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Efficient C-3 functionalization of 4-dimethylaminopyridine (DMAP). A straightforward access to new chiral nucleophilic catalysts

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ABSTRACT

Herein, the straightforward C-3 functionalization of 4-dimethylaminopyridine (DMAP) backbone is disclosed. An efficient halogen-metal exchange procedure from 3-bromo DMAP **1** is reported providing a large panel of C-3 functionalized DMAPs. In addition, a Pd-catalysed C–N cross-coupling reaction is also described furnishing new 3-amino DMAPs. These new functionalization pathways led to the resolution-free synthesis of three new chiral DMAP catalysts in few steps and a good overall yield. These new catalysts were evaluated into the Steglich rearrangement giving modest enantioselectivities (up to 20% ee).

Since the middle of the 1960s, 4-dimethylaminopyridine (DMAP) is well known as a powerful nucleophilic organocatalyst.[1] Indeed, since the first report dealing with the observation of the enhancement of esterification reaction rate, DMAP appeared as one of the most versatile nucleophilic organocatalyst.[2] Surprisingly, the first report dealing with the synthesis and application of a chiral DMAP catalyst was reported in 1996 by Vedejs and Chen.[3] They developed a chiral analog bearing a stereogenic center at the C-2 position of the pyridine moiety. However, its use as a catalyst in the resolution of secondary alcohol was significantly hampered by the C-2 substitution,[4] actually a stoichiometric amount of chiral DMAP was required to ensure decent yields. Over the past two decades several strategies have been developed to introduce a chiral moiety on the DMAP backbone. Among all these strategies, the C-3 functionalization position of the pyridine ring by a substituent bearing a stereogenic center,[5] a chiral axis[6] or a chiral relay[7] was mainly explored, while few reports dealt with the introduction of a chiral substituent at the C-4 position.[8] At last but not least, we have to mention the remarkable performances of ferrocene-based planar chiral DMAP analogs developed by Fu.[9] Interestingly, the C-2 functionalization of the pyridine ring does not disrupt the catalyst turnover and its impressive efficiency was described in a broad range of asymmetric processes (Fig. 1).

Although numerous efficient chiral catalysts have been reported, their synthesis remained laborious and usually required a final resolution step. Basically, two strategies have emerged on the preparation of chiral DMAP catalysts; the introduction of a chiral pattern in C-4 position was achieved by a SN_{Ar} strategy with halogenated pyridine derivative,[8] while the chiral C-2 and C-3 substituted derivatives were synthesized according to multi-step sequences from pyridine derivatives, followed by a tricky resolution step.[3,5,6,9] Surprisingly, the direct functionalization of the DMAP backbone and more interestingly the straightforward introduction of chiral

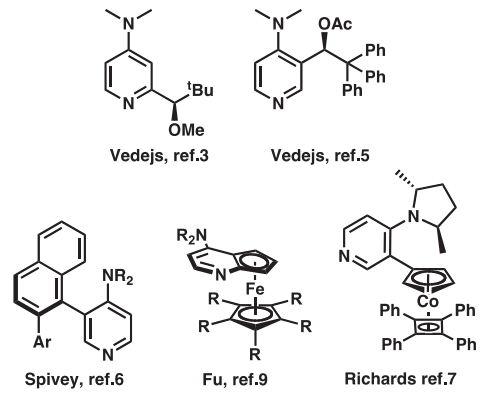

Figure 1. An overview of the most popular chiral DMAP catalysts previously reported.

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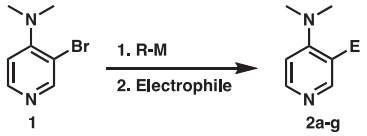
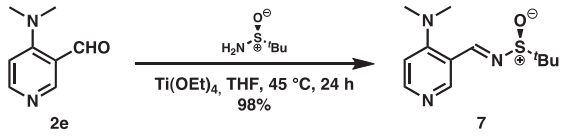
Table 1
Halogen-metal exchange with DMAP **1**[a]



