ORGANIC LETTERS

2009
Vol. 11, No. 16
3734−3737

A Sequential Indium-Mediated Aldehyde Allylation/Palladium-Catalyzed Cross-Coupling Reaction in the Synthesis of 2-Deoxy-β-*C*-Aryl Glycosides

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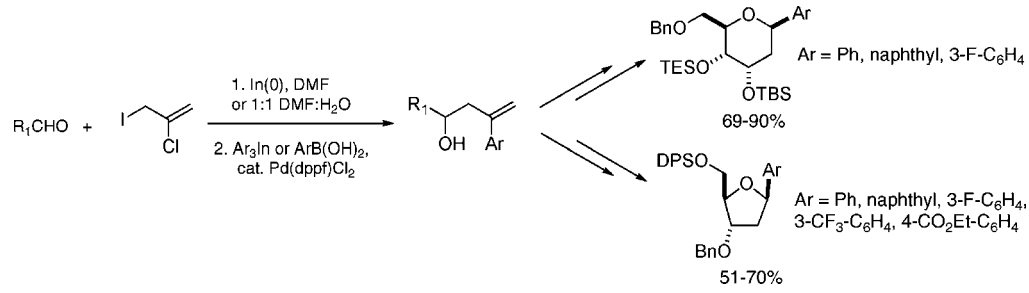
Received June 16, 2009

ABSTRACT



Indium-mediated allylation of aldehydes with 2-chloro-3-iodopropene, followed by a palladium-catalyzed cross-coupling reaction with triarylindium reagents or arylboronic acids, leads to aryl-substituted homoallylic alcohols in good to excellent yields and diastereoselectivities. The products obtained from reactions conducted with D-glyceraldehyde acetonide can be transformed into 2-deoxy-β-*C*-aryl ribofuranosides in high overall yields. Similarly, 2-deoxy-β-*C*-aryl allopyranosides may be prepared efficiently from 2,4-*O*-benzylidene erythrose.

C-Aryl glycosides are an important class of naturally occurring compounds with unique chemical and biological properties.[1] Possessing a carbon−carbon bond between aromatic and carbohydrate moieties, these substances are endowed with remarkable stability toward acid and enzymatic hydrolysis; this affords them a sufficient intracellular lifetime to allow trafficking to the nucleus, where they bind DNA to form stable complexes.[2] Indeed, numerous members of the glycosyl arene family have been shown to possess antibacterial, antitumor, and antifungal activities. These characteristics, in addition to limited availability from natural resources, mark these compounds as intriguing and timely targets for total synthesis.

Many previous approaches to the synthesis of *C*-aryl glycosides focus on achieving efficient formation of the aryl−glycosidic carbon−carbon bond.[3] Refinement of activating groups,[4] the use of lanthanide Lewis acids as

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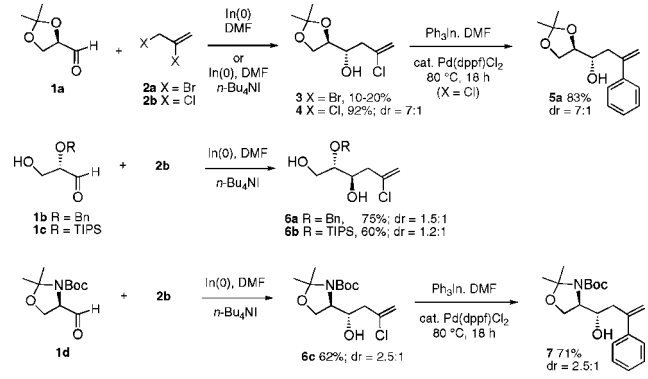
10.1021/ol901353f CCC: $40.75
Published on Web 07/24/2009

promoters,[5] and improvements in transition-metal-mediated couplings[6] have now made possible the total synthesis of complex natural products possessing the *C*-aryl glycoside functional group. Despite this progress, concerns about the use and disposal of environmentally hazardous reagents, solvents, and heavy metals have motivated chemists to investigate alternative "green" methods for forming carbon−carbon bonds, the backbone of all organic compounds.

Organoindium compounds have been shown to participate in a wide range of transition-metal-mediated processes for carbon−carbon bond formation.[7] These environmentally benign reagents are air- and moisture-stable and can undergo cross-coupling reactions in an atom-efficient manner.[8] Furthermore, the indium-mediated allylation of aldehydes and ketones in aqueous media is a powerful and stereoselective process that has been applied to the synthesis of a variey of complex natural products.[9] In this letter, we detail our findings on a sequential indium-mediated carbon−carbon bond-forming process that efficiently establishes the carbon backbone of 2-deoxy-*C*-aryl glycosides.

