VIP C–H Functionalization Very Important Paper

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Ruthenium–Porphyrin-Catalyzed Diastereoselective Intramolecular Alkyl Carbene Insertion into C–H Bonds of Alkyl Diazomethanes Generated In Situ from *N*-Tosylhydrazones**

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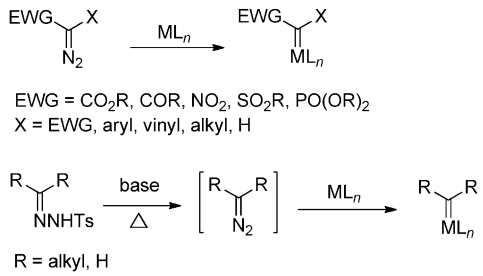
Abstract: *With a ruthenium–porphyrin catalyst, alkyl diazomethanes generated in situ from N-tosylhydrazones efficiently underwent intramolecular C(sp^3)–H insertion of an alkyl carbene to give substituted tetrahydrofurans and pyrrolidines in up to 99% yield and with up to 99:1 cis selectivity. The reaction displays good tolerance of many functionalities, and the procedure is simple without the need for slow addition with a syringe pump. From a synthetic point of view, the C–H insertion of N-tosylhydrazones can be viewed as reductive coupling between a C=O bond and a C–H bond to form a new C–C bond, since N-tosylhydrazones can be readily prepared from carbonyl compounds. This reaction was successfully applied in a concise synthesis of (+)-pseudoheliotridane.*

Metal-catalyzed carbene C–H insertion reactions are widely used in organic synthesis,[1] but related reactions involving alkyl carbenes are underdeveloped. As alkyl groups are electronically and structurally different from unsaturated acceptor/aryl groups (Scheme 1), new reactivity and selectivity of C–H insertion of alkyl carbenes and hence new applications can be envisioned. Alkyl carbene complexes of early transition metals feature a strong M=C bond with a nucleophilic C atom and do not undergo electrophilic carbene C–H insertion.[2] Although late-transition-metal complexes, such as dirhodium(II,II) carboxylates, are well-documented to catalyze carbene C–H insertion reactions of α-diazocarbonyl compounds,[1] to the best of our knowledge, metal-catalyzed carbene C(sp^3)–H insertion reactions of alkyl diazomethanes have not been reported.[3] Recent studies showed that $Pd^{0/II}$ complexes can catalyze reactions of carbenes generated from aryl diazomethanes or alkyl diazomethanes to give cross-coupling products.[4]



Scheme 1. Metal–acceptor carbenes from stabilized diazo compounds and metal–alkyl carbenes from alkyl diazomethanes. EWG = electron-withdrawing group, Ts = *p*-toluenesulfonyl.

A major challenge in metal-catalyzed alkyl carbene C–H insertion/transfer reactions is the low stability of alkyl diazomethanes, which are the common source of alkyl carbenes. To circumvent this difficulty, Morandi and Carreira reported the in situ generation of diazomethane from a water-soluble diazald derivative for the cyclopropanation of alkenes.[5] *N*-Tosylhydrazones have been reported for the in situ generation of the reactive alkyl diazomethanes and aryl diazomethanes.[4,6] Herein we describe the first example of metal-catalyzed intramolecular alkyl carbene C–H insertion in which alkyl diazomethanes generated in situ from alkyl *N*-tosylhydrazones are used as the carbene source. The protocol described herein can be used for the stereoselective synthesis of a wide variety of substituted tetrahydrofurans[7] and pyrrolidines.[8] The latter are commonly found in natural products and pharmaceuticals. As alkyl *N*-tosylhydrazones can be obtained by the treatment of alkyl-substituted ketones/aldehydes with tosylhydrazine, a one-pot reaction was developed for stereoselective intramolecular C–C bond formation from alkyl ketones/aldehydes.

