Reactivity of a Nickelacycle Derived from Aspartic Acid: Alkylations, Insertions, and Oxidations

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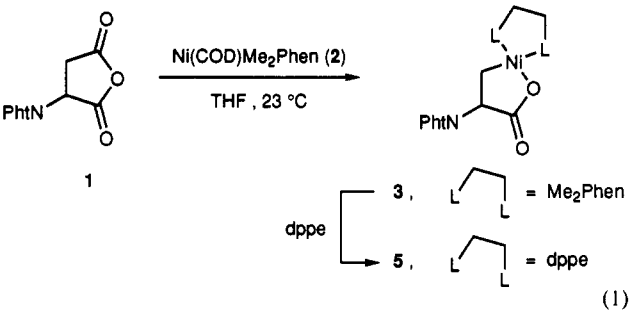
The five-membered nickelacycle derived from aspartic acid by oxidative addition followed by decarbonylation reacts with alkyl iodides and bromides to give α-amino acids, after hydrolysis of the reaction products. Carbonylation products were, however, observed with benzyl or allyl bromide. The involvement of radicals in the alkylation reaction pathway has also been explored. Oxidation of the nickelacycle with *N*-methylmorpholine *N*-oxide or dioxygen gave N-protected serine. On the other hand, benzoyl peroxide promoted the insertion of carbon monoxide or isocyanides into the Ni–C bond. Phenylacetylene and 1-octyne also insert into the Ni–C bond of the nickelacycle to give alkenyl or alkynyl products.

Introduction

The synthesis of five- or six-membered-ring nickelacycles has been carried out by means of the oxidative addition of succinic or glutaric anhydrides to Ni(0) complexes followed by decarbonylation.[1] Related metallacycles can be prepared by the oxidative cycloaddition of alkynes or alkenes with CO_2 or isocyanates in the presence of Ni(0) or Pd(0) complexes.[2] The intramolecular reactions of α,β- or β,γ-unsaturated carboxylic acids or amides with Ni(0) or Pd(0) complexes also lead to these types of metallacycles.[2b,3] Recently, the reactions of the five-membered-ring nickelacycle derived from succinic anhydride with certain alkyl halides in DMF in the presence of anhydrous MnI_2 have been reported.[4] An alkylation with methyl iodide has also been reported for a nickelacycle obtained in the reaction between Ni(COD)-$(py)_2$[5] and 2-cyclopentenecarboxylic acid.[2b] Herein we report the results of a study on the reactivity of a five-membered-ring nickelacycle derived from (±)-*N*-phthaloylaspartic anhydride (**1**) with alkyl halides, 1-alkynes, and several oxidants.

Results and Discussion

The oxidative addition of 1.5 equiv of Ni(COD)Me_2-Phen (**2**)[5] to anhydride **1** proceeds in THF at room temperature, leading regioselectively to the formation of nickelacycle **3** as an orange solid in 80% yield (eq 1).[6]



(1)

From the filtrate, complex $Ni(CO)_2Me_2Phen$ (**4**) was isolated, after concentration of the purple solution and cooling to −15 °C.[7] This complex results from the reaction of excess Ni(0) complex with the expelled CO. Complex **3** is very insoluble and was spectroscopically characterized after ligand exchange with dppe[5] in CH_2Cl_2 to give complex **5**. In its ^{31}P-decoupled ^1H NMR spectrum the diastereotopic CH_2 hydrogens appeared at δ 1.47 and 1.02. Hydrolysis of **3** or **5** afforded *N*-phthaloyl-α-alanine as the major product.[6]

Although isolation of nickelacycles **3** and **5** is possible, usually alkylation reactions were performed without isolation of any intermediates, by treatment of anhydride **1** with 1.5 equiv each of $Ni(COD)_2$ and Me_2Phen in THF at 23 °C for 5 h, followed by addition of excess alkyl halides (10–20 equiv) and stirring at 23 or 40 °C, followed by quenching of the mixture with aqueous acid. With Me_2-Phen as the ligand, we observed the best results. This ligand allows for regioselective oxidative addition and

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(1) (a) Uhlig, E.; Fehske, G.; Nestler, B. *Z. Anorg. Allg. Chem.* **1980**, *465*, 141. (b) Sano, K.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1983**, 115. (c) Sano, K.; Yamamoto, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2741. (d) Yamamoto, T.; Sano, K.; Yamamoto, A. *J. Am. Chem. Soc.* **1987**, *109*, 1092.

(2) (a) Behr, A. *Carbon Dioxide Activation by Metal Complexes*; Verlag Chemie: Weinheim, Germany, 1988; Chapter 3. (b) Hoberg, H.; Ballesteros, A.; Sigan, A.; Jegat, C.; Milchereit, A. *Synthesis* **1991**, 395. (c) Hoberg, H.; Nohlen, M. *J. Organomet. Chem.* **1990**, *382*, C6. (d) Hoberg, H.; Guhl, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1035.

(3) (a) Yamamoto, T.; Sano, K.; Osakada, K.; Komiya, S.; Yamamoto, A.; Kushi, Y.; Tada, T. *Organometallics* **1990**, *9*, 2390. (b) Osakada, K.; Doh, M.-K.; Ozawa, F.; Yamamoto, A. *Organometallics* **1990**, *9*, 2197. (c) Sano, K.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1982**, 695. (d) Yamamoto, T.; Igarashi, K.; Ishizu, I.; Yamamoto, A. *J. Chem. Soc., Chem. Commun.* **1979**, 554. (e) Yamamoto, T.; Igarashi, K.; Komiya, S.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 7448.

(4) (a) Schönecker, B.; Walther, D.; Fischer, R.; Nestler, B.; Bräunlich, G.; Eibissch, H.; Droescher, P. *Tetrahedron Lett.* **1990**, *31*, 1257. (b) Fischer, R.; Walther, D.; Bräunlich, G.; Undeutsch, B.; Ludwig, W. *J. Organomet. Chem.* **1992**, *427*, 395. (c) Walther, D.; Braünlich, G.; Ritter, U.; Fischer, R.; Schönecker, B. In *Organic Synthesis via Organometallics*; Dötz, K. H., Hoffman, R. W., Eds.; Wieweg: Braunschweig, Germany, 1991.

(5) Abbreviations: COD = *cis,cis*-1,5-cyclooctadiene; Me_2Phen = 2,9-dimethyl-1,10-phenathroline; dppe = 1,2-bis(diphenylphosphino)ethane; bpy = 2,2′-bipyridine; TMEDA = *N,N,N′,N′*-tetramethylethylenediamine; py = pyridine.

(6) Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1990**, *31*, 4783.

(7) The IR spectrum of complex **4** is in agreement with that of Ni-$(CO)_2$Phen: Plankey, B. J.; Rund, J. V. *Inorg. Chem.* **1979**, *18*, 957.

