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Highly Selective Iridium-Catalyzed Asymmetric Hydrogenation of Trifluoromethyl Olefins: A New Route to Trifluoromethyl-Bearing Stereocenters

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Abstract: Fluorine-containing compounds are useful in many applications ranging from pharmaceuticals to ferroelectric crystals. We have developed a new, highly enantioselective synthetic route to trifluoromethyl-bearing stereocenters in up to 96% *ee via* asymmetric hydrogenation using N,P-ligated iridium catalysts. We also hydrogenated an isomeric mixture of olefins; this reaction gave the hydrogenation product highly enantioselectively (87% *ee*), and only the *E* isomer was present after the reaction had reached 56% conversion.

Keywords: asymmetric catalysis; fluorine; hydrogenation; iridium; P,N ligands

Fluorine-containing compounds are useful in applications ranging from agrochemicals and pharmaceuticals to materials for liquid crystal displays (LCDs).[1] Among the fluoroorganic compounds, trifluoromethyl-substituted molecules have gained much attention, mainly because the electron-withdrawing ability of the trifluoromethyl group can significantly change the physical, chemical and biological properties of a compound. Therefore, much effort has been put towards the synthesis of CF_3-bearing stereocenters, but their formation is still limited in scope. The existing syntheses of CF_3-containing chiral centers rely mostly on chemical or biocatalytic resolutions of racemates or on the selective fluorination of chiral, non-fluorinated substrates.[2,3]

Chiral Rh and Ru catalysts have been used in the asymmetric hydrogenation of CF_3-substituted olefins. Because both types of catalysts require a coordinating group near the substrate double bond to obtain high enantioselectivity, all of the trifluoromethyl olefins hydrogenated so far have possessed functionality on or close to the double bond that bears the CF_3 group. In 1980, Koenig et al. reported the first successful asymmetric hydrogenation of a CF_3-substituted olefin by applying a chiral Rh catalyst in the hydrogenation of 2-acetoxy-3,3,3-trifluoromethyl-1-propene with good enantioselectivity (77%).[4] Ten years later, Burk reported a higher *ee* (>95%) for the reduction of the same substrate using Rh catalysts.[5] Kobayashi, Iseki and their co-workers enlarged the scope of functionalized trifluoromethyl olefin hydrogenation using a chiral Ru-(*R*)-BINAP catalyst.[6] They produced optically active 2-(trifluoromethyl)alkan-1-ols with *ee* values up to 83% and 2-(trifluoromethyl)propionic acid with 80% *ee* after derivatization; whereas they hydrogenated an unsaturated CF_3-substituted ester to an almost racemic product. To the best of our knowledge, there are no routes to obtain simple chiral fluoroalkanes, because all methods give optically active fluoroalkanes with additional functionality.

In the past decades, Ir complexes with chiral N,P ligands have proven to be efficient catalysts for the enantioselective hydrogenation of olefins.[7] As these catalysts hydrogenate both unfunctionalized and functionalized olefins, they have an advantage over Rh and Ru catalysts. Since the first chiral mimic of Crabtree's complex was reported by Pfaltz and his coworkers,[8] many groups have contributed to an ever-growing bank of chiral N,P-ligated Ir complexes that work very well in olefin hydrogenation, but have only been tested with a limited range of substrates.[9,10] Recently, the demand for new, optically active chiral centers has encouraged us[11] and others[12] to test the Ir-catalyzed asymmetric hydrogenation of more

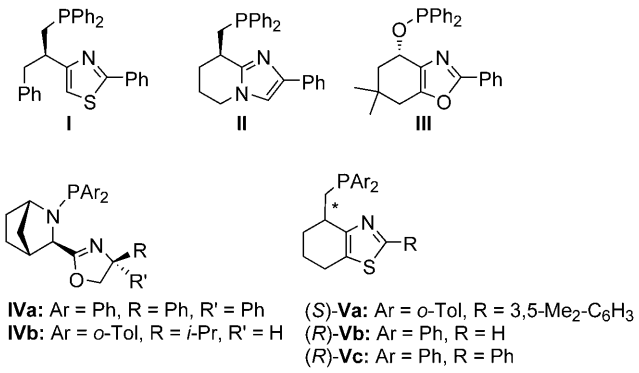
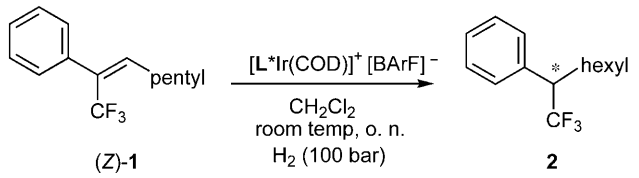


Figure 1. N,P-chelating ligands to iridium used in the hydrogenation studies.

