Ru^{V}-Acylimido Intermediate in $[Ru^{IV}(Por)Cl_2]$-Catalyzed C–N Bond Formation. Spectroscopic Characterization, Reactivity, and Catalytic Reactions

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Abstract: Metal-catalyzed C–N bond formation reactions via acylnitrene transfer have recently attracted much attention, but direct detection of the proposed acylnitrenoid/acylimido M(NCOR) (R = aryl or alkyl) species in these reactions poses a formidable challenge. Herein we report on Ru(NCOR) intermediates in C–N bond formation catalyzed by $[Ru^{IV}(Por)Cl_2]/N_3COR$, a catalytic method applicable to aziridine/oxazoline formation from alkenes, amination of substituted indoles, α-amino ketone formation from silyl enol ethers, amination of $C(sp^3)$–H bonds, and functionalization of natural products and carbohydrate derivatives (up to 99% yield). Experimental studies including HR-ESI-MS and EPR measurements, coupled with DFT calculations, lend evidence for the formulation of the Ru(NCOR) acylnitrenoids as a Ru^{V}-imido species.

Introduction

Catalytic nitrogen group transfer reactions via metal-imido or -nitrene intermediates, herein generally described as nitrenoids, represent an appealing method for C–N bond formation.[1] Acylnitrene (NCOR, R = aryl, alkyl) transfer is attractive for direct installation of useful functionalities such as *N*-acyl groups into hydrocarbon molecules; a hurdle to overcome is the proneness of acylnitrenes to undergo Curtius rearrangement,[2] which also poses challenges to direct detection of acylnitrenoid M(NCOR) intermediates in the catalytic processes. Worthy of note are the reports by Groves and co-worker[3] on stoichiometric aziridination of cyclooctene with $[Mn^{V}(Por)(N)]/(CF_3CO)_2O$ and by Carreira and co-workers[4] on stoichiometric amination of electron-rich alkenes with $L_nMn(N)/(CF_3CO)_2O$, all being proposed to involve $Mn(NCOCF_3)$ intermediates,[3,4] including $[Mn^{V}(TMP)(NCOCF_3)(CO_2CF_3)]$ by spectroscopic evidence.[3] As to catalytic reactions via acylnitrenoids, Mansuy and co-workers reported, in 1984, the styrene aziridination by $[Fe^{III}(TPP)Cl]/PhI{=}NCOCF_3$ (Figure 1aA).[5] In 2000, we reported C–H amination of ethylbenzene by, e.g., $Ru^{III}(Me_3tacn)/H_2NCOPh$.[6,7] Recently, there is a surge of interest in C–H amination with acyl azides N_3COR (**1**), dioxazolones,[8] H_2NCOCF_3, or *N*-substituted amides H(R′O)NCOR, as reported by Chang and others[9,10,12-15] employing directing group (DG) strategy (for intermolecular reactions) and by Warren and co-workers[11] using Cu^{I}(diketiminate)/N_3COR for hydrocarbons without DGs. These catalytic reactions proceed via proposed M(NCOR) intermediates (Figure 1aA, M = Fe,[5,9] Co,[10] Cu,[7a,11] Ru,[6,12] Rh,[13,14] Ir,[8,13c,15] Au[7b]). M(NCOR) (M = Cu,[16c,g] Ru,[16a,b,d,h] Ir[16e,f]) intermediates were also proposed in the corresponding catalytic reactions to give sufimides, oxazoles, oxazolines, lactams and amidines.[16] To the best of our knowledge, no example of M(NCOR) intermediates in catalytic reactions has been directly observed by spectroscopic analysis.[17]

Herein we describe spectroscopic studies including ESI-MS and EPR, and also DFT calculations, on Ru(NCOR) species involved in C–N bond formation reactions catalyzed by ruthenium porphyrin (Ru(Por)) complexes; these Ru(NCOR) species, generated in $[Ru^{IV}(Por)Cl_2]/N_3COR$(**1**) catalytic systems, could be formulated as Ru^{V}-imido complexes, being different from the sulfonyl/arylnitrenoids $[Ru^{VI}(Por)(NSO_2Ar)_2]$ [18] and $[Ru^{VI}(Por)(NAr)_2]$ [19] involved in stoichiometric or $[Ru^{II}(Por)(CO)]$-catalyzed reactions. The $[Ru^{IV}(Por)Cl_2]/N_3COR$ systems are applicable to catalytic C–N bond formation reactions using substrates without DGs to transform i) alkenes **2** to aziridines **3** or oxazolines **4**, ii) indoles **5** to C3-aminated derivatives **6**, iii) silyl enol ethers **7** to α-amino ketones **8**,

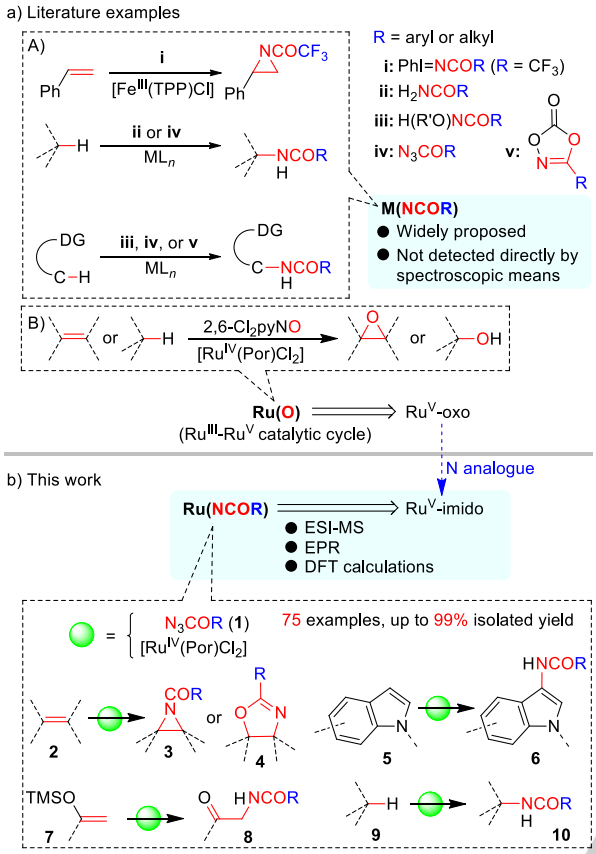


Figure 1. a) Literature examples: A) metal-catalyzed acylnitrene transfer reactions via proposed M(NCOR) intermediates, B) proposed $Ru^{V}(O)$ intermediates in $[Ru^{IV}(Por)Cl_2]$-catalyzed oxygen atom transfer reactions. b) $Ru^{V}(NCOR)$ active intermediates in this work, evidenced by experimental studies including ESI-MS and EPR measurements and DFT calculations, in $[Ru^{IV}(Por)Cl_2]$-catalyzed acylnitrene transfer reactions. Abbreviations: see the Supporting Information.

iv) hydrocarbons **9** to C(sp^3)–H amination products **10** (Figure 1b), together with functionalization of natural products and carbohydrate derivatives, with isolated product yields of up to 99% (a total of 75 examples). Notably, the $Ru^{V}(NCOR)$ species are unique examples of the nitrogen analogue of highly reactive $Ru^{V}(O)$ species [20,21] involved in, e.g., $[Ru^{IV}(Por)Cl_2]$-catalyzed oxygen atom transfer reactions (Figure 1aB).

