne moieties was not essential as shown by the reactions of alkenyl nitrones, which afforded similar products **115** and **116** in moderate yields. Moreover, the intermolecular reaction of nitrone **117** with diethyl acetylenedicarboxylate produced the corresponding cycloadduct **118** in 77% yield. This method was extended to an asymmetric cycloaddition using similar substrates bearing a chiral auxiliary on the nitrone moiety.[45] Representative examples are shown in Fig. 16B. Intramolecular reactions afforded single diastereomers with a high enantiomeric excess >95%. In contrast, the intermolecular reactions with diethyl acetylenedicarboxylate produced diastereomeric mixtures.

The formation of 4-oxidoisoquinolinium intermediates and its transition-metal complexes was confirmed by Jia, Li, and their coworkers (Fig. 17).[46] The stoichiometric reaction of *o*-ethynylphenyl nitrone **119** with $[Cp^*IrCl_2]_2$ in acetonitrile at 0–55 °C afforded the O-bound iridium complex of 4-oxidoisoqunolinium (**120**) in 84% yield. Notably, its structure was

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unambiguously confirmed by X-ray crystallography. A similar ruthenium complex was also obtained from **119** and [(*p*-cymene)$RuCl_2$]$_2$. Moreover, the catalytic isomerization of **119** also occurred in the presence of 1 mol% [Cp*$IrCl_2$]$_2$ in CH_2Cl_2 at room temperature, affording 4-oxidoisoquinolinium **121** in 87% yield. The catalytically generated **121** was further subjected to the (5 + 2) cycloaddition with *N*-methylmaleimide at room temperature for 4 h to afford *endo*-cycloadduct **122** in 85% yield. Similarly, the reaction of **121** with other electron-deficient alkenes such as ethyl acrylate and diethyl fumalate/maleate afforded the corresponding (5 + 2) cycloadducts with varied stereoselectivity. The intermolecular cycloaddition of *o*-alkynylphenyl nitrones with electron-deficient alkenes was also catalyzed by $Pd(OAc)_2$ (10 mol%) to afford (5 + 2) cycloadducts in good yields.[47]

The catalytic enantioselective reaction of *o*-ethynylphenyl nitrones with alkylideneindolinones was reported by Feng *et al.* (Fig. 18).[48] They developed a cooperative catalytic system involving a Pd catalyst for the cycloisomerization of *o*-ethynylphenyl nitrones and a chiral Co catalyst as a Lewis-acid activator of alkylideneindolinones. Typically, in the presence of catalysts (10 mol% each), the reaction of nitrone **123** and indolinone **124** was performed in CH_2Cl_2 at −10 °C for 8 h, affording **125** in 78% yield, with diastereomeric ratio of >19 : 1 and 95% enantiomeric excess. In the absence of a Co catalyst, **123** was converted into 4-oxidoisoquinolinium **126**, which was then converted into isolable methyl ether **127**. According to the X-ray analysis of the $CoL(THF)_2$ complex and the mechanism underlying the formation of **125**, the observed high selectivity was ascribed to the favored TS. This method can be applied to a variety of substrates without lowering the enantioselectivity. However, diminished diastereomeric ratios were observed when nitrones and indolinones bearing substituents on their aromatic rings were used (*e.g.*, **128** and **129**). In contrast, aryl substituents on the nitrone moiety had no impact on the stereoselectivity.

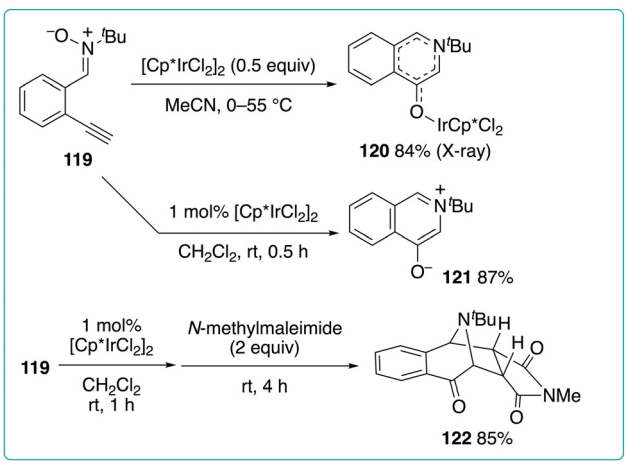

Fig. 17 Ir-mediated cycloisomerization of *o*-ethynylphenyl nitrone leading to 4-oxidoisoquinolinium and its O-bound iridium complex.

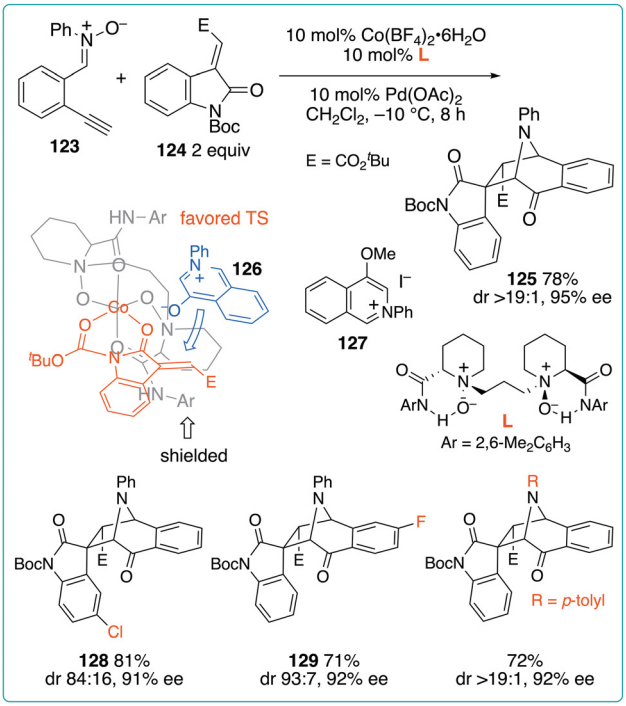

Fig. 18 Enantioselective reaction of *o*-ethynylphenyl nitrones with alkylideneindolinones using a Pd/Co cooperative catalyst system.

2.2 Applications of (5 + 2) cycloaddition

2.2.1 Natural product syntheses. The transformation of the oxidopyridinium (5 + 2) cycloadducts into tropolones was pioneered by the Katritzky group.[11a] Subsequently, Tamura *et al.* reported the synthesis of stipitatic acid and hinokitiol using the Katritzky method (Fig. 19).[49] The (5 + 2) cycloaddition of 1-methyl-5-methoxy-3-oxidopyridinium (**14**) with ethyl propiolate in THF under reflux afforded **130** in 87% yield. After the

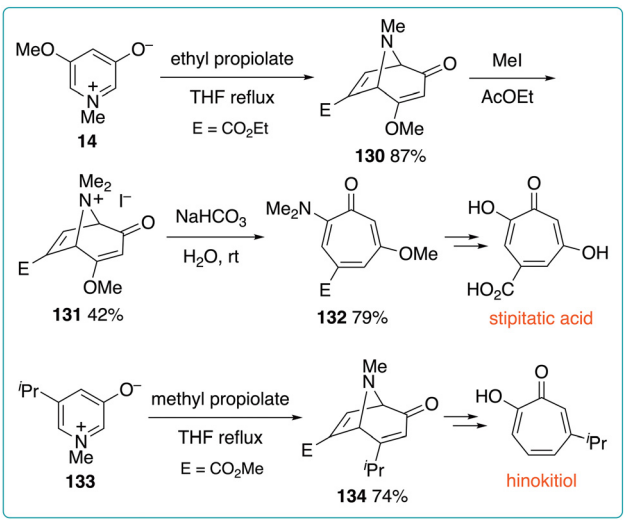

Fig. 19 Synthesis of stipitatic acid and hinokitiol *via* oxidopyridinium (5 + 2) cycloaddition with propiolates.

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methylation of **130** with iodomethane, the ring opening of resultant **131** proceeded in $NaHCO_3$ solution at room temperature to produce 2-dimethylamino-6-methoxytropone-4-carboxylate **132**. The subsequent functional group interconversions of **132** (three steps) afforded stipitatic acid. Similarly, hinokitiol was synthesized from 5-isopropyl-1-methyl-3-oxidopyridinium (**133**) *via* (5 + 2) cycloadduct **134**.

The total synthesis of a natural antiglaucoma compound, bao gong teng A, was achieved by Jung *et al.* (Fig. 20A).[50] The authors performed the (5 + 2) cycloaddition of 1-benzyl-3-oxidopyridium (**60**) with acrylonitrile to obtain *endo*- and *exo*-**135**. The desired isomer, *exo*-**135**, which was isolated in 54% yield, was hydrogenated using palladium black to afford **136** in 79% yield. Subsequent ketone reduction was performed using $NaBH_4$ to obtain the desired alcohol **137** in 56% yield along with its epimer (3% yield). Next, the cyano moiety of **137** was transformed into an acetoxy group *via* the silylation of the hydroxy group (100%), addition of MeMgI to the cyano group (71%), and Baeyer–Villiger oxidation (54%). The final debenzylation of **138** afforded bao gong teng A in 74% yield. The synthesis of C6-epimer of bao gong teng A through the oxidopyridinium (5 + 2) cycloaddition with 2-chloroacrylonitrile was also reported by Pei and Shen.[51] Subsequently, the asymmetric synthesis of (–)-bao gong teng A using a chiral auxiliary was reported by Pham and Charlton (Fig. 20B).[52] In this study, diastereoselective (5 + 2) cycloaddition of oxidopyridinium **60** with the acrylate of (*S*)-lactate (**139**) was developed. Although a very long reaction time (10 days) was required, the desired isomer, *exo*-**140**, was obtained with 65% selectivity. Subsequent transformations are similar to those employed in the racemic synthesis by Jung *et al.* (Fig. 20A). The hydrogenation of *exo*-**140** afforded **141**, which was subjected to reduction using a bulky hydride reagent, $LiAl(O^tBu)_3H$. The desired product **142** was obtained in 62% yield, along with its epimer (21% yield). After the silylation of the hydroxy group and the benzyl-to-Boc exchange, the chiral auxiliary was removed to afford carboxylic acid **143**. The final functional group manipulations gave (–)-bao gong teng A.