We used *N*-tosylhydrazone **1a** to establish the optimal reaction conditions. Treatment of the sodium salt of **1a**, generated in situ from **1a** and NaO*t*Bu, with the catalyst [Ru(TTP)(CO)] (1 mol%) in toluene at 110°C for 5 h afforded the 2,3-disubstituted tetrahydrofuran **2a** in 78% yield with excellent diastereoselectivity (*cis*/*trans* > 95:5; Scheme 2). The *cis* configuration of the major isomer was established by NMR spectroscopy. Other catalysts, including [Fe(TTP)Cl], [Ru(cymene)Cl_2], [Ru(salen)(CO)] (salen = *N*,*N*′-bis(3-bromosalicylidene)-1,2-cyclohexanediamino), [$Rh_2(CH_3CO_2)_4$], [Rh_2(esp)$_2$],[9] and $Cu(OTf)_2$, gave **2a** in 11–43% yield with diastereomeric ratios of 55:45–81:19 (see the Supporting Information). Other [Ru(Por)CO] catalysts (H_2por = porphyrin) were also effective: [Ru(TMP)(CO)] and [Ru(F_{20}-TPP)(CO)] afforded **2a** in 65 and 53% yield, respectively, with *cis*/*trans* ratios of around 95:5. In the absence of a metal catalyst, **2a** was obtained in 13% yield and

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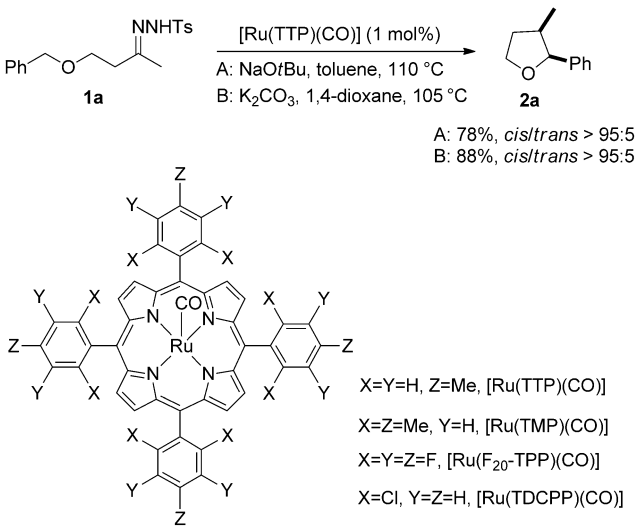


Scheme 2. [Ru(TTP)(CO)]-catalyzed cyclization of **1a** to give **2a** and the structure of porphyrins used in this study.

with a *cis*/*trans* ratio of 55:45. With [Ru(TTP)(CO)] as the catalyst, the screening of solvents and bases revealed that a combination of K_2CO_3 and 1,4-dioxane led to an improvement in the product yield to 88% (Scheme 2); other bases, including Li_2CO_3, Na_2CO_3, and Cs_2CO_3, were less effective. No coupling reaction of the diazo compound was observed in the cyclization.

Various *N*-tosylhydrazones **1b–m** derived from β-alkoxy ketones and aldehydes underwent cyclization to give the corresponding substituted tetrahydrofurans in moderate to high yields and with moderate to excellent diastereoselectivity (Table 1). The reaction tolerated a variety of functionalities, including hydroxy, halo, nitro, methoxy, acetal, and alkene groups. The cyclization of **1b–d**, with various benzyl substituents, gave the desired products in 73–91% yield and with excellent *cis* selectivity (*cis*/*trans* ≈ 95:5; Table 1, entries 1–3); electron-donating and electron-withdrawing groups on the phenyl ring had a minor effect on the product yield and diastereoselectivity. Alkyl-substituted *N*-tosylhydrazones **1e–g** were also reactive, and the aliphatic products of C–H bond insertion were obtained in 52–94% yield with *cis*/*trans* ratios of 66:34–83:17 (Table 1, entries 4–6). For **1e** and **1f**, which contain an alkene and a hydroxy functionality, respectively, no alkene cyclopropanation or carbene O–H insertion was observed.