Results

Ru(Por)-Catalyzed C–N Bond Formation

In this work, we found that $[Ru^{IV}(Por)Cl_2]$ served as active catalysts for C–N bond formation of various substrates with N_3COR by employing conveniently accessible $[Ru^{IV}(TDCPP)Cl_2]$ or $[Ru^{IV}(TTP)Cl_2]$ catalyst and benzoyl or naphthoyl azides **1a–g** (Figures 2–7; see the Supporting Information for more details); the former catalyst was reported to show high activity for hydrocarbon oxidation with 2,6-Cl_2pyNO[20c,22] and to catalyze cyclohexane amination with alkoxysulfonyl, alkoxycarbonyl, or phosphoryl azide.[23] The acyl azides **1** employed herein mainly bear electron-withdrawing *para*-substituents, as such substituents enhanced nitrene-transfer-reactivity

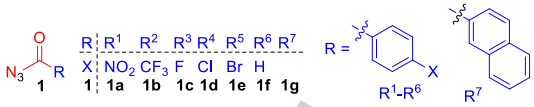


Figure 2. Acyl azides **1** used in this work.

of $[Ru^{VI}(Por)(NSO_2Ar)_2]$.[18] The substrates were generally used as limiting reagent in each type of the reactions or otherwise in selected examples.

Aziridination of Alkenes. For reaction of **1a** and aliphatic alkene **2a** (5 equiv) in DCE at 50 °C, $[Ru^{IV}(TDCPP)Cl_2]$ (3 mol%) afforded *N*-acyl aziridine **3aa** in 80% yield, higher than that obtained for $[Ru^{IV}(TTP)Cl_2]$ and other catalysts employed (≤45% yields, Table S1 in the Supporting Information). Using alkenes as limiting reagent, $[Ru^{IV}(TDCPP)Cl_2]$ (3 mol%) catalyzed the reactions of **1a–e** with aliphatic monosubstituted 1-alkenes **2a–c** and *p*-nitro-aryl alkene **2d** giving **3aa**, **3ba**, **3ca–ce**, **3da**,**dd** in 60–98% isolated yields (Figure 3). For monosubstituted 1-alkenes **2e–h**, **3ea–ha** were obtained in 51—87% yields. Cyclic aliphatic alkene **2i** (5 equiv) was converted to **3ia** in 91% yield by $[Ru^{IV}(TDCPP)Cl_2]$/**1a**; under similar conditions, a 99% yield of **3da** was obtained from **2d**. Prior to this work, there was lack of highly efficient metal catalyst for alkene aziridination via acylnitrene transfer; literature examples used styrene substrate (yield of aziridine product: 50% for $[Fe^{III}(TPP)Cl]/PhI{=}NCOCF_3$,[5] <5% for Cu-[24] and Fe[25]-catalyzed reactions with N_3COPh or N_3CO-2-pyridyl).

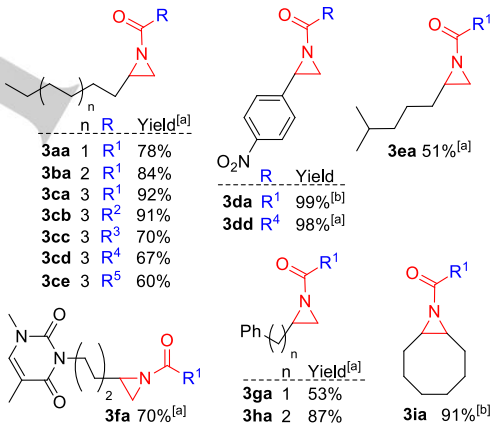


Figure 3. Aziridination of alkenes by $[Ru^{IV}(TDCPP)Cl_2]$/**1**. [a] Substrate as limiting reagent (substrate/**1** = 1:3). [b] Substrate/**1** = 5:1.

Oxazoline Formation from Alkenes. Oxazoline products were obtained by extending the $[Ru^{IV}(TDCPP)Cl_2]$(3 mol%)/N_3COR method to the following types of alkenes: i) aryl alkenes **2j–q** devoid of strongly electron-withdrawing group(s), ii) 3,4-dihydropyran **2r**, and iii) 1,1-disubstituted aliphatic alkenes **2s–u**. These reactions gave **4ja**,**jb**,**jd**,**jf**, **4kd–nd**,**pd**, **4qa**, **4sa–ua** in up to 97% isolated yield (acyl azides as limiting reagent) and **4od**,**rd** in 87–90% isolated yields (substrates as limiting reagent) (Figure 4); with **4od**,**qa**,**rd** (from *cis* alkenes) all adopting *cis* configuration and **4nd** (from *trans* alkene) adopting *trans* configuration. The reactions of styrenes **2j–l** gave **4ja**,**jb**,**jd**,**jf**,**kd**,**ld** in 93–97% isolated yields. Previously, **4ja**,**jd**,**jf** were obtained from styrene by using stoichiometric reagents [Mn(salen)(N)]/RCOCl (**4jf**: 74% yield)[26a] or $RCONH_2$/^{t}BuOI (**4ja** and its regioisomer: dr 86:14, 78% combined yield; **4jf**: 53% yield),[26b] or by using a "Ru-Cu"/dioxazolone catalytic system (**4jd**: 61% yield; **4jf**: 53% yield).[16a] The $[Ru^{IV}(TDCPP)Cl_2]$(3 mol%)/N_3COR catalytic system for a one-pot reaction of alkenes with acyl azides to give

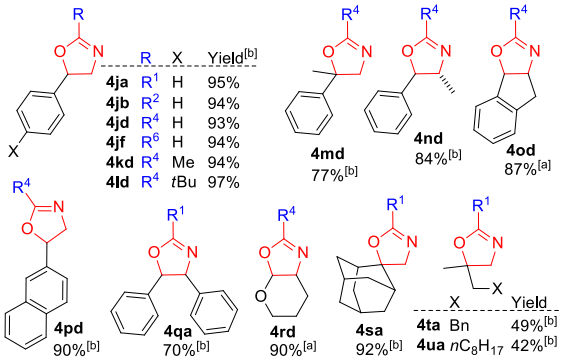


Figure 4. Oxazoline formation from alkenes by [Ru^{IV}(TDCPP)Cl$_2$]/**1**. [a] Substrate as limiting reagent (substrate/**1** = 1:3). [b] Substrate/**1** = 5:1.

oxazolines, which are valuable intermediates in organic synthesis,[27] does not require transition metal cocatalyst, unlike the "Ru-Cu"/dioxazolone catalytic system,[16a] which used [Ru(TTP)(CO)] (5 mol%) coupled with 15 mol% of $CuCl_2$ cocatalyst.[16a]

C(sp^2)–H Amination of Indoles. Treatment of *N*-phenyl indole **5a** (as limiting reagent) with **1b**,**d** and naphthyl analogue **1g** (3 equiv) and [Ru^{IV}(TTP)Cl$_2$] (0.5 mol%) in DCE at 70 °C gave C3-amino indoles **6ab**,**ad**,**ag** in 75–84% yields (Figure 5). The [Ru^{IV}(TTP)Cl$_2$](0.5 mol%)/**1b** method was applied to various indoles **5b–k** bearing electron-withdrawing or -donating groups, which afforded **6bd–kd** in 70–88% yields, with the structure of **6jd** determined by X-ray crystal analysis (Figure 5, inset). For *N*-tolyl indole, its amination by [Ru^{IV}(TDCPP)Cl$_2$](0.5 mol%)/**1d** under similar conditions led to <20% conversion (major product: **6fd**). In literature, reports on installing *N*-acyl amine groups by metal-catalyzed functionalization of indole C(sp^2)–H bonds are usually focused on indoles bearing DGs for C2-[28a,c-f] and C7[28b]-amination, except for the C2-amination of *N*-methylindole catalyzed by CuBr(20 mol%)/"H(R)NCOMe+*t*BuOO*t*Bu"[29a] leading to tertiary *N*-acyl amines (yields: 36–70%).[29a] The [Ru^{IV}(TTP)Cl$_2$]/N_3COR method resulted in C3-amination of indoles without DGs (Figure 5) to give secondary *N*-acyl amines[29b] in 70–88% yields.

