Synthesis of Ferrocene-Substituted 2-Azetidinones

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The photochemical reaction of alkoxychromium(0)carbene complexes and ferrocene mono- and disubstituted imines formed 2-azetidinones having one or two ferrocene moieties in good yields. Yields decrease when the carbene moiety bears an aminoferrocene moiety attached to the carbene carbon, while complex **9** having the ferrocene directly bonded to the carbene carbon was totally inert in these reactions. Access to β-lactams with the ferrocene tethered to the C3 position through a methylene group was gained using the lithium enolate derived from ethyl 3-ferrocenylpropanoate. The reaction of this enolate produced two unexpected processes. Thus, 2-azetidinone **15** having an hydroxyl group at the C3 position was obtained together with the expected β-lactam **14**, by reaction of the lithium enolate of ethyl 3-ferrocenylpropenoate and imine **1**. Additionally, unsaturated amide **17** was obtained by base-promoted Hoffmann-like breakage of the β-lactam ring formed in the reaction of the same enolate and imine **2**. Oxidation of the anion at the C3 of the 2-azetidinone ring on compound **14**, as well as the sterically driven ring-breakage of the C3 anion derived from the nonisolated 2-azetidinone **18**, should be responsible for this behavior.

Introduction

The search for β-lactams having new structures or novel variations of well-known basic structures remains unabated.[1] This is mainly because of the increased worldwide awareness about bacterial-resistance[2] and the search for other biological properties of these compounds apart from their antibacterial action. These compounds are potent inhibitors of mammalian serine proteases,[3] such as human leukocyte elastase (HLE)[4] or thrombin, cholesterol absorption inhibitors,[5] and inhibitors of human cytomegalovirus (HCMV, a β-herpes virus).[6] Moreover, development of synthetic methodology based on the 2-azetidinone nucleus has been steadily increased during the last 25 years meriting its own name: *the β-lactam synthon method*, a term coined by Ojima almost 20 years ago.[7] Surprisingly, 2-azetidinones having organometallic-moieties attached to the four membered ring are scarce.[8] 1,1′-Ferrocenyldicarboxiamidopenicillanic and cephalosporanic acids and several derivatives having the penicillin and cephalosporin nuclei acylated with different ferrocene-carboxylic acids have been prepared.[9,10] To the best of our knowledge, only one example of a monolactam *N*-substituted with a ferrocenyl tethered chain has been prepared.[11] Finally, some 3-unsubstituted-4-ferrocenyl-β-lactams have been reported while this work was in progress.[12]

Taking apart their potential as antibacterial agents, one of the more attractive aspects of these ferrocenyl-substituted compounds is their foreseeable role as electrochemical markers in biological processes.[13] In fact, the

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(8) (a) Alcaide, B.; Pérez-Castells, J.; Sánchez-Vigo, B.; Sierra, M. A. *Chem. Commun.* **1994**, 587. (b) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *Synlett.* **1994**, 183. (c) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *Tetrahedron: Asymmetry* **1994**, *5*, 809. (d) Baldoli, C.; Del Buttero, P.; Licandro, E.; Papagni, A. *Tetrahedron* **1996**, *52*, 4849.

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(10) Interestingly, almost all of the ferrocenyl-penicillins and -cephalosporins exhibited antibiotic activity, some being highly active, while others proved to be potent β-lactamase inhibitors.

(11) Tong, Y.-Y.; Fraústo da Silva, J. J. R.; Pombeiro, A. J. L.; Wagner, G.; Herrmann, R. *J. Organomet. Chem.* **1998**, *552*, 17.

(12) Ghatak, A.; Becker, F. F.; Banik, B. K. *Heterocycles* **2000**, *53*, 2769.

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electrochemical properties of ferrocene-derived biological substrates are extremely sensitive to environmental changes. For example, *N*-(2-ferrocene-ethyl)maleimide has been used recently as electroactive label into a nonelectroactive β-lactamase I. The labeling transforms the redox-inactive enzyme system into redox-active, rendering the labeled enzyme sensitive to changes in the enzyme's active site and, therefore, potentially useful for developing electrochemical biosensors.[14] We decided then, to develop synthetic approaches to 2-azetidinones having from one to three ferrocene units joined to the four membered ring.

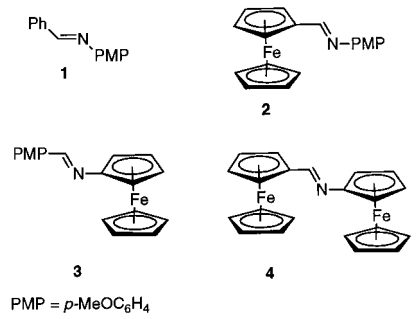
Current synthetic methodology to prepare the 2-azetidinone nucleus is mainly based on three different approaches: the Staüdinger ketene−imine cycloaddition in its many variants,[15] the enolate-imine approach,[16] including the cyclization of β-amino acids, and the isocyanate-olefin approach.[17] From these routes, we have chosen the photochemical reaction of chromium-carbene complexes with imines to study the compatibility of these processes with ferrocene moieties, as well as the photochemistry of ferrocene-substituted chromium(0)carbene complexes. The interaction of chromium(0)carbene complexes with different metal-substituted substrates[18] and catalysts[19] is a topic of current interest. Additionally, the reaction of enolates derived from ferrocenylpropionates with ferrocenylimines would allow us access to ferrocene-substituted 2-azetidinones. This approach is complementary to the photochemical reaction. As far as we know, the reactivity of this class of enolates toward imines was unknown at the beginning of this work.[20]

Reported herein is the successful implementation of both approaches for the preparation of mono- and disubstituted 2-azetidinones. Additional unexpected reactions of ferrocene-substituted 2-azetidinones, including the spontaneous oxidation of the 2-azetidinone ring as well as the base induced N1−C4 fragmentation of the β-lactam ring will be reported.