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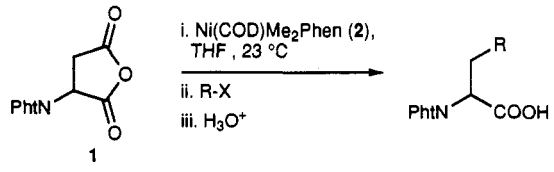
Table 1



entry no.	RX	amt of RX (equiv)	reacn time (h)[a]	R	yield (%)[b]
1	MeI	20	13	Me	69 (80)
2	EtBr	20	13	Et	81 (90)
3	EtI	20	15	Et	77 (79)
4	*n*-BuBr	18	144	*n*-Bu	51 (73)
5	*n*-BuBr	18	14[c]	*n*-Bu	49 (70)
6	*n*-BuI	10	40	*n*-Bu	49 (78)
7	*n*-BuI	10	15[c]	*n*-Bu	47 (71)
8	*i*-PrI	20	48	*i*-Pr	52 (86)
9	*c*-C_6H_{11}I	9	42	*c*-C_6H_{11}	42 (58)

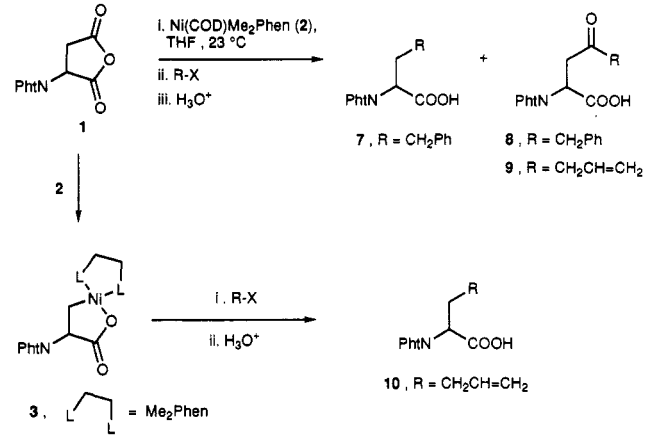
[a] The reactions were performed at 23 °C. [b] Corrected for conversion. [c] The reaction was carried out at 40 °C.

subsequent decarbonylation to proceed smoothly at room temperature. With other ligands on nickel, the decarbonylation reaction only proceeds at 60–70 °C or the undesired regioisomer was obtained.[6] Triphenylphosphine (2 equiv) led also to alkylation, although the products were isolated in lower yields.

The results obtained in the reactions with primary and secondary alkyl halides are summarized in Table 1. The alkylation reactions proceed satisfactorily with primary iodides (entries 1, 3, 6, and 7) or bromides (entries 2, 4, and 5) in the absence of additives or polar solvents. Shorter reaction times were obtained by performing the reaction at 40 °C. Secondary iodides gave also the alkylated derivatives (entries 8 and 9). However, more hindered substrates such as α-cholestanyl iodide[8] and menthyl iodide or bromide[9] were recovered unchanged or suffered elimination to afford mixtures of alkenes after several days at room temperature. The crude reaction mixtures were usually very clean. The only byproducts detected were small amounts of (±)-*N*-phthaloyl-α- and (±)-*N*-phthaloyl-β-alanines and (±)-*N*-phthaloylaspartic acid (**6**), resulting from the acid hydrolysis of the regioisomeric nickelacycles[6] and the starting anhydride **1**, respectively. In a few instances, small amounts of *N*-vinylphthalimide, resulting from decarboxylation of the nickelacycle **3**, were also detected by ^{1}H NMR analysis of the reaction mixtures. On the other hand, no alkylation took place with methyl *p*-toluenesulfonate, ethyl triflate, and propylene oxide under the same reaction conditions. Similarly unreactive toward the nickelacycle were alkenyl and aryl halides.

When the reaction of entry 3 (Table 1) was performed with optically active **1** as the substrate, the alkylated derivative L-*N*-phthaloylnorvaline was obtained with only 50% ee. Partial racemization in this reaction is probably due to β-hydride elimination–insertion of the nickelacycles. In fact, reaction of optically active **1** with Ni(0) complex **2** at 23 °C in THF, followed by acid hydrolysis, led to the formation of *N*-phthaloyl-α-alanine with 50–73% ee, depending on the reaction time and the amount of Ni(0)

Scheme 1



complex. The isolation of *N*-vinylphthalimide as a minor byproduct also points to the possible involvement of a reversible β-decarboxylation in the racemization. Additionally, the basic ligand also catalyzes the slow racemization of optically active anhydride **1**, leading to anhydride with 80% ee after 48 h at 23 °C in the presence of 1 equiv of Me_2Phen.[10] Finally, the observed loss of optical activity can also take place by a base-catalyzed process on the intermediate nickelacycle **3** or the oxidative addition product.[11]

In contrast with the results obtained with simple alkyl halides, benzyl bromide led to the formation of variable ratios of **7** and the ketone **8** (Scheme 1). Very recently a similar result has been reported in the reactions between the oxidative-addition product of Ni(COD)bpy or Ni(COD)TMEDA[5] with *cis*-4-cyclohexene-1,2-dicarboxylic anhydride and alkyl iodides.[12] With allyl bromide, ketone **9** was the only product observed in the crude reaction mixture. This compound underwent complete isomerization to the α,β-unsaturated ketone after esterification of the crude acid with benzyl bromide. However, when the reaction was performed with the isolated nickelacycle **3**, free of $Ni(CO)_2Me_2Phen$ (**4**), exclusive formation of the allylated derivative **10** was obtained in 60% yield (Scheme 1). This result indicates that complex **4** is not inert under the reaction conditions, since with certain substrates it can transfer CO to the nickelalactone **3**. Alternatively, the formation of ketones in these reactions could be explained by alkylation of the primary oxidative-addition product or by carbonylation of allyl or benzyl bromide to give acyl bromides which react with **3** to give the observed products.[13] However, this last reaction pathway seems unlikely, since acetyl or benzoyl chloride did not react with the nickelacycle **3** generated *in situ*.

Several processes of interest for organic synthesis catalyzed or mediated by Ni have been proposed to proceed by means of radical intermediates.[14–16] In particular, (η^3-

(8) Prepared from β-cholestanol by the method of Loibner and Zbiral: Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.

(9) (a) Yamashita, M.; Suzuki, N.; Yamada, H.; Soeda, Y.; Yamashita, H.; Nakatami, K.; Oshikawa, T.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 219. (b) Yamashita, M.; Soeda, Y.; Nobuyoshi, S.; Yamada, M.; Tsunekawa, K.; Oshikawa, T.; Inokawa, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1871.

(10) For the increased tendency toward racemization of phthaloyl amino acids, see: Anderson, G. W.; Callahan, F. M.; Zimmerman, J. E. *Acta Chim. Hung.* **1965**, *44*, 51. Liberek, B. *Tetrahedron Lett.* **1963**, 1103.

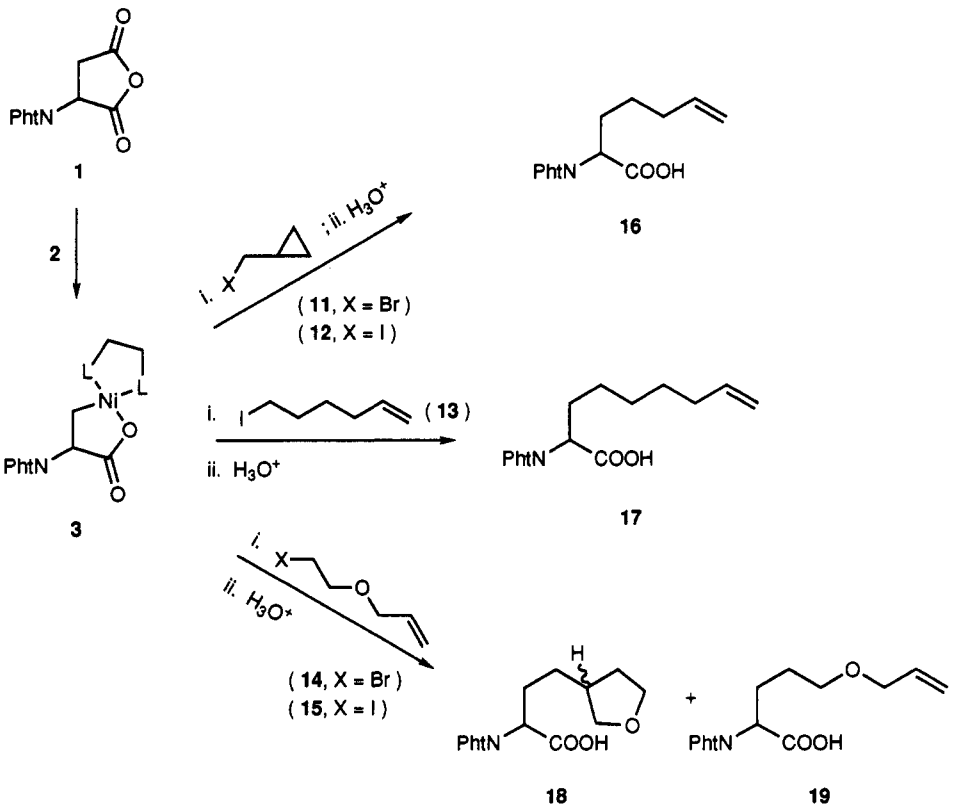
(11) Simple complexation with metal cations is known to enhance the CH acidity of amino acids: Buckingham, D. A.; Stewart, I.; Sutton, P. A. *J. Am. Chem. Soc.* **1990**, *112*, 845. Angus, P. M.; Goling, B. T.; Sargeson, A. M. *J. Chem. Soc., Chem. Commun.* **1993**, 979.

