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Efficient Synthesis of Symmetrical α,α-Disubstituted β-Amino Acids and α,α-Disubstituted Aldehydes via Dialkylation of Nucleophilic β-Alanine Equivalent

Daizong Lin, Guanghui Deng, Jiang Wang, Xiao Ding, Hualiang Jiang, and Hong Liu*

The Center for Drug Discovery and Design, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 201203, People's Republic of China

hliu@mail.shcnc.ac.cn

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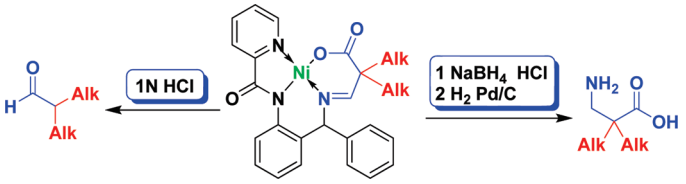

Homologation of the nucleophilic β-alanine equivalent β-Ala Ni(II)-PABP [Ni(II) complex of β-alanine Schiff base with 2-[*N*-(α-picolyl)amino]benzophenone (PABP), **1**] via alkyl halide alkylation was systematically studied as a general method for preparing symmetrically α,α-disubstituted β-amino acids. The dialkylation reactions could be easily performed and did not require inert atmosphere, dried solvents, and low temperatures, thereby affording the benefits of operationally convenient experimental procedure and high atom economy. Further, the methodology developed by us can also be used to generate symmetrical α,α-disubstituted aldehydes through an alternative decomposition method.

Introduction

α,α-Dialkyl β-alanines are useful building blocks in potent pharmaceutical drugs and functional materials.[1] For instance, α,α-dialkyl β-alanines are a constituent of cryptophycin fragment A,[2] adenosine analogues,[3] and inhibitors of protein kinase and diacylglycerol acyltransferase 1 (DGAT1).[4] Furthermore, the biological properties and applications of these substituted compounds, for example, as sterically constrained scaffolds for the rational design of peptides and proteins, still await systematic studies. Therefore, the development of efficient synthetic methods of these compounds has received much attention. To date, the Mannich reaction[5] and the alkylation of β-alanine derivatives[6] have commonly been utilized as synthetic routes to α,α-disubstituted β-amino acids; in addition, other routes such as the hydrogenation of 2-cyanoacetic acid derivatives,[7] Mitsunobu reaction,[8] and reductive amination[4] have been reported. These approaches employ relatively rare substances and therefore require restrained reaction conditions that might limit their broad synthetic applications. Although there exist a number of methods for the preparation of α,α-dialkyl β-alanines, these methods mainly focus on the synthesis of α,α-dimethyl β-alanine; thus, very few substituted variants have

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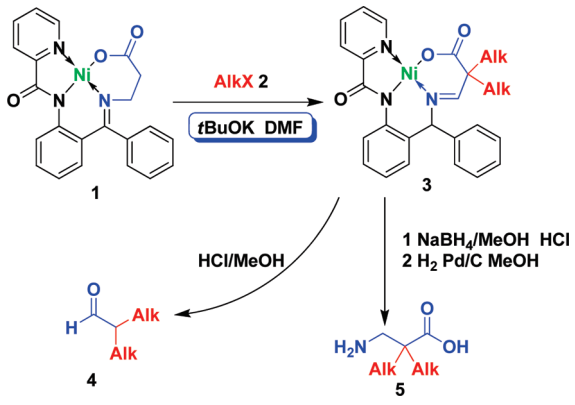
been synthesized until date. In particular, cyclic α,α-disubstituted β-amino acids are considered as good candidates for drug design.[9] However, despite the substantial interest in these amino acids and their applications in drug design, there are few synthetic approaches for preparing these compounds, with most of them being rather impractical.

During the preparation of α,α-disubstituted β-alanines in this study, we unexpectedly obtained α,α-disubstituted aldehydes. The α,α-disubstituted aldehydes are commonly utilized in organic synthesis and medical chemistry,[10] but there are few reports on the synthesis of these compounds.[11] We accidentally obtained α,α-disubstituted aldehydes while synthesizing β-amino acids. To our knowledge, this is the first example of the method to prepare aldehydes from β-Ala Ni(II)-PABP.

