

Enantioselective Synthesis of Axially Chiral Anilides through Rhodium-Catalyzed [2+2+2] Cycloaddition of 1,6-Diynes with Trimethylsilylnamides

Ken Tanaka,^{*,†} Kenzo Takeishi,[†] and Keiichi Noguchi[†]

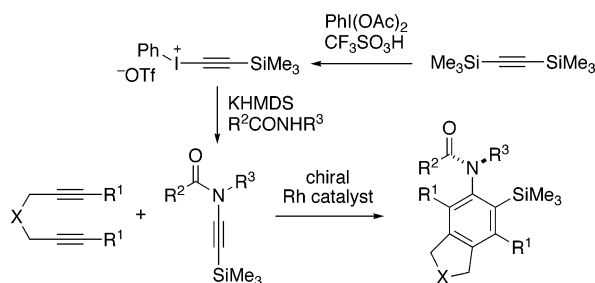
Department of Applied Chemistry, Graduate School of Engineering, and Instrumentation Analysis Center, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

Received January 17, 2006; E-mail: tanaka-k@cc.tuat.ac.jp

Axially chiral anilides are valuable structures for asymmetric reactions and biologically active compounds, and various asymmetric syntheses of them have been reported.^{1–3} These are mainly based on a chiral pool method or an optical resolution of racemic compounds,² although the straightforward enantioselective synthesis is highly desired.³

Taguchi's group and Curran's group reported the first catalytic enantioselective synthesis of axially chiral anilides through Pd-catalyzed N-allylation of achiral *o*-*tert*-butyl-NH-anilides, although high enantioselectivity could not be achieved (30–53% ee).⁴ Recently, Taguchi, Kitagawa, and co-workers reported the Pd-catalyzed enantioselective N-arylation of achiral *o*-*tert*-butyl-NH-anilides with high enantioselectivity (70–96% ee).⁵ In this Communication, we report an enantioselective synthesis of axially chiral anilides through a rhodium-catalyzed intermolecular [2+2+2] cycloaddition of 1,6-diynes with trimethylsilylnamides. It should be noted that the present reaction employs the readily prepared trimethylsilylnamides starting from commercially available bis(trimethylsilyl)-acetylene and trimethylsilyl group of the product anilides is expected to be utilized for further functionalization (Scheme 1).

Scheme 1



Recently, we reported the synthesis of axially chiral biaryl compounds through the cationic rhodium(I)/modified-BINAP complexes-catalyzed chemo-, regio-, and enantioselective intermolecular [2+2+2] cycloadditions.^{6,7} We anticipated that an intermolecular [2+2+2] cycloaddition of 1,6-diynes with trimethylsilylnamides would construct axial chirality upon the formation of benzene rings (Scheme 1).^{8,9}

We first investigated an intermolecular [2+2+2] cycloaddition of malonate-derived internal 1,6-diyne **1a** with trimethylsilylnamide **2a**, as shown in Table 1. Screening of various modified-BINAP ligands revealed that the highest enantioselectivity was achieved by using xyl-BINAP as ligand (entry 3). On the other hand, a terminal 1,6-diyne failed to react with **2a** due to the rapid homo [2+2+2] cycloaddition of the diyne.

Table 1. Screening of Modified-BINAP Ligands^a

entry	ligand	yield (%) ^b	ee (%)
1	(<i>R</i>)-BINAP	38	80
2	(<i>R</i>)-tol-BINAP	38	84
3	(<i>S</i>)-xyl-BINAP	32	97
4	(<i>S</i>)-H ₈ -BINAP	33	79
5	(<i>S</i>)-xyl-H ₈ -BINAP	13	90
6	(<i>S</i>)-Segphos ^c	21	12

^a [Rh(cod)₂]BF₄ (0.010 mmol), ligand (0.010 mmol), **1a** (0.10 mmol), **2a** (0.10 mmol), and CH₂Cl₂ (2.0 mL) were employed. ^b Isolated yield. ^c (4,4'-Bi-1,3-benzodioxole)-5,5'-diylbis(diphenylphosphine).

Table 2. Rhodium-Catalyzed Enantioselective [2+2+2] Cycloaddition of 1,6-Diynes with Nnamides^a

entry	1	2	R ²	R ³	3	yield (%) ^b	ee (%)
1	1a	2a	Ph	Bn	3aa	29 (66°)	97
2	1a	2b	Ph	<i>n</i> -Bu	3ab	15 (46°)	97
3	1a	2c	Ph	<i>i</i> -Pr	3ac	40 (52°)	87
4	1a	2d	Ph	Ph	3ad	79 (–°)	97
5	1a	2e	Me	Bn	3ae	21 (55°)	90
6 ^d	1d	2f	OMe	Bn	3df	69 (26°)	98
7	1b	2d	Ph	Ph	3bd	29 (56°)	98
8	1c	2d	Ph	Ph	3cd	62 (34°)	96
9	1d	2d	Ph	Ph	3dd	50 (38°)	84
10	1e	2a	Ph	Bn	3ea	19 (67°)	79
11	1e	2e	Me	Bn	3ee	30 (48°)	88

^a [Rh(cod)₂]BF₄ (0.025 mmol), (*S*)-xyl-BINAP (0.025 mmol), **1** (0.25 mmol), **2** (0.25 mmol), and CH₂Cl₂ (5.0 mL) were employed. ^b Isolated yield. ^c Recovery (%) of **2**. ^d Ligand: (*R*)-tol-BINAP.

