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TMP–Magnesium and TMP–Zinc Bases for the Regioselective Metalation of the Cinnoline Scaffold

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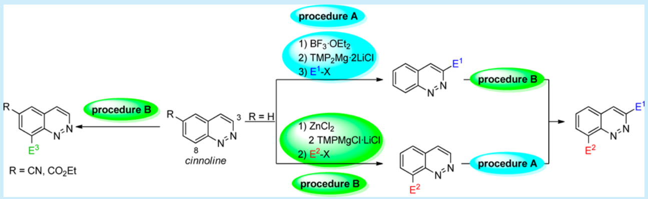
Supporting Information

ABSTRACT: A regioselective functionalization of cinnolines in positions 3 and 8 using metalations has been developed. This involves either the use of a frustrated Lewis pair consisting of $BF_3{\cdot}Et_2O$ and $TMP_2Mg{\cdot}2LiCl$ or the in situ generated base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$. Successive metalations allow the preparation of 3,8-disubstituted cinnolines. Various functionalizations by acylation, allylation, and cross-coupling reactions with aryl halides or alkenyl iodides were carried out successfully.



Due to their bioactivity, nitrogen-containing heterocycles are privileged structures in organic chemistry. They are present in numerous natural products, pharmaceuticals, and agrochemicals.[1] Among them, 1,2-benzodiazines or cinnolines have found various applications in materials and optics[2] and have important anticancer,[3] anti-inflammatory, and antifungal properties.[4] Consequently, the functionalization of these heterocyclic scaffolds is of special synthetic importance.[5]

The construction of the cinnoline (**1**) ring and especially its derivatives involves lengthy syntheses and the handling of diazonium species.[2,6] More recently, copper-catalyzed preparations of cinnolines have been reported by Willis[7] and Ge.[8]

There are only a few reports describing the direct metalation of cinnolines. Quéguiner showed that 3-, 4-chloro- and 3-, 4-methoxycinnolines can be lithiated with 2,2,6,6-tetramethylpiperidyllithium (TMP-Li) or lithium diisopropylamide (LDA).[9] The resulting heteroaryllithium species are sensitive intermediates that require handling at low temperature to avoid decomposition by competitive nucleophilic addition reactions.[10]

Recently, we have reported a range of sterically hindered TMP-magnesium bases such as $TMP_2Mg{\cdot}2LiCl$ (**2**) for the selective magnesiation of unsaturated substrates.[11] In addition, TMP-zinc bases, such as $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**3**),[12] were developed for the selective zincation of heterocycles.[13] Furthermore, we have shown that these bases are compatible with strong Lewis acids, such as $BF_3{\cdot}OEt_2$, forming frustrated Lewis pairs (FLP).[14] This considerably expands the synthetic scope of the original Zn- and Mg-TMP bases.

Herein, we report that the cinnoline scaffold can be regioselectively metalated using these new TMP-bases **2** and **3**. Preliminary results indicated that the reaction of cinnoline (**1**) with $TMP_2Mg{\cdot}2LiCl$ (**2**; 1.0 equiv, −78 °C, 10 min) leads to a preferential magnesiation at position 3 accompanied by substantial amounts of metalation at position 8 (ratio = 4:1). However, the addition of $BF_3{\cdot}OEt_2$ (1.1 equiv) to **1** prior to the magnesiation with $TMP_2Mg{\cdot}2LiCl$ (**2**; 1.1 equiv) leads to a highly selective metalation at position 3 (>98:2).

Thus, treatment of cinnoline (**1**) with $BF_3{\cdot}OEt_2$ (1.1 equiv, 0 °C, 15 min) and $TMP_2Mg{\cdot}2LiCl$ (**2**; 1.1 equiv, −78 °C, 10 min; procedure A) results in C(3)-selective magnesiation, and after transmetalation with $ZnCl_2$, a Pd-catalyzed Negishi cross-coupling[15] with ethyl 4-bromobenzoate (**4a**) furnishes the 3-substituted cinnoline **5a** in 74% yield (Table 1, entry 1). Other aryl bromides and iodides bearing electron-donating or electron-withdrawing substituents reacted as well, affording the 3-arylated cinnolines **5b**–**e** in 63–75% yield (entries 2–5).

