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New perfluoroalkylated cinchona derivatives: synthesis and use in base-catalysed Diels–Alder reactions

Fabienne Fache* and Olivier Piva

Laboratoire de Chimie Organique, Photochimie et Synthèse, Université Claude Bernard Lyon I, CNRS UMR 5622, Bât. J. Raulin, 43 bd du 11 novembre 1918, 69622 Villeurbanne cedex, France

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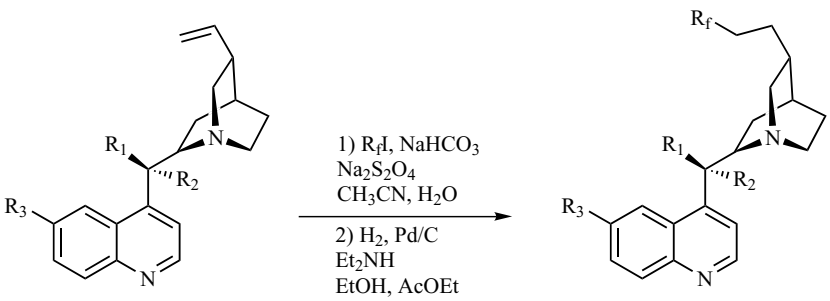
Abstract—Perfluorinated cinchona derivatives **1**–**4** were synthesised starting from commercially available compounds. They were tested in fluorous solvents in base catalysed Diels–Alder reactions and delivered adducts with ee up to 40%.

Techniques allowing an easy separation of the reaction products and a direct recycling of the catalytic system are very attractive. With that purpose, Fluorous Biphase Systems[1–3] (FBS) have been developed for few years. Nevertheless, as already pointed out by Pozzi et al.[4] they suffer from several drawbacks for industrial applications, such as possible environmental harmfulness of the solvent and ligand cost for asymmetric catalysis. Thus, there is a need for cheap, easily accessible perfluorinated ligands. In this paper, we wish to describe a straightforward method to obtain perfluoroalkylated cinchona derivatives directly from the chiral pool according to a two-step procedure (Scheme 1).

The iodoperfluoroalkylgroup was added under radical conditions on the double bond using the sodium dithionite method,[5,6] which turned out to be more efficient than the Rongalite® one.[7] The compounds thus prepared have been tested in an asymmetric base-catalysed Diels–Alder reaction[8] between anthrone **5** and *N*-methyl maleimide **6** (Scheme 2).

This reaction first described in 1989 by Kagan et al.[9,10] using various chiral β-amino alcohols furnished **7** as a single adduct in 61% ee at −50°C using quinidine as catalyst. Later, the same enantioselectivity was reached by Yamamoto et al.[11] with C_2-symmetry bis(hydroxymethyl)pyrrolidine at 20°C. More recently, the same



1a Cinchonidine: R_1=OH, R_2=H, R_3=H
2a Cinchonine: R_1=H, R_2=OH, R_3=H
3a Quinine: R_1=OH, R_2=H, R_3=OMe
4a Quinidine: R_1=H, R_2=OH, R_3=OMe

1b : R_1=OH, R_2=H, R_3=H, R_f=C_8F_{17} (isolated yield:40%)
2b : R_1=H, R_2=OH, R_3=H, R_f=C_8F_{17} (69%)
3b : R_1=OH, R_2=H, R_3=OMe, R_f=C_8F_{17} (35%)
3c : R_1=OH, R_2=H, R_3=OMe, R_f=C_4F_9 (41%)
4b : R_1=H, R_2=OH, R_3=OMe, R_f=C_8F_{17} (36%)

Scheme 1. Synthesis of perfluorinated alkaloids.

