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

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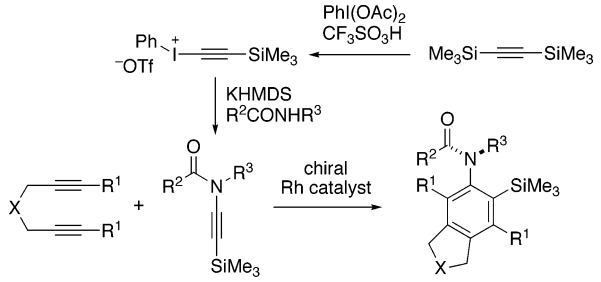
Axially chiral anilides are valuable structures for asymmetric reactions and biologically active compounds, and various asymmetric syntheses of them have been reported.[1−3] These are mainly based on a chiral pool method or an optical resolution of racemic compounds,[2] although the straightforward enantioselective 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 trimethylsilylynamides. It should be noted that the present reaction employs the readily prepared trimethylsilylynamides starting from commercially available bis(trimethysilyl)-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 trimethylsilylynamides 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 trimethylsilylynamide **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.

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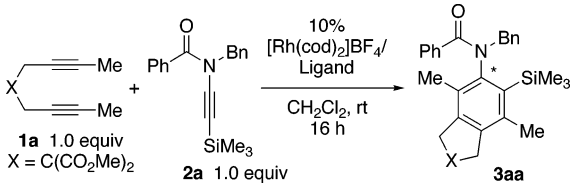
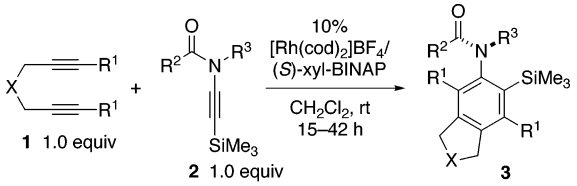
Table 1. Screening of Modified-BINAP Ligands[a]



entry	ligand	yield (%)[b]	ee (%)
1	(*R*)-BINAP	38	80
2	(*R*)-tol-BINAP	38	84
3	(*S*)-xyl-BINAP	32	97
4	(*S*)-H_8-BINAP	33	79
5	(*S*)-xyl-H_8-BINAP	13	90
6	(*S*)-Segphos[c]	21	12

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol), ligand (0.010 mmol), **1a** (0.10 mmol), **2a** (0.10 mmol), and CH_2Cl_2 (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 Ynamides[a]



1a R^1 = Me, X = $C(CO_2Me)_2$ **1d** R^1 = Me, X = $NSO_2(4\text{–}BrC_6H_4)$
1b R^1 = Me, X = $C(CH_2OMe)_2$ **1e** R^1 = Me, X = NTs
1c R^1 = Et, X = O

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

[a] $[Rh(cod)_2]BF_4$ (0.025 mmol), (*S*)-xyl-BINAP (0.025 mmol), **1** (0.25 mmol), **2** (0.25 mmol), and CH_2Cl_2 (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 trimethylsilylynamides (entries 1−6), the reaction of benzoyl- (**2a**, entry 1), acetyl- (**2e**, entry 5), and methoxycarbonyl- (**2f**, entry 6)[10] substituted *N*-benzylynamides furnished the corresponding axially chiral anilides with high

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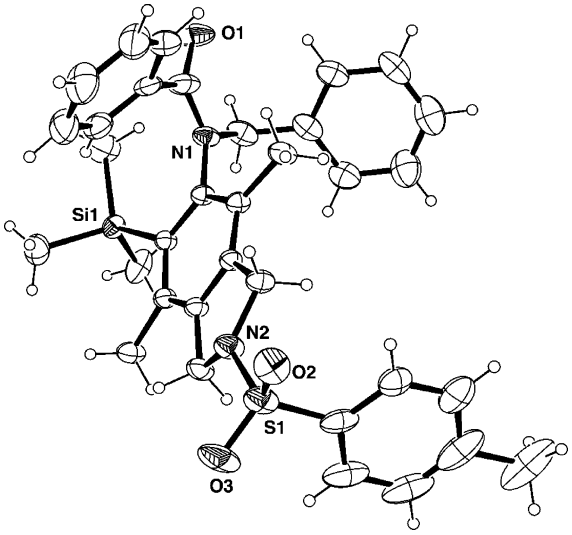
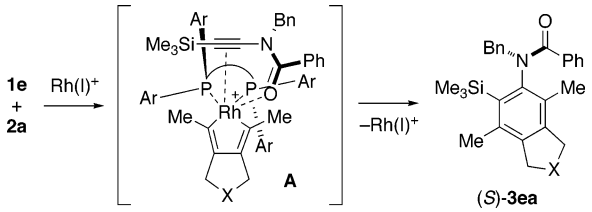


Figure 1. ORTEP diagram of (*S*)-(+)-**3ea**.

Scheme 2

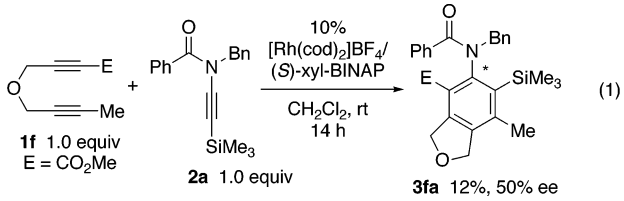


enantioselectivities. Furthermore, the reactions of not only benzyl- (**2a**, entry 1) but also primary alkyl- (**2b**, entry 2), secondary alkyl- (**2c**, entry 3), and phenyl- (**2d**, entry 4) substituted *N*-benzoylynamides furnished the corresponding axially chiral anilides with high enantioselectivities. 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 trimethylsilylynamide. 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 competetive 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 trimethylsilylynamides 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**,**e** could not be determined by chiral HPLC analysis.

(11) No regioisomer was generated other than **3fa**.

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