(−)-Frontalin: Synthesis using the Catalytic Enantioselective Addition of Dimethylzinc to a Ketone

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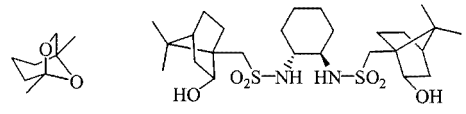
The first enantioselective synthesis of (−)-frontalin involving an enantioselective nucleophilic 1,2-addition of dimethylzinc to a functionalized α,β-unsaturated ketone, in the presence of titanium tetraisopropoxide and a substoichiometric amount of the chiral ligand 1,2-*trans*-bis(hydroxycamphorsulfonamido)cyclohexane (HOCSAC, **2**) as the key step, is described. The enantiomeric excess is as high as 89%.

Introduction

(1*S*,5*R*)-1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane [(−)-frontalin, **1**] is one of the semiochemicals[1] (aggregation pheromones) secreted from pine beetles of the *Dendroctonus* family.[2] This compound has also been isolated from other sources, such as the temporal gland of the male Asian elephant during the condition of musth,[3] and the bark of several angiosperm trees.[4] In the case of bark beetles, it was supposed that (−)-frontalin, as well as other pheromone components, was obtained by simple modifications of dietary precursors. However, according to different radiolabeled acetate derivative experiments,[5] in the case of male *Dendroctonus jeffreyi* it has been demonstrated that compound **1** is *de novo* synthesized in the anterior mid-gut tissue through the mevalonate pathway. Since these beetles destroy large areas of pine forest, frontalin has been used to control the progression of harmful insect infestations.[6]

Frontalin is a valuable simple target to test different asymmetric synthetic methods. Thus, although it possesses two stereocenters, the asymmetric key step is the construction of only one oxygen-substituted quaternary carbon stereocenter,[7] the second one being dictated by the formation of the bicyclic structure. All possible general strategies, such as diastereoselective[8] and enantioselective protocols, have been used in its preparation. Among the latter ones, it must be pointed out that enzymatic,[9] as well as antibody,[10] resolutions of different substrates are well established methodologies. However, the chemical enantioselective approaches have been restricted to those in which the construction of the stereocenter is performed by the formation of a carbon-oxygen bond, for example epoxidation[11] and dihydroxylation,[12] the only example of an enantioselective carbon-carbon bond-forming approach being, to the best of our knowledge, the allylation of benzyl pyruvate using an excess of a chiral diisopropyl tartrate-allyl-tin complex.[13]

On the other hand, we have found that *trans*-1,2-bis(hydroxycamphorsulfonamido)cyclohexane (HOCSAC, **2**) is, among other chiral sulfonamides, an extraordinary good ligand to perform enantioselective transformations. Thus, compound **2** has been used in substoichiometric amounts to carried out the enantioselective addition[14] of alkyl[15] and aryl[16] organozinc reagents to aldehydes[17] and ketones[18] in the presence of titanium tetraisopropoxide,[19] achieving excellent levels of enantioselectivity. We now describe the first catalytic enantioselective synthesis of (−)-frontalin which involves a carbon-carbon bond formation process by a nucleophilic alkylation of the appropriate ketone using HOCSAC (**2**) as the chiral promoter.



(−)-Frontalin **1** HOCSAC **2**

Results and Discussion

The enantioselective synthesis of (−)-frontalin started with the lithiation of chlorinated ketal **3**, using lithium powder and a substoichiometric amount of naphthalene,[20] to lead to the lithium bis-homoenolate[21] **4** (Scheme 1). Reaction of **4** with different cinnamoyl derivatives such as chloride, methyl ester or morpholine amide, yielded, after hydrolysis, the expected compound contaminated with by-products arising from a double addition processes. To avoid these by-products, the organolithium **4** was transmetal-

