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Selective 1,2-*syn* alkynylation of an open chain sugar: the prominent role of zinc chloride addition

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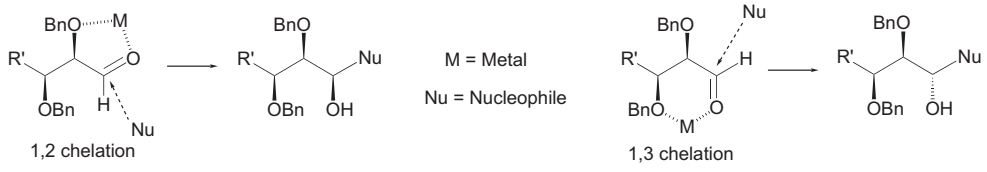
Abstract—Depending on the metal, solvent and protective groups, functionalized aldehydes may react through either Felkin or chelated transition states leading to the Felkin–Anh product or the 1,2-*anti* Felkin–Anh product, respectively. Zinc chloride addition proved to be a key aspect in order to favor 1,2-*syn* nucleophilic attack.

When adding organometallic reagents to chiral acyclic α- or/and β-alkoxyaldehydes, chelation can play a crucial role in reaction stereoselectivity. This aspect has received considerable attention since the work of Cram et al., Felkin and co-workers, and Anh, which originally explained the observed stereoselectivities.[1] When predicting diastereoselectivity for nucleophilic additions with α,β-*syn*-dialkoxyaldehydes, the task is complicated because of competition between the 1,2 and the 1,3 metal chelation processes. While 1,2 chelation favors the approach of nucleophilic reagents giving 1,2-*syn* adducts, a 1,3 one preferentially orients towards a 1,2-*anti* selectivity (Scheme 1). It is also important to note that lack of chelation can favor either 1,2-*syn* (Cram–Felkin–Ahn control) or 1,2-*anti* addition (*anti*-Cram–Felkin–Ahn control), depending on the nature of the group present in position 2, showing that perfectly controlled behavior is not trivial.[2]

In the course of our studies concerning the synthesis of *C*-glycosides, we needed to control the diastereoselectivity in the alkynylation of a chiral α,β-*syn*-dialkoxyaldehyde. We report here a 1,2-*syn* selective coupling of an open chain sugar aldehyde and diverse alkyne side chains. Although Carreira's procedure using zinc trifluoromethanesulfonate, triethylamine, and a chiral compound (*N*-methyl ephedrine) has proven to be efficient for this kind of addition,[3] we envisioned that the asymmetric centers already present in the sugar residue could be sufficient to induce a selective formation of the desired compounds. A few interesting cases of good diastereoselectivity with zinc derivatives have been observed with constrained cyclic carbohydrates derived aldehydes[2a,4] and with hemiacetals,[5] but only a few examples have been described with open chain sugar aldehydes.[2a,b,4b,6]

Keeping in mind our final goal toward *C*-glycoside synthesis, and in order to improve alkynylation reaction conditions, we chose the following functionalized aldehyde **1** (Scheme 2), available in three steps from the known diol **2**.[7]



Scheme 1.

Keywords: Alkynylation; 1,2-Dialkoxyaldehydes; Zinc chelation.
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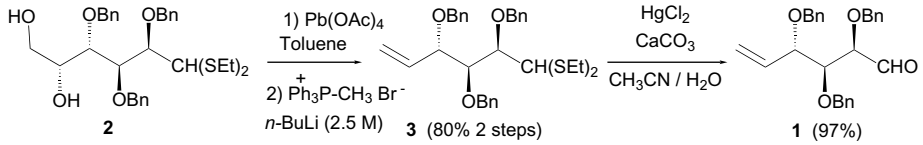
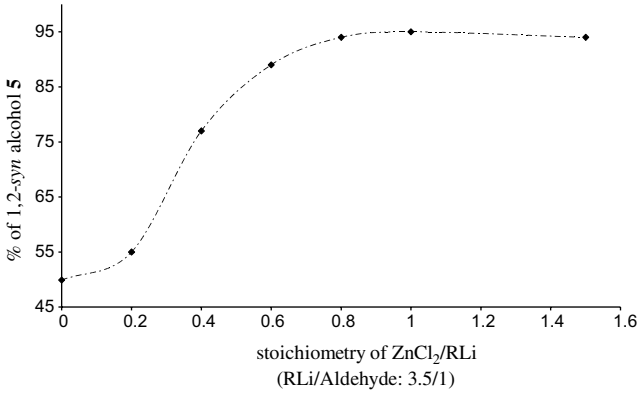


Scheme 2.

