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Lithium-Mediated Zincation of Pyrazine, Pyridazine, Pyrimidine, and Quinoxaline

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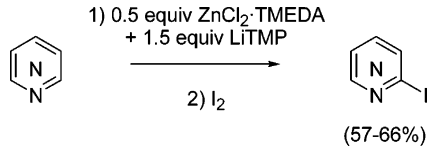

Deprotonation of pyrazine, pyridazine, pyrimidine, and quinoxaline using an in situ mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv) was studied. Pyrazine and pyrimidine were deprotonated in THF at room temperature, a result evidenced by trapping with I_2. The competitive formation of dimer observed in net hexane was reduced by using cosolvents (TMEDA or THF). Starting from quinoxaline, the dimer formation took place in THF also, and mixtures of mono- and diiodides were obtained whatever the solvent and conditions used. A similar competitive formation of a diiodide was noted with pyridazine; the use of THF at reflux temperature nevertheless afforded the 3-iodo derivative in good yield.

Substituted diazines are structural units present in many pharmaceutical synthetic intermediates and natural products.[1] Among the methods used to functionalize diazines,[1] deprotonation reactions using lithiated bases have been developed.[2] Metalation of diazines is a difficult challenge due to very facile nucleophilic addition reactions in relation with the low LUMOs energy levels of these substrates. Recourse to dialkylamides such as lithium diisopropylamide (LiDA) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP) generally allowed substituted diazines to be deprotonated. Concerning the parent diazines, metalation of pyrazine and pyridazine was found possible with an excess of LiTMP and very short reaction times at very low temperatures, while metalation of pyrimidine could only be accomplished using the in situ trapping technique.[3] More recently, Kondo described the unprecedented regioselective functionalization of pyridazine and pyrimidine at positions 4 and 5, respectively, using hindered phosphazene ^{t}Bu-P4 base and ZnI_2 as additive in toluene in the presence of a carbonylated compound as electrophile.[4] Knochel reported in 2006 the use of mixed lithium−magnesium amides such as (TMP)MgCl·LiCl for the deprotonation of diazines, a method still requiring low temperatures and not extendable to unsubstituted substrates.[5]

Kondo described in 1999 the deprotonation reactions of functionalized aromatics such as alkyl benzoates, ethyl thiophenecarboxylates, ethyl 2-furancarboxylate, pyridine, quinoline, and isoquinoline using a zincate, ^{t}Bu$_2$Zn(TMP)Li.[6] The reaction carried out in THF at rt proved to be chemoselective, but required 1 or 2 equiv of base, only TMP participating in the reaction.

Mulvey has reported since 2005 several examples of efficient deprotonation using lithium or sodium amido-zincates.[7] The term *alkali-metal-mediated zincation* has been introduced to depict these reactions since the reactivity ("synergy") exhibited by the zincates cannot be replicated by the homometallic compounds on their own.[8]

Herein, we describe the optimized deprotonation reaction of diazines using a zinc diamide−lithium amide mixture.

The addition of one molar equivalent (per lithium) of TMEDA or THF to a bulk nonpolar hydrocarbon in order to increase the opportunity for crystal growth proved to favor the deprotonation reactions of *N*,*N*-diisopropylcarboxamide[7c,d] and anisole[7g] using lithium amidozincates. We therefore decided to prepare a base from $ZnCl_2$·TMEDA,[9] much less hygroscopic than $ZnCl_2$, and to study its ability to deprotonate diazines. We chose to combine $ZnCl_2$·TMEDA with 3 equiv of LiTMP[10] and first turned to the deprotonation of pyrazine (**1**) (Table 1).

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(1) (a) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*, 1st ed.; Pergamon: New York, 1985. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH, New York, 2003; Chapter 6.

(2) (a) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187−304. (b) Godard, A.; Turck, A.; Plé, N.; Marsais, F.; Quéguiner, G. *Trends Heterocycl. Chem.* **1993**, *3*, 16−29. (c) Turck, A.; Plé, N.; Quéguiner, G. *Heterocycles* **1994**, *37*, 2149−2172. (d) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489−4505.