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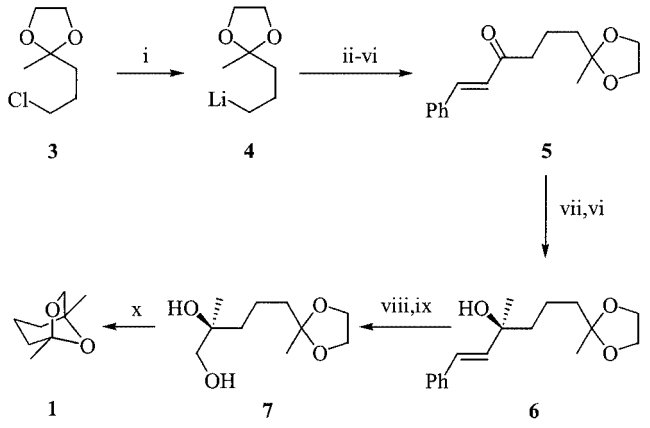
lated[22] to give a less-reactive system, although it was first necessary to eliminate the excess of lithium by filtration, since lithium is able to reduce different salts to their metallic state, thus preventing the transmetallation process. To achieve this, zinc and copper salts were successively added to the above solution containing the organolithium intermediate **4**. The resulting functionalized organometallic derivative was successfully trapped by reaction with cinnamyl chloride, to afford ketone **5** in 72% overall yield. In this case, it must be pointed out that the only by-product detected was 2-methyl-2-propyl-1,3-dioxolane, which arises from a proton abstraction of organolithium **4** from the reaction medium.



Scheme 1. (i) Li (excess), $C_{10}H_8$ (10% molar), THF, −78 °C, 30 min; (ii) filtration; (iii) $ZnBr_2$, 0 °C, 15 min; (iv) CuCN·2LiCl, 30 min; (v) PhCH=CHCOCl, 25 °C, 4 h; (vi) H_2O (72% **3** to **5**); (vii) Me_2Zn, Ti(O*i*Pr)$_4$, HOCSAC (**2**, 10% molar), PhMe, 25 °C, 24 h (81% yield, 89% *ee*); (viii) O_3, CH_2Cl_2, −78 °C; (ix) $NaBH_4$, MeOH, 0 °C, 16 h (75% yield for two steps, 88% *ee*); (x) HCl (2 M), C_6H_{14} (80% yield, 85% *ee*)

The asymmetric key step is the addition of dimethylzinc to the functionalized α,β-unsaturated ketone **5**. Enantioselective addition to ketones is much more difficult than that to the corresponding aldehydes for both steric and electronic reasons. However, chiral ligand HOCSAC (**2**) is the only one to overcome these problems, and it is able to promote the enantioselective addition of different organozinc reagents to ketones. Moreover, in other related methodologies using different chiral ligands there is a great dependence of the enantioselectivity upon the substrate structure, with modest levels of enantioselectivity for the functionalized compounds. This addition reaction merits a special comment, since it permits not only the use of simple ketones but also functionalized ones with a negligible decrease in the enantioselectivity. Thus, the reaction was carried out using an excess of dimethylzinc (1:2.4 molar ratio) and titanium tetraisopropoxide (1:1.3 molar ratio), and a substoichiometric amount of HOCSAC (10%). After one day, the starting ketone had been consumed and the expected tertiary alcohol **6** was isolated in 81% yield (Scheme 1). The enantiomeric excess (89%) was determined by HPLC using a racemic mixture of alcohol **6** as standard, the absolute configuration (*S*) being deduced by correlation of the finally obtained frontalin with the already described compound. The topicity of the addition is the same as that found for simple ketones.

Once the enantioselective key step had been successfully performed, it only remained to manipulate the structure to yield the desired product. Thus, ozonolysis[23] of the carbon-carbon double bond and reductive cleavage of the formed ozonide with sodium borohydride afforded the expected diol **7** with good yield (75%), with no loss of the enantiomeric excess, according to HPLC analysis. The final biphasic hydrolysis of the ketal functionality using hexane and hydrochloric acid yielded pure frontalin.[24] The absolute configuration of the compound was assigned by comparison of the optical rotation with the previously reported value and therefore the absolute configuration of compounds **7** and **6** was assigned as *S* (see above).

