Ruthenium-Catalyzed Asymmetric Electrophilic Fluorination of 1,3-Dicarbonyl Compounds

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Upon activation with $(Et_3O)PF_6$ (2 equiv), the ruthenium(II) complex $[RuCl_2(PNNP)]$ (**1**; PNNP is (1*S*,2*S*)-*N*,*N*′-bis(*o*-(diphenylphosphino)benzylidene)cyclohexane-1,2-diamine) catalyzes the electrophilic fluorination of 1,3-dicarbonyl compounds by *N*-fluorobenzenesulfonimide (NFSI). Oxygen donors, in particular Et_2O as cosolvent, increase the activity of the catalyst and, in some cases, the enantioselectivity. The absolute configuration of 2-*tert*-butoxycarbonyl-2-fluorocyclopentanone (**5a**), which is obtained with up to 93% ee in catalysis, was determined to be *R* by derivatization to (1*S*)-(−)-camphanic acid (1*R*,2*R*)-2-*tert*-butoxycarbonyl-2-fluoro-cyclopentyl ester (**7**) and X-ray analysis. A model for enantioselection is proposed on the basis of the known structures of the dicationic complex $[Ru(\mathbf{4a})(PNNP)]^{2+}$ (**2a**; **4a** is 2-*tert*-butoxycarbonylcyclopentanone), which is formed under catalysis conditions, and of its monocationic enolato analogue (**3a**). The stoichiometric reactions of **2a** and **3a** with NFSI in pure CH_2Cl_2 and in the presence of substrate, product, or Et_2O show that proton-transfer processes promoted by oxygen donors are pivotal in catalysis.

Introduction

The current most common methods to introduce a fluorine atom into an organic molecule are based on easy-to-handle electrophilic N−F reagents,[1,2] such as the commercially available 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis{tetrafluoroborate} (F-TEDA, also called *Selectfluor*) and *N*-fluorobenzenesulfonimide (NFSI), and on nucleophilic fluorine sources such as *N*,*N*-diethylaminosulfur trifluoride (DAST).[3] Following the increasing demand of bioactive fluoroorganic compounds with a C−F stereocenter,[4] methods for the stereoselective introduction of fluorine into organic molecules have been developed.[5] Enantioselective fluorination reactions have been originally developed using stoichiometric amounts of chiral N−F reagents derived from camphor- or cinchona alkaloids.[6] In 2000, we reported the first catalytic enantioselective process in which β-keto esters are fluorinated at the 2-position with F-TEDA in the presence of the chiral titanium complex (*R*,*R*)-$[TiCl_2(TADDOLato)(MeCN)_2]$.[7,8] The idea was to promote the enolization of the β-keto esters by a chiral transition metal Lewis acid, followed by fluorine transfer onto the coordinated enolate.[9] Since then, this reaction has been extended to other substrates (β-ketoamides, β-ketothioesters, β-ketophosphonates, and α-nitro esters)[10] and analogous heterofunctionalizations, encompassing electrophilic chlorination,[11,12] hydroxylation,[13] and sulfenylation.[14]

Besides a catalytic approach based on enantioselective phase-transfer catalysis,[15] several researchers have shown that a variety of chiral transition metal complexes efficiently catalyze electrophilic fluorination. Sodeoka's group reported a catalytic system for the enantioselective fluorination of 1,3-dicarbonyl compounds based on cationic palladium complexes.[16] Also copper(II) bis(oxazoline) complexes, as well as Ni(II) and Sc(III) complexes are now known to catalyze this reaction.[17] As these findings show that relatively soft late transition metal Lewis acids are suitable catalysts for this reaction, we tested

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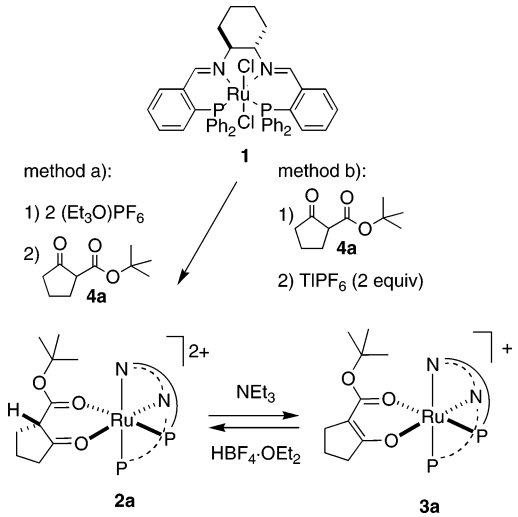
Scheme 1

