ORGANIC LETTERS

2012
Vol. 14, No. 15
3962–3965

Diastereoselective Addition of Arylzinc Reagents to Sugar Aldehydes

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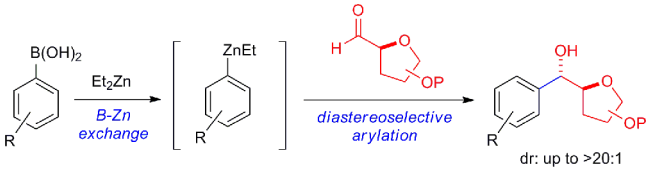
Received June 22, 2012

ABSTRACT



The diastereoselective arylation of sugar-derived aldehydes is described. The arylating reagents are generated in situ by a boron-to-zinc exchange reaction of arylboronic acids with Et_2Zn to generate arylethylzinc reagents. The exquisite reactivity of the arylzinc reagents allowed for an efficient and mild arylation, delivering the corresponding products in diastereoisomeric ratios of up to >20:1. The utility of the methodology is highlighted with an efficient formal synthesis of (+)-7-*epi*-goniofufurone, a member of the styryllactone family of natural products.

The addition of organozinc reagents to carbonyl compounds has been a subject of intense research over the past few years.[1] In this context, the addition of diethylzinc to aldehydes in the presence of an amino alcohol has been considered a test reaction for the development of new ligands and catalysts and hundreds of chiral ligands have been developed.[2,3] On the other hand, the addition of diarylzincs is a much more challenging reaction. The main reason is because diarylzinc reagents are far more reactive than the dialkyl ones and sometimes selectivity is difficult to achieve because of a competitive background addition that proceeds without the participation of the ligand. In order to circumvent these selectivity problems and achieve a neat aryl transfer to aldehydes, the generation of mixed arylalkylzinc compounds has been investigated. However the reaction of diphenylzinc with diethylzinc resulted in a species with decreased reactivity compared to the parent diphenylzinc.[4] One disadvantage associated with the Ar_2Zn/Et_2Zn system is that Ph_2Zn is the only commercially available arylzinc compound, thus limiting the reaction to the transfer of a phenyl group.

An interesting alternative for the generation of arylalkylzinc is the boron to zinc exchange reaction between

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(1) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856. (c) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 5. (d) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886. (e) Lemire, A.; Cote, A.; Janes, M. K.; Charette, A. B. *Aldrichimica Acta* **2009**, *43*, 71–83.

(2) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757–824.

(3) (a) Carreira, E. M.; Kvaerno, L. E. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, 2009. (b) Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, CA, 2009.

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(6) For selected recent references on the asymmetric addition of arylzincs to aldehydes, see: (a) Hatano, M.; Gouzu, R.; Mizuno, T.; Abe, H.; Yamada, T.; Ishihara, K. *Catal. Sci. Technol.* **2011**, *1*, 1149–1158. (b) Infante, R.; Nieto, J.; Andrés, C. *Org. Biomol. Chem.* **2011**, *9*, 6691–6699. (c) Schwab, R. S.; Soares, L. C.; Dornelles, L.; Rodrigues, O. E. D.; Paixao, M. W.; Godoi, M.; Braga, A. L. *Eur. J. Org. Chem.* **2010**, 3574–3578. (d) Godoi, M.; Alberto, E. E.; Paixao, M. W.; Soares, L. A.; Schneider, P. H.; Braga, A. L. *Tetrahedron* **2010**, *66*, 1341–1345. (e) DeBerardinis, A. M.; Turlington, M.; Ko, J.; Sole, M.; Pu, L. *J. Org. Chem.* **2010**, *75*, 2836–2850. (f) DeBerardinis, A. M.; Turlington, M.; Pu, L. *Org. Lett.* **2008**, *10*, 2709–2712. (g) Salvi, L.; Kim, J. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 12483–12493. (h) Wang, M.-C.; Wang, X.-D.; Ding, X.; Liu, Z.-K. *Tetrahedron* **2008**, *64*, 2559–2564. (i) Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.; Pericàs, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1098–1101. (j) Paixao, M. W.; Godoi, M.; Rhoden, C. R. B.; Westermann, B.; Wessjohann, L. A.; Lüdtke, D. S.; Braga, A. L. *J. Mol. Catal. A: Chem.* **2007**, *261*, 120–124. (k) Schmidt, F.; Rudolph, J.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 703–708.

