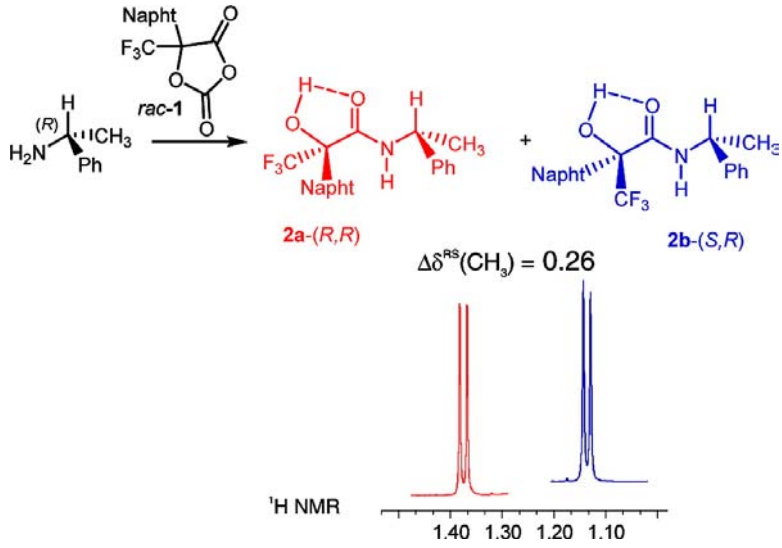
Letter

(1-Naphthyl)(trifluoromethyl) *O*-Carboxy Anhydride as a Chiral Derivatizing Agent: Eclipsed Conformation Enforced by Hydrogen Bonding

Olivier Thillaye du Boullay, Aure#lie Alba, Fatima Oukhatar, Blanca Martin-Vaca, and Didier Bourissou

Org. Lett., **2008**, 10 (20), 4669-4672• DOI: 10.1021/ol801930m • Publication Date (Web): 25 September 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ORGANIC LETTERS

2008
Vol. 10, No. 20
4669−4672

(1-Naphthyl)(trifluoromethyl) *O*-Carboxy Anhydride as a Chiral Derivatizing Agent: Eclipsed Conformation Enforced by Hydrogen Bonding

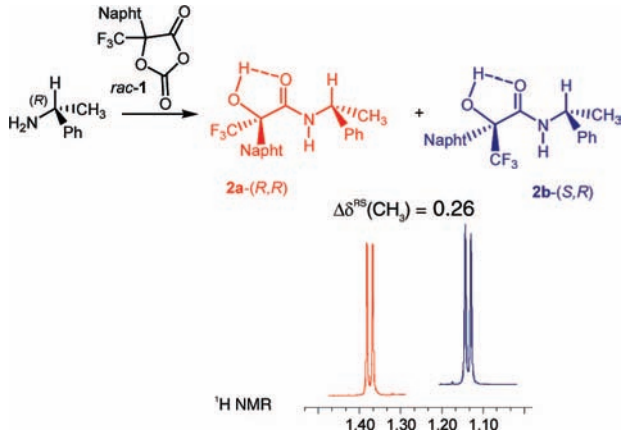
Olivier Thillaye du Boullay, Aurélie Alba, Fatima Oukhatar, Blanca Martin-Vaca,* and Didier Bourissou*

Laboratoire Hétérochimie Fondamentale et Appliquée du CNRS (UMR 5069)
Université Paul Sabatier, 118, route de Narbonne, 31062 Toulouse Cedex 09, France

dbouriss@chimie.ups-tlse.fr

Received August 19, 2008

ABSTRACT



The preparation of the (1-naphthyl)(trifluoromethyl) *O*-carboxy-anhydride 1 and its use as a chiral derivatizing agent with several α-chiral primary amines are reported. The very large $\Delta\delta^{RS}$ values observed in ^{1}H NMR have been correlated with a marked preference of the corresponding α-hydroxy-amides for the *eclipsed conformation*. In comparison, the related *O*-methylated amides are shown to adopt staggered conformations, which substantiates the critical role of intramolecular hydrogen bonding in maximizing the anisotropic effect.