'exotic' substrates. For example, we have successfully hydrogenated vinyl fluorides with good to excellent enantioselectivities.[11b] This was the first example of the Ir-catalyzed asymmetric hydrogenation of fluorinated compounds. To further develop this field, we set out to perform the Ir-catalyzed asymmetric hydrogenation of non-coordinating CF_3-substituted olefins, that is trifluoromethyl olefins with no additional functional groups.

Initially, we evaluated the asymmetric hydrogenation of the CF_3-substituted olefin (*Z*)-**1** by iridium catalysts of the N,P ligands **I**–**V** (Figure 1), as these catalysts are highly selective and efficient for the asymmetric hydrogenation of imines and trisubstituted olefins (Table 1).[10] The conversions and enantioselectivities varied widely with ligand structure. Most thiazole- (**I**,[10f] **Vc**[10d]) and imidazole-based (**II**[10g]) catalysts showed very good selectivities, whereas

Table 1. The asymmetric hydrogenation of CF_3-substituted olefin (*Z*)-**1**.[a]



Entry	Ligand (**L***)	Conv. [%]	*ee* [%]
1	**I**	95	**87**
2	**II**	88	**95**
3	**III**	27	60
4	**IVa**	8	47
5	**IVb**	79	27
6	(*S*)-**Va**	92	47
7	(*R*)-**Vb**	31	18
8	(*R*)-**Vc**	88	**96**

[a] *Reaction conditions:* 1.0 mol% catalyst, 16 h, room temperature, dry CH_2Cl_2, 100 bar H_2. Conversions were determined by ^1H NMR spectroscopy. *ee* values were determined by chiral GC/MS.

those with ligands **III**,[10a] **IV**[10c] and **Va**–**b** were less selective. The complexes of ligands **Va**[13] and **Vb**,[10d] which were included in order to evaluate an extremely bulky and a less bulky ligand, were both less selective than the complex of ligand **Vc**. When the hydrogen pressure was decreased from 100 to 50 bar, the Ir catalyst of ligand **Vc** retained selectivity (95% *ee*), whereas that of ligand **II** became less selective (85% *ee*). Additionally, a weakly coordinating solvent was not necessary, even in a non-coordinating solvent, 2,2,4-trimethylpentane, $[(\mathbf{Vc})Ir(COD)]^+[BAr_F]^-$ hydrogenated (*Z*)-**1** highly selectively.

We also evaluated the asymmetric hydrogenation of several other unfunctionalized CF_3-substituted olefins with CF_3 groups at the prochiral center. Chiral CF_3-containing products are especially interesting in 'flat-screen' technology. So far, there are no good methods to obtain these compounds and we therefore focused our efforts on them. Because some applications of chiral fluoroalkanes require varied alkyl chain lengths, four related olefins with alkyl chains of various lengths (Table 2, entries 1–4) were synthesized and hydrogenated using $[(\mathbf{Vc})Ir(COD)]^+[BAr_F]^-$. Overall, the enantioselectivies among these reductions were excellent, with *ee* values up to 96%, but the catalyst reactivity was lower when the alkyl chain was longer. A more bulky substrate that had a phenyl group on the alkyl chain (entry 5), was hydrogenated by $[(\mathbf{I})Ir(COD)]^+[BAr_F]^-$ in very good *ee* but to low conversion.

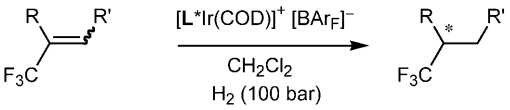
We also investigated the sensitivity of the hydrogenation reaction to changes of the aromatic moiety. *para*-Substitutions with electron-withdrawing (fluoro, entry 6) and electron-donating (methyl, entry 7) groups were examined. The catalyst $[(\mathbf{I})Ir(COD)]^+[BAr_F]^-$ hydrogenated these to similar conversions and with similar enantioselectivities to the unsubstituted olefin **1** (entry 3).

