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COMBINED DIRECTED METALATION – SUZUKI-MIYAURA CROSS COUPLING STRATEGIES. SYNTHESIS OF ISOMERIC CHROMENO-PYRIDINONES and RELATED ANNULATED ANALOGUES[§]

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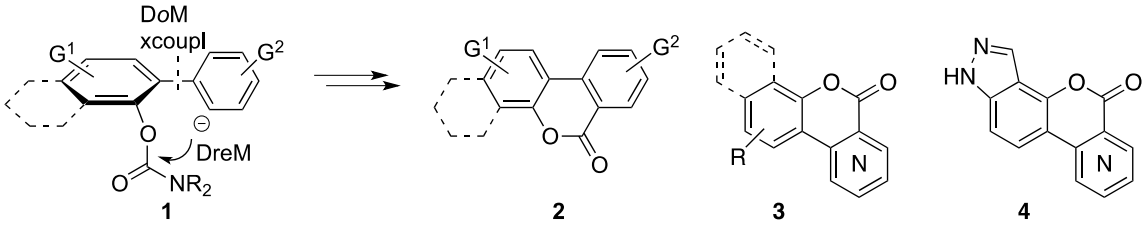
Abstract – A general strategy encompassing a Directed *ortho* Metalation (D*o*M) – Suzuki-Miyaura cross coupling and Directed remote Metalation (DreM) sequence for the synthesis of 5*H*-chromeno[4,3-*c*]pyridin-5-ones **5a-j**, 5*H*-chromeno[3,4-*b*]pyridin-5-ones **6a-j**, 5*H*-chromeno[3,4-*c*]pyridin-5-ones **13a-d**, 12*H*-benzo[7,8]chromenopyridin-12-ones **16a-c**, **17a-c**, and pyrido[3',4':4,5]pyrano[2,3-*e*]indazol-5(1*H*)-one analogues **18**, **28** is reported. Thus, using the powerful directed metalation group properties of aryl *O*-carbamates **9a-h**, **14a-c** metalation-boronation followed by Suzuki-Miyaura coupling with 3-bromopyridine affords a variety of azabiaryls **7a-i**, **8a-b**, **12a-c**, **15a-c** which, upon DreM reaction leads to several series of chromenopyridinones **5a-j**, **6a-j**, **13a-d** and pyridonaphthopyrones **16a-c**, **17a-c**. The synthesis of an unusual pyridopyranoindazolone **18** is also described.

Directed *ortho* metalation (D*o*M) and directed remote metalation (DreM), when combined with transition metal catalyzed cross coupling reactions, offer regioselective, efficient, versatile, and at times unique, strategies for distinct aromatic and heteroaromatic structural elements to be embodied in bioactive molecules and natural products.[1] As implementation of such tactics, we have recently reported the synthesis of the benzopyridopyranone, schumanniophytine[2] and a wide-ranging route to dibenzo-

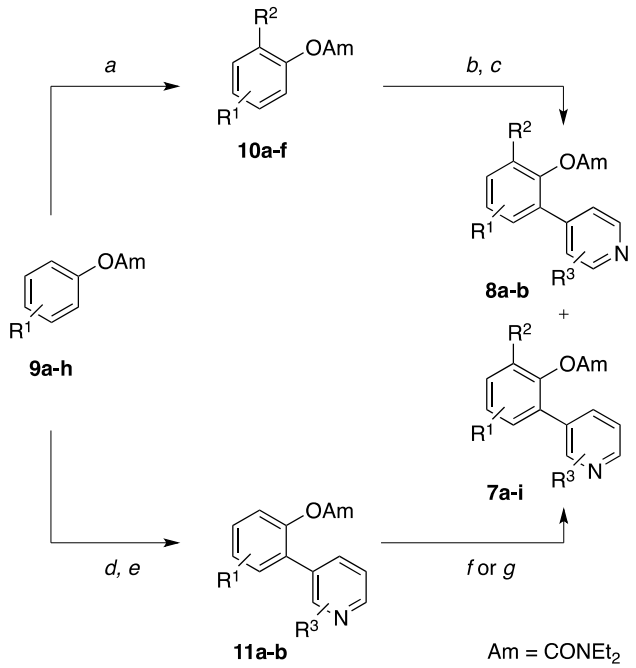
§ Dedicated to Ei-ichi Negishi, chemist extraordinaire, for an insightful early text in organometallic chemistry, friendship, and an impending Skimposium.