Amination of Silyl Enol Ethers. Reaction of trimethyl ((1-phenylvinyl)oxy)silane (**7a**) and various silyl enol ethers (**7b**-**7i**), as limiting reagents, with **1a**,**b**,**d**,**g** (3 equiv) catalyzed by [Ru^{IV}(TTP)Cl$_2$]

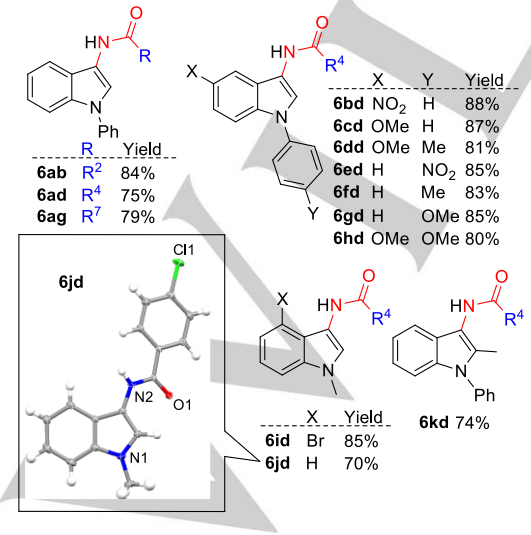


Figure 5. Amination of indoles by [Ru^{IV}(TTP)Cl$_2$]/**1**. Substrate as limiting reagent (substrate/**1** =1:3). Inset: crystal structure of **6jd** (CCDC 2022367).

(3 mol%) afforded **8aa**,**ab**,**ad**,**ag** and **8bd-id** in 67–81% yields (Figure 6). Use of [Ru^{IV}(TDCPP)Cl$_2$]/**1d** required a longer reaction time, e.g. 20 h for **7a** under similar conditions giving **8ad** in 73% yield. Previously, reactions of silyl enol ethers with stoichiometric amounts of Mn^{V}(N) complexes and excess $(CF_3CO)_2O$[4,30a] and photo-induced stoichiometric amination of silyl enol ethers with *N*-acyl iminoiodinanes ArI=NCOCF$_3$[30b] both gave α-(*N*-COCF$_3$ amino) ketones, instead of α-(*N*-arylcarbonyl amino) ketones **8**. The stoichiometric reaction of 4-chlorobenzoyl chloride with 1-(2-oxo-2-phenyl-ethyl) ammonium chloride furnished **8ad** in 78.5% yield,[31a] and photolysis of $N_3CH_2COC_6H_4$-*p*-Cl produced **8bd** in 30% yield[31b] (cf. product yields by [Ru^{IV}(TTP)Cl$_2$]/N_3COR: 79% for **8ad**, 81% for **8bd**). The Cu-,[32a] Ru-,[32b] and Rh[32c,d,e]-catalyzed amination of silyl enol ethers with PhI=NSO$_2$Ar possibly involve *N*-sulfonyl nitrenoids. A recently reported Ir-catalyzed *N*-alkoxycarbonyl nitrene transfer reaction of ^{t}BuMe$_2$SiC(Ph)=CHMe with $N_3COOCH_2CCl_3$ gave the amination product in 49% yield.[32f] The [Ru^{IV}(TTP)Cl$_2$]/N_3COR transformation of silyl enol ethers to α-amino ketones **8** (up to 81% yield, Figure 6) constitutes a unique method of preparing α-amino ketones featuring *N*-acyl groups via metal-catalyzed acylnitrene transfer.

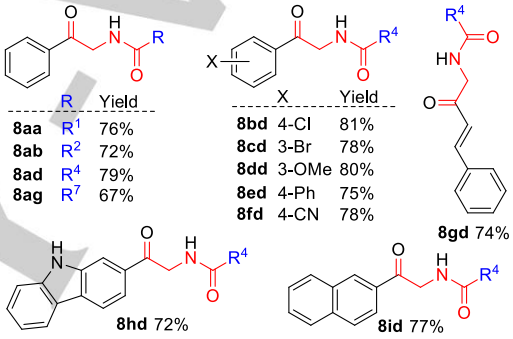


Figure 6. Amination of silyl enol ethers by [Ru^{IV}(TTP)Cl$_2$]/**1**. Substrate as limiting reagent (substrate/**1** =1:3).

Amination of C(sp^3)–H Bonds. Reactions of **1a**,**d** with 1,4-cyclohexadienes **9a**,**b** (10 equiv), bearing allylic C–H bonds, and [Ru^{IV}(TTP)Cl$_2$] or [Ru^{IV}(TDCPP)Cl$_2$] (3 mol%) in DCE at 70 °C afforded **10ad**,**bd**,**aa** in 58–68% yields (Figure 7). For phthalan **9c** and isochroman **9d**, bearing benzylic C–H bonds and used as limiting reagent, their reactions with **1a** and/or **1d** (3 equiv) gave **10cd**,**dd** in up to 78% yield for [Ru^{IV}(TTP)Cl$_2$] and **10cd**,**dd**,**da** in up to 92% yield for [Ru^{IV}(TDCPP)Cl$_2$]. [Ru^{IV}(TDCPP)Cl$_2$] can also catalyze reactions of **1a**,**b**,**d** with indan **9e** and tetralin **9f** (10 equiv) giving benzylic C(sp^3)–H amination products **10ea**,**eb**,**fa**,**fd** in 54–75% yields; no such reactions were observed for **9e**,**f** using [Ru^{IV}(TTP)Cl$_2$] as catalyst. The [Ru^{IV}(TDCPP)Cl$_2$]/**1a** amination of DHA **9g** and xanthene **9h** furnished **10ga**,**ha** in 60% and 96% yields. [Ru^{IV}(TDCPP)Cl$_2$]/**1a** can even catalyze C(sp^3)–H amination of cyclooctane **9i** to give **10ia**, albeit in a 12% yield. Amination of C(sp^3)–H bonds via metalloporphyrin-mediated nitrene transfer was previously confined to stoichiometric amination of indan by [Ru^{VI}(Por)(N)(OH)]/$(CF_3CO)_2O$ [33] and catalytic amination involving other types of proposed nitrenoids such as M(NSO$_2$Ar) and M(NAr) species.[1c,e,i,o] The C(sp^3)–H amination reactions by [Ru^{IV}(Por)Cl$_2$]/N_3COR (Por = TTP, TDCPP) to give *N*-acyl amines **10** in up to 96% yield (Figure 7) demonstrate the catalytic activity of a metalloporphyrin for such acylnitrene transfer reactions.

