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Functionalization of Methyl (*R*)-Phenylglycinate Through Orthopalladation: C−Hal, C−O, C−N, and C−C Bond Coupling

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The ortho functionalization of methyl *R*-phenylglycinate has been easily achieved using the known orthopalladated complex [Pd(μ-Cl){*R*-C_6H_4($CH(CO_2Me)NH_2$)-2}]$_2$ (**1**) as synthetic tool. Different functional groups have been introduced at the ortho position of the aryl ring. The reaction of (*R*)-**1** with X_2 or $PhI(OAc)_2$ gives XC_6H_4-($CH(CO_2Me)NH_2$)-2 (X = I, Br, OMe, OEt) through oxidative coupling, while the reaction with CO gives an isoindolone. (*R*)-**1** also reacts with one, two, or three alkyne molecules to give different metal-containing or metal-free heterocycles. The resulting functionalized amino esters or heterocycles retain the chirality of (*R*)-**1**, according with the values of the optical rotation and the obtained *ee* values ranging from 22%−87%. The X-ray structures of six representative compounds have also been determined.

Introduction

The CH bond activation process is at present one the most active research areas in chemistry because of its relevance in the functionalization of organic molecules.[1] A common problem in this context is the selectivity of the activation when several possibilities exist, and synthetic strategies must be developed to obtain the best performance. A classical solution is the ortho functionalization, which is easily achieved in aromatic substrates through the introduction of an ancillary coordinating group, namely, the directing group, on the starting substrate.[2] This strategy results in the formation of orthometalated complexes, which are very valuable tools in stoichiometric and/or catalytic processes.[1,3−17] Among different metals, cyclopalladated complexes[4] have proved to be efficient preparative reagents in metal-mediated organic synthesis,[3−17] and a large variety of different functional groups have been introduced, selectively, at the ortho position of the directing group. Therefore, the incorporation on a given molecule of methyl,[5] acetate, or methoxy,[6]

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(1) Recent reviews: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924. (c) Bercaw, J. E.; Labinger, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 6899. (d) Chen, G. S.; Labinger, J. A.; Bercaw, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 6915. (e) Bergman, R. G. *Nature* **2007**, *446*, 391. (f) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (g) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (h) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874. (i) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(2) (a) Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2370. (b) Clegg, W.; Dale, S. H.; Harrington, R. W.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2374.

(3) Recent reviews on orthometalation: (a) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (d) Bedford, R. B. *Chem. Commun.* **2003**, 1787. (e) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759. (f) Omae, I. *Coord. Chem. Rev.* **2004**, *248*, 995. (g) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553. (h) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (i) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055. (j) Dupont, J.; Consorti, C.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527. (k) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431. (l) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (m) Mohr, F.; Privér, S. H.; Bhargava, S. K.; Bennett, M. A. *Coord. Chem. Rev.* **2006**, *250*, 1851. (n) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (o) Albert, J.; Granell, J.; Muller, G. *J. Organomet. Chem.* **2006**, *691*, 2101. (p) Ghedini, M.; Aiello, I.; Crispini, A.; Golemme, A.; La Deda, M.; Pucci, D. *Coord. Chem. Rev.* **2006**, *250*, 1373. (q) Vicente, J.; Saura-Llamas, I. *Comments Inorg. Chem.* **2007**, *28*, 39. (r) Omae, I. *J. Organomet. Chem.* **2007**, *692*, 2608. (s) Nishiyama, H. *Chem. Soc. Rev.* **2007**, *36*, 1133. (t) Gagliardo, M.; Snelders, D. J. M.; Chase, P. A.; Klein Gebbink, R. J. M.; van Klink, G. P. M.; van Koten, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8558. (u) Horino, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2144. (v) Ma, L.; Wong, E. L.-M.; Che, C.-M. *Dalton Trans.* **2007**, 4884. (w) Chatani, N. Directed Metallation. In *Topics in Organometallic Chemistry*; Springer Verlag: Berlin, Germany, 2007; Vol. *24*. (x) Leis, W.; Mayera, H. A.; Kaska, W. C. *Coord. Chem. Rev.* **2008**, *252*, 1787. (y) Djukic, J. P.; Hijazi, A.; Flack, H. D.; Bernardinelli, G. *Chem. Soc. Rev.* **2008**, *37*, 406. (z) Djukic, J. P.; Sortais, J. B.; Barloy, L.; Pfeffer, M. *Eur. J. Inorg. Chem.* **2009**, 817.

(4) Pfeffer, M.; Dupont, J. In *Palladacycles, Synthesis, Characterization and Applications*; Wiley-VCH: Weinheim, Germany, 2008.

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arylsulfonyl,[7] ethoxycarbonyl,[8] halogen,[9] amide[10] or amine,[11] alkynyl,[12] alkenyl,[13] acyl,[14] and aryl[15] functional groups, as well as intramolecular cyclization processes[16] and mechanistic studies[17] have been reported. Using this methodology, the formation of C−C, C−O, C−N, C−S, or C−X (X = halogen) bonds have been achieved in a plethora of substrates, at designed positions, and under controlled conditions, giving proof of its versatility and capability.

We intend to use this methodology to functionalize a special class of substrates, such as the α-amino acids containing an aryl ring at the Cα (phenylglycine, for instance) or at the chain located at the Cα (phenylalanine or structural analogous), aiming to obtain the corresponding ortho-functionalized substrates.

The relevance of α-amino acids in chemistry and biology is unquestionable, since they are basic building blocks on peptides and proteins. Recent advances in structural biology allow to correlate the structure of a given amino acid with its physicochemical and biological properties.[18a−f] Most natural peptides display properties of pharmacological interest, although their use is limited because of their low selectivity. The number of allowed conformations in solution is at the origin of undesired interactions with different guests, this fact being responsible of the poor selectivity. Therefore, the introduction of conformational restrictions at a given amino acid could stabilize only some few conformations, increasing the stability of the peptide and its selectivity. One of the most interesting conformational restrictions is the introduction of substituents at the ortho positions of the aromatic rings of the phenylglycine[18g] or phenylalanine[18h] amino acids, this fact decreasing notably the rotation of this ring. Obviously, this restricted rotation could result in different properties, providing valuable information about the binomial structure−activity relationship.[18i−n] In addition to the classic methods of introduction of ortho-substituents, we intend to use here a complementary "organometallic" point of view, based on the sequence CH bond activation-functionalization, which could be advantageous.

However, this type of functionalization in α-amino acids is also a scarcely developed field, when it is compared with other classical ligands,[5−15] although some outstanding

(5) Selected examples on methylation reactions: (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

(6) Selected examples on introduction of methoxy and acetate groups: (a) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141. (b) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285.

(7) Example on introduction of arylsulfonyl groups: Zhao, X.; Dimitrijevic, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466.

(8) Example on introduction of ethoxycarbonyl groups: Yu, W. Y.; Sit, W. N.; Lai, K. M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304.

(9) Selected examples on halogenation reactions: (a) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (b) Li, J. J.; Mei, T. S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (c) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (d) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.

(10) Selected examples on amidation and carboamidation reactions: (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066.

(11) Example on amination reactions: Dick, A. R.; Remy, M. S.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2007**, *26*, 1365.

(12) Example on introduction of alkynyl groups: Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250.

(13) Selected examples on introduction of alkenyl groups: (a) Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009**, 3874. (b) Lee, G. T.; Jiang, X.; Prasad, K.; Repic, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1921. (c) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586.

(14) Example on acylation reactions: Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120.

(15) Selected examples on arylation reactions: (a) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651. (b) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (c) Campeau, L. C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (d) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (e) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (f) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046. (g) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211. (h) Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947. (i) Daugulis, O.; Zaitsev, V. G.; Shavashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382. (j) Scarborough, C. C.; McDonald, R. I.; Hartmann, C.; Sazama, G. T.; Bergant, A.; Stahl, S. S. *J. Org. Chem.* **2009**, *74*, 2613. (k) Zhou, H.; Chung, W.-J.; Xu, Y.-H.; Loh, T.-P. *Chem. Commun.* **2009**, 3472. (l) Zhou, H.; Xu, Y.-H.; Chung, W.-J.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355. (m) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720. (n) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (o) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047.

(16) Selected examples on cyclization reactions: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Wu, L.; Qiu, S.; Liu, G. *Org. Lett.* **2009**, *11*, 2707. (c) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 2337. (d) Joyce, L. L.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2792. (e) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (f) Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. *Chem. Eur. J.* **2009**, *15*, 7292. (g) Murai, M.; Miki, K.; Ohe, K. *Chem. Commun.* **2009**, 3466.

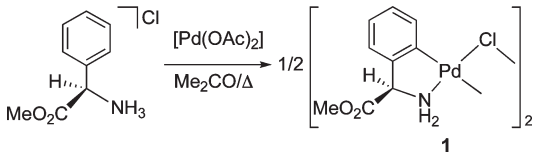
(17) Selected examples of mechanistic studies: (a) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790. (b) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974.

(18) Selected examples of structure−activity relationship: (a) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. *Curr. Med. Chem.* **2004**, *11*, 2785. (b) Sagan, S.; Karoyan, P.; Lequin, O.; Chassaing, G.; Lavielle, S. *Curr. Med. Chem.* **2004**, *11*, 2799. (c) Gibson, S. E.; Guillo, N.; Toser, M. J. *Tetrahedron* **1999**, *55*, 585. (d) Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389. (e) Galeazzi, R.; Mobbili, G.; Orena, M. *Curr. Org. Chem.* **2004**, *8*, 1799. (f) Maitly, P.; König, B. *Biopolymers (Pept. Sci.)* **2008**, *90*, 8; For a review of synthesis of modified arylglycines see:. (g) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889; For a review of synthesis of modified phenylalanines and structural analogous compounds:. (h) see reference [18c]. For recent selected references about the interest of ortho-substituted phenylglycines and phenylalanines see:(i) Ramón, R.; Alonso, M.; Riera, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2797. (j) Li, T.; Shiotani, K.; Miyazaki, A.; Tsuda, Y.; Ambo, A.; Sasaki, Y.; Jinsmaa, Y.; Marczak, E.; Bryant, S. D.; Lazarus, L. H.; Okada, Y. *J. Med. Chem.* **2007**, *50*, 2753. (k) Li, T.; Tsuda, Y.; Minoura, K.; In, Y.; Ishida, T.; Lazarus, L. H.; Okada, Y. *Chem. Pharm. Bull.* **2006**, *54*, 873. (l) Wang, W.; Zhang, J.; Xiong, C.; Hruby, V. J. *Tetrahedron Lett.* **2002**, *43*, 2137. (m) Soloshonok, V. A.; Tang, X.; Hruby, V. J. *Tetrahedron* **2001**, *57*, 6375. (n) Medina, E.; Moyano, A.; Pericás, M. A.; Riera, A. *Helv. Chim. Acta* **2000**, *83*, 972.

(19) (a) Vicente, J.; Saura-Llamas, I.; García-López, J. A.; Bautista, D. *Organometallics* **2009**, *28*, 448. (b) Vicente, J.; Saura-Llamas, I.; García-López, J. A.; Calmuschi-Cula, B. *Organometallics* **2007**, *26*, 2768. (c) Albert, J.; Cadena, J. M.; González, A.; Granell, J.; Solans, X.; Font-Bardia, M. *Chem.—Eur. J.* **2006**, *12*, 887 and refs cited therein. (d) Vicente, J.; Saura-Llamas, I.; Bautista, D. *Organometallics* **2005**, *24*, 6001. (e) Albert, J.; Cadena, J. M.; González, A.; Granell, J.; Solans, X.; Font-Bardia, M. *Chem. Commun.* **2003**, 528. (f) Albert, J.; Cadena, J. M.; González, A.; Granell, J.; Solans, X.; Font-Bardia, M. *J. Organomet. Chem.* **2002**, *663*, 277. (g) Fuchita, Y.; Yoshinaga, K.; Ikeda, Y.; Kinoshita-Kawashima, J. *J. Chem. Soc., Dalton Trans.* **1997**, 2495. (h) Hajipour, A. R.; Karami, K.; Pirisedigh, A.; Ruoho, A. E. *Amino Acids* **2009**, *37*, 537. (i) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (j) Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1634. (k) Ryabov, A. D.; Polyakov, V. A.; Yatsimirsky, A. K. *Inorg. Chim. Acta* **1984**, *91*, 59. (l) Vicente, J.; Saura-Llamas, I.; Grünwald, C.; Alcaraz, C.; Jones, P. G.; Bautista, D. *Organometallics* **2002**, *21*, 3587.

