# Synthesis of 2-Substituted Dihydropyran 3-*O*-Carbamates via Combined Metalation−Suzuki−Miyaura Cross-Coupling Reactions

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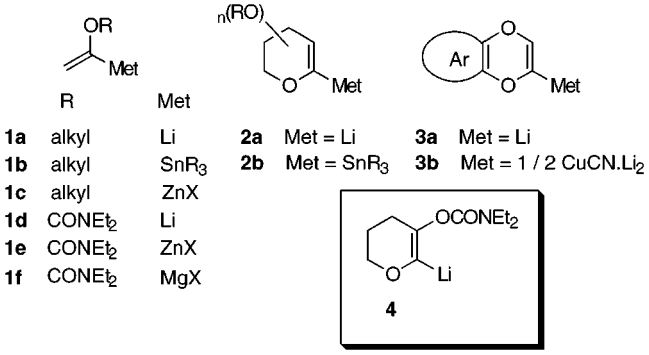
Treatment of 6-[(*N*,*N*-diethylcarbamoyl)oxy]-3,4-dihydro-2*H*-pyran (**8**) with *t*-BuLi followed by quench with a variety of electrophiles leads to 2-substituted products **9a**−**j** (Table 2) in modest to good yields. The thereby obtained 2-boronic acid (**11**) and iodo (**9j**) derivatives undergo Suzuki−Miyaura cross-coupling reactions to afford 2-aryl and -heteroaryl dihydropyran *O*-carbamates **12a**−**d** in excellent yields.

Recent manifestation of the deeply rooted Corey−Seebach acyl anion equivalent in the guise of an α-lithiovinyl ether **1a**[1] and related species **2a**[2] and **3a**[3] includes studies concerned with new methods of generation via stannane **1b** transmetalation,[4] transmetalation to cuprates **3b**,[5] zincates **1c**,[6] and stannanes **2b**[7] and application to glycals, especially as reflected in the synthesis of *C*-glycosides.[7,8] As part of methodological studies of α-lithiated *O*-vinyl carbamates **1d** and their zincate **1e** and Grignard **1f** counterparts as synthetically useful acyl anion equivalents,[9] we report on the electrophile quench and cross-coupling reactions of [(*N*,*N*-diethylcarbamoyl)-oxy]-6-lithio-3,4-dihydro-2*H*-pyran (**4**) which may serve as stepping stones to meet further challenges in the synthesis of *C*-substituted D-glucals and *C*-glycosides,[10] compounds of considerable interest in view of increasing presence of the *C*-glycosidic bond in natural products[11] and their potential use as antimetabolites.[11a,12] The formation of **4** may enjoy the combined benefit of α- and β-heteroatom-facilitation[1a,9] without suffering from the options of alternate α-lithiation or β-elimination.[13]




The synthesis of the requisite carbamate **8** (Scheme 1) starts from readily available hydroxy acetals **5a**[14] and **5b**[15] which, upon treatment with sodium hydride and *N*,*N*-diethylcarbamoyl chloride, afforded the corresponding *O*-carbamate acetals **6a** and **6b** in good yields. Hydrolysis of methyl acetal **6a** under the previously described mild acidic conditions[15] to produce hemiacetal **7** was efficient on small scale (96% yield on a 1 mmol scale), but proved troublesome upon scaling up, due to the poor solubility of **6a** in the reaction medium. Attempts to effect elimination from **6a** using a variety of conditions ($TiCl_4$/DBU, TMSI, TsOH/toluene/reflux) gave no reaction or complex product mixtures. To circumvent this problem, the benzyl acetal **6b** was prepared and subjected to catalytic hydrogenation to give **7** in good yields on scales up to 20 mmol. Dehydration of the hemiacetal **7** via its mesylate afforded the desired carbamate **8**[16] in good yield.

With the carbamate **8** in hand, a number of deprotonation/$CD_3OD$ quench experiments were undertaken in order to establish optimum conditions (Table 1). LDA and *n*-BuLi, with or without TMEDA, gave unsatisfactory results (entries 1, 2, and 3), whereas 2.2 equiv of *s*-BuLi/

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(16) Compound **8** is highly hygroscopic and slightly sensitive to acidic conditions.

