Regioselective Reactions of Organozinc Reagents with 2,4-Dichloroquinoline and 5,7-Dichloropyrazolo[1,5-*a*]pyrimidine

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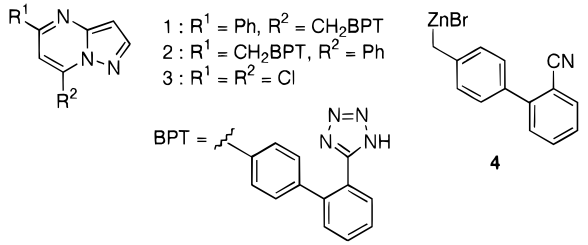
Strategies for controlling the regioselective reactions between 2,4-dichloroquinoline and organozinc reagents are described. 2,4-Dichloroquinoline has been found to react with benzylic zinc and phenylzinc reagents in the presence of catalytic amounts of palladium complexes to exclusively give α-substituted products. Several metal salts were examined as an additive for γ-selective coupling reactions. The most effective additive for selective coupling reaction at the γ-position has been found to be LiCl. These conditions for α- or γ-selective coupling reactions were applied to the reaction between 5,7-dichloropyrazolo[1,5-*a*]pyrimidine and a biphenylmethylzinc reagent in the synthesis of the angiotensin II receptor antagonists. This regioselectivity should be generally applicable to other α,γ-dichloroazine systems.

Introduction

Palladium-catalyzed cross-coupling reactions are versatile methods for C−C bond formation between formal electrophiles C−X (X = Cl, Br, I, OTf) and organometallics C−M (M = Li, Mg, Zn, Sn, B, Si, etc.).[1] Like organostannanes and organoboranes, organozinc reagents tolerate the presence of various organic functional groups in the reaction system. Recently, several new methods for preparing polyfunctional organozinc reagents have been developed,[1f,2] which allow organozinc reagents to be used more conveniently. Thus, the combination of reagents and palladium catalyst is a useful C−C bond formation method for preparing molecules containing several functional groups,[2,3] and these reactions are becoming more important not only in the area of natural product synthesis but also in medicinal chemistry.[4]

In the course of our investigation of nonpeptide angiotensin II receptor antagonists, we designed a series of pyrazolo[1,5-*a*]pyrimidines in which both 5- and 7-positions were substituted with biphenylmethyl and phenyl groups (**1** and **2**).[5] In the preliminary synthetic study of these compounds, we conducted the reaction of 5,7-dichloroderivative **3** with biphenylmethylzinc bromide **4** in the presence of a catalytic amount of $Pd(Ph_3P)_4$ in THF. This reaction gave a regioisomeric mixture of 5- and 7-substituted products. Generally, when two or more reaction centers are present in the cross-coupling reaction, it is difficult to produce each regioisomer selectively. To our knowledge, there have been few examples of such a regioselective cross-coupling reaction in the literature.[6] To develop a generally applicable method for controlling the regioselectivity of coupling reaction of α,γ-dichloroazines, we investigated the reaction of 2,4-dichloroquinoline **5** with a benzylic zinc reagent **6** under various conditions and then successfully established the conditions under which each regioisomeric coupling product would be selectively produced. Here we report the results of regioselective reactions of **5** with **6**, and application of the condition to synthesis of the pyrazolo[1,5-*a*]pyrimidines **1** and **2**.



Results and Discussion

The results of the reactions of 2,4-dichloroquinoline **5** with the benzylic zinc bromide **6** in the presence of various additives are summarized in Table 1. This coupling reaction does not proceed without any additive. The reactions in the presence of $Pd(Ph_3P)_4$ catalyst in THF or DMF proceeded at room temperature to exclusively give α-substituted product **8** (entries 1 and 2). A higher reaction temperature accelerated the reaction rate and improved the chemical yield (entry 3). This excellent α-selectivity was notable because it had been known that the reaction of the dichloro derivative **5** with various nucleophiles gave a regioisomeric mixture.[7] But recently, some examples of regioselective reaction of a similar α,γ-dichloroazine system were also reported. The Suzuki coupling reaction of 2,4-dichloropyridine in THF took place at only the α-position,[8] and Stille cross-coupling reaction of 2,4,6-tribromophosphinines with organotin

