Preparation of Enantioenriched Axially Chiral Anilides via [2+2+2] Cycloaddition of 1,6-Diynes with Trimethylsilylynamides

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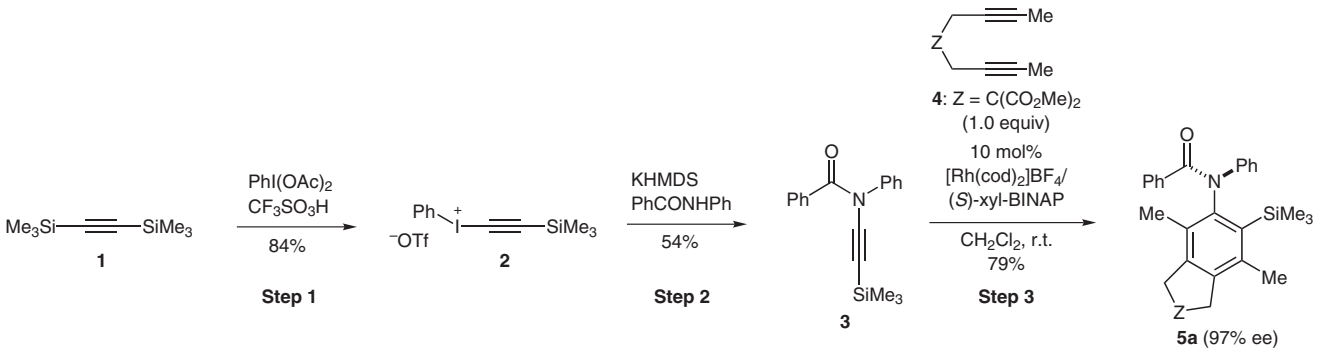
Abstract: The rhodium-catalyzed enantioselective [2+2+2] cycloaddition of 1,6-diynes with trimethylsilylynamides provides enantioenriched axially chiral anilides in poor to good yields with good to excellent enantioselectivity. Trimethylsilylynamides can be readily prepared in two steps starting from commercially available bis(trimethylsilyl)acetylene.

Key words: anilides, diynes, BINAP, rhodium, ynamides



Scheme 1 Preparation of enantioenriched axially chiral anilide **5a** via the rhodium-catalyzed [2+2+2] cycloaddition

Introduction

Axially chiral anilides are important compounds for asymmetric reactions and biologically active compounds.[1–4] Their previously reported enantioselective synthesis is based on two types of palladium-catalyzed N-functionalization of achiral *ortho-tert*-butyl-NH-anilides.[5,6] Taguchi's group and Curran's group reported the first catalytic enantioselective synthesis of axially chiral anilides with low to moderate enantioselectivity (30–53% ee) via palladium-catalyzed N-allylation.[5] Taguchi, Kitagawa, and co-workers reported the palladium-catalyzed enantioselective N-arylation with high enantioselectivity (70–96% ee), but this method is restricted to the synthesis of *N*-aryl anilides.[6]

In 2003, our research group first demonstrated that cationic rhodium(I)/BINAP-type bisphosphine complexes are highly effective catalysts for chemo- and regioselective [2+2+2] cycloadditions.[7] These catalysts were further applied to the synthesis of axially chiral biaryls via an enantioselective [2+2+2] cycloaddition.[8–11] This protocol was successfully extended to a practical synthesis of another important class of axially chiral anilides.[12]

The synthetic procedure, outlined in Scheme 1, constitutes three steps starting from commercially available bis(trimethylsilyl)acetylene (**1**). Treatment of **1** with $PhI(OAc)_2$ and CF_3SO_3H furnishes (trimethylsilyl)ethynyliodonium salt **2** in good isolated yield (Step 1).[13] N-Ethynylation of an NH-amide furnishes trimethylsilylynamide **3** in good isolated yield (Step 2).[14] Enantioselective aromatization via [2+2+2] cycloaddition of 1,6-diyne **4** with trimethylsilylynamide **3** (1.0 equiv) in the presence of 10 mol% of a cationic rhodium(I)/(*S*)-xyl-BINAP complex furnishes axially chiral anilide **5a** in good isolated yield with excellent enantioselectivity (Step 3).[12,15–17]

Scope and Limitations

Chiral BINAP-type ligands (Figure 1) were extensively screened at room temperature in the enantioselective [2+2+2] cycloaddition of malonate-derived internal 1,6-diyne **4** with *N*-benzyl-*N*-(trimethylsilylethynyl)benzamide leading to axially chiral anilide **5e**. The highest enantioselectivity (97% ee) was achieved using xyl-

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BINAP as the ligand, although the use of tol-BINAP (84% ee) and BINAP (80% ee) could furnish **5e** with synthetically acceptable ee values. The active catalyst can be readily prepared by mixing commercially available $[Rh(cod)_2]BF_4$ and (*S*)-xyl-BINAP in CH_2Cl_2 followed by treatment with hydrogen (1 atm) at room temperature.

