Journal of Fluorine Chemistry 130 (2009) 600–603

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Short communication

Ruthenium-catalysed asymmetric transfer hydrogenation of *para*-substituted α-fluoroacetophenones

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ARTICLE INFO

Article history:
Received 8 December 2008
Received in revised form 26 March 2009
Accepted 28 March 2009
Available online 5 April 2009

Keywords:
α-Fluoroacetophenone
1-Aryl-2-fluoroethanols
Asymmetric transfer hydrogenation
Ruthenium
TsDPEN
TsCYDN

ABSTRACT

The first examples of asymmetric transfer hydrogenation of α-fluoroacetophenones are reported. Eight *para*-substituted α-fluoroacetophenones have been reduced using four catalytic systems constructed of $[RuCl_2(p\text{-cymene})_2]_2$ or $[RuCl_2(\text{mesitylene})_2]_2$ in combinations with each of the ligands (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine ((*R*,*R*)-TsDPEN) and (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine ((*R*,*R*)-TsCYDN). All reactions were performed in both water and formic acid/triethylamine. The highest enantioselectivity was obtained using the (*R*,*R*)-TsDPEN ligand in a formic acid/triethylamine mixture, giving the (*S*)-1-aryl-2-fluoroethanols in high to moderate enantiomeric excess (97.5–84.5%). For this solvent system the presence of electron withdrawing groups in the *para* position reduced the enantioselectivity. Reactions performed in water generally gave lower enantioselectivity and reaction rate, although RuCl(mesitylene)-(*R*,*R*)-TsDPEN yielded the product alcohols with enantiomeric excess in the range of 95.5–76.5%.

1. Introduction

The importance and utilisation of optically pure secondary alcohols has been well recognised. Due to their somewhat troublesome preparation, fluorinated secondary alcohols have received considerably less attention. We have recently described routes to α-fluorinated ketones, rendering their corresponding alcohols easy accessible [1]. The potential use of such optically enriched fluorinated alcoholic building blocks is vast, and includes among others pharmaceuticals, advanced materials and agrochemicals [2–6].

Asymmetric transfer hydrogenation (ATH) using various metal complexes has emerged as an excellent alternative to established asymmetric reduction methods [7,8]. The easily available hydrogen sources, mild reaction conditions and simple experimental setup have made it an area of interest for both industrial and academic researchers [9–12]. Moreover, ATH can be performed in water [7,9,13–16], which is the ideal solvent seen from an environmental point of view, and potentially provides cost savings for commercial processes. In contrast to most transition metal catalysed reactions, asymmetric transfer hydrogenations have also been done in presence of air [16,17], without significant loss in enantioselectivity.

Acetophenones are usually the benchmark substrates for asymmetric reductions. Numerous investigations on the effects of different catalysts, metal species, solvent systems, additives, temperature and pH on the rate and selectivity of asymmetric transfer hydrogenations have been reported [7,9,10,13–21].

Sterk et al. [22] has described the ATH of trifluoromethylketones with mediocre enantioselectivity, but the ATH of monofluoroketones is an unexplored area. As part of our ongoing research, we have recently investigated chiral oxazaborolidine-catalysed borane reductions of a series of α-fluoroketones to the corresponding chiral secondary alcohols [23]. In order to develop a more robust and environmental friendly catalytic process, we have now turned our attention to ATH. Herein we wish to report an improved method for the preparation of enantioenriched 1-aryl-2-fluoroethanols using ruthenium catalysed asymmetric transfer hydrogenation.

2. Result and discussion

The α-fluoroketones **4a**–**e** (Scheme 1) were most conveniently prepared by fluorination of the corresponding trimethylsilyl enol ethers, **2a**–**e**, using Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) [1], while **4f**–**h** were obtained in highest yield by reacting the acetophenones, **1f**–**h**, with Selectfluor™ in methanol. The dimethoxyacetals, **3f**–**h** formed as the major products were hydrolysed using trifluoroacetic acid [1].