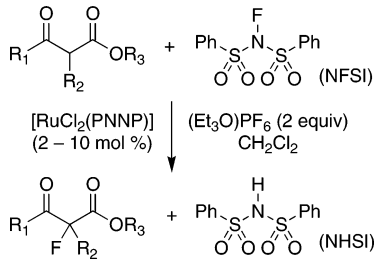


ruthenium complexes containing chiral tetradentate ligands PNNP. We previously reported that $[RuCl_2(PNNP)]$ (**1**; PNNP is (1*S*,2*S*)-*N*,*N*′-bis(*o*-(diphenylphosphino)benzylidene)cyclohexane-1,2-diamine)[18] forms, upon single chloride abstraction,[19,20] efficient catalysts for the cyclopropanation[20] and epoxidation[21] of olefins, as well as agents of nucleophilic fluorination of alkyl halides.[8,22] The abstraction of both chloro ligands from **1** with $(Et_3O)PF_6$ (2 equiv) produces a complex that catalyzes the hydroxylation of 1,3-dicarbonyl compounds such as *β*-keto esters and acyl lactams[13] and the Michael addition of *β*-keto esters to methyl vinyl ketone.[23,24]

The catalytically active species in the latter reactions is an elusive, highly oxophilic complex of tentative formulation $[Ru(OEt_2)_2(PNNP)]^{2+}$, which reacts with *β*-keto esters or acyl lactams to give the corresponding dicationic complexes $[Ru(O{-}O)(PNNP)]^{2+}$ (**2**, O−O is a chelating 1,3-dicarbonyl compound).[23] A remarkable feature of complexes of type **2** is that the 1,3-dicarbonyl compound (O−O) is bound to ruthenium in its non-enolized form (Scheme 1). Deprotonation of **2** with NEt_3 gives the corresponding enolato complexes **3**. We have previously reported the derivatives with 2-*tert*-butoxycarbonylcyclopentanone (**4a**) and α-acetyl-*N*-benzyl-*δ*-valerolactam (**4f**).[23] For complex **2a**, we estimated a pK_a^{aq} value (relative to Ph_3PH^+) between 1.9 and 4.6, depending on the reference value chosen for $pK_a^{aq}(Ph_3PH^+)$, from the acid−base equilibrium between **2a** and PPh_3.

Complexes of type **2** are ideal candidates to study the electrophilic atom-transfer reactions mentioned above, that is, hydroxylation, fluorination, and Michael addition, which involve O-, F-, and C-transfer to the ruthenium-coordinated 1,3-dicarbonyl compound. In fact, the solution structures of **2a** and **2f** have been determined by correlation with their enolato analogues **3a** and **3f**.[23] Following a preliminary communication,[25] we report here a full account of the asymmetric electrophilic fluorination catalyzed by Ru/PNNP complexes.

Scheme 2



Results and Discussion

In a first attempt, (*rac*)-$[Ru(acac)_2(PPh_3)_2]$ was tested as catalyst (5 mol %) for the electrophilic fluorination of ethyl 2-methyl-3-oxobutanoate (**4h**) with F-TEDA as the electrophilic fluorinating agent. The fluorinated *β*-keto ester **5h** was formed in trace amounts in acetonitrile solution and with 30% yield after 48 h in dichloromethane. Changing the fluorinating agent to *N*-fluorobenzenesulfonimide (NFSI) gave **5h** in 68% yield after 48 h, probably because NFSI is much more soluble in CH_2Cl_2 than F-TEDA. Therefore, NFSI was used as fluorinating agent for further screening. In the quest for a chiral catalyst, $[Ru(acac)_2(binap)]$,[26] $[Ru(OAc)_2(binap)]$,[27] and $[RuCl(\eta^6\text{-}p\text{-cymene})(binap)]PF_6$[28] (5−10 mol %) were then tested with **4h** as substrate. However, the yields did not exceed 52%, and the products were invariably racemic.

Eventually, nonracemic fluorinated products were obtained with the five-coordinate complex $[RuCl(PNNP)]PF_6$ (10 mol %),[20] which gave ethyl 2-fluoro-2-methyl-3-oxobutanoate (**5h**) with 81% yield and with an enantioselectivity of 27% ee after 24 h in CH_2Cl_2. The ether adduct $[RuCl(Et_2O)(PNNP)]PF_6$,[20b] generated by treating $[RuCl_2(PNNP)]$ (**1**) with $(Et_3O)PF_6$ (1 equiv), gave **5h** (6% yield) with 52% ee. Upon double chloride abstraction from the dichloro complex **1** with $(Et_3O)PF_6$ (2 equiv) (Scheme 2), **5h** was formed with 59% ee and in good yield after 24 h (Table 1, run 11), which prompted us to screen further substrates and optimize the catalysis conditions.

The catalyst formed from **1** and $(Et_3O)PF_6$ (2 equiv) was used to assess the scope of the reaction (Chart 1, Table 1). A total reaction time of 24 h had to be employed to achieve quantitative conversion of most substrates, indicating that the ruthenium catalyst is much slower than the titanium one.[7] The lower reactivity can be ascribed to the fact that ruthenium is a softer Lewis acid than titanium and that NFSI is a milder fluorinating agent than F-TEDA.[29,30] The substrate of choice is the cyclic *β*-keto ester **4a**, which is quantitatively converted to **5a** with 88% ee under the conditions described above (run 1), but with