Peese and Gin achieved the total synthesis of the hetisine C_{20}-diterpenoid alkaloid nominine *via* an intramolecular (5 + 2) cycloaddition of an oxidoisoquinolinium (Fig. 21).[53] They prepared oxidoisoquinolinium **147**, bearing a pendant cyclohexene moiety on its nitrogen atom, from cyanocyclohexene **144** and azide **145**. Tandem aza-Wittig reaction/reduction of **144** and **145** afforded **146** in 79% yield with a diastereomeric

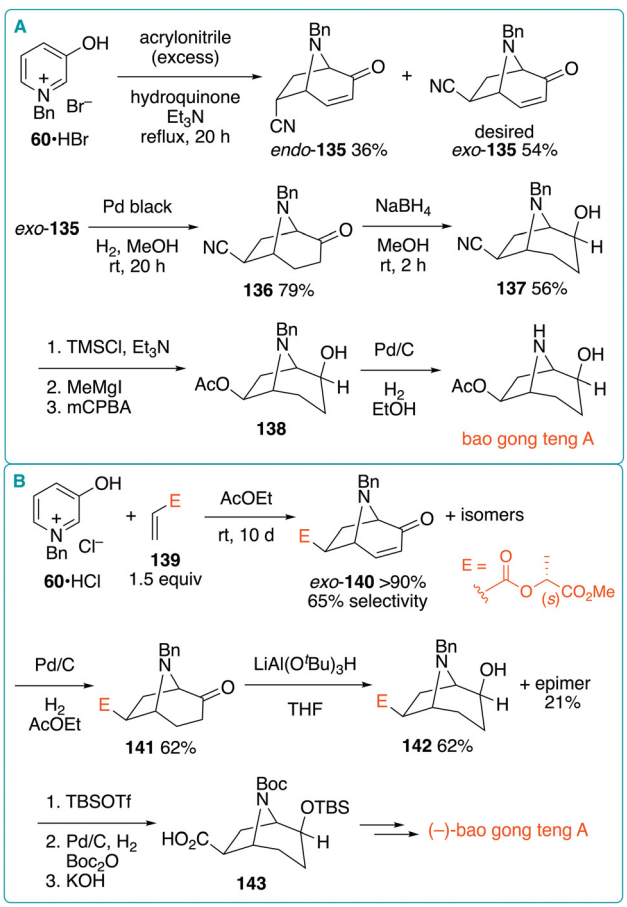

Fig. 20 (A) Racemic total synthesis of bao gong teng A. (B) Asymmetric total synthesis of bao gong teng A.

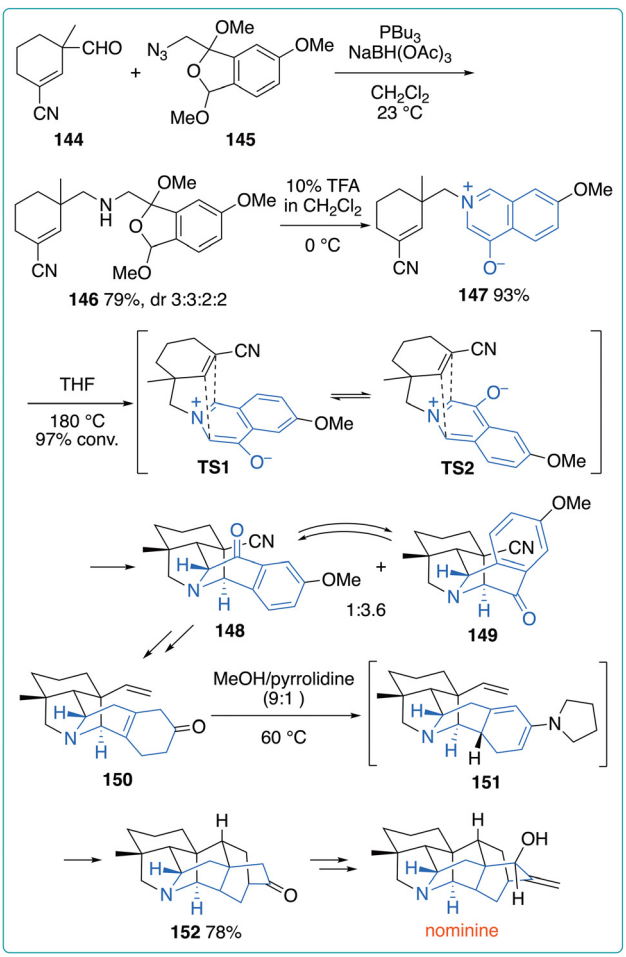

Fig. 21 Gin's total synthesis of nominine.

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ratio of 3 : 3 : 2 : 2. The treatment of **146** with 10% trifluoroacetic acid in methanol at 0 °C generated **147** in 93% yield. Heating **147** in THF at 180 °C promoted intramolecular (5 + 2) cycloaddition *via* TS1 and TS2, producing **148** and **149** with a 1 : 3.6 ratio. Because **148** and **149** were in equilibrium under the cycloaddition conditions, the undesired product **149** could be recycled by partial conversion into **148**. The desired isomer **148** was transformed into cyclohexenone **150** in several steps. Pyrrolidine-promoted intramolecular Diels–Alder cycloaddition occurred *via* dienamine **151**, affording **152** in 78% yield. After additional steps, **152** was converted into nominine. The same group also accomplished the enantioselective synthesis of nominine by employing enantioenriched **144**.[54]

The asymmetric total syntheses of three Sarpagine alkaloids were accomplished through the diastereoselective (5 + 2) cycloaddition of an oxidopyridinium with optically active 2-methylene-1,3-dithiolane 1,3-dioxide **61** by Krüger and Gaich (Fig. 22).[55] In the presence of Hünig's base, pyridinium salt **153** and **61** (93% ee) were allowed to react in dichloromethane at room temperature for 36 h, affording **154** in 77% yield with a 2 : 1 regioisomeric ratio. After the reduction of the sulfoxide and enone moieties, the resultant **155** was subjected to Pd-catalyzed cyclization to afford **156** in 88% yield. Subsequent manipulations converted **156** into the key intermediate **157**, which was transformed into (+)-vellosomine, (+)-*N*-methylvellosomine, and (+)-10-methoxyvellosomine, through Fisher indole synthesis using *N*-phenylhydrazones **158**. In the final step, the methyl vinyl ether moiety underwent hydrolysis to give the aldehyde with the desired configuration at the C16-position. Using this strategy, the same group completed the formal total synthesis of 16-epinormacusine B.[56] Taking advantage of the flexibility of this strategy, the Gaich group also synthesized non-natural analogs of Sarpagine alkaloids.[57]

Gaich *et al.* also applied their strategy to the total synthesis of a Stemona alkaloid, parvineostemonine (Fig. 23).[58] In this case, pyridinium salt **159** was used as an oxidopyridinium precursor to obtain (5 + 2) cycloadduct **160**. After the deoxygenation of the sulfoxide moieties, the desired product **161** was obtained in 86% yield with a 5.4 : 1 regioisomeric ratio. The conjugate allylation of the major isomer of **161** afforded **162** in 83% yield, which was then subjected to ring-closing metathesis using the Grubbs II catalyst to afford **163** in 77% yield. The subsequent removal of the dithioketal moiety and alkene hydrogenation afforded the key intermediate (–)-**164**, which was subjected to two-step lactonization to afford (+)-parvineostemonine in 62% yield. The minor isomer of **161** was similarly converted into (–)-parvineostemonine.

The studies by the Gin and Gaich groups demonstrated that the (5 + 2) cycloaddition of oxidopyridinium and oxidoisoquinolinium betaines serves as an effective strategy for the efficient construction of complex natural products. In the next section, the approach that has been used to create biologically active compounds is discussed.

2.2.2 Syntheses of medicinally relevant molecules. Carroll *et al.* revisited the (5 + 2) cycloaddition of oxidoisoquinolinium **34**.[59] The authors used **34**·HI as the oxidoisoquinolinium precursor for the cycloaddition of various dipolarophiles, including 1,4-quinones, at room temperature to improve product

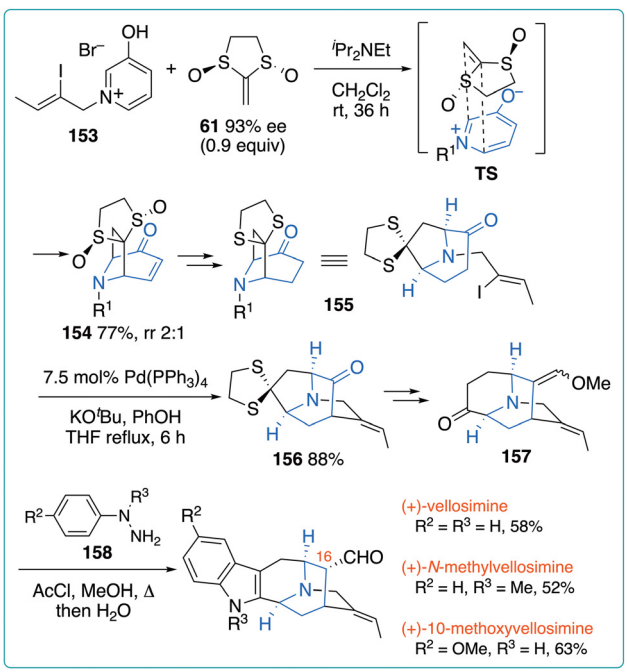

Fig. 22 Gaich's total synthesis of Sarpagine alkaloids.

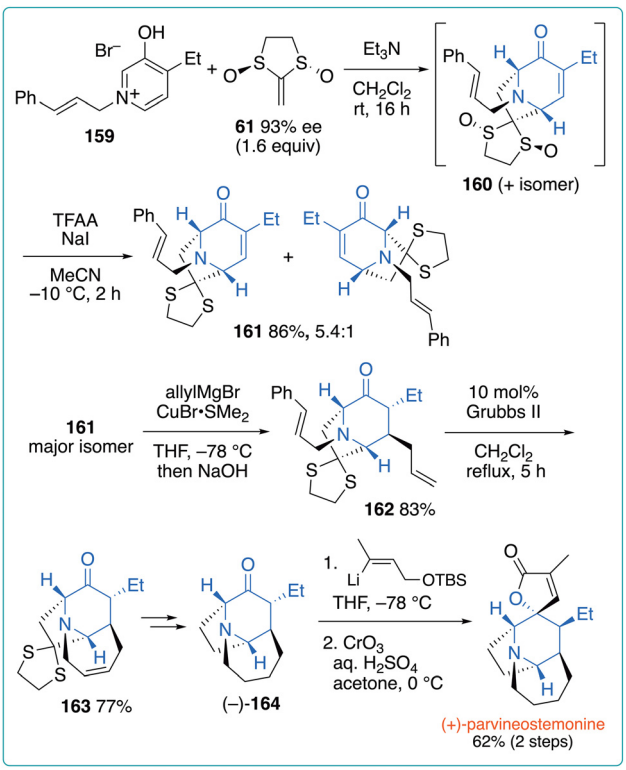

Fig. 23 Gaich's total synthesis of both enantiomers of parvineostemonine.

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yield. The reaction of **34**·HI and 1,4-naphthoquinone was performed in the presence of Et_3N to obtain hydroquinone-fused product **165a** in 92% yield (Fig. 24A). However, a similar reaction using 1,4-benzoquinone produced **165b** in moderate yield (53%). These products contain a dibenzoazabicyclo scaffold, similar to that of MK-801, an NMDA receptor antagonist. Therefore, the same group then synthesized MK-801 through the (5 + 2) cycloaddition of oxidoisoquinolinium with benzyne (Fig. 24B).[60] Treatment of **166**·HI and benzyne precursor **84** with CsF and triethylamine in acetonitrile at room temperature produced **167** in 74% yield. The debenzylation and ketone reduction of **167** proceeded upon treatment with ammonium formate and Pd/C to afford **168** in 88% yield. Finally, MK-801 was obtained in 88% yield by treating **168** with 55% hydrochloric acid and red phosphorus in acetic acid under reflux.

