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Intramolecular C(sp³)–H Bond Oxygenation by Transition-Metal Acylnitrenoids

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Abstract: This study demonstrates for the first time that easily accessible transition-metal acylnitrenoids can be used for controlled direct C(sp³)-H oxygenations. Specifically, a ruthenium catalyst activates N-benzoyloxycarbamates as nitrene precursors towards regioselective intramolecular C–H oxygenations to provide cyclic carbonates, hydroxylated carbamates, or 1,2-diols. The method can be applied to the chemoselective C–H oxygenation of benzylic, allylic, and propargylic C(sp³)–H bonds. The reaction can be performed in an enantioselective fashion and switched in a catalyst-controlled fashion between C–H oxygenation and C–H amination. This work provides a new reaction mode for the regiocontrolled and stereocontrolled conversion of C(sp³)-H into C(sp³)-O bonds.

Introduction

The direct functionalization of non-activated C(sp³)–H bonds represents an atom- and step-economic strategy for chemical synthesis, opening new opportunities for the streamlined synthesis of complex organic molecules. [1] One attractive mechanistic scenario proceeds through the direct or stepwise insertion of transition metal carbenoids (M=CR₂), nitrenoids (M=NR), or transition-metal oxo species (M=O) into C–H bonds (Figure 1a). [2] Intramolecular, ring-closing versions of transition metal carbenoid [3] and nitrenoid [4] C–H insertions are of particular current interest because they provide a synthetic tool for the regio- and stereocontrolled alkylation and amination of C(sp³)–H bonds under typically very mild reaction conditions and without the requirement for directing groups. Analogous intramolecular C(sp³)–H oxygenations [5] through metal oxo species would be highly desirable but are unfortunately not feasible owing to the lower valence of oxygen relative to nitrogen and carbon.

We hypothesized that intramolecular C–H oxygenations might be feasible from well-known metal N-acylnitrenoid intermediates as shown in Figure 1b. The design plan assumes a triplet metal nitrenoid which abstracts intramolecularly a hydrogen from a C(sp³)–H bond to form a diradical intermediate. The established pathway continues with a C–N bond formation under release of the metal catalyst. However, we envisioned that under certain circumstances, the lifetime of this intermediate might be long enough for a conformational reorganization of the radical intermediate. Considering that the spin at the nitrogen should be delocalized over the adjacent carbonyl group, we expected that a C–O bond formation could occur instead of the standard C–N bond formation. Such a C(sp³)–H oxygenation pathway through an intermediate transition metal nitrenoid has been elusive.

Herein we introduce a ring-closing C(sp³)–H oxygenation that proceeds through a transition-metal nitrenoid and a metal oxo intermediate.

Figure 1. Intramolecular C(sp³)–H insertion via carbenoids and nitrenoids.
permitted a regioselective intramolecular C–H oxygenation to generate cyclic carbonates, hydroxylated carbamates, or 1,2-diols (Figure 1c).

**Results and Discussion**

We commenced our study with the substrate 1aa, which bears a tosylate leaving group at a carbamate nitrogen (Table 1). Such N-toslyoxy carbamates were previously introduced by Lebel[9] as a source of metal nitrenes for C–H insertions and aziridinations and Davies[10] subsequently reported an enantioselective intramolecular C–H amination with a chiral dirhodium tetracarboxylate catalyst to provide non-racemic cyclic carbamates. We instead started with a recently developed class of ruthenium catalysts in which two bidentate N-(2-pyridyl)-substituted N-heterocyclic carbenes and two acetomine ligands are coordinated to the ruthenium center in a C₂-symmetric fashion.[11] A C(sp³)–H amination should afford cyclic carbamate 2a whereas the desirable C(sp³ )–oxygenation should furnish instead the cyclic carbonate 3a. When we reacted N-toslyoxy carbamate 1aa with catalytic amounts of a catalyst (2.0 mol%) containing CF₃ substituents at the coordinated pyridine ligands (RuCF₃)[9] in the presence of the base K₂CO₃, carbamate 2a was isolated in 30% yield but the desired carbonate 3a could not be detected (entry 1). Switching to a benzoate leaving group (1ab) afforded the carbamate 2a in 87% yield, thus revealing a very efficient intramolecular C(sp³ )–H amination (entry 2).

