Fused-Ring Systems

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Cobalt(II) Porphyrin-Catalyzed Intramolecular Cyclopropanation of N-Alkyl Indoles/Pyrroles with Alkylcarbene: Efficient Synthesis of Polycyclic N-Heterocycles

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Abstract: *A protocol on chemoselective cobalt(II) porphyrin-catalyzed intramolecular cyclopropanation of N-alkyl indoles/pyrroles with alkylcarbenes has been developed. The reaction enables the rapid construction of a range of nitrogen-containing polycyclic compounds in moderate to high yields from readily accessible materials. These N-containing polycyclic compounds can be converted into a variety of N-heterocycles with potential synthetic and biological interest. Compared to their N-tosylhydrazone counterparts, the use of bulky N-2,4,6-triisopropylbenzenesulfonyl hydrazones as carbene precursors allows cyclopropanation to occur under milder reaction conditions.*

Transition metal catalyzed reactions of heteroaromatics with α-diazocarbonyl compounds are powerful methods which can be used both to construct diverse heterocycles and in natural product synthesis.[1] However, the reactions involving alkyldiazomethanes are underexplored. In general, the low stability and inaccessibility of the alkyldiazomethanes, which are used to generate alkylcarbenes, presents a hurdle for development in this area. Recently, relatively stable N-tosylhydrazones have been used as precursors for in situ generation of nonstabilized diazo compounds in transition metal catalyzed or metal-free cross coupling reactions.[2,3] We have also reported that alkyldiazomethanes, generated in situ from N-tosylhydrazones, underwent ruthenium porphyrin catalyzed intramolecular carbene C–H insertion to give substituted tetrahydrofurans and pyrrolidines in high yields with excellent diastereoselectivity.[4] This in situ protocol, based on ruthenium porphyrin catalysts, circumvents the problem encountered in the isolation of labile nonstabilized diazo compounds (especially for alkyldiazomethanes), thereby expanding the scope of substrates for carbene-transfer reactions.

Nitrogen-containing polycyclic compounds are widely found in natural alkaloids and bioactive molecules.[5] The rigid structure of polycyclic compounds confers significant impact on their biological activities.[6] The synthetic approach to polycyclic N-heterocycles often requires a lengthy sequence of reactions. Thus, there has been considerable interest in the design of new and efficient methods for rapid construction of N-atom-containing polycyclic compounds from readily available starting materials. In this regard, transition metal catalyzed reaction of heteroaromatics with diazo compounds is an appealing strategy for the synthesis of complex N-heterocyclic compounds,[1] as numerous heteroaromatics are commercially available. Dirhodium carboxylates and copper complexes are well-known to be effective in catalyzing the reactions of indoles/pyrroles with α-diazocarbonyl compounds to give cyclopropanation products or C–H functionalization products.[1b,d,7] The chemoselectivity of this chemistry has been found to be dependent on N substitution of indoles/pyrroles. When the N substituent is an electron-withdrawing group, indoles/pyrroles preferentially undergo cyclopropanation, whereas N-alkyl-substituted indoles/pyrroles often result in C–H insertion products.[1b,d,7] The preferential C–H insertion for N-alkyl indoles/pyrroles is attributed to an electronically favorable zwitterionic intermediate wherein the positive charge is stabilized by the lone pair of electrons on the N atom of the indole/pyrrole, and the negative charge is stabilized by the acceptor group of the carbenoid component.[1b,d] The zwitterionic intermediate usually undergoes a rapid proton transfer to give C–H insertion products. As alkylcarbene does not have an acceptor group for stabilizing the zwitterionic intermediate, it is likely to undergo cyclopropanation with N-alkyl indoles/pyrroles. Described herein are the findings on cobalt(II) porphyrin-catalyzed intramolecular cyclopropanation of N-alkyl indoles/pyrroles with alkyldiazomethanes, generated in situ from hydrazones.[8,9] The reaction enables rapid construction of a range of nitrogen-containing polycycles in good yields from readily accessible materials (Scheme 1). These polycycles can be readily converted into a variety of N heterocycles having potential biological interest.

