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Asymmetric Ring-Closing Aminooxygenation of Alkenes en Route to 2-Amino-1,3-Diols with Vicinal Stereocenters

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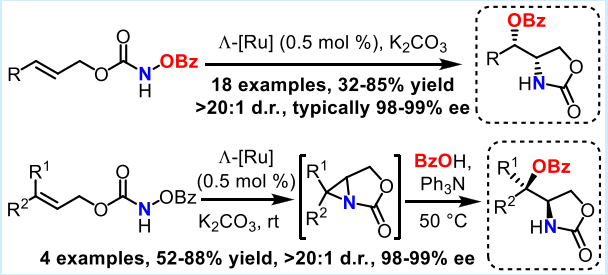
ABSTRACT: A ring-closing aminooxygenation of alkenes with *N*-benzoyloxycarbamates occurs with very high diastereoselectivity (typically >20:1 d.r.) and very high enantioselectivity (up to 99% ee). The reaction is catalyzed by a recently developed chiral-at-metal ruthenium complex at catalyst loadings of 0.5−1.0 mol %. The reaction is proposed to proceed through a ruthenium nitrenoid intermediate that depending on the nature of the substrate undergoes either an aminooxygenation (1,2-disubstituted alkenes) or stops at the stage of the aziridination (trisubstituted alkenes), which can then be ring opened with benzoic acid. The resulting chiral cyclic carbamates can be hydrolyzed under basic conditions to provide versatile chiral 2-amino-1,3-diols with vicinal stereocenters.



The catalytic asymmetric aminohydroxylation (AA) is a very straightforward method to introduce chiral vicinal amino alcohols, which are a frequent structural motif in pharmaceuticals, natural products, ligands, and auxiliaries.[1] Despite the versatility of the Sharpless AA,[2,3] the lack of regioselectivity, limitations with the substrate scope, and the requirement for toxic osmium have led to the development of other synthetic methods. Such enantioselective aminooxygenations of olefins include copper bis(oxazoline) (BOX) catalyzed intramolecular cyclizations to chiral indolines and pyrrolidines,[4] copper and iron BOX catalyzed oxaziridine additions,[5] intramolecular copper BOX catalyzed oxyazidations,[6] iron BOX catalyzed cyclizations of *N*-benzoyloxycarbamates,[7] the combination of iminium and enamine organocatalysis,[8] using chiral hypervalent iodine reagents,[9] and enzymatic aminohydroxylations of styrenes by an engineered hemoprotein.[10] In this letter, we report a ruthenium-catalyzed highly diastereoselective and highly enantioselective tethered[11] aminohydroxylation of *N*-benzoyloxycarbamates, leading to cyclic carbamates which can be hydrolyzed to 2-amino-1,3-diols with vicinal stereocenters.

Recently, we introduced a new class of "chiral-at-metal" ruthenium catalysts, bearing two bidentate *N*-(2-pyridyl)-substituted N-heterocyclic carbene ligands and two labile acetonitriles, with the overall chirality originating from a stereogenic ruthenium center.[12] Since these catalysts are suitable for C(sp^3)−H aminations[13,14] through intermediate ruthenium nitrenoid species, we questioned if we could trap them intramolecularly with an alkene. We initiated our study with the *N*-benzoyloxycarbamate **1a** shown in Table 1. When **1a** was reacted with Λ-**Ru** (2.0 mol %) in the presence of K_2CO_3 (3 equiv) in CH_2Cl_2 at room temperature, the carbamate **2a** was obtained in 76% NMR yield as a single diastereomer (>20:1 d.r.) and with 99% ee (entry 1).[15,16] The aziridine **3a** was formed as a side product in 21% NMR yield. For comparison, the acetoxycarbamate **1a′** provided the corresponding carbamate **2a′** with a lower yield and lower diastereoselectivity and no significant amounts of the aziridine **3a** (entry 2), while the tosyloxycarbamate **1a″** afforded both carbamate **2a″** (7%) and aziridine **3a** (12%) in low yields (entry 3). Thus, the benzoyloxycarbamate is the substrate of choice for this conversion with K_2CO_3 as base in CH_2Cl_2 as the solvent serving as the optimal standard conditions. For example, replacing K_2CO_3 with Na_2CO_3 results in slightly lower yield of **2a** (entry 4), whereas Et_3N provides **2a** with a higher yield but a reduced diastereoselectivity (entry 5). In the absence of any base, the reaction proceeds sluggishly with a reduced enantioselectivity (entry 6). Other solvents than CH_2Cl_2 such as THF (entry 7) or acetone (entry 8) provide carbamate **2a** with lower yields. Finally, we found that the reaction can be performed at a reduced catalyst loading of just 0.5 mol % without sacrificing the outcome (entry 9).

