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Phosphorodiamidate-Directed Metalation of *N*-Heterocycles using Mg- and Zn-TMP Bases

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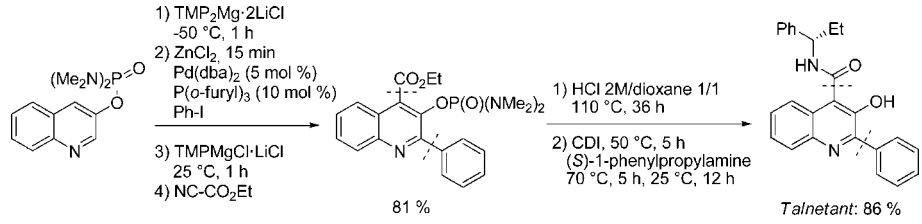
ABSTRACT



The strong directing ability of the *N,N,N′,N′*-tetramethyldiaminophosphorodiamidate group has been used to achieve selective metalations on various heterocycles such as pyridines, quinolines and quinoxalines with TMP-derived bases like TMPMgCl·LiCl, $TMP_2Mg·2LiCl$, and $TMP_2Zn·2MgCl_2·2LiCl$. This protocol was applied in the synthesis of etoricoxib, talnetant and a P-selectin inhibitor.

Heteroaromatics are important scaffolds in medicinal chemistry.[1] The skeletons of quinolines, pyridines, and quinoxalines are often found in pharmaceuticals such as the quinoline-based NK_3 receptor antagonist talnetant[2] (**1**; GSK), the pyridine-based COX-2 inhibitor etoricoxib[3] (**2**; Arcoxia, Merck), or the quinoxaline-based tachykinin receptor antagonist[4] (**3**; Mitsubishi Tanabe Pharma; Figure 1). Lithiations and magnesiations of these scaffolds using either a halogen/metal exchange[5] or directed metalation[6] have been reported. Lithiations often suffer from a lack of selectivity even when carried out at low temperatures.[5b,6e] Recently,

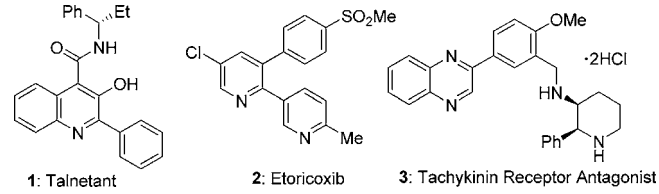


Figure 1. Pharmaceuticals containing a quinoline, pyridine, or quinoxaline skeleton.