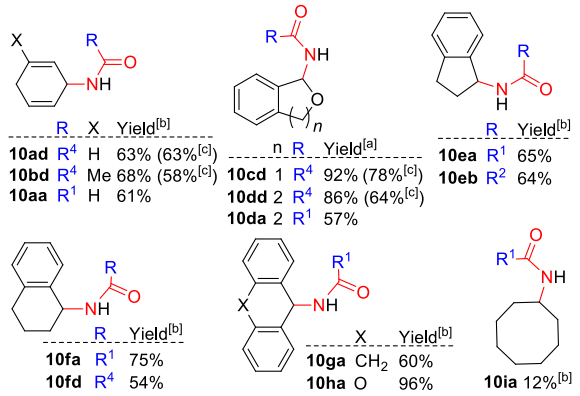
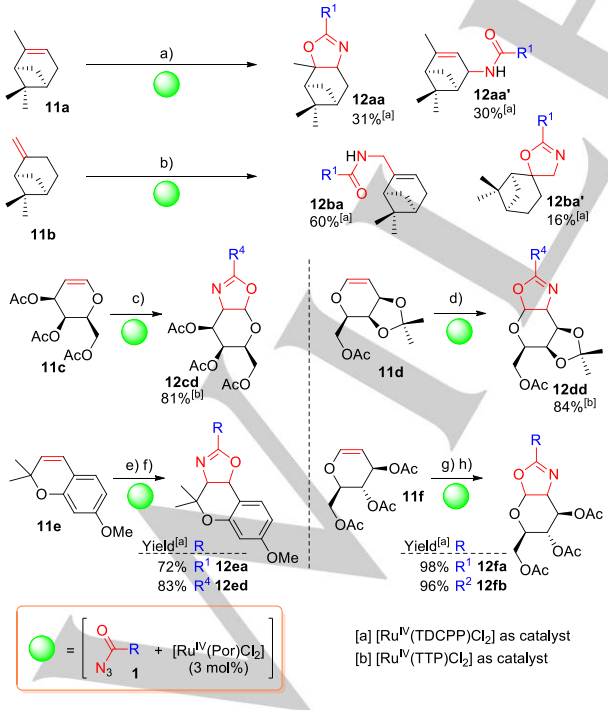


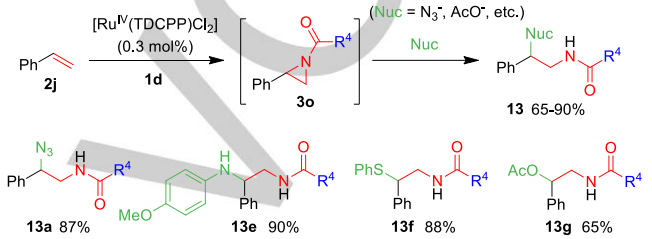
Figure 7. Amination of C(sp³)–H bonds by [Ru^{IV}(TDCPP)Cl$_2$]/**1**. [a] Substrate as limiting reagent (substrate/**1** =1:3). [b] Substrate/**1** = 10:1. [c] [Ru^{IV}(TTP)Cl$_2$] as catalyst.

Application to Functionalization of Natural Products and Carbohydrate Derivatives. The Ru(Por)/N$_3$COR method for catalytic acylnitrene transfer is applicable to functionalization of natural products and carbohydrate derivatives (as limiting reagents), including pinenes **11a**,**b** and chromene/carbohydrate derivatives **11c**–**f** (Scheme 1), which are not among the substrates employed in previous reports on metal-catalyzed acylnitrene transfer reactions.[5–16] Using [Ru^{IV}(TDCPP)Cl$_2$]/**1a**, **11a** was converted to oxazoline **12aa** and 2° C(sp³)–H amination product **12aa'** in ca. 1:1 ratio with combined yield of 61%, and **11b** was functionalized to give the 1° C(sp³)–H amination product **12ba** as the major product in 60% yield (oxazoline **12ba'**: 16% yield). For **11c**,**d**, their reactions catalyzed by [Ru^{IV}(TTP)Cl$_2$]/**1d** gave oxazolines **12cd**,**dd** in 81% and 84% yields, respectively. The [Ru^{IV}(TDCPP)Cl$_2$]/**1**-catalyzed reactions of **11e**,**f** led to isolation of oxazolines **12ea**,**ed**,**fa**,**fb** in yields of 72%–98%. The direct transformation of **11c**,**d**,**f** to oxazolines (**12cd**,**dd**,**fa**,**fb**) catalyzed by [Ru^{IV}(Por)Cl$_2$]/N$_3$COR is attractive in view of the previous transformation of **11c**,**f** to oxazoline derivatives by multistep reactions.[34]



Scheme 1. Catalytic functionalization of natural products and carbohydrate derivatives by [Ru^{IV}(Por)Cl$_2$]/N$_3$COR.

Application to Nucleophilic Ring-Opening of in Situ Generated N-Acyl Aziridines. Ring-opening reactions of *N*-acyl aziridines by nucleophiles give 1,2-bis-functionalized amino derivatives,[35] which are useful building blocks in organic synthesis or fine chemical engineering. In this work, the *N*-acyl aziridine **3o**, *in situ* generated by [Ru^{IV}(TDCPP)Cl$_2$](0.3 mol%)/**1d** aziridination of styrene, underwent ring-opening reactions with various nucleophiles (5 equiv) including NaN$_3$, NaCN, piperidine, indole, *p*-anisidine, thiophenol, and NaOAc, affording *N*-acyl amines **13a–g** in 65–90% yields (Scheme 2 and Figure S1). These reactions represent useful application of the Ru(Por)/N$_3$COR catalytic method in developing one-pot ring-opening reactions of *N*-acyl aziridines directly from their alkene precursors.

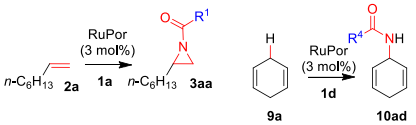


Scheme 2. Ring-opening reactions of **3o**, *in situ* generated from styrene aziridination by [Ru^{IV}(TDCPP)Cl$_2$](0.3 mol%)/**1d**, with nucleophiles.

Mechanistic Studies

Catalytic Activity of Ru^{III}(Por)Cl Species. In view of the Ru^{III}-Ru^{V} catalytic cycle in [Ru^{IV}(Por)Cl$_2$]-catalyzed oxygen atom transfer to hydrocarbons,[20b,c,21] analogous phenomenon possibly occurred for the acylnitrene transfer analogues. Indeed, [Ru^{III}(TDCPP)(Cl)(THF)], prepared by a procedure similar to that for crystallographically characterized [Ru^{III}(TDFPP)(Cl)(THF)],[21] catalyzed aziridination of **2a** with **1a** to give **3aa** in 82% yield and amination of **9a** with **1d** to afford **10ad** in 65% yield, similar to the corresponding yields using catalyst [Ru^{IV}(TDCPP)Cl$_2$] under the same conditions (Table 1). Time course experiments revealed that both [Ru^{IV}(TDCPP)Cl$_2$] and [Ru^{III}(TDCPP)(Cl)(THF)] catalyzed the reaction of **1a** with **2a** (5 equiv) to produce **3aa** in 62% yield (Figure S2), and the aziridination rate was faster for the Ru^{III} catalyst, consistent with pre-transformation of [Ru^{IV}(Por)Cl$_2$] to a Ru^{III} species such as [Ru^{III}(Por)Cl] before acylnitrene transfer occurred.