Recently, the Ni(II) complex of glycine Schiff base has been widely used to synthesize amino acids.[12] The PABP ligand was introduced by Soloshonok's group[13] and was utilized in the preparation of α-amino acids successfully.[14] In particular, PABP and the new generation of the ligand were shown to be very efficient for preparation of *sym*-α,α-disubstituted α-amino acids and therefore can be further applied for the synthesis of the corresponding β-derivatives.[15] Subsequently, a convenient one-pot, two-step protocol to generate novel nucleophilic β-alanine equivalent, namely β-Ala Ni(II)-PABP **1**, has been reported and employed in the synthesis of β-amino acids derivatives.[16] Herein, we report that the alkylation of β-Ala Ni(II)-PABP directly afforded a dialkylated product of the Ni(II) complex

SCHEME 1. Synthesis of α,α-Disubstituted β-Amino Acids and α,α-Disubstituted Aldehydes via a Ni(II) Complex



3, which can be hydrolyzed through two methods to yield α,α-disubstituted aldehydes **4** and amino acids **5**, respectively (Scheme 1).

Results and Discussion

Dialkylation of Ni(II) Complex 1 and 1-(Bromomethyl)-4-nitrobenzene 2a Using Various Bases and Solvents at Different Temperatures. We investigated the reaction of **1** with 1-(bromomethyl)-4-nitrobenzene **2a**, which was used as the model substrate, using 2-[*N*-(α-picolyl)amino]benzophenone as the achiral nucleophilic equivalent and optimized the reaction conditions, including bases, solvents, and temperatures, as summarized in Table 1. In the preparation of alkyl-substituted α-amino acid,[15] we selected potassium hydroxide as the base for alkylation of the Ni(II) complex **1** and performed the reaction in dimethyl formamide (DMF). However, we failed to obtain the Ni(II) complex of α,α-disubstituted β-amino acid **3a** (Table 1, entry 1). This result is likely due to the poor solubility of potassium hydroxide in DMF. Subsequently, we investigated a variety of alternative bases. DBU produced the same result as that of potassium hydroxide (Table 1, entry 2); therefore, we employed strong bases such as KH, *t*-BuONa, and *t*-BuOK (Table 1, entries 3−5). As we expected, 3 equiv of *t*-BuOK afforded the Ni(II) complex **3a** in 60% yield (Table 1, entry 5). With the view of industrial application, we determined if a smaller amount of equiv of the base provided similar yields. The reaction of benzylic bromide **2a** with **1** in the presence of 2 equiv of *t*-BuOK afforded the diallylated complex **3a** in 45% yield (Table 1, entry 4); similar results were obtained using 3 and 4 equiv of *t*-BuOK. Optimization of the solvents revealed that DMF was more superior than others solvents (Table 1, entries 5, 7, and 8). Further optimization studies established that the reaction with the base *t*-BuOK and DMF afforded good yields at various temperatures from +60 to −20 °C (Table 1, entries 5, 10−13). Lowering the temperature decreased the reaction rate and the conversion. Further, an increase in the reaction time lowered the yields of the target products. From the viewpoint of practical applications, we selected *t*-BuOK as a base and DMF as a solvent at ambient temperature and investigated the general utility of the dialkylation reaction (Table 1, entry 5).

Dialkylation between Ni(II) Complex 1 and 2. After the reaction conditions were optimized, the generality of the

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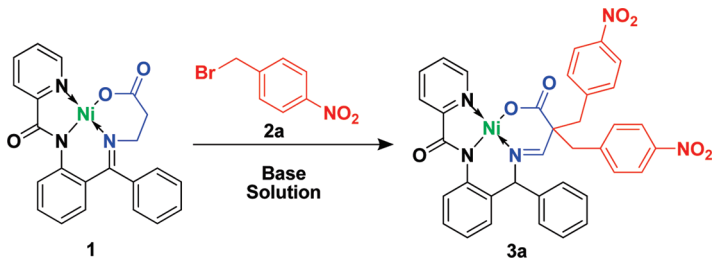
TABLE 1. Optimization of the Reaction Conditions[a]



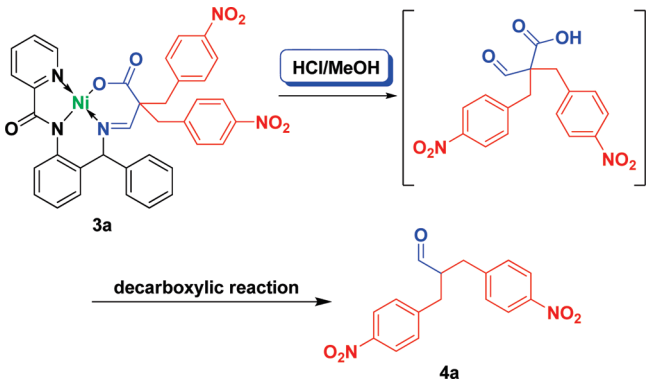
entry	base	solution	equiv of base	temp (°C)	yield (%)
1	KOH	DMF	10	20	0
2	DBU	DMF	3	20	0
3	KH	DMF	3	20	10
4	*t*-BuONa	DMF	3	20	30
5	*t*-BuOK	DMF	3	20	60
6	*t*-BuOK	DMF	2	20	45
7	*t*-BuOK	DMF	4	20	60
8	*t*-BuOK	CH_2Cl_2	3	20	0
9	*t*-BuOK	*t*-BuOH	3	20	0
10	*t*-BuOK	DMF	3	−20	47
11	*t*-BuOK	DMF	3	0	54
12	*t*-BuOK	DMF	3	40	60
13	*t*-BuOK	DMF	3	60	62

