A Novel Synthesis of Quinazolines by Cyclization of 1-(2-Isocyanophenyl)alkylideneamines Generated by the Treatment of 2-(1-Azidoalkyl)phenyl Isocyanides with NaH

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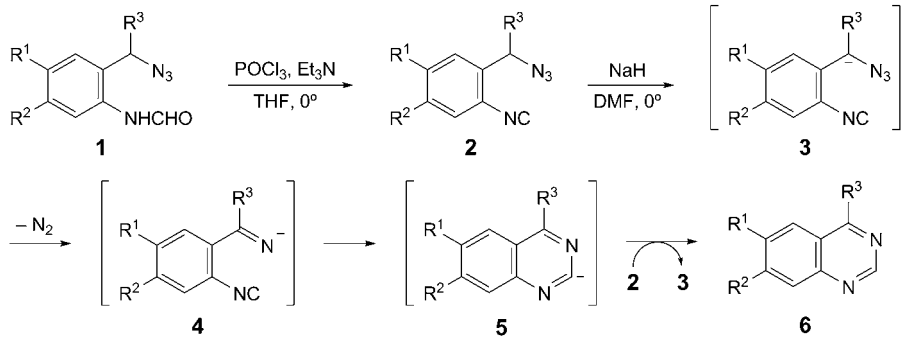
A new and efficient method for the synthesis of quinazolines has been developed. Thus, *N*-[2-(1-azidoalkyl)phenyl]formamides **1** are dehydrated with $POCl_3$ to give the corresponding 2-(1-azidoalkyl)-phenyl isocyanides **2**, which are then treated with NaH in DMF at 0° to give quinazolines **6** in satisfactory yields *via* cyclization of 1-(2-isocyanophenyl)alkylideneamine intermediates **4**. This methodology can be applied to the synthesis of the 7-azaanalogs of quinazolines, *i.e.*, pyrido[3,4-*d*]pyrimidines **9**.

Introduction. – Quinazolines are undoubtedly one of the most important classes of heterocycles, and they recently attract much attention, because a number of compounds with the quinazoline skeleton exhibit a variety of biological activities [1]. Quinazoline is a rather expensive chemical, and its new preparation by the reaction of benzene-1,2-dicarboxamide with iodobenzene diacetate as a key step has been reported [2]. Moreover, several new methods for the general preparation of quinazoline derivatives have recently been described [3][4]. For example, *Wang* and co-workers have reported a synthesis of 4-substituted quinazolines by the *N*-iodosuccinimide (NIS)-catalyzed reaction of 2-aminophenyl ketones with $AcNMe_2$ and NH_3 in the presence of excess *t*-BuOOH at 120° [3]. So, we became interested in pursuing a novel and convenient procedure for the preparation of quinazoline and its derivatives. We envisaged that the generation of 1-(2-isocyanophenyl)alkylideneamine would lead to the formation of quinazolines. In the course of our investigations, it was found that the reaction of 2-(1-azidoalkyl)phenyl isocyanides **2**, easily derived from *N*-[2-(1-azidoalkyl)phenyl]formamides **1**, with NaH could fulfill our expectations. We report herein the results of our study, which provided an efficient route to quinazolines. We have found that the present method is also applicable to the synthesis of the 7-azaanalogs of quinazolines, pyrido[3,4-*d*]pyrimidines **9**, which are of biological interest as well [5].

Results and Discussion. – The synthesis of quinazolines **6** from azido formamides **1** could be achieved as outlined in *Scheme 1*. Compounds **1** were easily accessible: *N*-[2-(azidomethyl)phenyl]formamide (**1a**) [6] is a known compound, and *N*-[2-(azidomethyl)-5-chlorophenyl]formamide (**1e**) was prepared from *N*-[3-chloro-6-(chloromethyl)phenyl]formamide [7] under the conditions for the preparation of **1a**. The other azido formamides **1** were prepared from the respective 2-aminophenyl ketones by easy

Scheme 1



four-step sequences. Thus, these ketones were *N*-formylated with HCO_2H, and subsequent reduction with $NaBH_4$ afforded the corresponding *N*-[2-(1-hydroxyalkyl)-phenyl]formamides. The latter were treated with $SOCl_2$, and the resulting chloro formamides were converted to **1** on treatment with NaN_3 (see *Exper. Part*).

The azido formamides **1**, thus obtained, were dehydrated with $POCl_3$ in the presence of Et_3N in THF at 0° to give the corresponding 2-(azidoethyl)phenyl isocyanides **2** in relatively good yields (*Table*; see [6]). When compounds **2** were treated with 1 equiv. of NaH in DMF at 0°, smooth deprotonation of the benzyl group, giving the benzyl anion intermediate **3**, denitrogenation, and subsequent intramolecular cyclization of the resulting alkylideneamine intermediate **3** by the attack of the anion on the isocyano C-atom took place within 10 min. Aqueous workup, followed by purification (recrystallization or column chromatography on SiO_2) gave the desired quinazolines **6** in generally good yields as compiled in the *Table* as well. However, the yield of product **6b** was much lower than those of the others (*Entry 2*). We speculate that this poor yield may be attributed to the lower acidity of the benzyl proton of the respective precursor **2b** due to its Me substituent.

