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Regio- and Diasteroselectivity of Rhodium-catalyzed Ring Opening Reaction of Oxabenzonorbornadienes with Heteroatom Nucleophiles

Ding Qiao YANG, He Ping ZENG*

Department of Chemistry, South China Normal University, Guangzhou 510631

Abstract: A new rhodium catalyzed ring opening reaction of oxabenzonorbornadienes and its derivatives was described. This reaction forms a new carbon-nitrogen bond *via* an intermolecular allylic displacement of the bridgehead oxygen with a piperazine's derivatives, which proceeds with very high regioselectivity.

Keywords: Ring opening, rhodium-catalyzed, oxabenzonorbornadienes, heteroatom nucleophiles.

A number of important bioactive molecules, which contain a substituted tetrahydronaphthalene core [1-3], led us to investigate the possibility of developing the ring-opening of the (un)substituted-oxabenzonornene systems. Since M. Lautens first reported the reductive [4-6] and alkylative nucleophilic ring opening of oxabenzonorbornadienes using nickel- and palladium-catalysts and a variety of nucleophiles, including asymmetric additions of aliphatic alcohols, phenols, carboxylates, aliphatic and aromatic amines and boronic acids. The stereocontrolled addition of heteroatom nucleophiles to different oxabenzonorbornadienes of the general structure **1a-c** uniquely gave *trans*-(un)substituted dihydronaphthalene products **2a-f** (**Scheme 1**), whereas the addition of boronic acids gave the corresponding *cis*-products [7-10]. In the present works, we report rhodium-catalyzing ring opening reaction of oxabenzonorbornadiene and its derivatives *via* piperazine's derivatives producing 2-(un)substituted dihydronaphthalen-1-ols in excellent yields (**Table 1**). Unlike all other nucleophiles, these nucleophiles under rhodium-catalyzing proceeded *endo* attack to give *trans* ring opening products. Extension of this reaction to other nucleophiles would allow to synthesize a broad range of enantioenriched dihydronaphthalene products, which could be further transformed into substituted benzofurans which are pharmaceutically interesting compounds.

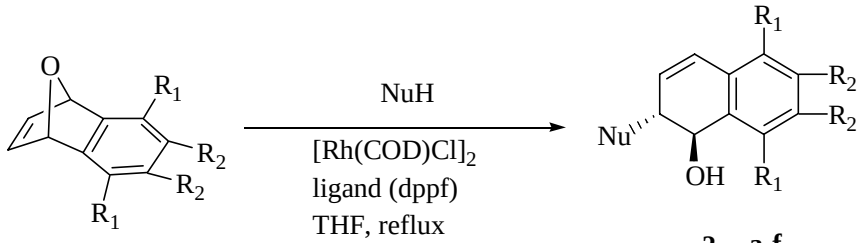
The compounds **2a-f** were syntheized from ring opening of oxabenzonorbonadienes by rhodium-catalyzing with ligand 1, 1′-bis(diphenylphosphino)ferrocene (dppf). The products formed were in the *trans* form rather than the *cis* products. The structure of the products were identified by IR, ^{1}H-NMR, ^{13}C-NMR, MS and HRMS.

Ring opening reaction of oxabenzonorbornadiene **1a** was carried out in a round bottom flask equipped with a reflux condenser, under dry nitrogen. Oxabenzonorborna-

*E-mail: zenghp@scnu.edu.cn

diene **1a**, (95 mg, 0.659 mmol) in anhydrous THF (2.5 mL), chloro(1, 5-cyclooctadiene)rhodium(I) dimmer $[Rh(COD)Cl]_2$(2.5 mol%) and 1, 1'-bis (diphenylphosphino) ferrocene (dppf) (5 mol%) were added simultaneously. When the reaction mixture was heated to boiling, hetero atom-nucleophiles 4-methylpiperazine (66 mg, 0.659 mmol) was added. Volatile nucleophiles were used in slightly excess (5 eq). The additive ammonium iodide was needed (2.5 eq), the nucleophile reagent is the derivatives of amine. The reaction mixture was refluxed continuously until the starting material was consumed (about 1-3 h). The reaction mixture was concentrated in *vacuo*, the crude mixture was purified by silica gel flate chromatography to obtain a brown oil **2a** (153 mg, 95%). **2b-f** were prepared in the same method.

Scheme 1



1 a-c **2 a-f**

a. R_1=H, R_2=H

b. R_1=H, R_2=OCH_3

c. R_1=OCH_3, R_2=H

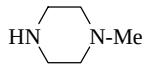
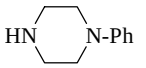
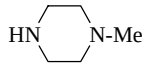
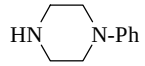
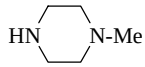
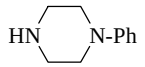
2a was obtained as a brown oil (153 mg, 95%) purified by flash chromatograph. R_f = 0.12 on silica gel plate (ethyl acetate : hexane : methanol 1:1:0.8 v/v). IR (KBr, cm^{-1}) 3420 (br), 2936 (w), 2805 (w), 1653 (w), 1556 (s), 1539 (s), 1456 (s), 1284(s), 1004 (w), 782 (s). ^{1}H-NMR (400 MHz, CD_3OD) δ 7.43 (t, 1H, J = 3.30 Hz), 7.24-7.26 (m，2H), 7.11 (t, 1H, J = 4.30 Hz), 6.65 (d, 1H, J = 9.80 Hz), 5.94 (q, 1H, J = 4.00 Hz), 4.87 (s，2H), 3.45-3.46 (m，1H), 2.71-2.73 (m, 2H), 2.63 (s, 2H), 2.46 (s, 3H), 2.47 (s，1H), 2.27 (s, 3H); ^{13}C-NMR (400 MHz, CD_3OD) δ 138.4, 133.6, 130.7, 129.2, 129.0, 128.2, 127.7, 126.5, 68.9, 66.9, 56.2, 45.9. FabMS *m/z*, 244 (M^+, 100), 226 (M-H_2O, 45), 187 (40), 145 (40), 115 (41), 99 (90), 84 (55), 70 (30), 56 (35); HRMS Calcd for $C_{15}H_{20}N_2O$, 244.1576. Found: 244.1579.

Conclusion

An efficient new rhodium-catalyzed ring opening reaction of (un)substituted oxabenzonorbornadienes to form a new carbon-heteroatom bond *via* an inter-molecular allylic displacement of the bridgehead oxygen was described. The nucleophiles were a variety of amines. In this reaction, if the heteroatom nucleophiles, containing oxygen or nitrogen electron donating atoms, only the *trans*-products were obtained, *i.e.* the reaction is highly

regioselective. The rhodium catalyst loadings were very low, only 0.25 mol% was required. The efforts to apply this method in the preparation of biologically active compounds are underway.

Table 1 Ring opening reaction of oxabenzonorbornadienes to form **2a**～**f**

Substrates	NuH	time(hr)	Prods.	[a] yield%
1a		3	**2a**	95
1a		3	**2b**	94
1b		2	**2c**	80
1b		3	**2d**	97
1c		3	**2e**	93
1c		2	**2f**	96

Conditions: 2.5 mol% $[Rh(COD)Cl]_2$, 5 mol% ligand(dppf), **1a** were dissolved in THF(2.0 mL) NH_4I (2.5 equiv.to **1a**), to piperazine derivatives 5 eq. [a]Isolated yield.

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