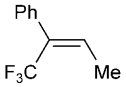
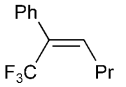
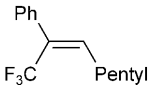
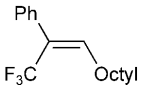
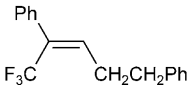
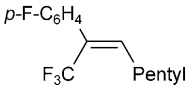
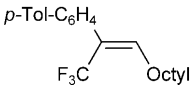
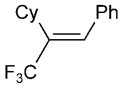
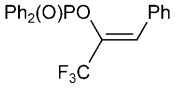
When a cyclohexyl substituent was present geminal to the CF_3 group, high conversion and good *ee* were obtained with catalyst $[(\mathbf{Va})Ir(COD)]^+[BAr_F]^-$ (entry 8). Thus the asymmetric hydrogenation does not require an aromatic substituent geminal to CF_3 group and so alkyl substituents can also be present there.

Our group has hydrogenated enol phosphinates with excellent stereoselectivities, and we therefore included one CF_3-substituted enol phosphinate in this study (entry 9).[11c,d] This was reduced in full conversion with excellent enantioselectivity. Chiral alkyl phosphinates are useful because they are easily transformed to the corresponding alcohols without loss of optical purity.[14]

During the course of this work, we noticed that catalyst $[(\mathbf{I})Ir(COD)]^+[BAr_F]^-$ hydrogenated the *cis* and *trans* isomers of CF_3-substituted olefins at different rates. This phenomenon has been observed with

Table 2. Asymmetric hydrogenation of CF_3-substituted olefins.[a]



Entry	L*	Olefin	Conv. [%]	*ee* [%]
1	(*R*)-**Vc**		94	**95** (−)
2	(*R*)-**Vc**		87	**92** (−)
3	(*R*)-**Vc**		88	**96** (−)
4	(*R*)-**Vc**		85	**95** (−)
5	(*R*)-**I**		21	**90** (−)
6	(*R*)-**I**		84	81 (−)
7	(*R*)-**I**		92	84 (−)
8	(*S*)-**Va**		96	74 (−)
9	(*R*)-**I**		>99[b]	**96** (+)

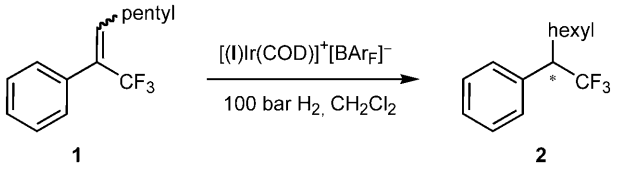
[a] *General reaction conditions:* 0.5–1.0 mol% catalyst, 72 h, room temperature, dry CH_2Cl_2, 100 bar H_2. Conversions were determined by ^{1}H NMR spectroscopy. *ee* values were determined by chiral HPLC or chiral GC/MS. For details see Supporting Information. Optical rotations are in parentheses. To date, the absolute configurations have not been correlated with optical rotations.

[b] The reaction was run at 50 bar H_2.

ruthenium catalysts by Iseki, Kobayashi and co-workers, but not for iridium catalysts.[6] As seen in Table 3, the hydrogenation of an isomeric mixture of olefin **1**, gives almost the same *ee* as the hydrogenation of the pure *Z* isomer. Apparently, *Z*-**1** reacts much faster than its *E* isomer, which was the only olefin isomer seen in the ^{1}H NMR spectrum after the reaction had reached 56% conversion. This is interesting because it offers the possibility to hydrogenate mixtures of *cis*/*trans* olefins, leaving the *E* isomer available for further functionalization.

In conclusion, we have developed a new, highly enantioselective synthetic route to building blocks

Table 3. Asymmetric hydrogenation of an isomeric mixture of CF_3-substituted olefins.[a]



1 2

Entry	Olefin	Conv. [%]	*ee* [%]
1	*E*-**1**	4	0
2	*Z*-**1**	95	87 (−)
3	*E*/*Z*-**1** (1:1)	56	83 (−)

[a] *Reaction conditions:* 1 mol% catalyst, room temperature, dry CH_2Cl_2, 100 bar H_2, 72 h.

with CF_3 at the chiral center. This synthetic route does not rely on additional functionality to direct its stereochemical course, and is therefore useful in the formation of chiral fluorine-containing molecules for a wide range of applications.

Experimental Section

General remarks, experimental details and preparation and spectral data of the new compounds can be found in the Supporting Information.

