Organometallics **2006,** *25,* 2917−2920

Synthesis and Diastereoselective *ortho*-Lithiation/Cyclopalladation of Enantiopure [2-Imidazolyl]-1′,2′,3′,4′,5′-pentamethylferrocenes and -1′,2′,3′,4′,5′-pentaphenylferrocenes

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Received February 26, 2006

Summary: Convenient synthetic routes to enantiomerically pure 1′,2′,3′,4′,5′-pentamethyl and -pentaphenylferrocenyl imidazolines are described. While the former complexes were diastereoselectively ortho-lithiated and subsequently functionalized by trapping with various electrophiles, the latter complexes could be diastereoselectively cyclopalladated, allowing the preparation of the first enantiomerically pure ferrocenyl palladacycles bearing C_5Me_5 or C_5Ph_5 spectator ligands. The planar chiral palladacycles have been shown to be promising catalysts for aza-Claisen rearrangement reactions of allylic trifluoroacetimidates.

Recently, we have described the first preparation of optically pure 2-ferrocenyl imidazolines and their diastereoselective *ortho*-metalation.[1] These new heterocyclic systems are currently investigated in our laboratory as chiral catalysts,[2] taking advantage of the strongly electron donating character of the ferrocene moiety, which significantly increases the basicity of the amidine functional group. To amplify this effect, we are interested in the corresponding 1′,2′,3′,4′,5′-pentamethylferrocene complexes, because a Cp* spectator ligand further magnifies the electron-donating properties of the metallocene backbone. Furthermore, the Cp* ring significantly increases the steric bulk of the metallocene moiety, which should have a conformational influence. To amplify the latter effect, we are also attracted by 1′,2′,3′,4′,5′-pentaphenylferrocenyl imidazolines.

In comparison to the rich and elaborate chemistry of enantiomerically pure ferrocene derivatives,[3] methods that permit entry to optically active 1′,2′,3′,4′,5′-pentamethyl- or 1′,2′,3′,4′,5′-pentaphenylferrocenes by asymmetric synthesis are relatively underdeveloped. Despite several complementary diastereo- or enantioselective *ortho*-metalation procedures for Cp′-unsubstituted ferrocenyl derivatives, which make use of various *ortho*-directing groups such as amines,[4] oxazolines,[5] sulfoxides,[6] acetals,[7] hydrazones,[8] oxazaphospholidine-oxides,[9] or amides,[10] providing access to numerous planar chiral derivatives, many of which have been successfully used as chiral ligands in asymmetric catalysis,[3] to the best of our knowledge, stereoselective *ortho*-metalations of 1′,2′,3′,4′,5′-pentamethylferrocene derivatives have been limited so far to Ugi type amines.[11] In addition, during the preparation of this communication the diastereoselective lithiations of enantiomerically pure 1′,2′,3′,4′,5′-pentamethylferrocenyl oxazolines[12] and of one acetal[13] have been described. The fact that 1′,2′,3′,4′,5′-pentamethylferrocenyl oxazolines have only very recently been reported might be due in part to the previously difficult accessibility of the carboxylic acid **3**.[14] The carboxylation of pentamethylferrocene **1** has been described to proceed by metalation with *n*-BuLi/*t*-BuOK and subsequent trapping with dry ice to furnish acid **3** in 86% yield based on 35% conversion.[15] In our hands this procedure led to inseparable mixtures of carboxylic acids due to a competing deprotonation of the methyl groups of the Cp* ligand. The published ^{1}H NMR data[15] are not consistent with pure acid **3** (four different Cp signals instead of two), and the chemical shifts are not in accordance with our ^{1}H NMR data.

Alternatively, **3** has been prepared in moderate yield by hydrolysis of the corresponding methyl ester, which was obtained by coordination of $[(C_5H_4CO_2CH_3)Na]$ to $[FeCp^*(NCCH_3)_3PF_6]$.[16] Since the latter complex is highly sensitive and because its preparation occurs photolytically, which significantly reduces the practicality of this procedure, acid **3** was prepared by us via a simple two-step sequence, which has previously been applied to the preparation of ferrocene carboxylic acid[17] and 1′,2′,3′,4′,5-pentaphenylferrocene carboxylic

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[2] For applications of imidazolines in catalysis see, for example: (a) Bastero, A.; Ruiz, A.; Claver, C.; Milani, B.; Zangrando, E. *Organometallics* **2002**, *21*, 5820. (b) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713. (c) Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brien E. M.; Spinelli, E. M. *Org. Lett.* **2003**, *5*, 595.