The growing interest for enantioselective synthesis in chemical and pharmaceutical fields has stimulated the development of simple and inexpensive methods for the determination of the enantiomeric excess of chiral compounds and the assignment of the absolute configuration of stereogenic centers. In this context, the use of chiral derivatizing agents (CDA) combined with multinuclear NMR analyses is one of the most efficient methods.[1] The MTPA and MPA derivatives introduced by Mosher[2] and Trost,[3] respectively, (Figure 1) have led to spectacular results especially with α-chiral primary amines and secondary alcohols. Further improvements have been possible exploiting the structural versatility of α-arylcarboxylic acids, as is nicely illustrated by the BPG[4] and CFTA[5] compounds.[6]

Current efforts focused on new CDA aim at increasing both their reactivity and resolution efficiency.[7] In this regard,

(1) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.

(2) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(3) (a) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.

(4) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669.

10.1021/ol801930m CCC: $40.75
Published on Web 09/25/2008

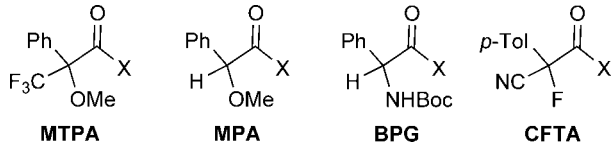


Figure 1. Structure of representative α-arylcarboxylic acid derivatives used as CDA (X = OH or Cl).

it is well-established that the eclipsed vs staggered conformations of the corresponding adducts have a major influence on the anisotropic effect induced by the aryl moiety.[4,5,8,9] Riguera et al. reported an elegant illustration of this phenomenon in the derivatization of α-chiral primary amines with MPA. The addition of barium(II) salts was demonstrated to shift the conformation of the ensuing amides from staggered to eclipsed, resulting in a significant increase of the anisotropic effect (Figure 2, compounds **A** and **B**).[8a] In

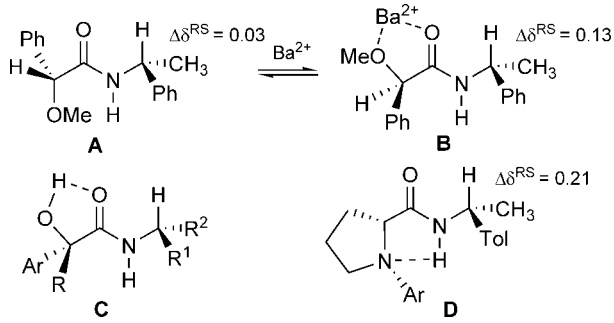


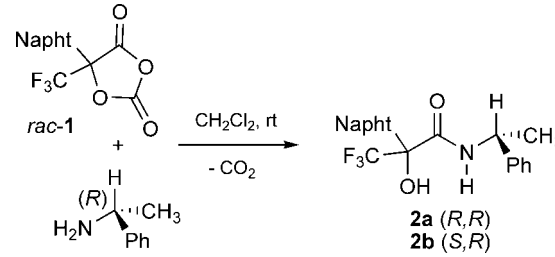
Figure 2. Control of the amide conformation by complexation to Ba^{2+} (**A**/**B**) or by intramolecular hydrogen bonding (**C** and **D**).

principle, the conformational equilibrium may also be controlled by replacing the methoxy group of the MTPA/MPA models by a hydroxyl group, thanks to the formation of a hydrogen bond between the proximal OH and C═O moieties (Figure 2, compound **C**). Note that a somewhat related approach has been recently studied by Choi et al. using *N*-(nitroaryl)prolines (NPP) as CDA.[10] As the result of intramolecular hydrogen bonding between the amide hydrogen and proline nitrogen atoms (Figure 2, adduct **D**), significantly larger chemical shift differences ($\Delta\delta^{RS}$) values were obtained than with MPA and MTPA derivatives.

