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A Route to 2-Substituted Tetrahydroquinolines via Palladium-Catalyzed Intramolecular Hydroamination of Anilino-alkynes

Nitin T. Patil, Huanyou Wu, and Yoshinori Yamamoto*

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

yoshi@mail.tains.tohoku.ac.jp

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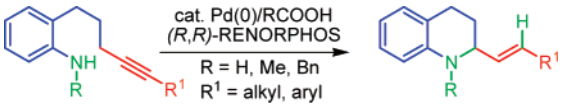

The cyclization of amino-alkynes **1** in which an amino group is attached to the aromatic ring, proceeded smoothly using a catalytic amount of $Pd(PPh_3)_4$ and benzoic acid in toluene at 120 °C, leading to the formation of the 2-substituted tetrahydroquinolines **2**. An asymmetric variant of the reaction using the chiral palladium catalyst (prepared in situ by mixing $Pd_2(dba)_3$·$CHCl_3$ and (*R*,*R*)-RENORPHOS) was also explored. The absolute configuration of the enantiomerically enriched tetrahydroquinolines, obtained in this way, was determined by converting them to the known compounds and was found to be *R*. The alkaloids such as (±)-galipinine, (±)-angustureine, and their optically active form were synthesized by using this reaction as a key step.

One of the most challenging topics in modern organic chemistry is the synthesis of natural products containing a heterocyclic ring. Despite the considerable exploration to date within this field, there is still a need for further development of alternative methods of preparation for biologically active heterocyclic compounds. Among numerous families of natural products, tetrahydroquinolines seem to attract considerable attention due to their abundant presence in plants[1] along with their promising biological activities.[2] Therefore their syntheses via newer and atom economical[3] approaches have been the subject of current research.[4] One of the approaches for the synthesis of this class of compounds involves the hydrogenation of quinolines.[5] The transition-metal-catalyzed process that involves C−N bond formation is desirable because the product is obtained generally under milder conditions with high atom economy.[6] Moreover, a catalytic asymmetric version of the process is possible with the help of chiral metal complexes, generated from metal and chiral ligands.

The transition-metal-catalyzed addition of amines to activated and nonactivated C−C unsaturated bonds, generally known as hydroamination,[7] has proven to be a valuable route for the formation of C−N bonds. Particularly noteworthy is the intramolecular cyclization of amines with tethered C−C bonds, which leads to the formation of a wide variety of nitrogen heterocycles. For example, the hydroamination/cyclization of aminoalkenes,[8] aminoallenes,[9] aminodienes,[10] and aminoalkynes[11] using transition metal and lanthanide complexes provides an

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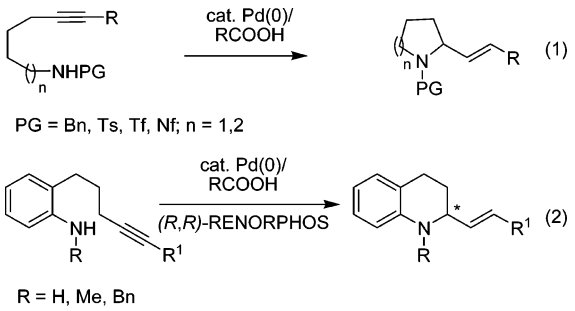
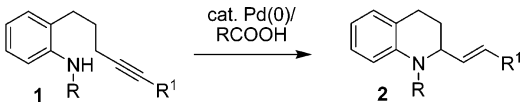
efficient way for synthesizing various nitrogen heterocycles. Recently, we reported[12] an entirely new method for the hydroamination of alkynes using a $Pd(PPh_3)_4$/PhCOOH combined catalyst system. The intramolecular catalytic asymmetric hydroamination of alkynes was also achieved using (*R*,*R*)-RENORPHOS ligand, which enabled us to synthesize the chiral nitrogen heterocycles (pyrrolidines and piperidines) in good to moderate yields and ee's (eq 1).[13] Herein we report the application of our methodology for the synthesis of 2-substituted tetrahydroquinolines (eq 2).