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[11] Abbenhuis, H. C. L.; Burckhardt, U.; Gramlich, V.; Togni, A.; Albinati, A.; Müller, B. *Organometallics* **1994**, *13*, 4481.

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[13] Wölfle, H.; Kopacka, H.; Wurst, K.; Ongania, K.-H.; Görtz, H.-H.; Preishuber-Pflügl, P.; Bildstein, B. *J. Organomet. Chem.* **2006**, *691*, 1197.

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[16] Labande, A.; Ruiz, J.; Astruc, D. *J. Am. Chem. Soc.* **2002**, *124*, 1782. Note that Geisler and Helmchen used $FeCl_2$ to prepare the ester in 59% yield (see ref 12).

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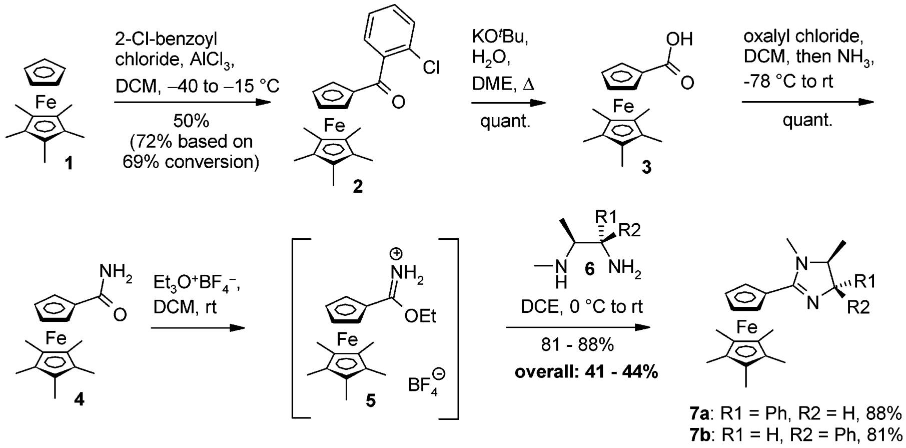
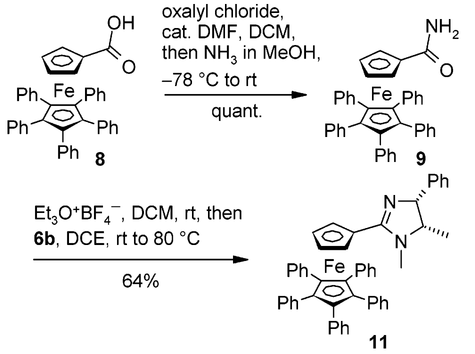
10.1021/om060187o CCC: $33.50

Scheme 1. Synthesis of 1′,2′,3′,4′,5′-Pentamethylferrocene Imidazolines



Scheme 2. Synthesis of 1′,2′,3′,4′,5′-Pentaphenylferrocene Imidazolines 11



Scheme 3. Diastereoselective *ortho*-Functionalization of 1′,2′,3′,4′,5′-Pentamethylferrocene Imidazolines

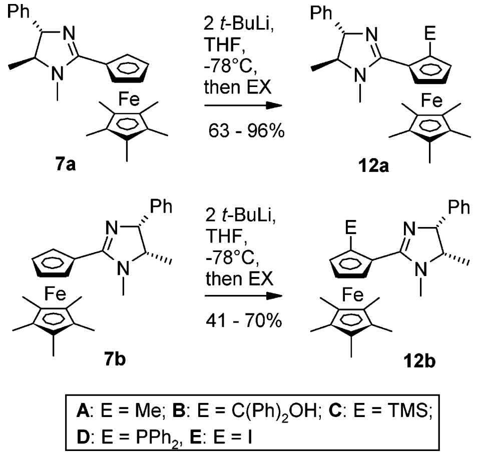


Table 1. Screening of Conditions for the Diastereoselective *ortho*-Metalation of 7a and 7b (EX = MeI)

