

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

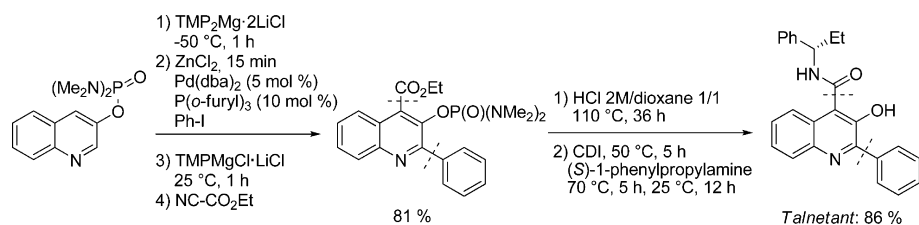
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ABSTRACT



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 $\text{TMPMgCl}\cdot\text{LiCl}$, $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$, and $\text{TMP}_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$. 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 NK₃ receptor antagonist talnetant² (**1**; GSK), the pyridine-based COX-2 inhibitor etoricoxib³ (**2**; Arcoxia, Merck), or the quinoxaline-based tachykinin receptor antagonist⁴ (**3**; Mitsubishi Tanabe Pharma; Figure 1). Lithiations and magnesiations of these scaffolds using either a

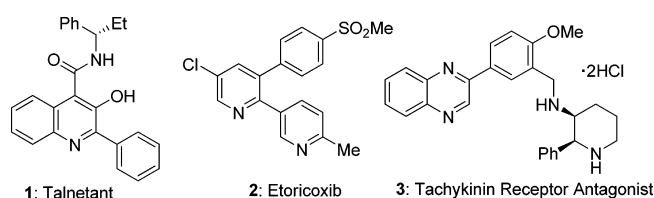


Figure 1. Pharmaceuticals containing a quinoline, pyridine, or quinoxaline skeleton.

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halogen/metal exchange⁵ or directed metalation⁶ have been reported. Lithiations often suffer from a lack of selectivity even when carried out at low temperatures.^{5b,6c} Recently,

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we have reported that the use of TMP (2,2,6,6-tetramethylpiperidyl)-derived bases allows the efficient magnesiation⁷ or zincation⁸ 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**), TMP₂Mg·2LiCl (**4b**), and TMP₂Zn·2MgCl₂·2LiCl (**4c**) using the P(O)(NMe₂)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 ZnCl₂ via Negishi cross-coupling reaction with 1-bromo-4-(methylthio)benzene in the presence of Pd₂(dba)₃ (1 mol %) and RuPHOS (2 mol %),¹¹ giving the biaryl **6a** in 74% yield (Table 1, entry 1). The

Table 1. Pyridines of Type **6** Obtained after Metalation with TMPMgCl·LiCl (**4a**) or TMP₂Zn·2MgCl₂·2LiCl (**4c**) and Subsequent Quenching with an Electrophile

entry	substrate	electrophile	product/yield ^a
1		<i>p</i> MeSC ₆ H ₄ Br	6a : E = <i>p</i> MeSC ₆ H ₄ , 74% ^{b, d}
2		<i>p</i> CF ₃ SO ₂ OC ₆ H ₄ I	6b : E = <i>p</i> CF ₃ SO ₂ OC ₆ H ₄ , 88% ^{c, e}
3		<i>p</i> ClC ₆ H ₄ I	6c : E = <i>p</i> ClC ₆ H ₄ , 79% ^{c, e}
4		CH ₂ =C(CH ₃)CH ₂ Br	6d : E = CH ₂ C(CH ₃)=CH ₂ , 74% ^{c, f}
5		C ₂ Cl ₃ F ₃	6e : E = Cl, 83% ^b
6		MeSSO ₂ Me	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 TMP₂Zn·2MgCl₂·2LiCl (0.75 equiv) was used (25 °C, 1 h). ^d Obtained by Pd-catalyzed cross-coupling reaction after transmetalation with ZnCl₂ (1.6 equiv) using Pd₂(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.