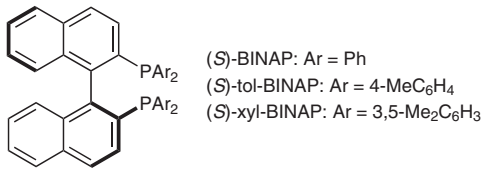


Figure 1 Chiral BINAP-type ligands

Scope of the present procedure is shown in Table 1. With respect to 1,6-diynes, not only malonate-derived 1,6-diyne (entries 1,5,7,8, and 9) but also 1,3-diol derivative (entry 2), sulfonamide-linked 1,6-diynes (entries 3,6,10, and 11), and ether linked 1,6-diyne (entry 4) furnished the corresponding axially chiral anilides with high enantioselectivity. With respect to trimethylsilylynamides, the reaction of not only phenyl (entries 1–4) but also benzyl (entries 5 and 6), primary alkyl (entry 7), and secondary alkyl (entry 8) substituted *N*-benzoylynamides furnished the corresponding axially chiral anilides with high enantioselectivity. Furthermore, not only benzoyl (entries 5 and 6) but also acetyl (entries 9 and 10), and methoxycarbonyl (entry 11) substituted *N*-benzylynamides furnished the corresponding axially chiral anilides with high enantioselectivity. Interestingly, the yield of anilides highly depends on the substituents of ynamides. Significantly increased yields were observed in the case of an *N*-phenyl (entries 1–4) or an *N*-methoxycarbonyl (entry 11) substituted anilide. The absolute configuration of (+)-**5f** (entry 6) was determined to be *S* by anomalous dispersion method. The anilides exist as an equilibrium mixture of *cis* and *trans* rotamers between the N-substituent and amido carbonyl oxygen group in $CDCl_3$ solution as shown in Figure 2.[3b] The *cis* rotamers are typically observed as major isomers of anilides (Table 1).

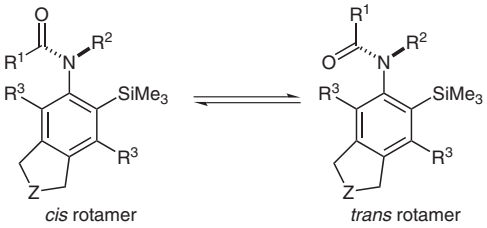
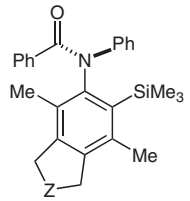
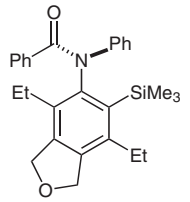
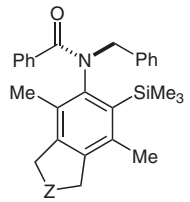
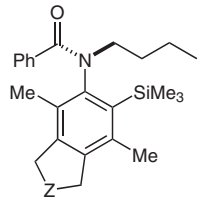
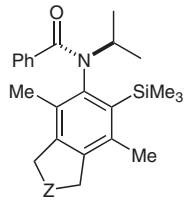
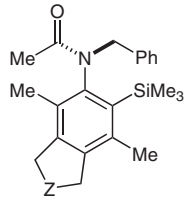
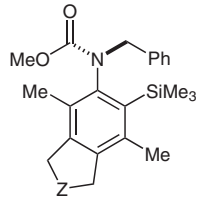


Figure 2 *Cis* and *trans* rotamers of axially chiral anilides

In these reactions, competetive homo [2+2+2] cycloadditions of 1,6-diynes leading to hexasubstituted benzenes **6** and **7** occur as side reactions (Figure 3). However, ynamides can be recovered unchanged by silica gel chromatography.

