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# Preparation of Polyfunctionalized Aromatic Nitriles from Aryl Oxazolines

A. Hess,[a] H. C. Guelen,[a] N. Alandini,[a] A. Mourati,[a] Y. C. Guersoy,[a] and P. Knochel*[a]

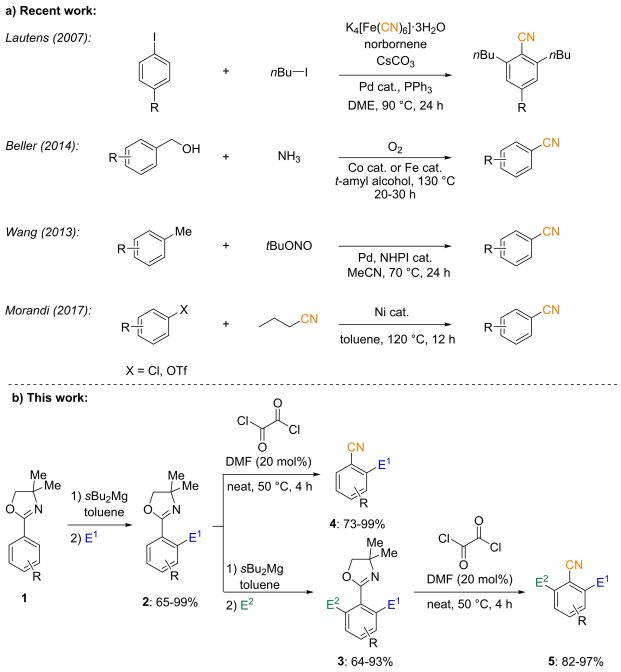
*Dedicated to Prof. Dr. Martin F. Semmelhack on the ocassion of his 80th birthday*

**Abstract:** A selective *ortho,ortho'*-functionalization of readily available aryl oxazolines by two successive magnesiations with $sBu_2Mg$ in toluene followed by trapping reactions with electrophiles, such as (hetero)aryl iodides or bromides, iodine, tosyl cyanide, ethyl cyanoformate or allylic bromides (39 examples, 62–99% yield) is reported. Treatment of these aryl oxazolines with excess oxalyl chloride and catalytic amounts of DMF (50 °C, 4 h) provided the corresponding nitriles (36 examples, 73–99% yield). Conversions of these nitriles to valuable heterocycles are reported, and a tentative mechanism is proposed.

The preparation of highly substituted aromatic compounds is of great importance for pharmaceutical, agrochemical and material science applications.[1] Especially, the selective preparation of ortho,ortho'-trisubstituted aromatics are of importance. Various C–H activation methods allowed such ortho,ortho'-functionalizations,[2] however unsymmetrical ortho,ortho'-derivatives were difficult to prepare.[3] Recently, we have shown that the magnesiation of various *N*-aryl azoles[4] including aryl oxazolines may be achieved by selective metalation using the powerful base $sBu_2Mg$ in toluene.[5] Although, such ortho,ortho'-arylated heterocycles were useful on themselves but the generation of heterocycle-free 1,2,3-trisubstituted arenes would greatly enhance their synthetic potential.[6] Thus, the preparation of newly ortho,ortho'-functionalized aryl oxazolines would be much more relevant, if the oxazoline moiety could be converted to a carboxylate derivative.[7] Such a conversion would valorize in general the chemistry of aryl oxazolines developed in pioneering work by Meyers, since this heterocycle is often difficult to cleave.[8]

Aromatic nitriles are key intermediates for the preparation of various N-heterocycles and represent valuable target molecules for various applications.[9] They are usually prepared from various precursors such as aromatic aldehydes,[10] hydrocarbons,[11] carboxylic acid derivatives,[12] halides[13] or benzylic derivatives (see representative preparations in Scheme 1).[14] In preliminary experiments,[5] we have noticed that aryl oxazolines may be converted under harsh conditions (refluxing of a 2:1 mixture of thionyl chloride and DMF at 75 °C for 2 h) to the corresponding aromatic nitriles.[15]

Herein, we report the successive magnesiations of aryl oxazolines of type **1** providing ortho-substituted aryl oxazolines of type **2** and ortho,ortho'-substituted aryl oxazolines of type **3** and their conversion to the corresponding nitriles **4** and **5** (Scheme 1).




