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# Lewis Acid-Triggered Selective Zincation of Chromones, Quinolones, and Thiochromones: Application to the Preparation of Natural Flavones and Isoflavones

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*Supporting Information*

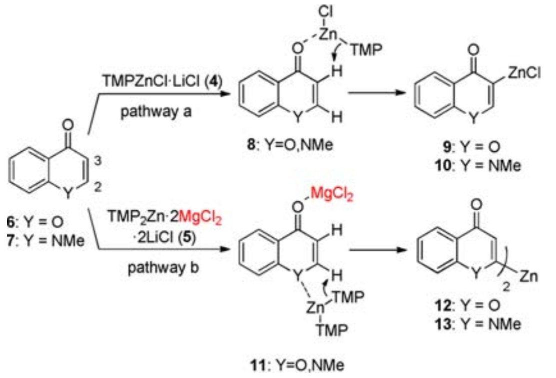
**ABSTRACT:** A Lewis acid-triggered zincation allows the regioselective metalation of various chromones and quinolones. In the absence of $MgCl_2$, a C(3) zincation is observed, whereas in the presence of $MgCl_2$ or a related Lewis acid, C(2) zincation occurs. Applications to a natural flavone, isoflavone, and quinolone are shown.

Chromones and quinolones are important classes of natural products[1] that have useful pharmaceutical properties, such as anti-neoplastic, antibacterial, and anti-HIV activity.[2] Typical representative natural products are chrysin (**1**),[3] the isoflavone biochanin A (**2**),[4] and the quinolone graveolinine (**3**).[5] Thiochromones, which are not found as natural products, also show useful bioactivities.[6,7] Consequently, the functionalization of these heterocyclic scaffolds is of special synthetic importance.

Lithiation at positions C(3) and C(2) of the chromone scaffold and further functionalizations have only been briefly described. Good metalation selectivity between positions C(2) and C(3) has yet not been achieved.[8,9] The lithiation of unsubstituted chromone with 2,2,6,6-tetramethylpiperidyllithium (TMP-Li) or lithium diisopropylamide (LDA) produces a complex mixture of products,[8,9] and therefore, the use of more selective metalating agents is desirable. Also, a selective zirconation[10] of chromone and a Pd-catalyzed direct intermolecular alkenylation[11] at position C(3) have been disclosed. A C(2)-selective lithiation of quinolone with LDA has also been described.[12]

We recently reported the preparation of new, highly chemoselective TMP bases such as $TMPZnCl\cdot LiCl$ (**4**)[13] and $TMP_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**5**).[14] These hindered zinc amides display an exceptional kinetic[15] basicity and tolerate a broad range of functional groups. We have also shown that various Lewis acids are compatible with such Mg- and Zn-TMP bases and constitute a new class of frustrated Lewis pairs.[16] Thus, the metalation regioselectivity of pyridines with TMP bases was triggered by the presence of $BF_3\cdot OEt_2$.[17] Also, magnesium salts,[18] triorganoboranes,[19] and catalytic amounts of $Sc(OTf)_3$[20] influence the reactivity of organometallics. On the basis of these recent advances, we envisioned that the presence (or absence) of Lewis acids may direct the zincation of chromone (**6**) or *N*-methylquinolone (**7**) to either C(2) or C(3). Theoretical calculations showed that the thermodynamically most acidic hydrogen is attached to C(2).[21] However, the most basic oxygen is located at the carbonyl group of these heterocycles. We anticipated that **4** would coordinate at this oxygen, leading through the complex-induced proximity effect (CIPE)[22] to complexes of type **8** (Scheme 1, pathway a). After metalation, the zinc reagents **9** and **10** would be obtained. In contrast, we expected that in the presence of **5** containing the strong Lewis acid $MgCl_2$, complexation of Mg at the carbonyl group would occur. In this case, the coordination of the TMP-Zn moiety would proceed at heteroatom Y(1), forming complex **11** and resulting in the C(2)-zincated heterocycle **12** or **13** after deprotonation (Scheme 1, pathway b).