entry	product	solvent	equiv base	equiv additive	conversion[a] [%]	*dr*
1	**12aA**	THF	1.1 *t*-BuLi		44	9:1
2	**12bA**	THF	1.1 *t*-BuLi		48	19:1
3	**12aA**	THF	1.0 *t*-BuLi	1.5 LDA	29	7:1
4	**12bA**	THF	1.0 *t*-BuLi	1.5 LDA	45	7:1
5	**12aA**	Et_2O	1.0 *t*-BuLi		46	3:1
6	**12aA**	THF	1.0 *s*-BuLi		64	2:1
7	**12aA**	Et_2O	1.0 s-BuLi		61	1:1
8	**12bA**	Et_2O	1.5 *s*-BuLi		72	3:1
9	**12aA**	Et_2O	1.0 *n*-BuLi		28	2:1
10	**12aA**	THF	2.0 *t*-BuLi		97	14:1
11	**12bA**	THF	2.0 *t*-BuLi		90	34:1

[a] Determined by ^1H NMR.

acid.[18] The unsubstituted Cp ring was functionalized by Friedel–Crafts acylation of **1**[19] with 2-chlorobenzoyl chloride promoted by $AlCl_3$ in DCM at low temperature (−40 to −15 °C).[20] Although **1** shows a distinct sensitivity toward oxidation, ketone **2** was obtained in 50% yield (72% based on 69% conversion) in a rapid reaction if working at high dilution. Following the described temperature profile is essential for reproducibility, since both longer reaction times and higher temperatures considerably decrease the yield due to oxidative decomposition. Acid **3** was subsequently obtained in high purity and in quantitative yield by hydrolytic cleavage of ketone **2** and was used to prepare amide **4** via the intermediate formation of the corresponding acid chloride (yield: 100%).

Activation of amide **4** with Meerwein's salt generated iminium ether intermediate **5**, which was subsequently added as a solution without purification to solutions of the respective diamines **6**[1] in dichloroethane, furnishing pentamethylferrocene imidazoline **7** in high yield (81–88%; overall yield of **7**: 41–44%).

We could adapt the imidazoline formation route as well to pentaphenylferrocene carboxylic acid **8** (Scheme 2), which was easily prepared according to the scalable procedure reported by Richards et al.[18] The C_5Ph_5 ligand is less electron donating than a Cp* moiety, resulting in a higher stability of **11** toward oxidation.

Recently, we have reported that *ortho*-lithiations of Cp′-unsubstituted 2-ferrocenylimidazolines provide only moderate diastereoselectivities (up to 5:1) using *n*-, *s*-, or *t*-BuLi in ethereal solvents at low temperature. The selectivities were significantly improved (up to 31:1) by using LDA as a metalation additive in combination with *t*-BuLi as a base.[1] In contrast, *ortho*-lithiations of the Cp* derivatives **7** proceed with high diastereoselectivity in the absence of metalation additives. Two equivalents of *t*-BuLi in THF at −78 °C emerged as the best reaction conditions in terms of diastereoselectivity and conversion (Scheme 3 and Table 1, entries 10, 11), while addition of LDA decreased both yield and diastereoselectivity.[21] Interestingly, an excess of *t*-BuLi improved the diastereomeric excess (entries 10, 11 versus 1, 2).

In THF the reaction mixtures turned rapidly intensively green using **7a** or blue-green in the case of **7b** after addition of the

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[18] Butler, D. C. D.; Richards, C. J. *Organometallics* **2002**, *21*, 5433.

[19] For the preparation of Cp*FeCp see: Bunel, E. E.; Valle, L.; Manriquez, J. M. *Organometallics* **1985**, *4*, 1680.

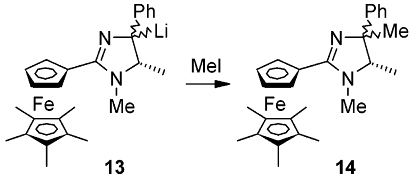
[20] For previous examples of Friedel–Crafts acylations of pentamethylferrocene see ref 15 and: Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950.