10.1021/ol301724x
Published on Web 07/24/2012

arylboronic acids and diethylzinc.[5] The B−Zn exchange occurs efficiently to generate the required mixed organozinc species in situ greatly expanding the number of transferable aryl groups,[6,7] since a vast number of arylboronic acids are commercially available or can be readily prepared.[8]

Despite their interesting reactivity, the synthetic potential of arylalkylzinc reagents has remained largely unexplored. Besides their use as nucleophiles for the addition to aldehydes, arylzincs have also found use in asymmetric Ni-catalyzed Negishi cross-couplings, in an elegant work developed by Smith and Fu.[9]

Considering the exquisite reactivity displayed by the arylethylzinc reagents and in connection with our recent interest on the use of carbohydrates for the synthesis of chiral molecules,[10] we hypothesized that a mild and selective arylation of enantiopure sugar-derived aldehydes would be possible to achieve. Herein we describe our results on the diastereoselective addition to chiral aldehydes bearing an α-oxygenated stereogenic center, readily available from carbohydrates (Scheme 1).

Our initial studies were focused on the screening of the reaction conditions in order to optimize both yield and diastereoselectivity. For the screening experiments phenylethylzinc was generated by the reaction of phenylboronic acid with Et_2Zn, and the enantiopure sugar aldehyde **1**, readily available from D-glucose, was chosen as the substrate.[11]

Under the first set of conditions tested, toluene was used as the solvent, and the desired product was obtained in 73% yield and with a very high diastereoselectivity (Table 1, entry 1, *dr* > 20:1). Attempts to improve the yield by increasing the reaction time (up to 24 h) or changing the solvent to dichloromethane, THF and hexane proved fruitless. When dichloromethane and hexane were used, the product **2** was obtained in good *dr* but in low yields (entries 2 and 4). When the more Lewis basic THF was employed as the solvent, the product yield was moderate, but a sharp decrease in the diastereoselectivity was observed (entry 3). Keeping toluene as the solvent and changing the temperature of the addition to 0 °C resulted in a decrease in the isolated yield, while maintaining high diastereoselectivity (entry 5).

Scheme 1. Diastereoselective Addition of Arylzinc Reagents to Sugar Aldehydes

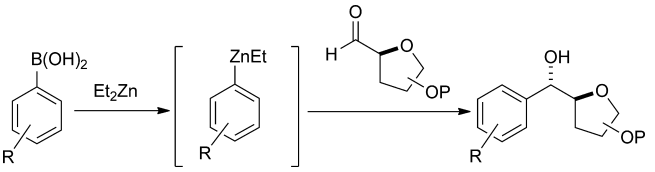
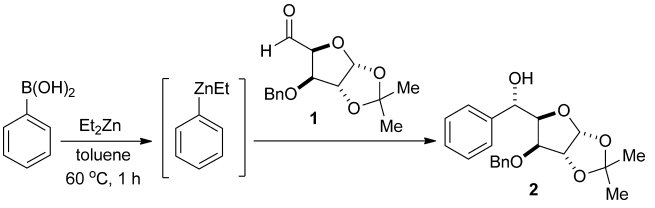


Table 1. Diastereoselective Addition of PhZnEt to Aldehyde **1**



entry	solvent	temp (°C)	time (h)	yield (%)[a]	*dr*[b]
1	toluene	25	3	73	>20:1
2	DCM	25	2	40	16:1
3	THF	25	2	60	5:1
4	hexane	25	2	20	14:1
5	toluene	0	4	43	>20:1
6	toluene	60	1	67	10:1
7	toluene	100	1	85	8:1

[a] Isolated yields. [b] Determined by ^{1}H NMR

Attempts to improve the yield by conducting the addition reaction at higher temperatures resulted in a decrease in the diastereoselectivity of the reaction (entries 6 and 7). Therefore, performing the reaction at room temperature for 3 h resulted in the best results in terms of yield and diastereoselectivity.