Solvents other than DMF were also studied. In THF and 1,2-dimethoxyethane (DME), the reactions proceeded much slower than those in DMF. However, if the reactions were allowed to proceed long enough (overnight and *ca.* 5 h, resp.) at room

Table. *Preparation of Quinazolines* **6**

Entry	**1**	**2**	Yield[a])	**6**	Yield[a])
1	**1a** ($R^1 = R^2 = R^3 = H$)	**2a** [6]	86	**6a**	69
2	**1b** ($R^1 = R^2 = H$, $R^3 = Me$)	**2b**	74	**6b**	34
3	**1c** ($R^1 = R^2 = H$, $R^3 = Ph$)	**2c**	79	**6c**	88
4	**1d** ($R^1 = R^2 = H$, $R^3 = 4\text{-Cl–}C_6H_4$)	**2d**	76	**6d**	87
5	**1e** ($R^1 = H$, $R^2 = Cl$, $R^3 = H$)	**2e**	75	**6e**	63
6	**1f** ($R^1 = H$, $R^2 = Cl$, $R^3 = 4\text{-Cl–}C_6H_4$)	**2f**	69	**6f**	88
7	**1g** ($R^1 = Cl$, $R^2 = H$, $R^3 = 4\text{-Me–}C_6H_4$)	**2g**	76	**6g**	85
8	**1h** ($R^1 = Cl$, $R^2 = H$, $R^3 = 4\text{-Cl–}C_6H_4$)	**2h**	82	**6h**	96
9	**1i** ($R^1 = MeO$, $R^2 = H$, $R^3 = Ph$)	**2i**	73	**6i**	95

[a]) Yields of isolated products [%].

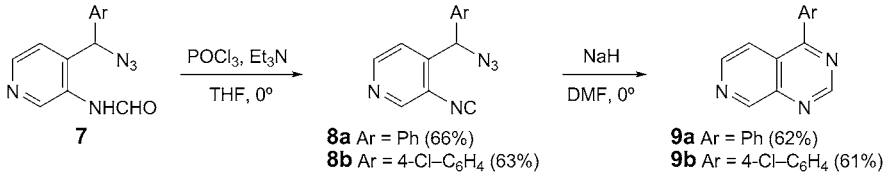
temperature, the desired products were obtained in slightly lower yields than those in DMF.

A possible pathway for the production of quinazolines **6** is also shown in *Scheme 1*. Trapping of the intermediate **5** by adding electrophiles such as MeI, Me_3SiCl, and BzCl to the reaction mixtures after confirmation of the disappearance of starting materials **1**, it was attempted to introduce a substituent at the 2-position of quinazolines. Unfortunately, however, all attempts failed; no desired products were obtained at all. Thus, we considered that deprotonation of **2** by **5** occurs to afford **6** and to regenerate **3**. When **2c** was treated with 0.1 equiv. of NaH in DMF at 0°, the reaction was complete in *ca.* 20 min to give the corresponding desired quinazoline **6c** in 75% yield. This result may support our consideration.

To investigate the utility of the present method, it was applied to the synthesis of 4-arylpyrido[3,4-*d*]pyrimidines **9** using *N*-{[4-aryl(azido)methyl]pyridin-3-yl}formamide **7** as precursors, which could be easily prepared from known (4-aminopyridin-3-yl)arylmethanones [8][9] by the same sequence as mentioned above for the preparation of azido formamides **1** from 2-aminophenyl ketones. After transformation of compounds **7** to the corresponding isocyanides **8**, these were subjected to the treatment with NaH under the same conditions as described for the preparation of quinazolines **6**. Moderate-to-fair yields of the desired products **9** were obtained by a similar workup and the subsequent purification as described for the isolation of **6**.

In conclusion, we have developed a novel method for the preparation of quinazolines, which can be conducted under mild conditions. The easiness of experimental operations and the ready availability of the starting materials make the present method attractive. We are currently exploring the possibility of applying this methodology to related heterocyclic systems to expand its potential scope.

Scheme 2



Experimental Part

General. All org. solvents used in this study were dried over appropriate drying agents and distilled prior to use. TLC: *Merck* silica gel *60 PF_{254}*. Column chromatography (CC): *Wako Gel C-200E.* M.p.: *Laboratory Devices MEL-TEMP II* melting-point apparatus; uncorrected. IR Spectra: *PerkinElmer Spectrum65* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *JEOL ECP500* FT NMR spectrometer or *JEOL LA400* FT NMR spectrometer (at 500 or 400 MHz, resp.); δ in ppm rel. to Me_4Si as internal standard, J in Hz. ^{13}C-NMR Spectra: *JEOL ECP500* FT NMR spectrometer, at 125 MHz, in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard. HR-MS (DART, pos.): *Thermo Scientific Exactive* spectrometer; in *m/z*.

2-(Aminophenyl)(4-chlorophenyl)methanone [10], *(2-amino-5-chlorophenyl)(4-methylphenyl)methanone* [11], *(2-amino-5-methoxyphenyl)phenylmethanone* [12], N-*[2-ethanoylphenyl]formamide* [13], N-*(2-benzoylphenyl)formamide* [14], N-*[3-chloro-6-(chloromethyl)phenyl]formamide* [7], N-*[2-(azido-*

methyl)phenyl]formamide (**1a**) [6], N-*(4-benzoylpyridin-3-yl)formamide* [8], and N-*[4-(4-chlorobenzoyl)pyridin-3-yl]formamide* [9] were prepared according to the reported procedures. All other chemicals used in this study were commercially available.

Other *(2-Aminophenyl)arylmethanones* were prepared from appropriate 2-aminobenzonitriles and arylmagnesium bromide as reported for the preparation of (2-aminophenyl)(4-chlorophenyl)methanone [10].

(2-Amino-4-chlorophenyl)(4-chlorophenyl)methanone. Yield: 64%. Yellow solid. M.p. 116–118° (hexane/$CHCl_3$). IR (KBr): 3450, 3338, 1629, 1611. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.17 (br. *s*, 2 H); 6.58 (*dd*, *J* = 8.4, 2.3, 1 H); 6.75 (*d*, *J* = 2.3, 1 H); 7.33 (*d*, *J* = 8.4, 1 H); 7.44 (*d*, *J* = 8.4, 2 H); 7.55 (*d*, *J* = 8.4, 2 H). Anal. calc. for $C_{13}H_9Cl_2NO$ (266.12): C 58.67, H 3.41, N 5.26; found: C 58.57, H 3.48, N 5.14.

N-*(2-Acylphenyl)formamides* were prepared by *N*-formylation of the respective 2-aminophenyl ketones with HCO_2H as described in [14].