The halogenation of the metalated cinnoline with either $(CBrCl_2)_2$ or iodine provides the bromocinnoline **5f** in 55% yield or the iodocinnoline **5g** in 51% yield (entries 6 and 7). Quenching the magnesiated species with $MeSO_2Me$ furnishes the thioether **5h** in 51% yield (entry 8). Additionally, after transmetalation with $ZnCl_2$,the corresponding zincated cinnoline is readily acylated in the presence of $CuCN{\cdot}2LiCl$[17] (1.1 equiv). The use of acyl chlorides bearing aryl, alkyl, or heteroaryl substituents affords the corresponding ketones **5i**–**k** in 53–58% yield (entries 9–11).

Complementary to the C(3)-selective magnesiation, a regioselective zincation of cinnoline (**1**) in position 8 can also be achieved. Thus, metalation of **1** with putative $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[18] (**3**; 1 equiv, 50 °C, 3 h) furnishes the 8-zincated cinnoline intermediate with high regioselectivity (95:5).[19] Subsequent cross-coupling with 4-iodoanisole (**4b**) leads to the 8-arylated cinnoline **6a** in 84% yield (Table 2, entry 1). Further examples illustrating this metalation sequence and cross-coupling with aryl iodides substituted in the *para*-, *meta*- and *ortho*-position proceeds in 60–70% yield (entries 2–4). A cross-coupling with (*E*)-iodooctene (**4l**) leads to the cinnoline **6e** in 65% yield

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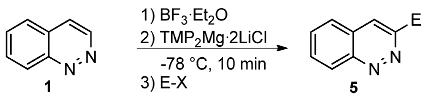
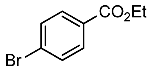
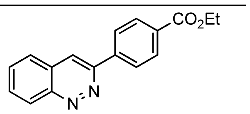
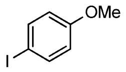
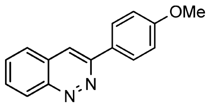
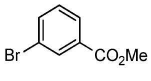
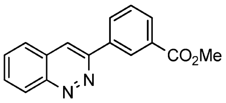
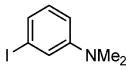
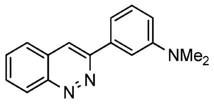
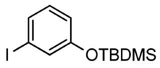
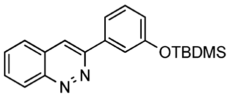
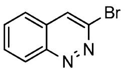
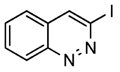
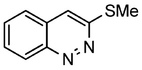
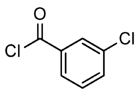
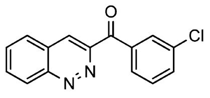
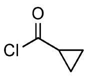
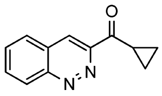
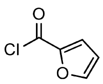
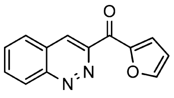
Table 1. Preparation of C(3)-Substituted Cinnolines by Magnesiation and Subsequent Quenching with Electrophiles

