ORGANIC LETTERS

2000
Vol. 2, No. 5
629−631

C_2-Symmetric Planar Chiral Ferrocene Diamides by (–)-Sparteine-Mediated Directed *ortho*-Lithiation. Synthesis and Catalytic Activity

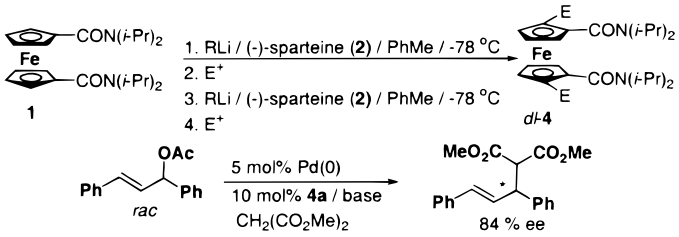
Radoslaw S. Laufer, Ulrich Veith,[1] Nicholas J. Taylor, and Victor Snieckus*,[2]

The Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario, N2L 3G1 Canada

snieckus@chem.queensu.ca

Received December 21, 1999

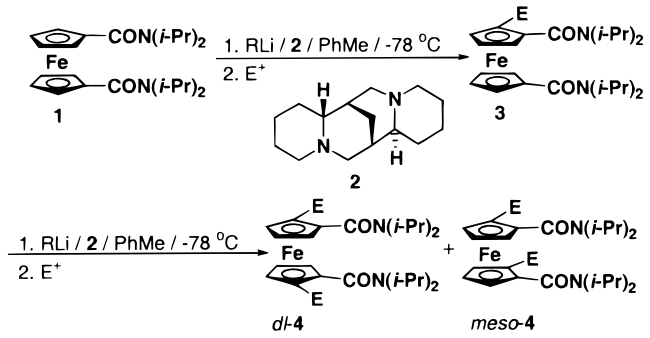
ABSTRACT



A variety of highly enantioenriched singly and doubly (4) functionalized derivatives of 1,1′-*N*,*N*,*N*′,*N*′-tetraisopropylferrocenedicarboxamide 1 have been synthesized by (–)-sparteine (2)-mediated directed *ortho*-metalation and Pd-catalyzed cross coupling reactions. The synthetic applications of these chiral ligands in asymmetric alkylation of benzaldehyde and Pd(0)-catalyzed allylic substitution have been demonstrated.

In 1996, we reported the first direct and highly enantioselective synthesis of planar chiral ferrocenecarboxamides by (−)-sparteine (**2**)-mediated[3] directed *ortho*-metalation (DoM)[4] which superseded diastereoselective metalation routes based on chiral auxiliary directed metalation groups (DMGs).[5] Herein we demonstrate this concept for the preparation of (a) highly enantioenriched 1,2,1′-trisubstituted chiral ferrocenes **3a**−**l** (Table 1, Scheme 1) which includes adaptation of Suzuki and Stille cross coupling protocols[6] to give 2-aryl-1,1′-ferrocenyl diamides (**3k**−**l**, Scheme 2) and (b) optically active C_2-symmetric derivatives **4a**−**c** via asym-

Scheme 1



(1) Present address: Process R & D, Lonza Ltd. Valais Works, CH-3930 Visp, Switzerland.

(2) Department of Chemistry, Queen's University K7L 3N6, ON, Canada.

(3) For a review on (−)-sparteine-assisted deprotonations, see: Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.

(4) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685.

(5) (a) Aratani, T.; Gonda, T.; Nozaki, H. *Tetrahedron Lett.* **1969**, 2265. (b) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffman, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389. (c) Rebiere, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 568. (d) Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835. (e) Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem.* **1997**, *62*, 6733. (f) Ganter, C.; Wagner, T. *Chem. Ber.* **1995**, *128*, 1157. (g) Richards, C. J. *Synlett* **1995**, 74. (h) Uemura, S.; Nishibayashi, Y. *Synlett* **1995**, 79. (i) Sammakia, T.; Lantham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10. (j) Sammakia, T.; Lantham, H. A. *J. Org. Chem.* **1995**, *60*, 6002. (k) Ahn, K. H.; Cho, C.-W.; Baek, H.-H.; Park, J.; Lee, S. *J. Org. Chem.* **1996**, *61*, 4937. (l) Enders, D.; Peters, R.; Lochtman, R.; Runsink, J. *Synlett* **1997**, 1462.