(20) (a) Bravo, J.; Cativiela, C.; Chaves, J. E.; Navarro, R.; Urriolabeitia, E. P. *Inorg. Chem.* **2003**, *42*, 1006. (b) Díaz-de-Villegas, M. D.; Urriolabeitia, E. P. *J. Chem. Educ.* **1999**, *76*, 77. (c) Cantín, O.; Cativiela, C.; Díaz-de-Villegas, M. D.; Navarro, R.; Urriolabeitia, E. P. *Tetrahedron: Asymmetry* **1996**, *7*, 2695. (d) Navarro, R.; Urriolabeitia, E. P.; Cativiela, C.; Díaz-de-Villegas, M. D.; López, M. P.; Alonso, E. *J. Mol. Catal A* **1996**, *105*, 111. (e) Navarro, R.; García, J.; Urriolabeitia, E. P.; Cativiela, C.; Díaz-de-Villegas, M. D. *J. Organomet. Chem.* **1995**, *490*, 35.

Scheme 1. Synthesis of Complex (*R*)-**1**[19g]



contributions have appeared recently,[19] showing the potential of this field. Most of the reported work describes only the orthopalladation reaction, while few of them are dedicated to the study of the reactivity of the Pd−C bond. Following our previous research in α-amino acids, and because of our interest in these ligands,[20] we report here the functionalization of enantiopure *R*-phenylglycine amino acid, as the methyl ester form. The oxidative coupling reaction and the insertion of small unsaturated molecules on the Pd−C bond have been studied, resulting in the synthesis of a wide prospect of structural situations, some of them unprecedented. A very interesting aspect, neglected in previous works, as far as we know, is the fate of the stereogenic information present in the starting ligand, that is, whether or not the chirality is preserved during the functionalization reaction. In most cases retention of the absolute configuration is observed, as inferred from the specific rotation and *ee* values obtained.

Results and Discussion

1. Characterization of ortho-Palladated Complex [Pd(μ-Cl){*R*-C$_6$H$_4$(CH(CO$_2$Me)NH$_2$)-2}]$_2$ (1). As starting point, we decided to study the reactivity of the palladated complex [Pd(μ-Cl){*R*-C$_6$H$_4$(CH(CO$_2$Me)-NH$_2$)-2}]$_2$ ((*R*)-**1**), which synthesis was previously reported by Fuchita et al. (Scheme 1).[19g] Complex (*R*)-**1** was prepared according to the mentioned procedure, by reaction of (*R*)-phenylglycinate methyl ester hydrochloride with Pd(OAc)$_2$ (OAc = acetate) in refluxing acetone. Purification by silica gel chromatography of the crude material obtained after solvent evaporation was needed for the isolation of (*R*)-**1** as pure yellow crystals (85% yield).

The identity of the compound (*R*)-**1** was determined from NMR spectroscopy data, by comparison with the original data reported by Fuchita et al.[19g] In addition, its molecular structure was confirmed by X-ray diffraction analysis. A drawing of the molecular structure is shown in Figure 1, selected bond distances and angles are collected in Table 1, and relevant crystallographic parameters are given in Table S1 (Supporting Information). Compound (*R*)-**1** crystallizes in the orthorhombic chiral space group $P2_12_12_1$, with a single molecule in the asymmetric part of the unit cell, reflecting that (*R*)-**1** is present in enantiomerically pure form. Refinement of the structure with *R* absolute configuration at both Cα atoms show correct values of the Flack parameter, meaning that ortho-palladation reaction occurs with a configuration retention. The value of specific rotation is $[\alpha]_D^{20}$ −333.4 ($CHCl_3$, c = 0.62), not reported before,[19g] and measured for crystals of (*R*)-**1**. In addition, the structure shows that (*R*)-**1** is a dimeric compound, containing two five-membered palladacycles. Each Pd center is coordinated to the chloride bridge atoms and to the respective N and C atoms of the orthometalated amino acid ligand, displaying a slightly distorted square planar geometry [C(1)−Pd(1)−N(1) 82.22(15)°, Cl(1)−Pd(1)−Cl(2) 87.94(4)°, Cl(1)−Pd(2)−Cl(2) 87.95(4)°, and C(10)−Pd(2)−N(2) 82.04(15)°]. Moreover, it has to be remarked that the cisoid arrangement of the two cyclopalladated moieties with respect to the chloride bridging system is not usually found in this type of structures.[4] A plausible explanation resides in the consideration that this ligand distribution minimizes both the molecular dipole and the intramolecular repulsions between ester groups.

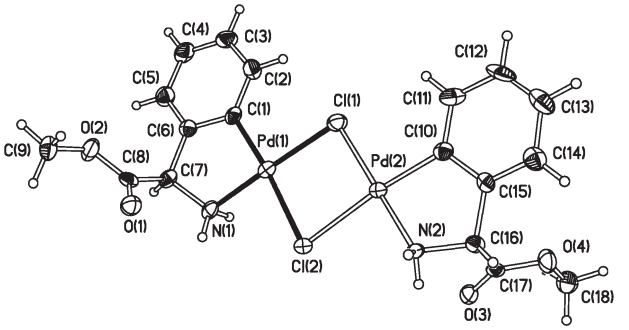


Figure 1. Structure of the complex (*R*)-**1**. Ellipsoids of non-hydrogen atoms have been drawn at 50% probability.

Table 1. Selected Bond Distances (Å) and Angles (deg) for (*R*)-**1**

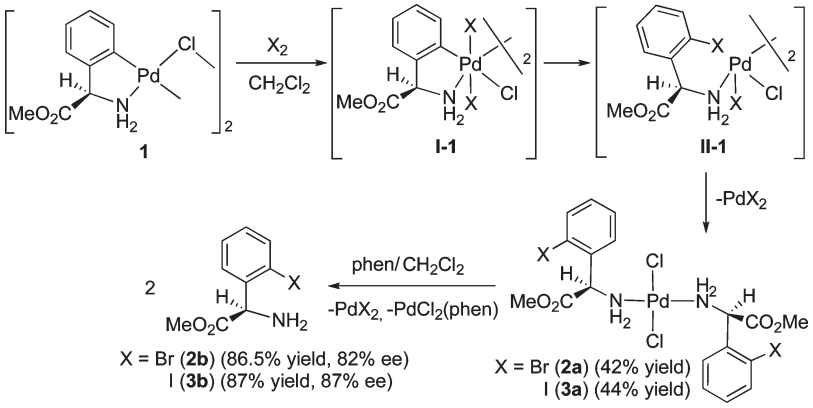
Pd1−C1	1.965(4)	Pd1−N1	2.048(3)
Pd1−Cl1	2.3279(11)	Pd1−Cl2	2.4811(11)
Pd2−C10	1.955(4)	Pd2−N2	2.031(3)
Pd2−Cl1	2.3264(11)	Pd2−Cl2	2.4824(11)
O1−C8	1.190(5)	O3−C17	1.193(5)
N1−C7	1.480(5)	N2−C16	1.476(5)
C1−Pd1−N1	82.22(15)	C1−Pd1−Cl1	97.36(13)
N1−Pd1−Cl2	92.63(10)	Cl1−Pd1−Cl2	87.94(4)
C10−Pd2−N2	82.04(15)	C10−Pd2−Cl1	97.33(13)
N2−Pd2−Cl2	92.81(9)	Cl1−Pd2−Cl2	87.95(4)
Pd1−Cl2−Pd2	88.23(3)	Pd1−Cl1−Pd2	95.86(4)

2. Reactions of (*R*)-1 in Oxidative Coupling Processes. Once the optical purity of (*R*)-**1** has been stablished, we have studied its reactivity. Aiming to achieve an easy and versatile method to synthesize new chiral functionalized amino acids, we decided to focus in study oxidative coupling reactions between the chiral palladated complex (*R*)-**1** and the halogens. Similar processes involving cyclopalladated complexes, containing aromatic tertiary amines, have been investigated.[3d,4,21] However, only very few studies employing cyclopalladated primary amines or α-amino acid complexes have been reported.[19b,d]

The formation of the palladium complexes **2a** and **3a** was initially observed after the addition of 2 equiv of halogen X_2 (X_2 = Br_2, I_2, respectively) to a solution of (*R*)-**1** in CH_2Cl_2. Both compounds are characterized as coordination complexes by spectroscopic methods (see Experimental Section). Further reaction of **2a** and **3a** with phenanthroline promoted the release of the corresponding free-metal halogenated amino acids (**2b** and **3b**, Scheme 2) in good yields, which were fully characterized.

(21) (a) Ryabov, A. D. *Synthesis* **1985**, 233. (b) Onishi, M.; Hiraki, K.; Iwamoto, A. *J. Organomet. Chem.* **1984**, *262*, C11. (c) Dunina, V. V.; Gorunova, O. N.; Grishin, Y. K.; Kuz'mina, L. G.; Churakov, A. V.; Kuchin, A. V.; Howard, J. A. K. *Russ. Chem. Bull.* **2005**, *54*, 2073. (d) Bartolome, C.; Espinet, P.; Martin-Alvarez, J. M.; Villafañe, F. *Inorg. Chim. Acta* **2003**, *347*, 49.

Scheme 2. Proposed Mechanism for the Synthesis of Compounds **2b** and **3b**



The mechanism that we propose for these reactions, see Scheme 2, is an alternative to the mechanism previously reported by Vicente et al.[19b] The reaction starts with the initial oxidative addition of X_2 to the Pd center, affording a plausible dimer of Pd(IV) centers I-1, which suffers reductive elimination through formation of two new C−X (X = Br, I) bonds, regenerating a Pd (II) complex (complex II-1). The resulting dimer complex II-1 eliminates the very insoluble $Pd(II)X_2$ salt, with concomitant formation of mononuclear **2a** and **3a**. The main difference with previous proposals[19b] resides in the nature of the intermediate II-1. We propose a dinuclear derivative, instead of a mononuclear one[19b] based on the known reactivity of $PdCl_2L_2$ or PdR_2L_2 complexes toward PdX_2, which affords dinuclear $[Pd(\mu\text{-}Cl)ClL]_2$ or $[Pd(\mu\text{-}Cl)RL]_2$ (R = C_6F_5 or C_6Cl_5; L = neutral ligand) through a symmetrization process.[22] The formation of **2a** or **3a** from II-1 could be considered as the inverse process, that is, the formation of two mononuclear complexes (one of them very insoluble) from the dinuclear. Finally, free amino acids **2b** and **3b** are obtained by the addition of phenanthroline to **2a** and **3a**, following reported procedures.[19b]

The $[\alpha]_D^{20}$ values for **2b** and **3b** were −42.6 ($CHCl_3$, c = 0.63) and −52.2 ($CHCl_3$, c = 0.63), respectively, meaning that these reactions occur with some degree of enantioselectivity. Aiming to determine the extent of the enantiomeric excess (*ee*) obtained in the synthesis of **2b** and **3b** we have applied several methods already reported on the literature. These methods are the following: (i) the Tony-James NMR protocol; (ii) the chiral shift reagent europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(*d*)-camphorate] [Eu(hfc)$_3$]; and (iii) the chiral derivatization using Mosher's acid chloride [*R*-(-)-α-methoxy-α-trifluoromethylphenylacetyl chloride], (*R*)-MTPA-Cl).[23] Among them, only Mosher's method works efficiently for the determination of the *ee* of **2b** and **3b**. When the NMR Tony-James protocol is applied,[23c,d] racemization was observed after the derivatization reaction. Similar results were obtained when the commercial (*R*)-phenylglycinate methyl ester hydrochloride was subjected to this NMR derivatization method. Some problems were also observed when using the chiral shift reagent Eu(hfc)$_3$ since,[23e] although the ^{1}H NMR signals of the aminoesters **2b** and **3b** underwent downfield shifts, these signals suffered severe broadening avoiding a proper integration and, consequently, the enantiomeric discrimination process. Therefore, only chiral derivatization with (*R*)-MTPA-Cl was successful, and this was applied as a general method. The method was carried out according to literature's procedure.[23b] The resulting (*R*)-MTPA-amides of **2b** and **3b** were analyzed by ^{19}F NMR spectroscopy, and the *ee* obtained were 82% and 87%, respectively (see Supporting Information). Obviously, the products are enriched in the (*R*)-enantiomer. Therefore, the synthetic reactions occur with the partial retention of the configuration.