pyranones,[3] which involved key D*o*M – Suzuki-Miyaura cross coupling – DreM sequences. In view of the interest of the chromone and dibenzopyranone motifs as bioactive molecule targets,[4] and as a rational extension of the previous work,[2,3] we have undertaken to establish a general protocol for the preparation of annulated- and aza-dibenzopyranones involving the conceptual framework **1** → **2** (Scheme 1) and herewith report the synthesis of several series of derivatives encompassing the structural types **3** and **4**.



Scheme 1. Synthesis of dibenzopyranones (**1**→**2**) and annulated and aza analogues (**3**, **4**) by D*o*M - Suzuki-Miyaura cross coupling – DreM sequences.

For the initial studies concerning the synthesis of the 5*H*-chromeno[3,4-*b*]pyridin-5-ones **5a-j** and the 5*H*-chromeno[4,3-*c*]pyridin-5-one **6a-j** series **(**Scheme 4), the necessary azabiaryls **7a-i** and **8a**,**b** (Scheme 2) were prepared in a straightforward manner starting from aryl *O*-carbamates **9a-h** which, in turn, were obtained from the corresponding commercially available phenols. In preparation for the *O*-carbamate remote anionic Fries rearrangement, the necessary avoidance of the anionic *ortho* Fries reaction[5] was secured by a D*o*M – silylation sequence of **9a-d**,**f** to furnish compounds **10a-d**,**f**. Sequential D*o*M – boronation and Suzuki-Miyaura cross coupling with 3-bromopyridines and 4-halopyridines yielded azabiaryls **7a-i** in good to excellent yields.[6] With exception of examples **11a-b**, attempts to invert the sequence for **9a-h** by TES electrophile introduction after the D*o*M – boronation – Suzuki coupling failed under standard *s*-BuLi/TMEDA, *t*-BuLi and LDA metalation conditions. On the other hand, the introduction of the TMS electrophile to give the D*o*M product **10e** proceeded smoothly and, not surprisingly, subsequent sequential D*o*M – boronation and Suzuki-Miyaura cross coupling with 4-bromopyridine and 3-chloro-4-iodopyridine afforded azabiaryls **8a-b** in good to excellent yields. For the methoxy-derivatives, an inverted sequence was employed (**9g,h**→**11a,b**→**7h,i**), to avoid the combined two DMGs in-between-metalation effect,[7] which would have resulted in the formation of a different regioisomers. In contrast to the reaction of derivatives **9a-f**, the TES silylation of **11a**,**b** to give **7h**,**i** proved to be efficient.