First the anilino-alkyne **1a**[14] was treated with $Pd(PPh_3)_4$ (20 mol %)/PhCOOH (50 mol %) in toluene at 120 °C for 4 h. The starting material completely disappeared in 4 h, giving the cyclization product **2a** in 98% isolated yield as a single *E*-stereoisomer (Table 1, entry 1). As anticipated, in the absence of benzoic acid no reaction took place even after heating at 120 °C for 24 h. The use of a methyl group on the amine nitrogen also worked well; however, the yield obtained was somewhat lower (entry 2). The substrate **1c**, in which there is no protecting group on nitrogen, also gave the cyclization product **2c** in 80% yield in just 2 h (entry 3). Not only aromatic alkynes but also aliphatic alkynes worked well to give **2d** in 78% yield (entry 4). Quite surprisingly, in the case of substrate **1e**, a mixture of *E*- and *Z*-isomers in a ratio of 2:1 was obtained (entry 5). The substrate **1f**, in which alkyne is attached to a ^{t}Bu group, proved to be inert under the standard reaction condition (entry 6). The substrates **1g**−**j**, in which the alkyne is attached to various aromatic ring, reacted with $Pd(PPh_3)_4$ catalyst under the standard conditions to give the corresponding tetrahydroquinolines **2g**−**j** in good to high yields (entries 7−10). It should be noted that an electron-withdrawing group such as Boc, Ts, or Nf on the amine nitrogen decreased dramatically the reactivity of the hydroamination and the desired product was not obtained at all. These results are in contrast to our previous results where the use of the Ts and Nf group was necessary.[12a,b,13]

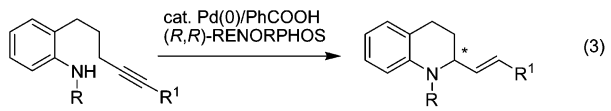
TABLE 1. Palladium-Catalyzed Synthesis of Tetrahydroquinolines[a]



entry	1	R	R^1	time (h)	2	yield (%)[b]
1	**1a**	Bn	Ph	4	**2a**	98
2	**1b**	Me	Ph	12	**2b**	63
3	**1c**	H	Ph	2	**2c**	80
4	**1d**	Me	^{n}Pr	24	**2d**	78
5	**1e**	H	^{n}Pr	24	**2e**	79[c]
6	**1f**	H	^{t}Bu	2	**2f**	0[d]
7	**1g**	H	*p*-CH_3-C_6H_4	24	**2g**	77
8	**1h**	H	*p*-OCH_3-C_6H_4	12	**2h**	90
9	**1i**	H	*p*-CF_3-C_6H_4	6	**2i**	71
10	**1j**	Me	benzo[1,3]dioxole	12	**2j**	87

[a] The reactions of aminoalkynes 1 (0.125 mmol) in the presence of $Pd(PPh_3)_4$(20 mol %) and $PhCO_2H$ (50 mol %) were carried out at 120 °C in toluene (1 M). [b] Isolated yields. [c] A mixture of *trans* and *cis* isomer in the ratio of 2:1 was obtained. [d] Complex mixture obtained.

It is clear that the scope and synthetic utility of this process would be enhanced dramatically if the reaction proceeded in an asymmetric manner. For this reason we have examined several nonracemic chiral ligands that were tested previously for similar reactions.[13] Once again, (*R*,*R*)-RENORPHOS gave better results, although the ee's obtained were not satisfactory. The reactions of **1a**, **1c**, and **1d** were conducted using $Pd_2(dba)_3$·$CHCl_3$ and (*R*,*R*)-RENORPHOS to give enantiomerically enriched tetrahydroquinolines **2a**, **2c**, and **2d**, respectively (eq 3).

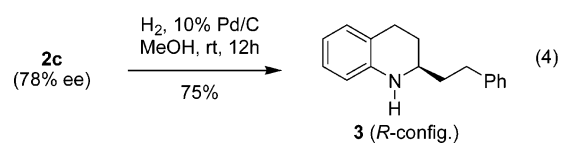


1a R = Bn, R^1 = Ph
1c R = H, R^1 = Ph
1d R = Me, R^1 = ^{n}Pr

2a R = Bn, R^1 = Ph, 73% yield, 60% *ee*
2c R = H, R^1 = Ph, 61% yield, 78% *ee*
2d R = Me, R^1 = ^{n}Pr, 48% yield, 52% ee

Unfortunately, lowering the amount of palladium catalyst as well as (*R*,*R*)-RENORPHOS ligand resulted into lowering of either yields or enantioselectivities. Although this process gave 2-substituted tetrahydroquinolines in modest yields and ee's, these data demonstrate the feasibility of enantioselective induction.

The absolute configuration of the hydroamination product **2c** (78% ee) was determined by transforming it into the known compound **3** (eq 4). It has been reported in the literature that



(+)-2-phenethyl-1,2,3,4-tetrahydroquinoline $[\alpha]^{23}_D = +73.1$ (*c* 1.0, $CHCl_3$) has *R* configuration.[4a] Since the optical rotation of **3** was found to be $[\alpha]^{25}_D = +52.3$ (*c* 0.55, $CHCl_3$), it was unequivocally confirmed that the absolute configuration of major

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(14) The starting materials were prepared from commercially available 2-iodoaniline, and the details are described in Supporting Information.