Under the conditions employed, insertion of the carbene into tertiary C–H bonds of *N*-tosylhydrazones gave the corresponding products with a quaternary carbon center in high yields (Table 1, entries 7–9). For example, the reaction of **1h** gave spiroketal **2h** in 80% yield and with d.r. > 95:5. The spiroketal is a structural subunit present in a broad range of bioactive natural products.[10] The optically active *N*-tosylhydrazone **1j** (96% *ee*) underwent stereospecific C–H insertion to give **2j** in 79% yield with complete retention of configuration. A similar stereospecific dirhodium(II,II)-catalyzed cyclization of diazocarbonyl compounds has also been reported.[11]

Table 1: Ruthenium–porphyrin-catalyzed cyclization of *N*-tosylhydrazones to give tetrahydrofurans and pyrrolidines.[a]

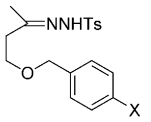
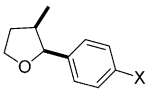
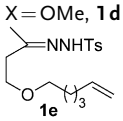
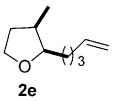
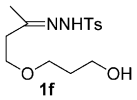
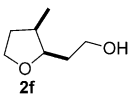
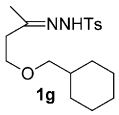
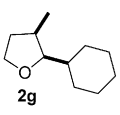
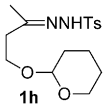
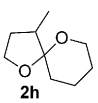
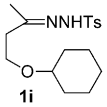
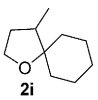
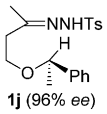
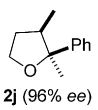
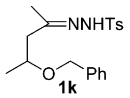
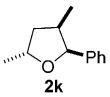
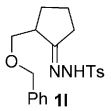
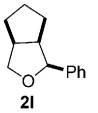
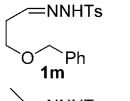
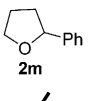
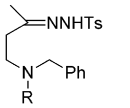
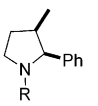
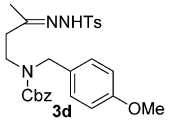
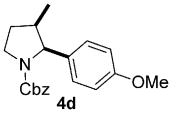
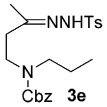
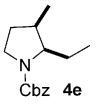
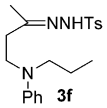
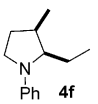
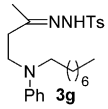
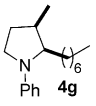
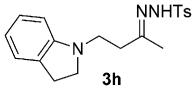
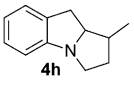
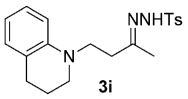
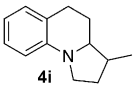
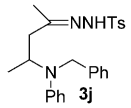
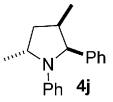
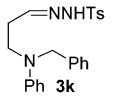
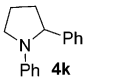
Entry	Substrate	Product	Yield [%][b]	*cis*/*trans*[c]
				
1	X = Br, **1b**	**2b**	91	> 95:5
2	X = NO_2, **1c**	**2c**	77	94:6
3	X = OMe, **1d**	**2d**	73	> 95:5
4	 **1e**	 **2e**	84	69:31
5	 **1f**	 **2f**	52	66:34
6	 **1g**	 **2g**	94	83:17
7	 **1h**	 **2h**	80	> 95:5[d]
8	 **1i**	 **2i**	78	
9	 **1j** (96% *ee*)	 **2j** (96% *ee*)	79	> 99:1
10	 **1k**	 **2k**	82	90:10[e]
11	 **1l**	 **2l**	54	> 99:1
12	 **1m**	 **2m**	43	
				
13	R = Ph, **3a**	**4a**	99	> 99:1
14	R = Cbz, **3b**	**4b**	92	> 99:1
15	R = Me, **3c**	**4c**	50	> 99:1
16	 **3d**	 **4d**	90	> 99:1
17	 **3e**	 **4e**	50	> 99:1
18	 **3f**	 **4f**	94	> 99:1

Table 1: (Continued)