Table 2. Diastereoselective *ortho*-Functionalization of 1′,2′,3′,4′,5′-Pentamethylferrocene Imidazolines

entry	product	EX	E	*dr*[a]	yield[b] [%]	*dr*[c]
1	**12aA**	MeI	Me	14:1	68	>99:1
2	**12bA**	MeI	Me	34:1	70	>99:1
3	**12aB**	Ph$_2$CO	Ph$_2$C(OH)	19:1	68	>99:1
4	**12bB**	Ph$_2$CO	Ph$_2$C(OH)	38:1	48	>99:1
5	**12aC**	Me$_3$SiCl	Me$_3$Si	29:1	96	>99:1
6	**12aD**	Ph$_2$PCl	Ph$_2$P	14:1	63	15:1
7	**12bD**	Ph$_2$PCl	Ph$_2$P	52:1	41	52:1
8	**12aE**	ICH$_2$CH$_2$I	I	19:1	66	19:1

[a] Diastereomeric ratio of the crude product determined by ^{1}H NMR (samples with low *dr* were prepared for comparison using conditions of entry 7 in Table 1). [b] Isolated yield after column chromatography. [c] Diastereomeric ratio of the isolated compound determined by ^{1}H NMR.

lithiating agent at −78 °C. This color change is most likely ascribed to a competing lithiation of the benzylic position in the heterocyclic system, yielding carbanion **13**, since we observed the formation of traces of imidazoline side product **14** with methyliodide (eq 1).



13 **14** (1)

The utility of our metalation protocol was demonstrated by *ortho*-methylation, -hydroxyalkylation, -silylation, -phosphinylation, and -iodination reactions, giving rise to the corresponding products in 48−96% yield and with high diastereoselectivities (14:1−52:1, Table 2).

It should be noted that imidazolines **7**, especially the *cis*-configured **7b**, are sensitive to air in a sense that they are oxidized to the corresponding imidazole. For the planar chiral derivatives, we have observed this behavior only for the *ortho*-methylated **12bA**.

Iodide **12aE** was further employed to prepare the air-stable palladacycle **15** as a dimeric iodide-bridged complex (geometrical isomers about the Pd(II) square planes, ratio 4:1) by oxidative addition to Pd$_2$(dba)$_3$·CHCl$_3$ in benzene at room temperature (Scheme 4).[22] Attempts of direct cyclopalladation of **7a** failed due to either oxidative decomposition (Pd(OAc)$_2$, HOAc) or low diastereoselectivities (Na$_2$PdCl$_4$, MeOH). Treatment of **15** with PPh$_3$ leads to the diastereomerically pure monomeric species **16**. To the best of our knowledge, **15** and **16** are the first cyclopalladated ferrocenes bearing a Cp* spectator ligand.

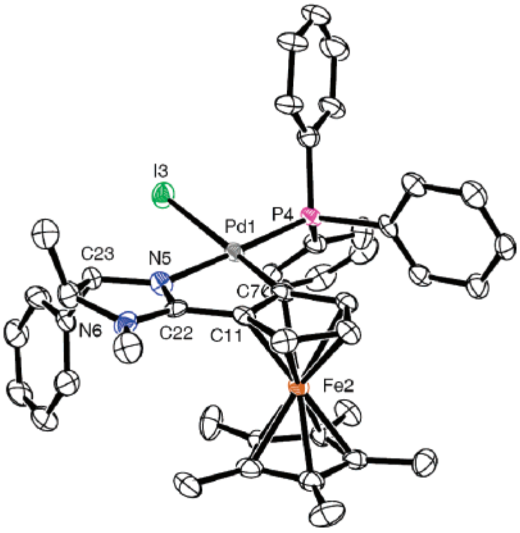
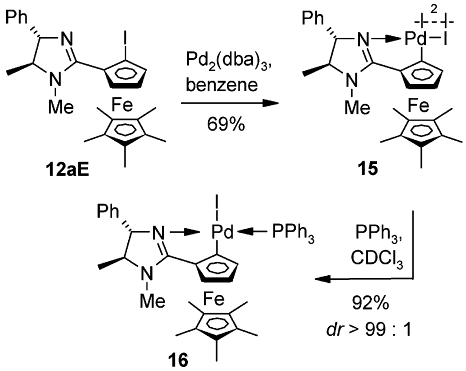


Figure 1. ORTEP drawing (ellipsoids at 50% probability level) of **16**. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)−C(7), 2.028 (6); Pd(1)−N(5), 2.115 (5); Pd(1)−P(4), 2.2655 (17); Pd(1)−I(2), 2.6963 (6); N(5)−C(22), 1.295 (8); N(6)−C(22), 1.346 (8); C(7)−Pd(1)−N(5), 79.6 (2); C(7)−Pd(1)−P(4), 97.84 (18); N(5)−Pd(1)−I(3), 93.48 (14); P(4)−Pd(1)−I(3), 88.67 (4); C(23)−N(5)−Pd(1), 135.9 (4); C(22)−N(5)−Pd(1), 115.7 (4); C(22)−N(5)−C(23), 107.9 (5); C(11)−C(22)−N(6): 128.6 (5).