Conclusion

The study presented here represents the first catalytic enantioselective synthesis of (−)-frontalin involving a carbon-carbon bond formation process as the asymmetric key step using a substoichiometric amount of chiral ligand. This synthesis emphasises that the enantioselective addition of organozinc reagents to ketones using HOCSAC might be potentially used in other syntheses since the system keeps its high enantioselectivity for different organozinc reagents and even for functionalized ketones.

Experimental Section

General Remarks: $[\alpha]_D$ values were recorded at room temperature (ca. 25 °C) on a DIP-1000 JASCO polarimeter (p.a. solvents, Panreac). FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. Mass spectra (EI) were obtained at 70 eV on a Shimazdu QP-5000 spectrometer, giving fragment ions in *m*/*z* with relative intensities (%) in parentheses. High resolution mass spectral analyses were performed by the Mass Spectrometry Service at the University of Alicante. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett Packard HP-5890 instrument equipped with a flame ionization detector and 12 m HP-1 capillary column (0.2 mm diam., 0.33 mm film thickness, OV-1 stationary phase), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$ = 275 °C, $T_{detector}$ = 300 °C, T_{column} = 60 °C (3 min) and 60−270 °C (15 °C/min), P = 40 kPa; t_R values are given in min under these conditions. The enantiomeric excesses (*ee*) were determined with a Hewlett Packard HP-1100 HPLC instrument equipped with a 25 cm OD-H or AD Chiralcel column (0.46 cm diameter); $t_R(R)$ and $t_R(S)$ values are given in min under these conditions. Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel; detection by UV_{254} light, staining with phosphomolybdic acid (25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2$·$4H_2O$, 60 mL concentrated H_2SO_4 and 940 mL H_2O) or with I_2; R_f values are given under these conditions. Column chromatography was performed using silica gel 60 of 35−70 mesh.

Chiral HOCSAC (**2**) was prepared from the corresponding cyclohexyldiamine and camphorsulfonyl chloride,[15] other reagents are commercially available (Acros, Aldrich, Strem) and were used as received. Solvents were dried by standard procedures.

2-Methyl-2-(4-oxo-6-phenylhex-5-en-1-yl)-1,3-dioxolane (5): A solution of the chlorodioxolane **3** (2.26 mL, 15 mmol) in THF (10 mL) was added to a green suspension of lithium powder (0.80 g, 1.12 mmol) and naphthalene (0.11 g, 0.32 mmol) in THF (20 mL) at −78 °C. After 30 min, the unreacted lithium was filtered off with a cannula, and a solution of $ZnBr_2$ (4.38 g, 19.5 mmol) in THF (15 mL) was added. The resulting solution was allowed to warm to 0 °C and after 15 min another solution of CuCN (1.175 g, 19.5 mmol) and LiCl (1.65 g, 39 mmol) in THF (10 mL) was added. After 15 min at the same temperature, a solution of cinnamoyl chloride (2.67 g, 16.05 mmol) in THF (5 mL) was added. The reaction mixture was stirred for 4 h, allowing the temperature to rise to 25 °C. Then, the mixture was quenched with a saturated solution of NH_4Cl (25 mL). The resulting mixture was extracted with diethyl ether (3 × 30 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and the solvents evaporated (15 Torr) to give a residue, which was purified by column chromatography, affording the pure title compounds **5** as yellow oil (2.81 g, 72%). t_R = 14.8, R_f = 0.26 (hexane/ethyl acetate, 4:1). IR (film): $\tilde{\nu}$ = 3045, 1612, 1449 (CH=C), 1714, 1661 (C=O), 1173 cm^{-1} (CO). ^1H NMR: δ = 1.33 (s, 3 H, CH_3), 1.65−1.85, 3.15−3.25 [2 m, 4 H and 2 H, respectively, $(CH_2)_3$], 3.90−4.00 (m, 4 H, 2 × CH_2O), 6.74, 7.55 (2 d, J = 16 Hz, 1 H each, CH=CHCO), 7.35−7.45, 7.50−7.55 (2 m, 2 H and 3 H, respectively, ArH) ppm. ^{13}C NMR: δ = 18.65, 23.65, 38.25, 40.6, 64.5 (2 C), 109.7, 126.05, 128.1 (2 C), 128.8 (2 C), 129.2, 130.25, 142.25 ppm. MS: m/z (%) = 260 [M^+] (<1), 131 (25), 103 (19), 99 (15), 87 (100), 77 (11). HRMS calcd. for $C_{16}H_{20}O_3$: 260.1412; found 260.1419.