The crystallization of **2b** or **3b** proved to be difficult, although a few crystals were grown from solutions containing the crude compound **2b**. However, determination of the structure of these crystals showed that **2b** has evolved in solution to the hydrobromide $[BrC_6H_4\{C(H)(CO_2Me)NH_3\}\text{-}2]Br$ **2c**. We are unaware of the source of the HBr which can originate the formation of **2c**.

A molecular drawing of **2c** is shown in Figure 2, selected bond distances and angles are given in Table 2, and crystallographic parameters concerning data collection and structure solution and refinement are collected in the Supporting Information. Compound **2c** crystallizes in the monoclinic space group $P2_1/c$, that is, a centrosymmetric space group, meaning that racemization had occurred during the crystallization process. The structure shows the incorporation of a bromine atom at the ortho position of the phenyl ring with respect to the amino acid fragment, as expected. All internal structural parameters do not show deviations from the expected values.

The methodology here presented is efficient for the synthesis of halo-amino acids, although the optical purity of the resulting species needs some improvements. Aiming to increase the scope of amino acids ortho-functionalized, we have tested other different oxidants. In the past years, iodine(III) reagents have been widely employed as oxidant species because of their low toxicity and

(22) For a review, see: (a) Usón, R.; Forniés, J. *Adv. Organomet. Chem.* **1988**, *28*, 219. For selected references, see:(b) Usón, R.; Forniés, J.; Martínez, F. *J. Organomet. Chem.* **1977**, *132*, 429. (c) Usón, R.; Forniés, J.; Navarro, R.; García, M. P. *Inorg. Chim. Acta* **1979**, *33*, 69. (d) Usón, R.; Forniés, J.; Martínez, F.; Tomás, M. *J. Chem. Soc., Dalton Trans.* **1980**, 888. (e) Mann, F. G.; Purdie, D. *J. Chem. Soc.* **1936**, 873.

(23) (a) Seco, J. M.; Quinoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17. (b) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451. (c) Pérez-Fuertes, Y.; Kelly, A. M.; Fossey, J. S.; Powell, M. E.; Bull, S. D.; James, T. D. *Nat. Protoc.* **2008**, *3*, 210. (d) Pérez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett.* **2006**, *8*, 609. (e) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

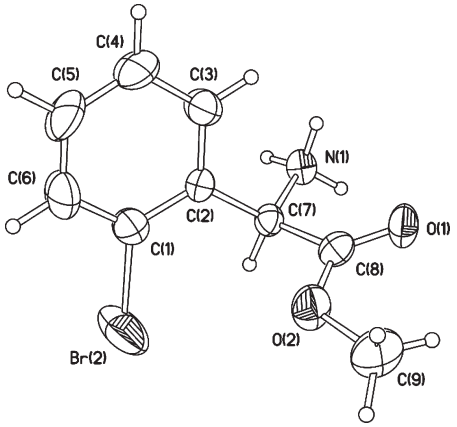


Figure 2. Structure of the cationic fragment of derivative **2c**. Ellipsoids of non-hydrogen atoms have been drawn at 50% probability.

Table 2. Selected Bond Distances (Å) and Angles (deg) for Compound **2c**

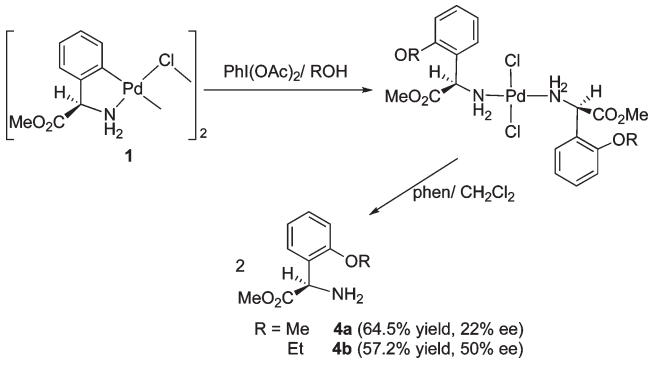
Br2−C1	1.899(6)	C1−C2	1.368(7)
C1−C6	1.381(8)	C2−C7	1.516(6)
C7−N1	1.490(6)	C7−C8	1.509(7)
C8−O1	1.189(6)	C8−O2	1.323(7)
C2−C1−Br2	120.4(4)	C6−C1−Br2	117.2(5)
N1−C7−C8	107.2(4)	N1−C7−C2	112.5(4)
C8−C7−C2	113.8(4)	O1−C8−O2	125.6(5)

milder reaction conditions when compared with other oxidants,[24] characteristics which confer a great potential for the functionalization of cyclometalated complexes.[1b,3l,4,6a,25]

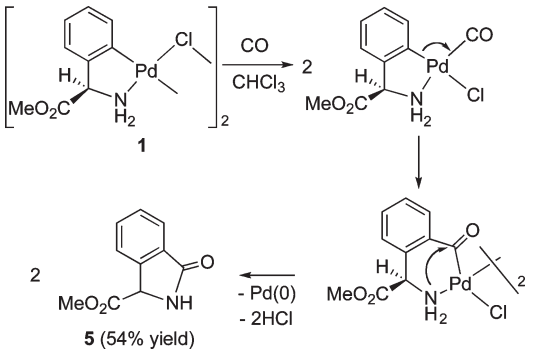
Therefore, we investigated the reaction between complex (*R*)-**1** and $PhI(OAc)_2$ in methanol or ethanol at room temperature. Following a workup very similar to that reported previously for other cyclopalladated complexes,[6] and after the addition of phenanthroline to release the ligands from the metal center, the free-metal α-amino acids **4a** or **4b** can be isolated in moderate yields (Scheme 3). In the compound **4a** the presence of the methoxy group in the ortho position of the α-amino acid was confirmed by the ^{1}H NMR and ^{13}C NMR spectra, which displayed new singlets at 3.70 ppm and at 54.89 ppm, respectively. In an analogous way, the presence of the ethoxy group in **4b** was inferred from the signals at 4.06 and 1.40 ppm in the ^{1}H NMR and at 14.71 and 63.64 ppm in the ^{13}C NMR.

The reaction mechanism operating here is most likely similar to that reported previously[6] and consists on an initial oxidation of (*R*)-**1** to a Pd (IV) species promoted by the $PhI(OAc)_2$, followed by the coordination of the methoxy or ethoxy groups to the electrophilic Pd(IV) center. The reductive elimination through formation of the C−O bond regenerates a Pd(II) complex to which the functionalized amino acid remains bonded. Subsequent addition of phenanthroline promotes the precipitation of the complex $[PdCl_2(phen)]$ and the release of the functionalized α-amino acids **4a** or **4b**. As described in previous paragraphs for **2b** and **3b** the reaction displayed somewhat enantioselectivity, according with the values for the specific rotation obtained, −13.2 ($CHCl_3$, c = 0.20) for **4a** and −14.1 ($CHCl_3$, c = 0.28) for **4b**. The *ee's*

Scheme 3. Synthesis of Compounds **4a** and **4b**



Scheme 4. Suggested Reaction Pathway for the Synthesis of **5**



were determined by Mosher derivatization and resulted in 22% and 50%, respectively (see Supporting Information), displaying a partial retention of the configuration. Anyway, the synthesis of optically enriched modified arylglycines **2**−**4** is noteworthy; it proved the inherent difficulties to obtain optically active arylglycines.[18g]

3. Reactivity of (*R*)-1 toward Small Unsaturated Molecules: CO, CNR. In compounds **2**−**4** there is no further reactivity between the ortho-directing group (the C(H)-$(CO_2R)NH_2$ fragment) and the new functional groups (Br, I, OR). However, the coupling of these two units is possible and could give very interesting heterocycles. This is usually the case when the orthopalladated complexes react with unsaturated molecules. Therefore, our next goal was to study the reactivity of (*R*)-**1** toward CO, isonitriles, and alkynes. Insertion reactions of CO and isonitriles into the Pd−C bond of palladated tertiary amines have been broadly investigated, and usually they allow for the synthesis of acyl or iminoacyl N-heterocycles.[3d,4,26] In contrast, few studies involving orthometalated primary amines or α-amino acids have been reported in the literature.[19a,b]

The reaction between (*R*)-**1** and CO (1 atm) ($CHCl_3$, 25 °C, Scheme 4) occurs with extensive decomposition (presence of black Pd^0). After elimination of the metallic residue, evaporation of the solution yields the air-stable metal-free isoindolone **5** (Scheme 4). The reaction

(24) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656.
(25) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836.

(26) See for example: (a) Thompson, J. M.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 2667. (b) Dupont, J.; Pfeffer, M.; Daran, J. C.; Jeannin, Y. *Organometallics* **1987**, *6*, 899. (c) Tollari, S.; Demartin, F.; Cenini, S.; Palmisano, G.; Raimondi, P. *J. Organomet. Chem.* **1997**, *527*, 93. (d) Rammah, M. M.; Othman, M.; Ciamala, K.; Strohmann, C.; Rammah, M. B. *Tetrahedron* **2008**, *64*, 3505.

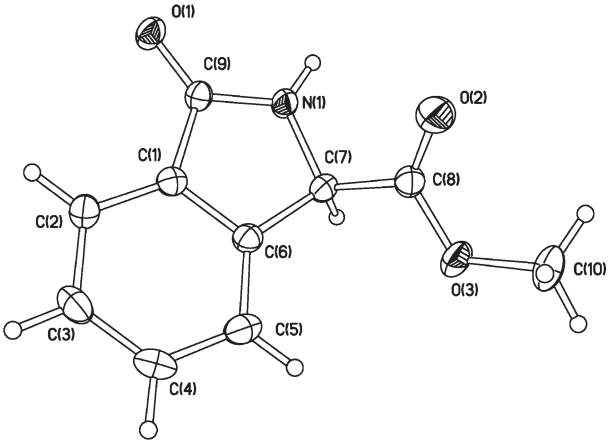


Figure 3. Molecular drawing of **5**. Ellipsoids of non-hydrogen atoms have been drawn at 50% probability.

Table 3. Selected Bond Distances (Å) and Angles (deg) for Compound **5**

C1−C6	1.380(2)	C1−C9	1.478(2)
C6−C7	1.515(2)	C7−N1	1.443(2)
C9−N1	1.340(2)	O1−C9	1.2367(19)
O1−C9−N1	126.03(16)	N1−C7−C6	102.10(13)
C6−C1−C9	108.65(15)	C1−C6−C7	108.57(15)

pathway is the classical CO migratory insertion into the activated Pd−C bond affording an acyl complex, followed by the intramolecular nucleophilic N-attack to the carbonyl carbon, promoting the release of isoindolone **5** via reductive elimination.

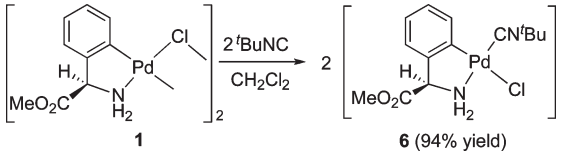
Compound **5** was characterized by NMR and IR spectroscopies. The IR spectrum displayed the presence a new strong absorption at 1691 cm^{-1}, attributed to the carbonyl of the amide group. This observation was further supported by the existence of a new signal at 169.64 ppm in the ^{13}C NMR spectrum assigned to the C of the amide group. Surprisingly, and in clear contrast with the observed behavior in **2**−**4**, the measured value of specific rotation for **5** is near zero $[\alpha]_D^{20}$ −0.30 ($CHCl_3$, c = 0.505), showing that a complete epimerization has occurred during the reaction. It seems likely that the acidity of the benzylic proton could be the responsible of the observed epimerization. In fact, both acid- and base-catalyzed epimerization of aryl glycines have been reported.[18g]

X-ray diffraction analysis of a single crystal of **5** confirmed the formation of the isoindolone skeleton. A molecular drawing of **5** is shown in Figure 3, selected bond distances and angles are given in Table 3, and crystallographic parameters concerning data collection and structure solution and refinement are collected in the Supporting Information.

Compound **5** crystallizes on the triclinic system, space group $P\bar{1}$. The presence of a crystallographic inversion center is in keeping with the formation of **5** as racemic mixture. The C(9)−O(1) bond distance [1.2367(19) Å] suggests a notable charge delocalization of the carbonyl group through the N atom of the amide and also through the aromatic group. The bond distance C(9)−O(1) is comparable to other distances reported for similar compounds.[27]

(27) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 51.