Cyclopropane-fused indolines are structural motifs in many natural products and bioactive molecules, and serve as useful building blocks in organic synthesis.[10] At the outset of our investigation, we examined cyclopropanation of the indolyl N-tosylhydrazone **1a** for the synthesis of the cyclopropane-fused indoline **2a** by using [Ru(TTP)(CO)] [H_2TPP = *meso*-tetrakis(4-tolyl)porphyrin] as the catalyst (Scheme 2).[4] The N-tosylhydrazone **1a** and its derivatives can be readily synthesized from commercially available indoles as shown in the literature.[11] Treatment of **1a** with K_2CO_3 (3 equiv) and [Ru(TTP)(CO)] (2 mol%) in 1,4-dioxane at 105 °C for 10 hours led to the cyclopropane **2a** in 20% yield. The structure of **2a** was inferred by the X-ray

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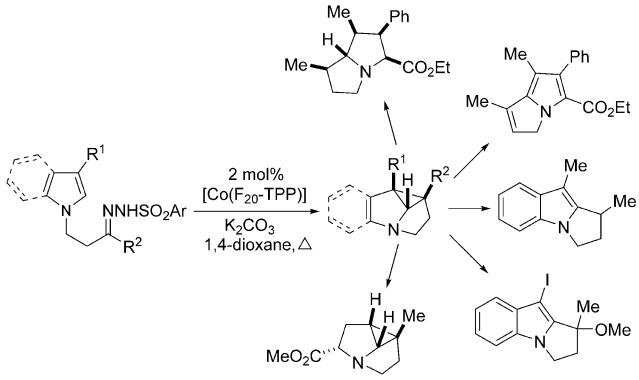
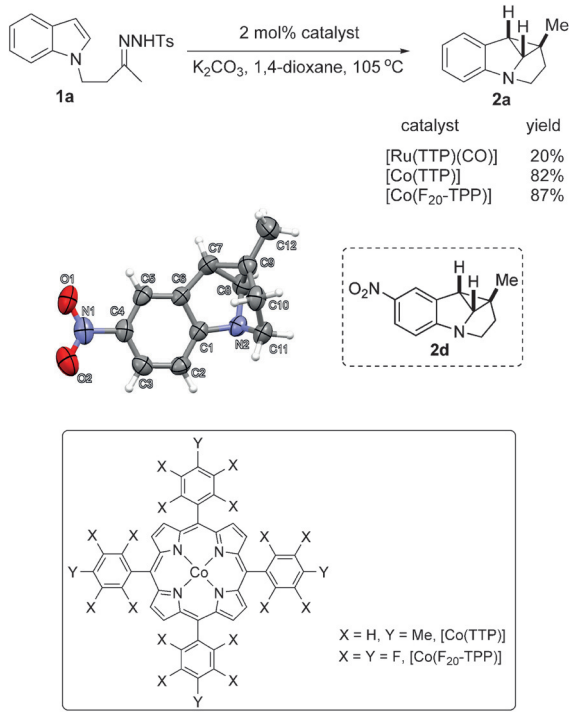


Scheme 1. [Co(Por)]-catalyzed cyclopropanation of N-alkyl indoles/pyrroles with alkyldiazomethanes generated in situ from hydrazones. See Scheme 2 for structure of catalyst.