(3) Plé, N.; Turck, A.; Couture, K.; Quéguiner, G. *J. Org. Chem.* **1995**, *60*, 3781−3786.

(4) Imahori, T.; Kondo, Y. *J. Am. Chem. Soc.* **2003**, *125*, 8082−8083.

(5) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem.* **2006**, *118*, 3024−3027; *Angew. Chem., Int. Ed.* **2006**, *45*, 2958−2961. Concerning lithium magnesates in the diazine series obtained by iodine−metal exchange, see: (b) Buron, F.; Plé, N.; Turck, A.; Marsais, F. *Synlett* **2006**, 1586−1588.

(6) (a) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539−3540. See also: (b) Imahori, T.; Uchiyama, M.; Sakamoto, T.; Kondo, Y. *Chem. Commun.* **2001**, 2450−2451. (c) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514−8515. (d) Uchiyama, M.; Matsumoto, Y.; Nobuto, D.; Furuyama, T.; Yamaguchi, K.; Morokuma, K. *J. Am. Chem. Soc.* **2006**, *128*, 8748−8750. (e) Uchiyama, M.; Matsumoto, Y.; Usui, S.; Hashimoto, Y.; Morokuma, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 926−929.

(7) (a) Barley, H. R. L.; Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E. *Angew. Chem.* **2005**, *117*, 6172−6175; *Angew. Chem., Int. Ed.* **2005**, *44*, 6018−6021. (b) Andrikopoulos, P. C.; Armstrong, D. R.; Barley, H. R. L.; Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E. *J. Am. Chem. Soc.* **2005**, *127*, 6184−6185. (c) Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem.* **2006**, *118*, 2430−2434; *Angew. Chem., Int. Ed.* **2006**, *45*, 2370−2374. (d) Clegg, W.; Dale, S. H.; Harrington, R. W.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem.* **2006**, *118*, 2434−2437; *Angew. Chem., Int. Ed.* **2006**, *45*, 2374−2377. (e) Armstrong, D. R.; Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem.* **2006**, *118*, 3859−3862; *Angew. Chem., Int. Ed.* **2006**, *45*, 3775−3778. (f) Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E.; O'Hara, C. T. *Angew. Chem.* **2006**, *118*, 6698−6700; *Angew. Chem., Int. Ed.* **2006**, *45*, 6548−6550. (g) Clegg, W.; Dale, S. H.; Drummond, A. M.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *J. Am. Chem. Soc.* **2006**, *128*, 7434−7435. (h) Armstrong, D. R.; Clegg, W.; Dale, S. H.; Graham, D. V.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E. *Chem. Commun.* **2007**, 598−600.

(8) For reviews, see: (a) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060−1075. (b) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem.* **2007**, *119*, 3876−3899; *Angew. Chem., Int. Ed.* **2007**, *46*, 3802−3824.

(9) Concerning the synthesis of a lithium zincate from $ZnCl_2$·TMEDA, see: Kjonaas, R. A.; Hoffer, R. K. *J. Org. Chem.* **1988**, *53*, 4133−4135.

(10) In the previously described bases of Kondo's type, Zn is surrounded by two *tert*-butyls and one TMP. We thought deprotonation of diazines, which are prone to nucleophilic addition, would be more likely if the use of alkyls was avoided.

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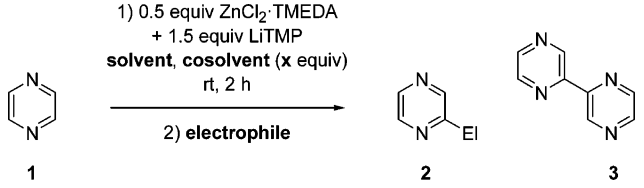
TABLE 1. Deprotonation of Pyrazine (1) Using an in Situ Prepared Mixture of $ZnCl_2$·TMEDA (0.5 Equiv) and LiTMP (1.5 Equiv)