Entry	Substrate	Product	Yield [%][b]	*cis*/*trans*[c]
19	 **3g**	 **4g**	98	>99:1
20	 **3h**	 **4h**	85	70:30[f]
21	 **3i**	 **4i**	99	71:29
22	 **3j**	 **4j**	98	90:10[e]
23	 **3k**	 **4k**	92	

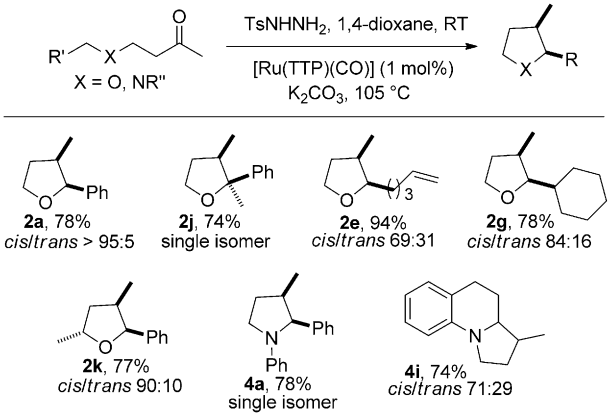
[a] Reaction conditions: **1**/K_2CO_3/[Ru(TTP)(CO)] = 1:3:0.01, 105 °C, 10 h, N_2 atmosphere. [b] Yield of the isolated product. [c] The *cis*/*trans* ratio was determined by ^{1}H NMR spectroscopy. [d] The configuration was not determined. [e] The product was obtained with a *cis*–*trans*/*cis*–*cis* ratio of 90:10. [f] The reaction was carried out at 90 °C; the product was obtained with a *trans*/*cis* ratio of 70:30. Cbz = carboxybenzyl.

The reaction of the β-substituted *N*-tosylhyrazone **1k** furnished the 2,3,5-trisubstituted tetrahydrofuran **2k** in 89% yield with a *cis*–*trans*/*cis*–*cis* ratio of 90:10. Thus, two new contiguous stereogenic centers were generated with a high level of diastereoselectivity (Table 1, entry 10). The analogous reaction of diazocarbonyl compounds under the catalysis of $[Rh_2(CH_3CO_2)_4]$ was reported to give the corresponding tetrahydrofurans with moderate diastereoselectivity (d.r. 75:25).[12] The *N*-tosylhydrazones **1l** and **1m** derived from a cyclic ketone and an aldehyde were also reactive and were converted into the corresponding cyclization products in 54 and 43% yield, respectively (Table 1, entries 11 and 12). In the reaction of **1l**, a fused bicyclic tetrahydrofuran was formed with exclusively *cis* selectivity.

The present catalytic method is applicable to the stereoselective synthesis of substituted pyrrolidines, which are a structural motif prevalent in natural alkaloids. Although α-diazoamides have been reported to undergo cyclization to give four- or five-membered lactams in the presence of a dirhodium(II,II) catalyst,[1a,c] direct access to pyrrolidines through carbene C–H insertion is unprecedented.

