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

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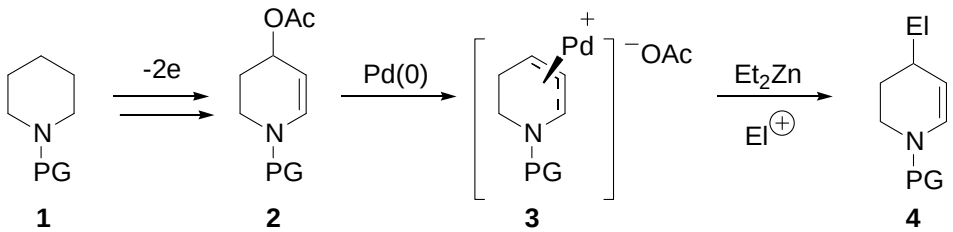
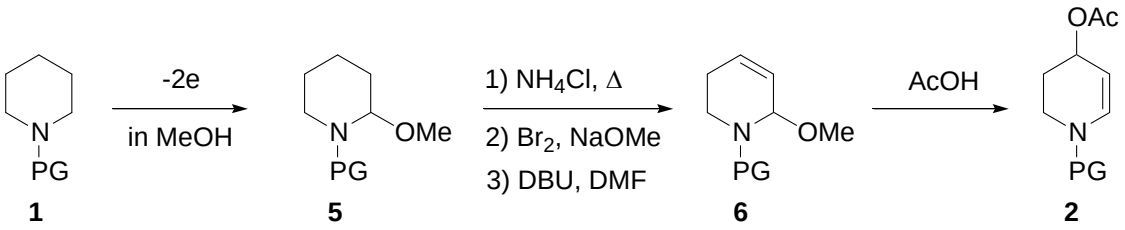
Abstract – Regioselective introduction of various electrophiles (aldehydes, ketones, and imines) into piperidine skeleton at the 4-position was achieved with a catalytic amount of $Pd(OAc)_2/PPh_3$ in the presence of excess Et_2Zn. In addition, enantioselective introduction of benzaldehyde into piperidine 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.[1] 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,[2] 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_2Zn.[3]

Scheme 1

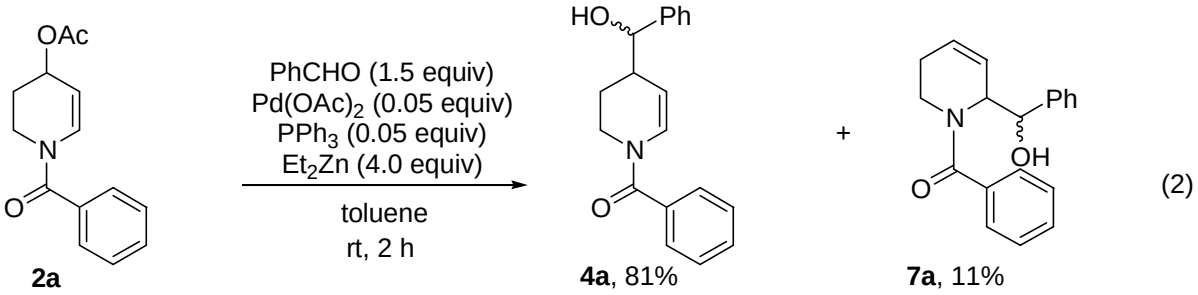


Compounds **2** were prepared as follows (Eq. 1). Electrochemical oxidation of *N*-protected piperidines **1** afforded 2-methoxypiperidines **5**. Subsequent removal of methanol from **5**, followed by bromomethoxylation and dehydrobromination gave *N*-protected 2-methoxy-3,4-didehydropiperidines **6**,[4] which were treated with AcOH to afford compounds **2** quantitatively.



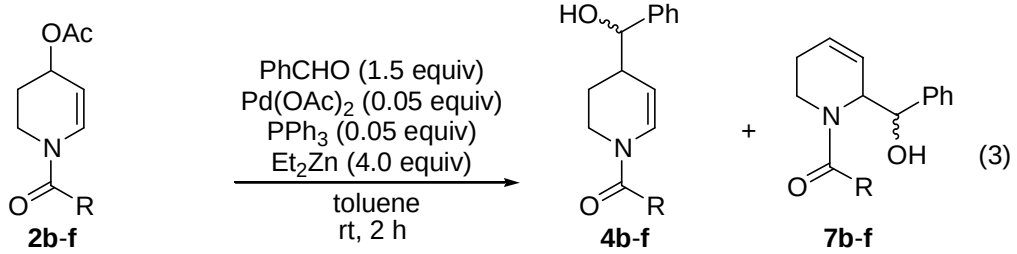
(1)

With *N*-benzoyl-2,3-didehydro-4-acetoxypiperidine (**2a**)[5] 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_2Zn in toluene (Eq. 2).[6] 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.