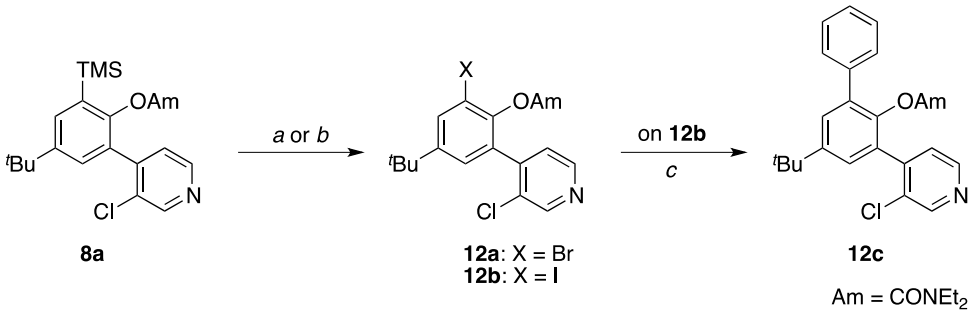


Scheme 2. Synthesis of azabiaryls **7a-f**,**h**,**i** and **8a**,**b**, and azateraryl **7g**. Reagents and conditions: (a) *s*-BuLi, TMEDA, THF, TMSCl, TESCl, -78 °C, 1 h, → rt; (b) *s*-BuLi, TMEDA, THF, B(O*i*-Pr)$_3$, -78 °C, 1 h, → rt, then 1 M HCl, pinacol; (c) [Pd(PPh$_3$)$_4$], halopyridine, Na_2CO_3, DME/H_2O, 90 °C, 16 h; (d) LDA, THF, B(O*i*-Pr)$_3$, -78 °C, 1 h, → 0 °C, then 1 M HCl, pinacol; (e) [Pd(PPh$_3$)$_4$], 3-bromopyridine, Na_2CO_3, DME/H_2O, 90 °C, 16 h; (f) LDA, THF, TESCl, -78 °C, 2 h, → rt; (g) *n*-BuLi, THF, -100 °C, 5 min, then TESCl, -100 °C, 90 min.

Table 1. Synthesis of azabiaryls **7a-f**,**h**,**i** and **8a**,**b**, and azateraryl **7g**.

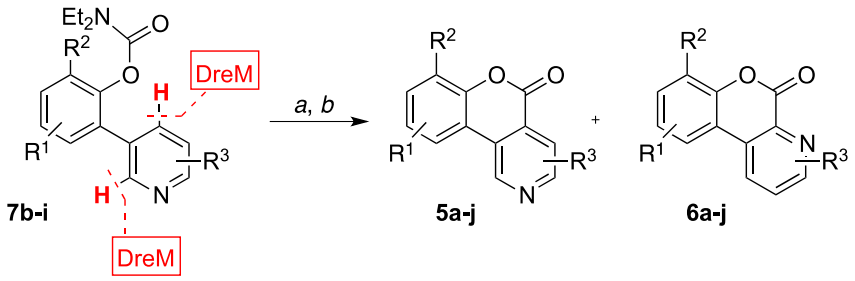
Starting Material			Product **10**, **11**		Product **7**, **8**			
	R^1	R^2	yield, %		R^1	R^2	R^3	yield, %
9a	H	TES	**10a**	51	**7a**	H	TES	H	49
9b	4-*t*-Bu	TES	**10b**	87	**7b**	4-*t*-Bu	TES	H	54
					7e	4-*t*-Bu	TES	2'-Cl	53
					7f	4-*t*-Bu	TES	6'-F	52
9c	4-OMe	TES	**10c**	92	**7c**	4-OMe	TES	H	74
9d	4-F	TES	**10d**	81	**7d**	4-F	TES	H	84
9e	4-*t*-Bu	TMS	**10e**	89	**8a**	4-*t*-Bu	TMS	3'-Cl	53
					8b	4-*t*-Bu	TMS	H	92
9f	4-Ph	TES	**10f**	70	**7g**	4-Ph	TES	H	46
9g	3-OMe	TES	**11a**	65	**7h**	3-OMe	TES	H	81
9h	3,5-OMe	TES	**11b**	62	**7i**	3,5-OMe	TES	H	81

The ready availability of silylated azabiaryl **8a** allowed a brief excursion to broaden the synthetic scope by virtue of sequential halo-ipsodesilylation[8] and Suzuki-Miyaura cross coupling chemistry (Scheme 3). Thus, treatment of **8a** with bromine and ICl smoothly led to the bromo-biaryl **12a** and iodo-biaryl **12b** derivatives respectively and the latter, upon cross-coupling with phenylboronic acid, furnished the corresponding azateraryl **12c** in 95% yield.



Scheme 3. Sequential halo-ipsodesilylation[8] and Suzuki-Miyaura cross coupling reactions to azateraryl **12c**. Reagents and conditions: (a) Br_2, CH_2Cl_2, 40 °C, 24 h, 59%; (b) ICl, CH_2Cl_2, rt, 3 h, 78%; (c) $[Pd(PPh_3)_4]$, $PhB(OH)_2$, Na_2CO_3, DME/H_2O, 90 °C, 4 h, 95%.

