Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 1747–1752

TETRAHEDRON: *ASYMMETRY*

Chiral derivatives of semisquaric acid as new modular ligands for asymmetric catalysis

Sílvia Ferrer, Mireia Pastó, Belén Rodríguez, Antoni Riera and Miquel A. Pericàs*

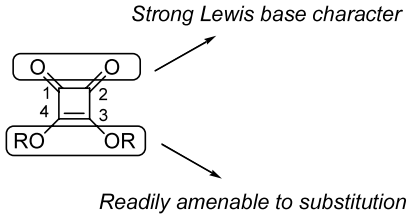
Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Departament de Química Orgànica/Parc Científic de Barcelona, Universitat de Barcelona, C/Josep Samitier, 1-5, 08028 Barcelona, Spain

Received 11 March 2003; accepted 11 April 2003

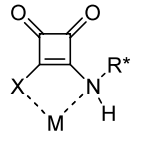
Abstract—A family of enantiomerically pure ligands based on the cyclobutenedione structure, and containing either an enantiomerically pure amino alcohol or a diamine as the chiral element, has been synthesized. As first examples of their application, these versatile and modularly constructed ligands have been tested in the transfer hydrogenation of acetophenone and in the reduction using borane of this same substrate.

1. Introduction

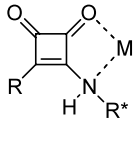
Modularly constructed ligands which allow the fast optimization of catalytic properties for a given application are widely recognized as a major advance in asymmetric synthesis.[1] Recently, we have been working on the development of chiral, yet purely synthetic amino alcohol ligands,[2] starting from readily available enantiomerically pure epoxides derived from Sharpless[3] and Jacobsen epoxidations.[4] The synthesis of the target ligands is modular in nature, thus fulfilling the condition of allowing the easy optimization of catalytic properties through structural modification for every particular situation. Herein we wish to report our work on the synthesis of a novel type of versatile chiral ligand containing a squaryl group as the structural building block. Squaric acid is an aromatic compound with unique properties and applications. Besides its important biological properties,[5] it has been employed in the development of advanced materials,[6] as a useful diene synthon in organic synthesis[7] and as a linker in the synthesis of oligosaccharides to a solid phase or a lipid.[8] Analysing its structure, squaric acid system possesses a rigid skeleton, two oxygen atoms with a pronounced Lewis base character, and two reactive positions that can be submitted to a variety of substitution processes either in a simultaneous or a sequential manner, providing the potential for the preparation of a large number of compounds by substituent variation.



In this sense, squaric acid derivatives are revealed as exceptionally versatile scaffolds for molecular recognition[9] and the synthesis of some chiral derivatives of squaric acid and their application to the enantioselective reduction of prochiral ketones has been already described.[10] In the reported catalytic applications, heteroatoms were present at the C-3 and C-4 carbons of the squaric acid skeleton, and both of them were presumably involved in the catalytic event.[11] The squaric acid system, however, allows an alternative mode of action: If a non basic substituent was introduced at either C-3 or C-4, participation of the carbonyl oxygen atoms in the molecular recognition concomitant to catalysis would be favoured and the squaryl group would act as a rigid, super-carbonyl group. In this way, new families of ligands with promising properties for asymmetric catalysis could be prepared.



Described action mode



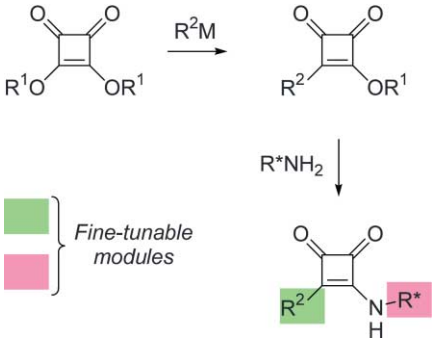
Alternative action mode

* Corresponding author. Tel.: +34-934037094; fax: +34-934037095; e-mail: mapericas@pcb.ub.es

0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00355-0

We wish to report here on the synthesis of highly modular catalytic ligands from a dialkyl squarate by a fully convergent, two stage procedure involving the initial monosubstitution of one alkoxy group by a C-sp^3 or a C-sp^2 nucleophile and the subsequent introduction of a chiral element by substitution of the remaining alkoxy group with an optically active diamine or with a (modular in itself) amino alcohol arising from Sharpless epoxidation.