In order to understand the high diastereoselectivity observed for the arylation of aldehyde **1**, a transition state involving coordination of the zinc atom to the carbonyl oxygen and at the furanoside oxygen is proposed (Figure 1). The substrate **1** might coordinate to the Lewis acidic PhZnEt as a bidentate Lewis base ligand, in an analogous manner that occurs for Lewis bases used in the standard diethylzinc additions.[1] In this working model, chelation would enhance the electrophilicity of the aldehyde, while the attack of the arylzinc reagent would occur

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(9) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 12645–12647.

(10) (a) Braga, H. C.; Wouters, A. D.; Zerillo, F. B.; Lüdtke, D. S. *Carbohydr. Res.* **2010**, *345*, 2328–2333. (b) Braga, H. C.; Stefani, H. A.; Paixão, M. W.; Santos, F. W.; Lüdtke, D. S. *Tetrahedron* **2010**, *66*, 3441–3446. (c) Braga, A. L; Severo Filho, W. A.; Schwab, R. S.; Rodrigues, O. E. D.; Dornelles, L.; Braga, H. C.; Lüdtke, D. S. *Tetrahedron Lett.* **2009**, *50*, 3005–3007. (d) Vieira, A. S.; Fiorante, P. F.; Hough, T. L. S.; Ferreira, F. P.; Lüdtke, D. S.; Stefani, H. A. *Org. Lett.* **2008**, *10*, 5215–5218.

(11) (a) Roy, A.; Achari, B.; Mandal, S. B. *Synthesis* **2006**, 1035–1039. (b) Gautam, D.; Kumar, D. N.; Rao, B. V. *Tetrahedron: Asymmetry* **2006**, *17*, 819–821.

at the less hindered side in the most energetically favorable conformation. Therefore, aryl transfer to the *si* face of the aldehyde would result in the formation of the main product observed. The stereochemistry of the new stereogenic center formed was assigned on the basis of literature NMR data.[12]

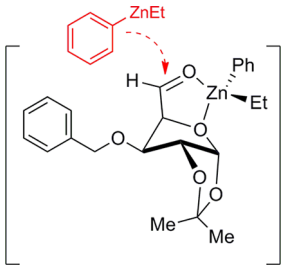
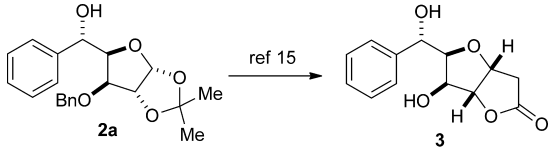


Figure 1. Proposed pathway to rationalize the high diastereoselectivity.

Importantly, the high diastereoselectivity of the arylation allows an efficient synthesis of a key intermediate in the synthesis of (+)-7-*epi*-goniofufurone, a styryllactone isolated from the bark of Goniothalamus giganteus.[13] The styryllactones are a family of natural products that present a broad range of biological activities that include anticancer, antibiotic, immunosuppressant, trypanocidal and antifertility activities.[14] Product **2a** was previously converted by Popsavin and co-workers to 7-*epi*-goniofufurone **3** in a three step sequence (Scheme 2).[15]

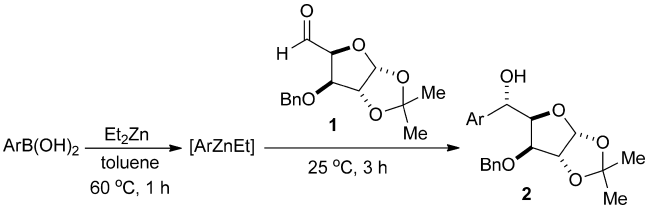
With the success obtained in the phenyl transfer to aldehyde **1**, we extended the scope of the methodology to a broader range of aryl groups. As shown in Table 2, a number of different arylboronic acids are suitable precursors for the generation of transferable aryl groups.