2-(4-Hydroxy-4-methyl-6-phenylhex-5-en-1-yl)-2-methyl-1,3-dioxolane (6): $Ti(OiPr)_4$ (1.65 mL, 5.6 mmol) and Me_2Zn (5.2 mL, 2 M in toluene, 10.3 mmol) were added at 0 °C under argon to a solution of HOCSAC (**2**, 0.235 g, 0.43 mmol) in toluene (5 mL). After 10 min, the resulting pale green solution was warmed up to 25 °C and then ketone **5** (1.12 g, 4.3 mmol) was added as a solution in toluene (2 mL). After 24 h, the solution was quenched by successive addition of MeOH (3 mL) and a saturated solution of NH_4Cl (5 mL). The resulting mixture was extracted with diethyl ether (3 × 20 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and the solvents evaporated (15 Torr) to give a residue, which was purified by column chromatography, affording the pure title compounds **6** as a colorless oil (0.96 g, 81%). t_R = 14.2, R_f = 0.14 (hexane/ethyl acetate, 4:1). $[\alpha]_D$ = +6.9 (c = 4.26, $CHCl_3$), ee = 89%. $t_R(S)$ = 29.4 and $t_R(R)$ = 39.1 (AD, UV 220 nm, hexane/2-propanol 97:3, flow 1 mL/min). IR (film): $\tilde{\nu}$ = 3080, 1494 (CH=C), 1052 cm^{-1} (CO). ^1H NMR: δ = 1.30, 1.38 (2 s, 3 H each, 2 × CH_3), 1.50−1.55, 1.60−1.70, 2.00−2.05 [3 m, 2 H each, respectively, $(CH_2)_3$], 3.90−4.05 (m, 4 H, 2 × CH_2O), 4.10−4.15 (m, 1 H, OH), 6.27, 6.59 (2 d, J = 16.1 Hz, 1 H each, CH=CHCO), 7.20−7.40 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 18.6, 23.7, 28.2, 39.35, 42.85, 64.55 (2 C), 73.15, 110.0, 126.35 (2 C), 127.0, 127.3, 128.5 (2 C), 136.6, 136.95 ppm. MS: m/z (%) = 276 [M^+] (<1), 157 (12), 156 (10), 147 (42), 141 (14), 129 (37), 128 (38), 115 (14), 99 (13), 91 (18), 87 (100), 59 (11). HRMS calcd. for $C_{17}H_{24}O_3$: 276.1725; found 276.1735.