Entry	R-M	Electrophile	*E*, Product	Yield[b] (%)
1	*t*-BuLi	EtOD	*D*, **2a**	60[c]
2	*n*-BuLi	EtOD	*D*, **2a**	80[c]
3	*i*-PrMgCl	EtOD	*D*, **2a**	99
4	*i*-PrMgCl	$CNCO_2Et$	CO_2Et, **2b**	86
5	*i*-PrMgCl	TMSCl	TMS, **2c**	98
6	*i*-PrMgCl	Trisyl azide	N_3, **2d**	55
7	*i*-PrMgCl	DMF	CHO, **2e**	81
8	*i*-PrMgCl	TsCN	CN, **2f**	74
9	*i*-PrMgCl	*n*-Bu_3SnCl	Sn(*n*-Bu)$_3$, **2g**	55
10	*i*-PrMgCl	Ar-CHO	CH(OH)Ar, **2h**	75
11	*i*-PrMgCl	**A**	(*R*)-**2i**	56[d]
12	*i*-PrMgCl	$Pd(PPh_3)_4$, PhI	Ph, **2j**	40

[a] Conditions: **1** (1 mmol), *i*-PrMgCl (1.2 mmol) in THF (7 mL), rt, 3 h, then electrophile (1.1 mmol). Ar = 3,4,5-trimethoxybenzaldehyde, **A** = (1*R*,2*S*,5*R*)-(−)-menthyl *para*-toluenesulfinate.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Product was obtained as a single enantiomer see Ref. 13.



Scheme 1. Synthesis of sulfinimine **7**.

substituents at C-3 still remained unexplored.[10] Herein, new C-3 functionalization pathways of the DMAP scaffold are disclosed as well as the synthesis of new non-racemic chiral DMAP derivatives without having to implement a resolution step. A preliminary evaluation of their performance in the course of asymmetric Steglich rearrangement will also be reported.[11]

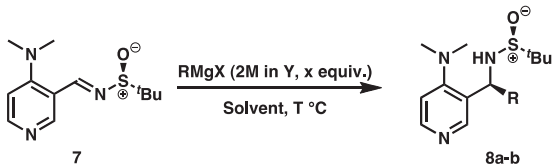
Our strategy focused on the use of the readily available 3-bromo-4-dimethylaminopyridine **1** as a key intermediate.[12] We decided to highlight the versatility of this intermediate through a halogen-metal exchange reaction and a Pd-catalyzed C–N cross-coupling reaction.

Firstly, we developed a straightforward halogen-metal exchange in order to introduce relevant functionalities at C-3 position of the pyridine ring within one step (Table 1).[13]

Initial experiments were performed using usual lithium bases, well known to promote smooth bromine–lithium exchange reactions. Unfortunately, all attempts to use *t*-BuLi, as previously reported by Vedejs and co-workers,[5a] failed. The best results were obtained when conducting the bromine–lithium exchange at −78 °C for 1 h. Subsequent deuteration of the intermediate lithiated species with EtOD afforded only 60% of the desired 3-deuterated DMAP **2a** along with significant amounts of unidentified side-products (entry 1). Under the same reaction conditions, *n*-BuLi furnished the corresponding deuterated product **2a** in somewhat higher yield (80%) but still with several by-products difficult to eliminate (entry 2). Finally, we tested *i*-PrMgCl, previously used by Knochel and others in bromide–magnesium exchange reactions for the preparation of pyridyl Grignard reagents.[14] To our delight, the room temperature exchange procedure gave the corresponding deuterated product **2a**, which was isolated in quantitative yield (entry 3). With this efficient halogen-metal exchange procedure in hand, several functional groups could be introduced straightforwardly on the DMAP scaffold. This methodology was successfully applied to the introduction of numerous substituents leading to the formation of ethyl ester **2b** (entry 4), trimethylsilyl derivative **2c** (entry 5), azide **2d** (entry 6) or aldehyde **2e** (entry 7), or tin derivative **2g** (entry 9) in good to excellent yields. Remarkably, a chiral sulfoxide group could be readily introduced in one step using (L)-*para*-toluenementhylsulfinate **A** as the electrophile under standard conditions giving access to the enantiomerically pure chiral catalyst **2i** without any resolution step in 56% yield (entry 11).[13] Finally, the synthetic utility of the Grignard reagent was also highlighted in the course of a Pd-catalyzed Corriu–Kumada cross-coupling with iodobenzene, affording the C-3-arylated DMAP **2j** in 40% yield (entry 12).

