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Directed *ortho* Metalation of Aryl Amides, *O*-Carbamates, and OMOM Systems. Directed Metalation Group Competition and Cooperation

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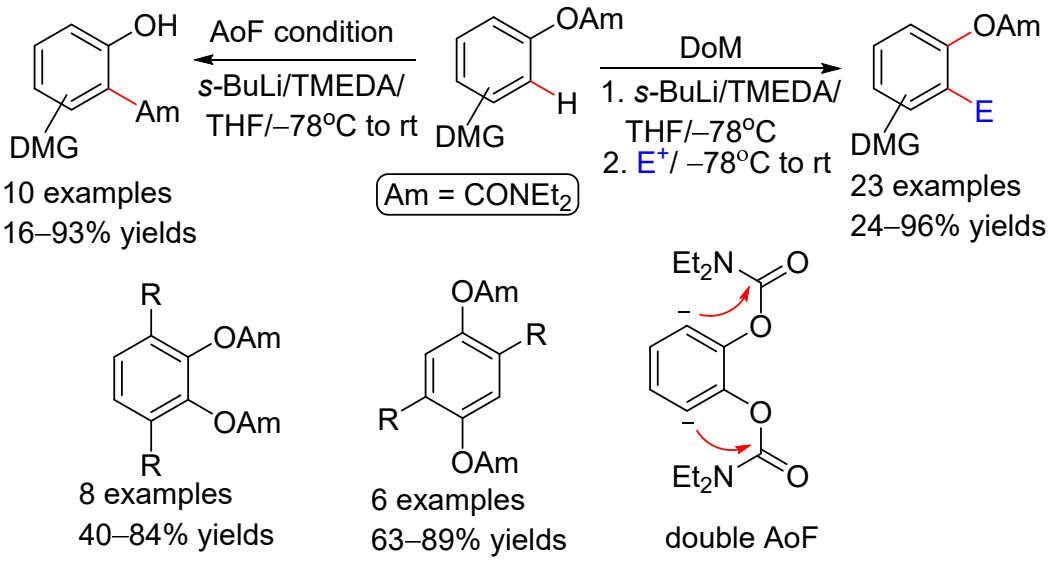
Abstract: A systematic study on the competitive metalation of four directed metalation group (DMG)-bearing derivatives (DMG = Cl, OMe, OMOM, and $CONEt_2$) in comparison with the $OCONEt_2$ DMG is described (Table 2). In addition, anionic ortho Fries (AoF) rearrangement (Table 3), the double metalation-electrophile quench of 1,2- and 1,4-*O*-carbamates (Scheme 2) and iterative metalation procedures (Scheme 3) is presented. The results provide new methodology for the synthesis of functionalized contiguously 1,2,3- and 1,2,3,4-substituted aromatic derivatives of difficult accessibility and potential broad utility. A comparison of the present methodology with previously developed routes is given in selected examples with emphasis on such substituted compounds (Table 5).

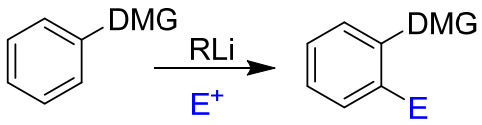


DoM = Directed *ortho* Metalation. AoF = Anionic *ortho* Fries

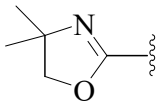
The Directed ortho Metalation (DoM) strategy has attained a prominent position, in concept and practice, for the construction of polysubstituted aromatics and heteroaromatics in both academic and industrial laboratories.[1]– [7] Among the extensive list of carbon- and heteroatom-based Directed Metalation Groups (DMGs) which have been developed,[1]–[4] a number may be considered to be adequately tested for reproducibility and widely adapted in synthesis. [1],[2] A hierarchal order of representative DMGs is shown in Table 1. The given order of ranking is based on the studies of numerous groups [1]– [3,],[8] – [18] using both inter- and intra-molecular competition experiments in which two DMG substrates and two DMGs on the same

substrate respectively are allowed to compete for one equivalent of base, followed by quench with a deuterium source (usually MeOD). While establishment of kinetic conditions (-78ºC, short reaction times) for the deprotonation is always sought, consideration of exothermicity of reaction and, significantly for the intramolecular experiments, resonance and inductive effects of one DMG on the other of metalation, give only qualitative character to these experiments. Nevertheless, the established hierarchy[19–36] has considerable value in allowing planning towards the synthesis of chosen substituted aromatics in context of *ortho*-, *meta*- and *para*-related DMG frameworks (Scheme 1). Thus, systems **1** and **3** are unexceptional in giving products of metalation as indicated by the arrows; *meta*-DMG system **2** has the beneficial but not completely invariable quality, observed for a number of DMGs, of metalation occurring synergistically in between the two DMGs.

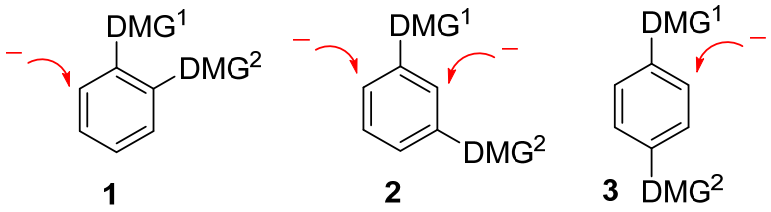
Table 1. Hierarchal Order of DMGs and Conditions for DoM [19–36]



DMG Power, Decreasing Order	DMG	Discovery [ref]	Conditions, temp
	$OP(O)(NR_2)_2$ ≥ $OCONR_2$	Nasman 1986[19] Snieckus 1983[20]	*s*-BuLi/TMEDA/THF/-103 to -93 ºC *s*-BuLi /THF/TMEDA /-78 ºC
	$SO_{(1,2)}$*t*-Bu	Stoyanovich1966[21] Snieckus 1989[10] Snieckus 1992[22]	*n*-BuLi/THF/none/-78 ºC *n*-BuLi/THF/-78 ºC
	$CONR_2$	Beak 1977[23]	*s*-BuLi/THF/TMEDA /-78 ºC
	CONHR	Hauser 1964[24]	*n*-BuLi/THF, Et_2O/TMEDA or none/-78 ºC
	SO_2NR_2	Hauser 1969[25]	*s*-BuLi /THF/none /-78 to 0 ºC
	n- SO_2NHR	Hauser 1968[26]	*n*-BuLi /THF/none/-10 to 25 ºC