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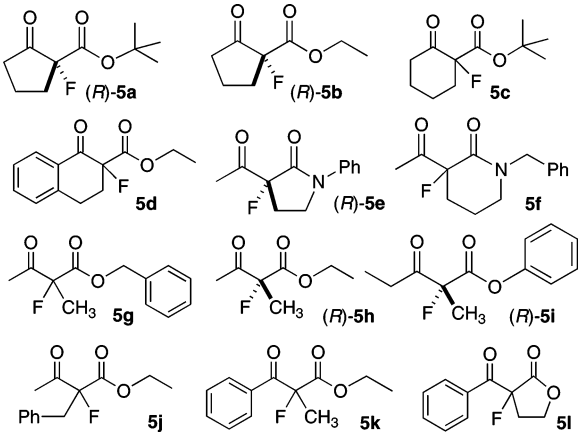
Table 1. Ruthenium-Catalyzed Asymmetric Fluorination[a]

run	substr.	enol (%)	yield (%)	ee (%)	abs. conf.[b]
1	**4a**	4	91	88	*R*
2[c]	**4a**		94	93	*R*
3[d]	**4a**		96	89	*R*
4	**4b**	3	82	58	*R*
5[c]	**4b**		84	65	*R*
6	**4c**	65	61	65	
7	**4d**	50	84	10	
8	**4e**	n.d.	90	8	*R*
9	**4f**	66	69	11	
10	**4g**	4	82	84	
11	**4h**	3	91[e]	59	*R*
12[c]	**4h**		96[e]	77	*R*
13	**4i**	3	34	53	*R*
14	**4j**	18	79	73	
15	**4k**	2	48	69	
16[c]	**4k**		65	24	
17	**4l**	5	60	71	

[a] Catalyst (10 mol %) prepared in situ from **1** and $(Et_3O)PF_6$ (2 equiv) in CH_2Cl_2, 24 h reaction time, unless otherwise stated. [b] See Experimental Section. [c] In CH_2Cl_2/Et_2O (1:1) as solvent, 4 h reaction time. [d] In CH_2Cl_2/Et_2O (1:1) as solvent, 2 mol % catalyst, 24 h reaction time. [e] Not isolated, conversion determined by NMR spectroscopy.

Chart 1



93% ee with optimized conditions (see below). These values compare to those obtained with titanium[7,8] (86% ee) and with Sodeoka's palladium[16a] system (92% ee).

Although cyclic substrates are fluorinated with higher enantiomeric excess than acyclic ones in general, the open-chain **5g** is formed with 84% ee (run 10). Cyclic β-keto esters containing five-membered rings give higher enantioselectivity than the corresponding ones bearing six-membered rings, as indicated by the comparison between **5a** and **5c** (runs 1, 6). A possible explanation is that the latter are enolized to a larger extent,[31] which makes them more reactive toward the electrophilic fluorinating agent and gives rise to a significant uncatalyzed (background) reaction. Moderately bulky groups at the ester functionality are beneficial to the enantioselectivity, as indicated by the comparison between **4a** and **4b** (runs 1, 4), and **4g**/**4h** (runs 10, 11). However, the COOPh group in **4i** reduces the activity drastically (run 13). Compared to the Ti/TADDOLato catalyst, the ruthenium system is superior for ethyl 2-benzyl-3-oxo-butanoate (**4j**) (73% ee vs 6% ee with titanium)[10c] and for lactone **4l** (71 vs 29% ee with ruthenium and titanium, respectively).[10d] Thus, the ruthenium catalyst tolerates bulky groups at the 2-position better than the titanium catalyst, albeit at the cost of activity.

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Table 2. Solvent Screening for the Fluorination of 4a[a]

run	solvent	time (h)	yield (%)	ee (%)
1	CH_2Cl_2	24	91	88
2[b]	CH_2Cl_2	24	88	86
3	1,2-dichloroethane	24	83	78
4	acetone	74	35	65
5	EtOH	48	33	5
6[c]	CH_2Cl_2/Et_2O (1:1)	4	94	93
7	CH_2Cl_2/THF (1:1)	4	93	85
8	CH_2Cl_2/dioxane (1:1)	3.5	84	83

[a] Reactions with 10 mol % of catalyst from **1**/2 $(Et_3O)PF_6$ at room temperature (method *a*). [b] Catalyst **2a** is formed in situ from **1** (10 mol %) and $TlPF_6$ (20 mol %) in the presence of **4a** (method *b*). [c] The same results were obtained with method *b*.

Effect of Oxygenated Solvents. In a parallel study of the Michael addition of 1,3-dicarbonyl compounds catalyzed by **1**/2 $(Et_3O)PF_6$, we recently found that oxygen-containing cosolvents enhance the reaction rate and—in some cases—the enantioselectivity.[23,24] Therefore, we screened the fluorination of **4a** in different solvents (Table 2). Although the solubility of the catalyst and NFSI restricted the solvent choice, significant differences were observed. Thus, the catalyst is less active and enantioselective in acetone and ethanol (runs 4, 5) as compared to dichloromethane, which can be ascribed—at least in part—to the strong coordination of these oxygen-containing solvents to the Ru/PNNP fragment.[21b] In contrast, 1:1 mixtures of CH_2Cl_2 with weakly coordinating oxygenated solvents (such as ethers) dramatically increase the reaction rate (runs 6−8). Quantitative conversion is obtained within 3.5−4 h, whereas a reaction time of 24 h is required in pure CH_2Cl_2. The CH_2Cl_2/Et_2O (1:1) mixture is superior to all other solvent systems, as it gives the fluorinated product **5a** in 94% yield and with 93% ee (Table 2, run 6). Pure diethyl ether as solvent is inapplicable because the Ru/PNNP complexes are insoluble in it.