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**Scheme 1. Synthesis of 5-[(*N*,*N*-Diethylcarbamoyl)oxy]-3,4-dihydro-2*H*-pyran (8)**

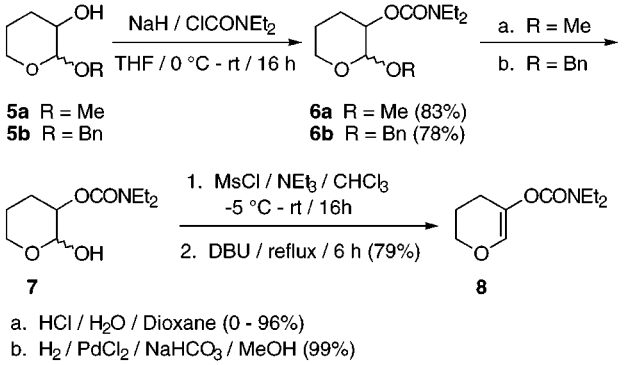
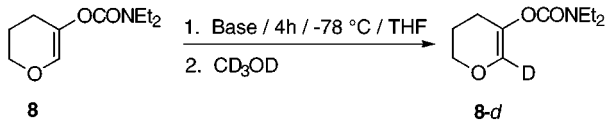



**Table 1. Lithiation/Deuteration Experiments on 8[a]**



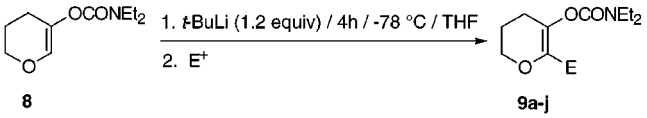

| entry | base | yld, %[b] | %D incorporation |
|---|---|---|---|
| 1 | 6 equiv LDA | 56 | <50 |
| 2 | 2.2 equiv *n*-BuLi | 56 | 72 |
| 3 | 2.2 equiv *n*-BuLi/TMEDA | 33[c] | 89 |
| 4 | 1.2 equiv *s*-BuLi/TMEDA | 87 | 66 |
| 5 | 1.65 equiv *s*-BuLi/TMEDA | 81 | 85 |
| 6 | 2.2 equiv *s*-BuLi/TMEDA | 83 | >99 |
| 7 | 2.2 equiv *s*-BuLi | 81 | 85 |
| 8 | 1.2 equiv *t*-BuLi | 87 | 95 |
| 9 | 1.65 equiv *t*-BuLi | 87 | 95 |
| 10 | 2.2 equiv *t*-BuLi | 91 | >99 |

[a] Experiments performed on a 1 mmol scale, lithiation over 4 h at −78 °C, quench with excess $CD_3OD$, stir for 15 min at −78 °C and for 1 h at rt. [b] Isolated yields after chromatography over neutral alumina. [c] Mixture with *N*,*N*-diethylvaleramide (30%).

TMEDA or *t*-BuLi gave high yields and almost complete deuterium incorporation (entries 6 and 10). Upon decreasing the equiv of base, *t*-BuLi (entry 8) proved to be more efficient than *s*-BuLi/TMEDA (entry 4), the percentage of deuterium incorporation remaining high (95%) with the former base when using only 1.2 equiv. Using a highly functionalized D-glucal, Friesen and co-workers[2a] found that 4 equiv of *t*-BuLi were necessary to achieve complete deuterium incorporation. This is probably due to coordination of the base to the polyoxygenated system and the lack of a powerful directing metalation group.

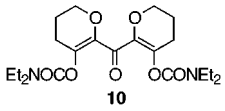
Various 6-substituted 5-[(*N*,*N*-diethylcarbamoyl)oxy]-3,4-dihydro-2*H*-pyrans (**9**) were prepared by lithiation of **8** using 1.2 equiv of *t*-BuLi followed by electrophilic quench (Table 2). Formyl and benzhydryl groups were smoothly introduced, whereas chloroformate and carbamoyl chloride quenches led to the expected products accompanied by small amounts of ketone **10**, resulting from competitive reaction of the products with the lithiated dihydropyran **4**. Silicon, sulfur, and selenium as well as bromo and iodo electrophiles gave diversely substituted dihydropyrans. Attempts to effect the anionic Fries rearrangement analogous to that observed for aryl *O*-carbamates[17] using *t*-BuLi/THF/−78 °C to room temperature to −78 °C followed by TMSCl quench led only to isolation of the starting material.