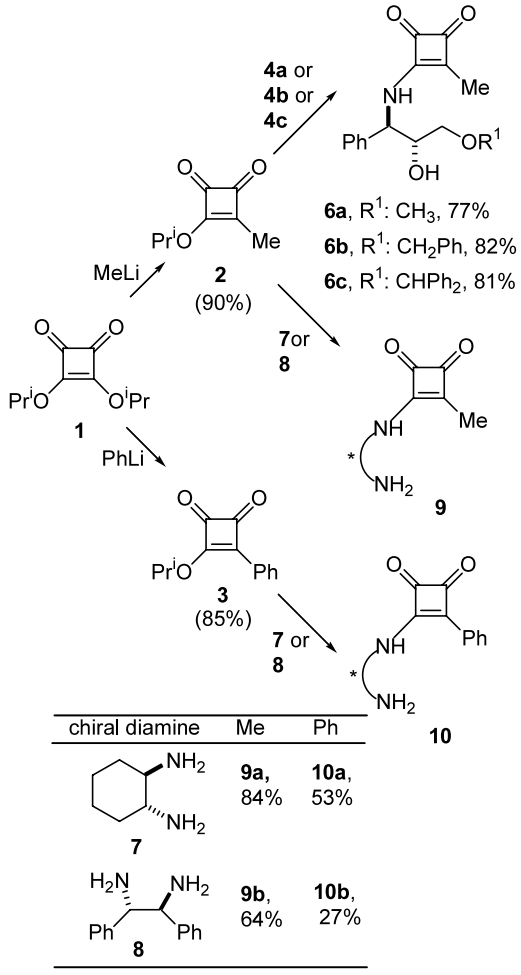
Preliminary results on the performance of these purely synthetic, enantiopure ligands in some catalytic processes such as transfer hydrogenation of ketones[12] and asymmetric carbonyl reduction using borane[13] are also reported.



2. Synthesis of the ligands

Diisopropyl squarate **1**, a readily available, stable, white solid was chosen as the scaffold for the construction of the target modular ligands for our studies. First, diester **1** was converted into a variety of alkyl- or aryl-cyclobutenediones as outlined in Scheme 1. This was accomplished by the initial treatment of **1** with 1 equiv. of an organolithium reagent (PhLi or MeLi) at low temperature to give, after acidic treament, the 3-isopropoxy-4-alkyl/aryl-3-cyclobutene-1,2-diones **2** and **3**[14] (Scheme 1). Interestingly, this broad-scope, well-documented procedure could allow the easy introduction of a great variety of C-substituents on the squarate skeleton if required. The intermediate monoesters **2** and **3** were converted into the target amide ligands by reaction with the appropriate enantiomerically pure amines. Two kinds of compounds were used for this purpose. On the one hand, β-amino alcohols **4a**–**c**, obtained by our previously described methodology,[2c] from enantiopure epoxycinnamyl alcohol **5** were selected as building blocks (Scheme 2). It is worth noting that these compounds contain two different sources of diversity: The primary alcohol protecting group R^1, able to accommodate a full range of steric and electronic characteristics, and the main chain substituent. While the last one has been specified as phenyl on this occasion, the variety of epoxy alcohols available in enantiomerically pure form through the Sharpless epoxidation is almost unlimited.

As shown in Scheme 1, reaction of monoester **2** with amino alcohols **4a**–**c** in ethanol smoothly led to monoamides **6a**–**c** in good yield (77–82%).



Scheme 1.

4

4a, R^1: CH_3
4b, R^1: CH_2Ph
4c, R^1: $CHPh_2$

5

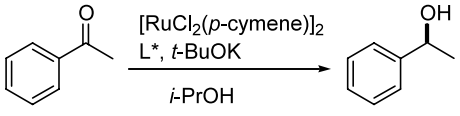
Scheme 2.

On the other hand, the commercialy available, enantiomerically pure diamines (1*R*,2*R*)-1,2-diaminocyclohexane **7** and (1*S*,2*S*)-1,2-diphenylethylenediamine **8** were also used as building blocks in front of cyclobutenediones **2** and **3** to afford, by reaction in EtOH at room temperature, the squaryl derivatives **9a**–**b** and **10a**–**b**, mostly in good yield. All new products were easily purified by either column chromatography or crystallization and were fully characterized. A characteristic feature in the NMR spectra of some derivatives is the splitting in some signals due to slowly interconverting rotamers, because of the amide character of the C–N bond, a fact that we had previously noted in similar situations.