The rate enhancement is general for the substrates tested in CH_2Cl_2/Et_2O solvent mixtures, that is, **4a**, **4b**, **4h**, and **4k**, whereas the effect on enantioselectivity is substrate specific (Table 1, runs 2, 5, 12, and 16). Besides **4a**, an improvement was observed for substrate **4b** (65% ee in CH_2Cl_2/Et_2O (1:1) vs 58% ee in CH_2Cl_2) and for **4h** (77% ee in the solvent mixture vs 59% ee in CH_2Cl_2), whereas **4k** gave lower enantioselectivity in CH_2Cl_2/Et_2O (1:1) (24% ee) than in pure CH_2Cl_2 (69% ee). Taking advantage of the rate enhancement in CH_2Cl_2/Et_2O (1:1), the catalyst loading with **4a** was reduced to 2 mol %, which produced **5a** in 96% yield and 89% ee within 24 h (Table 1, run 3).

The effect of oxygen-containing solvents prompted us to study the effect of small, controlled amounts of diethyl ether on the enantioselectivity of the catalytic fluorination of **4a**, which required the synthesis of **2a** under ether-free conditions. As the preparation of the catalyst from **1** and $(Et_3O)PF_6$ (2 equiv) produces Et_2O (1 equiv) along with EtCl (1 equiv) (method *a*), the double chloride abstraction was performed with $TlPF_6$ (2 equiv) in the presence of excess **4a** (10 equiv) (method *b*). The reaction yielded pure, ether-free **2a**, as determined by ^{31}P NMR spectroscopy after filtering off thallium(I) chloride, the only secondary product. A catalytic run performed by adding NFSI to the resulting solution gave **5a** with 86% ee (Table 2, run 2), which is slightly lower than with the standard activation method with $(Et_3O)PF_6$ (88% ee, run 1). Thus, even small amounts of diethyl ether increase the enantioselectivity of the catalytic fluorination of **4a** as compared to ether-free conditions. In the presence of a large excess of Et_2O (as in the CH_2Cl_2/Et_2O (1:1) solvent mixture), the enantioselectivity reaches 93% ee,

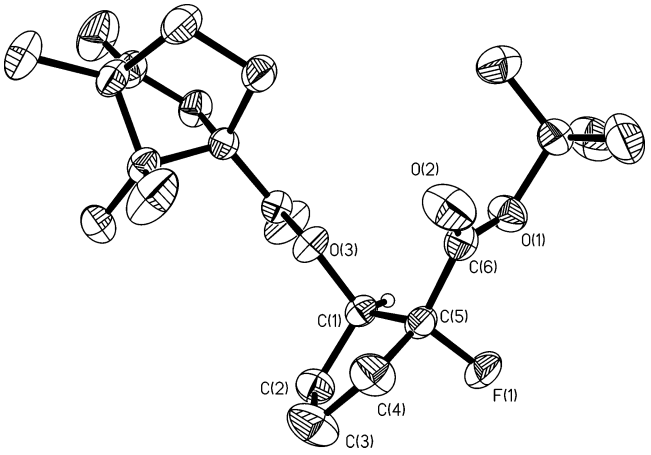
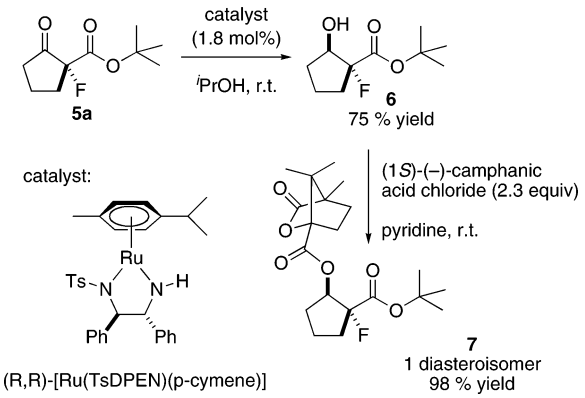


Figure 1. ORTEP drawing of (1*S*)-(−)-camphanic acid (1*R*,2*R*)-2-*tert*-butoxycarbonyl-2-fluoro-cyclopentyl ester (**7**), showing the *R* absolute configuration of the fluorinated stereogenic center.

Scheme 3



irrespective whether $(Et_3O)PF_6$ or $TlPF_6$ was used as chloride scavenger (run 6).