(12) Fischer, R.; Walther, D.; Kempe, R.; Sieler, J.; Schönecker, B. *J. Organomet. Chem.* **1993**, *447*, 131.

(13) Chiusoli, G. P. *Acc. Chem. Res.* **1973**, *6*, 442.

(14) (a) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic: New York, 1978. (b) Jolly, J. P. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, U.K., 1982; Vol. 4, Chapters 4.1 and 4.2.

Scheme 2



allyl)nickel(II) complexes are known to react with alkyl halides in polar solvents by a process for which a radical chain mechanism has been proposed.[15] We decided to study briefly the possible involvement of radical species in the alkylation of nickelacycle **3**. The lack of reaction of **3** with alkyl sulfonates excludes a simple S_N2 mechanism for the alkylation process. By using alkyl halides **11**–**15** with nickelacycle **3**, prepared *in situ*, the results summarized in Scheme 2 were obtained. These alkyl halides are known to generate alkyl radicals, which undergo rearrangement reactions with known rates ("radical clocks").[17] (Bromomethyl)cyclopropane (**11**) and (iodomethyl)cyclopropane (**12**) gave only the rearranged linear product **16**, albeit in low yield (26 and 45%, respectively). On the other hand, 5-hexenyl iodide (**13**) gave only unrearranged product **17** in 30% yield. In all these experiments, the other products of the reaction were *N*-phthaloyl-α- and *N*-phthaloyl-β-alanines and (±)-*N*-phthaloylaspartic acid (**6**). With 2-(allyloxy)ethyl bromide (**14**) and iodide (**15**) a 4.5:1 ratio of the rearranged cyclic species **18** and acyclic derivative **19** was obtained in 35 and 85% yield, respectively (Scheme 2). Tetrahydrofuran derivative **18** was obtained as a 1:1 mixture of diastereomers. In the reactions with **13** and **14**, the excess halides were recovered unchanged. However, with iodide **15** the recovered halide was contaminated with approximately 15% of 3-(iodomethyl)tetrahydrofuran (**20**). The cyclization of **15** is promoted, although quite inefficiently (3–5% yield), by Ni(0) complexes **2** and **4**. With 5-hexenyl or 2-(allyloxy)ethyl mesylates no reaction was observed.

If the reaction with alkyl halides proceeds though the formation of radicals, an apparent rate for radical trapping of 2×10^6 M^{-1} s^{-1} can be determined from the results of Scheme 2.[15a] This rate is an order of magnitude slower than the rate determined in the alkylation of (η^3-allyl)nickel(II) halide dimers in polar solvents.[18,19] The above results are thus consistent with the involvement of a radical intermediate in the carbon–carbon bond-forming step. However, unlike (η^3-allyl)nickel(II) complexes, the alkylation of nickelacycle **3** is not accelerated by irradiation with light or by addition of common radical initiators. Additionally, the alkylations were not inhibited by the addition of substantial amounts (0.2–1.0 equiv) of *m*-dinitrobenzene, a well-known inhibitor of radical chains.[15] Furthermore, although (η^3-allyl)nickel(II) halide complexes react smoothly with alkenyl and aryl halides,[15,16] no reaction was observed between **3**, or related nickelacycles, with the C_{sp^2} electrophiles. The results obtained with the radical clocks and the lack of reactivity observed with alkyl sulfonates can be explained by assuming that the reaction of nickelacycle **3** with the alkyl halides proceeds by electron transfer,[20] yielding a radical pair that collapses with a rate of 2×10^6 M^{-1} s^{-1} to afford the alkylated derivatives. However, the reactions performed

(15) (a) Hegedus, L. S.; Thompson, D. H. P. *J. Am. Chem. Soc.* **1985**, *107*, 5663. (b) Hegedus, L. S.; Miller, L. L. *J. Am. Chem. Soc.* **1975**, *97*, 459.

(16) Jolly, J. P. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, U.K., 1982; Vol. 6, Chapter 37.6. Billington, D. C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 3, Chapter 2.1.

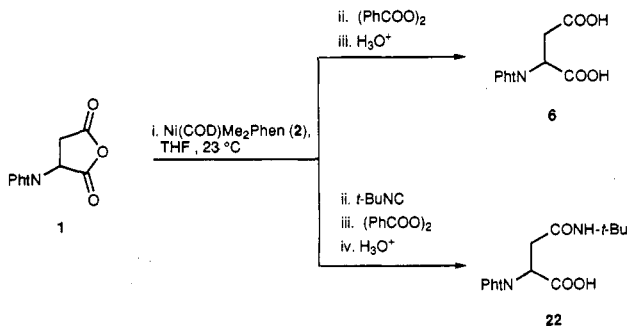
(17) (a) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206. (b) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

(18) On the basis of the 57:43 ratio of linear to cyclic products obtained in ref 15a with 2-(allyloxy)ethyl bromide and the more recently reported value for the rate of this radical rearrangement (9×10^6),[17b] the value 1.9×10^7 M^{-1} s^{-1} can be determined.[15a]

(19) For the rates of coligation of alkyl radicals with Ni(cyclam)$^{2+}$, see: Kelley, D. G.; Marchaj, A.; Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1993**, *113*, 7583.

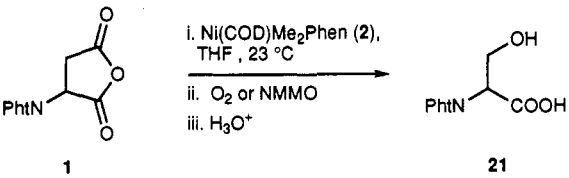
(20) For a discussion on the relevance of electron transfer to the mechanism of the alkylation of Ni(I) complexes related to the coenzyme F430, see: Stolzenberg, A. M.; Stershic, M. T. *J. Am. Chem. Soc.* **1988**, *110*, 5397. Lahiri, G. K.; Stolzenberg, A. M. *Inorg. Chem.* **1993**, *32*, 4409. Helvenston, M. C.; Castro, C. E. *J. Am. Chem. Soc.* **1992**, *114*, 8490.

Scheme 3



in the absence of Ni(0) complex **4** were slower, giving rise to the alkylated compounds in lower yields. Although the lower solubility of pure **3** in THF can account for this effect, a more important role for complex **4** in the alkylation reaction cannot be excluded at this time.

