Amino Acid Synthesis

Enantioselective H-Atom Transfer Reactions: A New Methodology for the Synthesis of β^2-Amino Acids**

Mukund P. Sibi and Kalyani Patil*

The development of new methods for the synthesis of β-amino acids and their derivatives is important.[1] Several enantioselective catalytic methods have been developed recently for the synthesis of β-substituted β-amino acids (β^3-amino acids).[2] In contrast, there are very few reports on enantioselective methods for the synthesis of α-substituted β-amino acids (β^2-amino acids).[3] This substitution pattern is of interest since it is present in naturally occurring amino acids as well as in compounds with potential therapeutic value.[4]

Enantioselective H-atom transfer,[5] an underdeveloped complementary strategy to enolate protonation,[6] is well suited to the preparation of β-amino acids. We showed recently that α-amino acrylates undergo radical addition followed by an enantioselective H-atom transfer in the presence of a chiral Lewis acid (**1**→**2**, Scheme 1).[5d] In this transformation, a stoichiometric amount of the Lewis acid is required to achieve good selectivity because of the low reactivity of the substrate. Development of a similar protocol starting with β-amino acrylate would provide access to α-substituted β-amino acids. At the outset, we were not certain if substrate **3** would be suitable for the catalytic process

[*] Prof. M. P. Sibi, K. Patil
Department of Chemistry
North Dakota State University
Fargo, ND 58105-5516 (USA)
Fax: (+1) 701-231-1057
E-mail: mukund.sibi@ndsu.nodak.edu

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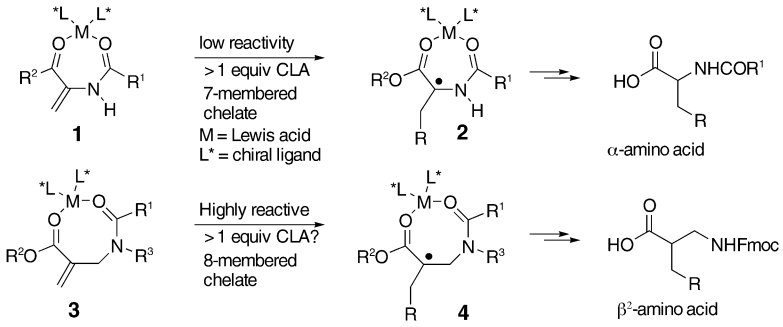
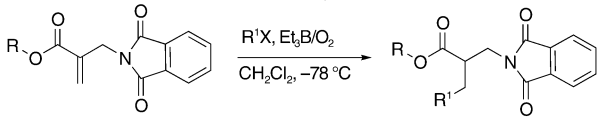


Scheme 1. Synthesis of amino acid derivatives from amino acrylates by radical addition and subsequent enantioselective H-atom transfer.

because of its high reactivity towards conjugate addition. The requirement of a very flexible eight-membered chelate[7] to control the face selectivity posed an additional concern. Herein, we report the successful development of catalytic methods for the synthesis of β^2-amino acids in high chemical yield and with high enantioselectivity by radical addition[8] followed by H-atom transfer.

We began our work by examining conjugate radical additions to acrylates **5** and **6**. These substrates were readily prepared in good overall yields in three steps.[9] The addition of various radicals was examined by using triethylborane/O_2 as an initiator in the absence of any Lewis acid activation (Table 1). As can be discerned from the results (entries 1–6),

Table 1: Radical addition to amino acrylates.[a]



5 R = Me
6 R = *t*Bu

7a–c R = Me
8a–c R = *t*Bu

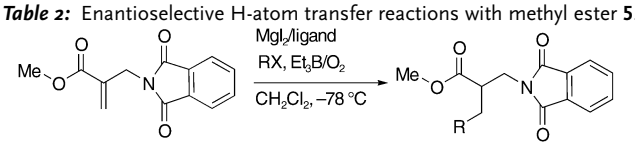
Entry	R	R^1	Compd	Yield [%],[b] No Lewis acid	MgI_2 (1 equiv)
1	Me	isopropyl-I	**7a**	99	78
2	Me	cyclohexyl-I	**7b**	95	80
3	Me	cycloheptyl-Br	**7c**	94	85
4	*t*Bu	isopropyl-I	**8a**	99	86
5	*t*Bu	cyclohexyl-I	**8b**	99	77
6	*t*Bu	cycloheptyl-I	**8c**	91	80

[a] For detailed reaction conditions see the Supporting Information. [b] Yields are for column-purified, isolated materials.