Absolute Configuration of 5a. To correlate the sense of induction with the known structures of **2a** and **3a**,[23] we determined the absolute configuration of the fluorinated product **5a**. The keto group in **5a** was reduced by transfer hydrogenation in isopropanol with (*R*,*R*)-[Ru(TsDPEN)(*p*-cymene)] as catalyst,[32] which gave alcohol **6** as a 92:8 mixture of diastereoisomers (Scheme 3). After separation by column chromatography, the major isomer was treated with enantiomerically pure (1*S*)-(−)-camphanic acid chloride to give ester **7** as a single diastereoisomer, which was crystallized by slow evaporation of a diethyl ether solution. An X-ray study revealed that the configuration of the stereogenic C−F center is *R* by internal comparison with the known absolute configuration of the (−)-camphanic acid scaffold (Figure 1). We have previously reported an X-ray study of **3a**, as well as a structural study of **2a** in solution based on NMR spectroscopy, whose results are summarized in Figure 2.[23] In both complexes, a phenyl group of PNNP shields the *si* face of the coordinated *β*-keto ester, and the observed *R* configuration of **5a** is in agreement with the attack of NFSI onto the exposed *re* face.

Stoichiometric Fluorination. Complexes **2a** and **3a**, which contain the best-performing substrate 2-*tert*-butoxycarbonylcyclopentanone (**4a**), were chosen to study the stoichiometric reactions with NFSI. These were run in pure CH_2Cl_2 or in CH_2Cl_2/Et_2O (1:1) as solvent (Table 3). Complex **2a**, which cannot be isolated, was prepared in situ by either method *a* or *b*. As previously observed,[23] the ^{31}P NMR spectra of **2a** and **3a** show their formation as a single diastereoisomer. Both complexes react with NFSI to give (*R*)-**5a**, that is with the same sense of induction as observed in the catalytic reaction. However, the stoichiometric reactions of **2a** (method *a*) with NFSI (1 equiv) give **5a** with 82% ee only, whereas 88−93% ee is observed in the corresponding catalytic reactions (entries 1, 2). Activation method *b* gave essentially the same results (entries 3, 4). The best value (97% ee) is obtained in the stoichiometric reaction of enolato complex **3a** with NFSI in CH_2Cl_2 (entry 5).[33] This almost perfect enantioselectivity confirms the effective steric shielding of the enolate *si* face by the PNNP ligand. However, enolato complex **3a** is unsuitable as catalyst precursor. Isolated

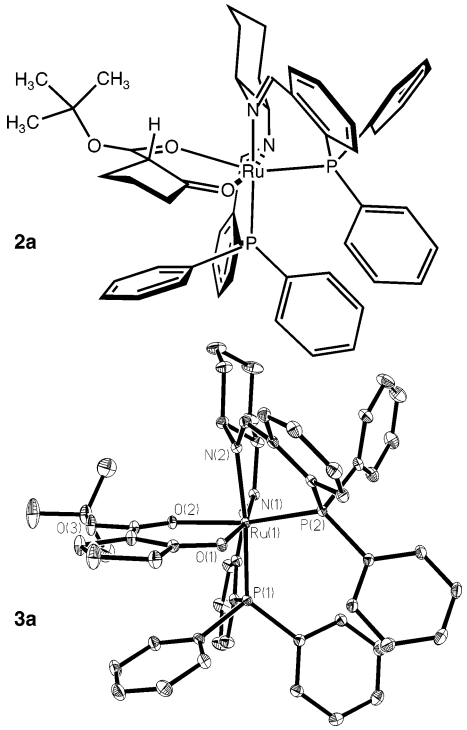


Figure 2. Comparison of **3a** (X-ray) and **2a** (as suggested by NMR spectroscopic studies).

Table 3. Complexes 2a and 3a in Stoichiometric (1:1) and Catalytic Fluorination[a]

				ee (%)	
entry	complex	scavenger	solvent	1:1	catalytic
1	**2a**	$(Et_3O)PF_6$	CH_2Cl_2	82	88
2	**2a**	$(Et_3O)PF_6$	CH_2Cl_2/Et_2O	82	93
3	**2a**	$TlPF_6$	CH_2Cl_2	81	86
4	**2a**	$TlPF_6$	CH_2Cl_2/Et_2O	81	93
5[b]	**3a**		CH_2Cl_2	97	47
6[b]	**3a**		CH_2Cl_2/Et_2O	93	35

[a] In the stoichiometric reactions, either $(Et_3O)PF_6$ (method *a*) or $TlPF_6$ (method *b*) were used as scavengers (see Experimental Section) to form **2a**, which was treated with NFSI (1 equiv) in the solvent indicated. In the catalytic runs 1−4, **2a** (10 mol %) was prepared as before, and then **4a** (10 equiv) and NFSI (1.08 equiv vs **4a**) were added in the specified solvent. [b] Stoichiometric: Isolated **3a** was reacted with NFSI (1 equiv). Catalytic: **3a** (0.1 equiv) and **4a** (0.9 equiv) were treated with NFSI (1.05 equiv) in the solvent indicated.

(32) (a) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (b) Haack, K-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285.

(33) We have previously reported an enantioselectivity of 83% ee for the same reaction.[25] In the meantime, we have improved the methods of isolation and purification of **3a**. Most probably, trace amounts of impurities were responsible for the lower enantiomeric excess obtained before.

3a (10 mol %) fluorinates **4a** with only 65% conversion after 24 h, and the enantioselectivity drops to 47% ee (entry 5).