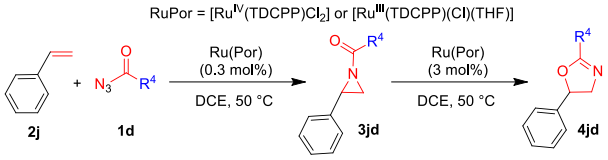
Table 1: Comparison of catalytic activity of [Ru^{III}(TDCPP)(Cl)(THF)] and [Ru^{IV}(TDCPP)Cl$_2$][a,b]



RuPor	Yield of **3aa** [%]	Yield of **10ad** [%]
[Ru^{III}(TDCPP)(Cl)(THF)]	82	65
[Ru^{IV}(TDCPP)Cl$_2$]	78	63

[a] Reaction conditions: same as those for the corresponding reactions in Figures 3 and 7. [b] [Ru^{IV}(TDCPP)Cl$_2$] is more convenient to handle.

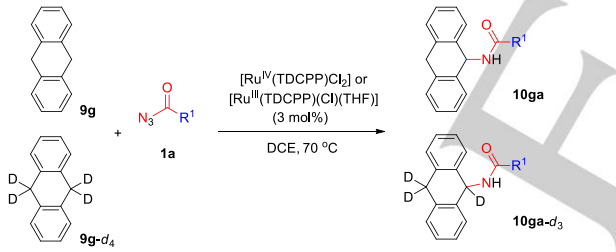
[Ru^{III}(TDCPP)(Cl)(THF)], like [Ru^{IV}(Por)Cl$_2$], also catalyzed reaction of **1d** and **2j** (5 equiv) to give oxazoline **4jd**; for both catalysts, upon reducing the loading from 3 to 0.3 mol%, this reaction afforded



Scheme 3. Reaction of **2j** with **1d** catalyzed by 0.3 mol% of [Ru^{IV}(TDCPP)Cl_2] or [Ru^{III}(TDCPP)(Cl)(THF)] to give **3jd**, and conversion of **3jd** to **4jd** upon treatment with these catalysts.

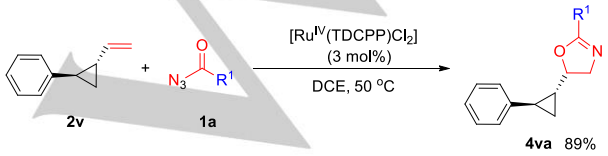
aziridine **3jd** (Scheme 3) as the major product, with **3jd/4jd** molar ratio of ca. 10:1 (combined yield: ca. 90%) in the crude reaction mixture as determined by ^{1}H NMR analysis. Both catalysts (3 mol%) can promote ring expansion of **3jd** to **4jd** (>95% yield, Scheme 3), reminiscent of previously reported analogues promoted by Lewis acids.[36] By using lower-valent [Ru^{II}(TDMPP)(CO)] (3 mol%) catalyst, the reaction of **1d** and **2j** (10 equiv) under similar conditions (DCE, 70 °C, 18 h) gave a crude mixture in which **4jd** was not detected, whereas **3jd** was detected with a 72% yield, by ^{1}H NMR analysis. For the reaction of *cis*-stilbene (**2q**) with **1a** catalyzed by [Ru^{IV}(TDCPP)Cl_2] (0.3 mol%), the corresponding aziridine product adopts *cis*-configuration, and no *trans*-counterpart was detected by NMR from the reaction mixture, indicating that the aziridination reaction is stereospecific.

Kinetic Isotope Effect (KIE). We examined the KIE for amination of DHA **9g** with **1a** by conducting competitive amination of an equimolar mixture of **9g** and **9g**-d_4 catalyzed by [Ru^{IV}(TDCPP)Cl_2] or [Ru^{III}(TDCPP)(Cl)(THF)] (Scheme 4), which gave a k_H/k_D value of 6.0 and 6.3, respectively. These KIE values fall in the range of k_H/k_D ~5–13 reported for the hydrogen atom abstraction by nitrenoids such as Ru(NSO_2Ar),[18] Fe(NAr),[37a] Fe(NSO_2Ar),[37c] and Ni(NR)[37b] species.



Scheme 4. KIE for Ru(Por)-catalyzed amination of DHA (**9g**) with**1a**.

Radical Clock Experiment. A cyclopropyl-containing alkene, *trans*-(2-vinylcyclopropyl)benzene (**2v**), was synthesized by the literature procedure;[38e] this alkene was previously employed as a radical clock[38a] (featuring cyclopropyl ring-opening or cyclopropylcarbinyl rearrangement) in Cu-,[38b,e] M(II) (M = Mn, Fe, Co, Ni)-,[38d,f,g] or Rh[38c]-catalyzed alkene transformations including sulfonyl nitrene transfer to alkenes to give *N*-sulfonyl aziridines.[38b,f] Reaction of **2v** with **1a** catalyzed by [Ru^{IV}(TDCPP)Cl_2] (3 mol%) in DCE at 50 °C under argon afforded oxazoline **4va** in 89% yield (Scheme 5). Cyclopropyl ring-opening products were not detected in the crude reaction mixture by NMR measurements.



Scheme 5. [Ru^{IV}(TDCPP)Cl_2]-catalyzed formation of oxazoline **4va** from **2v** and **1a**.

ESI-MS Studies. Reactions of [Ru^{IV}(TTP)Cl_2] with $N_3COC_6H_4$-*p*-X (X = NO_2, **1a**; Cl, **1d**, OMe, **1h**) were analyzed by ESI-MS. Treatment of [Ru^{IV}(TTP)Cl_2] in CH_2Cl_2/MeCN (1:1 v/v) with **1d** (100 equiv) at room temperature resulted in a new prominent signal at *m/z* 923.2 (cf. Figure S3a,b); this signal in the HR-ESI-MS analysis features *m/z* 923.1814 and is attributable to a Ru(NCOR) species, [Ru^{V}(TTP)($NCOC_6H_4$-*p*-Cl)]$^+$, based on the *m/z* value and isotope pattern (inset A, Figure S3b; Figure S8), coupled with its collision-induced dissociation (CID) spectrum showing fragmentation assignable to the loss of $NCOC_6H_4$-*p*-Cl ligand or COC_6H_4-*p*-Cl group (Figure S9a). Analogous phenomena were observed for the treatments of [Ru^{IV}(TTP)Cl_2] with **1a**,**h** under similar conditions, which generated new prominent signals at *m/z* 919.3 attributable to [Ru^{V}(TTP)($NCOC_6H_4$-*p*-NO_2)]$^+$ and at *m/z* 934.3 assignable to [Ru^{V}(TTP)($NCOC_6H_4$-*p*-OMe)]$^+$, respectively, as supported by the HR-ESI-MS and CID measurements (Figures S10–S12).