[a]Reactions were run with 0.47 mmol of **1** and 1.34 mmol of **2a** in 2 mL of solvent for 4 h.

reaction was investigated. The results are summarized in Table 2. The applications of halides show that the reaction has broad applicability. In general, functionalized benzyl bromide derivatives are excellent substrates for the reaction, regardless of their electronic effect. The aromatic system bearing electron-donating and electron-withdrawing groups is well tolerated (Table 2, entries 1−5). Further, we investigated the steric effect of benzyl bromide. Three regioisomeric benzyl bromine derivatives were applied in the dialkylation reaction, and equal yields were achieved (Table 2, entries 6−8). The reactivity of benzyl bromide for different allylic halides was as follows: allylic iodide > allylic bromide > allylic chloride, comparison of reactivities is shown in Table 2 (Table 2 entries 9−11), which was a typical characteristic of alkyl reactions. This method could be applied to other allylic halides to afford the corresponding products in moderate yields (Table 2, entries 12 and 13). The use of the activated alkyl halide, namely, iodomethane decreased the chemical yield (Table 2, entry 14) due to the low stability in the reaction conditions, and no product was obtained when the iodobutane was used (Table 2, entry 15). We found that the benzyl products were obtained in lower yields than the allylic ones. This result may be consistent with the view that activated stable alkyl halides with low steric hindrance afford dialkylated products in good yields. Under similar conditions, the cyclic compound (Table 2, entry 16) was obtained in lower yield (35%).

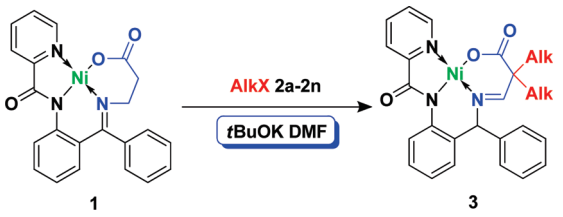
Decomposition of Products 3a and 3b. The analysis of ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra of the product **3a** revealed a C−N double bond shift in the structure. In addition, the hydrolysis of compound **3a** under standard conditions by stirring the suspension of **3a** in methanol/1 N HCl afforded the product 2,2-di(4-nitrobenzyl)acetaldehyde **4a** in high yield (90%) rather than, the target amino acid (α,α-disubstituted *β*-amino acids). To confirm this result, we performed single-crystal X-ray analysis of the major product **3a** formed by the reaction of Ni(II) complex **1** with **2a**. The results indicated a C−N double bond shift, which was due to a base-catalyzed 1,3-proton shift across the azaallylic system. The transposition of the imine-functionality increased the acidity of α-position to the carboxylic group resulting the bis-alkylation of the same methelyene, which explained the formation of α,α-disubstituted aldehydes. Under these conditions, the hydrolysis of compound **3** might generate *β*-aldehyde acids intermediates and undergo subsequent decarboxylation to produce α,α-disubstituted aldehydes (Scheme 2).

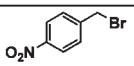
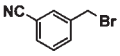
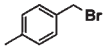
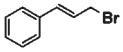
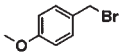
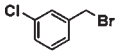
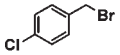
SCHEME 2. Decomposition of Ni(II) Complex 3 to Release Aldehyde 4



However, since various symmetrical α,α-disubstituted *β*-amino acids have several important applications, it was more important to develop a simple and practical method for preparing these compounds. Hydrogenation of the C−N double bond in **3b** was attempted under several conditions (Pd/C, $NaBH_4$, and Raney Ni). $NaBH_4$ catalyzed the hydrogenation of **3b**. Subsequently, methanol/1 N HCl was added to this reaction mixture at

