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Enantioselective Synthesis of α,β-Disubstituted-β-amino Acids

Mukund P. Sibi,* Narayanasamy Prabagaran, Sandeep G. Ghorpade, and Craig P. Jasperse

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105

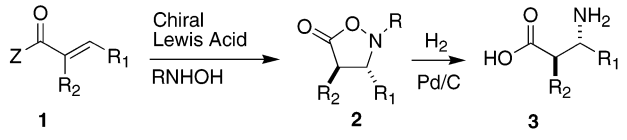
Received July 11, 2003; E-mail: mukund.sibi@ndsu.nodak.edu

We and others have recently reported novel catalytic methods for the synthesis of β-substituted-β-amino acids.[1,2] In contrast, there are fewer methods that provide access to α-substituted β-amino acids in high enantiomeric purity,[1] especially when both the α- and β-carbons contain carbon substituents. Since there are several naturally occurring α,β-disubstituted-β-amino acids, it is important to develop general methods for their synthesis.[3] This work reports a chiral Lewis acid-mediated conjugate amine addition protocol[4] for the synthesis of a variety of α,β-disubstituted-β-amino acids with high diastereo- and enantioselectivity (Scheme 1).

Successful implementation of **1** → **3** requires rotamer control in the substrate. Traditional templates such as oxazolidinones experience poor reactivity due to problematic $A^{1,3}$ interactions in either rotamer (Figure 1, **4** and **5**).[5] To relieve strain the C−C bond of the enoyl group twists, breaking conjugation which results in diminished reactivity at the β-carbon. Our hypothesis was that the use of an imide with an N−H group (**6**, R_3 = H), a template pioneered by Jacobsen,[2a,6] would eliminate the $A^{1,3}$ strain present in **4** and **5** and thus would allow for planar enoyl groups with normal reactivity. We also thought that s-cis/s-trans rotamer control between **6** and **7** would remain possible and that tunable reactivity should be available (R_4 = alkyl, aryl). Literature reports and our own work have shown that *N*-benzylhydroxylamine adds to enoyl groups in a concerted fashion.[4] We surmised that rotamer control for the substrate **1** combined with concerted addition of *N*-benzylhydroxylamine in the presence of a chiral Lewis acid should provide access to **2** with good relative as well as absolute stereocontrol.

Our experiments began with addition of *N*-benzylhydroxylamine to tiglates **8**−**17** with different achiral templates using catalytic amounts (30 mol %) of a chiral Lewis acid derived from ligand **18** and magnesium salts (eq 1). That the same isoxazolidinone product formed regardless of template streamlined our assessment of enantioselectivity. Results from these studies are shown in Table 1. Conjugate amine addition to pyrrolidinone (**8**) or oxazolidinone (**9**) derived tiglate gave low yields, although the diastereoselectivity and enantioselectivity were good (entries 1 and 2). Reaction with tertiary imide **10** (R_3 = CH_3) was also very slow and low-yielding and gave **19** with low selectivity (entry 3). By contrast, secondary imides **11**−**17** (R_3 = H) lacking the $A^{1,3}$ strain present in **8**−**10** were much more reactive and gave good yields. Our initial attempt with benzimide **11** (entry 4) gave excellent diastereoselectivity and good enantioselectivity, suggesting that even with R_3 = H, s-cis/s-trans rotamer control is satisfactory. Increasing the reaction temperature led to higher yield for **19** with a concomitant decrease in enantioselectivity (entry 5). In entries 6−8, electron-withdrawing groups were found to enhance reactivity (reaction time: 1 h for **13** and 8 h for **11** at room temperature) with little impact on selectivity. Reactions with imides containing alkyl R_4 substituents (**15**−**17**) gave higher selectivity as compared to aryl groups (entries 9, 10, and 14). When the magnesium counterion was varied (entries 11−13, 15−16), magnesium triflimide gave optimal enantioselectivity. When temperature, imide R_4, and chiral Lewis acid were all optimized (entries 9−16), the optimal substrate was determined to be **17**, which gave **19** with outstanding levels of selectivity (96% ee and 96% de, entry 16) using magnesium triflimide as a Lewis

