Functionalization of 2-Alkylidenetetrahydrofurans and 2-Alkylidenepyrrolidines by Palladium(0)-Catalyzed Cross-Coupling Reactions

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Abstract: 2-Alkylidenetetrahydrofurans and 2-alkylidenepyrrolidines were efficiently functionalized by bromination of the exocyclic double bond and subsequent palladium-catalyzed cross-coupling reactions.

Key words: bromination, cross-coupling, palladium, pyrrolidines, tetrahydrofurans

2-Alkylidenetetrahydrofurans[1,2] and 2-alkylidenepyrrolidines[3,4] represent important synthetic building blocks for the synthesis of pharmacologically relevant natural products and natural product analogues. The exocyclic double bond of 2-alkylidenetetrahydrofurans has been functionalized by cycloaddition reactions,[1a–1d] nucleophilic additions,[1e,f] cyclopropanations[1g] or hydrogenations.[1h,5h,i] 2-Alkylidenetetrahydrofurans are direct precursors of tetrahydrofuran natural products, such as methyl nonactate.[5] In addition, they were successfully transformed into naturally occurring spiroketals, such as chalcogran.[6] Recently, we have reported the functionalization of 2-alkylidenetetrahydrofurans by lithiation and subsequent alkylation.[7] Herein, we wish to report palladium-catalyzed cross-coupling reactions of 2-alkylidenetetrahydrofurans and 2-alkylidenepyrrolidines. This methodology allows a convenient functionalization of the exocyclic double bond and offers new synthetic vistas.

Our starting point was the development of a method for the bromination of the exocyclic double bond of 2-alkylidenetetrahydrofurans.[8] The required starting materials, tetrahydrofurans **2a**–**c**, were prepared by the recently reported cyclization of 1-bromo-2-chloroethane with the dianions of *tert*-butyl, methyl and ethyl acetoacetate (Scheme 1).[9]

The reaction of **2a**–**c** with NBS (1.3 equiv) resulted in selective bromination of the double bond and formation of the desired products **3a**–**c**. Bromination of both the double bond and carbon C-3 was observed in the reaction of **2c** with an excess of NBS (3.0 equiv); the dibrominated product was isolated in 93% yield (*E*-isomer: 70%, *Z*-isomer: 23%). The employment of other bromination reagents (e.g. Br_2) was unsuccessful. During the optimization, the reaction time (3 h), temperature (reflux) and solvent (CCl_4) proved to be important parameters.[10]

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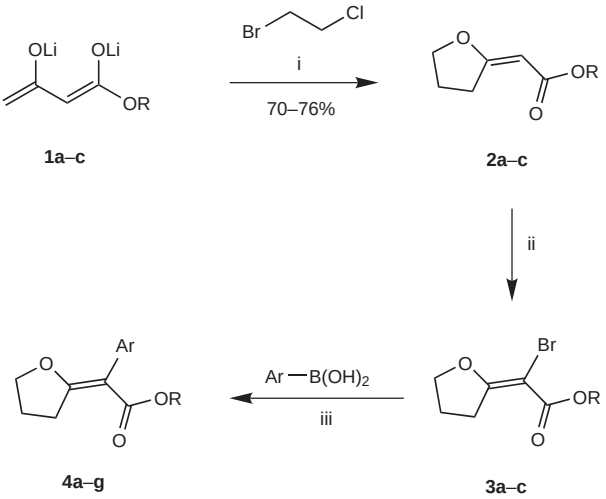


Scheme 1 Functionalization of 2-alkylidenetetrahydrofurans. *Reagents and conditions*: i: THF, 78 °C to 20 °C, 14 h, then reflux, 12 h, **2a** (R = *t*-Bu): 76%, **2b** (R = Me): 72%, **2c** (R = Et): 73%; ii: NBS (1.3 equiv), CCl_4, 3 h, **3a** (R = *t*-Bu): 73%, **3b** (R = Me): 84%, **3c** (R = Et): 84%; iii: $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (1.5 equiv), dioxane, reflux, 6 h.

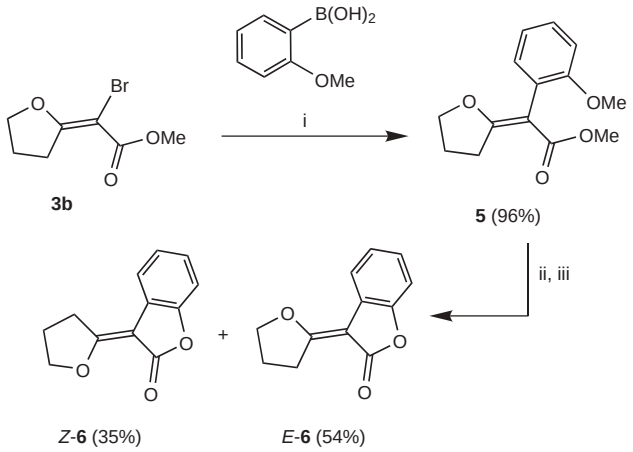
Table 1 Suzuki Reactions of 2-Alkylidenetetrahydrofurans