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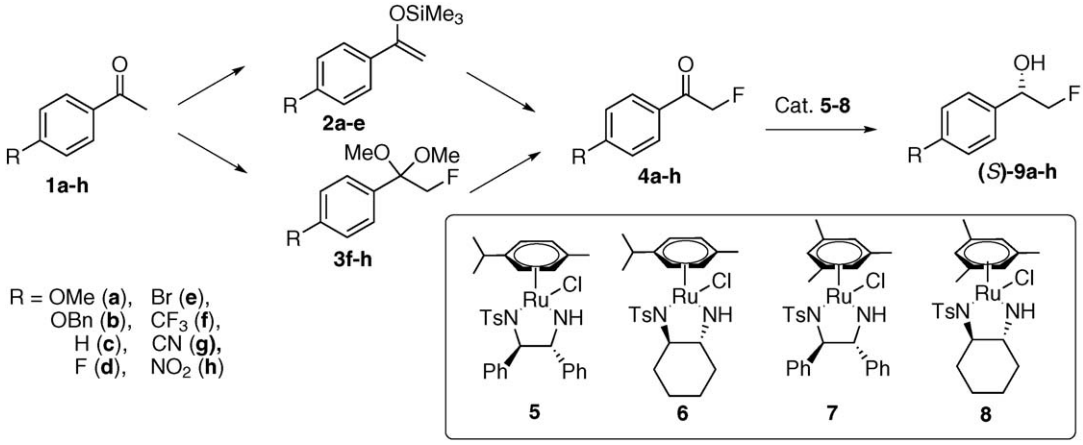
doi:10.1016/j.jfluchem.2009.03.011



Scheme 1. Preparation and asymmetric transfer hydrogenation of the fluoroketones, **4a**–**h**, using the catalysts **5**–**8**.

The ATH of **4a**–**h** were studied using four different catalysts, **5**–**8**, which were prepared by mixing the ruthenium arene complexes, $[RuCl_2(p\text{-cymene})]_2$ and $[RuCl_2(\text{mesitylene})]_2$ with (*R*,*R*)-TsDPEN and (*R*,*R*)-TsCYDN, respectively. The pre-catalyst $[RuCl_2(\text{mesitylene})]_2$ was synthesised from $RuCl_3$ and 1,3,5-trimethyl-1,4-cyclohexadiene according to literature procedures [24,25]. All reactions were performed without solvent degassing and without inert atmosphere protection [16].

Initially, **4a**–**h** were reduced with catalysts **5**–**8** in water at 40 °C using sodium formate as hydrogen donor. The reactions were monitored by HPLC for determination of conversion and enantiomeric excess. The results are summarised in Table 1. All reactions proceeded with preference of the (*S*)-enantiomer [23]. The ee of the reactions depended on both catalyst and substrate structure. The highest selectivity was obtained using catalyst **7**, giving the alcohols (*S*)-**9a**, (*S*)-**9c** and (*S*)-**9f** in ≥95% ee. The catalysts **5** and **8** gave comparable, but lower ee-values than was the case with **7**, while catalyst **6** gave only moderate enantioselectivity with ee-values ranging from 77.0 to 47.5%.

The effect of the substituents on the enantioselectivity seems complex. A general trend was that the reductions of **4c** (R = H) and **4f** (R = CF_3) gave some of the highest ee-values for all catalysts, whereas the reduction of **4g** (R = CN) and **4h** (R = NO_2) gave the lowest selectivities. Moderate enantioselectivity has also been the results in asymmetric transfer hydrogenation of 4-nitroacetophenone (**1h**) in similar catalytic systems [13,16,26].

The reaction rate was also dependant on both catalysts and substrate structures. Generally, the highest rates were observed in reductions using catalyst **5**, while catalyst **6** gave the longest reaction times. As expected, the ketones substituted with electron donating substituents tended to react slower than their more electron deficient counterparts [18]. Observed differences in conversion could also be due to the low solubility and crystalline nature of several of the α-fluoroacetophenones in water. Solubility effects might therefore overshadow electronic effects caused by the *para*-substituents.

A formic acid/triethylamine solvent mixture has previously been used in reductions of acetophenone using catalysts **5** and **7** [15,27]. The reactions yielded 1-arylethanols with high enantiomeric excess, but proceeded with a moderate reaction rate. The introduction of a fluorine atom in the α-position of the carbonyl group increases the electrophilicity at the reaction centre, and it was therefore considered worthwhile to investigate this solvent in reduction of **4a**–**h**. The reactions were performed using catalysts **5**–**8** at 40 °C, using S/C = 100, and a physical mixture of formic acid/triethylamine (5:2 mol ratio). The conversions and enantiomeric excess are summarised in Table 2.