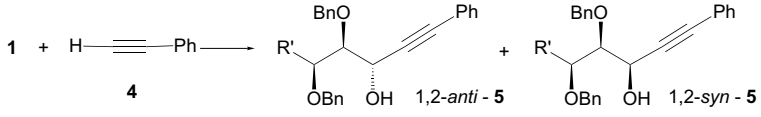
We then studied the reaction between aldehyde **1** and phenylacetylene, varying the solvent and the metal. The results are summarized in Table 1. The addition of lithium phenylacetylide to aldehyde **1** in THF at −78 °C gave a mixture of 1,2-*anti*- and 1,2-*syn*-propargylic alcohols **5** in 75% yield and in a ratio of 65:35 (Table 1, entry 1).[8] These two diastereoisomers were not separable by classical silica gel column chromatography. The use of a more metal complexing solvent to a lesser one (THF → Et_2O → toluene) showed evolution from a 1,2-*anti* favoring process to a 1,2-*syn* favoring one, due to enhanced 1,2 chelation (entries 2 and 3). The Grignard reagents proceeded with the same selectivity as previously observed with the lithium derivatives (entries 4 and 5). As the selectivities for lithium and magnesium acetylides remaining too low, we were prompted to shift to more 1,2 chelating metals.

The use of cerium derivatives prepared from the reaction of lithium phenylacetylide with cerium(III) chloride[9] (entry 6), known to favor 1,2-*syn* selectivity,[5f,10] gave disappointing results. The organocopper reagent did not give a better result (entry 7) and the aluminum derivative did not react with aldehyde **1** (entry 9). Alkynyltitanium reagents have been described to proceed with high levels of chelate organization,[2b] and in our hands, a good selectivity was obtained in favor of 1,2-*anti*-alcohol **5** (entry 8). The reaction between the alkynylzinc derivative and aldehyde **1** in THF at 0 °C was also carried out and we were pleased to observe a significant excess of the desired 1,2-*syn* alcohol (entry 10). The selectivity and the yield were improved by using zinc(II) chloride as the metal source and diethyl ether as solvent (entries 11 and 12).[11] Some precedents of 1,2-*syn* favoring effects with zinc have been reported in the literature,[5i,6a] giving excellent diastereoselectivities for simple aldehydes, but to the best of our knowledge, the use of more elaborate structures gave severe drops in selectivity.[2a,12] Finally, an organotin reagent was tested and presented a similar selectivity as previously seen for zinc, but in low yield (entry 13). This selectivity with an organotin reagent has previously been described



Scheme 3.

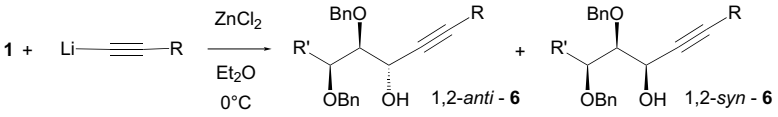
Table 1. Reactions between aldehyde **1** and phenylacetylides **4** with different metals