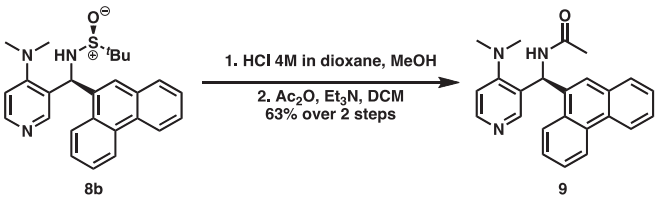
Then, with the aim of developing a straightforward access to new chiral nucleophilic catalysts, we decided to use aldehyde **2e** to introduce a stereogenic center at C-3 position. Our strategy relies on the use of the powerful Ellman's chiral auxiliary.[15] The corresponding chiral DMAP sulfinimine **7** was obtained in 98% yield under standard conditions (Scheme 1) and was then allowed to react with various Grignard reagents (Table 2).

Table 2
Addition of Grignard reagents to sulfinimine **7**[a]



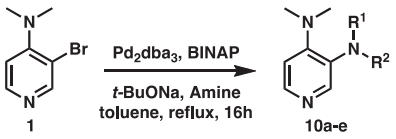
Entry	RMgX	Product	*Y*	*X*	Solvent	T (°C)	% Conv.[b]	Dr.[c]
1	Ph	**8a**	THF	1.2	THF	−78	100	82:18
2	Ph	**8a**	THF	1.2	Toluene	−78	100	75:25
3	Ph	**8a**	Et_2O	1.2	DCM	−78	53	91:9
4[d]	Ph	**8a**	Et_2O	1.2	DCM	−78	52	94:6
5	Ph	**8a**	Et_2O	2.4	DCM	−78	100	92:8
6	Ph	**8a**	Et_2O	2.4	DCM	−100	100	92:8
7	9-Phenanthrenyl	**8b**	Et_2O	2.4	DCM	−78	90	>95:5
8	9-Phenanthrenyl	**8b**	Et_2O	3.6	DCM	−78	100 (91)[e]	>95:5

[a] Conditions: **7** (0.91 mmol), RMgX (1.09 mmol), DCM (5 mL).
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR on the crude reaction mixture.
[d] Reaction was performed at 0.08 M instead of 0.16 M.
[e] Isolated yield.



Scheme 2. Preparation of catalyst **9**.[17b]

Table 3
Buchwald–Hartwig cross-coupling with **1**[a]



Entry	Amine	Product	Yield[b] (%)
1	Aniline	**10a**	45
2	α-Naphtylamine	**10b**	51
3	(*R*)-α-Methylbenzylamine	**10c**	84[c]
4	(*R*)-α-Methylnaphtylamine	**10d**	78[c]
5	Pyrrolidine	**10e**	50

[a] Conditions: **1** (1 equiv), amine (1.25 equiv) $Pd_2(dba)_3$ (2 mol %), BINAP (4 mol %), *t*-BuONa (1.5 equiv), toluene, 110 °C, 16 h.
[b] Isolated yield.
[c] Reaction proceeds without racemization.

As depicted in Table 2, we first studied the reaction parameters with phenylmagnesium bromide as the Grignard reagent. After extensive investigations, we were pleased to find out that the reaction carried out in DCM, with freshly prepared Grignard reagent in Et_2O afforded the corresponding sulfinamine in good yield with fairly good diastereoselectivity (up to 92:8, entry 6). We should notice that these results are in agreement with the report by Ellman and co-workers.[16]

