ORGANIC LETTERS

2006
Vol. 8, No. 26
5935−5938

Highly Enantioselective Transfer Hydrogenation of Fluoroalkyl Ketones

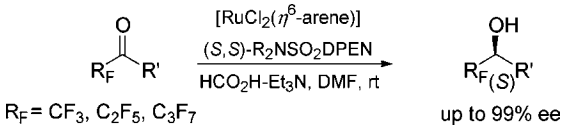
Damjan Šterk,[†] Michel Stephan,*[,†,‡] and Barbara Mohar*[,†]

Laboratory of Organic and Medicinal Chemistry, National Institute of Chemistry, Hajdrihova 19, SI-1001 Ljubljana, Slovenia, and PhosPhoenix SARL, 115, rue de l'Abbé Groult, F-75015 Paris, France

mstephan@phosphoenix.com; barbara.mohar@ki.si

Received September 26, 2006

ABSTRACT



The asymmetric transfer hydrogenation of fluoroalkyl ketones mediated by [Ru(η^6-arene)((*S*,*S*)-R_2NSO_2DPEN)] catalysts using HCO_2H–Et_3N afforded the corresponding alcohols with high ee's and in excellent yields.

Selectively fluorinated chiral organics have played an important role in the development of medicines, agrochemicals, and materials owing to the unique properties of the fluorine atom.[1] In particular, optically active α-trifluoromethyl alcohols are of interest as they are potentially useful in the synthesis of various trifluoromethyl-containing chiral structures.[2]

The preparation of fluoroalkyl alcohols via enantioselective reduction of the corresponding ketones is a convenient synthetic approach. Such compounds were prepared through hydroboration using a stoichiometric amount of DIP-chloride,[3] Rh- or Ru-catalyzed asymmetric hydrogenation at 10−50 atm of H_2,[4] or relying upon microorganisms.[5] However, these routes are not general to access a variety of substrates and suffer from obvious technical difficulties.

Asymmetric transfer hydrogenation has received considerable attention in the past decade with promising success since the discovery of the Ru(II)-*N*-tosyl-1,2-diphenylethylenediamine (Ru(II)-TsDPEN) catalyst by Noyori et al.[6]

We were interested to extend our ongoing research program in asymmetric reductions to the reduction of fluoroorganics. Accordingly, we undertook the task of investigating asymmetric transfer hydrogenation of a string of fluoroalkyl ketones using our Ru(II)-R_2NSO_2DPEN catalyst system. This catalyst system is prepared in situ by heating $[RuCl_2(\eta^6\text{-arene})]_2$ and (*S*,*S*)-R_2NSO_2DPEN ligands (**1a**−**d**) in DMF at 80 °C for 20 min. Noteworthy is that both enantiomers of DPEN are commercially available, and our catalysts proved to be excellent for the asymmetric transfer hydrogenation of various classes of ketones.[7] Bearing this in mind and on the basis of limited literature results,[8] we anticipated a high ee for the product alcohols in the

[†] National Institute of Chemistry.
[‡] PhosPhoenix SARL.

(1) (a) *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999. (b) Ma, J.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119−6146. (c) Mohar, B.; Šterk, D.; Ferron, L.; Cahard, D. *Tetrahedron Lett.* **2005**, *46*, 5029−5031 and references cited therein.

(2) (a) Mikami, K. In *Asymmetric Fluoroorganic Chemistry: Synthesis, Application and Future Directions*; Ramachandran, P. V., Ed.; American Chemical Society: Washington, DC, 2000; pp 255−269. (b) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1−16.

(3) Ramachandran, P. V.; Teodorović, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725−1738.

(4) (a) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529−13530. (b) Kuroki, Y.; Sakamaki, Y.; Iseki, K. *Org. Lett.* **2001**, *3*, 457−459. (c) Jeulin, S.; de Paule, S. D.; Ratovelomanana-Vidal, V.; Gênet, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320−325.

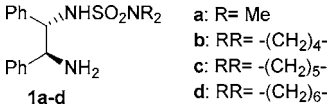
(5) (a) Fujisawa, T.; Onogawa, Y.; Sato, A.; Mitsuya, T.; Shimizu, M. *Tetrahedron* **1998**, *54*, 4267−4276. (b) Nakamura, K.; Matsuda, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* **1998**, *54*, 8393−8402. (c) Matsuda, T.; Harada, T.; Nakajima, N.; Itoh, T.; Nakamura, K. *J. Org. Chem.* **2000**, *65*, 157−163.