		Meyers 1975 [27] Gschwend 1975[28]	*n*-BuLi or *s*-BuLi/THF or Et_2O/none/ -45 to 0 °C
	CO_2H	Mortier 1994[29]	*s*-BuLi /THF/ TMEDA /-90 °C
	OMOM ≈ OMEM	Christensen 1975[30] Townsend 1981[31] Ronald 1982[32] Ellison 1973[33]	*n*-BuLi or *t*-BuLi/Et_2O/none/-20 to 25 °C *n*-BuLi/Et_2O/none/rt
	NH(BOC)	Gschwend 1979[34]	*t*-BuLi/ THF/none/-50 to -20 °C
	NH(Piv)	Muchoswki[35]	*n*-BuLi/ THF/none/-40 °C
	F	Gilman 1957[36]	*n*-BuLi/THF/none/ -50 °C

As part of a comprehensive study of the *N,N*-dialkyl *O*-carbamate DMG, we reported on its DoM chemistry for the general synthesis of *ortho*-disubstituted derivatives as well as its anionic *ortho*-Fries rearrangement to obtain salicylamides. [37] In that work, we restricted the study to the bare *O*-phenyl carbamate, methyl substituted derivatives, and naphthyl *O*-carbamates. Herein we describe results of a systematic study on the competitive metalation of four DMG-bearing derivatives (DMG = Cl, OMe, OMOM, and $CONEt_2$) in comparison with the $OCONEt_2$ DMG. In addition, we report results on the double metalation-electrophile quench of 1,2- and 1,4-*O*-carbamates for the synthesis of contiguously tetrasubstituted derivatives and iterative metalation procedures of potential value in synthesis of aromatic molecules.

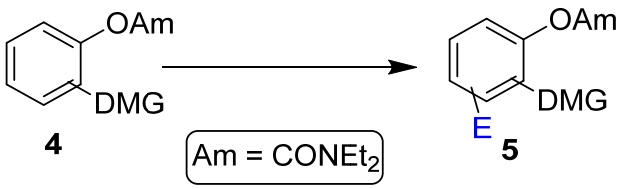


Metalation site indicated for $DMG^1 > DMG^2$
(**2** is an exception, see text)

Scheme 1. DoM Hierarchy of Isomeric DMG-substituted Aromatics

The studies on the four DMG-substituted *O*-carbamates are depicted in (Table 2). The variable conditions that can affect the reaction were brought under control by carrying out the reaction in the same flask and under the same temperature and solvent conditions for easy comparison. The structures of the products were assigned by analysis of their ^{13}C NMR spectra based on reduction of intensities of the signals for the substituted carbons compared to the corresponding signals in the starting materials (for details, see SI).[38]

Table 2. DoM Reactions of DMG-substituted Aryl *O*-Carbamates **4**



Entry	Compd	DMG	E^+	Product	DMG	E	Yield,%
1	**4a**	2-Cl	$ClCONEt_2$	**5a**	6-Cl	2-Am	78
2	**4a**	2-Cl	TMSCl	**5b**	2-Cl	6-TMS	79
3	**4a**	2-Cl	I_2	**5c**	2-Cl	6-I	93
4	**4b**	3-Cl	MeOD	**5d**	3-Cl	2-D	85 (80% d_1)
5	**4b**	3-Cl	PhCHO	**5e**	3-Cl	2-PhCH(OH)	81
6	**4b**	3-Cl	TMSCl	**5f**	3-Cl	2-TMS	89
7	**4c**	4-Cl	$ClCONEt_2$	**5g**	4-Cl	2-Am	77

8	**4d**	2-OMe	MeI	**5h**	2-OMe	6-Me	92
9	**4d**	2-OMe	$ClCONEt_2$	**5i**	6-OMe	2-Am	90
10	**4d**	2-OMe	TMSCl	**5j**	2-OMe	6-TMS	68
11	**4e**	3-OMe	MeOD	**5k**	3-OMe	2-D	93, 97% d_1
12	**4e**	3-OMe	MeI	**5l**	3-OMe	2-Me: 6-Me	90[b] (70:30)
13	**4e**	3-OMe	CO_2	**5m**	3-OMe	2-CO_2H 6-CO_2H	83[c] (76:24)
14	**4e**	3-OMe	I_2	**5n**	3-OMe, 5-OMe	2-I 2-I	75[d] (92:8)

15	**4f**	4-OMe	MeI	**5o**	4-OMe	2-Me	72
16	**4f**	4-OMe	DMF	**5p**	4-OMe	2-CHO	42[e]
17	**4f**	4-OMe	CO_2	**5q**	4-OMe	2- CO_2H	69
18	**4f**	4-OMe	$ClCONEt_2$	**5r**	4-OMe	2-Am	87
19	**4f**	4-OMe	TMSCl	**5s**	4-OMe	2-TMS	62
20	**4g**	2-OMOM	MeOD	**5t**	2-OMOM	6-D/3-D	88 (63% d_1)
21	**4g**	2-OMOM	$ClCONEt_2$	**5u**	6-OMOM	2-Am	48
22	**4h**	3-OMOM	MeOD	**5v**	3-OMOM	2-D	96 (55% d_1)
23	**4h**	3-OMOM	$ClCONEt_2$	**5w**	3-OMOM	2-Am	24[f]
24	**4i**	4-OMOM	MeOD	**5x**	4-OMOM	2-D	83 (66% d_1)
25	**4i**	4-OMOM	$ClCONEt_2$	**5y**	4-OMOM	2-Am	70
26	**4j**	3-OAm	MeOD	**5z**	3-OAm	2-D	76 (64% d_1)
27	**4k**	2-Am	MeOD	**5aa**	2-Am	6-D	86 (55% d_1)

28	**4k**	2-Am	ClCONEt$_2$	**5ab**	2-Am	6-Am 3-Am	80 (82:18)
29	**4l**	3-Am	MeOD	**5ac**	3-Am	2-D	85 (33% d_1)
30	**4l**	3-Am	ClCONEt$_2$	**5ad**	3-Am	2-Am	7[g]
31	**4m**	4-Am	MeOD	**5ae**	4-Am	2-D	85 (66 %d_1)
32	**4m**	4-Am	ClCONEt$_2$	**5af**	4-Am	2,4- di-Am: 3,4 di-Am	69 (3:2)

