DOI: 10.1002/ejoc.200500780

Solvent-Free Carbon–Oxygen Bond Formation Catalysed by $CeCl_3 \cdot 7H_2O$/NaI: Tetrahydropyranylation of Hydroxy Groups

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Keywords: Alcohols / Cerium / Lewis acids / Chemoselectivity / Synthetic methods / Protecting groups

An efficient and highly chemoselective method fo the protection of free hydroxy compounds with 3,4-dihydro-2*H*-pyran is reported. Since the deprotection of THP-ethers occurs very readily at room temperature, the successful use of this type of protecting group depends only upon how readily it can be introduced. For this we have examined the tetrahydropyranylation of alcohols and phenols catalysed by the $CeCl_3 \cdot 7H_2O$/NaI system surface under solvent-free conditions. The reaction presents the advantage of being performable under extremely mild conditions by use of catalytic amounts of an interesting Lewis acidic system consisting of the $CeCl_3 \cdot 7H_2O$/NaI catalyst combination, which can be easily separated from the reaction mixture. The advantages of this procedure, which utilizes cheap and "friendly" reagents, over the previously reported ones are discussed.

Introduction

As part of our research program on the development of new and general strategies for the synthesis of biologically important natural and unnatural substances, we have been involved with chemoselective transformations of polyfunctional compounds with the aid of protecting groups.[1] The protection of alcohols and phenols plays a key role in the synthesis of polyfunctional organic molecules. Numerous naturally occurring and synthetically and biologically interesting compounds such as nucleosides, carbohydrates, carbocycles, steroids, and alkaloids include hydroxy functions as parts of their structures[2] and several reactions of these compounds need some protection of their hydroxy groups in order to increase yields and to reduce undesired side reactions. Although over 150 hydroxy-protecting groups have been reported, few have found wide applications.[3] Novel OH protections are thus required as molecular targets increase in complexity and new fields such as supported-oligosaccharide synthesis emerge.[4] Tetrahydropyranyl (THP) ethers are frequently employed as protecting groups for hydroxy functionalities in multistep synthesis, thanks both to their ease of preparation and stability under a wide variety of reaction conditions and their subsequent ease of removal.[5] Furthermore, tetrahydropyranyl ethers are synthetically useful as building blocks for the synthesis of biologically important substances[6] and can also be used in perfume formulations.[7]

Acid-catalysed addition of alcohols and phenols to 3,4-dihydro-2*H*-pyran (DHP, **2**) in an organic solvent at room temperature is a useful procedure in organic synthesis (Scheme 1). When Brønsted acids[8] are used, incompatibility with other functions in the molecules is observed, and in many instances the reaction does not go to completion despite the additional of a large excess of the enol ether **2**.[9] These drawbacks of Brønsted acid promoters represent a severe limitation from a practical point of view, and heterogeneous acidic catalysts have consequently been developed.[10] As a result of their superior activity, Lewis acids have been advantageously used in place of Brønsted acids in such tetrahydropyranylations of hydroxy-containing compounds.[11] However, when classical Lewis acids ($BF_3 \cdot Et_2O$, $SnCl_4$, $TiCl_4$, $ZnBr_2$, ...) are used, stoichiometric amounts – or often more – of these reagents are required in order to achieve synthetically useful results. Furthermore, these Lewis acid-mediated protections not only have to be carried out under strictly anhydrous conditions, but they also release large amounts of environmentally hazardous wastes. To improve the potential of these Lewis acid-promoted reactions further, the development of processes compatible with the use of reduced amounts of the activator is highly desirable.

In recent years much attention has been paid to the development of water-resistant and environmentally mild Lewis acids, such as triflates.[12] In particular, attention has mostly focused on rare earth triflate-catalysed organic chemistry transformations, due to their mildness and effi-

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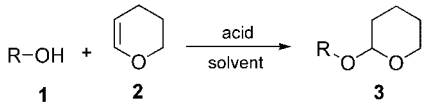


Scheme 1. A general method of tetrahydropyranylation of hydroxy compounds.

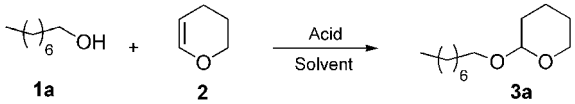
ciency.[13] All these salts are commercially available but rather expensive, and their use may not be economical, especially for large-scale synthetic operations. For this reason we considered using the cheap and readily available rare earth salt cerium trichloride heptahydrate, the activity of which increases dramatically in the presence of an iodide source.[14] Recent studies by us and by others have resulted in the development of various chemical transformations promoted by the $CeCl_3 \cdot 7H_2O$/NaI Lewis acid combination in organic synthesis.[15] After reactions and methodologies involving the $CeCl_3 \cdot 7H_2O$/NaI system to facilitate the cleavage of carbon–oxygen and silicon–oxygen bonds under neutral conditions, we also developed new methods for carbon–carbon[16] and nitrogen–carbon[17] bond-forming reactions promoted by the $CeCl_3 \cdot 7H_2O$/NaI system. On the other hand, only two procedures in which the $CeCl_3 \cdot 7H_2O$/NaI system promotes formation of a carbon–oxygen bond have been reported, to the best of our knowledge.[18] Thus, as a part of our ongoing research program to develop new methodologies involving cerium(III) salts, we investigated one of the most important carbon–oxygen bond-forming reactions in organic chemistry: the protection of hydroxy groups. In this paper we wish to report an efficient and versatile procedure for the conversion of alcohols and phenols into the corresponding THP ethers in the presence of catalytic amounts of the $CeCl_3 \cdot 7H_2O$/NaI system under solvent-free conditions.