Phase transfer limitations are less profound in the triethylamine system, since the α-fluoroacetophenones are soluble in the reaction medium. Less variance in rates was also observed within each catalytic system. The highest rates were observed in reductions using the catalysts **5** and **7**, where all starting materials were consumed within 2 h. Using catalyst **6**, the time needed to reach full conversion was increased to 24 h, whereas the reactions catalysed by **8** were terminated after 10 days, reaching only 20–66% conversion.

Reductions catalysed by **5**–**7** in formic acid/triethylamine gave overall higher selectivity than the reductions in water, and only the reduction of substrate **4f** (R = CF_3) resulted in lower ee-values. The

Table 1
Asymmetric transfer hydrogenation of **4a**–**h** using catalysts **5**–**8** in water.[a]

Substrate		Cat. 5		Cat. 6		Cat. 7		Cat. 8	
		Conv. (hours)	ee (%)	Conv. (hours)	ee (%)	Conv. (hours)	ee (%)	Conv. (hours)	ee (%)
4a	OMe	>99 (2)	90.0	18 (24)	67.0	>99 (5)	95.0	88 (5)[b]	87.0
4b	OBn	>99 (10)	88.0	49 (24)	74.0	71 (20)	90.0	83 (5)[b]	89.0
4c	H	>99 (2)	91.5	>99 (24)	81.5	>99 (2)	95.5	>99 (2)	90.5
4d	F	>99 (2)	87.0	>99 (24)	77.0	>99 (5)	91.0	82 (5)[b]	87.0
4e	Br	>99 (2)	87.0	>99 (24)	76.5	>99 (5)	90.5	>99 (5)	87.5
4f	CF_3	>99 (2)	91.5	>99 (24)	77.0	>99 (5)	96.0	>99 (2)	88.0
4g	CN	>99 (2)	66.0	>99 (24)	51.0	45 (20)	84.0	>99 (2)	68.5
4h	NO_2	>99 (2)	70.0	>90 (24)	47.5	99 (20)	76.5	>99 (5)	63.0

[a] A suspension of $[RuCl_2(\text{arene})]_2$ (0.001 mmol) and the ligand (0.0027 mmol) in H_2O (0.5 mL) were stirred at 40 °C for 1 h. Sodium formate (34 mg, 0.5 mmol) and the ketone (0.1 mmol) were then added and the mixture was stirred vigorously at 40 °C for the specified number of hours.
[b] Full conversion was obtained within 20 h reaction time.

Table 2
Asymmetric transfer hydrogenation of **4a–h** using catalysts **5–8** in formic acid/triethylamine.[a]

Substrate		**Cat. 5**		**Cat. 6**		**Cat. 7**		**Cat. 8**	
		Conv. (hours)	ee (%)	Conv. (hours)	ee (%)	Conv. (hours)	ee (%)	Conv. 10 days	ee (%)
4a	OMe	>99 (2)	95.5	>99 (24)	91.0	>99 (2)	96.0	29	44.0
4b	OBn	>99 (2)	96.5	>99 (24)	90.0	>99 (2)	97.5	28	64.0
4c	H	>99 (2)	97.0	>99 (24)	89.0	>99 (2)	97.0	30	72.0
4d	F	>99 (2)	92.0	>99 (24)	86.0	>99 (2)	93.5	24	41.0
4e	Br	>99 (2)	90.5	>99 (24)	83.5	>99 (2)	91.0	30	46.5
4f	CF_3	>99 (2)	91.0	>99 (24)	83.0	>99 (2)	90.5	20	25.0
4g	CN	>99 (2)	84.5	>99 (24)	75.5	>99 (2)	88.0	50	21.0
4h	NO_2	>99 (2)	85.0	>99 (24)	76.5	>99 (2)	84.5	66	29.0

[a] A suspension of the $[RuCl_2(arene)]_2$ (0.001 mmol) and ligand (0.0027 mmol) in CH_2Cl_2 (0.5 mL) were stirred at 20 °C for 30 min. After removal of CH_2Cl_2 by a stream of N_2, the ketone (0.1 mmol) in HCO_2H/Et_3N (5:2, 0.25 mL) was added. The reaction mixture was stirred vigorously at 40 °C for the specified time.

use of catalysts **5** and **7** yielded products with higher enantiomeric excess than was the case with **6**, and the alcohols, (*S*)-**9a–h**, could be obtained with ee-values ranging from 97.5 to 84.5%. On the other hand, catalyst **8**, which performed reasonable well in water, gave only moderate to low enantioselectivity in formic acid/triethylamine.

