Asymmetric Synthesis

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Diastereoselective Synthesis of Hexahydropyrrolo[2,1-*b*]oxazoles by a Rhodium-Catalyzed Hydroformylation/Silica-Promoted Deformylation Sequence**

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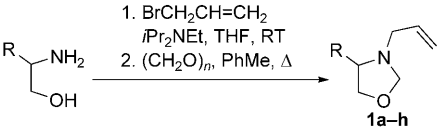
Iminium cations are intermediates in many synthetically important reactions, such as the Mannich,[1] Leuckart-Wallach,[2] Strecker,[3] and Vilsmeier–Haack[4] reactions to name just a few, which lead to formation of carbon–carbon bonds. Moreover, the ability of iminium cations to be generated at mild "physiological" conditions is widely employed in nature for the biosynthesis of a range of nitrogen-containing secondary metabolites (alkaloids).[5] Although the iminium cations are usually formed from a secondary amine and an aldehyde, an oxazolidine heterocycle can be considered a masked equivalent of an iminium cation. This property of oxazolidines has been successfully utilized for the synthesis of a variety of naturally occurring and synthetic pyrrolidine and piperidine derivatives.[6]

Herein, we report the novel synthesis of hexahydropyrrolo[2,1-*b*]oxazoles **2a**–**h**. This reaction proceeds diastereoselectively through a unique hydroformylation–deformylation pathway, involving the formation of a 1,3-oxazetidinium intermediate by addition of a carbonyl group to the iminium cation originated from the {N–CH_2–O} fragment of the oxazolidine heterocycle.

We recently demonstrated that *N*-(ethoxycarboxymethyl)oxazolidines, when subjected to carbonylation, undergo intramolecular reductive ring expansion, presumably by nucleophilic attack of the oxygen atom of the oxazolidine ring at the carbon atom of the ester functional group.[7] The initial aim of our research was to investigate whether we could utilize the nucleophilicity of the oxazolidine oxygen atom in reactions with electrophiles other than a carboxylic group. We prepared a range of substituted chiral *N*-allyl oxazolidines **1a**–**h** [Eq. (1)]. We envisioned that, upon introduction of the electrophilic functional group (formyl) by modification of the allylic fragment, the reaction intermediate would be subject to intramolecular attack by the oxygen atom of the oxazolidine ring.

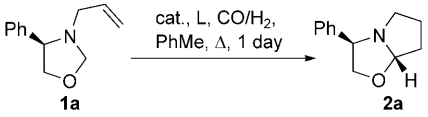
Applying hydroformylation conditions to model substrate **1a** with 0.5 mol% of [$Rh(CO)_2$(acac)] (acac = acetylacetonate) and 2 mol% xantphos ligand (xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene) as the catalyst system, in toluene at 80 °C under 25 atm carbon monoxide and 5 atm hydrogen gas, gave the reaction product in only 21% yield. The product, according to the spectral data, appeared to be (3*R*,7a*S*)-3-phenylhexahydropyrrolo[2,1-*b*]oxazole[8] **2a** (Table 1, entry 1). Surprisingly, no carbonyl group was incorporated into the product molecule, and the reaction resembled hydroalkylation of the allylic double bond.



(1)

1a R = (*R*)-Ph, **1b** R = (*S*)-Ph, **1c** R = (*R*)-*i*Bu, **1d** R = (*S*)-*i*Bu, **1e** R = (*R*)-Bn, **1f** R = (*S*)-Bn, **1g** R = (*R*)-*i*Pr, **1h** R = (*S*)-*i*Pr.

Table 1: Reaction of **1a** under carbonylative conditions.



Entry	Catalyst, [mol%]	Ligand L, [mol%]	CO [atm]	H_2 [atm]	*t* [°C]	Yield [%][a]
1	[$Rh(CO)_2$(acac)], 0.5	xantphos, 2	25	5	80	21
2	[$Rh(CO)_2$(acac)], 0.5	xantphos, 2	25	–	80	–[b]
3	[$Rh(CO)_2$(acac)], 2	xantphos, 8	25	10	70	43
4	[$Rh(CO)_2$(acac)], 5	xantphos, 20	25	10	70	71
5[c]	[$Rh(CO)_2$(acac)], 5	xantphos, 20	25	10	70	87
6	[$Rh(CO)_2$(acac)], 5	dppm, 20	25	10	70	–[b]
7	[{$Rh(CO)_2Cl$}$_2$], 5	xantphos, 20	25	10	70	39

[a] Yield of isolated product after purification by column chromatography on SiO_2. [b] No reaction occurred; starting material was recovered. [c] THF was used as the solvent. acac = acetylacetonate; xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene; dppm = bis(diphenylphosphino)methane.