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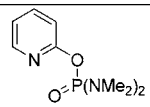
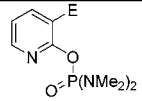
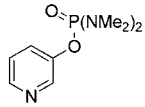
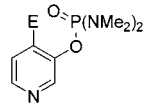
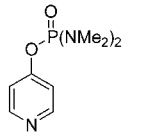
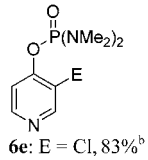
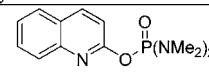
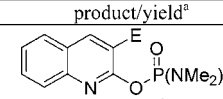
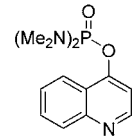
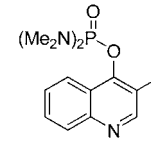
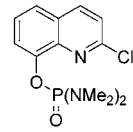
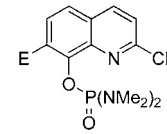
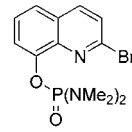
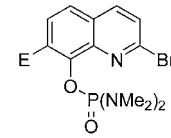
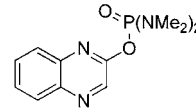
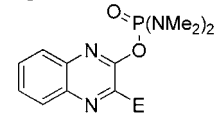
we have reported that the use of TMP (2,2,6,6-tetramethylpiperidyl)-derived bases allows the efficient magnesiation[7] or zincation[8] of functionalized aromatics and heteroaromatics. We have also reported that the use of a *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidate group as DMG (directed-metalation group)[9] allows fast and selective magnesiations of aromatics with unusual regioselectivity.[10] Herein, we report metalations of pyridines, quinolines, and quinoxalines performed with TMPMgCl·LiCl (**4a**), TMP_2Mg·2LiCl (**4b**), and TMP_2Zn·2$MgCl_2$·2LiCl (**4c**) using the $P(O)(NMe_2)_2$ group as DMG. Thus, the phosphorodiamidate **5a** (derived from 2-pyridinol) reacted with TMPMgCl·LiCl at 0 °C within 1 h and gave exclusively the 3-magnesiated heterocycle which reacted after transmetalation with $ZnCl_2$ via Negishi cross-coupling reaction with 1-bromo-4-(methylthio)benzene in the presence of $Pd_2(dba)_3$ (1 mol %) and RuPHOS (2 mol %),[11] giving the biaryl **6a** in 74% yield (Table 1, entry 1). The phosphorodiamidate **5b** prepared from 3-hydroxypyridine was best metalated at 25 °C using TMP_2Zn·2$MgCl_2$·2LiCl (**4c**). Deprotonations with TMPMgCl·LiCl (**4a**) or TMP_2Mg·2LiCl (**4b**) resulted in lower yields, even when the metalations were carried out at low temperatures (−20 to −50 °C). Thus, the pyridine **5b** was zincated selectively in position 4 at 25 °C within 1 h. The resulting zinc reagent was quenched via Negishi reaction using either 4-iodophenyl triflate or 4-chloroiodobenzene with a Pd catalyst ($Pd(dba)_2$ (5 mol %), P(2-furyl)$_3$ (10 mol %)),[14] yielding the arylated pyridines **6b** and **6c** in 79−88% yield (entries 2 and 3). An allylation of the zinc reagent was achieved with 3-bromo-2-methylpropene in the presence of CuCN·2LiCl[12] (10 mol %) furnishing the allylated pyridine **6d** in 74% yield (entry 4). Moreover, functionalization in position 3 was achieved after metalation of the phosphorodiamidate **5c** using TMPMgCl·LiCl (**4a**) (0 °C, 1 h). After addition of 1,1,2-trichlorotrifluoroethane, the desired 3-chloropyridine **6e** was isolated in 83% yield (entry 5). The addition of *S*-methyl methanesulfonothioate gave the thioether **6f** in 88% yield (entry 6). Furthermore, the phosphorodiamidate **7a** derived from 2-hydroxyquinoline was magnesiated regioselectively at position 3 and then thioethylated with $EtSSO_2Ph$[13] yielding the thioether **8a** in 85% yield (Table 2, entry 1). Remarkably,

Table 1. Pyridines of Type **6** Obtained after Metalation with TMPMgCl·LiCl (**4a**) or TMP_2Zn·2$MgCl_2$·2LiCl (**4c**) and Subsequent Quenching with an Electrophile

entry	substrate	electrophile	product/yield[a]
1	 **5a**	$pMeSC_6H_4Br$	 **6a**: E = $pMeSC_6H_4$, 74%[b, d]
2	 **5b**	$pCF_3SO_2OC_6H_4I$	 **6b**: E = $pCF_3SO_2OC_6H_4$, 88%[c, e]
3	**5b**	$pClC_6H_4I$	**6c**: E = $pClC_6H_4$ 79%[c, e]
4	**5b**	CH_2=C(CH_3)CH_2Br	**6d**: E = $CH_2C(CH_3)$=CH_2 74%[c, f]
5	 **5c**	$C_2Cl_3F_3$	 **6e**: E = Cl, 83%[b]
6	**5c**	$MeSSO_2Me$	**6f**: E = SMe, 88%[b]

[a] Yield of isolated, analytically pure product. [b] TMPMgCl·LiCl (1.5 equiv) was used (0 °C, 1 h). [c] TMP_2Zn·2$MgCl_2$·2LiCl (0.75 equiv) was used (25 °C, 1 h). [d] Obtained by Pd-catalyzed cross-coupling reaction after transmetalation with $ZnCl_2$ (1.6 equiv) using $Pd_2(dba)_3$ (1 mol %) and RuPHOS (2 mol %) as catalyst. [e] Obtained by Pd-catalyzed cross-coupling reaction using $Pd(dba)_2$ (5 mol %) and P(2-furyl)$_3$ (10 mol %) as catalyst. [f] A transmetalation with CuCN·2LiCl (10 mol %) was performed.