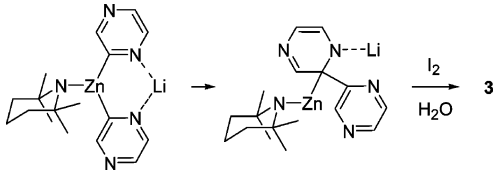
1 2 3

entry	solvent	cosolvent (equiv)	electrophile, El	**1**/**2**/**3** ratio[a]	compound (yield %)
1	THF	–	I_2, I	8/91/1	**2a** (59[b] [44[c]])
2	hexane	–	I_2, I	8/67/25	–
3	hexane	TMEDA (5)	I_2, I	3/96/1	–
4	hexane	THF (10)	I_2, I	2/97/1	–
5	THF	TMEDA (5)	I_2, I	2/97/1	**2a** (46[b])
6	THF	–	$ClPPh_2$, $P(O)Ph_2$	13/86/1	**2b** (52)

[a] Determined by ^1H NMR spectroscopy. [b] Decomposition of compound **2a** observed at rt. [c] Using 4 equiv of LiTMP, −75 °C, 6 min.[3]

The first experiment was carried out with 0.5 equiv of $ZnCl_2$·TMEDA and 1.5 equiv of LiTMP in THF at rt. Trapping with iodine after 2 h afforded the expected iodide **2a** in 59% yield (entry 1). The observation by Mulvey of a positive effect of a stoichiometric amount of TMEDA on the efficiency of deprotonations using lithium zincates in hexane[7c,d,g] led us to substitute THF by hexane. Under the same reaction conditions, the dimer **3** was identified together with the iodide **2a** by NMR analysis of the crude (entry 2). Thus, deprotonation occurred but was probably followed either by reaction of the zincated pyrazine with the pyrazine starting material or by 1,2-migration[11] of the pyrazyl group as depicted in Scheme 1. By adding 5 additional equiv of TMEDA (entry 3) or 10 equiv of THF (entry 4) to hexane,[12] the dimer **3** formation was lowered. A similar conversion was noted adding TMEDA to THF,[13] but the iodide **2a** was isolated in a moderate 46% yield (entry 5). With the use of chlorodiphenylphosphine as electrophile and THF without cosolvent, the phosphine oxide[14] **2b** was obtained in 52% yield (entry 6).

SCHEME 1. Proposed Pathway for the Formation of 3



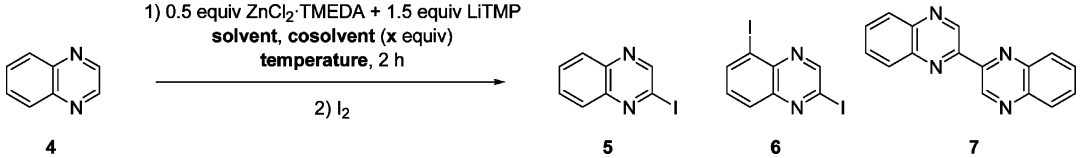
The degradation of the pyrazylzincate was not observed in THF at rt after 2 h,[15] while lithiopyrazine decomposes rapidly at −75 °C.[3] In addition, 4 equiv of LiTMP were necessary with the previously reported procedure to give a 44% yield of **2a**,[3] against 0.5 equiv of $ZnCl_2$·TMEDA and 1.5 equiv of LiTMP with our method to provide **2a** in 59% yield. The reason why the dimer **3** forms more easily when hexane is used instead of THF could be linked to stronger interactions between the pyrazine nitrogen and lithium in the absence of chelating solvent, activating the diazine ring for nucleophilic addition. Such interactions could be reduced using 5 additional equiv of TMEDA or 10 equiv of THF.

When the deprotonation of pyrazine (**1**) was conducted in hexane, the dimer **3** was identified along with the expected iodide **2a**. Starting from quinoxaline (**4**) (Table 2), the formation of a dimer (compound **7**) was also observed at rt (entry 1) or under reflux (entry 2) but, more importantly, both the monoiodide **5** and the diiodide **6** were obtained after trapping with iodine. This result was not significantly modified in the presence of 5 additional equiv of TMEDA (entry 3) or 10 equiv of THF (entry 4). Using bulk THF instead of hexane, the formation of the iodo derivatives **5** and **6** was favored (entries 5−7) with yields of 25 and 17%, respectively, under reflux (entry 6).