Table 1 Rhodium-Catalyzed Enantioselective [2+2+2] Cycloaddition of 1,6-Diynes with Trimethylsilylynamides

Entry	Product	Yield (%)[a]	ee (%)
1	 **5a**: Z = $C(CO_2Me)_2$	79 (–[b])	97
2	**5b**: Z = $C(CH_2OMe)_2$	29 (56[b])	98
3	**5c**: Z = $NSO_2(4\text{-}BrC_6H_4)$	50 (38[b])	84
4	 **5d**	62 (34[b])	96
5	 **5e**: Z = $C(CO_2Me)_2$	29 (66[b])	97
6	**5f**: Z = NTs	19 (67[b])	79
7	 **5g**: Z = $C(CO_2Me)_2$	15 (46[b])	97
8	 **5h**: Z = $C(CO_2Me)_2$	40 (52[b])	87
9	 **5i**: Z = $C(CO_2Me)_2$	21 (55[b])	90
10	**5j**: Z = NTs	30 (48[b])	88
11[c]	 **5k**: Z = $NSO_2(4\text{-}BrC_6H_4)$	69 (26[b])	98

[a] Yield of isolated product.
[b] Recovery (%) of trimethylsilylynamide.
[c] Ligand: (*R*)-tol-BINAP.

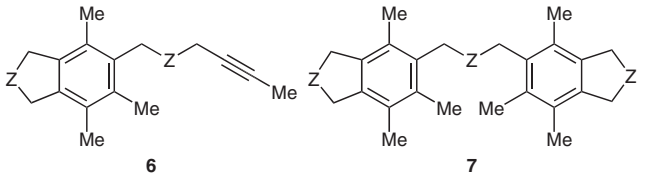


Figure 3 By-products of rhodium-catalyzed enantioselective [2+2+2] cycloadditions of 1,6-diynes with trimethylsilylynamides

Coordination of carbonyl group of trimethylsilylynamides to rhodium may play an important role in obtaining high ee values. Indeed, the use of 1,6-diynes bearing methoxycarbonyl group significantly decreased enantioselectivity of the corresponding anilides presumably due to the electronic repulsion between carbonyl groups of 1,6-diynes and trimethylsilylynamides (Figure 4).

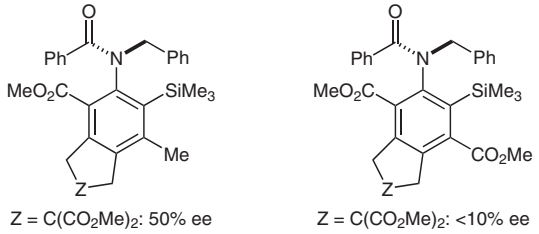


Figure 4 Axially chiral anilides obtained from 1,6-diynes bearing methoxycarbonyl groups

Axially chiral anilides inaccessible by the present method are shown in Figure 5. Terminal 1,6-diynes failed to react with trimethylsilylynamides due to the rapid homo [2+2+2] cycloaddition of the diynes. Terminal ynamides and cyclic ynamides failed to react with 1,6-diynes.

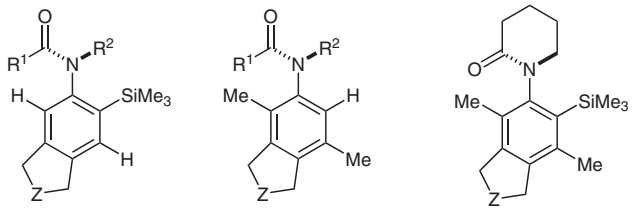


Figure 5 Axially chiral anilides inaccessible via rhodium-catalyzed [2+2+2] cycloaddition

In summary, the rhodium-catalyzed enantioselective [2+2+2] cycloaddition of 1,6-diynes with trimethylsilylynamides allows the preparation of enantioenriched axially chiral anilides. The trimethylsilyl group of these anilides is expected to be utilized for further functionalization.

Procedures

All reactions were carried out under argon or N_2 in oven-dried glassware with magnetic stirring. Anhyd CH_2Cl_2 (No. 27,099-7), used for the rhodium-catalyzed [2+2+2] cycloaddition, was obtained from Aldrich and used as received. BINAP-type ligands (xyl-BINAP, tol-BINAP, and BINAP) and $[Rh(cod)_2]BF_4$ were commercially available and can be handled in air. However, these compounds should be stored under inert atmosphere (argon or N_2), and $[Rh(cod)_2]BF_4$ should be stored at low temperature to suppress its decomposition. All other reagents were obtained from commercial sources and used as received unless otherwise indicated.

Phenyl(trimethylsilylethynyl)iodonium Triflate (2)[13]

Under N_2, $PhI(OAc)_2$ (6.31 g, 19.6 mmol) was dissolved in CH_2Cl_2 [30 mL, dried over 4 Å MS (Wako Pure Chemical Industries, Ltd.)] and the solution was cooled to 0 °C. CF_3SO_3H (5.60 g, 37.3 mmol) was added to this solution by using a glass pipette. After stirring at 0 °C for 30 min, bis(trimethylsilyl)acetylene (**1**; 3.16 g, 18.5 mmol) was added to this solution by using a glass pipette. After stirring at 0 °C for 2 h, the resulting solution was concentrated in vacuo at r.t. to give an oily residue. This oil was poured dropwise into stirred *n*-hexane (100 mL) at r.t. The resulting solid materials were collected by filtration, washed with Et_2O, and dried in vacuo to give phenyl(trimethylsilylethynyl)iodonium triflate (**2**) (7.04 g, 84%) as a colorless solid.

