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# Resin-Bound Chiral Derivatizing Agents for Assignment of Configuration by NMR Spectroscopy

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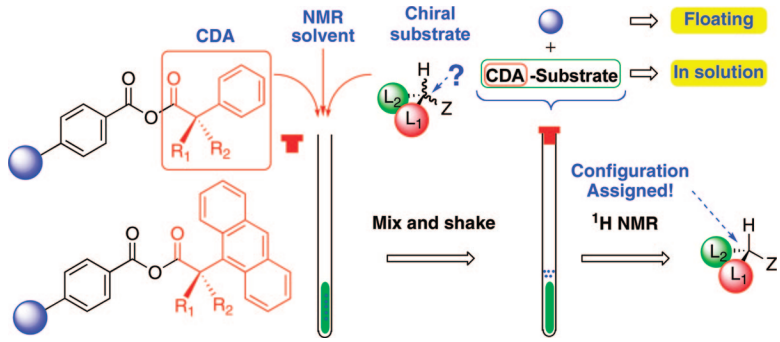


A general methodology for assigning the configuration of chiral mono- and polyfunctional compounds by NMR is presented. The approach is based on the use of polystyrene-bound chiral derivatizing agents (CDA-resins) specifically designed to achieve the high-yield formation of the covalent linkages (amide or ester bonds) between the substrate and the chiral auxiliary within the NMR tube, without the need for other manipulations, on a microscale level and in a short time. The deuterated NMR solvents ($CDCl_3$, $CD_3CN$, $CS_2/CD_2Cl_2$) are also the reaction solvents and separations, purifications or workups of any kind are not necessary prior to recording the spectra. The CDA-resins prepared included MPA, 9-AMA, BPG, MTPA, and 2-NTBA as auxiliary agents incorporated either as single enantiomers or as mixed combinations of the (*R*)- and the (*S*)-enantiomers at unequal and known ratios. The high versatility of these systems was successfully demonstrated in a variety of ways based on double and single derivatization, low temperature experiments, or the formation of metal complexes. The approach allowed the absolute configurations of chiral primary amines, primary and secondary alcohols, cyanohydrins, thiols, diols, triols, and amino alcohols to be determined. Extensive high-resolution magic angle spinning (HR-MAS) NMR experiments allowed the characterization of the new CDA-resins and enabled the study of their stability and regioselectivity.

## Introduction

NMR spectroscopy has contributed, with a variety of methods and chiral auxiliaries, to the assignment of absolute configuration of a large number of families of chiral compounds in the past decade.[1] The main procedures are based on the covalent attachment of a chiral derivatizing agent (CDA) of known configuration to the chiral substrate of unknown configuration. When applying these NMR methods to elucidate configurations, researchers can choose between methods that require either double or single derivatization.

The double derivatization methods are based on the preparation of two diastereomeric derivatives of the chiral substrate and the two enantiomers of the CDA, followed by comparison

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(1) (a) For comprehensive reviews, see: Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17, and references cited therein. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915. (c) Wenzel, T. J. *Discrimination of Organic Compounds Using NMR Spectroscopy*; Wiley-Interscience: Hoboken, 2007.



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of their $^1$H NMR spectra. The positive or negative sign of the $\Delta\delta^{RS}$ parameters[2] obtained for the $L_1$ and $L_2$ substituents on the stereogenic center allows us to infer its configuration. On the other hand, the single derivatization methods require the preparation of only one derivative and the necessary $\Delta\delta$ parameters can be obtained in several ways: by comparison between the spectrum of the original substrate and the spectrum of the derivative, by comparison between two spectra of the derivative taken at different temperatures, or by comparison between the spectrum of the derivative and the spectrum of an appropriate metal complex of the derivative.[1]

From an experimental point of view, all of the procedures outlined above require a series of time-consuming steps: (1) reaction between the substrate and the CDA in solution, usually in the presence of a coupling agent; (2) workup of the reaction mixture; and (3) separation, purification (i.e., CC, HPLC, TLC), and isolation of the derivative. This last step is usually associated with at least some loss of sample, which constitutes a problem when the available amount of substrate available is small. In the case of the double derivatization methods, these steps have to be repeated to prepare the second required derivative.

As a result of our search for new methods focused on avoiding some of the disadvantages outlined above, we present here our results on a methodology that allows the elucidation of absolute configurations by NMR in a very short time period and with minimum manipulations.[3] Essentially, the initial design of this method was based on the following ideas: (a) to employ solid matrix-bound chiral derivatizing agents; (b) to make use of deuterated NMR solvents as reaction media; and (c) to carry out rapid and high-yielding preparations of the derivatives inside the NMR tubes (they are the "reaction flasks") without interference by the solid matrix.

The development of the methodology first requires the binding of a CDA (i.e., a carboxylic acid) to a resin through an appropriate bond. Next, three components —the CDA-resin reagent, the chiral substrate of unknown configuration, and the deuterated solvent— are placed inside the NMR tube, where the substrate (i.e., amine, alcohol, etc.) acts as a nucleophile and reacts with the CDA-resin (electrophile). As a result, the CDA-substrate derivative (i.e., amide, ester, etc.) is liberated into solution while the solid matrix (the resin) behaves as the leaving group and remains out of solution (afloat). The NMR spectrum of this sample can now be obtained, and the experimental time is, in many cases, just few minutes.

The characterization of the new CDA-resins and studies on their stability and regioselectivity, carried out by high-resolution magic angle spinning (HR-MAS) NMR spectroscopy, are also presented.

## Results and Discussion

**1. Preparation of the CDA-Resin Reagents.** The mono- and polyfunctional compounds shown in Figures 1 and 1S (Supporting Information) that belong to families of compounds that are usually found as either synthetic or natural products were selected as chiral substrates. Next, appropriate CDAs for those substrates were chosen (Scheme 1a): 2-methoxy-2-phenylacetic acid (MPA, **1**); 2-(anthracen-9-yl)-2-methoxyacetic acid (9-AMA, **2**); Boc-phenylglycine (BPG, **3**); 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (MTPA, **4**);[1] and 2-*tert*-butoxy-2-(2-naphthyl)acetic acid (2-NTBA, **5**).[4]

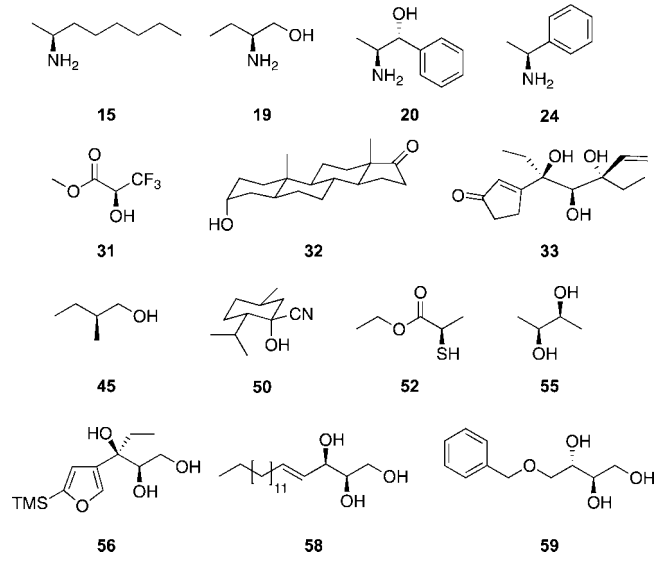



**FIGURE 1.** Selection of chiral substrates employed in this study: amines, secondary and primary alcohols, cyanohydrins, thiols, and polyfunctional compounds (amino alcohols, diols, and triols).