Scheme 5. Synthesis of Complex **6**



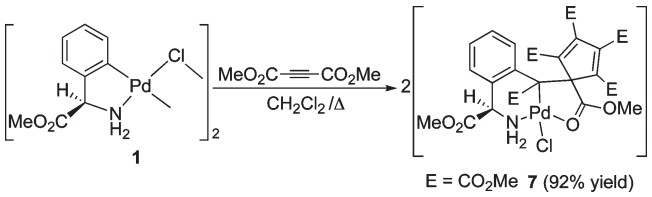
Isonitriles are small unsaturated molecules that react with orthopalladated complexes, giving interesting heterocycles.[4,19b,19d,19l] Aiming to enlarge the scope of accessible heterocycles, we have studied the reactivity of *tert*-butylisocyanide. The reaction between (*R*)-**1** and *tert*-butylisocyanide yielded the monomeric palladium complex **6**, in which the isocyanide ligand is coordinated to the metal (Scheme 5). The IR spectrum of **6** shows a strong absorption at 2212 cm^{-1} characteristic of the CN bond. The NMR spectra also confirmed the coordination of this ligand to the Pd center with the presence in the ^1H NMR of an intense signal at 1.45 ppm corresponding to the methyl groups of the *tert*-butyl unit. The measured specific rotation value of **6** was $[\alpha]_D^{20}$ +56.3 ($CHCl_3$, c = 0.38), showing that the coordination of the isonitrile, as expected, does not alter the optical properties. Several conditions were attempted to promote the insertion of the isonitrile and its further depalladation to release an organic heterocycle. Unfortunately, **6** seems to be quite stable, and all attempts were unsuccessful. This substrate was not explored further.

4. Reactivity of (*R*)-1 toward Small Unsaturated Molecules: Alkynes. As a further step, we decided to study for the first time the insertion of alkynes into the Pd−C bond of cyclopalladated α-amino acids. The insertion of alkynes and its mechanism have been extensively investigated employing several types of palladacycles, and it was concluded that, in general, the products obtained and the number of inserted alkynes depends on the reaction conditions, the electronic and steric properties of the alkynes, and the nature of the orthopalladated complexes employed.[4,28] Therefore we decided to study the reaction of (*R*)-**1** with three different types of alkynes: an alkyne containing strong electron-withdrawing substituents such as dimethyl acetylenedicarboxylate (DMAD), an electron-rich alkyne like 3-hexyne, and an intermediate case like diphenylacetylene.

The reaction of (*R*)-**1** with excess of DMAD in refluxing CH_2Cl_2 for 4 h results in the triple insertion of the alkyne affording **7** (see Scheme 6) in very good yield.

(28) See for representative examples: (a) Pfeffer, M. *Recl. Trav. Chim. Pay-Bas* **1990**, *109*, 567. (b) Pfeffer, M. *Pure Appl. Chem.* **1992**, *64*, 335. (c) Dupont, J.; Pfeffer, M. *J. Chem. Soc., Dalton Trans.* **1988**, 2421. (d) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *J. Chem. Soc., Chem. Commun.* **1986**, 488. (e) Wu, G.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1987**, *6*, 2386. (f) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *Organometallics* **1987**, *6*, 2029. (g) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *Organometallics* **1987**, *6*, 2043. (h) Spencer, J.; Pfeffer, M. *Tetrahedron: Asymmetry* **1995**, *6*, 419. (i) Spencer, J.; Pfeffer, M.; Kyritsakas, N.; Fischer, J. *Organometallics* **1995**, *14*, 2214. (j) Vicente, J.; Saura-Llamas, I.; Turpin, J.; Bautista, D.; Ramirez de Arellano, M. C.; Jones, P. G. *Organometallics* **2009**, *28*, 4175. (k) Vicente, J.; Saura-Llamas, I.; Turpin, J.; Ramírez de Arellano, M. C.; Jones, P. G. *Organometallics* **1999**, *18*, 2683. (l) Vicente, J.; Saura-Llamas, I.; Palin, M. G.; Jones, P. G. *J. Chem. Soc., Dalton Trans.* **1995**, 2535. (m) Vicente, J.; Saura-Llamas, I.; Ramírez de Arellano, M. C. *J. Chem. Soc., Dalton Trans.* **1995**, 2529. (n) van der Schaaf, P. A.; Sutter, J. P.; Grellier, M.; van Mier, G. P. M.; Spek, A. L.; van Koten, G.; Pfeffer, M. *J. Am. Chem. Soc.* **1994**, *116*, 5134.

Scheme 6. Synthesis of Complex **7**



Complex **7** was characterized by NMR spectroscopy in solution. The structure shown in Scheme 6 was proposed on the basis of these data and on previous work.[28a,c,j] It is noteworthy that, although **7** possesses two stereogenic centers, only one diastereoisomer was obtained, since only one set of resonances was observed in each spectrum. The ^{1}H and ^{13}C NMR spectra showed the presence of seven methoxy groups, one corresponding to the amino ester and six more attributed to the three inserted DMAD molecules, in addition to the signals assigned to the cyclopalladated unit and the amino and ester fragments. Moreover, the specific rotation value $[\alpha]_D^{20}$ was +37.4 ($CHCl_3$, c = 0.49), showing that the reaction occurs with some degree of diastereoselectivity. However, in this case the employ of the Mosher derivatization method does not work, and exact *ee* could not be measured. This protocol neither allows for *ee* determination of the rest of the ortho-palladated derivatives that we report in this manuscript (compounds **9**-**12**) and for the compound **8** (see below). The employ of chiral shift reagents or the Tony-James NMR methods were also unsuccessful.

Additional information was obtained from the crystal structure of the complex **7 OCMe$_2$**, elucidated by X-ray diffraction analysis. A molecular drawing of **7** is shown in Figure 4, selected bond distances and angles are presented in Table 4, and relevant crystallographic parameters are given in the Supporting Information. The complex crystallizes in the orthorhombic chiral space group $P2_12_12_1$, which indicates the presence of only one enantiomer in the crystal.

The structure shows the formation of a monomeric complex, which contains a cyclopentadiene unit and two metallacycles of five and six members. The formation of the cyclopentadiene entity is characteristic of reactions between alkynes and cyclopalladated complexes, and several examples are reported.[28a,c,j] The Pd atom displays a slightly distorted square-planar coordination environment, with the coordination positions occupied by one chloride ligand [Pd(1)−Cl(1) 2.3572(9) Å] and by the resulted tridentate ligand, which is bonded to the palladium through the nitrogen atom of the amino ester [Pd(1)−N(1) 1.987(3) Å], the carbon C(1) of the one DMAD molecule [Pd(1)−C(1) 2.067(3) Å], and the oxygen atom O(5) of a carboxylate group [Pd(1)−O(5) 2.053(2) Å]. Furthermore, a weak interaction between Pd(1) and the C(11) was observed with a bond distance of 2.602(3) Å and a bond angle of C(11)−C(1)−Pd(1) of 92.8(2)°. A similar interaction was reported for analogous cyclopalladated compounds.[28a,c,j] As expected, the length of the C=O bond that is bonded to the palladium through the oxygen O(5) atom [C(14)−O(5) 1.224(4) Å] is significantly longer than those found on the rest of the carboxylate groups. The relative arrangement of the different functional groups, which could be at the origin of the observed diastereoselectivity, seems to be driven by steric factors. Thus, the ester group at C(8) lies at one side of the molecular plane (upside in Figure 4) and probably forces the location of the ester group at C(1) on the other side of the molecular plane (downside in Figure 4) probably to minimize intramolecular steric interactions. In turn, the spatial location of the ester at C(1) drives the configuration around C(13) and the orientation of the ester directly bonded to it.

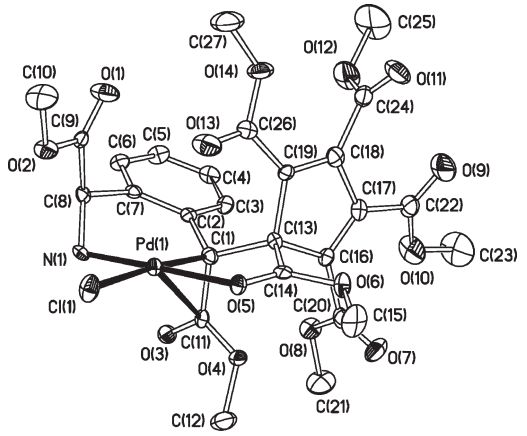
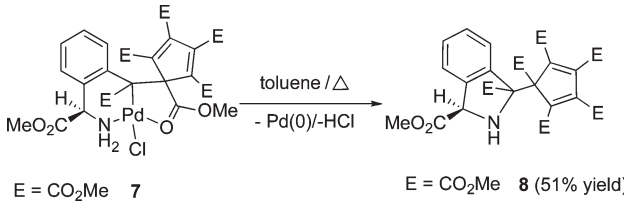


Figure 4. Structure of the organometallic part of **7 OCMe$_2$**. Ellipsoids of non-hydrogen atoms have been drawn at 50% probability. H atoms have been omitted by clarity.

Table 4. Selected Bond Distances (Å) and Angles (deg) for Compound **7 OCMe$_2$**

Pd1−C1	2.067(3)	Pd1−N1	1.987(3)
Pd1−Cl1	2.3572(9)	Pd1−O5	2.053(2)
Pd1−C11	2.602(3)	C14−O5	1.224(4)
C11−O3	1.213(4)	C1−C11	1.484(5)
C1−C13	1.585(5)	C1−C2	1.529(5)
C13−C14	1.520(5)	C13−C16	1.534(4)
C16−C17	1.334(5)	C17−C18	1.478(5)
C18−C19	1.341(5)	C13−C19	1.535(5)
C1−Pd1−N1	91.38(12)	O5−Pd1−C1	84.60(12)
N1−Pd1−Cl1	92.72(7)	O5−Pd1−N1	175.51(10)

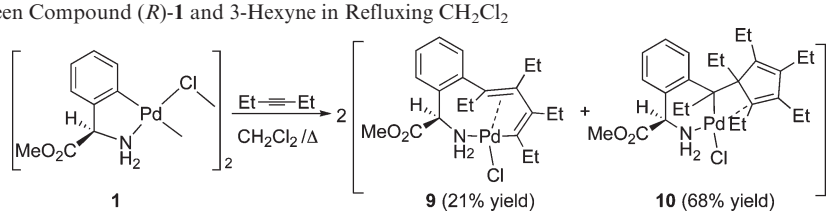
Scheme 7. Synthesis of Heterocycle **8**



Depalladation of **7** is easily achieved, resulting in the synthesis of new chiral aminoester-containing heterocycles (Scheme 7). Therefore, when **7** is refluxed in toluene for 1 h the formation of black Pd(0) is evident. Extraction with diethyl ether of the residue after solvent evaporation results in the formation of the metal-free compound **8** in moderate yield (51%), which was characterized by MS and NMR spectroscopy.

The NMR spectra showed, as expected, the presence of signals assigned to the presence of seven methoxy groups. The presence of only one peak assigned to the NH group on the ^{1}H NMR spectrum, together with the neutral nature of **8**, suggest that **8** is in fact a new heterocycle. The formation of the heterocycle is likely produced by nucleophilic attack of the N atom to the highly electron

Scheme 8. Reaction between Compound (*R*)-**1** and 3-Hexyne in Refluxing CH_2Cl_2



deficient metalated carbon (there is an ester group on this carbon) and concomitant C−N bond coupling. The reductive elimination also implies removal of HCl and formation of black Pd(0). Moreover, the NMR spectra show a single set of signals, showing that **8** is obtained as a single diastereoisomer. The measured value for the specific rotation $[\alpha]_D^{20}$ of +8.4 ($CHCl_3$, c = 0.47) implies somewhat enantioselectivity in the reaction but, once again, none of the checked methods for *ee* determination were successfully applied.

Prompted by these results, we decided to try an electron-rich alkyne, such as is 3-hexyne. Therefore, (*R*)-**1** and excess 3-hexyne were reacted together in refluxing CH_2Cl_2 for 4 h, yielding a mixture of two products, which after separation by silica gel chromatography were identified as complexes **9** and **10** (Scheme 8).

Complex **9** was obtained in a 21% of yield, and it is the result of the insertion of two molecules of 3-hexyne, as shown by NMR. The ^{1}H NMR spectrum displayed the presence of four triplets between 0.60 and 1.06 ppm, and four multiplets in the range of 1.49 and 2.34 ppm, signals attributed to the four methyl and methylene protons, respectively, of the ethyl groups. The $[\alpha]_D^{20}$ value of **9** is +182.6 ($CHCl_3$, c = 0.48).