[a] Yields of isolated products; [b] N,N-diethyl *O*-(2-methyl -3-methoxy)phenylcarbamate, (70%) and N,N-diethyl *O*-(6-methyl-3-methoxy)phenylcarbamate, (30%); [c] N,N-diethyl *O*-(2-carboxy-3-methoxy)phenyl-carbamate (76%, converted into 2-hydroxy-6-methoxybenzoic acid) and N,N-diethyl *O*-(2-carboxy-5-methoxy) phenylcarbamate (24%, converted to 2-hydroxy-5-methoxybenzoic acid) see SI; [d] N,N-diethyl *O*-(2-iodo-3-methoxy) phenylcarbamate, and N,N-diethyl *O*-(2-iodo-5-methoxy) phenylcarbamate, see SI; [e] Salicyldehyde, 58%; [f] N,N-Diethyl-2-hydroxy-6-methoxymethoxybenzamide was isolated (50%); [g] In addition, 1, 2-bis-N,N-diethyl-3-hydroxyphthalamide was obtained in 16% yield.

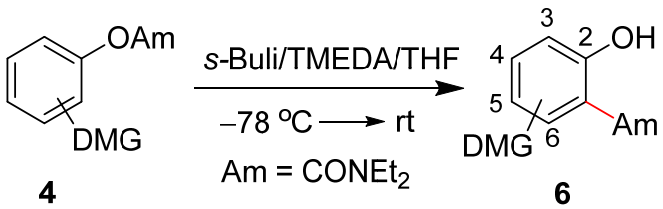
The chloro group is a very poor DMG on its own [1],[2] but contributes to regioselective 2-deprotonation when in a 1,3-relationship with a more powerful DMG. Thus, both 2- and 4-chloro *O*-carbamates **4a** and **4c** afford products **5a-c** and **5g** respectively while the 3-chloro derivative **4b** leads to 2-substituted products **5d-f** with selected electrophiles (entries 1–7). Similarly, the OMe DMG, originating with the discovery of the DoM reaction by Wittig and Gilman,[39]–[41] which has been widely and dependably used, [1], [42]–[44] does not interfere with clean deprotonation *ortho* to the *O*-carbamate as is seen in the conversion of 2- and 4-methoxy derivatives **4d** and **4f** into the corresponding products **5h-j** (entries 8-10) and **5o-s** (entries 15-19) while the 3-methoxy compound **4e** affords 2-substituted products **5k-n** (entries 11-14) albeit with less selectivity than the 3-chloro analogue **4b** (entries 5-6). The 2-, 3-, and 4-OMOM derivatives**, 4g, 4h,** and **4i** led to results showing less desirable regioselectivity. Thus, while **4g**, **4h** and **4i** all underwent highly regioselective deuteration to give compounds **5t, 5v**, and **5x** respectively (entries 20, 22 and 24), carbamoylation of these substrates gave variant observations. Good yield in the regioselective conversion of **4g** into **5u** (entry 21) was observed; however, treatment of **4h** with diethyl carbamoyl chloride afforded a mixture of 2-substituted product **5w** in addition to 2-hydroxy-6-OMOM benzamide (entry, 23, see footnote f, Table 2) which may have arisen by either A*o*F rearrangement or, perhaps less likely, by 2-carbamoylation followed by a de *O*-

carbamoylation reaction. The 4-OMOM derivative **4i**, on the other hand, gave **5y** (70%) (entry 25) as the major product, indicative of the greater DMG power of $OCONEt_2$ over OMOM. The 1,3-O-carbamoyl derivative **4j** was subjected to a metalation-deuteration experiment to cleanly afford the 2-deuterio product **5z** (76%, 66% d_1) (entry 26).

In the final series, the strong $CONEt_2$ DMG was tested in all three positional isomer variants (Table 2). The clear preference for a O-carbamate dominant DMG effect is seen in deuteration experiments on all three systems **4k, 4l,** and **4m** to give products **5aa, 5ac,** and **5ae** respectively (entries 27, 29, 31). Using the bulky $ClCONEt_2$ as the quenching reagent on **4k** afforded a mixture which also highly favored the *ortho* to O-carbamate substituted product **5ab** (entry 28). However, the 3-amide **4l** led to non-regioselective reaction to mixtures of isomer **5ad** (entry 30) and a phenol (see footnote [g]), resulting from an A*o*F rearrangement. The 4-amide **4m** gives deuterated (**5ae,** entry 31) and carbamoylated (**5af**, entry 32) products favoring regioselectivity for the *O*-carbamate DMG.

In order to extend and enhance the scope of the AoF rearrangement to DMG-substituted aromatics, a selected group of substrates from the above competition experiments was studied (Table 3). Thus, under the standard conditions (*s*-BuLi/TMEDA/THF/ -78^{o}) the 2-chloro and 2-methoxy *O*-carbamates **4a** and **4d** furnished the contiguously 1,2,3-substituted salicylamides **6a** and **6c** respectively (entries 1 and 3). The DoM (entry 7, Table 2) – AoF (entry 2, (Table 3), **4c** to **6b**) combination, was a pivotal tactic in the synthesis of the fungal metabolite ochratoxin B.[45]

Table 3. Competitive anionic *ortho* Fries Rearrangement of DMG-substituted Aryl *O*-Carbamates **4**



4 **6**

Entry	Compd	DMG	Product	DMG	Yld,%[a]
1	**4a**	2-Cl	**6a**	3-Cl	75
2	**4c**	4-Cl	**6b**	5-Cl	65
3	**4d**	2-OMe	**6c**	3-OMe	68
4	**4e**	3-OMe	**6d**	6-OMe: 4-OMe	68 (70: 30)
5	**4f**	4-OMe	**6e**	5-OMe	60
6	**4h**	3-OMOM	**6f**	6-OMOM	68
7	**4j**	3-OAm	**6g**	6-OAm	86
8	**4k**	2-Am	**6h**	3-Am	30
9	**4l**	3-Am	**6i**	6-Am	16
10	**6g**	6-OAm	**6j**	3-Am,6-OH	93

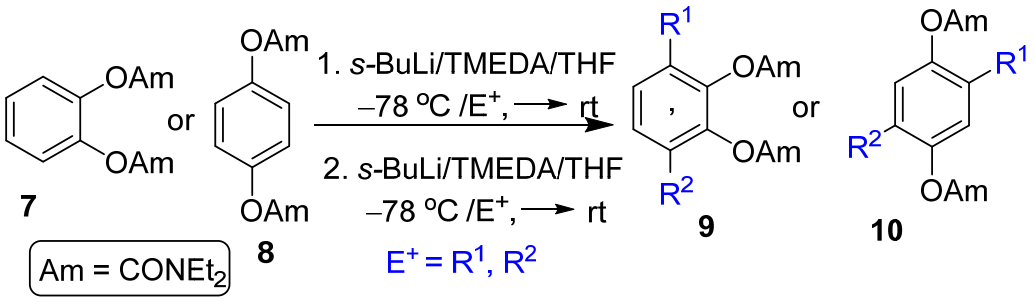
[a] Yields of isolated products.