Results and Discussion

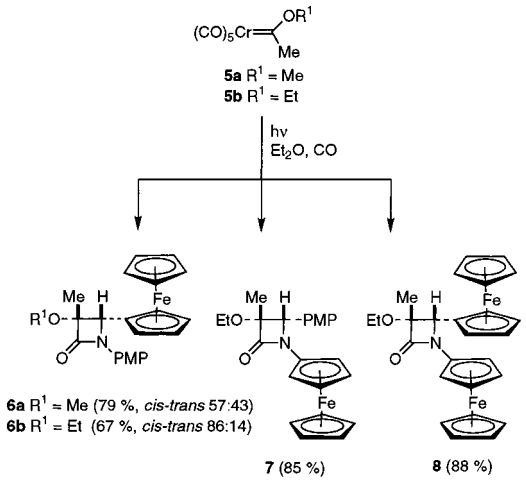
The imines **1**−**4** (Chart 1) used through this work were prepared by condensation of the corresponding aldehydes and amines. Compounds **2**−**4** were irradiated (400 W-Pyrex filter and Pyrex-well) in the presence of alkoxychromium(0)carbene complexes **5a**,**b** giving the corresponding ferrocene-substituted 2-azetidinones **6**−**8**.

Chart 1



Compounds **6**−**8** were obtained in good yields either exclusively (compounds **7** and **8**) or mainly (compounds **6)** as the cis-isomers. Thus, 2-azetidinones having ferrocene substituents at N1, C4, or both positions can be easily obtained in this way (Scheme 1).

Scheme 1



With these results in hand, the reaction of ferrocene-chromium(0)carbene complex **9** and imines **1** and **2** was attempted. Irradiation of complex **9** under different reaction conditions, including CO-pressure, different solvents (MeCN, Et_2O, and CH_2Cl_2), and different reaction times (up to 4 days) systematically returned unreacted starting materials. Therefore, we conclude that complex **9** was photochemically inert. The alternative approach to place a ferrocene moiety at the C3 position of the 2-azetidinone ring could be to use complex **10** having the ferrocene tethered to the carbene carbon through an oxygen. The preparation of complex **10** was undertook by acylation of pentacarbonyl[(methyl)[(tetramethylammonium) oxy]carbene]chromium(0) with acetyl bromide and further reaction with ferrocenemethanol. After several attempts, including the use of pivaloyl chloride as the acylating agent, 4-(dimethylamino)pyridine as catalyst, and different temperature and reaction times, this reaction produced small amounts of a compound having the spectroscopic properties (^{1}H NMR) expected for complex **10** (Chart 2). However, this compound was extremely unstable and could not be used to prepare the desired 2-azetidinone.

The chromium(0)carbene route to 2-azetidinones having ferrocene moieties attached to C3 of the four membered ring was then thwarted because of the lack of reactivity of complex **9** and the instability of compound **10**. We focused then on aminochromium(0)carbene com-

(13) (a) Di Gleria, K.; Hill, H. A. O. In *Advances in Biosensors*; Turner, A. P. F., Ed.; JAI Press: 1992; Vol. 2, pp 53−77. (b) Hill, H. A. O., Hunt, N. *Methods Enzymol.* **1993**, *227*, 501.

(14) Di Gleria, K.; Halliwell, C. M.; Jacob, C.; Hill, H. A. O. *FEBS Lett.*, **1997**, *400*, 155.

(15) For an excellent discussion on the Staudinger reaction, see ref 1c, pp 294−368.

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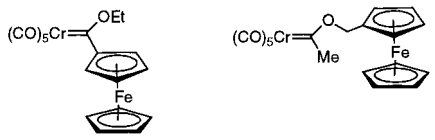
(17) Cossio, F. P.; Roa, G.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1995**, *117*, 12306, and the references therein.

(18) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591.

(19) (a) Sierra, M. A.; Mancheño, M. J.; Sáez, E.; del Amo, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 6812. (b) Sierra, M. A.; del Amo, J. C.; Mancheño, M. J.; Gómez-Gallego, M. *J. Am. Chem. Soc.* **2001**, 123, 851. (c) Sakurai, H.; Tanabe, K.; Narasaka, K. *Chem. Lett.* **1999**, 75. (d) Aumann, R.; Göttker-Schnetmann, I.; Fröhlich, R.; Meyer, O. *Eur. J. Org. Chem.* **1999**, *2545*, 5. (e) Göttker-Schnetmann, I.; Aumann, R. *Organometallics* **2001**, *20*, 346.

(20) While this work was in progress, Banik et al. reported the preparation of some 3-unsubstituted ferrocenyl β-lactams by the reaction of ethyl bromoacetate and ferrocenecarbaldehyde derived imines in the presence of indium. See ref 12.

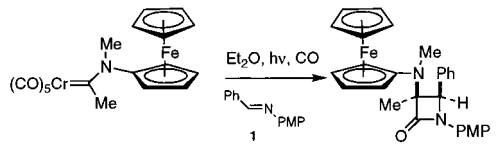
Chart 2



9 **10**

plex **11** having the ferrocene group attached to the amino moiety. Complex **11** was prepared from pentacarbonyl-[(methyl) [(tetramethylammonium)oxy]carbene]chromium-(0) by acylation with acetyl bromide, reaction with ferrocenylamine, followed by methylation of the carbene nitrogen with NaH/MeI. Photochemical reaction between complex **11** and imine **1** under CO pressure and after 40 h of irradiation gave the corresponding 2-azetidinone **12** as a *cis*−*trans* mixture (10:1) in low yield (23% isolated yield) (Scheme 2). Finally, chromium(0)carbene complex **11** allowed the preparation of the desired C3-ferrocene-substituted 2-azetidinone, albeit in low yield. The assignment of the stereochemistry of compounds **6**−**8** was derived from the accepted stereochemical model for the photochemical reaction of chromium(0)carbene complexes and imines.[21] To confirm that this model is also applicable in our case we run nOe experiments in compound **8**. Thus, irradiation of the C3-methyl group at 1.63 ppm resulted in a nOe enhancement of 3.3% in the signal corresponding to H4. Analogously, irradiation of the signal corresponding to H4 (δ 4.36 ppm) resulted in a nOe enhancement of 3.9% in the signal corresponding to the C3-methyl group. Therefore, H4 and the C3-methyl group should be in a cis-arrangement as predicted by the published model for these processes. We can conclude that the model is applicable to our case.