Suitable crystals for X-ray diffraction of complex **9** were obtained by slow diffusion of *n*-pentane into a saturated solution of **9** in dichloromethane at room temperature. A molecular drawing of **9** is shown in Figure 5, selected bond distances and angles are given in Table 5, and relevant crystallographic parameters are collected in the Supporting Information. Complex **9** crystallizes in the orthorhombic chiral space group $P2_12_12_1$, and possesses only one molecule in the asymmetric part of the unit cell, meaning that a single enantiomer is present in the crystal. The structure contains two metallacycle entities, and the palladium atom displays a slightly distorted square-planar geometry. The four coordination positions of the palladium atom are occupied by a chloride [Pd(1)−Cl(1) 2.3457(7) Å], and the tridentate ligand resulted from the insertion of the two molecules of 3-hexyne into the Pd−C bond. The resulting tridentate moiety is coordinated to the palladium center by a nitrogen [Pd(1)−N(1) 2.169(2) Å], the vinylic carbon C(16) [Pd(1)−C(16) 1.999(2) Å], and by an olefin unit [Pd(1)−C(7) 2.174(2) Å and Pd(1)−C(10) 2.159(3) Å]. All these distances fall in the usual range of distances found in other complexes with similar structural arrangements.[28a,j] The C(7)−C(10) bond distance [1.402(4) Å] is slightly longer than the C(13)−C(16) bond distance [1.315(4) Å] because of the coordination of the former bond to the metal center. It is remarkable that the ethyl substituents showed a *trans*+*cis* arrangement, in which the C=C group next to palladium exhibited a *cis* disposition, meanwhile the other C=C group showed a *trans* geometry. This situation was found previously in

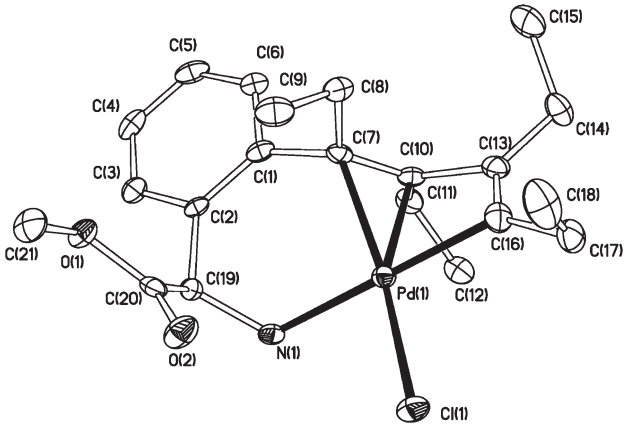


Figure 5. Molecular drawing of **9**. Ellipsoids of non-hydrogen atoms have been drawn at 50% probability. H atoms have been omitted by clarity.

Table 5. Selected Bond Distances (Å) and Angles (deg) for Compound **9**

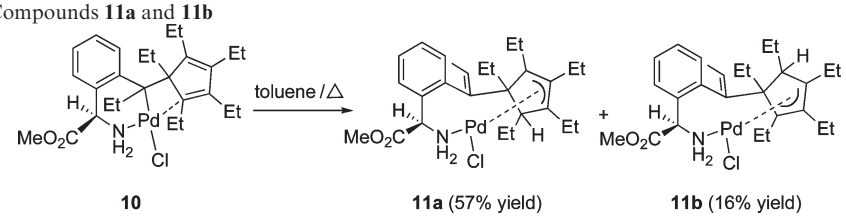
Pd1−N1	2.1693(18)	Pd1−C7	2.174(2)
Pd1−Cl1	2.3456(7)	Pd1−C10	2.159(3)
Pd1−C16	1.999(2)	C1−C7	1.520(4)
C7−C10	1.402(4)	C10−C13	1.501(4)
C13−C16	1.315(4)	C7−Pd1−N1	91.13(9)
N1−Pd1−C16	169.59(10)	C7−Pd1−C10	37.75(9)
N1−Pd1−Cl1	89.41(6)	C10−Pd1−C16	65.76(12)
C7−Pd1−C16	85.54(11)	C7−Pd1Cl1	162.57(7)
Cl1−Pd1−C16	96.74(8)	N1−Pd1−C7	91.13(8)

related complexes,[28a,j] and Maitlis et al. attributed the driving force of this isomerization to the fact that higher stabilization resulted in the case of the compound having *trans-cis* arrangement than in the isomer with the *cis-cis* orientation, because in the *cis-cis* geometry the C=C entity is not properly orientated to achieve a good overlap of π orbitals of the olefin with the d orbitals of the palladium.[29] Unfortunately, all the efforts to form a heterocycle from **9** by Pd elimination, including reaction with PPh_3 in MeOH,[28n] were unsuccessful. This lack of clear reactivity toward phosphine treatment has also been observed in complexes **10**, **11**, and **12**, avoiding the isolation of (in principle) interesting heterocycles.

The other product of the reaction, complex **10**, resulted from the insertion of three 3-hexyne molecules, and it was obtained in a 68% yield. The proposed structure for **10**, shown in Scheme 8, was assigned based on NMR data and comparison with previously reported tri-inserted complexes.[28a] Although **10** possess two chiral centers only one diastereoisomer is detected in solution by NMR methods. The measured value of specific rotation $[\alpha]_D^{20}$ is +36.0 ($CHCl_3$, c = 0.56) suggesting that the product is obtained diastereoselectively.

(29) Taylor, S. H.; Maitlis, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 4700.

Scheme 9. Synthesis of Compounds **11a** and **11b**



While phosphine-promoted decomposition of **10** was unsuccessful, its thermal treatment gave an unexpected result. When **10** was refluxed in toluene for 1 h the formation of two unprecedented, as far as we know, ortho-palladated species **11a** and **11b** in a 3:1 molar ratio was observed (Scheme 9).

These compounds have both identical MS spectra with the starting material indicating that palladium has not been eliminated, but clearly different NMR spectra are observed. Both compounds were separated by silica gel chromatography. The $[\alpha]_D^{20}$ values of **11a** and **11b** are +14.5 ($CHCl_3$, c = 0.46) and −89.0 ($CHCl_3$, c = 0.54), respectively. The structure of these constitutional isomers could not be completely inferred from the spectroscopic data; therefore, the molecular structure of **11b** was determined by single crystal X-ray diffraction analysis. A molecular drawing of **11b** is shown in Figure 6, and selected bond distances and angles are given in Table 6.

11b crystallizes in the chiral orthorhombic space group $P2_12_12_1$, showing that, once again, only one enantiomer is present in the crystal. It is remarkable that all crystallized complexes (**1**, **7**, **9**, **11b**) are enantiomerically pure, as deduced from their space groups. In **11b**, the Pd atom is located in a distorted square planar environment, surrounded by the chloride atom [Pd(1)−Cl(1) 2.4041(10) Å] and a terdentate ligand which is composed by the original amino ester, a methyl-vinyl link at the ortho position of the phenyl ring, and a fully ethyl-substituted cyclopentenyl unit, built from the insertion of the three molecules of 3-hexyne. This new ligand is bonded to the Pd atom through the N atom of the original methyl phenylglycinate moiety N(1) [Pd(1)−N(1) 2.122(3) Å] and through an η^3-allyl ligand C(2)−C(3)−C(4) [Pd(1)−C(2) 2.148(4) Å, Pd(1)−C(3) 2.092(4) Å and Pd(1)−C(4) 2.110(4) Å], which belongs to the cyclopentenyl fragment. The vinylic link C(16)−C(17) [1.328(5) Å] is not bonded to the Pd center. Therefore, this structure is not a classical example of cyclopentadiene formation from insertion of three alkynes, similarly to that described in **7** (Figure 4) or proposed for **10** (Scheme 8), (in fact, it is not a cyclopentadiene but a cyclopentenyl), suggesting that further transformations have occurred only at the cyclopentadiene moiety. Comparing with the structure proposed for **10** it is clear that the ethyl group at the palladated carbon [$-CH_2-CH_3$] has been transformed into the ethylidene [$=CH-CH_3$] fragment C(16)−C(17)−C(18), and that one of the carbons of the cyclopentadiene unit has been protonated, resulting in the formation of the cyclopentenyl unit.

To explain the formation of **11a** and **11b** by heating of **10** we propose the tentative mechanism shown in Scheme 10. The reaction starts with the formation of a hydride complex, as a result of the β-elimination at the ethyl group over the palladated carbon of **10**. Similar hydride complexes were previously proposed by Vicente et al.[28j] The subsequent attack of the hydride to both extremes of the cyclopentadiene unit caused the formation of the complexes **11a** and **11b**. According to these results, the structure of **11a** was assigned to a complex similar to **11b**, but containing the η^3-allyl five-membered moiety in the complementary position (see Scheme 9). However, we wish to stress that in the absence of mechanistic studies, no final conclusions regarding the mechanism can be made. Similar η^3-allylic five-membered ring complexes have been proposed several times as intermediates in the depalladation processes of related complexes; however, they have never been isolated before.[28a] The reason of why these complexes in particular are stable versus depalladation remains unclear at this point.

It is known that different alkynes usually give a different pattern of reactivity toward the same cyclopalladated substrate.[4,28] Using DMAD and 3-hexyne we have observed insertion of two and three alkynes, giving complex heterocycles. Aiming to obtain simpler molecules we have checked the reactivity of diphenylacetylene. The reaction of (*R*)-**1** with excess diphenylacetylene (Scheme 11) gives the monoinserted complex **12** (73%), which was characterized by NMR spectroscopy, elemental analysis, and

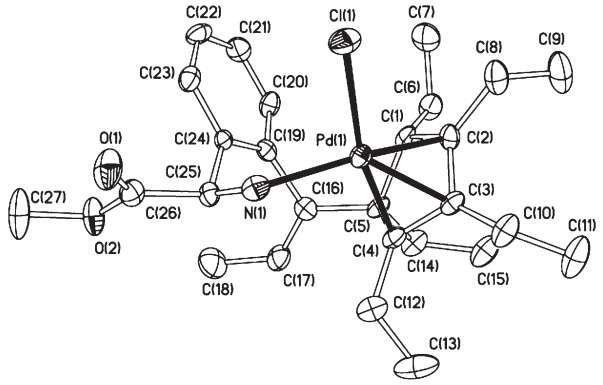
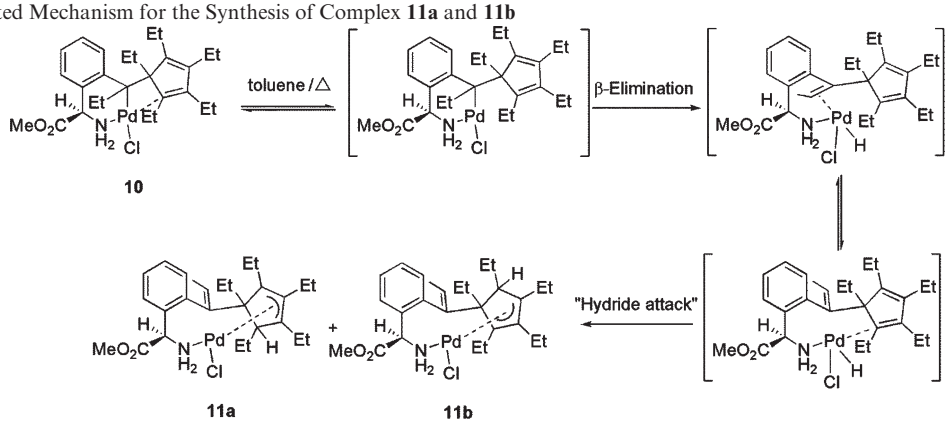


Figure 6. Structure of the complex **11b**. Ellipsoids of non-hydrogen atoms have been drawn at 50% probability. H atoms have been omitted by clarity.