phosphorodiamidate **5b** prepared from 3-hydroxypyridine was best metalated at 25 °C using TMP₂Zn·2MgCl₂·2LiCl (**4c**). Deprotonations with TMPMgCl·LiCl (**4a**) or TMP₂Mg·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-chloriodobenzene 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·2LiCl¹² (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 EtSSO₂Ph¹³ yielding the thioether **8a** in 85% yield (Table 2, entry 1). Remarkably,

Table 2. Quinolines and Quinoxalines of Type **8** Obtained after Metalation with TMPMgCl·LiCl (**4a**) or TMP₂Mg·2LiCl (**4b**) and Subsequent Quenching with an Electrophile

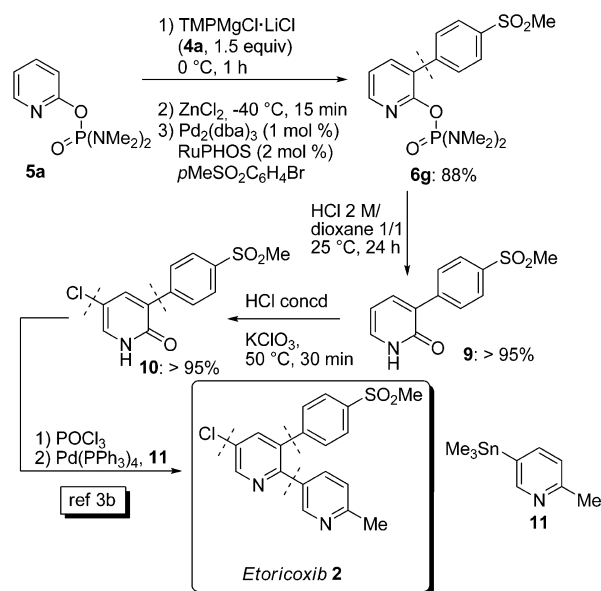
entry	substrate	electrophile	product/yield ^a
1		EtSSO ₂ Ph	8a : E = SEt, 85% ^b
2		<i>t</i> BuCOCl	8b : E = C(O) <i>t</i> Bu, 62% ^{b, d}
3		<i>p</i> IC ₆ H ₄ CO ₂ Et	8c : E = <i>p</i> CO ₂ EtC ₆ H ₄ , 83% ^{b, e}
4		CH ₂ =C(CH ₃)CH ₂ Br	8d : E = CH ₂ C(CH ₃)=CH ₂ , 87% ^{b, d}
5		<i>p</i> ClC ₆ H ₄ COCl	8e : E = <i>p</i> ClC ₆ H ₄ C(O), 74% ^{b, d}
6		<i>p</i> IC ₆ H ₄ OTIPS	8f : E = <i>p</i> TIPSOC ₆ H ₄ , 81% ^{b, e}
7		NC-CO ₂ Et	8g : E = CO ₂ Et, 77% ^b
8		<i>p</i> ClC ₆ H ₄ I	8h : E = <i>p</i> ClC ₆ H ₄ , 78% ^{c, e}
9		<i>p</i> IC ₆ H ₄ CO ₂ Et	8i : E = <i>p</i> CO ₂ EtC ₆ H ₄ , 79% ^{c, e}
10		CH ₂ =C(CH ₃)CH ₂ Br	8j : E = CH ₂ C(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 TMP₂Mg·2LiCl (1.5 equiv) was used (−30 °C, 1.5 h). ^d A transmetalation with CuCN·2LiCl (10 mol %) was performed after transmetalation with ZnCl₂ (1.6 equiv). ^e Obtained by Pd-catalyzed cross-coupling reaction after transmetalation with ZnCl₂ (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 $\text{TMPMgCl}\cdot\text{LiCl}$ (**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 $\text{CuCN}\cdot 2\text{LiCl}^{12}$ (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 ($\text{Pd}(\text{dba})_2$ (5 mol %), $\text{P}(2\text{-furyl})_3$ (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 $\text{TMPMgCl}\cdot\text{LiCl}$ (**4a**) at 0 °C within 1 h. A transmetalation with ZnCl_2 followed by the addition of methallyl bromide in the presence of $\text{CuCN}\cdot 2\text{LiCl}^{12}$ (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 $\text{TMPMgCl}\cdot\text{LiCl}$ (**4a**). After transmetalation with ZnCl_2 , a cross-coupling reaction with (4-iodophenoxy)(triisopropyl)silane in the presence of $\text{Pd}(\text{dba})_2$ (5 mol %) and $\text{P}(2\text{-furyl})_3$ (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 $\text{NC}-\text{CO}_2\text{Et}$ 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 $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ (**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 $\text{Pd}(\text{dba})_2$ (5 mol %) and $\text{P}(2\text{-furyl})_3$ (10 mol %)¹⁴ with either 4-chloriodobenzene 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 $\text{CuCN}\cdot 2\text{LiCl}^{12}$ (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 inhibitor¹⁶ (**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 $\text{TMPMgCl}\cdot\text{LiCl}$ (**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 $\text{Pd}_2(\text{dba})_3$ (1 mol %) and RuPHOS^{11} (2 mol %) gave the arylated pyridine **6g** in 88% yield. Cleavage of the directing group with an $\text{HCl}/\text{dioxane}$ mixture¹⁸ (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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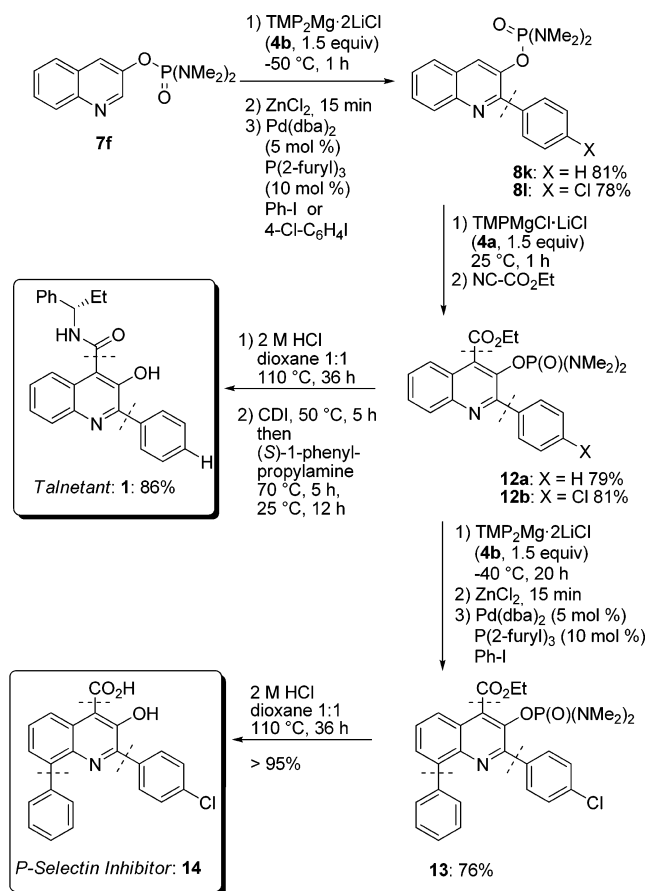
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Scheme 2. Synthesis of Talnetant and a P-Selectin Inhibitor