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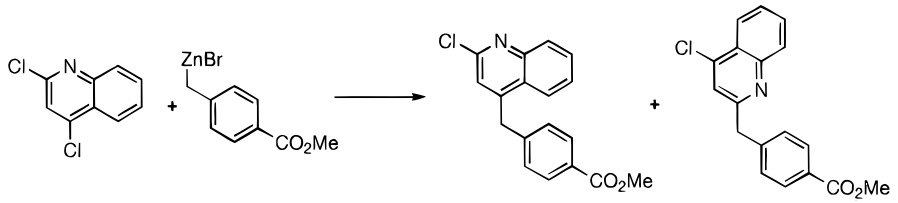
Table 1. Regioselective Reactions of 2,4-Dichloroquinoline and Benzyl Zinc Reagent 6 in the Presence of Various Additives



5 **6** **7** **8**

entry	additive (equiv)[a]	solvent	temp (°C)	time (h)	yield(%)[b] **7**	yield(%)[b] **8**
1	$Pd(Ph_3P)_4$ (0.05)	THF	rt	18	–	59
2	$Pd(Ph_3P)_4$ (0.05)	DMF	rt	18	–	60
3	$Pd(Ph_3P)_4$ (0.05)	THF	60	2	–	80
4	bipyridine (1.0)	THF	60	18	–	–
5	tBuOK (1.0)	THF	60	18	–	–
6	$CuBrMe_2S$ (1.0)	THF	−70−0	18	–	–[c]
7	$MgBr_2$ (1.0)	THF+DMPU[d]	rt	18	9.6	–
8	LiCl (1.5)	THF	rt	24	18	–
9	LiCl (4.0)	THF	rt	24	39	4.2
10	LiCl (1.0)	DMF	rt	24	65	–
11	LiCl (0.5)	DMF	rt	24	34	–
12	LiCl (2.0)	DMF	rt	24	77	<2.0
13	LiCl (4.0)	DMF	rt	6	83	<2.0
14	LiBr (2.0)	DMF	rt	24	77	4.0
15	LiI (2.0)	DMF	rt	24	54	5.0
16	$LiClO_4$ (2.0)	DMF	rt	16	–	–
17	LiCl (2.0)	DMF	rt	16	71	<2.0
18	NaCl (2.0)	DMF	rt	16	56	3.0
19	KCl (2.0)	DMF	rt	16	45	4.0
20	$MgBr_2$ (2.0)	DMF	rt	16	34	9

[a] Based on **5**. [b] Yields based on isolated products. [c] A homodimer of **6** was obtained. [d] *N*,*N*′-Dimethylpropyleneurea.

reagents occurred selectively at the α-position to the phosphorus.[9] In the latter example, coordination of the phosphorus to the palladium was hypothesized to control the regioselectivity. Similar coordination-controlled regioselectivity was proposed in the reaction of 2,4-dichloroquinoline with sodium alkoxide in toluene, which exclusively gave the 2-alkoxy-4-halogenoquinolines.[10] Taking these observations into account, in this case also, α-selective coupling reaction should be controlled by coordination of the quinoline nitrogen to the palladium.

We next attempted the γ-selective coupling reaction by direct nucleophilic substitution.[11] Several additives which have been reported to allow increase in the nucleophilicities of organozinc reagents[6b,12] resulted in no reaction or homodimer formation (entries 4−6). But when $MgBr_2$[13] was added to the reaction mixture, the γ-substituted product was obtained in low yield (entry 7). In the presence of 1.5 equiv of LiCl, the yield of the γ-substituted product was slightly improved (entry 8). Although an increased amount of LiCl gave a higher yield of **7** (entry 9), the choice of the solvent proved more critical in this reaction. When it was DMF, the yield and selectivity were dramatically improved (entry 10). This reaction was considered as an aromatic nucleophilic substitution reaction. The polar solvent DMF would be suitable for this reaction, because DMF assists in stabilizing partially ionized transition states and intermediate more effectively than THF. Various molar ratios of LiCl were examined in DMF solvent (entries 11−13). Although 4 equiv of LiCl provided the best result, 2 equiv of LiCl gave a comparable result with longer reaction times (entry 12).