10.1021/ol991381s CCC: $19.00
Published on Web 02/11/2000

Table 1. *n*-BuLi/(−)-Sparteine-Induced Mono-metalation of 1,1′-*N*,*N*,*N*′,*N*′-Tetraisopropylferrocenedicarboxamide (**1**)

entry	E^+	product	solvent	yield, %	ee, %
1	I_2	**3a**	Et_2O	53	59
2	I_2	**3a**	*t*-BuOMe	77	70
3	I_2	**3a**	PhMe	70	89
4	MeI	**3b**	Et_2O	56	68
5	MeI	**3b**	PhMe	71	92
6	$Ph_2C{=}O$	**3c**	Et_2O	77	64
7	$Ph_2C{=}O$	**3c**	PhMe	92	94
8	$Ph_2C{=}O$	**3c**	PhMe	72[a]	96
9	$Et_2C{=}O$	**3d**	PhMe	45	91
10	Bu_3SnCl	**3e**	PhMe	58	≥82[b]
11	Ph_2PCl	**3f**	PhMe	53	97[c]
12	$(PhS)_2$	**3g**	PhMe	71	89[c]
13	$(PhSe)_2$	**3h**	PhMe	82	71[c]
14	TMSCl	**3i**	PhMe	68[a]	*d*

[a] 2.1 equiv of both *n*-BuLi and **2** was used. [b] Enantiomeric resolution was not feasible, and ee was determined after conversion into **3c** by transmetalation with *n*-BuLi followed by benzophenone quench. [c] Undergoes racemization; therefore, % ee determination was carried out immediately after purification. [d] CSP HPLC enantiomeric resolution was not feasible, $[\alpha]^{23}_{578}$ +67.5 (*c* 0.54, $CHCl_3$).

metric metalation of 2-substituted 1,1′-*N*,*N*,*N*′,*N*′-tetraisopropylferrocenedicarboxamides **3f**,**g**,**i**[7] which results in diastereoselective amplification of enantioselectivity. We also report preliminary findings which show the potential of tri- (**3**) and tetrasubstituted (*dl*-**4**) ferrocene ligands in benchmark asymmetric alkylation and Pd-catalyzed allylic substitution reactions (Scheme 3).

These results are of potential significance in areas of asymmetric catalysis, enantioselective synthesis, and material science,[8] including spectacular industrial applications, wherein planar chiral ferrocenes are receiving flourishing application.[9]

Metalation of ferrocenyldiamide **1**[10] with *n*-BuLi/**2** in Et_2O furnished, almost exclusively, products from electrophilic trapping of monolithium anion, the 1,1′,2-trisubstituted derivatives **3a**−**c**, in good yields but with moderate enantioselectivities (Table 1 entries 1, 4, and 6).[11,12] Use of solvents of lower coordinating abilities allowed for the preparation of 1,1′,2-trisubstituted derivatives[13] in augmented optical and chemical yields (entries 1−3).[14] Toluene was found to give the optimal balance between the level of enantioinduction and chemical yield, e.g., 97% ee, 53% yield for E = PPh_2 (**3f**), without recrystallization.[15]

Reduction of the amount of (*n*-BuLi/**2**) to 2.2 equiv caused a slight decline in the chemical yield of the product but did not lead to erosion of ee (entry 8). The heteroatom-hinged phenyl derivatives **3f**−**h** (entries 11−13) were found to surrender their optical integrity on standing in solution.[4,16] To demonstrate the combined potential of the DoM−cross coupling strategy as a route to aryl-substituted ferrocenes,[17] the iodo (**3a**) and stannane (**3e**) ferrocene diamides were subjected to Suzuki[18] and Stille/Gronowitz[19] cross coupling

Table 2. *n*-BuLi/(−)-Sparteine-Induced Mono-metalation of 2-Substituted-1,1′-*N*,*N*,*N*′,*N*′-tetraisopropylferrocenedicarboxamide (**3f**,**g**,**i**)

(SM) ee, %	E^+	product	yield,%	*dl*:*meso*	ee, %
(**3i**) 0	TMSCl[a]	**4b**	86	51:49	72[b]
(**3i**) *c*	TMSCl[d]	**4b**	75	84:16	91[b]
(**3f**) 97	Ph_2PCl[e]	**4a**	45	>95:<5[f]	98[b,7]
(**3g**) 89	$(PhS)_2$[a]	**4c**	60	99:1	97[g]

[a] 2.1 equiv of *n*-BuLi/**2** was used. [b] Determined as optical purity (op). [c] $[\alpha]^{23}_{578}$ +67.5 (*c* 0.54, $CHCl_3$). [d] 4.2 equiv of *n*-BuLi/**2** was used. [e] 1.5 equiv of *n*-BuLi/**2** was used. [f] dr determined by ^{31}P NMR. [g] dr and ee determined using CSP HPLC.