Scheme 4. Preparation of the First Pentamethylferrocene Palladacycles



The structure of complex **16** was determined by X-ray crystallography (Figure 1), revealing the (S_p) configuration with regard to the planar chirality.[23,24] The palladium atom adopts a slightly distorted square-planar coordination geometry, and the PPh$_3$ ligand is positioned as expected *trans* to the imino type nitrogen atom. The Pd−ligand bond lengths are similar to those found in palladacyclic compounds containing imine or oxazoline donors. Two phenyl rings on the P atom and the one connected to the imidazoline ring get in close contact with three of the methyl substituents on Cp*. To optimize the contact distances, the Cp rings adopt a staggered conformation and the Cp and Cp* rings are slightly tilted toward each other (angle between ring planes 4.9°) in a way to increase the distances between the Cp* methyl group and the phenyl rings.

Suitable crystals for X-ray analysis could not be obtained so far for **12b**; the absolute configuration of **12bA** and **12bB** was therefore determined by NOE experiments.[25] Since the diastereoselective *ortho*-lithiation of **7a**/**7b** is responsible for the configuration with regard to the planar chirality, the absolute configuration can be assigned for all compounds **12a**/**12b**. The observed absolute configurations are in harmony with a mechanistic model presented by Richards et al. for *ortho*-lithiations of ferrocenyl oxazolines[5a] claiming that the substituent

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(21) The configuration of the major isomer with regard to the planar chirality could be reversed with LDA for Cp′-unsubstituted *trans*-configured imidazolines. The substituent at the imidazoline 4-position prefers the *exo* position for both *trans*- and *cis*-configured planar chiral imidazolines employing LDA as a metalation additive. The reduction of diastereoselectivity with LDA in the case of Cp* imidazolines means that the amount of product with an *exo* imidazoline 4-substituent is again increased, but to a much smaller degree.

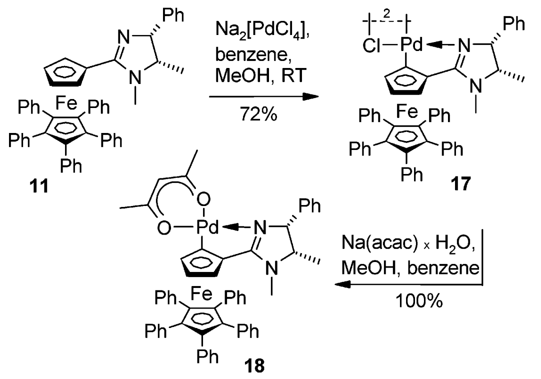
(22) For the cyclopalladation of related planar chiral iodo ferrocenyloxazolines see: Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648.

(23) Schlögl, K.; *Top. Stereochem.* **1967**, *1*, 39.

(24) Supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as deposition 299669. This material is available free of charge via the Internet at http://pubs.acs.org and http://www.ccdc.cam.ac.uk/products/csd/request/.

(25) For details see Supporting Information.

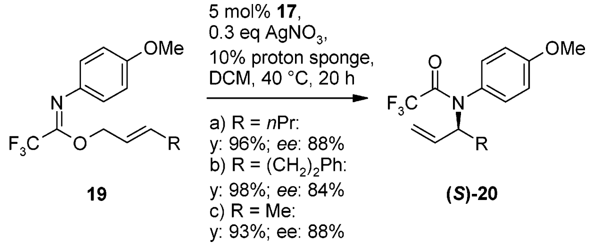
Scheme 5. Preparation of the First Pentaphenylferrocene Palladacycles



at the stereocenter next to the imino nitrogen atom should point to the *endo* position (to the metallocene) in order to minimize steric interactions with the coordinated alkyllithium base, which lies *exo* to the iron. This model is only partially valid for *ortho*-lithiations of Cp′-unsubstituted ferrocenyl imidazolines in the absence of LDA as metalation additive, and it is invalid in the presence of LDA.[1,21] Although a Cp* ligand adds much to the steric hindrance of a metallocene backbone, which should result in an increased repulsion of the imidazoline substituents, the diastereoselectivities for the *ortho*-functionalizations were improved in comparison to Cp′-unsubstituted ferrocenyl imidazolines.[1]