Results and Discussion

The procedure based on the Lewis acid catalytic activity of the $CeCl_3 \cdot 7H_2O$/NaI system represents an environmentally benign alternative to current chemical processes that use water-intolerant Lewis acids. The key to waste minimization in fine chemical synthesis lies in the widespread substitution of classical organic reactions employing stoichiometric amounts of reagents with cleaner and catalytic alternatives.[19] Furthermore, although performing organic reactions in an aqueous medium is a current challenge set to attract considerable attention in the coming years,[20] from the point of view of green chemistry it would be even more convenient to avoid the use of any solvent at all.[21] Given that the solvent-free approach finds useful applications when one reagent is a liquid and available in large quantities,[22] we believe that our $CeCl_3 \cdot 7H_2O$/NaI-catalysed tetrahydropyranylation of hydroxy compounds under solvent-free conditions could be particularly appealing.

Our initial efforts focused on achieving the optimum conditions for tetrahydropyranylation of 1-octanol (**1a**) as a model hydroxy compound in the presence of cerium trichloride as Lewis acid, and our results are summarized in Table 1. Comparing the results obtained, we noted that the reaction is sluggish when carried out in acetonitrile and in the presence of $CeCl_3 \cdot 7H_2O$ alone, even in stoichiometric amounts (Table 1, Entry 1). As is well known,[14] the addition of NaI increases the efficiency, and the yield is dramatically improved when the reaction mixture is stirred at a temperature of 50 °C (Table 1, Entries 2 and 3). An equimolar ratio of $CeCl_3 \cdot 7H_2O$ and NaI is found to give the best results, whereas use of an excess of sodium iodide salt results in lower yields (Table 1, Entry 4). Further experiments also showed that the amount of $CeCl_3 \cdot 7H_2O$/NaI can be reduced without an appreciable loss of activity, the optimum conditions being 2–5 mol-% of $CeCl_3 \cdot 7H_2O$/NaI. Finally, the reaction can be carried out in shorter times without solvent (Table 1, Entries 7, 8, and 9). This allowed us to adopt a very simple workup procedure for the recovery of the tetrahydropyranyl ether, with the reaction mixture being treated with an organic solvent (Et_2O) capable of dissolving the organic material but not the catalyst, which could then easily be removed by filtration. Because of the broad range of applications of the $CeCl_3 \cdot 7H_2O$/NaI system as catalyst in many organic transformations and the

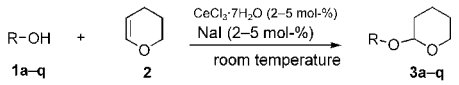
Table 1. Reaction between 1-octanol (**1a**) and 3,4-dihydro-2*H*-pyran (**2**) under different experimental conditions.[a]

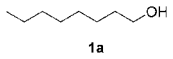
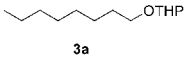
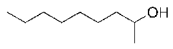
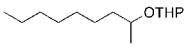
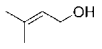
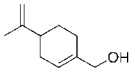
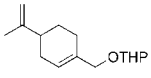
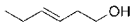
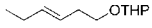
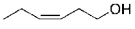
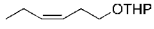
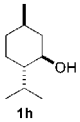
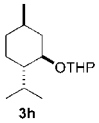