(6) (a) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, p 49. (b) Mitechell, T. N. ref 6a, p 167.

(7) Recently, Jendralla reported a synthesis of optically pure C_2-symmetric 2,2′-bis(diphenylphosphino)-1,1′-ferrocenedicarboxamide: Jendralla, H.; Paulus, E. *Synlett* **1997**, 471.

(8) (a) Hayashi. T., Togni, A. Eds. *Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Material Science*; VCH: Weinheim, 1995. (b) Kagan, H. B.; Riant, O. *Adv. Asymm. Synth.* **1997**, *2*, 189. (c) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH Publishers: New York; 1993.

(9) An asymmetric hydrogenation in the synthesis of (+)-biotin by Lonza: McGarrity, J.; Spindler, F.; Fuchs, R.; Eyer, M. (LONZA AG), EP-A 624 587-A2,1995; *Chem. Abstr.* **1995**, *122*, P81369q. Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475. Ciba-Geigy AG (Novartis) multiton synthesis of the herbicide (*S*)-Metolachlor: Spiendler, F.; Pugin, B.; Jalett, H.-P.; Buser, H.-P.; Pittelkow, W.; Blasser, H.-U. In *Catalysis of Organic Reactions*; Malz, R. E., Ed.; Marcel Dekker: New York, 1996, p 153. Spiendler, F.; Pugin, B. (Ciba-Geigy AG), EP-A 0 256982, 1988; *Chem. Abstr.* **1990**, *112*, 138725c.

(10) Prepared from 1,1′-ferrocenedicarboxylic acid (Aldrich), by sequential treatment with $(COCl)_2$/cat. DMF/PhMe and $HN(i\text{-}Pr)_2/Et_2O$ in 80% yield after recrystallization (Et_2O/hexane).

(11) In initial trials, double DoM−electrophile quench (2 equiv of *s*-BuLi/**2** in Et_2O/−78 °C/2 h and then 6 equiv of E^+/−78 °C to rt, 4 h) led to high yields of the 1,1′,2,2′-tetrasubstituted derivatives **4**; however, the reaction exhibited a prohibitively strong preference for the *meso* diastereomer and low levels of optical induction (e.g., E^+ = MeI 70% yield, *meso*:*dl* = 76:24, 53% ee; E^+ = TMSCl (**4b**) 99% yield, *meso*:*dl* = 96:4, 15% op (op = optical purity); E^+ = PPh_2Cl (**4a**) 49% yleid, *meso*:*dl* = >95:<5) (For other data, see Laufer, R. M.Sc. Thesis, University of Waterloo, 1998).

(12) Notably, *n*-BuLi·**2** is capable of effecting a double deprotonation of **1** but only in the presence of TMSCl as the electrophilic partner (e.g. in PhMe 71% yield of **4b**, *dl*:*meso* = 72:28, 97% op (Laufer, R. M.Sc. Thesis, University of Waterloo, 1998).

(13) (*S*) absolute configuration for carbinol **3c** was established by single-crystal X-ray crystallography. Crystal data for **3c**: $C_{37}H_{46}FeN_2O_3$, M = 624.4, orthorhombic, $P2_12_12_1$, a = 10.100(1) Å, b = 17.098(1) Å, c = 19.335(2) Å, V = 3338.9(8) Å^3, Z = 4; D_c = 1.242 g/cm^3, $F(000)$ = 1332, T = 160 K. Data were collected on a Siemens P4 diffractometer with Mo Kα radiation (λ = 0.710 73 Å); 6416 reflections were collected giving 3208 Friedel pairs. The structure was solved using Patterson and Fourier routines (SHELXTL IRIS) and refined by full-matrix least-squares on F resulting in final R, R_w, and GOF (for 5445 data with $F > 6.0\sigma(F)$) of 0.0238, 0.0272, and 2.05, respectively, for solution using the (*S*) model. The corresponding values for solution of the (*R*) model were 0.0433, 0.0492, and 3.70.

