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Formal Deoxygenative Hydrogenation of Lactams Using PN^{H}P-Pincer Ruthenium Complexes under Nonacidic Conditions

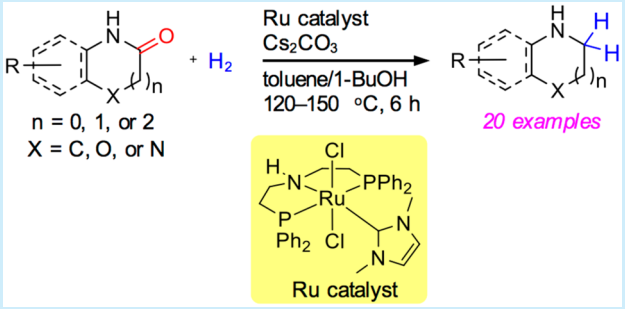
Osamu Ogata,*[,†] Hideki Nara,[†] Kazuhiko Matsumura,[†] and Yoshihito Kayaki*[,‡]

[†]Corporate Research and Development Division, Takasago International Corporation, 1-4-11 Nishi-Yawata, Hiratsuka, Kanagawa 254-0073, Japan

[‡]Department of Chemical Science and Engineering, School of Materials and Chemical Technology, Tokyo Institute of Technology, 2-12-1-E4-1 O-okayama, Meguro-ku, Tokyo 152-8552, Japan

Supporting Information

ABSTRACT: A formal deoxygenative hydrogenation of amides to amines with $RuCl_2(NHC)(PN^HP)$ (NHC = 1,3-dimethylimizadol-2-ylidene, PN^{H}P = bis(2-diphenylphosphinoethyl)-amine) is described. Various secondary amides, especially NH-lactams, are reduced with H_2 (3.0−5.0 MPa) to amines at a temperature range of 120−150 °C with 1.0−2.0 mol % of PN^{H}P−Ru catalysts in the presence of Cs_2CO_3. This process consists of (1) deaminative hydrogenation of secondary amides to generate primary amines and alcohols, (2) dehydrogenative coupling of the transient amines with alcohols to generate imines, and (3) hydrogenation of imines to give the formally deoxygenated secondary amine products.



The deoxygenative reduction of amides to amines has been one of the most fundamental transformations in organic synthesis.[1] While a stoichiometric amount of metal hydrides such as lithium aluminum hydride, boranes, or silanes[2] has been used, inevitable workup procedures, filtration, and repeated extraction were problematic on a manufacturing scale. Catalytic deoxygenative reduction of amides to amines with hydrogen gas is an ideal, environmentally benign approach to overcome these issues.[3] Heterogeneous catalysts have enabled the deoxygenative hydrogenation of amides, albeit often requiring forcing conditions of pressurized hydrogen and severe reaction temperature and suffering from limited functional group tolerance.[4] Homogeneous catalysts could also hydrogenate amides under relatively mild conditions; however, hydrogenolysis via C−N bond cleavage proceeded to give divided amines and alcohols in preference to C−O bond cleavage for the deoxygenation.[5] Since Cole-Hamilton and co-workers reported that a ruthenium complex with a triphos ligand catalyzed the selective deoxygenative hydrogenation of amides to amines in 2007,[6] related works based on the ruthenium−triphos system have been pursued extensively.[7] The hydrogenation of lactams by using a tailor-made triphos ligand was disclosed by Klankermayer,[7a] and a beneficial role of a catalytic amount of methanesulfonic acid[7b,c] on activation of the catalyst was observed. Beller and Zhou independently described the deoxygenative hydrogenation of amides assisted by $Yb(OTf)_3{\cdot}H_2O$[7d] and boron additives[7e] such as $B(C_6F_5)_3$ and $BF_3{\cdot}OEt_2$/TsOH. A similar promotional effect of $B(C_6F_5)_3$ as a Lewis acid was investigated in the amide hydrogenation using Ir[8] and Mn[9] complexes by Zhou and Milstein, independently. In view of the imperative addition of 0.2−1.5 equiv of expensive $B(C_6F_5)_3$ for excellent deoxygenation selectivity, the deoxygenative hydrogenation of amides using homogeneous catalysts without acidic additives is considered as an intriguing and eligible process.[10]

