

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

Naoki Ishida, David Nečas, Yusuke Masuda, and Masahiro Murakami*

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

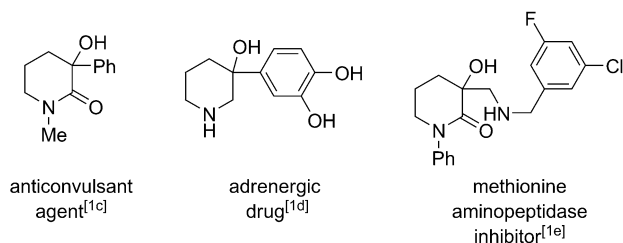
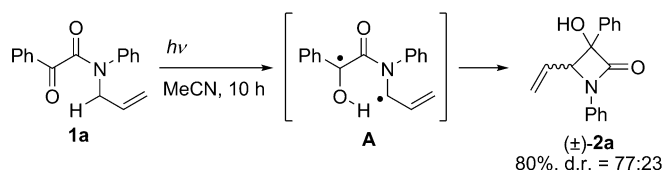


Figure 1. Biologically active piperidine derivatives.

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 -

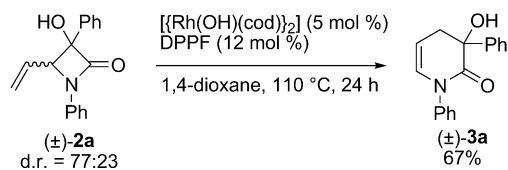
unsaturated ketones provides a mixture of a four-membered cyclic product and six-membered one together with other byproducts derived from Norrish-type fragmentation reactions.^[4] We initially examined a photocyclization reaction of N-allylglyoxylamides, in which a C=C bond is located at the δ,ϵ -position 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 ($\pm$)-**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 ($\pm$)-**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 ($\pm$)-**2a** was examined (Scheme 2). It has been known



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

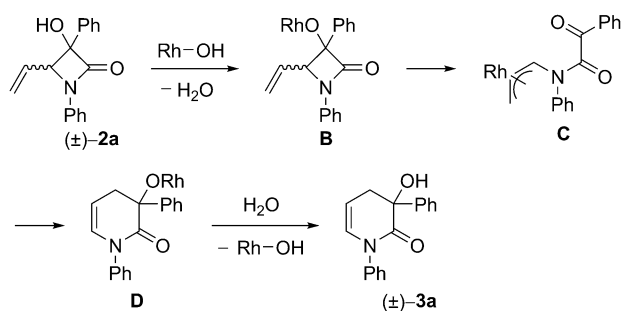
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that four-membered cyclic alcohols^[7] undergo a ring-opening reaction^[8] by cleavage of a C–C bond^[9] upon treatment with a transition-metal complex. Various unique restructuring reactions involving both cleavage and formation of a C–C bond have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

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



Scheme 3. Plausible mechanism of rearrangement of ($\pm$)-**2a** into ($\pm$)-**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,j] 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 recycles 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 ($\pm$)-**2a**) to release ($\pm$)-**3a** along with the rhodium hydroxide (or alkoxide **B**).

Thus, N-allylglyoxylamide **1a** was atom-economically cyclized to ($\pm$)-**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 ($\pm$)-**2a** as the ring strain. The second rearrangement reaction of ($\pm$)-**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 ($\pm$)-**2a** to **3a** (Scheme 4). Monodentate phosphoramidite ligands like **4**

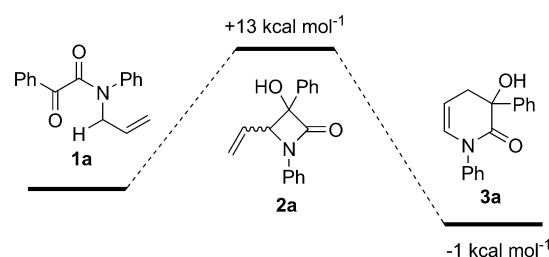
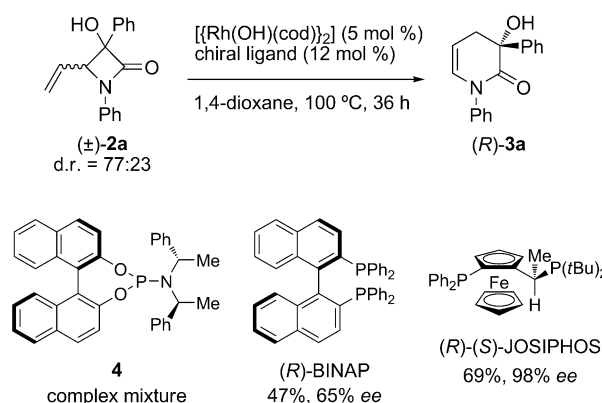


Figure 2. Energies of **1a**, **2a**, and **3a** estimated by DFT calculations.

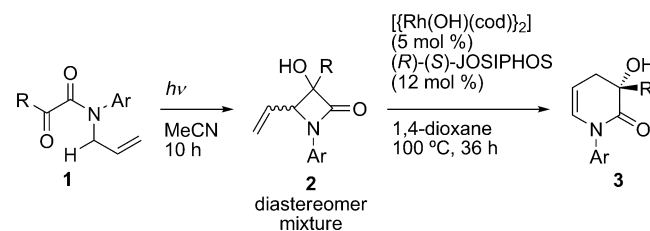


Scheme 4. Enantioselective restructuring of ($\pm$)-**2a** into (*R*)-**3a**.

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]ethylidene(*tert*-butyl)phosphine) gave the highly enantio-enriched (*R*)-**3a** (98% ee) in 69% yield. Thus, the chiral quaternary carbon center of ($\pm$)-**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 ($\pm$)-**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]

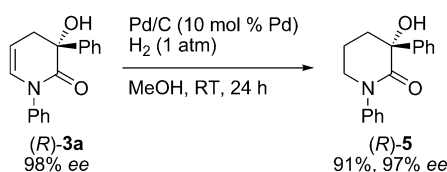


Entry	1 (R, Ar)	2 Yield [%] ^[b]	d.r. ^[c]	3 Yield [%] ^[b]	ee [%] ^[d]
1	1b (4-MeOC ₆ H ₄ , Ph)	83	78:22	67	97
2	1c (4-ClC ₆ H ₄ , Ph)	92	82:18	66	96
3	1d (4-FC ₆ H ₄ , Ph)	89	73:27	72	98
4	1e (4-CF ₃ C ₆ H ₄ , Ph)	54	68:32	67	96
5	1f (1-naphthyl, Ph)	73	39:61	60	96
6	1g (2-furyl, Ph)	82	79:21	60	98
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)-(-)-JOSIPHOS (12 mol %), 1,4-dioxane, 100 °C, 36 h. [b] Yield of isolated product. [c] Determined by ¹H 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

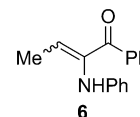
diastereomeric mixtures. Treatment of the resulting mixture with a chiral rhodium complex induces an enantioselective restructuring reaction of the four-membered lactam into the six-membered one through cleavage and formation of C–C bonds. In a formal sense, the allylic C–H bond is cleaved and atom-economically 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 sp²-carbonyl-carbon atom followed by decarbonylation and olefin migration.



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