The reactions of **3** with alkyl halides were carried out in the absence of oxygen. Otherwise, small amounts of the N-protected serine **21** were obtained by oxygen insertion into the Ni–C bond. This oxidation reaction could also be performed by using O_2 (1 atm) or *N*-methylmorpholine *N*-oxide (NMMO), leading to **21** in 37 and 47% yields, respectively (eq 2).[21] Previous syntheses

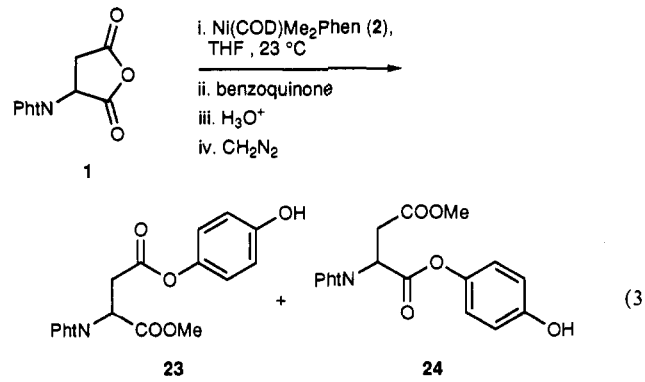


(2)

of serine from aspartic acid, in the optically active series, have been carried out by means of Baeyer–Villiger oxidation of a methyl ketone derived from protected aspartic acid.[22] The new procedure described herein allows for the synthesis of serine derivative **21** from aspartic acid in only two steps.

No oxidation was observed with ceric ammonium nitrate or *tert*-butyl hydroperoxide, while treatment with benzoyl peroxide,[23] followed by hydrolysis, gave the starting carboxylic acid **6** (Scheme 3). Control experiments showed that decarbonylation of the initially formed oxidative-addition product had taken place, since acid hydrolysis of the reaction mixture afforded the expected mixture of *N*-phthaloyl-α- and *N*-phthaloyl-β-alanines.[6] Thus, addition of benzoyl peroxide promotes the carbonylation of the intermediate nickelacycle **3**, probably by oxidation of the dicarbonyl Ni(0) complex **4**. Similarly, insertion of isocyanides can also be promoted by the addition of this oxidant. Thus, treatment of **3**, prepared as usual from anhydride **1** and complex **2**, with 2 equiv of *tert*-butyl isocyanide at room temperature for 2 h followed by addition of benzoyl peroxide (1.1 equiv) led, after hydrolysis, to (±)-*N*-phthaloyl-*N'*-*tert*-butylasparagine (**22**) in 80–90% yield (Scheme 3).[24]

Treatment of **3** with 1,4-benzoquinone gave a 4:1 ratio of diesters **23** and **24**, isolated in *ca.* 40% yield after methylation of the crude reaction mixture with excess diazomethane (eq 3). Again, the carbonyl group was



(3)

retained in this reaction. The poor regioselectivity observed in this reaction may be a consequence of the lower reactivity of the major nickelacycle toward hydroquinone. The assignment of the structures of the isolated esters was made by comparison with a 7:1 mixture of **23** and **24** prepared by reaction of anhydride **1** with hydroquinone, followed by methylation.[25] The structure for the major regioisomer **23** was secured by acetylation of the phenolic hydroxyl and oxidation with ceric ammonium nitrate,[26] yielding known methyl (±)-α-aspartate.[27]

The nickelacycles also react with some alkynes. Reaction of intermediate **3** with phenylacetylene at room temperature, followed by acid hydrolysis, led to a 1.5:1 mixture of **25** and **26** in 83% yield. When this reaction was performed at 66 °C, a 1:1.5 ratio of the same two products was obtained. Alkenyl **26** probably arises by insertion of the alkyne into the Ni–C bond, followed by hydrolysis of the alkenyl Ni(II) complex. The formation of alkyne **25** may be explained by an elimination reaction of the alkenyl Ni(II) complex. Accordingly, when the reaction between **3** and phenylacetylene was performed in the presence of pyrazole as a weakly acidic proton donor, the only product formed was alkene **26**, which was isolated as the methyl ester in 63% yield. On the other hand, reaction of **3** with 1-octyne yields only alkynyl derivative **27**, isolated in only 36% yield (eq 4). Internal alkynes, such as 4-octyne or dimethyl acetylenedicarboxylate, were not reactive with nickelacycle **3**.

Conclusions

The direct alkylation of the oxanickelacycle **3**, derived from an aspartic acid derivative, takes place smoothly with primary and secondary alkyl halides. The lack of reactivity of alkyl sulfonates and the results obtained with radical clocks point to the participation of a radical pair in the main reaction pathway. Oxidation of **3** with oxygen or

(21) For related oxidations of nickelacycles, see the following. (a) Oxidation with O_2: Herrera, A.; Hoberg, H. *Synthesis* **1981**, 831. Julia, M.; Lauron, H.; Verpeaux, J.-M. *J. Organomet. Chem.* **1990**, *387*, 365. (b) Oxidation with trimethylamine *N*-oxide: Hoberg, H.; Ballesteros, A. *J. Organomet. Chem.* **1991**, *387*, 365. See also ref 2b. (c) Oxidation with N_2O: Matsunaga, P. T.; Hillhouse, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 2075.

(22) Gani, D.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2393.

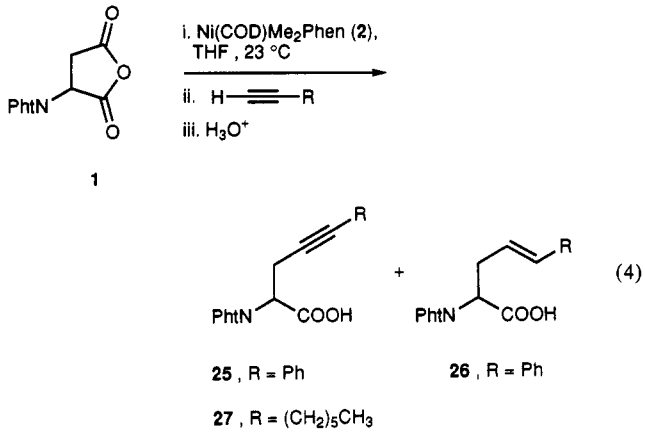
(23) For the use of benzoyl peroxide in oxidations catalyzed by Ni, see: Doyle, M. P.; Patrie, W. J.; Williams, S. B. *J. Org. Chem.* **1979**, *44*, 2955.

(24) Similarly, with a nickelacycle derived from (±)-glutamic anhydride, oxidation with benzoyl peroxide promoted the insertion of isocyanides: Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1993**, *34*, 4361.

(25) Nitrogen nucleophiles favor attack at the β-carbonyl group of aspartic acid anhydrides: King, F. E.; Kidd, D. A. A. *J. Chem. Soc.* **1951**, 243.

(26) Jacob, P.; Callery, P. S.; Shulzin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.

(27) Gani, D.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2393.



N-methylmorpholine *N*-oxide led to the formation of N-protected serine. Quite surprisingly, under certain conditions, products of carbonyl insertion were obtained. Benzoyl peroxide promotes the insertion of carbon monoxide or isocyanides into the Ni–C bond. 1-Alkynes also react with **3**, leading to insertion derivatives. These results demonstrate the synthetic potential of nickelacycles such as **3** in the straightforward preparation of N-protected α-amino acids from aspartic acid. However, in order to fully exploit these types of intermediates for the asymmetric synthesis of amino acids,[28] the racemization of the chiral nickel complexes has to be minimized. Further work directed to solve this problem by using a different N-protecting group is in progress.

Experimental Section

General Procedures. All reactions, except for the oxidations, were carried out under Ar. Solvents were dried by standard methods. Chromatographic purifications were carried out with columns packed with flash grade silica gel. Cyclooctadiene (COD) was distilled over CaH_2. $Ni(COD)_2$ was prepared by reduction of $Ni(py)_4Cl_2$ with Na in the presence of COD according to a known procedure.[29] Anhydride **1** was prepared in one step from aspartic acid and phthalic anhydride according to a known procedure.[25] Optically active anhydride **1** was prepared by dehydration of the N-protected aspartic acid with acetic anhydride according to a known procedure.[27] (Bromomethyl)cyclopropane (**11**),[30] (iodomethyl)cyclopropane (**12**),[30] 1-iodo-5-hexene (**13**),[31] 2-(allyloxy)ethyl iodide (**14**),[32] and 2-(allyloxy)ethyl bromide (**15**)[32] were prepared according to known procedures.

