Communications

Palladium-Mediated Three-Component Coupling Strategy for the Solid-Phase Synthesis of Tropane Derivatives[1]

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Solid-phase organic synthesis increasingly is being used for generating libraries of compounds for the purpose of identifying or optimizing lead compounds in drug discovery.[2] The development of general and high-yielding solid-phase organic synthesis methods is crucial to these efforts. Palladium-mediated carbon−carbon bond-forming processes are particularly appealing for library synthesis due to the mild reaction conditions, compatibility with a broad range of functionality, and high reaction yields. Accordingly, these reactions have been employed in a number of small molecule solid-phase synthesis efforts.[3] Herein, we report our preliminary studies on palladium-mediated three-component coupling processes for the display of diverse functionality through carbon−carbon bond formation.[4] In particular, we have focused on the display of functionality on a tropane template (Figure 1). The diverse pharmacological properties of tropane derivatives are well-known and include muscarinic cholinergic antagonists, antiemetics, and anticognition disorder agents.[5]

Our synthesis strategy involves the display of diverse functionality upon core structure **2**. The R_1 and R_2 substituents are sequentially introduced in the palladium-mediated three-component coupling process using commercially available aryl halides followed by aryl boronic acids or alkynes. The R_3 substituent is then attached to the tropane nitrogen by employing a final reductive amination or acylation step.

The scaffold **2** is synthesized from ethyl 3-α-hydroxy-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate, which has served as a key intermediate for the synthesis of a

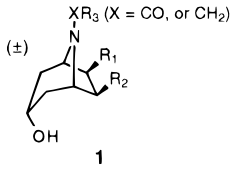

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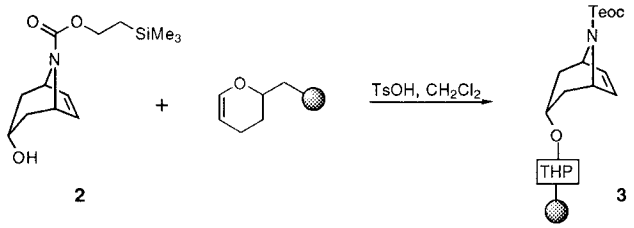
Figure 1.

number of tropane derivatives.[6] The scaffold **2** is coupled to dihydropyran-functionalized polystyrene support employing *p*-toluenesulfonic acid in CH_2Cl_2 (Scheme 1).[7] The exact loading level of the resin can be determined by recovery of alcohol **2** after subjecting a portion of resin **3** to cleavage with pyridinium *p*-toluenesulfonate in 1:1 1,2-dichloroethane/*n*-butanol.

Scheme 1



2 **3**

The first step in the palladium-mediated three-component coupling process follows the reaction pathway observed for the Heck reaction.[8] Oxidative addition of Pd(0) into the aryl halide bond is followed by insertion into the alkene of scaffold **3** to provide the (η^2-arene)-palladium(II) intermediate **4** (Scheme 1). While β-hydrogen elimination rapidly occurs in the standard Heck reaction, we anticipated that organopalladium intermediate **4** would be stable. The related intramolecular (η^2-arene)palladium(II) complexes $Pd[C_7H_8(\eta^2\text{-}Ar)](PPh_3)I$, where Ar = C_6H_5, *p*-$CH_3C_6H_4$, or *p*-$CH_3OC_6H_4$, from the reaction of norbornadiene with $Pd(PPh_3)_2(Ar)I$, have previously been isolated and characterized by NMR, IR, and X-ray diffraction.[9,10] For the norbornylpalladium complexes, the β-hydrogen atoms are not periplanar to the palladium substituent as is required for β-hydrogen elimination to occur. In analogy to the norbornylpalladium complexes, we found that organopalladium intermediate **4** also had an unusually long lifetime and was both air and thermally stable. Furthermore, intermediate **4** reacted with various nucleophiles to give cis-substituted products **5**.

The synthesis was initiated by treating resin **3** with excess $Pd(PPh_3)_4$ and aryl bromides at 66 °C for 48 h to form the stable organopalladium intermediate **4** (Scheme 2). Generally, for the formation of **4**, electron-rich aryl bromides reacted more rapidly than the electron poor aryl bromides as had previously been observed for the related

(1) Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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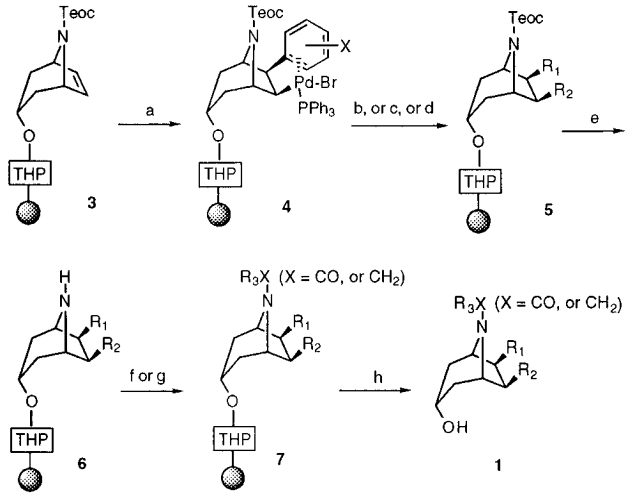
Scheme 2[a]