N-*[5-Chloro-2-(4-chlorobenzoyl)phenyl]formamide.* Yield: 98%. Yellow solid. M.p. 95–97° (hexane/$CHCl_3$). IR (KBr): 3307, 1704, 1640. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.12 (*d*, *J* = 8.4, 1 H); 7.49 (*d*, *J* = 8.4, 3 H); 7.63 (*d*, *J* = 8.4, 2 H); 8.50 (*s*, 1 H); 8.79 (*s*, 1 H); 10.77 (br. *s*, 1 H). Anal. calc. for $C_{14}H_9Cl_2NO_2$ (294.13): C 57.17, H 3.08, N 4.76; found: C 57.09, H 3.35, N 4.65.

N-*[4-Chloro-2-(4-methylbenzoyl)phenyl]formamide.* Yield: 89%. Pale-yellow solid. M.p. 95–96° (hexane/CH_2Cl_2). IR (KBr): 3318, 1702, 1642. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.47 (*s*, 3 H); 7.32 (*d*, *J* = 7.8, 2 H); 7.52–7.54 (*m*, 2 H); 7.63 (*d*, *J* = 7.8, 2 H); 8.42–10.04 (*m*, 3 H). Anal. calc. for $C_{15}H_{12}ClNO_2$ (273.71): C 65.82, H 4.42, N 5.12; found: C 65.79, H 4.48, N 5.03.

N-*[4-Chloro-2-(4-chlorobenzoyl)phenyl]formamide.* Yield: 86%. Yellow solid. M.p. 89–91° (hexane/Et_2O). IR (KBr): 3367, 1711, 1637. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.49–7.52 (*m*, 3 H); 7.55 (*dd*, *J* = 9.2, 2.3, 1 H); 7.67 (*d*, *J* = 8.4, 2 H); 8.47 (*d*, *J* = 2.3, 1 H); 8.64 (*d*, *J* = 9.2, 1 H); 10.43 (*s*, 1 H). Anal. calc. for $C_{14}H_9Cl_2NO_2$ (294.13): C 57.17, H 3.08, N 4.76; found: C 57.15, H 3.24, N 4.76.

N-*(2-Benzoyl-4-methoxyphenyl)formamide.* Yield: 90%. Yellow oil. R_f (AcOEt/hexane 1:1) 0.22. IR (neat): 3323, 1695, 1645. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.76, 3.77 (2*s*, combined 3 H); 7.06–10.26 (*m*, 10 H). Anal. calc. for $C_{15}H_{13}NO_3$ (255.27): C 70.58, H 5.13, N 5.49; found: C 70.52, H 5.13, N 5.30.

N-*[2-(Hydroxyalkyl)phenyl]formamides* and N-*{4-[Aryl(hydroxy)methyl]pyridin-3-yl}formamides* were prepared by the $NaBH_4$ reduction of the respective keto formamides in MeOH at r.t.

N-*[2-(1-Hydroxyethyl)phenyl]formamide.* Yield: 76%. Pale-yellow oil. R_f (AcOEt/hexane 1:2) 0.11. The ^{1}H-NMR data were identical to those reported in [15].

N-*{2-[Hydroxy(phenyl)methyl]phenyl}formamide.* Yield: 68%. White solid. M.p. 120–121° (hexane/THF) ([15]: 121–122°). IR (KBr): 3357, 1688. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.38 (*s*, 1 H); 5.82, 5.92 (2*s*, combined 1 H); 7.05–8.79 (*m*, 11 H).

N-*{2-[(4-Chlorophenyl)(hydroxy)methyl]phenyl}formamide.* Yield: 82%. Colorless amorphous. R_f (AcOEt/hexane 1:2) 0.19, IR (neat): 3319, 1675. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.95, 3.01 (2*s*, combined 1 H); 5.93 (*s*, 1 H); 7.05–8.58 (*m*, 10 H). Anal. calc. for $C_{14}H_{12}ClNO_2$ (261.70): C 64.25, H 4.62, N 5.35; found: C 64.04, H 4.69, N 5.08.

N-*{5-Chloro-2-[(4-chlorophenyl)(hydroxy)methyl]phenyl}formamide.* Yield: 92%. Colorless amorphous. R_f (AcOEt/hexane 1:2) 0.23. IR (neat): 3315, 1682. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.90, 2.99 (2*d*, *J* = 3.1, each, combined 1 H); 5.90 (*d*, *J* = 3.1, 1 H); 6.97–8.65 (*m*, 9 H). Anal. calc. for $C_{14}H_{11}Cl_2NO_2$ (296.15): C 56.78, H 3.74, N 4.73; found: C 56.73, H 3.81, N 4.80.

N-*{4-Chloro-2-[(hydroxy)(4-methylphenyl)methyl]phenyl}formamide.* Yield: 85%. Colorless viscous oil. R_f (AcOEt/hexane 1:1) 0.26. IR (neat): 3316, 1681. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.35 (*s*, 3 H); 3.11, 3.20 (2*d*, *J* = 2.9 and 3.4, resp., combined 1 H); 5.83, 5.85 (2*d*, *J* = 2.9 and 3.4, resp., combined 1 H); 7.00–8.68 (*m*, 9 H). Anal. calc. for $C_{15}H_{14}ClNO_2$ (275.73): C 65.34, H 5.12, N 5.08; found: C 65.34, H 5.14, N 5.04.

N-*{4-Chloro-2-[(4-chlorophenyl)(hydroxy)methyl]phenyl}formamide.* Yield: 77%. White solid. M.p. 117–118° (hexane/Et_2O). IR (KBr): 3318, 1680. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.89, 3.99 (2*d*, *J* = 3.1 each, combined 1 H); 5.82 (*s*, 1 H); 7.04–8.72 (*m*, 9 H). Anal. calc. for $C_{14}H_{11}Cl_2NO_2$ (296.15): C 56.78, H 3.74, N 4.73; found: C 56.53, H 3.99, N 4.51.

