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Palladium-Catalyzed Intramolecular Asymmetric Hydroamination of Alkynes

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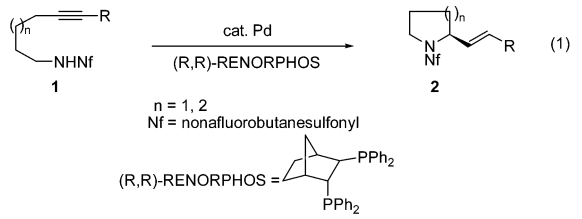
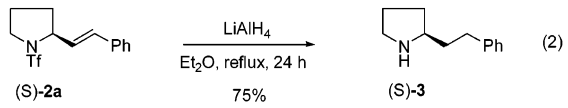
Nitrogen-containing heterocycles are the main components of many biologically important compounds. Their synthesis via the intramolecular hydroamination of C−C multiple bonds, an atom economical process,[1] is a subject of great interest in synthetic organic chemistry. The metal-catalyzed intramolecular hydroamination/cyclization of aminoalkenes,[2] aminoallenes,[3] aminodienes,[4] and aminoalkynes[5] has been abundantly documented. However, little progress has been made in the exploration of the enantioselective version of this process. To our knowledge, the only successful examples toward this goal involve the hydroamination/cyclization of aminoalkenes and aminodienes using lanthanide complexes.[4,6] Although good enantioselectivities (ee up to 69%) were achieved, the susceptibility of these complexes to moisture and oxygen constitute a serious drawback. Recently, the intermolecular enantioselective hydroamination of olefins catalyzed by late transition metals has been an area of intense investigation.[6a,7] As part of an ongoing program directed to the development of new methodologies for the transition metal-catalyzed addition of pronucleophiles to C−C multiple bonds in our laboratory,[8] we previously reported an efficient hydroamination of alkynes using catalytic amounts of $Pd(PPh_3)_4$.[5d] It was anticipated that the intramolecular reaction in the presence of a chiral palladium complex would lead to the synthesis of optically active cyclic amines. We now wish to report the first example of palladium-catalyzed intramolecular asymmetric hydroamination of alkynes. In this process, five- and six-membered nitrogen heterocycles are synthesized in high yields with high levels of enantioselectivity (eq 1).[9]



Using **1a** as a model substrate, initial studies aimed at developing reaction conditions revealed that benzene as solvent and tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$·$CHCl_3$] as the palladium precursor were the suitable starting point for the optimization of the chiral induction. At this early stage, a trial using the monodentate phosphine ligand (*S*)-neomenthyl-diphenylphosphine proved unsuccessful for the enantioselectivity. A variety of bidentate phosphine ligands were then examined; among MOP, BPPFOAc, DIOP, BINAP, BPPM, PYRPHOS, CHIRAPHOS, NORPHOS, and RENORPHOS tested, RENORPHOS gave the best combination of yield and enantioselectivity. The protecting groups, such as benzyl, acetyl, Boc, and tosyl, on the amino moiety gave unsatisfactory results. The trifluoromethanesulfonyl (Tf) group gave a better result, but nonafluorobutanesulfonyl (Nf) gave the best result under the Pd/L ratio of 1/2.5 (see Supporting Information). The scope of the reaction was evaluated using two sets of conditions, and the results are summarized in Table 1. The reaction of **1b** having a Nf protecting group proceeded in the presence of 5 mol % of $Pd_2(dba)_3$·$CHCl_3$ and 25 mol % of (*R*,*R*)-RENORPHOS (conditions A) to afford the vinylpyrrolidine **2b** in 68% yield and 83% ee (entry 2). It was interesting to note that by increasing the amounts of palladium precursor and ligand to 20 and 100 mol %, respectively (conditions B), better chemical and optical yields were obtained. Comparison of compounds **1c** and **1d** having methoxy and trifluoromethyl groups, respectively (entries 3 and 4, conditions A), shows that an electron-rich alkyne favors the reaction rate as the corresponding cyclized products **2c** and **2d** were obtained in 90% and 52% yield, respectively.[10] The enantiomeric excess, however, followed the opposite pattern. Perhaps the intermediate involved during the cyclization phase needs to adjust itself to the chiral environnement faster than the C−N bond formation step.[11] The reaction of **1e** having a pentyl-substituted alkyne under conditions B required a longer reaction time (5 days), and **2e** was obtained in 82% yield as a 1:1 mixture of cis and trans isomers (entry 5). However, at this stage, attempts to determine the enantiomeric excess all failed.[12] Compound **1f** with a one carbon-longer tether cyclized to give the vinylpiperidine **2f** in good yield and ee (entry 6, conditions A) or high yield and ee (entry 6, conditions B), indicating that five- and six-membered heterocycles can be synthesized with similar efficiency.[13] The reaction of **1g** having a benzene ring linker on the tether gave the tetrahydroisoquinoline **2g** in good yield and ee (entry 7, conditions A) or high yield and ee (entry 7, conditions B). The absolute configuration of **2a** (82% ee) was determined by transformation to the known compound **3** (eq 2). The literature[14] attributes the *R* configuration to (+)-2-phenethylpyrrolidine, although no value of ee is stated. Because the optical rotation of **3** was $[\alpha]^{22}_{D}$ −8.7 (*c* 0.75, $CHCl_3$), it was confirmed that the absolute configuration of **2a** is *S*.