When styrene (**2j**, 500 equiv) was added to the reaction mixtures of [Ru^{IV}(TTP)Cl_2] with the acyl azides, the signal assignable to the above-mentioned Ru(NCOR) species, such as the *m/z* 923.2 signal in Figure S3b, was suppressed, as exemplified by the ESI-MS spectrum of the reaction mixture of [Ru^{IV}(TTP)Cl_2] with **1d** in the presence of **2j** (Figure S3c), in which case the *m/z* 923.2 signal almost disappeared and there appeared a new prominent signal at *m/z* 1027.3. The new signal at *m/z* 1027.3 is assignable to [Ru^{III}(TTP)(L)]$^+$ (L = styrene aziridination product **3jd** or oxazoline product **4jd**) by considering the HR-ESI-MS (inset B, Figure S3c; Figure S13) and CID spectrum (Figure S9b, showing the fragmentation attributable to loss of coordinated **3jd** or **4jd**), along with the formation of **3jd** or **4jd** in the reaction of **1d** with **2j** (5 equiv) catalyzed by [Ru^{IV}(TTP)Cl_2] (0.3 mol%: **3jd**/**4jd** = 7.6:1; 3 mol%: **4jd** in 95% yield).

EPR Spectroscopy. We examined the X-band EPR spectrum of a reaction mixture of [Ru^{III}(TDCPP)(Cl)(THF)] with $N_3COC_6H_4$-*p*-Cl (**1d**) in CH_2Cl_2 at 100 K (Figure S14), which shows a new signal compared with the EPR spectrum of [Ru^{III}(TDCPP)(Cl)(THF)] in CH_2Cl_2 under similar conditions; the absence of an EPR signal for [Ru^{III}(TDCPP)(Cl)(THF)], and also for previously reported [Ru^{III}(TDFPP)(Cl)(THF)],[21] is possibly due to fast relaxation.[21] This new signal in the EPR spectrum, which features *g* values of 2.05, 1.97, 1.80 similar to those of Ru^{V} species (*S* = 1/2),[21,39] disappeared upon addition of styrene to the reaction mixture (Figure S14).

Density Functional Theory (DFT) Calculations

As the catalytic reactions by [Ru^{IV}(Por)Cl_2]/N_3COR are likely to involve pre-generation of Ru^{III} species (vide supra), we employed [Ru^{III}(TTP)Cl] as model active catalyst in the DFT calculations. The computed binding of $N_3COC_6H_4$-*p*-Cl (**1d**) by [Ru^{III}(TTP)Cl] gives [Ru^{III}(TTP)(Cl)($N_3COC_6H_4$-*p*-Cl)] (**I**, Ru–N_{N3COR} distance: 2.38 Å), which eliminates N_2 via transition state **TS1** with activation free energy ($\Delta G^{\ddagger}$) of 9.9 kcal mol^{-1} producing doublet species [Ru^{V}(TTP)($NCOC_6H_4$-*p*-Cl)(Cl)] (**II**, Figure 8).

The formulation of **II** as a Ru^{V}(NCOR) species, analogous to Ru^{V}(O) species for oxidations by [Ru^{IV}(Por)Cl_2]/2,6-Cl_2pyNO via a Ru^{III} species generated in situ,[20,21] was based on the EPR studies and the following calculation results for **II**: i) a doublet ground state with single unpaired electron configuration $(d_{xy})^2(d_{xz})^1(d_{yz})^0$ for Ru (d^3, *S* = 1/2), ii) a short Ru–N_{NCOR} distance of 1.78 Å comparable to the experimental and calculated Ru^{VI}–N_{NSO2Ar} distances of 1.79(3) Å and 1.82–1.83 Å, respectively, in [Ru^{VI}(TMP)($NSO_2C_6H_4$-*p*-OMe)$_2$],[40] iii) a Wiberg bond

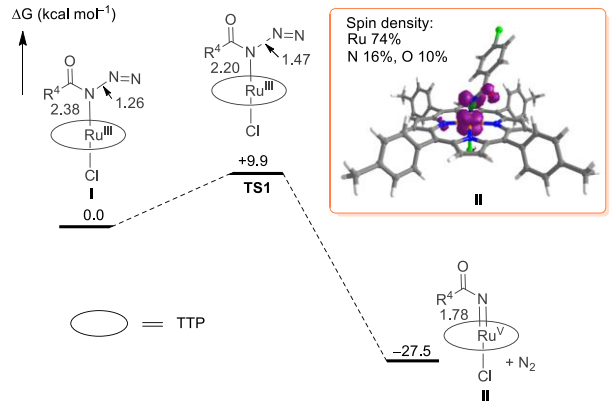


Figure 8. Computed energy profile for generation of **II** from **I** (selected bond distances in Å). Inset: Spin density plot (contour value: 0.005) for **II**.

order of 1.90, iv) a spin density of 74% on Ru (only 16% on N; Figure 8, inset).

Aziridination/Oxazoline Formation from Alkene. For aziridination of *p*-nitrostyrene **2d**, the computed free energy profile (Figure S15) shows that addition of **2d** to **II**, via transition state **TS2**, features $\Delta G^{\ddagger}$ 24.9 kcal mol^{-1} (lower than $\Delta G^{\ddagger}$ 29.4 kcal mol^{-1} for Curtius rearrangement of **II**, Figure S16), generating intermediate **Int1** (spin population on carbon: 0.75) which is 6.7 kcal mol^{-1} above the separate reactants. **Int1** can readily undergo ring closure, with a barrier of 2.6 kcal mol^{-1}, to give Ru-aziridine complex **III** from which the detachment of coordinated aziridine **3dd** is barrierless, indicating concomitant radical type C–N bond formation with simultaneous Ru–N bond breakage. We then computed the energy profiles for reaction of styrene **2j** with **II** to give aziridine **3jd** and its ring expansion to give oxazoline **4jd** (Figure 9) based on the experimental observations, i.e., transformation of **2j** by [Ru^{IV}(TTP)Cl$_2$](0.3 mol%)/**1d** to mainly afford **3jd** and treatment of in situ formed **3jd** with [Ru^{IV}(TTP)Cl$_2$] (3 mol%) (DCE, RT, ~12 h) giving **4jd** in >95% yield (see also Scheme 3). Addition of **2j** to **II**, via transition state **TS4**, to form Ru-aziridine complex **IV** needs to overcome a barrier of 22.2 kcal mol^{-1}, with a smaller barrier of 11.3 kcal mol^{-1} for detachment of the coordinated **3jd** from **IV**, in accord with formation of major product **3jd** from **2j** and **1d** catalyzed by 0.3 mol% of [Ru^{IV}(TTP)Cl$_2$]. At a higher catalyst loading (3 mol%), the following processes would be more likely to occur: i) binding of **3jd** to in situ generated [Ru^{III}(TTP)Cl] species to form adduct **V**, due to, for example, the electrostatic interaction between the carbonyl oxygen of **3jd** and the metal center; ii) transformation of Ru-aziridine complex from N-bound to O-bound form, i.e., **IV** (Ru–N 2.42 Å) → **V** (Ru–O 2.17 Å), with the latter being 13.9 kcal mol^{-1} more stable, unlike the corresponding process for **2d** (**IV′** → **V′**) which is disfavored by ΔG = 2.0 kcal mol^{-1} (Figure S17) presumably due to the strong electron-withdrawing *p*-NO$_2$ group of **2d**. In the subsequent ring-expansion step via transition state **TS6**, a barrier of 18.2 kcal mol^{-1} is needed to open the three-membered ring of the O-bound aziridine **3jd**.[41] Taking into account the thermal release (13.9 kcal mol^{-1}) in the **IV** → **V** transformation, this ring-expansion barrier can be readily overcome under the reaction conditions employed. The C–O bond formation and the oxazoline **4jd** detachment from the catalyst can proceed in a fast concerted manner by the proper geometry rearrangement in the transition state.

