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Cobalt-Porphyrin-Catalyzed Intramolecular Buchner Reaction and Arene Cyclopropanation of In Situ Generated Alkyl Diazomethanes

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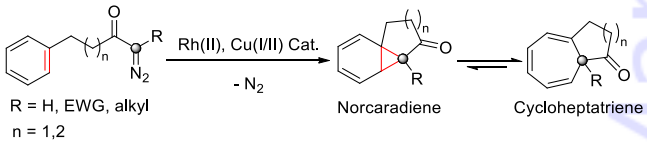
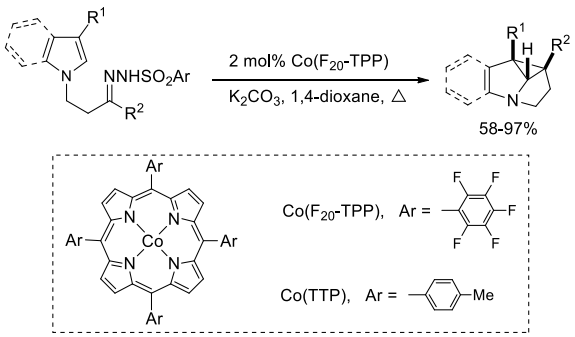
Abstract: Cobalt(II)-porphyrin catalyzed intramolecular Buchner reaction and arene cyclopropanation of alkyl diazomethanes generated in situ from *N*-tosylhydrazones gave a range of bicyclic cycloheptatriene fused pyrrolidines and tetracyclic cyclopropane fused pyrrolidines in good to high yields and with high chemo- and regioselectivities. The obtained cyclopropane fused pyrrolidines can be readily converted into other *N*-heterocycles with potential synthetic and biological interest.

Keywords: Carbenoids; Buchner reaction; Arene cyclopropanation; Cobalt catalysis; Heterocycles

Dearomatization is an appealing strategy for the construction of complex cyclic molecules as numerous aromatic compounds are commercially available or readily accessible.[1] Among the various dearomatization reactions, transition-metal-catalyzed Buchner reaction and arene cyclopropanation with diazo compounds are efficient methods for the construction of cycloheptatrienes and norcaradienes, both of which are useful building blocks in organic synthesis (Scheme 1).[2,3,4] It is generally conceived that the first step of Buchner reaction is the cyclopropanation of a benzenoid double bond with metal carbene to generate a norcaradiene. The initial product is prone to electrocyclic ring opening leading to a more stable tautomer cycloheptatriene. Intramolecular Buchner reaction could be controlled to stop at the arene cyclopropanation stage by destabilization of cycloheptatriene through tuning the linker between arene and diazo group or adjusting substituent (R) on metal carbene (Scheme 1). However, due to the facile tautomerization of norcaradiene to cycloheptatriene, reports on arene cyclopropanation [4] are sparse compared to Buchner reactions. Over the past decades, there have been extensive studies on Buchner reaction and arene cyclopropanation with α-diazocarbonyl compounds as carbene source. Dirhodium carboxylates and Cu(I/II) complexes have been reported to be highly effective catalysts for such reactions.[2]



Scheme 1. Metal-catalyzed intramolecular Buchner reaction with α-diazocarbonyl compounds.



Scheme 2. Intramolecular heteroaromatic cyclopropanation of *in situ* generated alkyl diazomethanes catalyzed by cobalt(II)-porphyrin.

