[18] D. J. Sexton, A. Muruganandam, D. J. McKenney, B. Mutus, *Photochem. Photobiol.* **1994**, *59*, 463.
[19] J. Aizenberg, A. J. Black, G. M. Whitesides, *Nature* **1998**, *394*, 868.
[20] C. M. Ruan, F. Yang, C. H. Lei, J. Q. Deng, *Anal. Chem.* **1998**, *70*, 1721.
[21] G. E. Poirier, *Chem. Rev.* **1997**, *97*, 1117.
[22] L. Jian, A. Glidle, A. Griffith, C. J. McNeil, J. M. Cooper, *Bioelectrochem. Bioenerg.* **1997**, *42*, 15.
[23] A. J. Guiomar, S. D. Evans, J. T. Guthrie, *Supramol. Sci.* **1997**, *4*, 279.
[24] Y. Hou, Y. Chen, N. A. Amro, K. Wadu-Mesthrige, P. R. Andreana, G. Liu, P. G. Wang, *Chem. Commun.* **2000**, 1831.
[25] S. Sortino, S. Giuffrida, G. De Guidi, R. Chillemi, S. Petralia, G. Marconi, G. Condorelli, S. Sciuto, *Photochem. Photobiol.* **2001**, *73*, 6.
[26] S. Sortino, G. Marconi, G. Condorelli, *Chem. Commun.* **2001**, 1226.
[27] D. W. Godwin, D. Che, D. M. O'Malley, Q. Zhou, *J. Neurosci. Methods* **1997**, *73*, 91.

Complete Stereospecific Cyclopropanation of α,β-Unsaturated Amides Promoted by Sm/CH_2I_2**

José M. Concellón,* Humberto Rodríguez-Solla, and Cecilia Gómez

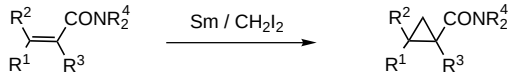
The cyclopropane ring is present in a great number of natural products.[1] In addition, the use of cyclopropanes in mechanistic studies[2] and their utility as synthetic intermediates[3] warrants the interest in these carbocycles from various fields in organic chemistry. The majority of the methodologies developed for the synthesis of cyclopropanes[4] rely on variants of the following reactions: Simmons–Smith cyclopropanation,[5] transition-metal catalyzed cyclopropanation of alkenes with diazomethane[6] or diazoesters,[7] and cyclopropanation of Michael acceptors.[8] However, these methods leave much to be desired: total control of diastereoselectivity in the synthesis of polysubstituted cyclopropanes is beyond reach, some methodologies call for toxic reagents, and in other cases, synthesis of cyclopropanes from unsaturated compounds in which the C=C bond is tri- or tetrasubstituted cannot be carried out.[9]

In particular, and to the best of our knowledge, the cyclopropanation of α,β-unsaturated amides in which the C–C double bond is tri- or tetrasubstituted has not been published. Only the transformation of mono- or disubstituted α,β-unsaturated amides into the corresponding cyclopropanecarboxamides has been described.[10] Consequently new methods for the diastereoselective construction of cyclopropylamides, in which the cyclopropane ring is polysubstituted, are of significant interest.

In their work on the synthetic applications of samarium(II) compounds Molander et al. reported the use of samarium amalgam/diiodomethane to cyclopropanate allylic alcohols with complete stereospecificity with respect to the olefin geometry.[11] Imamoto et al. described the cyclopropanation of lithium enolates derived from ketones by using SmI_2/CH_2I_2.[12] However, to the best of our knowledge, no cyclopropanation of α,β-unsaturated acid derivatives by using Sm/CH_2I_2 has been published.[13]

Recently, we described the SmI_2-promoted highly diastereoselective synthesis of vinyl halides,[14] α,β-unsaturated esters[15] and amides,[16] deuterated β,γ-unsaturated esters,[17] and vinylsilanes.[18] Here we report a new methodology for complete stereospecific cyclopropanation of α,β-unsaturated amides by using samarium and diiodomethane. The stereospecific synthesis of cyclopropylcarboxamides, in which the cyclopropane ring is di-, tri-, or tetrasubstituted, is achieved in high yield.

Treatment of several α,β-unsaturated amides **1** with samarium metal and diiodomethane at room temperature gave, after hydrolysis, the corresponding cyclopropylamides **2**, with complete stereospecificity and in high yield (Eq. (1), Table 1).