Our group has developed a PN^{H}P−pincer ruthenium complex, RuHCl(CO)(PN^{H}P) (**A**; Ru-MACHO; PN^{H}P = $(Ph_2PCH_2CH_2)_2NH$), as a potential catalyst for the hydrogenation of esters.[11] More recently, we also designed a Ru-MACHO derivative possessing a monodentate *N*-heterocyclic carbene (NHC) ligand, $RuCl_2(NHC)(PN^HP)$ (**B**), which exhibits outstanding catalytic activity for the hydrogenation of esters to alcohols even under an atmospheric pressure of hydrogen.[12] Aside from hydrogenation, the Ru-MACHO family has proven to be effective for hydrogen transfer to/from alcohols. For example, Ru-MACHO catalyzes the *N*-monomethylation of aromatic amines using methanol as a methylating agent[13] by a borrowing-hydrogen methodology.[14] The *N*-methylation involves dehydrogenation of methanol to formaldehyde, subsequent dehydrative condensation with an amine, and reduction of the imine, as outlined in Scheme 1. With the application of the borrowing-hydrogen system, we envisioned that the overall deoxygenative hydrogenation of amides could also be accomplished in the context of the *N*-alkylation of amines with alcohols formed by amide hydrogenolysis in a C−N bond cleavage mode.[7d]

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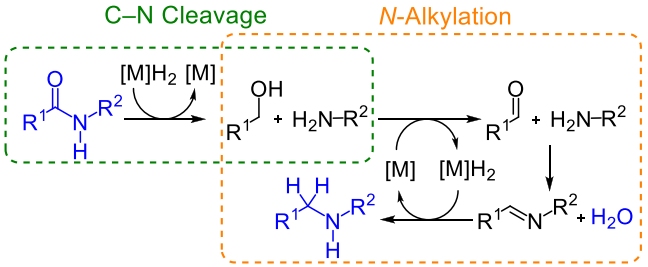
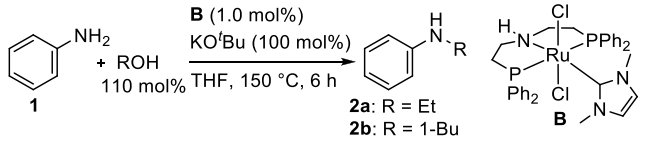
Scheme 1. Plausible Mechanism for Deoxygenative Hydrogenation of Amides Involving *N*-Alkylation of Amines



As a prerequisite for the cascade transformation, the dehydrogenation of alcohols should be compatible with the hydrogenation conditions. We initially investigated the influence of pressurized H_2 (3.0 MPa) on the *N*-alkylation of aniline in the presence of 1.0 mol % of **B** and 1.0 equiv of KO^{t}Bu in THF (Table 1). By using ethanol and 1-butanol as the alkylating agent, *N*-ethylaniline and *N*-butylaniline were successfully obtained in 70−71% and 87% yields, respectively, regardless of the presence or absence of hydrogen gas, after the reaction at 150 °C for 6 h.

Table 1. Comparison of the Catalytic Activity of B for *N*-Alkylation of Aniline with Alcohols in the Presence and Absence of Pressurized H_2[a]

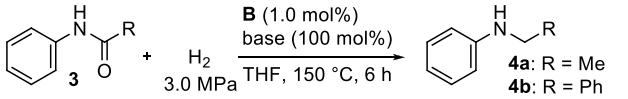


entry	H_2 (MPa)	R = Et[b] (%)	R = 1-Bu[b] (%)
1	none	71	87
2	3.0	70	87

[a]Standard conditions: aniline (1.0 mmol), **B** (0.01 mmol), KO^{t}Bu (1.0 mmol), ROH (1.1 mmol), THF (1.0 mL), 150 °C, 6 h. [b]Determined by GC.