Keywords: perfluorinated ligands; alkaloids; asymmetric catalysis; base-catalysed reactions; Diels–Alder reactions.
* Corresponding author. Fax: 00 33 (0)4 72 44 81 36; e-mail: fache@univ-lyon1.fr

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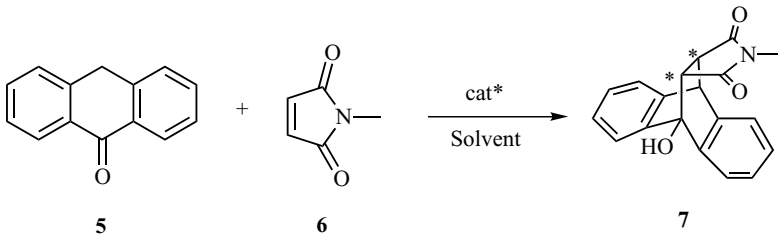

5 6 7

Scheme 2. Base-catalysed asymmetric Diels–Alder reaction.

group obtained 74% ee with a similar ligand bearing a (4-pyridyl)methyl group on the pyrrolidine nitrogen atom.[12] To our knowledge, this is the best result ever published in the literature for this reaction. We found this method of great interest as it was performed in the absence of metal derivatives and with only catalytic amounts of a chiral base. We therefore decided to test it under FBS conditions. Results are collected in Table 1.

The best ee value was 40%, obtained using **1b** (Table 1, entry 1), which has to be compared to Kagan's best result at the same temperature (35.5% ee with quinidine).[9] Nevertheless, in our case, decreasing the temperature to −15°C did not improve the enantioselectivity (Table 1, entry 3). Different solvent systems were also tested. In chloroform, whatever the fluorocatalyst, the reaction went slower than using the non-fluorinated alkaloids[9] (Table 1, entries 5 and 6). Turning up of the fluorinated side-chain could prevent the approach of the base towards the substrate and avoid the formation of the supposed intermediate oxyanion.[10] Thus, using α,α,α-trifluoromethylbenzene[14] increased the reaction rate and the reaction went to completion after 20 hours. Moreover, in this solvent, the reaction product **7** was insoluble and was then easily recovered by simple filtration. At 100% conversion, 75% of pure **7** was recovered in the precipitate with 59% ee (instead of 40% ee) with catalyst **1b**. This supposed an enrichment in one enantiomer by a selective precipitation. The filtrate has been reused without addition of catalyst: if the activity was maintained, the selectivity diminished (<20% ee). We also performed the reaction in a mixture of organic solvent/perfluorinated solvent without any advantage (i.e. Table 1, entries 6–8). Our fluorinated catalysts rather preferred the organic phase. According to empirical rules,[15] at least 60 wt.% of fluorine is required to ensure a good fluorophilicity of a molecule and thus increase its partition coefficient in favour of the fluorous phase. In our case, the fluorine content of the alkaloid derivatives was less than 45 wt.% and a fluorous ponytail in $C_{24}H_{49}$ will be necessary.

It should be noticed that the introduction of a perfluoroalkyl chain considerably changed the nature of the asymmetric induction of the base. Thus, in the results reported by Kagan et al.[9] quinidine gave the best enantioselectivity, whereas we measured the highest ee with the cinchonidine derivative. The only difference between these two compounds is due to the presence of a methoxy group, which does not considerably modify the percentage of fluorous content. However, it could change the fluorophilicity of the compounds and the general conformation of the molecules (repulsion between the electron pairs of fluorine and oxygen atoms).

Table 1. Base-catalysed asymmetric Diels–Alder reaction between **5** and **6**

	Catalyst[a]	Solvent	Time[b]	**7**[c] $[\alpha]_D$	ee (%)[d]
1	**1b**	C_6H_5–CF_3	20 h	+29	40
2	**1a**	C_6H_5–CF_3	1 h	+25	35
3	**1b**	C_6H_5–CF_3	6 days[e]	+21	29
4	**2b**	C_6H_5–CF_3	20 h	−23	32
5	**3a**	$CHCl_3$	30 min	−20	28
6	**3b**	$CHCl_3$	4 days	−11	15
7	**3b**	$CHCl_3/C_6F_{14}$[f]	4 days	−9	13
8	**3b**	C_6H_5–CF_3	20 h	−6	8
9	**3c**	$CHCl_3$	4 days	−9	13
10	**3c**	$CHCl_3/C_6F_{14}$[f]	4 days	−7	10
11	**4b**	C_6H_5–CF_3	20 h	+7	10

[a] 10% mol equiv.
[b] For total conversion.
[c] $[\alpha]_D = 71.4$ ($c = 1$, $CHCl_3$) for enantiomerically pure **7**.
[d] Measured by polarimetry and confirmed by ^1H NMR 500 MHz using a shift reagent[13]. Standard conditions : [**5**] = 0.1 M, 20°C.
[e] Reaction performed at −15°C.
[f] $CHCl_3/C_6F_{14} = 1/1$.