Cocaine is a potent stimulant of the central nervous system. It has been suggested that cocaine binds to dopamine transporters to inhibit dopamine reuptake, resulting in the reinforcing properties of the drug. Replacing the C3 benzoate in cocaine with an aryl group led to more potent analogs **169** (WIN series, Fig. 25A).[61] Kozikowski *et al.* developed similar compounds **170**, bearing an alkyl group instead of a C2 methoxycarbonyl group.[62] To synthesize **170**, they investigated the (5 + 2) cycloaddition of 1-methyl-3-oxido-4-phenylpyridinium (**171**) with chiral vinyl sulfoxide (*R*)-**58** in dioxane under reflux (Fig. 25A). Consequently, three diastereomers **172**, **173**, and **174** were obtained in 44%, 11%, and 22% yields, respectively. The Luche reduction of the major product **172** was followed by acetylation and deoxygenation to afford allylic acetate **175** in 88% yield. Subsequent S_N2' alkylation followed

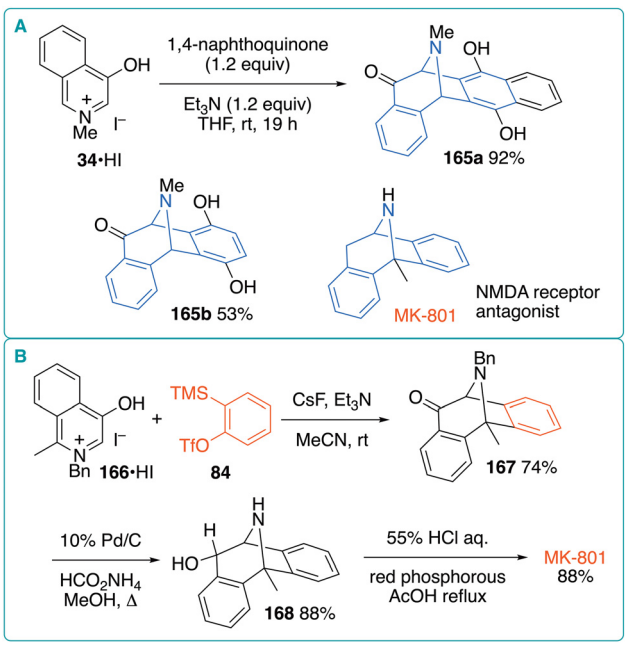

Fig. 24 (A) (5 + 2) cycloaddition of oxidoisoquinolinium with 1,4-quinones. (B) Synthesis of MK-801 *via* the (5 + 2) cycloaddition of oxidoisoquinolinium with benzyne.

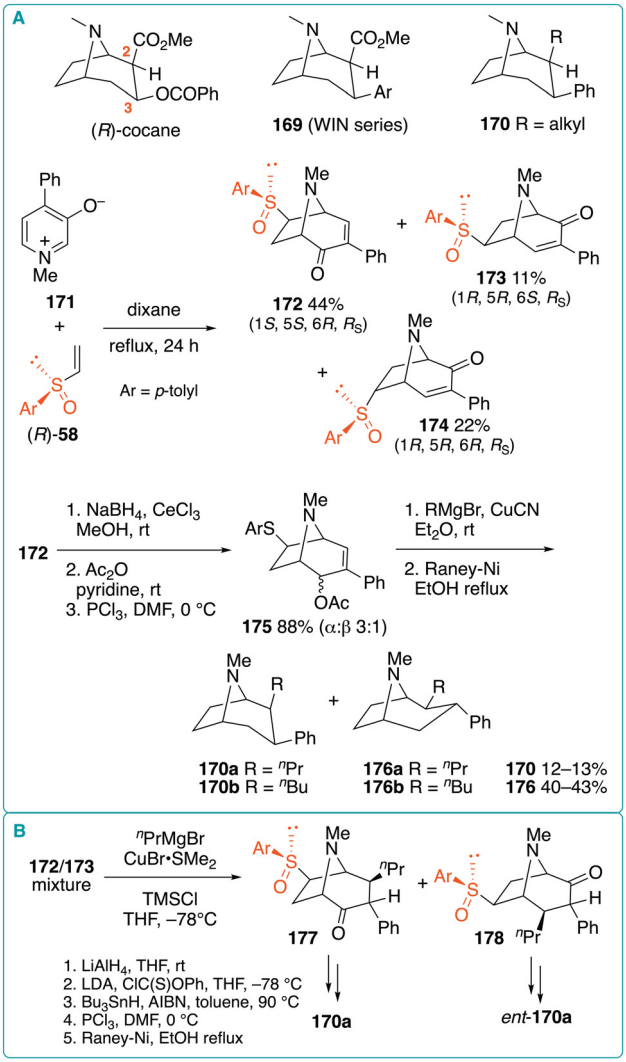

Fig. 25 (A) Enantioselective synthesis of 2-alkyl-3-phenyltropanes *via* the (5 + 2) cycloaddition of oxidopyridinium with chiral vinyl sulfoxide. (B) Alternative late-stage transformations of (5 + 2) cycloadducts.

by the treatment with RANEY®-Ni converted **175** into **170** (12–13% yield) and **176** (40–43% yield). Alternatively, a diastereomeric mixture of **172**/**173** was subjected to conjugate alkylation to afford **177** and **178** (Fig. 25B). These intermediates were separately converted into **170a** and its enantiomer *via* a five-step transformation sequence. Using this strategy, Kozikowski *et al.* synthesized a series of C2/C3-modified cocaine analogs and evaluated their biological activity.[63] There are several reports on the synthesis of biologically interesting tropanes *via* oxidopyridinium (5 + 2) cycloaddition with activated alkenes.[64]

To gain insights into the effect of the orientation of the nitrogen lone pair on binding affinity, Kozikowski *et al.* developed tricyclic cocaine analogs, in which the conformation of the N-lone pairs is restricted by introducing an additional ring moiety (Fig. 26).[65] Pyridinium salts **171**·HBr, bearing a 2-bromopropenyl substituent on the nitrogen atom, were subjected

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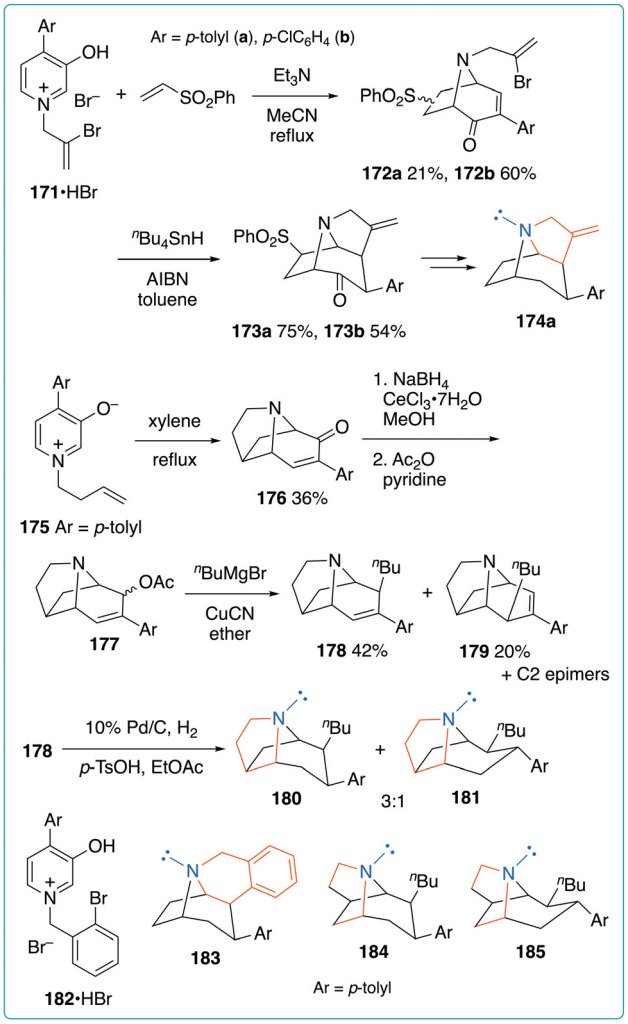

Fig. 26 Synthesis of constrained cocaine analogs *via* the (5 + 2) cycloaddition of 4-aryl-2-oxidopyridinium betaines.

to (5 + 2) cycloaddition with phenyl vinyl sulfone to obtain **172** in 21–60% yield as a mixture of regioisomers. According to a report by Ghosh and Hart,[66] the radical cyclization of **172** afforded the desired tricyclic products **173** in 54–75% yield. Although the partial reduction of the *p*-chlorophenyl moiety of **173b** occurred during the reductive desulfonylation step, *p*-tolyl analog **173a** was successfully converted into the constrained cocaine analog **174a**. An alternative tricyclic compound was also synthesized *via* the intramolecular (5 + 2) cycloaddition of betaine **175**. The resultant **176** was converted into allylic acetate **177**, which was subjected to S_N2' alkylation to afford **178** and **179** in 42% and 20% yields, respectively, along with C2 epimers. Finally, the hydrogenation of the major product **178** afforded **180** and **181** in a 3 : 1 ratio. Preliminary biological experiments showed that **174a** and **180** exhibited substantial affinity for the dopamine transporter. Therefore, the orientation of the N-lone pairs has no impact on the binding affinity. Moreover, the same group synthesized the benzo-fused constrained cocaine analog **183** from pyridinium salt **182**·HBr, as well as other analogs **184** and **185** from **175**.[67] The binding affinities of several monoamine transporters were investigated using the analogs described above. The binding affinities of the constrained analogs for the dopamine transporter were found to be 2.5- to 104-fold higher than that for cocaine.

2.2.3 Other applications. Natural-product-like scaffolds are promising starting points for drug discovery. New drug seeds can be created by combining several privileged scaffolds. Waldmann *et al.* proposed the enantiodivergent synthesis of pyrrolidine-fused tropanes having noted that the tropane scaffold is found in bioactive compounds such as cocaine and many natural products are known that contain a pyrrolidine ring. To this end, they applied the Cu-catalyzed enantioselective (3 + 2) cycloaddition of azomethine ylides to oxidopyridinium (5 + 2) cycloadducts (Fig. 27A).[68] In the presence of 2.5 mol% $[Cu(MeCN)_4]BF_4$, 3 mol% (*R*)-3,5-^{t}Bu$_2$-MeOBIPHEP as the chiral ligand, and 10 mol% *N*,*N*-diisopropylethylamine (DIPEA), *rac*-**11b** (2 equiv.) reacted with imine **186** in dichloromethane at room temperature to afford 1,3-dipolar cycloadduct (−)-**187** in 41% yield with 99% ee. The unreacted enantiomer of **11b** was recovered in 46% yield with 97% ee. The selectivity factor for this kinetic resolution was 119. Tropanes derived from phenyl vinyl sulphone and maleimides can be used as

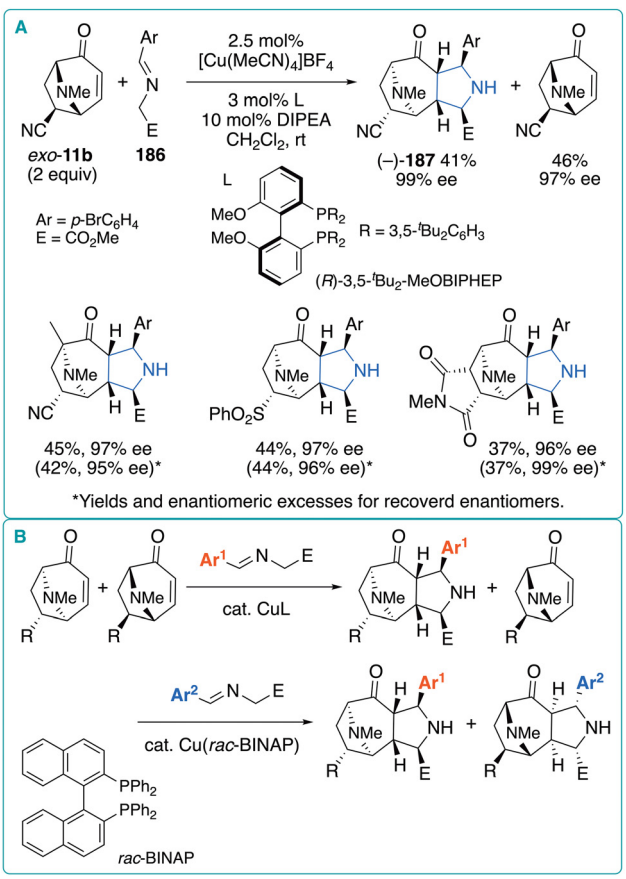

Fig. 27 (A) Kinetic resolution of oxidopyridinium (5 + 2) cycloadducts. (B) Enantiodivergent synthesis of pyrrolidine-fused tropanes.