Next, the scope of this cycloaddition was examined, as shown in Table 2. With regard to trimethylsilylnamides (entries 1–6), the reaction of benzoyl- (**2a**, entry 1), acetyl- (**2e**, entry 5), and methoxycarbonyl- (**2f**, entry 6)¹⁰ substituted *N*-benzylnamides furnished the corresponding axially chiral anilides with high

[†] Department of Applied Chemistry.
[‡] Instrumentation Analysis Center.

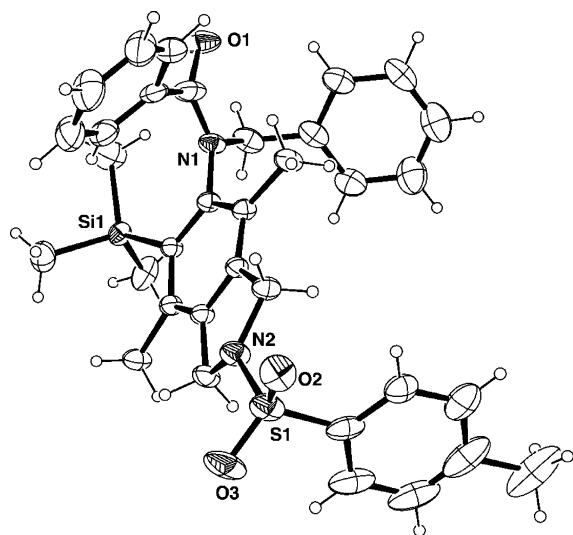
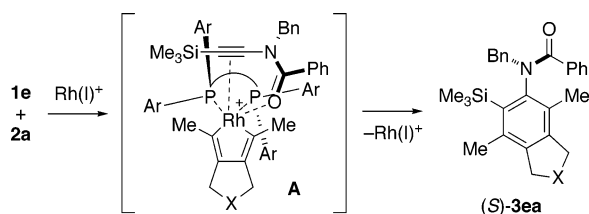


Figure 1. ORTEP diagram of (S)-(+)-3ea.

Scheme 2

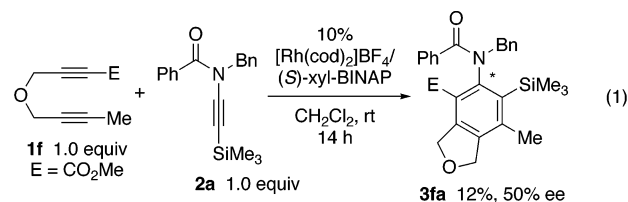


enantioselectivities. Furthermore, the reactions of not only benzyl- (2a, entry 1) but also primary alkyl- (2b, entry 2), secondary alkyl- (2c, entry 3), and phenyl- (2d, entry 4) substituted *N*-benzoylynamides furnished the corresponding axially chiral anilides with high enantioselectivities. Interestingly, the yield of anilides highly depends on the substituents on the ynamides. Significantly increased yields were observed in the case of a phenyl- (2d, entry 4) or a methoxycarbonyl- (2f, entry 6) substituted trimethylsilyl ynamide. On the other hand, no reaction was observed in the case of a terminal ynamide.

The generality of this cycloaddition was subsequently examined with regard to 1,6-diynes. Thus, not only malonate-derived 1,6-diyne 1a (entries 1–5) but also 1,3-diol derivative 1b (entry 7), ether-linked 1,6-diyne 1c (entry 8), and sulfonamide-linked 1,6-diynes 1d,e (entries 6 and 9–11) gave the corresponding axially chiral anilides with high enantioselectivities. Although competitive homo [2+2+2] cycloaddition of 1,6-diynes proceeded as the major side reaction, unreacted ynamides could be recovered by silica gel chromatography. The absolute configuration of (+)-3ea was determined to be *S* by the anomalous dispersion method (Figure 1).

Scheme 2 depicts a plausible mechanism of the selective formation of (S)-3ea. Enantioselectivity is determined by preferential formation of intermediate A, due to the coordination of the carbonyl group of 2a to rhodium and the steric interaction between the benzyl group of 2a and the *PAR*₂ group of (S)-xyl-BINAP. Reductive elimination of rhodium gives (S)-3ea and regenerates the rhodium catalyst.

Indeed, the use of methoxycarbonyl-substituted 1,6-diyne 1f decreased the ee of the corresponding anilide 3fa, presumably due to the electronic repulsion between carbonyl groups of 1f and 2a (eq 1).¹¹



In conclusion, we have developed a rhodium-catalyzed enantioselective intermolecular [2+2+2] cycloaddition of 1,6-diynes with trimethylsilyl ynamides for the synthesis of axially chiral anilides. Improvement of the product yield, utilization of trimethylsilyl group of the product anilides, and further application of the enantioselective [2+2+2] cycloaddition for the synthesis of axially chiral compounds are underway in our laboratory.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic files (PDF, CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) The ee's of the product anilides derived from ynamide 2f and 1,6-diynes 1a–c could not be determined by chiral HPLC analysis.
- (11) No regioisomer was generated other than 3fa.

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