(2)

In order to improve the regioselectivity, we screened a variety of *N*-protecting groups of **2** shown in Table 1 (Eq. 3). *p*-Chlorobenzoylated piperidine **2b** or *p*-trifluoromethylbenzoylated **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*-nitrobenzoylated one (**2d**) with benzaldehyde did not proceed at all (entry 3). On the other hand, compound **2e** protected with *p*-methoxybenzoyl 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).

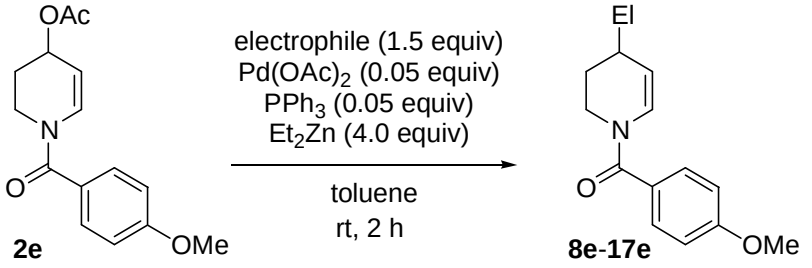


(3)

Table 1. Effect of *N*-protecting group on regioselectivity

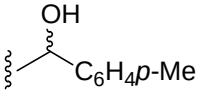
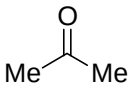
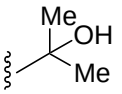
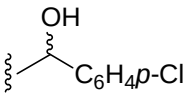
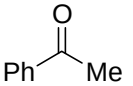
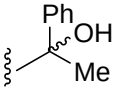
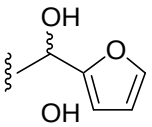
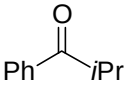
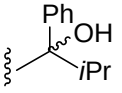
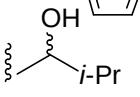
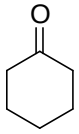
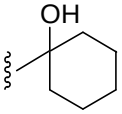
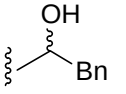
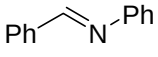
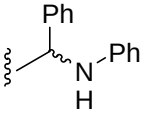
entry	4-acetate	R	product	(yield: %)		
1	**2b**	*p*-ClC_6H_4	**4b**	(71)	**7b**	(8)
2	**2c**	*p*-$CF_3C_6H_4$	**4c**	(66)	**7c**	(13)
3	**2d**	*p*-$NO_2C_6H_4$	**4d**	(0)	**7d**	(0)
4	**2e**	*p*-$MeOC_6H_4$	**4e**	(93)	**7e**	(0)
5	**2f**	OMe	**4f**	(54)	**7f**	(0)

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).

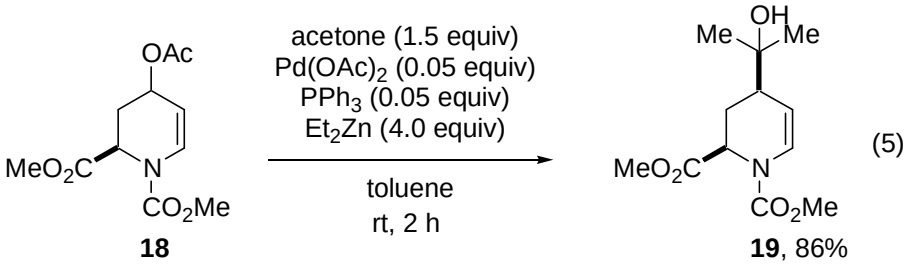


(4)

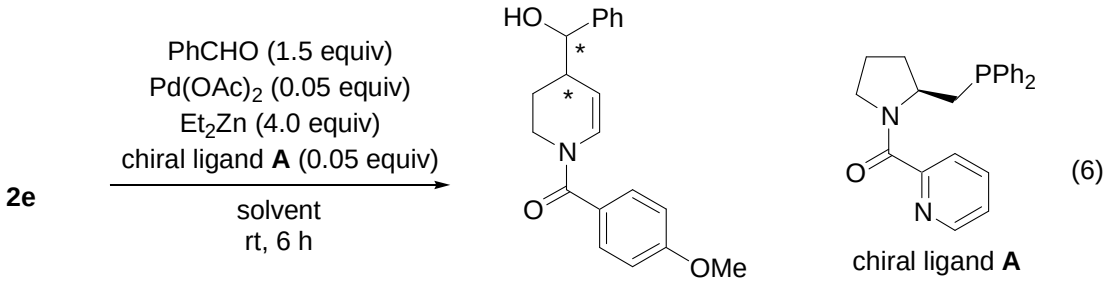
Table 2. Introduction of various electrophiles into **2e**

entry	electrophile	product		entry	electrophile	product	
		—El	(yield: %)			—El	(yield: %)
1	*p*-MeC_6H_4CHO		**8e** (70)	6			**13e** (86)
2	*p*-ClC_6H_4CHO		**9e** (67)	7			**14e** (78)
3	2-furyl-CHO		**10e** (70)	8			**15e** (65)
4	*i*-Pr-CHO		**11e** (69)	9			**16e** (64)
5	styrene oxide		**12e** (80)	10			**17e** (81)

