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Organocatalytic Preparation of Simple β-Hydroxy and β-Amino Esters: Low Catalyst Loadings and Gram-Scale Synthesis

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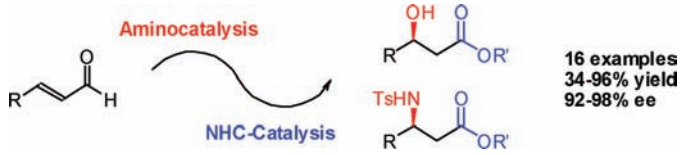
ABSTRACT



A combined amino- and *N*-heterocyclic carbene (NHC)-catalyzed one-pot reaction sequence for the synthesis of simple enantioenriched β-hydroxy and β-amino esters using commercially available catalysts at low catalyst loadings has been developed. The desired products were obtained in high yield and excellent enantiopurity. The generation of quaternary stereocenters and application in gram-scale synthesis were also realized, with no requirements of inert or anhydrous reaction conditions, thus making this transformation a highly practical protocol.

Due to their interesting biological properties and synthetic relevance, β-amino/β-hydroxy acids and their derivatives have attracted increased attention in the fields of chemistry and chemical biology.[1] Among useful methods for their preparation are the transition metal-catalyzed asymmetric hydrogenation processes.[2] However, these reactions are often quite substrate dependent and small variations in the side chain may lead to the necessity of new ligand design. Contrary to the progress made in hydrogenation processes, metal-free routes targeting these important classes of compounds remain elusive.

In 2004, Bode et al. reported a direct stereoselective transformation of racemic 2,3-epoxy aldehydes, obtained by sequential oxidation of the allylic alcohols, into β-hydroxy esters using a thiazolium salt based *N*-heterocyclic carbene (NHC) catalyst.[3a] Rovis et al. reported, independently, similar studies using a triazolium derived NHC catalyst for the generation of acylating agents.[3b] Later, both groups also applied these systems for redox-coupled peptide synthesis.[3c,d] In 2007, Cordóva and co-workers showed that by applying the Bode conditions, optically active β-hydroxy and β-amino esters could be obtained in one pot starting from α,β-unsaturated aldehydes, through the intermediacy of enantioenriched 2,3-epoxy and 2,3-aziridine aldehydes generated by asymmetric amino-catalysis.[4] However, the applied catalytic loadings of the chiral amine and achiral NHC precursor reached 10−20 and 40 mol %, respectively. On the basis of the reported yields (41−82%), these catalyst loadings correspond to catalytic turnovers of 2−8 cycles for

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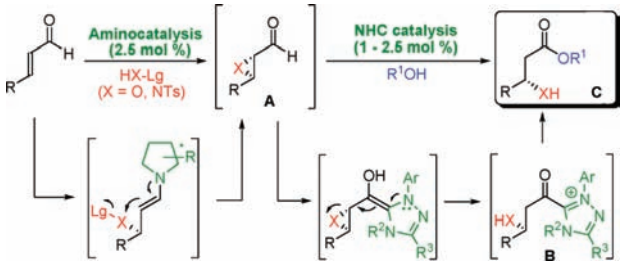
the amino catalyst and 1−2 cycles of the NHC-catalyst.[5] Nowadays, as atom economy has emerged as a guiding principle for the development of time-cost-effective reactions,[6] we aimed to develop a more efficient and practical protocol to β-hydroxy and β-amino esters by using combined amino-[4] and NHC-catalysis.[7] In the present work, we demonstrate that catalyst loadings of 2.5 mol % of the amino catalyst and 1−2.5 mol % of the NHC catalyst are generally sufficient to achieve high yields and excellent enantioselectivities in this transformation. It is notable that all catalysts applied may be purchased from commercial sources, and the reaction sequence does not require inert conditions, which greatly improves the practical aspects of the developed protocol.

The design of the reaction sequence is outlined in Scheme 1. The key intermediates, 2,3-epoxy and 2,3-aziridine aldehydes (**A**), are easily generated in an enantioselective manner by using a commercially available amino catalyst and α,β-unsaturated aldehydes by an improved protocol recently developed by our group.[8] Subsequent in situ generation of the NHC catalyst efficiently couples the amino-catalyzed epoxidation/aziridination of enals with an intramolecular redox reaction,[3] thereby facilitating the reductive ring-opening and the formation of an activated carboxylate (**B**). Final acyl-transfer in the presence of another nucleophilic species (R^1OH) furnishes the overall transformation from simple enals to β-hydroxy and β-amino esters (**C**) in one pot.