The formation of dizincated arenes has been described recently by deprotonation using a zincate: naphthalene was dideprotonated at both the 2 and 6 positions,[7f] and benzene at both the 1 and 4 positions,[7h] when treated with $^tBu_2Zn$(TMP)-Na·TMEDA in hexane. Even if dimetalated compounds such as 1,3- and 1,4-phenylenedisodiums, 2,5-furandiyldisodium, 2,5-furandiyldilithium, 2,5-thiophenediyldisodium, and 4,6-dibenzofurandiyldisodium have been evidenced, the generation of dideprotonated species is generally precluded by using a stoichiometric amount of base in a solvent of sufficient polarity such as THF.[16] Using polar additives or solvents with quinoxaline (**4**), the formation of the diiodide **6** was still observed (albeit lowered). Nevertheless, when detected in polar solvents, the kinetically formed dilithio species revert to the thermodynamically more stable monometal species.[16] In contrast, the dizincated substrates are still present after long reaction times, a result that could be attributed to their relative stability compared to that of the corresponding bis(alkali metal) compounds.

We next turned to the deprotonation of pyridazine (**8**) (Table 3) and first used as a deprotonation procedure treatment with 0.5 equiv of $ZnCl_2$·TMEDA and 1.5 equiv of LiTMP in THF at rt for 2 h. Under these conditions, a mixture of the 3-iodo **9** and 4-iodo **10** derivatives was obtained after trapping with iodine (entry 1). Increasing the reaction temperature to reflux resulted in the concomitant formation of the diiodide **11**, which was identified by its ^1H NMR, ^{13}C NMR, and mass spectra (entry 2). Adding 5 equiv of TMEDA favored the formation of the 3-iodo isomer **9**, which was isolated in 66% yield (entry 3). Replacing THF with hexane resulted in low conversions and competitive formation of the compound **11** whether the reaction

TABLE 2. Deprotonation of Quinoxaline (4) Using an in Situ Prepared Mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv)

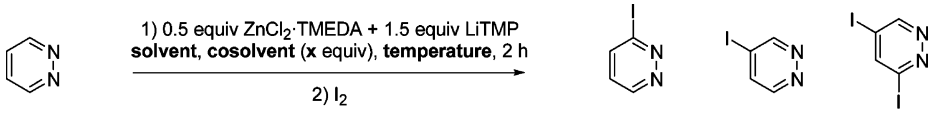


4 5 6 7

entry	solvent	cosolvent (equiv)	temp.	**4**/**5**/**6**/**7** ratio[a]	compound yield (%)
1	hexane	–	rt	27/38/25/10[b]	–
2	hexane	–	reflux	13/33/31/23[b]	**5** (20); **6** (4)
3	hexane	TMEDA (5)	reflux	29/19/18/34[b]	**7** (11)
4	hexane	THF (10)	reflux	19/43/22/16	–
5	THF	–	25 °C	9/58/18/15	–
6	THF	–	reflux	3/61/21/15[b]	**5** (25); **6** (17)
7	THF	TMEDA (5)	reflux	2/43/21/34[b]	–

[a] Determined by ^1H NMR spectroscopy. [b] Presence of numerous other products in the crude.

TABLE 3. Deprotonation of Pyridazine (8) Using an in Situ Prepared Mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv)



8 **9** **10** **11**

entry	solvent	cosolvent (equiv)	temp.	**8**/**9**/**10**/**11** ratio[a]	compound (yield %)
1	THF	–	rt	3/73/24/0	**9**, (– [16[b]])
2	THF	–	reflux	6/64/21/9	–
3	THF	TMEDA (5)	reflux	11/74/8/7	**9** (66)
4	hexane	–	rt	54/27/8/11	–
5	hexane	–	reflux	35/41/11/13	–
6	hexane	TMEDA (5)	reflux	17/58/11/14[c]	–
7	hexane	PMDTA (5)	reflux	24/65/11/0	–
8	hexane	THF (10)	reflux	5/83/12/0	**9** (30)

[a] Determined by ^{1}H NMR spectroscopy. [b] Using 4 equiv of LiTMP, −75 °C, 6 min.[3] [c] Traces of 3,6-diiodopyridazine (about 3%) were detected on the spectra of the crude mixture.

was conducted at rt (entry 4) or under reflux (entry 5), with (entry 6) or without TMEDA. The compound **11** was not detected, and better regioselectivities were observed by replacing TMEDA with PMDTA (entry 7) or THF (entry 8), but the iodide **9** was isolated in a moderate 30% yield using the latter.