[a] Key: (a) aryl bromide (X = H, 4-methoxy, 4-methyl, Pd-$(PPh_3)_4$, THF, 66 °C; (b) arylboronic acid, 2 N Na_2CO_3, PPh_3, THF or anisole, 66 °C; (c) formic acid, Et_3N, PPh_3, DMF, 66 °C; (d) phenylacetylene, CuI, Bu_4NCl, DMF, 66 °C; (e) Bu_4NF, THF, 50 °C; (f) benzaldehyde or isobutyraldehyde, $NaBH(OAc)_3$, DMF; (g) HATU, Et_3N, benzoic acid, HOAt, DMF; (h) TFA/H_2O (20:1).

norbornene and norbornadiene systems. Support-bound intermediate **4** is readily isolated by washing the resin with degassed THF to remove excess reactants and can be stored under nitrogen at ambient temperature. Because the palladium intermediate **4** is isolated, split synthesis strategies may be employed for library synthesis. This sequential coupling protocol also eliminates any potential for competing side reactions between the aryl halide that is employed to introduce the R_1 substituent and the nucleophile that is used to introduce the R_2 substituent.[11]

Reaction of the support-bound palladium intermediate **4** with diverse nucleophiles provides **5**, which incorporates both the R_1 and R_2 substituents. We first investigated the Suzuki coupling reaction[12] using arylboronic acids as the coupling partners, a number of which are available commercially. The reaction was carried out according to standard conditions using 2 M aqueous Na_2CO_3 as the base, PPh_3, and THF as the solvent with heating at reflux for 48 h. Excess PPh_3 was added to form a complex with the Pd(0) that results upon reductive elimination in order to prevent formation of palladium black. Complete conversion was observed for arylboronic acids that were electron poor or electron rich. Alternatively, the palladium substituent could be replaced with a hydrogen atom by treatment of **4** with formic acid as a hydride source in the presence of Et_3N in DMF to give support-bound **5i**.[13] In addition, in the presence of Bu_4NCl, Et_2NH, and CuI as catalyst, organopalladium intermediate **4** reacts with phenylacetylene in DMF to afford the corresponding *cis*,*exo*-5-aryl-6-alkynyl compound **5j**.[4c] Anisole was also evaluated as the solvent for the three-component coupling sequence, since it may be operationally preferable to use a higher boiling solvent in library synthesis.

Table 1

compd	R_1	R_2	R_3X	yield[a] (%)
1a	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5CO	63
1b	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	$(CH_3)_2CHCH_2$	69
1c	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	$C_6H_5CH_2$	73 (71)[b]
1d	C_6H_5	4-$CH_3OC_6H_4$	$C_6H_5CH_2$	60 (55)[b]
1e	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	$C_6H_5CH_2$	70 (68)[b]
1f	4-$CH_3OC_6H_4$	3-Cl-4-FC_6H_3	$C_6H_5CH_2$	70
1g	4-$CH_3OC_6H_4$	3-$CF_3OC_6H_4$	$C_6H_5CH_2$	66
1h	4-$CH_3OC_6H_4$	3-$NO_2C_6H_4$	$C_6H_5CH_2$	70
1i	4-$CH_3OC_6H_4$	H	$C_6H_5CH_2$	50
1j	4-$CH_3OC_6H_4$	$C_6H_5C{\equiv}C$	$C_6H_5CH_2$	50

[a] Yields are reported for pure products after chromatography and were determined by mass balance based on the initial loading level of alcohol **2**. [b] Yield when anisole is used as the solvent.

Removal of the [[(trimethylsilyl)ethyl]oxy]carbonyl (Teoc) group from intermediate **5** was next accomplished by treatment with *n*-Bu_4NF in THF at 50 °C for 20 h to provide amine **6**. IR analysis can be used to monitor reaction progress by following the disappearance of the carbamate carbonyl stretch. The R_3 substituent can then be introduced onto the secondary amine by acylation or reductive amination. Acylation with carboxylic acids was accomplished using *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) to provide **7** (X = CO).[14] Alternatively, reductive amination of **6** with aldehydes employing $NaBH(OAc)_3$ in DMF with 1% HOAc provided the corresponding tertiary amine **7** (X = CH_2).[15] Cleavage of the functionalized tropane derivatives from the solid support with 95:5 TFA/water for 30 min provided analytically pure derivatives **1a**−**j** after filtration through silica in 50−73% overall yield on the basis of the initial loading level of alcohol **2** (Table 1).

In summary, we have developed an expedient solid-phase method for the synthesis of tropane derivatives from scaffold **2** using three sets of commercially available components: (1) aryl halides, (2) arylboronic acids or terminal acetylenes, and (3) carboxylic acids or aldehydes. The results of further studies on the scope and generality of palladium-mediated multicomponent coupling strategies for library synthesis will be reported in due course.

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Supporting Information Available: Experimental details, including analytical data for all compounds described in this work (6 pages).

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(11) The cost of palladium reagent required for library synthesis is minimal even though the palladium reagent is not used catalytically because only small amounts of each of the compounds in a library are synthesized.

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