Scheme 1. Synthesis of β-Hydroxy/β-Amino Esters Using Combined Amino- and NHC-Catalysis



We initiated our screening using *trans*-2-nonenal **3a** as model substrate (Table 1). Full conversion into the 2,3-epoxy aldehyde was achieved after 24 h at rt with 2.5 mol % of the prolinol-derived catalyst **1** (Figure 1).[9] Following the

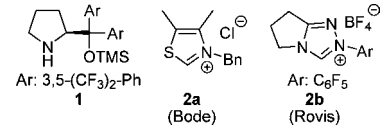
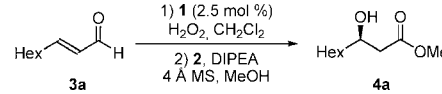


Figure 1. Catalysts used in this study.

Table 1. Optimization of the Reaction Conditions for the Synthesis of β-Hydroxy Ester **4a**[a]



entry	**2** (mol %)	DIPEA (mol %)	t (h)[b]	convn (%)[c]	ee (%)[d]
1[e,f]	**2a** (10)	8	15	<10	
2[e,g]	**2b** (10)	20	24	>95	92
3[e]	**2b** (10)	20	2	>95 (52)	94
4	**2b** (10)	20	2	>95 (70)	94
5	**2b** (5)	10	2	>95 (73)	94
6	**2b** (2.5)	5	4	>95 (75)	94
7[h]	**2b** (1)	2	16	>95 (84)	94

[a] Reactions performed at 0.1 mmol scale of **3a** in 0.2 mL of CH_2Cl_2 (see the Supporting Information). [b] Reaction time for the second step. [c] Conversion of 2,3-epoxy aldehyde as judged by ^{1}H NMR spectroscopy, isolated yield in parentheses. [d] Determined by chiral stationary phase GC. [e] Reaction performed in the absence of 4 Å MS. [f] Reaction performed at 30 °C. [g] Reaction performed with 10 mol % imidazole as additive at 40 °C. [h] Reaction performed at 0.5 mmol scale.

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Bode conditions, only traces of the product were observed (Table 1, entry 1). Instead, by using the Rovis protocol for the ring-opening/esterification sequence, full conversion of the 2,3-epoxy aldehyde was achieved furnishing the β-hydroxy ester **4a** (entry 2) in 92% ee. Moreover, complete conversion was achieved within 2 h of stirring at room temperature (rt) even without additives, providing the product **4a** in slightly higher enantioselectivity (entry 3). However, the isolated yield of **4a** was only moderate (52% yield, entry 3).

Careful analysis of the reaction conditions revealed that the remaining water from the aqueous peroxide solution competes as a nucleophilic species during the final acylation step. Full selectivity favoring the methyl ester product **4a** could be attained by using 4 Å MS to remove excess water in the reaction mixture prior to the addition of the NHC catalyst (entry 4). We were able to lower the catalyst loading of the NHC catalyst to 5 mol % giving product **4a** in 73% isolated yield and 94% ee (entry 5). Further reduction of catalyst loading also proved to be possible; however, slightly longer reaction times were required (entry 6 and 7). Under optimal conditions, as low as 2.5 mol % of amino catalyst **1** and 1 mol % of NHC catalyst **2b** were sufficient to provide clean turnover of **3a** into product **4a**, in a one-pot fashion (84% yield and 94% ee, entry 7).

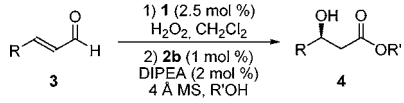
With the optimized reaction conditions in hand, the scope of the described reaction sequence was explored by varying the R-group in enal **3** and the nucleophilic species used in the final acyl transfer step (R′OH). The results are outlined in Table 2. It appears that both linear and γ-branched enals **3a**−**c** as well as functionalized enals **3d**−**f** provided the desired β-hydroxylated methyl esters **4a**−**f** in high yields (58−80%) and excellent enantioselectivities (92−98% ee) (Table 2, entries 1−6). Cinnamaldehyde **3g** required a slightly higher loading of the amino catalyst **1** (10 mol %, entry 7). The use of other alcohols as nucleophiles was also compatible with the reaction sequence affording a range of different β-hydroxy esters (entries 8−10) in 34−64% yield and 94% ee. The low yield observed in the formation of **4j** can be rationalized by the increased steric bulk and reduced nucleophilicity of *i*PrOH.