Using catalysts **5–7** in formic acid/triethylamine, a trend regarding the effect of substituents on the enantioselectivity could be noticed. A drop in ee of the product alcohols were observed going from **4a–c** to substrates bearing more electron withdrawing substituents. Fujii et al. [27] has previously reduced a series of *para*-substituted acetophenones using (*S*,*S*)-**7** as catalyst in formic acid/triethylamine. At 28 °C using a catalyst/substrate ratio of 200:1, reduction of **1a** (60 h), **1c** (20 h) and **1g** (14 h) gave the corresponding alcohols in 97, 98 and 90% ee, respectively [27]. The ee of the products in our study are comparable to that obtained in reductions of the corresponding acetophenones. Substituting a methyl- with a fluoromethyl group increases the size of the substituent, and alters the electron density at the carbonyl carbon. It was noteworthy that the reduction of α-fluoroacetophenone (**4c**) was completed in less than 2 h using catalyst **5**, whereas acetophenone (**1c**) under identical conditions in our hands required 20 h to reach full conversion with 97% ee. Evidently, the introduction of one electron withdrawing fluorine increases the reaction rate significantly. Somewhat surprisingly the enantiodiscrimination process was not affected to a large extent by this substitution. The fact that the relative difference in activation energy leading to the (*R*)- and (*S*)-enantiomers is almost equal in the acetophenone and the α-fluoroacetophenone series, implies that the drop in selectivity for substrates containing electron withdrawing aromatic substituents is not solely related to the electronic content of the carbonyl carbon. This effect can rather be explained by other factors such as change in π–π interactions, solvation effects or dispersion interactions as suggested by Brandt et al. [28].

3. Conclusion

Asymmetric transfer hydrogenation of *para*-substituted α-fluoroacetophenones, **4a–h**, using the RuCl-(*p*-cymene)-(*R*,*R*)-TsDPEN and RuCl-(mesitylene)-(*R*,*R*)-TsDPEN provides the corresponding chiral 1-aryl-2-fluoroethanols, **9a–h**, in high to moderate ee. The formic acid/triethylamine system was found to give higher enantioselectivity than for reactions in water using sodium formate as hydrogen donor. Compared to the acetophenone series, the introduction of a fluorine atom in α-position to the ketone increased the reaction rates significantly without affecting enantioselectivity. ATH of α-fluoroacetophenones represent a fast, selective, robust and environmental friendly method towards enantioenriched 1-aryl-2-fluoroethanols.

4. Experimental

4.1. General experimental procedures

Solvents and reagents were used as received from the suppliers. $[RuCl_2(p\text{-cymene})]_2$, (*R*,*R*)-TsDPEN, (*R*,*R*)-TsCYDN and ruthenium(III) chloride hydrate were from Aldrich, while 1,3,5-trimethyl-1,4-cyclohxadiene was from Alfa Aesar. $[RuCl_2(mesitylene)]_2$ [24,25], and α-fluoroacetophenones [1], were prepared as described previously. Reactions were performed in an incubator shaker from Brunswic Scientific Co. Inc. NMR spectra were recorded with Bruker Avance DPX 400 operating at 400 MHz for ^1H, 375 MHz for ^{19}F and 100 MHz for ^{13}C. The ee of the alcohols were determined by HPLC using an Agilent 1100 series system equipped with a Bruker DAD detector and a Chiracel OD column (0.46 cm × 25 cm), mobile phase: hexane/2-propanol, 98:2, flow rate 1.0 mL/min [23].

4.2. Asymmetric transfer hydrogenation in water

A suspension of $[RuCl_2(arene)]_2$ (0.001 mmol) and the ligand (0.0027 mmol) in H_2O (0.5 mL) were stirred at 40 °C for 1 h. Sodium formate (34 mg, 0.5 mmol) and the α-fluoroacetophenone (0.1 mmol) was then added and the mixture was stirred vigorously at 40 °C for the specified number of hours. Samples were withdrawn from the reaction mixture, extracted with Et_2O and filtered through silica before analysis by HPLC for determination of conversion and enantiomeric excess.