N-*{2-[Hydroxy(phenyl)methyl]-4-methoxyphenyl}formamide.* Yield: 78%. Colorless viscous oil. R_f (AcOEt/hexane 2:3) 0.21. IR (neat): 3331, 1674, 1605. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.34, 3.53 (2*d*,

$J =$ 3.1 each, combined 1 H); 3.73, 3.76 (2*s*, combined 3 H); 5.857, 5.862 (2*s*, combined 1 H), 6.66–8.33 (*m*, 10 H). Anal. calc. for $C_{15}H_{15}NO_3$ (257.28): C 70.02, H 5.88, N 5.44; found: C 69.84, H 5.96, N 5.31.

N-*{4-[Hydroxy(phenyl)methyl]pyridin-3-yl}formamide.* Yield: 65%. White solid. M.p. 143–145° (hexane/THF). IR (KBr): 3293, 1678. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.21, 3.60 (2 br. *s.* combined 1 H); 5.93, 5.94 (2*s*, combined 1 H); 7.01–9.37 (*m*, 10 H). Anal. calc. for $C_{13}H_{12}N_2O_2$ (228.25): C 68.41, H 5.30, N 12.27; found: C 68.15, H 5.40, N 12.20.

N-*{4-[(4-Chlorophenyl)(hydroxy)methyl]pyridin-3-yl}formamide.* Yield: 65%. White solid. M.p. 138–140° (hexane/THF). IR (KBr): 3289, 3249, 1688, 1606. ^{1}H-NMR (500 MHz, (D_6)DMSO): 5.94, 6.03 (2*s*, combined 1 H); 6.43 (br., 1 H); 7.28–9.80 (*m*, 9 H). Anal. calc. for $C_{13}H_{11}ClN_2O_2$ (262.69): C 59.44, H 4.22, N 10.66; found: C 59.27, H 4.27, N 10.50.

N-*{2-[Azido(phenyl)methyl]phenyl}formamide* (**1c**) (*Representative Procedure*). To a stirred soln. of *N*-{2-[hydroxy(phenyl)methyl]phenyl}formamide (2.0 g, 8.6 mmol) in THF (11 ml) at −40° was added a soln. of $SOCl_2$ (1.1 g, 9.0 mmol) in THF (5 ml) dropwise. After stirring for 30 min at the same temp., the temp. was raised to −20°, and stirring was continued for 1.5 h. Na_2CO_3 (0.3 g) was added, and the mixture was filtered under reduced pressure. The filtrate was concentrated by evaporation to give a residue (1.9 g), which was used for the next step without any purification. The residue was dissolved in DMF, and NaN_3 (0.59 g, 9.0 mmol) was added under stirring, which was continued for 7 d at r.t. H_2O (30 ml) was added, and the mixture was extracted with AcOEt (3 × 20 ml). The combined extracts were washed with H_2O (3 × 20 ml) and brine (20 ml), and dried (Na_2SO_4) and concentrated by evaporation. The residue was purified by CC (SiO_2) to give **1c** (1.5 g, 70%). White solid. M.p. 103–104° (hexane/CH_2Cl_2). IR (KBr): 3314, 2101, 1687. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.82, 5.92 (2*s*, combined 1 H); 7.05–8.80 (*m*, 11 H). Anal. calc. for $C_{14}H_{12}N_4O$ (252.27): C 66.65, H 4.79, N 22.21; found: C 66.65, H 4.77, N 22.15.

N-*[2-(1-Azidoethyl)phenyl]formamide* (**1b**). Yield: 71%. Yellow oil. R_f (AcOEt/hexane 1:1) 0.47. IR (neat): 3287, 2104, 1693, 1604. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.64 (*d*, $J = 6.1$, 3 H); 4.64–4.72 (*m*, 1 H); 7.18–8.58 (*m*, 6 H). Anal. calc. for $C_9H_{10}N_4O$ (190.20): C 56.83, H 5.30, N 29.46; found: C 56.62, H 5.30, N 29.20.

N-*{2-[Azido(4-chlorophenyl)methyl]phenyl}formamide* (**1d**). Yield: 60%. White solid. M.p. 100–102° (hexane/CH_2Cl_2). IR (KBr): 3224, 2106, 1656. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.79 (*s*, 1 H); 7.05–8.38 (*m*, 10 H). Anal. calc. for $C_{14}H_{11}ClN_4O$ (286.72): C 58.65, H 3.87, N 19.54; found: C 58.42, H 3.90, N 19.40.

N-*[2-(Azidomethyl)-5-chlorophenyl]formamide* (**1e**) was prepared from *N*-[3-chloro-6-(chloromethyl)phenyl]formamide [7] in 87% yield as described for the preparation of N-*[2-(azidomethyl)phenyl]formamide* (**1a**) from *N*-[2-(chloromethyl)phenyl]formamide and NaN_3 [6]. Yellow oil. R_f (AcOEt/hexane 1:5) 0.57. IR (neat): 3288, 2106, 1693. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.34, 4.36 (2*s*, combined 2 H); 7.18–8.56 (*m*, 5 H). Anal. calc. for $C_8H_7ClN_4O$ (210.62): C 45.62, H 3.35, N 26.60; found: C 45.47, H 3.38, N 26.48.

N-*{2-[Azido(4-chlorophenyl)methyl]-5-chlorophenyl}formamide* (**1f**). Yield: 64%. Yellow oil. R_f (AcOEt/hexane 1:2) 0.25. IR (neat): 3286, 2102, 1693. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.76, 5.77 (2*s*, combined 1 H); 7.18–8.39 (*m*, 9 H). Anal. calc. for $C_{14}H_{10}Cl_2N_4O$ (321.16): C 52.36, H 3.14, N 17.45; found: C 52.16, H 3.40, N 17.40.

N-*{2-[Azido(4-methylphenyl)methyl]-4-chlorophenyl}formamide* (**1g**). Yield: 67%. Colorless oil. R_f (AcOEt/hexane 1:1) 0.30. IR (neat): 3292, 2103, 1693. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.36 (*s*, 3 H); 5.70 (*s*, 1 H); 7.05–8.34 (*m*, 9 H). Anal. calc. for $C_{15}H_{13}ClN_4O$ (300.74): C 59.91, H 4.36, N 18.63; found: C 59.86, H 4.60, N 18.37.