(6) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562−7563. (b) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522.

(7) Šterk, D.; Stephan, M.; Mohar, B. *Tetrahedron: Asymmetry* **2002**, *13*, 2605−2608.

10.1021/ol062358r CCC: $33.50
Published on Web 11/18/2006

reduction of fluoroalkyl ketones. Such fluorinated ketones are either commercially available or easily accessible in 1−2 steps according to reported literature procedures.[3,9]



Thus, a variety of fluoroalkyl ketones were reduced on a 1 mmol scale under our standard conditions at room temperature using HCO_2H-Et_3N (5:2) in DMF and catalyzed by [Ru(η^6-arene)((*S*,*S*)-R_2NSO_2DPEN)] with a substrate/catalyst molar ratio (S/C) of 200−2000. The results of transfer hydrogenation of selected fluoroalkyl ketones are presented in Table 1. To the best of our knowledge, this present work constitutes the first extended study of asymmetric reduction of various classes of fluoroalkyl ketones under transfer hydrogenation conditions.

As we have previously reported, transfer hydrogenation using our [Ru(η^6-arene)((*S*,*S*)-R_2NSO_2DPEN)] catalysts with HCO_2H-Et_3N can be best carried out in polar media such as DMF, DMA, NMP, and the like.[7] The η^6-arene ligand (i.e., benzene, *p*-cymene, mesitylene, 1,3,5-triethylbenzene, hexamethylbenzene) can influence the outcome of the reduction. For example, the catalyst possessing η^6-arene = benzene leads in general to 10−20% lower ee's, and the one with η^6-arene = hexamethylbenzene is less active compared to the rest. The modification of the R_2NSO_2 group in the R_2NSO_2DPEN ligand can serve to fine tune the enantioselectivity (ee enhancement up to 2%) against a selected target. These observations are also valid for the fluoroalkyl ketones in Table 1.

In general, Ru(II)-R″SO_2DPEN catalysts with R″ = Ar, R_F, or R_2N only reduce activated ketones (i.e., aryl ketones, α- and *β*-keto esters, α,*β*-unsaturated ketones, 1,2-diketones)[10] with high optical and chemical yields. As can be seen from Table 1, various classes of fluoroalkyl ketones can be reduced using our catalytic system leading to very high ee's and in a consistent manner. Thus, alkyl, arylmethyl, (2-aryl)ethyl, and (alkoxycarbonyl)methyl trifluoromethyl ketones and their perfluoroalkyl higher homologues were reduced to their corresponding alcohols with up to 99% ee within 2 h using a S/C = 200.

Fluoroalkyl ketones constitute suitable substrates for transfer hydrogenation compared to their nonfluorinated counterparts, and trifluoromethyl ketones are reduced in a faster rate than phenyl ketones. For example, using [Ru(*p*-cym)((*S*,*S*)-**1c**)], benzyl trifluoromethyl ketone was reduced with 97% ee (*S*) in 2 h with a S/C = 200 (entries 9−12), whereas phenyl acetone was reduced with ∼5% ee and 13% conversion in 2 h using a S/C = 100 (Figure 1). As an exception to this trend, 2,2,2-trifluoroacetophenone was reduced in 2 h albeit with 38% ee (*R*) (entry 7), and acetophenone was reduced with 95% ee (*S*) using a S/C = 100 in 24 h (50% conversion).[7] Here, the sense of asymmetric induction is unchanged. Thus, one can conclude that in the particular case of 2,2,2-trifluoroacetophenone the CF_3 group behaves as a smaller group to the Ph. It is noteworthy to mention that octafluoroacetophenone was exceptionally reactive and was reduced in the presence or absence of the catalyst giving rise to the racemic alcohol (entry 8).

Reduction of cyclohexyl trifluoromethyl ketone using [Ru(mesitylene)((*S*,*S*)-**1d**)] led to 66% ee (*S*) (entries 5 and 6). In this case, the sense of asymmetric induction is opposite to the one observed with 2,2,2-trifluoroacetophenone and follows the general observed trend of enantioselectivity.