From a synthetic viewpoint, α-hydroxy-amides **C** can be readily accessed by reacting α-chiral primary amines with *O*-carboxy anhydrides (OCA).[11−13] The (1-naphthyl)(trifluoromethyl) OCA **1** was thus considered a promising CDA. Here we report its synthesis (in both racemic and enantiomerically pure forms) and its derivatization with several α-chiral primary amines. The very large $\Delta\delta^{RS}$ values observed in ^{1}H NMR have been correlated with a marked preference of the α-hydroxy-amides for the *eclipsed conformation*, as deduced from detailed spectroscopic analyses performed on the α-methylbenzylamine adducts **2a**/**2b**. In comparison, the related *O*-methylated adducts **4a**/**4b** (obtained from the MTPA analog **3**) are shown to adopt a staggered conformation, which substantiates the critical role of *intramolecular hydrogen bonding* in enforcing the eclipsed conformation.

The OCA **1** was readily prepared in racemic form from the corresponding α-hydroxy-acid and isolated in 68% yield after recrystallization.[14] Reaction of **1** with (*R*)-α-methylbenzylamine[15] afforded an equimolar mixture of α-hydroxy-amides **2a** and **2b** that were separated by silica-gel chromatography and fully characterized (Scheme 1). Notably, the

Scheme 1. Reaction of *rac*-**1** with (*R*)-α-Methylbenzylamine



two diastereomers are readily distinguishable in the ^{1}H NMR spectrum, with differences in chemical shifts up to 0.26 ppm

(5) (a) Takeuchi, Y.; Segawa, M.; Fujisawa, H.; Omata, K.; Lodwig, S. N.; Unkefer, C. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4617. (b) Takahashi, T.; Fukushima, A.; Tanaka, Y.; Takeuchi, Y.; Kabuto, K.; Kabuto, C. *Chem. Comm.* **2000**, 787.

(6) For recent examples of CDA different from α-arylcarboxylic acids, see: (a) Pérez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett.* **2006**, *8*, 609. (b) Rodríguez-Escrich, S.; Popa, D.; Jimeno, C.; Vidal-Ferran, A.; Pericás, M. A. *Org. Lett.* **2005**, *7*, 3829.

(7) For recent examples reporting alternative coupling methodologies see: (a) Porto, S.; Seco, J. M.; Espinosa, J. F.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2008**, *73*, 5714. (b) Katritzky, A. R.; Mohapatra, P. P.; Fedoseyenko, D.; Duncton, M.; Steel, P. J. *J. Org. Chem.* **2007**, *72*, 4268.

(8) (a) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2006**, *71*, 1119. (b) Latypov Sh., K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 877. (c) Seco, J. M.; Latypov Sh., K.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1997**, *62*, 7569. (d) Latypov Sh., K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569. (e) Latypov Sh., K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 1538.

(9) The situation may be further complicated if different rotamers with opposite anisotropic effects coexist in solution.

(10) Ahn, H. C.; Choi, K. *Org. Lett.* **2007**, *9*, 3853.

(11) Reaction of OCA with primary or secondary amines has been demonstrated to yield α-hydroxy-amides. (a) Toyoka, K.; Takeuchi, Y.; Kubota, S. *Heterocycles* **1989**, *29*, 5. (b) Branch, C. L.; Finch, S. C.; Pearson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1491. (c) Sinay, P. *Carbohydr. Res.* **1971**, *16*, 113.

(12) *O*-carboxy-anhydrides have also been involved recently for the dynamic kinetic resolution of monosubstituted α-hydroxy carboxylic acids: Tang, T.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870.