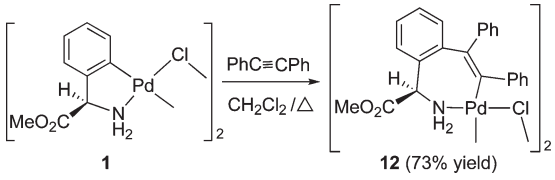
Table 6. Selected Bond Distances (Å) and Angles (deg) for Compound **11b**

Pd1−Cl1	2.4041(10)	Pd1−N1	2.122(3)
Pd1−C2	2.148(4)	Pd1−C3	2.092(4)
Pd1−C4	2.110(4)	C5−C16	1.555(4)
C1−C5	1.571(5)	C1−C2	1.533(5)
C2−C3	1.396(5)	C3−C4	1.423(5)
C4−C5	1.552(5)	C16−C19	1.489(5)
C16−C17	1.328(5)	C17−C18	1.491(5)
Cl1−Pd1−N1	89.21(9)	Cl1−Pd1−C4	166.84(11)
N1−Pd1−C2	162.69(13)	Cl1−Pd1−C3	128.76(12)
Cl1−Pd1−C2	102.82(11)	C3−Pd1−C4	39.59(14)
C2−Pd1−C4	64.13(15)		

Scheme 10. Suggested Mechanism for the Synthesis of Complex **11a** and **11b**



Scheme 11. Synthesis of Complex **12**



MS spectrometry. The ^{1}H NMR spectrum displayed the presence of 14 aromatic protons, 4 from the C_6H_4 unit of the amino acid and 10 from the phenyl groups of the alkyne. The measure of the specific rotation $[\alpha]_D^{20}$ +231.5 ($CHCl_3$, c = 0.07) shows that **12**, as observed for **7**, **9**, **10**, **11a**, and **11b**, was obtained with a degree of diastereoselectivity.

Attempts to depalladate **12**, aiming to obtain the corresponding heterocycle, gave unclear decomposition pathways, and no defined compounds could be isolated and characterized.

Conclusion

In summary, the reactivity toward different substrates, halogens, I(III) reagents, CO, isonitriles, and alkynes, of the orthopalladated [Pd(μ-Cl){*R*-C_6H_4(CH(CO_2Me)NH_2)-2}]$_2$ (*R*)-**1** has been studied. Either through oxidative coupling processes (halogens, I(III) reagents) or through insertion reactions (CO, alkynes), amino esters derived from methyl phenylglycinate functionalized at the ortho position of the phenyl ring have been obtained in remarkably mild conditions. In some cases the organometallic intermediate is very stable and does not allow the isolation of the organic derivative. Two main types of organic structures are accessible through this methodology: one identical to the phenylglycinate (functionalized at the ortho position) and another one heterocyclic, derived from the coupling between the N atom and the new functional group. The X-ray analysis of six new products are also reported, one of them unprecedented. Therefore, it is clear that this methodology has been successfully applied to the synthesis of new amino esters. Moreover, the new functionalized free amino esters are enantioenriched in the (*R*)-enantiomer, with the exception of the compound **5**, displaying *ee* values from 22 to 87%.

Study of the fate of the stereogenic information of the obtained products, the reactivity of (*R*)-**1** with other substrates, the possibility to develop catalytic versions of these functionalizations, as well as the functionalization of other cyclopalladated complexes are currently under investigation in our laboratory.

Experimental Section

General Methods. Elemental analyses were carried out on a Perkin-Elmer 2400-B microanalyzer. Infrared spectra (4000−200 cm^{-1}) were recorded on a Perkin-Elmer 883 IR spectrophotometer from nujol mulls between polyethylene sheets. The ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded in CD_2Cl_2, $CDCl_3$ or acetone-d_6 solutions at 25 °C on Bruker Avance-300 and Avance-400 spectrometers (δ, ppm; J, Hz); ^{1}H and ^{13}C{^{1}H} spectra were referenced using the solvent signal as internal standard. The ^{1}H SELNO-1D NMR experiments were performed with optimized mixing times (D8), depending of the irradiated signal. Electrospray Ionization (ESI)/Atmospheric Pressure Chemical Ionization (APCI) mass spectra were recorded using an Esquire 3000 ion-trap mass spectrometer (Bruker Daltonic GmbH, Bremen, Germany) equipped with a standard ESI/APCI source. Samples were introduced by direct infusion with a syringe pump. Nitrogen served both as the nebulizer gas and the dry gas. Helium served as a cooling gas for the ion trap and collision gas for MS_n experiments. Other mass spectra (MALDI-DIT) were recorded from CH_2Cl_2 solutions on a Bruker MicroFlex spectrometer. **1** was prepared following reported procedures.[19g]

Synthesis of Compound 2a. To a suspension of (*R*)-**1** (150 mg, 0.245 mmol) in dichloromethane (4 mL), Br_2 (0.025 mL, 0.490 mmol) was added. The mixture was stirred for 24 h at room temperature, filtered through a plug of Celite, and purified by silica gel chromatography using ethyl acetate/hexane (3:7) as eluent. The yellow band was collected and evaporated to dryness affording the compound **2a** as a yellow solid. Obtained: 50.4 mg, 0.103 mmol (42.1% yield). $[\alpha]_D^{20}$ −98.4 ($CHCl_3$, c = 0.64). Anal. Calcd for $C_{18}H_{20}Cl_2Br_2N_2O_4Pd$ (664.42): C, 32.54; H, 3.04; N, 4.21. Found: C, 32.67; H, 3.17; N, 4.09. Mass Spect. (ESI+) [m/z]: 243.9 [$NH_2CHCO_2MeC_6H_4Br$]$^+$. IR (ν, cm^{-1}): 1734 (ν_{CO}), 3276, 3218 (ν_{NH}). ^{1}H NMR ($CDCl_3$): δ = 3.65 (m, 1H, NH_2), 3.69 (s, 3H, OMe), 4.02 (dd, 1H, NH_2, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 4.8 Hz), 5.11 (dd, 1H, CH, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 5.2 Hz), 7.27 (dd, 1H, C_6H_4, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.6 Hz), 7.33 (td, 1H, C_6H_4, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz), 7.39 (m, 1H, C_6H_4), 7.57 (m, 1H, C_6H_4). ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 53.31 (s, OMe), 60.62 (s, CH), 123.50 (s, CH), 128.22 (s, CH), 130.80 (s, CH), 131.56 (s, CH), 133.73 (s, C), 134.64 (s, C), 170.24 (s, CO).

Synthesis of Compound 2b. 1,10-Phenanthroline hydrate (120 mg, 0.606 mmol) was added to a solution of complex **2a** (403 mg, 0.606 mmol) in dichloromethane (24 mL), the resulting mixture was stirred for 3 h, and the crude of the reaction was filtered to remove the orange solid formed, which was identified as [$PdCl_2$(phen)]. The resulting orange solution was evaporated

to dryness, and diethyl ether (10 mL) was added, generating a suspension which was filtered through a plug of Celite and evaporated to dryness, affording **2b** as orange solid. Obtained: 256.0 mg, 1.050 mmol (86.5% yield). $[\alpha]_D^{20}$ −42.6 ($CHCl_3$, c = 0.63). 82% of *ee* (91% (*R*)-**2b**). Anal. Calcd for $C_9H_{10}BrNO_2$ (244.09): C, 44.29; H, 4.13; N, 5.74. Found: C, 44.64; H, 4.27; N, 5.35. Mass Spect. (ESI+) [*m*/*z*]: 244.0 $[M(Br^{79})]^+$, 246.0 $[M(Br^{81})]^+$. IR (ν, cm^{-1}): 1735 (ν_{CO}). ^1H NMR ($CDCl_3$): δ = 3.50 (m, 2H, NH_2), 3.67 (s, 3H, OMe), 5.12 (s, 1H, CH), 7.13 (td, 1H, C_6H_4, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.7 Hz), 7.27 (td, 1H, C_6H_4, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz), 7.40 (m, 1H, C_6H_4), 7.52 (m, 1H, C_6H_4). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 53.00 (s, OMe), 57.72 (s, CH), 123.90 (s, C), 128.20 (s, CH), 129.31 (s, CH), 130.13 (s, CH), 133.46 (s, CH), 136.93 (s, C), 171.94 (s, CO).

Synthesis of Compound 3a. I_2 (124 mg, 0.490 mmol) was added to a suspension of (*R*)-**1** (150 mg, 0.245 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for 12 h at room temperature affording a dark solution, which was filtered through a plug of Celite and evaporated to dryness, yielding compound **3a** as a yellow solid. Obtained: 63.0 mg, 0.108 mmol (44.2% yield). $[\alpha]_D^{20}$ −118.0 ($CHCl_3$, c = 0.52). Anal. Calcd for $C_{18}H_{20}Cl_2I_2N_2O_4Pd$ (758.42): C, 28.50; H, 2.66; N, 3.70. Found: C, 28.67; H, 3.24; N, 3.62. Mass Spect. (ESI+) [*m*/*z*]: 291.9 $[NH_2CHCO_2MeC_6H_4I]^+$. IR (ν, cm^{-1}): 1733 (ν_{CO}), 3217 br (ν_{NH}). ^1H NMR ($CDCl_3$): δ = 3.58 (s br, 1H, NH_2), 3.72 (s, 3H, OCH_3), 4.11 (s br, 1H, NH_2), 5.17 (dd, 1H, CH, $^3J_{HH}$ = 8.0 Hz), 7.09 (td, 1H, C_6H_4, $^3J_{HH}$ = 9.6 Hz, $^4J_{HH}$ = 2.0 Hz), 7.30−7.38 (m, 2H, C_6H_4), 7.90 (d, 1H, C_6H_4, $^3J_{HH}$ = 10.4 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 53.36 (s, OMe), 64.18 (s, CH), 99.40 (s, CH), 129.07 (s, CH), 129.79 (s, CH), 130.89 (s, CH), 138.19 (s, C), 140.59 (s, C), 170.43 (CO).

Synthesis of Compound 3b. Compound **3b** was prepared similar to **2b**, starting from 1,10-phenanthroline hydrate (124 mg, 0.622 mmol) and **3a** (472 mg, 0.622 mmol), yielding the corresponding iodide compound as a yellow oil. Obtained: 316.0 mg, 1.090 mmol (87.1% yield). $[\alpha]_D^{20}$ −52.2 ($CHCl_3$, c = 0.63). 87% of *ee* (93.5% (*R*)-**3b**). Anal. Calcd for $C_9H_{10}INO_2$ (291.08): C, 32.54; H, 3.04; N, 4.21. Found: C, 31.88; H, 3.53; N, 4.56. Mass Spect. (ESI+) [*m*/*z*]: 292.0 $[M+H]^+$. IR (ν, cm^{-1}): 1734 (ν_{CO}). ^1H NMR ($CDCl_3$): δ = 2.76 (m, 2H, NH_2), 3.73 (s, 3H, OMe), 5.05 (s, 1H, CH), 6.94 (m, 1H, C_6H_4), 7.22 (m, 1H, C_6H_4), 7.34−7.36 (m, 1H, C_6H_4), 7.87 (d, 1H, C_6H_4, $^3J_{HH}$ = 7.8 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 52.03 (s, OMe), 62.52 (s, CH), 99.90 (s, C), 127.60 (s, CH), 129.01 (s, CH), 129.83 (s, CH), 140.86 (s, CH), 142.43 (s, C), 173.34 (s, CO).

Synthesis of Compound 4a. $PhI(OAc)_2$ (526 mg, 1.63 mmol) was added to a suspension of (*R*)-**1** (250 mg, 0.407 mmol) in MeOH (15 mL), the mixture was stirred for 20 h at room temperature, and the resulting brown suspension was filtered. The orange solution was evaporated to dryness, the residue was dissolved in dichloromethane (20 mL) and washed with Na_2SO_3 10% (3 × 15 mL) and with saturated NaCl solution (2 × 10 mL). The organic phase was dried on anhydrous $MgSO_4$, filtered, and 1,10-phenanthroline hydrate (120 mg, 0.407 mmol) was added. The resulting mixture was stirred for 3 h, and the crude of the reaction was filtered to remove the orange solid formed, which was identified as $[PdCl_2(phen)]$. The yellow solution was evaporated to dryness, and diethyl ether (10 mL) was added, generating a suspension which was filtered through a plug of Celite and evaporated to dryness, affording **4a** as colorless oil. Obtained: 102.5 mg, 0.525 mmol (64.5% yield). $[\alpha]_D^{20}$ −13.2 ($CHCl_3$, c = 0.20). 22% of *ee* (61% (*R*)-**4a**). Mass Spect. (MALDI+-DIT) [*m*/*z*]: 196.0 $[M+H]^+$. IR (ν, cm^{-1}): 1733 (ν_{CO}). ^1H NMR ($CDCl_3$): δ = 1.75 (s br, 2H, NH_2), 3.70 (s, 3H, OMe), 3.84 (s, 3H, OMe), 4.76 (s, 1H, CH), 6.89−6.98 (m, 2H, C_6H_4), 7.23−7.27 (m, 2H, C_6H_4). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 52.27 (s, OMe), 54.89 (s, OMe), 55.45 (s, CH), 110.97 (s, CH), 120.91 (s, CH), 128.67 (s, CH), 129.05 (s, C), 129.18 (s, CH), 156.74 (s, C), 175.06 (CO).