In summary, we have synthesised new easily accessible perfluoro catalysts and used them in an asymmetric Diels–Alder reaction with anthrone with enantioselectivity up to 40%. We have shown that α,α,α-trifluoromethylbenzene was a solvent of choice for such a reaction and allowed easy separation of the reaction products. Moreover, the recycling of the catalytic system appeared possible. Further studies are currently under progress in our laboratory to improve the recycling techniques and to find new applications to these catalysts.[16]

Preparation of perfluoroalkylated cinchona derivatives:[17] 6 mmol of $NaHCO_3$ (504 mg), 2.4 mmol of the desired perfluoroalkyliodide and 2 mmol of the alkaloid were dissolved in 5 ml CH_3CN and 1 ml H_2O. After 10 min, 2.6 mmol of $Na_2S_2O_4$ (453 mg) was added to the reaction medium and the mixture was allowed to stir in the dark at room temperature for 24 h. The white precipitate thus obtained was washed with MeOH and CH_2Cl_2. After filtration and flash chromatography (eluent CH_2Cl_2/MeOH: 92/8) the iodo intermediate was obtained in nearly 40% yield. The pure iodo compound (1 mmol) was then hydrogenated under 10 bar H_2 in a 1:1 EtOH/AcOEt mixture (24 ml) over Pd/C (10%, 100 mg) and in the presence of Et_2NH (150 mg). After 24 h, the pure product was isolated quantitatively after filtration and flash-chromatography (eluent CH_2Cl_2/MeOH :92/8).

Typical catalysed asymmetric Diels–Alder reaction procedure: 0.125 mmol of perfluoro alkaloid was added at room temperature to a solution of 245 mg (1.25 mmol) of **5** and 139 mg (1.25 mmol) of **6** in 12 ml of solvent. The reaction completion was controlled by TLC. **7** was obtained after flash-chromatography on silica gel (eluent petroleum ether/AcOEt: 60/40) in isolated yield better than 90%.

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17. All the compounds have been fully characterised. The disappearance of the double bond signals was noticed by ^1H NMR. Selected data: **1b**: ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -81.31$ (s, 3F), −114.89 (br.s, 2F), −122.42 (br.s, 6F), −123.26 (br.s, 2F), −123.88 (br.s, 2F), −126.65 (br.s, 2F), HRMS: calculated for $C_{27}F_{17}H_{23}N_2O$: 714.15389, found: 714.15375, $[\alpha]_D^{21} = +6$ ($c = 0.9$, $CHCl_3$). **2b**: ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -81.27$ (s, 3F), −114.74 (br.s, 2F), −122.41 (br.s, 6F), −123.23 (br.s, 2F), −123.72 (br.s, 2F), −126.63 (br.s, 2F), HRMS: calculated for $C_{27}F_{17}H_{23}N_2O$: 714.15389, found: 744.15406, $[\alpha]_D^{21} = +34$ ($c = 1.14$, $CHCl_3$). **3b**: ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -81.31$ (t, $J = 10$ Hz, 3F), −114.88 (br.s, 2F), −122.45 (br.s, 6F), −123.27 (br.s, 2F), −123.92 (br.s, 2F), −126.66 (br.s, 2F), HRMS: calculated for $C_{28}F_{17}H_{25}N_2O_2$: 744.16445, found: 744.16493, $[\alpha]_D^{21} = -8$ ($c = 1.03$, $CHCl_3$). **3c**: ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -81.61$ (s, 3F), −115.10 (s, 2F), −124.89 (s, 2F), −126.57 (s, 2F), HRMS: calculated for $C_{24}F_9H_{25}N_2O_2$: 544.177230, found: 544.17797, $[\alpha]_D^{21} = +1$ ($c = 0.3$, $CHCl_3$). **4b**: ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -81.28$ (t, $J = 9.4$ Hz, 3F), −114.77 (br.s, 2F), −122.38 (br.s, 6F), −123.22 (br.s, 2F), −123.79 (br.s, 2F), −126.63 (br.s, 2F), HRMS: calculated for $C_{28}F_{17}H_{25}N_2O_2$: 744.16445, found: 744.16435, $[\alpha]_D^{21} = +30$ ($c = 1.04$, $CHCl_3$).