With regard to the choice of the solid matrix, carboxypolystyrene resin **6** presents the adequate requirements (i.e., high loading, stability, functionalization) as solid matrix and forms polymer-bound anhydrides[5] with the selected CDAs through its acid chloride derivative **7** (Scheme 1b). The resulting CDA-resins **8**−**12** present good swelling properties in deuterated solvents and float on $CDCl_3$, and the attack by nucleophiles to the anhydride is regioselective. Experimental procedures, as well as results on other resins that were also tested (i.e., 1-hydroxybenzotriazole resin **13** and sulfamylbutyryl resin **14,** Scheme 1c), can be found in the Experimental Section and Supporting Information.

**2. HR-MAS Analysis: Characterization of the CDA-Resins.** The structural characterization of CDA-resins **8**−**11** was achieved by a combination of 1D and 2D HR-MAS NMR spectroscopy, which was the technique of choice because it constitutes a powerful tool to overcome the analytical difficulties associated with solid-phase matrices.[6] In this technique, rotation of the solvent-swollen resin at an angle of 54.7° significantly reduces the line-broadening, leading to $^1$H spectra that are amenable to analysis. These studies confirmed the attachment of the chiral auxiliaries to the polystyrene resins. To illustrate the application of this technique, the on-resin analysis of **8** is described below.

Comparison of the $^1$H HR-MAS spectrum of **8** with that of the starting resin **6** reveals the presence of four new peaks corresponding to the proton resonances of the MPA moiety

(2) $\Delta\delta^{RS}$ for a substituent is the difference between its chemical shift in the (*R*)-CDA derivative minus its chemical shift in the (*S*)-CDA.

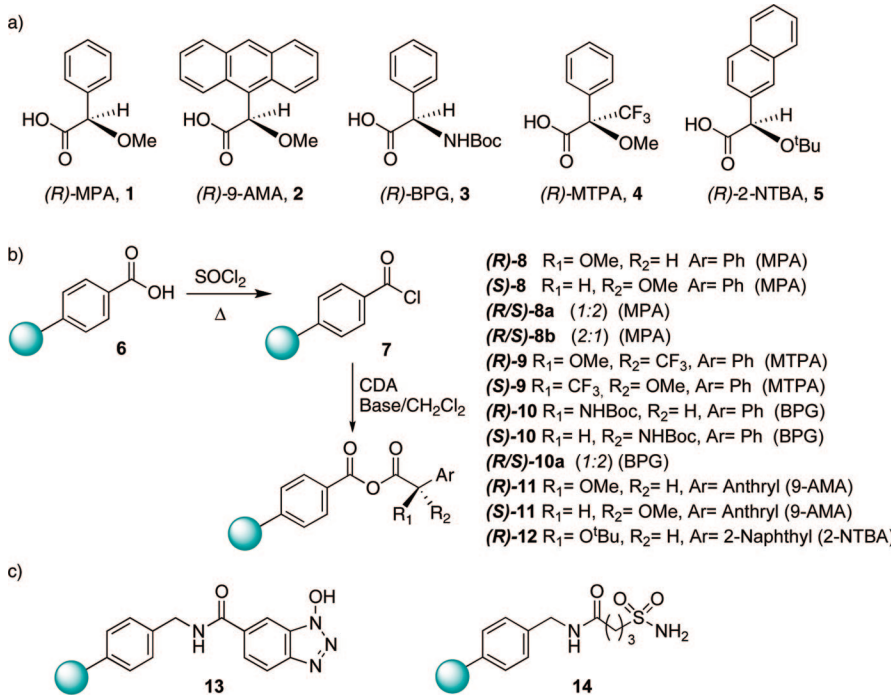
(3) A short communication on this subject has been published: Porto, S.; Durán, J.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2003**, *5*, 2979.

(4) Porto, S.; Seco, J. M.; Ortiz, A.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2007**, *9*, 5015.

(5) (a) Shambhu, M. B.; Digenis, G. A. *Tetrahedron Lett.* **1973**, *18*, 1627. (b) Leznoff, C. C.; Dixit, D. M. *Can. J. Chem.* **1977**, *55*, 3351. (c) Kurth, M. J.; Ahlberg-Randall, L. A.; Takenouchi, K. *J. Org. Chem.* **1996**, *61*, 8755.

(6) (a) Keifer, P. A. *Drugs Future* **1998**, *23*, 301. (b) Shapiro, M. J.; Gounarides, J. S. *Prog. Nucl. Magn. Reson. Spectrosc.* **1999**, *35*, 153. (c) Lippens, G.; Warras, R.; Wieruszeski, J. M.; Rousselot-Pailley, P.; Chessari, G. *Comb. Chem. High Throughput Screen.* **2001**, *4*, 333. (d) Lippens, G.; Bourdonneau, M.; Dhalluin, C.; Warrass, R.; Richert, T.; Seetharaman, C.; Boutillon, C.; Piotto, M. *Curr. Org. Chem.* **1999**, *3*, 147. (e) Warras, R.; Lippens, G. *J. Org. Chem.* **2000**, *65*, 2946. (f) Yao, N.-H.; He, W.-Y.; Lam, K. S.; Liu, G. *J. Comb. Chem.* **2004**, *6*, 214.

**SCHEME 1. (a) Chiral Derivatizing Agents (CDAs), (b) Preparation of Different CDA-Resins from 6, (c) Other Resins Tested**




(Figure 2a). The signals at 7.38 and 7.52 ppm were assigned to the aromatic protons of the phenyl ring and the signals at 5.05 and 3.50 ppm to the methine and the methoxy protons, respectively. The chemical shifts of the carbon resonances were determined by 2D-heteronuclear HSQC and HMBC experiments, which provided one-bond proton-carbon correlations (HSQC) or two- and three-bonds proton-carbon correlations (HMBC). The HMBC spectrum of **8** is shown in Figure 2b along with the assignments of the carbon resonances. Analogous studies allowed the characterization of the MTPA, BPG, and 9-AMA resins.