The above observations are puzzling in two respects. First, enolato complex **3a** gives the highest enantioselection in the stoichiometric F-transfer but features low enantioselectivity as catalyst. The main difference between **2a** and **3a** as precatalysts is that the first catalytic cycle of the reaction with NFSI produces $(PhSO_2)_2NH$ (NHSI) in the case of **2a** and $(PhSO_2)_2N^-$ (NSI^-) with **3a**. Therefore, the effects of NHSI and NSI^- had to be assessed. The second surprising feature is that the enantioselectivity of the stoichiometric (1:1) reaction between NFSI and **2a** is lower than that of the catalytic fluorination under analogous conditions. This implies that the enantioselectivity of fluorine transfer increases during the course of catalysis, a phenomenon that we have previously observed.[25,34] These issues are discussed in the following two sections.

Effect of $(PhSO_2)_2N^-$. In the reaction of **3a** with NFSI, NSI^- is formed along with the fluorinated β-keto ester. Analogously, when **3a** is used as catalyst precursor, the first catalytic cycle produces NSI^- (1 equiv vs **3a**). To assess the effect of NSI^- in catalysis, we studied its coordinating properties toward ruthenium. $[Ru(OEt_2)_2(PNNP)]^{2+}$, prepared in situ from **1** and $(Et_3O)PF_6$ (2 equiv), was treated with $(Ph_4P)((PhSO_2)_2N)$ in CD_2Cl_2. As indicated by the AB patterns in the ^{31}P NMR spectrum of the reaction solution, three new complexes (**8a**, **8b**, and **8c**) were formed. The ^1H NMR spectrum showed signals that are diagnostic for the PNNP ligand in *cis*-β configuration, namely a doublet and a singlet for the imine protons (*H*C═N) and a multiplet for the *H*C−N cyclohexyl protons for each of the complexes. Besides **5a**, the reaction of enolato complex **3a** with NFSI (1 equiv) in CD_2Cl_2 gives **8a** and **8b** quantitatively, as indicated by the ^{31}P and ^1H NMR spectra of the reaction solution. The ^{19}F NMR spectrum shows that the fluorinated β-keto ester **5a** is not coordinated to ruthenium. On the basis of the ESI mass spectrum of the reaction solution, we formulate **8** as ruthenium PNNP complexes containing coordinated NSI^-. A ruthenium complex featuring a coordinated bis(trifluoromethylsulfonyl)imide anion has been recently reported,[35] and several bis(arylsulfonyl)amido complexes of Ag(I), Au(I), and Hg(II) are known.[36]

When added to a catalytic run in a 1:1 ratio to the catalyst, NSI^- reduces the enantioselectivity to 64% ee (Table 4, run 2). Interestingly, a stronger base than NSI^-, such as NEt_3, leaves the enantioselectivity unchanged when added in equimolar amount to ruthenium (run 4), and even a NEt_3/**4a** ratio of 1:1 affects the ee only moderately (run 5). Furthermore, the effect of NSI^- on enantioselectivity does not originate from a base-catalyzed background reaction, as **4a** does not react with NFSI in the presence of NSI^- in CH_2Cl_2. Also acids ($HBF_4 \cdot OEt_2$ and camphorsulfonic acid) do not catalyze the fluorination of **4a** by NFSI. Finally, NHSI does not affect the enantioselectivity, even when added in a 50 mol % ratio to the β-keto ester (run 3). It should be noted that NHSI, contrary to water, is a weak acid in dichloromethane. We find that NHSI does not protonate **3a** to a significant extent in CD_2Cl_2 and that the NSI^- anion, introduced as its tetraphenylphosphonium salt (1 equiv), cleanly deprotonates **2a** to **3a**.[37] Therefore, NHSI is mainly present in its nonionized form and not as the bis(benzenesulfonyl)amide anion NSI^- when **2a** is used as catalyst.

Table 4. Influence of Additives on the Catalytic Fluorination of 4a[a]

run	additive (mol %)	time (h)	yield (%)	ee (%)
1	−	24	91	88
2[b]	NSI^- (10)	24	92	64
3	NHSI (50)	23	83	87
4	NEt_3 (10)	23	86	88
5	NEt_3 (100)	96	32	73

[a] The reactions were carried out with **2a** as catalyst (10 mol %) from method *a* in CH_2Cl_2. [b] NSI^- is the bis(benzenesulfonyl)amide anion $(PhSO_2)_2N^-$.

Table 5. Enantioselectivity Increase during Catalytic Fluorination of 4a[a]

conversion (%)	ee (%)
15	65
56	76
76	82
94	85

[a] For reaction conditions, see Table 1.

We conclude that $(PhSO_2)_2N^-$, which is present only in a basic environment (for instance, with **3a** as catalyst), reduces the enantioselectivity by coordination to ruthenium. The formation of $(PhSO_2)_2N^-$ is irrelevant in the case of the stoichiometric reaction because its coordination occurs after fluorine transfer. The above results suggest that, in catalysis, the coordination of $(PhSO_2)_2N^-$ to the Ru/PNNP fragment produces a less enantioselective catalytic species.