Based on the fact that the Ru-MACHO analogue can serve as a hydrogen transfer catalyst even under hydrogen, we next tried to obtain the *N*-ethylation product directly from acetanilide (1.0 mmol) as a benchmark substrate without addition of alcohols (Table 2). When KO^{t}Bu was used as a base under reaction conditions similar to the *N*-alkylation with alcohols in Table 1, aniline was obtained in 18% yield as the hydrogenation product but *N*-ethylaniline was not generated (entry 1). Switching the base to sodium ethoxide resulted in formation of *N*-ethylaniline in 77% yield (entry 2). Addition of ethanol in the presence of KO^{t}Bu also provided the same product selectively in 96% yield (entry 3), and satisfactory productivity (84% yield) was attainable even with a reduced loading (0.2 mol %) of the catalyst under a lower hydrogen pressure (1.0 MPa) and at a lower temperature of 120 °C (entry 4). The employment of 1-PrOH or 1-BuOH instead of EtOH gave *N*-ethylaniline in 11% and 12% yields (entries 5 and 6) in association with the formation of *N*-propylaniline (87%) or *N*-butylaniline (80%), respectively. The fact that both added alcohols and ethanol proved to be responsible for the formation of secondary anilines supports the expected mechanism involving the deaminative hydrogenation of acetoanilide to aniline, followed by the *N*-alkylation with the alcohol via the borrowing hydrogen sequence, as opposed to the direct deoxygenative hydrogenation. The use of Cs_2CO_3 without alcoholic additives was not effective to obtain *N*-ethylaniline from acetoanilide (4% yield; entry 7). In the reaction of benzanilide, a low amount of *N*-benzylaniline was detected under identical conditions, and a reasonable yield of 52% was obtained at a higher reaction temperature of 180 °C (entries 8 and 9). Considering the less favorable intermolecular *N*-alkylation step in the reduction of acyclic carboxamides, lactams were next exploited for the combined hydrogenation/hydrogen transfer system accessible to synthetically useful cyclic amines.

Table 2. Formal deoxygenative Hydrogenation of Anilides[a]



entry	R	base	additive	conv (%)	yield[b] (%)
1	Me	KO^{t}Bu	none	29	0 (18[c])
2	Me	NaOEt	none	>99	77 (23[c])
3	Me	KO^{t}Bu	EtOH[d]	97	96 (3[c])
4[e]	Me	KO^{t}Bu	EtOH[d]	98	84 (10[c])
5	Me	KO^{t}Bu	1-PrOH[f]	>99	11 (<1[c])
6	Me	KO^{t}Bu	1-BuOH[g]	92	12 (<1[c])
7	Me	Cs_2CO_3	none	>99	4 (96[c])
8	Ph	Cs_2CO_3	none	>99	14 (84[c])
9[h]	Ph	Cs_2CO_3	none	97	50 (47[c])

[a]Standard conditions: substrate (1.0 mmol), **B** (0.01 mmol), base (1.0 mmol), H_2 (3.0 MPa), THF (1.0 mL), 150 °C, 6 h. [b]Determined by GC. [c]Yield of aniline. [d]EtOH 117 μL (2.0 mmol). [e]Ru cat **B** (0.002 mmol), 120 °C, H_2 (1.0 MPa). [f]1-PrOH 75 μL (1.0 mmol). [g]1-BuOH 92 μL (1.0 mmol). [h]H_2 (1.0 MPa), 180 °C.

The apparent deoxygenation was applicable to a lactam substrate, 3,4-dihydro-2(1*H*)-quinolinone (Table 3). Although the reaction hardly proceeded in the presence of KO^{t}Bu (entry 1) as tested with acetanilide, Cs_2CO_3 was found to be effective for the reduction to afford the expected cyclic amine in 89% yield (entry 2). In separate NMR experiments, deprotonation of the lactam was observed after the treatment with an equimolar amount of KO^{t}Bu in THF-d_8 at 150 °C, as distinct from Cs_2CO_3 (see Figures S63 and S64). These results imply that the formation of amidate anions stemming from KO^{t}Bu could retard the reduction. While decreasing the amount of Cs_2CO_3 and the reaction temperature led to lower yields (entries 3 and 4), amine formation was accelerated by changing the solvent. Performing screening experiments summarized in Table S1, the addition of 1-BuOH allowed an increase in the yield from 29% to 87% without the formation of *N*-butylated amine (entry 5). The optimal yield of 96% under comparatively mild conditions was achieved in a mixed solvent of toluene/1-BuOH (entry 6). The reaction was accelerated by increasing the amount of Cs_2CO_3 from 20 to 50 mol %, and an almost quantitative yield was attained within 4 h (entries 7 and 8).