Encouragingly, small amounts (4%) of the desired carbonate 3a could also be identified. We next attempted to increase the yield of the desired carbonate by modifying the catalyst. Accordingly, using a ruthenium catalyst with a mononuclear N-(2-pyridyl)–substituted N-heterocyclic carbene ligand (RuH) improved the yield of the carbonate 3a to 18% (entry 3). Increasing the steric bulk by introducing a trimethylsilyl (TMS) group into the pyridine ligand (RuTMS) further raised the yield of the carbonate 3a to 79% (entry 4). Finally, using an even more bulky tripropylsilyl (TEPS) group (RuTEPS) [see X-ray structure] provided the optimal result with the formation of carbonate 3a in 85% isolated yield (entry 5). Increasing the bulkiness of the catalyst further by replacing the TEPS group with a tri-n-propylsilyl group (RuTPPS) did not provide improved results but a lower catalytic activity (entry 6). Some control experiments were performed. Introducing an electron-donating methoxy (1ac) or electron-withdrawing CF₃ (1ad) group into the benzoyl moiety resulted in reduced yields (entries 7 and 8). Reducing the catalyst loading, adding water or molecular sieves, or performing the reaction under air resulted in a reduction of the carbonate yield (entries 9–12). Finally, without base the reaction proceeded very sluggishly (entry 13).

The proposed mechanism starts with the reaction of the ruthenium catalyst with the N-benzyloxycarbamate substrate 1 under base-promoted release of benzoic acid to provide a ruthenium nitrenoid intermediate (I, Figure 2).[10] This nitrenoid species subsequently performs a 1,5-hydrogen atom transfer (HAT) from the benzylic C–H bond to the nitrenoid nitrogen to generate the diradical II. In this diradical intermediate II, the nitrogen radical is conjugated to the adjacent carbonyl group so that a delocalization of the spin can be expected. If the lifetime of this diradical is long enough, a conformational change will now allow a radical–radical recombination with the oxygen moiety of the ruthenium N-coordinated amide, thereby forming a new C–O bond (III). This is consistent with the observed trend that a more sterically crowded catalyst active site shifts the otherwise preferred C–N to the previously elusive C–O bond formation. Presumably the competing C–N bond formation is suppressed by the bulky ruthenium catalyst which is directly coordinated to the nitrogen while the oxygen is more remote and thus less sensitive to steric effects. The formed iminocarbonate III then dissociates from the ruthenium and provides the cyclic carbonate 3 upon hydrolysis of the exocyclic imine.

Experimental and computational results validate the proposed mechanism. Ruthenium nitrenoid substrate have been reported to efficiently transfer the nitrene unit to phosphines and sulfides.[11] Indeed, when we performed the ruthenium-catalyzed reaction with substrate 1ab under

![X-ray structure of RuTES](image-url)
Evidence for the intermediate formation for the iminocarbonate IV, which we were not able to isolate, stems from a reaction shown in Figure 2d. When we used substrate 1c, in which the phenyl group is functionalized with a para-methoxy group, we obtained under ruthenium catalysis the carbamate 6c instead of the cyclic carbonate. This product can be rationalized by a ring opening hydrolysis of the protonated intermediate iminocarbonate IV[14] In summary, the control experiments provide strong support for the proposed radical pathway, which can explain the competing C–O and C–N bond formations.

With the optimal conditions in hand, we investigated the scope of this reaction. N-Benzoyloxycarbamates derived from 2-phenylethanol with substituents in the phenyl moiety were investigated first. As shown in Figure 3, cyclic carbonates with electron-withdrawing bromine (3d, 88%), chlorine (3e, 87%), or fluorine (3f, 85%) substituents in para-position of the phenyl moiety were obtained in high yields. Substituents are also accommodated in meta-position as demonstrated for an electron-withdrawing CF₃ (3g, 70%) and an electron-donating methoxy group (3h, 62%). As already discussed in the mechanistic section (Figure 2), for a substrate with a methoxy substituent in the para-position of the phenyl moiety, the intermediate iminocarbonate hydrolyzes to a ring-

Figure 2. Proposed mechanism and supporting experiments. Reactions performed under standard conditions shown in Table 1. [a] Formed together with the corresponding acyclic carbamate. See the Supporting Information for more details.

