ORGANIC LETTERS

2010
Vol. 12, No. 10
2198−2201

Combined Directed *ortho* Metalation−Halogen Dance (HD) Synthetic Strategies. HD−Anionic *ortho* Fries Rearrangement and Double HD Sequences

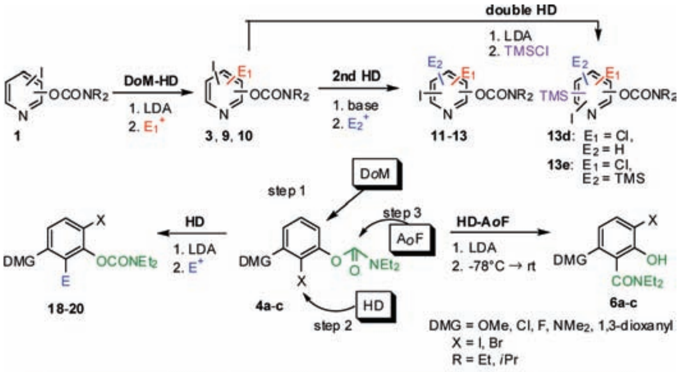
Ricarda E. Miller,[†] Toni Rantanen,[‡] Kevin A. Ogilvie,[‡] Ulrich Groth,[†] and Victor Snieckus*,[‡]

Fachbereich Chemie and Konstanz Research School of Chemical Biology, Universität Konstanz, Fach 720, D-78457 Konstanz, Germany, and Queen's University, 90 Bader Lane, Chernoff Hall, Kingston, ON K7L 3N6, Canada

snieckus@chem.queensu.ca

Received February 26, 2010

ABSTRACT



DoM = Directed *ortho* Metalation; HD = Halogen Dance; AoF = Anionic *ortho* Fries rearrangement.

A general and efficient directed *ortho* metalation (DoM)−halogen dance (HD)−electrophile quench sequence for the synthesis of trisubstituted pyridyl *O*-carbamates is described. A second HD sequence furnishes highly functionalized tetrasubstituted pyridines. Furthermore, a hitherto unobserved double HD rearrangement is reported. Under similar LDA conditions, aromatic *O*-carbamates with OMe, Cl, and F substituents (4a−c) undergo either a HD−electrophile quench sequence, 4a−c → 18−20, or a HD−anionic *ortho* Fries rearrangement, 4a−c → 6a−c, respectively.

The combination of two or more reactions, either sequentially with and without the isolation of intermediates or in one pot, is an increasingly significant quest of the modern synthetic organic chemist.[1] In our continuing efforts to enhance the utility of the directed *ortho* metalation (DoM) reaction[2] and its link to other effective synthetic tactics,[3] we have undertaken a study aimed to bridge DoM to the halogen dance (HD)[4] in pyridine and benzenoid ring systems to establish a synthetic methodology for the preparation of contiguously and usefully functionalized derivatives. Schlosser and Quéguiner have contributed significantly to the HD of haloaromatics and halopyridines (mainly Cl, F, I),[4,5] and the reaction has witnessed sparse application in natural product synthesis.[6]

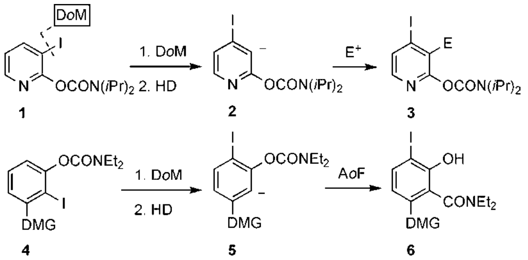
As part of our long-standing interest in the DoM chemistry of aryl and pyridyl systems of one of the most powerful directed metalation groups (DMG),[2,7,8] the *O*-carbamate, we considered the potential of hitherto unknown DoM−HD chemistry of aryl and pyridyl *O*-carbamates, e.g., **1** → **2** → **3** (Scheme 1). We now report results that demonstrate (a) the capability of all three isomeric pyridyl *O*-carbamates to undergo this useful combined chemistry and their further HD reactions; (b) the hitherto unknown one-pot HD-anionic *ortho*-Fries rearrangement, **4** → **5** → **6**; and (c) first examples

---

[†] Universität Konstanz.
[‡] Queen's University.