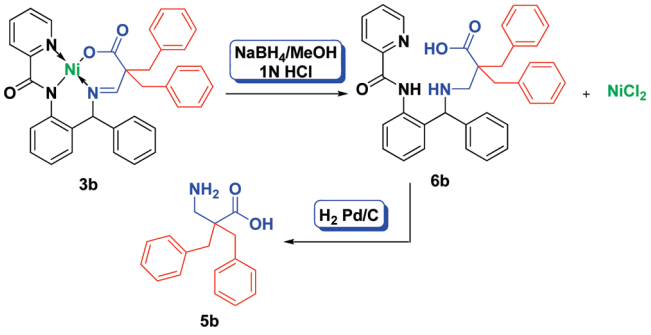
TABLE 2. Dialkylation of Ni(II) Complex 1 with Alkylating Agent 2[a]



Entry	Halide	Products	Yield	Entry	Halide	Products	Yield
1		**3a**	64%	9		**3i**	60%
2		**3b**	60%	10		**3i**	78%
3		**3c**	50%	11		**3i**	90%
4		**3d**	52%	12		**3j**	65%
5		**3e**	56%	13		**3k**	70%
6		**3f**	40%	14	CH_3I	**3l**	13%
7		**3g**	43%	15		**3m**	0
8		**3h**	45%	16		**3n**	35%[b]

[a]Reactions were run with 0.466 mmol of **1**, 1.34 mmol of **2a**−**2m** in 2 mL of DMF under 1.34 mmol of *t*-BuOK for 4 h. [b]Reaction was run with 0.466 mmol of **1**, 0.67 mmol of **2n** in 2 mL of DMF under the 1.34 mmol of *t*-BuOK for 4 h.

SCHEME 3. Hydrogenation and Decomposition of Ni(II) Complex 3 to Release Amino Acids 5



room temperature, and the product **6b** was obtained in 70% yield; Pd/C then catalyzed the hydrogenolysis of **6b** to the target amino acid **5b**, which was obtained in 62% yield (Scheme 3).

Conclusion

In conclusion, we have successfully synthesized dialkylated products of Ni(II) complexes of *β*-alanine Schiff base and developed a practical and highly efficient route to synthesize sterically constrained symmetrically α,α-disubstituted *β*-amino acids and α,α-disubstituted aldehydes. The dialkylation reactions were conducted under normal conditions without recourse to inert atmosphere, dried solvents, and low temperatures, thereby providing the key advantages of simple experimental procedure and attractive cost structure. The method has been shown to be particularly successful for the preparation of symmetrical α,α-disubstituted *β*-amino acids and α,α-disubstituted aldehydes.

Experimental Section

General Procedures for the Synthesis of 3a. The Ni(II) complex of *β*-alanine **1** (200 mg, 0.47 mmol) was dissolved in DMF (2 mL). *t*-BuOK (157 mg, 1.34 mmol) was added under ambient conditions. The mixture was then stirred at room temperature for 0.5 h, the 1-(bromomethyl)-4-nitrobenzene **2a** (288 mg, 1.34 mmol) was added in three batches within 1 h, and the reaction mixture was continually stirred for 4 h. The reaction was quenched by pouring the crude reaction mixture over 30 mL of aq satd NH_4Cl. The suspension was extracted with dichloromethane (3 times). The combined organic layers were dried with $MgSO_4$, concentrated, and purified by column chromatography on silica gel (dichloromethane/methanol = 100/1) to give **3a** as a dark red solid.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-di-(4-nitrobenzyl)-3-oxopropanoic Acid Schiff Base Complex 3a: dark red solid; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J = 8.4 Hz, 2H),