Scheme 2

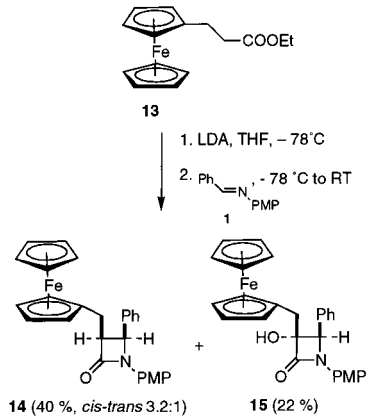


11 **12** (23 %, *cis-trans* 10:1)

It is worth to note the inertia of complex **9** toward the photocarbonylation reaction. Other reactions carried out with this complex such as the thermal reaction with alkynes[22] and olefins,[23] also produce results that fall out from the usual chemistry of alkoxychromium(0)carbene complexes. It is relevant to state that the value of the oxidation potential $E_{1/2}$ of complex **9** falls by ca. 200 mV from the values of other alkoxychromium(0)carbene complexes having aromatic substituents (for example aryl, 2-thienyl, or 2-furyl).[24] It has been suggested that this complex has a redox orbital that encompasses both potential redox centers (the ferrocene and the chromium moieties). This may point to a strong interaction between the donor (iron) and acceptor (chromium) centers that may inactivate the excited species before the CO insertion occurred. This would render the complex photochemically inactive.[25]

Access to ferrocene-substituted 2-azetidinones having the ferrocene moiety linked to the four-membered ring by a carbon chain required a different synthetic strategy. The classical Staudinger reaction between 3-ferrocenylpropanoyl chloride derived ketene and imines **1** and **4** did not give any positive result. Even though different reaction conditions were assayed,[26] only complex reaction mixtures were obtained. However, when ethyl 3-ferrocenylpropanoate, **13**, (2.2:1 ester/imine ratio) was reacted with an excess of LDA and the resulting enolate condensed with imine **1**, the resulting reaction mixture contained the expected 2-azetidinone **14** as a *cis*−*trans* mixture of isomers (3.2:1 ratio) and a new compound **15** having a β-lactam structure, together with ethyl 4-ferrocenyl-2-ferrocenylmethyl-3-oxo-butanoate, **16**. This last product was derived from the self-condensation of the ester enolate that was used in excess. The unexpected compound **15** shows signals attributable to the 2-azetidinone carbonyl group in ^{13}C NMR (δ 167.2 ppm) and IR (ν = 1726 cm^{-1}). However, this compound lacked the signal attributable to H3-methyne in compound **14** (determined unambiguously by ^{1}H-^{1}H-COSY experiment) that appeared at δ 3.55 ppm. Additionally, the H4-resonance appeared in this new compound at δ 4.93 ppm as a singlet instead of a doublet like the signal attributable to H4 (δ 5.05 ppm, J = 5.4 Hz) in compound **14**. These and the remaining spectroscopic and analytical data allow us to assign the structure of 3-hydroxy-2-azetidinone **15** for this new compound (Scheme 3).

Scheme 3



13

14 (40 %, *cis-trans* 3.2:1) **15** (22 %)

Encouraged by these results, we reacted the enolate derived from compound **13** with imine **2**. The reaction

(21) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784.

(22) (a) Dötz, K. H.; Dietz, R.; Neugebauer, D. *Chem. Ber.* **1979**, *112*, 1486. (b) Zora, M.; Güngör, E. Ü. *Tetrahedron Lett.* **2001**, *42*, 4733.

(23) Connor, J. A.; Lloyd, J. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 17.

(24) (a) Lloyd, M. K.; McCleverty, J. A.; Orchard, D. G.; Connor, J. A.; Hall, M. B., Hillier, I. H.; Jones, E. M.; McEwen, G. K. *J. Chem. Soc., Dalton Trans*, **1973**, 1743. (b) Casey, C. P.; Albin, L. D.; Saeman, M. C.; Evans, D. H. *J. Organomet. Chem.* **1978**, *155*, C37.

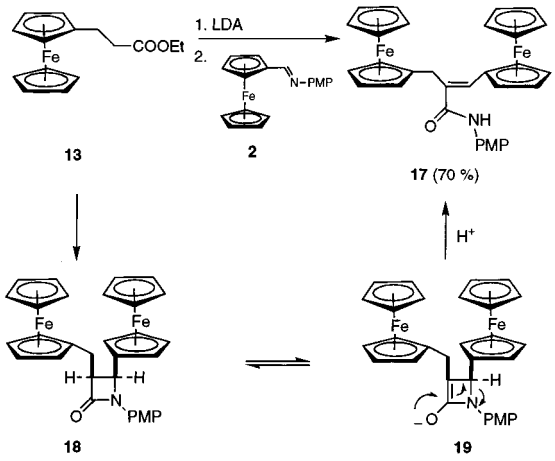
(25) It has been suggested that the irradiation of chromium(0)-carbene complex with visible light activate the MLCT band and promotes one-electron from a metal d-centered HOMO to a π*-carbene centered LUMO which is formally one-electron oxidation. This oxidation results in a CO insertion and thence the ketene-like chemistry of this compounds. See (a) Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105. For a study of the mechanism of the reaction of alkoxychromium(0)-carbenes and imines, see (b) Arrieta, A.; Cossío, F. P.; Fernández, I.; Gómez-Gallego, M.; Lecea, B.; Mancheño, M. J.; Sierra, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 11509.

(26) Apart from the standard acid chloride/Et$_3$N-imine reaction in direct and inverse addition, other conditions including the use of the systems acid/cyanuric chloride and acid/diethylchlorophosphate gave none of the desired β-lactam product. For the reaction with cyanuric chloride, see (a) Van der Veen, J. M.; Bari, S. S.; Bhawal, B. M.; Bose, A. K. *J. Org. Chem.* **1989**, *54*, 5758. For the diethylchlorophosphate variant, see (b) Manhas, M. S.; Lal, B.; Amin, S. G.; Bose, A. K. *Synth. Commun.* **1976**, *6*, 435.