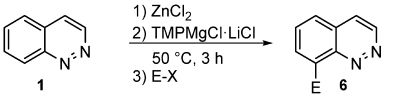


1 → **5**

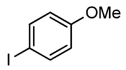
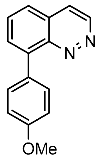
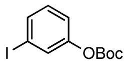
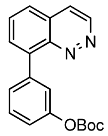
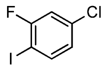
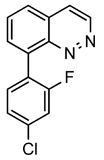
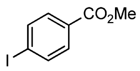
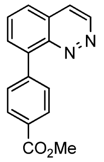
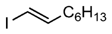
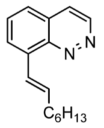
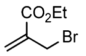
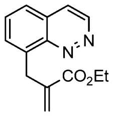
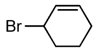
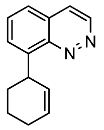
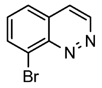
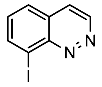
entry	electrophile	product, yield[a]
1	 **4a**	 **5a**: 74%[b]
2	 **4b**	 **5b**: 75%[c]
3	 **4c**	 **5c**: 69%[b]
4	 **4d**	 **5d**: 73%[c]
5	 **4e**	 **5e**: 63%[c]
6	$(CBrCl_2)_2$	 **5f**: 55%
7	I_2	 **5g**: 51%
8	$MeSO_2SMe$	 **5h**: 51%
9	 **4f**	 **5i**: 53%[d]
10	 **4g**	 **5j**: 58%[d]
11	 **4h**	 **5k**: 53%[d]

[a] Isolated yield of analytically pure product. [b] Pd-catalyzed cross-coupling using 5 mol % of $Pd(PPh_3)_4$ and 0.8 equiv of electrophile. [c] Pd-catalyzed cross-coupling using 2 mol % of $Pd(dba)_2$, 4 mol % of P(*o*-furyl)$_3$,[16] and 0.8 equiv of electrophile. [d] $CuCN \cdot 2LiCl$ (1.1 equiv) was used.

Table 2. 8-Substituted Products Obtained by Regioselective Zincation and Subsequent Reaction with Electrophiles

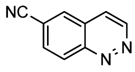
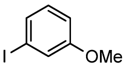
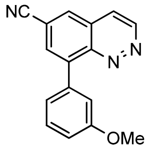
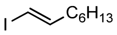
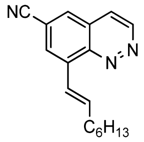
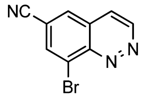
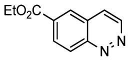
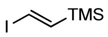
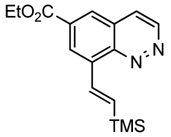
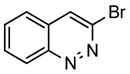
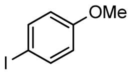
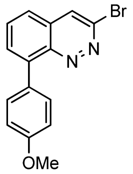
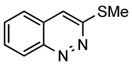
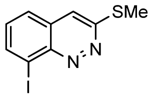
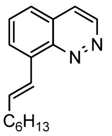
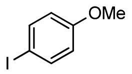
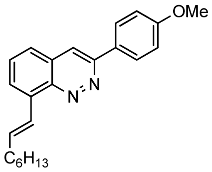


1 → **6**

entry	electrophile	product, yield[a]
1	 **4b**	 **6a**: 84%[b]
2	 **4i**	 **6b**: 70%[b]
3	 **4j**	 **6c**: 65%[b]
4	 **4k**	 **6d**: 60%[b]
5	 **4l**	 **6e**: 65%, *E*:*Z* > 99:1[b]
6	 **4m**	 **6f**: 61%[c]
7	 **4n**	 **6g**: 53%[c]
8	$Br_2 \cdot$dioxane	 **6h**: 46%
9	I_2	 **6i**: 52%

[a] Isolated yield of analytically pure product. [b] Pd-catalyzed cross-coupling using 2 mol % of $Pd(dba)_2$, 4 mol % of P(*o*-furyl)$_3$, and 0.8 equiv of electrophile. [c] $CuCN \cdot 2LiCl$ (1.1 equiv) was used.

Table 3. Preparation of Disubstituted Cinnoline Derivatives

entry	substrate	electrophile	product, yield[a]
1	 **7a**	 **4o**	 **8a**: 72%[b]
2	**7a**	 **4l**	 **8b**: 68%, *E*:*Z* > 99:1[b]
3	**7a**	Br_2·dioxane	 **8c**: 59%
4	 **7b**	 **4p**	 **8d**: 57%, *E*:*Z* = 99:1[c]
5	 **5f**	 **4b**	 **8e**: 65%[b]
6	 **5h**	I_2	 **8f**: 48%
7	 **6e**	 **4b**	 **8g**: 68%, *E*:*Z* > 99:1[b]

[a] Isolated yield of analytically pure product. [b] Pd-catalyzed cross-coupling using 2 mol % of Pd(dba)$_2$, 4 mol % of P(*o*-furyl)$_3$, and 0.8 equiv of electrophile. [c] Pd-catalyzed cross-coupling using 2 mol % of Pd(dba)$_2$, 4 mol % of P(*o*-furyl)$_3$, and 0.7 equiv of electrophile.