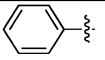
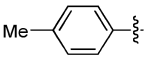
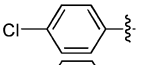
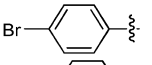
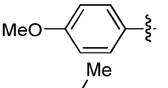
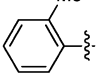
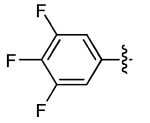
Scheme 2. Structure of Product **2a** and Styryllactone (+)-7-*epi*-Goniofufurone **3**



Both electron-rich and electron-poor aryl groups are transferred, resulting in the desired products in good yields and in very good diastereomeric ratios. In all cases studied, the reaction was complete within 3 h. High conversion was observed by TLC analysis; however, the isolated yields were slightly reduced because of high water solubility of the products. Halogen substituents are well tolerated in the reaction with use of 4-chlorophenyl- and 3,4,5-trifluorophenylboronic acids resulting in smooth addition, delivering the products **2c** and **2g** with excellent diastereoselectivity (entries 3 and 7). A decrease in the selectivity of the addition was observed with the 4-bromophenyl and with the more sterically demanding *ortho*-tolyl derivative, resulting in a *dr* of 14:1 and 16:1, respectively (entries 4 and 6).

Table 2. Scope of the Aryl Transfer Reaction to Aldehyde **1**



entry	Ar	product yield (%)[a]	*dr*[b]
1		**2a**- 73	>20:1
2		**2b**- 68	>20:1
3		**2c**- 72	>20:1
4		**2d**- 73	14:1
5		**2e**- 75	>20:1
6		**2f**- 70	16:1
7		**2g**- 66	>20:1

[a] Isolated yields. [b] Determined by ^{1}H NMR

Our optimized conditions represent an advance over previously reported organometallic additions to aldehyde **1**, using PhMgBr.[12,15,16] Despite, in some cases, the benzylic alcohol **2a** being obtained in moderate to good diastereoisomeric ratios (1.6 to 14:1), the Grignard addition was reported only for the introduction of a phenyl group. Our methodology allows the mild and highly diastereoselective transfer of a broader range of aryl groups, since a number of arylzinc reagents can be efficiently prepared from the corresponding boronic acids, opening the door for the synthesis of natural product analogues for structure activity relationship studies.

(12) (a) Gracza, T.; Szolcsányi, P. *Synthesis* **1994**, 1359–1368. (b) Gracza, T.; Szolcsányi, P. *Molecules* **2000**, *5*, 1386–1398.

(13) Fang, X. F.; Anderson, J. E.; Chang, C. J.; Fanwik, P. E.; McLaughlin, J. L. *J. Nat. Prod.* **1991**, *54*, 1034–1043.

(14) de Fatima, A.; Modolo, L. V.; Conegero, L. S.; Pilli, R. A.; Ferreira, C. V.; Khon, L. K.; de Carvalho, J. E. *Curr. Med. Chem.* **2006**, *13*, 3371–3384.

(15) Popsavin, V.; Benedekovic, G.; Sreco, B.; Popsavin, M.; Francuz, J.; Kojic, V.; Bogdanovic, G. *Org. Lett.* **2007**, *9*, 4235–4238.

(16) Prakash, K. R. C.; Rao, S. P. *Tetrahedron* **1993**, *49*, 1505–1510.

With the success achieved in the arylation of enantiopure aldehyde **1**, derived from D-glucose, we turned our attention to test our protocol with two different sugar aldehydes (Table 3). The arylation of aldehyde **4**, obtained from D-mannose,[17] proceeded in good yield but with only moderate diastereoselection for the majority of cases studied (entries 1, 3, 5 and 9). An exception to this behavior was the reaction performed using *ortho*-tolylboronic acid as the precursor of the transferable aryl group, which delivered the product **6d** in 78% yield and in a *dr* of >20:1 (entry 7). Also worth noting is that heating the reaction mixture to 60 °C was necessary in order to achieve good yields of the product **6**.

