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Synthesis of optically active amino sugar derivatives using catalytic enantioselective hetero-Diels–Alder reactions

Wei Zhuang, Jacob Thorhauge and Karl Anker Jørgensen*

Center for Metal Catalyzed Reactions, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark. E-mail: kaj@kemi.aau.dk

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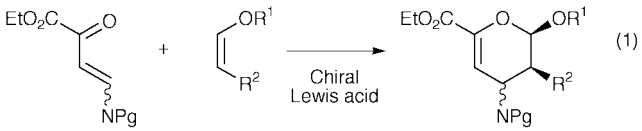
A new synthetic method for the formation of optically active amino sugars using catalytic enantioselective inverse-electron demand hetero-Diels–Alder reactions of γ-amino-protected β,γ-unsaturated α-keto esters with vinyl ethers is presented; the catalytic reactions proceed in good yield with high diastereo- and enantioselectivity and fully control of the stereochemistry at the amino-carbon center.

Sugars containing nitrogen atoms have a variety of different biological activities; they are, *e.g.* among the largest group of carbohydrate mimetics and belong to the strongest known inhibitors of glycosidases found.[1] Furthermore amino sugars are also applied as pharmaceuticals such as for treatment of diabetes[2] and promising drugs against influenza.[3]

The synthesis of optically active amino sugars normally takes its starting point from naturally occurring carbohydrates.[4] or amino acids.[5] A simple and convenient procedure for the formation of optically active amino sugars and their derivatives (**3**) could be the catalytic enantioselective inverse-electron demand hetero-Diels–Alder (HDA) reaction of γ-amino-protected β,γ-unsaturated α-keto esters **1** with vinyl ethers **2** [eqn. (1)]. This approach has previously been used in diastereoselective reactions.[6]



1 **2** **3**

Here, we present the first catalytic enantioselective synthesis of amino sugars **3** by inverse-electron demand HDA reactions using C_2-bisoxazoline-Lewis acid complexes as catalysts.[7,8]† The reaction has been developed for two different protected γ-amino β,γ-unsaturated α-keto esters **1a**, **b** which have the protected γ-amino substituent, *trans* or *cis*, respectively, as these by reaction, *e.g.* ethyl vinyl ether **2a**, will give the two different diastereomers of the optically active amino sugars **3a** and **4a**, respectively [eqn. (2)]. The (*S*)-Bu^t-BOX-Cu(OTf)$_2$ [(*S*)-**5a**] and (*R*)-Ph-BOX-Zn(OTf)$_2$ [(*R*)-**5b**] complexes are found to be good catalysts for the reaction among different C_2-bisoxazoline–Lewis acid complexes tested.

Table 1 Reaction of γ-amino-protected β,γ-unsaturated α-keto esters **1a**, **b** with ethyl vinyl ether **2a** in the presence of (*S*)-Bu^t-BOX-Cu(OTf)$_2$ [(*R*)-**5a**] and (*R*)-Ph-BOX-Zn(OTf)$_2$ [(*S*)-**5b**] at room temperature (r.t.)

Entry	Substrate	Cat./mol%	Yield[a] (%)	*endo*-de[b] (%)	Ee[c] (%)
1	**1a**	(*S*)-**5a**/10[e]	**3a**/98	88	98
2	**1a**	(*S*)-**5a**/5[e]	**3a**/67	95	> 99
3	**1a**	(*S*)-**5a**/10[e,f]	**3a**/94	90	> 99
4	**1a**	(*S*)-**5a**/10[g]	**3a**/82	29	99
5	**1b**	(*S*)-**5a**/10[g]	**4a**/96	74	94[d]
6	**1b**	(*R*)-**5b**/10[e]	**4a**/99	70	70[d]

[a] Isolated yield. [b] Diastereomeric excess measured by ^{1}H NMR. [c] Enantiomeric excess measured by chiral HPLC using a Daicel Chiralpak OJ column. [d] Enantiomeric excess measured by chiral GC using a Chrompack ChiralsilDex CB column. [e] Et_2O as solvent. [f] Reaction temperature 0 °C [g] THF as solvent.