The reaction of pipecolinic acid derivative **18** with acetone proceeded regio- and stereo-selectively to afford *cis*-2,4-disubstituted product **19** in high yield (Eq. 5).[7] The relative stereoconfiguration of **19** was deduced by NOE correlation.[8]



Chiral phosphine ligand **A**[9] was used to introduce chirality in product **4e**.[10] Use of toluene as a solvent gave diastereomer mixture of **4e** in low enantioselectivities, while CH_2Cl_2 led to moderate improvement in enantioselectivities of **4e** (Eq. 6).[12]



solvent	yield	diastereomer ratio and ee
toluene	70%	75 (11% ee) : 25 (20% ee)
CH_2Cl_2	62%	80 (44% ee) : 20 (36% ee)

In summary, efficient regioselective introduction of various electrophiles into piperidine skeleton at the 4-position was achieved with a catalytic amount of $Pd(OAc)_2/PPh_3$ in the presence of excess Et_2Zn. 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.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

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

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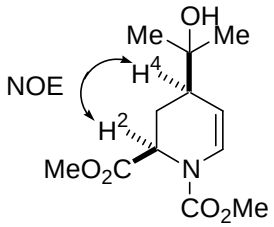
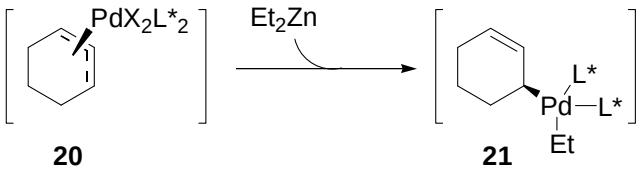
5. Characterization data of **2a**: Colorless oil. IR (neat): 3447, 2937, 1738, 1645, 1578 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.92-2.21 (m, 5H), 3.41-3.53 (m, 1H), 4.28 (br s, 1H), 5.00 (br s, 1H), 5.20-5.29 (m, 1H), 6.68 (br s, 1H), 7.29-7.57 (m, 5H). MS [HR-FAB(+)]: *m/z* calcd for $C_{14}H_{16}NO_3$ 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), PPh_3 (0.015 mmol, 3.4 mg), 1M Et_2Zn 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 NH_4Cl and extracted with AcOEt (10 mL x 3). The combined organic layer was dried over $MgSO_4$ 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, 2920, 1655, 1490 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 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 $C_{19}H_{20}NO_2$ 294.1494 $[M+H]^+$ found 294.1493. **7a:** IR (neat): 3420,

2931, 1716, 1645 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 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}. ^1H NMR (300 MHz, $CDCl_3$) δ 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.



9. K. Hiroi, Y. Suzuki, and I. Abe, *Tetrahedron: Asymmetry*, 1999, **10**, 1173.
10. It was proposed in ref 11 that a plausible intermediate in the asymmetric reaction of cyclohexenyl acetate with benzaldehyde might be η^1-allylpalladium species **21** generated from η^3-allylpalladium species **20** with Et_2Zn.



20 **21**

11. G. P. Howell, A. J. Minnaard, and B. L. Feringa, *Org. Biomol. Chem.*, 2006, **4**, 1278.
12. Characterization data of **4e** obtained in CH_2Cl_2 (The absolute stereoconfiguration is not determined). Colorless oil. $[\alpha]^{19}_D$ −9.1 (*c* 1.07, $CHCl_3$). IR (neat): 3420, 2934, 1732, 1651 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 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 mmϕ, 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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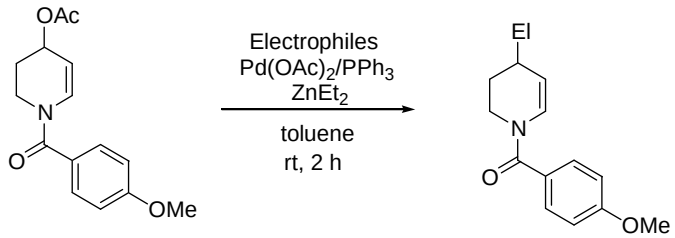

Electrophiles = Aldehydes, Ketones, and Imine