A Rh-Catalyzed C–H Insertion Reaction for the Oxidative Conversion of Carbamates to Oxazolidinones**

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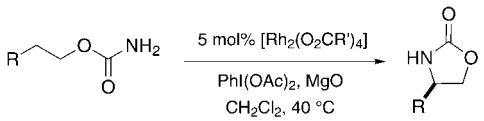
Vicinal amino alcohols are common structural units in both naturally occurring molecules and pharmaceutical agents.[1] These groups also appear as auxiliaries in asymmetric synthesis and in ligands for metal catalysts.[2, 3] The large and varied number of applications for β-hydroxy amines in synthetic, medicinal, materials, and coordination chemistry has fueled interest in the development of methods for their construction.[2a, 4] We have found a unique, metal-catalyzed C–H insertion process that makes possible the preparation of such compounds from readily available carbamate starting materials [Eq. (1)]. This methodology utilizes catalytic quan-

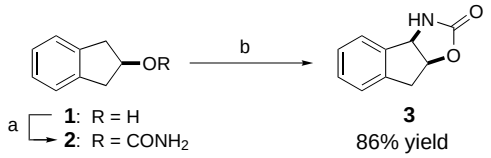


(1)

tities of a Rh^{II} carboxylate complex and an inexpensive commercial oxidant, $PhI(OAc)_2$. The product oxazolidinones are versatile, crystalline materials that can be opened under hydrolytic conditions to furnish 1,2-amino alcohols.[5, 6]

Transition metal promoted methods for the oxidative conversion of saturated hydrocarbons to amines or amine derivatives have limited precedence.[7, 8] In one seminal example, both iron and rhodium catalysts were found to react with the iodoimine of 2,5-diisopropylbenzenesulfonamide to furnish a substituted benzisothiazoline product.[9] This reaction is believed to occur through intramolecular metal–nitrene insertion into an isopropyl methine C–H bond, though no mechanistic data has been offered in support of this claim.[10] More recently, reports of metal-catalyzed intermolecular allylic and benzylic C–H oxidation with $PhI{=}NSO_2Ar$ reagents have been described.[7c–e,h–k] These processes are hampered, however, by the poor shelf life of the iodoimine starting materials, a restricted substrate profile, and the need to often employ large excesses of hydrocarbon substrates.

We wished to explore the use of simple carbamate materials as precursors for the synthesis of substituted oxazolidinones. The crystalline indanol derivative **2** used for our initial studies was afforded easily upon treatment of alcohol **1** with $CCl_3C(O)NCO$ followed by K_2CO_3/MeOH (Scheme 1).[11]



Scheme 1. a) $CCl_3C(O)NCO$; K_2CO_3/MeOH; b) 5 mol% $[Rh_2(OAc)_4]$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C, 12 hr.

Control experiments indicate that **2** does not react with $PhI(OAc)_2$ after >10 hr at 40 °C.[12] We were pleased to find, however, that a stirred suspension of **2**, $PhI(OAc)_2$, and 5 mol% $[Rh_2(OAc)_4]$ at 25 °C produced ~15% of the desired oxazolidinone **3**. Analysis of the unpurified reaction mixture by ^{1}HNMR spectroscopy indicated that the sample comprised mostly starting material **2**. Subsequent studies demonstrated that the conversion of **2** into **3** could be improved slightly by warming the mixture of reactants to 40 °C, an observation that intimated a possible problem with slow catalyst turnover. Following a series of control experiments, we concluded that AcOH, generated as a by-product from $PhI(OAc)_2$, reduced the catalytic activity of $[Rh_2(OAc)_4]$. The need to scavenge AcOH from the reaction mixture prompted the screening of K_2CO_3, Na_2HPO_4, 2,6-di-*tert*-butyl-4-methylpyridine, BaO, and MgO as base additives. Of these reagents, MgO proved uniquely effective and, in addition, was the most desirable from a cost and convenience standpoint. Thus, the reaction of **2** performs optimally when a CH_2Cl_2 suspension containing $PhI(OAc)_2$ (1.4 equivalents), 5 mol% $[Rh_2(OAc)_4]$, and MgO (2.3 equivalents) is stirred for 12 hr at 40 °C (Scheme 1).[13] Reactions conducted under these conditions on scales >1.5 mmol furnish the product oxazolidinone **3** as analytically pure material in 86% yield.