The 3- and 4-methoxy O-carbamates **4e** and **4f** led to the corresponding isomers **6d** and **6e** (entries 4 and 5) with the former conversion lacking regioselectivity**.** Analogous to the corresponding 3-OMe derivative **4e**, the 3-OMOM **4h** and, more synthetically interesting, the 3-*O*-carbamate **4j**, afforded the in-between A*o*F rearrangement products **6f** (68% yield, entry 6) and **6g** (86% yield, entry 7) respectively. To conclude this study, two isomeric amide aryl O-carbamates **4k** and **4l** were subjected to the anionic *ortho*-Fries to afford **6h** (entry 8) and **6i** (entry 9) respectively, albeit both were obtained in low yields, the latter being a side product in the carbamoylation experiment (Table 2, entry 30). The availability of the phenol **6g** allowed a test of the anionic Fries in the presence of an acidic phenol group and this reaction, under 3 equiv *s*-BuLi/TMEDA conditions, led smoothly to the formation of the resorcinol **6j** in 93% yield.

Our original results concerning the generation of dianions of mono- and di-DMG containing derivatives [46] and thiophene 2-carboxamides [47] encouraged a more detailed study on the dilithiation reaction [48]

of the 1,2-di- and 1,4-di- O-carbamates **7** and **8** (Table 4). Dilithiated aromatics, generally generated by metal-halogen exchange processes,[49]– [53] are relatively unknown [54], [55] and underdeveloped species.[56]

Table 4. Dilithiation of Aryl 1,2- and 1,4-di-O-carbamates [a]



Entry	Compd	E^+	Product	R^1	R^2	Yld[b],%
1	**7**	MeOD	**9a**	D	D	84[c]
2	**7**	$ClCONEt_2$	**9b**	Am	Am	40
3	**7**	$ClCONEt_2$	**9c**	H	Am	61
4	**7**	TMSCl	**9d**	TMS	TMS	58
5	**7**	TMSCl	**9e**	H	TMS	78
6	**7**	$(MeS)_2$	**9f**	SMe	SMe	44
7	**7**	a) TMSCl; b. $ClCONEt_2$	**9g**	TMS	Am	55
8	**7**	a) TMSCl; b) $(MeS)_2$	**9h**	TMS	SMe	62

9	**8**	MeOD	**10a**	D	D	83[d]
10	**8**	$ClCONEt_2$	**10b**	Am	Am	63
11	**8**	TMSCl	**10c**	TMS	TMS	67
12	**8**	TMSCl	**10d**	H	TMS	78
13	**8**	$(MeS)_2$	**10e**	SMe	SMe	71
14	**8**	MeI	**10f**	Me	Me	89

[a] Dilithiation of the aryl dicarbamates **7** and **8** was effected under standard conditions (2.2 equiv l-BuLi/2.2 equiv TMEDA/THF/-78°C). Subsequent treatment with electrophiles led to 2,5-disubstitued products **9a-h** and **10a-f**; [b] Yields correspond to purified (chromatographed and/or distilled and recrystallized) materials; [c] Entry 1: 57% d_2, 43% d_1; [d] Entry 9: 64.2% d_2, 35.8% d_1.

Dicarbamates **7** and **8** (Table 4), readily obtained from catechol and hydroquinone respectively (see SI) were studied under conditions of 2 equiv of *s*-BuLi/TMEDA/THF/-78 ° C metalation conditions followed by quench with excess of electrophile. Using these conditions, followed by deuteration, resulted in formation of mono- and di-deuterated products in almost equal amounts (MS analysis) indicating incomplete dianion formation and therefore forecasting inefficient reactions with other electrophiles. Consistent with this observation, quenching with $ClCONEt_2$ and TMSCl respectively afforded disubstituted 1,2-di-O-carbamates **9b** and **9d** in modest yields. In order to establish mono anion reactivity, treatment of **7** with 1 equiv of s-BuLi/TMEDA under the same conditions followed by slightly more than 1 equiv of electrophiles resulted in the formation of monosubstituted product **9c** and **9e** respectively. The reasonably good yield of **9e** may be due to the compatibility or slow rate of reactivity of TMSCl with alkyllithium reagents. [57]–[60]

The last cases of dilithiation and electrophile quench experiments on **7** involved a $(MeS)_2$ quench and provided product **9f** (entry 6) in low yield. Sequential introduction of two electrophiles was also successful. Thus, by treatment of **7** with TMSCl followed by $ClCONEt_2$ and TMSCl followed by $(MeS)_2$ furnished the more diversely substituted products **9g** and **9h** (entries 7 and 8) respectively. The dianionic *ortho,ortho*-Fries rearrangement of **7**, carried out by treatment with 2 equiv of base and warming the