Various counteranions for lithium cation were examined in DMF solvent (entries 14−16). Whereas the reactions in the presence of Cl^-, Br^-, I^-, which are known to coordinate with zinc ion,[14] gave **7** in good yields (entries 13−15), ClO_4^-, which has little coordination ability, gave no coupling product (entry 16). These results suggest that the halogen ligands increase the zinc−carbon bond polarity through coordination to the zinc and then enhance the reactivity of **6** toward electrophilic species. The lithium cation was more effective than sodium, potassium, or magnesium salts (entries 17 vs 18, 19 and 20) for increasing the reactivity of **6**.

The structures of the regioisomers **7** and **8** were confirmed by NOE studies. The product from the palladium-catalyzed reaction was assigned as the 2-substituted **8** from the NOE observed between the benzylic methylene protons and the proton at the 3-position of quinoline. On the other hand, the NOE study of **7** showed

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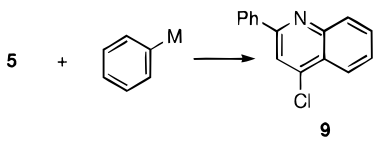
Table 2. Regioselective Coupling Reactions of 2,4-Dichloroquinoline and Various Phenyl Metal Reagents

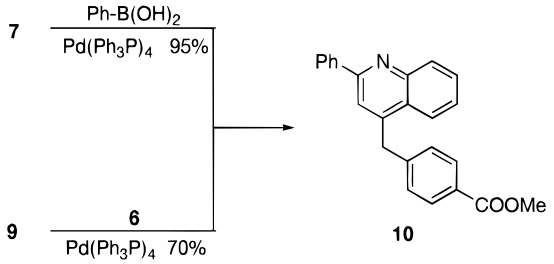


9

entry	phenyl reagent	additive	**9**, yield[a]
1	$PhZnCl$	$Pd(Ph_3P)_4$ (0.05)	94
2	$PhSn(Me)_3$	$Pd(Ph_3P)_4$ (0.05)	79
3	$PhB(OH)_2$	$Pd(Ph_3P)_4$ (0.05)	74
4	$PhZnCl$	LiCl (2.0)	–

[a] Yields are based on isolated products.

Scheme 1



NOE's between the benzylic methylene protons and the protons at both 3- and 5-positions of quinoline.

Thus, regioselectivity in the cross-coupling reaction between **5** and **6** could be controlled or switched by using two different additives, $Pd(PPh_3)_4$ for the α-coupling product and LiCl for the γ-coupling product.

The general applicability of the palladium-catalyzed α-selective coupling reaction of 2,4-dichloroquinoline with various organometallics was investigated using the phenylorganometallics (Table 2). As was expected, palladium-catalyzed reactions (entries 1−3) exclusively gave α-coupling product **9**, suggesting that the regioselectivity is not affected by the kind of organometal. On the other hand, no coupling product was obtained in the reaction using LiCl. This is in marked contrast to the reactivity and regioselectivity observed for the benzylic zinc reagent **6**. This difference would be due to the lower reactivity of phenylzinc than benzylzinc reagent **6**.

The structure of **9** was confirmed by two independent preparations of compound **10** (Scheme 1). The γ-coupling product **7**, whose structure was previously determined by NOE study, reacted with phenylboronic acid in the presence of palladium catalyst to give **10**. The cross-coupling product from the reaction of **9** with the benzylzinc bromide **6** showed the same analytical and spectral properties as those of the product obtained from **7**.