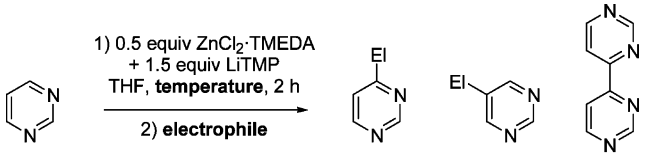
The degradation of the pyridazylzincate was not observed in THF or hexane after 2 h at reflux, with or without additives, while lithiopyridazine decomposes rapidly at −75 °C.[3] Our method gave the iodide **9** in a better yield than using LiTMP (66% yield after interception with iodine against 16% using the lithium amide).[3] LiTMP being more selective than the more hindered lithium zincate, the incomplete regioselectivity of the deprotonation could be in relation with the size of the deprotonating agent.[3] The formation of the diiodide **11** could be due to a competitive deprotonation of the iodide **9** or **10** during the addition of the THF iodine solution. Nevertheless, a faster addition of the electrophile solution not favoring the monoiodides formation,[17] the diiodide **11** could rather result from a dideprotonation, as noted with quinoxaline (**4**).

The deprotonation of pyrimidine (**12**) was finally investigated (Table 4). The reaction was performed in THF at temperatures ranging from 0 °C to reflux (entries 1−4). After trapping with iodine, mixtures of the 4-iodo **13a**, the 5-iodo **14a**, and the 4,4′-dimer **15** were obtained whatever the temperature. The 4,4′-dimer formation being minimal at 25 °C, a good 97% regioselectivity was observed for the iodide **13a**, which was isolated in 57% yield (entry 2). Using the same deprotonation conditions, the phosphine **13b** was produced in 42% yield after interception with chlorodiphenylphosphine (entry 5). As previously noted with pyrazine (**1**), the formation of dimer was favored in hexane.

Whereas 4-pyrimidyllithium could only be generated using the in situ trapping technique,[3] the pyrimidylzincate was accumulated in THF at 25 °C (4% of the 4,4′-dimer after 2 h).

In conclusion, pyrazine, pyridazine, and pyrimidine were deprotonated on treatment with 0.5 equiv of $ZnCl_2$·TMEDA and 1.5 equiv of LiTMP in THF at rt or reflux, a result evidenced by trapping with I_2. Since $(TMP)_2Zn$ and LiTMP give lower conversion and degradation, respectively, we assumed that the deprotonating species was $(TMP)_3ZnLi$·TMEDA.[18] The competitive formation of dimers sometimes observed in net hexane (e.g., with pyrazine) was reduced by adding cosolvents (TMEDA or THF). Competitive formation of diiodides was noted with quinoxaline and pyridazine.

TABLE 4. Deprotonation of Pyrimidine (12) Using an in Situ Prepared Mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv)



12 **13** **14** **15**

entry	temp. (°C)	electrophile, El	**12**/**13**/**14**/**15** ratio[a]	compound (yield %)
1	0	I_2, I	4/75/6/15	–
2	25	I_2, I	0/93/3/4	**13a** (57 [0[b]])
3	40	I_2, I	0/91/4/5	–
4	reflux	I_2, I	0/71/8/21	**13a** (16)
5	25	$ClPPh_2$, PPh_2	0/75/0/15	**13b** (42)

[a] Determined by ^{1}H NMR spectroscopy. [b] Using LiTMP, whatever the temperature.

The main advantage of this methodology is the relative stability of the organometallic species formed: hydrogen−lithium exchange has to be performed at low temperature (−75 °C) in order to prevent side nucleophilic addition while hydrogen−zinc exchange proceeds at rt or more.