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 Stille¹¹ 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.

(20) CDI: *N,N'*-carbonyldiimidazole. See also: Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351.

(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.

Thus, 3-hydroxyquinoline was first converted into the corresponding phosphorodiamidate **7f**.¹⁰ The metalation with $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ (**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-chloriodobenzene in the presence of $\text{Pd}(\text{dba})_2$ (5 mol %) and $\text{P}(\text{2-furyl})_3$ (10 mol %),¹⁴ furnished the quinolines **8k,l** in up to 81% yield. A subsequent metalation at the C4 position with $\text{TMPMgCl}\cdot\text{LiCl}$ (**4a**, 25 °C, 1 h) and a reaction with $\text{NC-CO}_2\text{Et}$ 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 mixture¹⁶ for 36 h. The reaction of the resulting acid with (*S*)-phenylpropylamine and CDI²⁰ 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 $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ (**4b**, -40 °C, 20 h)^{7d} followed by a transmetalation (ZnCl_2) and a subsequent cross-coupling reaction with iodobenzene ($\text{Pd}(\text{dba})_2$ (5 mol %), $\text{P}(\text{2-furyl})_3$ (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 $\text{TMPMgCl}\cdot\text{LiCl}$ (**4a**), $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ (**4b**), or $\text{TMP}_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$ (**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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