Extension of this method to other carbamate starting materials illustrates the potential value of this C–H oxidation reaction (Table 1). Substrates containing both benzylic and tertiary C–H centers are cyclized to oxazolidinone products in yields of 74–84% (entries 1–5). $[Rh_2(OAc)_4]$ can be used as the catalyst with a number of these starting materials; in some cases, however, the readily prepared triphenylacetate (tpa) complex, $[Rh_2(tpa)_4]$,[14] is a more effective promoter at a 5 mol% loading. The enhanced performance of $[Rh_2(tpa)_4]$ is ascribed to its greater resistance towards oxidation under the reaction conditions. As evident in entry 6, cyclization of less reactive substrates such as *n*-butylcarbamate requires use of this more robust catalyst.[15] By contrast, carbamates derived from tertiary cycloalkanols with unactivated CH_2 centers (entries 7 and 8) are converted efficiently into oxazolidinones with $[Rh_2(OAc)_4]$.[16] Collectively, our findings indicate that substrates having some degree of conformational constraint generally afford superior results.

The carbamate prepared from (*S*)-2-methyl-1-butanol (**4**) was employed as a probe to examine the mechanism of oxazolidinone formation (Figure 1).[17] Direct insertion of a nitrene or nitrenoid intermediate into the methine center of **4**

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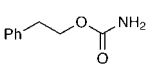
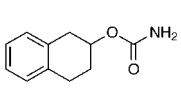
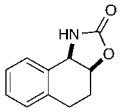
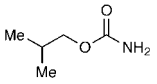
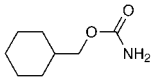
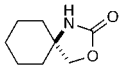
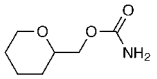
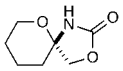
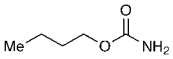
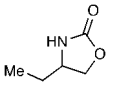
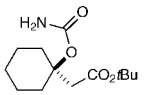
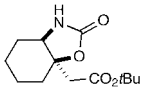
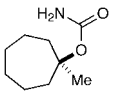
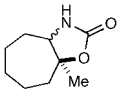
Table 1. Oxidative cyclization of carbamates.

Entry	Substrate	Product	Catalyst[a]	Yield[b]
1			**B**	74
2			**B**	77[c]
3			**A**	83
4			**A**	77
			B	79
5			**A**	82
			B	84
6			**B**	44
7			**A**	82
8			**A**	83[d]

[a] Catalyst: **A** = $[Rh_2(OAc)_4]$, **B** = $[Rh_2(tpa)_4]$. [b] All reactions conducted for 12 h with 5 mol% of catalyst, 1.4 equiv $PhI(OAc)_2$, and 2.3 equiv MgO in CH_2Cl_2 at 40 °C (~0.2 M in substrate). [c] Exclusive product as determined by ^1H NMR spectroscopy of the unpurified reaction mixture; *cis* stereochemistry assigned based on ^1H coupling constants. [d] Product isolated as an 8:1 mixture of *cis*:*trans* isomers; *cis* stereochemistry established by X-ray crystallography. Full experimental details are in the Supporting Information.

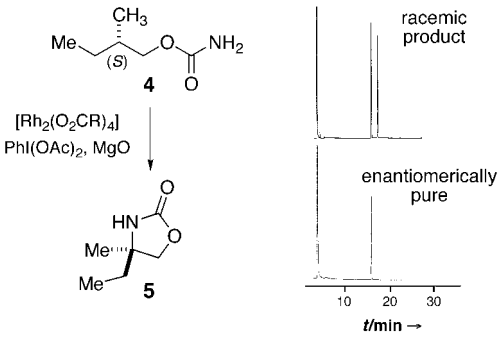
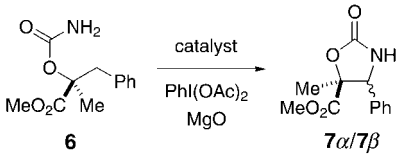


Figure 1. Cyclization of **4** into **5**. Gas chromatograms of the oxazolidinone **5** from racemic (top) and optically pure (bottom) carbamate **4**.

should occur with retention of configuration.[18, 19] Alternatively, cyclization of **4** through a pathway involving a discrete tertiary radical species is likely to produce a mixture of enantiomeric oxazolidinones. Chiral GC analysis of the product obtained from **4** displayed only a single peak in the chromatogram (Figure 1). This result provides definitive evidence that C–N bond formation is stereospecific. Moreover, the observed reactivity is consistent with that of a nitrene-type oxidant. In practice, stereospecific C–H insertion makes possible the synthesis of chiral α,α-disubstituted alkyl amines from enantiomerically pure, β-branched primary alcohols.[20] The potential of this method is considerable given the limited number of asymmetric methods available for preparing this important class of compounds and related quaternary α-amino acids.[21]