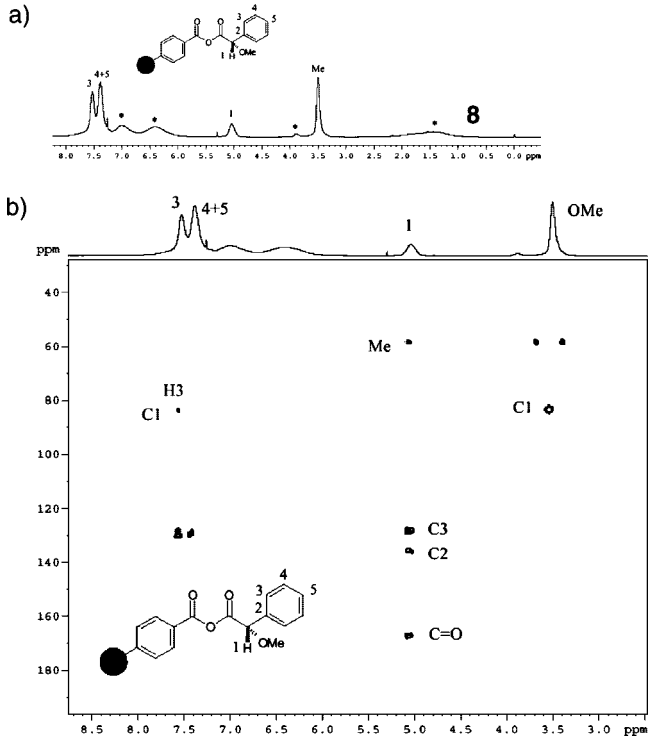



**FIGURE 2.** (a) $^1$H HR-MAS and (b) HR-MAS H-C HMBC spectra of CDA-resin **8**.

**Stability of the CDA-Resins.** In order to determine the stability of the CDA-resins, the $^1$H HR-MAS spectra of recently prepared samples were compared with those of samples kept under Ar at −22 °C for 1 year. The spectrum of a fresh sample of **8** shows only the signals corresponding to the MPA linked to the resin (Figure 3a). After 1 year, however, additional sharp signals were observed close to those of MPA bonded to the resin, and these can be ascribed to the presence of free auxiliary in solution, which results from decomposition of the CDA-resin (Figure 3b). A CPMG (Carr-Purcell-Meiboom-Gill) experiment showed that the intensity of the signals of the linked MPA were preferentially reduced in intensity, while the new signals decreased by a lesser amount, further confirming that they belong to a molecule that is not bound to the solid matrix (Figure 3c). It is estimated that 5% decomposition of the resin had occurred after that period, as deduced from the different intensity ratios of the signals at 5.04 and 4.79 ppm (corresponding to the Hα of free and bound MPA, respectively).

Similar studies performed with CDA-resins **9** and **10** demonstrated the high stability of these systems: $^1$H HR-MAS spectra obtained 1 year after sample preparation showed that decomposition had not occurred. Finally, CDA-resin **11** showed less than 10% decay after that period.

**Regioselectivity of the Nucleophilic Attack.** The existence of two carbonyl groups in the CDA-resin, both of which can act as electrophiles, led us to study the regioselectivity of the attack of the nucleophile on the mixed anhydride by HR-MAS.

When a chiral amine is derivatized with CDA-resins **8** and **10**, only the corresponding MPA or BPG amide is observed in solution, without the presence of free MPA or BPG, thus suggesting that the amine attacks only the carbonyl group next to the auxiliary (Figure 4a,b). The possibility of acid-base equilibria between the carboxylic leaving group and the amine was considered. In such a case, a proportion of the amine could neutralize the acid residue of the resin, leading to a loss of

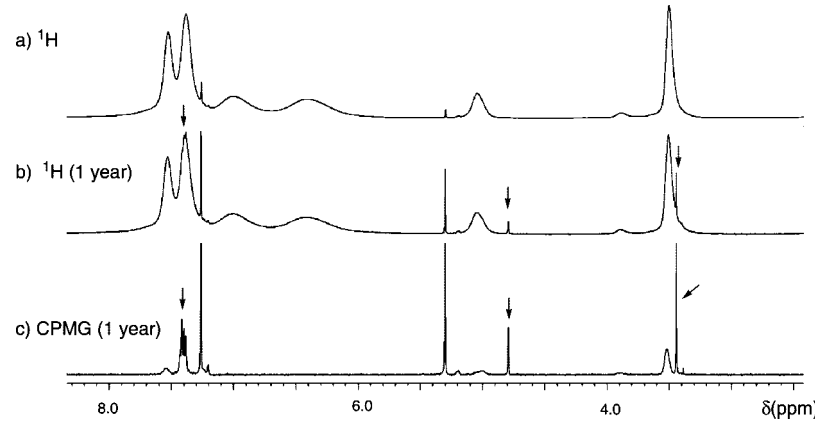



**FIGURE 3.** (a) $^1$H HR-MAS spectra of recently prepared and (b) 1-year-old CDA-resin **8**. (c) Experiment with the CPMG sequence. Arrows show the signals corresponding to the free compound.

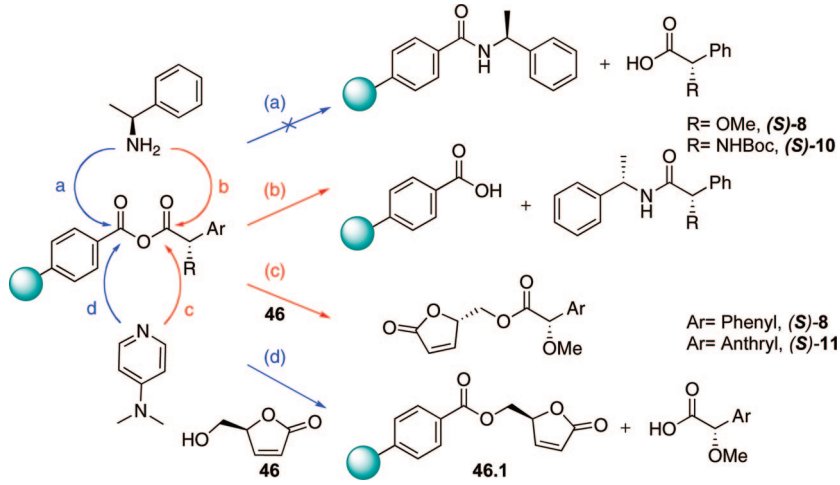



**FIGURE 4.** Potential nucleophilic attacks on CDA-resins.

substrate, and the resulting salt would remain undetected in solution NMR spectra. HR-MAS experiments, employed to determine the presence/absence of the ammonium salt in the resin, did not show any signal that would correspond to it.[7]

When substrates bearing hydroxy or thiol groups are derivatized with resins **8** and **11**, free auxiliary is observed in solution. These reactions are catalyzed by DMAP, which generates an acyl pyridinium intermediate. This active species reacts with the alcohol/thiol to give the final derivative, which can be observed by solution $^1$H NMR spectroscopy (Figure 4c). The presence of the free auxiliary in solution can be explained by either partial hydrolysis of the active intermediate or attack by DMAP on the other carbonyl group (Figure 4d). In the latter case, the active intermediate that is generated is attached to the resin and the final nucleophilic attack by the substrate would produce the ester derivative covalently linked to the resin.