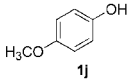
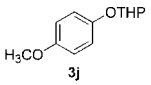
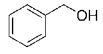
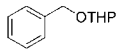
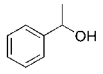
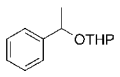
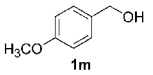
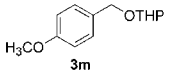
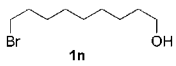
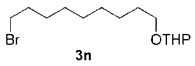
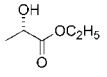
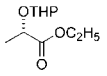
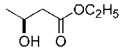
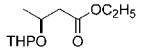
Entry	Catalyst	Solvent	Time [h]	Temp. [°C]	Yields [%]
1	$CeCl_3 \cdot 7H_2O$ (1 equiv.)	CH_3CN	96	25	35
2	$CeCl_3 \cdot 7H_2O$ (1 equiv.)/ NaI (1 equiv.)	CH_3CN	48	25	48
3	$CeCl_3 \cdot 7H_2O$ (1 equiv.)/ NaI (1 equiv.)	CH_3CN	20	50	95
4	$CeCl_3 \cdot 7H_2O$ (1 equiv.)/ NaI (1.8 equiv.)	CH_3CN	25	50	82
5	$CeCl_3 \cdot 7H_2O$ (1.8 equiv.)/ NaI (1.8 equiv.)/SiO_2	no solvent	20	25	65
6	$CeCl_3 \cdot 7H_2O$ (0.1 equiv.)/ NaI (0.1 equiv.)	CH_3CN	15	50	90
7	$CeCl_3 \cdot 7H_2O$ (0.1 equiv.)/ NaI (0.1 equiv.)	no solvent	6.5	25	98
8	$CeCl_3 \cdot 7H_2O$ (0.05 equiv.)/ NaI (0.05 equiv.)	no solvent	6	25	97
9	$CeCl_3 \cdot 7H_2O$ (0.02 equiv.)/ NaI (0.02 equiv.)	no solvent	6	25	98

[a] All reactions were carried out by stirring mixtures of **1a** (10 mmol), DHP (13 mmol) and catalyst for the selected reaction times. Yields of products were estimated by GC/MS.

Table 2. Tetrahydropyranylation of hydroxy compunds **1a–q** with DHP (**2**) in the presence of 2–5 mol-% of $CeCl_3 \cdot 7H_2O$/NaI system under solvent-free conditions.



Entry	Substrate	Time/h	Product[a]	Yield (%)[b]
1	 **1a**	6	 **3a**	98
2	 **1b**	8	 **3b**	94
3	 **1c**	8	 **3c**	92
4	 **1d**	48	 **3d**	> 99
5	 **1e**	8	 **3e**	92
6	 **1f**	6	 **3f**	96
7	 **1g**	26	 **3g**	73
8	 **1h**	24	 **3h**	76[c]

Entry	Substrate	Time/h	Product[a]	Yield (%)[b]
9	 **1i**	26	 **3i**	> 99
10	 **1j**	29	 **3j**	> 99
11	 **1k**	25	 **3k**	91
12	 **1l**	48	 **3l**	83
13	 **1m**	23	 **3m**	87
14	 **1n**	24	 **3n**	> 99
15	 **1o**	10	 **3o**	72[c]
16	 **1p**	24	 **3p**	75[c]
17	 **1q**	24	 **3q**	0[d]

[a] All products were identified by their IR, NMR, and GC/MS spectra. [b] All yields refer to pure isolated compounds. [c] As a mixture of two epimers in about 1:1 ratio in all cases. [d] Only starting material was recovered.

high efficiencies obtained, several efforts have been devoted to the recovery and recycling of the catalyst.[16d,16e] We thus repeated our procedure for the tetrahydropyranylation of **1a** with DHP (**2**) five times without noting any appreciable decrease in activity.

Application of our method to the preparation of THP-ethers from different alcohols and phenols was investigated. The scope and efficiency of the procedure are summarized in Table 2, and in all cases the yields of these ethers are satisfactory and comparable to those observed with different heterogeneous Lewis acid catalysts. However, our $CeCl_3 \cdot 7H_2O$/NaI system has the advantages of being effective at room temperature and avoiding the use of solvents.

It can thus be observed that primary and secondary alcohols are smoothly transformed into the corresponding THP-ethers and that the reaction proceeds with excellent yields under solvent-free conditions, even in cases involving sterically hindered alcohols (Table 2, Entries 7 and 8). Even allylic and benzylic alcohols give the corresponding tetrahydropyranyl ether adducts in excellent yields (Table 2, Entries 3, 4, 11, 12, and 13). Interestingly, in the case of racemic perillyl alcohol (**1d**) the exocyclic double bond is not attacked and the *exo-endo* isomerization phenomenon does not occur (Table 2, Entry 4). Analogously, no (*Z*)/(*E*) isomerization of the double bond in **1f** has been observed (Table 2, Entry 6).[23] Furthermore, alcohols bearing the hydroxy group bonded to a carbon stereogenic centre (Table 2, Entries 8, 15, and 16) can be protected, giving adducts with complete retention of configuration.[24] Particularly interestingly, the $CeCl_3 \cdot 7H_2O$/NaI system does not cause dehydration[25] during the conversion of β-hydroxy carbonyl compound **1p** into the corresponding THP-ether **3p** under our conditions. In these hydroxy compound substrates (**1h**, **1o**, and **1p**), which include a stereogenic centre, the tetrahydropyranylation generates adducts with a new stereogenic centre, however low diastereoselectivity is ob-

served (Table 2, Entries 8, 15, and 16), and the corresponding THP-ethers are isolated as diastereomeric mixtures in about 1:1 ratio. We have also observed that our tetrahydropyranylation procedure is compatible with the presence of several functionalities such as ester (**1o** and **1p**) and bromo (**1n**) groups. In the latter case no halogen exchange reaction[26] occurred under these conditions. Unfortunately, the reaction with tertiary alcohols shows the typical issue associated with highly hindered substrates,[27] and only starting material was recovered without any trace of dehydration product (Table 2, Entry 17).

