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Enantioselective radical reactions. Evaluation of nitrogen protecting groups in the synthesis of β^2 -amino acids

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Abstract

We have investigated the effect of nitrogen protecting groups in radical addition trapping experiments leading to β^2 -amino acids. Of the three N-protecting groups examined, the phthalimido group was optimal with respect to both yields and enantioselectivity. Additionally, radical additions to more complex acrylates were also investigated, which provided access to functionalized β^2 -amino acids in modest selectivity.

1. Introduction

β -Amino acids are key components of compounds with potential therapeutic value. Thus, the development of new methods for the asymmetric synthesis of β -amino acids is important.¹ Many 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 We have recently developed a novel enantioselective H-atom transfer⁴ methodology that provided access to a variety of β^2 -amino acids in good yields and selectivity (Scheme 1).

The main shortcoming of the above transformation, with a few exceptions, is that these reactions can not be carried out under catalytic conditions. The starting esters are very reactive and the rate of background reaction is very high. We surmised that variation of the nitrogen protecting group could allow for tuning of the reactivity and enable selective reactions using low catalytic loading. Herein we report the effect of the nitrogen protecting group on the enantioselective H-atom transfer reactions leading to β^2 -amino acids. Additionally, we also present a few examples of addition/H-atom transfer reactions with β -substituted amino acrylates.

2. Results and discussion

Our work began with the preparation of three differentially protected methylamino acrylates **7**, **8**, and **10** to evaluate the effect of the nitrogen protecting group on reactivity and selectivity in enantioselective H-atom transfer reactions. These compounds were prepared according to a literature procedure (Scheme 2).⁵ Substrates **7** and **8** were synthesized by treating the corresponding bromide with succinimide and potassium carbonate. The bis-protected Boc compound **9**, was prepared from the corresponding bromide and then converted to **10** by cleavage with Sc(OTf)₃.

In a previous work, we have shown that radical addition to **1** proceeds smoothly in the presence, or absence, of a Lewis acid to furnish **2** (Scheme 1). Of the different chiral Lewis acids examined, a combination of magnesium iodide and bisoxazoline derived from amino indanol

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provided optimal results. Furthermore, the nature of the H-atom donor had minimal impact on enantioselectivity while tributyltin hydride was the best of the three reagents examined. Based on this background information, our present work began with the addition of various radicals to substrates **7** and **8** in the presence of MgI_2 as a Lewis acid (equation in Table 1) using tributyltin hydride as a H-atom donor and triethylborane/oxygen as the initiator.⁶ The results from these experiments are shown in Table 1. As can be discerned from the table, primary, secondary, and tertiary radicals (entries 1–3) gave good yields of the products, when methyl ester **7** was used as the substrate. Similarly, radical additions to the *tert*-butyl ester **8** were equally effective.

We also carried out H-atom transfer reactions using a stoichiometric amount of MgI_2 and ligand **13**, the optimal chiral Lewis acid from our previous study. Results from the experiments with **7** and **8** as substrates are shown in Table 1. As can be noted from the data in the table, the chemical yields for these experiments varied from modest to good (entries 1–7). Additionally, they were generally less efficient than the corresponding reaction with MgI_2 . The enantioselectivities in the H-atom transfer reactions were disappointing with 39% being the highest. In contrast to the reactions with phthalimido protected acrylates, where the *tert*-butyl ester was superior to the methyl ester, there was very little difference in selectivity in reactions with methyl **7** and *tert*-butyl substituted esters **8** with a succinimido protecting group.⁷ Reactions with substoichiometric amounts of the chiral Lewis acid (30 mol %) gave very low selectivity.

We then evaluated the reactions with methylamino acrylate **10** containing a carbamate protecting group. The results from these experiments are tabulated in Table 2. As can be seen from the table, the yields for radical addition to **10** were high under racemic conditions. Chiral reactions were also examined with substrate **10** (Table 2). The yields obtained in these reactions were also very high; however, the enantioselectivity was low. A maximum selectivity of 60% was observed for the addition of an ethyl radical (Table 2, entry 1). From the limited amount of data at hand, a small radical provided better enantioselectivity in the addition/H-atom transfer experiments (compare entry 1 with 2). Overall, the protecting group changes did not lead to modulation of the reactivity of the starting material. Of the three different nitrogen protecting groups evaluated, the phthalimido group gave the best results with regard to selectivity.

We were also interested in synthesizing highly functional β^2 -amino acids by radical addition to β -substituted acrylates. The starting material to probe this goal was readily prepared from Baylis–Hillman adduct **15**. The synthesis of compound **17** is shown in Scheme 3.⁸

Three key issues need to be addressed in these conjugate radical addition experiments: (1) the reactivity of the β -functionalized substrates, (2) the enantioselectivity for the radical addition step, and (3) the diastereoselectivity during the hydrogen atom transfer step. Initially, we investigated racemic reactions with **17** by adding isopropyl radical (Table 3). In the absence of a Lewis acid, the radical addition to **17** was not efficient (Table 3, entry 1). However, radical addition was more efficient in the presence of a Lewis acid, but dependent on its nature. Although $\text{Yb}(\text{OTf})_3$ proved to be an inefficient Lewis acid (entry 3), MgI_2 provided the product in good yield and high diastereoselectivity (entry 2). The addition of a bulky *tert*-butyl radical was also efficient providing the product in 80% yield (entry 4). In this case, the starting material was also obtained as a minor product. The diastereoselectivity obtained in this reaction was lower than that obtained for the isopropyl radical addition.

