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# Enantioselective Construction of 3-Hydroxypiperidine Scaffolds by Sequential Action of Light and Rhodium upon N-Allylglyoxylamides**

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***Abstract:*** *3-Hydroxypiperidine scaffolds were enantioselectively constructed in an atom-economical way by sequential action of light and rhodium upon N-allylglyoxylamides. In a formal sense, the allylic C–H bond was selectively cleaved and enantioselectively added across the ketonic carbonyl group with migration of the double bond (carbonyl-ene-type reaction).*

A piperidine scaffold is one of the structural motifs most prevalent among biologically active compounds, including natural products (Figure 1).[1] Although a wide variety of methods have been developed for the construction of

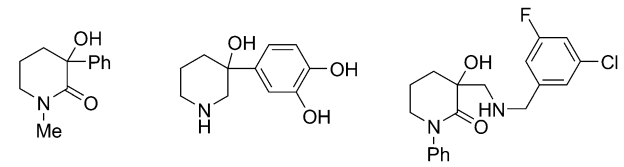
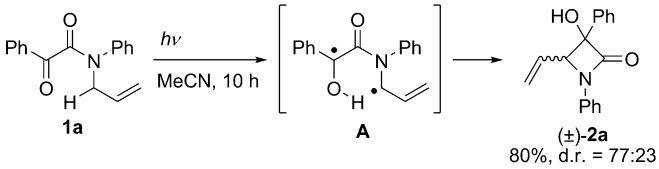



***Figure 1.*** Biologically active piperidine derivatives.

piperidine scaffolds,[2] there is still a strong demand for catalytic asymmetric procedures offering straightforward access starting from simple molecules. We herein report enantioselective construction of 3-hydroxypiperidine scaffolds by the sequential action of light and rhodium upon N-allylglyoxylamides. In a formal sense, the allylic C–H bond is selectively cleaved and added across the ketonic carbonyl group with migration of the double bond (carbonyl-ene type reaction), thus forming the six-membered ring with a chiral quaternary carbon center in an atom-economical way.

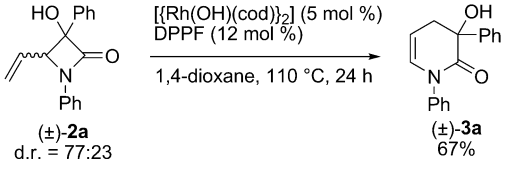
It has been reported that N-alkylglyoxylamide derivatives undergo photocyclization upon UV irradiation to furnish β-lactams and/or oxazolidinones.[3] Photoirradiation of δ,ε-unsaturated ketones provides a mixture of a four-membered cyclic product and six-membered one together with other byproducts derived from Norrish-type fragmentation reactions.[4] We initially examined a photocyclization reaction of N-allylglyoxylamides, in which a C=C bond is located at the δ,ε-position of the ketonic carbonyl group. The substrate amide **1a** (for structure see Scheme 1) was synthesized through a conventional amide-forming reaction of commercially available phenylglyoxylic acid with aniline followed by a simple N-allylation reaction. When a benzene solution of **1a** in an ordinary Pyrex tube was irradiated using an LED lamp ($\lambda = 365$ nm), the four-membered lactam (±)-**2a** was produced in 43% yield [diastereomeric ratio (d.r.) = 67:33] together with various byproducts including the six-membered lactam **3a** and olefin isomerized acyclic amides. In contrast, photoirradiation of an acetonitrile solution of **1a** with the same lamp selectively furnished **2a** in 80% yield with d.r. value of 77:23 (Scheme 1). The vinyl and the hydroxy




***Scheme 1.*** Photocyclization of the N-allylglyoxylamide **1a**.

groups of the major diastereomer were *cis* to each other. Mechanistically, the formation of (±)-**2a** from **1a** can be explained by a conventional pathway of a Norrish–Yang-type cyclization reaction,[5] wherein **1a** initially absorbs a photon to be promoted into an excited state. The excited carbonyl oxygen atom of the benzoyl group abstracts the γ-hydrogen via a six-membered cyclic transition state to produce the 1,4-biradical species **A**. The two radical centers intramolecularly couple to furnish the strained β-lactam scaffold.[6]