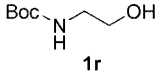
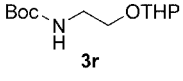
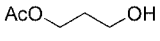
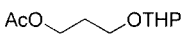
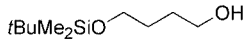
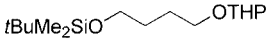
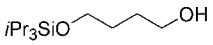
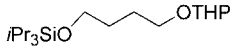
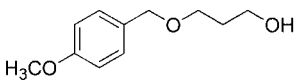
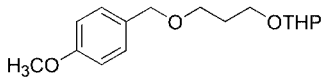
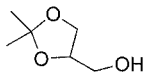
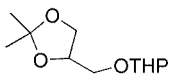
Our $CeCl_3 \cdot 7H_2O$/NaI-catalysed tetrahydropyranylation was successfully applied to a variety of alcohol and phenol derivatives (Table 2, Entries 11 and 12), providing fairly good yields of the corresponding THP-ethers. We also investigated the role of electron density on the phenol moiety in the protection reaction: no apparent difference in reactivity was detected in the presence of electron-donating substituents on the aromatic moiety, whereas the presence of an electron-withdrawing group on the aromatic ring retarded the protection of the hydroxy group, while no reaction occurred between *p*-nitrophenol and 3,4-dihydro-2*H*-pyran.[28]

Given these results, and to evaluate the efficiency of the tetrahydropyranylation procedure further, a series of alcohols was protected in the presence of other protective groups. The results are summarized in Table 3. It is important to note not only that a tetrahydropyranyl ether is obtained in the presence of *N*-*tert*-butoxycarbonyl and acetate groups (Table 3, Entries 1 and 2), but also that hydroxy groups can be selectively protected in the presence of *p*-methoxybenzyl[29] and trialkylsilyl ethers,[30] which have been recently reported to be cleaved by stoichiometric amounts of the $CeCl_3 \cdot 7H_2O$/NaI system. Finally, our procedure is mild enough to be useful for substrates containing acid-sensitive protecting groups such as 1,3-dioxolanes[31] (Table 3, Entry 6).

These results have established that the ability of the $CeCl_3 \cdot 7H_2O$/NaI system to mediate organic reactions either catalytically or stoichiometrically constitutes one of the most powerful strategies to achieve both selectivity and efficiency in synthetic chemistry. Unfortunately, the mechanism of this effective catalyst for tetrahydropyranylation of alcohols and phenols is not clear. Undoubtedly the presence of NaI is essential too for this reaction, and no THP-ether formation took place in absence of iodide. We believe that the acceleration effect caused by addition of inorganic iodide cannot be rationalized simply in terms of a halogen exchange reaction because we have observed that CeI_3 alone shows activity significantly lower than that of the $CeCl_3 \cdot 7H_2O$/NaI system.[32] The mechanistic role of NaI thus appears to be intriguing and complex, and the exact nature of the reactive species obtained on treatment of the substrates with the $CeCl_3 \cdot 7H_2O$/NaI system is not known.

Even though it is premature to speculate on the exact mechanism, we have obtained some evidence that our car-

Table 3. Compatibility of the tetrahydropyranylation with other protecting groups of amines and alcohols.

Entry	Substrate	Time [h]	Product[a]	Yield (%)[b]
1	 **1r**	19	 **3r**	76
2	 **1s**	10	 **3s**	83
3	 **1t**	48	 **3t**	67
4	 **1u**	46	 **3u**	85
5	 **1v**	25	 **3v**	93
6	 **1z**	7	 **3z**	> 99

[a] All products were identified by their IR, NMR, and GC/MS spectra. [b] Isolated yields.

bon–oxygen bond formation is promoted by the solid $CeCl_3 \cdot 7H_2O$/NaI system. Having established, in fact, what appeared to be the optimal conditions, we switched our attention to the water of crystallization in the cerium(III) salt. The water (from $CeCl_3 \cdot 7H_2O$) is an important component of the reaction system, and when anhydrous cerium(III) chloride salt[33] has been employed the THP-ether products are not observed. It is also worth noting that, in contrast to the results proposed by Patel et al.,[34] the tetrahydropyranylation is not catalysed by water alone: no trace of THP-ether has been observed on simple addition of water to the mixture of hydroxy compound **1** and dihydropyran **2**. These experimental findings indicate that our $CeCl_3 \cdot 7H_2O$/NaI system functions as a water-tolerant oxophilic Lewis acid catalyst under solvent-free conditions. However, according to a paper published by Spencer,[35] investigations aimed at confirming the effective catalyst do not preclude the existence of a Brønsted acid-catalysed pathway in our procedure. In fact, the presence of the weak base 2,6-di-*tert*-butyl-4-methylpyridine, which only binds to protons and is unable to coordinate to metal cerium, due to the bulky *tert*-butyl groups,[36] significantly retards the tetrahydropyranylation under our conditions. THP-ethers are thus produced catalytically in our procedure, but the real active species have not been recognized, and the characterization of all these species is being studied in our laboratories.