(14) Typical procedure for lithiation of **1**: A solution of (−)-sparteine (0.91 mL, 4.2 mmol) or TMEDA (0.64 mL, 4.20 mL) in PhMe (20 mmol) was stirred at rt (5 min), cooled to −78 °C, and treated with *n*-BuLi (solution in hexane, 4.2 equiv). After 10 min of stirring at −78 °C, a solution of **1** (0.44 g, 1.0 mmol) in PhMe (4.5 mL) was added dropwise (ca. 1 drop/10 s). The stirring was continued (1−2 h) at −78 °C, and the reaction mixture was quenched by addition of an electrophile (6 mmol) and allowed to warm to rt (or 0 °C for **3f**), treated with saturated aqueous NH_4Cl, extracted with Et_2O or CH_2Cl_2, washed with brine, dried ($MgSO_4$), concentrated in vacuo, and purified by flash chromatography on silica gel (deactivated with 2% Et_3N for diphenylphosphine derivative **3f**). Diphenylphosphine derivatives **3f** and **4a** were found to be air-sensitive but could be stored indefinitely as solids under argon at −20 °C.

(15) Toluene offers greatly improved solubility of ferrocenyldiamide **1**. The opposite solvent effect was observed in (−)-sparteine-assisted DoM of *N*,*N*-diisopropylferrocenecarboxamide (ref 4).

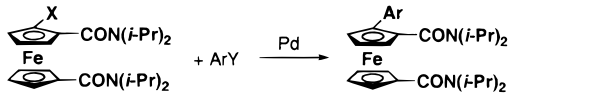
(16) Derivative **3g** undergoes racemization at rt, $t_{1/2} \approx 9$ h at rt (either in 90:10 or 98:2 hexane:*i*-PrOH).

(17) Quesnelle, C. A.; Familioni, O. B.; Snieckus, V. *Synlett* **1994**, 349 and references therein.

(18) $Pd(PPh_3)_4$/ 2M aqueous Na_2CO_3/DME/85 °C/5 d.

conditions with (2,4-dimethoxyphenyl)boronic acid[20] and bromobenzene, respectively, to give aryl derivatives **3k** (20% yield, unchanged ee, together with 70% of unreacted **3a**) and **3l** (35% yield in addition to 51% of **1**)[21] (Scheme 2).

Scheme 2

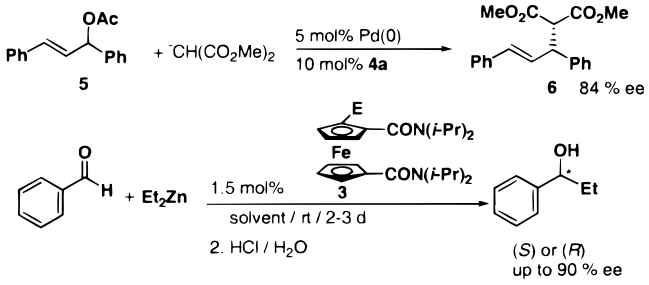


X = I (89 % ee) **3a** ArY = 2,4-$(MeO)_2$PhB(OH)$_2$ **3k** 20% yld, 89% ee
X = *n*-Bu_3Sn **3e** ArY = PhBr **3l** 35% yld

Highly diastereo- and enantioenriched, tetrasubstituted ferrocenyldiamides *dl*-**4** were prepared by subjecting 1,2,1′-trisubstituted ferrocenes **3** to a further (−)-sparteine-assisted asymmetric DoM reaction. Electrophilic quench furnished products **4a**−**c** with diastereoselective amplification of enantioselectivity (e.g., entry 1 in Table 2).[22,23] The (*R*,*R*) absolute configuration of products **4a**−**c** must be dictated by the (*R*) stereochemistry of the corresponding chiral precursors **3f**,**g**,**i**. Noteworthy is the relatively greater optical stability of 1,1′,2,2′-tetrasubstituted dervatives; for example, in solution, 2,2′-bis(diphenylthio)-1,1′-ferrocenediamide **4c** maintained its enantioenrichment at a 70% level even after 20 days of standing[24] compared to 2-(diphenylthio)-1,1′-ferrocenediamide **3g** which, under the same conditions, undergoes complete racemization within 1.5 days.[16]

In a preliminary study of the utility in asymmetric synthesis, chiral 1,1′-bis(diphenylphosphino)-2,2′-ferrocenyldiamide **4a** was tested as an auxiliary ligand for enantioselective Pd-catalyzed allylic substitution of (±)-phenylcinnamyl acetate (**5**) (Scheme 3).[25] The reactions were conducted using 2.5 mol % of [Pd(η^3-C_3H_5)Cl]$_2$ as the Pd source under Trost's alkylation conditions (3.0 equiv of *N*,*O*-bis(trimethylsilyl)acetamide/0.03 equiv of AcOK/3.0 equiv of $CH_2(CO_2Me)_2$/CH_2Cl_2 /rt/10 h)[26] or employing sodiodimethylmalonate (3.0 equiv of $NaCH(CO_2Me)_2$/THF/rt/36 h). In both cases, alkylated product **6** was obtained in essentially quantitative yield and with good enantiocontrol (96% yield, 84% ee (*R*)).[27]