Hexyl, (2-phenyl)ethyl, benzyl, (pyridin-2-yl)methyl, (pyridin-4-yl)methyl, (pyrimidin-4-yl)methyl, and (benzoxazol-2-yl)methyl trifluoromethyl ketones were reduced using [Ru(η^6-arene)((*S*,*S*)-**1a**−**d**)] with high ee's (93−99% (*S*)) (entries 1−4, 9−12, and 15−25). With low catalyst loading (S/C = 2000), benzyl trifluoromethyl ketone was reduced with 97% ee in 20 h (entry 11). Benzyl perfluoropropyl ketone was reduced equally well with a high ee as in the case of the trifluoromethyl analogue (entries 13 and 14). Although a S/C = 200 and 2 h were sufficient for the complete reduction of hexyl, (2-phenyl)ethyl, benzyl, and (pyridin-2-yl)methyl trifluoromethyl ketones, in the case of (pyridin-4-yl)methyl and (benzoxazol-2-yl)methyl trifluoromethyl ketones, 8 h was needed to achieve full conversion, and with (pyrimidin-4-yl)methyl trifluoromethyl ketone, a S/C = 25 and 4 h were required.

In addition, we investigated the reduction of 1-(pyridin-2-yl)ethyl trifluoromethyl ketone as we anticipated a dynamic kinetic resolution to occur during the reaction (entries 18−20). In a preliminary experiment using HCO_2H-Et_3N (5:2), a dr of 54:46 was obtained with 99% and 94% ee, respectively. Interestingly, the dr ratio was significantly improved reverting to HCO_2H-Et_3N (3:2). Thus, a dr of 78:22 was attained with 99% and 84% ee, respectively. The ee of the major (+)-*erythro* enantiomer was increased to 100% by recrystallization.

Transfer hydrogenation of 1,1,1-trifluoro-5,5-dimethyl-2,4-hexanedione occurred regioselectively with the sole reduction of the trifluoromethylcarbonyl group (entries 26 and 27). The product alcohol was obtained with excellent ee (99%).

γ-Fluorinated *β*-keto esters are interesting substrates to undergo reduction to the chiral *γ*-fluoro *β*-hydroxy esters which are useful building blocks. Several research groups were active in developing methods for their reduction.[4c,11] From the first result of the test substrate ethyl 2,2,2-

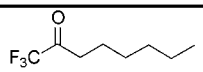
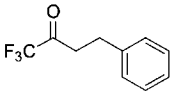
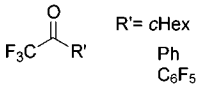
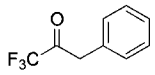
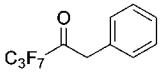
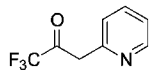
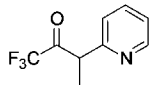
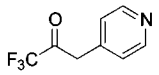
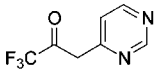
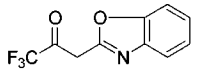
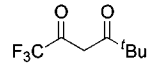
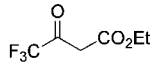
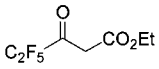
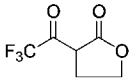
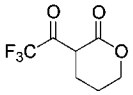
(8) (a) Tada, K.; Miura, T. JP 2003034665, 2003; *Chem. Abstr.* **2002**, *137*, 369737. (b) Šterk, D.; Stephan, M.; Mohar, B. *Tetrahedron Lett.* **2004**, *45*, 535−537.

(9) (a) Linderman, R. J.; Lonikar, M. S. *J. Org. Chem.* **1988**, *53*, 6013−6022. (b) Xavier, C. *J. Org. Chem.* **1987**, *52*, 5026−5030. (c) Kawase, M.; Teshima, M.; Saito, S.; Tani, S. *Heterocycles* **1998**, *48*, 2103−2109. (d) Archer, S.; Perianayagam, C.; Sevenard, D. V.; Lork, E. *J. Fluorine Chem.* **2004**, *125*, 125−128. (e) Archer, S.; Perianayagam, C. *J. Med. Chem.* **1979**, *22*, 306−309.

(10) (a) Zanotti-Gerosa, A.; Hems, W.; Groarke, M.; Hancock, F. *Platinum Metals Rev.* **2005**, *49*, 158−165 and references cited therein. (b) Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986−987. (c) Mohar, B.; Valleix, A.; Desmurs, J.-R.; Felemez, M.; Wagner, A.; Mioskowski, C. *J. Chem. Soc., Chem. Commun.* **2001**, 2572−2573.