8.02 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 5.4 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.39−7.45 (m, 1H), 7.31−7.37 (m, 1H), 7.32 (s, 1H), 7.30 (s, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.15 (m, 2H), 7.09 (m, 1H), 7.03 (dd, J_1 = 0.9 Hz, J_2 = 7.2 Hz, 1H), 6.54 (d, J = 7.2 Hz, 2H), 5.00 (s, 1H), 4.14 (d, J = 13.8 Hz, 1H), 3.88 (d, J = 12.9 Hz, 1H), 3.21 (d, J = 12.9 Hz, 1H), 3.05 (d, J = 13.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 44.1, 44.6, 59.3, 77.8, 123.2, 123.6, 124.1, 125.9, 126.0, 126.6, 127.8, 128.2, 128.5, 128.9, 129.7, 130.6, 131.7, 137.1, 140.5, 140.6, 142.5, 144.4, 147.3, 147.4, 152.4, 167.4, 171.9, 173.7; MS (EI, m/z) 699 $[M]^+$; HRMS (EI) calcd for $C_{36}H_{27}N_5NiO_7$ $[M]^+$ 699.1264, found 699.1256.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-dibenzyl-3-oxopropanoic Acid Schiff Base Complex 3b: dark red solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 6.4 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.56 (s, 1H), 7.29−7.37 (m, 6H), 7.10−7.27 (m, 6H), 7.00−7.08 (m, 2H), 6.87−6.95 (m, 3H), 6.47 (d, J = 7.6 Hz, 2H), 4.91 (s, 1H), 4.08 (d, J = 14.0 Hz, 1H), 3.72 (d, J = 13.2 Hz, 1H), 3.08 (d, J = 13.2 Hz, 1H), 2.88 (d, J = 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.2, 45.2, 59.4, 77.4, 122.8, 123.0, 125.4, 126.2, 127.0, 127.2, 128.1, 128.7, 128.9, 129.5, 130.9, 135.4, 137.4, 137.9, 139.9, 140.7, 144.8, 152.7, 167.7, 172.9, 174.7; MS (EI, m/z) 609 $[M]^+$; HRMS (EI) calcd for $C_{36}H_{29}N_3NiO_3$ $[M]^+$ 609.1562, found 609.1546.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-di-(3-cyanobenzyl)-3-oxopropanoic Acid Schiff Base Complex 3c: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 5.1 Hz, 1H), 7.88 (m, 1H), 7.79 (s, 1H), 7.22−7.68 (m, 12H), 7.00−7.11 (m, 3H), 6.93 (t, J = 7.5 Hz, 1H), 6.57 (d, J = 6.0 Hz, 2H), 4.96 (s, 1H), 4.09 (d, J = 14.1 Hz, 1H), 3.78 (d, J = 13.5 Hz, 1H), 3.13 (d, J = 13.5 Hz, 1H), 2.94 (d, J = 14.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.8, 44.6, 59.1, 77.7, 113.0, 113.3, 117.7, 118.4, 123.3, 123.6, 126.3, 126.7, 127.8, 128.1, 128.4, 129.0, 129.4, 130.0, 131.1, 132.8, 134.2, 135.2, 136.8, 137.2, 138.5, 140.3, 140.5, 144.7, 152.4, 167.8, 172.0, 173.5; MS (EI, m/z) 659 $[M]^+$; HRMS (EI) calcd for $C_{38}H_{27}N_5NiO_3$ $[M]^+$ 659.1467, found 659.1461.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-di-(4-methylbenzyl)-3-oxopropanoic Acid Schiff Base Complex 3d: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 5.7 Hz, 1H), 7.88 (t, J = 7.5 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.54 (s, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.14−7.32 (m, 8H), 7.00−7.07 (m, 4H), 6.68 (d, J = 7.5 Hz, 2H), 6.48 (d, J = 7.2 Hz, 2H), 4.90 (s, 1H), 4.03 (d, J = 13.8 Hz, 1H), 3.66 (d, J = 13.2 Hz, 1H), 3.03 (d, J = 13.2 Hz, 1H), 2.84 (d, J = 13.8 Hz, 1H), 2.37 (s, 3H), 1.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 21.0, 43.9, 44.8, 59.7, 77.5, 122.8, 123.0, 125.4, 125.9, 127.2, 127.9, 128.0, 128.2, 128.6, 129.0, 129.5, 129.6, 130.8, 132.5, 134.3, 136.8, 137.1, 137.6, 139.8, 140.8, 144.9, 152.9, 167.8, 173.1, 174.9; MS (EI, m/z) 637 $[M]^+$; HRMS (EI) calcd for $C_{38}H_{33}N_3NiO_3$ $[M]^+$ 637.1857, found 637.1889.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-di-(4-methoxybenzyl)-3-oxopropanoic Acid Schiff Base Complex 3e: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 5.4 Hz, 1H), 7.79 (t, J = 7.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.54 (s, 1H), 7.36 (m, 1H), 7.13−7.28 (m, 6H), 7.00−7.05 (m, 4H), 6.87 (d, J = 8.4 Hz, 2H), 6.49 (d, J = 7.5 Hz, 2H), 6.42 (d, J = 8.4 Hz, 2H), 4.92 (s, 1H), 3.95 (d, J = 13.8 Hz, 1H), 3.79 (s, 3H), 3.60 (d, J = 13.2 Hz, 1H), 3.43 (s, 3H), 3.00 (d, J = 13.2 Hz, 1H), 2.80 (d, J = 13.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.3, 44.2, 54.8, 55.2, 60.0, 77.4, 114.2, 122.9, 123.0, 125.5, 125.9, 127.1, 127.5, 127.9, 128.0, 128.2, 128.7, 129.0, 129.4, 130.6, 131.9, 137.5, 139.8, 140.8, 144.9, 152.8, 158.8, 159.0, 167.8, 173.2, 174.9; MS (EI, m/z) 669 $[M]^+$; HRMS (EI) calcd for $C_{38}H_{33}N_3NiO_5$ $[M]^+$ 669.1774, found 669.1779.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-di-(2-chlorobenzyl)-3-oxopropanoic Acid Schiff Base Complex 3f: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, J = 4.2 Hz, 1H), 7.99 (s, 1H), 7.82 (m, 1H), 7.80 (s, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.41−7.50 (m, 2H), 7.27−7.38 (m, 4H), 7.13−7.23 (m, 3H), 6.94−7.05 (m, 3H), 6.87 (m, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.49 (d, J = 7.2 Hz, 2H), 4.89 (s, 1H), 3.92 (d, J = 14.4 Hz, 1H), 3.63 (s, 2H), 3.57 (d, J = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.1, 42.1, 53.4, 60.5, 77.9, 122.9, 123.2, 125.6, 126.1, 127.1, 127.2, 127.8, 128.0, 128.6, 128.8, 129.2, 129.9, 130.5, 131.7, 132.5, 133.8, 135.2, 137.7, 140.0, 140.2, 144.7, 152.8, 167.6, 173.1, 174.1; MS (EI, m/z) 677 $[M]^+$; HRMS (EI) calcd for $C_{36}H_{27}Cl_2N_3NiO_3$ $[M]^+$ 677.0783, found 677.0781.