Scheme 1



Z = template; R = Bn; R_1 = alkyl, aryl; R_2 = alkyl, aryl, halo

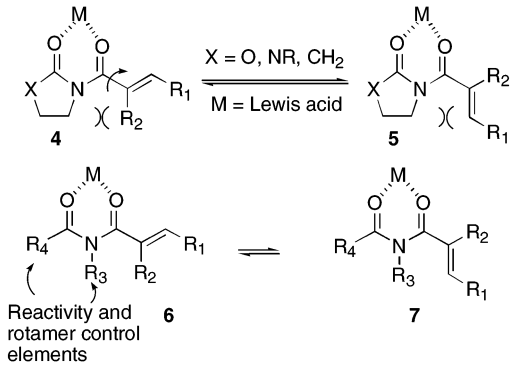
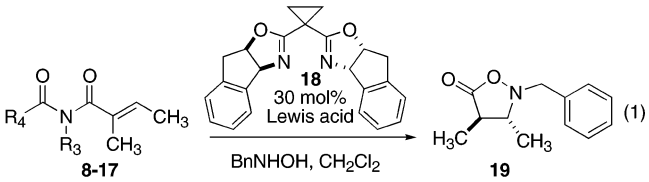


Figure 1.

Table 1. Evaluation of Imides in Conjugate Amine Addition[a]



ent	SM	R_3	R_4	Lewis acid	*T*, °C	yld[b]	de[c]	ee[d]
1	**8**	-$CH_2CH_2CH_2$-		$Mg(ClO_4)_2$	−40	10	95	70
2	**9**	-CH_2CH_2O-		$Mg(ClO_4)_2$	−40	8	95	40
3	**10**	Me	Ph	$Mg(ClO_4)_2$	−40	10	60	18
4	**11**	H	Ph	$Mg(ClO_4)_2$	−40	47	94	75
5	**11**	H	Ph	$Mg(ClO_4)_2$	25	66	90	45
6	**12**	H	3,5-$(CF_3)_2$Ph	$Mg(ClO_4)_2$	25	70	92	40
7	**13**	H	3,5-$(NO_2)_2$Ph	$Mg(ClO_4)_2$	25	66	90	44
8	**14**	H	4-NO_2Ph	$Mg(ClO_4)_2$	25	62	94	46
9	**15**	H	*tert*-butyl	$Mg(ClO_4)_2$	25	45	92	57
10	**16**	H	cyclohexyl	$Mg(ClO_4)_2$	25	64	88	67
11	**16**	H	cyclohexyl	$Mg(ClO_4)_2$	−40	76	92	88
12	**16**	H	cyclohexyl	$Mg(NTf_2)_2$	−40	66	90	96
13	**16**	H	cyclohexyl	MgI_2	−40	62	90	70
14	**17**	H	isopropyl	$Mg(ClO_4)_2$	25	78	94	54
15	**17**	H	isopropyl	$Mg(ClO_4)_2$	−40	76	96	90
16	**17**	H	isopropyl	$Mg(NTf_2)_2$	−40	72	96	96

[a] For details on the synthesis and characterization of starting materials and products, and reaction conditions, see the Supporting Information. [b] Isolated yield after column chromatography. [c] Diastereomeric excess determined by ^1H NMR (500 MHz). [d] Determined by chiral HPLC.

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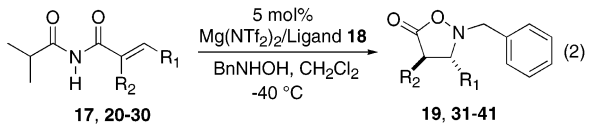
Table 2. Breadth and Scope Studies



17, 20-30 **19, 31-41**

entry	SM	R_1	R_2	product	yield (%)[a]	de[b]	ee %[c]
1[d]	**17**	methyl	methyl	**19**	95	96	96
2	**20**	methyl	ethyl	**31**	70	98	86
3	**21**	methyl	bromo	**32**	76	99	76
4	**22**	methyl	phenyl	**33**	90	95	90
5	**23**	ethyl	methyl	**34**	82	96	90
6	**24**	*n*-propyl	methyl	**35**	92	95	89
7[e]	**25**	isopropyl	methyl	**36**	28	95	81
8[f]	**26**	isobutyl	methyl	**37**	64	95	77
9	**27**	*n*-heptyl	methyl	**38**	73	96	87
10	**28**	ethyl	ethyl	**39**	72	96	60
11[e]	**29**	phenyl	methyl	**40**	38	95	76
12[e]	**30**	phenyl	phenyl	**41**	49	93	84