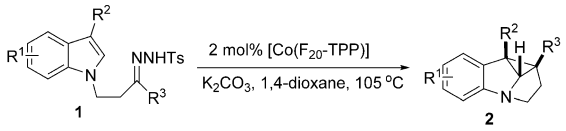


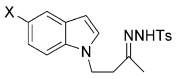
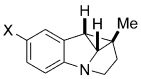
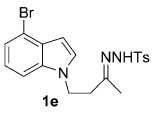
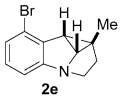
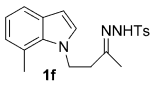
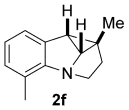
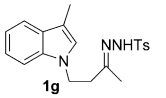
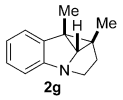
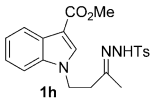
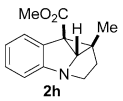
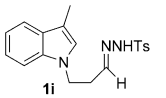
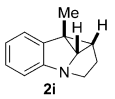
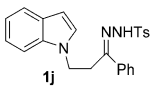
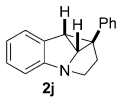
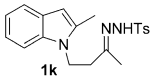
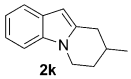
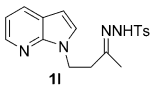
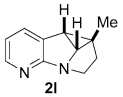
Scheme 2. [Co(Por)]-catalyzed intramolecular cyclopropanation of **1a** to give **2a**. X-ray crystal structure of **2d** (an analogue of **2a**) is shown. Thermal ellipsoids shown at 50% probability. Ts = 4-toluenesulfonyl.

crystal structure of its analogue **2d** (Scheme 2).[12] The major side-product of the reaction was found to be alkenes, presumably derived from 1,2-hydride migration of a carbene intermediate. The use of [Ir(TTP)Me], $[Rh_2(CH_3CO_2)_4]$, $[Rh_2(esp)_2]$,[13] and $Cu(OTf)_2$ as catalysts led to similar results (see the Supporting Information). However, under the same reaction conditions, [Co(TTP)] gave **2a** in 82% yield. Screening of other cobalt complexes, including [Co(F_{20}-TPP)] [H_2(F_{20}-TPP) = *meso*-tetrakis(pentafluorophenyl)porphyrin], [Co(PC)] (PC = phthalocyanine), $CoCl_2$, Co(OAc)$_2$·4 H_2O, [Co(salen)] [salen = *N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino], revealed that [Co(F_{20}-TPP)] was the choice catalyst, thus giving **2a** in 87% yield (see Scheme 2 and the Supporting Information).

With [Co(F_{20}-TPP)] as the catalyst, the substrate scope for the intramolecular cyclopropanation was examined. As depicted in Table 1, a range of N-tosylhydrazones derived from different indoles underwent intramolecular cyclopropanation to give the corresponding tetracyclic cyclopropane-fused indolines in moderate to high yields. The reaction was observed to tolerate a variety of functionalities including halo, nitro, methoxy, and ester groups. The indoles bearing electron-donating groups, **1b** and **1g**, exhibited high reac-

Table 1: Cobalt(II) porphyrin-catalyzed intramolecular cyclopropanation of indolyl N-tosylhydrazones to form cyclopropane-fused indolines.[a]



Entry	Substrate	Product	Yield [%][b]
			
1	X = H, **1a**	**2a**	87
2	X = OMe, **1b**	**2b**	97
3	X = Cl, **1c**	**2c**	92
4[c]	X = NO_2, **1d**	**2d**	83
5			88
6			71
7			84
8[c]			58
9			86
10			83
11			71
12			33

[a] **1**/K_2CO_3/[Co(F_{20}-TPP)] = 1:3:0.02, 105 °C, 10 h, under N_2. [b] Yield of isolated product. [c] Reaction time = 48-72 h.