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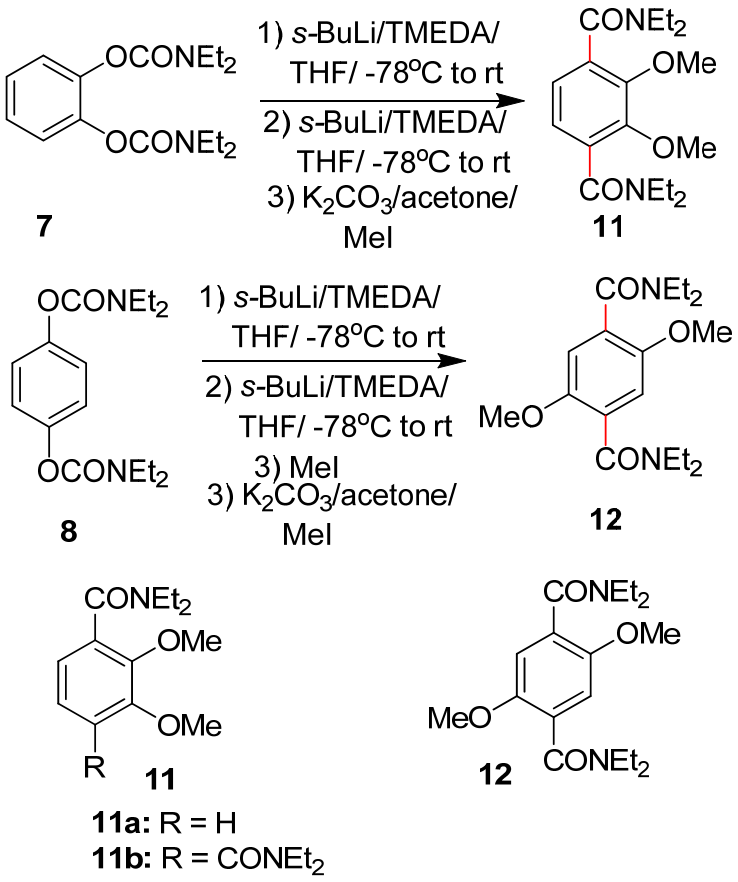
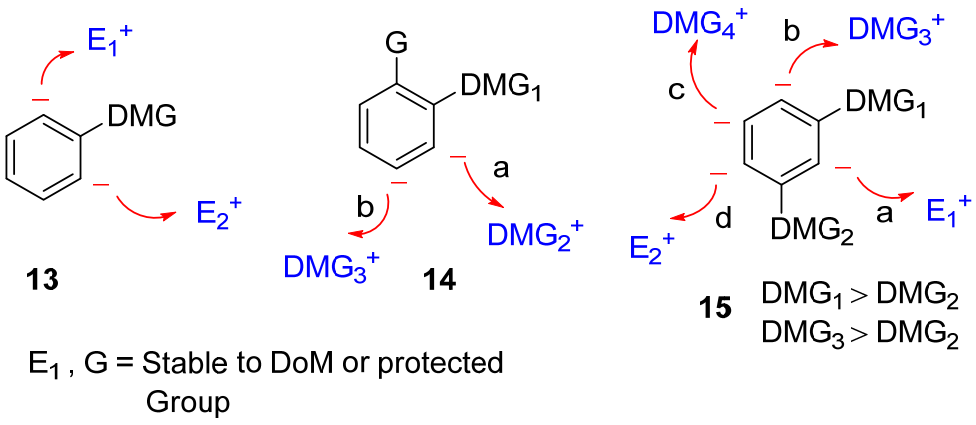
solution to room temperature gave, after standard methylation, the terephthalamide **11a** (22% yield) in addition to the known benzamide **11b** (9% yield). [61]

Similarly, the 1,4-di-O-carbamate **8** was subjected to the 2 equiv of s-BuLi/TMEDA metalation conditions and electrophile quench reactions to afford a series of symmertrically substituted products **10a-f** (entries 9-14). In addition, whereas 1,2-di-O-carbamate **7** had given an inseparable and therefore uncharacterizable mixture of methylated products, **8** afforded, upon treatment with MeI, dimethylated derivative **10f** in high yield (entry 14). Mono anion generation of **8** was accomplished as shown by its treatment with TMSCl to furnish product **10d** (entry 12). A double anionic *ortho* Fries rearrangement of **8** was also achieved to give, after treatment with methyl iodide, the paraphthalamide **12** in low yield.



Iterative Metalation

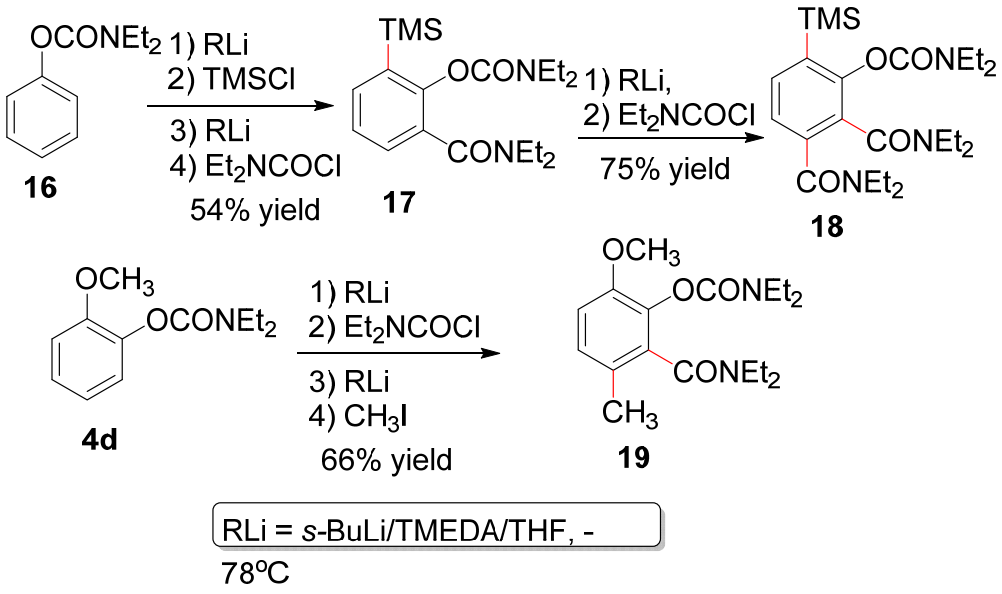
Consideration of DoM reactions in context of iterative, multiple metalations reveals an overabundance of possibilities. Thus, in the basic consideration (Scheme 2), sequential metalation-electrophile quench with two different or same electrophiles can furnish, with the caveat that E_1 must be stable to the strongly basic conditions or a suitably protected group, a 1,2,3-substituted aromatic as conceptualized in **13**. The presence of an unreactive or protected group G as in **14** provides the opportunity to introduce a second DMG_2 (step a) by use of an appropriate electrophile (as has been demonstrated for the $ClCONEt_2$ DMG in examples collected in (Table 1). The thus introduced DMG_2, if relatively strong, [37] may serve for further DoM reaction (step b) to introduce DMG_3. The continuation of this first step of walk-around-the-ring anionic chemistry may be envisaged. With regard to two DMGs, the *ortho*-, *meta*- and *para*-relations may be envisaged, of which only the *meta*-DMG_1-DMG_2 isomer is considered in **15**. Thus, synergistic effects of DMG_1 and DMG_2 affect the introduction of E_1 (step a). Given that $DMG_1 > DMG_2$ in metalation power, a DMG_3 may be introduced (step b) and consideration of $DMG_3 > DMG_2$ will allow a further metalation and DMG_4 introduction (step c). Conceptualization **15** has been previously achieved in our laboratories. [62], [63]