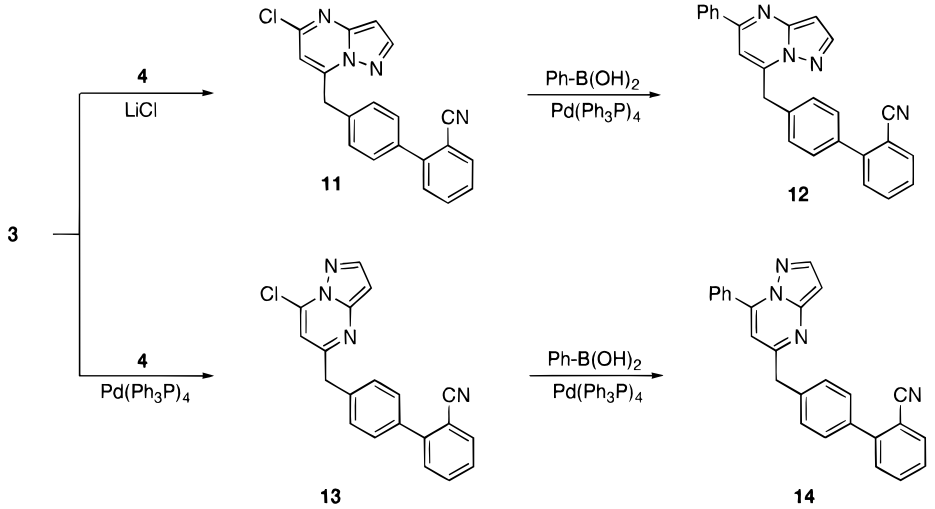
The above procedure was applied to the synthesis of regioisomeric pyrazolo[1,5-*a*]pyrimidines **12** and **14** as shown in Scheme 2. Dichloro derivative **3** was treated with the organozinc reagent **4** in the presence of 2 equiv of LiCl to exclusively give **11** in 52% yield. Coupling reaction of **3** with **4** in the presence of a catalytic amount of $Pd(Ph_3P)_4$ in DMF solvent gave 52% of **13** and 7% of **11**. The same reaction which was performed in THF showed no regioselectivity (vide supra). DMF was the preferred solvent for giving the α-selective cross-coupling product in the palladium-catalyzed reaction. Although the reason for the lower α-regioselectivity of 5,7-dichloropyrazolo[1,5-*a*]pyrimidine than 2,4-dichloroquinoline was unclear, we speculate that the lower basicity of 5,7-dichloropyrazolo[1,5-*a*]pyrimidine may diminish the coordination-controlled reaction pathway. The products **11** and **13** were independently coupled with phenylboronic acid in the presence of palladium catalyst affording 5,7-disubstituted products **12** and **14** in 90 and 77%, respectively.

Structure determination of these regioisomeric products was carried out by regiospecific synthesis of 5-phenyl derivative **12** as shown in Scheme 3. According to the literature, β-keto ester **15** and 3-aminopyrazole were condensed to give 5-phenylpyrazolo[1, 5-*a*]pyrimidin-7-(4*H*)-one **17**,[15] which was then converted to 7-chloro derivative **18** by treatment with phosphorus oxychloride. Coupling reaction of **18** with **4** gave the product whose analytical and spectral properties were identical to those of **12**.

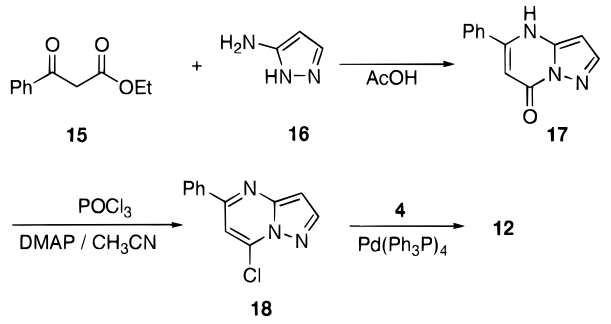
Conclusions

The reaction conditions for controlling the regioselectivities of the reactions of 2,4-dchloroquinoline and 5,7-dichloropyrazolo[1,5-*a*]pyrimidine with organozinc reagents were developed: $Pd(Ph_3P)_4$ for α-position to the aromatic nitrogen, and LiCl for γ-position. While regioselectivities have been demonstrated only in two systems, 2,4-dichloroquinoline and 5,7-dichloropyrazolo[1,5-*a*]py-

Scheme 2



Scheme 3



rimidine, the reaction should have synthetic utility in other α,γ-dichloroazine systems.