Motivated by the studies of Otera and Alcaide[10] and others[11] on the tin-mediated Barbier-type allylation of aldehydes with 2,3-dibromopropene, and hoping to avoid the use of toxic metals and acidic conditions required for such couplings, our initial investigations centered around the indium-mediated allylation of readily available D-glyceraldehyde acetonide (**1a**) with 2,3-dihalopropenes. Stirring a DMF (or 1:1 DMF:H_2O) solution of **1a** with 1.5 equiv of 2,3-dibromopropene **2a** and 1 equiv of indium metal led to the desired homoallylic alcohol product in a disappointing 20% yield (Scheme 1). Careful study of the reaction revealed

Scheme 1. Glyceraldehyde Allylation with 2,3-Dihalopropenes



that addition of the indium metal to **2a** in the presence or absence of glyceraldehyde acetonide led to a vigorous exothermic reaction and the visible production of gas. We reasoned that, upon formation, the 2-bromoallylindium reagent undergoes a rapid decomposition to indium bromide and allene. In contrast, Li has previously reported the high-yielding allylation of aldehydes with 3-bromo-2-chloropropene in water.[12] Since 2,3-dichloropropene is commercially available and inexpensive, we decided to investigate the allylation of D-glyceraldehyde acetonide with this reagent in the presence of an iodide source to generate the more reactive 3-iodo-2-chloropropene in situ. Indeed, addition of indium metal (1 equiv) and TBAI (1 equiv) to a 2 M DMF solution of glyceraldehyde and 2,3-dichloropropene (**2b**, 1.5 equiv) led to homoallylic alcohol **4** in 92% yield and 7:1 diastereoselectivity; the major diastereomer was assigned the *anti* stereochemistry in analogy with previously reported indium allylations of glyceraldehyde.[13] The allylation reaction takes place with similar efficiency (89% yield) and diastereoselectivity (dr = 6.5:1) in 1:1 DMF:H_2O when 2-chloro-3-iodopropene[14] is employed as the allyl source. Subsequent cross-coupling of **4** with 1 equiv of Ph_3In in the presence of $Pd(dppf)Cl_2$ (5 mol %) at 80 °C for 18 h proceeded uneventfully,[7j] providing an 83% yield of **5a**, the spectral data of which matched closely those reported for the same compound by Wang et al.[13] Similarly, treatment of Garner's aldehyde **1d** with **2b** in the presence of indium

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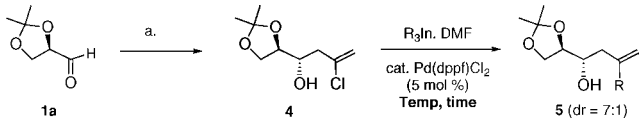
metal led to *anti*-vinyl chloride **6c** in 62% yield and 2.5:1 diastereoselectivity, in line with the previous allylation studies of Paquette;[15] palladium-catalyzed cross-coupling of **6c** with Ph_3In furnished alcohol **7** in 71% yield. However, allylation of either 2-*O*-benzyl-L-glyceraldehyde[16a] (**1b**) or 2-*O*-triisopropylsilyl-L-glyceraldehyde[16b] (**1c**) was essentially nondiastereoselective (dr = 1.2−1.5:1), producing vinyl chlorides **6a** and **6b**, respectively, in moderate yields.

Ultimately, it was revealed that both the allylation and cross-coupling reactions could be performed sequentially without purification of the intermediate homoallylic alcohol: crude **4** obtained from a simple extractive work up of the allylation reaction was directly treated with the reagents for cross-coupling, and the reaction was heated for 16−36 h. To explore the scope of this process, we tested cross-coupling with a variety of aryl- and heteroarylindium reagents. Both electron-rich (Table 1, entries 2 and 6) and electron-deficient

Table 1. Scope of the Sequential Glyceraldehyde Allylation/Arylindium Cross-Coupling Reaction[a]



entry	R	temp (°C)	time (h)	**5**	**5**[b] (% yield from **1a**)
1	Ph	80	18	a	75
2	4-MeO-C_6H_4	80	16	b	68
3	4-Me-C_6H_4	80	36	c	78
4	4-Cl-C_6H_4	80	17	d	86
5	3-F-C_6H_4	80	18	e	88
6	2-furyl	80	22	f	65
7	3-CF_3-C_6H_4	80	20	g	58
8	2-naphthyl[c]	90	18	h	87
9	4-CO_2Me-C_6H_4[c]	90	21	i	69
10	3-pyridyl[c]	90	18	j	51
11	2-Me-C_6H_4	100	48	k	<10
12	1-naphthyl	100	48	l	<5
13	Bu	80	24	m	--

