Asymmetric Construction of Quaternary Carbon Stereocenter by Pd-Catalyzed Intramolecular α-Arylation

Takafumi ARAO, Kazuhiro KONDO,* and Toyohiko AOYAMA*

Graduate School of Pharmaceutical Sciences, Nagoya City University; 3–1 Tanabe-dori, Mizuho-ku, Nagoya 467–8603, Japan. Received August 28, 2006; accepted September 30, 2006; published online October 4, 2006

The catalyst comprised of $Pd(OAc)_2$ and H_8-BINAP provides good reaction conversions for a catalytic enantioselective intramolecular α-arylation of *N*-(2-bromophenyl)-*N*-methyl-2-arylpropanamide to form the quaternary carbon with up to 68% enantioselectivity.

Key words enantioselective intramolecular α-arylation; quaternary carbon; H_8-BINAP; chiral N-heterocyclic carbene

The creation of quaternary carbon streocenters with enantiocontrol remains a great challenge in organic synthesis.[1—6] We have been quite recently developing a novel N-heterocyclic carbene ligand[7,8] **1** based on the concept of chiral mimetic.[7—13] The N-heterocyclic carbene ligand **1** has been found to construct quaternary carbon streocenters with up to 65% enantioselectivity in Pd-catalyzed enantioselective intramolecular α-arylation of *N*-(2-bromophenyl)-*N*-methyl-2-arylpropanamide **2** (Chart 1). The enantioselectivity obtained is, to the best of our knowledge, the high level in the reported literature,[14,15] although the chemical yield is moderate. Since the chemical yield in the reactions with carben ligand **1** was moderate, we focused on screening a number of phosphine ligands, although it is reported that the use of phosphine ligand is not good by Hartwig.[14] We here would like to report our further investigation on the enantioselective intramolecular α-arylation for improvement of the previous results.

After intensive screening of phosphine ligands, we found that both the yield and the enantioselectivity of the arylation were brought to acceptable levels by using H_8-BINAP as a ligand (entry 3). The representative ligand effects are shown in Table 1. Next, screening of Pd sources, bases and solvents was undertaken (Table 2), and the combination of $Pd(OAc)_2$ as Pd source, NaO*t*-Bu as base and toluene as solvent was found to be best. This optimization exhibited good reaction conversion and enantioselectivity (entry 6: yield 98%, 68% ee). Having optimized the reaction conditions, the substrates which were reported by Hartwig[14] were investigated as shown in Fig. 1. Amides **2b**—**e** possessing various substituents on the Ar group were found to be employable, exhibiting >81% reaction conversions and 51—67% enantioselectivities.

In summary, we have found the use of H_8-BINAP as a ligand, compared with carbene ligand **1**, improved reaction conversions in an enantioselective intramolecular α-arylation[16—20] of *N*-(2-bromophenyl)-*N*-methyl-2-arylpropanamide **2**. Ligand tunings are now ongoing in order to improve enantioselectivity.

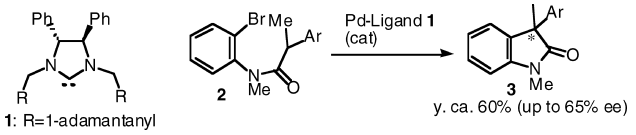
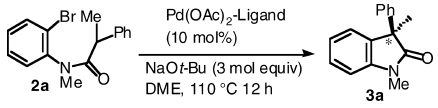


Chart 1. Enantioselective Intramolecular α-Arylation of Amide **2**

Table 1. Effects of Ligands[a]



Entry	Ligand	Yield of **3a** (%)	Ee[b] of **3a** (%)
1	(*S*)-BINAP	89	55
2	(*S*)-tol-BINAP	88	59
3	(*S*)-H_8-BINAP	86	62
4	(*S*)-SEGPHOS	90	44
5	(*S*)-DM-SEGPHOS	90	47
6	(*S*)-DTBM-SEGPHOS	90	17[c]

a) The reactions of **2a** were performed using 10 mol% of $Pd(OAc)_2$, 10 mol% of the ligand and 3 mol eq of NaO*t*-Bu in DME at 110 °C for 12 h. *b*) Determined by HPLC analysis. *c*) The product **3a** with opposite absolute configuration was obtained.

Experimental

General IR spectra were measured on a SHIMADZU FTIR-8100 diffraction grating IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM-EX-270 NMR spectrometer, operating at 270 MHz for

Table 2. Optimization of Reaction Conditions[a]

Entry	Pd	Base	Solvent	Yield of **3a** (%)	Ee[b] of **3a** (%)
1	$Pd_2(dba)_3\cdot CHCl_3$	NaO*t*-Bu	DME	86	55
2	$Pd(OAc)_2$	LiO*t*-Bu	DME	96	12
3	$Pd(OAc)_2$	KO*t*-Bu	DME	33[c]	48
4	$Pd(OAc)_2$	NaO*t*-Bu	1,4-Dioxane	71[c]	44
5	$Pd(OAc)_2$	NaO*t*-Bu	CF_3–C_6H_5	38[c]	61
6	$Pd(OAc)_2$	NaO*t*-Bu	Toluene	98	68

a) The reactions of **2a** were performed using 10 mol% of Pd, 10 mol% of (*S*)-H_8-BINAP and 3 mol eq of base in solvent at 110 °C for 12 h. *b*) Determined by HPLC analysis. *c*) Remainder of mass balance was the unreacted amide **2a**.