3. Catalysis

As the starting point, to examine the efficiency of these new ligands in asymmetric catalysis we tested them in the transfer hydrogenation of acetophenone **11**. Asymmetric transfer hydrogenation of prochiral ketones is one of the most attractive methods for the synthesis of optically active secondary alcohols.[12] The most common catalysts for this reaction are ruthenium complexes, but derivatives of samarium,[15] rhodium[16] and iridium[17] have been also employed. In these processes, diamines,[18] amino alcohols[19] and other chiral compounds incorporating phosphorus and nitrogen[20] have been used as chiral ligands. Noyori has developed one of the most efficient versions of the reaction using Ru (II) complexes of chiral monoarylsulfonylated-1,2-diamines.[21] It is worth noting that the nature of the amine functionality largely controls the enantioselectivity of the process. This fact prompted us to examine, in this catalytic process, ligands **9a**, **9b**, **10a** and **10b** which have similar electronic characteristics with respect to Noyori's ligands (in both cases ligands contain a primary amine group and a secondary one substituted with an electron-withdrawing group). In this set of experiments, the chiral catalysts were prepared in situ by heating a mixture of [$RuCl_2$(*p*-cymene)] and the ligand in a 0.012 M solution of *t*-BuOK in 2-propanol for 1.5 h. After the catalyst solution had cooled to room temperature acetophenone was added (a ketone/Ru/ligand/*t*-BuOK molar ratio of 20:2:1:4 was used) and the transfer hydrogenations were performed at room temperature. Results are summarized in Table 1. Fast and essentially quantitative reductions to phenylethanol were achieved when using a 5% molar amount of catalyst, although the asymmetric induction was low. In any case, this set of experiments showed that both the steric bulk of the alkyl group on the squaroyl system and the steric bulk of the substituents on the amine skeleton affect the enantioselectivity of the process, bulkier substituents on either moiety leading to improved selectivities.

Table 1. Asymmetric transfer of acetophenone

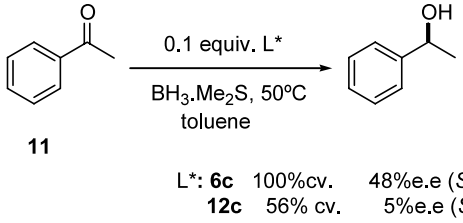


11

Ligand	Conversion (%)	E.e. (%)[a]	Configuration
9a	91	13	*S*
9b	96	21	*S*
10a	90	17	*S*
10b	94	29	*S*

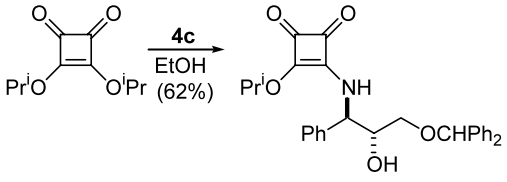
[a] Determined by chiral GC analysis.

The next catalytic process that was evaluated was asymmetric carbonyl reduction using borane.[13] The catalyst for this process was formed in situ by mixing the ligand (0.1 equiv.) and $BH_3{\cdot}Me_2S$ (1.2 equiv.) at 0°C, and the subsequent reduction of acetophenone was performed at 50°C in toluene. Ligand **6c** was initially used in these experiments. It behaved as a very active catalyst and led (*S*)-1-phenylethanol of 48% e.e., as shown in Scheme 3.



Scheme 3.

As we have already mentioned, *N*-squarylprolinols have shown good stereoinduction in the asymmetric reduction of prochiral ketones.[10] In order to test if the presence of an alkyl substituent at C-4 on the squaroyl skeleton (in **6c**) had provoked some change in the action mode of the derived ligands, we decided to prepare the amide/ester ligand **12c**, and to test its use in the reaction. This ligand was synthesized in a strightforward manner by selective reaction of squaric acid diisopropyl ester **1** with β-amino alcohol **4c**. Thus, treatment of **1** with 1 equiv. of **4c** in ethanol at room temperature gave the corresponding squaric acid amide/ester **12c** in good yield (Scheme 4). The reaction was remarkably clean: The secondary hydroxy group did not interfere in the process, and no diamide product could be detected under these reaction conditions.



1 **12c**

Scheme 4.

Very interestingly, when **12c** was used as catalyst in the oxazaborolidine-mediated reduction of acetophenone, it behaved as a much less active and a much less enantioselective catalyst than **6c** (Scheme 3). Thus, the apparently innocent alkyl substituent on the squaroyl nucleus seems to play a key role in the enantioface discrimination as well as in the catalytic efficiency on the hybrid ligands reported here. Although these results are only preliminary, they suggest that a change can be induced in the action mode of squaroyl amides by supressing the possibility of coordination by heteroatom substituents at C-4 while participating in catalytic cycles.