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substrates without loss of yield and enantioselectivity. Moreover, a one-pot, tandem 1,3-dipolar cycloaddition using two imines with different aryl substituents afforded separable pseudo-enantiomeric products (Fig. 27B). For the second cycloaddition, *rac*-BINAP was used as the ligand.

The (5 + 2) cycloadducts derived from oxidopyridinium betaines and vinyl sulfones are highly versatile platforms for the synthesis of tropanone derivatives.[69] Marsden *et al.* investigated the divergent transformations of vinyl-sulfone-derived (5 + 2) cycloadducts to construct a tropane-based molecular library (Fig. 28A).[70] To this end, they transformed **188** into **189** *via* hydrogenation, **190** *via* intramolecular Michael addition, and **191** *via* Rh-catalyzed conjugate arylation. In addition, the reductive Heck cyclization of *N*-(*o*-bromophenyl)methyl derivative **192**, leading to tetracyclic derivative **193**, was performed under conditions similar to those reported by the Grigg group.[71] Furthermore, diverse fused tropane derivatives were prepared by converting saturated and unsaturated tropanones, such as **188** and **189**. Selected examples are shown in Fig. 28B.

The trifluoromethyl (CF_3) group is one of the most common fluoroalkyl moieties, and its introduction into bioactive compounds can modify biological properties such as lipophilicity, metabolic stability, and binding affinity to target receptors.[72] Thus, CF_3-substituted tropanes are promising candidates for drug discovery. Yamamoto *et al.* reported the dearomative transformation of CF_3-substituted pyridine-3-ols *via* oxidopyridinium cycloaddition.[73] The authors investigated the transformation of pyridin-3-ols bearing a CF_3 group at different positions and found that the regio- and stereoselectivity changed depending on the substitution positions (Fig. 29). The N-methylation of 2-(trifluoromethyl)pyridin-3-ol **194** was conducted using MeOTf in toluene at 90 °C for 1 h, and the resultant pyridinium and *N*-methylmaleimide (1 equiv.) were treated with triethylamine (2 equiv.) in toluene at 110 °C for 16 h in the same pot, affording a mixture of *endo*- and *exo*-**195** in 87% yield with a 4.8 : 1 ratio. Similarly, 6-(trifluoromethyl)pyridin-3-ol **196** was subjected to one-pot N-methylation/(5 + 2) cycloaddition to afford a mixture of *endo*- and *exo*-**197** in 95% yield with a lower stereoselectivity of 2.1 : 1. In contrast, the transformation of 5-(trifluoromethyl) pyridin-3-ol **198** exclusively produced *exo*-**199** in 68% yield. Thus, the position of the CF_3 group has a notable impact on the stereoselectivity. Furthermore, a similar reaction of **194** with phenyl vinyl sulfone exclusively afforded *exo*-**200** in 84% yield, whereas an 8 : 1 mixture of *exo*-**201** and *endo*-**202** was obtained in 78% yield from **196**. The latter result suggests that

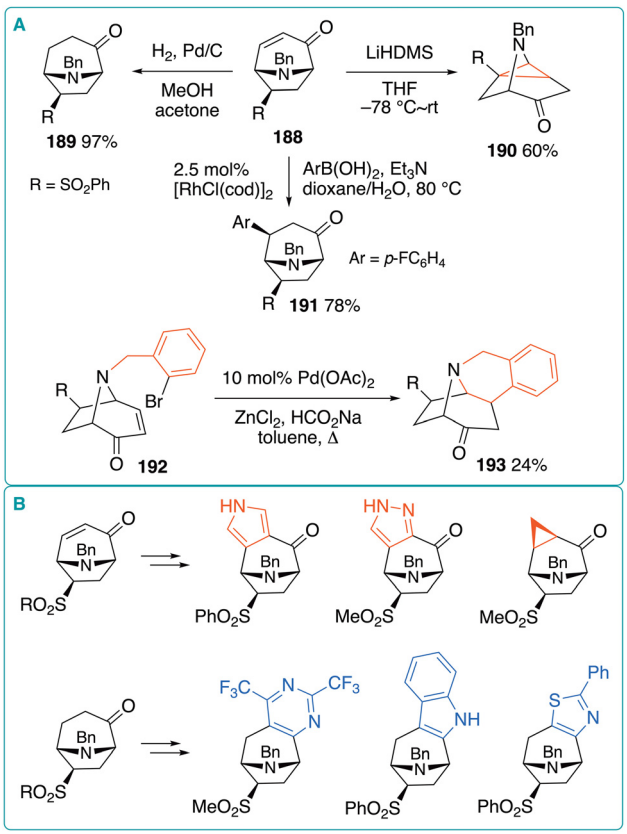

Fig. 28 (A) Transformations of oxidopyridinium (5 + 2) cycloadducts derived from phenyl vinyl sulfone. (B) Divergent transformations of saturated and unsaturated tropanones into fused tropane derivatives.

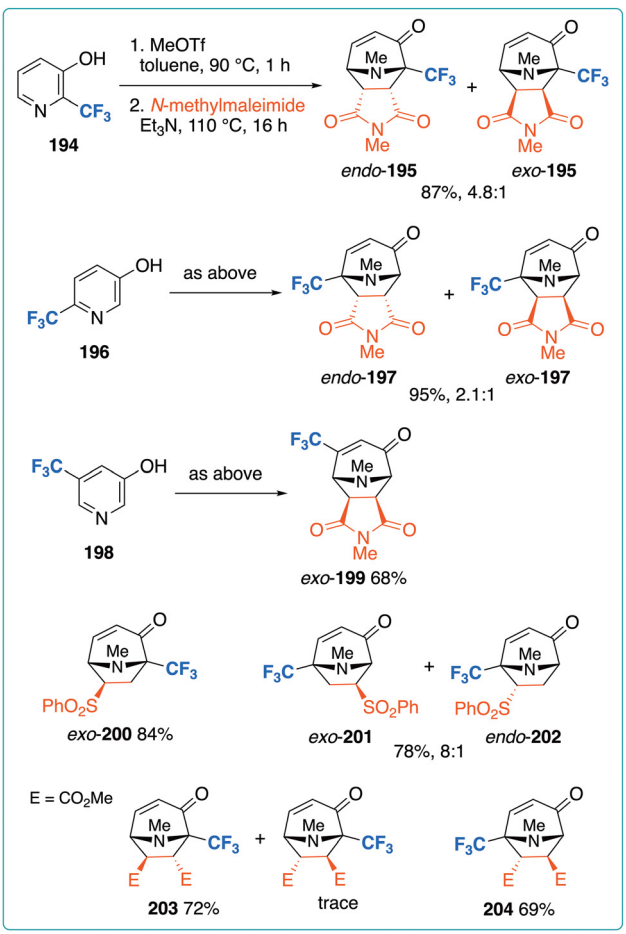

Fig. 29 Dearomative transformation of trifluoromethyl-substituted pyridin-3-ols into the corresponding tropane derivatives.

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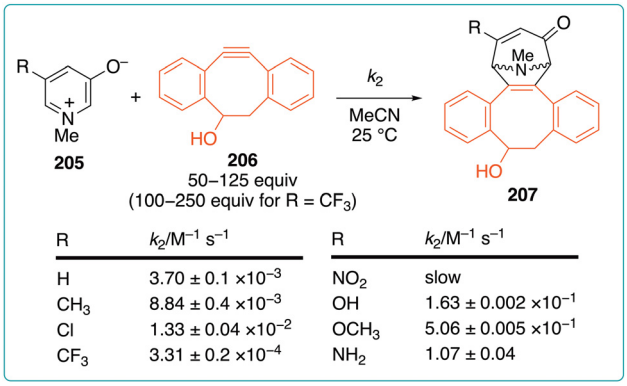

R	k_2/M^{-1} s^{-1}	R	k_2/M^{-1} s^{-1}
H	3.70 ± 0.1 ×10^{-3}	NO_2	slow
CH_3	8.84 ± 0.4 ×10^{-3}	OH	1.63 ± 0.002 ×10^{-1}
Cl	1.33 ± 0.04 ×10^{-2}	OCH_3	5.06 ± 0.005 ×10^{-1}
CF_3	3.31 ± 0.2 ×10^{-4}	NH_2	1.07 ± 0.04

Fig. 30 Kinetic study of the (5 + 2) cycloaddition of oxidopyridinium betaines with 4-dibenzocyclooctynol.

the bulky CF_3 group altered the regioselectivity of the cycloaddition, such that the sulfonyl group adopted a position distal to the CF_3 group. A similar stereocontrolling effect of the CF_3 group was observed in the reaction with dimethyl fumarate: in this case, products **203** and **204**, in which the CF_3 and adjacent methoxycarbonyl groups were mutually *trans*, were selectively obtained from **194** and **196**, respectively.

The use of 3-oxidopyridinium betaines as bioorthogonal dipoles was reported by Pezacki *et al.* (Fig. 30).[74] They performed the (5 + 2) cycloaddition of betaines **205**, bearing a substituent R at the 5-position with 4-dibenzocyclooctynol **206** in acetonitrile at 25 °C, and bimolecular rate constants k_2 were determined through UV/Vis absorption spectroscopy under pseudo-first-order kinetic conditions. This study demonstrated that the introduction of electron-donating groups at the 5-position led to significant rate increases. The stability of the most reactive derivative (**205**, R = OMe) in an aqueous medium relevant to chemical biology was quantitatively investigated by UV/Vis spectroscopy in 9 : 1 phosphate-buffered saline (pH 7.4)/DMSO with equimolar concentrations of dithiothreitol: under these conditions, less than 5% decrease in absorbance was observed after 18 h, demonstrating the stability of **205** under biological conditions.