In 2014, we reported that alkyl diazomethanes, *in situ* generated from *N*-tosylhydrazones, are effective carbene source for intramolecular sp^3 C-H insertion to give substituted tetrahydrofurans and pyrrolidines in high yields and with excellent diastereoselectivity.[5] In 2015, May and co-workers reported a rhodium(II)-catalyzed hydrazone-initiated alkylcarbene/alkyne cascade reaction to form

polycyclic products.[6] With chiral Rh(I)/BINAP catalyst, Pla-Quintana and co-workers achieved an enantioselective cascade reaction of alkyl diazomethanes.[7] Very recently, we found that alkyl diazomethanes underwent chemoselective cyclopropanation with *N*-alkyl indoles/pyrroles with cobalt(II)-porphyrin as catalyst (Scheme 2), which enables rapid construction of a range of nitrogen-containing polycycles in good yields from readily accessible materials.[8] These works have demonstrated that alkyl diazomethanes can be used for various carbene transfer reactions with diastereo- and chemo-selectivity. Despite these advances, the alkylcarbene chemistry remains largely underdeveloped compared to that of acceptor-carbenes. So far the reports on metal-catalyzed alkylcarbene transfer reactions are rare. To further explore the reactivity and selectivity of alkylcarbenes, we turned our attention to Buchner reaction and arene cyclopropanation. Herein, is described a cobalt-porphyrin catalyzed intramolecular Buchner reaction and cyclopropanation of arenes with alkylcarbene.

We first examined the use of aniline-derived *N*-tosylhydrazone **1a** as substrate for intramolecular Buchner reaction. The target product **2a** has a cyclohepta[*b*]pyrrole structure which is found in some bioactive compounds (Figure 1). However, chemoselectivity of the reaction could be a challenge as there are several potential side reactions including 1) 1,2-hydride shift of carbene intermediate to form alkene **3a** (**3a'** and **3a''**), such a reaction has been observed in our previous work;[5,8] 2) tosylation of *N*-tosylhydrazones (**4a**);[9] 3) intramolecular aromatic C-H bond insertion (**5a**), similar reaction was found to be major when analogous *α*-diazocarbonyl compounds were used as substrates in dirhodium(II) catalysis.[10]

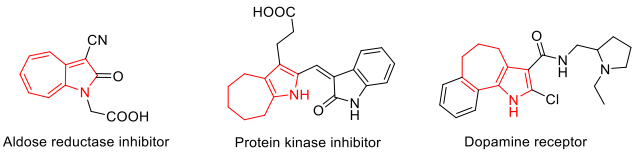
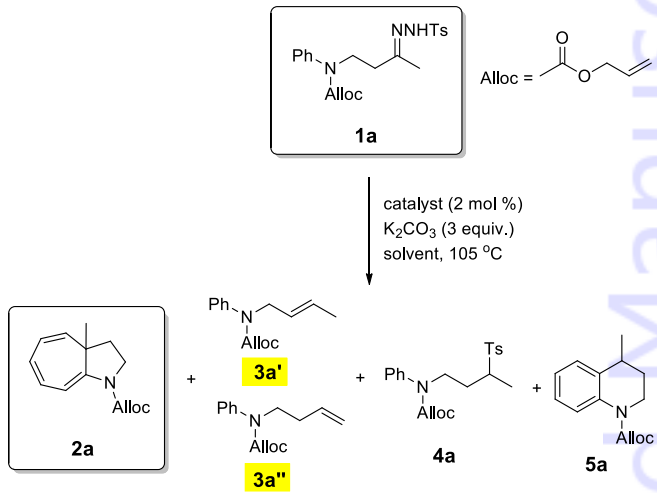


Figure 1. Examples of bioactive compounds containing cyclohepta[*b*]pyrrole structure.