Entry	Conditions	Yield[a] (%)	Ratio[b] 1,2-*anti*-**5**/1,2-*syn*-**5**
1	*n*-BuLi, THF, −78 → 0 °C	75	65/35
2	*n*-BuLi, Et_2O, −78 → 0 °C	75	50/50
3	*n*-BuLi, toluene, −78 → 0 °C	71	40/60
4	*n*-BuLi, $MgBr_2{\cdot}OEt_2$, THF, −78 → 0 °C	56	63/37
5	*n*-BuLi, $MgBr_2{\cdot}OEt_2$, Et_2O, −78 → 0 °C	74	42/58
6	*n*-BuLi, $CeCl_3$, THF, −78 °C → rt	53	67/33
7	*n*-BuLi, $MgBr_2{\cdot}OEt_2$, $CuBr{\cdot}SMe_2$, THF, −78 °C → rt	56	50/50
8	*n*-BuLi, $ClTi(O\text{-}i\text{-}Pr)_3$, THF, −40 °C → rt	53	74/26
9	*n*-BuLi, $Al(Et)_2Cl$, THF, −78 °C → rt	—	—
10	*n*-BuLi, $ZnBr_2$, THF, 0 °C → rt	23	23/77
11	*n*-BuLi, $ZnBr_2$, Et_2O, 0 °C → rt	37	17/83
12	***n*-BuLi, $ZnCl_2$, Et_2O, 0 °C → rt**	**79**	**7/93**
13	*n*-BuLi, $SnMe_3Cl$, THF, −78 → 0 °C	33	16/84

[a] Yield after purification by silica gel column chromatography.
[b] Determined by HPLC on inverse phase Nucleodur column eluting with MeOH/H_2O: 78/22.

Table 2. Reactions between aldehyde **1** and various zinc acetylides



Entry	R	Conditions	Yield[a] (%)	Ratio 1,2-*anti*-**6**/1,2-*syn*-**6**
1	Ph	Et_2O, 0 °C → rt	79	7/93
2	*n*-C_3H_7	Et_2O, 0 °C → rt	47	17/83
3	*n*-C_5H_{11}	Et_2O, 0 °C → rt	32	14/86
4	$SiMe_3$	Et_2O, 0 °C → rt	85	<6/>94
5	CO_2Et	Et_2O, 0 °C → rt	<5	—
6	$CH_2OTBDMS$	Et_2O, 0 °C → rt	55	14/86

[a] Yield after purification by silica gel column chromatography.

but only in the alkynylation of a chiral β-alkoxyaldehyde in the presence of a Lewis acid.[13]

In order to better determine the species involved in our selective 1,2-*syn* alkynylation with the alkynylzinc derivative, we first verified that LiCl, originally formed in situ in our procedure, was not the major influence on reaction diastereoselectivity. Use of reaction conditions in entry 2 with excess amount of added LiCl did not change the ratio in diastereoisomers. This may be due to solubility problems, indicating that lithium is probably not involved in the chelated species. A study with various amounts of zinc(II) chloride using the typical procedure was then done and the profile in Scheme 3 clearly shows that an increase in zinc(II) chloride concentration is essential for major formation of the 1,2-*syn* product.

We then selected the optimized reaction conditions (Table 1, entry 12) to extend our approach to various alkynes. The results are reported in Table 2.[14] Although reactions with alkynes containing an alkyl chain were less efficient compared to phenylacetylide in terms of reactivity and selectivity (entries 2 and 3), they still remain a good approach to these kinds of compounds. In contrast, trimethylsilylacetylide zinc led to the 1,2-*syn* alcohol as the major product in good yield (entry 4). This result is extremely interesting because the trimethylsilyl group can be replaced with another side chain. When an ester function was tested using the same approach, we met serious problems (entry 5). Even if this lithium acetylide was described before,[15] it seems in our case that the necessary temperature increase to generate the zinc derivative, and further reaction with an aldehyde is accompanied with by-products. A different promoter system was cited but we preferred our simple and easy method.[16] A functionalized acetylide was also tested and the corresponding 1,2-*syn* alcohol **6** was obtained as the major isomer (entry 6).

In summary, we have described a selective 1,2-*syn* addition of various acetylides to a chiral α,β-*syn*-dialkoxyaldehyde using zinc(II) chloride as an efficient promoter. The observed results are very encouraging, creating the possibility of applying this reaction to more complex molecules. We believe this method is convenient for the diastereoselective synthesis of biologically active compounds.