Scheme 2. Conceptual Framework of Walkaround around-the-ring Strategies

In the present study, contemplation of the *ortho* and *para* two DMG isomer systems leads to considerable numbers of combinations. Two cases, based on the *O*-

carbamoyl DMG were tested in iterative protocols (Scheme 3). Thus, the original N,N-diethyl phenyl O-carbamate **16**, upon sequential metalation, silylation, metalation and carbamoylation with equivalent amounts of base and electrophile and maintaining the -78 °C, gave the trisubstituted substance **17** in reasonable yield. An attempt to carry out a third metalation and quench with $ClCONEt_2$ in the same pot to obtain **18** failed. However, isolation and purification of **17** followed by use of the standard conditions for deprotonation and treatment with $ClCONEt_2$ gave the contiguously tetrasubstituted aromatic molecule **18** in good yield.



Scheme 3. Iterative DoM Strategies Exemplified

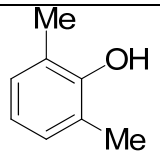
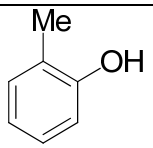
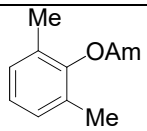
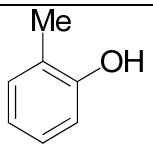
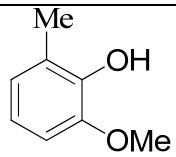
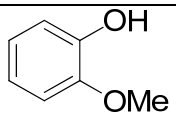
In the second tested case for iterative DoM reactions, the 2-methoxy O-carbamate **4d** was subjected to the one pot, two metalation-electrophile quench sequences using $ClCONEt_2$ and MeI as quenching reagents to afford a further case of a contiguously tetrasubstituted product **19** in acceptable yield. Both products may be amenable to further DoM chemistry.

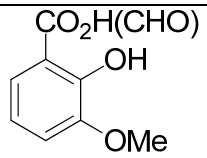
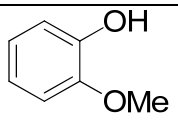
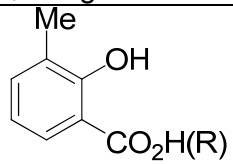
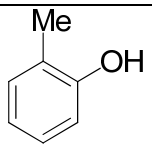
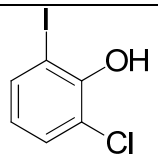
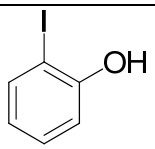
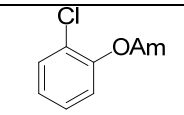
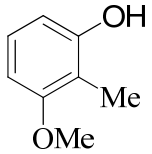
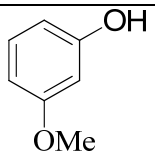
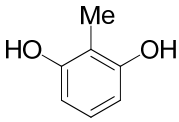
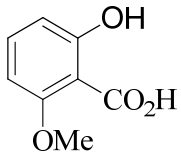
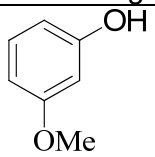
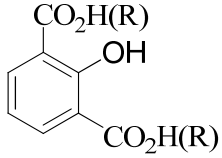
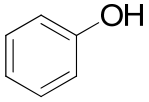
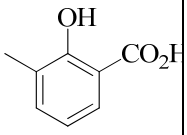
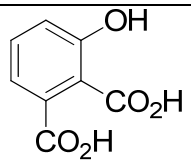
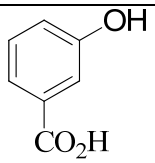
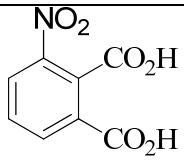
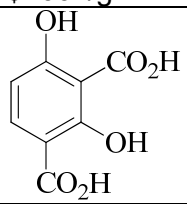
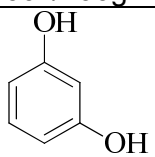
Summary, Comparative Analysis, and Conclusions

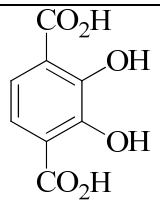
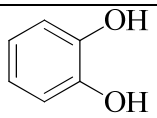
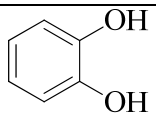
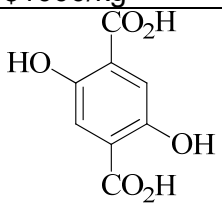
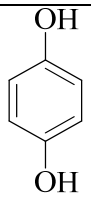
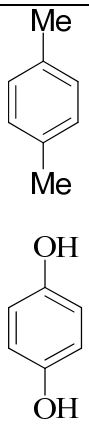
The predisposition for the formation of 1,2,3-substituted products by DoM and AoF processes (to highlight at random, **5d-f, 5v-w**, **5ad (**Table 2) and **6a, 6c, 6g,** (Table 4) and their conversion into phenol [20, 64, 65] and benzaldehyde and benzoic acid derivatives [20, 64, 65] presents methodology of considerable advantage over other routes for the preparation of such contiguously substituted aromatics. In addition, potential for the synthesis of more highly substituted products owing to the nature of readily available starting materials may be gleaned from Tables 2 and 3 as well as from the dilithiation reactions which lead to tetrasubstituted products, especially those of contiguous 1,2,3,4-substitution (Table 4).

To provide an awareness of the *O*-carbamate DoM methodologies in comparison to other synthetic procedures, a brief compilation of selected cases with focus on 1,2,3-trisubstituted systems are depicted in Table 5.