(11) (a) Sayo, N.; Akutagawa, S.; Saito, T.; Noyori, R.; Kumobayashi, H.; Takaya, H. EP295109, 1988; *Chem. Abstr.* **1989**, *111*, 39010. (b) von Arx, M.; Mallat, T.; Baiker, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2302−2305. (c) Xu, C.; Yuan, C. *Tetrahedron* **2005**, *61*, 2169−2186.

Table 1. Transfer Hydrogenation of Fluoroalkyl Ketones[a]

entry	ketone	$[RuCl_2(\eta^6\text{-arene})]_2$, arene=	ligand	S/C	time, h	% ee [b]	config
1		*p*-cymene	**1c**	200	2	93 [d]	*S* [f]
2		mesitylene	**1c**	200	2	94 [d]	*S* [f]
3		mesitylene	**1a**	200	2	94	*S* [f]
4		mesitylene	**1c**	200	2	96 (100) [e]	*S* [f]
5	 R'= *c*Hex	mesitylene	**1c**	200	2	65	*S* [f]
6		mesitylene	**1d**	200	2	66	*S* [f]
7	Ph	*p*-cymene	**1c**	200	2	38	*R* [f]
8	C_6F_5	mesitylene	**1c**	200	<0.5	~racemic	-
9		benzene	**1c**	200	2	68	*S* [f]
10		*p*-cymene	**1c**	200	2	97	*S* [f]
11		*p*-cymene	**1c**	2000	20	97	*S* [f]
12		mesitylene	**1c**	200	2	97	*S* [f]
13		mesitylene	**1a**	200	2	98	*S* [f]
14		mesitylene	**1c**	200	2	96	*S* [f]
15		benzene	**1c**	200	2	82	*S* [g]
16		*p*-cymene	**1b**	200	2	98	*S* [g]
17		mesitylene	**1c**	200	2	99 (100) [e]	*S* [g]
18		mesitylene	**1c**	200	8	99/ 94 (dr 54:46)	*erythro/threo* [h]
19		mesitylene	**1c**	200 [c]	8	99 (100) [e]/ 84 (dr 78:22)	*erythro/threo* [h]
20		hexamethylbenzene	**1c**	200 [c]	8	99/ 53 (dr 80:20)	*erythro/threo* [h]
21		*p*-cymene	**1b**	200	8	98	*S* [g]
22		mesitylene	**1c**	200	8	98	*S* [g]
23		mesitylene	**1c**	25	4	98	*S* [g]
24		*p*-cymene	**1b**	200	6	96 (100) [e]	*S* [h]
25		*p*-cymene	**1c**	200	8	95	*S* [h]
26		benzene	**1b**	200	2	77	*S* [f]
27		*p*-cymene	**1b**	200	2	99 (100) [e]	*S* [f]
29		*p*-cymene	**1c**	200	2	98	*S* [f]
30		*p*-cymene	**1c**	2000	20	98	*S* [f]
31		*p*-cymene	**1b**	200	2	98	*S* [g]
32		mesitylene	**1c**	200	2	99	*S* [g]
33		1,3,5-triethylbenzene	**1c**	200	2	99	*S* [g]
34		mesitylene	**1c**	200	8	97/ 81 (dr 89:11)	(1'*S*,3*S*) [g]/ (1'*S*,3*R*) [g]
35		*p*-cymene	**1c**	200	4	96 (100) [e]/ 94 (dr 88:12)	(1'*S*,3*S*) [i]/ (1'*S*,3*R*) [g]
36		mesitylene	**1c**	200	4	97/ 95 (dr 89:11)	(1'*S*,3*S*) [i]/ (1'*S*,3*R*) [g]

[a] HCO_2H-Et_3N (5:2) (420 μL) was added to a mixture of the ketone (1 mmol) and the preformed $[RuCl(\eta^6\text{-arene})((S,S)\text{-}R_2NSO_2DPEN)]$ in DMF (1 mL) and was left under stirring at 25 °C until GC indicated 100% conversion. Isolated yield: 85−98%. [b] Determined by chiral GC unless otherwise noted. [c] HCO_2H-Et_3N (3:2) used. [d] Determined by ^{19}F NMR of its (1*S*)-camphanic acid ester. [e] ee after upgrading by recrystallization. [f] Assigned by comparing the sign of the optical rotation of the isolated product with the lit. data. [g] Assigned by analogy with the t_R of chiral GC analysis of related homologous alcohols of the table. [h] Determined by X-ray analysis. [i] Determined by X-ray analysis of its (1*S*)-camphanic acid ester. For further details, see Supporting Information.