3. Advances in (5 + 4) and (5 + 6) cycloaddition

3.1 (5 + 4) cycloaddition with 1,3-dienes

The (5 + 4) cycloaddition of 3-oxidopyridinium betaines with 1,3-dienes has been underdeveloped in relation to the (5 + 2) cycloadditions discussed in the previous sections although the expected products are fascinating bridged nitrogen heterocycles. As a synthetic application, Cha *et al.* reported the construction of the tricyclic core of sarain A *via* (5 + 4) cycloaddition (Fig. 31A).[75] The key reaction was performed upon treatment of **20**·HCl and cyclopentadiene with triethylamine, affording (5 + 4) cycloadducts **208a** and **208b** in 58% and 4% yields, respectively, along with (5 + 2) cycloadduct **209** (27% yield). The enamine moiety of **208a** was reduced using $NaBH_3CN$/TFA to produce **210**

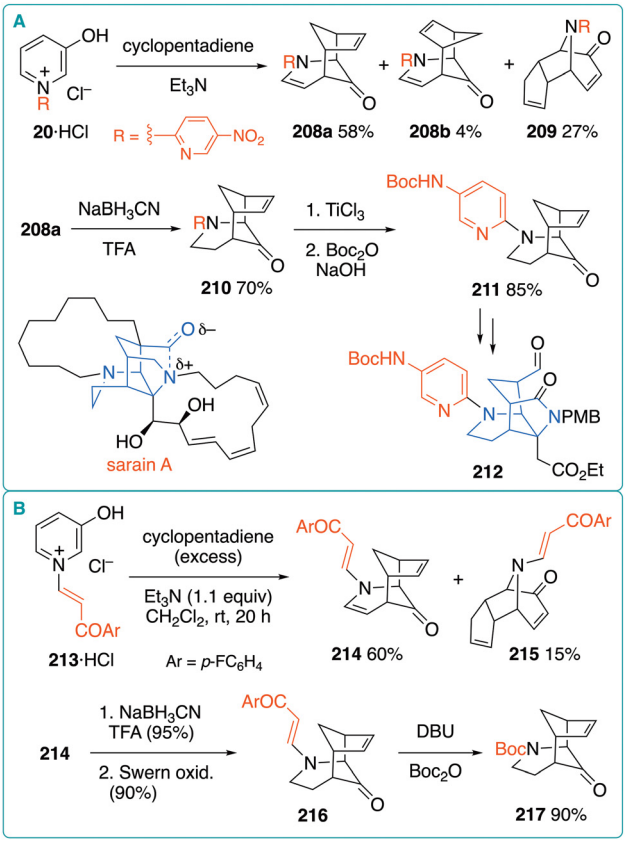

Fig. 31 (A) Construction of the tricyclic core of sarain A *via* the (5 + 4) cycloaddition of 1-(5-nitropyridin-2-yl)-3-oxidopyridinium with cyclopentadiene. (B) (5 + 4) cycloaddition of 3-oxidopyridinium bearing an (*E*)-β-(4′-fluorobenzoyl)vinyl group with cyclopentadiene and subsequent transformations.

in 70% yield. Because the 5-nitropyridin-2-yl-substituted products were less soluble in common organic solvents, the nitro group of **210** was reduced to an amine, and **211** was obtained in 85% yield after Boc protection of the resultant amino group. After many steps, including the oxidative ring opening of the cyclopentene moiety, **211** was transformed into the tricyclic core model of sarain A (**212**). However, the removal of the *N*-Boc-5-aminopyridin-2-yl group was not achieved. Therefore, the Cha group examined the use of a 3-oxidopyridinium with the removable *N*-group (Fig. 31B). After screening several (*E*)-β-(benzoyl) vinyl-substituted betaines for the (5 + 4) cycloaddition with cyclopentadiene, *p*-fluorophenyl analog **213** was found to be optimal. The desired (5 + 4) cycloadduct **214** was obtained in 60% yield along with the undesired (5 + 2) cycloadduct **215** (15% yield). After the reduction of the enamine moiety of **214**, the benzoylvinyl group of the resultant **216** was replaced with a readily removable Boc group in high yield. Thus, **217** was transformed into a tricyclic core model of sarain A in a manner similar to the conversion of **211** into **212**.

Electron-withdrawing N-substituents on 3-oxidopyridinium betaines are necessary for efficient (5 + 4) cycloaddition with 1,3-dienes. This requirement limits the application of (5 + 4) cycloaddition products in natural product synthesis, as illustrated

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above (Fig. 31). To address this limitation, Harmata *et al.* developed the (5 + 4) cycloaddition of 1-methyl-3-oxidopyridinium bearing an ester substituent at the 5-position, thereby eliminating the need for electron-withdrawing groups on the nitrogen atom (Fig. 32A).[76] They conducted the N-methylation of methyl nicotinate (**218**) with methyl triflate in dichloromethane at ambient temperature, and the resultant pyridinium was directly used for the subsequent (5 + 4) cycloaddition with 2,3-dimethylbuta-1,3-diene (10 equiv.) in the presence of triethylamine (3 equiv.) in acetonitrile at 85 °C (sealed tube). Using this approach, the target product **219** was quantitatively obtained. DFT calculations were performed to identify the most stable transition state (also see below). A representative range of 1,3-dienes is shown in Fig. 32A. The parent 1,3-butadiene and exocyclic dienes were used to obtain the corresponding products in high yield. The use of penta-1,3-diene afforded **220** as a 1 : 1 diastereomeric mixture in 70% yield. In contrast, the reaction with 1-phenylbuta-1,3-diene produced **221** in 86% yield with a regioisomeric ratio of 10 : 1. The use of 2-methylbuta-1,3-diene led to the formation of the regioisomers of **222** in 80% yield with a ratio of 1.2 : 1. To realize an intramolecular (5 + 4) cycloaddition, the same authors prepared a pyridinium salt bearing a pendant 1,3-diene on the nitrogen atom from ethyl nicotinate (**223**) and triflate **224** (Fig. 32B). The subsequent reaction was conducted in the same manner as the intermolecular reaction, affording the desired tricyclic product **226** in 84% yield, albeit with low diastereoselectivity.

Given that the (5 + 4) cycloaddition of 1-alkyl-substituted 1,3-butadienes regioselectively proceeded, further scope studies were conducted by the Harmata group.[77] 1-Alkyl-substituted 1,3-butadienes were subjected to (5 + 4) cycloaddition with 3-oxidopyridinium **227** to regioselectively obtain the corresponding products **228** in 61–97% yields with diastereomeric ratios ranging from 38 : 62 to 56 : 44 (Fig. 33A). In addition to alkyl substituents, a benzoate substituent was also compatible. When vinylcyclohexene derivative **229** was used as the 1,3-diene component, tetracyclic product **230** was obtained in 94% yield with a 37 : 63 diastereomeric ratio. The use of sorbyl acetate as the diene component produced a mixture of four isomeric cycloadducts. In contrast, the reaction of butadienyl phenyl sulfide **231** afforded *endo*-cycloadduct **232** in 41% yield with a 75 : 25 regioisomeric ratio.

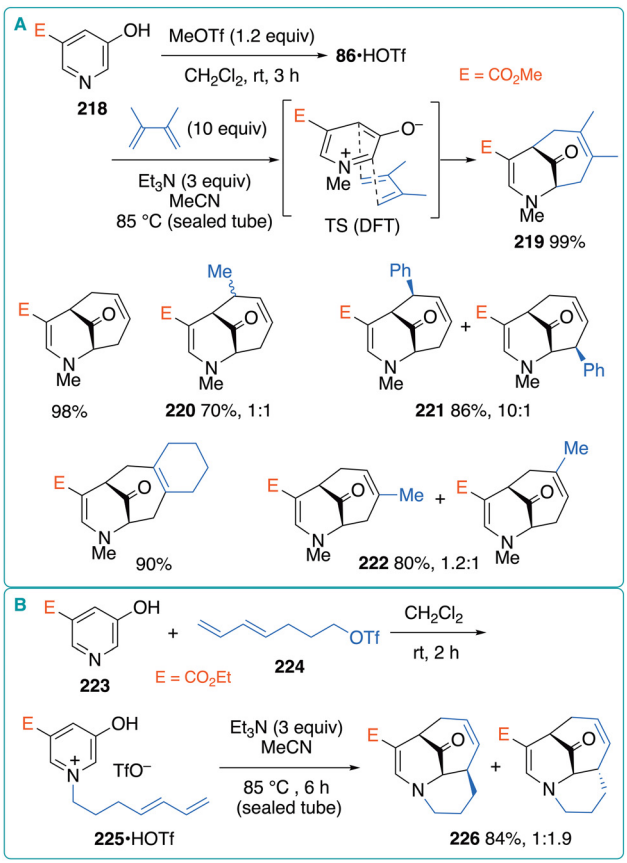

Fig. 32 (A) Tandem N-methylation/(5 + 4) cycloaddition of methyl nicotinate with 1,3-dienes. (B) Intramolecular (5 + 4) cycloaddition of a pyridinium salt derived from ethyl nicotinate.

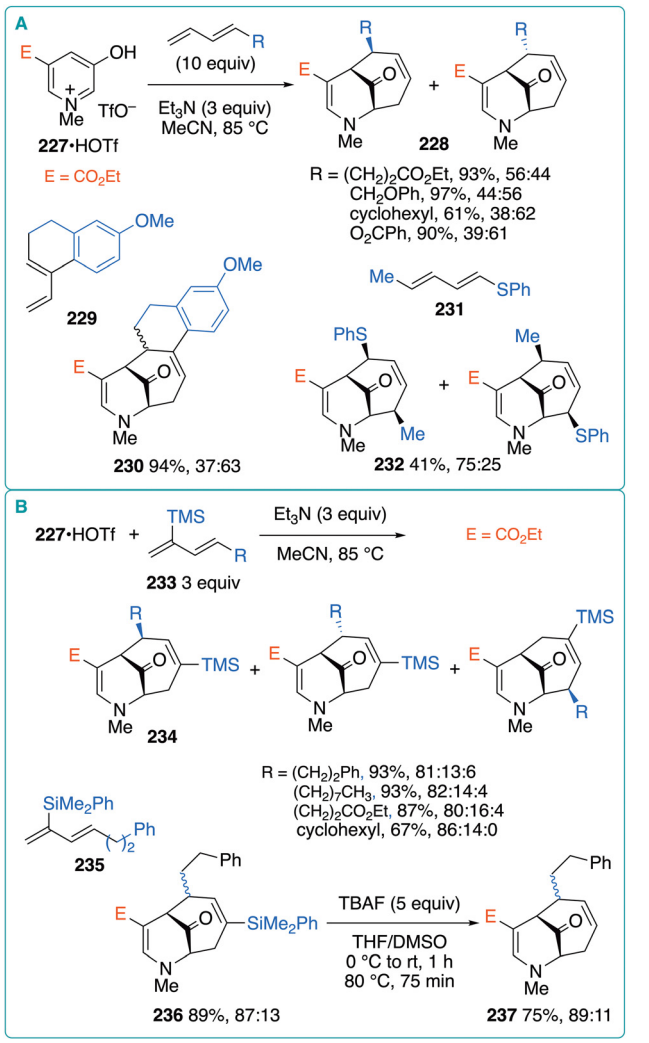

Fig. 33 (A) (5 + 4) cycloaddition of ester-substituted oxidopyridinium with unsymmetrical 1,3-dienes. (B) (5 + 4) cycloaddition of ester-substituted oxiopyridinium with dienylsilanes.

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Moreover, dienylsilanes **233** were used as the diene component with the expectation that steric interactions between the bulky TMS group and ester substituent on the betaine would lead to improved diastereoselectivity (Fig. 33B).[78] Actually, the reaction using **227**·HOTf and **233** produced **234** as the major isomer. The use of diene **235** with a much bulkier dimethylphenylsilyl group resulted in the formation of **236** as the major isomer in 89% yield with an 87 : 13 diastereomeric ratio. The treatment of **236** with tetra(*n*-butyl)ammonium fluoride (TBAF) afforded desilylation product **237** in 75% yield with an 89 : 11 diastereomeric ratio.