4. Conclusion

In summary, the synthesis of chiral derivatives of squaric acid incorporating either enantiomerically pure

amino alchols that arise from Sharpless epoxidation, or other optically active diamines, has led to the development of a new family of highly modular ligands for asymmetric catalysis. We have demostrated that our synthetic approach to this ligand system based on the cyclobutenedione scaffold is highly flexible and opens many possibilities for structural variation towards an efficient ligand design. From the catalysis point of view, initial results have already demostrated the interest of the design principle introduced here. Further work on the structural refining of ligands of the general types **6**, **9**–**10** now on course in our laboratories will be reported on due course.

5. Experimental

5.1. Instruments and materials

Optical rotations were measured at room temperature on a Perkin–Elmer 241MC automatic polarimeter (concentration in g/100 mL). Melting points were determined on a Gallenkamp apparatus and have not been corrected. Infrared spectra were recorded on a Nicolet 510FT-IR instrument using NaCl film or KBr pellet techniques. NMR spectra were acquired on a Varian XL-200 or Varian Unity-300 instruments. ^{1}H NMR were obtained at 200 or 300 MHz (s = singlet, d = doublet, t = triplet, dt = double triplet, m = multiplet and b = broad); ^{13}C NMR were obtained at 50.3 or 75.4 MHz. ^{1}H chemical shifts are quoted relative to TMS and ^{13}C shifts relative to solvent signals. Carbon multiplicities have been assigned by ditorsionless enhancement by polarization transfer (DEPT) experiments. High-resolution mass spectra (CI) were measured by the Servicio de Espectrometría de Masas de la Universidad de Santiago de Compostela. Chromatographic separations were carried out using NEt_3-pretreated (2.5% v/v) SiO_2 (70–230 mesh) and eluting with hexane/ethyl acetate mixtures of increasing polarity. *i*PrOH was distilled over magnesium under nitrogen prior to use. Catalytic reactions were performed under nitrogen using standard Schlenk techniques. (2*S*,3*S*)-2,3-Epoxy-3-phenylpropanol, **5**, was prepared according to the procedure described for Sharpless et al.,[3b] β-amino alcohols **4a**–**c** were prepared according to the procedure described by Puigjaner et al.[2c] and 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione **2** and 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione **3** were prepared according to the procedure described by Edwards et al.[14a]

5.2. Preparation of 3-hydroxyamino-4-methyl-3-cyclobutene-1,2-diones

A solution or suspension of the amino alcohol and the squaric acid derivative in EtOH was stirred at room temperature until the reaction was completed. The solvent was evaporated in vacuo and the crude product was purified by column chromatography.

5.2.1. 3-((1*R*,2*R*)-2-Hydroxy-3-methoxy-1-phenylpropylamino)-4-methylcyclobut-3-ene-1,2-dione, 6a. The general procedure was followed using 0.098 g (0.54 mmol) of (1*R*,2*R*)-1-amino-3-methoxy-1-phenylpropan-2-ol **4a** and 0.1 g (0.65 mmol) of 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione (**2**) in EtOH (4 mL). Reaction was completed after 22 h. The crude product was chromatographed through a SiO_2 column using hexane/EtOAc (40:60) yielding 0.115 g (77%) of **6a** as an oil that on standing becomes a solid.

Mp: 112–114°C; $[\alpha]_D = -45.1$ (*c* 1.99, $CHCl_3$); ^{1}H NMR δ 8.0–7.8 and 7.8–7.6 (br m, 1H, NH), 7.5–7.2 (m, 5H), 5.6–5.4 and 5.0 (m, 1H), 4.2 (m, 1H), 3.38 (s, 3H), 3.33 (s, 2H), 1.97 (s, 3H); ^{13}C NMR δ 193.2 and 193 (C), 184.6 and 183.8 (C), 168.6 and 168.5 (C), 137.6 and 137 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 127.3 (CH), 126.8 (CH), 73.6 and 72.6 (CH_2), 71.8 and 71.3 (CH), 62.1 and 60.7 (CH), 59.3 (CH_3), 10.6 and 9.7 (CH_3); IR (film) 3235, 1786, 1726, 1597, 1452, 1192, 1115, 953, 760, 704 cm^{-1}; MS (CI) *m*/*z*: 293 (M^++18, 100%), 276 (M^++1, 78%); HRMS (CI) calcd for $C_{15}H_{17}NO_4 \cdot H^+$ 276.1236, found 276.1246.