LDA metalation of **7b-i** under previously developed conditions[3b,5a] followed by treatment with conc. HCl:EtOH (1:1) mixture led to results shown in Scheme 4 and Table 2. Since pyridine ring C-H acidity is difficult to predict for **7** in view of inherent *O*-carbamate and pyridine nitrogen coordination effects and biaryl rotational barriers,[9] formation of mixtures of isomeric products resulting from C-2 and C-4 deprotonation – remote anionic Fries rearrangement was expected. Furthermore, protodesilylation during the acid-catalyzed lactonization step was anticipated. Thus, for *t*-Bu and Ph-azabiaryls **7b** and **7g**, besides equal amounts of the two expected isomers **5a - 6a** and **5c - 6c**, the protodesilylated products **5b** and **6b** and **5d** and **6d**, respectively were isolated, the former pair in about 50% yield while the latter products in less than 10% yields. For the fluoro-derivative **7d**, the [3,4-*b*]-isomer **6j** was obtained exclusively, albeit in low yield which may be due to competing benzyne formation[10] and polymerization reactions.



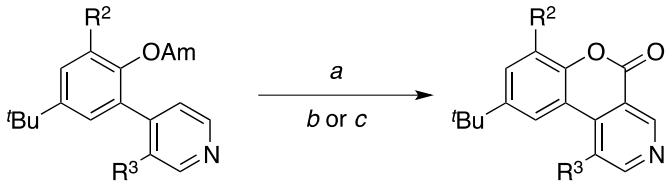
Scheme 4. Remote anionic Fries rearrangement – lactonization synthesis of **5a-j** and **6a-j**. Reagents and conditions: (a) LDA, THF, 0 °C → rt, 1 h; (b) EtOH, conc. HCl, 80 °C, 16 h, 3-76% (2 steps).

For chloro (**7e**) or fluoro (**7f**) pyridine, bearing only one remote metalation site, the formation of single regioisomers **5e** and **5f** was expected and observed, however, in low yields due to formation of an unidentified black material suggesting competitive formation of reactive intermediate pyridyne species.[11] As for the above cases **5b - 6b** and **5d - 6d**, the formation of the desilylated isomer of **5e** was observed; however, this was not the case for **5f**. Most interestingly, for **7h**,**i** bearing 3-methoxy groups, the exclusive formation of the isomer **5g**,**h** was observed.[12] The 4-methoxy biaryl (**7c**) led to the formation of both isomers with isomer **6i** being favored.

Table 2. Remote anionic Fries rearrangement – lactonization sequence to **5a-j** and **6a-j**

Starting Material	R^1	R^2	R^3	Product **5**, **6** yield, %			
7b	4-*t*-Bu	TES	H	**5a**	23	**6a**	20
7b	4-*t*-Bu	H	H	**5b**	18	**6b**	22
7g	4-Ph	TES	H	**5c**	37	**6c**	41
7g	4-Ph	H	H	**5d**	3	**6d**	4
7e	4-*t*-Bu	H	2'-Cl	**5e**	12	**6e**	0
7f	4-*t*-Bu	TES	6'-F	**5f**	24	**6f**	0
7h	3-OMe	TES	H	**5g**	62	**6g**	0
7i	3,5-OMe	TES	H	**5h**	76	**6h**	0
7c	4-OMe	TES	H	**5i**	17	**6i**	27
7d	4-F	TES	H	**5j**	0	**6j**	29

The 4-azabiaryl *O*-carbamates **8a** and **12a**,**c** were also subjected to the same LDA metalation conditions followed by lactonization (HCl or HOAc) to furnish chromenopyridinones **13a-d** (Scheme 5, Table 3). For **8a**, depending on the lactonization conditions, two different products **13a** and **13b** were obtained, with **13a** being the result of protodesilylation, a result which was not observed under the EtOH/HCl conditions. The yields of products **13a-d** were again found to be very low for halogen-substituted pyridines due to formation of unidentified black material suggesting competitive formation of reactive pyridyne species as discussed above.[11]