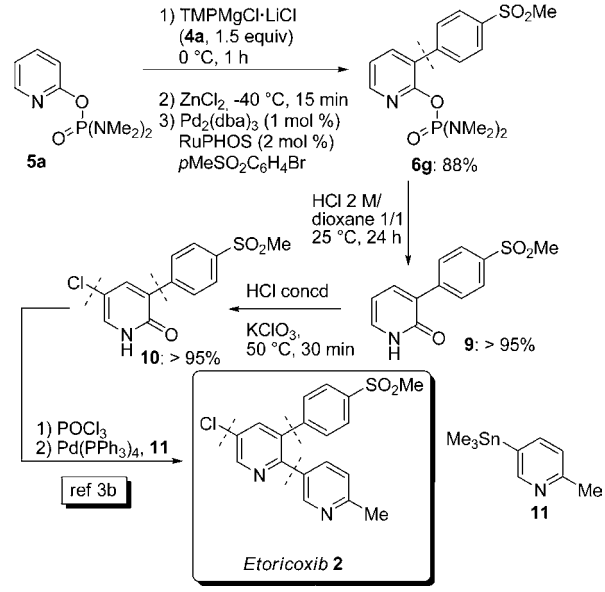
Table 2. Quinolines and Quinoxalines of Type **8** Obtained after Metalation with TMPMgCl·LiCl (**4a**) or TMP_2Mg·2LiCl (**4b**) and Subsequent Quenching with an Electrophile

entry	substrate	electrophile	product/yield[a]
1	 **7a**	$EtSSO_2Ph$	 **8a**: E = SEt, 85%[b]
2	 **7b**	*t*BuCOCl	 **8b**: E = C(O)*t*Bu, 62%[b, d]
3	**7b**	$pIC_6H_4CO_2Et$	**8c**: E = $pCO_2EtC_6H_4$, 83%[b, e]
4	 **7c**	CH_2=C(CH_3)CH_2Br	 **8d**: E = $CH_2C(CH_3)$=CH_2, 87%[b, d]
5	**7c**	$pClC_6H_4COCl$	**8e**: E = $pClC_6H_4C(O)$, 74%[b, d]
6	 **7d**	pIC_6H_4OTIPS	 **8f**: E = $pTIPSOC_6H_4$, 81%[b, e]
7	**7d**	NC-CO_2Et	**8g**: E = CO_2Et, 77%[b]
8	 **7e**	$pClC_6H_4I$	 **8h**: E = $pClC_6H_4$, 78%[c, e]
9	**7e**	$pIC_6H_4CO_2Et$	**8i**: E = $pCO_2EtC_6H_4$, 79%[c, e]
10	**7e**	CH_2=C(CH_3)CH_2Br	**8j**: E = $CH_2C(CH_3)$=CH_2, 71%[c, d]

[a] Yield of isolated, analytically pure product. [b] TMPMgCl·LiCl (1.5 equiv) was used (0 °C, 1 h). [c] TMP_2Mg·2LiCl (1.5 equiv) was used (−30 °C, 1.5 h). [d] A transmetalation with CuCN·2LiCl (10 mol %) was performed after transmetalation with $ZnCl_2$ (1.6 equiv). [e] Obtained by Pd-catalyzed cross-coupling reaction after transmetalation with $ZnCl_2$ (1.6 equiv) using $Pd(dba)_2$ (5 mol %) and P(2-furyl)$_3$ (10 mol %) as catalyst.