Harmata *et al.* envisioned that the intramolecular (5 + 4) cycloaddition (*cf.* Fig. 32B) would provide a straightforward route to the ABC-ring system of natural alkaloid daphnicyclidin A. However, the reaction of **225**·HOTf afforded the desired (5 + 4) cycloadduct with unsatisfactory diastereoselectivity. Therefore, they reinvestigated the influence of the substituted dienes on the intramolecular (5 + 4) cycloaddition (Fig. 34A).[79] The alkylation of **223** with triflate **239** was conducted under neat conditions (no solvent, 80 °C, 18 h) to quantitatively afford pyridinium salt **240**·HOTf, which was treated with triethylamine (3 equiv.) in acetonitrile at 85 °C for 9 h. Under these conditions, cycloadduct **241** was obtained in 80% yield as the sole product. Thus, the methyl substituent at the 5′-position is beneficial for diastereocontrol. The terminal methyl substituent of **242**·HOTf was also found to be effective: cycloadduct **243** was obtained with high diastereoselectivity, albeit with moderate yield (51%). The reaction of pyridinium **244**·HOTf, which has a TMS substituent at the 6′-position, produced cycloadduct **245** in 66% yield as the sole diastereomer. A higher reaction temperature was required for the reaction of pyridinium salts with shorter two-carbon tethers between the nitrogen and diene moieties. The reaction of **246**·HOTf was conducted using sodium benzoate as a base in benzonitrile at 220 °C for 0.5 h, affording the desired ABC-ring unit **247** in 74% yield with complete diastereoselectivity. Moreover, the same group prepared pyridinium salt **249**, possessing a pendant 3-sulfolene, from **223** and triflate **248** (Fig. 34B).[80] The treatment of **249** with sodium benzoate in benzonitrile at 180 °C for 1 h successfully produced the ABCE-ring unit **251** in 70% yield, *via* the formation of exocyclic diene **250** with concomitant extrusion of SO_2.

Burns and Boittier performed DFT calculations to investigate the reaction of 5-methoxycarbonyl-substituted oxidopyridinium **86** with 1,3-butadiene (Fig. 35).[81] In accordance with the DFT analysis by Harmata *et al.*,[76] two TSs were found for the (5 + 4) cycloaddition leading to **252**. Among these, TS1 for the *exo*-approach was slightly more efficient than TS2 for the *endo*-approach. TS3 for the (5 + 2) cycloaddition can be located 4.1 kcal mol^{-1} above TS1, and (5 + 2) cycloadduct **253** is 12.8 kcal mol^{-1} less stable than (5 + 4) cycloadduct **252**. Moreover, the [3,3]-sigmatropic rearrangement of **253** led to the formation of **252** *via* TS4. Accordingly, (5 + 4) cycloadduct **252** should be produced selectively.

Jørgensen *et al.* achieved the enantioselective (5 + 2) cycloaddition of oxidopyridinium betaine **22** with acrolein derivatives using proline-derived organocatalyst **69** (Fig. 10).[35] Although dienamine **71** is involved in the enantioselective cycloaddition, no (5 + 4) cycloadduct was observed. It was considered that **71** attacks betaine **22** to produce iminium intermediate **72**, which reversibly generates (5 + 2) intermediate **73** or (5 + 4) intermediate **254** (Fig. 36A). Because catalyst restoration from **254** is impossible, a (5 + 2) cycloadduct (*endo*-**70**) was selectively obtained upon catalyst release from **73**. To achieve the enantioselective (5 + 4) cycloaddition, the same group investigated the reaction of dienal **255** (Fig. 36B).[82] In the presence of catalyst **256** (20 mol%) and pivalic acid (1 equiv.), **255** and the oxidopyridinium dimer of **23** were allowed to react in *o*-dichlorobenzene (*o*DCB) at

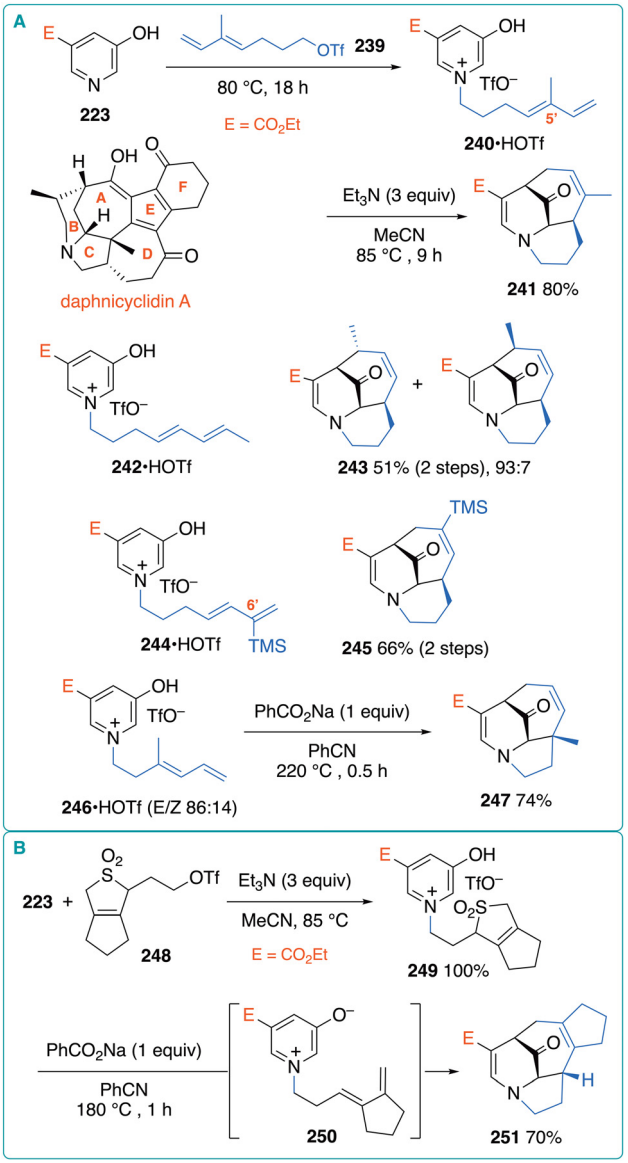

Fig. 34 (A) Intramolecular (5 + 4) cycloaddition of ester-substituted oxidopyridiniums with pendant 1,3-dienes. (B) Intramolecular (5 + 4) cycloaddition of ester-substituted oxidopyridinium with a pendant 3-sulfolene.

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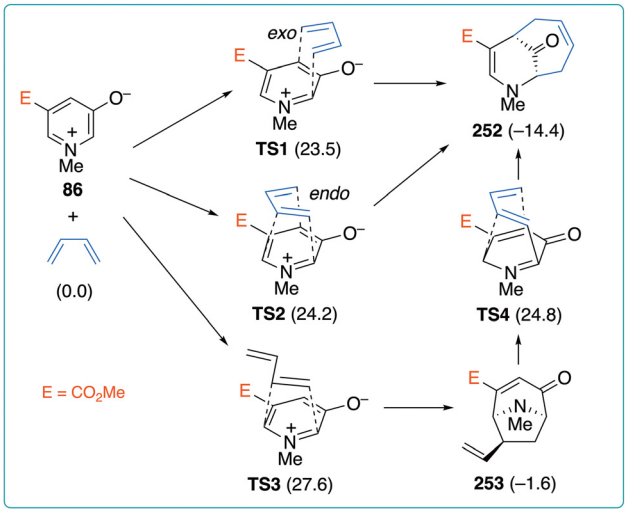

Fig. 35 DFT calculations of the (5 + 4) and (5 + 2) cycloaddition of 1-methyl-3-methoxycarbonyl-3-oxidopyridinium with 1,3-butadiene [Gibbs energies (kcal mol^{-1}) are shown in parentheses].

room temperature for one day. However, rather than the expected (5 + 4) product **258**, cyclopentene-fused cycloheptenone **261** was obtained in 52% yield with 59% ee. This result was rationalized as the intramolecular attack of the enamine moiety on the formyl group generating iminium intermediate **259**, which is hydrolyzed to afford aminoaldehyde **260**. The subsequent E1cB elimination of H_2O from **260** ultimately produces **261**. Although the product yields were low to moderate, several alkyl substituents on the dienal component were compatible; however, tricyclic product **262** was obtained in low yield with low enantioselectivity. The enantioselectivity was improved when (hetero)aromatic substituents were introduced into the dienal components (*i.e.*, **263–265**).

In the above examples, oxidopyridinium betaines possessing *N*-heteroaryl or 5-alkoxycarbonyl substituents were essential for efficient (5 + 4) cycloadditions. In contrast, Yamamoto *et al.* reported that highly reactive *o*-quinodimethane could be used as the 1,3-diene component for the (5 + 4) cycloaddition of various oxidopyridinium betaines.[83] As the *o*-quinodimethane precursor, [(trimethylsilyl)methyl] benzyl acetate (**267**) was used with 1-(pyrimidin-2-yl)-3-oxidopyridinium dimer **266** (Fig. 37A). These substrates were treated with KF (3.6 equiv.) in DMF at 100 °C for 3 h, affording the expected (5 + 4) cycloadduct **268** in 80% yield. More importantly, the *N*-pyrimidyl group was not necessary. N-Methylated pyrimidinium **269**·HI and **267** were treated with KF (4 equiv.) in DMF at 100 °C for 5 h, affording **270** in 72% yield from 5-chloropyridin-3-ol. In this method, KF was used as the activator of **267** and as the base for the deprotonation of **269**·HI. Similarly, 5-phenyl, 5-methoxycarbonyl, and 6-trifluoromethyl derivatives were obtained in 52–65% yield. The same authors also showed that sultine **271** could be used as a precursor of *o*-quinodimethane (Fig. 37B).

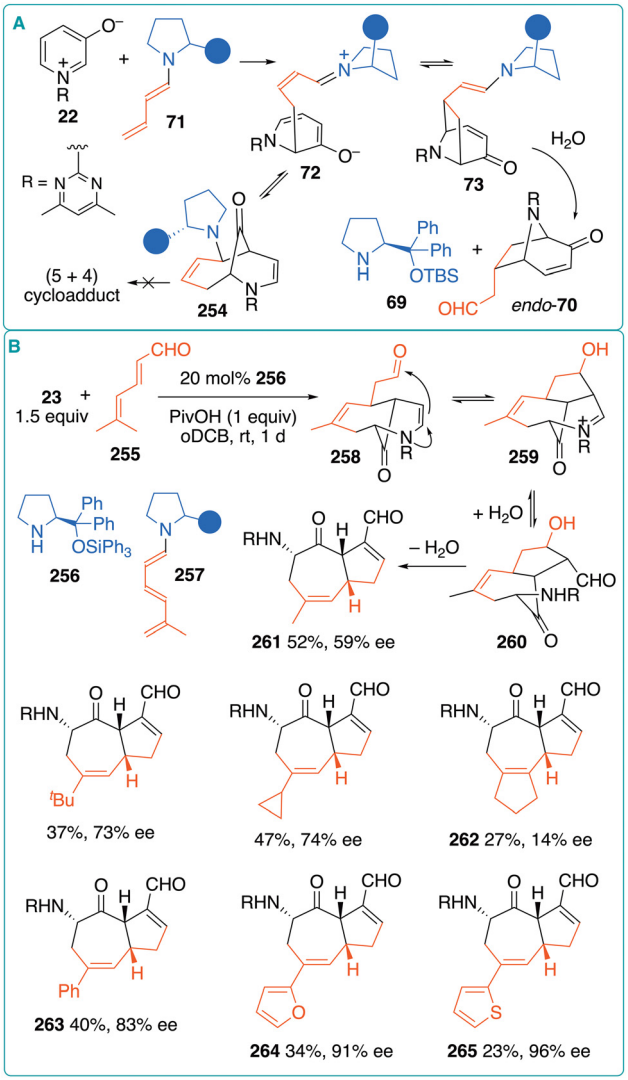

Fig. 36 (A) Mechanistic rationale explaining why no (5 + 4) cycloadduct is obtained from dienamine intermediate and oxiopyridinium. (B) Enantioselective formation of cyclopentene-fused cycloheptenones *via* (5 + 4) cycloaddition using dienals.