Table 5. Competitive Methods for the Synthesis of Substituted Aromatics

		Synthetic Method				
		DoM			Other	
		Starting Material (SM)	ArOAm Product [b] (oy)[c]	Steps to TM[d] (oy)[c]	Starting Material (SM)	Steps to TM[e] (oy)[c] [ref]
1	 $10s/100 g	 $100s/kg	 (50%) [66b]	3		2, 36% [66a]
2	 $ 100s/g	 $100s/kg	**5h** (92 %)	3 (55%)		N/A[f]

3	 $10s/g		**5i** (90 %)	3 (54%)		N/A[f]
4	 $10s/100g		**41b** (70 %)	3 (42%)		4, 30% [67]
5	 $10s-100s/g	 $70s-200s/100g	**5c** (93 %)	3 (56%)	 Am = CONH(*i-Pr*	5, [68][g]
6	 $10/g	 $60s-100s/100g	**5l** (~70%)	3 (42%)		4, 26% [69]
7	 $100s/g		**5m** (~76%)	3 (45%)		N/A[f]
8	 $100s/g		**5ab** (~82%)	3 (~50%)	 $10s/100g	2, 46-61% [70]
9	 $100s/g	 $40s-60s/100g	**6i** (16 %)	3 (10%)	 $10s/100g	5, [71a]; 6, 9% [71b]
10			**6j** (93 %)	3 (52%)		N/A[f]

11	 $1000/kg		**9b** (40 %)	2 (35%)		1, 35-56% [72]
12	 $10s-100s/g		**10b** (63%)	3 (37%)		1. 22-93% [73]

[a] From various commercial sources (April, 2017 prices) given in factor of 10/g in USD. Two values indicate different suppliers; [b] Structure number corresponds to the O-carbamate product obtained from the given obtained using SM; [c] oy = overall yield; [d] An approximate yield based on carbamate to phenol conversion at 85% which represents average yield for the Schwartz reagent (see, ref: [64]; [e] Calculated from the most efficient reported route. [f] No commercial source or reported synthesis. [g]oy not available; last step (deprotection) proceeds in 94% yield.

2,6-Dimethylphenol (entry 1), a relative simple an inexpensive molecule, available by high pressure/temperature industrial chemistry from *ortho*-cresol in two steps and 36% yield [66a] and is available from the same starting material in same number of steps and 50% yield [66b] by the *ortho*-lithiation of N,N-diethyl *O*-(2-tolylcarbamate (**6,** Scheme 2 [37]).

On the other hand, the expensive, commercially available but, to the best of our knowledge, unreported 2-methoxy-6-methylphenol (entry 2) may be prepared from commercially available 2-methoxyphenol via the corresponding *O*-carbamate derivative **5h** in 3 steps and estimated 55% overall yield. The commercially available 2-hydroxy-3-methoxybenzoic acid and its corresponding aldehyde (entry 3) have an extensive history as natural products of biological and ecological significance.
Both compounds may be prepared by DoM chemistry from 2-methoxyphenol via **5i** in reasonable overall yield. The corresponding 2-hydroxy-3-methyl benzoic acid and aldehydes (entry 4) are surprisingly inexpensive at least based on the reported [67]

synthesis which is carried out over four steps in atom-uneconomical fashion. According to the carbamate DoM route via **41b**, this molecule should be available in three steps and 42% overall yield.

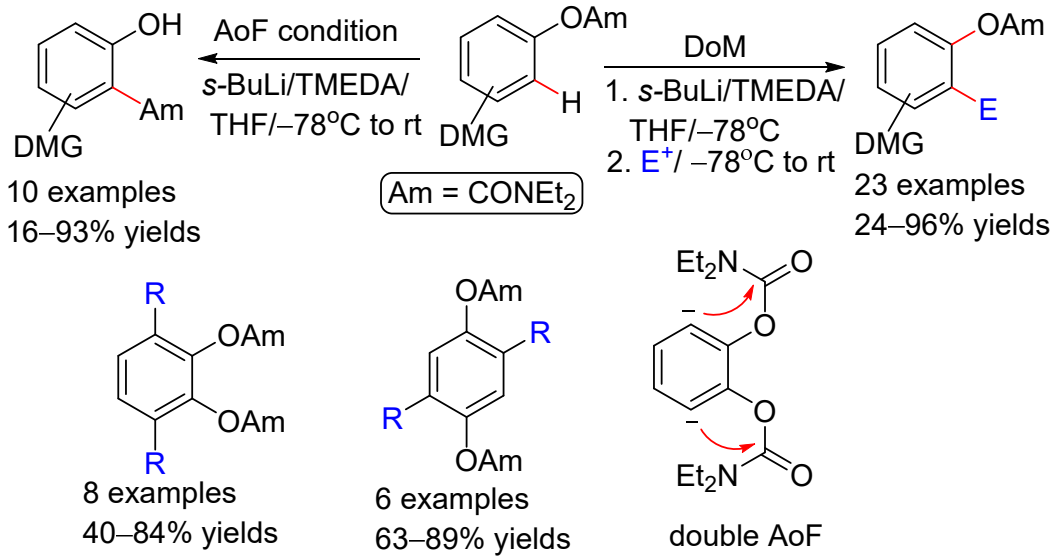
The synthesis of the expectedly expensive differentially halogenated phenol (entry 5) is a good illustration of the value of DoM chemistry since it has been prepared from 2-iodophenol (via **5c**) in acceptable yield; [68a] it has been also prepared from the less costly 2-chloro-phenol in unreported yield.[68b] The in-between two DMG facility is a hallmark of the DoM approach as may be gleaned from the synthesis of 3-methoxy-2-methyl- and 2-carboxy-phenol (entries 6 and 7). Starting from common 3-methoxyphenol, target molecule 3-methoxy-2-methyl phenol is obtained either via the carbamate (**5l**) (three steps, 42% overall yield) or 2,6-dihydroxytoluene (complicated four steps, 26% overall yield).[69] The corresponding 2-carboxylic acid (entry 7) may be obtained via O-carbamate **5m** in modest 45% yield; its synthesis is not reported. The expensive 2-hydroxyisophthalic diester (entry 8) maybe prepared by several classical routes, [70a, 70b] the best and most recent of which requires the acceptably priced 3-methylsalicylic acid as starting material.[70a] Alternatively, it should be available in 3 steps and overall ~50% yield via D*o*M-A*o*F chemistry (**5ab**) followed by hydrolysis. 3-Hydroxyphthalic acid (entry 9) and its anhydride are available by a route [71] based on traditional aromatic chemistry from the modestly priced 3-nitrophthalic acid. The O-carbamate route, via **6i** does not promise an efficient route but it may also be prepared relatively efficiently by DoM chemistry from 2-methoxybenzamide.[61]

Entries 10-12 give examples of contiguously tetrasubstituted aromatics which may be prepared by *O*-carbamate DoM tactics. The routes follow starting with O-dicarbamates prepared from corresponding diphenols which lead to DoM products **6j, 9b**, and **10b** and should provide, by reduction and hydrolysis reactions, the respective isophthalic (entry 10) and terphthalic (entries 11 and 12) target molecules in reasonably short routes and modest yields. Previous syntheses,[72,73] although developed on scale for commercial production, require high temperatures, dangerous materials, and corrosive reagents and proceed in variable yields.