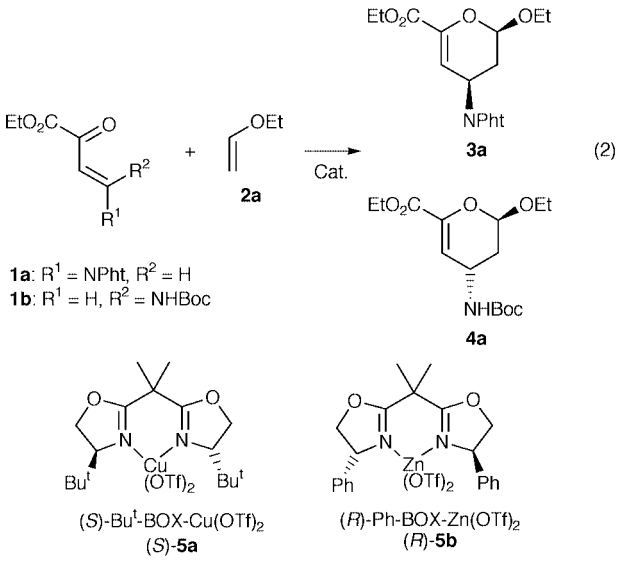


Table 1 presents some results obtained for the reaction of **1a**, **b** with **2a**. It appears that the γ-amino-protected β,γ-unsaturated α-keto esters **1a**, **b** react with ethyl vinyl ether **2a** in the presence of the (*S*)-**5a** catalyst giving the protected amino sugars **3a** and **4a**, respectively, in high yield, diastereo (de) and enantiomeric excess (ee) at room temperature. The reaction of **1a** with **2a** can proceed with 5 mol% of the catalyst with very high diastereoselectivity giving only one detectable enantiomer by chiral HPLC of **3a** (entry 2). The reaction can take place in several solvents and high yield, de and ee are obtained in, *e.g.* Et_2O and THF (entries 1, 4). However, it is notable that the de is reduced when THF is the solvent compared with Et_2O, and that the reaction performed in CH_2Cl_2 gives the *exo*-diastereomer as the major diastereomer (de_{exo} 43% and with 90% ee_{exo}). The reaction of **1b** leads to the other diastereomer of the protected amino sugar (**4a**) and this reaction proceeds also with high yield, de and ee using (*S*)-**5a** as the catalyst and **4a** is obtained in 96% yield, 74% de and 94% ee (entry 5). The yield of **4a** is slightly improved in the presence of (*R*)-**5b** as the catalyst, while the de is the same and the ee is reduced compared to (*S*)-**5a** as the catalyst (entry 6). The absolute configuration of a related series of compounds has been determined previously.[8e]

The application of this catalytic enantioselective approach for the preparation of various types of different amino sugar derivatives is shown in the following equations. In eqn. (3) the reaction of **1a** with *cis*-1-acetoxy-2-ethoxyethene **2b** in the presence of (*S*)-**5a** and (*R*)-**5b** as the catalysts is presented. The reaction proceeds in a highly regio-, diastereo- and enantioselective manner giving **3b** in 82% yield, 85% de and 99% ee when (*S*)-**5a** is the catalyst and an improvement in yield, and reduction in ee when (*R*)-**5b** is the catalyst. The reaction in eqn. (3) shows that it is possible to introduce two different

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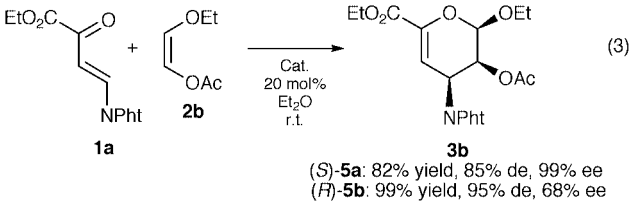
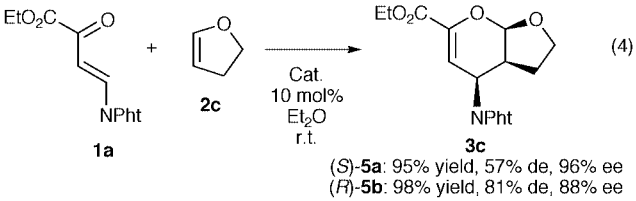


(3)

protected hydroxy functionalities in the amino sugar fragment by this reaction.

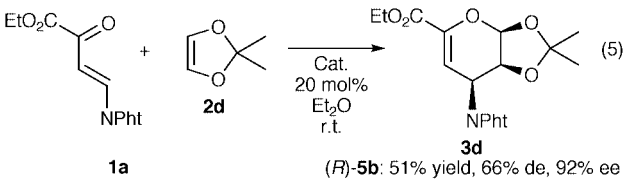
The results for the reaction of **1a** with 2,3-dihydrofuran **2c** is presented in eqn. (4). Both catalysts give good yield of the



(4)

amino sugar **3c**; the (*S*)-**5a** catalyst gives the highest ee (96%) of the major diastereomer, formed with a de of 57%, while (*R*)-**5b** leads to the highest de (81%), and with only a slight reduction to 88% ee. It is notable that the same enantiomer of **3b** and **3c** in eqns. (3) and (4) are obtained using the (*S*)-**5a** and (*R*)-**5b** catalysts.