On the other hand, when the arylation reaction was extended to aldehyde **5**,[18] which is prepared from D-ribose, exceptional levels of diastereoselectivity resulted (Table 3). For all the reactions studied, diastereomeric ratios of >20:1 were observed, and the products **7a**–**e** were formed in yields ranging from 72 to 78%. The substitution pattern of the aryl group seems to be irrelevant for the reaction outcome, since the same high levels of selectivity were achieved with electron-withdrawing (entry 4), electron-donating (entries 6) and *ortho*-substituted (entry 8) aryl groups. Once again, performing the reaction at higher temperature resulted in optimized yields, without any decrease in the diastereoselectivity of the addition. The stereochemistry of the newly formed stereocenter was assigned by analogy with the stereochemical outcome observed for the arylation of aldehyde **1**, assuming that aldehydes **4** and **5** undergo reaction through analogous chelation-controlled transition states. An unequivocal proof of the absolute stereochemistry remains to be achieved. Several attempts to prepare suitable derivatives for X-ray crystallography analysis have so far proven fruitless.

In summary, we have developed a diastereoselective addition of arylzinc reagents to enantiopure sugar-derived aldehydes. High diastereoselectivity was achieved using aldehydes **1** and **5**, which are derived from D-glucose and D-ribose, respectively, while only moderate *dr* are observed for aldehyde **4**, derived from D-mannose, except when an *ortho* substituent is present in the arylzinc reagent. Our protocol further expands the utility of the B–Zn exchange reaction of arylboronic acids and allows the synthesis of interesting chiral molecules, as exemplified by our formal synthesis of (+)-7-*epi*-goniofufurone. Further efforts to expand the reaction to other substrates and for the synthesis of natural products and analogues are underway.

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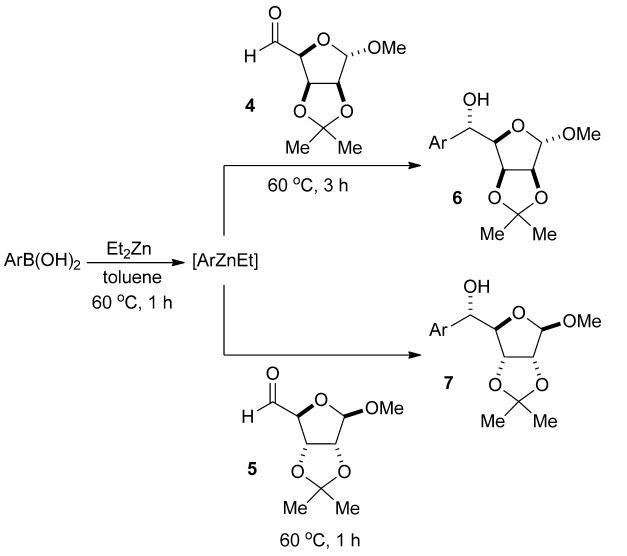
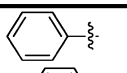
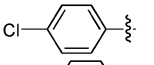
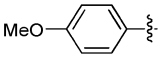
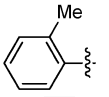
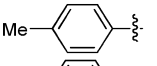
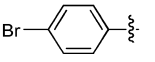
(18) (a) Evans, M. E.; Parrish, F. W. *Carbohydr. Res.* **1973**, *28*, 359–364. (b) Zhong, Y. L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622–2624.

Table 3. Diastereoselective Arylation of Aldehydes **4** and **5**



entry	aldehyde	Ar	product yield (%)[a]	*dr*[b]
1	**4**		**6a**- 78	5:1
2	**5**		**7a**- 78	>20:1
3	**4**		**6b**- 75	7:1
4	**5**		**7b**- 77	>20:1
5	**4**		**6c**- 74	4:1
6	**5**		**7c**- 77	>20:1
7	**4**		**6d**- 78	>20:1
8	**5**		**7d**- 76	>20:1
9	**4**		**6e**- 79	3:1
10	**5**		**7e**- 72	>20:1

[a] Isolated yields. [b] Determined by ^{1}H NMR

Acknowledgment. We are grateful to FAPESP, CNPq and FAPERGS for financial support. CAPES and CNPq are also acknowledged for a PhD fellowship to A.D.W. and research fellowship to D.S.L., respectively.

Supporting Information Available. Full experimental procedures, analytical data and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.