Experimental Section

General. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere. Tetrahydrofuran (THF), ether, xylene and *N*,*N*-dimethylformamide (DMF) were dried over 4-Å molecular sieves. Flash chromatography was performed on silica gel (Merck Kieselgel: Art9385). 5,7-Dichloropyrazolo[1,5-*a*]pyrimidine,[16] 2,4-dichloroquinoline,[17] and 4′-(bromomethyl)-1,1′-biphenyl-2-carbonitrile[18] were prepared by literature methods. Zinc dust, $Pd(Ph_3P)_4$, $ZnCl_2$ in THF solution, methyl 4-(bromomethyl)benzoate, and *n*-butyllithium in *n*-hexane solution were purchased from Aldrich, Inc.

Preparation of Benzylic Zinc Bromide Stock Solution (6). A suspension of zinc dust (1.634 g, 25 mmol) and 1,2-dibromoethane (87 μL, 1 mmol) in DMF (5 mL) was stirred for 10 min at 70 °C. After the mixture was cooled to room temperature, chlorotrimethylsilane (100 μL, 0.8 mmol) was added and stirred for 30 min at room temperature. To this activated zinc dust was added dropwise methyl 4-(bromomethyl)benzoate (5.14 g, 22 mmol) in DMF (20 mL) over a period of 120 min at 0 °C. After 2 h of stirring at 0 °C, the total volume of this mixture was adjusted to 40 mL, which gave about 0.5 M stock solution of the zinc reagent. This stock solution was stable for a few weeks in the refrigerator under N_2 atmosphere. THF stock solution could be obtained by the similar procedure.

General Procedure for Coupling Reactions of 2,4-Dichloroquinoline (5) and Benzylic Zinc Bromide (6) in the Presence of Variety of Additives. LiCl as an additive: To the solution of **5** (199 mg, 1 mmol) and **6** (2.4 mL, 1.2 mmol) in DMF (5 mL) was added LiCl (85 mg, 2 mmol). After stirring 24 h at room temperature, the mixture was poured into saturated aqueous ammonium chloride and ice and extracted with three 30 mL portions of EtOAc. The combined extracts were washed with water (20 mL) and saturated brine (20 mL) and then dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (toluene: EtOAc = 20:1 as an eluent) to give 240 mg (77%) of **7** as white prisms: mp 137−138 °C; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 4.46 (s, 2H), 7.12 (s, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.54 (ddd, J = 1.4, 7.0, 8.3 Hz, 1H), 7.73 (ddd, J = 1.4, 7.0, 8.4 Hz, 1H), 7.92−8.07 (m, 4H); IR (Nujol): 2924, 2854, 1716, 1284 cm^{-1}. Anal. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; Cl, 11.37; N, 4.49. Found: C, 69.39; H, 4.66; Cl, 11.09; N, 4.52.

$Pd(Ph_3P)_4$ as an additive: A mixture of **5** (397 mg, 2 mmol), **6** (4.2 mL, 2.1 mmol), and $Pd(Ph_3P)_4$ (120 mg, 0.1 mmol) in THF (5 mL) was stirred for 2 h at 60 °C. The reaction mixture was worked up and purified by a similar procedure to that described in the preparation of **7** to give 249 mg (80%) of **8** as white crystals: mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 4.36 (s, 2H), 7.29 (s, 1H), 7.34 (d, J = 7.8 Hz, 2H), 7.61 (ddd, J = 1.0, 7.05, 8.4 Hz, 1H), 7.77 (ddd, J = 1.5, 7.05, 8.55 Hz, 1H), 8.00 (m, 2H), 8.09 (dd, J = 1.0, 8.4 Hz, 1H), 8.18 (dd, J = 1.5, 8.3 Hz, 1H); IR (Nujol): 3438, 1730, 1273 cm^{-1}. Anal. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; Cl, 11.37; N, 4.49. Found: C, 69.37; H, 4.54; Cl, 11.33; N, 4.51.