Scheme 3



Furthermore, the 1,1′,2-ferrocenyldiamides **3c**,**d**,**k** exhibit moderate to good catalytic activities in the reaction of Et_2-Zn with PhCHO (Table 3, Scheme 3).[28−30]

Table 3. Ferrocenyldiamide-Catalyzed (**3c**,**d**,**k**) Et_2Zn Addition to PhCHO

entry	E	ligand (ee, %)	solvent	yield, %	ee, %[a]
1	$Ph_2C(OH)$	**3c** (96)	hexane	98	61(*S*)
2	$Ph_2C(OH)$	**3c** (96)	PhMe	98	12(*R*)
3	$Ph_2C(OLi)$	**3c**·Li (95)	PhMe	70	47(*S*)[b]
4	$Et_2C(OH)$	**3d** (90)	hexane	37	60(*S*)
5	2,4-di(MeO)Ph	**3k** (89)	PhMe	43	90(*S*)

[a] By CSP HPLC. [b] $[\alpha]^{23}_D$ −21.7 (*c* 3.43, $CHCl_3$), see ref 29b.

In summary, a direct and highly efficient enantioselective synthesis of mono- (**3a**−**h**) and C_2-symmetric, homoleptic (**4a**−**c**) ferrocene diamides from achiral ferrocenyldicarboxamide **1** using sparteine-mediated DoM and combined DoM−cross coupling (**3k**,**l**) have been demonstrated. The preliminary results for use in asymmetic synthesis and the current intense activity in ferrocene-based catalysis[8,9] stimulate our continuing efforts in this area.

Acknowledgment. We warmly thank Dr. Heiner Jendralla for exchange of correspondence and helpful comments on this manuscript. We are grateful to NSERC Canada for support under the Industrial Research Chair (Monsanto/Searle) and Research Grant programs. R.L. is an Ontario Graduate Scholar, 1996−1997.

Supporting Information Available: Experimental procedures and details of compound characterization. This material is available free of charge via Internet at http://pubs.acs.org.

OL991381S

(19) $PdCl_2$(dppf)/CuO/DMF/150 °C/18 h; Gronowitz, S.; Bjork, P.; Malm, J.; Hornfeldt, A.-B. *J. Organomet. Chem.* **1993**, *460*, 127.
(20) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763.
(21) Ee for **3l** was not determined because of availability of only an approximate value for ee of the ferrocenyltin **3e**.
(22) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
(23) Typical procedure is analogous to that used for the monometalation of **1** (ref 14)
(24) **4c** undergoes very slow racemization at rt, $t_{1/2}$ > 40 d at rt (90:10 hexane:*i*-PrOH).
(25) For reviews on catalyzed allylic substitution reactions, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355. (c) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203.
(26) Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143.
(27) Enantiomeric excess determined by CSP HPLC (Chiralcell OD, eluent = *n*-hexane/*i*-PrOH 99:1, flow 0.2 mL/ min, t_R(minor) 58.78, t_R-(minor) 63.50 min), $[\alpha]^{23}_D$ +15.9 (*c* 0.71, EtOH).
(28) Noyori, R. *Asymmetric catalysis in organic synthesis*; Wiley: New York, 1994.
(29) (a) In a typical reaction, to a stirred solution of PhCHO (0.1 mL, 1.6 mmol) and a ferrocenyl ligand (0.05 mmol) in either hexane (15 mL) or PhMe (5 mL) under an inert atmosophere was added Et_2Zn (1.6 mL, 1.0 M in hexane, 1.6 mmol) at rt, and the resultant mixture was stirred at rt for 48−72 h before addition of 0.2 M aqueous HCl at 0 °C. After the standard workup, the crude material was analyzed by CSP HPLC (Chiralcel OD column, eluent 99:1 *n*-hexane/*i*-PrOH, flow 0.5 mL/min, t_R 27.20 and 29.66 min). (b) For the value of the optical rotation, see: Packard, R. H.; Kenyon, J. *J. Chem. Soc.* **1914**, 1115. Also see: Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
(30) Quite unusual and, to our knowledge, previously unobserved is the variation in the enatiotopicity of the reaction as a function of the solvent (entry 1 vs entry 2) and use of lithium salt of carbinol **3c** (entry 2 vs entry 3). We currently do not have an explanation for this observation.