To optimize the reaction conditions, we increased the amount of [$Rh(CO)_2$(acac)] to 5 mol% and the amount of the xantphos ligand up to 20 mol%; at the same time, we decreased the temperature of the reaction from 80 to 70 °C and changed the carbon monoxide/hydrogen gas ratio. As a

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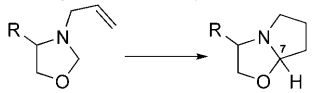
result, the performance of the reaction was improved (Table 1, entries 3 and 4). Switching the solvent to THF improved the reactivity even further, providing **2a** in 87% yield (Table 1, entry 5).

Even though the reaction does not seem to involve a hydroformylation process, our attempts to apply Ir and Pd complexes as the catalysts, as well as the use of bis(diphenylphosphino)methane (dppm) as a ligand (Table 1, entry 6) resulted in quantitative recovery of the starting material **1a**. The use of $[\{Rh(CO)_2Cl\}_2]$ as a source of the rhodium metal proved to be less efficient than $[Rh(CO)_2(acac)]$ and led to a lower yield of **2a** (Table 1, entry 7).

With the optimized conditions in hand, we examined the scope of the cyclization reaction of *N*-allyl oxazolidines **1a–h**. The cyclization reaction gave hexahydropyrrolo[2,1-*b*]oxazoles **2a–h** in good yields with a variety of substituents at the 3-position of the hexahydropyrrolo[2,1-*b*]oxazole (Table 2). However, replacement of an aromatic functional group (R = Ph or Bn) by an aliphatic *i*Bu or *i*Pr substituent resulted in somewhat lower yields of **2** (Table 2, entries 3, 4, 7, and 8).

Table 2: Reaction of **1a–g** under carbonylative conditions.[a]

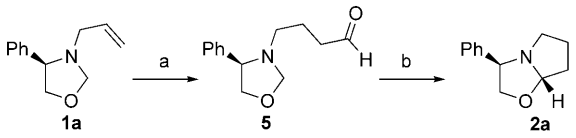


Entry	Product	R	7-CH[b]	d.r.[c]	Yield [%][d]
1	**2a**	(*R*)-Ph	*S*	25:1	87
2	**2b**	(*S*)-Ph	*R*	25:1	82
3	**2c**	(*R*)-*i*Bu	*S*	6:1	63
4	**2d**	(*S*)-*i*Bu	*R*	6:1	61
5	**2e**	(*R*)-Bn	*S*	9:1	85
6	**2f**	(*S*)-Bn	*R*	11:1	75
7	**2g**	(*R*)-*i*Pr	*S*	11:1	72
8	**2h**	(*S*)-*i*Pr	*R*	10:1	73

[a] Reaction conditions: Substrate (1 mmol), $[Rh(CO)_2(acac)]$ (5 mol%), xantphos (20 mol%), CO (25 atm), H_2 (10 atm), THF (10 mL), 70°C, 1 day. [b] Configuration of the major diastereoisomer confirmed by transient 1D NOE experiments. [c] Determined by ^{1}H NMR spectroscopy. [d] Yield of isolated product after purification by column chromatography on SiO_2.

On the basis that no carbonyl group was introduced into the product of the reaction, our initial hypothesis on the reaction mechanism involved hydroalkylation of the allylic double bond, with formation of a Rh hydride intermediate through initial activation of the sp^3 C–H bond. In this case, the Rh hydride would undergo oxidative addition to the double bond, eliminating the need for hydrogen gas for the reaction. However, in the absence of hydrogen gas no reaction occurred (Table 1, entry 2), indicating that initial formation of the Rh hydride by the reaction of the catalyst with dihydrogen is a prerequisite for the transformation.