Conclusions

In conclusion, in the course of our studies in developing new methods for transformations of organic functional groups containing oxygen, we have established an efficient and inexpensive method for introducing the tetrahydropyranyl protecting group by use of the $CeCl_3 \cdot 7H_2O$/NaI system as a water-tolerant and heterogeneous catalyst. While the treatment of tetrahydropyranyl ethers with $CeCl_3 \cdot 7H_2O$ in methanol provides a method for detetrahydropyranylation,[37] our $CeCl_3 \cdot 7H_2O$/NaI combination represents an useful system for catalyzing the preparation of THP-ethers under solvent-free conditions. In addition, the simplicity of our approach, the low cost of reagents and the fact that no precautions to exclude moisture or oxygen from the reaction system need to be taken suggest to us that the $CeCl_3 \cdot 7H_2O$/NaI combination could find applicability in further organic transformations. In fact, after wide scientific work regarding the use of the $CeCl_3 \cdot 7H_2O$/NaI system as a promoter in the cleavage of carbon–oxygen bonds, to which different groups including ourselves have made substantial contributions, we are now describing in this paper a new method for carbon–oxygen bond formation catalysed by the same $CeCl_3 \cdot 7H_2O$/NaI system. As in Rosini's procedure,[18a] the catalyst functions as a promoter of formation of the carbon–oxygen bond when the substrates possess a carbon–carbon double bond.

The applicability of the $CeCl_3 \cdot 7H_2O$/NaI to other synthetic problems is currently under study and will constitute the subject of future reports.

Experimental Section[38]

General Remarks: ^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz on a Varian Gemini 200 spectrometer and are reported as follows: chemical shift, δ (ppm) [multiplicity, number of protons, and coupling constant J (Hz)]. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as the internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$ at 50 MHz on Varian Gemini 200 spectrometer, with use of the central resonance of $CDCl_3$ (δ_C = 77.0 ppm) as the internal reference. Infrared spectra were recorded on a Perkin–Elmer FTIR Paragon 500 spectrometer as thin films on NaCl plates. Only the characteristic peaks are quoted. Mass spectra were recorded on a Hewlett–Packard 5988 gas chromatograph with a mass-selective detector (MSD HP 5790 MS), utilizing electron ionization (EI) at an ionizing energy of 70 eV. A fused silica column (30 m × 0.25 mm HP-5; cross-linked 5% Ph-Me siloxane, 0.10 μm film thickness) was used with a helium carrier flow of 30 mL min^{-1}. The temperature of the column was varied, after a delay of 3 min from the injection, from 65 °C to 300 °C with a slope of 15 °C min^{-1}.

Most solvents and reagents were used without purification unless mentioned otherwise. Solvents (EtOAc and hexanes) for flash chromatography were distilled. Cerium(III) chloride heptahydrate, sodium iodide and 3,4-dihydro-2*H*-pyran are commercially available and were used without further purification. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a Baker silica gel (230–400 mesh) column with 30% ethyl acetate in hexane as the eluent. Analytical thin layer chromatography was performed with precoated glass-backed plates (Merck Kieselgel 60 F254) and visualized with UV light (254 nm) and/or by dipping the plates into Von's reagent (1.0 g of ceric sulfate and 24.0 g of ammonium molybdate in 31 mL of sulfuric acid and 470 mL of water).

The hydroxy compounds used as starting materials were obtained from commercial sources or (**1t** and **1u**) were synthesized by reported methods in the literature.[39] All the obtained tetrahydropyranyl ethers were characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry, while the compounds **3a**,[10d] **3b**,[7] **3c**,[40] **3e**,[7] **3f**,[7] **3g**,[10d] **3h**,[12] **3i**,[10d] **3j**,[10b], **3k**,[10d] **3l**,[10d] **3m**,[41] **3n**,[42] **3o**,[43] **3p**,[43] **3q**,[44] **3r**,[45] **3s**,[11d] **3v**,[28] and **3z**[12] are all known, and their structures are consistent with their published physical data.

General Procedure for the Tetrahydropyranylation (compounds 3a–z): The hydroxy compound (**1a**–**z**, 1.0 mmol), 3,4-dihydro-2*H*-pyran (1.1 mmol), $CeCl_3 \cdot 7H_2O$ (2–5 mol-%) and NaI (2–5 mol-%) were placed successively in a flask. After having been stirred at room temperature for the time needed, the reaction mixture was treated whilst stirring with Et_2O (20 mL), and the catalyst mixture was removed by filtration. The filtered extracts were concentrated under reduced pressure, and the crude product was then purified by silica gel chromatography (hexanes/EtOAc).