Next, we investigated the scope for this ruthenium-catalyzed asymmetric aminooxygenation, starting with 1,2-disubstituted alkenes (Scheme 1). *N*-Benzoyloxycarbamates of phenyl-

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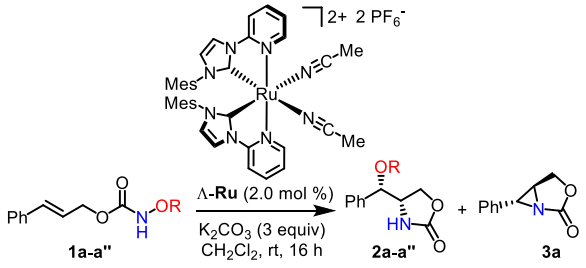
Table 1. Initial Experiments and Optimization[a]



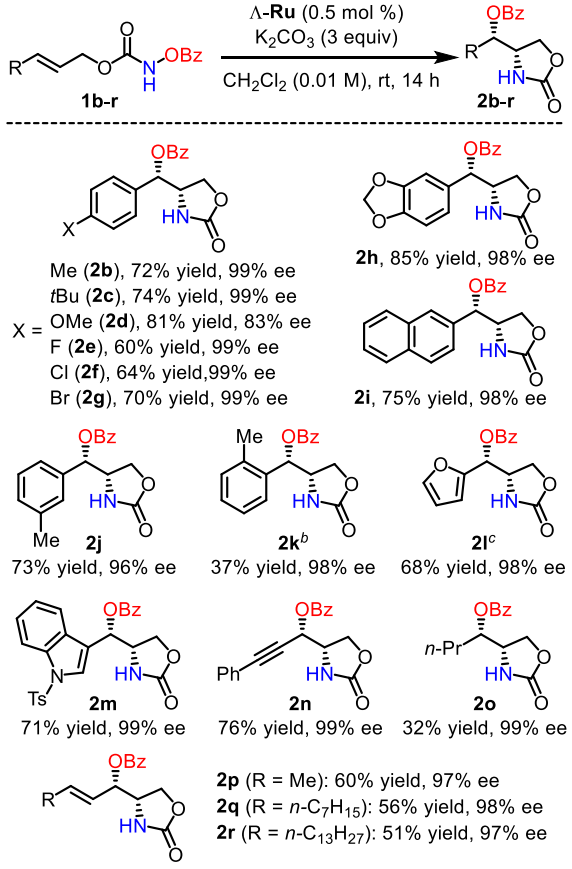
			yield (%)[b]			
entry	R	conditions	2	3a	d.r.[b]	ee (%)[c]
1	Bz	standard	76	21	>20:1	99
2	Ac	standard	58	<1	3.5:1	99
3	Ts	standard	7	12	n.d.	n.d.
4	Bz	Na_2CO_3 as base	69	22	>20:1	99
5	Bz	Et_3N as base	86	3	4.1:1	98
6	Bz	no base	52[d]	1	>20:1	86
7	Bz	THF as solvent	39	4	10:1	99
8	Bz	acetone as solvent	28	1	>20:1	99
9[e]	Bz	0.5 mol % cat.	75 (72)[f]	18	>20:1	99

[a]Conditions: **1a-a''** (0.05 mmol), cat. (2.0 mol %), and base (0.15 mmol) in solvent at rt for 16 h under N_2. Complete conversion except for entry 6. [b]Determined by ^1H NMR of the crude product. [c]Ee of the major diastereomer shown. [d]78% conversion. [e]Modified conditions: **1a** (0.2 mmol), cat. (0.5 mol %) in CH_2Cl_2 (0.01 M). [f]Isolated yield in parentheses. n.d. = not determined.

modified cinnamyl alcohols were tested first. Substituents at the *para*-position of the phenyl moiety provided the corresponding rearranged benzoylated cyclic carbamates **2b–g** in 60–81% yield and with high enantioselectivities of 99% ee, except for the electron-donating *para*-methoxy derivative **2d** which was obtained with reduced 83% ee. However, a very electron-rich benzodioxole derivative provided the amino-oxygenation product **2h** in 85% yield and with a high enantioselectivity of 98% ee. The benzannulated 2-naphthyl derivative **2i** formed with 75% yield and 98% ee. A methyl group in the *meta*-position of the phenyl moiety was well tolerated (**2j**, 73% yield, 96% ee), whereas a methyl group in *ortho*-position reduced the yield to 37% but with 98% ee (**2k**). A furane derivative **2l** (68% yield, 98% ee), indole derivative **2m** (71% yield, 99% ee), and an alkynyl derivative **2n** (76% yield, 99% ee) also formed in good yields and with very high enantioselectivities. A *N*-benzoyloxycarbamate of an aliphatic allyl alcohol provided the benzoylated cyclic carbamate **2o** with a reduced yield of 32% but excellent 99% ee. 1,3-Dienes can also be subjected to this aminooxygenation protocol as shown for the alkene products **2p–r** which formed in 51–60% yield and 97–98% ee.