**Scheme 1.** a) Recent cyanation methods. b) Regioselective magnesiations of aryl oxazolines **1** using $sBu_2Mg$ in toluene furnishing ortho- and *ortho,ortho'*-substituted oxazolines **2** and **3** and subsequent conversion to the corresponding nitriles **4** and **5**.

[a] *A. Hess, H. C. Guelen, N. Alandini, A. Mourati, Y. C. Guersoy, Prof. P. Knochel*
*Department Chemie*
*Ludwig-Maximilians-Universität München*
*Butenandtstrasse 5–13, Haus F, 81377 München (Germany)*
*E-mail: paul.knochel@cup.uni-muenchen.de*

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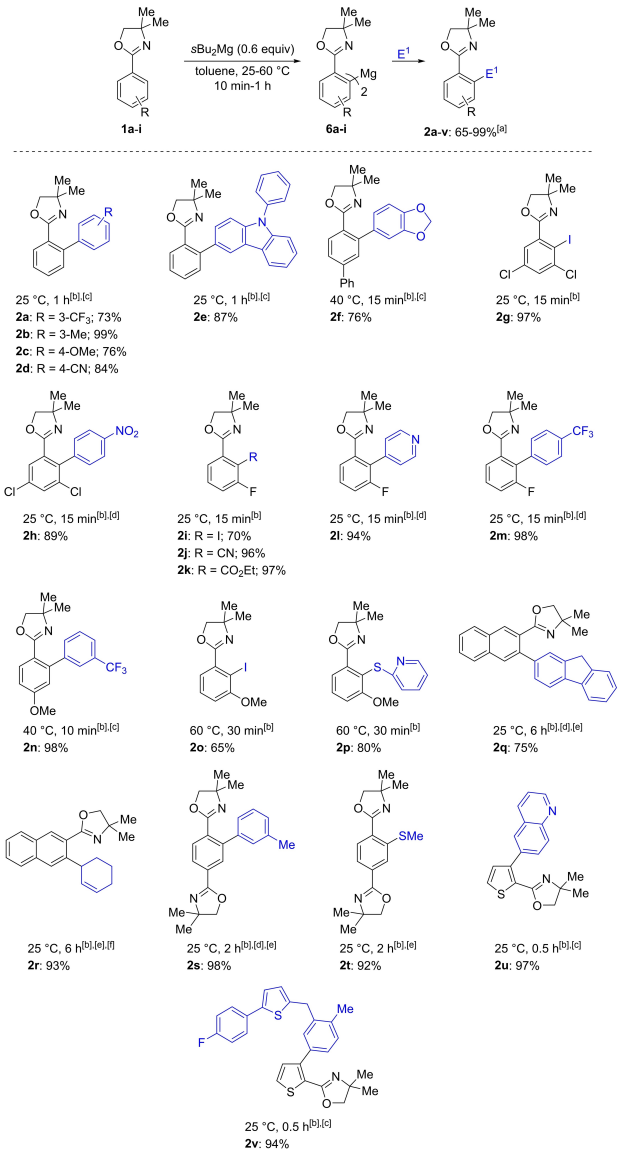
First, we have prepared a range of mono-ortho-substituted aryl oxazolines of type **2** starting from aryl oxazolines of type **1**[16] by magnesiation with $sBu_2Mg$[5,17] in toluene (0.48 M) prepared by the reaction of *s*BuMgCl with *s*BuLi (Scheme 2). In a typical experiment, we treated the phenyl oxazoline **1a** with $sBu_2Mg$ (0.6 equiv) for 1 h at 25 °C leading to the diarylmagnesium intermediate **6a** in toluene,[5] which after transmetalation with $ZnCl_2$ (1 M in THF, 1.1 equiv) and Negishi cross-coupling[18] with 1-iodo-3-trifluorobenzene (0.83 equiv, 55 °C, 2 h) and $PdCl_2$(dppf) (5 mol%, dppf = diphenylphosphinoferrocene) furnished the ortho-substituted oxazoline **2a** in 73% yield of analytically pure isolated product. Similarly, starting from **1a** and **1b**,[19] we have prepared the related 2-arylated oxazolines **2b–f** in 76–99% yield.