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-di-(3-chlorobenzyl)-3-oxopropanoic Acid Schiff Base Complex 3g: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 5.4 Hz, 1H), 7.83 (m, 1H), 7.65 (d, J = 7.2 Hz, 1H), 7.56 (s, 2H), 7.28−7.38 (m, 5H), 7.19−7.26 (m, 4H), 6.97−7.06 (m, 3H), 6.71 (t, J = 7.8 Hz, 1H), 6.65 (d, J = 7.5 Hz, 1H), 6.58−6.61 (m, 2H), 4.94 (s, 1H), 4.06 (d, J = 13.8 Hz, 1H), 3.71 (d, J = 13.2 Hz, 1H), 3.04 (d, J = 13.2 Hz, 1H), 2.86 (d, J = 13.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.0, 45.0, 59.1, 77.6, 123.0, 123.3, 125.8, 126.5, 127.0, 127.5, 127.7, 127.8, 128.0, 128.2, 129.0, 129.1, 129.4, 130.3, 130.5, 134.8, 135.2, 137.4, 139.3, 140.0, 140.6, 145.1, 152.7, 168.0, 172.5, 174.0; MS (EI, m/z) 677 $[M]^+$; HRMS (EI) calcd for $C_{36}H_{27}Cl_2N_3NiO_3$ $[M]^+$ 677.0783, found 677.0773.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-di-(4-chlorobenzyl)-3-oxopropanoic Acid Schiff Base Complex 3h: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, J = 7.8 Hz, 1H), 7.81−7.89 (m, 2H), 7.66 (d, J = 7.2 Hz, 1H), 7.54 (s, 1H), 7.22−7.43 (m, 9H), 6.99−7.09 (m, 4H), 6.84 (d, J = 8.1 Hz, 2H), 6.47 (d, J = 6.9 Hz, 2H), 4.94 (s, 1H), 4.02 (d, J = 13.8 Hz, 1H), 3.67 (d, J = 13.2 Hz, 1H), 3.02 (d, J = 13.2 Hz, 1H), 2.84 (d, J = 13.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.6, 44.3, 59.6, 77.8, 123.0, 123.4, 125.6, 127.0, 127.7, 128.1, 128.3, 128.9, 129.2, 131.0, 132.1, 133.4, 133.7, 133.8, 135.7, 137.2, 140.2, 140.7, 144.5, 152.8, 167.7, 172.6, 174.2; MS (EI, m/z) 677 $[M]^+$; HRMS (EI) calcd for $C_{36}H_{27}Cl_2N_3NiO_3$ $[M]^+$ 677.0783, found 677.0793.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-diallyl-3-oxopropanoic Acid Schiff Base Complex 3i: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12−8.16 (m, 2H), 7.88 (m, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.60 (s, 1H), 7.29−7.47 (m, 7H), 7.02−7.12 (m, 2H), 6.43 (m, 1H), 5.90 (m, 1H), 5.33 (d, J = 9.9 Hz, 1H), 5.17−5.22 (m, 3H), 5.04 (d, J = 17.1 Hz, 1H), 3.45 (dd, J_1 = 13.8 Hz, J_2 = 7.8 Hz, 1H), 3.24 (dd, J_1 = 13.2 Hz, J_2 = 7.2 Hz, 1H), 3.05 (dd, J_1 = 14.1 Hz, J_2 = 4.8 Hz, 1H), 2.34 (dd, J_1 = 14.1 Hz, J_2 = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.7, 44.6, 55.8, 77.2, 119.0, 122.0, 123.1, 123.5, 126.0, 126.1, 127.1, 128.2, 128.3, 129.1, 129.3, 131.6, 134.5, 138.2, 140.3, 140.6, 145.3, 153.2, 167.9, 172.2, 177.1; MS (EI, m/z) 509 $[M]^+$; HRMS (EI) calcd for $C_{28}H_{25}N_3NiO_3$ $[M]^+$ 509.1249, found 509.1251.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-dicinnamyl-3-oxopropanoic Acid Schiff Base Complex 3j: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 5.4 Hz, 1H), 7.67−7.73 (m, 2H), 7.17−7.42 (m, 12H), 6.96−7.13 (m, 9H), 6.62 (m, 2H), 6.30 (m, 1H), 5.12 (s, 1H), 3.20−3.34 (m, 2H), 2.89 (dd, J_1 = 13.2 Hz, J_2 = 6.9 Hz, 1H), 2.55 (dd, J_1 = 13.8 Hz, J_2 = 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 41.7, 41.8, 57.6, 77.3, 122.9, 123.2, 125.5, 125.8, 126.0, 126.2, 126.3, 127.3, 127.6, 128.0, 128.6, 129.1, 133.8, 136.1, 136.5, 137.4, 137.7, 139.7, 140.4, 144.6, 152.7, 167.9, 172.4, 175.4; MS (EI, m/z) 661 $[M]^+$; HRMS (EI) calcd for $C_{40}H_{33}N_3NiO_3$ $[M]^+$ 661.1875, found 661.1899.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-di-(3,3-dimethylallyl)-3-oxopropanoic Acid Schiff Base Complex 3k: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (m, 2H), 7.86 (t, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.30−7.44 (m, 6H), 7.23 (d, J = 7.2 Hz, 2H), 7.00−7.10 (m, 2H), 6.15 (m, 1H), 5.15 (br, 1H), 5.09 (s, 1H), 2.81−2.88 (m, 2H), 2.61 (dd, J_1 = 13.8 Hz, J_2 = 9.0 Hz, 1H), 2.42 (dd, J_1 = 14.4 Hz, J_2 = 9.3 Hz, 1H), 1.74 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.2, 18.4, 25.9, 26.0, 36.6, 37.0, 57.7, 77.5, 118.9, 120.2, 123.0, 123.4, 125.9, 126.2, 127.1, 128.2, 128.5, 128.7, 129.0, 129.2, 135.4, 138.4, 139.8, 140.1, 140.6, 145.2, 153.2, 167.9, 172.9, 175.6; MS (EI, m/z) 565 $[M]^+$; HRMS (EI) calcd for $C_{32}H_{33}N_3NiO_3$ $[M]^+$ 565.1875, found 565.1874.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2,2-dimethyl-3-oxopropanoic Acid Schiff Base Complex 3l: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (d, J = 8.1 Hz, 1H), 8.13 (d, J = 5.1 Hz, 1H), 7.89 (t, J = 7.5 Hz, 1H), 7.80 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.42−7.47 (m, 2H), 7.31−7.39 (m, 5H), 7.13 (d, J = 7.5 Hz, 1H), 7.05 (m, 1H), 5.24 (s, 1H), 2.58 (s, 3H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 30.1, 48.6, 77.0, 123.1, 123.6, 126.0, 126.3, 127.1, 128.3, 128.4, 128.5,128.7, 129.0, 129.2, 129.3, 138.1, 140.5, 140.6, 145.4, 153.2, 168.2, 174.8, 180.0; MS (EI, m/z) 457 $[M]^+$; HRMS (EI) calcd for $C_{24}H_{21}N_3NiO_3$ $[M]^+$ 457.0936, found 457.0941.