8a, 12a,c **13a-d**

Am = $CONEt_2$

Scheme 5. Remote anionic Fries rearrangement – lactonization sequence to **13a-d**. Reagents and conditions: (a) LDA, THF, 0 °C → rt, 1 h; (b) EtOH, conc. HCl, 80 °C, 16 h, 37% (2 steps); (c) i) glacial AcOH, 75 °C, 10 min, → 0 °C, ii) H_2O added, → 75 °C, 60 min, 8-51% (2 steps).

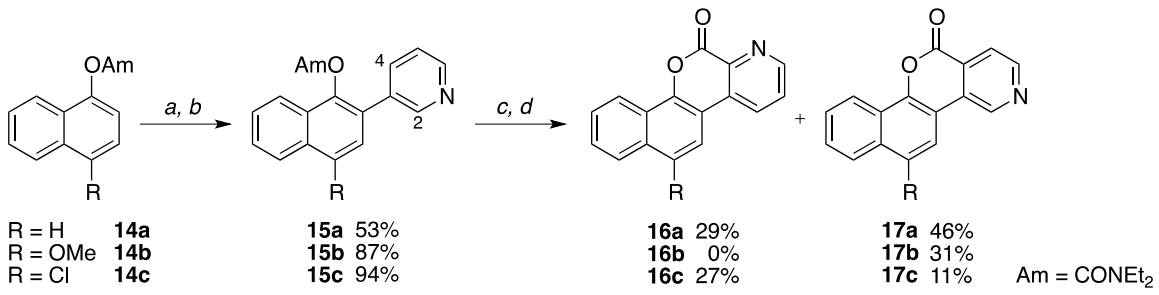
Table 3. Remote anionic Fries rearrangement – lactonization sequence to **13a-d**

Starting Material	R^2	R^3	Product yield, %	
8a	H	Cl	**13a**	37[a]
8a	TMS	Cl	**13b**	51[b]
12a	Br	Cl	**13c**	37
12c	Ph	Cl	**13d**	8

[a] conditions (b) were employed (Scheme 5)
[b] conditions (c) were employed (Scheme 5)

With these results in hand, the synthesis of more complex pyridonaphthopyrones was undertaken (Scheme 6). Thus the 6-OMe and the 6-Cl pyridyl naphthalene *O*-carbamates **14a-c**, prepared from commercially available 1-naphthol, 4-chloronaphthalen-1-ol and 4-methoxynaphthalen-1-ol, were subjected to metalation-boronation which, upon Suzuki-Miyaura cross-coupling with 3-bromopyridine gave the coupled products **15a-c** in good to excellent yield.[13]