**Table 2. Synthesis of 2-Substituted-3-(Carbamoyloxy)dihydropyrans 9a−j[a]**

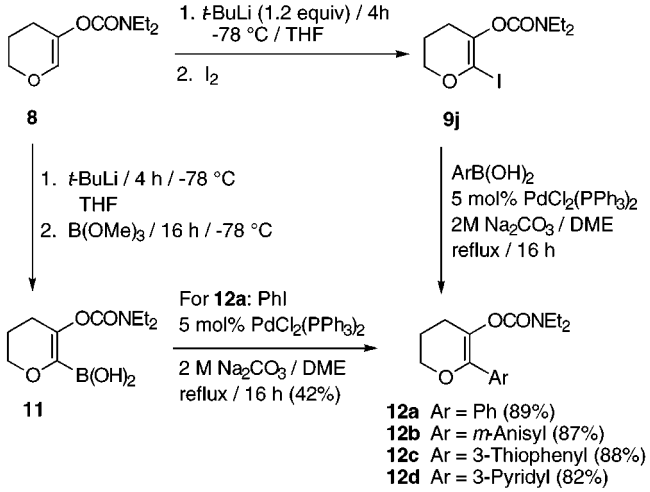



| $E^+$ | product | E | yield, %[b,c] |
|---|---|---|---|
| DMF | **9a** | CHO | 66 |
| PhCHO | **9b** | CH(OH)Ph | 80 |
| 4-MeO-$C_6H_4CHO$ | **9c** | CH(OH)-$C_6H_4$-4-OMe | 81 |
| $ClCO_2Et$ | **9d** | $CO_2Et$ | 56[d] |
| $ClCONMe_2$ | **9e** | $CONMe_2$ | 53[e] |
| TMSCl | **9f** | TMS | 40 |
| PhSeSePh | **9g** | SePh | 71 |
| PhSSPh | **9h** | SPh | 62 |
| $BrF_2C$-$CF_2Br$ | **9i** | Br | 76 |
| $I_2$ | **9j** | I | 80 |

[a] Experiments performed on a 1 mmol scale, lithiation over 4 h at −78 °C, electrophilic quench at −78 °C, and then hydrolysis after 2 h at −78 °C. [b] Isolated yields after chromatography. [c] Yields within experimental error were obtained using 2.2 equiv of *t*-BuLi. [d] 15% of byproduct **10** was also isolated. [e] 9% of byproduct **10** was also isolated.




**Scheme 2. Cross-Coupling Reactions of 9j and 11**




While attempts to effect Negishi cross coupling[6] (transmetalation of **4** with $ZnCl_2$ followed by reaction with iodobenzene using $Pd(PPh_3)_4$ as catalyst) were unsuccessful, conversion into the boronic acid **11** followed by Suzuki cross-coupling[18] with iodobenzene gave the 6-phenyl derivative **12a** in 42% yield accompanied by starting material (31%), which complicated product isolation. This problem was circumvented by reversing the cross-coupling procedure. Thus, a selection of cross-coupling reactions were performed on the iodo derivative **9j** using several readily available arylboronic acids to give cross-coupled products **12a**−**d** in excellent yields (Scheme 2).

We conclude, from the above observations, that the lithiated carbamate **4** is a useful species for formation of diversely substituted products **9a**−**j** and **12a**−**d** by direct reaction with electrophiles and Suzuki cross-coupling, respectively. The latter may serve as a model for the

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preparation of *C*-aryl glycosides of natural origin.[11] A further methodological connection may be the nickel-catalyzed carbamate−Grignard cross-coupling reaction of **9** and **12**.[19]

## Experimental Section

**General Procedures.**[20] **Materials.** 3,4-Dihydro-2*H*-pyran was obtained from Aldrich Chemical Co. and used without further purification. Diethylcarbamoyl chloride and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene also obtained from Aldrich were distilled and stored under an atmosphere of argon prior to use.

Unless otherwise noted, standard workup and chromatography denotes the following. The reaction mixture was diluted with $Et_2O$ (20 mL) and extracted with $H_2O$ (5 mL) and satd aq NaCl solution (5 mL). The organic extract was dried ($Na_2SO_4$), subjected to filtration, and evaporated to dryness in vacuo to give crude material which was purified by flash column chromatography (hexane/EtOAc 3:1, 1% $NEt_3$ eluent).

The 2-alkoxy-3-hydroxytetrahydropyrans **5a** and **5b** were prepared from 3,4-dihydro-2*H*-pyran using known procedures.[14,15]

**2-Methoxytetrahydropyran-3-ol (5a):**[14] colorless oil (20 g, 69% yield), as a mixture of diastereoisomers; bp 76−80 °C (9−10 mmHg); $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 4.17 (d, $J$ = 5.6 Hz, 1H), 3.94−3.87 (m, 2H), 3.50 (s, 3H), 3.48−3.40 (m, 1H), 2.31 (br s, 1H), 2.12−2.00 (m, 2H), 1.90−1.46 (m, 4H).

**2-(Benzyloxy)tetrahydropyran-3-ol (5b):**[15] colorless oil (30 g, 58% yield), as a mixture of diastereoisomers; bp 138−140 °C (1−2 mmHg); $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.45−7.27 (m, 5H), 4.75 (app d, app $J$ = 11 Hz, 1H), 4.6 (app d, app $J$ = 11 Hz, 1H), 4.30 (d, $J$ = 5.6 Hz, 1H), 3.99−3.80 (m, 1H), 3.58−3.45 (m, 2H), 2.20−1.45 (m, 6H).