Amination of C(sp^3)–H Bond. Considering the higher catalytic activity of [Ru^{IV}(TDCPP)Cl$_2$] relative to [Ru^{IV}(TTP)Cl$_2$] in C(sp^3)–H amination (vide supra), we conducted DFT calculations on reaction of DHA (**9g**) with [Ru^{V}(TDCPP)(NCOC$_6$H$_4$-*p*-NO$_2$)(Cl)] (**II′**).[42] Compared to generation of **II** (Figure 10), similar formation of **II′** from [Ru^{III}(TDCPP)(Cl)(N$_3$COC$_6$H$_4$-*p*-NO$_2$)] (**I′**, Ru–N$_{N3COR}$ distance: 2.60 Å) via transition state **TS9** (Figure S18a) is slightly more difficult, with $\Delta G^{\ddagger}$ of 16.1 kcal mol^{-1} (cf. 9.9 kcal mol^{-1} for generating **II**). Previously a

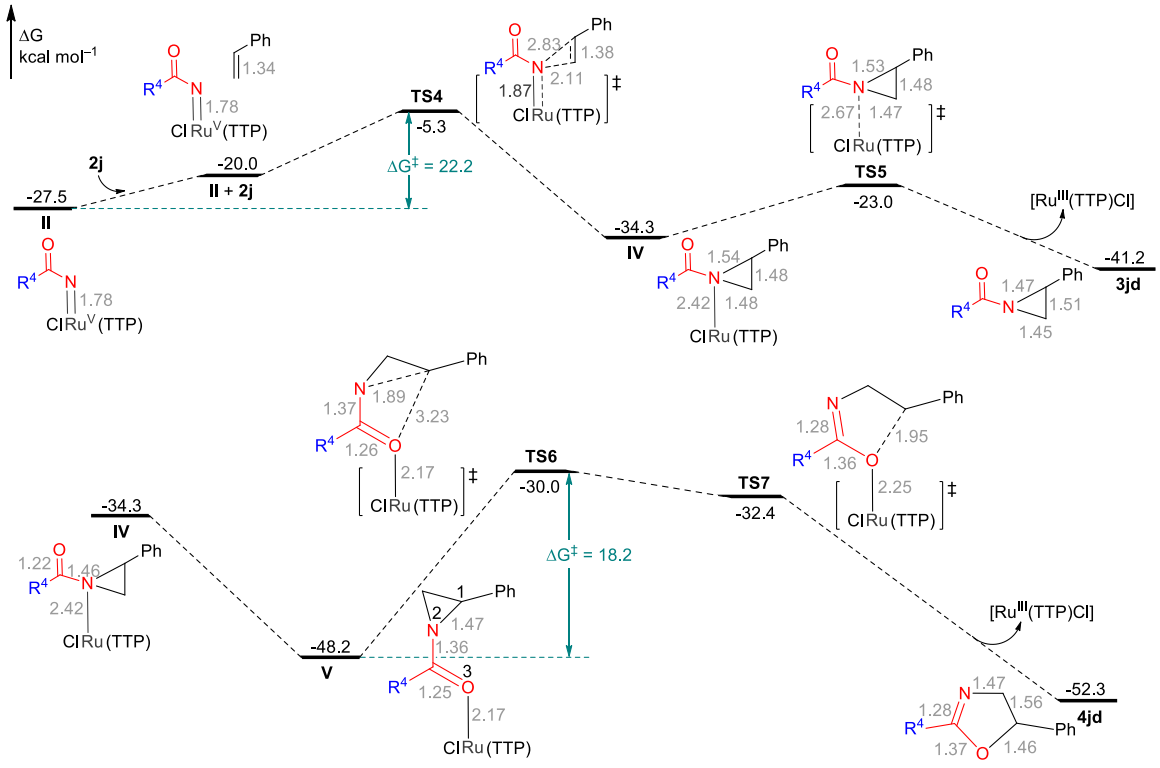


Figure 9. Computed energy profile for oxazoline formation from styrene (**2j**) and **II** (selected bond distances in Å; C1, N2 and O3 for **V** are shown).

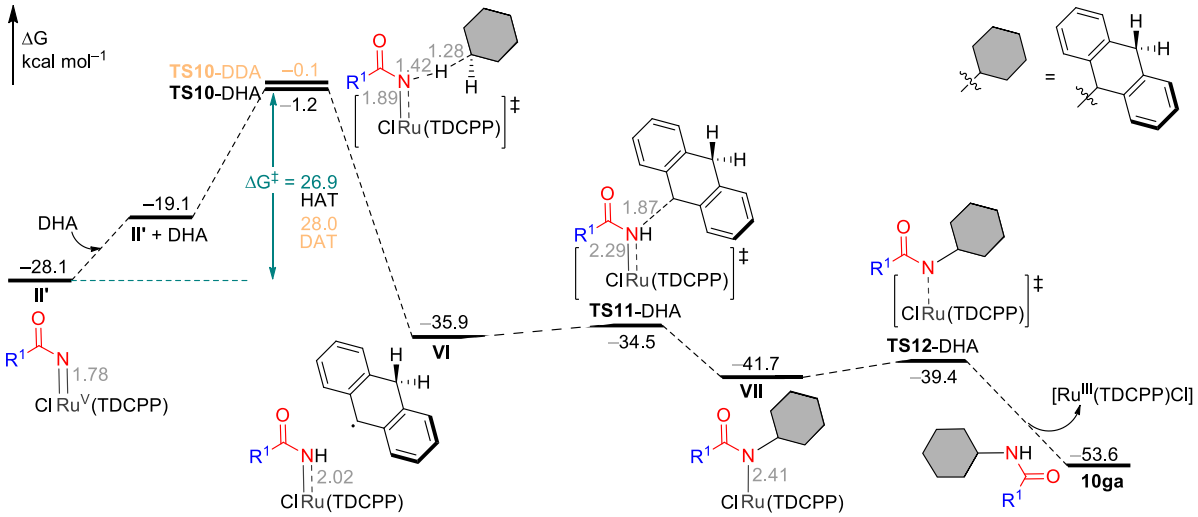


Figure 10. Computed energy profile for C–H amination of DHA (**9g**) by **II'** (ΔG‡ in RDS for DAT in orange; selected bond distances in Å).

computed barrier of 18.14 kcal mol^{-1} was reported for the generation of a Ir(NCOMe) species from its Ir(N_3COMe) precursor.[15b] The computed Ru–N_{NCOR} distance in **II'** is 1.777 Å, similar to that in **II** (1.784 Å, Figure S18b). The spin density of **II'** (Ru 54%, N 29%, O 17%, inset of Figure S18a), like that of **II**, is also mainly localized at Ru. For the acylnitrene C–H insertion of **II'** with **9g**, the computed pathway (Figure 10) shows that the rate-determining step (RDS) lies in the hydrogen atom transfer (HAT) to give species **VI** via transition state **TS10**-DHA with ΔG‡ of 26.9 kcal mol^{-1}. In the carbon radical rebound step giving species **VII** via transition state **TS11**-DHA, only a barrier of 1.4 kcal mol^{-1} is encountered. The product release step via transition state **TS12**-DHA can also occur in a facile manner with a barrier of 2.3 kcal mol^{-1}. For **9g**-d_4 (DDA), the calculated ΔG‡ of 28.0 kcal mol^{-1} in the RDS, i.e., deuterium atom transfer (DAT, Figure 10) is 1.1 kcal mol^{-1} higher than that for the HAT counterpart. Based on this difference, the computationally determined KIE is 6.4, in good agreement with the experimental value of 6.0.