The related ruthenium complexes with the tridentate PN^{H}P ligand were applied to this reaction. As shown in entries 9 and 10, the complexes possessing a carbon monoxide ligand instead of NHC showed slightly lower activities than that of **B**. Presumably, the strong σ-donating property of NHC enhances the hydricity of active catalytic intermediates[5m] and therefore facilitates the initial deaminative hydrogenation of the amide substrate. Meanwhile, the formal deoxygenative reduction also

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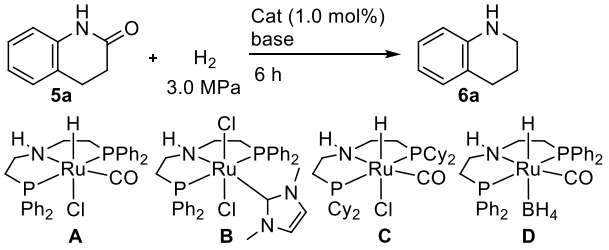
Table 3. Formal Deoxygenative Hydrogenation of 3,4-Dihydro-2(1*H*)-quinolinone[a]



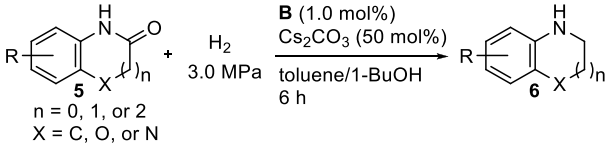
entry	cat.	temp (°C)	base (mol %)	solvent	yield[b] (%)
1	**B**	150	KO^{t}Bu (100)	THF	1
2	**B**	150	Cs_2CO_3 (100)	THF	89
3	**B**	150	Cs_2CO_3 (20)	THF	72
4	**B**	120	Cs_2CO_3 (20)	THF	29
5	**B**	120	Cs_2CO_3 (20)	THF/1-BuOH[c]	87
6	**B**	120	Cs_2CO_3 (20)	toluene/1-BuOH[d]	96
7[e]	**B**	120	Cs_2CO_3 (20)	toluene/1-BuOH[d]	73
8[e]	**B**	120	Cs_2CO_3 (50)	toluene/1-BuOH[d]	99
9	**A**	120	Cs_2CO_3 (20)	toluene/1-BuOH[d]	87
10	**C**	120	Cs_2CO_3 (20)	toluene/1-BuOH[d]	81
11	**D**	120	none	toluene/1-BuOH[d]	14

[a]Standard conditions: substrate (1.0 mmol), **B** (0.01 mmol), base, H_2 (3.0 MPa), THF (2.0 mL), 6 h. [b]Isolated yield. [c]Solvent: THF/1-BuOH (2.0 mL/0.92 mL). [d]Solvent: toluene/1-BuOH (2.0 mL/0.92 mL). [e]4 h.

proceeded under neutral conditions by using a hydroborate complex (**D**), albeit with a low yield of 14% (entry 11).

The deoxygenation was also achieved by hydrogenating a variety of benzo-fused lactams under the optimized conditions using 1.0 mol % of **B** in the presence of 50 mol % of Cs_2CO_3 (Table 4). Chloro- and fluoro-substituted lactams were converted selectively into the corresponding cyclic amines without deterioration in 95% and 94% yields, respectively (entries 1 and 3), whereas 6-bromo-3,4-dihydroquinolin-2(1*H*)-one was reduced to the deoxygenated amine, 6-bromo-1,2,3,4-tetrahydroquinoline, in a slightly lower yield of 73%, as a consequence of concurrent debromination (entry 2 and the Supporting Information). The hydrogenation of a sterically congested lactam having two methyl substituents adjacent to the carbonyl group led to a 28% yield of 3,3-dimethyl-1,2,3,4-tetrahydroquinoline and 67% of the unreacted substrate was recovered (entry 4). In addition to an excellent yield (96%) attained with a methoxy-substituted lactam (entry 5), an acid-susceptible silyloxy substituent tolerated the hydrogenation conditions to give the desired 1,2,3,4-tetrahydroquinoline derivative in 80% yield (entry 6). Notably, a lactam fused with aniline was transformed while keeping the unprotected amino group intact (entry 7). The electronic effects of the substituents on the arene ring on the hydrogenation were not obvious for the 3,4-dihydroquinolin-2(1*H*)-one derivatives. The lactams having a heteroatom on the ring were also amenable to the formal deoxygenative hydrogenation, furnishing *N*-protected 1,2,3,4-tetrahydroquinoxaline and benzo-fused morpholine in 90% and 98% yields, respectively (entries 8 and 9). When a phenyl group was placed at the amide nitrogen, the corresponding amino alcohol could be obtained selectively in 70% yield, possibly due to retardation of transient iminium formation from less nucleophilic *N*,*N*-diarylamine and aldehyde moieties (entry