Acknowledgements

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11. *Typical procedure* (example for entry 12): Zinc(II) chloride (102.4 mg, 0.751 mmol) was fused under high vacuum. After cooling, anhydrous diethyl ether (1.5 mL) was then introduced under argon. To this solution was added a solution of lithium phenylacetylide (prepared from phenylacetylene (51.1 mg, 0.5 mmol) and *n*-BuLi (0.31 mL, 0.5 mmol, 1.6 M solution in hexanes) in diethyl ether (2 mL)) at 0 °C. The solution was stirred for 45 min at 0 °C before the addition of a solution of aldehyde **1** (60.2 mg, 0.145 mmol) in diethyl ether (1 mL). The solution was stirred for 2.5 h at 0 °C, diluted with diethyl ether and quenched with a saturated NH_4Cl solution. The organic layer was washed with brine, dried, and evaporated under reduced pressure. Purification by silica gel column chromatography (petroleum ether/ethyl acetate: 95/5 → 90/10) led to **5** (59.3 mg, 0.114 mmol, 79%) as a mixture of 1,2-*syn*- and 1,2-*anti*-isomers in a 93:7 ratio.
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14. (a) *syn* **6**–**1**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42–7.21 (m, 20H, Har), 5.97 (ddd, 1H, =CH, J = 7.6, 10.2, 17.4 Hz), 5.46 (dd, 2H, $=CH_2$, J = 10.2, 17.4 Hz), 4.84 (d, 1H, CH–O, J = 3.6 Hz), 4.81–4.62 (m, 6H, CH_2–O), 4.12 (dd, 1H, CH–O, J = 6.5, 7.6 Hz), 4.00–3.89 (m, 2H, CH–O), 2.81 (br s, 1H, OH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 138.3 (quat C), 138.1 (quat C), 138.0 (quat C), 135.9 (=CH), 131.6 (CH), 128.4 (CH, 2C overlap), 128.3 (CH, 2C overlap), 128.2 (CH, 2C overlap), 128.1 (CH), 128.0 (CH), 127.7 (CH, 2C overlap), 127.6 (CH), 127.5 (CH), 122.4 (quat C), 119.9 ($=CH_2$), 88.1 (quat C), 86.0 (quat C), 82.6 (CH–O), 81.5 (CH–O), 80.6 (CH–O), 75.3 (CH_2–O), 74.8 (CH_2–O), 70.1 (CH_2–O), 63.7 (CH–O). HRMS (ES) Calcd for $C_{35}H_{34}O_4Na$: 541.2355. Found: 541.2369; (b) *syn* **6**–**2**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.20 (m, 15H, Har), 6.05–5.85 (m, 1H, =CH), 5.46 (dd, 2H, $=CH_2$, J = 11.1, 16.3 Hz), 4.74 (d, 1H, CH–O, J = 2.9 Hz), 4.71–4.52 (m, 6H, CH_2–O), 4.29 (dd, 1H, CH–O, J = 5.3, 6.3 Hz), 3.90–3.76 (m, 2H, CH–O), 2.55 (br s, 1H, OH), 2.20 (dt, 2H, CH_2, J = 2.1, 7.3 Hz), 1.61–1.44 (m, 2H, CH_2), 0.97 (t, 3H, CH_3, J = 7.3 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): 138.9 (quat C), 138.7 (quat C), 138.6 (quat C), 136.5 (=CH), 128.9 (CH), 128.8 (CH, 2C overlap), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 120.3 ($=CH_2$), 87.4 (quat C), 83.4 (CH–O), 81.9 (CH–O), 81.0 (CH–O), 79.5 (quat C), 75.7 (CH_2–O), 75.0 (CH_2–O), 70.6 (CH_2–O), 64.0 (CH–O), 22.4 (CH_2), 21.3 (CH_2), 14.0 (CH_3). HRMS (ES) Calcd for $C_{32}H_{36}O_4Na$: 507.2511. Found: 507.2501; (c) *syn* **6**–**3**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38–7.15 (m, 15H, Har), 6.06–5.80 (m, 1H, =CH), 5.43 (dd, 2H, $=CH_2$, J = 10.3, 17.0 Hz), 4.80–4.45 (m, 7H, CH–O and CH_2–O), 4.20–4.05 (m, 2H, CH–O), 3.90–3.80 (m, 1H, CH–O), 2.52 (br s, 1H, OH), 2.22 (t, 2H, CH_2, J = 7.1 Hz), 1.55–1.45 (m, 2H, CH_2); 1.40–1.22 (m, 4H, CH_2), 0.86 (t, 3H, CH_3, J = 7.1 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): 138.9 (quat C), 138.6 (quat C), 138.3 (quat C), 136.1 (=CH), 128.7 (CH), 128.5 (CH, 2C overlap), 128.3 (CH, 2C overlap), 128.1 (CH), 127.8 (CH, 2C overlap), 127.7 (CH), 120.1 ($=CH_2$), 87.2 (quat C), 83.1 (CH–O), 81.6 (CH–O), 80.8 (CH–O), 79.0 (quat C), 75.4 (CH_2–O), 75.0 (CH_2–O), 70.3 (CH_2–O), 63.7 (CH–O), 31.2 (CH_2), 28.3 (CH_2), 22.3 (CH_2), 18.9 (CH_2), 14.1 (CH_3). HRMS (ES) Calcd for $C_{34}H_{40}O_4Na$: 535.2824. Found: 535.2810; (d) *syn* **6**–**4**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.27–7.16 (m, 15H, Har), 5.88 (ddd, 1H, =CH, J = 7.6, 9.6, 17.5 Hz), 5.46 (dd, 2H, $=CH_2$, J = 9.6, 17.5 Hz), 4.72–4.48 (m, 6H, CH_2–O and CH–O), 4.20 (d, 1H, CH_2–O, J = 11.6 Hz), 3.98 (dd, 1H, CH–O, J = 6.1, 7.6 Hz), 3.82–3.72 (m, 2H, CH–O), 2.60 (d, 1H, OH, J = 6.1 Hz), 0.10 (s, 9H, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): 138.6 (quat C), 138.4 (quat C), 138.3 (quat C), 136.1 (=CH), 128.6 (CH, 2C overlap), 128.5 (CH, 2C overlap), 128.4 (CH), 128.3 (CH), 127.9 (CH, 2C overlap), 127.8 (CH), 120.1 ($=CH_2$), 104.1 (quat C), 91.1 (quat C), 82.7 (CH–O), 81.8 (CH–O), 80.9 (CH–O), 75.6 (CH_2–O), 75.1 (CH_2–O), 70.4 (CH_2–O), 63.9 (CH–O), 0.0 (CH_3). HRMS (ES) Calcd for $C_{32}H_{38}O_4SiNa$: 537.2454. Found: 537.2437; (e) *syn* **6**–**6**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30–7.10 (m, 15H, Har), 5.94–5.76 (m, 1H, =CH), 5.46 (dd, 2H, $=CH_2$, J = 10.9, 16.3 Hz), 4.70–4.44 (m, 6H, CH_2–O and CH–O), 4.24 (d, 1H, CH_2–O, J = 1.7 Hz), 4.17 (d, 1H, CH_2–O, J = 11.6 Hz), 3.98 (dd, 1H, CH–O, J = 6.1, 7.4 Hz), 3.80–3.70 (m, 2H, CH–O), 2.52 (d, 1H, OH, J = 5.7 Hz), 0.78 (s, 9H, CH_3), 0.0 (s, 6H, CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): 138.8 (quat C), 138.7 (quat C), 138.6 (quat C), 136.4 (=CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH, 2C overlap), 128.0 (CH), 120.4 ($=CH_2$), 85.2 (quat C), 84.0 (quat C), 82.8 (CH–O), 81.8 (CH–O), 81.0 (CH–O), 75.7 (CH_2–O), 75.3 (CH_2–O), 70.6 (CH_2–O), 63.7 (CH–O), 52.2 (CH_2–O), 26.2 (CH_3), 18.7 (quat C), 0.0 (CH_3). HRMS (ES) Calcd for $C_{36}H_{47}O_5SiNa$: 587.3193. Found: 587.3181.
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