2-(4,5-Dihydroxy-4-methylpent-1-yl)-2-methyl-1,3-dioxolane (7): A solution of the alkene **6** (0.30 g, 1.10 mmol) in CH_2Cl_2 (15 mL) was cooled to −78 °C. The effluent stream from an ozone generator was bubbled into the dichloromethane solution (ca. 30 mL/min) for 1 h, until the blue color of ozone was noticeable. MeOH (15 mL) and $NaBH_4$ (0.38 g, 10 mmol) were added at 0 °C to the above solution, and the temperature was allowed to rise to 25 °C overnight. The reaction was then quenched by addition of water (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (5 × 20 mL), the combined organic layers were dried over anhydrous $MgSO_4$ and the solvents evaporated (15 Torr) to give a residue, which was purified by column chromatography, affording the pure title compounds **7**[9d] as a colorless oil (0.17 g, 75%). t_R = 11.05, R_f = 0.46 (hexane/ethyl acetate, 1:1). $[\alpha]_D$ = −2.1 (c = 1.0, Et_2O), ee = 88% {ref.:[9d] $[\alpha]_D$ = −1.8 (c = 1.2, Et_2O), 90%}. $t_R(S)$ = 3.25 and $t_R(R)$ = 4.00 (OD-H, UV 200 nm, hexane/2-propanol 97:3, flow 1 mL/min). IR (film): $\tilde{\nu}$ = 3383, 3410 (OH), 1152, 1055 cm^{-1} (CO). ^1H NMR: δ = 1.08, 1.32 (2 s, 3 H each, 2 × CH_3), 1.30−1.75 [m, 6 H, $(CH_2)_3$], 2.45−2.65 (m, 2 H, 2 × OH), 3.28, 3.34 (2 d, J = 11.0 Hz, 1 H each, CH_2OH), 3.85−4.00 (m, 4 H, 2 × CH_2O) ppm. ^{13}C NMR: δ = 18.6, 23.4, 24.0, 39.1, 40.2, 64.6 (2 C), 70.0, 72.7, 110.2 ppm. MS: m/z (%) = 189 [M^+ − Me] (<1), 87 (34), 72 (12), 71 (14), 43 (100).

1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (1): HCl (1 mL, 2 M) was added at 25 °C to a solution of the dioxolane **7** (0.50 g, 0.24 mmol) in hexane (2 mL). After 1 h, the organic layer was decanted, dried over anhydrous $MgSO_4$ and the solvents evaporated (15 Torr) to give pure frontalin (**1**)[24] as a colorless oil (0.29 g, 85%). $[\alpha]_D$ = −51.6 (c = 0.4, Et_2O), ee = 85% {ref.:[9d] $[\alpha]_D$ = −52.1 (c = 0.5, Et_2O), 90%}. $t_R(S)$ = 3.30 and $t_R(R)$ = 4.40 (OD-H, UV 200 nm, hexane/2-propanol 99:1, flow 1 mL/min).

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[1] [1a] K. Mori, *Eur. J. Org. Chem.* **1998**, 1479−1489. [1b] W. Francke, W. Schroder, *Curr. Org. Chem.* **1999**, *3*, 407−443.
[2] [2a] G. W. Kinzer, F. A. Fentiman, F. T. Page, R. L. Foltz, J. P. Vite, G. B. Pitman, *Nature* **1969**, *221*, 477−478. [2b] J. A. A. Renwick, J. P. Vite, *Nature* **1969**, *224*, 1222−1223. [2c] D. L. Wood, L. E. Browne, B. Ewing, K. Lindahl, W. D. Bedard, P. E. Tilden, K. Mori, G. B. Pitman, P. R. Hughes, *Science* **1976**, *192*, 896−898.
[3] L. E. L. Rasmussen, J. Lazar, D. R. Greenwood, *Biochem. Soc., Trans.* **2003**, *31*, 137−141.
[4] D. P. W. Huber, R. Gries, J. H. Borden, H. D. Pierce, *J. Chem. Ecol.* **1999**, *25*, 805−816.
[5] [5a] G. M. Hall, C. Tittiger, G. J. Blomquist, G. L. Andrews, G. S. Mastick, L. S. Barkawi, C. Bengoa, S. J. Seybold, *Insect Biochem. Mol. Biol.* **2002**, *32*, 1525−1532. [5b] S. J. Seybold, C. Tittiger, *Annu. Rev. Entomol.* **2003**, *48*, 425−453.
[6] [6a] T. L. Payne, J. C. Dickens, J. V. Richerson, *J. Chem. Ecol.* **1984**, *10*, 487−492. [6b] M. P. Chatelain, J. A. Schenk, *Environ. Entomol.* **1984**, *13*, 1666−1674. [6c] J. H. Borden, L. C. Borden, L. J. Chong, H. D. Pierce, B. D. Johnston, A. C. Oehlschlager, *Can. J. For. Res.* **1987**, *17*, 118−128.
[7] For reviews on enantioselective formation of quaternary carbon stereocenters, see: [7a] K. Fuji, *Chem. Rev.* **1993**, *93*, 2037−2066. [7b] E. J. Corey, A. Guzmán-Pérez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388−401. [7c] J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591−4597. [7d] D. J. Ramón, M. Yus, *Curr. Org. Chem.* submitted.
[8] For different examples, see: [8a] T. Fujisawa, I. Takemura, Y. Ukaji, *Tetrahedron Lett.* **1990**, *31*, 5479−5482. [8b] E. A. Mash, J. A. Fryling, *J. Org. Chem.* **1991**, *56*, 1094−1098. [8c] H. Nem-