N-*{2-[Azido(4-chlorophenyl)methyl]-4-chlorophenyl}formamide* (**1h**). Yield: 83%. Pale-yellow solid. M.p. 98–100° (hexane/$CHCl_3$). IR (KBr): 3275, 2104, 1694. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.75, 5.78 (2*s*, combined 1 H); 7.12–8.31 (*m*, 9 H). Anal. calc. for $C_{14}H_{10}Cl_2N_4O$ (321.16): C 52.36, H 3.14, N 17.45; found: C 52.35, H 3.28, N 17.40.

N-*{2-[Azido(phenyl)methyl]-4-methoxyphenyl}formamide* (**1i**). Yield: 70%. Yellow oil. R_f (AcOEt/hexane 1:1) 0.21. IR (KBr): 3257, 2101, 1689. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.81, 3.83 (2*s*, combined, 3 H); 5.78, 5.80 (2*s*, combined 1 H); 6.86–8.17 (*m*, 10 H). Anal. calc. for $C_{15}H_{14}N_4O_2$ (282.30): C 63.82, H 5.00, N 19.85; found: C 63.93, H 5.04, N 20.13.

N-*{4-[Azido(phenyl)methyl]pyridin-3-yl}formamide* (**7a**). Yield: 60%. Yellow oil. R_f (THF/hexane 1:1) 0.35. IR (neat): 3239, 2103, 1695. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.87 (*s*, 1 H); 7.23–9.02 (*m*, 10 H). Anal. calc. for $C_{13}H_{11}N_5O$ (253.26): C 61.65, H 4.38, N 27.65; found: C 61.61, H 4.40, N 27.60.

N-*{4-[Azido(4-chlorophenyl)methyl]pyridin-3-yl}formamide* (**7b**). Yield: 62%. Yellow oil. R_f (THF/hexane 1:1) 0.24. IR (neat): 3239, 2105, 1695. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.86, 5.88 (2*s*, combined 1 H); 7.18–8.98 (*m*, 9 H). Anal. calc. for $C_{13}H_{10}ClN_5O$ (287.70): C 54.27, H 3.50, N 24.34; found: C 54.10, H 3.53, N 24.28.

Isocyanobenzenes **2** were prepared by dehydration of **1** with $POCl_3$ as described in [16].

1-(Azidomethy)l-2-isocyanobenzene (**2a**). Green oil. R_f (CH_2Cl_2/hexane 1:1) 0.46. ^{1}H-NMR Data: identical to those reported in [6].

1-(1-Azidoethyl)-2-isocyanobenzene (**2b**). Pale-green oil. R_f (CH_2Cl_2/hexane 1:5) 0.50. IR (neat): 2121, 2101. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.57 (*d*, $J = 6.9$, 3 H); 5.09 (*q*, $J = 6.9$, 1 H); 7.35 (*td*, $J = 7.6$, 1.5, 1 H); 7.41 (*d*, $J = 7.6$, 1 H); 7.46 (*td*, $J = 7.6$, 1.5, 1 H), 7.52 (*d*, $J = 7.6$, 1 H). HR-MS: 173.0806 ($[M+H]^+$, $C_9H_9N_4^+$; calc. 173.0827).

1-[Azido(phenyl)methyl]-2-isocyanobenzene (**2c**). Pale-green oil. R_f (CH_2Cl_2/hexane 1:5) 0.20. IR (neat): 2119, 2102. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.09 (*s*, 1 H); 7.32–7.35 (*m*, 3 H); 7.36–7.40 (*m*, 4 H); 7.47 (*td*, $J = 7.6$, 1.5, 1 H); 7.62 (*d*, $J = 7.6$, 1 H). HR-MS: 235.0982 ($[M+H]^+$, $C_{14}H_{11}N_4^+$; calc. 235.0983).

1-[Azido(4-chlorophenyl)methyl]-2-isocyanobenzene (**2d**). Pale-green oil. R_f (CH_2Cl_2/hexane 1:3) 0.47. IR (neat): 2127, 2103. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.07 (*s*, 1 H); 7.26–7.29 (*m*, 2 H); 7.34–7.40 (*m*, 4 H); 7.48 (*td*, $J = 7.6$, 1.5, 1 H); 7.59 (*d*, $J = 7.6$, 1 H). HR-MS: 269.0565 ($[M+H]^+$, $C_{14}H_{10}ClN_4^+$; calc. 269.0594).

1-(Azidomethy)l-4-chloro-2-isocyanobenzene (**2e**). Pale-green liquid. R_f (CH_2Cl_2/hexane 1:3) 0.18. IR (neat): 2119. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.55 (*s*, 2 H); 7.37–7.38 (*m*, 2 H); 7.48 (*s*, 1 H). HR-MS: 193.0278 ($[M+H]^+$, $C_8H_6ClN_4^+$; calc. 193.0281).

1-[Azido(4-chlorophenyl)methyl]-4-chloro-2-isocyanobenzene (**2f**). Green oil. R_f (CH_2Cl_2/hexane 1:5) 0.30. IR (neat): 2104. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.00 (*s*, 1 H); 7.25 (*d*, $J = 8.4$, 2 H); 7.36 (*d*, $J = 8.4$, 2 H); 7.39 (*d*, $J = 2.3$, 1 H); 7.46 (*dd*, $J = 8.4$, 2.3, 1 H); 7.54 (*d*, $J = 8.4$, 1 H). HR-MS: 303.0203 ($[M+H]^+$, $C_{14}H_9Cl_2N_4^+$; calc. 303.0204).

1-[Azido(4-methylphenyl)methyl]-5-chloro-2-isocyanobenzene (**2g**). Green oil. R_f (CH_2Cl_2/hexane 1:3) 0.26. IR (neat): 2128, 2103. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.35 (*s*, 3 H); 5.98 (*s*, 1 H); 7.21 (br. *s*, 4 H); 7.28–7.32 (*m*, 2 H); 7.65 (br. *s*, 1 H). HR-MS: 283.0729 ($[M+H]^+$, $C_{15}H_{12}ClN_4^+$; calc. 283.0750).