(7) CDA-resin (***R/S*)-8a** was treated with (*S*)-1-phenylethylamine (**24**), and once the reaction was complete, the resin was filtered off and washed with dichloromethane, and a $^1$H HR-MAS spectrum was recorded. No signals attributed to the amine were observed, thus strongly suggesting the absence of salt. Experiments carried out with BPG-resin (**10**) yielded analogous results. Parallel experiments were performed in order to further check the possibility of the formation of the salt: (a) A solution (in $CDCl_3$) of benzylamine and toluene (internal reference) in a known ratio (by NMR) was submitted to the usual reaction with **(*S*)-8**. After reaction, quantification by NMR showed virtually the same amide/toluene ratio (see spectra in Figure 2S in the Supporting Information). (b) When carboxypolystyrene resin **6** was soaked with a solution of benzylamine in $CDCl_3$ for 10 min (2:1 resin-amine ratio), only 3% (approximate) disappearance of the amine was detected by NMR. Results with DMAP were the same.

In order to ascertain which carbonyl group is involved in the reaction, HRMAS studies on resins **8** and **11** were performed after reaction with alcohol **46** (followed by filtration and washes with dichloromethane). The $^1$H HRMAS spectrum of resin **(*R*)-8**, after derivatization, does not show any signal that can be assigned to the ester linked to the resin (**46.1**). This finding indicates that the reactions between substrates bearing hydroxy groups and CDA-resin **8** take place with total regioselectivity. Thus, the presence of small amounts of free MPA in solution can be explained by the partial hydrolysis of the acyl pyridinium intermediate. Analogous results were obtained in the study of the $^1$H HR-MAS spectra of the reaction involving resin **11**.

HR-MAS studies were performed as described above with resin **9** and alcohol **46**, and the results were clearly different. New signals that corresponded to the alcohol covalently linked to the resin appeared in the $^1$H HR-MAS spectra. Thus, in this case (MTPA as CDA), attack of DMAP on the carbonyl groups of the mixed anhydride of the resin is not selective, most likely due to the higher steric hindrance of the auxiliary. The outcome is a decrease in the reaction yield through loss of the substrate, and as a consequence, MTPA-resins are not recommended in these cases.

**3. Use of the CDA-Resins: General Procedure of the "Mix and Shake" Method.** The appropriate amount of the CDA-resin (the average amount of resin employed in standard experiments was 20 mg) and the substrate of unknown config-

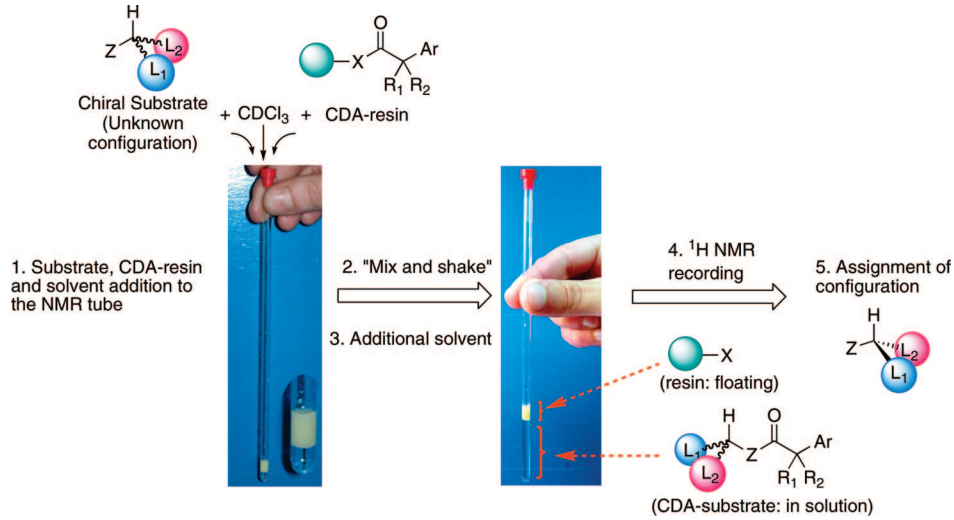



**FIGURE 5.** General procedure for the use of the CDA-resins in the "mix and shake" method.

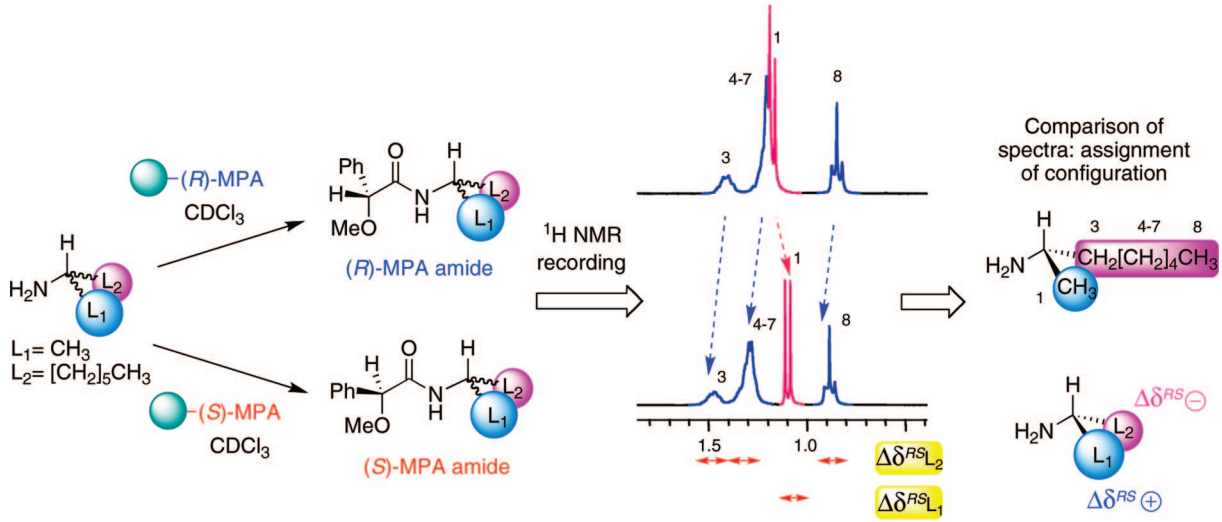



**FIGURE 6.** Assignment of the configuration of (*S*)-octan-2-amine (**15**) by the double derivatization method and the use of two resins [**(*R*)-** and **(*S*)-8**].

uration were added to the NMR tube together with a small amount of the dry deuterated solvent (i.e., 150 $\mu$L, $CDCl_3$). After soaking and shaking the heterogeneous mixture[8] for several minutes (see below for the appropriate timing according to the specific substrate), additional dry solvent was added (i.e., 600 $\mu$L altogether) and the NMR spectrum was taken directly. The CDA is now linked to the substrate in solution while the free resin floats on the surface without causing any interference in the recording of the spectrum. Other manipulations such as filtration, separation, or purification are not required. This general approach is represented schematically in Figure 5.