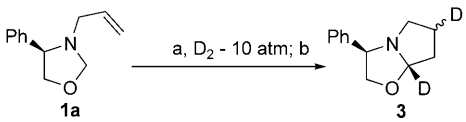
Valuable information on how the cyclization reaction occurs was obtained during our attempts to shorten the reaction time. After a reaction time of 7 h, the main product, according to NMR spectroscopic data,[9] was the aldehyde **5** [Eq. (2)]. This result demonstrates that the cyclization reaction is slower than the hydroformylation step. An attempt to isolate **5** resulted in the formation of (3*R*,7a*S*)-3-phenylhexahydropyrrolo[2,1-*b*]oxazole **2a** solely, suggesting that cyclization was induced by contact with silica used for the chromatographic separation.[10] Therefore, although hydroformylation did take place, the subsequent cyclization reaction was accompanied by decarbonylation.



(2)

a) $[Rh(CO)_2(acac)]$ - 5 mol %, Xantphos - 20 mol %, CO - 25 atm, H_2 - 10 atm, THF, 70 °C, 1 day
b) Chromatographic separation on SiO_2

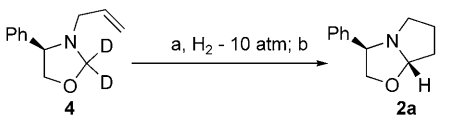
To gain more insight into the mechanism of the reaction, we conducted an experiment using deuterium gas instead of molecular hydrogen [Eq. (3)]. In this case, the isolated product was 5,7-dideuterated 3-phenylhexahydropyrrolo-[2,1-*b*]oxazole **3** (see the Supporting Information, S90–S92).[11]



(3)

a) $[Rh(CO)_2(acac)]$ - 5 mol %, Xantphos - 20 mol %, CO - 25 atm, THF, 70 °C, 1 day;
b) Chromatographic separation on SiO_2

On the other hand, when dideuterated oxazolidine **4** was used for the cyclization reaction [Eq. (4)], all deuterium labels were lost, providing **2a** as the product. This result lends additional support to the fact that no hydrogen-atom transfer occurred from the oxazolidine ring to the allyl fragment during the cyclization process. Furthermore, the presence of deuterium at the 7-position in 3-phenylhexahydropyrrolo[2,1-*b*]oxazole **3** [Eq. (3)] and the loss of both deuterium atoms [Eq. (4)] clearly demonstrate that the reaction proceeds through a double C–H activation of hydrogen atoms within the {N–CH_2–O} fragment.



(4)

a) $[Rh(CO)_2(acac)]$ - 5 mol %, Xantphos - 20 mol %, CO - 25 atm, THF, 70 °C, 1 day;
b) Chromatographic separation on SiO_2

On the basis of these results, we surmised that the mechanism of the cyclization reaction of the initially formed aldehyde **5** may have involved generation of a heteroatom-stabilized carbene (Fischer carbene)[12] upon activation of a

C–H bond of the {N–CH_2–O} fragment, followed by reductive elimination of dihydrogen.[13] The following decarbonylation of the aldehyde and subsequent hydride transfer would then explain the origin of a deuterium atom at the 7-position in 3-phenylhexahydropyrrolo[2,1-*b*]oxazole **3** [Eq. (3)].

To validate this hypothesis by providing evidence for decarbonylation of the aldehyde **5**, we conducted an additional isotope labeling experiment using $^{13}CO/H_2$ gas mixture and (4*R*)-*N*-allyl-4-isopropyloxazolidine **1g** as a substrate.[14] However, as is clearly shown by the ^{13}C NMR spectra of the aldehyde (Figure 1a) and the cyclic product **2g** (Figure 1b), cyclization proceeded with retention of the ^{13}C-labeled carbon atom of the carbonyl group, thus refuting the carbene-based mechanism.

