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Stereoselective indium-mediated allylation of erythrulose derivatives in aqueous media

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Abstract

A range of erythrulose derivatives has been allowed to react with allyl bromide and metallic indium in THF or aqueous THF. Some of these allylations are highly stereoselective.

The allylation of carbonyl compounds with allyl halides and activated metals under Barbier type conditions is an established method for the synthesis of homoallylic alcohols.[1] Within these nucleophilic additions, those conducted in aqueous media have been a particularly active research topic in recent years. Either in pure water or in water-containing organic solvents, allyl halides are able to add to carbonyl compounds under promotion of metals such as tin, zinc, indium and others.[2] The use of indium in organic synthesis is a quite recent development.[1b,2,3] The physicochemical properties of this element, most particularly its low ionization potential, make it very prone to insertion into carbon–halogen bonds.[3] The first example of an indium-mediated allylation in an aqueous solvent was reported in 1991, when Li and Chan described allylations of various aldehydes and methyl ketones in water. They showed that indium gave rise to a smooth reaction without the need of a promoter and that yields were consistently better with indium than with tin.[4] A further interesting feature, pointed out by several groups,[5] is that indium-mediated allylations are equally successful with carbonyl compounds bearing free hydroxyl groups. In addition, chiral α- or β-hydroxy and α-acylamino aldehydes often react in these conditions with a high stereoselectivity. Interestingly, protection of the free hydroxyl groups causes marked variations in the degree and/or sense of the stereoselectivity.[5] This has been attributed by some authors to chelate formation between the substrate and the indium atom of an intermediate organometallic reagent. According to their opinion, chelation is still operative in water and acquires its maximum efficiency when a free hydroxyl group in the immediate vicinity of the carbonyl function is involved.[5a,b,d] More recently, it has been found that indium-mediated stereoselective allylations are also possible with α-alkoxy ketones.[6]

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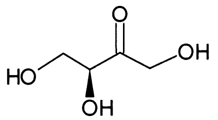
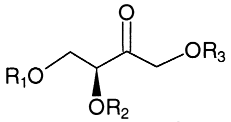
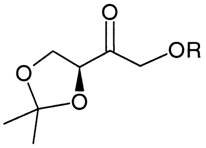
The ketotetrose L-(S)-erythrulose **1** and protected derivatives thereof **2** are useful precursors for the synthesis of many types of chiral, polyfunctionalized compounds.[7] We have recently shown that nucleophilic additions of organometallic reagents, including allylmetal derivatives, display a high stereoselectivity under chelation-control conditions.[7a,b,d] These additions were performed, however, on fully protected erythrulose derivatives **2** (R_1–R_3=silyl or benzyl) under anhydrous conditions. The excellent diastereoselectivity displayed by some allylating reagents in aqueous media[2] prompted us to try the same type of reaction on derivatives **2** with both free and protected hydroxyl groups. Aside from the synthetic utility, we further desired to test once more the possible concurrence of α- versus β-chelation, a question which has not yet received a satisfactory answer.[7d]



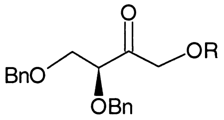
1



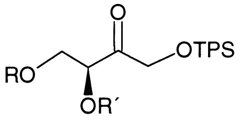
2



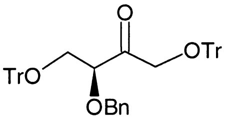
3 R = H
4 R = TPS
5 R = Tr



6 R = H
7 R = TPS
8 R = Tr

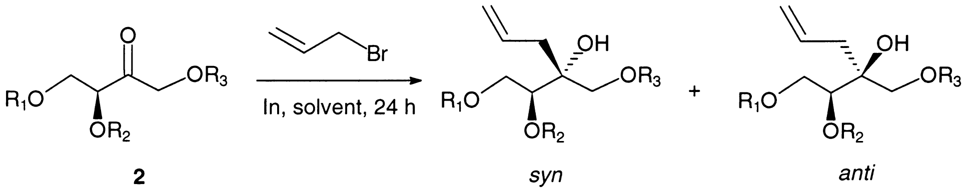


9 R = R´ = H
10 R = H R´ = Bn
11 R = TPS R´ = H



12

General reaction



In addition to **1** itself, erythrulose derivatives **3**–**12** were selected for the purpose of our work. The syntheses of most of these protected derivatives have been recently described,[7c,d] while those of the remaining ones will be reported in due course. Allyl bromide was allowed to react with these ketones in the presence of metallic indium either in THF, aqueous THF or pure water. Table 1 shows the observed diastereomeric ratios (d.r.). The two diastereoisomeric allylation products have been arbitrarily designated as *syn* or *anti*.[8] The *syn* product is that predicted by Cram's cyclic chelation model.[7d] Whenever possible, all reactions were performed in the three solvent systems. Exceptions were products **4**–**8**, **11** and **12**, which were not assayed in water because of their very low solubility in this solvent. It is noteworthy that compounds **4**–**8** and **12**, where all hydroxyl groups are protected, displayed a low diastereoselectivity. In contrast, compounds **9**–**11**, which have free hydroxyl groups, behaved in a quite *syn* stereoselective way. The case of **9** is particularly worth mentioning, as it displays one of the highest d.r. values registered to date in indium-mediated allylations (>19:1). Erythrulose acetonide **3**, which has a free hydroxyl on the α′ side of the carbonyl group, showed also an appreciable stereoselectivity but with the opposite sense. In contrast, the parent sugar **1**, which displays three free hydroxyl groups, behaved in an almost stereorandom way.