Discussion

The development of metal-catalyzed acylnitrene transfer (MCAT) to organic substrates, compared with stoichiometric analogues by $L_nMn^V(N)/(CF_3CO)_2O$ or $L_nMn^V(N)/RCOCl$,[3,4,26a,30a,43] has met with formidable challenges[5,6] until recently;[7–16] the overwhelming majority of the recent examples deal with C–H amination and are based on substrates bearing directing groups (DGs) that can bind to the metal center. Examples on the use of MCATs for other reactions such as alkene aziridination are sparse. The [Ru^{IV}(Por)Cl_2]/N_3COR method is applicable to various MCAT reactions including alkene aziridination described in this work and to substrates without DGs.

For the MCAT reactions in literature, the proposed M(NCOR) intermediates[5–16] include high-valent M^V(NCOR) (M = Rh, Ir) species, which were studied by DFT calculations[13c–e,14,15b] but not directly observed by spectroscopic means. Ru^V(NCOR) species are involved in the MCAT reactions by [Ru^{IV}(Por)Cl_2]/N_3COR based on the following findings: i) [Ru^{IV}(Por)Cl_2] gave catalytic results similar to those for [Ru^{III}(Por)(Cl)(THF)] (Table 1 and Scheme 3). ii) ESI-MS analysis revealed new signals attributable to [Ru^V(Por)(NCOR)]$^+$ (Figure S3 and Figures S9 and S10), which almost vanished in the presence of styrene affording species assignable to **3jd** or **4jd** (Figure S3c and Figure S9b). iii) Reaction of Ru^{III}(Por)Cl complex with N_3COR generated a new EPR signal characteristic of Ru^V species (S = 1/2, Figure S14),[21,39] which disappeared upon treatment with styrene (Figure S14) and could be ascribed to Ru^V(NCOR) species.[44] Formation of this Ru^V(NCOR) species is reminiscent of Ru^V(O) formation by oxidizing Ru^{III}(Por)X (X = Cl, Ph) complex with 2,6-Cl_2pyNO[20] or *m*-CPBA.[21] iv) The KIE study for C–H amination revealed a k_H/k_D value (Scheme 4) comparable to that reported for H-atom abstraction by nitrenoids.[18,37] v) DFT calculations provide support for formation of Ru^V(NCOR) species (**II** and **II'**) with relatively small barriers (9.9 and 16.1 kcal mol^{-1}) and for their acylnitrene transfer to hydrocarbons with reasonable barriers (22.2–26.9 kcal mol^{-1}, Figures 9 and 10, Figure S15; see also ref 42). Also, no radical intermediate is located in oxazoline formation from styrene and **II** (Figure 9), in line with the radical clock experiment (Scheme 5; note also the almost barrierless ring closure of radical intermediate **Int1** in Figure S15). In addition, the DFT calculated doublet ground state (S = 1/2) for the Ru^V(NCOR) species is consistent with the EPR measurements, and the computed KIE (k_H/k_D 6.4, from Figure 10) compares well with that measured experimentally (k_H/k_D 6.0–6.3, Scheme 4). The intermediacy of Ru^V(NCOR) species supported by porphyrin ligand can account for the effect of porphyrin on the catalytic activity by considering steric factor and/or electronic factor including increase in electrophilicity of Ru^V(NCOR) by electron-withdrawing groups.

Conclusion

Mechanistic studies on acylnitrene transfer by [Ru^{IV}(Por)Cl_2]/N_3COR, including ESI-MS and EPR spectroscopic analysis, KIE and radical clock measurements, and DFT calculations, provide evidence for a Ru^V(NCOR) intermediate, a nitrogen analogue of highly reactive Ru^V(O) species.[20,21] The [Ru^{IV}(Por)Cl_2]/N_3COR catalytic system can transform alkenes, indoles, silyl enol ethers, and C(sp^3)–H bonds, including natural products and carbohydrate derivatives, to aziridines/oxazolines, C3-aminated indoles, α-amino ketones, and *N*-acyl amines, respectively, in up to 99% yield. In view of tunable reactivity of M(NCOR) species by altering metal center,

supporting ligand(s), and/or acyl group, coupled with accommodation of reactivity by varying substrate types, the present work reveals a promising potential of metalloporphyrin-catalyzed acylnitrene transfer in synthetic applications, and, particularly, sheds light on putative M(NCOR) intermediates widely proposed in literature.[5–16]

Acknowledgements

This work was supported by Hong Kong Research Grants Council (HKU 17301817, 17304019) and Basic Research Program-Shenzhen Fund (JCYJ20170412140251576 and JCYJ20180508162429786). We also acknowledge the funding support from "Laboratory for Synthetic Chemistry and Chemical Biology" under the Health@InnoHK Program launched by Innovation and Technology Commission, The Government of Hong Kong Special Administrative Region of the People's Republic of China. We thank Dr. Xiao-Yong Chang for assistance in the X-ray crystal structure determination of compound **6jd**.

Keywords: Acylnitrene transfer • C–N bond formation • porphyrinoids • ruthenium • Ru^{V}-imido complex

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[42] DFT calculations on the aziridination of **2d** and **2j** by **II′** revealed $\Delta G^{\ddagger}$ values of 17.5 and 16.2 kcal mol^{-1}, respectively, lower than the corresponding values of 24.9 and 22.2 kcal mol^{-1} by **II**, in line with the higher catalytic activity of $[Ru^{IV}(TDCPP)Cl_2]$ than $[Ru^{IV}(TTP)Cl_2]$ for the aziridination reactions.

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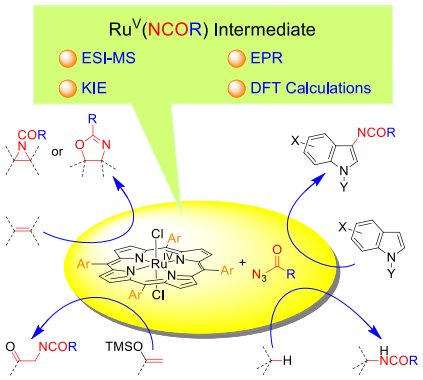

Evidence for M(NCOR) species in catalysis. Experimental studies including ESI-MS, EPR spectroscopy and KIE, and also DFT calculations point to the intermediacy of a porphyrin-supported Ru^{V}(NCOR) species in $[Ru^{IV}(Por)Cl_2]$-catalyzed C–N bond formation reactions with acyl azides N_3COR (up to 99% yield). The $[Ru^{IV}(Por)Cl_2]/N_3COR$ catalytic method is applicable to various substrates including alkenes, indoles, silyl enol ethers, and $C(sp^3)$–H bonds.