ORGANIC LETTERS

2008
Vol. 10, No. 18
4057−4060

Rhodium-Catalyzed Asymmetric Ring-Opening Alkynylation of Azabenzonorbornadienes

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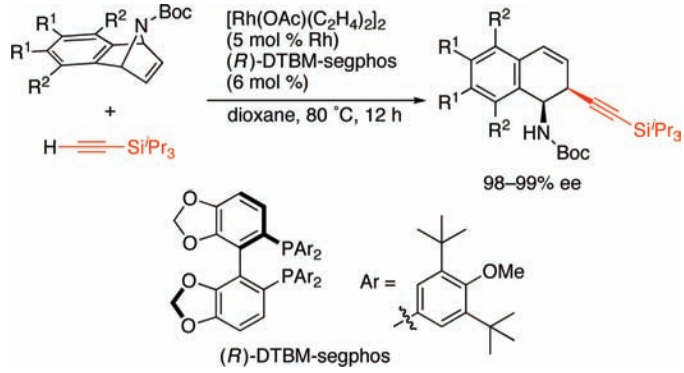
Received July 9, 2008

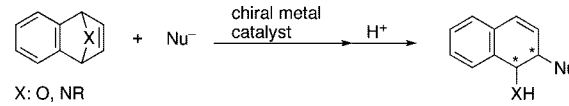
ABSTRACT



Asymmetric ring-opening alkynylation of *meso*-azabenzonorbornadienes with (triisopropylsilyl)acetylene giving 2-alkynyl-1-aminodihydronaphthalenes took place in high yields with high enantioselectivity in the presence of a rhodium/(*R*)-DTBM-segphos catalyst.

Transition-metal-catalyzed asymmetric addition of carbon- and heteroatom-nucleophiles to oxa- and azabicyclic alkenes has provided a useful strategy for enantioselective synthesis of chiral building blocks.[1] Lautens and co-workers have extensively studied rhodium- and palladium-catalyzed asymmetric transformations of these bicyclic alkenes, where enantioposition-selective addition of nucleophiles brings about desymmetrization of their meso structure and subsequent ring-opening reactions provide a route to optically active compounds bearing multiple stereocenters (Scheme 1).[2−4] On the other hand, Cheng and co-workers have reported[5] the use of a terminal alkyne, as one of the important carbon-nucleophiles, for the nickel-catalyzed ring-opening reaction of the oxa- and azabicyclic

Scheme 1



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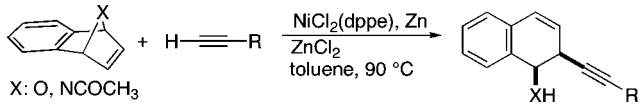
10.1021/ol801549t CCC: $40.75
Published on Web 08/19/2008

alkenes, where racemic 2-alkynyl-1,2-dihydronaphthalene derivatives were produced in high yields with high diastereoselectivity (Scheme 2).

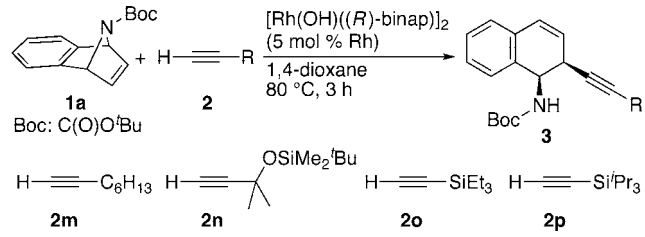
Scheme 2. Nickel-Catalyzed Ring-Opening Alkynylation Reported by C.-H. Cheng



The catalytic addition of terminal alkynes to unsaturated bonds has attracted much attention in organic synthesis because of its high synthetic utility realizing the high atom efficiency.[6] There have been many reports on the asymmetric alkynylation of unsaturated bonds with diverse transition metal catalysts.[7] Of the transition metals, rhodium is most versatile, catalyzing the addition of terminal alkynes to alkynes,[8] allenes,[9] vinyl ketones,[10] aldehydes,[11] and ketones.[11] In this context, we recently reported rhodium-catalyzed asymmetric alkynylation of conjugate enones[12] and allenes,[13,14] and we have extended our studies to asymmetric addition to other unsaturated bonds. Here, we report the highly enantioselective alkynylation of azabenzonorbornadienes involving a ring-opening step, which is realized by use of a sterically bulky silylacetylene and an axially chiral biarylbisphosphine/rhodium catalyst.