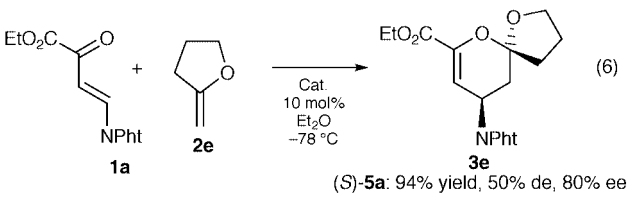
The catalytic enantioselective reaction of the activated cyclic alkene **2d** with **1a** gives **3d** in moderate yield (51%) and de (66%), and with high ee (92%) [eqn. (5)]. The highest yield of



(5)

3d is obtained with the chiral zinc(II) catalyst (*R*)-**5b**, while catalyst (*S*)-**5a** only gives 12% isolated yield of **3d**, but formed in a highly enantioselective manner as 97% ee is obtained.

The catalytic enantioselective HDA reaction can also be used for the preparation of optically active spiro-amino sugars. The spiroacetal functionality is found in natural products such as pheromones, steroidal compounds, anti-parasitic agents and polyether antibiotics[9] and eqn. (6) shows how the reaction of



(6)

1a with the exo-cyclic vinyl ether **2e** catalyzed by (*S*)-**5a** leads to high yield, de and ee of the spiro-amino sugar **3e**.

The present work has shown a new development in catalytic enantioselective HDA reactions for the preparation of optically active amino sugars. It is demonstrated that the approach can be used for the synthesis of a series of different types of protected amino sugars in good yield with control of both the diastereo- and enantioselectivity. The new synthetic procedure introduces a new approach for the formation important amino sugars from simple substrates. Furthermore, can the products obtained also be considered as cyclic γ-amino acid esters. Further work is in progress in developing optically active highly functionalized molecules using this approach.

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Notes and references

† *Representative procedure* for the catalytic enantioselective HDA reaction: to a flame dried Schlenk tube was added $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) and bisoxazoline (*S*)-**5a** (16.2 mg, 0.055 mmol). The mixture was dried under vacuum for 1–2 h and freshly distilled anhydrous solvent (2.0 mL) was added and the solution was stirred for 0.5–1 h. Subsequently, **1a** (137 mg, 0.5 mmol) and **2a** (70 μL, 1.5 eq.) were added. After stirring overnight at r.t., the reaction mixture was filtered through a pad of silica with EtOAc and pentane (1 : 1), concentrated *in vacuo*, and the product purified by flash chromatography (30% EtOAc in pentane) to afford compound **3a** in 98% yield, 88% de and 98% ee detected by HPLC using a Daicel Chiralpak OJ column hexane–Pr^iOH (95 : 5), $[\alpha]^{20}_D$ = +27.0° (*c* = 0.0074 g mL^{-1} in $CDCl_3$); ^1H NMR ($CDCl_3$): δ 7.79–7.76 (m, 2H, Ar), 7.69–7.67 (m, 2H, Ar), 5.94 (dd, 1H, *J* 3.0, 1.5 Hz, C=CH), 5.16–5.09 (m, 2H, OCHO and CHN), 4.19 (dq, 2H, *J* 5.4, 7.2 Hz, $CO_2CH_2CH_3$), 4.01 (dq, 1H, *J* 9.0, 7.2 Hz, $OCHHCH_3$), 3.61 (dq, 1H, *J* 9.0, 7.2 Hz, $OCHHCH_3$), 2.54 (ddd, 1H, *J* 12.8, 9.9, 8.7 Hz, CHH), 2.08 (ddt, 1H, *J* 12.8, 6.3, 1.5 Hz, CHH), 1.25 (t, 3H, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.18 (t, 3H, *J* 7.2 Hz, OCH_2CH_3)' ^{13}C NMR ($CDCl_3$): δ 167.4, 162.0, 143.7, 134.1, 131.7, 123.3, 109.4, 99.8, 64.9, 61.3, 42.9, 31.0, 15.0, 14.1.

Enone **1a** made according to ref. 6(*b*). **1b** was prepared as described in ref. 6(*f*) except for the last isomerization step which was performed by a simple destillation. Alkenes were obtained from commercial sources or synthesized using literature procedures.[10]

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