1-[Azido(4-chlorophenyl)methyl]-5-chloro-2-isocyanobenzene (**2h**). Light-blue solid. M.p. 85–86° (hexane/Et_2O). IR (KBr): 2106. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.99 (*s*, 1 H); 7.28 (*d*, $J = 8.3$, 2 H); 7.29–7.34 (*m*, 2 H); 7.38 (*d*, $J = 8.3$, 2 H); 7.62 (*d*, $J = 2.0$, 1 H). HR-MS: 303.0197 ($[M+H]^+$, $C_{14}H_9Cl_2N_4^+$; calc. 303.0204).

1-[Azido(phenyl)methyl]-5-methoxy-2-isocyanobenzene (**2i**). Green oil. R_f (CH_2Cl_2/hexane 1:2) 0.57. IR (neat): 2103, 1607. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.84 (*s*, 3 H); 6.04 (*s*, 1 H); 6.82 (*dd*, $J = 9.2$, 2.3, 1 H); 7.11 (*d*, $J = 2.3$, 1 H); 7.29–7.39 (*m*, 6 H). HR-MS: 265.1088 ($[M+H]^+$, $C_{15}H_{13}N_4O^+$; calc. 265.1089).

4-[Azido(phenyl)methyl]-3-isocyanopyridine (**8a**). Brown oil. R_f (THF/hexane 1:2) 0.50. IR (neat): 2119, 2106. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.00 (*s*, 1 H); 7.32–7.43 (*m*, 5 H); 7.66 (*d*, $J = 5.3$, 1 H); 8.62 (*s*, 1 H); 8.69 (*d*, $J = 5.3$, 1 H). HR-MS: 236.0928 ($[M+H]^+$, $C_{13}H_{10}ON_5^+$; calc. 236.0936).

4-[Azido(4-chlorophenyl)methyl]-3-isocyanopyridine (**8b**). Green oil. R_f (THF/hexane 1:4) 0.52. IR (neat): 2107. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.98 (*s*, 1 H); 7.27 (*d*, $J = 8.4$, 2 H); 7.39 (*d*, $J = 8.4$, 2 H); 7.69 (*d*, $J = 5.3$, 1 H); 8.65 (*s*, 1 H); 8.70 (*d*, $J = 5.3$, 1 H). HR-MS: 270.0550 ($[M+H]^+$, $C_{13}H_9ClN_5^+$; calc. 270.0546).

Quinazoline (**6a**) (*Representative Procedure*). To a stirred suspension of NaH (60% in mineral oil; 35 mg, 0.88 mmol) in DMF (2 ml) at 0° was added a soln. of **2a** (0.14 g, 0.88 mmol) in DMF (1.5 ml) dropwise. After stirring for 10 min at the same temp., H_2O (15 ml) was added. The mixture was extracted with AcOEt (3×10 ml), and the combined extracts were washed with H_2O (3×10 ml) and brine (10 ml), and dried (Na_2SO_4) and concentrated by evaporation. The residue was purified by CC (SiO_2) to give **6a** (79 mg, 69%). White solid. M.p. 45–47° (hexane/CH_2Cl_2) ([17]: 48°). Identified by a direct comparison with a sample purchased from *Tokyo Chemical Industry Co., Ltd.*

4-Methylquinazoline (**6b**). White solid. M.p. 34–36° (hexane/CH_2Cl_2) ([18]: 34–35°). ^{1}H-NMR Data: identical to those reported in [18].

4-Phenylquinazoline (**6c**). White solid. M.p. 99–101° (hexane/CH_2Cl_2) ([18]: 100–101°). ^{1}H- and ^{13}C-NMR data: identical to those reported in [19].

4-(4-Chlorophenyl)quinazoline (**6d**). White solid. M.p. 123–125° (hexane/CH_2Cl_2) ([17]: 122°). ^{1}H-NMR Data: identical to those reported in [17].

7-Chloroquinazoline (**6e**). White solid. M.p. 92–94° (hexane/CH_2Cl_2) ([20]: 93–94°). ^{1}H-NMR Data: identical to those reported in [21].

7-Chloro-4-(4-chlorophenyl)quinazoline (**6f**). White solid. M.p. 160–162° (hexane/Et_2O). IR (KBr): 3065, 1604, 1557, 1475. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.57–7.59 (*m*, 3 H); 7.73 (*d*, *J* = 8.4, 2 H); 8.03 (*d*, *J* = 9.2, 1 H); 8.12 (*d*, *J* = 2.3, 1 H); 9.36 (*s*, 1 H). ^{13}C-NMR: 121.35; 128.09; 128.11; 129.10 (2 overlapped Cs); 131.23; 135.08; 136.81; 140.21; 151.77; 155.55; 167.11. HR-MS: 275.0123 ($[M+H]^+$, $C_{14}H_9Cl_2N_2^+$; calc. 275.0143). Anal. calc. for $C_{14}H_8Cl_2N_2$ (275.13): C 61.12, H 2.93, N 10.18; found: C 60.85, H 2.81, N 10.08.

6-Chloro-4-(4-methylphenyl)quinazoline (**6g**). White solid. M.p. 163–164° (hexane/CH_2Cl_2). IR (KBr): 3065, 1556, 1486. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.49 (*s*, 3 H); 7.41 (*d*, *J* = 7.6, 2 H); 7.68 (*d*, *J* = 7.6, 2 H); 7.84 (*dd*, *J* = 9.2, 2.3, 1 H); 8.06 (*d*, *J* = 9.2, 1 H); 8.13 (*d*, *J* = 2.3, 1 H); 9.36 (*s*, 1 H). ^{13}C-NMR: 21.46; 123.72; 125.91; 129.55; 129.85; 130.62; 133.33; 133.71; 134.55; 140.74; 149.61; 154.83; 167.64. HR-MS: 255.0688 ($[M+H]^+$, $C_{15}H_{12}ClN_2^+$; calc. 255.0689). Anal. calc. for $C_{15}H_{11}ClN_2$ (254.71): C 70.73, H 4.35, N 11.00; found: C 70.57, H 4.48, N 10.90.