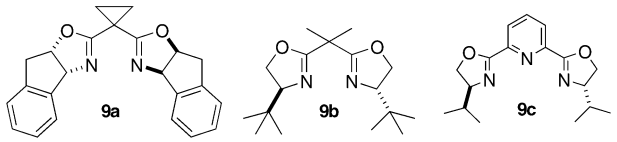
both substrates are very reactive and undergo very efficient uncatalyzed radical addition even at −78 °C. Reactions were also carried out with a stoichiometric amount of MgI_2 which was present as a representative Lewis acid (Table 1, entries 1–6).[10] The results show that the uncatalyzed reactions are slightly more efficient than reactions mediated by a Lewis acid. The results also suggest that the reactions catalyzed by chiral Lewis acids have to be substantially faster than the background reaction to achieve enantioselective H-atom transfer.

Enantioselective H-atom transfer reactions catalyzed by chiral Lewis acids derived from bisoxazolines and magnesium salts were evaluated.[11] Addition of an isopropyl radical to **5** in the presence of **9a** and MgI_2 (100 mol%) gave the product in good yield and with modest enantioselectivity (Table 2, entry 1). A change of ligand to either **9b** or **9c** did not lead to improvements in selectivity (entries 2 and 3). The effect of the H-atom donor on the level of selectivity was also examined and was found to have very little impact.[12] This trend is similar to that observed in our previous work on α-amino acids.[5d] The addition of a series of acyclic and cyclic radicals to **5** was investigated with **9a** as the ligand.

Table 2: Enantioselective H-atom transfer reactions with methyl ester **5**.



5 **7a–i**



9a **9b** **9c**

Entry	RX	Ligand	Compd	Yield [%][a]	*ee* [%][b]
1	isopropyl-I	**9a**	**7a**	91	40
2	isopropyl-I	**9b**	**7a**	98	6
3	isopropyl-I	**9c**	**7a**	76	−6
4	CH_3OCH_2-Br	**9a**	**7d**	85	30
5	CH_3CH_2-I	**9a**	**7e**	91	40
6	MeC(O)Br	**9a**	**7f**	80	55
7	*tert*-butyl-I	**9a**	**7g**	81	20
8	cyclopentyl-Br	**9a**	**7h**	68	60
9	cyclohexyl-I	**9a**	**7b**	71	79
10	cycloheptyl-Br	**9a**	**7c**	70	75
11	1-adamantyl-I	**9a**	**7i**	64	27
12[c]	isopropyl-I	**9a**	**7a**	95	20
13[c]	cyclohexyl-I	**9a**	**7b**	76	40

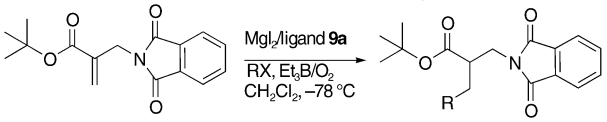
[a] Yields of isolated products. 100 mol% catalyst was used. [b] Enantiomeric excess determined by chiral HPLC analysis. A negative value indicates that the enantiomer opposite to that of the starting material is favored. [c] Reaction with 30 mol% chiral Lewis acid.

Reactions with the primary radicals methoxymethyl and ethyl were chemically efficient but selectivities were low (entries 4 and 5). Addition of the acetyl radical was not highly selective either (entry 6). The yield from the addition of the bulky *tert*-butyl radical was high, but the reaction gave the product in only 20% *ee* (entry 7). The observed trend of lower selectivity with bulkier radicals is the same as that found in our previous work on the synthesis of α-amino acids. Reactions with cyclic radicals were more rewarding: the addition products were formed in good yield and high *ee* values (entries 8–10). Addition of the bulky adamantyl radical occurred with a low enantioselectivity similar to that observed for the *tert*-butyl radical (entry 11). Reactions in the presence of 30 mol% of the chiral Lewis acid gave lower *ee* values for the products than when 100 mol% of the Lewis acid was used

(compare entries 1 and 9 with entries 12 and 13, respectively). These results clearly suggest that background reactions compete with the catalyzed reactions.

