Stereoselective α-Alkylations of β-Dicarbonyl Compounds with Chiral Auxiliaries

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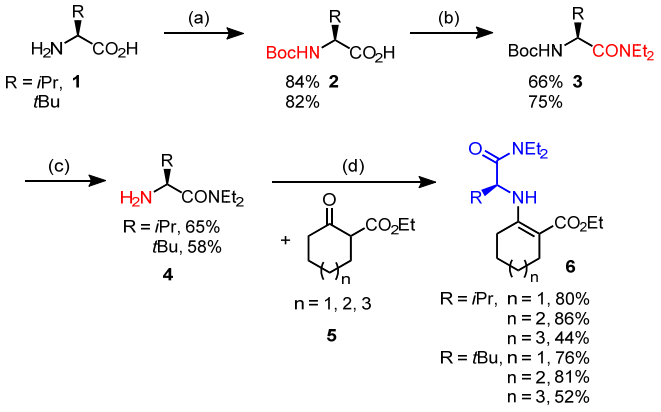
Herein we report on the functionalization of commercially available amino acids to dialkyl amides and their further application with cyclic β-oxoesters to get enamino esters. In two model reactions for asymmetric C–C forming reactions, up to 60% *ee* was achieved.

Introduction

Chiral auxiliaries based on amino acids were previously identified as useful reagents for stereoselective synthesis. Dialkyl amides of amino acids have been previously investigated as excellent chiral auxiliaries for the construction of quaternary stereocenters at ambient temperatures. Enamino esters **6** prepared from these auxiliaries were used in copper-catalyzed asymmetric Michael reactions in our preliminary work with up to 90% yield and 99% *ee*.[1] These products where very useful for the synthesis of various hetero cyclic compounds, especially for hexahydroisoquinolone and tetrahydroisoindole derivatives.[2] One advantage of this method is the recyclability of the auxiliary by hydrolysis and extraction from organic solvents. The aim of this study is to extend the scope of this type of reaction towards α-alkylations with propargyl halides and diazoacetates. By investigation of different dialkyl amides and metal based precatalysts, we were able to identify appropriate conditions to synthesize compounds **7** and **8** with acceptable enantiomeric excesses.

Preparation of Various Enamino Esters from Amino Acids

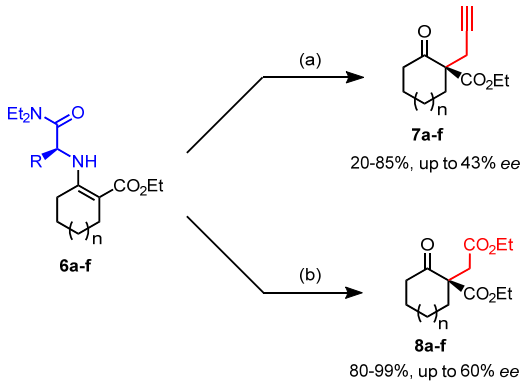
According to a published procedure[1] the amino function of commercially available L-valine or L-*tert*-leucine was protected by di-*tert*-butyldicarbonate. After work up, the protected amino acid was submitted to amidation with dicyclohexylcarbodiimide and diethyl amine to give the protected dialkylamide. The next step was the deprotection with trifluoroacidic acid in dichloromethane and subsequent vacuum distillation with a Kugelrohr apparatus to yield the expected products. Finally, the dialkylamide was converted with β-oxoesters under acidic conditions in toluene to furnish six different enamino esters **6a-f**.



Scheme 1. Synthesis of enamino esters **6**. (a) Boc_2O, Na_2CO_3, MeOH/H_2O (1:1), rt, 16 h. (b) DCC, $HNEt_2$, DCM, 0°C→rt, 16 h. (c) TFA/DCM (1:1), rt, 20 h. (d) cat. HCl, molecular sieves 4 Å, toluene, 60°C.

Screening

For examination of the potential, the enamino esters were tested towards asymmetric copper catalysis. Two model reactions were carried out and the optimal reaction conditions were identified.



Scheme 2. (a) 5 mol% $Cu(OAc)_2 \cdot H_2O$, propargylic bromide, K_2CO_3, molecular sieves 4 Å, acetone, 23°C, 24 h, then HCl–H_2O, 0°C, 30 min. (b) 5 mol% $Cu(OAc)_2 \cdot H_2O$, ethyldiazoacetate, MTBE, 10°C, 20 h, then HCl–H_2O, 0°C, 30 min.

As shown in Table 1, the recation with diazoacetate gave better results than the propargylation. Futhermore, the six membered rings enamino esters **8a** and **8b** gave the best results so far. But there are also promising results on the propargylation of enamino esters in copper catalyzed reactions.

Table 1. Experimental results.

entry	7 or 8	n	R	yield/%	*ee*/%[a]
1	7a	1	*i*Pr	85	36
2	7b	2	*i*Pr	73	43
3	7c	3	*i*Pr	45	21
4	7d	1	*t*Bu	75	25
5	7e	2	*t*Bu	81	32
6	7f	3	*t*Bu	20	12
7	8a	1	*i*Pr	93	51
8	8b	2	*i*Pr	99	60
9	8c	3	*i*Pr	80	45
10	8d	1	*t*Bu	91	48
11	8e	2	*t*Bu	96	55
12	8f	3	*t*Bu	83	43

[a] Enantiomeric excess was determined by GLC on a chiral phase.

Conclusion

A known concept was transformed to a new strategy to generate quaternary stereocenters. Application of the enamino esters on alkylation reactions with diazoacetates and on propargylations gave promising results. Although it is still hard to get higher *ee*'s we could achieve in the case of the propargylation up to 43% *ee* and in the case of the alkylation up to 60% *ee*. We were able to show within the optimiziation process the potential of the enamino auxiliaries.

[1] J. Christoffers, A. Mann, *Chem. Eur. J.* **2001**, 7, 1014.
[2] a) J. Christoffers, H. Scharl, W. Frey, *Org. Lett.* **2004**, 7, 1171; b) J. Christoffers, J. Sluiter, J. Schmidt, *Synthesis* **2011**, 895.