standard conditions in the presence of 2 equivalents of PPh₃,
the iminophosphorane 4 was formed in 88% yield so that this experiment supports the intermediate formation of the ruthenium nitrenoid species I (Figure 2a). Experimental support for a radical pathway comes from a reaction with the alkene substrate (Z)-1b which was converted to the cyclic carbonate (E)-3b under complete Z→E isomerization of the configuration (Figure 2b).[12,13] This can be explained with a conversion of the Z-isomer to the thermodynamically more stable E-isomer at the stage of the diradical intermediate II, which for the alkene substrate 1b involves a configurationally fluxional allylic radical. A trapping experiment of substrate (E)-1b with 4-methoxy-TEMPO which afforded the TEMPO adduct 5 (11%) provides a further indication for a radical pathway (Figure 2c). Finally, density functional theory (DFT) calculations were performed and provide additional support for the proposed radical mechanism with a 1,5-HAT from a triplet state of the ruthenium intermediate I being the favored pathway (I→II) (see Supporting Information for details on the calculations).[11–17]
opened C–H hydroxylated carbamate instead of forming a cyclic carbonate (1c → 6c, 53% yield). A methoxy group in ortho-position of the phenyl ring increases the yield of the C–H hydroxylated carbamate to 82% (6i). For some substrates, mixtures of cyclic carbonate and C–H hydroxylated carbamate were observed. For those cases, a basic hydrolysis was applied before silica gel chromatography to isolate the corresponding diols. For example, 1-aryl-1,2-ethanediols were obtained with the aryl group being ortho-tolyl (7j, 59% yield), para-tolyl (7k, 71% yield), para-tert-butylphenyl (7l, 66%), 4-biphenyl (7m, 67%), 1,3-benzodioxol-5-yl (7n, 60%), 2-naphthyl (7o, 79%), or 1-naphthyl (7p, 72%). A 2-thiophene moiety leads to lower 48% yield (7q). The oxygenated C(sp³)–H bond can also be flanked by an alkynyl group. Both E- and Z-configured alkenes 1b afford the diol (E)-7b in a diastereocconvergent reaction in 78% and 72% yield, respectively. Additional examples for an allylic C–H hydroxylation are the obtained isopropenyl substituted cyclic carbonate 3r (38%) and the hydroxylated terpene nopol 7s (45% yield). C–H oxygenation in propargylic position is also feasible as shown for the cyclic carbonate 3t (67%), whereas unactivated C–H groups do not provide any C–H oxygenation product (such as 3u and 3v, 0%). However, the C–H oxygenation is applicable to tertiary C–H groups as shown for compounds derived from the drugs naproxen (7w, 62%), ibuprofen (7x, 52%), flurbiprofen (7y, 50%), and the sterically congested tertiary alcohol 7z (40%). N-Benzoyloxy carbamates of 2-phenylethanol with one (3za, 37%) or two methyl substituents (3zb, 68%) in the 1-position also provide the cyclic carbonate. Overall, the developed C–H oxygenation can be applied to benzylic, allylic, and propargylic secondary and tertiary C(sp³)–H bonds with yields of up to 88%. A few substrates provide only modest C–H oxygenation yields which can be explained with a certain degree of competing C–H amination. Depending on the nature of the substrate, the intermediate iminocarbonate either hydrolyzes to the cyclic carbonate, the hydroxylated carbamate, or a mixture of both. Both can be converted to the corresponding vicinal diols by a basic hydrolysis, resulting in an overall vicinal C(sp³)–H hydroxylation of the initial alcohol starting materials.

In preliminary experiments, we also started to investigate the enantioselective version of this C–H functionalization. The class of ruthenium catalysts used in this study, although containing only achiral ligands, feature a stereogenic metal center, which results in overall chirality with a ∆ (left-handed helical twist of the bidentate ligands) and Λ (right-handed helical twist) enantiomer.32] Whereas for all preceding experiments a racemic mixture of RuTES was employed, we next synthesized non-racem RuTES according to a recently developed chiral-auxiliary-mediated method.39] Indeed, when enantiomerically pure Λ-RuTES (2.0 mol %) was reacted with the N-benzoyloxy carbamate 1ab under standard conditions, the cyclic carbonate (R)-3a was obtained with an enantiomeric excess of 90:10 er (Figure 4). Interestingly, when the same nitrene precursor 1ab was instead reacted with the enantiomerically pure catalyst Λ-RuCF₃ (2.0 mol %) under identical reaction conditions, the cyclic carbamate (S)-2a was obtained in 88% yield and with 89:11 er. Thus, depending on a single functional group at the catalyst, either an enantioselective C–H oxygenation or enantioselective C–H amination[19,20,21] can be obtained starting from an identical nitrene precursor. A catalyst-dependent switch between C–H amination and oxygenation was recently also reported by Lu and co-workers in a photo-redox dual catalysis reaction from N-benzoyloxy carbamates.32] White and co-workers reported a catalyst-controlled diastereoselective allylic C–H amination versus oxygenation using a combination of palladium(II) catalyst and Lewis acid.33] However, experiments in both reports were not performed in an enantioselective fashion and occurred by different mechanisms.

**Conclusion**

We here introduced a novel reactivity of transition metal nitrenoids complexes, leading to C–H oxygenation instead of the expected and established C–H nitrogenation. Metal-catalyzed intramolecular carbene and nitrene insertions previously only allowed for the formation of C–C and C–N bonds, respectively, whereas the here reported work expands on this limitation. Furthermore, we demonstrated that the reactivity of the transition metal nitrenoids towards C–H oxygenation or nitrogenation can be tuned simply by changing one substituent on the ruthenium catalyst scaffold and also provides a handle for creating new stereogenic centers in an enantioselective fashion. We believe that this new reaction mode of transition metal nitrenoids will provide untapped opportunities for the streamlined synthesis of alcohols by regiocontrolled and stereocontrolled C(sp³)–H oxygenation. Furthermore, cyclic carbonates are useful building blocks for a variety of transformations.34]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H functionalization · enantioselectivity · nitrenoids · oxygenation · ruthenium

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