resulted in the smooth conversion of the starting materials into a new compound that was isolated in a 70% yield. Strikingly, this new compound lacked the expected 2-azetidinone ring as shown by the spectroscopic data. Instead, analytical and spectroscopic data for this compound were fully consistent with the propenamide **17**. The *E*-stereochemistry of compound **17** has been tentatively assigned based on the absence of nOe enhancement observed in the CH_2-allylic moiety upon irradiation of the vinylic proton at 7.18 ppm. It seems clear that compound **17** arises from the expected 2-azetidinone **18** by N1−C4 bond breakage (Scheme 4). This type of bond rupture is observed when 4-aryl-β-lactams are submitted to Pd-catalyzed hydrogenation or metal-NH_3 hydrogenation,[27] but it is otherwise rare.[28] Thus, the enolate derived from ester **13** produces in its reaction with imines two different, unexpected results that possibly are related to each other. In fact, the reaction between ester **13** and imines **1** and **2** is carried out by generating the enolate in the presence of an excess of LDA (usually 2:1 LDA/ester ratio). This excess of base was essential to obtain good conversions after many reactions tested. The excess of LDA generates the C3-carbanion in the formed 2-azetidinones **14** since this position is acid.[29] 3-Hydroxy-β-lactam **15** should be formed by oxidation of this carbanion.[30] The stereoselectivity observed in this reaction is also a characteristic of the reactions of carbanions at the C3 of the 2-azetidinone ring with electrophiles.[31] The nature of the oxidant agent is unknown but, to the best of our knowledge, none of the many reactions carried out to prepare 2-azetidinones by the enolate-imine approach have resulted in the oxidation of the C3 position.[16] That points to the ferrocene moiety as responsible for this outcome, but further work will be required to confirm or discard this hypothesis.[32]

The formation of compound **17** should be analogous. However, in this case, the anion **19** fragments through a

Scheme 4



Hoffmann-type elimination instead of experimenting an oxidation process. This points to an intrinsic instability of the intermediate β-lactam **18**. It seems reasonable that the simultaneous presence of two bulky ferrocenes at the C3 and C4 carbons provokes an increase in the steric energy of the compound. Planarization of the four-membered ring by formation of the anion **19** should result in an increase of the steric hindrance. This energy would be released by breaking the β-lactam ring to form compound **17**.[33]

In conclusion, the combination of methodologies reported through this work allows the preparation of 2-azetidinones having one or two ferrocene moieties joined to any of the three positions of the four membered ring. Chromium(0)carbene complexes react smoothly with ferrocene imines **2**−**4** which allow to place ferrocene subtituents at the N1, C4, or simultaneously at N1 and C4 positions of the β-lactam ring. Yields decrease for aminoferrocenechromium(0)complexes and compound **9** having the ferrocene bonded to the carbene carbon was totally inert in these reactions. Access to β-lactams with the ferrocene tethered to the C3 position through a methylene group was gained using the enolate derived from ethyl 3-ferrocenylpropenoate. Additionally, the reactions of this enolate produced two unexpected processes, namely, the spontaneous oxidation of the C3 carbon of the 2-azetidinone ring, and the base-promoted Hoffmann-like breakage of the β-lactam ring. Further work to determine the redox properties of β-lactams synthesized through this work, as well as to incorporate other

(27) (a) Ojima, I.; Chen, H.-J. C.; Nakahashi, J. *J. Am Chem. Soc.* **1988**, *110*, 278. (b) Ojima, I.; Chen, H.-J. C.; Qiu, X. *Tetrahedron* **1988**, *44*, 5307. (c) Hatanaka, N.; Abe, R.; Ojima, I. *Chem. Commun.* **1981**, 344.

(28) Usually, this kind of rupture requires that the 2-azetidinone has a masked functionality that makes the N1−C4 reactive. For 4-amino-2-azetidinones, see (a) Perelman, H.; Mizsak, S. A. *J. Am. Chem. Soc.* **1962**, *84*, 4988. (b) Opitz, G.; Koch, J. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 152. (c) Kawamura, Y.; Sanemitsu, Y. *J. Org. Chem.* **1993**, *58*, 414. 4-Alkoxy- and 4-sulfinyl-2-azetidinones: (d) Kita, Y.; Shibata, N.; Yoshida, N.; Kawano, N.; Matsumoto, K. *J. Org. Chem.* **1994**, *59*, 938. (e) Kita, Y.; Shibata, N.; Kawano, N.; Yoshida, N.; Matsumoto, K.; Takebe, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2321. An analogous fragmentation induced by NaH was observed in 4-benzoyl-2-azetidinones: (f) Alcaide, B.; Domínguez, G.; Martín-Domenech, A.; Plumet, J.; Monge, A.; Pérez-García, V. *Heterocycles* **1987**, *26*, 1461.

(29) See, among others, (a) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575. (b) Alcaide, B.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1996**, *61*, 7125. (c) Bose, A. K.; Narayanan, C. S.; Manhas, M. S. *Chem. Commun.* **1970**, 975. (d) Hart, D. J.; Ha, D.-C. *Tetrahedron Lett.* **1985**, *26*, 5493.

(30) 3-Hydroxy-2-azetidinones have been prepared by MoOOH-oxidation of their C3-enolate anions. See Palomo, C.; Aizpurua, J. M.; Miranda, J. I.; Mielgo, A.; Odriozola, J. M. *Tetrahedron Lett.* **1993**, *34*, 6325. For some examples of anodic oxidation of the 2-azetidinone ring, see (a) Suda, K.; Hotoda, K.; Aoyagi, M.; Takanami, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1327. (b) Suda, K.; Hotoda, K.; Watanabe, J.; Shiozawa, K.; Takanami, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1283, and the pertinent references therein.

(31) Enolate anions derived from β-lactams are attacked by electrophiles by the face opposite to the substituent at the C4 position. See, for example, (a) Coggins. P.; Simpkins, N. S. *Synlett.* **1992**, 313. (b) Gasparsksi, C. M.; Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 2741. (c) Roe, J. M.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 359. (d) Sadeghpour, B. M.; Pellicciari, R.; Marchioro, C.; Rossi, T.; Tamburini, B.; Tarzia, G.; Ursini, A. *Tetrahedron Lett.* **1995**, *51*, 10715.

(32) It would be very attractive to consider that the hydroxy group present in compound **15** has its origin in the attack of water onto the C3 position of β-lactam **14**. This process would be catalyzed by *i*Pr_2-NH, and it would be analogous to the diastereoselective addition of nucleophiles to the C3 position of *N*-(tosyloxy)-β-lactams catalyzed by tertiary amines reported by Miller. However, the lack of leaving group in compound **14** makes this option albeit attractive little probable. (a) Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548. (b) Guzzo, P. R.; Miller, M. J. *Tetrahedron* **1994**, *50*, 8275.