(±)-(2,9-Dimethyl-1,10-phenanthroline)(3-phthalimido-2-oxo-1-oxabutane-1,4-diyl)nickel (3) and (±)-(1,2-Bis(diphenylphosphino)ethane)(3-phthalimido-2-oxo-1-oxabutane-1,4-diyl)nickel (5). A solution of anhydride **1** (143 mg, 0.58 mmol) and Me_2Phen (182 mg, 0.87 mmol) in THF (10 mL) was added to $Ni(COD)_2$ (240 mg, 0.87 mmol). The resulting mixture was stirred at 23 °C for 1.5 h to give a dark red suspension. The suspension was filtered off and washed with Et_2O (3 × 3 mL) to give an air-sensitive orange solid in *ca.* 80% yield (determined by acid hydrolysis and isolation of *N*-phthaloyl-α-alanine): IR (Nujol) 1768, 1708, 1662, 1385, 1325, 725 cm^{-1}. The purple filtrate was concentrated and cooled to −15 °C to give a purple solid, characterized as dicarbonyl(2,9-dimethyl-1,10-phenanthroline)-nickel: IR (Nujol) 1983, 1890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 8.2 Hz, 2 H), 7.76 (s, 2 H), 7.69 (d, J = 8.1 Hz, 2 H), 3.26 (s, 6 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 196.76, 159.65, 144.21, 134.65, 127.54, 125.32, 124.24, 27.66. Complex **3** was transformed into **5** as follows: complex **3** (obtained from 0.29 mmol of **1** and 0.44 mmol of $Ni(COD)Me_2Phen$) was treated with a solution of 1,2-bis(diphenylphosphino)ethane (dppe; 175 mg, 0.44 mmol) in CH_2Cl_2 (3 mL) and stirred at 23 °C for 16 h. The yellow suspension was filtered, and the solid was recrystallized from CH_2Cl_2 (−15 °C for 3 days) to give **3** in *ca.* 30% yield, after washing with Et_2O (2 × 1 mL), as a yellow air-sensitive solid: IR (Nujol) 1710, 1650, 1380, 1325 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02–7.30 (m, 24 H), 4.96 (ddd, J = 11.9, 7.2, 1.1 Hz, 1H, CH α), 2.4–2.0 (m, 2 H, PCH_2), 1.9–1.8 (m, 2 H, PCH_2), 1.52–1.42 (m, 1 H, CH β), 1.04–0.98 (m, 1 H, CH β'); $^1H\{^{31}P\}$ NMR (300 MHz, $CDCl_3$) δ 8.01–7.30 (m, 24 H), 4.96 (dd, J = 11.9, 7.2 Hz, 1 H), 2.3–2.1 (m, 2 H), 1.9–1.7 (m, 2 H), 1.47 (dd, J = 11.8, 9.8 Hz, 1 H), 1.02 (dd, J = 9.7, 7.2 Hz, 1 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 181.65 (d, J = 10 Hz), 167.74, 133.59, 128.65 (m, 10 C, P–Ph), 133.16, 131.71, 129.95, 122.79, 53.89, 29.67 (dd, J = 30.4, 20.4 Hz, P–CH_2), 22.21 (dd, J = 29.4, 11.1 Hz, P–CH_2), 21.86 (dd, J = 57.7, 23.8 Hz, CH_2 β); ^{31}P NMR (121 MHz, $CDCl_3$) δ 59.33 (d, J = 7.8 Hz, 1 P), 35.20 (d, J = 7.8 Hz, 1 P). Hydrolysis of **3** or **5** with 1.2 M aqueous HCl at 23 °C gave (±)-*N*-phthaloyl-α-alanine as the major product in *ca.* 80% yield: ^1H NMR (200 MHz, DMSO-d_6) δ 7.95–7.81 (m, 4 H), 4.86 (q, J = 7.3 Hz, 1 H), 1.55 (d, J = 7.3 Hz, 3 H); $^{13}C\{^1H\}$ NMR (50 MHz, DMSO-d_6) δ 171.00, 167.12, 134.71, 131.29, 123.25, 46.96, 14.78. This compound was identical with a sample prepared from (±)-alanine.

Alkylation of Nickelacycle 3 (Table 1, Schemes 1 and 2). General Procedure. Anhydride **1** (186 mg, 0.76 mmol) was added to a solution of $Ni(COD)_2$ (275 mg, 1.0 mmol) and Me_2-Phen (208 mg, 1.0 mmol) in THF (15 mL). The reaction mixture was stirred at 23 °C for 5 h. Excess alkyl halide (10–20 equiv) was added, and stirring was continued at 23 or 40 °C. The mixture was treated with 1.2 M aqueous HCl and extracted with EtOAc (3×). The combined EtOAc solution was extracted with 5% aqueous $NaHCO_3$, acidified with 1.2 M HCl, and extracted with EtOAc (3×). The solution was dried (Na_2SO_4) and evaporated to give the crude N-protected amino acids.

(±)-2-Phthalimidobutyric acid (Table 1, entry 1) was characterized after benzylation with benzyl bromide (1 equiv) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 1 equiv) at 23 °C. Chromatography (6:1 hexane–EtOAc) gave the benzyl ester as a pale yellow oil: IR (neat) 3065, 3035, 2980, 1780, 1750, 1720, 1390, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2 H), 7.75–7.70 (m, 2 H), 7.31–7.29 (m, 5 H), 5.21 (AB system, part A, J = 17.9 Hz, 1 H), 5.15 (AB system, part B, J = 17.9 Hz, 1 H), 4.82 (t, J = 7.9 Hz, 1 H), 2.30 (quint, J = 7.6 Hz, 2 H), 0.94 (t, J = 7.4 Hz, 3 H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 169.12, 167.66, 135.29, 134.09, 131.74, 128.45, 128.20, 127.95, 123.42, 67.28, 53.83, 22.12, 10.84; MS m/z 324 (M^+ + 1, 0.5), 217 (32), 188 (100), 160 (36), 91 (72), 76 (29); high-resolution mass spectrum calcd for $C_{19}H_{17}NO_4$ m/z 323.1158, found m/z 323.1146.

(±)-2-Phthalimidopentanoic acid (Table 1, entries 2 and 3): ^1H NMR (200 MHz, DMSO-d_6) δ 7.92–7.82 (m, 4 H), 4.73 (dd, J = 9.9, 5.7 Hz, 1 H), 2.22–1.94 (m, 2 H), 1.23 (sext, J = 7.7 Hz, 2 H), 0.84 (t, J = 7.3 Hz, 3 H); $^{13}C\{^1H\}$ NMR (50 MHz, DMSO-d_6) δ 170.62, 166.44, 134.83, 131.11, 123.36, 51.37, 30.05, 19.06, 13.19. Methylation with excess diazomethane in Et_2O, followed by chromatography (10:1 hexane–EtOAc), gave the methyl ester as a colorless oil: IR (neat) 2955, 2870, 1775, 1750, 1715, 1390, 720 cm^{-1}; MS m/z 261 (M^+, 2), 202 (44), 160 (100), 130 (29), 104 (11); high-resolution mass spectrum calcd for $C_{14}H_{15}NO_4$ m/z 261.1001, found m/z 261.1005. Scalemic *N*-phthalimidopentanoic acid was similarly transformed into the methyl ester ($[\alpha]_D$ −10.4°, $[\alpha]_{436}$ −20.0° (ee 50%)), which was shown to be identical spectroscopically with a sample prepared from L-phthalimidopentanoic acid ($[\alpha]_D$ −20.96°, $[\alpha]_{436}$ −40.4° (*c* 1, $CHCl_3$)).