**Scheme 1. $MgCl_2$-Triggered Regioselective Zincation of 6 and 7**



Herein we report the successful realization of these regioselective zincations of **6** and **7** according to Scheme 1. Thus, treatment of **6** with **4** resulted in C(3)-selective zincation to produce the zinc reagent **9**. After iodolysis, 3-iodochromone (**14a**) was isolated (Table 1, entry 1). Transmetalation of **9** with $CuCN\cdot 2LiCl$[23] and subsequent reaction with allylic bromides provided chromones **14b** and **14c** (entries 2 and 3). The corresponding reaction with pivaloyl chloride afforded the expected ketone **14d** (entry 4). Pd-catalyzed Negishi cross-coupling[24] with aryl iodides or aryl bromides led to the cross-coupling products **14e**–**i** (entries 5–9).

C(2)-selective zincation was also achieved. Thus, the reaction of **6** with **5** led to regiospecific metalation at C(2), providing the bis-heterocyclic zinc reagent **12**, and subsequent iodolysis gave product 2-iodochromone (**15a**) (Scheme 2). Similarly,

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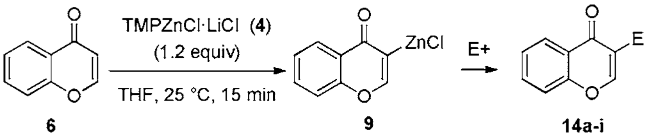
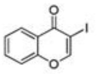
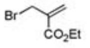
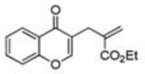
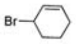
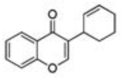
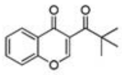
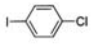
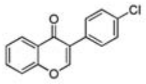
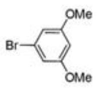
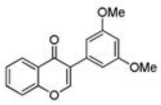
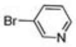
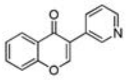
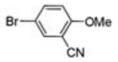
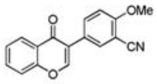
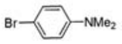
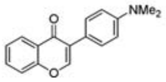
### Table 1. Products Obtained by Zincation of 6 with 4 and Subsequent Reactions with Electrophiles



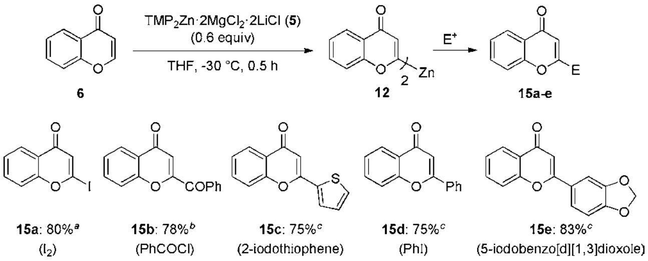
| entry | electrophile | | product | yield[a] |
|---|---|---|---|---|
| 1 | $I_2$ | **14a** |  | 77% |
| 2 |  | **14b** |  | 87%[b] |
| 3 |  | **14c** |  | 75%[b] |
| 4 | *t*BuCOCl | **14d** |  | 74%[b] |
| 5 |  | **14e** |  | 90%[c] |
| 6 |  | **14f** |  | 85%[d] |
| 7 |  | **14g** |  | 77%[d] |
| 8 |  | **14h** |  | 93%[e] |
| 9 |  | **14i** |  | 83%[e] |

[a] Yields of isolated, analytically pure products. [b] Obtained after transmetalation with 1.2 equiv of CuCN·2LiCl (−40 °C, 30 min). [c] Obtained by using 2% Pd(dba)$_2$, 4% tfp,[25] and 1.2 equiv of ArI (25 °C, 1 h). [d] Obtained by using 2% Pd(OAc)$_2$, 4% SPhos,[26] and 1.2 equiv of ArBr (48 h, 50 °C). [e] Obtained by Negishi cross-coupling using 2% Pd(OAc)$_2$, 4% XantPhos,[27] and 1.2 equiv of ArBr (48 h, 50 °C).

Cu-mediated acylation or Pd-catalyzed Negishi cross-coupling furnished the expected C(2)-substituted chromones **15b−e**.

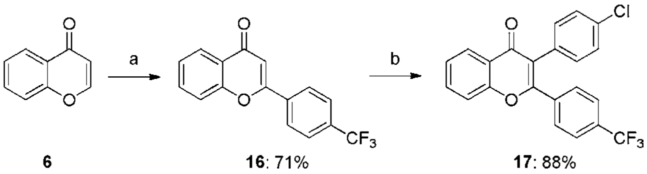
2,3-Disubstituted chromones can be readily prepared by two successive metalation/cross-coupling sequences (Scheme 3). Pd-catalyzed cross-coupling of C(2)-zincated chromone **12** with *p*-iodobenzotrifluoride first afforded flavone **16** (Scheme 3), from which 2,3-disubstituted chromone **17** was obtained after treatment with **4** and subsequent Negishi cross-coupling reaction.