At the outset, we examined the catalytic activity of a panel of transition metal catalysts towards the Buchner reaction of **1a**. Treatment of *N*-tosylhydrazone **1a** with K_2CO_3 (3 equiv.) and Co(TTP) (2 mol %) in 1,4-dioxane at 105 °C for 15 h led to cycloheptatriene fused pyrrolidine **2a** in 93% yield (Table1, entry 1), comparable yield was obtained with Co(F_{20}-TPP) as catalyst. When Co(PC) (PC = phthalocyanine) was used as catalyst, **2a** was obtained in moderate yield and low chemoselectivity (entry 3). The use of Co(salen) [salen = *N,N'*-bis(salicylidene)-1,2-cyclo-hexanediamine], $Co(OAc)_2{\cdot}4H_2O$, $Rh_2(OAc)_4$, Ru(TTP)CO or $[Ru(cymene)Cl_2]_2$ as catalyst led to alkene **3a** as major product (entry 4-8). When Ir(TTP)Me or CuI was used as catalyst, both alkene products **3a** (**3a'** and **3a''**) and tosylation product **4a** were obtained as major products (entry 9-10). The absence of catalyst led to low product yield and poor chemoselectivity (entry 11). With Co(TTP) as catalyst, the effect of solvent was examined (entry 12-14). The use of toluene and $PhCF_3$ led to **2a** in 75% and 59% yield respectively, along with alkene **3a** in 12-32% yield. When 1,2-dichloroethane was used as solvent, trace amount of **2a** was obtained. Screening of bases revealed that K_2CO_3 was the best, whereas other bases, including NaH, LiO^{t}Bu and TMSONa, were less effective (see Supporting Information).

Table 1. Screening of catalyst and reaction condition.[a]