2-[(4-Isopropenylcyclohex-1-enyl)methoxy]tetrahydro-2*H*-pyran (3d): ^{1}H NMR: δ = 1.40–2.30 (m, 16 H, CH_2 and CH_3), 3.45–3.55 (m, 2 H, CH_2O), 3.80–3.95 (m, 2 H, CH_2), 4.55–4.65 (m, 1 H, CH), 4.73 (s, 2 H, CH_2), 5.74 (s, 1 H, =CH) ppm. ^{13}C NMR: δ = 19.7, 20.9, 25.7, 26.3, 26.9, 28.0, 30.2, 42.4, 61.8, 71.0, 96.5, 108.1, 126.4, 131.8, 149.9 ppm. IR (neat): $\tilde{\nu}$ = 3086, 1661, 1355 cm^{-1}. MS: m/z = 236 [M]$^+$, 182, 155, 115, 101, 85 (100), 69, 57, 45, 41. $C_{15}H_{24}O_2$ (236.35): calcd. C 76.23, H 10.24; found C 76.19, H 10.21.

***tert*-Butyldimethyl[4-(tetrahydro-2*H*-pyran-2-yloxy)butoxy]silane (3t):** ^{1}H NMR: δ = 0.76 (s, 6 H, 2 × CH_3), 0.93 (s, 9 H, 3 × CH_3), 1.45–1.90 (m, 10 H, 5 × CH_2), 3.30–3.45 (m, 1 H, CH_2), 3.45–3.55 (m, 1 H, CH_2), 3.60–3.70 (m, 2 H, CH_2), 3.70–3.80 (m, 1 H, CH_2),

3.85–3.95 (m, 1 H, CH_2), 4.50–4.60 (m, 1 H, CH) ppm. ^{13}C NMR: δ = –5.2, 18.3, 19.6, 25.5, 25.9, 26.1, 29.6, 30.7, 62.2, 63.0, 67.4, 98.7 ppm. IR (neat): $\tilde{\nu}$ = 2942, 2878, 1431, 1280, 1050 cm^{-1}. MS: *m*/*z* = 330 $[M]^+$, 315, 273, 173, 143, 101, 85 (100), 69, 57, 43. $C_{15}H_{32}O_3Si$ (288.50): calcd. C 62.45, H 11.18; found C 62.39, H 11.10.

Triisopropyl[4-(tetrahydro-2*H*-pyran-2-yloxy)butoxy]silane (3u): ^1H NMR: δ = 0.95–1.15 (m, 21 H, CH and CH_3), 1.45–1.85 (m, 10 H, 5 × CH_2), 3.35–3.45 (m, 1 H, CH_2), 3.45–3.55 (m, 1 H, CH_2), 3.65–3.80 (m, 3 H, CH and CH_2), 3.82–3.90 (m, 1 H, CH_2), 4.56–4.60 (m, 1 H, CH) ppm. ^{13}C NMR: δ = 12.0, 18.0, 20.0, 25.5, 26.0, 29.5, 31.0, 62.0, 63.5, 67.5, 99.3 ppm. IR (neat): $\tilde{\nu}$ = 2945, 2893, 1420, 1248, 1104 cm^{-1}. MS: *m*/*z* 330 $[M]^+$, 287, 173, 157, 101, 85, 69, 43 (100). $C_{18}H_{38}O_3Si$ (330.58): calcd. C 65.40, H 11.59; found C 65.36, H 11.57.

Acknowledgments

Work was carried out in the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni" and the National Project "Studio degli Aspetti Teorici ed Applicativi degli Aggregati di Molecole Target su Siti Catalitici Stereoselettivi" supported by the MIUR, Rome, by the University of Bologna and by the University of Camerino. M. P. gratefully acknowledges the Pfizer Ascoli Piceno Plant for a postgraduate fellowship.