1 **2** (1)

These results show that this cyclopropanation reaction: a) takes place in high yield; b) is general and can be carried out starting from aliphatic (linear, branched, or cyclic) or aromatic α,β-unsaturated amides; c) is unaffected by the presence of bulky groups R^3 on the carbonyl amide (entries 3, 10, and 11); d) can be carried out starting from α,β-unsaturated amides **1**, in which the C=C bond is di-, tri-, or tetrasubstituted; e) takes place with complete stereospecificity—*trans*- and *cis*-cyclopropanamides are obtained from (*E*)- and (*Z*)-α,β-unsaturated amides, respectively (entries 1, 2 and 10, 11); f) takes place with very high chemoselectivity—selective cyclopropanation of the C=C bond conjugated with the carbonyl group is achieved in polyunsaturated amides (entry 5).[19]

The diastereoisomeric purity of compounds **2** was determined on the crude reaction products by ^1H NMR spectroscopy (300 MHz) and GC-MS, which showed the presence of a

[*] Dr. J. M. Concellón, H. Rodríguez-Solla
Departamento de Química Orgánica e Inorgánica
Facultad de Química, Universidad de Oviedo
33071 Oviedo (Spain)
Fax: (+34) 98-510-3446
E-mail: jmcg@sauron.quimica.uniovi.es
Dr. C. Gómez
Departamento de Química Orgánica
Facultad de Ciencias, Universidad de Alicante
Apartado 99, 03080 Alicante (Spain)

[**] We acknowledge financial support from II Plan Regional de Investigación del Principado de Asturias (PB-EXP01-11) and Ministerio de Ciencia y Tecnología (BQU2001-3807). We thank Dr. Francisco J. González for valuable discussions and Robin Walker for revising the English manuscript. J.M.C. thanks Carmen Fernández-Flórez for her time. H.R.S. thanks Principado de Asturias for a predoctoral fellowship.

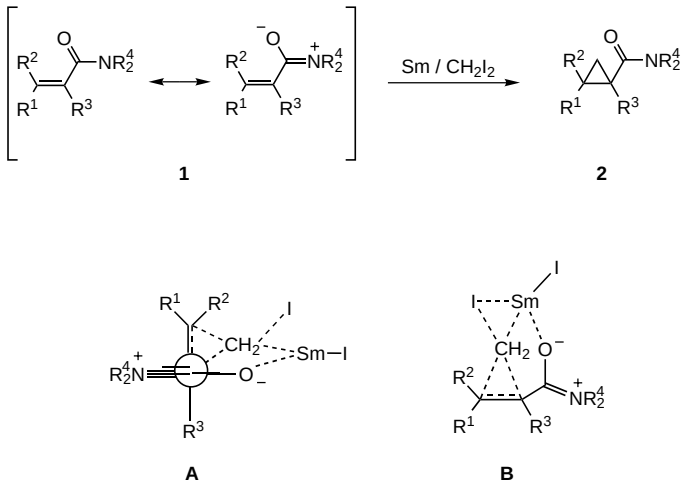
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/02/4111-1917 $ 20.00+.50/0

Table 1. Synthesis of cyclopropanecarboxamides by using Sm/CH_2I_2.

Entry	2[a]	R^1	R^2	R^3	R^4	Yield [%][b]
1	**2a**	Ph	H	H	Et	79
2	**2b**	H	Ph	H	Et	71
3	**2c**	Ph	H	H	*i*Pr	72
4	**2d**	Me(CH)Ph	H	H	Et	75
5	**2e**	(*E*)-MeCH=CH	H	H	Et	73
6	**2f**	Ph	H	Me	Et	73
7	**2g**	C_7H_{15}	H	Me	Et	69
8	**2h**	Bu	H	Et	Et	66
9	**2i**	cyclohexyl	H	Me	Et	72
10	**2j**	*p*-$MeOC_6H_4$	H	Me	*i*Pr	83
11	**2k**	H	*p*-$MeOC_6H_4$	Me	*i*Pr	85
12	**2l**	Ph	Et	Me	Et	70
13	**2m**	$PhCH_2$	Me	Me	Et	69
14	**2n**	-$(CH_2)_5$-		Me	Et	74

[a] All products were obtained with complete stereospecificity. Diastereoisomeric purity was determined by GC-MS, and ^1H and ^{13}C NMR (300 MHz) analysis of the crude products **2**. [b] Yield after column chromatography based on compound **1**.