Experimental Section

Deprotonation of Pyrazine. To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.53 mL, 3.0 mmol) in THF (3 mL) were successively added BuLi (1.6 M hexanes solution, 3.0 mmol) and $ZnCl_2$·TMEDA[19] (0.25 g, 1.0 mmol). The mixture was stirred for 10 min at 0 °C before introduction of pyrazine (0.16 g, 2.0 mmol). After 2 h at room temperature, a solution of I_2 (0.76 g, 3.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of $Na_2S_2O_3$ (2 mL) and extraction with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

Iodopyrazine (2a). 2a was obtained according to the pyrazine deprotonation procedure and isolated after purification by flash chromatography on silica gel (CH_2Cl_2) as a pale-yellow powder

(11) Concerning 1,2-migration of zincates, see: Harada, T.; Chiba, M.; Oku, A. *J. Org. Chem.* **1999**, *64*, 8210−8213.

(12) Seggio, A.; Lannou, M.-I.; Chevallier, F.; Nobuto, D.; Uchiyama, M.; Golhen, S.; Roisnel, T.; Mongin, F. In press.

(13) The effect of TMEDA is generally weakened when used in THF: Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448−454.

(14) The oxidation of (diphenylphosphino)pyrazine could not be avoided.

(15) The ^{1}H NMR spectra of the crude only shows the presence of residual pyrazine.

(16) Schlosser, M. *Angew. Chem.* **2005**, *117*, 380−398; *Angew. Chem., Int. Ed.* **2005**, *44*, 376−393.

(17) The reverse addition was not attempted, due to the low solubility of the pyridazylzincate.

(18) The in situ prepared mixture of $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv) in THF was analyzed by NMR: the ^{13}C spectra showed that the main species in solution are LiTMP and $(TMP)_2Zn$.

(19) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679−682.

(0.24 g, 59%); mp 90 °C dec. ^{1}H NMR ($CDCl_3$): δ 8.38 (dd, 1H, J = 1.3 and 2.8), 8.50 (d, 1H, J = 2.8), 8.86 (d, 1H, J = 1.3). These values are consistent with the literature.[3] ^{13}C NMR ($CDCl_3$): δ 118.6, 143.1, 146.0, 153.4. HRMS: calcd for $C_4H_3N_2I$ ($M^{+\bullet}$) 205.9341, found 205.9355.

Bipyrazine (3). 3 was obtained according to the pyrazine deprotonation procedure and identified in the crude mixture. ^{1}H NMR ($CDCl_3$): δ 8.56 (s, 4H), 9.46 (s, 2H). These values are consistent with the literature.[20] HRMS: calcd for $C_8H_6N_4$ ($M^{+\bullet}$) 158.0592, found 158.0590.

(Diphenylphosphino)pyrazine Oxide (2b). 2b was obtained according to the pyrazine deprotonation procedure using $ClPPh_2$ (0.54 mL, 3.0 mmol) instead of I_2 as electrophile. The product was isolated after purification by flash chromatography on silica gel (pentane/EtOAc, 70:30 to 0:100) as a white powder (0.29 g, 55%); mp 120 °C. ^{1}H NMR ($CDCl_3$): δ 7.49 (m, 6H), 7.86 (dd, 4H, J = 7.8 and 11.8), 8.69 (m, 2H), 9.40 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 128.7 (d, 4C, J_P = 12), 131.2 (d, 2C, J_P = 105), 132.1 (d, 4C, J_P = 10), 132.5 (d, 2C, J_P = 3), 144.9 (d, J_P = 15), 146.4 (d, J_P = 3), 148.7 (d, J_P = 20), 152.4 (d, J_P = 125). ^{31}P NMR ($CDCl_3$): δ 20.1. HRMS: calcd for $C_{16}H_{13}N_2OP$ ($M^{+\bullet}$) 280.0765, found 280.0753.