Synthesis of Compound 4b. Compound **4b** was prepared in a similar way to **4a** starting from $PhI(OAc)_2$ (526 mg, 1.63 mmol), (*R*)-**1** (250 mg, 0.407 mmol) in EtOH (15 mL). Compound **4b** was obtained as yellow oil. Obtained: 97.4 mg, 0.466 mmol (57.2% yield). $[\alpha]_D^{20}$ −14.1 ($CHCl_3$, c = 0.28). 50% of *ee* (75% (*R*)-**4b**). Mass Spect. (ESI+) [*m*/*z*]: 210.0 $[M+H]^+$. IR (ν, cm^{-1}): 1734 (ν_{CO}), 3285 br (ν_{NH}). ^1H NMR ($CDCl_3$): δ = 1.40 (t, 3H, CH_3, $^3J_{HH}$ = 9.4 Hz), 1.69 (s br, 1H, NH_2), 1.97 (s br, 1H, NH_2), 3.70 (s, 3H, OMe), 4.05 (m, 2H, OCH_2), 4.68 (s, 1H, CH), 6.86−6.96 (m, 2H, C_6H_4), 7.23−7.26 (m, 2H, C_6H_4). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.71 (s, CH_3), 52.20 (s, OMe), 55.45 (s, CH), 63.64 (s, OCH_2), 111.67 (s, CH), 120.73 (s, CH), 128.61 (s, CH), 129.47 (s, CH), 134.23 (s, C), 156.04 (s, C), 171.21 (CO).

Synthesis of Compound 5. A suspension of (*R*)-**1** (197.6 mg, 0.323 mmol) in chloroform (7 mL) was stirred under a CO atmosphere for 15 h, then the dark suspension was filtered through a plug of Celite, and the yellow solution was evaporated to dryness. The residue was dissolved in dichloromethane (3 mL), and the addition of *n*-hexane (20 mL) caused the precipitation of **5** as a white solid. Crystals of **5** were obtained by the diffusion of *n*-hexane (10 mL) into a saturated solution of **5** in dichloromethane (5 mL). Obtained: 67.3 mg, 0.352 mmol (54.5% yield). $[\alpha]_D^{20}$ −0.3 ($CHCl_3$, c = 0.50). Anal. Calcd for $C_{10}H_9NO_3$ (191.18): C, 62.49; H, 5.26; N, 7.29. Found: C, 62.15; H, 5.40; N, 7.39. Mass Spect. (MALDI+-DIT) [*m*/*z*]: 192.2 $[M+H]^+$. IR (ν, cm^{-1}): 1749 (ν_{CO}), 1691 (ν_{CO}), 3198 (ν_{NH}). ^1H NMR ($CDCl_3$): δ = 2.06 (s br, 1H, NH), 3.77 (s, 3H, OMe), 5.28 (s br, 1H, CH), 7.47 (t, 1H, C_6H_4, $^3J_{HH}$ = 6.6 Hz), 7.54 (t, 1H, C_6H_4, $^3J_{HH}$ = 6.6 Hz), 7.64 (m, 1H, C_6H_4), 7.79 (m, 1H, C_6H_4). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 53.45 (s, OMe), 53.84 (s, CH), 123.99 (s, CH), 124.87 (s, CH), 129.42 (s, CH), 132.61(s, CH), 141.29 (s, C), 144.92 (s, C), 169.60 (*C*OOMe), 169.64 (*C*O).

Synthesis of Compound 6. ^{t}BuNC (0.037 mL, 0.327 mmol) was added to a solution of complex (*R*)-**1** (100 mg, 0.163 mmol) in CH_2Cl_2 (20 mL). The resulting mixture was stirred for 45 min at room temperature. After the reaction time, the mixture was concentrated to 2 mL, and pentane (20 mL) was added to cause the precipitation of compound **6**. The orange solid was collected, washed with *n*-pentane (2 × 20 mL), and dried in vacuo. Obtained: 119.3 mg, 0.306 mmol (94% yield). Λ_M (Ω^{-1} cm^2 mol^{-1}) = 0.969 (5.37×10^{-4} M). $[\alpha]_D^{20}$ +56.3 ($CHCl_3$, c = 0.38). Mass Spect. (MALDI+-DIT) [*m*/*z*]: 353.69 $[M-Cl]^+$. IR (CH_2Cl_2, ν, cm^{-1}): 1743 (ν_{CO}), 2212 (ν_{CN}), 3281, 3334 (ν_{NH}). ^1H NMR ($CDCl_3$): δ = 1.45 (s, 9H, ^{t}Bu), 3.76 (s, 3H, OMe), 4.45 (m, 1H, NH), 4.84 (m, 1H, NH), 4.99 (m, 1H, CH), 6.85−6.92 (m, 1H, C_6H_4), 6.99 (td, 1H, C_6H_4, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.2 Hz), 7.03−7.05 (m, 1H, C_6H_4), 7.16 (d, 1H, C_6H_4, $^3J_{HH}$ = 7.6 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 29.01 (s, C*Me*$_3$), 52.30 (s, OMe), 63.72 (s, CH), 65.12 (s, *C*Me$_3$), 123.16 (s, C_6H_4), 123.85 (s, C_6H_4), 126.11 (s, C_6H_4), 136.27 (s, C_6H_4), 147.38 (s, C_6H_4), 148.63 (s, C_6H_4), 169.75 (s, CO).

Synthesis of Compound 7. To a solution of (*R*)-**1** (100 mg, 0.163 mmol) in dichloromethane (20 mL), excess of dimethyl acetylenedicarboxylate was added (0.160 mL, 1.304 mmol). The resulting mixture was refluxed for 4 h, then was concentrated under vacuum to a volume of 1 mL. The addition of *n*-pentane (2 × 20 mL) caused the precipitation of **7** as an orange solid. Crystals were obtained by diffusion of *n*-pentane (10 mL) into a solution of **7** in acetone (2 mL). Obtained: 219.7 mg, 0.300 mmol (92% yield). $[\alpha]_D^{20}$ +37.4 ($CHCl_3$, c = 0.49). Anal. Calcd for $C_{27}H_{28}ClNO_{14}Pd \cdot H_2O$ (732.39 + 18.02): C, 43.22; H, 4.03; N, 1.87. Found: C, 43.23, H, 3.98, N, 1.86. Mass Spect. (MALDI+ DIT) [*m*/*z*]: 696.2 $[M-Cl]^+$. IR (ν, cm^{-1}): 1723 vs, 1705 s, 1678 s, 1636 s (ν_{CO}), 3225, 3446 (ν_{NH}). ^1H NMR (acetone-d_6): δ = 3.51 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.29 (m, 1H, NH), 4.39 (m, 1H, NH), 4.74 (m, 1H, CH), 6.93 (m, 1H, C_6H_4), 7.01−7.12 (m, 3H, C_6H_4). $^{13}C\{^1H\}$ NMR (acetone-d_6): δ = 52.57 (s, OMe), 53.05 (s, OMe), 53.13, (s, OMe), 53.21

(s, OMe), 53.34 (s, OMe), 53.77 (s, OMe), 57.50 (s, OMe), 58.86 (s, CH), 79.31 (s, C), 83.00 (s, C), 125.25 (s, C), 126.26 (s, C), 126.40 (s, CH), 127.91 (s, C), 128.03 (s, C), 129.18 (s, CH), 130.91 (s, C), 135.64 (s, CH), 137.32 (s, CH), 138.00 (s, C), 161.87 (s, CO), 162.70 (s, CO), 163.33 (s, CO), 164.77 (s, CO), 170.85 (s, CO), 172.63 (s, CO), 184.29 (s, CO).

Synthesis of Compound 8. Compound **7** (125 mg, 0.171 mmol) was refluxed for 1 h in toluene (10 mL), evaporated to dryness, and the obtained residue was extracted with Et_2O (3 × 10 mL). The resulting red solution was concentrated under vacuum to a volume of 2 mL and precipitated by addition of *n*-pentane, affording **8** as a red solid. Obtained: 51.4 mg, 0.087 mmol (51% yield). Λ_M (Ω^{-1} cm^2 mol^{-1}) = 10.756 (6.20×10^{-4} M). $[\alpha]_D^{20}$ +8.4 ($CHCl_3$, c = 0.47). Complex **8** was crystallized from $CHCl_3/Et_2O$, giving crystals of **8** $CHCl_3$, which were used for analytic and spectroscopic purposes. Anal. Calcd for $[C_{27}H_{27}NO_{14}]$ $CHCl_3$ (708.43): C, 47.44; H, 3.98; N, 1.98. Found: C, 46.91, H, 4.19, N, 1.59. Mass Spect. (ESI+) [*m*/*z*]: 590.1 $[M]^+$. IR (ν, cm^{-1}): 1780, 1727, 1697, 1644 br (ν_{CO}), 3237 (ν_{NH}). ^{1}H NMR ($CDCl_3$): δ = 2.77 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.67 (s, 6H, OMe), 3.76 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.38 (m, 1H, NH), 5.15 (s br, 1H, CH), 7.24−7.29 (m, 3H, C_6H_4), 7.50 (d, 1H, C_6H_4, $^3J_{HH}$ = 7.6 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 52.38 (s, OMe), 52.47 (s, OMe), 52.49 (s, OMe), 52.52 (s, OMe), 52.76 (s, OMe), 52.92 (s, OMe), 53.35 (s, OMe), 62.85 (s, CH), 73.49 (s, C), 76.41 (s, C), 124.30 (s, CH), 124.44 (s, CH), 128.10 (s, CH), 128.89 (s, CH),132.02 (s, C), 132.04 (s, C), 137.74 (s, C), 139.15 (s, C), 161.21 (s, CO), 162.54 (s, CO), 163.22 (s, CO), 163.79 (s, CO), 163.92 (s, CO), 170.54 (s, CO), 170.84 (s, CO).

Synthesis of Compounds 9 and 10. Excess of 3-hexyne (0.296 mL, 2.616 mmol) was added to a solution of (*R*)-**1** (200 mg, 0.327 mmol) in dichloromethane (20 mL), and the mixture was refluxed for 4 h. The resulting yellow solution was concentrated under vacuum and washed with *n*-pentane (2 × 20 mL) to remove the unreacted 3-hexyne, affording a mixture of compounds **9** and **10** which were separated by silica gel chromatography as follows:

Compound 9. A first orange band was eluted with ethyl acetate/*n*-hexane (90:10); this fraction was collected and concentrated under vacuum to a volume of 1 mL. Addition of *n*-pentane (10 mL) caused the precipitation of compound **9** as a microcrystalline orange solid. Crystals were obtained by diffusion of *n*-pentane (5 mL) into a solution of **9** in dichloromethane (1 mL). Obtained: 64.6 mg, 0.137 mmol (21% yield). $[\alpha]_D^{20}$ +182.6 ($CHCl_3$, c = 0.48). Complex **9** was crystallized from CH_2Cl_2/Et_2O, giving crystals of **9** CH_2Cl_2, used for analytic and spectroscopic purposes. Anal. Calcd for $[C_{21}H_{30}ClNO_2Pd]CH_2Cl_2$ (565.28): C, 47.59; H, 5.81; N, 2.52. Found: C, 48.38, H, 5.96, N, 3.08. Mass Spect. (ESI+) [*m*/*z*]: 434.2 $[M-Cl]^+$. IR (ν, cm^{-1}): 1737 (ν_{CO}), 3265, 3327 (ν_{NH}). ^{1}H NMR (acetone-d_6): δ = 0.66 (t, 3H, CH_3, $^3J_{HH}$ = 7.4 Hz), 0.87 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 0.98 (t, 3H, CH_3, $^3J_{HH}$ = 7.2 Hz), 1.06 (t, 3H, CH_3, $^3J_{HH}$ = 7.2 Hz), 1.49−1.55 (m, 2H, CH_2), 1.72−1.78 (m, 2H, CH_2), 2.02−2.11 (m, 2H, CH_2), 2.21−2.34 (m, 2H, CH_2), 3.58 (s, 3H, OMe), 4.72 (m, 1H, NH), 4.88 (m, 1H, CH), 5.33 (m, 1H, NH), 7.08−7.11 (m, 1H, C_6H_4), 7.19−7.33 (m, 3H, C_6H_4). $^{13}C\{^1H\}$ NMR (acetone-d_6): δ = 12.85 (s, CH_3), 15.05 (s, CH_3), 15.08 (s, CH_3), 15.12 (s, CH_3), 22.94 (s, CH_2), 24.29 (s, CH_2), 27.68 (s, CH_2), 33.18 (s, CH_2), 52.86 (s, OMe), 59.98 (s, CH), 94.68 (s, C), 112.22 (s, C), 128.14 (s, CH), 128.97 (s, CH), 133.28 (s, CH), 133.43 (s, CH), 133.84 (s, C), 137.27 (s, C), 138.55 (s, C), 142.64 (s, C), 172.11 (s, CO).