oto, T. Yamada, H. Ishibashi, K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3149−3151. [8d] F. A. Davis, G. V. Reddy, B.-C. Chen, A. Kumar, M. S. Haque, *J. Org. Chem.* **1995**, *60*, 6148−6153. [8e] Y. Nishimura, K. Mori, *Eur. J. Org. Chem.* **1998**, 233−236. [8f] N. Maezaki, T. Shogaki, M. Uchida, K. Tokuno, T. Imamura, T. Tanaka, C. Iwata, *Chem. Pharm. Bull.* **1998**, *46*, 217−221. [8g] C. Kouklovsky, O. Dirat, T. Berranger, Y. Langlois, M. E. Tran-Huu-Dau, C. Riche, *J. Org. Chem.* **1998**, *63*, 5123−5128. [8h] M. Majewski, P. Nowak, *Tetrahedron: Asymmetry* **1998**, *9*, 2611−2617. [8i] P. Bravo, E. Corradi, M. Frigerio, S. V. Meille, W. Panzeri, C. Pesenti, F. Viani, *Tetrahedron Lett.* **1999**, *40*, 6317−6320. [8j] R. M. Kanada, T. Taniguchi, K. Ogasawara, *Tetrahedron Lett.* **2000**, *41*, 3631−3635. [8k] P. Bravo, M. Frigerio, T. Ono, W. Panzeri, C. Peseti, A. Sekine, F. Viani, *Eur. J. Org. Chem.* **2000**, 1387−1389. [8l] P. Ambrosi, A. Arnone, P. Bravo, L. Bruché, A. De Cristofaro, V. Francardi, M. Frigerio, E. Gatti, G. S. Germinara, W. Panzeri, F. Pennacchio, C. Pesenti, G. Rotundo, P. F. Roversi, C. Salvadori, F. Viani, M. Zanda, *J. Org. Chem.* **2001**, *66*, 8336−8343. [8m] S.-s. Jew, D.-Y. Lim, J.-Y. Kim, S.-j. Kim, E.-y. Roh, H.-J. Yi, J.-M. Mo, B.-s. Park, B.-s. Jeong, H.-g. Park, *Tetrahedron: Asymmetry* **2002**, *13*, 155−159. [8n] M. Trzoss, J. Shao, S. Bienz, *Tetrahedron* **2002**, *58*, 5885−5894.

