REGIOSELECTIVE INTRODUCTION OF ELECTROPHILES INTO PIPERIDINE DERIVATIVES AT THE 4-POSITION†

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Abstract – Regioselective introduction of various electrophiles (aldehydes, ketones, and imines) into piperidine skeleton at the 4-position was achieved with a catalytic amount of Pd(OAc)$_2$/PPh$_3$ in the presence of excess Et$_2$Zn. In addition, enantioselective introduction of benzaldehyde into piperidine derivatives was accomplished by using chiral phosphine ligand with moderate enantioselectivity.

Piperidines possessing substituents at the 4-position are useful synthetic intermediates for a variety of natural products and drug candidates. Accordingly, it is worthwhile to develop convenient methods for introduction of substituents at the 4-position of piperidine skeleton. Although some methods for the nucleophilic substitution are known, the electrophilic substitution has not been reported to date. We wish to report herein regioselective introduction of various electrophiles (aldehydes, ketones, and imines) into piperidine derivatives at the 4-position. Our strategy for generation of nucleophilic species from piperidine derivatives is shown in Scheme 1. First, electrochemical preparation of N-protected 2,3-didehydro-4-acetoxypiperidine 2, followed by generation of π-allyl palladium 3 from 2 by Pd(OAc)$_2$/PPh$_3$ and then, successive umpolung of 3 mediated by Et$_2$Zn.

Scheme 1

\[
\begin{align*}
\text{NPG} & \quad \text{OAc} \quad -2e & \quad \text{Pd(0)} & \quad \text{Et}_2\text{Zn} & \quad \text{El}^\ominus \\
1 & \quad 2 & \quad 3 & \quad 4
\end{align*}
\]
Compounds 2 were prepared as follows (Eq. 1). Electrochemical oxidation of N-protected piperidines 1 afforded 2-methoxypiperidines 5. Subsequent removal of methanol from 5, followed by bromomethoxylation and dehydrobromination gave N-protected 2-methoxy-3,4-didehydropiperidines 6, which were treated with AcOH to afford compounds 2 quantitatively.

\[
\begin{array}{ccc}
\text{N} & \text{OAc} \\
\text{PG} & \text{PG} & \text{PG} \\
1 & 5 & 2
\end{array}
\]

With N-benzyloxy-2,3-didehydro-4-acetoxypiperidine (2a) in hand, we first examined the reaction of 2a with benzaldehyde using a catalytic amount of Pd(OAc)\(_2\)/PPh\(_3\) in the presence of excess Et\(_2\)Zn in toluene (Eq. 2). The reaction proceeded smoothly within 2 h to afford 4-substituted piperidine 4a as a major product in 81% and 2-substituted 7a as a minor product in 11% yields.

In order to improve the regioselectivity, we screened a variety of N-protecting groups of 2 shown in Table 1 (Eq. 3). p-Chlorobenzyloxy piperidine 2b or p-trifluoromethylenzoxy piperidine 2c mainly afforded 4-substituted piperidine 4b or 4c along with some amount of 2-substituted 7b or 7c, respectively (entries 1 and 2). However the reaction of p-nitrobenzyloxy one (2d) with benzaldehyde did not proceed at all (entry 3). On the other hand, compound 2e protected with p-methoxybenzyl group gave exclusively 4-substituted piperidine 4e in excellent yield (entry 4), and 2f protected with methoxycarbonyl group also gave 4-substituted 4f in moderate yield (entry 5).
Next, the electrophilic substitution of 2e with various electrophiles was examined (Eq. 4). These results are summarized in Table 2. Some aromatic (entries 1-3) and aliphatic aldehydes (entry 4) gave the corresponding coupling products 8e-11e in good yields. Styrene oxide, which was transformed into phenylacetaldehyde under the reaction conditions, afforded 12e in 80% yield (entry 5). Moreover, acyclic (entries 6-8) and cyclic ketones (entry 9) gave 4-substituted products 13e-16e in good to high yields, while benzylideneaniline gave amine 17e in high yield (entry 10).
The reaction of pipercolinic acid derivative 18 with acetone proceeded regio- and stereo-selectively to afford cis-2,4-disubstituted product 19 in high yield (Eq. 5). The relative stereoconfiguration of 19 was deduced by NOE correlation.

![Chemical structure](image1)

Chiral phosphine ligand A^9 was used to introduce chirality in product 4e. Use of toluene as a solvent gave diastereomer mixture of 4e in low enantioselectivities, while CH₂Cl₂ led to moderate improvement in enantioselectivities of 4e (Eq. 6).

![Chemical structure](image2)

In summary, efficient regioselective introduction of various electrophiles into piperidine skeleton at the 4-position was achieved with a catalytic amount of Pd(OAc)₂/PPh₃ in the presence of excess Et₂Zn. In addition, enantioselective introduction of benzaldehyde into 2e at the 4-position was accomplished by use of chiral phosphine ligand A with moderate enantioselectivity. Further improvement of diastereo- and enantio-selectivity is underway.

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REFERENCES AND NOTES

† Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.


5. Characterization data of 2a: Colorless oil. IR (neat): 3447, 2937, 1738, 1645, 1578 cm⁻¹. $^1$H NMR (300 MHz, CDCl₃) $\delta$ 1.92-2.21 (m, 5H), 3.41-3.53 (m, 1H), 4.28 (br s, 1H), 5.00 (br s, 1H), 5.20-5.29 (m, 1H), 6.68 (br s, 1H), 7.29-7.57 (m, 5H). MS [HR-FAB(+)]: $m/z$ calcd for C₁₄H₁₆NO₃ 246.1130 [M+H]⁺ found 246.1108.