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(±)-2-Phthalimidoheptanoic acid (Table 1, entries 4–7): ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.98–7.78 (m, 4 H), 4.71 (dd, J = 8.8, 6.8 Hz, 1 H), 2.20–2.05 (m, 2 H), 1.28–1.08 (m, 6 H), 0.85–0.70 (m, 3 H). Methylation with excess diazomethane in Et_2O, followed by chromatography (10:1 hexane–EtOAc) gave the methyl ester as a colorless oil: IR (neat) 2960, 2930, 2860, 1780, 1750, 1720, 1390, 720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88–7.83 (m, 2 H), 7.75–7.71 (m, 2 H), 4.83 (dd, J = 9.6, 6.2 Hz, 1 H), 3.71 (s, 3 H), 2.30–2.15 (m, 2 H), 1.45–1.26 (m, 6 H), 0.88–0.78 (m, 3 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 169.94, 167.67, 134.12, 131.82, 123.48, 52.59, 31.01, 28.58, 25.92, 22.30, 13.85; MS m/z 289 (M^+, 1), 230 (34), 160 (100), 130 (22), 104 (17), 41 (29); high-resolution mass spectrum calcd for $C_{16}H_{19}NO_4$ m/z 289.1314, found m/z 289.306.

(±)-*N*-Phthaloylleucine (Table 1, entry 8): ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.95–7.82 (m, 4 H), 4.77 (dd, J = 11.4, 4.4 Hz, 1 H), 2.17 (ddd, J = 14.0, 11.4, 4.2 Hz, 1 H), 1.91–1.77 (m, 1 H), 1.52–1.35 (m, 1 H), 0.86 (d, J = 6.5 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C{^{1}H} NMR (50 MHz, DMSO-d_6) δ 170.79, 167.44, 134.84, 131.08, 123.38, 50.11, 36.72, 24.62, 22.95, 20.80. The spectroscopic data are in agreement with those reported.[33]

(±)-3-Cyclohexyl-2-phthalimidopropionic acid (Table 1, entry 9): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90–7.65 (m, 4 H), 5.00 (dd, J = 11.1, 4.5 Hz, 1 H), 2.35–2.22 (m, 2 H), 2.07–1.93 (m, 1 H), 1.87–1.80 (m, 10 H). Methylation with excess diazomethane in Et_2O, followed by chromatography (10:1 hexane–EtOAc), gave the methyl ester as a colorless oil: IR (neat) 2930, 2855, 1770, 1760, 1720, 1390, 1260, 720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89–7.87 (m, 2 H), 7.77–7.74 (m, 2 H), 4.98 (dd, J = 11.2, 4.5 Hz, 1 H), 3.72 (s, 3 H), 2.35–2.21 (m, 1 H), 2.11–1.90 (m, 1 H), 1.89–1.75 (m, 2 H), 1.72–1.46 (m, 4 H), 1.25–0.80 (m, 7 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 170.35, 167.70, 134.10, 131.85, 123.49, 52.64, 49.93, 35.89, 34.32, 33.64, 31.68, 26.34, 26.08, 25.83; MS m/z 315 (M^+, 1), 256 (11), 219 (11), 174 (100), 163 (25), 130 (22); high-resolution mass spectrum calcd for $C_{18}H_{21}NO_4$ m/z 315.1471, found m/z 315.1475.

(±)-*N*-Phthaloylhomophenylalanine (7) and (±)-5-Phenyl-2-phthalimido-4-oxopentanoic Acid (8) (Scheme 1). Methylation with excess diazomethane in Et_2O, followed by chromatography (10:1 hexane–EtOAc), gave partially purified samples of the methyl esters. Methyl ester of **7**: IR (neat) 3030, 2955, 1780, 1750, 1720, 1390, 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.82 (m, 2 H), 7.75–7.71 (m, 2 H), 7.22–7.08 (m, 5 H), 4.90–4.86 (m, 1 H), 3.72 (s, 3 H), 2.71–2.55 (m, 4 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 169.68, 167.62, 140.22, 134.09, 131.81, 128.36, 126.03, 123.45, 52.70, 51.87, 32.64, 29.95. Methyl ester of **8**: IR (neat) 3030, 2960, 1780, 1750 (br), 1725, 1390, 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2 H), 7.73–7.70 (m, 2 H), 7.25–7.16 (m, 5 H), 5.46 (dd, J = 7.7, 6.3 Hz, 1 H), 3.75 (m, 2 H), 3.69 (s, 3 H), 3.52 (dd, J = 17.7, 6.3 Hz, 1 H), 3.19 (dd, J = 17.7, 7.7 Hz, 1 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 203.73, 169.16, 167.09, 134.13, 133.18, 131.68, 129.40, 128.68, 127.08, 123.48, 52.91, 50.09, 47.48, 40.79.

(±)-2-Phthalimido-4-oxo-6-heptenoic Acid (9) (Scheme 1). Benzylation with benzyl bromide (1 equiv) and DBU (1 equiv) at 23 °C, followed by chromatography (6:1 hexane–EtOAc), gave the benzyl ester of (±)-2-phthalimido-4-oxo-5-heptenoic acid: IR (neat) 3025, 2960, 2920, 2850, 1780, 1745 (br), 1720, 1390, 720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86–7.80 (m, 2 H), 7.76–7.69 (m, 2 H), 7.33–7.20 (m, 5 H), 6.89 (dq, J = 15.8, 6.8 Hz, 1 H), 6.11 (dq, J = 15.8, 1.6 Hz, 1 H), 5.61 (dd, J = 8.2, 5.8 Hz, 1 H), 5.17 (s, 2 H), 3.62 (dd, J = 17.5, 5.8 Hz, 1 H), 3.41 (dd, J = 17.6, 8.2 Hz, 1 H), 1.87 (dd, J = 6.8, 1.6 Hz, 3 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 195.31, 168.86, 167.38, 144.04, 135.07, 134.15, 131.36, 128.32, 127.99, 123.54, 67.73, 47.83, 38.75, 18.27; MS m/z 286 (6), 228 (38), 271 (77), 160 (21), 91 (93), 69 (100); high-resolution mass spectrum calcd for $C_{22}H_{19}NO_5$ m/z 377.1263, found m/z 377.1271.

(±)-2-Phthalimido-5-hexenoic acid (10) (Scheme 1): IR (neat) 3500–2500 (br), 2930, 1770, 1720, 1390, 1250, 1025, 995, 720 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.92–7.81 (m, 4 H), 5.75 (ddt, J = 17.0, 10.4, 6.5 Hz, 1 H), 5.01–4.84 (m, 2 H), 4.73 (t, J = 7.5 Hz, 1 H), 2.18 (t, J = 6.9 Hz, 2 H), 2.04 (m, 2 H); ^{13}C{^{1}H} NMR (50 MHz, DMSO-d_6) δ 170.45, 167.43, 137.17, 134.81, 131.13, 123.34, 115.60, 51.18, 29.93, 27.25; MS m/z 260 (M^+ + 1, 4), 259 (M^+, 7), 205 (92), 187 (98), 174 (60), 173 (30), 160 (75), 148 (87), 132 (81), 130 (100), 57 (95), 84 (57), 76 (80), 66 (95); high-resolution mass spectrum calcd for $C_{14}H_{13}NO_4$ m/z 259.0845, found m/z 259.0846.