Table 4. Formal Deoxygenative Hydrogenation of Benzo-Fused Lactams[a]



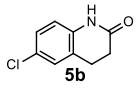
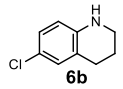
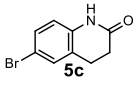
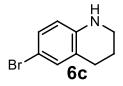
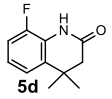
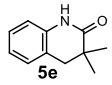
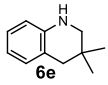
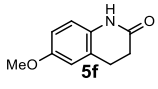
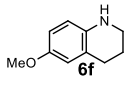
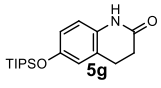
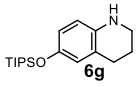
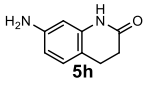
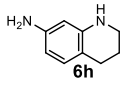
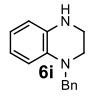
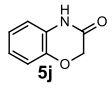
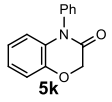
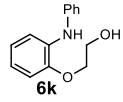
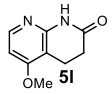
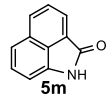
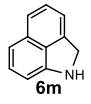
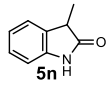
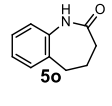
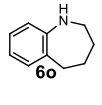
Entry	Substrate	Product	Temp (°C)	Yield (%)[b]
1			120	95
2[c]			120	73
3[d]			150	94
4[e]			150	28
5			120	96
6[f]			150	80
7[g]			150	93
8[h]			150	90
9			120	98
10[i]			120	70
11			150	96
12			150	80
13[j]			140	76
14[k]			150	55

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Table 4. continued

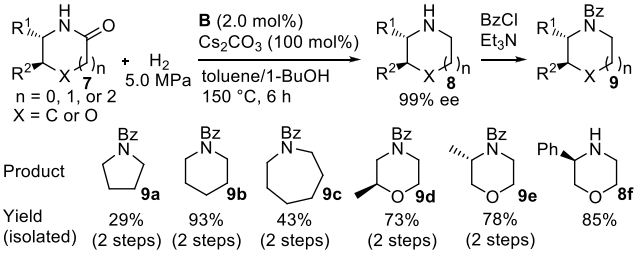
[a]Standard conditions: substrate (1.0 mmol), **B** (0.01 mmol), Cs_2CO_3 (0.5 mmol), H_2 (3.0 MPa), toluene (2.0 mL), 1-BuOH (0.92 mL), 6 h. [b]Isolated yield. [c]1-BuOH (0.18 mL). [d]**B** (0.02 mmol), H_2 (5.0 MPa), 1-BuOH (0.46 mL). [e]Substrate (0.30 mmol), **B** (0.006 mmol), Cs_2CO_3 (0.14 mmol), H_2 (5.0 MPa), toluene (0.58 mL), 1-BuOH (0.27 mL). [f]0.50 mmol scale, **B** (0.01 mmol), H_2 (5.0 MPa). [g]Without 1-BuOH, **2** (0.02 mmol). [h]0.50 mmol scale, **B** (0.01 mmol). [i]0.50 mmol scale. [j]**B** (0.02 mmol). [k]**B** (0.02 mmol), KO^{t}Bu (1.0 mmol), THF (5.0 mL), 1-BuOH (0.46 mL), 10 h.

10). This result also corroborates the step-by-step mechanism involving the hydrogenation/borrowing hydrogen reactions, as proposed in Scheme 1. The pyridine-fused lactam was reduced analogously to the corresponding cyclic amine (entry 11).