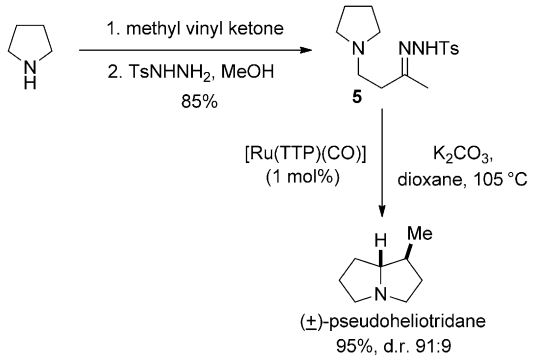
The treatment of *N*-tosylhydrazone **3a** with K_2CO_3 in the presence of [Ru(TTP)(CO)] (1 mol%) in 1,4-dioxane at 105 °C for 9 h gave the *cis* pyrrolidine **4a**[13] as a single isomer in 99% yield (Table 1, entry 13). When *N*-tosylhydrazone **3c** was used, both insertion into a benzylic C–H bond and insertion into a primary C–H bond of the methyl group were observed (Table 1, entry 15). In contrast to the reactions of alkyl-substituted *N*-tosylhydrazones **1e**–**g** (Table 1, entries 4–6), which gave the corresponding tetrahydrofurans with moderate diastereoselectivity, the amino analogues **3e**–**g** underwent cyclization to give the desired products with excellent *cis* selectivity (*cis*/*trans* > 99:1) and in up to 98% yield (Table 1, entries 17–19). *N*-Tosylhydrazones **3h** and **3i** bearing indoline and 1,2,3,4-tetrahydroquinoline moieties were converted into the tricyclic pyrrolidines **4h** and **4i** in 85 and 99% yield, respectively, and with d.r. values around 70:30 (Table 1, entries 20 and 21). The *N*-tosylhydrazone **3k** derived from an aldehyde was also a suitable substrate and was converted into **4k** in 92% yield (Table 1, entry 23). The formation of alkene side products derived from 1,2-hydride migration of the carbene intermediate was detected (2–20% yield) in the cyclization of **1a**–**m**. However, for the cyclization of **3a**–**k** (except **3e**) to form pyrrolidines, no alkenes were detected. The reaction of **3e** gave product **4e** in 50% yield along with an alkene side product in 45% yield. This result with **3e** can be attributed to N-substitution with Cbz, which decreased the ability of the nitrogen atom to activate the adjacent C–H bond.

Since *N*-tosylhydrazones can be obtained by the treatment of carbonyl compounds with $TsNHNH_2$, we explored the [Ru(TTP)(CO)]-catalyzed cyclization reaction directly from carbonyl compounds in a one-pot fashion. A solution of the carbonyl compound and $TsNHNH_2$ in dioxane was stirred at room temperature for 3 h, and then K_2CO_3 and [Ru(TTP)(CO)] were added, and the mixture was heated at 105 °C for 10 h. Seven examples were examined, and the corresponding cyclization products were formed in 74–94% yield (Scheme 3). When the [Ru(TTP)(CO)]-catalyzed cyclization of **1a** was scaled up to a 2 g scale, **2a** was obtained in 85% yield after a reaction time of 15 h.

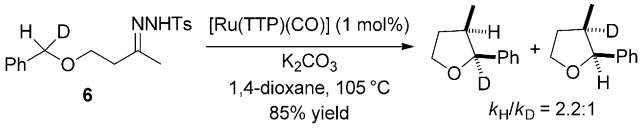


Scheme 3. One-pot ruthenium–porphyrin-catalyzed intramolecular C–H insertion of ketones. The reactions were carried out with a 1:1.05:10:0.01 ketone/$TsNHNH_2$/K_2CO_3/[Ru(TTP)(CO)] ratio. The yields given are for the isolated product.

To illustrate the synthetic utility of the [Ru(TTP)(CO)]-catalyzed alkyl carbene C(sp^3)–H insertion, we undertook a short synthesis of the pyrrolizidine alkaloid (±)-pseudoheliotridane (Scheme 4). The *N*-tosylhydrazone **5** was synthesized in two steps (Michael addition and condensation) from pyrrolidine. Treatment of **5** under the aforementioned reaction conditions gave (±)-pseudoheliotridane in 95% yield (73% overall yield) with d.r. 91:9. Thus, this synthetic



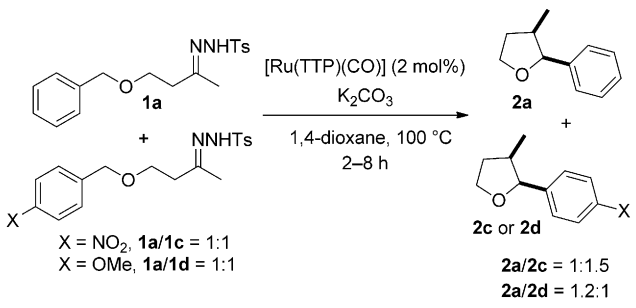
Scheme 4. Synthesis of (±)-pseudoheliotridane by the [Ru(TTP)(CO)]-catalyzed cyclization of **5**.