(33) This fact offers the opportunity to deform the four membered ring by steric hindrance. This may cause the piramidalization of the amide nitrogen and hence an inhibition of the amide resonance. Should this hypothesis be right it would be a new entry into the so-called *anti-Bredt* β-lactams. This is a very attractive family of compounds and it has been scarcely studied. See (a) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073. (b) Buynak, J. D.; Rao, A. S.; Adam, G.; Nidamarthy, S. D.; Zhang, H. *J. Am. Chem. Soc.* **1998**, *120*, 6846. For a failed approach to these compounds based on the intramolecular Staudinger reaction of iminochromium(0)carbene complexes, that resulted in an entry into bridged *antiBredt* δ-lactams, see Alcaide, B.; Casarrubios, L.; Domínguez, G.; Sierra, M. A.; Monge, A. *J. Am. Chem. Soc.* **1995**, *117*, 5604.

electroactive moieties in these compounds, is now underway in our laboratories.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, on a Varian XL-300S (299.94 MHz for ^{1}H and 75.43 MHz for ^{13}C), a Bruker 250-AC (250.13 MHz for ^{1}H and 62.90 MHz for ^{13}C), a Bruker 200-AC (200.13 MHz for ^{1}H and 50.03 for ^{13}C MHz), and a Bruker Avance-300 (300.13 MHz for ^{1}H and 75.48 MHz for ^{13}C) spectrometers. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm) or $CDCl_3$ (^{13}C, 77.0 ppm). IR spectra were taken on a Perkin-Elmer 781 spectrometer. Mass spectra were carried out on a GC-MS HP-5989 (60 eV) mass spectrometer using methanol as solvent. Melting points were measured on an electrothermal digital melting point apparatus (Gallenkamp) and are uncorrected. Flame-dried glassware and standard Schlenck techniques were used for all the reactions. Merck silica gel (230−400 Mesh) was used as the stationary phase for purification of crude reaction mixtures by flash chromatography. Identification of products was made by TLC (Kieselgel 60F-254), UV light ($\lambda = 254$ nm), and phosphomolibdic acid solution in 95% EtOH and iodine were also used to develop the plates. All commercially available compounds were used without further purification. The following products were prepared according to literature methods: pentacarbonyl[(ethoxy)(methyl)carbene]chromium(0),[34] pentacarbonyl[(methoxy)(methyl)carbene] chromium(0),[35] pentacarbonyl[(ethoxy)(ferrocenyl)carbene]chromium(0),[36] 3-ferrocenylpropanoic acid,[37] ferrocenylamine.[38]

General Procedure for the Synthesis of Imines 1−4. Imines **1**−**4** were synthesized in quantitative yield by refluxing stoichiometric amounts of the corresponding amine and aldehyde for 2 h in EtOH under an argon atmosphere. The resulting product was used as obtained without further purification.

***N*-*p*-Anisylferrocenemetanimine 2.** From ferrocenecarbaldehyde and *p*-methoxyphenylamine was obtained as a red solid. ^{1}H NMR δ 3.75 (s, 3H), 4.16 (s, 5H), 4.39 (s, 2H), 4.71 (s, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 7.06 (d, $J = 8.7$ Hz, 2H), 8.25 (s, 1H). ^{13}C NMR δ 55.5, 68.8, 69.2, 71.0, 80.7, 114.3, 121.6, 145.9, 157.6, 159.6. IR (CCl_4) 1620, 1506, 1464, 1242, 1035 cm^{-1}.

***N*-Ferrocenyl-*p*-anisylmetanimine, 3.** From *p*-methoxybenzaldehyde and ferrocenylamine was obtained as a red solid. ^{1}H NMR δ 3.85 (s, 3H), 4.17 (s, 5H), 4.21 (s, 2H), 4.54 (s, 2H), 6.93 (d, 2H, $J = 8.7$ Hz), 7.75 (d, 2H, $J = 8.7$ Hz), 8.55 (s, 1H). ^{13}C NMR δ 55.4, 62.6, 66.9, 69.5, 105.8, 114.2, 129.6, 129.8, 157.4, 161.6. IR (KBr) 1603, 1514, 1311, 1275, 1163 cm^{-1}.

***N*-Ferrocenylferrocenemetanimine, 4.** From ferrocenecarbaldehyde and ferrocenylamine was obtained as a red solid. ^{1}H NMR δ 4.17 (s, 5H), 4.19 (m, 2H), 4.21 (s, 5H), 4.42 (t, $J =$ 1.9 Hz, 2H), 4.49 (t, $J = 1.9$ Hz, 2H), 4.72 (t, $J = 1.9$ Hz, 2H), 8.44 (s, 1H). ^{13}C NMR δ 62.2, 66.7, 68.5, 69.2, 69.4, 70.9, 81.3, 106.6, 158.2. IR (KBr) 1608, 1439, 1408, 1250, 1105 cm^{-1}.

Pentacarbonyl[(*N*-ferrocenyl-*N*-methylamino)(methyl)carbene]chromium(0), 11. (1) Pentacarbonyl[(*N*-ferrocenylamino)(methyl)carbene]chromium(0). To a solution of 1.01 g (3.3 mol) of pentacarbonyl[(methyl)[(tetramethylammonio)oxy]carbene]chromium(0) in 20 mL of CH_2Cl_2 was added dropwise 0.25 mL (3.3 mmol) of acetyl bromide at −40 °C. After stirring for 1 h at this temperature, a solution of 0.55 g (2.74 mmol) of ferrocenylamine in 10 mL of CH_2Cl_2 was added to the mixture and then stirred at −20 °C overnight. After allowing the mixture to reach room temperature, Al_2O_3 was added to the solution, and the solvent evaporated and was chromatographed on silica gel under argon atmosphere (hexane:EtOAc, 9:1) to yield 1.02 g (89%) of pentacarbony[(*N*-ferrocenylamino) (methyl)carbene]chromium(0). ^{1}H NMR δ 2.63 (s, 3H), 4.19 (s, 2H), 4.27 (s, 5H), 4.37 (s, 2H), 10.04 (br s, 1H). ^{13}C NMR δ 37.3, 65.6, 66.8, 69.9, 94.1, 217.9, 223.0, 288.4. IR (CCl_4) 3363, 2054, 1971, 1930 cm^{-1}.