trifluoroacetoacetate, we were pleased to find that our catalyst system (S/C = 2000) is able to furnish under mild conditions the corresponding γ-trifluoro β-hydroxy ester with a superior ee (98%) (entries 29 and 30) compared to the results of other metal-catalyzed hydrogenations (using 1 mol % of [RuBr-(*S*-difluorphos)] at 10 bar H_2, 110 °C, 1 h, 70% ee[4c] and using $[RuHCl(binap)_2]$, S/C = 1000, at 80 kg/cm^2 H_2, 30 °C, 16 h, 46% ee[11a]) or transfer hydrogenations (using [Ru-(*p*-cym)(TsDPEN)], S/C = 500, HCO_2H-Et_3N (5:2), THF, 35 °C, 15 h, 96% ee).[8a] Reduction of ethyl 4,4,5,5,5-pentafluoro-3-oxopentanoate revealed similar efficiency of the catalyst (99% ee) (entries 31−33). Further investigation with α-trifluoroacetyl-lactones (C_4 and C_5) showed that a dynamic kinetic resolution occurred during the transfer hydrogenation (entries 34−36). With the lactone C_4, a dr of 89:11 (syn/anti) was obtained with 97% (*S*,*S*-syn) and 81% (anti) ee, respectively. Lactone C_5 behaved in a similar manner giving rise to a dr of 88:12 (syn/anti) with 96% (*S*,*S*-syn) and 94% (anti) ee, respectively. The 96% ee of the major *S*,*S*-syn-enantiomer was increased to 100% by recrystallization, and its absolute configuration was confirmed by X-ray analysis of its (1*S*)-camphanic acid ester.

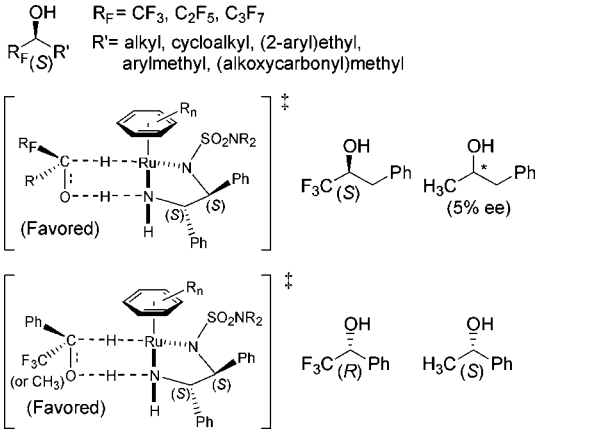


Figure 1. General sense of asymmetric transfer hydrogenation catalyzed by [Ru(η^6-arene)((*S*,*S*)-R_2NSO_2DPEN)].

The analysis of the results of transfer hydrogenation using our Ru(II)-R_2NSO_2DPEN catalyst of 2,2,2-trifluoroacetophenone, cyclohexyl, or alkyl trifluoromethyl ketones, ethyl 2,2,2-trifluoroacetoacetate and ethyl benzoylacetate,[7] brings us to establish the relative order of magnitude of group bulkiness as follows: Ph > CF_3 > *c*Hex > CH_2. Interestingly enough, in the reduction of trifluoromethyl ketones with DIP-chloride, the CF_3 group behaves as though it is bulkier than Ph.[3]

In summary, this work constitutes the first extended study of asymmetric reduction of various classes of fluoroalkyl ketones under transfer hydrogenation conditions. Chiral α-trifluoromethyl alcohols and their perfluoroalkyl higher homologues were prepared in excellent optical (up to 100% ee) and chemical yields (85−100%) through ketone reduction catalyzed by our Ru(II)-R_2NSO_2DPEN (0.05−0.5 mol %) complexes using HCO_2H−Et_3N in DMF at room temperature. Several fluoroalkyl ketones were asymmetrically reduced for the first time. This asymmetric approach allows easy isolation of the chiral fluoroalkyl alcohol in either enantiomeric form, and new opportunities for industrial synthetic implementation may evolve. Further synthetic applications of this catalytic system are in progress.

Acknowledgment. Financial support from the Ministry of Higher Education, Science and Technology of the Republic of Slovenia through grant P1-242 is kindly acknowledged. We thank as well Dr. Barbara Modec (University of Ljubljana) for X-ray structure analysis.

Supporting Information Available: Experimental procedures and characterization data for chiral fluoroalkyl alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062358R