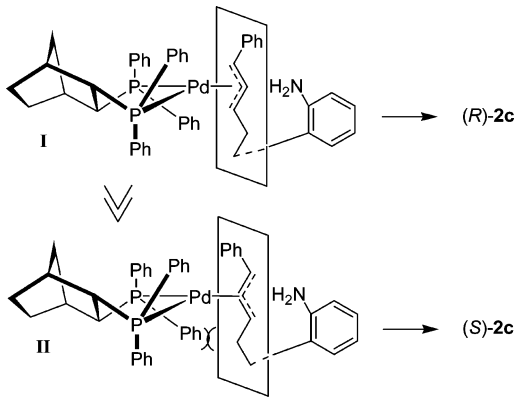
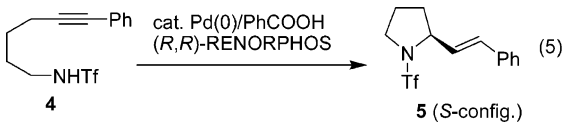


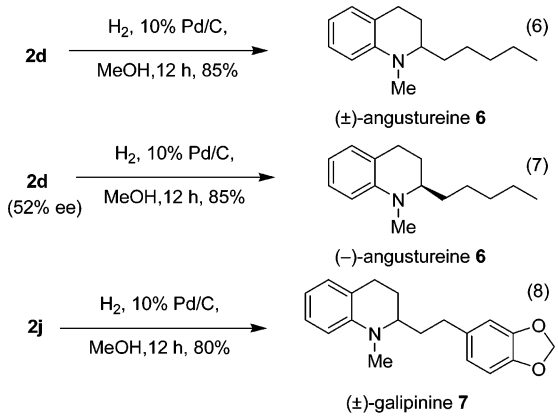
FIGURE 1. Proposed transition state models.

isomer **2c** is *R*. Previously, we reported that the reaction of the aliphatic amino alkyne **4**, in the presence of $Pd_2(dba)_3$·$CHCl_3$/(*R*,*R*)-RENORPHOS catalyst, afforded the pyrrolidine **5** with *S* configuration (eq 5).[13] Although in the present case the product having *R*-configuration was obtained, the direction of chiral induction is same as that of previous findings.



The observed enantioselectivity in the intramolecular hydroamination of alkyne could be rationalized in terms of transition state models **I** and **II** as shown in Figure 1. In **I**, the space at the lower front side of the catalyst allows the alkyl chain attached to the π-allyl to move freely. In **II**, a phenyl ring emanating from the phosphorus atom at the backside of the catalyst restricts the movement of the tether. Accordingly, the reaction proceeds through a transition state model **I** to give (*R*)-**2c** predominantly.

It was envisaged that the hydrogenation of **2d** and **2j** would lead to the formation of (±)-angustureine and (±)-galipinine, respectively.[15] Accordingly, **2d** and **2j** were independently subjected to hydrogenation with 10% Pd/C in methanol at room temperature after 12 h, giving (±)-angustureine **6** and (±)-galipinine **7** in 85% and 80% yields, respectively (eqs 6 and 8). In order to synthesize the enantiomerically enriched tetrahydroquinoline, **2d** having 52% ee was subjected to hydrogenation to afford (−)-angustureine **6** in 75% yield, $[\alpha]^{26}_D = -3.5$ (*c* 0.50, $CHCl_3$), [lit.[15a] $[\alpha]^{25}_D = -7.16$ (*c* 1.00, $CHCl_3$)] (eq 7).



In conclusion, we have developed a method for the synthesis of 2-substituted tetrahydroquinolines via the Pd(0)-catalyzed intramolecular hydroamination of anilino-alkynes. The application of this methodology was implemented for the synthesis of alkaloids such as (±)-angustureine and (±)-galipinine. The method reported herein will be applicable for the synthesis of natural products containing tetrahydroquinoline moiety. We have also shown the possibility of asymmetric induction, which gave chiral tetrahydroquinolines. However, the enantioselectivity obtained in all cases was not very high, and moreover high catalyst loading was needed. Research directed toward ligand design, synthesis, and application for the present reaction is now underway in our laboratories.

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Supporting Information Available: Experimental details and characterization data including ^{1}H NMR and ^{13}C NMR of compounds **1a**−**d**,**g**−**j**, **2a**−**d**,**g**−**j**, **3**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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