Oxidopyridinium dimer **266** and sultine **271** were simply heated in 1,2-dichloroethane (DCE) under reflux to afford **268** in 73% yield. Symmetrically substituted sultines were used to obtain the corresponding (5 + 4) cycloadducts in high yields. Moreover, 5-halogenated pyridinium salts **272**·HCl and **271** were treated with AcONa as the base in refluxing DCE to obtain the corresponding cycloadducts **273** in 63–94% yield. The stereoselective transformations of (5 + 4) cycloadduct **268** at its enamine and carbonyl moieties were also achieved as shown in Fig. 37C.

3.2 (5 + 6) Cycloaddition with fulvenes

Katritzky *et al.* reported that the reaction of *N*-(5-nitropyridin-2-yl)-substituted oxidopyridinium betaine with 6,6-dimethylfulvene produced (5 + 6) cycloadduct **26**, instead of the corresponding (5 + 4) or (5 + 2) cycloadduct involving the

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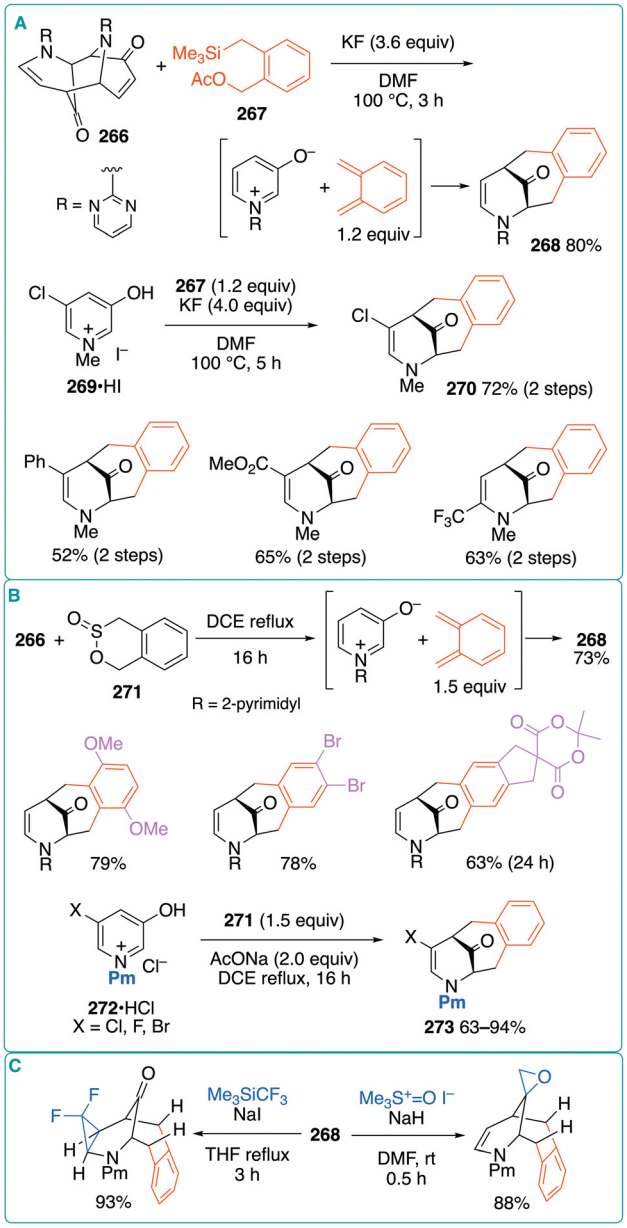

Fig. 37 (A) (5 + 4) cycloaddition using [(trimethylsilyl)methyl]benzyl acetate as the *o*-quinodimethane precursor. (B) (5 + 4) cycloaddition using sultines as the o-quinodimethane precursors. (C) Stereoselective transformation of the representative cycloadduct.

cyclopentadienyl moiety of the fulvene (Fig. 4B).[17b] The generality of this (5 + 6) cycloaddition was later investigated by Radhakrishnan and coworkers (Fig. 38A).[84] *N*-(Pyrimidin-2-yl)-substituted pyridinium salt **274**·HBr and 6,6-diphenylfulvene (**275**) were treated with triethylamine in THF at 0 °C to room temperature, affording (5 + 6) cycloadduct **277** in 68% yield *via* a 1,5-H shift of the initially generated intermediate **276**. The reactions using 6,6-dialkylfulvenes also afforded the corresponding products in similar yields. In addition, 5-nitropyridin-2-yl-substituted pyridinium salts were used to obtain the corresponding (5 + 6) cycloadducts in similar yields. Interestingly, the sterically demanding adamantane-derived fulvene **279** was allowed to react with oxidopyridinium betaine **278** under the same conditions to produce cycloadduct **280** in 36% yield, without a subsequent 1,5-H shift (Fig. 38B). The structure of **280** was unambiguously confirmed by X-ray crystallography. In addition, (5 + 2) cycloadduct **281** was also obtained in 26% yield.

Yamamoto *et al.* also revisited the (5 + 6) cycloaddition of oxidopyridium **274** with 6,6-dimethylfulvene (**282**) and observed a different outcome (Fig. 39A).[20d] In the presence of triethylamine, **274**·HCl and **282** (2 equiv.) were heated in THF under reflux for 23 h, affording a 1.5 : 1 mixture of the known (5 + 6) cycloadduct **283** and minor product **284** in 60% combined yield. Because the similar peak patterns of cyclopentadienyl methylene protons were observed in their ^{1}H NMR spectra, it was assumed that **283** and **284** are mutually isomeric. DFT calculations suggest that the cycloaddition of **274** and **282** proceeds *via* an ambimodal TS, from which post-TS bifurcation occurs to generate both (5 + 4) cycloadduct **285** and initial (5 + 6) product **286** (Fig. 39B). The former is 12.9 kcal mol^{-1} less stable than the latter, and **285** can be converted into **286** *via* a [3,3]-sigmatropic rearrangement. The subsequent 1,5-H shift from **286** produces the experimentally observed major product **283**, which is 2.3 kcal mol^{-1} more stable than **286**. Moreover, two additional 1,5-H shifts from **283** would produce isomeric product **284**, which is only 0.5 kcal mol^{-1} less stable than **283**. According to these results, the experimentally observed minor product can be assigned to **284**.

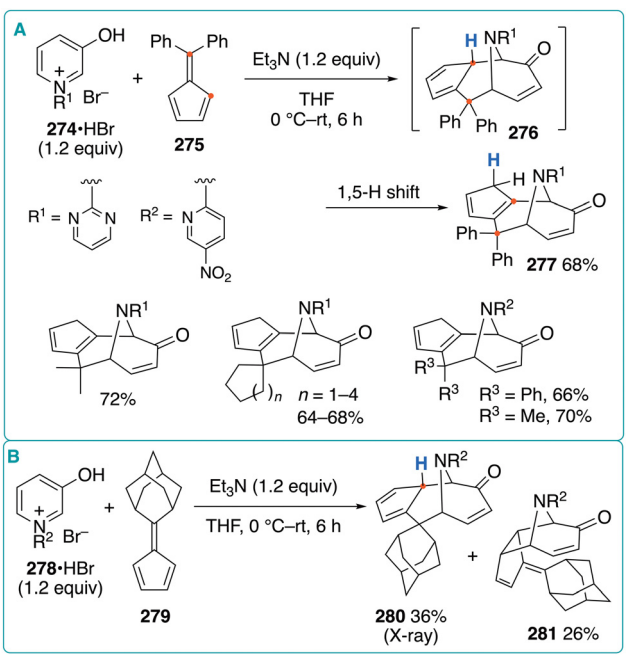

Fig. 38 (A) (5 + 6) cycloaddition of N-heterocycle-substituted oxidopyridinium betaines with fulvenes. (B) Reaction of *N*-(5-nitropyridin-2-yl)-substituted oxidopyridinium with adamantane-derived fulvene.

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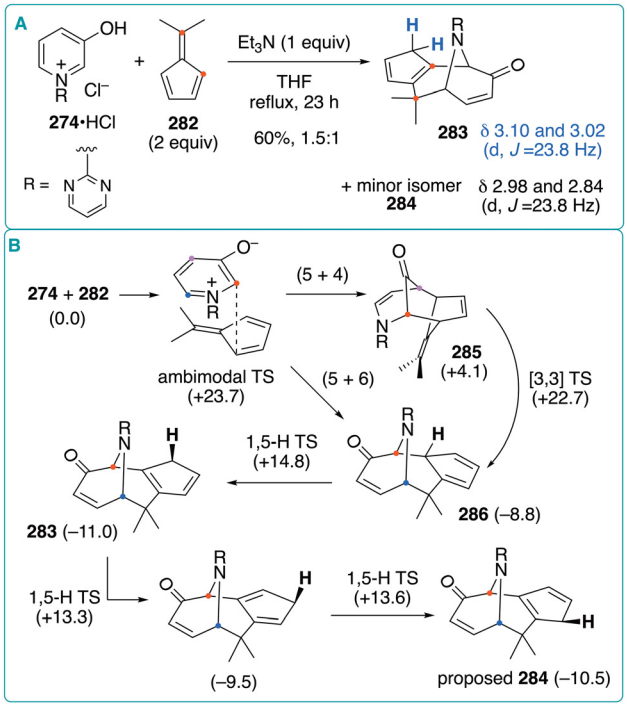

Fig. 39 (A) (5 + 6) cycloaddition of *N*-(pyrimidin-2-yl)-substituted oxidopyridinium betaine with 6,6-dimethylfulvene. (B) DFT analysis of the formation of isomeric (5 + 6) products from *N*-(pyrimidin-2-yl)-substituted oxidopyridinium betaine and 6,6-dimethylfulvene [Gibbs energies (kcal mol^{-1}) are indicated in parentheses].