[a] Isolated yield after chromatography. [b] Diastereomeric excess determined by ^{1}H NMR (500 MHz). [c] Determined by chiral HPLC. [d] 5 g scale. [e] Reactions at 0 °C using 30 mol % of catalyst. [f] 10 mol % of catalyst

acid.[7] *These results clearly demonstrate that a highly enantioselective method for the synthesis of disubstituted-β-amino acids is at hand.*

The results from breadth and scope studies for the preparation of a variety of isoxazolidinones (**19**, **31**−**41**) using 5 mol % of the catalyst and isopropyl-substituted imides are shown in Table 2 (eq 2). As illustrated earlier, amine addition to the tiglate **17** gave **19** with 96% ee (entry 1). Reaction with a bulkier α-ethyl group was equally effective (entry 2). Bromo (entry 3) as well as phenyl substituents (entry 4) at the α-position are also well tolerated in the reaction, leading to products **32** and **33** with good and high selectivity, respectively. Reactions with several substrates with changes in the β-substituent were examined next (entries 5−9). All of these gave isoxazolidinones with high selectivity. The chemical efficiency with the bulky β-isopropyl group (**25**) was low (entry 7). Amine addition to **28**, containing α,β-diethyl groups, gave **39** in good yield. However, the enantioselectivity was modest (entry 10). Reactions with a β-phenyl substituent were also examined (entries 11 and 12). These are relatively unreactive substrates, and reactions were carried out at 0 °C to get modest yields. However, the enantioselectivity for **40** and **41** remained good. The results from these studies demonstrate that a variety of substituted isoxazolidinones can be prepared with high diastereo- and enantioselectivity.

The product isoxazolidinones can be easily converted to the corresponding amino acids by a simple hydrogenolysis. Catalytic hydrogenolysis of **19** using Pd/C on a 5 g scale gave **(**2*R*,3*R*)-3-amino-2-methylbutanoic acid **42** in 90% yield. Compounds **31**, **36**, **37**, and **40** were also converted to the corresponding amino acids by hydrogenolysis. Thus α,β-disubstituted-β-amino acids can be synthesized in four steps from the unsaturated acids in good overall yields and high enantiopurity using chiral catalysis.

We have a tentative cis octahedral model (**43***)* for the observed stereochemistry based on the identity of **42** (Figure 2). Interestingly,

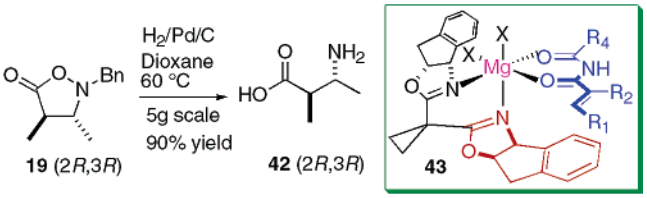


Figure 2. Stereochemical model for amine addition.

the addition of the nitrogen occurs on the re face of the β-carbon, as is also the case for additions of both amines[4a] and radicals[8] to oxazolidinone crotonates and cinnamates when activated by MgX_2/**18**. This suggests by analogy that even in the case of tiglates, reaction still occurs from s-cis rotamers **6** rather than s-trans rotamers **7**. The high diastereoselectivity results from the fact that protonation of the α-carbon is concerted with addition of nitrogen to the β-carbon.[4]

In conclusion, we have developed a novel and practical chiral catalytic method for the synthesis of α,β-disubstituted-β-amino acids in good overall yields and enantioselectivity. The availability of highly enantioenriched isoxazolidinones provides access to syn disubstituted as well as α,α,β-trisubstituted compounds by base-mediated inversion or alkylation protocols.[9] Experiments along these lines as well as extension of the methodology to the synthesis of more complex amino acids and optimization of the protocol for less reactive substrates is underway.

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Supporting Information Available: Characterization data for compounds **8**−**42** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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