6-Chloro-4-(4-chlorophenyl)quinazoline (**6h**). Pale-yellow solid. M.p. 125–127° (hexane/Et_2O). IR (KBr): 3037, 1559, 1486. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.59 (*d*, *J* = 8.4, 2 H); 7.73 (*d*, *J* = 8.4, 2 H); 7.86 (*dd*, *J* = 9.2, 2.3, 1 H); 8.05 (*d*, *J* = 2.3, 1 H); 8.08 (*d*, *J* = 9.2, 1 H); 9.37 (*s*, 1 H). ^{13}C-NMR: 123.46; 125.35; 129.17; 130.81; 131.17; 133.75; 134.84; 134.90; 136.83; 149.64; 154.75; 166.31. HR-MS: 275.0128 ($[M+H]^+$, $C_{14}H_9Cl_2N_2^+$; calc. 275.0143). Anal. calc. for $C_{14}H_8Cl_2N_2$ (275.13): C 61.12, H 2.93, N 10.18; found: C 60.96, H 3.04, N 9.78.

6-Methoxy-4-phenylquinazoline (**6i**). Yellow solid. M.p. 101–103° (hexane/Et_2O). IR (KBr): 3062, 1619, 1537, 1504, 1234. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.85 (*s*, 3 H); 7.37 (*d*, *J* = 2.3, 1 H); 7.55–7.61 (*m*, 4 H); 7.79–7.81 (*m*, 2 H); 8.03 (*d*, *J* = 9.2, 1 H); 9.27 (*s*, 1 H). ^{13}C-NMR: 55.62; 104.10; 124.03; 125.47; 128.70; 129.55; 129.85; 130.37; 137.45; 147.32; 152.88; 158.39; 166.56. HR-MS: 237.1019 ($[M+H]^+$, $C_{15}H_{13}N_2O^+$; calc. 237.1028). Anal. calc. for $C_{15}H_{12}N_2O$ (236.27): C 76.25, H 5.12, N 11.86; found: C 76.04, H 5.15, N 11.84.

*4-Phenylpyrido[3,4-*d*]pyrimidine* (**9a**). Yellow solid. M.p. 87–88° (hexane/CH_2Cl_2). IR (KBr): 3030, 1557, 1542, 1384. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.61–7.64 (*m*, 3 H); 7.83–7.85 (*m*, 2 H); 7.96 (*d*, *J* = 5.4, 1 H); 8.77 (*d*, *J* = 5.4, 1 H); 9.54 (*s*, 1 H); 9.61 (*s*, 1 H); ^{13}C-NMR: 118.12; 125.51; 128.96; 129.92; 130.87; 135.78; 145.29; 145.40; 154.46; 156.00; 168.24. HR-MS: 208.0864 ($[M+H]^+$, $C_{13}H_{10}N_3^+$; calc. 208.0874). Anal. calc. for $C_{13}H_9N_3$ (207.23): C 75.35, H 4.38, N 20.28; found: C 75.10, H 4.58, N 20.26.

*4-(4-Chlorophenyl)pyrido[3,4-*d*]pyrimidine* (**9b**). Yellow solid. M.p. 141–142° (hexane/CH_2Cl_2). IR (KBr): 3061, 1554, 1536, 1381. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.61 (*d*, *J* = 8.4, 2 H); 7.80 (*d*, *J* = 8.4, 2 H); 7.91 (*d*, *J* = 5.4, 1 H); 8.78 (*d*, *J* = 5.4, 1 H); 9.52 (*s*, 1 H); 9.61 (*s*, 1 H). ^{13}C-NMR: 117.67; 125.31; 129.08; 129.32; 131.24; 134.18; 137.44; 145.45; 154.59; 155.96; 166.97. HR-MS: 242.0481 ($[M+H]^+$, $C_{13}H_9ClN_3^+$; calc. 242.0485). Anal. calc. for $C_{13}H_8ClN_3$ (241.68): C 64.61, H 3.34, N 17.39; found: C 64.40, H 3.18, N 17.27.

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REFERENCES

[1] K.-F. Chen, K.-C. Pao, J.-C. Su, Y.-C. Chou, C.-Y. Liu, H.-J. Chen, J.-W. Huang, I. Kim, C.-W. Shiau, *Bioorg. Med. Chem.* **2012**, *20*, 6144; K. Juvale, M. Wiese, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6766; M. H. P. Verheij, A. J. Thompson, J. E. Van Muijlwijk-Koezen, S. C. R. Lummis, R. Leurs, I. J. P.

de Esch, *J. Med. Chem.* **2012**, 55, 8603; S. Lü, W. Zheng, L. Ji, Q. Luo, X. Hao, X. Li, F. Wang, *Eur. J. Med. Chem.* **2013**, *61*, 84; S. Mowafy, N. A. Farag, K. A. M. Abouzid, *Eur. J. Med. Chem.* **2013**, *61*, 132; J.-H. He, H.-Y. Liu, Z. Li, J.-H. Tan, T.-M. Ou, S.-L. Huang, L.-K. An, D. Li, L.-Q. Gu, Z.-S. Huang, *Eur. J. Med. Chem.* **2013**, *63*, 1; S. Li, X. Wang, Y. He, M. Zhao, Y. Chen, J. Xu, M. Fang, J. Chang, H. Hing, C. Qi, *Eur. J. Med. Chem.* **2013**, *67*, 293; M. T. Conconi, G. Marzaro, L. Urbani, I. Zanusso, R. D. Liddo, I. Castagliuolo, P. Brun, F. Tonus, A. Ferrarese, A. Guiotto, A. Chilin, *Eur. J. Med. Chem.* **2013**, *67*, 373; L. Xu, W. A. Russu, *Bioorg. Med. Chem.* **2013**, *21*, 540; T.-A. N. Pham, Z. Yang, Y. Fang, J. Luo, J. Lee, H. Park, *Bioorg. Med. Chem.* **2013**, *21*, 1349; A. I. Sánchez, V. Martínez-Barrasa, C. Burgos, J. J. Vaquero, J. Alvarez-Builla, E. Terricabras, V. Segarra, *Bioorg. Med. Chem.* **2013**, *21*, 2370; F. Zhao, Z. Lin, F. Wang, W. Zhao, X. Dong, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5385; X. Zhang, M. Su, Y. Chen, J. Li, W. Lu, *Molecules* **2013**, *18*, 6491.