### Scheme 2. Preparation of C(2)-Substituted Chromones from 6 Using 5 and Subsequent Reactions with Electrophiles



[a] Obtained using 1.2 equiv of $I_2$ (25 °C, 15 min). [b] Obtained after transmetalation with 1.2 equiv of CuCN·2LiCl (−40 °C, 30 min). [c] Obtained using 2% Pd(dba)$_2$, 4% tfp, and 1.2 equiv of ArI (25 °C, 1 h).

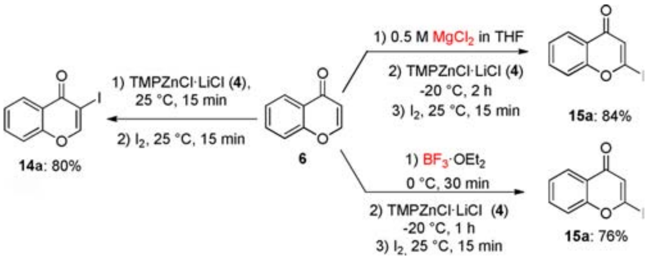
### Scheme 3. Preparation of 2,3-Disubstituted Chromone 17[a]



[a] Reagents and conditions: (a) (1) 0.6 equiv of **5** (THF, −30 °C, 1 h); (2) 2% Pd(dba)$_2$, 4% tfp, and 1.2 equiv of ArI (25 °C, 1 h). (b) (1) 1.2 equiv of **4** (THF, 25 °C, 30 min); (2) 2% Pd(dba)$_2$, 4% tfp, and 1.2 equiv of ArI (25 °C, 1 h).

To provide additional support for our mechanistic picture in Scheme 1, we added the Lewis acid $MgCl_2$ to **4**. This completely inverted the regioselectivity of zincation, providing **15a** after iodolysis. A similar selectivity reversal was achieved by adding $BF_3$·$OEt_2$ as a Lewis acid, which also afforded **15a** after iodolysis (Scheme 4).

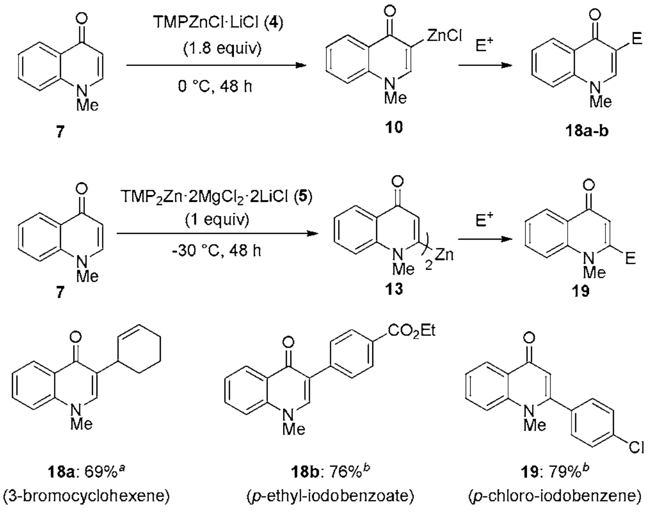
### Scheme 4. Reversal of Regioselective Zincation of 6 by 4 upon Addition of Lewis Acid



Our metalation procedure was extended to **7**, which was deprotonated with **4** to give C(3)-zincated intermediate **10**. Cu-mediated allylation of **10** afforded the desired *N*-methyl-4-quinolone **18a**, and Pd-catalyzed cross-coupling of **10** provided arylated quinolone **18b**. Inverse zincation regioselectivity was observed in the presence of $MgCl_2$. Thus, metalation of **7** with **5** gave the C(2)-zincated *N*-methyl-4-quinolone **13**, which was converted to **19** by a Negishi cross-coupling reaction (Scheme 5).