All attempts to *ortho*-lithiate C_5Ph_5 derivative **11** failed, since the starting material was always recovered unchanged. However, in contrast to pentamethylferrocene derivatives **7**, **11** could be directly diastereoselectively *ortho*-palladated, furnishing the air-stable palladacycle **17** as a dimeric chloride-bridged complex (*trans*/*cis* isomers about the Pd(II) square planes, Scheme 5). To determine the diastereoselectivity of the cyclopalladation, **17** was treated with an excess of Na(acac), leading to the monomeric complex **18** ($dr = 16{:}1$).[26] To the best of our knowledge, **17** and **18** are the first cyclopalladated or *ortho*-metalated ferrocenes bearing a pentaaryl-Cp spectator ligand.[27]

Scheme 6. Aza-Claisen Rearrangement of Trifluoroacetimidates 19



The absolute configuration was assigned by NOESY experiments of **18**.[25,28] Like for the above-discussed lithiations of the pentamethylferrocenyl imidazolines **7**, the cyclopalladation reaction occurs from a stereochemical point of view in a way that the phenyl group connected to the imidazoline 4-position points toward the spectator Cp ligand (*endo*).

Preliminary results show that **17** after activation with silver nitrate catalyzes the rearrangement of allylic trifluoroacetimidates **19** (aza-Claisen rearrangement)[22,29] in excellent yield and with high enantioselectivity (Scheme 6) in DCM at 40 °C within 20 h. Further work is ongoing in order to improve the catalyst system.

In conclusion, we have described the first enantiomerically pure 1′,2′,3′,4′,5′-pentamethyl- and 1′,2′,3′,4′,5′-pentaphenylferrocenyl imidazolines. While the 1′,2′,3′,4′,5′-pentamethyl derivatives could be *ortho*-lithiated with good diastereoselectivity, the 1′,2′,3′,4′,5′-pentaphenylferrocenyl complexes were inert toward *ortho*-lithiations, but could be diastereoselectively *ortho*-palladated. Our synthetic routes allowed the preparation of the first enantiomerically pure ferrocenyl palladacycles possessing C_5Me_5 or C_5Ph_5 spectator ligands. The planar chiral palladacycles have been shown to be promising catalysts for aza-Claisen rearrangement reactions of allylic trifluoroacetimidates.

Acknowledgment. This work was financially supported by ETH Research Grant TH-30/04-2F and by F. Hoffmann-La Roche. Moreover, we are indebted to F. Hoffmann-La Roche for the donation of laboratory equipment. We thank Prof. B. Jaun and co-workers for performing the NOE(SY) experiments and the groups of Profs. E. M. Carreira and P. Chen for sharing laboratory equipment.

Supporting Information Available: Experimental procedures, characterization data for all new products, X-ray data, and interpretations of the NOE(SY) experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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[26] Only few direct diastereoselective cyclopalladations of chiral ferrocenes are known: (a) Kuz'min, L. G.; Struchkov, Y. T.; Troitskaya, L. L.; Sokolov, V. I.; Reutov, O. A. *Isv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 1528. (b) López, C.; Bosque, R.; Solans, X.; Font-Bardia M. *Tetrahedron: Asymmetry* **1996**, *7*, 2527. (c) Zhao, G.; Xue, F.; Zhang, Z.-Y.; Mak, T. C. W. *Organometallics* **1997**, *16*, 4023. (d) Zhao, G.; Wang, Q.-G., Mak, T. C. W. *Tetrahedron: Asymmetry* **1998**, *9*, 1557. (e) Zhao, G.; Wang, Q.-G.; Mak, T. C. W. *Organometallics* **1998**, *17*, 3437.

[27] For the diastereoselective palladation of a (η^4-tetraphenylcyclobutadiene)cobalt complex see: Stevens, A. M.; Richards, C. J. *Organometallics* **1999**, *18*, 1346.

[28] Crystals suitable for X-ray analysis were not obtained so far for either **17** or **18**.

[29] (a) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, *5*, 1809. (b) Prasad, R. S.; Anderson, C. E.; Richards, C. J.; Overman, L. E. *Organometallics* **2005**, *24*, 77.