**Application to Primary Amines.** Primary amines showed excellent behavior as nucleophiles with **(*R*)-8** and **(*S*)-8** (MPA) and **(*R*)-10** and **(*S*)-10** (BPG) resins.[9] A 2:1 equiv CDA-resin/amine ratio gave optimum results [i.e., 44 $\mu$mol = 20 mg of resin **8** (known loading); 22 $\mu$mol of amine], and the reaction times ranged from 5 to 10 min (rt) for all of the amines studied (MPA resins were tested with amines **15**−**27**; BPG resins with **17**, **20**, and **21**; see structures in Figure 1 and 1Sa in the Supporting Information). It is worth noting that amino alcohols **19** and **20** reacted in a totally regioselective way through the amino group alone, while the hydroxy group did not undergo any reaction. The configuration of the amino chiral center was accordingly established in the usual way.[1a,b]

Given the fact that the CDA-resins used in this approach consist of a single CDA enantiomer, two "in tube" derivatizations (double derivatization method) are necessary and the configurations are deduced by comparison of the spectra of the two diastereomeric amides (Figure 6).

Other effective ways to assign the configuration of amines are possible through the use of these resins. One consists of making use of a CDA-resin incorporating the two CDA enantiomers with a known excess of one of them [i.e., **(*R*/*S*)-8a** (1:2) or **(*R*/*S*)-8b** (2:1)]. Thus, only one "in tube" derivati-

(8) Although shaking by hand is an option, the use of a mechanical mixing device is recommended. Rotation of the tube while the tube is held with a certain slope proved to be a highly efficient procedure. An example is shown in the Supporting Information.

(9) Treatment of the chiral amines with MTPA-resins **9** did not give favorable results. When submitted to the reaction conditions, these resins showed anomalous behavior when compared to that of MPA and BPG resins: the resins lost the floating properties and yielded heterogeneous mixtures that did not allow acceptable spectra to be acquired. These results do not represent a handicap because MTPA is not the most suitable CDA for amines, with BPG and MPA being much better choices (BPG amides generate the largest $\Delta\delta^{RS}$ values: see ref 1 and references therein).

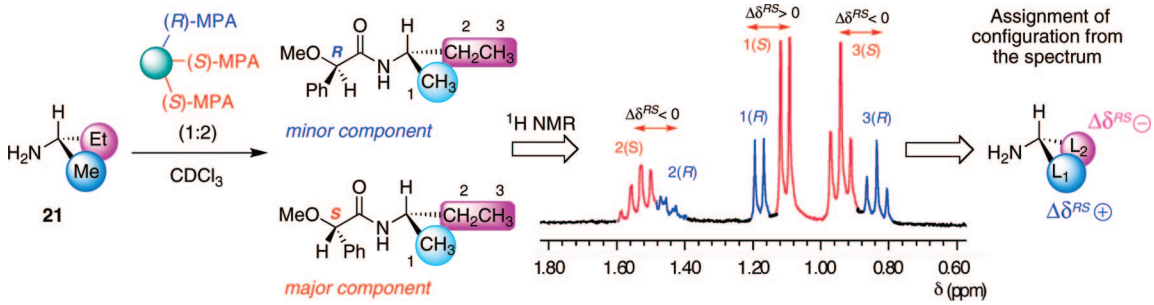



**FIGURE 7.** Assignment of the configuration of (*S*)-butyl-2-amine (**21**) by the double derivatization method and use of a single (*R*/*S*)-resin [(***R*/*S*)-8a**].

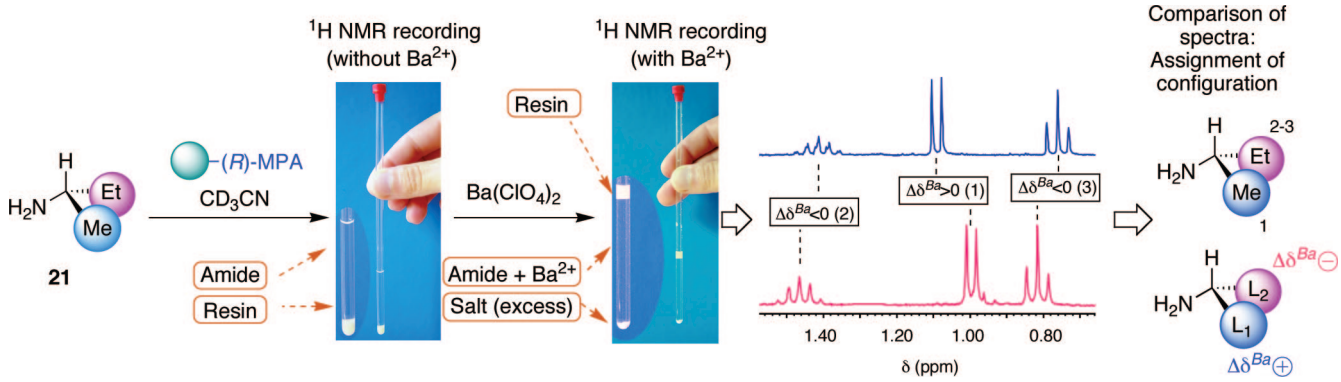



**FIGURE 8.** Assignment of the configuration of (*S*)-butyl-2-amine (**21**) by single derivatization with **(*R*)-8** and formation of a barium(II) complex.

zation is necessary because it produces a mixture of the (*R*)- and the (*S*)-CDA derivative, the signals of which can be identified in the spectrum of the mixture by integration. An example of the application of this strategy to (*S*)-butyl-2-amine (**21**) using resin **(*R*/*S*)-8a** is represented in Figure 7. No measurable kinetic resolution was detected under these conditions. The advantage of his approach lies in the fact that it requires half the amount of substrate, half the time, and half the cost when compared to the double derivatization approach.

The formation of barium(II) complexes of a single MPA amide derivative has proven to be another extremely effective method for the configurational assignment of chiral amines by way of $\Delta\delta^{Ba}$ parameters.[10] In this method, the comparison that allows the configuration to be established is made between the spectra of the amide before and after the addition of a barium(II) salt [e.g., $Ba(ClO_4)_2$], which shifts the conformational equilibrium by forming a complex. $CD_3CN$ is the most suitable deuterated solvent for this approach, and MPA-resins (**8**) proved to have appropriate characteristics (although different to that of $CDCl_3$) when soaked in this solvent.

The procedure follows the general steps adapted specifically for this application. The amine and the MPA-resin are introduced into an NMR tube together with a small amount of $CD_3CN$ (i.e., 150 $\mu$L). In this case, the resin does not float (as it did in the case of $CDCl_3$) but lies at the bottom of the tube (Figure 8). The mixture is shaken for 30 min approximately[11] and the MPA amide is formed. Extra $CD_3CN$ is then added to give the appropriate volume in the NMR tube (i.e., 450 $\mu$L) and the first spectrum is recorded. The resin does not interfere with this process, as it is still located at the bottom of the tube. $Ba(ClO_4)_2$ is subsequently added until saturation is achieved and the solution is shaken. At that point, the resin recovers the floating properties (sonication helps to speed up this process) and the second spectrum can be recorded. Comparison between the spectra and calculation of the $\Delta\delta^{Ba}$ parameters enabled the determination of the configuration.