5.2.2. 3-((1*R*,2*R*)-3-Phenylmethoxy-2-hydroxy-1-phenylpropylamino)-4-methylcyclobut-3-ene-1,2-dione, 6b. The general procedure was followed using 0.144 g (0.56 mmol) of (1*R*,2*R*)-1-amino-1-phenyl-3-(phenylmethoxy)propan-2-ol **4b** and 0.114 g (0.74 mmol) of 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione (**2**) in EtOH (4.5 mL). Reaction was completed after 22 h. The crude product was chromatographed using hexane/EtOAc (70:30) yielding 0.16 g (82%) of **6b** as an oil.

$[\alpha]_D = -8.7$ (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 8.2–8.0 and 8.0–7.8 (br m, 1H, NH), 7.4–7.1 (m, 15H), 5.6–5.4 and 5.0–4.8 (m, 1H), 4.6–4.3 (m, 2H), 4.2 (m, 1H), 3.6–3.2 (m, 2H), 1.97 and 1.89 (s, 3H); ^{13}C NMR δ 192.9 and 192 (C), 184.6 and 183.7 (C), 169.0 and 168.2 (C), 137.7 and 137.2 (C), 136.9 (C), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.1 (CH), 126.8 (CH), 73.6 (CH_2), 71.7 and 71.2 (CH), 69.7 (CH_2), 61.9 and 61.0 (CH), 10.5 and 9.4 (CH_3); IR (film) 3316, 3033, 2921, 1786, 1732, 1597, 1497, 1454, 1097, 750, 700 cm^{-1}; MS (CI) *m*/*z*: 369 (M^++18, 25%), 368 (M^++17, 100%), 351 (M^+, 39%); HRMS (CI) calcd for $C_{21}H_{21}NO_4$ 351.1470, found 351.1473.

5.2.3. 3-((1*R*,2*R*)-3-Diphenylmethoxy-2-hydroxy-1-phenylpropylamino)-4-methylcyclobut-3-ene-1,2-dione, 6c. The general procedure was followed using 0.07 g (0.21 mmol) of (1*R*,2*R*)-1-amino-1-phenyl-3-(diphenylmethoxy)propan-2-ol **4c** and 0.042 g (0.27 mmol) of 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione **2** in EtOH (2 mL). Reaction was completed after 4.5 h. The crude product was chromatographed using hexane/EtOAc (60:40) yielding 0.072 g (81%) of **6c** as an oil that on standing becomes a solid.

Mp: 73–76°C; $[\alpha]_D = -21.8$ (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 8.0–7.8 (br m, 1H, NH), 7.6–7.0 (m, 10H). 5.29 (bs, 1H), 5.0 and 5.6 (m, 1H), 4.2 (m, 1H), 3.4 (m, 2H), 1.9 (bs, 3H); ^{13}C NMR δ 193 (C), 184 (C), 168 (C), 141 (C), 137 (C), 128.6 (CH); 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 126.9 (CH), 126.8 (CH), 126.6 (CH), 84.9 (CH), 72 and 71.8 (CH), 70 and 69.0 (CH_2), 62.2 and 62 (CH), 10.5 and 10.4 (CH_3); IR (KBr) 2925, 1786, 1734, 1597, 1495, 1452, 1094, 744, 702 cm^{-1}; MS

(CI) m/z: 445 (M^++18, 60%), 428 (M^++1, 100%); HRMS (CI) calcd for $C_{27}H_{25}NO_4 \cdot H^+$ 428.1862, found 428.1851.

5.3. Preparation of 3-diamino-4-alkyl/aryl-3-cyclobutene-1,2-diones

5.3.1. 3-((1*R*,2*R*)-2-Aminocyclohexylamino)-4-methylcyclobut-3-ene-1,2-dione, 9a. To a solution of (1*R*,2*R*)-1,2-diaminocyclohexane **7** (0.17 g, 1.45 mmol) in EtOH (5 mL) was added slowly a solution of 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione **2** (0.22 g, 1.45 mmol) in EtOH (5 mL). The mixture was stirred at room temperature for 12 h. The solvent was evaporated in vacuo and the crude purified by crystallization in Et_2O yielding 0.27 g (84%) of **9a**.