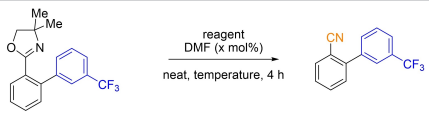
Also, the 3,5-dichlorophenyl oxazoline **1c** and the 3-fluorophenyl oxazoline **1d** were magnesiated with $sBu_2Mg$ at 25 °C for 15 min furnishing the diarylmagnesium intermediates **6c** and **6d**.[19] Trapping with various electrophiles such as iodine, tosyl cyanide, ethyl cyanoformate or (hetero)aryl iodides (Negishi cross-coupling using $Pd(dba)_2$ (3 mol%, dba = dibenzylideneacetone and tfp (6 mol%, tfp = tri(*o*-furyl)phosphine) gave the expected products **2g–m** in 70–98% yield. Electron-rich substituted aryl oxazolines such as **1e** and **1f** as well as the 2-naphthyl oxazoline **1g**[20a] were metalated with $sBu_2Mg$ as well as with TMPMgCl·LiCl[20b,21] and were trapped with typical electrophiles providing the ortho-substituted oxazolines **2n–2r** in 65–98% yield. Finally, the 1,4-bisoxazolyl benzene **1h**[22] or thienyl oxazoline **1i** were converted to the ortho-substituted oxazolines **2s–2v** in 92–98% yield. With these oxazolines in hand, we have performed optimization experiments for their conversion to the corresponding nitriles. Thus, we have submitted the oxazoline **2a** to various conditions, leading to nitrile **4a**. We have noticed that thionyl chloride (used as solvent) was ineffective in the absence of DMF (entry 1 of Table 1) or in the presence of DMF (20 mol%) at 25 °C (entry 2). Heating to 50 °C, which presumably generates an intermediate immonium reagent ($Me_2N{=}C(H)Cl_2$); Vilsmeier reagent)[23] led to the nitrile **4a** in 64% calibrated GC-yield (entry 3).

Switching thionyl chloride to oxalyl chloride as solvent (0.2 M solutions) already provided **4a** at 25 °C (entries 4 and 5). Increasing the reaction temperature to 50 °C afforded the desired nitrile **4a** in quantitative GC-yield (98% isolated yield; entry 6). Using toluene as solvent and oxalyl chloride in small excess (2.0 equiv) was not satisfactory (entry 7). With these optimized conditions in hand, we have converted ortho-substituted aryl oxazolines **2a–b,d–l,n–v** to the corresponding nitriles **4a–u** in 73–99% yield (Scheme 3). Various functional groups like a CN, $NO_2$, $CO_2Et$, cyclohexenyl or thiopyridyl were compatible with the mild reaction conditions of this cyanation procedure.



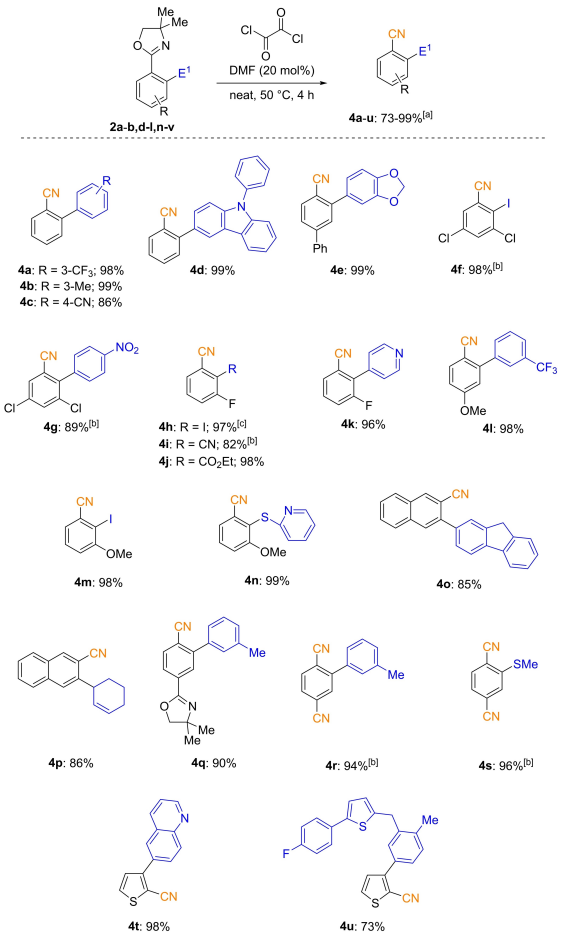

**Scheme 2.** Regioselective magnesiation of oxazolines **1a–i** with $sBu_2Mg$ leading, via diarylmagnesium intermediates **6a–i**, to functionalized oxazolines **2a–v**. [a] All yields refer to analytically pure isolated compounds. [b] Magnesiation conditions. [c] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv) and a palladium-catalyzed cross-coupling with [$PdCl_2$(dppf)] (5 mol%) and an aryl bromide or iodide (0.83 equiv). [d] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv) and a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (3 mol%), tfp (6 mol%) and an aryl bromide or iodide (0.83 equiv). [e] TMPMgCl·LiCl (2.0–3.0 equiv) was used for the magnesiation.[20] [f] The reaction was catalyzed by CuCN·2LiCl (20 mol%).

