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REGIOSELECTIVE FUNCTIONALIZATION OF CHIRAL NICKELACYCLES DERIVED FROM N-PROTECTED ASPARTIC AND GLUTAMIC ANHYDRIDES[#]

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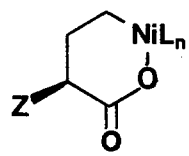
Summary: The electrophilic cleavage of the nickelacycles resulting from oxidative addition of Ni(0) complexes to *N*-protected aspartic and glutamic anhydrides, followed by decarbonylation, gives rise regioselectively to derivatives of α-and ß-alanine or α- and γ-aminobutyric acid, respectively.

The developing of synthetic strategies for the preparation of enantiomerically pure amino acids has attracted considerable interest in recent years.[1] Much of the attention has been focused on glycine synthons, although the use of alanine equivalents, and related synthons, has considerable synthetic potential.[2] In this regard, the preparation of chiral nickelacycles **1** and **2** would provide valuable starting materials for the elaboration of important natural and unnatural amino acids.[1,3]

1 , Z = NR_2

3 , Z = H



2 , Z = NR_2

4 , Z = H

Herein, we wish to report on the regioselective generation of oxanickelacycles **1** and **2** (n = 1 or 2), starting from readily available *N*-protected aspartic and glutamic acid anhydrides, and their electrophilic cleavage. It is hoped that these nickelacycles will be of synthetic use as synthons for α-alanine and α-aminobutyric acid,

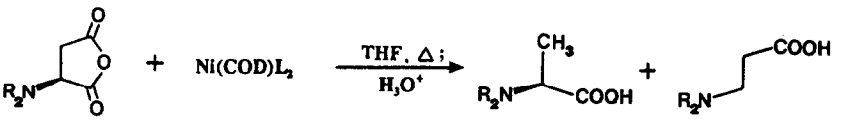
Recently it was reported that Ni(COD)(bpy)[5] reacts with succinic anhydride to give the oxidative addition product, which after decarbonylation affords nickelacycle **3**.[6,7] A related reaction sequence transforms glutaric anhydride into the six-membered ring nickelacycle **4**, which can suffer isomerization to a five-membered ring complex by a ß-hydride elimination/insertion process.[7]

The utilization of aspartic or glutamic anhydrides[8] in the above reaction addresses the question of the regiochemical control in the oxidative addition step to the unsymmetrical anhydrides, and the compatibility of the highly reactive Ni(0) complexes with the NH functionality and the protective groups. In the event, treatment of Cbz-aspartic anhydride with the complex Ni(COD)(bpy) in THF at 23 °C gave a dark red suspension of oxidative addition products. Hydrolysis with aq HCl gives the expected Cbz-Asp-OH. Decarbonylation was achieved after heating in THF for several hours, yielding a 1:1 mixture of Cbz-α-Ala-OH and Cbz-ß-Ala-OH in

[#] This Letter is dedicated to the memory of Prof. John K. Stille.

88 % yield,[9] after acid quenching of the crude reaction mixture.[10] Selected results of this oxidative addition-decarbonylation process are summarized in Table 1.

Table 1. *Oxidative addition and Decarbonylation of N-Protected Aspartic Anhydrides.*[a]



Asp α-Ala ß-Ala

entry	R,R [a b]	L_2	product ratio α-Ala	ß-Ala	yield[b] (%)
1	Cbz,H	bpy	1	1	88
2		Me_2Phen	2	1	61
3		TMEDA	9	1	60
4		PCy_3	1	1	78
5		dppf	1	3	54
6	TFA,H	TMEDA	2	1	86
7	Pht	bpy	1	3	91
8		Me_2Phen	11	1	91
9		TMEDA	1	1	82
10		PCy_3[c]	1	10	82
11			1	28	91[d]
12		PPh_3[c]	4	1	80

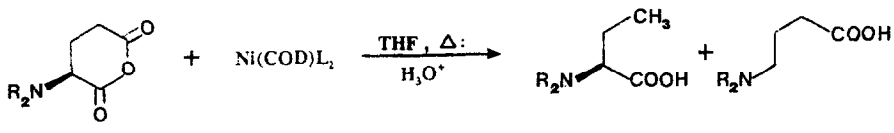
(a) Unless otherwise stated, the reactions were carried out in THF under reflux for 4-8 h with 1.1-1.5 equiv of Ni(0) complex, prepared *in situ* from $Ni(COD)_2$ and 1 equiv of the corresponding ligand (except for entry 12, where 2 equiv were used). (b) Yields were determined by 300 MHz ^{1}H NMR, and were confirmed in several instances by isolation of the amino acids or the methyl esters derivatives (CH_2N_2, Et_2O). The only other constituent of the crude reaction mixture was the *N*-protected aspartic acid. (c) Reaction run at 23 °C. (d) Reaction in benzene at 23 °C for 25 h.