Scheme 1. Mechanistic proposal for the conversion of **1** into **2**. **A** and **B** depict the proposed transition state.

single diastereoisomer. The relative *trans* or *cis* configuration of substituents on the cyclopropane ring was established by analysis of ^1H NMR coupling constants between the cyclopropane protons of compounds **2a**–**e**,[20] or by NOE experiments in the case of tri- and tetrasubstituted cyclopropanes (**2j**, **k** and **2l**).

Exposure of the substrate to Sm/CH_2I_2 for extended periods of time appears to have no detrimental effect on either the yield or the diastereoselectivity of the isolated products.[21] When the same reaction conditions were used to obtain cyclopropylesters from α,β-unsaturated esters, no cyclopropanation was observed at room temperature or at reflux.

The formation of products **2** may be explained by assuming the formation of Sm^{II} carbenoids (e.g. $ISmCH_2I$). Such species have been proposed as intermediates in the cyclopropanation of allylic alcohols[11] and in the generation of the SmI_2 from samarium metal and diiodomethane.[22] Our experimental results can be explained using a model similar to the staggered model previously proposed by Houk and co-workers for the addition of carbenoids to olefins,[23] and which was also utilized to explain the cyclopropanation of allylic alcohols (Scheme 1).[11] Tentatively, we propose a transition-state model **A** (similar to the Houk model), in which the coordination of the divalent samarium atom with the oxygen atom of the amide group provides the obtained cyclopropylamide **2**, whilst maintaining the geometry about the C=C bond. Another view of the same transition state is shown in **B**. Indirect support for this mechanism is the non-cyclopropanation of α,β-unsaturated esters, because of the decreased ability of the oxygen atom of the carbonyl group in esters relative to that in amides to coordinate with the Sm^{II} center.

In conclusion, an easy, rapid, and general cyclopropanation of α,β-unsaturated amides with complete stereospecificity by using samarium/diiodomethane has been developed. This cyclopropanation reaction is achieved from α,β-unsaturated amides in which the C=C bond is di-, tri-, or tetrasubstituted. Studies designed to prepare enantiopure cyclopropylcarboxamides are currently in progress.

Experimental Section

To a suspension of Sm (1.4 mmol) in THF (15 mL) was added the α,β-unsaturated amide **1** (0.4 mmol) in THF (2 mL) and diiodomethane (1.4 mmol) at 0 °C. After stirring at room temperature for 2 h the reaction mixture was quenched by the addition of 0.1 M aqueous HCl (5 mL). Standard workup afforded the crude cyclopropanecarboxamides **2**, which were purified by flash column chromatography on silica gel (hexane/EtOAc 5:1).

Received: January 21, 2002 [Z 18547]

[1] a) "Biochemistry of the Cyclopropyl Group": H. W. Liu, C. T. Walsh in *The Chemistry of the Cyclopropyl Group* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1987**, chap. 16, pp. 959–1025; b) R. Faust, *Angew. Chem.* **2001**, *113*, 2312–2314; *Angew. Chem. Int. Ed.* **2001**, *40*, 2251–2253; c) W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589–8627; d) J. Salaün, *Top. Curr. Chem.* **2000**, *207*, 1–67.

[2] a) G. Maier, S. Senger, *Angew. Chem.* **1994**, *106*, 605–606; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 558–559; b) L. Dechoux, E. Doris, *Tetrahedron Lett.* **1994**, *35*, 2017–2020; c) R. B. Silverman, Y. Zelechonok, *J. Org. Chem.* **1992**, *57*, 6373–6374.

[3] "Carbocyclic Three- and Four-Membered Ring Systems": *Methods of Organic Chemistry (Houben-Weyl) 4th ed. 1952–, Vol. E* **1997**, p. 17a–f.

[4] For some reviews, see: a) "Preparation of Cyclopropyl Derivatives": T. Tsuji, S. Nishida in *The Chemistry of the Cyclopropyl Group* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1987**, pp. 308–373; b) J. Salaün, *Chem. Rev.* **1989**, *89*, 1247–1270.