Coupling Reactions of 2,4-Dichloroquinoline and Phenyl Organometallics. Entry 1: To a solution of phenyl bromide (210 mL, 2.0 mmol) in THF (5 mL) at −78 °C was added dropwise *n*-butyllithium (2.1 mmol) in *n*-hexane. The resulting mixture was stirred for 0.5 h at −78 °C. Next, 2.1 mL of 1 M $ZnCl_2$ solution in THF was added to this mixture, and the reaction was stirred at −78 °C for another 1 h. **5** (300 mg, 1.5 mmol) and $Pd(Ph_3P)_4$ (87 mg, 0.075 mmol) were added to the mixture which was then stirred for 16 h at room temperature. The reaction mixture was worked up and purified by a similar procedure to that described in the preparation of **7** to give 337 mg (94%) of **9** as white crystals: mp 60−61 °C; ^{1}H NMR ($CDCl_3$) δ 7.47−7.63 (m, 3H), 7.61 (ddd, J = 1.6, 6.9, 8.4 Hz, 1H), 7.77 (ddd, J = 1.6, 6.9, 8.4 Hz, 1H), 7.97 (s, 1H), 8.11−8.25 (m, 4H); IR (Nujol): 2923, 1578, 1545, 1488 cm^{-1}. Anal. Calcd for $C_{15}H_{10}ClN$: C, 75.16; H, 4.20; Cl, 14.79; N, 5.84. Found: C, 75.11; H, 4.32; Cl, 14.66; N, 5.87. **Entry 2:** A solution of **5** (397 mg, 2 mmol), phenyltrimethyltin (390 mL, 2.1 mmol), and $Pd(Ph_3P)_4$ (120 mg, 0.01 mmol) in toluene (10 mL) was refluxed for 16 h. The reaction mixture was worked up and purified by a similar procedure to that described in the preparation of **7** to give **9** (378 mg, 79%). **Entry 3:** A solution of **5** (300 mg, 1.5 mmol), phenylboronic acid (220 mg, 1.8 mmol), Na_2CO_3 (335 mg, 3.16 mmol), and $Pd(Ph_3P)_4$ (120 mg, 0.01 mmol) in 7 mL of toluene and 2 mL of H_2O was refluxed for 16 h. The reaction mixture was worked up and purified by a similar procedure to that described in the preparation of **7** to give **9** (265 mg, 74%).

Methyl 4-(2-phenylquinolin-4yl)methylbenzoate (10). This compound was prepared from **7** according to the procedure described for the coupling reactions of 2,4-dichloroquinoline and phenylboronic acid. Colorless needles. Yield 95%. mp111−112 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 4.53 (s, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.42−7.54 (m, 4H), 7.63 (s, 1H), 7.68−7.73 (m, 1H), 7.93−8.00 (m, 3H), 8.08−8.12 (m, 2H), 8.20 (d, J = 8.1 Hz, 1H); IR (Nujol): 2951, 2923, 2854, 1714, 1594, 1282 cm^{-1}. Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.36; H, 5.55; N, 3.93.