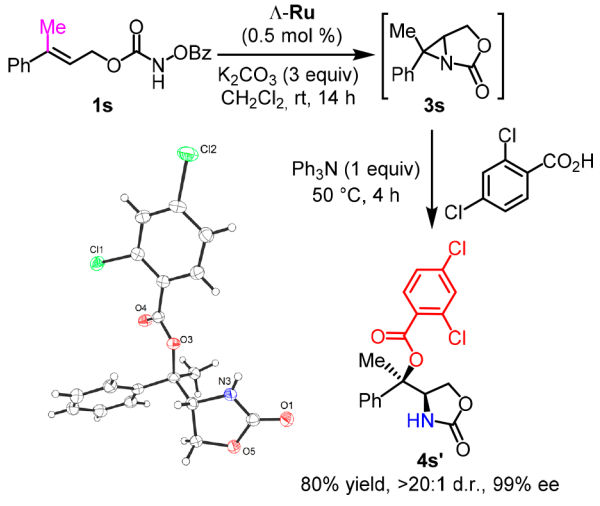
We next investigated trisubstituted alkene substrate **1s** and were surprised to find that under the standard reaction conditions the aziridine **3s** was formed exclusively as determined by crude ^1H NMR after workup (Scheme 2). However, this aziridine is unstable and in our hands was difficult to purify so that we reacted it without purification with 2,4-dichlorobenzoic acid in the presence of Ph_3N to obtain the benzoylated cyclic carbamate **4s'** in 80% yield over two steps with >20:1 d.r. and 99% ee. The relative and absolute configuration of this product were assigned by single crystal X-ray diffraction and revealed an opposite absolute configuration

Scheme 1. Substrate Scope with Disubstituted Alkenes[a]



[a]All products formed as single diastereomers (>20:1 d.r.). [b]Catalyst loading of 1.0 mol % was used. [c]Reaction at 4 °C with 1.0 mol % catalyst.

Scheme 2. Initial Reaction of a Trisubstituted Alkene and Stereochemical Verification by Single Crystal X-ray Diffraction



at the two stereocenters compared to the results with disubstituted alkenes. Scheme 3 shows a few examples in which we applied this two-step procedure to trisubstituted alkene substrates (**1s**, **1t**, **1v**), with the difference that the aziridine intermediates **3s**, **3t**, and **3v** were treated with benzoic acid instead of 2,4-dichlorobenzoic acid. As a result, the

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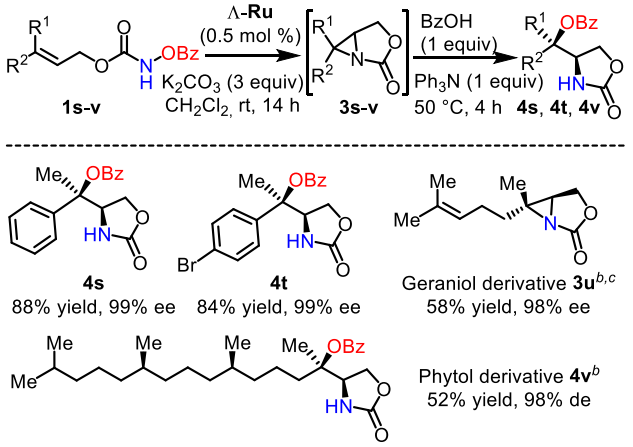
Scheme 3. Substrate Scope with Trisubstituted Alkenes[a]