**Preparation of 2-Alkoxy-3-(carbamoyloxy)tetrahydropyrans 6a and 6b.** A solution of the appropriate *trans*-2-alkoxy-3-hydroxytetrahydropyran **5a**[14] or **5b**[15] (80 mmol) in dry THF (100 mL) was added dropwise over 45 min to a stirred suspension of NaH (4.8 g of a 60% dispersion in mineral oil (washed four times with 20 mL of dry hexane, prior to use) 120 mmol) in dry THF (300 mL) at 0 °C under a dry argon atmosphere. The resulting mixture was stirred for 7 h at room temperature and cooled to 0 °C, before a solution of *N*,*N*-diethylcarbamoyl chloride (15.2 mL, 120 mmol) in dry THF (50 mL) was added dropwise over 20 min. The reaction mixture was slowly warmed to room temperature, stirred for an additional 16 h, and poured onto 250 mL of satd aqueous $NaHCO_3$ mixed with ca. 250 mL of ice. After separation of the phases, the aqueous phase was extracted with $CH_2Cl_2$ (4 × 250 mL). The organic extracts were combined and washed with 100 mL of satd aqueous NaCl, dried ($Na_2SO_4$), and concentrated in vacuo yielding 23.1 g of a yellow oil. Distillation afforded pure products.

***trans*-2-Methoxy-3-[(*N*,*N*-diethylcarbamoyl)oxy]tetrahydropyran (6a):** colorless oil (25 g, 83% yield); bp 137−140 °C (10−11 mmHg); IR (film): 2937, 1698, 1476, 1426, 1380, 1314, 1273, 1178, 1146, 1115, 1044, 987, 879, 771 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 4.65−4.49 (m, 1H), 3.95−3.79 (m, 1H), 3.59−3.47 (m, 1H), 3.41 (s, 3H), 3.30 (q, $J$ = 7.2 Hz, 4H), 2.02−1.71 (m, 3H), 1.46−1.40 (m, 1H), 1.15 (t, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 155.1, 115.2, 113.4, 99.0, 68.8, 60.2, 54.9, 41.7, 24.1, 21.0, 13.6; MS (CI): *m*/*z* (%) 232 (M + H, 100), 200 (94), 114 (26). HRMS: *m*/*z* calcd for $C_{11}H_{21}NO_4$: 231.1471; found: 231.1474.

***trans*-2-(Benzyloxy)-3-[(*N*,*N*-diethylcarbamoyl)oxy]tetrahydropyran (6b):** colorless oil (19.2 g, 78% yield); bp 148−158 °C (0.1 mmHg); IR (film): 3386, 2956, 2879, 1684, 1450, 1381, 1316, 1277, 1182, 1083, 1015, 1044, 987, 877, 773 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.40−7.17 (m, 5H), 4.72 (app d, $J$ = 11 Hz, 1H), 4.70−4.68 (m, 1H), 4.55 (app d, $J$ = 11 Hz, 1 H), 3.95−3.82 (m, 1H), 3.58−3.52 (m, 1H), 3.32−3.25 (m, 4H), 2.02−1.40 (m, 4H), 1.15 (t, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ 155.9, 155.6, 95.3, 92.4, 71.9, 60.2, 54.9, 41.7, 24.1, 21.0, 13.6; MS (CI): *m*/*z* (%) 308 (M + H, 100), 275 (75), 114 (25); HRMS: *m*/*z* calcd for $C_{17}H_{25}NO_4$: 307.1783; found: 307.1789.

**3-[(*N*,*N*-Diethylcarbamoyl)oxy]-2-hydroxytetrahydropyran (7).** Sodium hydrogen carbonate (1.84 g, 21.90 mmol) and palladium(II) chloride (0.13 g, 0.73 mmol, 5 mol %) were added to a degassed solution of *trans*-2-(benzyloxy)-3-[(*N*,*N*-diethylcarbamoyl)oxy]tetrahydropyran (**6b**) (4.5 g, 14.64 mmol) in MeOH (20 mL) at room temperature. The system was evacuated and then purged with hydrogen. This procedure was repeated three times, the reaction mixture was stirred at room temperature for 16 h, and subjected to filtration through Celite, and the filtrate was evaporated to dryness yielding 3.16 g (99%) of a pale yellow oil. $^1$H NMR analysis of the crude product showed only the presence of **7** as a 1:1 mixture of diastereoisomers, which was used in the next step without further purification: bp 138−140 °C (0.5 mmHg); IR (film): 3386, 1684, 1277, 1225, 1182, 1083, 1015 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 5.00−4.65 (m, 1H), 4.57−4.51 (m, 1H), 4.04−3.93 (m, 1H), 3.59−3.30 (m, 4H), 2.14−2.00 (m, 1H), 1.98−1.56 (m, 3H), 1.14 (t, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (67 MHz, $CDCl_3$): $\delta$ 155.6, 155.4, 94.7, 91.9, 71.5, 70.7, 62.4, 60.8, 41.6, 41.2, 25.7, 24.5, 22.8, 22.6, 14.8, 13.6, 13.1; MS (CI): *m*/*z* (%) 217 (20), 199 (45), 100 (75); HRMS: *m*/*z* calcd for $C_{10}H_{19}NO_4$: 217.1314; found: 217.1315.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-3,4-dihydro-2*H*-pyran (8).** Methanesulfonyl chloride (1.87 mL, 40 mmol) was added dropwise to a cooled (−5 °C) solution of 3-[(*N*,*N*-diethylcarbamoyl)oxy]-2-hydroxytetrahydropyran (**7**) (2.62 g, 12.06 mmol) and $NEt_3$ (5.04 mL, 36.18 mmol) in dry $CHCl_3$ under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The resulting orange solution was treated with DBU (2.71 mL, 18.09 mmol), and the reaction mixture was refluxed (6 h). After cooling to room temperature, the black reaction mixture was washed with water (25 mL), 1 N aqueous HCl (50 mL), and satd aqueous NaCl (50 mL), dried over $Na_2SO_4$, and evaporated to dryness yielding 2.10 g of a yellow oil. The crude product was purified by column chromatography (hexane/ethyl acetate (3:1/1% $NEt_3$ eluent) and distillation to give 1.9 g (79%) of **8**: a colorless oil; bp 115 °C (0.2 mmHg); IR (film): 3080, 1712, 1274 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 6.53 (s, 1H), 3.92 (t, $J$ = 5.2 Hz, 2H), 3.30 (q, $J$ = 7.1 Hz, 4H), 2.28 (td, $J$ = 6.4, 1.5 Hz, 2H), 1.97−1.92 (m, 2H), 1.15 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 154.8, 136.9, 132.3, 65.4, 42.2, 41.8, 23.7, 22.1, 14.2, 13.5; MS (CI): *m*/*z* (%) 200 (M + H, 100), 100 (74); HRMS: *m*/*z* calcd for $C_{10}H_{17}NO$: 199.1208; found: 199.1211.