[9] [9a] P. Ferraboschi, S. Casati, P. Grisenti, E. Santaniello, *Tetrahedron: Asymmetry* **1993**, *4*, 9−12. [9b] W. Kroutil, I. Osprian, M. Mischitz, K. Faber, *Synthesis* **1997**, 156−158. [9c] S.-T. Chen, J.-M. Fang, *J. Org. Chem.* **1997**, *62*, 4349−4357. [9d] R. Chênevert, D. Caron, *Tetrahedron: Asymmetry* **2002**, *13*, 339−342.

[10] B. List, D. Shabat, G. Zhong, J. M. Turner, A. Li, T. Bui, J. Anderson, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **1999**, *121*, 7283−7291.

[11] T. H. Chan, L. M. Chen, D. Wang, L. H. Li, *Can. J. Chem.* **1993**, *71*, 60−67.

[12] [12a] J. A. Turpin, L. O. Weigel, *Tetrahedron Lett.* **1992**, *33*, 6563−6564. [12b] B. Santiago, J. A. Soderquist, *J. Org. Chem.* **1992**, *57*, 5844−5847. [12c] T. Taniguchi, K. Nakamura, K. Ogasawara, *Synthesis* **1997**, 509−511.

[13] M. Scholl, R. H. Grubbs, *Tetrahedron Lett.* **1999**, *40*, 1425−1428.

[14] For a review on enantioselective 1,2-additions, see: M. Yus, D. J. Ramón, *Recent Res. Devel. Org. Chem.* **2002**, *6*, 297−378.

[15] M. Yus, D. J. Ramón, O. Prieto, *Tetrahedron: Asymmetry* **2002**, *13*, 2291−2293.

[16] O. Prieto, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2003**, in press.

[17] [17a] D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **1997**, *8*, 2479−2496. [17b] O. Prieto, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2000**, *11*, 1629−1644. [17c] M. Yus, D. J. Ramón, O. Prieto, *Tetrahedron: Asymmetry* **2002**, *13*, 1573−1579.

[18] [18a] D. J. Ramón, M. Yus, *Tetrahedron Lett.* **1998**, *39*, 1239−1242. [18b] D. J. Ramón, M. Yus, *Tetrahedron* **1998**, *54*, 5651−5666. [18c] M. Yus, D. J. Ramón, O. Prieto, *Tetrahedron: Asymmetry* **2003**, *14*, 1103−1114.

[19] For a review on enantioselective reactions promoted by titanium derivatives, see: D. J. Ramón, M. Yus, *Recent Res. Devel. Org. Chem.* **1998**, *2*, 489−523.

[20] For reviews on arene-catalyzed lithiation, see: [20a] M. Yus, *Chem. Soc. Rev.* **1996**, *25*, 155−161. [20b] D. J. Ramón, M. Yus, *Eur. J. Org. Chem.* **2000**, 225−237. [20c] M. Yus, *Synlett* **2001**, 1197−1205. [20d] D. J. Ramón, M. Yus, *Rev. Cubana Quím.* **2002**, *14*, 76−115.

[21] [21a] D. J. Ramón, M. Yus, *Tetrahedron Lett.* **1990**, *31*, 3763−3766. [21b] D. J. Ramón, M. Yus, *Tetrahedron Lett.* **1990**, *31*, 3767−3770. [21c] D. J. Ramón, M. Yus, *J. Org. Chem.* **1991**, *56*, 3825−3831. [21d] M. Yus, D. J. Ramón, *J. Chem. Soc., Chem. Commun.* **1991**, 398−400.

[22] For reviews on functionalized organometallics obtained by transmetallation processes, see: [22a] P. Knochel, J. J. Almena Perea, P. Jones, *Tetrahedron* **1998**, *54*, 8275−8319. [22b] M. Yus, D. J. Ramón, *Latv. J. Chem.* **2002**, 79−92.

[23] L. A. Flippin, D. W. Gallagher, K. Jalali-Araghi, *J. Org. Chem.* **1989**, *54*, 1430−1432.

[24] M. Yus, D. J. Ramón, *J. Org. Chem.* **1992**, *57*, 750−751.

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