[2] S. Verbeeck, W. A. Herrebout, A. V. Gulevskaya, B. J. van der Veken, B. U. W. Maes, *J. Org. Chem.* **2010**, *75*, 5126.

[3] Y. Yan, Y. Zhang, C. Feng, Z. Zha, Z. Wang, *Angew. Chem., Int. Ed.* **2012**, *51*, 8077.

[4] Z.-Y. Xing, Y. Fu, F. Ye, *ARKIVOC* **2012**, (*ix*), 280; S. K. Panja, N. Dwivedi, S. Saha, *Tetrahedron Lett.* **2012**, *53*, 6167; J. Ju, R. Hua, J. Su, *Tetrahedron* **2012**, *68*, 9364; Y. Lv, Y. Li, T. Xiong, W. Pu, H. Zhang, K. Sun, Q. Liu, Q. Zhang, *Chem. Commun.* **2013**, *49*, 6439; X. Su, C. Chen, Y. Wang, J. Chen, Z. Lou, M. Li, *Chem. Commun.* **2013**, *49*, 6752.

[5] J. B. Smail, B. D. Palmer, G. W. Rewcastle, W. A. Denny, D. J. McNamara, E. M. Dobrusin, A. J. Bridges, H. Zhou, H. D. H. Showalter, R. T. Winters, W. R. Leopold, D. W. Fry, J. M. Nelson, V. Slintak, W. L. Elliot, B. J. Roberts, P. W. Vincent, S. J. Patmore, *J. Med. Chem.* **1999**, *42*, 1803; B. Lippa, G. S. Kauffman, J. Arcari, T. Kwan, J. Chen, W. Hungerford, S. Bhattacharya, X. Zhao, C. Williams, J. Xiao, L. Pustilnik, C. Su, J. D. Moyer, L. Ma, M. Campbell, S. Steyn, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3081; S. J. Mantell, K. R. Gibson, S. A. Osborne, G. N. Maw, H. Rees, P. G. Dodd, B. Greener, G. W. Harbottle, W. A. Million, C. Poinsard, S. England, P. Carnell, A. M. Betts, R. Monhemius, R. L. Prime, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2190; M. J. van Eis, J.-P. Evenou, P. Floersheim, C. Gaul, S. W. Cowan-Jacob, L. Monovich, G. Rummel, W. Schuler, W. Stark, A. Strauss, A. von Matt, E. Vangrevelinghe, J. Wagner, N. Soldermann, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7367; C. D. Cox, I. T. Raheem, B. A. Flores, D. B. Whiteman, *US Pat. Appl. Publ.* **2011**, 20110319409; *Chem. Abstr.* **2011**, *156*, 92460; L. Wie, S. V. Malhotra, *MedChemComm* **2012**, *3*, 1250.

[6] G. Facchin, R. A. Michelin, M. Mozzon, S. Pugliese, P. Sgarbossa, A. Tassan, *Inorg. Chem. Commun.* **2002**, *5*, 915.

[7] K. Kobayashi, D. Iitsuka, S. Fukamachi, H. Konishi, *Tetrahedron* **2009**, *65*, 7523.

[8] K. Kobayashi, T. Kozuki, S. Fukamachi, H. Konishi, *Helv. Chim. Acta* **2010**, *93*, 2086.

[9] K. Kobayashi, T. Kozuki, M. Konishi, T. Suzuki, M. Tanmatsu, H. Konishi, *Helv. Chim. Acta* **2011**, *94*, 1234.

[10] K. Kobayashi, Y. Okamura, S. Fukamachi, H. Konishi, *Tetrahedron* **2010**, *66*, 7961.

[11] M. Okabe, R.-C. Sun, *Tetrahedron* **1995**, *51*, 1861.

[12] M. C. Carter, D. G. Alber, R. C. Baxter, S. K. Bithell, J. Budworth, A. Chubb, G. S. Cockerill, V. C. L. Dowdell, E. A. Henderson, S. J. Keegan, R. D. Kelsey, M. J. Lockyer, J. N. Stables, L. J. Wilson, K. L. Powell, *J. Med. Chem.* **2006**, *49*, 2311.

[13] K. Kobayashi, S. Fujita, S. Fukamachi, H. Konishi, *Synthesis* **2009**, 3378.

[14] K. Kobayashi, K. Yoneda, K. Miyamoto, O. Morikawa, H. Konishi, *Tetrahedron* **2004**, *60*,11639.

[15] I. Fleming, M. A. Loreto, I. H. M. Wallace, *J. Chem. Soc., Perkin Trans. 1* **1986**, 349.

[16] Y. Ito, K. Kobayashi, N. Seko, T. Saegusa, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73.

[17] T. Higashino, *Chem. Pharm. Bull.* **1961**, *9*, 635.

[18] B. C. Uff, B. L. Joshi, F. D. Popp, *J. Chem. Soc., Perkin Trans. 1* **1986**, 2295.

[19] C.-H. Yang, K. H. Fang, W.-L. Su, S.-P. Wang, S.-K. Su, I.-W. Sun, *J. Organomet. Chem.* **2006**, *691*, 2767.

[20] W. L. F. Armarego, *J. Chem. Soc.* **1962**, 561.

[21] M. Akazome, J. Yamamoto, T. Kondo, Y. Watanabe, *J. Organomet. Chem.* **1995**, *494*, 229.

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