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Enantioselective Michael Additions of Grignard Reagents to Cinnamamides deriving from N-Fluoroalkyl (R)-(-)-2-Aminobutan-1-ol. Determination of Diastereomeric Excess by means of ^{19}F NMR

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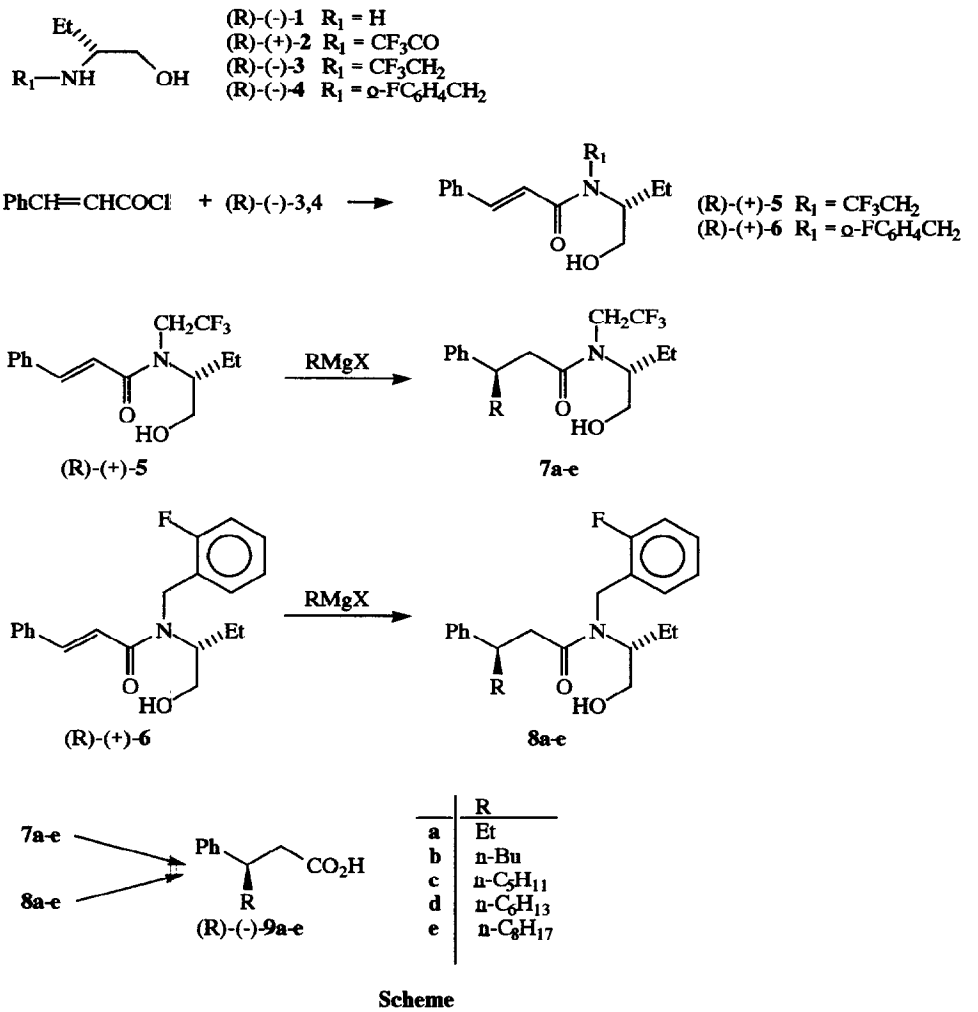
Abstract : N-Alkylation of (R)-(-)-2-aminobutan-1-ol **1** (a readily available reagent) with ortho-fluorobenzyl chloride, followed by reaction with cinnamoyl chloride, afforded the cinnamamide (R)-(+)-**6**. Michael addition of n-alkyl magnesium halides to the latter gave the corresponding adducts (R,R)-**8a-e** whose diastereomeric excesses were higher than 92% as evidenced by ^{19}F NMR. Acidic hydrolysis of these adducts yielded the corresponding β-phenylalkanoic acids (R)-(-)-**9a-e**.