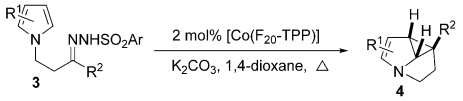
tivity, thus giving **2b** (97%) and **2g** (84%), respectively (entries 2 and 7). Electron-withdrawing groups (**1d** and **1h**) render indoles less reactive than their electron-donating counterparts, thus leading to the corresponding products **2d** (83%) and **2h** (58%), for which longer reaction times were required for completion (entries 4 and 8). The reaction is compatible with C3-substituted indoles, thus giving corresponding cyclopropanes bearing two adjacent, all-carbon quaternary centers in moderate to high yields (entries 7 and 8), the access to which remains a formidable challenge. The N-tosylhydrazones **1i** and **1j** derived from aldehyde and phenyl ketone, respectively, were also reactive, thus giving the corresponding cyclopropanation products **2i** (86%) and **2j** (83%; entries 9 and 10). When the 2-methylindole **1k** was used, a primary C–H insertion product was obtained in 71% yield without cyclopropanation being observed (entry 11). The reaction of the 7-azaindolyl hydrazone **1l** afforded the cyclopropanation product, albeit in moderate yield (entry 12).

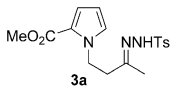
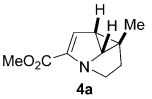
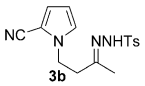
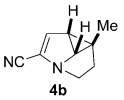
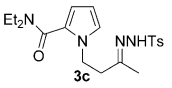
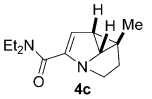
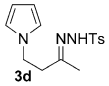
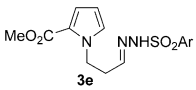
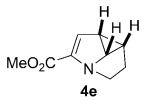
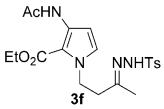
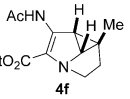
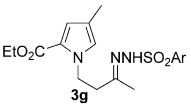
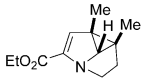
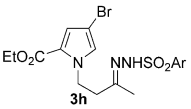
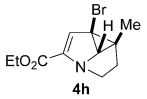
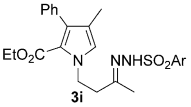
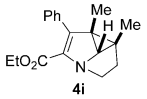
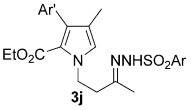
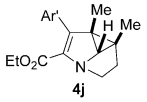
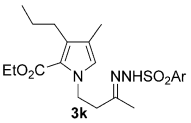
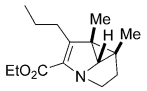
We next extended this catalysis to intramolecular cyclopropanation of pyrroles to synthesize cyclopropane-fused pyrrolines (Table 2). Treatment of the N-tosylhyrazone **3a** with K_2CO_3 in the presence of 2 mol% [Co(F_{20}-TPP)] in 1,4-dioxane at 105°C for 10 hours gave cyclopropane-fused pyrroline **4a** in a 75% yield along with a trace amount of an sp^2 C–H insertion product (entry 1). Changing the β-substitution from ester to cyanide and amide led to similar product yields (entries 2 and 3). However, when the β substituent is a hydrogen atom, only the carbene C–H insertion product was obtained in 65% yield (entry 4). This result revealed that when there is no electron-withdrawing substituent, the pyrrole moiety is very electron-rich, thus favoring formation of zwitterionic intermediate through the reaction with an alkylcarbene and subsequent proton transfer to give C–H insertion products.[1b,d] The hydrazone **3e**, derived from an aldehyde, was also reactive and gave the corresponding cyclopropanation product **4e** in 74% yield (entry 5). The cobalt(II) porphyrin-catalyzed cyclopropanation is compatible with disubstituted and trisubstituted pyrroles to give the corresponding multisubstituted polycycles in good yields (entries 6–11). For example, treatment of 2,3-disubstituted pyrrole (**3f**), 2,4-disubstituted pyrroles (**3g**,**h**), and 2,3,4-trisubstituted pyrroles (**3i**–**k**) with a catalytic amount of [Co(F_{20}-TPP)] led to the corresponding tricyclic cyclopropane-fused pyrrolines in 61–85% yields (entries 6–11). This efficient approach for generating multisubstituted polycycles is appealing since the starting hydrazones can be readily synthesized in two steps (Michael addition and condensation) from readily accessible substituted pyrroles.