Next, a restructuring reaction of the vinyl-substituted β-lactam (±)-**2a** was examined (Scheme 2). It has been known




***Scheme 2.*** Rhodium-catalyzed rearrangement of (±)-**2a** into (±)-**3a**. cod = 1,5-cyclooctadiene.

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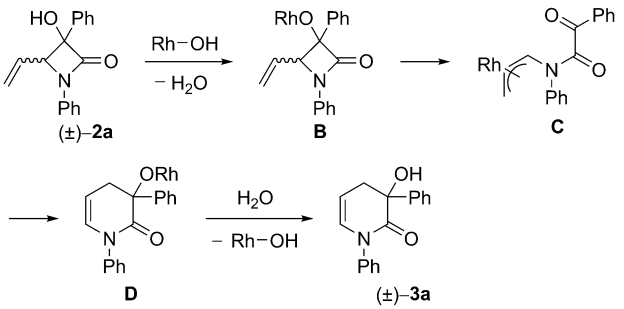
that four-membered cyclic alcohols[7] undergo a ring-opening reaction[8] by cleavage of a C–C bond[9] upon treatment with a transition-metal complex. Various unique restructuring reactions involving both cleavage and formation of a C–C bond have been reported based on the ring-opening process.[8b–e] We found that the restructuring of the diastereomeric mixture of (±)-**2a** took place when treated with a rhodium catalyst prepared in situ from [{Rh(OH)(cod)}$_2$] (5 mol%) and DPPF (1,1′-bis(diphenylphosphino)ferrocene, 12 mol%) in 1,4-dioxane at 110 °C. The 3,4-dihydropyridone (±)-**3a** was obtained in 67% yield upon isolation.[10]

A plausible mechanistic pathway of the rearrangement reaction of (±)-**2a** to (±)-**3a** is depicted in Scheme 3. Initially, the hydroxide ligand on rhodium is exchanged with the hydroxy group of (±)-**2a** to generate the rhodium alkoxide **B**




***Scheme 3.*** Plausible mechanism of rearrangement of (±)-**2a** into (±)-**3a**.

and water. There are two modes available to open the strained four-membered ring of **B** through β-carbon elimination: 1) cleavage of the bond bound to the allylic sp$^3$-carbon atom[9h,l] and 2) cleavage of the bond bound to the carbonyl sp$^2$-carbon atom. The bond bound to the allylic sp$^3$-carbon atom is preferentially cleaved[11] to furnish the ring-opened allylrhodium species **C**. It recyclizes by intramolecular nucleophilic addition to the carbonyl group at the terminal methylene carbon atom to construct the six-membered lactam scaffold, which would be far less strained than the four-membered lactam **B**. The rhodium alkoxide **D** is protonated by water (or (±)-**2a**) to release (±)-**3a** along with the rhodium hydroxide (or alkoxide **B**).

Thus, N-allylglyoxylamide **1a** was atom-economically cyclized to (±)-**3a** by the sequential action of light and a rhodium catalyst. The energetics of the whole transformation was roughly estimated by DFT calculations (Figure 2). The first photocyclization step is energetically uphill by about 13 kcal mol$^{-1}$. The light energy is absorbed by **1a** and is stored in the four-membered structure of (±)-**2a** as the ring strain. The second rearrangement reaction of (±)-**2a** is energetically downhill by about 14 kcal mol$^{-1}$, which would be mainly ascribed to the release of the ring strain of the four-membered structure.