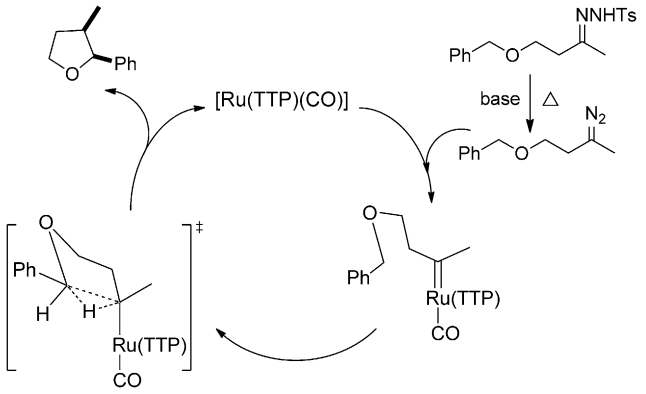
Scheme 5. KIE for the [Ru(TTP)(CO)]-catalyzed cyclization of **6.**

route proved highly efficient in terms of the simplicity of the starting materials, the high overall yield, the low number of reaction steps, and the convenient manipulation of intermediates.[14]

To gain insight into the reaction mechanism, we examined the kinetic isotope effect (KIE) by using the monodeuterated *N*-tosylhydrazone **6** (Scheme 5). Analysis of the C–H and C–D insertion products (total yield: 85%) by ^{1}H NMR spectroscopy showed a k_H/k_D ratio of 2.2:1. This KIE value is comparable to those of the dirhodium(II,II)-catalyzed intra- and intermolecular carbene C–H insertion of diazocarbonyl compounds ($k_H/k_D = (1–3.5):1$)[15] and intramolecular nitrene C–H insertion of sulfamates ($k_H/k_D = 1.9$):[16] reactions generally conceived to proceed through a concerted C–H insertion pathway.[1,17] In this study, excellent stereospecificity was observed (Table 1, entry 9). We next performed a competitive cyclization of **1a** and **1c** (Scheme 6; see also the Supporting Information) and obtained **2a** and **2c** in a 1:1.5 ratio. Likewise, the competitive cyclization of **1a** and **1d** gave **2a** and **2d** in a ratio of 1.2:1. Thus, a change in the *para* substituent on the phenyl ring from an electron-withdrawing to an electron-donating substituent has only a minor effect on the overall transformation.[15a,18]



Scheme 6. Competition experiments: [Ru(TTP)(CO)]-catalyzed cyclization of **1a** and **1c**/**1d**.



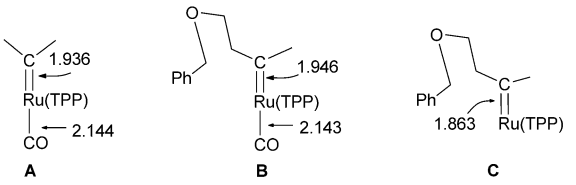
Scheme 7. Proposed reaction mechanism of the alkyl carbene C–H insertion catalyzed by [Ru(TTP)(CO)].

A proposed mechanism is depicted in Scheme 7. In this study, the reaction of [Ru(TTP)(CO)] with **1a** (2 equiv) gave **2a** in 81% yield with 83% of [Ru(TTP)(CO)] recovered (the IR spectrum of the recovered catalyst showed a strong band at $\tilde{\nu}$ =1937 cm^{-1}), thereby lending support to [Ru(TTP)(CO)-(CR^{1}R^2)] as a reaction intermediate responsible for intramolecular carbene C–H insertion.

To examine the effect of a *trans* CO ligand on the ruthenium–alkyl carbene moiety, we undertook DFT calculations on [Ru(TPP)(CO)(C{CH$_3$}$_2$)] (**A**), [Ru(TPP)(CO)-(C{CH$_3$}CH$_2$CH$_2$OCH$_2$Ph)] (**B**), and [Ru(TPP)(C{CH$_3$}-CH$_2$CH$_2$OCH$_2$Ph)] (**C**). The structures of **A**–**C** were optimized at the B3LYP/6-31G(d):lanl2dz level of theory, and selected geometrical parameters are depicted in Table 2.