In our next set of experiments we used the *tert*-butyl ester **6** as the substrate and investigated the addition of various radicals of different size in the presence MgI_2/**9a** as the chiral Lewis acid catalyst. The results of these experiments are presented in Table 3. The reactions with primary radicals

Table 3: Enantioselective H-atom transfer reactions with *tert*-butyl ester **6**.[a]



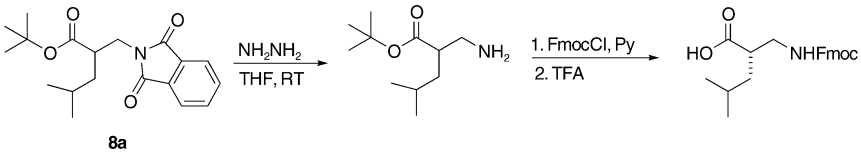
6 **8a–j**

Entry	RX	Compd	100 mol% LA[b] Yield [%][c]	100 mol% LA[b] *ee* [%][d]	30 mol% LA[b] Yield [%][c]	30 mol% LA[b] *ee* [%][d]
1	CH_3OCH_2-Br	**8d**	85	68	78	36
2	$ClCH_2$-I	**8e**	84	36	84	34
3	CH_3CH_2-I	**8f**	82	36	83	62
4	isopropyl-I	**8a**	91	62	95	84
5	*tert*-butyl-I	**8g**	85	92	88	71
6	$ClCH_2CH_2CH_2(CH_3)_2C$-Br	**8h**	72	98	70	50
7	cyclopentyl-I	**8i**	86	94	74	47
8	cyclohexyl-I	**8b**	95	88	86	90
9	1-adamantyl-I	**8j**	71	97	72	61

[a] For detailed reaction conditions see the Supporting Information. [b] LA = Lewis acid. [c] Yields are for column-purified, isolated materials. [d] *ee* values were determined by chiral HPLC.

were efficient but their enantioselectivity was modest (entries 1–3). Interestingly, addition of the ethyl radical occurred more selectively with substoichiometric amounts of the Lewis acid (*ee* = 62%, entry 3) than with 100 mol% of the Lewis acid. The isopropyl radical behaved similarly and led to a higher *ee* value of 84% when 30 mol% of the catalyst was used (entry 4).[13] Substrate **6**, a *tert*-butyl ester, reacted with higher selectivity than the corresponding methyl ester (compare entry 5 in Table 3 with entry 7 in Table 2). Reactions with tertiary and cyclic radicals gave excellent yields and proceeded with high enantioselectivity (entries 5–9). The functionalized tertiary radical gave the highest selectivity (98%, entry 6). These results demonstrate that a variety of β^2-amino acids can be prepared with high levels of selectivity by employing a novel enantioselective H-atom transfer reaction. Disappointingly, there was no clear correlation between the catalytic loading and level of selectivity.[14]

The absolute stereochemistry of **8a** was assigned by converting it into a known β^2-amino acid[15] by using standard reactions (Scheme 2). This sequence also establishes that the



8a

Scheme 2. Conversion of **8a** into a β^2-amino acid. Fmoc = 9-fluorenylmethoxycarbonyl, Py = pyridine, TFA = trifluoroacetic acid.

products of the radical reaction can be converted into compounds that can be employed in solid-phase peptide synthesis.