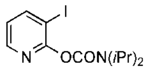
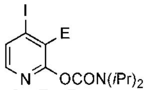
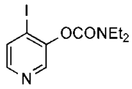
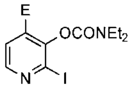
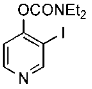
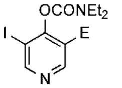
10.1021/ol100493v © 2010 American Chemical Society
Published on Web 04/16/2010

Scheme 1. HD of Pyridyl and Aryl *O*-Carbamates[a]



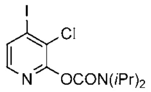
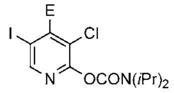
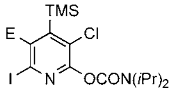
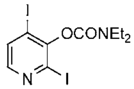
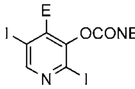
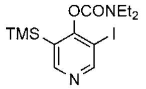
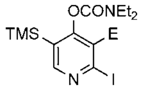
[a] DoM = directed *ortho* metalation; AoF = anionic *ortho* Fries rearrangement.

Table 1. Halogen Dance on Isomeric Pyridine *O*-Carbamates[a]

substrate	method[d]	E	product	yield (%)[b]
				
1	A	MeOD	**3a**, E = D	88
1	A	MeI	**3b**, E = Et	73[c]
1	A	C_2Cl_6	**3c**, E = Cl	77
1	A	I_2	**3d**, E = I	33[e]
				
7	B	MeOH	**9a**, E = H	90
7	B	ClCONEt$_2$	**9b**, E = CONEt$_2$	68
7	B	C_2Cl_6	**9c**, E = Cl	68
7	B	I_2	**9d**, E = I	95
				
8	C	TMS	**10a**, E = TMS	82
8	C	ClCONEt$_2$	**10b**, E = CONEt$_2$	58
8	C	C_2Cl_6	**10c**, E = Cl	65
8	C	I_2	**10d**, E = I	95

[a] For additional E quench examples, see Supporting Information. [b] Isolated yields. [c] Instead of the expected E = Me product, the ethyl product was obtained as a result of lateral metalation. [d] Methods. A: LDA (2.2 equiv)/−78 °C/60 min. B: LDA (1.1 equiv)/−78 °C/30 min. C: LDA (1.1 equiv)/−78 °C/45 min. [e] The low yield in the case of **3d** arises from extensive halogen scrambling during the reaction, presumably due to the presence of an extra equivalent of base, which is not quenched by the electrophile as in **3a**−**c**. After electrophile addition, immediate quench with MeOH was required to attain this meager yield.

Table 2. Secondary Directed *ortho* Metalation−Halogen Dance Sequence on Primary HD Products **3c**, **9d**, and **10d**

substrate	method	E	product	yield [%][a]
				
3c	A	H_2O	**13a**, E = H	75
3c	A	MeI	**13b**, E = Me	77
3c	A	Br_2	**13c**, E = Br	50[b]
3c	A	TMSCl (1.1 equiv)		56
3c	A	TMSCl (3.0 equiv)	**13d**, E = H **13e**, E = TMS	34
				
9d	B	H_2O	**12a**, E = H	69
9d	B	MeI	**12b**, E = Me	61
9d	B	TMSCl	**12c**, E = TMS	88
9d	B	Cl_3CCCl_3	**12d**, E = Cl	77
				
10d	C	MeOH	**11a**, E = H	87
10d	C	TMSCl	**11b**, E = TMS	60
10d	C	BrH_2CCH_2Br	**11c**, E = Br	58

[a] Isolated yields. [b] An inseparable mixture of products **13c**:**13a** (3:1) was obtained. Calculated yield is based on the NMR spectrum of this mixture. [c] Methods. A: LDA (2.2 equiv)/−78 °C/30 min. B: LDA (2.2 equiv)/−78 °C/15 min. C: LiTMP (2.2 equiv)/−78 °C/30 min.

of DoM−double HD reactions. Taken in sum, this work provides new and unique methodology for the synthesis of polysubstituted aromatics and pyridines.