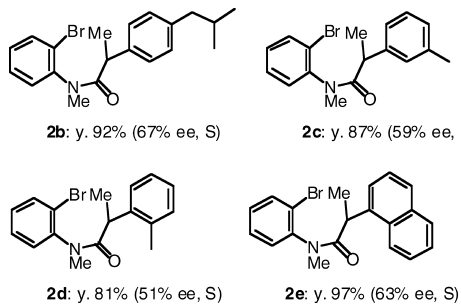


Fig. 1. Enantioselective α-Arylation of Several Amides **2b**—**e** under the Optimized Conditions

* To whom correspondence should be addressed. e-mail: kazuk@phar.nagoya-cu.ac.jp; aoyama@phar.nagoya-cu.ac.jp

^{1}H-NMR and at 68 MHz for ^{13}C-NMR. ^{1}H- and ^{13}C-NMR spectra were reported in δ units, parts per million (ppm) downfield from tetramethylsilane (δ=0). EI- and FAB-MS spectra were measured on a JEOL JMS-SX-102A instrument. Specific rotations (in deg cm^3 g^{-1} l^{-1}) were determined on a JASCO DIP-1000 digital polarimeter.

All reagents were available from commercial sources and used without further purification. In general, all reactions were performed under an argon atmosphere. H_2O was used without purification. 1,2-Dimethoxyethane (DME), 1,4-dioxane and toluene were distilled from Na/benzophenone ketyl under a nitrogen atmosphere. Silica gel column chromatography was performed on Fuji silysia BW200.

The *N*-(bromophenyl)-*N*-methyl-2-arylpropanamide **2c** was prepared according to the same procedure reported.[14)]

N-(2-Bromophenyl)-*N*-methyl-2-(3-tolyl)propanamide (**2c**): A yellow oil. IR (neat): ν: 1666, 1661 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ: 1.40 (d, J=6.9 Hz, 0.9H), 1.42 (d, J=6.9 Hz, 2.1H), 2.25 (s, 3H), 3.16 (s, 2.1H), 3.18 (s, 0.9H), 3.30 (q, J=6.9 Hz, 0.7H), 3.50 (q, J=6.9 Hz, 0.3H), 6.61—6.88 (m, 2.7H), 6.91—7.46 (m, 4.3H), 7.56 (br d, J=7.9 Hz, 0.3H), 7.70 (dd, 1.6, 7.7 Hz, 0.7H). ^{13}C-NMR ($CDCl_3$): δ: 19.91, 20.52, 21.32, 21.34, 36.10, 36.13, 43.21, 44.00, 123.48, 124.06, 124.33, 124.81, 127.19, 127.23, 127.82, 127.92, 127.97, 128.06, 128.37, 128.53, 129.37, 129.40, 129.89, 130.81, 133.27, 133.72, 137.40, 137.70, 140.15, 141.33, 142.04, 142.31, 173.49, 173.69. EI-MS: m/z=252 (M^+−Br), 119 (bp). FAB-MS: m/z=334 (M^++1), 332 (M^++1). HR-MS (M^+−Br) Calcd for $C_{17}H_{18}NO$: 252.1388, Found: 252.1384.

Reresentative Procedure for the Enantioselective Intramolecular α-Arylation of Amide 2a (Entry 6, Table 2) To a stirred solution of *N*-(2-bromophenyl)-*N*-methyl-2-phenylpropanamide[14)] (**2a**) (63.6 mg, 0.200 mmol) in toluene (1.0 ml) were added H_8-BINAP (12.6 mg, 0.0200 mmol), Pd $(OAc)_2$ (4.5 mg, 0.0200 mmol) and NaO*t*-Bu (57.7 mg, 0.600 mmol) at r.t. and the mixture was stirred for 12 h at 110 °C. After being cooled to r.t., the mixture was filtered through a layer of silica gel and evaporated. Purification by silica gel column (EtOAc/hexane, 1 : 8) gave (3*S*)-1,3-dimethyl-3-phenyl-1,3-dihydro-indol-2-one (**3a**) (46.5 mg, 98%, 68% ee). The spectral data of **3a** were comparable to those reported.[14)]

The spectral data of the (*S*)-oxindoles **3b**, **3d** and **3e** were comparable to those reported.[14)] The physical data of the oxindole **3c** were shown as follows.

(3*S*)-1,3-Dimethyl-3-(3-tolyl)-1,3-dihydro-indol-2-one (**3c**): A colorless oil. $[\alpha]_D^{29}$ +68° (c=1.19, THF). IR (neat): ν: 1720, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ: 1.77 (s, 3H), 2.30 (s, 3H), 3.24 (s, 3H), 6.90 (d, J=7.6 Hz, 1H), 7.00—7.20 (m, 6H), 7.31 (ddd, J=1.3, 7.6, 7.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ: 21.64, 23.78, 26.53, 52.11, 108.17, 122.65, 123.54, 124.04, 127.16, 127.90, 128.26, 134.91, 137.98, 140.56, 143.07, 179.36. EI-MS: m/z=251 (M^+), 236 (bp, M^+−Me). HR-MS (M^+) Calcd for $C_{17}H_{17}NO$: 251.1310, Found 251.1312.

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