(±)-2-Phthalimido-6-heptenoic acid (16) (Scheme 2). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95–7.82 (m, 4 H), 5.73 (ddt, J = 17.1, 10.3, 6.7 Hz, 1 H), 5.09–4.84 (m, 2 H), 4.72 (t, J = 7.8 Hz, 1 H), 2.15–1.98 (m, 4 H), 1.38–1.23 (m, 2 H). Methylation with excess diazomethane in Et_2O, followed by chromatography (8:1 hexane–EtOAc), gave the methyl ester as a colorless oil: IR (neat) 2920, 2885, 1780, 1745, 1715, 1390, 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.86 (m, 2 H), 7.76–7.73 (m, 2 H), 5.75 (ddt, J = 17.0, 10.3, 6.7 Hz, 1 H), 5.03–4.82 (m, 3 H), 3.73 (s, 3 H), 2.30–2.22 (m, 2 H), 2.18–2.04 (m, 2 H), 1.48–1.40 (m, 2 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 169.82, 167.67, 137.86, 134.17, 131.86, 123.55, 115.13, 52.68, 52.04, 32.94, 28.19, 25.63; MS m/z 288 (M^+ + 1, 17), 228 (38), 219 (77), 187 (41), 160 (51), 148 (100), 41 (20); high-resolution mass spectrum calcd for $C_{16}H_{17}NO_4$ m/z 287.1158, found m/z 287.1157.

(±)-2-Phthalimido-8-nonenoic Acid (17) (Scheme 2). Methylation with excess diazomethane in Et_2O, followed by chromatography (5:1 hexane–EtOAc), gave the methyl ester as a colorless oil: IR (neat) 2930, 2855, 1775, 1745, 1720, 1390, 720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.91–7.83 (m, 2 H), 7.78–7.70 (m, 2 H), 5.76 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H), 5.00–4.79 (m, 3 H), 3.73 (s, 3 H), 2.35–1.92 (m, 4 H), 1.60–1.23 (m, 6 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 169.94, 167.70, 138.82, 134.16, 131.87, 123.54, 114.34, 52.66, 52.18, 33.56, 28.62, 28.56, 28.36, 26.15; MS m/z 256 (5), 219 (5), 160 (56), 104 (89), 76 (100); high-resolution mass spectrum calcd for $C_{18}H_{21}NO_4$ m/z 315.1471; found m/z 315.1474.

(±)-2-Phthalimido-4-(tetrahydro-3-furanyl)butanoic Acid (18) (Scheme 2). Methylation with excess diazomethane in Et_2O of the 4.5:1 ratio of cyclic to linear products, followed by chromatography (5:1 hexane–EtOAc), gave the methyl esters of the major compound as a 1:1 mixture of diastereomers: IR (neat) 2950, 2930, 2850, 1780, 1745, 1720, 1395, 720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.86 (m, 2 H), 7.77–7.74 (m, 2 H), 4.86–4.80 (m, 1 H), 3.90–3.68 (m, 4 H), 3.78 (s, 3 H), 3.34–3.28 (m, 1 H), 2.30–1.99 (m, 4 H), 1.53–1.33 (m, 2 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 169.62, 167.63, 134.26, 131.67, 123.60, 73.27 (73.05), 67.88, 52.78, 52.12 (52.07), 38.82 (38.75), 32.38 (32.03), 30.10 (29.97), 27.85 (27.68) (signals in parentheses are for the diastereomer); MS m/z 318 (M^+ + 1, 7), 317 (M^+, 8), 258 (45), 219 (24), 160 (100). From the recovered halide, 3-(iodomethyl)tetrahydrofuran (**21**) was detected by GC–MS as the higher retention peak, with MS m/z 212 (M^+) and 55 (M^+ – I – CH_2O).

Synthesis of (±)-*N*-Phthaloylserine (21) by Oxidation of Nickelacycle 3 (Eq 2). (a) Oxidation with O_2. A mixture prepared from anhydride **1** (133 mg, 0.54 mmol), Me_2Phen (170 mg, 0.81 mmol), and Ni(COD)$_2$ (224 mg, 0.81 mmol) in THF (10 mL) at 23 °C for 13 h was saturated with O_2 and stirred under O_2 (1 atm) for 18 h at 23 °C. After the usual workup (hydrolysis and extraction) **21** was obtained in 32% yield.

(b) Oxidation with NMMO. To the mixture prepared from anhydride **1** (158 mg, 0.64 mmol), Me_2Phen (201 mg, 0.97 mmol), and Ni(COD)$_2$ (266 mg, 0.97 mmol) in THF (14 mL) at 23 °C for 8.5 h was added NMMO (284 mg, 2.42 mmol) in DMF (3 mL). The resulting mixture was stirred at 23 °C for 60 h. After the usual workup, **21** was obtained in 47% yield: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.98–7.82 (m, 4 H), 4.84 (dd, J = 9.8, 5.2 Hz, 1H), 4.05 (dd, J = 11.4, 9.9 Hz, 1 H), 3.97 (dd, J = 11.7, 5.4 Hz, 1 H). Methylation with excess diazomethane in Et_2O gave the methyl ester: IR (KBr) 3580–3370 (br), 1780, 1745, 1715, 1400, 1255, 720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90–7.86 (m, 2 H), 7.77–7.73 (m, 2 H), 5.03 (t, J = 5.0 Hz, 1 H), 4.21–4.19 (m, 2 H), 3.78 (s, 3 H), 3.58–3.40 (br s, 1 H); ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ

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168.47, 168.04, 134.45, 131.70, 123.75, 61.04, 54.73, 52.85; MS *m/z* 250 ($M^+ + 1$, 2), 249 (M^+, 1), 219 (86), 190 (91), 187 (100), 172 (52), 104 (96). The spectroscopic data are in agreement with those of a sample prepared from L-serine.[33]

(±)-*N*-Phthaloylaspartic Acid β-*tert*-Butyl Amide (22) (Scheme 3). A mixture prepared from anhydride **1** (110 mg, 0.45 mmol), Me_2Phen (140 mg, 0.67 mmol), and $Ni(COD)_2$ (185 mg, 0.67 mmol) in THF (8 mL) at 23 °C for 5 h was treated with *tert*-butyl isocyanide (150 μL, 110 mg, 1.33 mmol). After being stirred at 23 °C for 2 h, addition of benzoyl peroxide (177 mg, 0.73 mmol) led to a dark green reaction mixture, which was stirred at 23 °C for 5 h. After the usual workup (hydrolysis and extraction), **22** was obtained in 80–90% yield: ^1H NMR (200 MHz, DMSO-d_6) δ 7.90–7.71 (m, 4 H), 5.19 (dd, J = 8.1, 6.6 Hz, 1 H), 3.00 (dd, J = 14.9, 6.6 Hz, 1 H), 2.66 (dd, J = 14.9, 8.2 Hz, 1 H), 1.14 (s, 9 H); $^{13}C\{^1H\}$ NMR (50 MHz, DMSO-d_6) δ 170.17, 168.16, 166.92, 134.72, 131.17, 123.23, 49.89, 48.42, 35.66, 29.27. The structure was confirmed by comparison with a sample prepared by reaction of anhydride **1** with excess *tert*-butylamine in THF at 23 °C.