Table 2: Calculated bond distance, bond-dissociation energy (BDE), and electrostatic potential charge of the carbene carbon atom (C(Q)) of the Ru=C(carbene) moiety in complexes **A**–**C**.

	A	B	C
Ru=C distance [Å]	1.936	1.946	1.863
BDE [kcal mol^{-1}]	41.7	38.1	100.4
C(Q) [e]	0.337	0.324	0.316

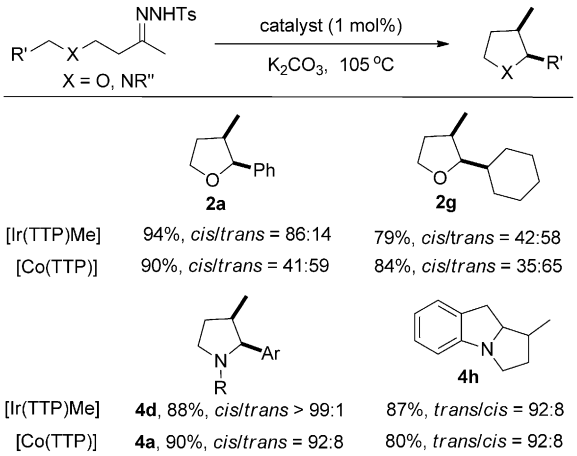


Natural bond orbital (NBO)[19] and charge decomposition analyses (CDA)[20] were used to analyze the orbital correlation diagram and the carbene electrostatic potential charges of **A**–**C** (Table 2; see also the Supporting Information, including Figure S1).

The calculated Ru=C distances of **A**–**C** are comparable to those of analogous ruthenium–carbene complexes whose structures have been determined by X-ray crystal-structure analysis.[21] Both **A** and **B** show significantly longer Ru=C distances (1.936 and 1.946 versus 1.863 Å) and lower Ru=C BDE values (38.1–41.7 versus 100.4 kcal mol^{-1}) than those of

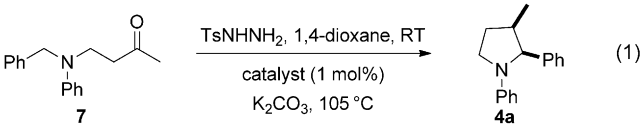
C (Table 2), in line with the significant *trans* effect of the CO ligand on the ruthenium–alkyl carbene moiety.[21,22] DFT calculations on the [Ru(Por)CO]-catalyzed cyclization of **1a** revealed that C–H insertion via **B** is thermodynamically and kinetically more favorable than that via **C** (the activation energy via **B** and **C** is 14.1 and 37.5 kcal mol^{-1}, respectively; see the Supporting Information). The relatively low activation energy via **B** stands in contrast to the high reaction temperature of 105 °C (Table 1), thus suggesting that the decomposition of *N*-tosylhydrazones to generate alkyl diazomethanes in situ is crucial in the aforementioned [Ru(Por)(CO)] catalysis. NBO analysis (Table 2) revealed that the carbene carbon atom is electrophilic, as evidenced by the positive partial electrostatic potential (ESP) charge of 0.337 e.

Are [Ru(Por)(CO)] catalysts unique? We found that [Ru(TDCPP)(IPr)$_2$] (Ipr = *N*,*N*′-diisopropylimidazol-2-ylidene; see Table S1), [Ir(Por)Me], and [Co(Por)] are also effective in catalyzing the alkyl carbene C–H insertion reactions. As shown in Scheme 8, the cyclization of **1a**,**g** catalyzed by [Ir(TTP)Me] and [Co(TTP)] gave **2a**,**g** with