[1] K. Jarowicki, P. J. Kocienski, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2495–2527.
[2] a) A. Studer, S. Hadida, R. Ferritto, S.-Y. Kim, P. Jegar, P. Wipf, D. P. Curran, *Science* **1997**, *275*, 823–826; b) B. M. Trost, D. L. Van Vrauken, *Chem. Rev.* **1996**, *96*, 395–422.
[3] P. J. Kocienski, *Protecting Groups*, 4th ed., Thieme, Stuttgart, **2005**.
[4] R. Palmacci, M. C. Hewitt, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2001**, *40*, 4433–4437.
[5] C. B. Reese, in: *Protective Groups in Organic Chemistry* (Ed.: J. F. W. McOmie), Plenum Press, London, **1973**, chapter 3.
[6] a) V. Debal, T. Cuvigny, M. Larcheveque, *Synthesis* **1976**, 391–393; b) E. J. Corey, R. H. Wollenberg, *J. Org. Chem.* **1975**, *40*, 2265–2666.
[7] C. Anselmi, M. Centini, M. Mariani, A. Sega, P. Pelosi, *J. Agric. Food Chem.* **1992**, *40*, 853–856.
[8] a) D. Tanner, P. Somfai, *Tetrahedron* **1987**, *43*, 4395–4406; b) G. Olah, A. Hasain, B. P. Singh, *Synthesis* **1985**, 703–704; c) Y. Morizawa, I. Mori, T. Hiyama, H. Nozaki, *Synthesis* **1981**, 899–901; d) K. F. Bernardy, M. B. Floyd, J. F. Poletto, M. J. Weiss, *J. Org. Chem.* **1979**, *44*, 1438–1447; e) E. J. Corey, H. Niwa, J. Knolle, *J. Am. Chem. Soc.* **1978**, *100*, 1942–1943; f) M. Miyashita, A. Yoshikoshi, P. A. Grieco, *J. Org. Chem.* **1977**, *42*, 3772–3774.
[9] As much as 20% of the starting hydroxy compound may be present at equilibrium, which, once reached, can be shifted towards the THP product by adding excess finely powdered potassium carbonate, and stirring the reaction mixture at room temperature. As the acid concentration gradually diminishes, the reaction goes to completion.
[10] a) A. Hegedüs, I. Vígh, Z. Hell, *Synth. Commun.* **2004**, *34*, 4145–4152; b) R. Ballini, F. Bigi, S. Carloni, R. Maggi, G. Sartori, *Tetrahedron Lett.* **1997**, *38*, 4169–4172; c) P. Kumar, C. H. Dinesh, R. S. Reddy, B. Pandey, *Synthesis* **1993**, 1069–1070; d) S. Hoyer, P. Laszlo, M. Orlovic, E. Polla, *Synthesis* **1986**, 655–656.
[11] a) M. M. Heravi, F. K. Behbahani, H. A. Oskooie, R. H. Shoar, *Tetrahedron Lett.* **2005**, *46*, 2543–2545; b) Y. J. Kim, R. S. Varma, *Tetrahedron Lett.* **2005**, *46*, 1467–1469; c) A. T. Khan, L. H. Choudhury, S. Ghosh, *Tetrahedron Lett.* **2004**, *45*, 7891–7894; d) J. S. Yadav, B. V. Subba Reddy, D. Guaneshwar, *New J. Chem.* **2003**, *27*, 202–204; e) V. V. Namboodiri, R. S. Verma, *Chem. Commun.* **2002**, 342–343; f) N. Deka, J. C. Sarma, *Synth. Commun.* **2000**, *30*, 4435–4441; g) M. A. Reddy, L. R. Reddy, N. Bhanumathi, K. R. Rao, *Synth. Commun.* **2000**, *30*, 4323–4328; h) N. Rezai, F. A. Meybodi, P. Salehi, *Synth. Commun.* **2000**, *30*, 1799–1805; i) G. Maity, S. C. Roy, *Synth. Commun.* **1993**, *23*, 1667–1671.
[12] J. R. Stephens, P. L. Butler, C. H. Claw, M. C. Oswald, R. C. Smith, R. S. Mohan, *Eur. J. Org. Chem.* **2003**, 3827–3831.
[13] Kobayashi, S., in: *Lanthanides: Chemistry and Use in Organic Synthesis* (Ed.: S. Kobayashi), Springer: Berlin, **1999**; p. 63–118.
[14] G. Bartoli, E. Marcantoni, L. Sambri, *Synlett* **2003**, 2101–2116, and references therein.
[15] a) W.-D. Z. Li, Y. Peng, *Org. Lett.* **2005**, *7*, 3069–3072, and references cited therein; b) L. M. Urbaneja, N. Krause, *Eur. J. Org. Chem.* **2004**, 4467–4470.
[16] a) G. Bartoli, M. Bosco, S. Giuli, A. Giuliani, L. Lucarelli, E. Marcantoni, L. Sambri, E. Torregiani, *J. Org. Chem.* **2005**, *70*, 1941–1944; b) G. Bartoli, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri, *Synthesis* **2004**, 895–900; c) G. Bartoli, M. Bosco, A. Giuliani, E. Marcantoni, A. Palmieri, M. Petrini, L. Sambri, *J. Org. Chem.* **2004**, *69*, 1290–1297; d) G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri, E. Torregiani, *J. Org. Chem.* **2003**, *68*, 4594–4597; e) G. Bartoli, M. Bosco, M. C. Bellucci, E. Marcantoni, L. Sambri, E. Torregiani, *Eur. J. Org. Chem.* **1999**, 617–620.
[17] a) G. Bartoli, M. Bartolacci, A. Giuliani, E. Marcantoni, M. Massaccesi, E. Torregiani, *J. Org. Chem.* **2005**, *70*, 169–174; b) G. Bartoli, M. Bosco, E. Marcantoni, M. Petrini, L. Sambri, E. Torregiani, *J. Org. Chem.* **2001**, *66*, 9052–9055.
[18] a) E. Marotta, E. Foresti, T. Marcelli, F. Peri, P. Righi, N. Scardovi, G. Rosini, *Org. Lett.* **2002**, *4*, 4451–4453; b) J. S. Yadav, B. V. S. Reddy, K. Bhaskar Reddy, M. Satyanarayana, *Tetrahedron Lett.* **2002**, *43*, 7009–7012.
[19] P. T. Anastas, M. M. Kirchoff, T. C. Williamson, *Appl. Catal. A* **2001**, *221*, 3–19.
[20] T. Okuhara, *Chem. Rev.* **2002**, *102*, 3641–3666.
[21] P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **1998**.
[22] J. O. Metzger, *Angew. Chem. Int. Ed.* **1998**, *37*, 2975–2978.
[23] J.-M. Conia, P. Amice, *Bull. Soc. Chim. Fr.* **1970**, 2972–2980.
[24] $[\alpha]_D$ values were compared with those of authentic samples.
[25] G. Bartoli, M. C. Bellucci, M. Petrini, E. Marcantoni, L. Sambri, E. Torregiani, *Org. Lett.* **2000**, *2*, 1791–1793.
[26] A. Motoji, H. Takaoki, K. Takeo, *Chem. Lett.* **1994**, 1789–1792.
[27] N. Hamada, T. Sato, *Synlett* **2004**, 1802–1804.
[28] A. Semwal, S. K. Nayak, *Synthesis* **2005**, 71–74.
[29] G. Bartoli, M. C. Bellucci, M. Bosco, A. Cappa, E. Marcantoni, L. Sambri, E. Torregiani, *J. Org. Chem.* **1999**, *64*, 5696–5699.
[30] G. Bartoli, M. Bosco, E. Marcantoni, L. Sambri, E. Torregiani, *Synlett* **1998**, 209–211.
[31] G. Bartoli, M. Bosco, E. Marcantoni, F. Nobili, L. Sambri, *J. Org. Chem.* **1997**, *62*, 4183–4184.
[32] a) S. Fukuzawa, T. Tsuruta, T. Fujinami, S. Sakai, *J. Chem. Soc., Perkin Trans. 1* **1987**, 1473–1477; b) S. Fukuzawa, T. Fujinami, S. Sakai, *J. Chem. Soc., Chem. Commun.* **1985**, 777–778.
[33] T. Imamoto, N. Takeda, *Org. Synth.* **1998**, *76*, 228–238.
[34] V. Kavala, A. Kumar Samal, B. K. Patel, *Arkivoc* **2005**, 20–29.
[35] T. C. Wabnitz, J.-Q. Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484–493.
[36] For the use of 2,6-di-*tert*-butyl-4-methylpyridine, see: a) A. G. M. Barrett, D. C. Braddock, J. P. Henshke, E. R. Walker, *J. Chem. Soc., Perkin Trans. 1* **1999**, 873–878; b) T. K. Hollis, B. Bosnich, *J. Am. Chem. Soc.* **1995**, *117*, 4570–4581.
[37] G. Sudhakar Reddy, P. Neelakautan, D. S. Iyengar, *Synth. Commun.* **2000**, *30*, 4107–4111.