**Application to Secondary Alcohols.** MPA and 9-AMA have proven to be the CDAs of choice for alcohols.[1,12] Subsequently, resins **8** and **11** were selected as candidates to perform the formation of the required ester derivatives in NMR tubes.

The optimized derivatization procedure for this functional group consists of the addition of the CDA-resin (2 equiv), the alcohol (1 equiv), and $CDCl_3$ (100 $\mu$L) to the NMR tube [i.e., 44 $\mu$mol = 20 mg of resin **8** (known loading); 22 $\mu$mol of alcohol]. A solution of DMAP (1 equiv) in $CDCl_3$ (i.e., 100 $\mu$L) is also added to the tube, and the resulting mixture is agitated for 10 min in the case of MPA (1 h if 9-AMA is used).[13] After the addition of an extra quantity of $CDCl_3$ (400 $\mu$L) the spectrum can be recorded.

The double derivatization method for alcohols is based on the analysis of $\Delta\delta^{RS}$ parameters obtained from the comparison of two spectra corresponding to the diastereomeric esters formed by reaction with two enantiomeric CDA-resins [i.e., **(*R*)-8/(*S*)-8** or **(*R*)-11/(*S*)-11**], in an analogous way to that already depicted for amines in Figure 6. A selection of chiral alcohols with a variety of structural features (including aliphatic, cyclic, aromatic) was tested (MPA resins were employed with alcohols **28**−**41**; 9-AMA resins with **28** and **30**; see Figures 1 and 1Sb

(10) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2006**, *71*, 1119.

(11) The longer time needed (30 min) when compared to $CDCl_3$ (10 min) is ascribed to the fact that the swelling takes place more slowly in $CD_3CN$.

(12) For a comparative study showing the advantages of MPA versus MTPA, see: Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569.

(13) Most likely due to the higher steric hindrance.

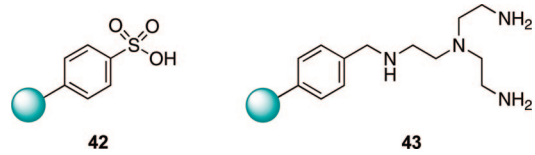



**FIGURE 9.** Scavenger resins employed in this study.

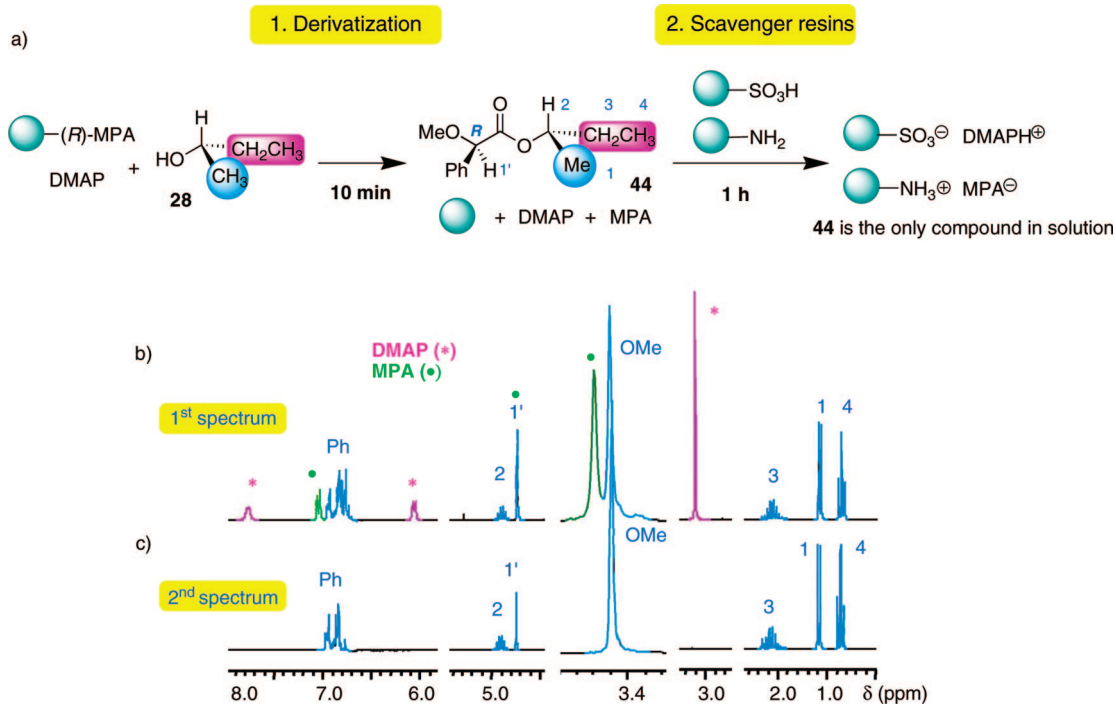



**FIGURE 10.** (a) Derivatization of (*S*)-2-butanol (**28**) with **(*R*)-8**. (b) $^1$H NMR (250 MHz) of the reaction mixture. The signals correspond to the MPA ester **44** (blue), DMAP (violet), and MPA (green). (c) After treatment with the scavenger resins. The signals correspond only to the MPA ester **44** (blue).

in the Supporting Information). Racemization, decomposition, or formation of byproducts was not detected in any case. The derivatization of triol **33** warrants particular attention as it shows the expected selectivity: the monoester at the secondary alcohol was the only product obtained.

As a result of the experimental conditions, NMR signals due to the presence of DMAP and MPA (or 9-AMA)[14] are observed in the spectra (Figure 10b). These signals are easily identified and usually do not interfere in the assignment of configuration. Nevertheless, we looked for a simple way to remove these signals without taking the solution out of the NMR tube.

Thus, we explored the addition to the tube of other resins that would retain these side products and therefore leave a "clean" solution for NMR assignment. Scavenger resins **42** (a sulfonic acid resin)[15] and **43** [a tris(2-aminoethyl)amine resin][16] proved to be compatible with the "in tube" process and removed effectively the DMAP and MPA that were present in the solution (Figure 9).

From an experimental point of view, these scavengers are added to the tube (2 equiv of **42** and 2 equiv of **43**) once the CDA ester is formed and the resulting mixture is then shaken for about 1 h (Figure 10). The spectrum of the ester can then be directly recorded without any further manipulation (i.e., filtration).

The double derivatization with a single resin was also tested. "In tube" derivatization of the alcohol with a CDA-resin consisting of unequal amounts of the two CDA enantiomers [i.e., **(*R/S*)-8a** (1:2 *R/S* ratio); **(*R/S*)-8b** (2:1 *R/S* ratio)] allows the assignment of configuration from only one NMR spectrum, in a similar way to that shown before for amines, by interpretation of the $\Delta\delta^{RS}$ signs.[1]

The derivatization of alcohols with the CDA-resins was successfully achieved in other solvents, which allowed us to resort to other approaches in order to assign the absolute configuration. So, the derivatization took place in $CD_3CN$, meaning that the methodology based on the use of barium(II) complexes could be applied in an analogous way to that already described for amines. Only one derivative [with either (*R*)- or (*S*)-CDA] is required, and comparison of its spectrum with the one obtained after the addition of $Ba(ClO_4)_2$ yields the absolute configuration (by interpretation of $\Delta\delta^{Ba}$ signs).[17]

(14) The excess of CDA-resin, together with DMAP, employed in order to achieve complete transformation of the alcohol to the ester is the origin of the "free" CDA found in the solution.