The initial studies were undertaken with the pyridine **1** (Table 1). The decision to use **1** was dictated by the poor reproducibility[9] of the previously reported synthesis[8b] of the corresponding *N*,*N*-diethyl pyridine 3-iodo-2-*O*-carbamate, which is ascribed to intermolecular carbamoyl transfer reactions to the 3-lithiopyridine species, presumably due to base *N*-coordination and the excellent leaving group ability of the 2-pyridol anion.[9,10] In contrast, the more hindered *N*,*N*-diisopropyl pyridyl *O*-carbamate underwent metalation smoothly to afford the requisite starting material **1** in acceptable yields. In an experiment critical to establish the extent of anion formation, treatment of **1** with the required 2.2 equiv of LDA at −78 °C for 60 min followed by MeOD quench afforded the corresponding HD product **3a**. Presumably, the first equivalent of LDA is complexed to the pyridine nitrogen and 2-carbamate oxygen. Application of the methodology to other electrophiles led to the trisubstituted pyridines **3b**−**d**. The isomeric *O*-carbamates **1**, **7**, and **8** each required individual optimization of HD reaction times, and thus extension of the methodology to the 3- and 4-pyridyl *O*-carbamates **7** and **8** under the conditions of only 1.1 equiv of LDA (presumably owing to absence of the coordination mentioned above) and 30 and 45 min metalation time, respectively, was carried out to provide the products **9a**−**d** and **10a**−**d**, respectively. Of potential significance for transition-metal-catalyzed cross-coupling reactions, perhaps most favorably for the Suzuki−Miyaura process,[11] is the availability of differential halogen-substituted products **3c,d**, **9c,d**, and **10c,d** for the attainment of regioselective coupling reactions.

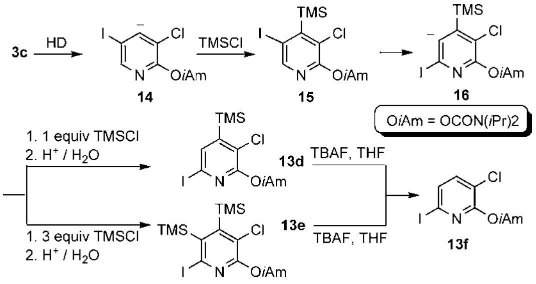
Recognition of the potential of further HD reactions for some of these products led to examination of the metalation chemistry of selected substrates **3c**, **9d**, and **10d** (Table 2). Although deprotonation of pyridyl-4-*O*-carbamate **10d** with LDA at −78 °C was unsuccessful, use of LiTMP at this temperature resulted in a smooth reaction to afford the HD products **11a**−**c** in 58−87% yields. In case of the pyridyl 3-*O*-

---

(1) (a) Transition metals in the synthesis of heterocycles: Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Tandem/cascade reactions in total synthesis: Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (c) Domino reactions: Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(2) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Macklin, T.; Snieckus, V. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, pp 106−118.

Scheme 2. Double HD Reactions of Substrate **3c**

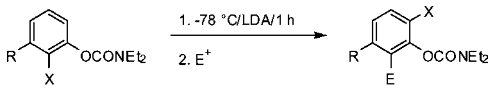


carbamate **9d**, metalation using LDA, LiTMP, or LDA/TMEDA (1.1 equiv of each) combinations at −78 °C afforded only unreacted starting material (TLC and GC/MS analysis). However, treatment with 2.2 equiv of LiTMP at −78 °C followed by proton quench gave the HD product **12a** in 69% yield. Standardization of this stoichiometry for LDA (2.2 equiv) provided HD products **12b**−**d** in good yields. The requirement for 2 equiv of base is presently not understood.

The 3-chloro-4-iodo 2-pyridyl-*O*-carbamate (**3c**) was the final substrate to be subjected to a secondary HD study. Although LDA-metalation (2.2 equiv) followed by protonation and methylation produced the desired HD products, **13a** and **13b**, respectively, in good yields, bromination with Br_2 or $BrCH_2CH_2Br$ led to inseparable mixtures of **13c** and the protonated side product **13a**. However, unexpected and interesting results were observed using TMSCl as the electrophile. Thus, using the standard LDA metalation conditions on **3c** followed by quench with 1.1 equiv of TMSCl, (Scheme 2) gave a silylated product (56% yield) that, based on NMR studies, was suggestive of structure **13d** rather than the expected 4-TMS-5-iodo 2-pyridine *O*-carbamate as the product of the reaction.