5-Chloro-7-[[2′-cyanobiphenyl-4-yl]methyl]pyrazolo-[1,5-*a*]pyrimidine (11). To a suspension of zinc dust (activated with 1, 2-dibromoethane and chlorotrimethylsilane as same manner described in the preparation of **6**; 330 mg, 5 mmol) in DMF (1.0 mL) at 0 °C was added dropwise 4′-(bromomethyl)-1,1′-biphenyl-2-carbonitrile (1.02 g, 3.75 mmol) in DMF (5 mL) over a period of 30 min. The resulting mixture was stirred for 1 h at 0 °C and then left standing for 1 h at 0 °C. The supernatant was transferred to a solution of **3** (376 mg, 2.0 mmol) and LiCl (206 mg, 4.9 mmol) in DMF (2 mL) and stirred for 1 h at room temperature. The reaction mixture was worked up and purified by a similar procedure to that described in the preparation of **7** to give 360 mg (52%) of **11** as colorless prisms: mp 154−155 °C; ^{1}H NMR ($CDCl_3$) δ 4.56 (s, 2H), 6.49 (s, 1H), 6.68 (d, J = 2.4 Hz, 1H), 7.42−7.82 (m, 8H), 8.18 (d, J = 2.4 Hz, 1H); IR (Nujol): 2924, 2855, 2226, 1606, 1540 cm^{-1}. Anal. Calcd for $C_{20}H_{13}ClN_4$: C, 69.67; H, 3.80; Cl, 10.28; N, 16.25. Found: C, 69.68; H, 3.94; Cl, 10.14; N, 16.31.

5-Phenyl-7-[[2′-cyanobiphenyl-4-yl]methyl]pyrazolo-[1,5-*a*]pyrimidine (12). This compound was prepared from **5** according to the procedure described for the coupling reactions of 2,4-dichloroquinoline and phenylboronic acid. Colorless prisms. Yield 90%. mp 152−153 °C; ^{1}H NMR ($CDCl_3$) δ 4.64 (s, 2H), 6.78 (d, J = 2.4 Hz, 1H), 6.97 (s, 1H), 7.42−7.80 (m, 11H), 7.98−8.04 (m, 2H), 8.19 (d, J = 2.4 Hz, 1H); IR (Nujol): 2925, 2229, 1621, 1555 cm^{-1}. Anal. Calcd for

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$C_{26}H_{18}N_4$: C, 80.81; H, 4.69; N, 14.50. Found: C, 80.77; H, 4.80; N, 14.36.

7-Chloro-5-[[2′-cyanobiphenyl-4-yl]methyl]pyrazolo-[1,5-*a*]pyrimidine (13). A solution of **4** (3.0 mmol; prepared by the same method as described for the synthesis of **11**), **3** (452 mg, 2.4 mmol), and $Pd(Ph_3P)_4$ (110 mg, 0.1 mmol) in DMF (10 mL) was stirred for 4 h at 60 °C. The reaction mixture was worked up and purified by a similar procedure to that described in the preparation of **7** to give 430 mg (52%) of **13** as colorless prisms: mp 145−148 °C; ^{1}H NMR ($CDCl_3$) δ 4.23 (s, 2H), 6.76 (d, J = 2.2 Hz, 1H), 6.85 (s, 1H), 7.41−7.80 (m, 8H), 8.20 (d, J = 2.2 Hz, 1H); IR (Nujol): 3434, 2228, 1616 cm^{-1}. Anal. Calcd for $C_{20}H_{13}ClN_4$·0.1toluene: C, 70.23; H, 3.93; Cl, 10.01; N, 15.83. Found: C, 70.01; H, 4.14; Cl, 9.72; N, 15.61.

7-Phenyl-5-[[2′-cyanobiphenyl-4-yl]methyl]pyrazolo-[1,5-*a*]pyrimidine (14). This compound was prepared from **13** according to the procedure described for the coupling reactions of 2,4-dichloroquinoline and phenylboronic acid as colorless needles. Yield 77.3%. mp 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 4.28 (s, 2H), 6.73 (d, J = 2.4 Hz, 1H), 6.77 (s, 1H), 7.40−7.55 (m, 9H), 7.60−7.66 (m, 1H), 7.74−7.77 (m, 1H), 7.96−7.99 (m, 2H), 8.14 (d, J = 2.1 Hz, 1H); IR (Nujol): 2924, 2854, 2228, 1617, 1603 cm^{-1}. Anal. Calcd for $C_{26}H_{18}N_4$: C, 80.81; H, 4.69; N, 14.50. Found: C, 80.94; H, 4.97; N, 14.24.

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Supporting Information Available: ^{1}H NMR spectra of compounds **7** and **8**, including NOE spectra (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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