magnesiations at the 3 position of the quinoline proceed *without* protection of the kinetically more favored C2 position. Thus, the quinoline **7b** smoothly reacted with TMPMgCl·LiCl (**4a**) at 0 °C within 1 h. The corresponding magnesium reagent was then transmetalated with $ZnCl_2$ and subsequently acylated with pivaloyl chloride in the presence of CuCN·2LiCl[12] (10 mol %) giving the heteroaromatic ketone **8b** in 62% yield (entry 2). A cross-coupling reaction of the Zn-reagent derived from **7b** with ethyl 4-iodobenzoate in the presence of a Pd-catalyst ($Pd(dba)_2$ (5 mol %), P(2-furyl)$_3$ (10 mol %)[14]) furnished the 3-arylated quinoline **8c** in 83% yield (entry 3). Moreover, the regioselective functionalization of the C7 position was possible using this protocol. Thus, the 2-chloroquinoline **7c** is readily magnesiated with TMPMgCl·LiCl (**4a**) at 0 °C within 1 h. A transmetalation with $ZnCl_2$ followed by the addition of methallyl bromide in the presence of CuCN·2LiCl[12] (10 mol %) led to the allylated quinoline **8d** in 87% yield (entry 4). The addition of 4-chlorobenzoyl chloride under the same conditions furnished the ketone **8e** in 74% yield (entry 5). The 2-bromoquinoline **7d** also underwent a smooth magnesiation at 0 °C with TMPMgCl·LiCl (**4a**). After transmetalation with $ZnCl_2$, a cross-coupling reaction with (4-iodophenoxy)(triisopropyl)silane in the presence of $Pd(dba)_2$ (5 mol %) and P(2-furyl)$_3$ (10 mol %)[14] led to the arylated bromoquinoline **8f** in 81% yield (entry 6). The introduction of an ethyl ester in position 7 was achieved by reacting the 7-magnesiated quinoline **7d** with NC−CO_2Et leading to the ester **8g** in 77% yield (entry 7). Magnesiations or lithiations on quinoxalines are often difficult to achieve as these systems are prone to undergo nucleophilic substitution reactions.[8a,15] However, quinoxaline **7e** bearing a phosphorodiamidate group as DMG was smoothly magnesiated with TMP_2Mg·2LiCl (**4b**) at −50 °C in 1.5 h without any dimerization side reaction. After a transmetalation with $ZnCl_2$ it underwent a Negishi cross-coupling in the presence of a $Pd(dba)_2$ (5 mol %) and P(2-furyl)$_3$ (10 mol %)[14] with either 4-chloroiodobenzene or ethyl 4-iodobenzoate leading to the 2-arylated quinoxalines **8h** and **8i** in up to 79% yield (entries 8 and 9). Treatment of the quinoxalylzinc reagent with methallyl bromide in the presence of CuCN·2LiCl[12] (10 mol %) furnished the allylated quinoxaline **8j** in 71% yield (entry 10).

Scheme 1. Synthesis of Etoricoxib



As an application, we have prepared etoricoxib (**2**), talnetant (**1**), and a P-selectin inhibitor[16] (**14**) (Schemes 1 and 2). For the preparation of etoricoxib (**2**), a phosphorodiamidate DMG group was first attached at 2-pyridinol leading to **5a** in 90% yield.[10] In a second step, **5a** was selectively metalated in the 3-position using TMPMgCl·LiCl (**4a**; 1.5 equiv, 0 °C, 1 h).[17] After Zn-transmetalation, a subsequent cross-coupling reaction with 4-bromophenyl methyl sulfone in the presence of $Pd_2(dba)_3$ (1 mol %) and RuPHOS[11] (2 mol %) gave the arylated pyridine **6g** in 88% yield. Cleavage of the directing group with an HCl/dioxane mixture[18] (25 °C, 24 h) led to the pyridone **9** in 95% yield.

Chlorination at the C5 position was achieved by reacting **9** with $KClO_3$ in the presence of concd HCl[19] furnishing