Carbamoylnitrenes, generated in thermolytic or photolytic decomposition reactions of azidoformates, react as powerful, indiscriminate oxidants.[17c, 18a,b] In the Rh-catalyzed process, the regioselective formation of a single product from substrates capable of generating other oxazolidinone and/or oxazinone derivatives (e.g., entries 2, 4, and 6, Table 1) is evidence against a free nitrene intermediate.[17c, 18a, 22] Additional data that strongly support this conclusion were obtained from reactions with carbamate **6** [Eq. (2)]. The use



	7α:**7**β
$[Rh_2(OAc)_4]$	2:1
$[Rh_2(tpa)_4]$	1:2.6

(2)

of $[Rh_2(OAc)_4]$ as a catalyst to effect the cyclization of **6** afforded a 2:1 mixture of diastereomeric products, **7*α*** and **7*β*** (79%). In contrast, the $[Rh_2(tpa)_4]$ complex yielded **7*α*** and **7*β*** in a 1:2.6 ratio (74%).[23] Collectively, these observations confirm that the Rh catalyst is in some way mediating C–N bond formation, and that a free carbamoylnitrene is not the active oxidant. Such a reaction mechanism, in which the metal complex influences the actual C–H insertion step, has significant ramifications for the future development of catalyst systems that enable control over reaction chemo-, regio-, and stereoselectivity.[24] We believe that our findings represent the most compelling experimental documentation recorded to date for a concerted, metal-directed N-atom insertion process.[10]

We have described a unique catalytic method for the oxidative cyclization of carbamates to oxazolidinones. The reaction is performed conveniently on the benchtop using readily accessible substrates and catalysts, an inexpensive commercial oxidant, and a common absorbent. C–H insertion is stereospecific, thereby facilitating the preparation of α-branched alkylamines from optically pure alcohol starting materials. Importantly, our data indicate that the active oxidizing species does not display the indiscriminate reactivity patterns characteristic of a carbamoylnitrene. The ability to use simple Rh carboxylate complexes to perform selective intramolecular alkane oxidations has created myriad opportunities for investigations in catalyst design, mechanism, and target-directed synthesis. Efforts along each of these lines are currently in progress.

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[12] A suspension of **2**, $PhI(OAc)_2$, and MgO in CD_2Cl_2 was heated in an NMR tube. ^{1}HNMR spectroscopy indicated only the presence of starting materials. Interestingly, carboxamides react rapidly with $PhI(OAc)_2$ to afford isocyanates, see: R. M. Moriarty, C. J. Chany II, R. K. Vaid, O. Prakash, S. M. Tuladhar, *J. Org. Chem.* **1993**, *58*, 2478 – 2482.

[13] Substitution of $PhI(OAc)_2$ with other iodine(III) oxidants ($PhI{=}O$, $PhI(O_2CCF_3)_2$, $PhI(OMe)_2$, 2-iodosobenzoic acid) gave inferior product conversions under otherwise identical reaction conditions (carbamate, Rh catalyst, MgO). These results are ascribed to the poor solubility and/or instability of these reagents. Control experiments show that none of these oxidants react with carbamates to give oxazolidinone products in the absence of catalyst.

[14] $[Rh_2(tpa)_4]$ is prepared easily from $[Rh_2(OAc)_4]$ and Ph_3CCO_2H, see: S.-i. Hashimoto, N. Watanabe, S. Ikegami, *Tetrahedron Lett.* **1992**, *33*, 2709 – 2712. For a general review of Rh^{II} carboxylate compounds, see: T. R. Felthouse, *Prog. Inorg. Chem.* **1982**, *29*, 73 – 166.

[15] ^{1}HNMR spectroscopy shows a ~1:1 mixture of unreacted *n*-butylcarbamate and the corresponding 4-ethyloxazolidinone. The higher product yields for carbamates having either benzylic or tertiary C–H centers suggest that substrate reactivities parallel the C–H homolytic bond strengths. Additional results from our studies, however, do not necessarily support this conclusion. Details will be provided in a full account of this work.

[16] Carbamates prepared from some secondary alcohols, such as cyclohexanol, yield only small amounts of the corresponding ketones. We are exploring conditions under which such substrates can react to afford oxazolidinone products and will report these findings in due course.

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[22] Irradiation of a 0.2 M CH_2Cl_2 solution of cyclohexylmethylcarbamoyl azide at ~25 °C (450 W medium pressure Hg arc lamp, H_2O cooled) afforded a complex mixture that included both oxazolidinone and oxazinone products.

[23] Diastereomeric product ratios were determined by ^{1}HNMR spectroscopy. The stereochemical assignments for compounds **7*α*** and **7*β*** are based on difference nuclear overhauser effect (nOe) measurements.

[24] Numerous examples illustrate the influence of catalyst structure on reaction selectivity in the analogous C–H insertion reactions of diazoalkanes. For a comprehensive reference, see: M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley-Interscience, New York, **1998**.

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