Selective C-4 attack by the Ni(0) complex was obtained by using more sterically demanding ligands (entries 2, 3, and 8), although replacement of the *N*-protecting group by the more electron-withdrawing TFA or Pht increases the amount of C-1 attack (compare entries 3, 6, and 9).[11] Particularly interesting was the observation that addition of PCy_3, presumably giving the coordinatively unsaturated complex $Ni(COD)PCy_3$, directs the reaction to C-1, leading, after decarbonylation and acid hydrolysis, to Pht-ß-Ala-OH.[8b] This result is in contrast with the selective C-4 attack observed with PPh_3 (2 equiv) (entry 12)[12] and may be a consequence of the coordination of the unsaturated Ni(0) complex with the imide protective group. Accordingly, utilization of benzene as solvent results in an increase of the regioselectivity for oxidative addition through the C-1 carbonyl. On the other hand, no reaction was observed with $Ni(COD)_2$ itself, or when Me_2bpy or bqy were used as ligands.

The reaction of (*R*)-MTPA-(*S*)-aspartic anhydride[13] with Ni(0) to give (*R*)-MTPA-(*S*)-Ala-OH was also briefly examined to determine the degree of C-2 epimerization during the reaction sequence. Satisfactory results were obtained with PCy_3 and PPh_3 (80-90% de, determined by ^{1}H and ^{19}F NMR), while TMEDA gave ca. 50% de, and Me_2Phen led to a 1:1 mixture of diastereoisomers.[14]

The oxidative addition of Ni(0), with concomitant decarbonylation, to *N*-protected glutamic anhydrides was also studied (Table 2). In this instance good to excellent selectivity in the oxidative addition through the C-5 carbonyl was obtained for Cbz-glutamic anhydride. This trend was reversed again with PCy_3 and the phthalimido protective group, yielding Pht-γ-Abu-OH as the major product (Table 2, entry 6).

Table 2. *Oxidative Addition and Decarbonylation of N-Protected Glutamic Anhydrides.*[a]

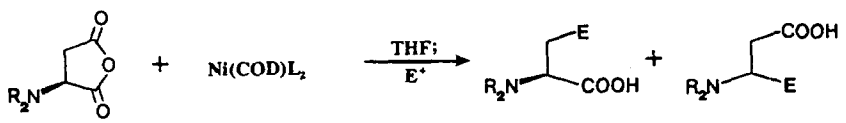


Glu α-Abu -Abu

entry	R,R[8b]	L_2	product ratio α-Abu	γ-Abu	yield[b] (%)
1	Cbz,H	bpy	5	1	75
2		Me_2Phen	4	1	65
3		TMEDA	>50	<1	96
4		PCy_3	>50	<1	40
5	Pht	bpy	3	1	46
6		PCy_3	1	3	91

(a) The reactions were carried out as in Table 1, but for 2-2.5 h. (b) See comment b in Table 1. Additionally small amounts (*ca.* 4-10 %) of Cbz-pyroglutamic acid were also obtained in several runs.

Having established the regiochemical control in the oxidative addition step, the deuteriation of the five-membered ring nickelacycles was also studied. Reaction of the decarbonylated metalacycles with DCl (20% D_2O solution) at 23 °C gave 3-*d*-alanines **5** (as in entry 3, Table 1 but at 23 °C, 43% yield, 93% *d*) and *rac*-**6** (entry 8, Table 1, 23 °C, 70-80% yield, 80-84 % *d*) (Eq 1).[15] The corresponding *rac*-Pht-3-*d*-ß-Ala-OH (**7**)[15] was also prepared by using Ni(COD)(bpy) (entry 7, Table 1, 23 °C, 38 % yield, 91 % *d*) .[16] These results demonstrate the usefulness of the described reaction sequence for the selective labeling of alanines by decarboxylation of aspartic acids.[17] Furthermore, treatment of *rac*-Pht-aspartic anhydride with Ni(COD)(Me_2Phen) (Table 1, entry 8), followed by addition of *N*-bromosuccinimide at 23 °C gave *rac*-Pht-3-bromo-Ala-OH (**8**)[15] in 80 % yield (Eq 1).[18]



5, E = D, R = Cbz, H
6, E = D, R = Pht
8, E = Br, R = Pht

7, E = D, R = Pht

(Eq 1)

Further experiments directed towards the determination of the synthetic potential of these and related nickelacycles are in progress.