(13) As part of a research program on biodegradable polymers, we have recently reported the remarkable reactivity of the OCAs derived from lactic and glutamic acids towards Ring-Opening Polymerization, giving access to poly(α-hydroxy-acids) in very mild conditions: (a) Bonduelle, C.; Martin-Vaca, B.; Cossío, F. P.; Bourissou, D. *Chem.−Eur. J.* **2008**, *14*, 5304. (b) Thillaye du Boullay, O.; Bonduelle, C.; Martin-Vaca, B.; Bourissou, D. *Chem. Commun.* **2008**, 1786. (c) Thillaye du Boullay, O.; Marchal, E.; Martin-Vaca, B.; Cossío, F. P.; Bourissou, D. *J. Am. Chem. Soc.* **2006**, *128*, 16442.

(14) See Supporting Information.

for the methyl group and 0.58 ppm for the H_{ortho} of the phenyl ring. These values are markedly larger than those usually observed, with previous CDA typically leading to $\Delta\delta^{RS}$ < 0.21 ppm for the methyl group of $ArCH(Me)NH_2$ (Ar = phenyl, para-tolyl, 1-naphthyl).[2−5,8d,16] To rationalize the large $\Delta\delta^{RS}$ values obtained with **1**, we sought to determine the conformations of **2a** and **2b**.

The absolute configuration (*S*,*R*) of **2b** was first deduced from an X-ray diffraction analysis (Figure 3), suitable crystals

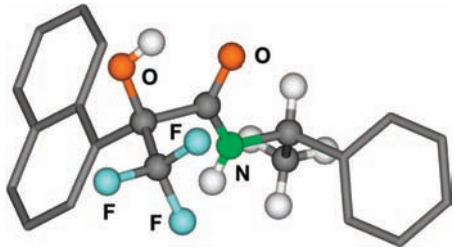


Figure 3. Molecular structure of **2b**.

being obtained from pentane solution at 0 °C. This study also provided the first indication of the conformation of the α-hydroxy-amide. As expected, the C−C(═O)−NH−$C_α$ skeleton is almost perfectly planar, the amide fragment adopts a *Z* conformation and the vicinal N−H/C−H bonds are approximately antiperiplanar (HNCH torsion angle 152.4°). In addition, the O−C−C═O fragment adopts a synperiplanar (*sp*) conformation (OCCO torsion angle 13.6°), indicating the presence of an intramolecular hydrogen bond.[17] As a result of this *eclipsed conformation*, the 1-naphthyl and trifluoromethyl groups eclipse the methyl and phenyl groups, respectively.

According to multinuclear NMR and IR analyses, the *sp-Z* conformation observed for **2b** in the solid state is also favored in $CDCl_3$ solution for both diastereomers **2a** and **2b**. Indeed, the $^3J_{HH}$ coupling constants (8.0 Hz) are diagnostic for an antiperiplanar arrangement of the vicinal N−H and C−H bonds ($^3J_{HH}$ = 7.0−9.0 Hz).[4,16,18] In addition, NOESY and $^{19}F\{^1H\}$ HOESY experiments unambiguously supported the eclipsed *sp* conformation, cross-relaxation peaks being observed for the CF_3 group and H_{peri} atom of the naphthyl on the one hand, and the CH_3 group and H_{ortho} of the phenyl on the other hand (Figure 4). Lastly, the presence of an intramolecular hydrogen bond between the OH and C═O groups is supported by the sharp signals observed for the hydroxyl group both in ^1H NMR (δ_{OH} = 5.28 ppm for **2a** and 5.37 ppm for **2b**) and in IR (ν_{OH} = 3421 cm^{-1} for **2a** and **2b**), no noticeable displacements being detected upon dilution.

(15) The α-methylbenzylamine was chosen as a representative α-chiral primary amine available in enantiopure form and presenting diagnostic signals ^1H NMR.

(16) Chinchilla, R.; Falvello, L. R.; Nájera, C. *J. Org. Chem.* **1996**, *61*, 7285.