4.3. Asymmetric transfer hydrogenation in formic acid/triethylamine

A suspension of the $[RuCl_2(arene)]_2$ (0.001 mmol) and ligand (0.0027 mmol) in CH_2Cl_2 (0.5 mL) were stirred at 20 °C for 30 min. After removal of CH_2Cl_2 by a stream of N_2, the ketone (0.1 mmol) in a physical mixture of HCO_2H/Et_3N (5:2 mol ratio, 0.25 mL) was added. The reaction mixture was stirred vigorously at 40 °C for the specified number of hours. Samples were withdrawn from the reaction mixture and the solvent was removed under a stream of N_2. The samples were then dissolved in the HPLC-eluent, filtered through silica and analysed by HPLC for determination of conversion and enantiomeric excess.

References

[1] E. Fuglseth, T.H. Krane Thvedt, M. Førde Møll, B.H. Hoff, Tetrahedron 64 (2008) 7318–7323.
[2] K.L. Kirk, J. Fluorine Chem. 127 (2006) 1013–1029.
[3] P. Kirsch, M. Bremer, Angew. Chem. Int. Ed. 39 (2000) 4216–4235.
[4] F. Leroux, P. Jeschke, M. Schlosser, Chem. Rev. 105 (2005) 827–856.
[5] S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330.
[6] A.M. Thayer, Chem. Eng. News. 84 (2006), 15-24-27-32.

[7] X. Wu, J. Liu, D.D. Tommaso, J.A. Iggo, C.R.A. Catlow, J. Bacsa, J. Xiao, Chem. Eur. J. 14 (2008) 7699–7715.
[8] X. Wu, X. Li, A. Zanotti-Gerosa, A. Pettman, J. Liu, A.J. Mills, J. Xiao, Chem. Eur. J. 14 (2008) 2209–2222.
[9] X. Wu, J. Xiao, Chem. Commun. (2007) 2449–2466.
[10] S. Gladiali, E. Alberico, Chem. Soc. Rev. 35 (2006) 226–236.
[11] T. Ikariya, K. Murata, R. Noyori, Org. Biomol. Chem. 4 (2006) 393–406.
[12] J.M.J. Williams, C. Bubert, S.M. Brown, A.J. Blacker, WO 2002044111 (2001).
[13] Y. Ma, H. Liu, L. Chen, X. Cui, J. Zhu, J. Deng, Org. Lett. 5 (2003) 2103–2106.
[14] J. Mao, B. Wan, F. Wu, S. Lu, Tetrahedron Lett. 46 (2005) 7341–7344.
[15] X. Wu, X. Li, W. Hems, F. King, J. Xiao, Org. Biomol. Chem. 2 (2004) 1818–1821.
[16] X. Wu, D. Vinci, T. Ikariya, J. Xiao, Chem. Commun. (2005) 4447–4449.
[17] E. Alza, A. Bastero, S. Jansat, M.A. Pericas, Tetrahedron: Asymm. 19 (2008) 374–378.
[18] N.A. Cortez, G. Aguirre, M. Parra-Hake, R. Somanathan, Tetrahedron Lett. 48 (2007) 4335–4338.
[19] H.Y. Rhyoo, H.J. Park, W.H. Suh, Y.K. Chung, Tetrahedron Lett. 43 (2002) 269–272.
[20] P. Vaestilae, A.B. Zaitsev, J. Wettergren, T. Privalov, H. Adolfsson, Chem. Eur. J. 12 (2006) 3218–3225.
[21] F. Wang, H. Liu, L. Cun, J. Zhu, J. Deng, Y. Jiang, J. Org. Chem. 70 (2005) 9424–9429.
[22] D. Sterk, M. Stephan, B. Mohar, Org. Lett. 8 (2006) 5935–5938.
[23] E. Fuglseth, E. Sundby, P. Bruheim, B.H. Hoff, Tetrahedron: Asymm. 19 (2008) 1941–1946.
[24] M.J. Palmer, J.A. Kenny, T. Walsgrove, A.M. Kawamoto, M. Wills, Perkin Trans. 1 (2002) 416–427.
[25] M.A. Bennett, A.K. Smith, Dalton Trans. (1974) 233–241.
[26] J. Canivet, G. Labat, H. Stoeckli-Evans, G. Suss-Fink, Eur. J. Inorg. Chem. (2005) 4493–4500.
[27] A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 118 (1996) 2521–2522.
[28] P. Brandt, P. Roth, P.G. Andersson, J. Org. Chem. 69 (2004) 4885–4890.