Role of Oxygen-Containing Molecules. As mentioned above, the observation that the stoichiometric (1:1) reaction between NFSI and **2a** is less enantioselective than catalytic fluorination under analogous conditions implies that the enantioselectivity of fluorine transfer increases during the course of the reaction. The latter phenomenon has been independently observed by monitoring the enantioselectivity during a catalytic run (Table 5). Furthermore, a set of reactions with limiting amounts of NFSI was run to confirm the dependency of the enantioselectivity on the degree of conversion of β-keto ester **4a** to its fluorinated analogue **5a**. To disentangle the effects of substrate, product, and solvent, two reaction series (in pure CH_2Cl_2 as solvent and CH_2Cl_2/Et_2O (1:1) solvent mixture) were performed under standard catalysis conditions, that is, by activation of **1** with $(Et_3O)PF_6$ (2 equiv).

In pure CH_2Cl_2 as solvent, **5a** is formed in 70, 81, 84, and 86% ee for 0.10, 0.25, 0.5, and 0.75 equiv of NFSI, respectively. In CH_2Cl_2/Et_2O (1:1), 73, 90, 91, and 91% ee is obtained with 0.10, 0.25, 0.5, and 0.75 equiv of NFSI, respectively. In both series, the enantiomeric excess of **5a** increases with increasing

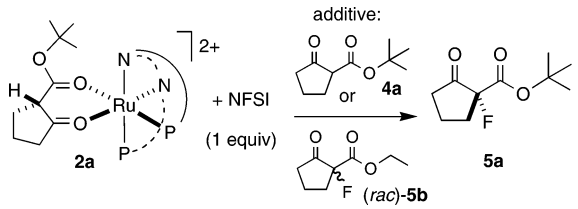
(34) As a first hypothesis, we attributed this behavior to the formation of a ruthenium(III) complex during the catalytic reaction.[25] Attempts to reproduce the original preparation of the alleged enolato complex of ruthenium(III) by chloride abstraction from **1** with $(Et_3O)PF_6$ (2 equiv), followed by oxidation with $AgPF_6$ (1 equiv or in excess) and addition of **4a** (1 equiv or in excess), with or without adding NEt_3, always yielded **2a** in low purity instead. In addition, we treated the enolato complex **3a** with different one-electron oxidants. Although a Ru(III) complex is possibly formed under such conditions, it is reduced back to the ruthenium(II) complex **2a** in the presence of a large excess of β-keto ester, which does not support the possibility of Ru(II) → Ru(III) oxidation during catalysis—at least at low substrate conversion.

(35) Williams, D. B.; Stoll, M. E.; Scott, B. L.; Costa, D. A.; Oldham, W. J. *Chem. Commun.* **2005**, 1438.

(36) See, for instance: Jones, P. G.; Blaschette, A.; Lautner, J.; Thoene, C. *Z. Anorg. Allg. Chem.* **1997**, *623*, 775.

(37) In CD_2Cl_2, NHSI is a slightly weaker acid than **2a**. The ^{31}P NMR spectrum of a CD_2Cl_2 solution of **3a** and NHSI (1 equiv) shows the signals of **3a** exclusively, and the N−*H* acidic proton gives a broad signal with approximately the expected intensity at δ 4.4 in the ^1H NMR spectrum. When a 10-fold excess of NHSI is added, the ^{31}P NMR doublets broaden and shift from the position observed for **3a** (δ 63.4 and 52.5) to δ 62.8 and 52.2, that is, toward those of **2a** (δ 61.2 and 51.3), which we take as an indication that **3a** is protonated to a small extent. Upon addition of Et_2O (CD_2Cl_2/Et_2O ratio = 7:1), however, the signals return to their original shape, indicating that only **3a** is present.

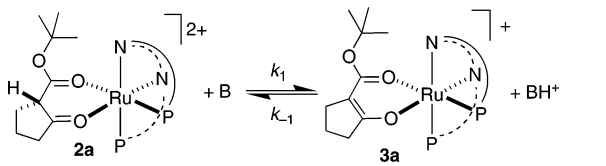
Table 6. Stoichiometric Fluorination in the Presence of an Excess of β-keto Ester[a]



run	additive (9 equiv)	solvent	ee (%)
1	**4a**	CH_2Cl_2	66
2	**4a**	CH_2Cl_2/Et_2O (1:1)	57
3	(*rac*)-**5b**	CH_2Cl_2	79
4	(*rac*)-**5b**	CH_2Cl_2/Et_2O (1:1)	86

[a] Complex **2a** was prepared by method *b*.

Table 7. Estimated Rate and Equilibrium Constants for Dissociation of 2a[a]



additive (B)	solvent	k_1 (s^{-1})	k_{-1} (s^{-1})	**2a**:**3a**
–	CD_2Cl_2	2.6 ± 0.4	28 ± 5	92:8
4a (8 equiv)	CD_2Cl_2	3.0	27	90:10
5a (8 equiv)	CD_2Cl_2	3.1	32	91:9
–	CD_2Cl_2/Et_2O	2.3 ± 0.8	18 ± 3	89:11
4a (8 equiv)	CD_2Cl_2/Et_2O	5.5 ± 1.1	38 ± 8	87:13
5a (8 equiv)	CD_2Cl_2/Et_2O	14 ± 4	74 ± 7	85:15

[a] From line width analysis of the ^{31}P NMR spectra (Lorentz lines).