General Procedure for the Asymmetric Hydrogenation of CF_3-Substituted Olefins (Table 2)

A vial was charged with substrate (0.1–0.5 mmol) and catalyst (0.5–2 mol%), and CH_2Cl_2 (2 mL) was added. The vial was placed in a high-pressure steel apparatus, which was purged three times with H_2 before it was pressurized to 50–100 bar, left at room temperature and held at this pressure for 12–72 h. The pressure was released and the solvent was evaporated off. At this point, the conversion was measured by ^{1}H NMR spectroscopy. Then 1.5 mL of Et_2O:pentane (1:1) were added, and the resulting solution was filtered through a short plug of silica. The silica plug was rinsed with 3 mL Et_2O:pentane (1:1). The solvent was evaporated and the *ee* was determined by GC-MS or HPLC.

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References

[1] a) M. Schlosser, *Angew. Chem.* **1998**, *110*, 1538–1556; *Angew. Chem. Int. Ed.* **1998**, *37*, 1496–1513; b) B. E.

Smart, *J. Fluorine Chem.* **2001**, *109*, 3–11; c) M. Hird, J. W. Goodby, R. A. Lewis, K. J. Toyne, *Mol. Cryst. Liq. Cryst.* **2003**, *401*, 115–132; d) W. R. Dolbier Jr. , *J. Fluorine Chem.* **2005**, *126*, 157–163; e) A. M. Thayer, *Chem. Eng. News* **2006**, *84*, 15–24; f) a special issue has been devoted to "Fluorine in the Life Sciences": *ChemBioChem* **2004**, *5*, 559–722; g) Y. Suzuki, T. Hagiwara, I. Kawamura, N. Okamura, T. Kitazume, M. Kakimoto, Y. Imai, Y. Ouchi, H. Takezoe, A. Fukuda, *Liq. Cryst.* **2006**, *33*, 1344–1349.

[2] a) P. Bravo, G. Resnati, *Tetrahedron: Asymmetry* **1990**, *1*, 661–692; b) K. Mikami, Y. Itoh, M. Yamanaka, *Chem. Rev.* **2004**, *104*, 1–16; c) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119–6146; d) M. Shimizu, T. Hiyama, *Angew. Chem.* **2005**, *117*, 218–234; *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231.

[3] a) M. Kimura, T. Yamazaki, T. Kitazume, T. Kubota, *Org. Lett.* **2004**, *6*, 4651–4654; b) K. Tojo, Y. Aoki, M. Yasutake, T. Hirose, *J. Fluorine Chem.* **2006**, 620–626; c) R. Motoki, D. Tomita, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2006**, *47*, 8083–8086; d) T. Konno, T. Takehana, M. Mishima, T. Ishihara, *J. Org. Chem.* **2006**, *71*, 3545–3550; e) H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Lett.* **2007**, *36*, 666–667.

[4] K. E. Koenig, G. L. Bachman, B. D. Vineyard, *J. Org. Chem.* **1980**, *45*, 2362–2365.

[5] M. J. Burk, *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519.

[6] a) K. Iseki, Y. Kuroki, T. Nagai, Y. Kobayashi, *J. Fluorine Chem.* **1994**, *69*, 5–6; b) K. Iseki, Y. Kuroki, T. Nagai, Y. Kobayashi, *Chem. Pharm. Bull.* **1996**, *44*, 477–480.

[7] a) X. Cui, K. Burgess, *Chem. Rev.* **2005**, *105*, 3276–3296; b) K. Källström, I. Munslow, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 3194–3200; c) S. J. Roseblade, A. Pfaltz, *C. R. Chim.* **2007**, *10*, 178–187; d) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402–1411; e) T. L. Church, P. G. Andersson, *Coord. Chem. Rev.* **2008**, *252*, 513–531.

[8] a) R. H. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331–337; b) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem.* **1998**, *110*, 3047–3050; *Angew. Chem. Int. Ed.* **1998**, *37*, 2897–2899.