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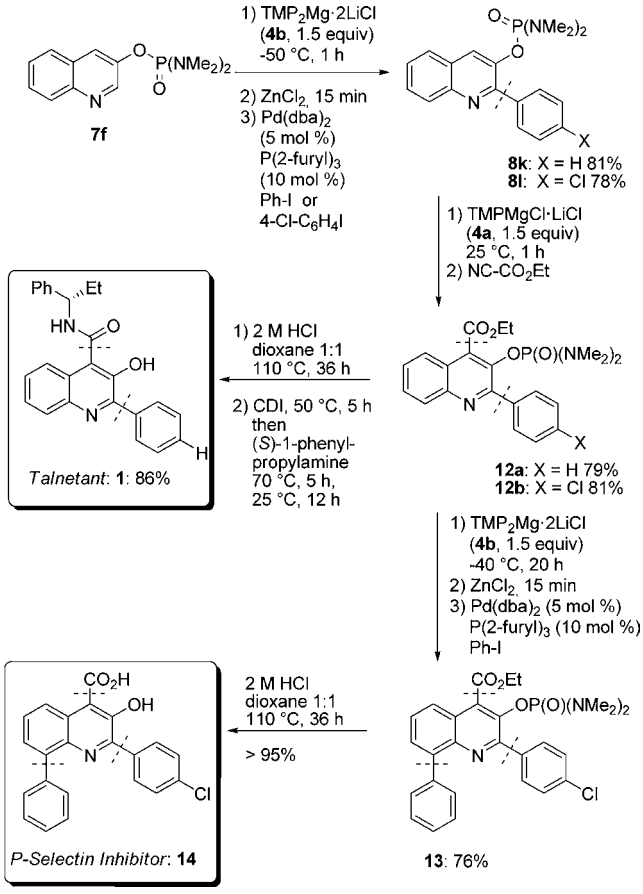
Scheme 2. Synthesis of Talnetant and a P-Selectin Inhibitor



quantitatively the 5-chloropyridine **10**. The final product was obtained using a literature procedure.[3b] Thus, the reaction of this pyridone with $POCl_3$ gave the corresponding 2,5-dichloropyridine which by Stille[11] reaction with the tin reagent **11** derived from 5-bromo-2-picoline furnished etoricoxib (**2**; Scheme 1). Similarly, we have prepared two pharmaceuticals bearing a quinoline salicylic acid spine. Thus, 3-hydroxyquinoline was first converted into the corresponding phosphorodiamidate **7f**.[10] The metalation with TMP_2Mg·2LiCl (**4b**) occurred selectively at the C2 position (−50 °C, 1 h). Transmetalation with $ZnCl_2$, followed by a cross-coupling reaction with either iodobenzene or 4-chloroiodobenzene in the presence of $Pd(dba)_2$ (5 mol %) and P(2-furyl)$_3$ (10 mol %),[14] furnished the quinolines **8k**,**l** in up to 81% yield. A subsequent metalation at the C4 position with TMPMgCl·LiCl (**4a**, 25 °C, 1 h) and a reaction with NC−CO_2Et gave the desired esters **12a**,**b** in 79−81% yield. Cleavage of the DMG and the ester is achieved by refluxing **12a** in a HCl/dioxane mixture[16] for 36 h. The reaction of the resulting acid with (*S*)-phenylpropylamine and CDI[20] furnished talnetant (**1**) in 86% yield (Scheme 2). Completing the synthesis of the P-selectin inhibitor **14** required a phenylation of the C8 position. Thus, the treatment of **12b** with TMP_2Mg·2LiCl (**4b**, −40 °C, 20 h)[7d] followed by a transmetalation ($ZnCl_2$) and a subsequent cross-coupling reaction with iodobenzene ($Pd(dba)_2$ (5 mol %), P(2-furyl)$_3$ (10 mol %)) yielded the highly functionalized quinoline **13** in 76% yield. Combined deprotection/saponification is achieved by refluxing **13** (2 M HCl; dioxane, 110 °C, 36 h) leading to the P-selectin inhibitor (**14**) quantitatively (Scheme 2).

In summary, we have shown that phosphorodiamidate-substituted *N*-heterocycles can be smoothly and regioselectively magnesiated or zincated with TMPMgCl·LiCl (**4a**), TMP_2Mg·2LiCl (**4b**), or TMP_2Zn·2$MgCl_2$·2LiCl (**4c**) and readily functionalized in positions difficult to substitute otherwise. This method was used to prepare three pharmaceutically relevant structures. Further studies on phosphate DMGs are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures, characterization data of all compounds, and X-ray data for **1**, **6b**, and **12a** is provided.[21] This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) CCDC 766951 (**1**), 766952 (**6b**), and 766953 (**12b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.