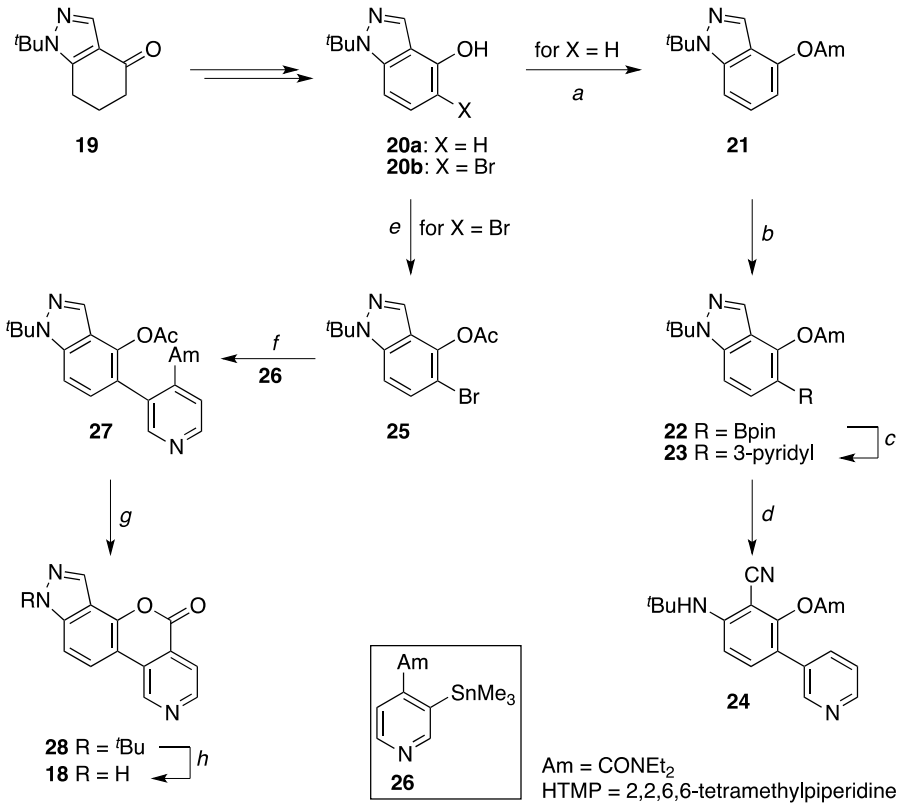
The DreM – lactonization sequence on **15a-c**, carried out under the standard LDA conditions, afforded pyridonaphthopyrones **16a-c** and **17a-c**. The yields and isomer distribution of products, while random and not rationalized without additional data, are undoubtedly related to the electronic nature of the substituent and the *O*-carbamate and pyridyl ring rotational barrier effects of the naphthalenylpyridines **15a-c**. Thus, with the reasonable assumption of high yielding lactonization, the lowest combined yields of products are for the substituted DreM products of **15b**, to give the single isomer **17b** in 31% yield, and **15c**, to give **16c**,**17c** in a combined 38% yield. The low yield for the chloro derivatives **16c**,**17c** may be due to competitive benzyne formation and further decomposition as well known to occur under LDA conditions for their simple aromatic counterpart compounds.[11] The through-bond electronic effect of the OMe groups on the pyridyl C-2' vs C-4' C-H acidity, favoring isomer **16b** over **17b** is difficult to appreciate without calculational data but is supported by a different study.[13]



Scheme 6. Synthesis of pyridonaphthopyrones **16a-c** and **17a-c**. Reagents and conditions: (a) *s*-BuLi, TMEDA, THF, B(O*i*-Pr)$_3$, -78 °C, 1 h, → rt, then 1 M HCl, pinacol, (not isolated); (b) [Pd(PPh$_3$)$_4$], 3-bromopyridine, Na_2CO_3, DME/H_2O, 90 °C, 16 h, 53-94% (2 steps); (c) LDA, THF, 0 °C → rt, 1 h (not isolated); (d) EtOH, conc. HCl, 80 °C, 16 h, yield 31-75% (2 steps).

To extend the scope of the D*o*M – Suzuki-Miyaura cross coupling – DreM strategy, the synthesis of a pyrazole-annulated pyridochromone **18** variant was undertaken (Scheme 7). α-Bromination of **19** gave the corresponding α-brominated cyclohexanone,[14] whose conversion by HBr elimination as well as other direct oxidative means to **20a** proved to be unsuccessful.[13] However, bromination conditions using $CuBr_2$ (2 equiv)[15] and dehydrobromination with Li_2CO_3/LiBr in DMF[16] afforded phenol **20a** (69% yield, over