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1. For a recent review, see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Pergamon: Oxford, 1989.
2. For recent developments, see: (a) *Nucleophilic alanine equivalents*: Baldwin, J. E.; Moloney, M. G.; North, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 833; *Tetrahedron* **1989**, *45*, 6309; 6319. Jackson, R. F. W.; Wythes, M. J.; Wood, A. *Tetrahedron Lett.* **1989**, *30*, 5941. Jackson, R. F. W.; James, K.; Wythes, M. J.; Wood, A. *J. Chem. Soc., Chem. Commun.* **1989**, 644. Hegedus, L. S.; Schwindt, M. A.; De Lombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264. (b) *Nucleophilic d⁴-aminobutyric acid equivalents and related synthons*: El Marini, A.; Roumestant, M.-L.; Pappalardo, L.; Viallefont, P. *Bull. Soc. Chim. Fr.* **1989**, 554. Attwood, M. R.; Carr, M. G.; Jordan, S. *Tetrahedron Lett.* **1990**, *31*, 283. (c) *Electrophilic alanine equivalents*: Pansare, S. V.; Vederas, J. C. *J. Org. Chem.* **1989**, *54*, 2311. Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073. (d) For the palladium-catalyzed reaction of an electrophilic aspartic acid synthon, see: Salituro, F. G.; McDonald, I. A. *J. Org. Chem.* **1988**, *54*, 6138.
3. Wagner, I.; Musso, H. *Angew. Chem. Int. Ed. Eng.* **1983**, *22*, 816.
4. A recent report stresses the synthetic utility of a succinic acid derived nickelacycle as a propionic acid equivalent: Schönecker, B.; Walther, D.; Fischer, R.; Nestler, B.; Bräunlich, G.; Eibisch, H.; Droescher, P. *Tetrahedron Lett.* **1990**, *31*, 1257.
5. Abbreviations: (*Ligands*) COD = 1,5-cyclooctadiene; bpy = 2,2'-bipyridine; Me_2bpy = 4,4'-dimethyl-2,2'-bipyridine; Me_2Phen = 2,9-dimethyl-1,10-phenanthroline; bqy = 2,2'-biquinoline; PCy_3 = tricyclohexylphosphine; TMEDA = *N,N,N',N'*-tetramethylethylenediamine; dppf = 1,1'-bis(diphenylphosphino)ferrocene. (*N-protective groups*) Cbz = benzyloxycarbonyl; TFA = trifluoroacetyl; Pht = phthaloyl; MTPA = α-methoxy-α-trifluoromethylphenylacetyl. (*Amino acids*) Asp = aspartic; Glu = glutamic; Ala = alanine; Abu = aminobutyric.
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8. (a) Preparation of protected amino acids: Wünch, E.; Ed. *"Methoden der Organischen Chemie. Houben-Weyl"*, Vols. 15/1 and 15/2, G. Thieme: Stuttgart, 1972. (b) Cbz and TFA derivatives are optically pure compounds. Pht derivatives are racemic.
9. Determined by ^{1}H NMR after hydrolysis of the decarbonylated products. The resulting amino acids were characterized by ^{1}H and ^{13}C NMR and by comparison with authentic samples.
10. The air sensitive nickelacycles are insoluble in NMR solvents.
11. (a) A moderate (ca. 1.4:1) selectivity for nucleophilic α-attack (C-1) by methanol was reported for **5**: see ref. 8a (Vol. 15/1, p. 322). (b) For the regioselective reduction of **5** with $NaBH_4$, see: McGarvey, G. J.; Hiner, R. N.; Matsubara, Y.; Oh, T. *Tetrahedron Lett.* **1983**, *24*, 2733.
12. A similar result was obtained with $Ni(PPh_3)_4$, prepared *in situ* by reduction of $NiCl_2(PPh_3)_2$ with Zn-Cu in the presence of 2 equiv of PPh_3: Sugimoto, T.; Misaki, Y.; Kajita, T.; Yoshida, Z.; Kai, Y.; Kasai, N. *J. Am. Chem. Soc.* **1987**, *109*, 4106.
13. Prepared in quantitative yield by dehydration (DCC or Ac_2O) of optically pure (*R*)-MTPA-(*S*)-aspartic acid, synthetized by acylation of (*S*)-aspartic acid bis(trimethylsilyl) ester. Details of this procedure will be published shortly.
14. It is not clear at this moment if this result is a consequence of a base catalyzed epimerization (see: Buckingham, D. A.; Stewart, I.; Sutton, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 845) or it takes place by means of a ß-hydride elimination/insertion process.[7] Experiments to ascertain this point are in progress.
15. These compounds have been fully characterized. NMR data for selected compounds: *rac*-**6**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95-7.80 (m, 4 H), 4.85 (t, J = 7.3 Hz, 1 H), 1.55 (br d, J = 7.2 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.1, 168.0, 134.2, 131.8, 123.5, 47.2, 14.7 (t, J = 20.1 Hz). *rac*-**7**: ^{1}H NMR (300 Mz, DMSO-d_6) δ 7.95-7.80 (m, 4 H), 3.77 (t, J = 7.3 Hz, 1H), 2.59 (d, J = 7.3 Hz, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.9, 167.4, 134.1, 131.9, 123.4, 33.2 (t, J = 22.4 Hz), 32.4. *rac*-**8**: ^{1}H NMR (300 Mz, DMSO-d_6) δ 8.00-7.80 (m, 4 H), 5.18 (dd, J = 11.0, 5.0 Hz, 1 H), 4.11 (dd, J = 10.7, 5.0 Hz, 1 H), 4.03 (t, J = 10.8 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.4, 167.2, 134.3, 131.6, 123.8, 53.4, 28.3.
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17. The preparation of α-alanine from aspartic acid mimics the action of the enzyme aspartic acid ß-decarboxylase. For a leading reference, see: Chang, C.-C.; Laghai, A.; O'Learly, M. H.; Floss, H. G. *J. Biol. Chem.* **1982**, *257*, 3564.
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