[5] a) T. Morikawa, H. Sasaki, R. Hanai, A. Shibuya, T. Taguchi, *J. Org. Chem.* **1994**, *59*, 97–103; b) A. B. Charette, J. F. Marcoux, *Synlett* **1995**, 1197–1207; c) A. B. Charette, J. F. Marcoux, *J. Am. Chem. Soc.* **1996**, *118*, 4539–4549.

[6] a) R. Paulissen, A. J. Hubert, P. Teyssie, *Tetrahedron Lett.* **1972**, *13*, 1465–1468; b) M. Suda, *Synthesis* **1981**, 714–714; c) J. E. A. Luithle, J. Pietruszka, *J. Org. Chem.* **1999**, *64*, 8287–8297.

[7] M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**, pp. 163–288.

[8] A. H. Li, L. X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341–2372.

[9] E. V. Dehmlow, K. Eulenberg, *Liebigs Ann. Chem.* **1978**, 1112–1115.

[10] For recent reports on the cyclopropanation of α,β-unsaturated amides see: a) S. Goumri-Magnet, T. Kato, H. Gornitzka, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **2000**, *122*, 4464–4470; b) S. Ye, L. Yuan, Z. Z. Huang, Y. Tang, L. X. Dai, *J. Org. Chem.* **2000**, *65*, 6257–6260; c) A. Mamai, J. S. Madalengoitia, *Tetrahedron Lett.* **2000**, *41*, 9009–9014.

  1433-7851/02/4111-1918 $ 20.00+.50/0

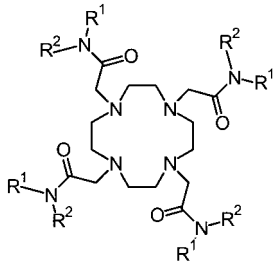
[11] a) G. A. Molander, J. B. Etter, *J. Org. Chem.* **1987**, *52*, 3942 – 3944; b) G. A. Molander, L. S. Harring, *J. Org. Chem.* **1989**, *54*, 3525 – 3532.
[12] T. Imamoto, N. Takiyama, *Tetrahedron Lett.* **1987**, *28*, 1307 – 1308.
[13] Previously, it was indicated that the cyclopropanation promoted by samarium carbenoids takes place exclusively with allylic alcohols, and other functionalized olefinic substrates are inert (see ref. [11b]).
[14] J. M. Concellón, P. L. Bernad, J. A. Pérez-Andrés, *Angew. Chem.* **1999**, *111*, 2528 – 2530; *Angew. Chem. Int. Ed.* **1999**, *38*, 2384 – 2386.
[15] J. M. Concellón, J. A. Pérez-Andrés, H. Rodríguez-Solla, *Angew. Chem.* **2000**, *112*, 2866 – 2868; *Angew. Chem. Int. Ed.* **2000**, *39*, 2773 – 2775.
[16] J. M. Concellón, J. A. Pérez-Andrés, H. Rodríguez-Solla, *Chem. Eur. J.* **2001**, *7*, 3062 – 3068.
[17] J. M. Concellón, P. L. Bernad, H. Rodríguez-Solla, *Angew. Chem.* **2001**, *113*, 4015 – 4017; *Angew. Chem. Int. Ed.* **2001**, *40*, 3897 – 3899.
[18] J. M. Concellón, P. L. Bernad, E. Bardales, *Org. Lett.* **2001**, *3*, 937 – 939.
[19] The product of double cyclopropanation was obtained in 2% yield (GC-MS).
[20] "Nuclear Magnetic Resonance and Infrared Spectra of Cyclopropanes and Cyclopropenes": D. G. Morris in *The Chemistry of the Cyclopropyl Group* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1987**, chap. 3, pp. 101 – 172.
[21] When the reaction time is increased, the yield of some Simmon – Smith cyclopropanations decrease: C. D. Poulter, E. C. Fiedrich, S. Winstein, *J. Am. Chem. Soc.* **1969**, *91*, 6892 – 6894.
[22] a) J. L. Namy, P. E. Caro, P. Girard, H. B. Kagan, *Nouv. J. Chim.* **1981**, *5*, 479 – 484; b) T. Imamoto, H. Koto, T. Takeyama, *Tetrahedron Lett.* **1986**, *27*, 3243 – 3246; c) T. Tabuchi, J. Inanaga, M. Yamaguchi, *Tetrahedron Lett.* **1986**, *27*, 3891 – 3894.
[23] a) M. N. Paddon-Row, N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1982**, *104*, 7162 – 7166; b) J. Mareda, N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1983**, *105*, 6997 – 6999.