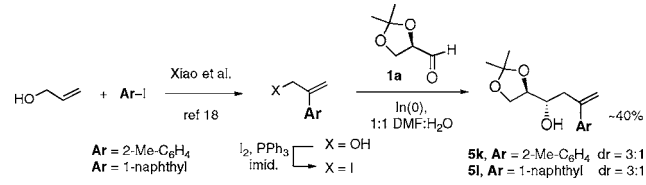
[a] Reaction conditions: (a) 2,3-dichloropropene (1.5 equiv), In (1 equiv), TBAI (1 equiv), DMF (2 M), rt, 6 h. [b] Isolated yield after silica gel chromatography. [c] The corresponding arylboronic acid ($ArB(OH)_2$) was employed for the cross-coupling reaction. Conditions: 1.5 equiv of $ArB(OH)_2$, 3 equiv of Na_2CO_3 (2 M), 5 mol % of $Cl_2Pd(dppf)$, 3:1 toluene:EtOH, 90 °C, 18−21 h.

(entries 4, 5, and 7) arylindiums cross-couple efficiently. However, sterically hindered arylindiums (entries 11 and 12) such as tris-2-tolylindium or tris-1-naphthylindium provided negligible yields (<10%) of coupled products even at elevated temperatures (100 °C) and with extended reaction times (48 h). The use of alternative catalyst systems, such as Fu's P(*t*-Bu)$_3$/Pd_2(dba)$_3$ and PCy_3/$Pd(OAc)_2$ systems[17a] or Nolan's NHC/$Pd(OAc)_2$ complexes,[17b] afforded no significant improvement in the yields of **5k** and **5l** obtained (∼10−20%).

Employing tributylindium (entry 13) in the cross-coupling led to the formation of reduced products due to a facile β-hydride elimination/reductive elimination sequence. However, arylboronic acids could be efficiently used in place of arylindium reagents (entries 8−10) when slightly modified reaction conditions were employed for the cross-coupling (1.5 equiv of $ArB(OH)_2$, 3 of equiv Na_2CO_3 (2 M), 3:1 toluene:EtOH, 90 °C, 18−21 h). Optimal yields were obtained with 1 equiv of triarylindium reagent or 1.5 equiv of arylboronic acid. Employing decreased amounts of these reagents led to significantly increased reaction times and lower overall yields.

Although this method did not furnish products containing sterically encumbered, *ortho*-substituted aryl groups, these substrates could be prepared by an alternate route involving Xiao's α-regioselective Heck arylation of allyl alcohol,[18] allylic iodide formation, and indium-mediated glyceraldehyde allylation in aqueous media (Scheme 2). This procedure

Scheme 2. Synthesis of Substrates Containing Sterically-Hindered Aryl Moieties



afforded alcohols **5k**,**l** in ∼40% overall yield and 3:1 diastereoselectivity.

2-Deoxy-β-*C*-aryl glycofuranosides have recently gained heightened importance as non-natural nucleoside analogues.[19,20] Given that our arylated products contain the carbon backbone of 2-deoxyribose, we envisioned that they could be transformed into *C*-aryl ribofuranosides in a straightforward manner. Benzylation of **5a**, acetonide deprotection, and regioselective silylation of the primary hydroxyl group took place in 80% overall yield. Oxidative cleavage of the alkene (cat. OsO_4, NMO, acetone/H_2O; KIO_4, pH 6.5 buffer) gave **9a** as a mixture of C.1 anomers; stereoselective ketol reduction (Et_3SiH, TESOTf, CH_2Cl_2, −78 °C) then provided the target 1-phenyl-2-deoxyribofuranoside **10a** with >10:1 β:α stereoselectivity. The undesired diastereomer at

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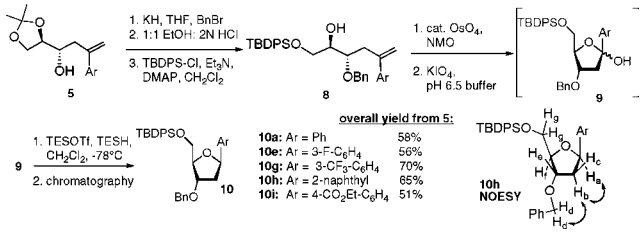
C.3 formed in the allylation step could be easily separated at this stage by silica gel chromatography; the overall yield of **10a** from compound **5a** was 58% (Scheme 3). Compounds