To further demonstrate the practicality and efficiency of the developed reaction sequence, a scale-up reaction was performed. Gram-scale synthesis of β-functionalized esters could be achieved, as exemplified by the synthesis of **4a** (80% yield, 94% ee) from enal **3a** (entry 11).

An efficient synthesis of β-amino esters could also be realized by using this strategy. A literature survey revealed only a single report (containing one entry only) where combined amino-NHC catalysis was used for the one-pot synthesis of β-amino esters. Moreover, the catalytic turnover was low and the selectivity moderate (41% yield, 61% ee).[5a] To develop a more convenient and catalyst-efficient process, we merged the optimized ring-opening conditions with a highly efficient aziridination protocol recently reported by our group that requires only 2.5 mol % amino catalyst.[8a] Initial screening showed that 2.5 mol % of NHC catalyst precursor **2b** was needed to complete the reaction within 24 h. Contrary to the synthetic protocol for β-hydroxy esters **4**, the addition of DIPEA was not needed, since the active NHC catalyst was effectively generated by the remaining NaOAc from the aziridination step.

As presented in Table 3, the scope of the aziridination/NHC catalysis sequence was similar to the previous protocol involving the epoxidation, furnishing the nonproteinogenic amino esters **5a**−**e** (entry 1−5) in 77−96% yields and 93−96% ee. Moreover, it was shown that the other nucleophilic quenching reagents are compatible, as demonstrated for the use of EtOH, providing the ethyl ester **5f**, a key intermediate applied in the asymmetric total synthesis of Indolizidine 209D. Notably, this intermediate has been

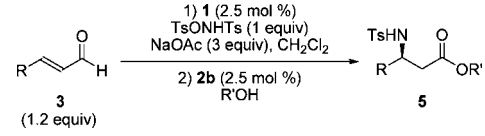
Table 2. Scope of the Enantioselective Epoxidation/Ring-Opening/Acyl Substitution Sequence[a]



entry	**1** (R)	R′OH	yield (%)[b]	ee (%)[c]
1	**3a** (*n*Hex)	MeOH	**4a**: 84	94
2	**3b** (*n*Pr)	MeOH	**4b**: 73	94
3	**3c** (*i*Pr)	MeOH	**4c**: 64	98
4[d]	**3d** (*E*-3-hexenyl)	MeOH	*ent*-**4d**: 71	95
5	**3e** (CH_2OBn)	MeOH	**4e**: 58	92
6	**3f** (C_2H_4Ph)	MeOH	**4f**: 80	94
7[e]	**3g** (Ph)	MeOH	**4g**: 66	93
8	**3a** (*n*Hex)	EtOH	**4h**: 64	94
9	**3a** (*n*Hex)	CD_3OD	**4i**: 58	94
10	**3a** (*n*Hex)	*i*PrOH	**4j**: 34	94
11[f]	**3a** (*n*Hex)	MeOH	**4a**: 80	94

[a] Reactions were performed at 0.5 mmol scale of **3** in 1 mL of CH_2Cl_2 (see the Supporting Information). [b] Isolated yield. [c] Determined by chiral stationary phase GC/HPLC. [d] Performed at 0.25 mmol scale using *ent*-**1** as amino catalyst, 2 mol % NHC catalyst, and 4 mol % DIPEA. [e] 10 mol % of catalyst **1** was used. [f] Performed at 10 mmol (1.40 g) scale of **3a**.

Table 3. Scope of the Enantioselective Aziridination/Ring-Opening/Acyl Substitution Sequence[a]

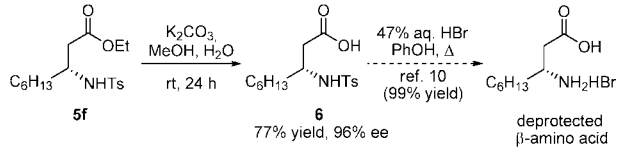


entry	**1** (R)	R′OH	yield (%)[b]	ee (%)[c]
1	**3a** (*n*Hex)	MeOH	**5a**: 91	96
2	**3c** (*i*Pr)	MeOH	**5b**: 96	95
3	**3h** (Et)	MeOH	**5c**: 95	96
4	**3i** (*Z*-3-hexenyl)	MeOH	**5d**: 89	96
5	**3e** (CH_2OBn)	MeOH	**5e**: 77	93
6	**3a** (*n*Hex)	EtOH	**5f**: 85	96[d]

[a] Reactions performed at 0.1 mmol scale of **3** in 0.5 mL of CH_2Cl_2 (see the Supporting Information). [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] The ee was determined after transformation into **5a** (see the Supporting Information for details).