Furthermore, under the same metalation conditions on **3c** but using an excess (3.0 equiv) of TMSCl resulted in the formation of a product (34% yield) exhibiting no pyridine protons and two TMS signals in its ^1H NMR spectrum that, based on the tentatively assigned **13d**, was likewise tentatively assigned structure **13e**. These results were found to be reproducible. Correlation of the two products was achieved by separate treatment with TBAF to give the same fully desilylated product that, on the basis of characteristic pyridine ^1H NMR chemical shifts and coupling constants, was assigned structure **13f**, thus establishing the halogen substitution in products **13d** and **13e**. Since the available data did not allow unequivocal assignment of the position of the TMS substituent in **13d**, structural confirmation was achieved by an X-ray single crystal analysis (see Supporting Information), which by inference also established structures **13e** and **13f**. These products represent results of double HD reactions that take advantage of the in situ compatibility of LDA and TMSCl,[12] favorable relative rates, and driving force due to the formation of the early double DMG-stabilized lithio species. Thus, the cascade begins by initial HD of **3c** to intermediate **14**, which undergoes silylation to **15** and a rapid second HD to **16**, presumably driven by iodo-TMS hindrance effects. Species **16** is quenched by a proton source to afford **13d** (1.1 equiv of TMSCl) or with an excess of TMSCl to afford **13e** (3 equiv of TMSCl). These previously unobserved initial results of double HD reactions are under further study.

Table 3. DoM−HD Reactions of Aryl *O*-Carbamates **4a**−**c** and **17a**



compound	R	X	LDA (equiv)	E	E^+	product	yield (%)[a]
4a	Cl	I	1.1	MeOH	H	**18a**	89
4a	Cl	I	1.1	MeOD	D	**18b**	87
4a	Cl	I	1.1	$C_2Br_2F_4$	Br	**18c**	73
4b	OMe	I	2.1[b]	MeOH	H	**19a**	71
4b	OMe	I	2.1[b]	DMF	CHO	**19b**	71
4c	F	I	1.1	MeOH	H	**20a**	49
4c	F	I	1.1	DMF	CHO	**20b**	44
17a	Cl	Br	1.1	MeOH	H	**21a**	86
17a	Cl	Br	1.1	TMSCl	TMS	**21b**	79
17b	Cl	Cl	1.1	MeOH	H		

[a] Yields of isolated products. [b] Multiple tries with only 1 equiv of LDA failed, possibly as a result of OMe-coordination.

Stimulated by these first results of the combined DoM−HD reactions in the pyridine *O*-carbamate series, we turned our attention to analogous studies on aryl *O*-carbamates.[4,13] The 2-iodo double DMG *O*-carbamates **4a**−**c** and **17a**−**b** (Table 3) were prepared by metalation−halogenation of the corresponding *O*-carbamates (see Supporting Information) and subjected to the HD conditions established in the pyridine series as described above. For **4a**, the reactions proceeded cleanly and efficiently to give, after protonation and deuteration, products **18a** and **18b**. Synthetic utility was established by quenching the intermediate HD species of **4a**−**c** and **17a** with a variety of electrophiles to furnish the respective tetrasubstituted *O*-carbamates **18c**, **19b**, **20b**, and **21b**, the last representing an example of a bromine HD reaction[14] (Table 3). A chloro HD on compound **17b** was not observed under similar conditions. The efficiency of these processes lends further credence that the generation of the in-between, two-DMG stabilized lithiated species may be the ascribed driving force for the process.

With these synthetically useful results in hand, we continued the metalation walk-around-the-ring tour with the

---

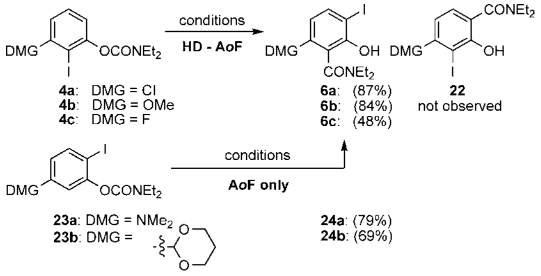
(3) (a) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (b) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750. (c) Lane, C.; Snieckus, V. *Synlett* **2000**, 1294. (d) Hurst, T.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J.-C.; Marder, T. B.; Snieckus, V. *Chem. Eur. J.* **2010**, accepted.