A stereochemical model for the H-atom transfer reactions must be consistent with four key observations: 1) the effect of the ester substituent (*tert*-butyl versus methyl) on selectivity, 2) the increased enantioselectivity observed with bulky radicals and with **6** as the substrate, 3) the absolute stereochemistry of the addition product, and 4) the effect of catalytic loading on selectivity. We propose an eight-membered chelate model with a tetrahedrally coordinated magnesium ion to account for most of these observations (Figure 1).[16] In this model, the conformation of the ester substituent (*S-cis* or *S-trans*) is dependent on its size and is controlled by the ligand.[17] Substrate **6**, which has a bulky *tert*-butyl ester substituent, is predominantly in an *S-trans* arrangement.[18] The conformation of **5**, which has a smaller methyl ester substituent, is not fixed but is predominantly *S-trans*. After radical addition from the top face (see structure **B**), the face selectivity of the H-atom transfer is dependent

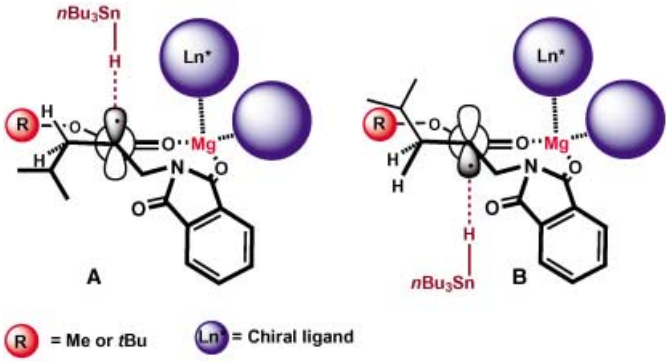


Figure 1. Stereochemical model.

upon the size of the ester substituent as well as that of the radical fragment. The high enantioselectivities observed in reactions between bulky radicals and **6** suggests that the local conformation of the substituent at the carbon atom β to the radical center[19] has a large impact on the selectivity. Metzger and co-workers.[7a] also noted unusual relationships between selectivity and the size of the radical fragment. Steric interactions between the *tert*-butyl ester and the radical fragment in the complex force the radical to adopt the orientation shown in Figure 1A. H-atom transfer

then occurs *anti* to the radical fragment. This analysis is consistent with the dependence of the level of enantioselectivity on the steric bulk of the radical fragment. In reactions with **5**, steric interactions between the methyl group of the ester and the radical fragment are less demanding (both models **A** and **B** are feasible) but reactions occur predominantly through model **A**.

The absolute stereochemistries of **8a** and **7a** were determined to be *S* (see above). The proposed model predicts the correct face selectivity (*S*) for H-atom transfer in reactions with both **5** and **6**. In the methyl ester (**5**) series, the lower selectivity of reactions with 30 mol% of the catalyst suggests that background reactions compete effectively with the catalyzed process. In contrast, there is no discernable relationship between catalytic loading and selectivity in the reactions with **6**. The broad range of results observed with these reactions is more difficult to explain and further work is required.

In conclusion, we have developed a novel and efficient enantioselective H-atom transfer process to prepare α-substituted β-amino acids (β^2-amino acids) in high enantiomeric purity. Work is underway to develop more efficient catalytic reactions and to extend the methodology to more complex substrates.

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Keywords: amino acids · asymmetric catalysis · enantioselective H-atom transfer · Lewis acids · radical reactions

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[10] Several other Lewis acids were evaluated. They gave similar results to those obtained with MgI_2. The details of these experiments will be reported in a separate full account.

[11] Several ligand–Lewis acid combinations were also evaluated. Of these, magnesium salts with ligand **9a** gave the best results.

[12] Of the three H-atom donors tested (Bu_3SnH, Ph_3SnH, and $(TMS)_3SiH$; TMS = trimethylsilyl), tributyltin hydride gave the addition products most efficiently (clean with very few byproducts) and with the highest enantioselectivity.

[13] The catalytic loading was varied from 10 to 100 mol%. The enantioselectivity remained nearly constant (ca. 80% *ee*) for loadings between 20 and 75 mol%.

[14] The higher enantioselectivities observed for **8a** and **8f** at 30 mol% catalytic loading are not an experimental artifact. Further experimentation is required to identify the origin(s) of this anomaly.

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[16] This model is similar to that proposed by Metzger and coworkers in their work on diastereoselective H-atom transfer reactions with methylene glutarates (see ref. [7a]).

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