Deprotonation of Quinoxaline. To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.53 mL, 3.0 mmol) in THF (3 mL) were successively added BuLi (1.6 M hexanes solution, 3.0 mmol) and $ZnCl_2$·TMEDA[19] (0.25 g, 1.0 mmol). The mixture was stirred for 10 min at 0 °C before introduction of quinoxaline (0.26 g, 2.0 mmol). After 2 h at reflux, a solution of I_2 (0.76 g, 3.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of $Na_2S_2O_3$ (2 mL) and extraction with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

2-Iodoquinoxaline (5). 5 was obtained according to the quinoxaline deprotonation procedure and isolated after purification by flash chromatography on silica gel (heptane/CH_2Cl_2, 50:50 to 0:100) as a pale-yellow powder (0.13 g, 25%). mp 101 °C. ^{1}H NMR ($CDCl_3$): δ 7.8 (m, 2H), 8.0 (m, 2H), 8.96 (s, 1H). These values are consistent with the literature.[21] ^{13}C NMR ($CDCl_3$): δ 118.2, 128.9, 129.6, 130.5, 131.0, 141.1, 144.9, 152.2. HRMS: calcd for $C_8H_5N_2I$ ($M^{+\bullet}$) 255.9497, found 255.9495.

2,5-Diiodoquinoxaline (6). 6 was obtained according to the quinoxaline deprotonation procedure and isolated after purification by flash chromatography on silica gel (heptane/CH_2Cl_2, 50:50 to 0:100) as a pale-yellow powder (0.13 g, 17%); mp 199−200 °C. ^{1}H NMR ($CDCl_3$): δ 7.50 (dd, 1H, J = 7.3 and 8.3), 8.04 (dd, 1H, J = 1.2 and 8.3), 8.37 (dd, 1H, J = 7.3 and 1.2), 9.02 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 102.1, 119.3, 129.8, 132.1, 141.0, 141.3, 145.1, 153.2. HRMS: calcd for $C_8H_4N_2I_2$ ($M^{+\bullet}$) 381.8464, found 381.8447. The structure of **6** was elucidated on the basis of HMBC NMR spectroscopy.

2,2′-Biquinoxaline (7). 7 was obtained according to the quinoxaline deprotonation procedure and identified in the crude mixture. ^{1}H NMR ($CDCl_3$): δ 7.85 (m, 4H), 8.24 (m, 4H), 10.10 (s, 2H). These values are consistent with the literature.[22] HRMS: calcd for $C_{16}H_{10}N_4$ ($M^{+\bullet}$) 258.0905, found 258.0910.

Deprotonation of Pyridazine. To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.53 mL, 3.0 mmol) in THF (3 mL) were successively added BuLi (1.6 M hexanes solution, 3.0 mmol), $ZnCl_2$·TMEDA[19] (0.25 g, 1.0 mmol), and TMEDA (1.5 mL, 10 mmol). The mixture was stirred for 10 min at 0 °C before introduction of pyridazine (0.16 g, 2.0 mmol). After 2 h at reflux, a solution of I_2 (0.76 g, 3.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of $Na_2S_2O_3$ (2 mL) and extraction with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

3-Iodopyridazine (9). 9 was obtained according to the pyridazine deprotonation procedure and isolated after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 100:0 to 70:30) as a yellow powder (0.27 g, 66%); mp 130 °C dec. ^{1}H NMR ($CDCl_3$): δ 7.16 (dd, 1H, J = 8.6 and 5.0), 7.88 (dd, 1H, J = 8.6 and 1.2), 9.14 (dd, 1H, J = 1.2 and 5.0). These values are consistent with the literature.[3] ^{13}C NMR ($CDCl_3$): δ 125.8, 127.3, 137.4, 150.6. HRMS: calcd for $C_4H_3N_2I$ ($M^{+\bullet}$) 205.9341, found 205.9335.

4-Iodopyridazine (10). 10 was obtained according to the pyridazine deprotonation procedure and identified in the crude mixture. ^{1}H NMR ($CDCl_3$): δ 8.20 (dd, 1H, J = 5.4, 2.2), 8.92 (d, 1H, J = 5.4), 9.49 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 101.1, 135.6, 151.2, 158.4.

3,5-Diiodopyridazine (11). 11 was obtained according to the pyridazine deprotonation procedure and identified in the crude mixture. ^{1}H NMR ($CDCl_3$): δ 8.31 (d, 1H, J = 1.7), 9.35 (d, 1H, J = 1.6). ^{13}C NMR ($CDCl_3$): δ 100.8, 124.3, 145.1, 157.1. HRMS: calcd for $C_4H_2N_2I_2$ ($M^{+\bullet}$) 331.8307, found 331.8298.