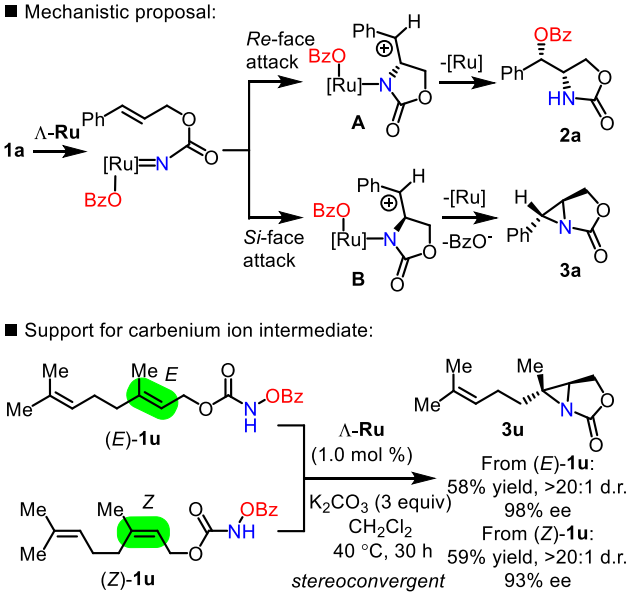


[a]All products formed as single diastereomers (>20:1 d.r.). [b]Reaction at 40 °C with 1.0 mol % catalyst. [c]The relative configuration of **3u** was determined by NMR spectroscopy. See Supporting Information for more details.

aminooxygenated products **4s** and **4t** and the phytol derivative **4v** were all obtained as single diastereomers, with high enantioselectivities (98−99% ee) and yields ranging from 52% to 88%. The geraniol derivative **3u** is stable and could be isolated as a single diastereomer in 58% yield and with 98% ee.

A proposed mechanism is shown in Scheme 4. The ruthenium catalyst activates the *N*-benzoyloxycarbamate substrate (shown for **1a**) to form a ruthenium nitrenoid intermediate with the benzoate leaving group remaining coordinated to the ruthenium. A subsequent addition of the nitrene to the *Re*-face of the prochiral alkene leads to the intermediate carbocation **A** at the newly formed carbon stereocenter.[17] The following transfer of the benzoate from the ruthenium center to the carbocation will then produce product **2a**. On the other hand, a nitrene addition to the *Si*-face of the prochiral alkene leads to the carbocation intermediate **B** with an opposite absolute configuration at the newly installed carbon stereocenter. For steric and/or stereoelectronic reasons, intermediate **B** then apparently prefers to undergo an aziridine formation instead of a benzoate transfer. These two pathways can rationalize the opposite configurations observed for the aminooxygenation products **2** as compared to aziridines **3** and aminooxygenation products **4**. Support for a carbenium ion mechanism stems from experiments using the geraniol substrate (*E*)-**1u** and its diastereomer (*Z*)-**1u** which afford in a stereoconvergent reaction the same product **3u**, supporting the proposed mechanism through a carbenium ion intermediate in which the second step occurs under thermodynamic control. This mechanism reveals that the observed high enantioselectivities for the aminooxygenation products **2** are not due to an especially high asymmetric induction but instead are the result of two distinct pathways after the initial *Si*- or *Re*-addition of the nitrene to the prochiral alkenes, resulting in the formation of the distinct products **2** and **3** which can be easily separated by standard methods.

Scheme 4. Mechanistic Proposal and Supporting Experiments



In conclusion, we here reported a practical method for the asymmetric aminooxygenation of alkenes starting from *N*-benzoyloxycarbamates of allylic alcohols catalyzed by a recently introduced chiral-at-metal ruthenium NHC catalyst. The aminooxygenation products are formed with excellent diastereoselectivity (typically >20:1 d.r.) and enantioselectivities (often 98−99% ee). The reaction is proposed to proceed through a ruthenium nitrenoid intermediate that, depending on the nature of the substrate, either undergoes an aminooxygenation (1,2-disubstituted alkenes) or stops at the stage of the aziridination (trisubstituted alkenes), which can then be ring opened with benzoic acid. The resulting chiral cyclic carbamates can be hydrolyzed under basic conditions to provide versatile chiral 2-amino-1,3-diols with vicinal stereocenters.[18]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02452.

Experimental procedures, analytical data, HPLC traces, crystallographic data, NMR spectra (PDF)

Accession Codes

CCDC 1940059 and 1942447 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(15) Xu reported the formation of **2a** from an analogous 2,4-dichlorobenzoyloxycarbamate under chiral iron catalysis, but with significantly lower enantiomeric excess. See ref 7.
(16) For comparison, the *Z*-configured diastereomer of **1a** provides the carbamate **2a** only in low yields and with low stereoselectivity. See Supporting Information for more details.
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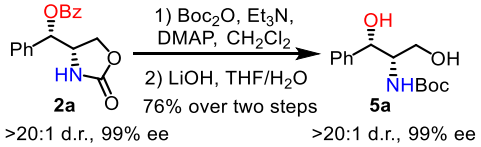
(18) The cyclic carbamates can be hydrolyzed without loss of diastereomeric and enantiomeric excess. See an example below:



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