(2) Pentacarbonyl[(*N*-ferrocenyl-*N*-methylamino)(methyl)carbene]chromium(0), 11. To a suspension of 57 mg (2.39 mmol) of NaH (60% mineral oil) in 50 mL of THF at −78 °C was added 0.5 g (1.19 mol) of pentacarbonyl[(*N*-ferrocenylamino)(methyl)carbene]chromium(0) in one portion. Then, the mixture was stirred at −40 °C for 2.5 h. Afterward the solution was cooled to −78 °C, and 0.15 mL (2.39 mmol) of methyl iodide was added by a syringe. The reaction mixture was allowed to reach room temperature and was stirred overnight, quenched with 20 mL of degassed water, extracted with CH_2Cl_2, and submitted to flash column chromatography (SiO_2, Hexane:EtOAc 19:1) under argon to yield 223 mg (43%) of compound **11**. ^{1}H NMR δ 2.36 (s, 3H), 4.10 (s, 2H), 4.17 (s, 2H), 4.27 (s, 5H), 4.42 (s, 3H). ^{13}C NMR δ 42.8, 57.3, 64.7, 65.8, 70.1, 104.2, 217.9, 229.4, 284.3. IR (KBr) 2052, 1973, 1911, 1888 cm^{-1}.

Ethyl 3-ferrocenylpropanoate, 13. Method A. (1) Ethyl 3-Ferrocenylpropenoate. To a solution of 0.59 g (5.9 mmol) of diisopropilamine in 5 mL of THF at −78 °C was added dropwise 4.02 mL (6.43 mmol) of *n*-butyllithium (1.6 M in hexanes), and the mixture was stirred for 30 min. Then, 0.57 mL (5.9 mmol) of EtOAc was added at −78 °C, and the solution was stirred at this temperature for 1 h. Afterward the mixture was transferred via cannula to a solution of 0.5 g (2.34 mmol) of ferrocenecarbaldehyde in 5 mL of THF, stirred for 4 h at −78 °C and then allowed to reach room temperature overnight, quenched with water, and extracted with diethyl ether. After removal of the solvent, the crude reaction was chromatographed (SiO_2, Hexane:EtOAc 8:2) to yield 157 mg (24%) of ethyl 3-ferrocenylpropenoate as a red oil. ^{1}H NMR δ 1.26 (t, $J =$ 7.1 Hz, 3H), 4.10 (s, 5H), 4.18 (q, $J = 7.1$ Hz, 2H,), 4.33 (t, $J = 1.9$ Hz, 2H), 4.42 (t, $J = 1.9$ Hz, 2H), 5.97 (d, $J = 15.8$ Hz, 2H), 7.50 (d, $J = 15.8$ Hz, 2H). IR (film) 1707, 1632, 1396, 1367, 1290, 1246 cm^{-1}.

(2) Ethyl 3-Ferrocenylpropanoate. A solution of ethyl 3-ferrocenylpropenoate (157 mg, 0.55 mmol) and 6 mg of Pd-(C) in 20 mL of EtOH was stirred in a Parr apparatus under hydrogen pressure (40 psi) for 10 h to yield 147 mg (93%) of a yellow oil identified as ester **13**. ^{1}H NMR δ 1.19 (t, 3H, $J =$ 7.2 Hz), 2.45 (m, 2H), 2.60 (m, 2H), 3.97 (s, 4H), 4.04 (s, 4H), 4.07 (q, $J = 7.2$ Hz, 2H). ^{13}C NMR δ 14.2, 24.8, 35.7, 60.3, 67.3, 67.9, 68.5, 87.5, 173.1. IR (film) 1736 cm^{-1}.

Method B. To a solution of 3-ferrocenyl propanoic acid (2.1 g, 8.14 mmol) in 50 mL of dry acetone was added 1.25 mL (8.95 mmol) of Et_3N. Then, 1.50 g (8.14 mmol) of cyanuric chloride was added in one portion at room temperature, and the mixture stirred for 2.5 h. Afterward 2 mL of dry EtOH was added, and the solution was allowed to stir overnight, was filtered through a short pad of Celite, and the solvent removed under reduce pressure. After flash column chromatography (SiO_2, Hexane:EtOAc 4:1) accomplished by vacuum distillation was obtained 1.45 g (62%) of ester **13**.

General Procedure for the Synthesis of β-Lactams 6, 7, 8, 12. Photochemical reactions were conducted by using a 450 W-medium-pressure mercury lamp through a Pyrex filter. All the reactions were carried out in dry degassed MeCN or Et_2O in a sealed pressure Pyrex tube under CO pressure (90 psi). In a typical experiment a solution of the carbene complex (0.20 mmol) and the stoichiometric amount of imine in 20 mL of CH_3CN was irradiated as indicated for each case (all the reactions were monitored by TLC until the disappearance of the starting material). The solvent was removed in vacuo and the residue was dissolved in a mixture of hexane:EtOAc (1:1) and exposed to direct sunlight until a clear solution was obtained. The solution was filtered through a short pad of Celite, the solvent was eliminated, and the desired β-lactam

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was purified by flash column chromatography accomplished in some cases by crystallization from hexane to yield pure compounds.