(4) Discovery: (a) Vaitiekunas, A.; Nord, F. F. *Nature* **1951**, *168*, 875. (b) Mallet, M.; Quéguiner, G. *Tetrahedron* **1979**, *35*, 1625. (c) Daykin, L. M.; Siddle, J. S.; Ankers, A. L.; Batsanov, A. S.; Bryce, M. R. *Tetrahedron* **2010**, *66*, 668. Reviews: (d) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376. (e) Schnürch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046. (f) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161. Other major contributors: (g) Gronowitz, L. *Adv. Heterocycl. Chem.* **1963**, *14*, 1. (h) Pieterse, M. J.; den Hertog, H. J. *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 855. (i) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139.

(5) For HD on picolinamides, see: Cochennec, C.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Synthesis* **1995**, 321, and references therein.

(6) Caerulomycin: (a) Sammakia, T.; Stangeland, E. L.; Withcomb, M. C. *Org. Lett.* **2002**, *4*, 2385. (b) Trecourt, F.; Gervais, B.; Mallet, M.; Quéguiner, G. *J. Org. Chem.* **1996**, *61*, 1673. (±)-Mappicine: (c) Comins, D. L.; Saha, J. K. *J. Org. Chem.* **1996**, *61*, 9623. WS75624 B: (d) Stangeland, E. L.; Sammakia, T. *J. Org. Chem.* **2004**, *69*, 2381.

Scheme 3. One-Pot Sequential HD−A*o*F Reactions



expectation that the next deprotonation of **4b** would be followed by an A*o*F process to give the iodo salicylamides **6** (Scheme 3).[15] Discouragingly, treatment of **4b** with 1.1 equiv of LDA (−78 °C/THF/1 h) at 0.01−0.1 M concentration gave, in addition to unreacted starting material (23% yield), deiodinated 3-methoxy *N*,*N*-diethyl phenyl *O*-carbamate (48% yield). Surprisingly, under highly concentrated conditions (0.5 M) a new product was obtained (84% yield) for which the assignment as **6b** or **22** was insecure based on ^{1}H NMR (δ = 6.50 ppm, dd, 7.67 ppm, dd) and ^{13}C NMR (δ = 76.2 ppm, 115.1 ppm) data and comparison with model compounds (see Supporting Information). The uncertainty in structural assignment forced an X-ray structure determination (see Supporting Information), which proved that the product of the reaction of **4b** is **6b**, the result of a sequential HD−A*o*F rearrangement reaction.

This delightful observation prompted application of similar reaction conditions to the chloro and fluoro *N*,*N*-diethyl *O*-carbamates **4a** and **4c**, which gave the analogous products **6a** and **6c**, respectively, in good yields. Interestingly, in contrast to the HD−A*o*F product **6b**, the products **6a** and **6c** were obtained in highest yields under dilute conditions (for X-ray crystal structure verification as well as optimization and temperature dependence studies, see Supporting Information).

The availability of dimethylamino and 1,3-dioxanyl *N*,*N*-diethyl *O*-carbamates **23a** and **23b** from D*o*M reactions allowed determination of 1,3-synergistic $OCONEt_2$−DMG effects on the A*o*F rearrangement. Despite the presence of weak second DMG effects and undoubtedly as a consequence of the sizeable iodo group that offers a steric enhancement, **23a** and **23b** underwent smooth A*o*F rearrangement to afford the salicylamides **24a** and **24b** (for X-ray, see Supporting Information), respectively, in good yields.

These results suggest that differentiation between sequential HD−A*o*F and simple A*o*F is possible and that the driving force for these reactions is the generation of the 2-lithiated species: by HD in the series **4a−c** and directly in the series **23a−b**. Recent studies by Collum established the intramolecularity of the A*o*F rearrangement.[7d] The classical HD proceeds via a sequence of intermolecular lithium−halogen exchange processes.[16] As a mechanistic contribution, we have established intramolecularity for the A*o*F component of the present reaction, see SI.