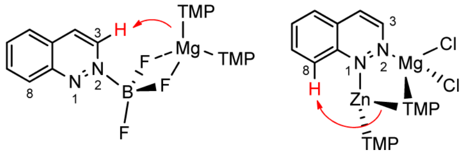
(*E*/ > 99:1; entry 5). Copper(I)-mediated allylation with ethyl 2-(bromomethyl)acrylate[20] (**4m**) or 3-bromocyclohexene (**4n**) affords the allylated cinnolines **6f–g** in 53–61% yield (entries 6 and 7). Bromination and iodination of the 8-zincated cinnoline furnishes the sensitive halogenated derivatives **6h–i** in 46–52% yield (entries 8 and 9).

Functionalized cinnolines bearing a cyano or an ester group such as **7a**,**b** can be readily prepared[6b] and zincated using in situ generated TMP$_2$Zn·2MgCl$_2$·2LiCl (**3**; 1.0 equiv, 25 °C, 1 h; procedure B). Using this procedure, 6-cyanocinnoline (**7a**) undergoes regioselective metalation at position 8. The resulting zinc species reacts with various electrophiles to afford the functionalized cinnoline derivatives **8a–c** in 59–72% yield (Table 3, entries 1–3). The mild metalation conditions also tolerate the presence of an ester group in substrate **7b**. After metalation and subsequent cross-coupling with the alkenyl iodide **4p**, the 6,8-disubstituted cinnoline **8d** is obtained in 57% yield (entry 4).

Finally, a double functionalization via successive metalation can be achieved, and the 3-functionalized cinnolines (**5f**, **5h**; see Table 1) can be readily zincated (procedure B) affording the corresponding 3,8-disubstituted cinnolines (**8e**,**f**) in 48–65% yield (entries 5 and 6). Additionally, 8-substituted cinnoline **6e** undergoes a second metalation and a subsequent cross-coupling with 4-iodoanisole (**4b**) to furnish the corresponding disubstituted cinnoline **8g** in 68% yield (entry 7).

The observed regioselectivity in the case of a metalation at position 3 is best explained by assuming a complexation of BF$_3$ at the most sterically accessible nitrogen N(2). This coordination acidifies the proton in position 3 sufficiently so that a deprotonation occurs exclusively in this position (Scheme 1).

Scheme 1. BF$_3$·OEt$_2$- and MgCl$_2$-Triggered Selective Metalations of Cinnoline (1) at Positions 3 and 8 Using TMP$_2$Mg·2LiCl (2) and TMP$_2$Zn·MgCl$_2$ (3)



By using the much less active TMP$_2$Zn·2MgCl$_2$·2LiCl (**3**), position 3 is now only activated by MgCl$_2$ (instead of BF$_3$·OEt$_2$) due to complexation at N(2). This may not be sufficient activation to initiate the deprotonation at position 3, and coordination of zinc from **3** at N(1) directs the zincation at position 8.[21]

In conclusion, we have developed a new general method for the regioselective metalation of the cinnoline scaffold by implementation of two complementary metalation procedures (BF$_3$·OEt$_2$ and TMP$_2$Mg·2LiCl (**2**) or TMP$_2$Zn·2MgCl$_2$·2LiCl (**3**)) allowing either a magnesiation at C(3) or a selective zincation at C(8). Additionally, a second selective metalation of prefunctionalized cinnoline derivatives can be performed, leading to highly functionalized compounds. Extension of this method to the metalation of related heterocycles is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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