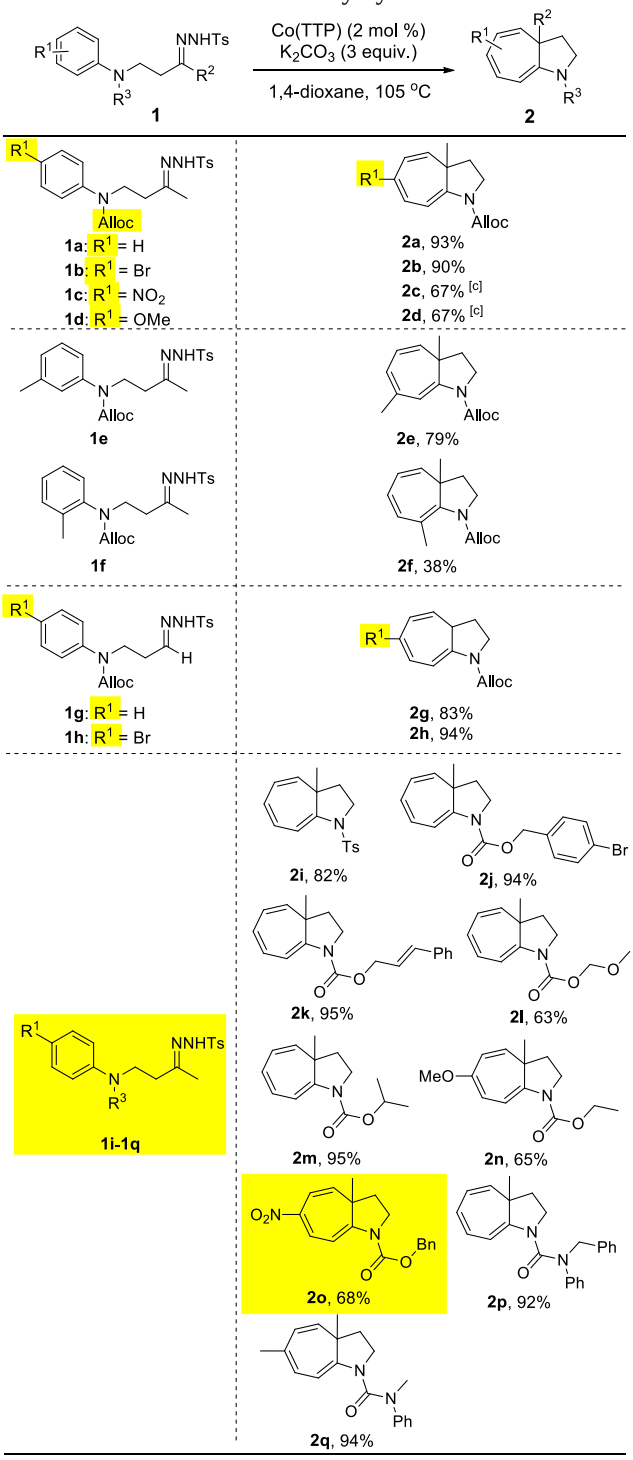


Entry	Catalyst	Solvent	Overall Yield [%][b]	Ratio[b] **2a**:**3a**:**4a**:**5a**
1	Co(TTP)	dioxane	94	99:1:0:0
2	Co(F_{20}-TPP)	dioxane	99	97:3:0:0
3	Co(PC)	dioxane	52	63:37:0:0
4	Co(salen)	dioxane	60	15:85:0:0
5	$Co(OAc)_2{\cdot}4H_2O$	dioxane	40	7:93:0:0
6	$Rh_2(OAc)_4$	dioxane	23	14:86:0:0
7	Ru(TTP)CO	dioxane	89	4:96:0:0
8	$[Ru(cymene)Cl_2]_2$	dioxane	79	11:89:0:0
9	Ir(TTP)Me	dioxane	90	1:77:22:0
10	CuI	dioxane	70	2:55:43:0
11	None	dioxane	22	15:67:18:0
12	Co(TTP)	Toluene	87	86:14:0:0
13	Co(TTP)	$PhCF_3$	91	65:35:0:0
14	Co(TTP)	DCE[c]	3	67:33:0:0

[a] The reaction was carried out with **1a** (0.2 mmol), K_2CO_3 (3 equiv.) and catalyst (2 mol %) in 1 mL solvent under N_2.

[b] Determined by ^{1}H NMR.
[c] 1,2-Dichloroethane, reaction was carried out at 84 °C.

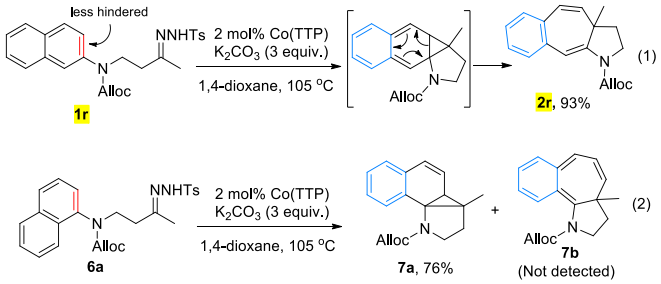
Table 2. Co(TTP)-catalyzed intramolecular Buchner reaction of aniline derived *N*-tosylhydrazones [a,b]



[a] The reaction was carried out with **1** (0.2 mmol), K_2CO_3 (3 equiv.) and Co(TTP) (2 mol %) in 1 mL 1,4-dioxane under N_2.
[b] Isolated yield.
[c] Byproduct alkene was observed in around 20% yield.

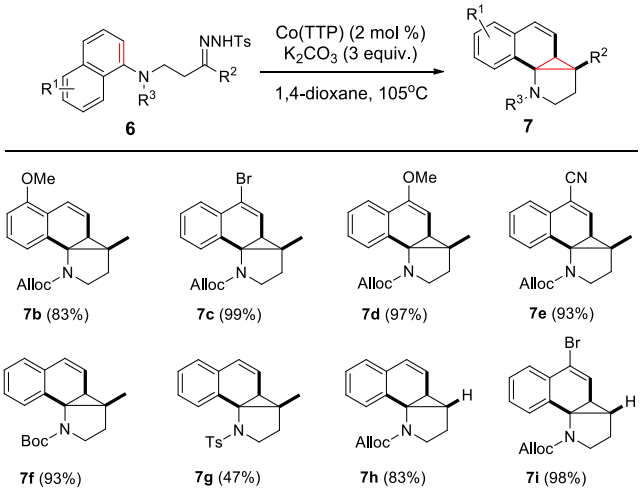
With the optimised conditions, we examined the substrate scope of the Co(II)-catalyzed Buchner reaction. As depicted in Table 2, various *N*-tosylhydrazones derived from different anilines underwent intramolecular Buchner reactions to give cycloheptatriene fused pyrrolidines in good to high yields. The reaction is tolerant of a variety of functional groups (Table 2). When para-substituent R^1 of arene is H or Br, corresponding cycloheptatriene fused pyrrolidine **2a** and **2b** were obtained in 93% and 90% yield, respectively. However, when R^1 is electron-withdrawing group (NO_2), the reaction furnished Buchner product **2c** in 68% yield. These results are indicative of the electrophilic nature of the as formed cobalt-alkylcarbene intermediate. In the reaction of **1c**, alkene was found to be the major byproduct (around 20% yield) revealing that 1,2-hydride migration of carbene intermediate would become competitive when substrate is less reactive. Interestingly, when R^1 is the electron-donating methoxy group (**1d**), similar result (**2d**) was obtained. This suggests that electronic properties of arene substituents may not be the sole factors affecting the Buchner reaction. Monitoring the reaction course by TLC revealed that aryl substitution has little influence on the reaction rate as all of the reactions of **1a**-**1d** required around 15 h for completion. This indicates that the cyclopropanation/tautomerization step might not be rate-determining in the Co(II)-catalyzed Buchner reaction of *N*-tosylhydrazones.