Deprotonation of Pyrimidine. To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.53 mL, 3.0 mmol) in THF (3 mL) were successively added BuLi (1.6 M hexanes solution, 3.0 mmol) and $ZnCl_2$·TMEDA[19] (0.25 g, 1.0 mmol). The mixture was stirred for 10 min at 0 °C before introduction of pyrimidine (0.16 g, 2.0 mmol). After 2 h at 25 °C, a solution of I_2 (0.76 g, 3.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aq saturated solution of $Na_2S_2O_3$ (2 mL) and extraction with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

4-Iodopyrimidine (13a). 13a was obtained according to the pyrimidine deprotonation procedure and isolated after purification by flash chromatography on silica gel (CH_2Cl_2/EtOAc, 100:0 to 80:20) as a yellow powder (0.23 g, 57%); mp 112 °C dec. ^{1}H NMR ($CDCl_3$): δ 7.76 (dd, 1H, J = 1.3 and 5.3), 8.21 (d, 1H, J = 5.3), 8.83 (d, 1H, J = 1.3). ^{13}C NMR ($CDCl_3$): δ 129.6, 133.1, 156.1, 158.6. HRMS: calcd for $C_4H_3IN_2$ ($M^{+\bullet}$) 205.9341, found 205.9335.

5-Iodopyrimidine (14a). 14a was obtained according to the pyrimidine deprotonation procedure and identified in the crude mixture. ^{1}H NMR ($CDCl_3$): δ 8.77 (s, 2H), 8.94 (s, 1H).

4,4′-Bipyrimidine (15). 15 was obtained according to the pyrimidine deprotonation procedure and identified in the crude mixture. ^{1}H NMR ($CDCl_3$): δ 8.44 (dd, 2H, J = 1.5 and 5.0), 8.97 (d, 2H, J = 5.0), 9.36 (d, 2H, J = 1.5). These values are consistent with the literature.[3,23] HRMS: calcd for $C_8H_6N_4$ ($M^{+\bullet}$) 158.0592, found 158.0575.

4-(Diphenylphosphino)pyrimidine (13b). 13b was obtained according to the pyrimidine deprotonation procedure using $ClPPh_2$ (0.54 mL, 3.0 mmol) instead of I_2 as electrophile. The product was isolated after purification by flash chromatography on silica gel (heptane/EtOAc, 70:30 to 30:70) as a pale-yellow oil (0.22 g, 42%). ^{1}H NMR ($CDCl_3$): δ 7.02 (dd, 1H, J = 1.5 and 5.2), 7.41 (m, 10H), 8.53 (dd, 1H, J = 3.0 and 5.2), 9.22 (br dd, 1H, J = 1.5 and 3.0). ^{13}C NMR ($CDCl_3$): δ 124.4 (d, 2C, J_P = 12), 129.0 (d, 4C, J_P = 8), 129.9 (2C), 134.0 (d, J_P = 9), 134.6 (d, 4C, J_P = 20), 156.1, 158.3 (d, J_P = 9), 175.3 (d, J_P = 5). ^{31}P NMR ($CDCl_3$): δ −3.7. HRMS: calcd for $C_{16}H_{13}N_2P$ ($M^{+\bullet}$) 264.0816, found 264.0811.

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Supporting Information Available: General procedures and copies of the ^{1}H, ^{13}C, and ^{31}P NMR spectra of **2b**, **6**, **13a**, and **13b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Fort, Y.; Becker, S.; Caubère, P. *Tetrahedron* **1994**, *50*, 11893−11902.

(21) Sugimoto, O.; Mori, M.; Moriya, K.; Tanji, K.-I. *Helv. Chim. Acta* **2001**, *84*, 1112−1118.

(22) Sugimoto, O.; Sudo, M.; Tanji, K.-I. *Tetrahedron* **2001**, *57*, 2133−2138.

(23) Ioachim, E.; Medlycott, E. A.; Polson, M. I. J.; Hanan, G. S. *Eur. J. Org. Chem.* **2005**, 3775−3780.