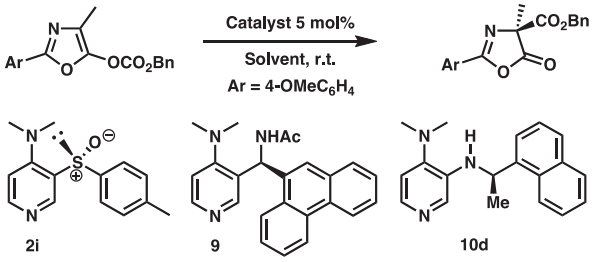
With these optimized conditions in hand, the anthracenyl pattern was successfully introduced in 91% yield with excellent diastereoselectivity (>95:5, entry 8). Then, a one pot deprotection–acylation reaction sequence gave the corresponding enantiomerically pure DMAP analog **9** in 63% yield without any erosion of the optical purity (Scheme 2).[17]

Then, we turned our attention to the use of the bromo derivative **1** in metal catalyzed cross-coupling reactions. To the best of our knowledge, reactions involving **1** as the reaction partner in cross-coupling reaction are limited to sporadic examples.[6] Moreover, the introduction of an amino group through a Buchwald–Hartwig cross-coupling reaction on the DMAP backbone remains, to date, unexplored. Thus, this strategy would lead to a new class of DMAP analogs bearing an amino group at C-3 position.

As shown in Table 3, the introduction of an amino group was successfully achieved using Pd_2dba_3/BINAP/*t*-BuONa as a catalytic system, affording various 3-amino DMAP derivatives **10a–e** in moderate to excellent yields. However, the scope of amine derivatives underlined some limitations. In particular, this process was found to be highly dependent on the steric hindrance of the amine. The reaction is restricted to primary and strained secondary amines (ie., pyrrolidine, entry 5).[18] As shown in entries 3 and 4, the introduction of amines bearing an α-stereogenic center was successfully achieved, yielding to new chiral DMAP analogs **10c** and **10d** in good yield without racemization.

Having developed several synthetic pathways providing straightforward access to chiral DMAP derivatives, we decided to evaluate chiral catalysts **2j**, **9**, and **10d** in the Steglich rearrangement.

Table 4
Steglich rearrangement[a]



Entry	Catalyst	Time (h)	Solvent	Yield[b] (%)	ee[c] (%)
1	**2i**	24	*t*-Amyl-OH	60	10
2	**9**	8	*t*-Amyl-OH	80	<5
3	**10d**	6	*t*-Amyl-OH	99	20
4	**10d**	6	THF	86	16
5	**10d**	6	DCM	40	20

[a] Conditions: Azalactone enol carbonate (0.1 mmol), catalyst (5 mol %), solvent (2 mL).
[b] Isolated yield.
[c] Determined by HPLC using chiral column.

As summarized in Table 4 and despite all our efforts, no or poor enantioselectivities (not exceeding 20% ee) were obtained. Noteworthy, in all cases a decent turnover of the catalyst was observed, pointing out the good nucleophilic properties of our DMAP catalysts.

Herein, we described a new and efficient access to C-3 functionalized DMAPs from the readily available 3-bromo dimethylaminopyridine **1** thanks to a straightforward room temperature bromine–magnesium exchange reaction. Several DMAPs bearing various functional groups at C-3 position as well as relevant chiral appendages were obtained in good yields. From the same key intermediate **1**, an efficient Pd-catalyzed C–N cross-coupling reaction was also developed leading to new chiral 3-amino DMAP derivatives. Both halogen-metal exchange and cross-coupling approaches led to a short- step synthesis of three new chiral catalysts without any resolution step. These three catalysts were evaluated in the Steglich rearrangement and despite decent catalytic activities, the enantiomeric excesses remained modest. However, the straightforward access to these catalysts prompts us to go further into and new original applications of these catalysts are currently underway in our laboratory.

Acknowledgments

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17. (a) Determined by HPLC analysis using chiral column: Chiralpak AD-H, heptane/*i*-PrOH, 4:1, 1 mL min^{-1}). Retention times of enantiomers: 6.86 and 19.81 min. (b) The absolute configuration of the stereogenic center was determined according to Ellman's model as described in Ref. 16.
18. The cross coupling of *N*-methylaniline as well as C-2 substituted pyrrolidine was ineffective under these conditions.