The compilation of Table 5 places O-carbamate DoM methodology against other reported reaction paths for the construction of polysubstituted aromatics. We

emphasize selected groups of contiguously 1,2,3- and 1,2,3,4-substituted derivatives in order to highlight the meagre availability of these structural classes from commercial sources. Although yields via DoM chemistry are partially estimates based on average yields expected by reduction and hydrolysis of phenol and amide functional groups, these approximations should be sufficient for decisions made in a synthetic endeavors of polysubstituted aromatic targets.

In conclusion, work presented in in this and the sequel report [37] demonstrates the superiority of the *O*-carbamate function as an *ortho* director over the chloro, methoxy, tertiary amide and methoxymethoxy groups in DoM chemistry and leads to the conclusion that it is the functionality of paramount choice among the oxygen-based DMGs. Routes the synthesis of a variety of substituted aryl O-carbamates have been demonstrated by DoM and AoF rearrangement reactions. Especially valuable are processes which lead to contiguously 1,2,3- and 1,2,3,4-substituted aromatic arrays that are difficult to achieve or unavailable by alternative and traditional methods. The competitive and advantageous nature of O-carbamates DoM reactions is illustrated in selected examples of comparison with those previously reported (Table 5). Although considerable results are already available, the further application of the described methodology in synthesis may be anticipated.



DoM = Directed *ortho* Metalation. AoF = Anionic *ortho* Fries

Experimental

Standard Procedures

Procedure 1. Lithiation of *O*-Aryl Carbamates with *s*-BuLi/TMEDA. A solution of the carbamate in dry THF (5-10 mL) was added dropwise by syringe injection to a stirred solution of a 1:1 *s*-BuLi-TMEDA complex in dry THF at -78°C (or -90°C as indicated) under nitrogen. After a reaction period (5 min to 1h as indicated), the mixture was treated with an electrophile. The resulting solution was then allowed to warm to rt over 8 h after which a few mL of aqueous NH_4Cl solution was added and the THF was removed in vacuo. Subsequent standard workup gave the crude product. The details of the lithiation procedures which follow the above standard procedure are summarized in the order as follows: name and number of molar equivalents of alkyllithium reagent used, reaction temperature, lithiation time, and name and number of molar equivalents of electrophile used.

Procedure 2. Lithiation of *O*-Aryl Carbamates with LDA. To a THF solution of freshly distilled diisopropylamine (1.1 equiv) was added *n*-BuLi (1.1 equiv) at 0°C under nitrogen and the solution was stirred for 30 min. The resulting solution of lithium diisopropylamide was cooled to -78° C and the required carbamate (1.0 equiv) in THF (5 mL) was added by syringe injection. After 1 h, an electrophile was added and the resulting solution was allowed to warm to rt over 8 h and processed in the normal manner (as described in Procedure 1) to give the crude product.

Relative Directed Metalation Abilities of Chloro, Methoxy, Carbamoyloxy, Tertiary Amide and Methoxymethoxy Groups by Intramolecular Competition Experiments.

The intramolecular competition in metalation of methoxymethoxy (MOM) and the tertiary amide ($CONEt_2$) positioned *ortho*, *meta* and *para* with respect to a

carbamoyloxy group ($OCONEt_2$) was examined. The sites of lithiation were determined by analysis of the ^{13}C NMR spectra show a reduction in intensities of the signals for the substituted carbons in the products compared to the corresponding signal in the starting materials according to the method of Beak.[3]

The position of substitution was assigned by using established additivity of individual ^{13}C NMR substituent chemical shifts either from the literature [4], [5] or as determined (Table 5). The shift value expresses the direction and magnitude of a carbon's chemical shift difference from δ 128.5 ppm, the shift of benzene. The experimental chemical shift difference $(\Delta\delta)$ of aromatic carbons of O-phenyl carbamate were found to fit reasonably well with the chemical shift difference $(\Delta\delta)$ of aromatic carbons of phenyl acetate. These findings were also confirmed by comparing the ^{13}C NMR spectrum of N, N-diethyl *O*-(N,N-diethyl carbamoyl)phenyl carbamate following the method of Beak.[3] The method is exemplified by the calculations of chemical shift values of aromatic carbons in compounds **5i** and **5ab.**

Directed ortho Metalation (DoM) Reactions

Standard Procedures

Procedure 1. Lithiation of *O*-Aryl Carbamates with *s*-BuLi/TMEDA. A solution of the carbamate in dry THF (5-10 mL) was added dropwise by syringe injection to a stirred solution of a 1:1 *s*-BuLi-TMEDA complex in dry THF (60 ML) at -78°C under nitrogen. After a reaction period 1h, the mixture was treated with a THF solution of an electrophile. The resulting reaction mixture was then allowed to warm to rt over 8 h after which a few mL of aqueous NH_4Cl solution was added and the THF was removed in vacuo. Subsequent standard workup gave the crude product. The details of the lithiation procedure which follow the above standard procedure

are summarized in the order as follows: name and number of molar equivalents of alkyllithium reagent used, reaction temperature, lithiation time, and name and number of molar equivalents of electrophile used.

Anionic *ortho*-Fries Rearrangement: 1,3- or 1,4- 0 --> C Carbamoyl Migration

Lithiation of the appropriate carbamate was carried out with *s*-BuLi (Procedure **1**): or LDA (Procedure **2**). Standard workup and column chromatography using 1:1 (v/v) EtOAc-hexane as eluent/distillation/recrystallization] and the resulting lithiated carbamate, without being quenched with electrophiles, was allowed to warm to room temperature over 8 h. Processing in usual manner as described in Procedure **1** or **2** gave the crude product.

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