4	R	Ar	Yield (%)[a]
a	*t*-Bu	Ph	87
b	*t*-Bu	4-MeC_6H_4	88
c	*t*-Bu	4-$(MeO)C_6H_4$	77
d	*t*-Bu	4-ClC_6H_4	87
e	*t*-Bu	2-Thienyl	81
f	Me	4-ClC_6H_4	92
g	Me	2-Thienyl	62

[a] Yields of isolated products, *E*:*Z* >98:2

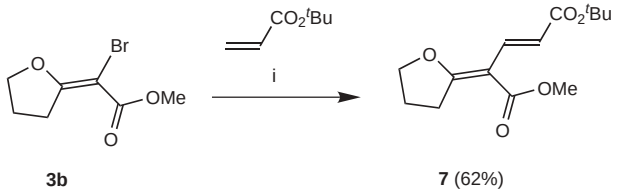
Palladium-catalyzed cross coupling reactions of **3a**,**b** were studied (Scheme 1, Table 1). Stille reactions of **3a** with Me_3SnPh or Bu_3SnPh proved unsuccessful under a variety of conditions. In contrast, the Suzuki reaction of **3a** with $PhB(OH)_2$ in the presence of $Pd(PPh_3)_4$ (3 mol%) afforded the desired 2-alkylidenetetrahydrofuran **4a**. The best yields (up to 87%) were obtained when $Pd(PPh_3)_4$, phenylboronic acid, K_3PO_4 and dioxane (reflux) were

used.[11] The reaction of **3a** with 4-tolyl-, 4-methoxyphenyl-, 4-chlorophenyl and 2-thienylboronic acid afforded the functionalized 2-alkylidenetetrahydrofurans **4b**–**e**. The functionalized products **4f**–**g** were prepared from **3b**. All Suzuki reactions proceeded in good to very good yields (62–92%) and with very good *E*-diastereoselectivity.



Scheme 2 Sequential Suzuki reaction and lactonization. *Reagents and conditions*: i: $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (1.5 equiv), dioxane, reflux, 6 h; ii: BBr_3, CH_2Cl_2; iii: *t*-BuOK, H_2O.

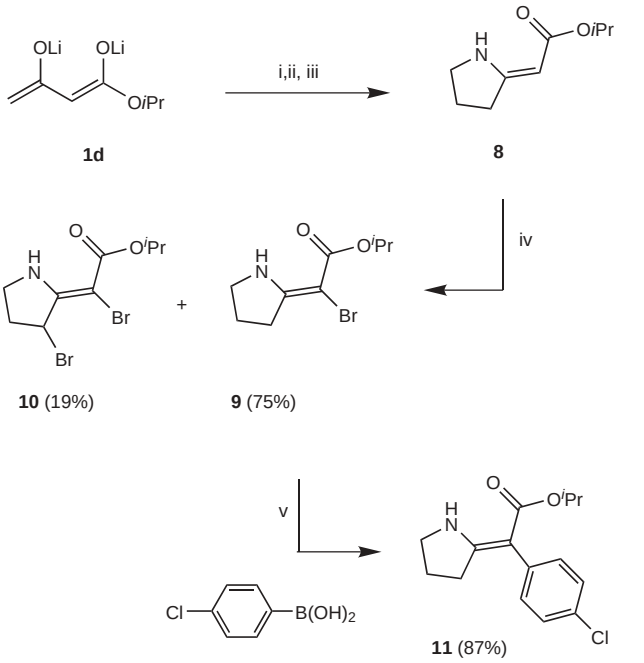
The application of our methodology to the synthesis of 2-alkylidenetetrahydrofuran **6**, a saturated analogue of the natural product calycine,[12,13] was studied next (Scheme 2). The reaction of **3b** with 2-methoxyphenylboronic acid afforded **5**. Sequential treatment of **5** with BBr_3 (CH_2Cl_2) and *t*-BuOK (H_2O) afforded **6** as a separable mixture of *E*/*Z*-isomers.



Scheme 3 Heck reaction of **3b**. *Reagents and conditions*: i: $Pd(PPh_3)_4$ (3 mol%), Et_3N, DMF, 100 °C, 25 h.

Alkenyl substituted 2-alkylidenetetrahydrofurans were successfully prepared by Heck reactions. For example, the reaction of **3b** with *tert*-butyl acrylate afforded, under standard conditions, the desired alkenyl substituted tetrahydrofuran **7** (Scheme 3).