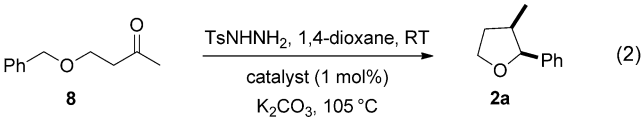


Scheme 8. Iridium–porphyrin- and cobalt–porphyrin-catalyzed cyclization of *N*-tosylhydrazones. The reactions were carried out with a 1:3:0.01 *N*-tosylhydrazone/K_2CO_3/([Ir(TTP)Me] or [Co(TTP)]) ratio. The yield was determined by ^{1}H NMR spectroscopy with 4-iodoanisole as an internal standard. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

lower diastereoselectivity than that observed with [Ru(TTP)(CO)] as the catalyst. On the other hand, the [Ir(TTP)Me]-catalyzed cyclization of **3d** to **4d** and [Co(TTP)]-catalyzed cyclization of **3a** to **4a** proceeded with diastereoselectivity comparable to that observed with [Ru(TTP)(CO)]. Catalysts [Ir(TTP)Me] and [Co(TTP)] both gave **4h** with a diastereomeric ratio of 92:8, which is higher than that observed with [Ru(TTP)(CO)]. These two catalysts are also effective for the one-pot cyclization of ketones. For example, the treatment of ketone **7** with [Ir(TTP)Me] or [Co(TTP)] under one-pot reaction conditions afforded **4a** in good yield with high diastereoselectivity [Eq. (1)]. Likewise, the reaction of **8** gave **2a** in good yield with good diastereoselectivity [Eq. (2)]. Thus, the [M(Por)X] core (M = metal ion; Por = porphyrin dianion; X = ligand *trans* to the alkyl carbene) is



[Ir(TTP)Me]: 72%, d.r. > 99:1
[Co(TTP)]: 55%, d.r. 93:7



[Ir(TTP)Me]: 92%, d.r. 88:12
[Co(TTP)]: 66%, d.r. 71:29

effective in capturing the reactive M–alkyl carbene moiety for subsequent C–H insertion reactions. By varying the structure of [M(Por)X], it may be possible to tune both the reactivity and selectivity of alkyl carbene C–H insertion.

In summary, alkyl diazomethanes generated in situ from *N*-tosylhydrazones are an effective carbene source for metalloporphyrin-catalyzed intramolecular C(sp^3)–H bond insertion to give a variety of substituted tetrahydrofurans and pyrrolidines with good diastereoselectivity. With [Ru(Por)(CO)] as the catalyst, good tolerance of diverse functionalities was observed, and the operational procedure is simple without the need for slow addition with a syringe pump. The synthetic utility of the reaction was demonstrated in a short synthesis of a pyrrolizidine alkaloid, (±)-pseudoheliotridane.

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Keywords: alkyl carbenes · alkyl diazomethanes · C–H insertion · homogeneous catalysis · ruthenium

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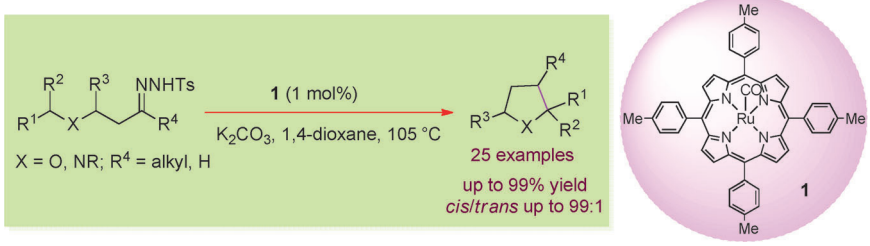
Communications

C–H Functionalization

A. R. Reddy, C.-Y. Zhou, Z. Guo, J. Wei, C.-M. Che* ——— ■■■■–■■■■

Ruthenium–Porphyrin-Catalyzed Diastereoselective Intramolecular Alkyl Carbene Insertion into C–H Bonds of Alkyl Diazomethanes Generated In Situ from *N*-Tosylhydrazones



Nose to tail: With a ruthenium–porphyrin catalyst, alkyl diazomethanes generated in situ from *N*-tosylhydrazones underwent efficient intramolecular C(sp^3)–H insertion to give substituted tetrahydrofurans and pyrrolidines (see scheme) in a reaction that can be viewed as a reductive coupling between C=O and C–H bonds to form a new C–C bond. This transformation was applied in a concise synthesis of (±)-pseudoheliotridane.