[9] a) J. Blankenstein, A. Pfaltz, *Angew. Chem.* **2001**, *113*, 4577–4579; *Angew. Chem. Int. Ed.* **2001**, *40*, 4445–4447; b) D. R. Hou, J. Reibenspies, T. J. Colacot, K. Burgess, *Chem. Eur. J.* **2001**, *7*, 5391–5400; c) P. G. Cozzi, N. Zimmermann, R. Hilgraf, S. Schaffner, A. Pfaltz, *Adv. Synth. Catal.* **2001**, *343*, 450–454; d) M. C. Perry, X. Cui, M. Powell, D. Hou, J. Reibenspies, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113–123; e) W. Tang, W. Wang, X. Zhang, *Angew. Chem.* **2003**, *115*, 973–976; *Angew. Chem. Int. Ed.* **2003**, *42*, 943–946; f) T. Bunlaksananusorn, K. Polburn, P. Knochel, *Angew. Chem.* **2003**, *115*, 4071–4073; *Angew. Chem. Int. Ed.* **2003**, *42*, 3941–3943; g) A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wüstenberg, N. Zimmermann, *Adv. Synth. Catal.* **2003**, *345*, 33–43; h) P. G. Cozzi, F. Menges, S. Kaiser, *Synlett* **2003**, *6*, 833–836; i) W. J. Drury III, N. Zimmermann, M. Keenan, M. Hayashi, S. Kaiser, R. Goddard, A. Pfaltz, *Angew. Chem.* **2004**, *116*, 72–76; *Angew. Chem. Int. Ed.* **2004**, *43*, 70–74; j) N. End, C. Stoessel, U. Berens, P. di Pietro, P. G. Cozzi, *Tetrahedron: Asymmetry* **2004**, *15*, 2235–2239; k) C. J. Wang, X. Sun, X. Zhang, *Angew. Chem.* **2005**, *117*, 5013–5015; *Angew. Chem. Int. Ed.* **2005**, *44*, 4933–4935; l) S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem.* **2006**, *118*, 5318–5321; *Angew. Chem. Int. Ed.* **2006**, *45*, 5194–5197; m) M. N. Cheemala, P. Knochel, *Org. Lett.* **2007**, *9*, 3089–3092; n) J. Zhou, J. W. Ogle, Y. Fan, V. Banphavichit (Bee), Y. Zhu, K. Burgess, *Chem. Eur. J.* **2007**, *13*, 7162–7170.

[10] a) K. Källström, C. Hedberg, P. Brandt, A. Bayer, P. G. Andersson, *J. Am. Chem. Soc.* **2004**, *126*, 14308–14309; b) A. Trifonova, J. S. Diesen, C. J. Chapman, P. G. Andersson, *Org. Lett.* **2004**, *6*, 3825–3827; c) A. Trifonova, J. S. Diesen, P. G. Andersson, *Chem. Eur. J.* **2006**, *12*, 2318–2328; d) C. Hedberg, K. Källström, P. Brandt, L. K. Hansen, P. G. Andersson, *J. Am. Chem. Soc.* **2006**, *128*, 2995–3001; e) J. J. Verendel, P. G. Andersson, *Dalton Trans.* **2007**, *47*, 5603–5610; f) P. Cheruku, A. Paptchikhine, M. Ali, J.-M. Neudörfl, P. G. Andersson, *Org. Biomol. Chem.* **2008**, *6*, 366–373; g) P. Kaukoranta, M. Engman, C. Hedberg, J. Bergquist, P. G. Andersson, *Adv. Synth. Catal.* **2008**, *350*, 1168–1176.

[11] a) K. Källström, I. Munslow, C. Hedberg, P. G. Andersson, *Adv. Synth. Catal.* **2006**, *348*, 2575–2578; b) M. Engman, J. S. Diesen, A. Paptchikhine, P. G. Andersson, *J. Am. Chem. Soc.* **2007**, *129*, 4536–4537; c) P. Cheruku, S. Gohil, P. G. Andersson, *Org. Lett.* **2007**, *9*, 1659–1661; d) P. Cheruku, J. Diesen, P. G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 5595–5599.

[12] a) N. S. Goulioukina, T. M. Dolgina, G. N. Bondarenko, I. P. Beletskaya, M. M. Ilyin, V. A. Davankov, A. Pfaltz, *Tetrahedron: Asymmetry* **2003**, *14*, 1397–1401; b) S.-M. Lu, X.-W. Han, Y.-G. Zhou, *Adv. Synth. Catal.* **2004**, *346*, 909–912.

[13] P. Kaukoranta, K. Källström, P. G. Andersson, *Adv. Synth. Catal.* **2007**, *349*, 2595–2602.

[14] T. Hayashi, K. Kanehira, M. Kumada, *Tetrahedron Lett.* **1981**, *22*, 4417–4420.