**General Metalation Procedure.** *t*-BuLi (0.46 mL, 1.2 equiv, 0.60 mmol or 0.86 mL, 2.2 equiv, 1.1 mmol, 1.29 M in pentane) was added dropwise to a stirred solution of **8** (100 mg, 0.50 mmol) in THF (2 mL) at −78 °C, and the reaction mixture was stirred at this temperature for 4 h. A solution of the electrophile (0.75 mmol) in THF (1 mL) was then added, and the whole was stirred at −78 °C for 2 h, quenched with water at −78 °C, and allowed to warm to room temperature. Standard workup and chromatography gave the pure product.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-formyl-3,4-dihydro-2*H*-pyran (9a):** pale yellow oil; IR (film): 2936, 1709, 1646, 1275 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 9.73 (s, 1H), 4.07 (t, $J$ = 5.1 Hz, 2H), 3.39−3.31 (m, 4H), 2.53 (t, $J$ = 6.6 Hz, 2H), 2.07−1.97 (m, 2H), 1.21 and 1.17 (2t, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (67 MHz, $CDCl_3$): $\delta$ 182.7, 152.8, 147.3, 143.9, 65.6, 42.3, 41.9, 25.1, 21.4, 14.3, 13.1; MS (CI): *m*/*z* (%) 327 (M + $CONEt_2$, 100), 228 (M + H, 8), 100 (20); HRMS: *m*/*z* calcd for $C_{11}H_{17}NO_4$: 227.1157; found: 227.1155.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-(1-hydroxybenzyl)-3,4-dihydro-2*H*-pyran (9b):** pale yellow oil; IR (film): 3426, 2975, 1693, 1272, 1166, 1100, 1024 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.48−7.43 (m, 2H), 7.37−7.22 (m, 3H), 5.52 (d, $J$ = 6.4 Hz, 1H), 3.96 (t, $J$ = 5.2 Hz, 2H), 3.32−3.24 (m, 4H), 3.04

(19) Preliminary experiments on the parent *O*-carbamate **8** with PhMgCl using $Ni(acac)_2/PPh_3$ in refluxing toluene conditions (Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066) gave 5-phenyl-3,4-dihydro-2*H*-pyran in 33% yield, Bower, J. F.; Wong, P. L.; Snieckus, V. Unpublished results.

(20) See, Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763.