Compound 10. A second band was collected after elution with ethyl acetate/methanol (99:1), was concentrated under vacuum to a volume of 1 mL, and precipitated with *n*-pentane (10 mL), yielding **10** as a yellow solid. Obtained: 245.3 mg, 0.444 mmol (68% yield). $[\alpha]_D^{20}$ +36.0 ($CHCl_3$, c = 0.56). Anal. Calcd for $C_{27}H_{40}ClNO_2Pd$ (552.49): C, 58.70; H, 7.30; N, 2.54. Found: C, 58.97, H, 7.10, N, 2.50. Mass Spect. (MALDI+-DIT) [*m*/*z*]: 516.3 $[M-Cl]^+$. IR (ν, cm^{-1}): 1749 (ν_{CO}), 3226, 3299 (ν_{NH}). ^{1}H NMR (acetone-d_6): δ = 0.32 (t, 3H, CH_3, $^3J_{HH}$ = 7.2 Hz), 0.37 (t, 3H, CH_3, $^3J_{HH}$ = 7.8 Hz), 0.63 (t, 3H, CH_3, $^3J_{HH}$ = 7.4 Hz), 0.84 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 1.08 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 1.49 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 2.08−2.15 (m, 2H, CH_2), 2.29−2.35 (m, 6H, CH_2), 2.43−2.48 (m, 4H, CH_2), 3.65 (s, 3H, OMe), 4.61 (m, 1H, NH), 4.75 (m, 1H, CH), 4.86 (m, 1H, NH), 6.99−7.12 (m, 3H, C_6H_4), 7.49 (dd, 1H, C_6H_4, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.2 Hz). $^{13}C\{^1H\}$ NMR (acetone-d_6): δ = 6.72 (s, CH_3), 10.92 (s, 2 CH_3), 12.76 (s, CH_3), 13.88 (s, CH_3), 16.23 (s, CH_3), 19.28 (s, CH_2), 20.61 (s, CH_2), 20.71 (s, CH_2), 21.41 (s, CH_2), 22.62 (s, CH_2), 36.83 (s, CH_2), 51.93 (s, OMe), 58.43 (s, CH), 75.90 (s, C), 77.68 (s, C), 124.95 (s, CH), 127.18 (s, CH), 128.10 (s, C), 128.79 (s, C), 129.64 (s, CH), 131.71 (s, CH), 135.48 (s, C), 138.36 (s, C), 139.63 (s, C), 140.86 (s, C), 168.91 (s, CO).

Synthesis of Compounds 11a and 11b. A solution of **10** (125 mg, 0.226 mmol) in toluene (10 mL) was refluxed for 1 h; after cooling the solution was evaporated to dryness, and the residue was extracted with Et_2O (2 × 10 mL). The yellow solution was evaporated under vacuum and purified by silica gel chromatography as follows:

Compound 11a. Elution with ethyl acetate afforded a first band corresponding to **11a**. This fraction was collected and evaporated to dryness yielding compound **11a** as a yellow solid. Obtained: 71.3 mg, 0.129 mmol (57% yield). $[\alpha]_D^{20}$ + 14.5 ($CHCl_3$, c = 0.46). Compound **11a** was crystallized from $CHCl_3/Et_2O$, giving crystals of **11a** $CHCl_3$, used for analytical and spectroscopic purposes. Anal. Calcd for $[C_{27}H_{40}ClNO_2Pd]$ $CHCl_3$ (669.09): C, 50.06; H, 6.15; N, 2.08. Found: C, 50.61; H, 6.33; N, 2.17. Mass Spect. (ESI+) [*m*/*z*]: 516.3 $[M-Cl]^+$. IR (ν, cm^{-1}): 1732 (ν_{CO}), 3265, 3380 (ν_{NH}). ^{1}H NMR ($CDCl_3$): δ = 0.35 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 0.68 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 1.04 (t, 3H, CH_3, $^3J_{HH}$ = 7.5 Hz), 1.13 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 1.31 (t, 3H, CH_3, $^3J_{HH}$ = 7.5 Hz), 1.34 (d, 3H, c = CH-*CH*$_3$, $^3J_{HH}$ = 6.7 Hz), 1.58−1.65 (m, 2H, CH_2), 1.82−1.88 (m, 2H, CH_2), 2.00−2.06 (m, 2H, CH_2), 2.10−2.19 (m, 2H, CH_2), 2.23−2.31 (m, 2H, CH_2), 2.91 (m, 1H, CH), 3.62 (s, 3H, OMe), 3.66 (m, 1H, NH), 5.29 (d, 1H, CH, $^3J_{HH}$ = 13.2 Hz), 5.74 (q, 1H, c = *CH*-CH$_3$, $^3J_{HH}$ = 6.7 Hz), 7.10−7.13 (m, 1H, C_6H_4), 7.16−7.18 (m, 1H, C_6H_4), 7.25−7.35 (m, 2H, C_6H_4). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 10.18 (s, CH_3), 11.26 (s, CH_3), 13.00 (s, CH_3), 13.77 (s, CH_3), 13.80 (s, CH_3), 14.05 (s, CH_3), 19.00 (s, CH_2), 20.03 (s, CH_2), 20.57 (s, CH_2), 22.61 (s, CH_2), 29.25 (s, CH_2), 51.76 (s, OMe), 56.02 (s, CH), 59.32 (s, CH), 65.59 (s, C), 92.79 (s, C), 105.43 (s, C), 119.65 (s, C), 124.68 (s, CH), 126.12 (s, CH), 127.20 (s, CH), 127.79 (s, CH), 129.28 (s, CH), 133.99 (s, C), 140.99 (s, C), 141.5 (s, C), 172.97 (s, CO).

Compound 11b. A second band, corresponding to compound **11b**, was collected with ethyl acetate/methanol (98:2). The eluted band was concentrated under vacuum to dryness, yielding **11b** as a yellow solid. Obtained: 20.0 mg, 0.036 mmol (16% yield). $[\alpha]_D^{20}$ −89.0 ($CHCl_3$, c = 0.54). Anal. Calcd for $C_{27}H_{40}ClNO_2Pd$ (552.49): C, 58.70; H, 7.30; N, 2.54. Found: C, 58.73; H, 6.95; N, 2.34. Mass Spect. (ESI+) [*m*/*z*]: 516.3 $[M-Cl]^+$. IR (ν, cm^{-1}): 1739 (ν_{CO}), 3220, 3305 (ν_{NH}). ^{1}H NMR ($CDCl_3$): δ = 0.71 (t, 3H, CH_3, $^3J_{HH}$ = 7.2 Hz), 0.94 (t, 3H, CH_3, $^3J_{HH}$ = 7.4 Hz), 1.09 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 1.12 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 1.21 (t, 3H, CH_3, $^3J_{HH}$ = 7.6 Hz), 1.35 (d, 3H, C = CH-*CH*$_3$, $^3J_{HH}$ = 6.6 Hz), 1.96−2.11 (m, 6H, CH_2), 2.32−2.38 (m, 4H, CH_2), 2.43 (m, 1H, CH), 2.68 (m, 1H, NH), 3.41 (m, 1H, NH), 3.65 (s, 3H, OMe), 4.56 (m, 1H, CH), 5.93 (q, 1H, C = *CH*-CH$_3$, $^3J_{HH}$ = 6.6 Hz), 6.93−6.95 (m, 1H, C_6H_4), 7.12−7.15 (m, 1H, C_6H_4), 7.29−7.31 (m, 2H, C_6H_4). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 11.99 (s, CH_3), 12.22 (s, CH_3), 13.06 (s, CH_3), 14.49 (s, CH_3), 14.96 (s, CH_3), 15.90 (s, CH_3), 19.44 (s, CH_2), 20.52 (s, CH_2), 21.10 (s, CH_2), 23.30 (s, CH_2), 26.82 (s, CH_2), 52.78 (s, OMe), 54.33 (s, CH), 57.59 (s, CH), 65.72 (s, C), 90.89 (s, C), 106.10 (s, C), 120.60 (s, C), 126.60 (s,

CH), 127.80 (s, CH), 128.40 (s, CH), 128.86 (s, CH), 131.73 (s, CH), 136.22 (s, C), 141.73 (s, C), 142.96 (s, C), 173.84 (s, CO).

Synthesis of Compound 12. Excess of diphenylacetylene (232 mg, 1.304 mmol) was added to a solution of (*R*)-**1** (100 mg, 0.163 mmol) in dichloromethane (20 mL), the reaction mixture was refluxed for 5 h, and the crude was concentrated to a volume of 2 mL. Addition of *n*-pentane (30 mL) caused the precipitation of a dark yellow solid, which was washed with *n*-pentane (4 × 10 mL) to eliminate the excess of alkyne, and dried in vacuo affording **12** as a yellow solid. Obtained: 121.0 mg, 0.238 mmol (73% yield). $[\alpha]_D^{20}$ +231.5 ($CHCl_3$, c = 0.07). Anal. Calcd for $[C_{25}H_{20}NO_2PdCl]\cdot 0.5H_2O$ (517.31): C, 58.04; H, 4.10; N, 2.71. Found: C, 58.08, H, 4.41, N, 2.48. Mass Spect. (MALDI+-DIT) [*m*/*z*]: 508.3 $[M]^+$. IR (ν, cm^{-1}): 1735 (ν_{CO}), 3248, 3305 (ν_{NH}). ^1H NMR (acetone-d_6): δ = 3.85 (s, 3H, OMe), 4.65 (s br, 1H, NH), 4.86 (m, 1H, CH), 5.35 (s br, 1H, NH), 6.88−7.19 (m, 14H, C_6H_4+Ph), 7.19−7.85 (m, 6H, C_6H_4+Ph). This complex was unstable in solution, and no reliable ^{13}C NMR spectrum could be recorded.

X-ray Crystallography. Crystals of **1**, **2c**, **5**, **7**, **9**, and **11b** of quality for X-ray measurements were grown by diffusion of *n*-hexane into CH_2Cl_2 (**1**, **2b** (see text), and **5**), *n*-pentane into CH_2Cl_2 (**9**), *n*-pentane into acetone (**7**), and by evaporation of *n*-pentane (**11b**) solutions of the crude products at −15 °C. On each case, a single crystal was mounted at the end of a quartz fiber in a random orientation, covered with perfluorinated oil, and placed under a cold stream of N_2 gas. Data collection were performed on an Oxford Diffraction Xcalibur2 diffractometer using graphite-monocromated Mo Kα radiation (λ = 0.71073 Å). In all cases, a hemisphere of data were collected based on ω-scan or ϕ-scan runs. The diffraction frames were integrated using the program or CrysAlis RED,[30] and the integrated intensities were corrected for absorption with SADABS.[31] The structures were solved and developed by Patterson and Fourier methods.[32] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were placed at idealized positions and treated as riding atoms. Each H atom was assigned an isotropic displacement parameter equal to 1.2 times the equivalent isotropic displacement parameter of its parent atom. The structures were refined to F_o^2, and all reflections were used in the least-squares calculations.[33]

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Supporting Information Available: ^{19}F NMR spectra of Mosher's determinations and tables of crystallographic parameters, data collection, and data refinement for **1**, **2c**, **5**, **7**, **9**, and **11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(30) *CrysAlis RED*, version 1.171.27p8; Oxford Diffraction Ltd.: Oxford, U.K., 2005.

(31) Sheldrick, G. M. *SADABS, Program for absorption and other corrections*; Göttingen University: Göttingen, Germany, 1996.

(32) *SHELXS-86* Sheldrick, G. M. *Acta Crystallogr*. **1990**, *A46*, 467.

(33) Sheldrick, G. M. *SHELXL-97: FORTRAN program for the refinement of crystal structures from diffraction data*; Göttingen University: Göttingen, Germany, 1997; Molecular graphics were done using the commercial package *SHELXTL-PLUS*, Release 5.05/V; Siemens Analytical X-ray Instruments, Inc.: Madison, WI, 1996.