Ni(II)-2-[*N*-(α-picolyl)amino]diphenylmethanamine/2-formylindan-2-carboxylic Acid Schiff Base Complex 3n: dark red solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J = 8.1 Hz, 1H), 8.12 (d, J = 4.8 Hz, 1H), 7.94 (s, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.15−7.48 (m, 11H), 6.98−7.06 (m, 2H), 5.24 (s, 1H), 4.80 (d, J = 15.6 Hz, 1H), 4.56 (d, J = 15.6 Hz, 1H), 4.16 (d, J = 16.8 Hz, 1H), 3.24 (d, J = 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.0, 49.2, 60.0, 76.4, 123.2, 123.7, 124.3, 124.6, 124.8, 126.1, 126.8, 127.2, 127.6, 128.5, 128.8, 129.2, 138.0, 138.6, 140.4, 140.6, 140.7, 141.1, 145.4, 153.2, 168.2, 173.0, 180.6; MS (EI, m/z) 531 $[M]^+$; HRMS (EI) calcd for $C_{30}H_{23}N_3NiO_3$ $[M]^+$ 531.1093, found 531.1131.

Procedure for the Synthesis of 4a. The complex **3a** was hydrolyzed by stirring a suspension in a mixture of aqueous 1 N HCl (1 mL) and methanol (15 mL) for 30 min at room temperature until the red color of the solution disappeared. The reaction was evaporated to dryness and purified by flash column chromatography (petroleum ether/ethyl acetate) to give **4a** as a white solid.