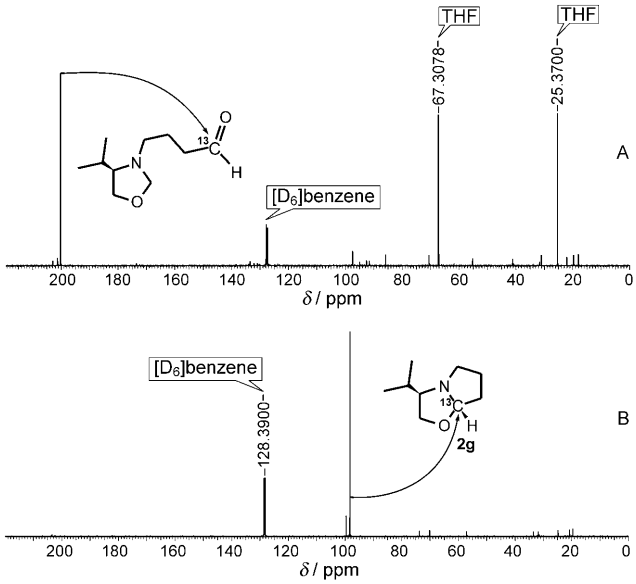
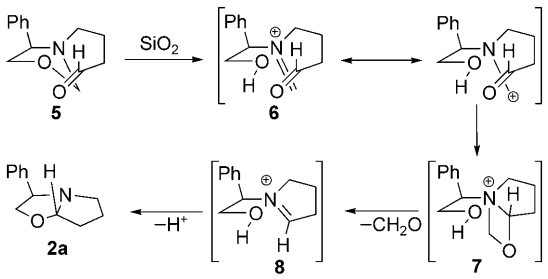


Figure 1. ^{13}C NMR spectra of the ^{13}C-labeled aldehyde (A) and cyclic product **2g** (B).

An alternative mechanism, which would involve hydrolytic cleavage of the oxazolidine ring and reaction of the generated amine with the carbonyl group, was repudiated on the basis of an experiment carried out with (4*S*,5*R*)-3,4-dimethyl-5-phenyloxazolidine and 3-phenylpropanal in THF in the presence of silica gel. The experiment did not produce any of the expected (4*S*,5*R*)-3,4-dimethyl-2-phenethyl-5-phenyloxazolidine.

Taking into account all of the aforementioned results, we propose a mechanism for the cyclization reaction of the aldehyde **5**, (Scheme 1). Addition of the Lewis and Brønsted acidic silica gel to the reaction mixture generates the iminium ion **6**, which then undergoes an addition to the carbonyl group to form the 1,3-oxazetidinium ion **7**. Subsequent fragmentation of the highly unstable 1,3-oxazetidinium intermediate results in the formation of cyclic iminium ion **8** and formaldehyde. Finally, nucleophilic attack of the oxygen atom leads to the formation of (3*R*,7a*S*)-3-phenylhexahydropyrrolo[2,1-*b*]oxazole **2a**.



Scheme 1. Proposed mechanism for the deformylative cyclization of 4-(oxazolidin-3-yl)butanals upon contact with silica gel.

An unusual, yet possible[15] interaction of the carbonyl group with the generated iminium cation, bringing about the formation of a 1,3-oxazetidinium intermediate, seemed to occur favorably in an intramolecular fashion, as opposed to an intermolecular process, which, as mentioned above, would give no reaction product. Moreover, the cyclization of aldehyde **5** under an atmosphere of H_2/CO was relatively slow in toluene or benzene, and even slower in THF. However, addition of silica gel immediately prompted the cyclization process. Although the formation of the five-membered heterocyclic system in the presence of silica gel occurred relatively fast, the possible restrictions imposed by the length of the carbonyl-terminated aliphatic chain are yet to be determined.

In summary, we have developed a new rhodium-catalyzed reaction of *N*-allyl oxazolidines to provide hexahydropyrrolo-[2,1-*b*]oxazoles in good yields by hydroformylation and subsequent SiO_2-initiated diastereoselective cyclization. The reaction may proceed by a unique hydroformylation–deformylation sequence in which the formyl functional group virtually substitutes for the {CH_2–O} fragment of the oxazolidine heterocycle.

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[9] NMR spectroscopy was carried out on a sample taken from the reaction of **1a** for 7 h in [D_8]THF (see the Supporting Information, S76–S81). At the same time, reaction of **1a** for 7 h in C_6D_6 gave an approximately 1.5:1 mixture of **5** and **2a** (see the Supporting Information, S93–S94).

[10] The smooth conversion of **5** into **2a** upon treatment of the reaction mixture with silica gel was confirmed by GC and GCMS analysis (see the Supporting Information, S82–S86).

[11] Owing to the nonstereoselective nature of the hydroformylation reaction, 5,7-dideuterated 3-phenylhexahydro-pyrrolo[2,1-*b*]oxazole **3** was isolated as a mixture of diastereoisomers. Indeed, the ^{13}C NMR spectrum of the deuterated compound **3** reveals two distinctive signals for the 3-position and two overlapping triplets for the 5-position (see the Supporting Information, S91).

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