In principle, the high *syn* stereoselectivity of **9** and **11** is in a good agreement with an α-chelation control.[7d] Further support of the involvement of α-chelation comes from the results of a competition

Table 1
Stereoselective allylations of erythrulose derivatives **1**, **3**–**12**[a]

Compound	**H_2O[b]**	**H_2O / THF[b]**	**THF[b]**
1	62:38 (54)	62:38 (59)	50:50 (58)
3	26:74 (83)	21:79 (85)	**16:84 (90)**
4	---	25:75 (92)	33:67 (85)
5	---	25:75 (91)	28:72 (?)
6	---	30:70 (80)	30:70 (81)
7	---	57:43 (87)	70:30 (87)
8	---	57:43 (75)	63:37 (82)
9	**> 95:5 (89)**	**> 95:5 (95)**	**> 95:5 (87)**
10	79:21 (90)	**90:10 (90)**	67:33 (87)
11	---	**90:10 (88)**	**86:14 (85)**
12	---	33:67 (75)	31:69 (73)

[a] Standard, non-optimized reaction conditions: The ketone (1 mmol) was dissolved in the appropriate solvent (10 ml). Indium (230 mg, 2 mg-atom) and allyl bromide (260 μl, 3 mmol) was added and the suspension was stirred at room temp. for 24 h. [b] d.r. *syn*:*anti* (% yield). The d.r. was determined by high-field $^1H/^{13}C$ NMR. When the minor diastereomer was not detectable, the d.r. is expressed as >95:5.

experiment, which showed that **9** is much more reactive than **7**.[9] However, β-hydroxy ketone **10** reacts with the same sense of stereoselectivity as **9**, a fact which cannot be so easily reconciled with a putative β-chelation model. As we have recently shown for erythrulose derivatives in anhydrous media,[7d] no clear-cut evidence exists to date which supports without any doubt the participation of chelates in nucleophilic additions to β-oxygenated carbonyl groups. Very recently, Paquette has postulated the existence of β-chelation control in order to explain the high stereoselectivity of indium-mediated allylations of β-hydroxy aldehydes in aqueous media.[5d] However, support of his proposal relies mainly on the high stereoselectivity and not on additional data. Furthermore, his results have been obtained in reactions with β-chiral β-hydroxy aldehydes with no stereogenic centre at Cα. Substrate **10**, however, is an α-chiral α-alkoxy β-hydroxy ketone and its features may not be comparable with those of the aforementioned aldehydes.[7d] Although a high stereoselectivity suggests in fact a reduced internal mobility of the bonds around the carbonyl group, the true origin of this enhanced rigidity is not quite clear in reactions such as those under study, which occur on a heterogeneous system. Single electron transfer (SET) from the metal surface to either the carbonyl substrate or the allyl halide has been suggested to be the initial step.[5] Very recently, the mechanism of the allylation of β-keto esters with zinc in THF/aq NH_4Cl has been investigated.[10] The data presented seem to indicate the intermediacy of free radicals, generated most likely through SET processes on the metal surface, but the origin of the stereoselectivity is still unclear. More data have still to be collected for a sound mechanistic view to be feasible. Work in this direction is in progress.

Acknowledgements

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References

1. (a) Blomberg, C. *The Barbier Reaction and Related One-Step Processes*, Springer Verlag, Berlin, 1993. (b) Cintas, P. *Activated Metals in Organic Synthesis*, CRC Press, Boca Raton, 1993, pp 154–172. (c) Yamamoto, Y.; Asao, N. *Chem. Rev*. **1993**, *93*, 2207–2293.
2. Li, C. J. *Tetrahedron* **1996**, *52*, 5643–5668, and references therein.
3. Cintas, P. *Synlett* **1995**, 1087–1096.
4. Li, C. J.; Chan, T. H. *Tetrahedron Lett*. **1991**, 7017–7020.
5. (a) Gordon, D. M.; Whitesides, G. M. *J. Org. Chem*. **1993**, *58*, 7937–7938. (b) Binder, W. H.; Prenner, R. H.; Schmid, W. *Tetrahedron* **1994**, *50*, 749–758. (c) Chan, T. H.; Lee, M. C. *J. Org. Chem*. **1995**, *60*, 4228–4232. (d) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc*. **1996**, *118*, 1931–1937. (e) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem*. **1997**, *62*, 4293–4301.
6. (a) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc*. **1996**, *118*, 1917–1930. (b) Loh, T. P.; Ho, D. S. C.; Chua, G. L.; Sim, K. Y. *Synlett* **1997**, 563–564.
7. (a) Carda, M.; González, F.; Rodríguez, S.; Marco, J. A. *Tetrahedron: Asymmetry* **1992**, *3*, 1511–1514. (b) Carda, M.; González, F.; Rodríguez, S.; Marco, J. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1799–1802. (c) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann. Chem*. **1996**, 1801–1810. (d) Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Castillo, E.; Murga, J. *J. Org. Chem*. **1998**, *63*, 698–707.
8. (a) The configurations of the allylation products have been determined from a network of mutual chemical correlations via interchange of protecting groups, as well as through chemical correlations with previously described allylation products.[7d] All details are part of the projected Ph.D. Thesis of E.C. and will be described in due course.
9. When **7** and **9** (1 equiv. each) were allowed to compete for 1 equiv. of indium and 1.5 equiv. of allyl bromide, **9** reacted completely at room temperature whereas **7** was almost quantitatively recovered.
10. Ahonen, M.; Sjöholm, R. *Acta Chem. Scand*. **1997**, *51*, 785–790.