1-Anisyl-4-ferrocenyl-3-methyl-3-methoxy-2-azetidinone, 6a. From 50 mg (0.2 mmol) of pentacarbonyl[(methoxy)(methyl)carbene]chromium(0) carbene complex and 80 mg (0.2 mmol) of imine **2**, after 24 h, was obtained 48 mg (79%) of compound **6a** as a mixture of isomers *cis:trans* (57:43 ratio). Isomer *cis*-**6a**: ^{1}H NMR δ 1.57 (s, 3H), 3.18 (s, 3H), 3.73 (s, 3H), 4.04 (br s, 7H), 4.19 (m, 1H), 4.25 (m, 1H), 4.74 (s, 1H), 6.85 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 9.0 Hz, 2H).^{13}C NMR δ 19.7, 54.3, 55.6, 60.1, 67.4, 67.7, 68.7, 68.8, 69.1, 82.8, 87.7, 114.2, 120.6, 130.7, 156.8, 166.9. Isomer *trans*-**6a**: ^{1}H NMR δ 1.02 (s, 3H), 3.44 (s, 3H), 3.75 (s, 3H), 3.83 (br s, 1H), 3.96 (s, 5H), 4.09 (br s, 2H), 4.16 (br s, 1H), 4.96 (s, 1H), 6.90 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 8.9 Hz, 2H).^{13}C NMR δ 15.7, 53.0, 55.6, 63.3, 64.0, 67.2, 67.7, 68.4, 69.2, 83.8, 90.7, 114.2, 22.3, 130.7, 157.4, 167.1. IR (KBr) 1747, 1512, 1250 cm^{-1}. Anal. Calcd for $C_{22}H_{23}FeNO_3$: C, 65.20; H, 5.72; N, 3.46. Found: C, 65.40; H, 5.84; N, 3.40.

1-Anisyl-3-ethoxy-4-ferrocenyl-3-methyl-2-azetidinone, 6b. From 53 mg (0.2 mmol) of pentacarbonyl[(ethoxy)(methyl)carbene]chromium(0) carbene complex and 80 mg (0.2 mmol) of imine **2**, after 18 h, was obtained after flash column chromatography 50 mg (67%) of compound **6b** as an inseparable mixture of isomers *cis:trans* (86:14 ratio). Isomer *cis*-**6b**: ^{1}H NMR δ 0.98 (t, J = 7.0 Hz, 3H), 1.59 (s, 3H), 3,36 (m, 1H), 3.54 (m, 1H), 3.75 (s, 3H), 4.07 (br s, 7H), 4.24 (br s, 1H), 4.38 (br s, 1H), 4.69 (s, 1H), 6.92 (d, J = 9 Hz, 2H), 7.48 (d, J = 9 Hz, 2H). ^{13}C NMR δ 15.6, 20.5, 55.5, 62.1, 66.1, 67.7, 68.4, 69.2, 70.3, 84.0, 87.5, 114.2, 120.4, 130.8, 156.7, 167.1. IR (KBr) 1746, 1512, 1248 cm^{-1}. The ^{1}H NMR data for *trans*-isomer was indistinguishable from that of *cis*-isomer but for signals listed bellow. *trans*-**6b**: ^{1}H NMR δ 1.23 (t, J = 7.0 Hz, 3H), 3.75 (s, 3H) and 4.97 (s, 1H). Anal. Calcd for $C_{23}H_{25}FeNO_3$: C, 65.88; H, 6.01; N, 3.34. Found: C, 66.00; H, 6.14; N, 3.25.

4-*p*-Anisyl-3-ethoxy-1-ferrocenyl-3-methyl-2-azetidinone, 7. From 53 mg (0.2 mmol) of pentacarbonyl[(ethoxy)(methyl)carbene]chromium(0)carbene complex and 61 mg (0.2 mmol) of imine **3** after 24 h was obtained after flash column chromatography 71 mg (85%) of compound **7** as a single isomer (*cis:trans* 100:0). Isomer *cis*-**7**: ^{1}H NMR δ 0.77 (t, J = 7.0 Hz, 3H), 1.60 (s, 3H), 3.06 (m, 1H), 3.37 (m, 1H), 3.75 (s, 3H), 3.82 (m, 1H), 3.93 (m, 2H), 4.10 (s, 5H), 4.47 (s, 1H), 4.58 (m, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H). ^{13}C NMR δ 15.2, 19.0, 55.2, 58.6, 61.6, 64.3, 65.1, 68.9, 69.4, 88.5, 93.2, 113.7, 126.5, 129.3, 159.7, 167.2. IR (KBr) 1736, 1506, 1250 cm^{-1}. $C_{23}H_{25}FeNO_3$: C, 65.88; H, 6.01; N, 3.34. Found: C, 65.90; H, 5.94; N, 3.40.

3-Ethoxy-1,4-diferrocenyl-3-methyl-2-azetidinone, 8. From 53 mg (0.2 mmol) of pentacarbonyl[(ethoxy)(methyl)carbene]chromium(0) carbene complex and 79.3 mg (0.2 mmol) of imine **4** after 24 h was obtained 88 mg (88%) of compound **8** as a single isomer (*cis:trans* 100:0). Isomer *cis*-**8**: ^{1}H NMR δ 1.12 (t, J = 7.0 Hz, 3H), 1.63 (s, 3H), 3.67 (m, 2H), 3.94 (m, 2H), 4.00 (s, 5H), [4.09 (s) and 4.09−4.25 (m), 8 H], 4.36 (s, 1H), 4.39 (br s, 2H), 4.48 (br s, 1H). ^{13}C NMR δ 15.9, 19.9, 59.6, 60.5, 61.9, 64.6, 64.8, 66.8, 67.3, 68.8, 69.0, 69.5, 70.1, 81.7, 87.6, 93.1, 167.5. IR (KBr) 1740, 1502, 1215 cm^{-1}. $C_{26}H_{27}Fe_2NO_2$: C, 62.81; H, 5.47; N, 2.82. Found: C, 62.90; H, 5.59; N, 2.92.

1-Anisyl-3-(*N*-ferrocenyl-*N*-methylamino)-3-methyl-4-phenyl-2-azetidinone, 12. From 100 mg (0.2 mmol) of aminocarbene complex **11** and 49 mg (0.2 mmol) of imine **1** after 40 h was obtained 25 mg (23%) of compound **12** as an inseparable mixture of isomers *cis:trans* (10:1 ratio). *cis*-**12**: ^{1}H NMR δ 1.15 (s, 3H), 2.95 (s, 3H), 3.65 (s, 3H), 3.88−4.03 (m, 4H), 4.13 (s, 5H), 4.98 (s, 1H), 6.68 (d, J = 9 Hz, 2H), 7.09−7.29 (m, 7H).^{13}C NMR δ 13.0, 38.1. 55.4, 59.4, 60.2, 63.9, 64.1, 64.3, 68.4, 69.1, 110.2, 114.2, 118.9, 127.9, 128.1, 128.7, 130.6, 135.0, 156.1, 166.5. IR (KBr) 1742, 1512, 1215 cm^{-1}. The ^{1}H NMR data for *trans*-isomer was indistinguishable from that of *cis*-isomer but for signals listed bellow. Isomer *trans*-**12**: ^{1}H NMR δ 1.8 (s, 3H) and 3.67 (s, 3H). $C_{28}H_{28}FeN_2O_2$: C, 70.01; H, 5.88; N, 5.83. Found: C, 70.34; H, 5.94; N, 6.01.