(d, $J$ = 6.6 Hz, 1H), 2.30 (t, $J$ = 6.5 Hz, 2H), 1.99−1.86 (m, 2H), 1.14 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 154.4, 146.8, 140.8, 128.3, 128.0, 127.0, 125.9, 68.3, 66.1, 42.3, 41.7, 23.9, 22.3, 14.2, 13.3; MS (CI): $m/z$ (%) 288 (M + H − $H_2O$, 100); HRMS: $m/z$ calcd for $C_{17}H_{23}NO_4$: 305.1627; found: 305.1632.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-(*p*-anisylhydroxymethyl)-3,4-dihydro-2*H*-pyran (9c):** pale yellow oil; IR (film): 3438, 2975, 1713, 1272, 1168, 1099, 1076, 1036 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.40 (d, $J$ = 8.8 Hz, 2H), 6.89 (d, $J$ = 8.8 Hz, 2H), 5.47 (d, $J$ = 6.2 Hz, 1H), 3.96 (t, $J$ = 5.2 Hz, 2H), 3.79 (s, 3H), 3.39−3.28 (br m, 4H), 2.95 (d, $J$ = 6.5 Hz, 1H), 2.27 (t, $J$ = 6.5 Hz, 2H), 1.97−1.92 (m, 2H), 1.15 and 1.14 (2t, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 158.7, 154.4, 146.8, 132.9, 128.2, 127.1, 113.5, 67.8, 66.1, 55.1, 42.3, 41.7, 23.9, 22.3, 14.2, 13.3; MS (CI): $m/z$ (%) 318 (M + H − $H_2O$, 100); HRMS: $m/z$ calcd for $C_{18}H_{25}NO_5$: 335.1733; found: 335.1748.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-(ethoxycarbonyl)-3,4-dihydro-2*H*-pyran (9d):** pale yellow oil; IR (film): 2936, 1723, 1656, 1290, 1175, 1074 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 4.23 (q, $J$ = 7.2 Hz, 2H), 4.06 (t, $J$ = 5.1 Hz, 2H), 3.37−3.23 (m, 4H), 2.34 (t, $J$ = 6.7 Hz, 2H), 2.03−1.97 (m, 2H), 1.28 (t, $J$ = 7.1 Hz, 3H), 1.22−1.10 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 161.6, 153.3, 139.6, 137.2, 66.0, 60.8, 42.1, 41.7, 25.7, 21.8, 14.1, 13.9, 13.3; MS (CI): $m/z$ (%) 371 (M + $CONEt_2$, 100), 300 (M + $C_2H_5$, 15), 272 (M + H, 34), 100 (32); HRMS: $m/z$ calcd for $C_{13}H_{21}NO_5$: 271.1420; found: 271.1391.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-(*N*,*N*-dimethylcarbamoyl)-3,4-dihydro-2*H*-pyran (9e):** pale yellow oil; IR (film): 2994, 1713, 1650, 1273, 1145, 1068 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 4.02 (t, $J$ = 5.1 Hz, 2H), 3.28−3.21 (m, 4H), 3.03 (s, 3H), 2.95 (s, 3H), 2.37 (t, $J$ = 6.6 Hz, 2H), 2.04−1.96 (m, 2H), 1.09 (t, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 164.2, 153.7, 140.5, 129.3, 65.9, 42.2, 41.9, 37.8, 34.4, 23.7, 21.9, 13.9, 13.3; MS (CI): $m/z$ (%) 370 (M + $CONEt_2$, 100), 299 (M + $C_2H_5$, 18), 271 (M + H, 44); HRMS: $m/z$ calcd for $C_{13}H_{22}N_2O_4$: 270.1580; found: 270.1575.