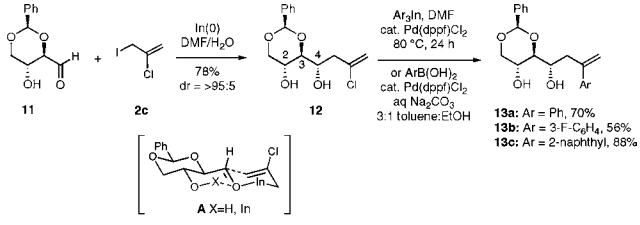
Scheme 3. Synthesis of 2-Deoxy-*C*-arylfuranosides **10** from **5**



5e, **5g**, **5h**, and **5i** can be transformed into *C*-aryl glycosides **10e**, **10g**, **10h**, and **10i** in an analogous manner in 51−70% overall yields. The stereochemistry of the products was confirmed by analysis of cross peaks observed in the NOESY spectrum of **10h** (see Supporting Information for details).

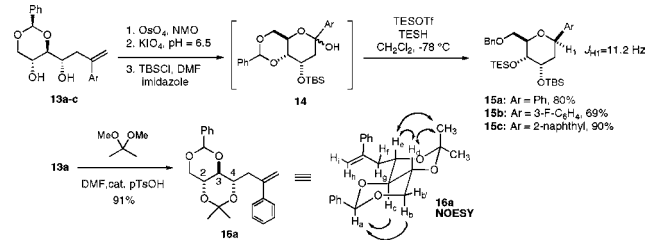
To extend this process to the synthesis of *C*-aryl pyranosides, we investigated allylation reactions of glucose-derived aldehyde **11**[21] with 2,3-dichloropropene under our standard conditions. Vinyl chloride **12** was obtained in low (30%) yield; however, when 2-chloro-3-iodopropene **2c** was used as the allyl source and the reaction was conducted under aqueous conditions (1:1 DMF:H_2O), a 78% yield of **12** was obtained. In both cases, only a single diastereomer was evident by ^{1}H NMR, indicating <95:5 diastereoselectivity for the reactions. We suspect that a highly organized transition state, such as that represented by structure **A** in Scheme 4, is responsible for the high level of diastereose-

Scheme 4. Diastereoselective Allylation of 2,4-*O*-Benzylidene Erythrose **11**



lection observed in this process.[13d] The resulting 2,3-*anti*, 3,4-*anti* stereorelationship was deduced by analysis of the NOESY spectrum of acetonide derivative **16a** (vide infra, Scheme 5). Subsequent palladium-catalyzed cross-coupling

Scheme 5. Synthesis of 2-Deoxy β-*C*-Aryl Glycosides **15a**−**c**



of **12** with triphenylindium led to styrene **13a** in 70% yield. Suzuki coupling of **12** with 3-fluorophenylboronic acid or 2-naphthaleneboronic acid gave rise to **13b** and **13c** in 56% and 88% yields, respectively.

Compound **13a**, containing the carbon backbone of 2-deoxyallose, was then subjected to standard olefin oxidative cleavage conditions, and subsequent silyl protection of the C.3 alcohol produced ketol **14a**. Treatment with excess Et_3SiH and TESOTf at −78 °C led to reduction of the C.1 ketol and opening of the benzylidene acetal in a regioselective fashion to provide β-*C*-aryl glycoside **15a** in 80% overall yield from **13a** (Scheme 5). Compounds **13b** and **13c** could be similarly transformed into *C*-glycosides **15b** and **15c** in 69−90% overall yields. The 11.2 Hz coupling constant observed for the anomeric protons in **15a**−**c** confirmed the β-orientation of the aryl groups at C.1 of the carbohydrates. Importantly, the differential protection of the three hydroxyl groups on glycosides **15a**−**c** allows for regioselective unmasking for subsequent O-glycosylation reactions.

The sequential indium-mediated aldehyde allylation/palladium-catalyzed cross-coupling process efficiently established the carbon backbone of 2-deoxy-*C*-aryl ribofuranosides and allopyranosides, and subsequent transformations stereoselectively furnish glycosides with differential hydroxyl protection. We are currently exploring the utility of this method in the context of natural product synthesis.

Acknowledgment. We thank the National Institutes of Health (SC2 GM081064-01), the ACS Petroleum Research Fund (No. PRF 45277-B1), and the Henry Dreyfus Teacher-Scholar Award for their generous support of our research program.

Supporting Information Available: Detailed experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for all compounds in Table 1 and Schemes 1−5, as well as NOESY spectra for compounds **10h** and **16a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901353F

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