We then examined induction of enantioselectivity by using chiral ligands in the rhodium(I)-catalyzed restructuring reaction of a diastereomeric mixture of (±)-**2a** to **3a** (Scheme 4). Monodentate phosphoramidite ligands like **4**

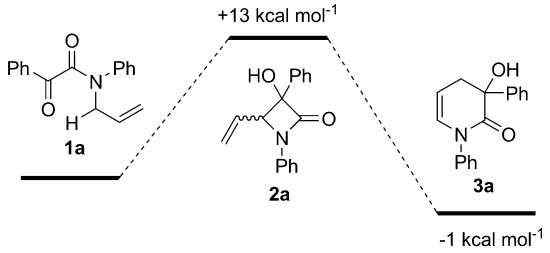
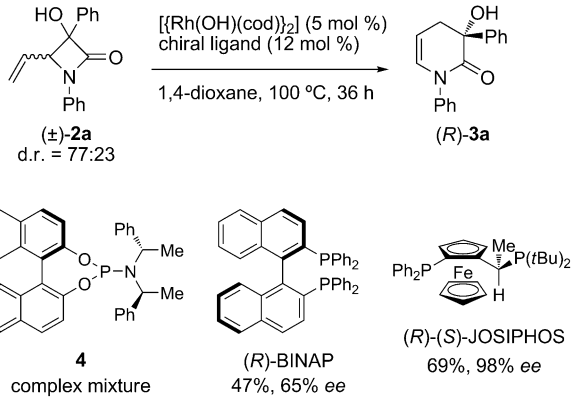



***Figure 2.*** Energies of **1a**, **2a**, and **3a** estimated by DFT calculations.



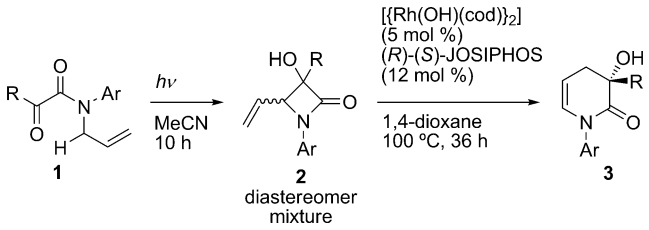

***Scheme 4.*** Enantioselective restructuring of (±)-**2a** into (*R*)-**3a**.

failed to afford **3a** selectively. Diphosphine ligands with biaryl backbones, such as (*R*)-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), produced **3a** with moderate enantioselectivities. (*R*)-(*S*)-JOSIPHOS (1-[(2-diphenylphosphino)ferrocenyl])ethyldi(*tert*-butyl)phosphine) gave the highly enantioenriched (*R*)-**3a** (98% *ee*) in 69% yield. Thus, the chiral quaternary carbon center of (±)-**2a** was formally deracemized to create the chiral quaternary carbon center of (*R*)-**3a**. The restructuring mechanism shown in Scheme 3 is compatible with this stereochemical outcome; the chiral centers of (±)-**2a** once disappear upon ring opening from **B** to **C**, and a new chiral quaternary carbon center is created in an enantioselective manner at the subsequent C–C bond-forming step from **C** to **D**.

The substrate scope of the sequential procedure from **1** to **3** was examined and the results are summarized in Table 1. First, variously substituted N-allyl-N-arylglyoxylamides (**1b**–**m**) were subjected to the photocyclization reaction under the reaction conditions almost identical to those for **1a**. The β-lactams **2b**–**m** were produced in yields ranging from 54 to 92% as the diastereomeric and racemic mixture. In case of N-alkyl-N-allylglyoxylamides, photoirradiation induced γ-hydrogen abstraction at both N-alkyl and N-allyl sites, thus giving a mixture of constitutional isomers of β-lactams. An *N*-*p*-toluenesulfonyl derivative afforded the desired vinyl-β-lactam together with various unidentified byproducts. We then examined the rhodium-catalyzed rearrangement reaction of **2b**–**m**, which produced the corresponding 3,4-dihydropyridones **3b**–**m**. Of note were the high enantioselectivities, ranging from 96 to 98%, which were generally attained.