Mp: 60–62°C; $[\alpha]_D = +73.8$ (c 1.13, $CHCl_3$); ^{1}H NMR δ 4.1 (m, 1H), 3.5 (m, 1H), 2.3–0.8 (m, 11H); ^{13}C NMR δ 62.0 (CH), 56.0 (CH), 55.0 (CH_3), 25.0 (CH_2), 23.0 (CH_2), 24.6 (CH_2), 9.5 (CH_2); IR (KBr) 3234, 2935, 1785, 1735, 1654 cm^{-1}; MS (CI) m/z: 227 (M^++18, 50%), 115 (100%)

5.3.2. 3-((1*S*,2*S*)-2-Amino-1,2-diphenylamino)-4-methylcyclobut-3-ene-1,2-dione, 9b. To a solution of (1*S*,2*S*)-1,2-diphenylethylenediamine **8** (0.34 g, 1.6 mmol) in EtOH (5 mL) was added slowly a solution of 3-isopropoxy-4-methyl-3-cyclobutene-1,2-dione (**2**) (0.25 g, 1.6 mmol) in EtOH (5 mL). The mixture was stirred at room temperature for 24 h. The solvent was evaporated in vacuo and the crude crude product was chromatographed through a SiO_2 column using hexane/EtOAc (60/40) yielding 0.38 g (64%) of **9b**.

Mp: 75–79°C; $[\alpha]_D = +19.5$ (c 1.1, $CHCl_3$); ^{1}H NMR δ 7.6–7.0 (m, 10H), 4.7 (d, $J = 7$ Hz, 1H), 4.4 (d, $J = 7$ Hz, 1H), 2.0 (br m, NH), 1.7 (s, 3H); ^{13}C NMR δ 189.1 (C), 188.21 (C), 179.25 (C), 164.0 (C), 136.7 (C), 134.7 (C), 124.8–121.7 (CHs Ar), 59.8 (CH), 55.9 (CH), 5.8 (CH_3); IR (film) 3276, 1784, 1734, 1597 cm^{-1}; MS (CI) m/z: 324 (M^++18, 100%), 307 (M^++1, 60%).

5.3.3. 3-((1*R*,2*R*)-2-Aminocyclohexylamino)-4-phenylcyclobut-3-ene-1,2-dione, 10a. To a solution of (1*R*,2*R*)-1,2-diaminocyclohexane **7** (0.16 g, 1.4 mmol) in CH_2Cl_2 (5 mL) was added slowly a solution of 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione **3** (0.3 g, 1.4 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 12 h. The solvent was evaporated in vacuo and the crude crude product was chromatographed through a SiO_2 column using hexane/EtOAc (10/90) yielding 0.2 g (53%) of **10a**.

Mp: 65–67°C; $[\alpha]_D = -48.5$ (c 1.2, $CHCl_3$); ^{1}H NMR δ 7.7–7.1 (m, 5H), 4.7 (br m, 3H), 2.2–0.9 (m, 10H); ^{13}C NMR δ 187 (C), 172 (C), 168 (C), 143 (C), 128–125 (CHs Ar), 62 (CH), 57 (CH), 34 (CH_2), 32 (CH_2), 24 (CH_2), 23 (CH_2); IR (KBr) 3250, 3086, 2932, 1773, 1734, 1676, 1653 cm^{-1}; MS (CI) m/z: 253 (M^+−17, 100%).

5.3.4. 3-((1*S*,2*S*)-2-Amino-1,2-diphenylamino)-4-phenylcyclobut-3-ene-1,2-dione, 10b. To a solution of (1*S*,2*S*)-1,2-diphenylethylenediamine **8** (0.3 g, 1.4 mmol) in CH_2Cl_2 (5 mL) was added slowly a solution of 3-isopropoxy-4-phenyl-3-cyclobutene-1,2-dione (**3**) (0.3 g, 1.4 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 24 h. The solvent was evaporated in vacuo and the crude crude product was chromatographed through a SiO_2 column using hexane/EtOAc (85/15) yielding 0.14 g (27%) of **10b**.

Mp: 83–86°C; $[\alpha]_D = +45.5$ (c 1.32, $CHCl_3$); ^{1}H NMR δ 7.8.7–6.8 (m, 15H), 4.7 (d, 1H), 4.3 (d, 1H), 1.2 (br m, 3H); ^{13}C NMR δ 128.9 (CH), 128.7 (CH), 128.1 (CH), 127.9 (CH), 126.5 (CH), 70 (CH), 62 (CH); IR (KBr) 3855, 3021, 2925, 1767, 1734, 1609 cm^{-1}; MS (CI) m/z: 366 (M^+−2, 49%), 350 (M^+−18, 100%).