Note: Although workup and crystallization procedures can be carried out in air, compound **2** should be stored under a dry inert atmosphere to avoid its decomposition.

N-Phenyl-*N*-(trimethylsilylethynyl)benzamide (3)[12]

Under argon, KHMDS (0.5 M in toluene, 9.80 mL, 4.90 mmol) was added to a solution of *N*-phenylbenzamide (0.863 g, 4.37 mmol) in toluene [40 mL, dried over 4 Å MS (Wako Pure Chemical Industries, Ltd.)] at 0 °C. After warming to r.t., phenyl(trimethylsilylethynyl)iodonium triflate (**2**; 2.21 g, 4.91 mmol) was added in four portions. The resulting mixture was stirred for 15 h at r.t. and filtered through a plug of silica gel. Purification by silica gel column chromatography (silica gel 60 N, spherical, neutral, Kanto Chemical Co.; hexane–EtOAc, 40:1) gave **3** (0.688 g, 54%) as a yellow solid; mp 70–71 °C.

IR (neat): 2975, 2200, 1680, 1260, 840, 720 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.78 (m, 2H), 7.55–7.22 (m, 8H), 0.06 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 139.5, 133.5, 131.6, 129.04, 129.02, 127.7, 127.2, 125.0, 97.2, 75.0, –0.3.

HRMS (EI): *m/z* $[M - CH_3]^+$ calcd for $C_{17}H_{16}NOSi$: 278.1001; found: 278.0956.

Note: KHMDS should be used as a base for the synthesis of trimethylsilylynamides employed in Table 1. According to our experiments, *n*-BuLi did not furnish the desired trimethylsilylynamides in satisfactory yield.

(–)-5-(Benzoylphenylamino)-4,7-dimethyl-6-(trimethylsilyl) indan-2,2-dicarboxylic Acid Dimethyl Ester (5a, *cis/trans* = 60:40)[12] (Scheme 1)

Under argon, (*S*)-xyl-BINAP (18.4 mg, 0.0250 mmol) and $[Rh(cod)_2]BF_4$ (10.2 mg, 0.0250 mmol) were dissolved in CH_2Cl_2 (1 mL) and the mixture was stirred at r.t. for 5 min. H_2 was introduced to the resulting solution in a Schlenk tube. After stirring at r.t. for 30 min, the resulting solution was concentrated to dryness and redissolved in CH_2Cl_2 (1.0 mL). To this solution was added, dropwise over 1 min, a solution of diyne **4** (59.1 mg, 0.250 mmol) and trimethylsilylynamide **3** (73.3 mg, 0.250 mmol) in CH_2Cl_2 (1 mL) at r.t., and washed the remaining substrates away by using CH_2Cl_2 (3 mL). The mixture was stirred at r.t. for 42 h. The resulting solution was concentrated and purified by silica gel preparative TLC (Wakogel B-5F, Wako Pure Chemical Industries, Ltd.; hexane–EtOAc–Et_3N, 10:1:2), which furnished **5a** (118 mg, 79%, 97% ee) as a colorless oil; $[\alpha]_D^{25}$ –32.6 ($CHCl_3$, *c* = 1.14, 97% ee). CHIRALPAK AD: hexane–*i*-PrOH (80:20); 1.0 mL/min; t_R: 11.8 min (minor isomer) and 23.9 min (major isomer).

IR (neat): 2900, 1720, 1640, 1430, 1230, 840, 710 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.58–6.91 (m, 10 H, *cis*; 8 H, *trans*), 6.68–6.56 (m, 2 H, *trans*), 3.84–3.70 (m, 6 H, *cis* and *trans*), 3.70–3.38 (m, 4 H, *cis* and *trans*), 2.32 (s, 3 H, *trans*), 2.25 (s, 3 H, *cis*), 2.18 (s, 3 H, *trans*), 1.95 (s, 3 H, *cis*), 0.22 (s, 9 H, *trans*), 0.16 (s, 9 H, *cis*),

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 172.1, 172.0, 169.8, 169.0, 146.3, 145.3, 143.1, 142.9, 141.6, 141.5, 139.5, 139.0, 138.8, 138.2, 137.7, 136.6, 136.1, 135.6, 130.3, 130.0, 129.8, 129.3, 129.0, 128.2, 128.0, 127.9, 127.4, 125.0, 124.4, 124.3, 123.9, 58.9, 53.1, 40.7, 40.5, 40.2, 21.0, 20.3, 15.3, 15.1, 2.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{31}H_{35}NO_5Si$ + Na: 552.2182; found: 552.2241.