(17) The hydrogen atom of the hydroxyl group could be positioned between the two oxygen atoms without any constraint.

(18) Helmchen, G.; Ott, R.; Sauber, K. *Tetrahedron Lett.* **1972**, *37*, 3873.

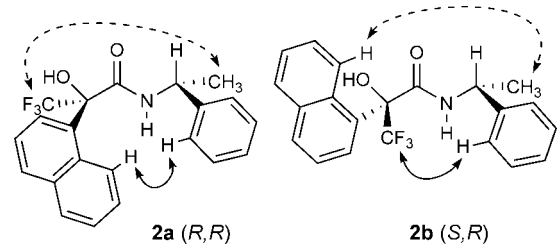


Figure 4. NOE interactions observed for **2a** and **2b** in NOESY and $^{19}F\{^1H\}$ HOESY experiments.

This hydrogen bond, which enforces the eclipsed conformation, is likely to explain the large $\Delta\delta^{RS}$ observed between **2a** and **2b** by maximizing the anisotropic effect of the naphthyl group (Figure 5). In this regard, the OCA **1** markedly differs from other CDA that usually favor the staggered conformation. The situation encountered in **2a**/**2b** is reminiscent of the eclipsed conformation induced by Riguera et al. upon complexation of both oxygen atoms of MPA-derived amides with barium(II) salts.[8a]

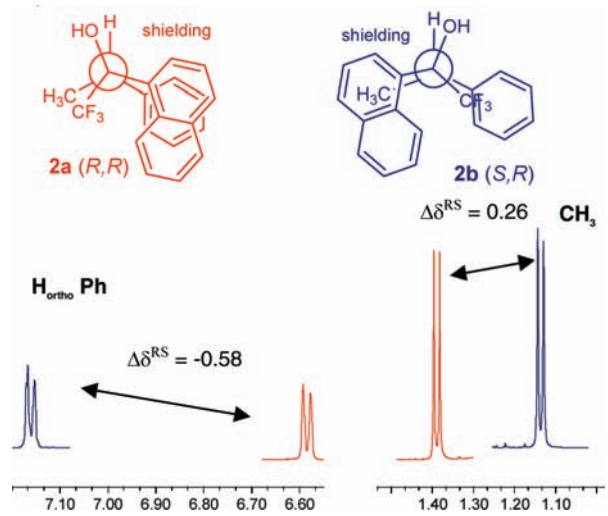
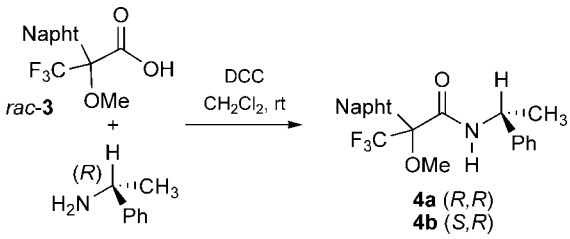


Figure 5. Extended Newman projections of **2a**/**2b** and ^1H NMR spectra (aromatic and methyl regions) of **2a**/**2b** illustrating the eclipsed conformation and the resulting strong anisotropic effect of the naphthyl ring.

At this stage, one may argue that the larger anisotropic effect of the naphthyl versus the phenyl ring[19] could also have a significant effect. This prompted us to investigate the 1-naphthyl analogue **3** of MTPA (Scheme 2).[14] The spectroscopic study performed on the corresponding *O*-methylated amides derived from the (*R*)-α-methylbenzylamine **4a**/**4b**, revealed a preference for a *staggered conformation* with the MeO−C−C═O fragment adopting an antiperiplanar

(19) Latypov Sh., K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504.

Scheme 2. Reaction of **3** with (*R*)-α-Methylbenzylamine



conformation. As a result, very low $\Delta\delta^{RS}$ are observed in the ^{1}H NMR spectra (0.01 ppm for the methyl group), confirming thus the critical role played by the hydrogen bond in **2a** and **2b**.