The reaction of azabenzonorbornadiene **1a** was examined with several terminal alkynes **2** under one of the standard reaction conditions[14a] for the rhodium-catalyzed alkynylation using $[Rh(OH)((R)\text{-binap})]_2$[15] as a catalyst. It was found that yields and enantioselectivity of the alkynylation products are strongly dependent on the steric bulkiness of the terminal alkynes (Table 1). Treatment of **1a** with 1-octyne (**2m**) in 1,4-dioxane in the presence of $[Rh(OH)((R)\text{-binap})]_2$ (5 mol % of Rh) at 80 °C for 3 h gave only 15% yield of the corresponding 2-alkynyl-1,2-dihydronaphthalene **3am**, whose enantiomeric excess was 3% (entry 1). The addition of a bulky propargylic ether **2n** gave a moderate yield (58%) of **3an** with 35% ee (entry 2). By use of sterically bulky silylacetylenes, both the yield and ee of the product **3** were improved to a considerable extent. Thus, the reaction of **1a** with (triethylsilyl)- (**2o**) and (triisopropylsilyl)acetylene (**2p**) gave the corresponding alkynylation products **3ao** in 67% yield with 82% ee and **3ap** in 81% yield with 86% ee, respectively (entries 3 and 4). The higher yield with the

Table 1. Rhodium-Catalyzed Asymmetric Ring-Opening Alkynylation of Azabenzonorbornadiene **1a**[a]



entry	alkyne	product **3**	yield (%)[b]	ee (%)[c]
1	**2m**	**3am**	15	3
2	**2n**	**3an**	58	36
3	**2o**	**3ao**	67	82
4	**2p**	**3ap**	81	86

[a] Reaction conditions: **1a** (0.40 mmol), alkyne **2** (0.20 mmol), $[Rh(OH)((R)\text{-binap})]_2$ (5 mol % of Rh), in 1,4-dioxane (0.4 mL) at 80 °C for 3 h. [b] Isolated yield (%). [c] Determined by HPLC analysis with a chiral stationary phase column: Chiralcel OD-H.

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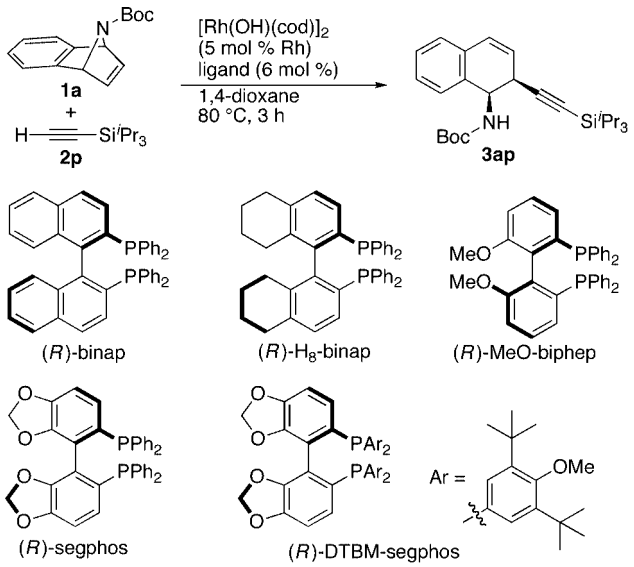
sterically more bulky substituent on terminal alkynes is ascribed to the suppression of side reactions, dimerization and oligomerization of the terminal alkynes, by the sterically bulky groups on the alkynes. A similar relationship between the yield of alkynylation and the steric bulkiness of the alkyne substituent has been observed in the addition to α,β-unsaturated ketones.[12a,16]

A series of axially chiral biarylbisphosphines related to binap were examined for the reaction of azabenzonorbornadiene **1a** with (triisopropylsilyl)acetylene **2p** to find the catalyst capable of bringing about higher enantioselectivity (Table 2). The reaction was catalyzed by 5 mol % rhodium

Table 2. Effects of Ligands[a]

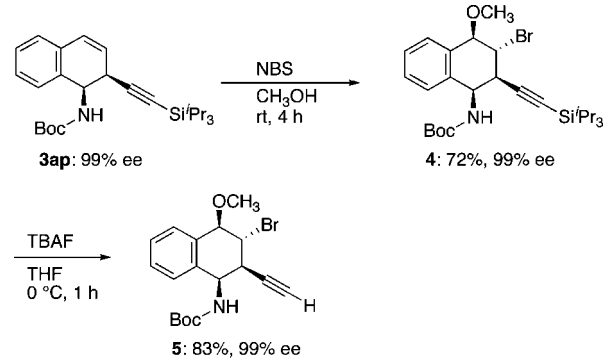


entry	ligand	isolated yield (%)	ee (%)[b]
1[c]	(*R*)-binap	81	86 (−)
2	(*R*)-H$_8$-binap	87	89 (−)
3	(*R*)-MeO-biphep	94	77 (−)
4	(*R*)-segphos	90	80 (−)
5	(*R*)-DTBM-segphos	49	98 (−)
6[d]	(*R*)-DTBM-segphos	93	99 (−)