Finally, we examined the functionalization of thiochromone (**20**). Theoretical calculations showed that the difference in acidity of the hydrogens attached to C(2) and C(3) is much higher in **20** than in **6** or **7**.[21] This strong thermodynamic preference for deprotonation at C(2) in **20** affects the zincation

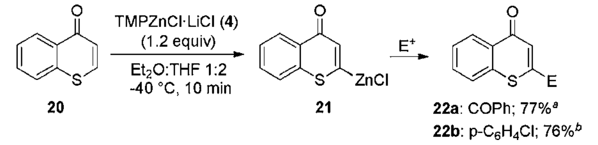
### Scheme 5. Selective Metalation of 7 and Subsequent Reactions with Electrophiles



[a]Obtained after transmetalation with 1.2 equiv of CuCN·2LiCl (−40 °C, 30 min). [b]Obtained after using 2% Pd(dba)$_2$, 4% tfp, and 1.2 equiv of ArI (25 °C, 1 h).

regioselectivity. Thus, metalation of **20** with **4** in THF produced a mixture of C(2)- and C(3)-zincated products. The reactivity of **4** can be influenced by reducing the solvent polarity. This reduced polarity might also affect the complexation at the sulfur atom. With a less polar solvent mixture (THF/Et$_2$O), it was possible to direct the metalation completely to C(2).[28] Zincation of **20** with **4** in 2:1 THF/Et$_2$O gave the C(2)-zincated intermediate **21**. Transmetation with CuCN·2LiCl and subsequent quenching with PhCOCl led to ketone **22a**, and Pd-catalyzed cross-coupling with *p*-chloroiodobenzene gave thiochromone **22b** (Scheme 6).

### Scheme 6. Products Obtained by Zincation of 20 with 4 and Subsequent Reactions with Electrophiles

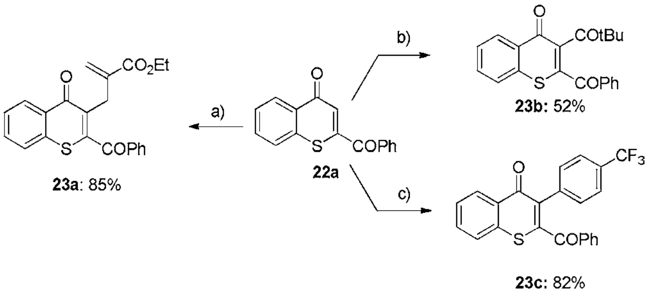


[a]Obtained after transmetalation with 1.2 equiv of CuCN·2LiCl (−40 °C, 30 min). [b]Obtained using 2% Pd(dba)$_2$, 4% tfp, and 1.2 equiv of ArI (25 °C, 1 h).

The preparation of 2,3-disubstituted thiochromones was readily achieved. Thus, zincation of **22a** with **4** provided the expected thiochromone, which underwent Cu-mediated allylation, Cu-mediated acylation, or Pd-catalyzed Negishi cross-coupling to give 2,3-disubstituted thiochromones **23a−c** (Scheme 7).

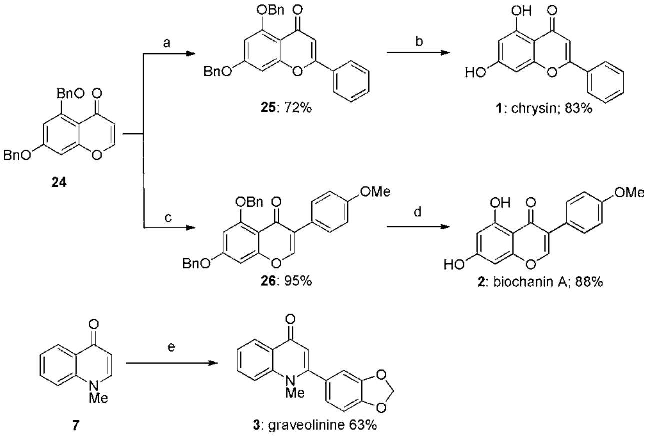
As an application of this metalation methodology, we prepared several naturally occurring chromones and quinolones, such as chrysin (**1**)[3] and biochanin A (**2**),[4] starting from the common chromone precursor **24**.[29] Regioselective metalation of **24** with **5** provided C(2) zincation, and Negishi cross-coupling with iodobenzene then gave flavone **25**. On the other hand, metalation of **24** with **4** led to the C(3)-zincated intermediate, and subsequent Pd-catalyzed cross-coupling with *p*-iodoanisole provided isoflavone **26**. Removal of the benzyl protection groups[30] gave the natural products **1** and **2**, respectively. The quinolone graveolinine (**3**)[5] was prepared by Negishi cross-coupling of C(2)-zincated quinolone **13** (Scheme 8).