two steps) which, upon carbamoylation, gave the desired *O*-carbamate **21** in good overall yield. D*o*M reaction followed by quench with triisopropyl borate and further treatment with pinacol provided the *ortho*-B-pinacolate **22** in 86% yield,[13] which was subjected to Suzuki-Miyaura cross coupling with 3-bromopyridine to furnish the pyridoindazole **23** in 99% yield. However, and perhaps not surprisingly in view of the higher acidity of indazole C-3 H over pyridine C-2/C-4 hydrogens,[17] treatment with LDA as well as other bases (*s*-BuLi, LiTMP) failed to induce either of the potential DreM reactions, resulting instead in the formation of the ring cleavage product **24** in quantitative yield. To overcome this impasse, an alternative, non-DreM approach was undertaken. Thus the bis α-bromination product of **19** was converted into the *ortho*-bromophenol **20b**,[13] which was acylated to **25** and the latter was subjected to a Stille cross coupling with the requisite *ortho*-stannylated benzamide **26** to give the azabiayl **27** in good overall yield (64%, four steps from cyclohexanone **19**). Lactonization (conc. HCl, EtOH 1:1) to give **28**, followed by de *t*-butylation (H_2SO_4) afforded the interesting pyridopyranoindazolone **18** in 66% yield.



Scheme 7. Synthesis of pyridopyranoindazolones **18** and **28**. Reagents and conditions: (a) KO*t*Bu, $ClCONEt_2$, THF, rt, 17 h, 68%; (b) *s*-BuLi, TMEDA, THF, $B(Oi\text{-}Pr)_3$, -78 °C, 1 h, → rt, then 1 M HCl, pinacol, 86%; (c) $[Pd(PPh_3)_4]$, 3-bromopyridine, Na_2CO_3, DME/H_2O, 90 °C, 16 h, 99%; (d) HTMP, *n*-BuLi, THF, -78 °C, 1 h, → rt, 2 h, 94%; (e) KO*t*Bu, Ac_2O, THF, 99%; (f) $[Pd(PPh_3)_2Cl_2]$, **26**, LiCl, CuI, DMF, 130 °C, 3 h, 88%; (g) EtOH, conc. HCl, 80 °C, 16 h, 89%; (h) H_2SO_4, 90 °C, 1 h, 74%.

In summary, the combined D*o*M – Suzuki-Miyaura – DreM strategy[1-3] has been extended to effective and

general syntheses of new heterocyclic systems 5*H*-chromeno[4,3-*c*]pyridin-5-ones and 5*H*-chromeno[3,4-*b*]pyridin-5-ones (**5a-j, 6a-j**, Scheme 4), 5*H*-chromeno[3,4-*c*]pyridin-5-ones (**13a-d**, Scheme 5), 12*H*-benzo[7,8]chromenopyridin-12-ones (**16a-c**, **17a-c**, Scheme 6), and pyrido[3',4':4,5]pyrano[2,3-*e*]indazol-5(1*H*)-one analogues (**18**, **28**, Scheme 7). While occurring in modest yields, the DreM reaction provides a method for intramolecular carbamoyl translocation to the alternate ring of a biaryl or azabiaryl. Alternative, direct cross coupling with more highly substituted benzamide or aryl boronic acid partners may be of lower efficacy due to steric requirements.[18] In the course of this work, new D*o*M chemistry of an indazole 4-*O*-carbamate (**21**, Scheme 7) has been achieved. Complete synthetic studies with bioactivity data will be published in due course.