The substrate scope could be expanded to 5- and 7-membered lactams. Benzo[*cd*]indol-2(1*H*)-one was reduced to the 5-membered cyclic amine in 80% yield (entry 12), whereas 3-methyloxindole was transformed into 3-methylindole in 76% yield as the dehydrative condensation product from amino aldehyde via hydrogenolysis of the C−N bond (entry 13). In the reaction of 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one in the presence of Cs_2CO_3, a ring-opening hydrogenolysis product of amino alcohol was obtained selectively in 70% yield, suggesting that the reaction rate of its intramolecular *N*-alkylation was slower than that of 5- and 6-membered lactams. By applying KO^{t}Bu in a mixed solvent of THF and 1-BuOH, the 7-membered cyclic amine was obtained in an acceptable yield of 55% (entry 14).[15]

To further demonstrate the synthetic utility of this catalytic system, the formal deoxygenative hydrogenation of nonfused lactams was performed using 2.0 mol % of **B** with 100 mol % of Cs_2CO_3 under 5.0 MPa of hydrogen at a temperature of 150 °C for 6 h. After benzoyl protection of the hydrogenation products, cyclic amine derivatives were successfully isolated, as summarized in Scheme 2. Among five- to seven-membered

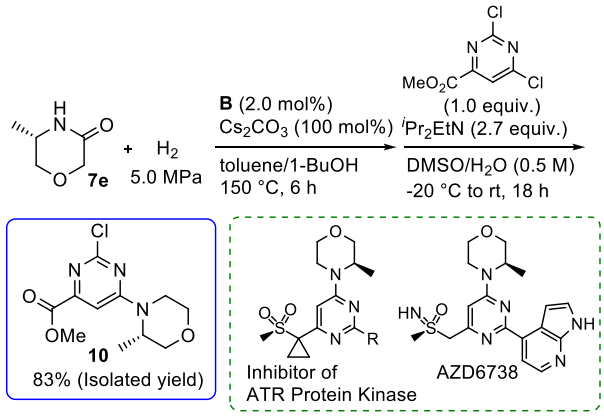
Scheme 2. Formal Deoxygenative Hydrogenation of Nonfused Lactams



lactams, 2-piperidone was efficiently reduced to piperidine (**9b**) in 93% yield. Encouraged by this result, we took a forward step for the hydrogenation of enantiomerically pure lactams, which could be synthesized from easily available chiral amino alcohols and α-halo acid chlorides[16] and tested access to optically active morpholines as important chiral building blocks of biological and pharmacological agents.[17] (*S*)-6-Methyl-3-morpholinone, (*S*)-5-methyl-3-morpholinone, and (*R*)-5-phenyl-3-morpholinone were converted into (*S*)-2-methymorpholine (73% yield), (*S*)-3-methylmorpholine (78% yield), and (*R*)-3-phenylmorpholine (85% yield), respectively, without erosion of the optical purity of 99% ee.

This protocol is applicable to synthesize chiral 4-(4-pyrimidyl)-3-methylmorpholine derivatives which are the important skeleton accessible to the bioactive compounds shown in Scheme 3.[18,19] In marked contrast to the $LiAlH_4$

Scheme 3. One-Pot Synthesis of Chiral 4-(4-Pyrimidyl)morpholine



reduction, for which hazardous workup procedures and careful handling to isolate less stable chiral methylmorpholine are inevitable, the deoxygenative hydrogenation of lactam could be performed coupled with the subsequent nucleophilic amine functionalization in a one-pot synthesis.

In summary, the formal deoxygenative hydrogenation of amides under nonacidic conditions was achieved by using the NHC-ligated PN^{H}P−Ru complex. The powerful hydridicity of the Ru catalyst contributes to the smooth hydrogenolysis of the C−N bond of hardly reducible amides and the subsequent reduction of imines generated from aldehydes and amines. The balanced hydrogenation and *N*-alkylation via hydrogen transfer by the same catalyst are particularly significant for the selective formation of deoxygenated amines. Actually, the sequential reaction performed with a range of lactams demonstrated the versatility with respect to the operational simplicity, the functional group tolerance originating from nonacidic conditions, and the maintenance of stereochemical integrity. Further studies to advance the eurhythmic hydrogenation/hydrogen transfer processes are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03878.

Experimental section and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: osamu_ogata@takasago.com.
*E-mail: ykayaki@o.cc.titech.ac.jp.

ORCID

Yoshihito Kayaki: 0000-0002-4685-8833

Notes

The authors declare no competing financial interest.

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