In a recent paper, [1] we described the asymmetric Michael addition of organomagnesium reagents to the α, β-ethylenic amides obtained by reaction of cinnamoyl chloride with various N-alkyl derivatives of (R)-(-)-2-aminobutan-1-ol (R)-(-)-**1**. Acidic hydrolysis of the resulting Michael adducts yielded optically active β-phenylalkanoic acids of type **9** (see scheme), and whose enantiomeric excesses (ee, %) most generally were in the range 72-100%. In each case, the ee was determined as the ratio of the specific rotation we observed to that reported for the optically pure compound. When the optically active acid of type **9** was a new compound, we had no simple method in hand for determining its enantiomeric excess. In order to overcome this problem, we decided to synthesize N-alkyl N-cinnamoyl derivatives of (R)-(-)-**1**, in which the N-alkyl group contained fluorine. It was expected that the diastereomeric excesses (de, %) of the Michael adducts deriving from these cinnamamides could be determined by means of ^{19}F NMR. Indeed, ^{19}F NMR spectrometry has attracted much interest as an analytical tool in asymmetric synthesis in the past few years. For instance, this technique has been used for the determination of the ee's of chiral alcohols by examination of their esters deriving from α-methoxy α-trifluoromethyl phenylacetic acid (Mosher acid).[2-4] The ee of chiral α-fluoroacids was similarly determined by examination of their amides deriving from optically active α-methyl benzylamine.[5] Thus, in the above cases, determination of the ee of the end product implied its derivatization into a diastereomeric mixture, which is obviously a further chemical step. Whereas in our case, the ee's of the end products **9** could be assumed to be equal to the de of the immediately preceding diastereomeric intermediates.

Treatment of the aminoalcohol (R)-(-)-**1**[6,7] with excess trifluoroacetic anhydride in ether and in the presence of anhydrous sodium carbonate, for 1 hr at -10°C and 2 hrs at 20°C, afforded the crystalline trifluoroacetamide (R)-(+)-**2**.[6] Reduction of the latter with excess lithium tetrahydroaluminate in refluxing ether for 10 hrs gave the liquid N-(2,2,2-trifluoroethyl) base (R)-(-)-**3**.[6] On the other hand, treatment of ortho-fluorobenzyl chloride with an approximately fourfold molar amount of the aminoalcohol (R)-(-)-**1** at 90°C for 2 hrs yielded the crystalline N-alkyl base (R)-(-)-**4**.[6] The cinnamamides (R)-(+)-**5**[6] and (R)-(+)-**6**[6] were next prepared in high yields by N-acylation of (R)-(-)-**3** and (R)-(-)-**4**, respectively, by means of cinnamoyl chloride in a biphasic mixture of methylene dichloride and aqueous sodium carbonate solution for 3 hrs at room temperature.



Scheme

The Michael adducts **7a-e** and **8a-e** were obtained by reaction of the cinnnamamides (R)-(+)-**5** and (R)-(+)-**6**, respectively, with a sixfold molar excess of the corresponding n-alkylmagnesium reagent in ether at 0°C for 4 hrs (see Scheme). In some cases, the amount of the Grignard reagent used was reduced to a threefold molar excess without any decrease in the yield of the resulting Michael adduct. The adducts **7**, **8a-e** were isolated in yields ranging from 50 to 79% after purification by column chromatography over silica gel, using cyclohexane/ether (8:2) or cyclohexane/ethyl acetate (8:2) as an eluent (see Table 1).

The levorotary β-phenylalkanoic acids (-)-**9a-e** were next obtained by acidic hydrolysis (6N H_2SO_4/acetic acid, reflux, 6 hrs)[1] of the corresponding amides **7a-e** and **8a-e**. Since all the Michael additions proceeded with the same mechanism and since the known acids (-)-**9a,b** have the absolute (R) configuration,[1,8] it can be assumed that the other three acids **9c-e** also have the (R) configuration.

R	Michael adducts 7, 8a-e	Yield (%) a)	$[\alpha]_D$ b)	de (%) c)	Resulting acids 9a-e	Yield (%) d)	$[\alpha]_D$ obs. e)	Lit. $[\alpha]_D$ (Ref.)	ee (%)
Et	**7a**	62	-32	94	**9a**	62	-42.8	-49.96 (8)	85.6
n-Bu	**7b**	70	-23.1	86	**9b**	42	-30	+37.05 (8)	81
n-C_5H_{11}	**7c**	50	-23.7	88	**9c**	63	-30		
n-C_6H_{13}	**7d**	70	-20.1	87	**9d**	30	-27.8		
n-C_8H_{17}	**7e**	73	-19	88	**9e**	60	-28.2		
Et	**8a**	60	-3.81	92.2	**9a**	74	-45	-49.96 (8)	90
n-Bu	**8b**	70	-2	94.4	**9b**	61	-38	+37.05 (8)	100
n-C_5H_{11}	**8c**	68	-1	95	**9c**	76	-30.5		
n-C_6H_{13}	**8d**	77	+1.3	97	**9d**	60	-26.45		
n-C_8H_{17}	**8e**	79	+1	96	**9e**	60	-21.5		

a) Yield after chromatography. b) Taken in PhH as a solvent. c) The de's were determined by means of ^{19}F NMR. d) Yield after distillation. e) Specific rotations were taken at 22°C in PhH, at 589 nm for **9a,c-e** and 578 nm for **9b**.

Table 1.-Enantioselective syntheses of β-phenylalkanoic acids **9a-e**.