### Scheme 7. Preparation of 2,3-Disubstituted Thiochromones 23a−c[a]



[a]Reagents and conditions: (a) (1) 1.2 equiv of **4** (THF, −20 °C, 15 min); (2) CuCN·2LiCl (−40 °C, 0.5 h); (3) ethyl 2-(bromomethyl)-acrylate (−40 °C, 10 min). (b) (1) 1.2 equiv of **4** (THF, −20 °C, 15 min); (2) CuCN·2LiCl (−40 °C, 30 min); (3) *t*BuCOCl (−40 to 25 °C, 4 h). (c) (1) 1.2 equiv of **4** (THF, −20 °C, 15 min); (2) 2% Pd(dba)$_2$, 4% tfp, 1.2 equiv of ArI (25 °C, 1 h).

### Scheme 8. Preparation of Chrysin (1), Biochanin A (2), and Graveolinine (3)[a]

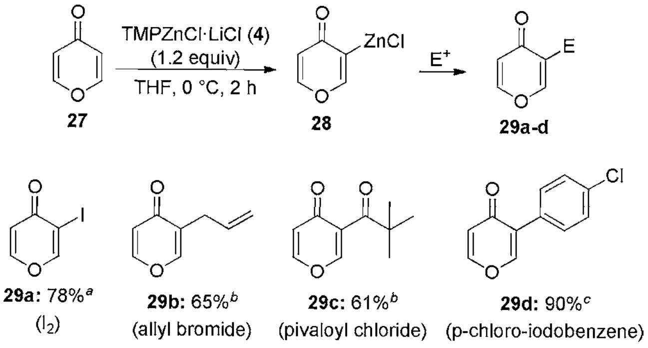


[a](a) (1) 1.2 equiv of **5** (−30 °C, 1 h); (2) 2% Pd(dba)$_2$, 4% tfp, 1.2 equiv of PhI (25 °C, 1 h). (b) H$_2$, 20% Pd/C, EtOH. (c) 2 equiv of **4** (25 °C, 0.5 h); (2) 2% Pd(dba)$_2$, 4% tfp, 1.2 equiv of ArI (25 °C; 1 h). (d) H$_2$, 20% Pd/C, EtOAc. (e) (1) 1.0 equiv of **5** (−20 °C, 48 h); (2) 2% Pd(dba)$_2$, 4% tfp, 1.2 equiv of ArI (25 °C, 1 h).

We have also briefly studied the metalation of 4-pyrone (**27**) using **4**, which gave **28** by C(3)-selective zincation. Quenching with iodine or allyl bromide, acylation with pivaloyl chloride, and cross-coupling with *p*-chloroiodobenzene provided the expected products **29a−d** (Scheme 9).

In summary, we have shown that the regioselectivity of zincation of chromone (**6**) and *N*-methyl-4-quinolone (**7**) can be directed either to C(2) or C(3) depending on the reaction conditions. Thus, the use of TMPZnCl·LiCl (**4**) leads to C(3)-zincated intermediates, whereas the presence of Lewis acids (MgCl$_2$ or BF$_3$·OEt$_2$) leads to metalation at C(2). For thiochromone (**20**), the use of 2:1 THF/Et$_2$O was essential for controlling the regioselectivity of C(2) zincation. Applications to the syntheses of a naturally occurring flavone, isoflavone, and quinolone have been shown. Extension of this

**Scheme 9. Preparation of 3-Substituted Pyronones 29a−d**



27 28 29a-d

**29a**: 78%[a] ($I_2$) **29b**: 65%[b] (allyl bromide) **29c**: 61%[b] (pivaloyl chloride) **29d**: 90%[c] (p-chloro-iodobenzene)

[a] Obtained using 1.2 equiv of $I_2$ (25 °C, 15 min). [b] Obtained after transmetalation with 1.2 equiv of CuCN·2LiCl (−40 °C, 30 min). [c] Obtained using 2% $Pd(dba)_2$, 4% tfp, and 1.2 equiv of ArI (25 °C, 1 h).

methodology to related heterocycles is currently under investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

Full experimental details, $^1H$ and $^{13}C$ spectra, and computational details. 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.

## ■ ACKNOWLEDGMENTS

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