2,2-Di(4-nitrobenzyl)acetaldehyde Complex 4a: white solid; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.74 (s, 1H), 8.17 (d, J = 8.7 Hz, 4H), 7.32 (d, J = 8.7 Hz, 4H), 3.13−3.20 (m, 3H), 2.85 (d, J = 12.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 34.5, 54.0, 123.9, 129.8, 145.7, 147.0, 201.4; MS (EI, m/z) 314 $[M]^+$; HRMS (EI) calcd for $C_{16}H_{14}N_2O_5$ $[M]^+$ 314.0903, found 314.0919.

Procedure for the Synthesis of 6b. The complex **3b** (200 mg, 0.328 mmol) was dissolved in methanol (10 mL), and then $NaBH_4$ (13 mg, 0.34 mmol) was added under ambient conditions. The reaction mixture was stirred at room temperature for 0.5 h, and then 1 N HCl (1 mL) was added. The reaction mixture was stirred at room temperature until the red color of the solution disappeared and then evaporated to dryness. Water (20 mL) was added to the residue to form a clear solution, and then this solution was separated by column chromatography on C18-reversed phase (230−400 mesh) silica gel. Pure water as eluent was employed to remove the green $NiCl_2$ and excess HCl, and then methanol/water (4/1) was used to obtain the product **6b** as a white solid. The column chromatography was washed with 100 mL of methanol for further use.

2,2-Dibenzyl-3-(2-(*N*-(α-picolyl)amino)diphenylmethanamino)-propanoic Acid Complex 6b: white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.88 (s, 1H), 8.55 (d, J = 4.0 Hz, 1H), 8.22 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.90 (m, 1H), 7.50 (m, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.09−7.26 (m, 14H), 6.99−7.03 (m, 2H), 6.93 (d, J = 7.6 Hz, 1H), 4.74 (s, 1H), 3.38 (d, J = 13.2 Hz, 1H), 3.32 (d, J = 14.0 Hz, 1H), 2.72−2.78 (m, 3H), 2.55 (d, J = 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.5, 44.4, 51.0, 51.1, 63.2, 122.6, 124.0, 125.4, 126.5, 126.8, 127.1, 127.3, 127.9, 128.4, 128.5, 128.6, 128.9, 129.9, 130.1, 132.1, 134.9, 136.8, 137.7, 138.7, 147.9, 149.6, 162.4, 177.4; MS (EI, m/z) 555 $[M]^+$; HRMS (EI) calcd for $C_{36}H_{33}N_3O_3$ $[M]^+$ 555.2522, found 555.2514.

Procedure for the Synthesis of 5b. In a hydrogenation flask were placed compound **6b** and methanol (10 mL) before the addition of Pd/C. The resulting mixture was pressurized to hydrogen and mechanically stirred at room temperature for 4 h. The reaction mixture was filtered, and the filtrate was concentrated in a rotary evaporator to afford the crude product. The crude residue was purified by column chromatography on C18-reversed phase (230−400 mesh) silica gel (water/ methanol = 11/9) to give **5b** as a white solid in 62% yield, and the column chromatography was washed with 100 mL of methanol for further use.

α,α-Dibenzyl-*β*-alanine complex 5b: white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.47 (m, 10H), 3.41 (s, 1H), 3.22 (d, J = 13.5 Hz, 2H), 2.96 (s, 2H), 2.87 (d, J = 13.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 43.0, 44.7, 52.2, 129.9, 131.1, 132.6, 137.7, 179.2; MS (ESI, m/z) 268 $[M - H]^+$; HRMS (ESI) calcd for $C_{17}H_{18}NO_2$ $[M - H]^+$ 268.1338, found 268.1346.

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Supporting Information Available: Detailed experimental procedures, characterization data, copies of ^{1}HNMR and ^{13}CNMR spectra for all products, and crystallographic information files (CIF) of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.