***Table 1:*** Enantioselective synthesis of **3**.[a]

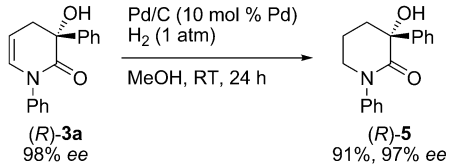



| Entry | **1** (R, Ar) | **2** Yield [%][b] | d.r.[c] | **3** Yield [%][b] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | **1b** (4-MeOC$_6$H$_4$, Ph) | 83 | 78:22 | 67 | 97 |
| 2 | **1c** (4-ClC$_6$H$_4$, Ph) | 92 | 82:18 | 66 | 96 |
| 3 | **1d** (4-FC$_6$H$_4$, Ph) | 89 | 73:27 | 72 | 98 |
| 4 | **1e** (4-CF$_3$C$_6$H$_4$, Ph) | 54 | 68:32 | 67 | 96 |
| 5 | **1f** (1-naphthyl, Ph) | 73 | 39:61 | 60 | 96 |
| 6 | **1g** (2-furyl, Ph) | 82 | 79:21 | 60 | 98 |
| 7 | **1h** (2-thienyl, Ph) | 80 | 76:24 | 75 | 98 |
| 8 | **1i** (Me, Ph) | 86[e] | 78:22 | 66[f] | 98 |
| 9 | **1j** (Ph, 4-MeOC$_6$H$_4$) | 79 | 78:22 | 69 | 98 |
| 10 | **1k** (Ph, 4-CF$_3$C$_6$H$_4$) | 90 | 72:28 | 75 | 97 |
| 11 | **1l** (Ph, 4-MeO$_2$CC$_6$H$_4$) | 64 | 69:31 | 65 | 97 |
| 12 | **1m** (Ph, 4-ClC$_6$H$_4$) | 88 | 79:21 | 68 | 96 |

[a] Reaction conditions,: step 1: *hν* (LED lamp, 365 nm), MeCN, RT, 10 h; step 2: [{Rh(OH)(cod)}$_2$] (5 mol%), (*R*)-(*S*)-JOSIPHOS (12 mol%), 1,4-dioxane, 100°C, 36 h. [b] Yield of isolated product. [c] Determined by $^1$H NMR analysis. [d] Determined by HPLC analysis using a chiral stationary phase. The absolute stereochemistry of **3b** was assigned by X-ray crystallographic analysis of the corresponding ester of (1*S*)-camphanic acid. The others are assigned by analogy. [e] 18 h. [f] 60 h.

Furyl, thienyl, and methyl groups were used as the substituent R. Both electron-donating and electron-withdrawing substituents were allowed on the N-aryl groups. Although glyoxylamides possessing substituents at the alkene moiety underwent photocyclization to give the corresponding β-lactams, the rearrangement reaction failed to afford 3,4-dihydropyridones, probably because of steric reasons.

The enamide moiety of the resulting (*R*)-**3a** underwent hydrogenation with a catalytic amount of Pd/C under an atmospheric pressure of hydrogen in MeOH (Scheme 5). The




***Scheme 5.*** Hydrogenation of (*R*)-**3a**.

stereochemical integrity of the quaternary benzylic carbon center was retained to afford (*R*)-**5** in 91% yield with 97% *ee*.

In summary, we have described the enantioselective synthesis of 3-hydroxy-3,4-dihydropyridin-2(1*H*)-ones by the sequential action of light and rhodium upon N-allylglyoxylamides. The initial photoirradiation prompts an endergonic photocyclization reaction (an addition reaction of the C–H bond across the carbonyl group) to furnish β-lactams in diastereomeric mixtures. Treatment of the resulting mixture with a chiral rhodium complex induces an enantioselective restructuring reaction of the four-membered lactam into the six-membered one through cleavage and formation of C–C bonds. In a formal sense, the allylic C–H bond is cleaved and atom-economically added across the ketonic carbonyl group with migration of the double bond (carbonyl-ene-type reaction).

**Keywords:** asymmetric synthesis · C–C activation · homogeneous catalysis · nitrogen heterocycles · rhodium

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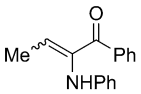
[10] The diastereomers of **2a** were separated by preparative HPLC and the rearrangement reaction of diastereomerically pure *trans*- and *cis*-**2a** was conducted separately. Both diastereomers gave similar results, thus affording **3a** in 64 and 65% yields, respectively. See the Supporting Information for details.

[11] A small amount of the enamide **6** (ca. 10%) was obtained as the byproduct. It would be generated through cleavage of the bond bound to the $sp^2$-carbonyl-carbon atom followed by decarbonylation and olefin migration.

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