[a] Reaction conditions: **1a** (0.40 mmol), alkyne **2p** (0.20 mmol), [Rh(OH)(cod)]$_2$ (5 mol % of Rh), ligand (6 mol %) in 1,4-dioxane (0.4 mL) at 80 °C for 3 h. [b] Determined by HPLC analysis with a chiral stationary phase column: Chiralcel OD-H. [c] [Rh(OH)((*R*)-binap))]$_2$ (5 mol % of Rh) was used. [d] [Rh(OAc)(C$_2$H$_4$)$_2$]$_2$ was used as a catalyst precursor.

catalysts generated in situ by mixing [Rh(OH)(cod)]$_2$[17] with (*R*)-H$_8$-binap,[18] (*R*)-MeO-biphep,[19] and (*R*)-segphos[20] to give **3ap** in high yields (87−94%), the enantioselectivity ranging between 77% and 89% ee (entries 2−4). A sterically bulky bisphosphine ligand (*R*)-DTBM-segphos[20] displayed very high enantioselectivity (98% ee), although the yield was modest (49% yield; entry 5). The employment of [Rh(OAc)(C$_2$H$_4$)$_2$]$_2$[21] as a catalyst precursor combined with (*R*)-DTBM-segphos gave the higher yield (93%) of **3ap** with 99% ee (entry 6). The relative and absolute configuration of **3ap** was determined to be 1*R*,2*S* by X-ray analysis of tetrahydronaphthalene amine **4**, which was obtained by the reaction of **3ap** with *N*-bromosuccinimide (NBS) in methanol (Scheme 3, Figure 1). [22] The silyl group of **4** was readily

Scheme 3. Transformation of Compound **3ap**



removed by treatment with tetrabutylammonium fluoride (TBAF) to give terminal alkyne **5** without loss of enantiomeric purity.

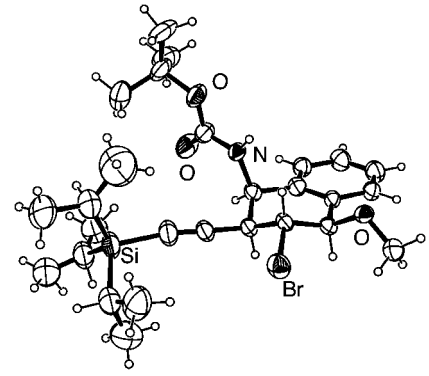


Figure 1. ORTEP illustration of compound **4** with thermal ellipsoids drawn at the 30% probability level.

Table 3 summarizes the results obtained for the reaction of several azabenzonorbornadienes **1** with (triisopropylsilyl)-acetylene **2p**, which was carried out in the presence of rhodium/(*R*)-DTBM-segphos as a catalyst (5 mol % of Rh). *meso*-Azabenzonorbornadienes **1b**−**1f** bearing substituents (Me, MeO, F, and Br) on the benzene ring gave the corresponding dihydronaphthalene amines **3bp**−**3fp** in high yields (83−94%) with excellent enantioselectivity (98−99% ee) (entries 2−6).

(16) In the addition to α,β-unsaturated ketones, the use of DTBM-segphos is another important factor to realize high chemical yields. See ref 12a.

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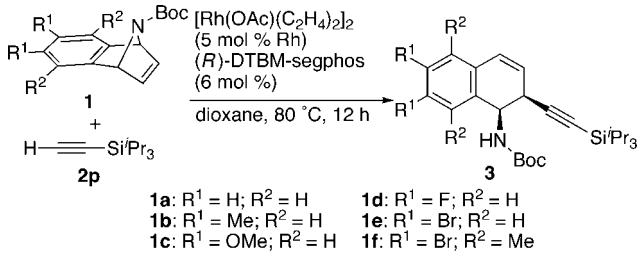
Table 3. Asymmetric Ring-Opening Alkynylation of Azabenzonorbornadienes **1** with (Triisopropylsilyl)acetylene **2p**[a]



1a: R^1 = H; R^2 = H **1d**: R^1 = F; R^2 = H
1b: R^1 = Me; R^2 = H **1e**: R^1 = Br; R^2 = H
1c: R^1 = OMe; R^2 = H **1f**: R^1 = Br; R^2 = Me

entry	1	product	isolated yield (%)	ee (%)[b]
1[c]	**1a**	**3ap**	93	99
2	**1b**	**3bp**	94	99
3	**1c**	**3cp**	91	99
4	**1d**	**3dp**	90	99
5	**1e**	**3ep**	83	98
6	**1f**	**3fp**	88	99

[a] Reaction conditions: **1** (0.40 mmol), alkyne **2p** (0.20 mmol), [Rh(OAc)(C$_2$H$_4$)$_2$]$_2$ (5 mol % of Rh), (*R*)-DTBM-segphos (6 mol %) in 1,4-dioxane (0.4 mL) at 80 °C for 12 h. [b] Determined by HPLC. [c] For 3 h.

In summary, we have succeeded in a ring-opening reaction of azabenzonorbornadienes with (triisopropylsilyl)acetylene with very high enantioselectivity by use of a rhodium/(*R*)-DTBM-segphos catalyst.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the substrates and products (pdf and cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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