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Catalytic Enantioselective Conjugate Additions Using Enantiopure β-Amino Disulfides and β-Amino Thiolates

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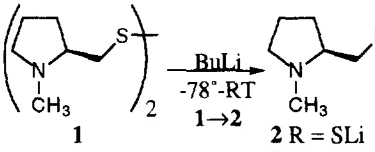
Abstract: The enantioselective conjugate addition of diethylzinc to chalcone catalysed by nickel(II) using an enantiopure β-amino thiolate **2** or β-amino disulfide **1** to achieve ee's of up to 50% is described. Copyright © 1996 Elsevier Science Ltd

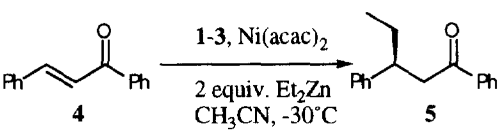
The asymmetric formation of carbon-carbon bonds by the use of the enantioselective conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a particularly valuable synthetic method. The importance of this approach has led to considerable interest and numerous stoichiometric processes have been reported.[1] In contrast, relatively few reports on the synthetically more useful catalytic enantioselective conjugate addition have appeared. In the area of organocopper reagents the scalemic catalysts that have been recorded thus far includes dialkylaminotropones,[2] arenethiolates,[3] thiosugars[4] and amidophoshines.[5] The enantioselective conjugate addition of dialkylzinc reagents to enones in the presence nickel(II) has been carried out using scalemic catalysts including β-amino alcohols,[6] pyridine alcohols,[7] amino amides,[8] δ-amino alcohols,[9] and β-diamines.[10] While these protocols represent significant advances in catalytic enantioselective conjugate additions, there still does not exist a general solution of achieving efficient procedures.

Recently, we reported the beneficial effects of a sulfur chelation site on the level of asymmetric induction for bidentate amine ligands and catalysts in diorganozinc[11] and organocuprate[12] addition reactions. We anticipated that catalysts with a β-amino disulfide or a β-amino thiolate moiety would give improved enantioselectivities in the catalytic enantioselective conjugate addition of diethylzinc to chalcone **4** in the presence of nickel acetonylacetate. Herein, we report the first use of an enantiopure β-amino disulfide **1**[11] β-amino thiolate **2** in such processes to achieve ee's of up to 50%. In contrast, the corresponding β-amino alcohol, N-methylprolinol **3** gave an ee of only 6%.

Initial experiments were carried out using the thiolate **2** which was generated *in situ* by the treatment of the disulfide **1** with butyllithium in THF (see Scheme 1).[13] The thiolate **2** was then investigated as a scalemic catalyst in the Ni(II) promoted conjugate addition of diethylzinc to chalcone **4** (see Scheme 2). In the absence of Ni(II) the conjugate addition product **5** was obtained as the racemate (entry 1, Table). Increasing the amount of Ni(II) from 1 to 7 mol% resulted in an increase in the enantioselectivitiy to 18 and 37% ee, respectively (entries 2 and 3). In contrast to the observations of Soai *et al.* for β-amino alcohols[6a] no improvements in the enantioselectivity could be achieved by running the reaction in the presence of 2,2'-bipyridine (entry 4). Improved enantioselectivities were realised by the use of the disulfide **1** directly and a maximum ee of 50% was achieved (entry 7). The use of N-methylprolinol **3** as the scalemic catalyst gave a high yield of the addition product **5** but in only 6% ee of the *(R)* isomer (entry 8), this contrasts with catalysts **1** and **2** which gave the *(S)* enantiomer. The improvement of enantioselectivity from amino alcohol **3** (6% ee) to the disulfide **1** (50% ee) indicates the beneficial effects of a sulfur chelation site in catalysts for these processes.



Scheme 1



Scheme 2

Table: Enantioselective conjugate additions of diethylzinc to chalcone **4** using catalysts **1-3**

Entry	Catalyst (%)	% Ni(II)	Yield (%)	% ee	config.
1	**2** (20)‡	0	51	0	-
2	**2** (17)	1	43	18	*(S)*
3	**2** (17)	7	87	37	*(S)*
4	**2** (17)§	7	47	34	*(S)*
5	**2** (25)	7	42	16	*(S)*
6	**1** (16)	3	22	44	*(S)*
7	**1** (17)	7	85	50	*(S)*
8	**3** (17)	7	90	6	*(R)*

‡ At room temperature. § With 7 mol% 2,2'-bipyridine.

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