In conclusion, we have demonstrated the first HD process of isomeric iodo pyridine *O*-carbamates, compounds that are readily available by D*o*M chemistry. The D*o*M−HD−electrophile quench sequence (Table 1), as well as subsequent HD reactions of its products (Table 2), allows access to diverse tri- and tetra-substituted pyridines that have valuable functionalities for further manipulation and are difficult to obtain by alternative available routes.[17] In addition, we have established the first D*o*M−double HD process of iodo pyridine 2-*O*-carbamate (Scheme 2). Finally, we have found the hitherto unobserved sequential HD−anionic *ortho* Fries (A*o*F) rearrangement of conveniently synthesized D*o*M-derived starting materials that lead to continuously substituted, difficult to access salicylamides (Scheme 3). The conjunction of D*o*M−HD−A*o*F reactions reinforces the value of D*o*M protocols, of continued interest in pyridines,[18] from which the development and application of further new synthetic aromatic and heteroaromatic chemistry may be anticipated. On the basis of the present work, we note that the HD reaction appears to be fast even at low temperatures and therefore suggest giving due consideration to the occurrence of potential HD reactions in the strong base chemistry of halopyridines as well as haloaromatics.

Acknowledgment. We are most grateful to NSERC Canada Discovery Grant Program and the Graduiertenschule Chemical Biology Konstanz for financial support and scientific encouragement. We thank Michael Burgert (Universität Konstanz) for expert X-ray assistance. R.M. is grateful for a fellowship from the Studienstiftung des Deutschen Volkes (German National Academic Foundation).

Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100493V

---

(7) For applications, see: (a) James, C. A.; Coelho, A. L.; Gevaert, M.; Forgione, P.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4080. James, C. A.; Snieckus, V. *J. Org. Chem.* **2009**, *74*, 4094. (b) Anionic Fries rearrangement: Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935. (c) Chromenopyridines: Macklin, T. K.; Reed, M. A.; Snieckus, V. *Eur. J. Org. Chem.* **2008**, *9*, 1507. Macklin, T. K.; Panteleev, J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 2097. For recent thorough mechanistic studies, see: (d) Ma, Y.; Collum, D. *J. Am. Chem. Soc.* **2007**, *129*, 14818.

(8) (a) Tsukazaki, M.; Snieckus, V. *Heterocycles* **1993**, *35*, 689. (b) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.

(9) First observed in the studies of Tsukazaki, M. *Ph.D. Thesis*, University of Waterloo, ON, Canada, 1995.

(10) The significance of *N*-coordination for driving new regioselectivity is nicely demonstrated by the work of Fort; see: Gros, P.; Choppin, S.; Mathieu, J.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 234.

(11) *Metal-Catalyzed Cross-Coupling Reactions II*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.

(12) Compatibility of LDA and TMSCl first established by Martin and Quéguiner: (a) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *109*, 6155. (b) Marsais, F.; Laperdrix, B.; Gũngõr, T.; Mallet, M.; Quéguiner, G. *J. Chem. Res., Miniprint* **1982**, 2863. A similar one-pot D*o*M-HD reaction of pyrimidine with an excess of base was described by Quéguiner: (c) Ple, N.; Turck, A.; Couture, C.; Quéguiner, G. *Tetrahedron* **1994**, *50*, 10299.

(13) Noteworthy are the extensive contributions of Schlosser (review): (a) Schlosser, M. *Eur. J. Org. Chem.* **2001**, *21*, 3975. For a single report concerning a combined HD−A*o*F of a iodo quinoline *O*-carbamate, see: (b) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2005**, *70*, 373.

(14) Fröhlich, J.; Hametner, C.; Kalt, W. *Monatsh. Chem.* **1996**, *127*, 325.

(15) Typically, *O*-carbamates are metalated with *s*-BuLi/TMEDA under standard conditions and the resulting lithiated species are allowed to warm to room temperature (10−12 h); see ref 7b. In the present studies, LDA is used as the base to prevent lithium-halogen exchange reactions.

(16) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059.

(17) *Handbook of Heterocyclic Chemistry*; Katritzky, A. R., Pozharskii, A. F., Eds.; Pergamon: Oxford, 2000; pp 545−546.

(18) (a) Bentabed-Ababsa, G.; Ely, S. C. S.; Hesse, S.; Nassar, E.; Chevallier, F.; Nguyen, T. T.; Derdour, A.; Mongin, F. *J. Org. Chem.* **2010**, *75*, 839. (b) von Kieseritzky, F.; Lindström, J. *Synthesis* **2010**, 63.