Reaction with 1,4-Benzoquinone (Eq 3). A mixture prepared from anhydride **1** (112 mg, 0.46 mmol), Me_2Phen (142 mg, 0.68 mmol), and $Ni(COD)_2$ (188 mg, 0.68 mmol) in THF (10 mL) at 23 °C for 10 h was treated with 1,4-benzoquinone (180 mg, 1.67 mmol) in THF (3 mL) to give a light brown reaction mixture. After being stirred for 15 h at 23 °C, the mixture was hydrolyzed and extracted with EtOAc. Esterification with excess diazomethane and chromatography (4:1 hexane–EtOAc) gave a 4:1 mixture of esters **23** and **24** in *ca.* 40% yield. The structure was confirmed by comparison with a 7:1 mixture of the same esters prepared from anhydride **1** and hydroquinone in the presence of pyridine (1 equiv each) and 4-(dimethylamino)pyridine (catalytic amount) in THF under reflux. The major isomer **23** showed the following spectroscopic data: IR (KBr) 3640–3200, 2960, 2930, 1780, 1755, 1720, 1605, 1510, 1470, 1445, 1395, 1190, 1110, 720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.89–7.84 (m, 2 H), 7.75–7.71 (m, 2 H), 6.88–6.84 (m, 2 H), 6.74–6.69 (m, 2 H), 6.4–6.2 (br, 1 H), 5.48 (dd, J = 8.6, 6.2 Hz, 1 H), 3.77 (s, 3 H), 3.59 (dd, J = 16.6, 6.2 Hz, 1 H), 3.30 (dd, J = 16.6, 8.6 Hz, 1 H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.23, 168.64, 167.33, 153.89, 143.29, 134.44, 131.41, 123.73, 122.05, 115.85, 53.27, 48.11, 34.13; MS *m/z* 369 (M^+, 3), 260 (55), 232 (79), 200 (100). The regiochemistry of the major compound **23** was determined as follows: A 4:1 mixture of **23** and **24** (16 mg, 0.04 mmol) was dissolved in acetic anhydride (0.5 mL), and a catalytic amount of concentrated H_2SO_4 was added. After being stirred at 23 °C for 15 h, the mixture was poured into ice–water. Extractive workup and chromatography (4:1 hexane–EtOAc) gave a 4:1 mixture of the corresponding acetates (12 mg, 73%) as a semisolid. The major acetate showed the following spectroscopic data: IR (neat) 2950, 2930, 1760, 1720, 1505, 1495, 1175, 1210, 1180, 1150, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.86 (m, 2 H), 7.76–7.73 (m, 2 H), 7.08–7.06 (m, 4 H), 5.48 (dd, J = 8.5, 6.2 Hz, 1 H), 3.77 (s, 3 H), 3.61 (dd, J = 16.6, 6.2 Hz, 1 H), 3.32 (dd, J = 16.6, 8.6 Hz, 1 H), 2.26 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.19 (d, J = 6.1 Hz), 168.47 (br s), 168.37 (br s), 167.18 (br s), 148.25 (t, J = 5.7 Hz), 147.76 (t, J = 5.8 Hz), 134.42 (dd, J = 163.9, 6.8 Hz), 131.73 (t, J = 6.3 Hz), 123.77 (dd, J = 170.5, 4.9 Hz), 122.77 (dd, J = 168.3, 7.1 Hz), 122.55 (dd, J = 162.0, 7.8 Hz), 53.24 (q, J = 148.2 Hz), 48.20 (dt, J = 139.0, 4.9 Hz), 34.34 (td, J = 133.4, 5.6 Hz), 21.02 (q, J = 130.0); MS *m/z* 411 (M^+, 1), 260 (81), 232 (96), 200 (100). Oxidation of the above mixture of acetates (13 mg, 0.035 mmol) in acetonitrile (1.5 mL) with ceric ammonium nitrate (66 mg, 0.12 mmol) in water (1 mL) at 23 °C for 1.5 h, followed by extractive workup and chromatography, gave α-methyl (±)-*N*-phthaloylaspartate as a semisolid (5 mg, 71%): IR (neat) 3500–2800, 2960, 2930, 2855, 1780, 1760, 1745, 1400, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.86 (m, 2 H), 7.77–7.74 (m, 2 H), 5.38 (dd, J = 8.5, 6.2 Hz, 1 H), 3.75 (s, 3 H), 3.44 (dd, J = 17.1, 6.2 Hz, 1 H), 3.16 (dd, J = 17.1, 8.4 Hz, 1 H). The spectroscopic data were in agreement with those reported for this ester.[27]

(±)-5-Phenyl-2-phthalimido-4-pentynoic Acid (25) and (±)-(*E*)-5-Phenyl-2-phthalimido-4-pentenoic Acid (26) (Eq 4). **25**: ^1H NMR (300 MHz, DMSO-d_6) δ 7.95–7.78 (m, 4 H), 7.25–7.20 (m, 5 H), 5.12 (dd, J = 9.5, 6.7 Hz, 1 H), 3.40–3.15 (m, 2 H). **26**: ^1H NMR (300 MHz, DMSO-d_6) δ 7.95–7.78 (m, 4 H), 7.25–7.20 (m, 5 H), 6.37 (d, J = 16.0 Hz, 1 H), 6.19 (m, 1 H), 4.93 (dd, J = 9.9, 5.6 Hz, 1 H), 3.10–2.90 (m, 2 H). Benzylation with enzyl bromide (1 equiv) in the presence of DBU (1 equiv) at 23 °C gave a mixture of esters, which could not be separated by chromatography. Benzyl ester of **25**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.89–7.86 (m, 2 H), 7.73–7.71 (m, 2 H), 7.35–7.14 (m, 10 H), 5.26–5.16 (m, 3 H), 3.45 (dd, J = 17.3, 10.7 Hz, 1 H), 3.33 (dd, J = 17.4, 5.2 Hz, 1 H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) (only significant signals) δ 167.77, 167.26, 84.49, 82.85, 67.76, 51.10, 20.58. Benzyl ester of **26**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.78 (m, 2 H), 7.70–7.67 (m, 2 H), 7.35–7.14 (m, 10 H), 6.42 (dt, J = 15.8, 1.3 Hz, 1 H), 6.09 (m, 1H), 5.26–5.16 (m, 2 H), 5.07 (dd, J = 9.0, 6.8 Hz, 1 H), 3.21–3.15 (m, 2 H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) (only significant signals) δ 168.82, 167.56, 67.66, 52.02, 32.66. When the reaction between the nickelacycle and phenylacetylene was carried out in the presence of pyrazole, **26** was isolated as the only compound. Esterification with excess diazomethane and chromatography (6:1 hexane–EtOAc) gave the methyl ester of **26** as a pale yellow oil: IR (neat) 3015, 2960, 2930, 1780, 1750, 1720, 1390, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2 H), 7.71–7.67 (m, 2 H), 7.22–7.20 (m, 5 H), 6.42 (d, J = 15.7, 1 H), 6.15–6.05 (m, 1 H), 5.02 (m, 1 H), 3.76 (s, 3 H), 3.18–3.13 (m, 2 H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 169.16, 167.46, 136.62, 134.06, 133.49, 131.60, 128.30, 127.25, 126.08, 124.70, 123.42, 52.70, 51.76, 32.59; MS *m/z* 322 ($M^+ - 15$, 1). 276 (5), 174 (28), 130 (56), 129 (100), 128 (41), 77 (43), 76 (41), 50 (43); high-resolution mass spectrum calcd for $C_{20}H_{17}NO_4$ *m/z* 335.1158, found *m/z* 335.1160.

(±)-2-Phthalimido-4-undecynoic Acid (27) (Eq 4). Esterification with excess diazomethane and chromatography (10:1 hexane–EtOAc) gave the methyl ester of **27** as a colorless oil: IR (neat) 2950, 2925, 2850, 1775, 1750, 1720, 1390, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88–7.86 (m, 2 H), 7.76–7.73 (m, 2 H), 4.84 (dd, J = 10.1, 5.6 Hz, 1 H), 3.73 (s, 3 H), 2.30–2.18 (m, 2 H), 1.35–1.20 (m, 10 H), 0.88–0.82 (m, 3 H); $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ 169.49, 167.19, 134.93, 130.91, 123.47, 78.90, 75.11, 52.47, 51.33, 31.01, 28.16, 27.96, 25.41, 21.89, 13.79; MS *m/z* 281 (100), 219 (25), 160 (98); high-resolution mass spectrum calcd for $C_{20}H_{23}NO_4$ *m/z* 341.1627, found *m/z* 341.1626.

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