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-(trimethylsilyl)-3,4-dihydro-2*H*-pyran (9f):** pale yellow oil; IR (film): 2975,0.1712, 1266 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 3.80 (t, $J$ = 5.2 Hz, 2H), 3.25 (q, $J$ = 7.1 Hz, 4H), 2.22 (t, $J$ = 6.6 Hz, 2H), 1.90−1.82 (m, 2H), 1.25−1.08 (m, 6H), 0.09 (s, 9H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 154.2, 149.7, 140.7, 65.1, 41.6, 41.3, 24.3, 22.2, 13.9, 13.2, −1.9; MS (CI): $m/z$ (%) 271 (30), 256 (15), 100 (100); HRMS: $m/z$ calcd for $C_{13}H_{25}NO_3Si$: 271.1604; found: 271.1602.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-(phenylseleno)-3,4-dihydro-2*H*-pyran (9g):** pale yellow crystals; mp 95 °C; IR (film): 2974, 1713, 1274, 1134, 1078 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.49−7.45 (m, 2H), 7.26−7.18 (m, 3H), 4.02 (t, $J$ = 5.1 Hz, 2H), 3.30 (q, $J$ = 7.1 Hz, 4H), 2.45 (t, $J$ = 6.6 Hz, 2H), 2.02−1.91 (m, 2H), 1.16−1.07 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 153.9, 138.1, 134.8, 131.7, 129.5, 128.9, 126.7, 68.2, 42.1, 41.8, 25.2, 22.5, 14.2, 13.3; MS (CI): $m/z$ (%) 384 (48), 382 (29), 356 (100), 354 (69); HRMS: $m/z$ calcd for $C_{16}H_{21}NO_3Se$: 353.0694; found: 353.0698.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-(phenylthio)-3,4-dihydro-2*H*-pyran (9h):** colorless crystals; mp 90 °C; IR (film): 2975, 1713, 1273 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.40−7.36 (m, 2H), 7.29−7.16 (m, 3H), 4.04 (t, $J$ = 5.1 Hz, 2H), 3.28 (q, $J$ = 7.1 Hz, 4H), 2.45 (t, $J$ = 6.6 Hz, 2H), 2.03−1.99 (m, 2H), 1.17−1.12 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 153.8, 140.1, 135.6, 133.9, 129.1, 128.8, 126.3, 67.8, 42.2, 41.8, 25.5, 22.4, 14.1, 13.3; MS (CI): $m/z$ (%) 308 (M + H, 33), 100 (27), 57 (100); HRMS: $m/z$ calcd for $C_{16}H_{21}NO_3S$: 307.1242; found: 307.1269.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-bromo-3,4-dihydro-2*H*-pyran (9i):** pale yellow oil; IR (film): 2975, 1715, 1268, 1155, 1060, 750 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 4.13 (t, $J$ = 5.1 Hz, 2H), 3.30 (q, $J$ = 7.1 Hz, 4H), 2.38 (t, $J$ = 6.5 Hz, 2H), 2.07−1.97 (m, 2H), 1.17−1.14 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 153.2, 128.4, 127.3, 69.6, 42.2, 41.7, 25.2, 22.3, 14.1, 13.3; MS (CI): $m/z$ (%) 279 (M + H, 30), 230 (65), 181 (65), 101 (100); HRMS: $m/z$ calcd for $C_{10}H_{16}BrNO_3$: 277.0314; found: 277. 0359.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-iodo-3,4-dihydro-2*H*-pyran (9j):** pale yellow oil; IR (film): 2974, 1714, 1274, 1192, 1140, cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 4.09 (t, $J$ = 5.1 Hz, 2H), 3.36−3.33 (m, 4H), 2.46 (t, $J$ = 6.6 Hz, 2H), 2.07−2.02 (m, 2H), 1.22−1.15 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 153.2, 134.3, 102.9, 69.5, 42.1, 41.8, 25.0, 22.2, 14.3, 13.3; MS (CI): $m/z$ (%) 326 (M + H, 34), 158 (28), 100 (100); HRMS: $m/z$ calcd for $C_{10}H_{16}INO_3$: 325.1479; found: 325.1499.