To further substantiate the utility of OCA-**1**, enantiomerically pure forms (*S*)-**1** and (*R*)-**1** were prepared after resolution of the α-hydroxy-acid precursor with α-methylbenzylamine (ee >99.6% after three recrystallizations in 2-propanol).[14,20] A range of α-chiral primary amines with diverse structures were then reacted with both *rac*-**1** and (*S*)-**1**, and the resulting $\Delta\delta^{RS}$ values were determined (Figure 6). The proton chemical shift differences follow the same trend for all the prepared α-hydroxy-amides, and are all consistent with the eclipsed hydrogen-bonded conformation established with α-methylbenzylamine. This includes the amino-alcohol adduct **11**, illustrating (i) the complete selectivity of OCA **1** for amines vs alcohols in the absence of coupling reagents and (ii) its applicability to substrates featuring hydroxyl groups also susceptible to hydrogen-bonding toward the amide moiety. Moreover, all the obtained $\Delta\delta^{RS}$ values are significantly larger than those reported with classical CDA such as MTPA, MPA and even surpass those achieved with NPP.[10]

In conclusion, the (1-naphthyl)(trifluoromethyl) *O*-carboxyanhydride **1** was found to induce considerable ^{1}H NMR differentiation with a wide range of α-chiral primary amines. In marked contrast to related CDA such as MTPA and MPA, the use of **1** leads to *O*-unprotected adducts in which *eclipsed*

(20) The absolute configuration of enantiomerically pure **1** was determined by derivatization with (*R*)-α-methylbenzylamine and comparison with the known adducts **2a**/**2b** by ^{1}H NMR.

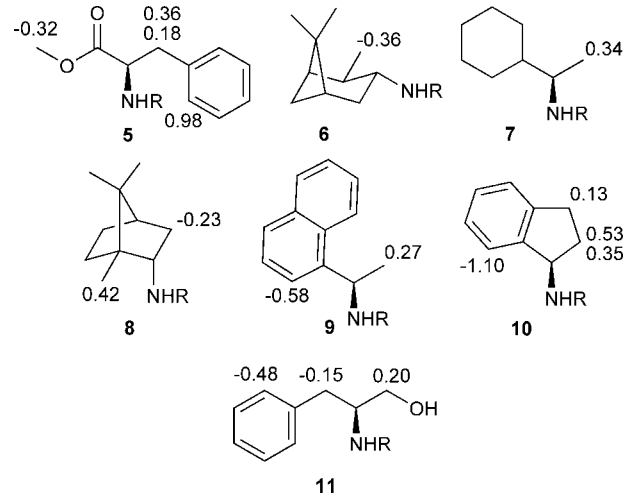


Figure 6. $\Delta\delta^{RS}$ values obtained for diastereomeric amides **5**−**11** [R = COC(OH)CF$_3$(1-naphthyl)] derived from the corresponding α-chiral primary amines. (^{1}H NMR spectra were recorded at 25 °C, in $CDCl_3$)].

conformations are enforced by *intramolecular hydrogen bonding*. As a result, the anisotropic effect of the naphthyl group is much larger than in the related *O*-methylated amides for which the staggered conformation is classically favored. Accordingly, this OCA may be considered as a promising CDA and further improvements may be expected in both reactivity and resolution efficiency by varying the substitution pattern.

Acknowledgment. The CNRS and UPS are warmly acknowledged for financial support of this work. Discussions with Y. Robin (ISOCHEM) are sincerely appreciated. We also thank P. Lavedan (NMR), C. Zedde (HPLC), Dr. S. Bontemps, and Dr. H. Gornitzka (X-ray diffraction analyses) for their assistance.

Supporting Information Available: Experimental details, spectroscopic characterization for all new compounds, and crystallographic data for **2a** and **4a**.This material is available free of charge via the Internet at http://pubs.acs.org.

OL801930M