Synthesis of β-Lactams 14 and 15 and β-Ketoester 16. To a solution of LDA (1.4 mmol) in anhydrous THF at −78 °C was added dropwise a solution of the ester **13** (200 mg, 0.7 mmol) in 8 mL of THF. The mixture was stirred at this temperature for 15 min, and then, a solution of imine **1** (67 mg, 0.32 mmol) was added. Afterward the solution was allowed to reach room temperature and stirred overnight, quenched with water, and extracted with Et_2O. After removal of the solvent, the crude reaction was chromatographed (SiO_2, Hexane:EtOAc) to yield sequentially compounds **16**, **14**, and **15**. Analytically pure compounds **14** and **15** were obtained by crystallization from hexane.

1-*p*-Anisyl-3-ferrocenylmethyl-4-phenyl-2-azetidinone, 14 [58 mg (40%), 3.2:1 ratio of *cis:trans* mixture]. Isomer *cis*-**14** (from an inseparable mixture): ^{1}H NMR δ 2.15 (dd, J_1 = 15.1 Hz, J_2 = 9.0 Hz, 1H), 2.65 (dd, J_1 = 15.1 Hz, J_2 = 4.8 Hz, 1H), 3.31 (br s, 1H), 3.55 (m, 1H), 3.68 (s, 3H), 3.84 (br s, 1H), 3.96 (s, 4H), 4.03 (br s, 3H), 5.05 (d, J = 5.4 Hz, 1H), 6.69 (d, J = 9 Hz, 2H), 7.10−7.30 (m, 7H). ^{13}C NMR δ 25.2, 55.4, 56.4, 58.7, 68.8, 69.0, 85.9, 114.3, 118.4, 127.8, 128.4, 128.7, 131.1, 134.8, 155.9, 166.7. IR ($CHCl_3$) 1736, 1512, 1248 cm^{-1}. The ^{1}H NMR data for *trans*-isomer was indistinguishable from that of *cis*-isomer but for signals listed bellow. Isomer *trans*-**14**: ^{1}H NMR δ 2.81 (dd, J_1 = 14.6 Hz, J_2 = 9.1 Hz, 1H), 2.94 (dd, J_1 = 14.6 Hz, J_2 = 5.0 Hz, 1H), 3.66 (s, 3H), 4.56 (d, J = 2.0 Hz, 1H). $C_{27}H_{25}FeNO_2$: C, 71.85; H, 5.58; N, 3.10. Found: C, 71.95; H, 5.66; N, 3.00.

1-*p*-Anisyl-3-ferrocenylmethyl-3-hydroxy-4-phenyl-2-azetidinone, 15 (33 mg, 22%). ^{1}H NMR δ 2.32 (d, J = 15.0 Hz, 1H), 2.63 (d, J = 15.0 Hz, 1H), 3.35 (s, 1H), 3.52 (br s, 1H), 3.68 (s, 3H), 3.94 (s, 6H), 4.05 (br s, 1H), 4.13 (br s, 1H), 4.93 (s, 1H), 6.71 (d, J = 9.0 Hz, 2H), 7.12−7.21 (m, 4H), 7.31−7.37 (m, 3H). ^{13}C NMR δ 32.3, 55.4, 68.1, 68.6, 68.7, 68.9, 69.5, 69.8, 79.5, 86.5, 114.3, 119.1, 127.3, 128.6, 128.8, 130.7, 134.2, 156.3, 167.2. IR (CCl_4) 3293, 1726, 1514, 1248 cm^{-1}. MS (ESI) m/z (%) 467 (M^+, 100), 468 (33). $C_{27}H_{25}FeNO_3$: C, 69.39; H, 5.39; N, 3.00. Found: C, 69.30; H, 5.40; N, 2.90.

Ethyl 4-Ferrocenyl-2-ferrocenylmethyl-3-oxo-butanoate, 16 (28 mg, 8% based on the starting ester 13). ^{1}H NMR δ 1.16 (t, J = 7.0 Hz, 3H), 2.42−2.70 (m, 4H), 2.84 (d, J = 7.3 Hz, 2H), 3.49 (t, J = 7.3 Hz, 1H), 3.92−3.98 (m, 8H), 4.01 (s, 5H), 4.04 (s, 5H), 4.07 (q, J = 7.0 Hz, 2H). ^{13}C NMR δ 14.1, 23.2, 28.8, 44.4, 61.1, 61.4, 67.3, 67.7, 68.0, 68.5, 68.6, 68.7, 84.8, 87.5, 169.1, 204.3. IR (CCl_4) 1713, 1740 cm^{-1}.

***E*-*N*-*p*-Anisyl-3-ferrocenyl-2-(ferrocenylmethyl)propenamide, 17.** Following the general procedure from ester **13** (158 mg, 0.5 mmol) and imine **2** (80 mg, 0.25 mmol) were obtained 10 mg of unreacted starting material, 25 mg of ester **16** (10% based on the starting ester **13**), and 98 mg (70%) of a single isomer of amide **17** as an orange solid. ^{1}H NMR δ 3.62 (s, 2H), 3.71 (s, 3H), 4.11−4.12 (br s, 13H), 4.21 (br s, 1H), 4.32 (br s, 2H), 4.51 (br s, 2H), 6.78 (d, J = 8.5 Hz, 2H), 7.18 (br s, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.47 (br s, 1H). ^{13}C NMR δ 28.0, 55.4, 67.8, 68.6, 69.1, 69.3, 70.0, 70.1, 79.2, 86.4, 94.0, 114.1, 121.7, 134.5, 156.2, 167.3. IR (KBr) 3384, 3018, 1658, 1512 cm^{-1}. $C_{31}H_{29}Fe_2NO_2$: C, 66.58; H, 5.23; N, 2.50. Found: C, 66.42; H, 5.24; N, 2.40. MS (ESI) m/z (%) 559 (M^+, 100), 560 (40).

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