**Table 1.** Optimization of the dehydration reaction of oxazoline **2a** to nitrile **4a**.

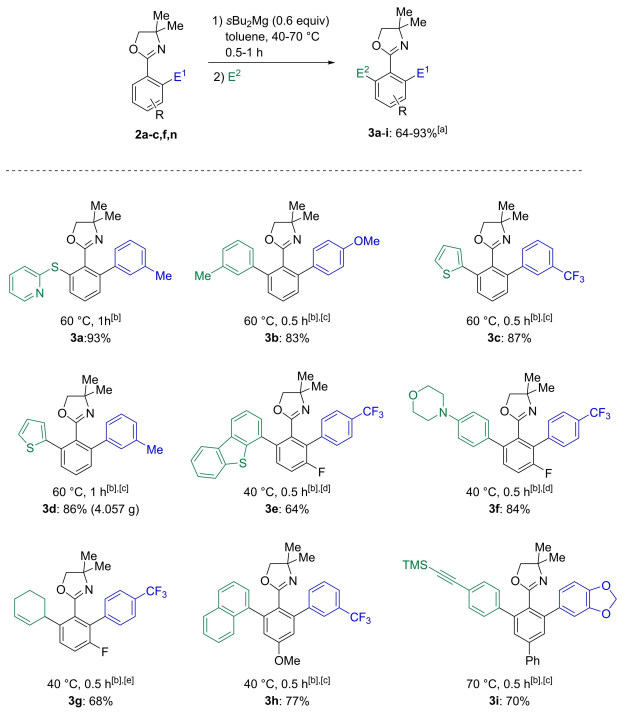



| Entry | Reagent | DMF [mol%] | *T* [°C] | Yield [%][a] |
|---|---|---|---|---|
| 1 | $SOCl_2$ | 0 | 25 | 0 |
| 2 | $SOCl_2$ | 20 | 25 | 0 |
| 3 | $SOCl_2$ | 20 | 50 | 64 |
| 4 | $(COCl)_2$ | 0 | 25 | traces |
| 5 | $(COCl)_2$ | 20 | 25 | 47 |
| 6 | $(COCl)_2$ | 20 | 50 | 100 (98)[b] |
| 7 | $(COCl)_2$[c] | 20 | 50 | 47 |

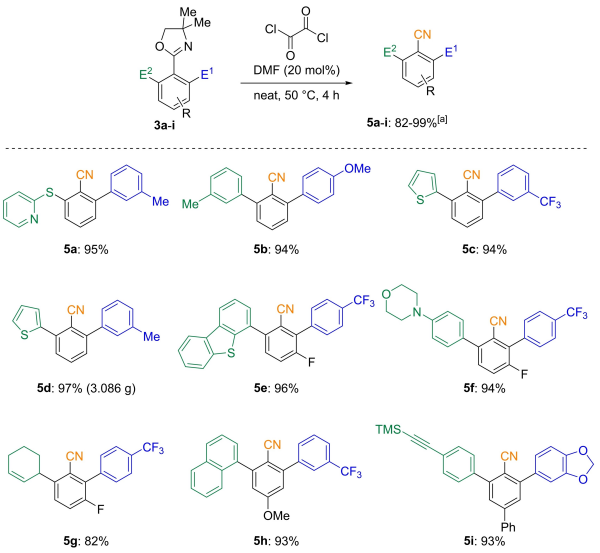
[a] Calibrated GC yield using undecane as internal standard. [b] Isolated yield. [c] 2.0 equiv of $(COCl)_2$ in toluene were used.




**Scheme 3.** Transformation of ortho-functionalized oxazolines **2a–b,d–l,n–v** to the corresponding nitriles **4a–u**. [a] All yields refer to isolated compounds. [b] $SOCl_2$/DMF 2:1 (70 °C, 4 h) was used. [c] 5 h reaction time.