It is worth noting that when 2,4-disubstituted and 2,3,4-trisubstituted pyrrolyl N-tosylhydrazones were used as substrates, the [Co(F_{20}-TPP)]-catalyzed reaction took place at 105°C, thus leading to the corresponding cyclopropanation products in low yields, presumably because of the instability of these cyclopropanes under high temperature. This issue can be remedied by using the bulky N-2,4,6-triisopropylbenzenesulfonyl hydrazone, which enables the cyclopropanation to take place at 70°C and runs to completion after 3 hours (Table 2, entries 7–11). The lower reaction temperature may be attributed to steric hindrance of the bulky substitution, which facilitates the decomposition of N-2,4,6-triisopropylbenzenesulfonyl hydrazone to a diazo compound.[14]

Since N-arenesulfonylhydrazones can be readily prepared simply by mixing carbonyl compounds and arenesulfonyl hydrazide, we examined the [Co(F_{20}-TPP)]-catalyzed cyclo-

Table 2: Cobalt(II) porphyrin-catalyzed intramolecular cyclopropanation of pyrrolyl N-arenesulfonylhydrazones to form cyclopropane-fused pyrrolines[a]

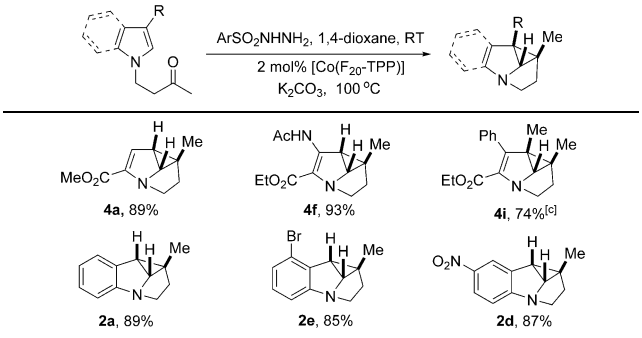


Entry	Substrate	Product	Yield [%][b]
1			75
2			77
3			78
4			65
5[c]			74
6			85
7[c]			71
8[c]			79
9[c]			85
10[c,d]			61
11[c]			78

[a] **3**/K_2CO_3/[Co(F_{20}-TPP)] = 1:3:0.02, 105°C, 2–10 h, under N_2. [b] Yield of isolated product. [c] Ar = 2,4,6-triisopropylphenyl, T = 70°C, reaction time = 3 h. [d] Ar′ = 2,6-dibromophenyl.

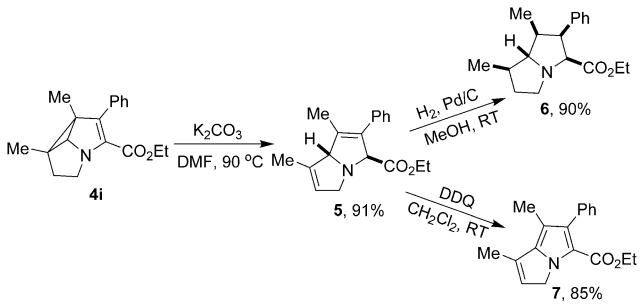
propanation directly from carbonyl compounds in a one-pot fashion. After screening reaction conditions and arenesulfonyl hydrazides, we found that the one-pot reaction of carbonyl compounds with mesitylenesulfonyl hydrazide (1.05 equiv), K_2CO_3 (5 equiv), and [Co(F_{20}-TPP)] (2 mol%) gave the best results (see the Supporting Information). Six examples were studied and the corresponding cyclopropanation products were obtained in high yields (Table 3). The [Co(F_{20}-TPP)]-catalyzed cyclopropanation could be scaled up to the gram level. For example, **3i** (1.6 g) could be used to generate **4i** in 80% yield.