(15) Smith, R. A.; Bhargava, A.; Browe, C.; Chen, J.; Dumas, J.; Hatoum-Mokdad, H.; Romero, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2951.

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(17) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2002**, *67*, 4579.

The "in tube" derivatization of alcohols also occurred in $CS_2$/$CD_2Cl_2$ (4:1) (the resins float in this mixture). As a result, the methodology based on the use of low temperature $^1$H NMR of a single MPA derivative could be applied. Only one derivative [with either (*R*)- or (*S*)-MPA: resins **(*R*)-8** or **(*S*)-8** respectively] is required and comparison of its spectra at two different temperatures (e.g., 303 and 203 K) provides the configuration through interpretation of $\Delta\delta^{T1T2}$ signs.[18]

**Application to Other Monofunctional Compounds: Primary Alcohols, Cyanohydrins, and Secondary Thiols.** The $^1$H NMR spectra of the 9-AMA esters of $\beta$-chiral primary alcohols and interpretation of the $\Delta\delta^{RS}$ signs allows determination of their configuration.[19] The substrates tested with 9-AMA resins (**11**) are alcohols **45**−**49** (Figures 1, 4, and 1Sc in the Supporting Information) and the experimental approaches (including those with scavenger resins)[20] are analogous to those described above for secondary alcohols.

With regard to cyanohydrins, it is known that the $\Delta\delta^{RS}$ parameters obtained from both $^1$H and $^{13}$C NMR spectra of their MPA esters allow the assignment of their absolute configuration.[21] We assessed the feasibility of the "in tube" derivatization of cyanohydrins [**50** and **51**, Figures 1 and 1Sd (Supporting Information)] with MPA-resins **8** in $CDCl_3$, using experimental protocols similar to those already described for alcohols. Indeed, the formation of the MPA esters occurred in high yields within 15 min, and evidence for the formation of the carbonyl precursors or racemization was not detected.[22] These results represent a great advantage to the usual coupling procedures in solution,[21] where it is difficult to avoid the regeneration of the parent aldehyde or ketone. Once formed in the NMR tube, the MPA esters proved to be perfectly stable [scavenger resins may be added to remove DMAP and MPA (1 h)].

Finally, another family of monofunctional compounds, thiols, were studied. The $\Delta\delta^{RS}$ parameters obtained from the $^1$H NMR spectra of MPA thioesters of secondary thiols allow the assignment of their absolute configurations.[4,23] We carried out the derivatization of thiols **52** and **53** [Figures 1 and 1Se (Supporting Information)] with MPA-resins **8** in $CDCl_3$, using experimental protocols similar to those already described for secondary alcohols. The formation of the MPA thioesters occurred after 10 min shaking and scavenger resins could be added to remove DMAP and MPA (1 h).

**Application to Polyfunctional Compounds: Amino Alcohols, Diols, And Triols.** We explored the expansion of the "in tube" methodology to polyfunctional compounds,[24] namely to amino alcohols, diols and triols. A selection of these substrates [Figures 1 and 1Sf-h (Supporting Information)] was derivatized with CDA-resins **8** and **11** (MPA resins were tested with **20**, **54**−**66**; 9-AMA resins with **55**).

Amino alcohols and diols of different structural types (amino and hydroxy groups at the 1,2- and 1,3-*sec,sec* or 1,2-*sec,prim* positions) were successfully transformed into the bis-MPA derivatives (1 equiv of amino alcohol, 3 equiv of MPA-resin, 1 equiv of DMAP, $CDCl_3$, rt, 20 min; 1 equiv of diol, 3 equiv of CDA-resin, 2 equiv of DMAP, $CDCl_3$, rt, 90 min). The spectra showed a complete transformation without any byproducts. Optionally, the DMAP and MPA signals could be removed by employing the scavenger resins. When 9-AMA resins (**11**) are used with diol **55**, the protocol to follow is similar to that outlined above for MPA, with the only change being an increase in the reaction time to 4 h. As expected, with triols **56** and **64** only the primary and secondary hydroxy groups were transformed into the esters.

Finally, triols belonging to the structural type 1,2,3-*prim, sec,sec* (**58**, **59**, **65**, and **66**) were also efficiently derivatized with MPA in $CDCl_3$ and transformed into the tris-MPA derivatives according to protocols similar to those used with diols (1 equiv of triol, 4 equiv of CDA-resin, 2 equiv of DMAP, 8 h; scavenger resins optional).

## Conclusions

The polymer-bound auxiliary reagents presented in this work allow the derivatization steps needed to determine absolute configuration by NMR spectroscopy of a variety of functional groups in a rapid, simple, and totally reliable way. The CDA-resins are easily prepared, effortlessly handled and are very stable. Furthermore, the different enantiomeric compositions of the CDAs attached to them allow their use in a wide range of procedures.

The advantages of these CDA-resins, when compared to the standard coupling procedures, seem clear: external reaction flasks (other than the NMR tubes), coupling agents (i.e., DCC or EDC), large volumes of solvents, filtrations, chromatographic separations or other on the bench manipulations are not required; undesired byproducts (i.e., ureas) are not produced; the transformations take place at rt and in high yields; the reactions are fast (5−10 min in the case of amines) and have been tested at a microscale level (less than 0.5 mg of substrate).

The use of HR-MAS NMR spectroscopy completed the structural characterization of the CDA-resins and yielded important information concerning their stabilities and the regiochemistry of the reactions.

## Experimental Section

**HR-MAS Studies.** The resin samples (3 mg) were introduced into a 4 mm rotor and swollen in $CDCl_3$. The spectra were acquired

(18) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 877.

(19) (a) Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Commun.* **2007**, 1456. (b) Latypov, S. K.; Ferreiro, M. J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 4771.

(20) Unsaturated lactone **46** was transformed quantitatively into the 9-AMA ester with the resin. When the scavenger resins were subsequently used, the formation of a byproduct [identified as 5-methylenefuran-2(5*H*)-one] was detected. In fact, basic resin **43** was found to be the cause of the elimination reaction. Thus, when scavenger resins are used, special attention must be paid if functional groups prone to react with them are present.

(21) Louzao, I.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Commun.* **2006**, 1422.

(22) The decomposition of cyanohydrins in the presence of DMAP has been documented. For instance, see: Mathews, B. R.; Jackson, W. R.; Jayatilake, G. S.; Wilshire, C.; Jacobs, H. A. *Aust. J. Chem.* **1988**, *41*, 1697.

(23) 2-*tert*-Butoxy-2-(2-naphthyl)acetic acid (2-NTBA), which has proved to be an excellent agent for determining the absolute configuration of thiols, was also selected to be linked to the resin. However, the lower yields obtained in the reactions, together with the longer reaction times needed (most likely related to the steric hindrance of the bulky *tert*-butoxy group), discouraged us from pursuing its use as a CDA-resin.