**Scheme 4.** Regioselective magnesiation of ortho-functionalized oxazolines **2a–c,f,n** with $sBu_2Mg$ leading to ortho,ortho'-functionalized oxazolines **3a–i**. [a] All yields refer to isolated compounds. [b] Magnesiation conditions. [c] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv) and a palladium-catalyzed cross-coupling with [$PdCl_2$(dppf)] (5 mol%) and an aryl halide (0.83 equiv). [d] Obtained after transmetalation with $ZnCl_2$ (1.1 equiv) and a palladium-catalyzed cross-coupling with $Pd(dba)_2$ (3 mol%), tfp (6 mol%) and an aryl halide (0.83 equiv). [e] Reaction was catalyzed by CuCN·2LiCl (20 mol%).

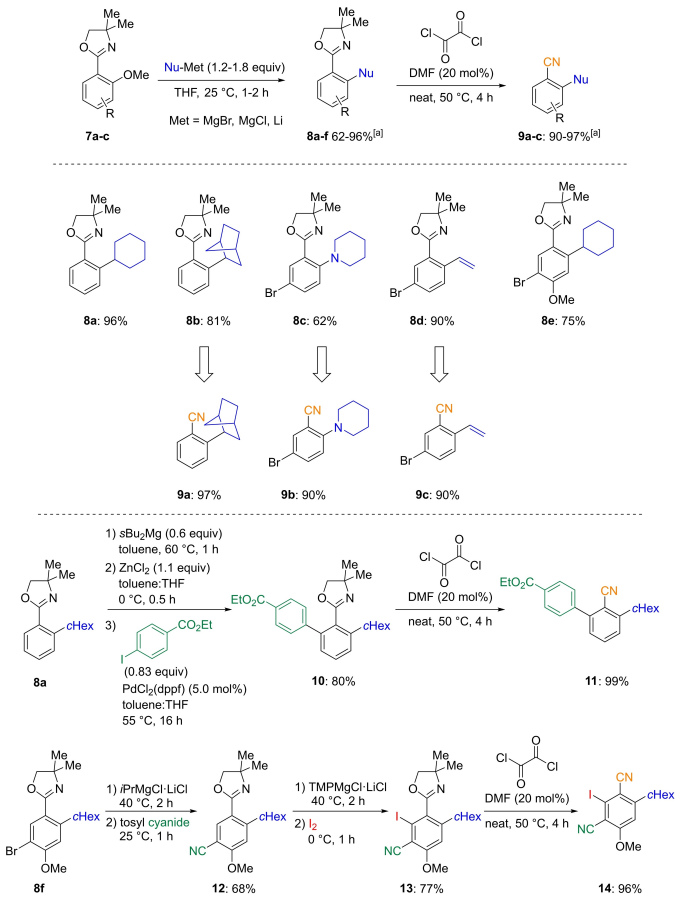



**Scheme 5.** Transformation of *ortho,ortho'*-functionalized oxazolines **3a-i** to the corresponding nitriles **5a–i**. [a] All yields refer to isolated compounds.

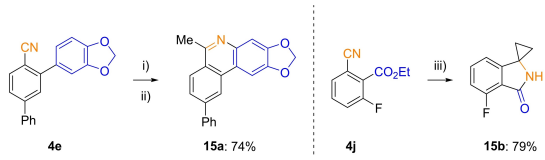
After these encouraging results, we have prepared various ortho,ortho'-disubstituted oxazolines **3a–i** using $sBu_2Mg$ (0.6 equiv) in toluene between 40–70 °C with 0.5-1 h reaction time in 64–93% isolated yield. (Scheme 4). To our delight, the aryl oxazolines **3a–i** were readily converted in the corresponding nitriles **5a–i** in 82–99% yield (Scheme 5). Remarkably, the scale-up of this cyanation was performed in the case of **3d** providing the nitrile **5d** in multigram-scale (3.1 g were prepared) in 97% isolated yield.

Furthermore, we have treated ortho-methoxy substituted aryl oxazolines **7a** and **7b** with various nucleophiles, as previously described by Meyers,[24] resulting in substituted products of type **8**. Thus, the reaction of the reaction of **7a** with cHexMgCl or *exo*-norbornylmagnesium bromide[25] (25 °C, 1 h) produced the alkylated derivatives **8a–8b** in 81–96% yield (Scheme 6).