The Amide Protons of an Ytterbium(III) dota Tetraamide Complex Act as Efficient Antennae for Transfer of Magnetization to Bulk Water**

Shanrong Zhang, Lydie Michaudet, Shawn Burgess, and A. Dean Sherry*

Current diagnostic contrast agents (CAs) for magnetic resonance imaging (MRI) are largely based on paramagnetic gadolinium complexes that shorten the relaxation time of bulk-water protons in tissue by rapid exchange of at least one gadolinium-bound inner sphere water molecule with bulk solvent.[1] Recently, Balaban et al.[2] demonstrated that image contrast can be altered by applying a frequency-selective RF pulse at the resonance frequency of an NH or OH group of an intrinsic amino acid, sugar, nucleotide, or other metabolite prior to collection of the imaging data. An advantage of a chemical exchange saturation transfer (CEST) agent over a paramagnetic relaxation agent is that image contrast can be switched on and off at will. A disadvantage is that the amount of CEST agent required to produce significant water contrast is unrealistically high,[3] although a later report demonstrated that the CEST effect can be amplified considerably by using polymers that contain a large number of amide NH groups.[4] As the chemical shifts of diamagnetic NH or OH protons are typically within 5 ppm of that of bulk water, it may ultimately prove difficult to avoid off-resonance direct saturation of the bulk-water signal or indirect saturation via water tightly bound to tissue macromolecules. The latter effect provides the basis of magnetization-transfer (MT) imaging.[5]

We recently reported that the weakly paramagnetic complex $[Eu(\mathbf{2})]^{3+}$, which has a bound-water signal near $\delta =$ 50 ppm with an exchange lifetime of $\tau_M^{298} \approx 350$ μs, acts as an MT contrast agent.[6] Aime et al.[7] also demonstrated that the MT effect can be used to measure pH by using two different exchange sites (OH in $[Eu(\mathbf{3})]^-$ and NH in $[Yb(\mathbf{3})]^-$) to eliminate the concentration dependence. Although paramagnetic systems offer the advantage over diamagnetic systems of having exchangeable protons that are shifted well away from the bulk-water signal,[2, 3] they suffer from a similar lack of sensitivity. One way to increase the sensitivity of a paramagnetic MT agent and thereby make it more practical would be to increase the number of exchangeable protons[4] at a hyperfine-shifted site. Here the Yb^{3+} complex of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide (**1**), which has eight exchangeable, hyperfine-shifted amide protons, is reported as a prototype high-sensitivity MT agent. The eight amide protons of this complex should in principle allow a fourfold reduction in concentration compared to an agent with a single exchangeable bound water molecule.[8]



$R^1 = H_a$, $R^2 = H_b$ **1**
$R^1 = H$, $R^2 = CH_2COOEt$ **2**
$R^1 = H$, $R^2 = CH_2COO^-$ **3**

A crystal of $[Yb(\mathbf{1})(H_2O)](CF_3SO_3^-)_3 \cdot 4H_2O$ was grown from water at room temperature and studied by X-ray diffraction at 153 K (Figure 1).[9] The geometry around the Yb^{3+} ion is a typical square antiprism with average N-C-C-N and N-C-C-O torsion angles of 58.3 and $-22.5°$, respectively. The Yb^{3+} ion is nine-coordinate with average macrocyclic Yb–N and Yb–O bond lengths of 2.608 and 2.301 Å, respectively, and a Yb^{3+}–O_{water} distance of 2.335 Å. The Yb^{3+} – macrocyclic ligand distances are similar to those

[*] Prof. A. D. Sherry, Dr. S. Zhang, Dr. L. Michaudet
Department of Chemistry, University of Texas at Dallas
PO Box 830688, Richardson, TX 75083 (USA)
Fax: (+1) 972-883-2925
E-mail: sherry@utdallas.edu
Prof. A. D. Sherry, Dr. S. Burgess
Department of Radiology, Rogers Magnetic Resonance Center
5801 Forest Park Road, Dallas, TX 75235 (USA)

[**] This work was supported in part by grants from the Robert A. Welch Foundation (AT-584), the National Institutes of Health (CA-84697), and the Division of Research Resources, National Institutes of Health (RR-02584). We thank Professor Silvio Aime for providing a copy of his manuscript prior to publication.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.