[38] The Experimental Section of this work is part of the degree thesis of Andrea Bellotti at the University of Bologna Faculty of Industrial Chemistry.
[39] K. C. Nicolaou, C. V. C. Prasad, C.-K. Hwang, M. E. Duggan, C. A. Veale, *J. Am. Chem. Soc.* **1989**, *111*, 5321–5330.
[40] S. A. Gajare, D. P. Sabde, M. S. Shingare, R. D. Wakharkar, *Synth. Commun.* **2002**, *32*, 1549–1555.
[41] R. R. Fraser, P. Hanbury, C. Royes-Zamora, *Can. J. Chem.* **1967**, *45*, 2481–2487.
[42] D. J. Hodgson, K. Y. Y. Lao, B. Dawson, P. H. Buist, *Helv. Chim. Acta* **2003**, *86*, 3688–3697.
[43] M. Hamdani, B. De Jeso, H. Delenze, B. Maillard, *Tetrahedron: Asymmetry* **1991**, *2*, 867–870.
[44] B. Karimi, J. Maleki, *Tetrahedron Lett.* **2002**, *43*, 5353–5355.
[45] B. R. Holloway, R. Howe, D. J. Lecount, B. S. Rao, Patent number EP0565317, 1993; *Chem. Abstr.* **1993**, *120*, 106544.
Received: October 7, 2005
Published Online: January 3, 2006