The ^{19}F NMR spectra[9] of the cinnamamides (R)-(+)-**5** and (R)-(+)-**6** both comprised two unequal signals ($\Delta\delta \approx 1.9$ ppm for **5** and $\Delta\delta \approx 1.2$ ppm for **6**) which were due to the presence in solution of two amide conformers (s-Z and s-E) for each compound. The ^{19}F NMR spectra of the Michael adducts **7a-e** and **8a-e** each revealed the presence of four signals, two big ones corresponding to both amide conformers of the more abundant (R,R) diastereomer, and two small ones corresponding to the minor (S,R) diastereomer, each small signal being located very close to a big one. The diastereomeric ratios of a given adduct had the same value for each pair of conformers. As a matter of example, the ^{19}F NMR data of some adducts are displayed in Table 2. The de' s (%) of the Michael adducts **7a-e** and **8a-e** are given in Table 1.

In principle, the de of each adduct should be equal to the ee of the corresponding final β-phenylalkanoic acid **9a-e**. The ee of each known acid (-)-**9a,b** was determined as the ratio of the specific rotation we observed to that reported for the optically pure compound. It can be seen from Table 1 that the ee of each acid **9a,b** was in reasonably good agreement with the de value of the corresponding Michael adducts **7a,b** and **8a,b.**

All Grignard reagents added to the cinnamamides (R)-(+)-**5** and (R)-(+)-**6** in a highly diastereoselective manner. Thus, the de's of the Michael adducts deriving from the N-(2,2,2-trifluoroethyl) cinnamamide **5** were in the range 86-94%. Even better results were obtained with the N-(2-fluorobenzyl) cinnamamide **6** which led to adducts having de's higher than 92%.

Adduct	δ(ppm)[9]	Relative abundance (%) Diastereomers	Conformers A and B
7e	-70.60	(R,R) 93.6	(A) 60
	-70.50	(S,R) 6.4	(A) 60
	-68.35	(S,R) 6.6	(B) 40
	-67.84	(R,R) 93.4	(B) 40
8b	-121.00	(S,R) 2.8	(A) 36
	-120.03	(R,R) 97.2	(A) 36
	-118.69	(S,R) 2.8	(B) 64
	-118.56	(R,R) 97.2	(B) 64
8c	-120.10	(S,R) 2.7	(A) 36
	-120.04	(R,R) 97.3	(A) 36
	-118.72	(S,R) 2.7	(B) 64
	-118.59	(R,R) 97.3	(B) 64

Table 2.- ^{19}F NMR data of the Michael adducts **7e** and **8b,c**.

Conclusion

From the above results and by comparison with those we described earlier,[1] it appears that the N-(2-fluorobenzyl) base (R)-(-)-**4** is a promising chirality transfer vector for the asymmetric Michael addition of Grignard reagents to the corresponding α,β-ethylenic amides. Although it contains only one asymmetric centre, the chirality transfer reagent **4** can help creating a new asymmetric centre in a highly enantioselective manner. Other important advantages are that the compound **4** is rather cheap and readily available in both enantiomeric forms, and besides allows for the straightforward determination of the optical purity of the target products by means of ^{19}F NMR spectrometry. We are currently investigating the scope of such Michael additions using the base (R)-(-)-**4** and various types of α,β-ethylenic acids and nucleophiles.

References and Notes

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4. Meyers, A.I. ; Schmidt, W. ; McKennon, M.J. *Synthesis*, **1993**, 250-62.
5. Kitazume, T. ; Sato, T. ; Kobayashi, T. ; Tain Lin, J. *J. Org. Chem.*, **1986**, *51*, 1003-6.
6. Physical properties and yields of purified compounds. (R)-(-)-**1**, liquid, $[\alpha]_D$ -10 (5, MeOH) ; (R)-(+)-**2**, m.p. 90°C (needles from CH_2Cl_2), $[\alpha]_D$ +22 (1, MeOH), 60% ; (R)-(-)-**3**, liquid, b.p. 95°C (30 mm), $[\alpha]_D$ -9.7 (6, MeOH), 70.5% ; (R)-(-)-**4**, m.p. 65°C (cyclohexane), $[\alpha]_D$ -23.7 (3.25, MeOH), 70% ; (R)-(+)-**5**, liquid, $[\alpha]_D$ +3 (2, MeOH), 83% ; (R)-(+)-**6**, liquid, $[\alpha]_D$ +12.9 (2, MeOH), 87%.
7. Both enantiomers of the base **1** were obtained in kilogram quantities from SmithKline Beecham Laboratories, Mayenne (France).
8. Mukaiyama, T. ; Iwasawa, N. *Chem. Lett.*, **1981**, 913-6.
9. ^{19}F NMR Spectra were recorded either with or without proton decoupling, on a Bruker AC 400 instrument operating at 373.5 MHz. Samples (ca. 10 mg) were dissolved in $CDCl_3$ (ca. 0.5 mL). Chemical shifts are reported in ppm upfield from $CFCl_3$ in $CDCl_3$ as a reference.