previously synthesized by a five-step sequence starting from homochiral L-aspartic acid in 63% overall yield.[10a] Finally, it was shown that the obtained β-amino esters can be easily converted to the parent amino acid by saponification by using K_2CO_3 in a H_2O/MeOH mixture, as demonstrated for the synthesis of amino acid **6** (Scheme 2). Tosyl deprotection

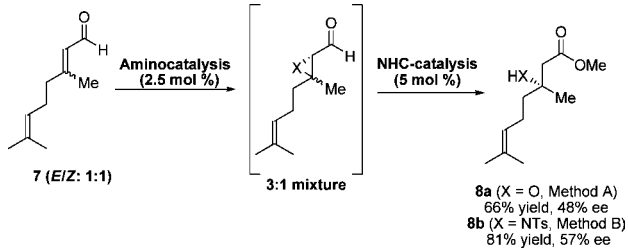
Scheme 2. Synthesis of Tosyl-Protected β-Amino Acid **6**



without racemization can be realized by using aq HBr, PhOH, and heating, as reported for **6**.[10]

Next, we investigated the possibility to form β-hydroxy or β-amino esters carrying a quaternary stereocenter using the present reaction conditions (Scheme 3). Access to these

Scheme 3. Formation of β-Hydroxy or β-Amino Esters Carrying a Quaternary Stereocenter Using Amino-NHC Catalysis[a]



[a] Method A: (I) **1** (2.5 mol %), H_2O_2 (0.13 mmol), **7** (0.1 mmol) in CH_2Cl_2 (0.2 mL), rt, 24 h. (II) **2b** (5 mol %), DIPEA (10 mol %), MeOH, 4 Å MS. Method B: (I) **1** (2.5 mol %), TsONHTs (0.1 mmol), **7** (0.12 mmol), NaOAc (0.3 mmol), CH_2Cl_2 (0.5 mL), rt, 20 h. (II) **2b** (5 mol %), MeOH.

important products presents a challenging task in organic synthesis, since quaternary stereocenters cannot be attained by hydrogenation processes. As a proof of concept, the commercially available citral **7** was used as the enal substrate. Due to the initial 1:1 *E*/*Z* ratio of the double bond geometry of **7**, a mixture of diastereomers of the 2,3-epoxy/aziridine aldehydes was formed. Consistent with previous reports by our group,[8b] the observed diastereomeric ratio of the intermediates is higher (~3:1 dr in favor of the *trans*-isomer) than the initial *E*/*Z* ratio of **7**, suggesting an isomerization during the reaction. Subsequent ring-opening by NHC-catalysis allowed the formation of the desired products **8**, carrying tertiary hydroxy or amino moieties, in 66−81% yield and 48−57% ee. The moderate enantioselectivity is rationalized by the presence of a significant amount of the minor diastereomer of the epoxy or aziridine aldehyde, leading to the buildup of the wrong enantiomer of the product, hence eroding the overall enantioselectivity of the reaction sequence. However, when diastereomerically pure starting materials are used, such erosion should not be observed.

Due to the importance of the amide bond in biologically active molecules, several attempts were made to include the use of *N*-centered nucleophiles for the final acylation. However, applying the optimized reaction protocol and employing several *N*-nucleophiles under various conditions was unsuccessful.

In conclusion, we have developed a combined amino- and NHC-catalyzed one-pot reaction sequence for the synthesis of β-hydroxy and β-amino esters using commercially available catalysts at low catalyst loadings. The desired products were obtained in high yields and excellent enantioselectivities, even on gram-scale, with no requirements of inert or anhydrous reaction conditions. Moreover, we extended the concept to include more challenging substrates such as β,β-disubstituted enals, thereby allowing simple access to β-hydroxy and β-amino esters carrying quaternary stereogenic centers.

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Supporting Information Available: Detailed experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Jefford, C. W.; Wang, J.-B. *Tetrahedron Lett.* **1993**, *34*, 3119. Direct deprotection of β-tosylamino esters to the free amino acid is also possible using a similar protocol: (b) Calvisi, G.; Dell'Uomo, N.; De Angelis, F.; Dejas, R.; Giannessi, F.; Tinti, M. O. *Eur. J. Org. Chem.* **2003**, 4501. As a reviewer correctly pointed out, the HBr deprotection method is unlikely to tolerate more functionalized substrates, including some of the proteinogenic side chains. The availability of the starting materials also limits the presented protocol to be most useful for preparation of simple β-amino esters. However, some of the same restrictions are present with alternative methods (see refs 1 and 2).