The known 2-alkylidenepyrrolidine **8** was prepared by reaction of the dianion **1d** with 1-bromo-2-chloroethane to give *iso*propyl 6-chloro-1,3-dioxohexanoate, subsequent displacement of the chloride by treatment with NaN_3 (DMSO) and cyclization by treatment with PPh_3–THF (Staudinger–Aza–Wittig reaction).[14] The reaction of **8** with NBS–CCl_4 gave a separable mixture of **9** (75%) and



Scheme 4 Functionalization of 2-alkylidenepyrrolidine **8**, *Z*:*E* = 3:1 for all products. *Reagents and conditions*: i: $Br(CH_2)_2Cl$, THF, 78 °C to 0 °C; ii: NaN_3, DMSO, 50 °C, 12 h; iii: PPh_3, THF, reflux, 6 h; iv: NBS (1.3 equiv), CCl_4, reflux, 3 h; v: $Pd(PPh_3)_4$ (3 mol%), K_3PO_4 (1.5 equiv), dioxane, reflux, 6 h.

10 (19%). The Suzuki reaction of **9** with 4-chlorophenylboronic acid afforded the desired *Z*-configured pyrrolidine **11** in 87% yield (Scheme 4). All 2-alkylidenepyrrolidines were formed with *Z*-selectivity, due to the formation of a stable intramolecular hydrogen bond NHO.

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(10) **Typical Experimental Procedure for 3a:** *N*-Bromosuccinimide (0.879 g, 4.9 mmol) was added to a CCl_4 solution (40 mL) of **2a** (0.700 g, 3.8 mmol) at r.t. The reaction mixture was stirred under reflux for 3 h. The reaction mixture was allowed to cool to r.t. and Et_2O (20 mL) was added. The solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 100:1 to 1:1) to give **3a** as a colorless solid (0.732 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, O*t*-Bu), 2.21 (quint, *J* = 7.2 Hz, 2 H, CH_2), 3.13 (t, *J* = 7.8 Hz, 2 H, CH_2), 4.37 (t, *J* = 7.2 Hz, 2 H, OCH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.10 (CH_2), 28.46 (CH_3), 32.54 (CH_2), 72.83 (C-5), 81.65 (C), 85.80 (Br-*C*=C), 163.38 (O=C-O), 170.80 (O-*C*=C). IR (KBr): ν = 2975 (w, C-H), 1694 (s, C=C-O), 1613 (s, C=C-C=O), 1370 (m), 1295 (s), 1250 (w), 1243 (w), 1210 (m), 1170 (s), 1067 (s), 1039 (w), 1023 (w), 955 (w), 934 (w), 864 (w). MS (EI, 70 eV): *m/z* (%) = 263 (19)[M^+], 206 (100), 190 (92), 162 (4) cm^{-1}. The exact molecular mass *m/z* = 262.0205 ± 2 mD [M^+] for $C_{10}H_{15}O_3Br$ was confirmed by HRMS (EI, 70 eV). Anal. Calcd for $C_{10}H_{15}O_3Br$ (263.131): C, 45.65; H, 5.75. Found: C, 45.38; H, 6.03. All products gave satisfactory spectroscopic and analytical and/or high-resolution mass data.

(11) **Typical Experimental Procedure for 4a:** Tetrakis(triphenylphosphine)palladium (0.20 g, 0.017 mmol) was added to a 1,4-dioxane solution (5 mL) of **3a** (0.150 g, 0.57 mmol), K_3PO_4 (0.726 g, 3.42 mmol) and phenylboronic acid (0.209 g, 1.71 mmol) at r.t. The reaction mixture was stirred under reflux for 6 h. The solution was allowed to cool to r.t. and a sat. solution of NH_4Cl (20 mL) was added. The solution was extracted with Et_2O (4 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane–EtOAc = 100:1 to 25:1) to give **4a** as a slightly yellow solid (0.128 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, O*t*-Bu), 2.11 (quint, *J* = 7.2 Hz, 2 H, CH_2), 3.21 (t, *J* = 7.8 Hz, 2 H, CH_2), 4.17 (t, *J* = 6.9 Hz, 2 H, OCH_2), 7.20–7.34 (m, 5 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.36 (CH_2), 28.46 (CH_3), 31.74 (CH_2), 71.92 (C-5), 79.83 (C), 106.37 (*C*=C-O), 126.35, 127.60, 130.60 (CH, Ph), 136.18 (C, Ph), 167.92 (O=C-O), 170.73 (O-*C*=O). IR (neat): ν = 3079 (w), 2974 (m), 2921 (w), 2907 (w, C-H), 1687 (s, C=C-O), 1608 (s, C=C-C=O), 1492 (m), 1474 (m), 1452 (m), 1420 (w), 1384 (m), 1368 (m), 1321 (m), 1301 (m), 1269 (m), 1251 (m), 1231 (m), 1157 (s), 1113 (m), 1063 (s), 1038 (s), 956 (m), 930 (m), 880 (w), 839 (m), 812 (m), 778 (m), 756 (m), 697 (m), 654 (w), 508 (w) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 260 (23) [M^+], 203 (100), 186 (79), 169 (4), 157 (1). The exact molecular mass *m/z* = 260.1412 ± 2 mD [M^+] for $C_{16}H_{20}O_3$ was confirmed by HRMS (EI, 70 eV).

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