MgI_2 was selected as the optimal Lewis acid, and chiral reactions were performed using ligands **13** or **19** (Table 4). The combination of MgI_2 and ligand **13** at -78°C resulted in recovered starting material (Table 4, entry 1). When the temperature was increased to 0°C , a moderate

yield of the product was obtained with high diastereoselectivity and a modest level of enantioselectivity (entry 2). Ligand **19** provided lower diastereoselectivity as well as poor ee (entry 3) in the addition/H-atom transfer experiment.

3. Conclusion

Herein, we have investigated two alternative nitrogen protecting groups in radical addition trapping experiments leading to β^2 -amino acids. These changes did not allow us to lower the catalytic loadings. Of the three N-protecting groups examined, the phthalimido group was optimal with respect to both yields and enantioselectivity. Additionally, radical additions to more complex acrylates were also investigated, which provided access to functionalized β^2 -amino acids in modest selectivity.

Acknowledgements

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6. The reaction in the absence of Lewis acid also proceeded equally well providing yields in the 70–80% range for both the methyl ester **7** and the tert-butyl ester **8**.
7. General procedure for enantioselective hydrogen atom transfer reactions using stoichiometric chiral Lewis acid: A suspension of MgI_2 (0.2 mmol) and chiral ligand (0.2 mmol) in dichloromethane (1 mL) was stirred at room temperature for 45 min. This mixture was then cooled in a dry ice/acetone bath. The corresponding acrylate (0.2 mmol) solution in 1.5 mL dichloromethane was added to the

suspension and stirred for 30 min. To this solution were added the radical precursor (2 mmol), Bu_3SnH (2 mmol), and Et_3B /hexane solution (1.0 M, 1.0 mL/5 mmol). At once, 5.0 mL O_2 was added. After complete consumption of starting material (TLC, ~3 h), the reaction was diluted with ether (20 mL). Silica gel (~2.5 g) was added and the mixture concentrated. The resulting powder was washed with hexanes (100 mL) and the product was eluted with ether (60 mL). Evaporation of the ether fraction yielded the crude product as a colorless oil or solid. Silica gel chromatography furnished the desired compound in good yield. The enantiomeric purity was determined by HPLC.

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Scheme 1.

Scheme 2.

Scheme 3.

Table 1

Radical addition to succinimides: racemic and chiral reactions

Entry	R_1	RX	Pdt.	MgI_2 Yield(%) ^a	1 equiv MgI_2 and ligand 13	
					Yield(%) ^a	ee(%) ^b
1	Me (7)	EtI	11a	70	69	21
2	Me (7)	<i>i</i> -PrI	11b	95	66	33
3	Me (7)	<i>t</i> -BuI	11c	72	55	15
4	<i>t</i> -Bu (8)	EtI	12a	60	78	31
5	<i>t</i> -Bu (8)	<i>i</i> -PrI	12b	76	50	39
6	<i>t</i> -Bu (8)	<i>c</i> -PentI	12c	82	61	27
7	<i>t</i> -Bu (8)	<i>c</i> -HexI	12d	78	50	15

^a Isolated yields after column chromatography.^b Determined by chiral HPLC.

Table 2Radical addition to *N*-Boc derivative

Entry	RX	Pdt.	MgI_2 Yield (%) ^a	MgI_2 and ligand 13	
				Yield (%) ^a	ee (%) ^b
1	EtI	14a	99	90	60
2	<i>i</i> -PrI	14b	91	95	35
3	<i>c</i> -PentI	14c	98	88	12
4	<i>c</i> -HexI	14d	96	85	10

^a Isolated yields after column chromatography.^b Determined by chiral HPLC for the corresponding benzoate.

Table 3Radical addition to β -substituted acrylates

Entry	LA	RX	Pdt.	Yield (%) ^a	dr ^b
1	—	<i>i</i> -PrI	18a	7 (85)	4:1
2	MgI ₂	<i>i</i> -PrI	18a	92	15:1
3	Yb(OTf) ₃	<i>i</i> -PrI	18a	22 (60)	5:1
4	MgI ₂	<i>t</i> -BuI	18b	80 (16)	7:1

Numbers in parentheses represent recovered starting material.

^a Isolated yields after column chromatography.^b Determined by NMR.

Table 4

Radical addition to β -amino acrylate **17**

Entry	Ligand	Yield (%) ^a	dr ^b	ee (%) ^c
1	13	(91) ^d	—	—
2	13	60	10:1	30 ^e
3	19	70	5:1	15

^a Isolated yields after column chromatography.^b Determined by NMR.^c Determined by chiral HPLC.^d Recovered starting material.^e Reaction was performed at 0°C .