Treatment of **7b** with piperidyllithium or vinylmagnesium bromide provided the aminated and vinylated products **8c** and **8d** respectively (62-90% yield). Applying the cyanation procedure afforded the aryl nitriles **9a–c** in 90–97% yield (Scheme 7). Treatment of the alkylated oxazoline **8a** with $sBu_2Mg$ (60 °C, 1 h) and subsequent Negishi cross-coupling furnished the ortho,ortho'-functionalized aryl oxazoline **10** in 80% yield, which was converted to the corresponding aromatic nitrile **11** in 99% yield. Reacting the readily available 2-methoxy oxazo-

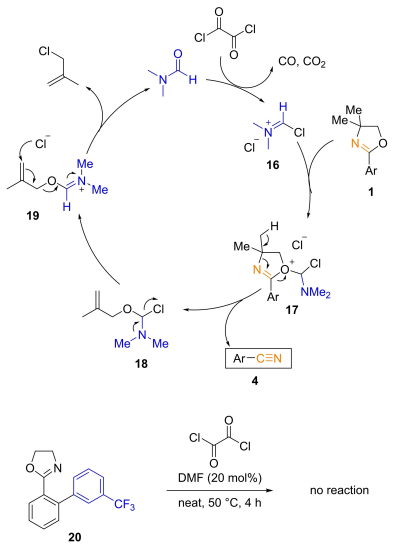



**Scheme 6.** Nucleophilic aromatic substitution on *ortho*-(methoxy)aryl oxazolines **7a-c** furnishing functionalized aryl oxazolines **8a–e** and subsequent transformation to the corresponding nitriles **9a–c**. Multiple functionalizations on aryl oxazolines **8a** and **8e** and subsequent transformation to the corresponding nitriles **11** and **14**. [a] All yields refer to isolated compounds.




**Scheme 7.** Transformation of aryl nitriles **4e** and **4j** to cyclic derivatives **15a** and **15b**. All yields refer to isolated compounds.Reaction conditions: i) MeLi (2.0 equiv), THF, 0 °C, 15 min. ii) $H_2O$, $I_2$ (4.0 equiv), $K_2CO_3$ (3.0 equiv), THF, 60 °C, 2 h. iii) Ti(O*i*Pr)$_4$ (1.1 equiv), EtMgBr (2.0 equiv), $Et_2O$, 25 °C, 1 h.

line **7c** with cHexMgCl (25 °C, 1 h) furnished the ortho-substituted oxazoline (**8e**) in 75% yield. Br/Mg-exchange with *i*PrMgCl·LiCl[26] produced an intermediate functionalized aryl magnesium derivative, which after treatment with tosyl cyanide (25 °C, 1 h) gave the nitrile **12** in 68% yield. Subsequent magnesiation with TMPMgCl·LiCl followed by an iodolysis of the intermediate Grignard species led to the polyfunctional aryl iodide **13** in 77% yield, which was converted by the usual procedure into the penta-substituted dinitrile **14** in 96% yield demonstrating the versatility of this approach for preparing highly substituted aryl nitriles.




**Scheme 8.** Tentative reaction mechanism of the conversion of aryl oxazoline **1** to the aromatic nitrile **4**.

Some of these nitriles were converted to cyclized derivatives by diverse methods. Thus, the nitrile **4e** was converted to the phenanthridine **15a** by an imino radical cyclization in 74% yield.[27] Treatment of **4j** using the Kulinkovich procedure (Ti(O*i*Pr)$_4$ and EtMgBr)[28] in ether (25 °C, 1 h) furnished a spirocyclic lactam **15b** in 79% yield.[29]

A tentative reaction mechanism was proposed in Scheme 8. Thus, DMF was first converted with oxalyl chloride to the Vilsmeier-reagent **16**. Its reaction with the aryl oxazoline **1** provided the oxonium ion **17** which by a fragmentation led to the aryl nitrile **4** and to the amino-derivative **18** which gave the iminium chloride **19** regenerating DMF and methallyl chloride in a further fragmentation step. Interestingly, the use of an aryl oxazoline such as **20** missing the two methyl groups necessary in the fragmentation process leading to a nitrile, gave no reaction under our standard conditions.

In summary, a new method for preparing highly functionalized tri-, tetra- and penta-substituted aromatic nitriles by using successive magnesiations with *s*Bu$_2$Mg in toluene followed by trapping with a broad range of electrophiles associated with an efficient conversion of the oxazolyl directing group to a nitrile using oxalyl chloride and catalytic amounts of DMF (50 °C, 4 h) is reported.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** aryl nitriles · aryl oxazolines · cyanation · directed metalation · Grignard reagents

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