5.4. Preparation of squaric acid amide esters

5.4.1. 3-((1*R*,2*R*)-3-Diphenylmethoxy-2-hydroxy-1-phenylpropylamino) - 4 - isopropoxycyclobut - 3 - ene - 1,2-dione, 12c. To a suspension of (1*R*,2*R*)-1-amino-1-phenyl-3-(diphenylmethoxy)propan-2-ol **4c** (0.132 g, 0.39 mmol) in EtOH (2.5 mL) was added one solution of diisopropyl squarate **1** (0.079 g, 0.40 mmol) in EtOH (1.5 mL). The mixture was stirred at room temperature for 21 h. The solvent was evaporated in vacuo and the crude product was chromatographed through a SiO_2 column using hexane/EtOAc (70:30) yielding 0.115 g (62%) of **12c** as an oil that on standing becomes a solid.

Mp: 70–72°C; $[\alpha]_D = -15.2$ (c 5.2, $CHCl_3$); ^{1}H NMR δ 8.0 (br m, 1H, NH), 7.4–7.0 (m, 15H), 5.4–5.0 (m, 1H), 5.25 (s, 1H), 5.2–5.0 (m, 1H), 4.4–4.2 (m, 1H), 3.5–3.1 (m, 2H), 1.35 (d, 3H, $J = 6.2$ Hz), 1.14 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR δ 189.3 (C), 182.7 (C), 177.6 (C), 172.2 (C), 141.3 (C), 137.3 (C), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 126.6 (CH), 84.2 (CH), 77.6 (CH), 71.4 (CH), 69.3 (CH_2), 60.7 (CH), 22.8 and 22.5 (CH_3); IR (film) 3341, 1806, 1705, 1599, 1495, 1454, 1410, 1331, 1095, 1030, 758, 702 cm^{-1}; MS (CI) m/z: 488 (M^++17, 75%), 472 (M^++1, 44%); HRMS (CI) calcd for $C_{29}H_{29}NO_5$ 471.2046, found 471.2053.

5.5. Catalysis

5.5.1. Transfer hydrogenation of acetophenone. Typical procedure: The appropiate amount of ligand (0.025 mmol) was added to the catalyst precursor $[RuCl_2(p\text{-cymene})]_2$ (0.025 mmol) (Ru atom/ligand = 2/1) in 8.3 mL of a solution of potassium terbutoxyde in 2-propanol (0.012 mol/l) and stirred at 82°C for 1.5 h under an inert atmosphere. After the mixture had cooled to room temperature, ketone (0.5 mmol) was added and the resulting mixture stirred overnight at room temperature. The reaction was quenched by the addition of 3 drops of 1 M HCl solution. The enantiomeric excesses were determined from the crude mixture by GC analysis.

5.5.2. Catalytic reduction of acetophenone. Typical procedure: To a solution of the chiral ligand (0.05 mmol) in toluene (2.5 mL) under an argon atmosphere at 0°C was added $BH_3 \cdot Me_2S$ (0.055 mL). The reaction mixture

was stirred for 2 h at room temperature and for another 1 h at 55°C, to form an oxazaborolidine catalyst. A solution of the acetophenone (0.5 mmol) in toluene (1 mL) was added slowly over a period of 1 h and stirred for another 2 h. The reaction mixture was cooled to 0°C and quenched with 2.5 mL of 1N HCl solution. The organic layer was then extracted with ethyl acetate (3×5 mL) and subjected to GC analysis.

Conditions of the GC analyses: β-DEX 120, 30 m length, 0.25 mm internal diameter, isotherm temperature program, He as a carrier gas (2.4 mL/min). For 1-phenylethanol: β-DEX 120, 100°C, t_R(*R* isomer) = 52.1 min, t_R(*S* isomer) = 55.7 min.

Acknowledgements

Financial support from DGI-MCYT (BQU2002-02459) and DURSI (2001SGR50) is gratefully acknowledged. BR thanks University of Barcelona for a fellowship.