(24) (a) For diols, see: Freire, F.; Calderón, F.; Seco, J. M.; Fernández-Mayoralas, A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2007**, *72*, 2297. (b) Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2005**, *70*, 3778. (c) Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2005**, *7*, 4855. (d) Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Eur. J.* **2005**, *11*, 5509. For amino alcohols, see: (e) Leiro, V.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Commun.* **2005**, 5554. For other approaches to diols and polyols, see: (f) Higashibayashi, S.; Kishi, Y. *Tetrahedron* **2004**, *60*, 11977. (g) Fukui, H.; Fukushi, Y.; Tahara, T. *Tetrahedron Lett.* **2003**, *44*, 4063. (h) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379. (i) Ghosh, I.; Kishi, Y.; Tomoda, H.; Omura, S. *Org. Lett.* **2004**, *6*, 4719. For triols, see: (j) Lallana, E.; Freire, F.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2006**, *8*, 4449.

on a 500 MHz spectrometer equipped with a 4 mm HR-MAS probe at 25 °C. The samples were spun at 4 kHz. Proton and carbon chemical shifts were referenced to the residual solvent signals at 7.26 and 77.1 ppm, respectively. 1D spectra were acquired using 32K data points, which were zero-filled to 64K data points prior to Fourier transformation. Absolute value COSY, phase sensitive HSQC and magnitude mode HMBC spectra were acquired using gradient-selection techniques. Acquisition data matrices were defined by 1K × 128 points in $t_2$ and $t_1$, respectively, and multiplied by appropriate window functions and zero-filled to 2K × 512 matrices prior to Fourier transformation.

**Preparation of Acid Chloride Resin (7).** Carboxypolystyrene resin (**6**) (500 mg, 2 mmol) was added to dry $CH_2Cl_2$ (2 mL) and stirred under a flow of Ar (30 min). Thionyl chloride (6 mL, 82 mmol) was added, and the resulting mixture was heated at 65 °C (4 h). The resin was filtered off under Ar, washed with dry $CH_2Cl_2$ (8 × 3 mL), and dried overnight under vacuum.

**Preparation of CDA-Resins.** Acid chloride resin (**7**) (500.0 mg, 1.9 mmol) was added to dry $CH_2Cl_2$ (2 mL), and the mixture was stirred under a flow of Ar (30 min). The CDA [MPA (**1**), 9-AMA (**2**), BPG (**3**), or MTPA (**4**)] (2.3 mmol) and dry DIPEA (2.3 mmol) were dissolved in $CH_2Cl_2$ (2 mL with **1**, **3**, and **4**; 4 mL with **2**) in a dry flask and added to the flask containing the resin. The mixture was stirred under a flow of Ar (1 h with **1**, **3**, and **4**; 6 h with **2**). The resin was filtered off under Ar, washed with dry $CH_2Cl_2$ (8 × 3 mL), dried overnight under vacuum, and stored at −22 °C under an Ar atmosphere. Average yields: 88% for **8**; 80% for **9** and **10**; 70% for **11**.

**Determination of the Loadings of the CDA-Resins.** The corresponding CDA-resin (30.0 mg) and toluene (75 μmol, 6.9 mg) were introduced into an NMR tube. $CDCl_3$ (250 μL) and dry benzylamine (225 μmol, 24.1 mg) were added. The mixture was shaken (2 h). After the addition of extra $CDCl_3$ (350 μL), the NMR spectrum was recorded, the signals were integrated, and the loading was calculated. Average loadings: 2.2 mmol/g for **8**; 1.7 mmol/g for **9** and **10**; 1.4 mmol/g for **11**.

**"In Tube" Derivatization of Primary Amines.** The CDA-resin (**8** or **10**) (20 mg, 44 μmol) and the amine (22 μmol) were added to the NMR tube together with dry $CDCl_3$ (150 μL). After soaking and shaking the mixture for 5−10 min, extra $CDCl_3$ (450 mL) was added. The NMR spectrum was recorded. When the method with barium(II) was used, $CD_3CN$ was the solvent and the mixture was shaken for 30 min. Extra $CD_3CN$ was added, and the first spectrum was recorded. $Ba(ClO_4)_2$ was added until saturation was achieved. Sonication may help the resin to float.

**"In Tube" Derivatization of Primary and Secondary Alcohols, Cyanohydrins, and Secondary Thiols.** The CDA-resin (**8**) (20 mg, 44 μmol) and the substrate (22 μmol) were added to an NMR tube together with dry $CDCl_3$ (100 μL). In a dry vial, DMAP (22 μmol) was dissolved in $CDCl_3$ (100 μL), and the solution was added to the NMR tube. After the mixture was shaken for 10 min (1 h in case of resin **11**; 15 min in case of cyanohydrins; 30 min in case of compound **33** due to low solubility), extra $CDCl_3$ (400 μL) was added. The NMR spectrum was recorded. In cases where scavenger resins were used, resins **42** and **43** (44 μmol of each) and extra $CDCl_3$ (200 μL) were added to the tube. After the mixture was shaken for 1 h, the new spectrum was recorded.

Alternative way of using the scavenger resins: the above protocol applies until the addition of the DMAP and the shaking of the mixture for 10 min. At this point, resins **42** and **43** (44 μmol of each) and extra $CDCl_3$ (200 μL) were added to the tube. After the mixture was shaken for 1 h, extra $CDCl_3$ (450 μL) was added and the NMR spectrum was recorded.

In the methods requiring just a single derivatization, the reactions were carried out in a way similar to the procedures described above. $CD_3CN$ and $CS_2/CD_2Cl_2$ (4:1) were used as solvents in the barium(II) and low temperature approaches, respectively (30 min reaction times in both cases).

**"In Tube" Derivatization of Amino Alcohols.** CDA-resin **8** (30 mg, 66 μmol) and the amino alcohol (22 μmol) were added to the NMR tube together with dry $CDCl_3$ (200 μL). A solution of DMAP (22 μmol) in $CDCl_3$ (100 μL) was then added. After the mixture was shaken for 20 min, extra $CDCl_3$ (300 μL) was added and the NMR spectrum was recorded.

**"In Tube" Derivatization of Diols and Triols.** In the case of diols, resin **8** (30 mg, 66 μmol) and the diol (22 μmol) were added to the NMR tube together with dry $CDCl_3$ (200 μL). A solution of DMAP (44 μmol) in $CDCl_3$ (100 μL) was also added. After the mixture was shaken for 90 min, extra $CDCl_3$ (300 μL) was then added and the NMR spectrum was recorded. In the case of triols, the procedure followed similar steps but the following changes were introduced: 16.5 μmol of triol, 66 μmol resin **8** (30 mg), 33 μmol of DMAP, 8 h.

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**Supporting Information Available:** Other CDA-resins studied; optimization of the synthesis of CDA-resins; Figures 1S and 2S; picture of mechanical mixing device; experimental section; spectroscopic data, including FT-IR data of CDA-resins; and $^1H$ and $^{13}C$ NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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