Table 3: One-pot cobalt(II) porphyrin catalyzed intramolecular cyclopropanation of ketones.[a,b]



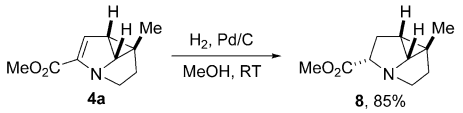
[a] Ketone/$ArSO_2NHNH_2$/K_2CO_3/[Co(F_{20}-TPP)] = 1:1.05:5:0.02; Ar = mesitylene. [b] Determined by ^{1}H NMR spectroscopy using 4-iodoanisole as an internal standard. [c] $ArSO_2NHNH_2$ = 2,4,6-triisopropylbenzenesulfonyl hydrazide, T = 70 °C.

The as obtained cyclopropanation products could be converted into a range of N-heterocycles of interest in medicinal chemistry. For example, **4i** readily underwent cyclopropane ring opening by treatment with K_2CO_3 in DMF at 90 °C to generate the 5,7*a*-dihydro-3*H*-pyrrolizine **5** in 91% yield, and then hydrogenation of **5** gave the polysubstituted pyrrolizidine **6** in 90% yield (Scheme 3). The present catalysis thus facilitates rapid construction of polysubstituted pyrrolizidines which are commonly found in naturally occurring pyrrolizidine alkaloids possessing a wealth of bioactivities.[15] Treatment of **5** with DDQ at room temperature gave the 3H-pyrrolizine **7** in 85% yield. Pyrrolizine derivatives have been found to display various

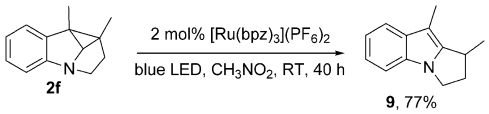


Scheme 3. Cyclopropane ring opening of **4i** and subsequent transformations. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMF = *N*,*N*-dimethylformamide.

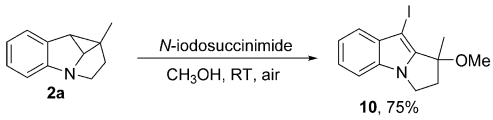
bioactivities such as anti-inflammation and antitumor activity.[16] Hydrogenation of **4a** with H_2, catalyzed by Pd/C, led to the cyclopropane-fused pyrrolizidine **8** in 85% yield (Scheme 4). The cyclopropane-fused indoline **2f** can undergo cyclopropane ring opening under visible-light photolysis to give **9** in 77% yield (Scheme 5),[17] the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole moiety of which is widely found in bioactive molecules.[18] Treatment of **2a** with *N*-iodosuccinimide in methanol under air led to the functionalized 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole **10** in 75% yield (Scheme 6).[19]



Scheme 4. Hydrogenation of **4a**.



Scheme 5. Cyclopropane ring opening of **2f** under visible-light photolysis. bpz = 2,2′-bipyrazine.



Scheme 6. Cyclopropane ring opening of **2a** by *N*-iodosuccinimide.

In conclusion, we have developed an efficient method for rapid construction of a range of nitrogen-containing polycycles from simple starting materials by a cobalt(II) porphyrin-catalyzed intramolecular cyclopropanation of N-alkyl indoles/pyrroles with alkyldiazomethanes generated in situ from hydrazones. A series of polycyclic cyclopropane-fused indolines and pyrrolines were obtained in moderate to high yields and with high chemoselectivity. Further elaboration of the as obtained polycycles provides straightforward access to a variety of N-heterocycles, including polysubstituted pyrrolizidines and other complex N-heterocycles. The use of bulky 2,4,6-triisopropylbenzenesulfonyl hydrazones as carbene precursors enables the cyclopropanation to occur under milder reaction conditions than those needed for their N-tosylhydrazone counterparts.

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