The Co(II) catalyzed Buchner reaction was found to be highly regioselective. For example, the reaction of *N*-tosylhydrazone **1e** bearing a *meta* methyl substitution gave the sole isomeric product **2e** derived from the attack of carbene to the π bond most remote to *meta* substituent. The analogous reaction of *α*-diazocarbonyl compounds catalyzed by $Rh_2(OAc)_4$ was reported to give corresponding cycloheptatriene in high yields but with moderate regioselectivity (rr = 70:30).[11] For the reaction of **1f** having an *ortho* methyl substituent, corresponding **2f** was obtained as sole isomer in 38% yield presumably due to steric hindrance. Besides the ketone-based substrates, aldehyde-based *N*-tosylhydrazones **1g** and **1h** were also reactive towards the Buchner reaction leading to corresponding products **2g** and **2h** in 83% and 94% yield, respectively. The effect of *N*-substitution was also examined. Various *N*-substituents (**2i**-**2q**) were found to be compatible with the Co(II)-catalyzed Buchner reaction, including Alloc, Cbz, Ts and carbamide, all of which can be readily removed according to literature method.[12]



Notably, when the two naphthylamine derived *N*-tosylhydrazones **1r** and **6a** were used (eq. 1 and 2), in which amino substitution is respectively at 2 and 1 position of naphthalene, two different types of products (**2r** and **7a**) were formed. Like aniline derived *N*-tosylhydrazones, **1r** underwent cyclopropanation with the less sterically hindered double bond of naphthalene and subsequent electrocyclic ring opening to give the Buchner product **2r** in 93% yield with high regio- and chemo-selectivity. In contrast, the reaction of **6a** stopped at the cyclopropanation stage to give a tetracyclic compound **7a** in 76% yield, no Buchner product **7b** was observed. The electrocyclic ring opening of **7a** to **7b** might be kinetically and thermodynamically disfavoured by a concomitant dearomatization.

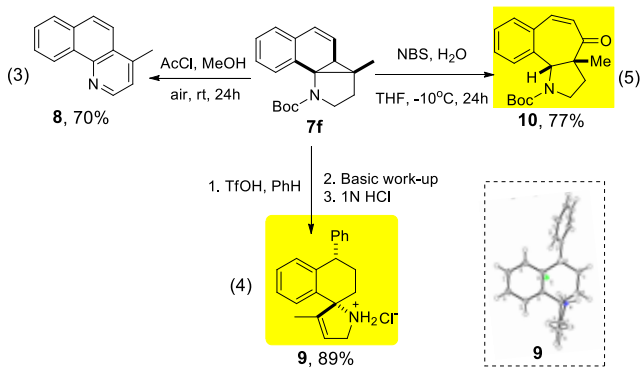
Table 3. Co(TTP)-catalyzed intramolecular arene cyclopropanation of naphthylamine derived *N*-tosylhydrazones[a,b]



[a] The reaction was carried out with **6** (0.2 mmol), K_2CO_3 (3 equiv.) and Co(TTP) (2 mol %) in 1 mL 1,4-dioxane under N_2.
[b] Isolated yield.