ACKNOWLEDGEMENTS

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6. Representative example: To a solution of *s*-BuLi (4.89 mL, 6.86 mmol) was added a solution of TMEDA (0.790 g, 6.85 mmol) in THF (60 mL) at -78 °C and the whole was stirred for 10 min, before *O*-carbamate **10e** (2.00 g, 6.23 mmol, in 3.0 mL THF) was added. After 1 h at -78 °C, B(O*i*-Pr)$_3$ (2.32 g, 16.2 mmol) was added, the mixture was stirred for an additional 30 min, warmed to 0 °C, and acidified (< pH 5, 1 M aq HCl), and the whole was extracted (EtOAc), dried ($MgSO_4$) and concentrated. To the crude residue, 4-bromopyridine hydrochloride (1.21 g, 6.23 mmol), [Pd(PPh$_3$)$_4$] (0.140 g, 0.121 mmol), Na_2CO_3 (1.32 g, 12.5 mmol), degassed DME (20 mL) and degassed Na_2CO_3 (16 mL, 2 M aq solution) was added and the mixture was heated at 90 °C for 12 h, water was added, and the whole was extracted with EtOAc, dried and concentrated. Flash column chromatography (pet ether/EtOAc 1/1) followed by recrystallization (MeOH) yielded 2.28 g (5.72 mmol, 92%) of compound **8b** as a colourless solid; mp 86-89 °C (MeOH); IR (ATR) cm^{-1}: 1702; ^{1}H-NMR ($CDCl_3$, 400 MHz, 293K) δ 0.15 (s, 9H), 0.71 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H), 1.19 (s, 9H), 3.06 (br s, 2H), 3.32 (q, *J* = 7.2 Hz, 2H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.21 (d, *J* = 6.0 Hz, 2H), 7.38 (d, *J* = 2.4 Hz, 1H), 8.43 (d, *J* = 6.0 Hz, 2H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz, 293K) δ -0.71, 12.6, 13.9, 31.4, 34.5, 41.1, 41.4, 123.9, 127.1, 128.7, 131.8, 132.7, 146.8, 147.9, 149.6, 151.7, 153.3 ppm; LRMS (70 eV), *m/z* (%) = 398(40)[M$^+$], 100(100)[CONEt$_2^+$]; Anal. Cacld for $C_{23}H_{34}N_2O_2Si$ requires: C 69.30, H 8.60, N 7.03. Found: C 68.98, H 8.38, N 6.74.

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12. Representative example. A solution of LDA (1.88 mL, 2.25 mmol, freshly prepared 1.2 M solution in THF) was added to a solution of aryl-*O*-carbamate **7i** (0.250 g, 0.562 mmol) in THF (5.0 mL) at 0 °C, and the reaction mixture was warmed to rt, stirred for 1 h, quenched with water, and the whole was neutralized with 1 M HCl solution, extracted (EtOAc), dried ($MgSO_4$), and concentrated to give the crude phenol, which was purified by flash column chromatography (EtOAc). A solution of this material in a mixture of conc. HCl (4.0 mL, 80 equiv) and EtOH (equal volume to HCl) was

heated to 90 °C for 12 h, cooled, diluted with water, neutralized with satd aq Na_2CO_3 and the whole was extracted (EtOAc), dried ($MgSO_4$), and evaporated to dryness. Flash column chromatography (EtOAc) followed by recrystallization (EtOAc) yielded 0.109 g (0.424 mmol, 76%) of compound **5h** as a colorless solid; mp 188-189 °C (EtOAc); IR (ATR) cm^{-1}: 1727, 1615, 1597; ^{1}H-NMR ($CDCl_3$, 400 MHz, 293K) δ 3.92 (s, 3H), 4.08 (s, 3H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 8.18 (d, *J* = 4.8 Hz, 1H), 8.77 (d, *J* = 4.8 Hz, 1H), 10.2 (s, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz, 293K) δ 55.8, 56.1, 94.2, 96.1, 121.4, 125.0, 129.4, 147.2, 149.3, 154.0, 159.1, 160.3, 162.0 ppm; FAB (70 eV), *m/z* (%) = 258(100)[M^++1]; Anal. Cacld for $C_{14}H_{11}NO_4$ requires: C 65.37, H 4.31, N 5.44. Found: C 65.44, H 4.32, N 5.62.

13. Metalation-electrophile quench reactions with other electrophiles as well as the anionic Fries rearrangement of **21** occur smoothly providing a hitherto unexplored D*o*M playground. These reactions as well as an alternative route to isomeric pyridonaphthopyrones **16a-c**, **17a-c** will be reported in a full account of our studies.
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17. For H-D exchange studies for pyridine under various conditions, see J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Am. Chem. Soc.*, 1969, **91**, 5501. Calculated values (in DMSO): indazole pK_a = 36.3 (3-H), pyridine pK_a = 40.3 (C-4), 43.6 (C-2), see K. Shen, Y. Fu, J.-N. Li, L. Liu, and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568 and references therein.
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