**Bis[5-[(*N*,*N*-diethylcarbamoyl)oxy]-3,4-dihydro-2*H*-pyran-6-yl] Ketone (10):** pale yellow oil; IR (film): 2976, 2928, 2880, 1718, 1273 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 3.96 (t, $J$ = 5.2 Hz, 4H), 3.28 (q, $J$ = 7.0 Hz, 8H), 2.39 (t, $J$ = 6.6 Hz, 4H), 1.97−1.88 (m, 4H), 1.13 (t, $J$ = 7.0 Hz, 12H); $^{13}$C NMR (63 MHz, $CDCl_3$): $\delta$ = 184.0, 153.7, 143.4, 137.1, 66.3, 42.3, 25.3, 22.4, 14.2, 13.5; MS (CI): $m/z$ (%) 425 (M + H, 44), 299 (38), 214 (71), 100 (100); HRMS: $m/z$ calcd for $C_{21}H_{32}N_2O_7$: 424.2210; found: 424.2203.

**Preparation of 12a−d. General Cross-Coupling Procedure.** To a thoroughly degassed solution of 5-[(*N*,*N*-diethylcarbamoyl)oxy]-6-iodo-3,4-dihydro-2*H*-pyran (**9j**) (50 mg, 0.154 mmol) and bis(triphenylphosphine)palladium(II) chloride (5.4 mg, 0.008 mmol) in DME (3 mL) was added a previously degassed 2 M aq $Na_2CO_3$ solution (0.23 mL, 0.46 mmol). The reaction mixture was stirred for 10 min, a specific boronic acid (0.308 mmol) was added, and the whole was stirred for 15 min at room temperature and then heated to reflux for 16 h under an atmosphere of argon. Standard workup and chromatography gave the coupled product.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-phenyl-3,4-dihydro-2*H*-pyran (12a)** (38 mg, 89% yield): pale yellow oil; IR (film): 2957, 1702, 1275, 1192, 1138, cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.50−7.46 (m, 2H), 7.36−7.21 (m, 3H), 4.13 (t, $J$ = 5.1 Hz, 2H), 3.36−3.15 (m, 4H), 2.45 (t, $J$ = 6.6 Hz, 2H), 2.08−2.00 (m, 2H), 1.17−1.01 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 153.8, 144.6, 133.9, 128.7, 127.9, 127.7, 127.6, 66.2, 41.9, 41.4, 24.7, 22.7, 14.3, 13.3; MS (CI): $m/z$ (%) 375 (M + $CONEt_2$, 43), 276 (M + H, 100); HRMS: $m/z$ calcd for $C_{16}H_{21}NO_3$: 275.1521; found: 275.1545.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-*m*-anisyl-3,4-dihydro-2*H*-pyran (12b)** (41 mg, 87% yield): pale yellow oil; IR (film): 2949, 1703, 1278, 1173, 1136 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.19 (t, $J$ = 7.9 Hz, 1H), 7.06 (d, $J$ = 7.9 Hz, 1H), 7.04 (s, 1H), 6.79 (dd, $J$ = 8.1, 2.5, Hz, 1H), 4.12 (t, $J$ = 5.1 Hz, 2H), 3.76 (s, 3H), 3.30−3.15 (m, 4H), 2.47 (t, $J$ = 6.6 Hz, 2H), 2.07−2.02 (m, 2H), 1.14−0.99 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 159.1, 154.2, 144.5, 135.1, 128.8, 128.7, 120.1, 114.3, 112.5, 66.2, 55.1, 41.9, 41.5, 24.7, 22.7, 13.9, 13.3; MS (CI): $m/z$ (%) 305 (25), 135 (30), 100 (100); HRMS: $m/z$ calcd for $C_{17}H_{23}NO_4$: 305.1627; found: 305.1627.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-(3-thiophenyl)-3,4-dihydro-2*H*-pyran (12c)** (38 mg, 88% yield): pale yellow oil; IR (film): 2957, 1705, 1272, 1179, 1142, cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 7.41 (s, 1H), 7.23 (d, $J$ = 6.6 Hz, 2H), 4.11 (t, $J$ = 5.1 Hz, 2H), 3.38−3.28 (m, 4H), 2.44 (t, $J$ = 6.6 Hz, 2H), 2.08−1.98 (m, 2H), 1.17 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 153.9, 141.2, 134.7, 128.3, 126.4, 124.5, 122.6, 65.9, 41.9, 41.5, 24.5, 22.6, 14.2, 13.3; MS (CI): $m/z$ (%) 282 (10), 111 (55), 100 (100); HRMS: $m/z$ calcd for $C_{14}H_{19}NO_3S$: 281.1102; found: 282.1163.

**5-[(*N*,*N*-Diethylcarbamoyl)oxy]-6-(3-pyridyl)-3,4-dihydro-2*H*-pyran (12d)** (35 mg, 82% yield): pale yellow oil; IR (film): 2974, 1709, 1271, 1184, 1142, cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 8.76 (d, $J$ = 1.8 Hz, 1H), 8.47 (dd, $J$ = 4.8, 1.7 Hz, 1H), 7.82−7.77 (m, 1H), 7.27−7.21 (m, 1H), 4.14 (t, $J$ = 5.1 Hz, 2H), 3.31−3.23 (m, 4H), 2.46 (t, $J$ = 6.6 Hz, 2H), 2.09−2.04 (m, 2H), 1.15−1.02 (m, 6H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 153.9, 148.8, 142.1, 134.8, 134.6, 130.3, 129.9, 122.2, 69.3, 42.1, 41.9, 24.7, 22.6, 14.2, 13.7; MS (CI): $m/z$ (%) 276 (30), 100 (100); HRMS: $m/z$ calcd for $C_{15}H_{20}N_2O_3$: 276.1474; found: 276.1480.

**Preparation of Boronic Acid 11.** *t*-BuLi (0.50 mL (1.2 equiv, 0.60 mmol, 1.20 M in pentane) was added dropwise to a stirred solution of **8** (100 mg, 0.50 mmol) in THF (2 mL) at −78 °C and the reaction mixture stirred for 4 h at −78 °C. A solution of trimethyl borate (0.12 mL, 1.10 mmol) was added

in one portion, and the reaction mixture was stirred at −78 °C for 2 h, allowed to warm to room temperature over 16 h, cooled to −40 °C, and quenched with satd aq $NH_4Cl$. Standard workup and chromatography gave **11** as a yellow oil (110 mg, 90% yield) which was used immediately without further purification.

**Cross-Coupling of 11 with Iodobenzene.** To a thoroughly degassed solution of iodobenzene (50 mg, 0.154 mmol) and bis(triphenylphosphine)palladium(II) chloride (7 mg, 0.02 mmol) in DME (3 mL) was added a previously degassed solution of 2 M aq $Na_2CO_3$ (0.31 mL, 0.61 mmol). The reaction mixture was stirred for 10 min, boronic acid **11** (100 mg, 0.41 mmol) was added, and the whole was stirred for 15 min at room temperature and then heated at reflux for 16 h under an atmosphere of argon. Standard workup and chromatography gave **12a** (47 mg, 42% yield) as a pale yellow oil whose spectoscopic properties were identical to those given above.

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**Supporting Information Available:** Copies of the $^1H$ and $^{13}C$ NMR spectra for compounds **7**, **8**, **9b**−**j**, and **12a**−**d** and $^1H$ NMR spectra for compounds **5a**,**b**, **6a**,**b**, and **9a** (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for the ordering information.

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