In contrast to the well-studied Buchner reaction, arene cyclopropanation remains far less explored due to facile tautomerization of norcaradiene. In this work, we performed a study on this transformation by designing substrates analogous to **6a** (Table 3). Firstly, we examined the effect of naphthalene substitution (R^1) on the intramolecular arene cyclopropanation. Several naphthylamine derived *N*-tosylhydrazones bearing electron-donating (OMe) and withdrawing (Br and CN) groups respectively were examined with Co(TTP) as catalyst. The results revealed that electronic property of the substituents has only a slight influence on the arene cyclopropanation as similar product yields (83-99%) were obtained (**7b**-**7e**). In contrast with the Buchner reaction of **1c**-**1d** (Table 2), no byproduct alkenes were observed in the cyclopropanation of **6b**-**6e**. A possible explanation for this phenomenon could be that naphthalene, compared to benzene, is more reactive due to lower resonance energy,[13] which would facilitate the cyclopropanation reaction, thus suppressing the competitive side reaction of 1,2-hydride shift of carbene intermediate. High product yields were also obtained when the *N*-substituent was Boc (**7f**, 93% yield). However, the use of Ts as N protecting group has detrimental effect on the reaction leading to **7g** in 47% yield, and retro-Michael addition product was found to be the major byproduct. *N*-tosylhydrazones derived from aldehydes were also reactive towards the cyclopropanation giving corresponding products in high yields (**7h** and **7i**). The relative stereochemistry of compound **7f** was determined by NOE experiments (spectra are provided in the Supporting Information).

The thus obtained tetracyclic cyclopropane products can be readily converted to other *N*-heterocycles. Treatment of **7f** with acyl chloride in MeOH under open air led to benzo[*h*]quinoline **8** in 70% yield (eq. 3). Benzo[*h*]quinolines are commonly used as ligand in the preparation of luminescent cyclometalated Ir complexes.[14] They have also been found to display central nervous system action and antibacterial activity.[15] When **7f** was subjected to TfOH in benzene, a tricyclic spiro-2,5-dihydro-1*H*-pyrrole **9** [16] was obtained in 89% yield presumably through cyclopropane ring opening and arylation with benzene (eq. 4). Compound **7f** also underwent cyclopropane ring opening by treating with NBS and H_2O to give a tricycle-fused pyrrolidine **10** in 77% yield (eq. 5), its analogues have often been found in bioactive compounds.[17]



Scheme 3. Ring opening and related transformations of **7f**

In conclusion, we have demonstrated that alkyl diazomethanes generated *in situ* from *N*-tosylhydrazones are effective carbene source for Co(II)-porphyrin catalyzed intramolecular Buchner reaction and arene cyclopropanation in chemo- and regio-selective manner. The unique tetracyclic *N*-heterocycles obtained from intramolecular cyclopropanation of naphthylamine derived *N*-tosylhydrazones can be readily converted to other *N*-heterocycles with potential synthetic and biological interests. To our best knowledge, this work represents the first example of metal catalyzed Buchner reaction and arene cyclopropanation via intermediacy of alkylcarbene.

Experimental Section

General procedure for Co(TTP)-catalyzed intramolecular Buchner reaction and arene cyclopropanation reaction of alkyl diazomethanes *in situ* generated from *N*-tosylhydrazones

A reaction vessel was charged with *N*-tosylhydrazone (0.2 mmol), potassium carbonate (83 mg, 3 equiv), Co(TTP) (3 mg, 2 mol %) and dry 1,4-dioxane (1.0 mL). The mixture was stirred at 105 °C until the substrate was fully consumed. The reaction mixture was cooled to room temperature and filtered, the filtrate was concentrated, and the residue was purified by silica gel column chromatography to give corresponding products.

Acknowledgements

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