6. A typical experimental procedure: A solution of piperidine derivative 2a (0.3 mmol, 73.5 mg), Pd(OAc)₂ (0.015 mmol, 3.4 mg), PPh₃ (0.015 mmol, 3.4 mg), 1M Et₂Zn in hexane (1.2 mmol, 1.2 mL), and benzaldehyde (0.45 mmol, 48 mg) in toluene (2.0 mL) was stirred for 2 h under a nitrogen atmosphere. The resulting mixture was poured into saturated aqueous NH₄Cl and extracted with AcOEt (10 mL x 3). The combined organic layer was dried over MgSO₄ and extracted with AcOEt (10 mL x 3). The combined organic layer was dried over MgSO₄ and concentrated in vacuo, the residue was chromatographed on silica gel (hexane/AcOEt = 3/1) to afford 4a in 81% and 7a in 11% yield as colorless oil, respectively. 4a: IR (neat): 3450, 2937, 1738, 1645 cm⁻¹. $^1$H NMR (300 MHz, CDCl₃) $\delta$ 1.92-2.10 (m, 2H), 2.52-2.65 (m, 1H), 3.31-3.42 (m, 1H), 3.50-3.63 (m, 1H), 3.95-4.13 (m, 1H), 4.45-4.51 (m, 1H), 5.08-5.15 (m, 1H), 6.45-6.55 (m, 1H), 7.20-7.61 (m, 10H). MS [HR-FAB(+)]: $m/z$ calcd for C₁₉H₂₀NO₂ 294.1493 [M+H]⁺ found 294.1493. 7a: IR (neat): 3420, 2937, 1738, 1645 cm⁻¹. $^1$H NMR (300 MHz, CDCl₃) $\delta$ 1.92-2.21 (m, 5H), 3.41-3.53 (m, 1H), 4.28 (br s, 1H), 5.00 (br s, 1H), 5.20-5.29 (m, 1H), 6.68 (br s, 1H), 7.29-7.57 (m, 5H). MS [HR-FAB(+)]: $m/z$ calcd for C₁₄H₁₆NO₃ 246.1130 [M+H]⁺ found 246.1108.
2931, 1716, 1645 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.43-1.73 (m, 1H), 2.16-2.27 (m, 1H), 3.13-3.25 (m, 1H), 3.25-3.47 (m, 2H), 4.39-4.53 (m, 1H), 4.81-4.92 (m, 2H), 5.82-5.88 (m, 1H), 7.20-7.61 (m, 10H).

7. Characterization data of 19. Colorless oil. IR (neat): 3504, 2959, 1716, 1655, 1448 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.19 (s, 3H), 1.22 (s, 1.2H), 1.23 (s, 1.8H), 1.45 (br s, 1H), 1.72-1.84 (m, 1H), 2.08-2.14 (m, 1H), 2.39-2.47 (m, 1H), 3.75 (s, 3H), 3.76 (s, 1.2H), 3.80 (s, 1.8H), 4.82-4.85 (m, 0.4H), 4.90 (d, \(J\)=8.5 Hz, 0.6H), 4.97-5.00 (m, 1H), 6.87 (d, \(J\)=8.5 Hz, 0.6H), 7.00 (d, \(J\)=8.5 Hz, 0.4H). MS [HR-FAB(+)]: \(m/z\) calcd for C\(_{12}\)H\(_{20}\)NO\(_5\) 258.1341 [M+H]\(^+\) found 258.1339.

8. NOE correlation was observed between H\(^2\) and H\(^4\).


10. It was proposed in ref 11 that a plausible intermediate in the asymmetric reaction of cyclohexenyl acetate with benzaldehyde might be \(\eta^1\)-allylpalladium species 21 generated from \(\eta^3\)-allylpalladium species 20 with Et\(_2\)Zn.

\[
\begin{align*}
\text{20} & \quad \xrightarrow{\text{Et}_2\text{Zn}} \quad \text{21} \\
\text{PdX}_2\text{L}^* & \quad \text{Et}_2\text{Zn} \\
\text{Pd} & \quad \text{L}^* \\
\end{align*}
\]


12. Characterization data of 4e obtained in CH\(_2\)Cl\(_2\) (The absolute stereoconfiguration is not determined). Colorless. \([\alpha]\)\(^D\)\(_{25}\)=−9.1 (c 1.07, CHCl\(_3\)). IR (neat): 3420, 2934, 1732, 1651 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.70 (br s, 1H), 1.99 (br s, 2H), 2.59-2.64 (m, 1H), 3.52-3.61 (m, 1H), 3.84 (s, 3H), 3.99-4.04 (m, 1H), 4.43-4.58 (m, 1H), 5.05-5.19 (br s, 1H), 6.60 (br s, 1H), 6.90 (d, \(J\)=8.7 Hz, 2H), 7.22-7.40 (m, 5H), 7.45 (d, \(J\)=8.7 Hz, 2H). MS [HR-FAB(+)]: \(m/z\) calcd for C\(_{20}\)H\(_{22}\)NO\(_3\) 324.1600 [M+H]\(^+\) found 324.1598. The diastereoselectivity and optical purity of 4e were determined by chiral HPLC: Daicel Chiralcel OJ-H column (4.6 mm\(^φ\), 250 mm), \(n\)-hexane : \(i\)-PrOH = 3 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: Major diastereomer 12.9 min (rich), 22.9 min and minor diastereomer 27.5 min (rich), 38.5 min.
Regioselective Introduction of Electrophiles into Piperidine Derivatives at the 4-Position

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Electrophiles = Aldehydes, Ketones, and Imine