References

1. (a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; John Wiley & Sons: New York, 1994; (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.
2. (a) Pericas, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gomez, M.; Jimenez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164–4178; (b) Pasto, M.; Riera, A.; Pericas, M. A. *Eur. J. Org. Chem.* **2002**, 2337–2341; (c) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902–7911; (d) Sola, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078–7082; (e) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970–4982.
3. (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1–299; (b) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
4. Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp. 159–202.
5. (a) Sherertz, E. F.; Sloan, K. B. *Arch. Dermatolog. Res.* **1988**, *288*, 57–60; (b) Tietze, L. F.; Arlt, M.; Beller, M.; Gluesenkamp, K. H.; Jaehde, E.; Rajewsky, M. F. *Chem. Ber.* **1991**, *124*, 1215–1221; (c) Tietze, L. F.; Schroeter, C.; Gabius, S.; Brinck, U.; Goerlach-Graw, A.; Gabius, H. *J. Bioconjugate Chem.* **1991**, *2*, 148–153.
6. de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566.
7. (a) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2002**, *124*, 11616–11617; (b) Paquette, L. A.; Tae, J. *J. Org. Chem.* **1998**, *63*, 2022–2030.
8. Blixt, O.; Norberg, T. *Carbohydr. Res.* **1999**, *319*, 80–91.
9. (a) Quinonero, D.; Frontera, A.; Tomas, S.; Suner, G. A.; Morey, J.; Costa, A.; Ballester, P.; Deya, P. M. *Theor. Chem. Acc.* **2000**, *104*, 50–66; (b) Prohens, R.; Tomas, S.; Morey, J.; Deya, P. M.; Ballester, P.; Costa, A. *Tetrahedron Lett.* **1998**, *39*, 1063–1066; (c) Tomas, S.; Prohens, R.; Vega, M.; Rotger, M. C.; Deya, P. M.; Ballester, P.; Costa, A. *J. Org. Chem.* **1996**, *61*, 9394–9401; (d) Tomas, S.; Rotger, M. C.; Gonzalez, J. F.; Deya, P. M.; Ballester, P.; Costa, A. *Tetrahedron Lett.* **1995**, *36*, 2523–2526.
10. (a) Zhang, J.; Zhou, H. B.; Lu, S. M.; Luo, M. M.; Xie, R. G.; Choi, M. C. K.; Zhou, Z. Y.; Chan, A. S. C.; Yang, T. K. *Tetrahedron: Asymmetry* **2001**, *12*, 1907–1912; (b) Zhou, H.-B.; Zhang, J.; Lu, S.-M.; Xie, R.-G.; Zhou, Z.-Y.; Choi, M. C. K.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron* **2001**, *57*, 9325–9333; (c) Zhou, H.; Lu, S.; Xie, R.; Chan, A. S. C.; Yang, T. K. *Tetrahedron Lett.* **2001**, *42*, 1107–1110.
11. In Ref. 10 the proposed transition states for the asymmetric borane reduction involc heteroatoms at C-3 and C-4.
12. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; VCH: New York, 1994; (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045–2061; (c) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051–1069.
13. (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986–2012; (b) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784.
14. (a) Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Org. Chem.* **1993**, *58*, 3942–3952; (b) Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350–5358.
15. Evans, D. A.; Nelson, S. G.; Gagne, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800–9801.
16. (a) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186–2187; (b) Touchard, F.; Bernard, M.; Fache, F.; Delbecq, F.; Guiral, V.; Sautet, P.; Lemaire, M. *J. Organomet. Chem.* **1998**, *567*, 133–136.
17. Petra, D. G. I.; Kamer, P. C. J.; Spek, A. L.; Schoemaker, H. E.; Van Leeuwen, P. W. N. M. *J. Org. Chem.* **2000**, *65*, 3010–3017.
18. (a) Touchard, F.; Fache, F.; Lemaire, M. *Eur. J. Org. Chem.* **2000**, 3787–3792; (b) Schwink, L.; Ireland, T.; Puntener, K.; Knochel, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1143–1163.
19. (a) Palmer, M. J.; Kenny, J. A.; Walsgrove, T.; Kawamoto, A. M.; Wills, M. *J. Chem. Soc., Perkin Trans.* **2002**, 416–427; (b) Everaere, K.; Mortreux, A.; Bulliard, M.; Brussee, J.; Van der Gen, A.; Nowogrocki, G.; Carpentier, J.-F. *Eur. J. Org. Chem.* **2001**, 275–291; (c) Nordin, S. J. M.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem. Eur. J.* **2001**, *7*, 1431–1436; (d) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J.-W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. E.; Van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2000**, *6*, 2818–2829.
20. (a) Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Organomet. Chem* **1999**, *572*, 163–168; (b) Gao, J. x.; Xu, P. p.; Yi, X. d.; Yang, C. b.; Zhang, H.; Cheng, S. h.; Wan, H. l.; Tsai, K. r.; Ikariya, T. *J. Mol. Cat. A* **1999**, *147*, 105–111; (c) Braunstein, P.; Fryzuk, M. D.; Naud, F.; Rettig, S. J. *J. Chem. Soc., Dalton Trans.* **1999**, 589–594; (d) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817–3818.
21. (a) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931–7944; (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102; (c) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563.