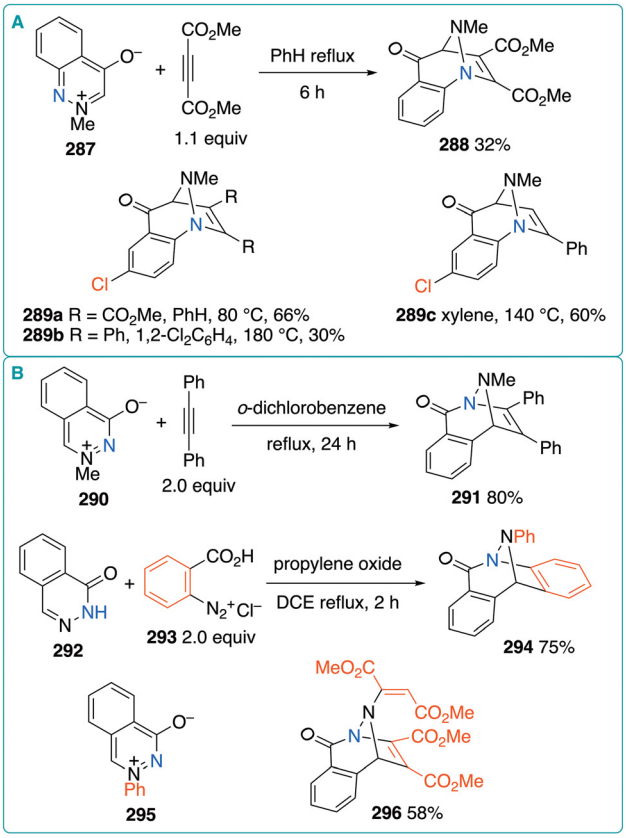

Fig. 40 (A) (5 + 2) cycloaddition of 2-methyl-4-oxidocinnolinium betaines with alkynes. (B) (5 + 2) cycloaddition of 1-oxidophthalazinium betaines with alkynes and benzyne.

4. Cycloadditions of related six-membered N-heterocyclic betaines

In this section, the reactions of six-membered N-heterocyclic betaines relevant to 3-oxidopyridiniums are briefly discussed. Early examples of cycloadditions involving benzodiazine-derived betaines are shown in Fig. 40. In 1969, Ames and Novitt reported that the reaction of 2-methyl-4-oxidocinnolinium **287** with DMAD afforded (5 + 2) cycloadduct **288** in 32% yield (Fig. 40A).[85] In 1975, Katritzky *et al.* investigated the (5 + 2) cycloaddition of 6-chloro-2-methyl-4-oxidocinnolinium with alkynes.[86] The reaction with DMAD afforded **289a** in 66% yield, which was higher than the yield of **288**. Although the reaction with less reactive diphenylacetylene required a higher reaction temperature (180 °C), **289b** was obtained, albeit in a significantly lower yield (30%). The use of phenylacetylene as the unsymmetrical alkyne led to the regioselective formation of **289c** in 60% yield. The Katritzky group also reported the reaction of 3-methyl-1-oxidophthalazinium **290** with diphenylacetylene,[86] which afforded the corresponding (5 + 2) cycloadduct **291** in 80% yield (Fig. 40B). Moreover, the reaction of the parent phthalazine-1(2*H*)-one (**292**) with benzyne, derived from diazonium **293**, produced **294** in 75% yield. One possibility is that **292** reacts with one benzyne molecule to generate betaine **295**, which then reacts with a second benzyne molecule to produce **294**. Similarly, the reaction of **292** with DMAD afforded 1 : 2 product **296** in 58% yield.

Joule *et al.* found that the reaction of oxidopyrazinium **297** with dipolarophiles afforded cyclic enamides **299** through the tautomerization of the initial (5 + 2) cycloadduct **298** (Fig. 41A).[87] The reaction with methyl acrylate selectively afforded *exo*-**299a** in 85% yield, whereas *exo*- and *endo*-**299b** were obtained in 25% and 29% yields, respectively, from the reaction with acrylonitrile. Cycloaddition with methyl propiolate or indene selectively produced **299c** or *endo*-**299d** in 75% and 40% yields, respectively. As a model reaction for the synthesis of quinocarcin, the reaction of betaine **300** with methyl acrylate was conducted to afford *exo*-**301**, bearing a benzylidene moiety, in moderate yield. The Joule group further investigated the reactivity of more sterically hindered oxidopyraziniums (Fig. 41B). The reaction of tetramethyl oxidopyrazinium **302** with methyl acrylate proceeded with opposite regioselectivity to that observed in the reaction of **297**.[88] As a result, *exo*-cycloadduct **303** was obtained in 58% yield, and its structure was unambiguously confirmed by X-ray crystallography. The reaction of trimethyl analog **304** with methyl methacrylate produced tricyclic product **307** in 59% yield.[89] A follow-up theoretical study suggested that the initial (5 + 2) cycloadduct **305** undergoes skeletal rearrangement to generate betaine

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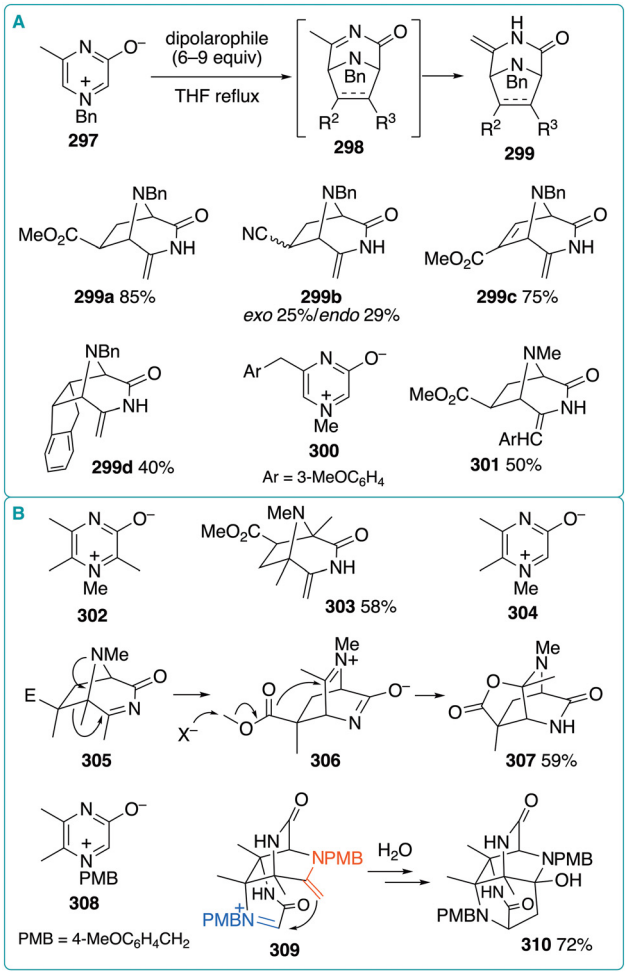

Fig. 41 (A) (5 + 2) cycloaddition of oxidopyrazinium betaines with dipolarophiles. (B) Reactions of highly hindered oxidopyrazinium betaines.

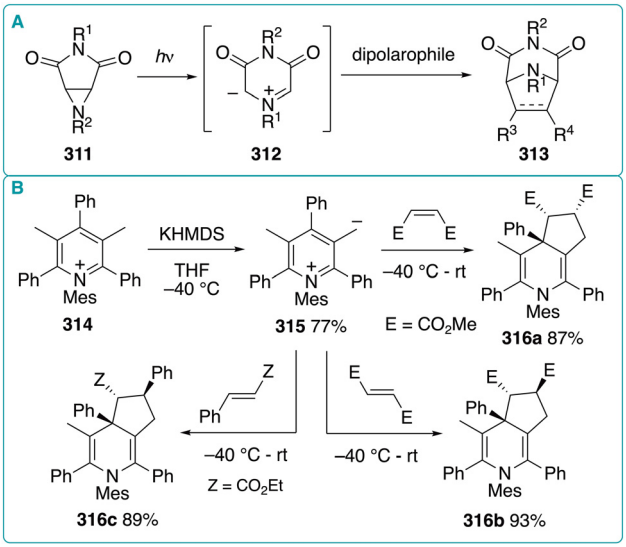

Fig. 42 (A) (5 + 2) cycloaddition of azomethine ylides derived from imide-fused aziridines. (B) (3 + 2) cycloaddition of pyridinium betaines generated from deprotonation of 1-aryl-3,4-dialkylpyridiniums.

intermediate **306**, from which lactonization proceeds to afford **307**.[90] Moreover, *N*-PMB derivative **308** underwent dimerization to produce tetracyclic product **310** *via* an intramolecular reaction between the enamine and iminium moieties in **309**.

In relation to oxidopyrazinium betaines, cyclic azomethine ylides **312** were also used for natural product syntheses. The photolysis of bicyclic aziridines **311** generated ylides **312**, which were trapped by dipolarophiles to afford (5 + 2) cycloadducts **313** (Fig. 42A).[91] This method has been applied to the asymmetric total synthesis of natural products, such as (–)-quinocarcin, (–)-tetrazomine, and (–)-lemonomycin.[92] Recently, new pyridinium betaines derived from 1-aryl-3,4-dialkylpyridiniums were reported by Hansmann *et al.* (Fig. 42B).[93] For example, pyridinium **314** was treated with potassium hexamethyldisilazide (KHMDS) at −40 °C to generate betaine **315** in 77% yield. In contrast to oxidopyridinium betaines, **315** underwent the (3 + 2) cycloaddition with activated alkenes to afford **316a–c** in high yields with excellent regio- and diastereoselectivities.

5. Conclusions

Katritzky's pioneering studies revealed the multifaceted cycloaddition reactivities of oxidopyridinium betaines. The most investigated reaction of oxidopyridinium betaines is the (5 + 2) cycloaddition, in which acrylates, acrylonitrile, vinyl sulfones, and styrene are commonly used as the dipolarophiles. Although 1-alkyl-3-oxidopyridinium betaines showed limited scope, 1-(heteroaryl)-3-oxidopyridiniums were found to exhibit significantly improved reactivity toward various alkenes. Moreover, the latter class of betaines was used for the (5 + 4) cycloaddition with 1,3-butadienes and (5 + 6) cycloaddition with fulvenes. The (5 + 2) cycloaddition has been continuously studied to improve its scope and selectivity, leading to the development of enantioselective methods, intramolecular cycloadditions, and some modern methods involving solid-phase synthesis, ultrasound irradiation, and mechanochemical techniques. Consequently, oxidopyridinium (5 + 2) cycloadditions have been successfully applied to the total synthesis of natural products and the creation of medicinally important molecules. In contrast, the development of (5 + 4) and other cycloadditions has been slower than that of the (5 + 2) cycloaddition. Nevertheless, Harmata *et al.* reported a breakthrough discovery that 1-methyl-5-(alkoxycarbonyl)-3-oxidopyridinium betaines exhibit high reactivity toward the (5 + 4) cycloaddition with 1,3-butadienes. They also demonstrated the synthetic utility of their method by applying it to the synthesis of natural product subunits.

A potential limitation of this methodology is the limited availability of oxidopyridinium betaine precursors (*i.e.*, pyridine-3-ol and its derivatives). Therefore, new methods to generate betaines from readily available precursors should be devel-

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oped. The transition-metal-mediated generation of 4-oxidoisoquinoliniums from alkynes is one viable approach.

In addition to experimental studies, modern theoretical investigations using DFT methods have been reported that provide insights into the reactivity and selectivity of oxidopyridinium betaines. It is expected that combined experimental and computational studies will accelerate the development of new methods and applications in a wide range of research areas such as drug discovery, chemical biology, and materials science, to which this exciting methodology can add so much.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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