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References

(1) For the pioneering work on axially chiral N-substituted *ortho-tert*-butyl anilides, see: Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131.

(2) For the synthesis of axially chiral anilides, see: (a) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **1998**, *63*, 2634. (b) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295. (c) Kondo, K.; Fujita, H.; Suzuki, T.; Murakami, Y. *Tetrahedron Lett.* **1999**, *40*, 5577. (d) Ates, A.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 5130.

(3) For the asymmetric synthesis of axially chiral anilides through enantiotopic deprotonation, see: (a) Hata, T.; Koide, H.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2000**, *2*, 1907. (b) Koide, H.; Hata, T.; Yoshihara, K.; Kamikawa, K.; Uemura, M. *Tetrahedron* **2004**, *60*, 4527. (c) Bennett, D. J.; Pickering, P. L.; Simpkins, N. S. *Chem. Commun.* **2004**, 1392.

(4) For the stereoselective synthesis of axially chiral *N*-aryl indoles, see: Kamikawa, K.; Kinoshita, S.; Matsuzaka, H.; Uemura, M. *Org. Lett.* **2006**, *8*, 1097.

(5) (a) Kitagawa, O.; Kohriyama, M.; Taguchi, T. *J. Org. Chem.* **2002**, *67*, 8682. (b) Terauchi, J.; Curran, D. P. *Tetrahedron: Asymmetry* **2003**, *14*, 587.

(6) (a) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676. (b) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923.

(7) For our first report on the cationic rhodium(I)/modified-BINAP-catalyzed inter- and intramolecular [2+2+2] cycloadditions, see: Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697.

(8) For the enantioselective synthesis of axially chiral biaryls, see: (a) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 6510. (b) Tanaka, K.; Nishida, G.; Ogino, M.; Hirano, M.; Noguchi, K. *Org. Lett.* **2005**, *7*, 3119. (c) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2005**, *7*, 4737. (d) Nishida, G.; Suzuki, N.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2006**, *8*, 3489. (e) Tanaka, K.; Suda, T.; Noguchi, K.; Hirano, M. *J. Org. Chem.* **2007**, *72*, 2243. (f) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. Angew. Chem. Int. Ed. **2007**, *46*, 3951. (g) Tanaka, K.; Otake, Y.; Wada, A.; Hirano, M. *Org. Lett.* **2007**, *9*, 2203.

(9) For the enantioselective synthesis of axially chiral spiranes, see: Wada, A.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2007**, *9*, 1295.

(10) For the synthesis of cyclophanes, see: (a) Tanaka, K.; Toyoda, K.; Wada, A.; Shirasaka, K.; Hirano, M. *Chem. Eur. J.* **2005**, *11*, 1145. (b) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K. *Eur. J. Org. Chem.* **2006**, 3575. For enantioselective synthesis of planar-chiral metacyclophanes, see: (c) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 1522.

(11) For the enantioselective construction of central chiralities, see: (a) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2006**, *8*, 907. (b) Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917. (c) Tanaka, K.; Osaka, T.; Noguchi, K.; Hirano, M. *Org. Lett.* **2007**, *9*, 1307. (d) Tanaka, K.; Nishida, G.; Sagae, H.; Hirano, M. *Synlett* **2007**, 1426.

(12) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586.

(13) Stang, P. J. In *Modern Acetylene Chemistry*; Stang, P. J.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **1995**, 67.

(14) Martinez-Esperón, M. F.; Rodriguez, D.; Castedo, L.; Saá, C. *Org. Lett.* **2005**, *7*, 2213.

(15) For a recent review of ynamides, see: Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575.

(16) For the $RhCl(PPh_3)_3$-catalyzed [2+2+2] cycloadditions of ynamides leading to amide-substituted chiral biaryls, see: Tracey, M. R.; Oppenheimer, J.; Hsung, R. P. *J. Org. Chem.* **2006**, *71*, 8629.

(17) For the $RhCl(PPh_3)_3$-catalyzed [2+2+2] cycloadditions of ynamides for the synthesis of nitrogen heterocycles, see: (a) Witulski, B.; Stengel, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 2426. (b) Witulski, B.; Alayrac, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3281.