A plausible mechanism is shown in Scheme 1, although it is highly speculative. Hydropalladation of **1a** with the hydridopalladium species generated from Pd^0 and benzoic acid would produce the vinylpalladium intermediate **4**, which would undergo β-elimination to give allene **5** coordinated with the hydridopalladium. Subsequent hydropalladation of **5** would furnish the π-allylpalladium species **6**. Nucleophilic attack of the amine on the π-allyl moiety would give the product **2a** along with the hydridopalladium catalyst.

To obtain insight into the mechanism of the present chiral induction, aminodiene **7** and aminoallene **8** were prepared, and their reactivity was examined. When **7** was submitted to conditions A, the cyclized product **2b** was obtained in only 15% yield and 24% ee (eq 3). Under the same conditions, **8** gave exclusively *trans*-(**9**) in 85% yield after 12 h (eq 4).[15] In this case, however, no asymmetric induction was observed at all. It is generally thought

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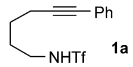
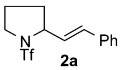
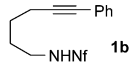
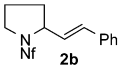
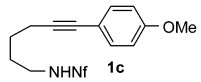
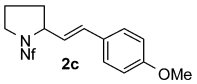
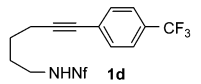
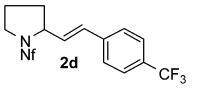
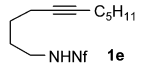
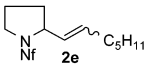
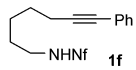
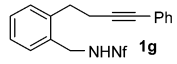
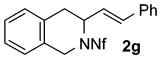
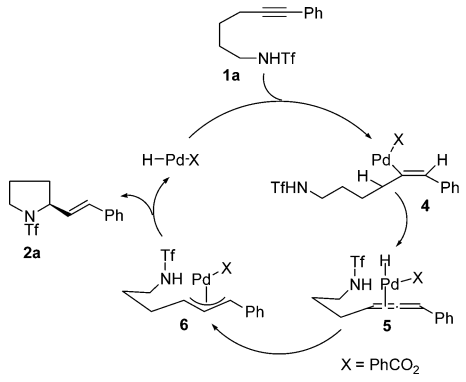
Table 1. Catalytic Intramolecular Asymmetric Hydroamination of Alkynes

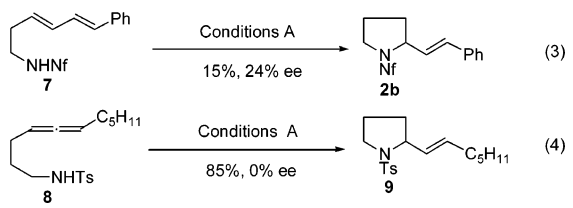
entry	substrate	product	cond.[a]	yield[b] (%)	ee[c] (%)
1	 **1a**	 **2a**	A	65	82[d]
2	 **1b**	 **2b**	A B	68 93	83 91
3	 **1c**	 **2c**	A B	90 90	47 81
4	 **1d**	 **2d**	A B	52 85	77 88
5	 **1e**	 **2e**	B	82	-[e]
6	 **1f**	 **2f**	A B	63 92	77 90
7	 **1g**	 **2g**	A B	70 90	72 87

[a] Conditions A: 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 10 mol % of $PhCO_2H$, and 25 mol % of (*R*,*R*)-RENORPHOS in benzene at 100 °C for 72 h. Conditions B: 20 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 40 mol % of $PhCO_2H$, and 100 mol % of (*R*,*R*)-RENORPHOS in benzene/hexane (2:1) at 80 °C for 72 h. [b] Isolated yield. [c] The ee was determined by chiral HPLC. [d] 30 mol % of ligand was used. [e] The ee was not determined.

Scheme 1. Plausible Mechanism



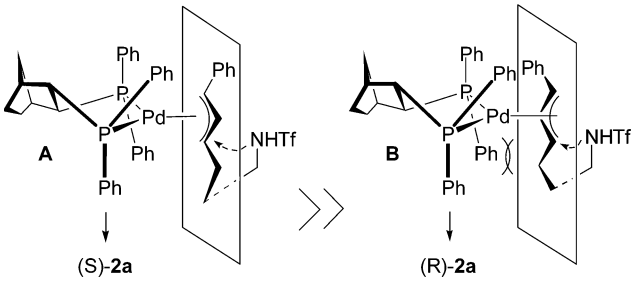
Scheme 2



that the palladium-catalyzed hydroamination of dienes[7b] and allenes[3b] takes place through the formation of π-allyl intermediates. The precise reason for the different observations in Scheme 2 and in the above alkyne case is not clear at present.

Probable transition state models are shown in Scheme 3. In A, the space at the lower front side of the catalyst allows the alkyl

Scheme 3. Probable Transition State Models



chain attached to the π-allyl to move freely. In B, 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 A to give (*S*)-**2a** predominantly.

In conclusion, we have developed the first palladium-catalyzed intramolecular asymmetric hydroamination of alkynes. Various optically active nitrogen heterocycles were prepared by using readily available aminoalkynes. Application to the synthesis of natural products is underway in our laboratory and will be reported in due course.

Supporting Information Available: Spectroscopic and analytical data of new compounds and information on procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The reaction shown in eq 1 is a formal 1,3-addition of N−H to a triple bond involving the shift of one proton similar to known allylic amination reactions.
(10) The starting material **1d** was recovered in ca. 40% yield.
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(12) Efforts to determine the ee of **2e** were undertaken using GC with different chiral columns. However, no satisfactory separation of enantiomers could be obtained.
(13) The synthesis of seven-membered rings was not achieved under these conditions.
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(15) **8** was used because the determination of the ee of the product from the corresponding Nf-protected compound proved difficult.

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