NFSI added. The largest effect is observed in CH_2Cl_2/Et_2O (1:1), where the enantioselectivity goes from 73% ee in the first reaction (which is, in fact, stoichiometric in NFSI) to 91% ee at 75% conversion. This suggests that, besides the solvent, the accumulation of free fluorinated product **5a** during catalysis influences the enantioselectivity of the overall catalytic reaction.

The first and last turnovers of catalysis were simulated to test how the **4a**/**5a** ratio affects the enantioselectivity of stoichiometric fluorine transfer. Thus, ether-free **2a** (prepared by method *b*, see Experimental Section) was treated with NFSI (1 equiv) in the presence of either excess β-keto ester **4a** or its closely related fluorinated analogue[38] (*rac*)-**5b** both in pure CH_2Cl_2 and in CH_2Cl_2/Et_2O (1:1) (Table 6). The results in both solvent systems show that excess substrate **4a** decreases the enantioselectivity (66 and 57% ee in CH_2Cl_2 and CH_2Cl_2/Et_2O, respectively) with respect to the analogous reactions without additives (81−82% ee, Table 3, runs 1−4). Most interesting is run 4, in which the combined presence of **5b** and Et_2O leads to 86% ee, which is much higher than that with excess **4a** and is close to the best catalytic results.

Overall, the qualitative trends show that the enantioselectivity is higher in the presence of excess **5b** than with excess **4a**, which explains the enantioselectivity increase during the catalytic reaction, and that the effect is enhanced by the addition of Et_2O. As the enolato complex **3a** gives the highest enantioselectivity in stoichiometric fluorine transfer, we speculated that this effect might be related to the acid−base equilibrium between **2a** and **3a**. Thus, we studied briefly both the thermodynamic and kinetic aspects of this equilibrium in the presence of free β-keto ester **4a** and of its fluorinated analogue **5a**.

β-Keto Esters 4a and 5a as Weak Bases. When prepared under ether- and acid-free conditions[39] from **1**, β-keto ester **4a** (1 equiv), and $TlPF_6$ at concentrations above 0.04 M in CD_2Cl_2, **2a** is formed along with small amounts[40] of the enolato analogue **3a** and of the diaqua complex $[Ru(OH_2)_2(PNNP)]^{2+}$.[41] Selective irradiation and ^{31}P,^{31}P NOESY exchange NMR spectroscopic experiments indicate that **2a** and **3a** are slowly exchanging at room temperature and that the diaqua complex is not involved in the process. The exchange rate constants were estimated from the line widths of the ^{31}P NMR signals (Table 7). The rate constant for the formation of **3a**, k_1, is particularly relevant to our discussion. In pure CD_2Cl_2, its value increases to a very small extent (if at all) in the presence of excess of **4a** (8 equiv) or of **5a** (8 equiv). Diethyl ether as additive (0.1 mL) even causes a slight decrease of k_1, unless either **4a** or **5a** are added. The largest change is observed when fluorinated β-keto ester **5a** (8 equiv) is added to **2a** in the presence of Et_2O. Under these conditions, a 5-fold increase of k_1 is observed (with respect to **2a** in CD_2Cl_2), and 15% enolato complex **3a** is formed. The above observations indicate that Et_2O accelerates proton transfer in the presence of fluorinated β-keto ester **5a**, which behaves as a slightly stronger base than **4a**.[42] As the concentration of **5a** steadily increases during catalytic fluorination, the increasing rate of formation (and, concentration) of the highly selective enolato complex **3a** may explain why the enantiomeric excess of **5a** increases with conversion.[43]

It should be noted that the tautomerization of the closely related β-diketones is slow even in aqueous solution and catalyzed by metal ions—in particular by Cu(II)—and the catalytic efficiency has been associated with the ease of proton loss from the metal-bound diketone,[44] that is with its acidity enhancement upon coordination. We have found that the Ru/PNNP fragment increases the acidity of β-keto ester **4a** by at least 6 orders of magnitude.[23] Still, the proton transfer is expected to be slow in dichloromethane, which explains the dramatic effect exerted by oxygenated proton shuttles whose pK_a matches that of the β-keto ester complex.

In sum, the overall chemical evidence prompts us to sketch a hypothetical catalytic cycle (Scheme 4), which, albeit merely a working hypothesis for future mechanistic studies, explains our experimental observations. The highly oxophilic[19,20a,b,21,41] Ru/PNNP fragment binds β-keto ester **4a**, which displaces the weakly bound fluorinated product **5a** (step *a*).[45] Complex **2a** can either react directly with NFSI (step *b*) or be deprotonated to enolato complex **3a** (step *c*), which is then fluorinated (step *d*). The accumulation of **5a** during catalysis increases the

(38) The structurally closely related ethyl ester **5b** was chosen as a model product to allow for the independent determination of the enantiomeric excess of **5a** formed in the stoichiometric fluorination of **2a**. The use of excess **5a** with known ee would have implied calculating the incremental enantiomeric excess, a procedure that amplifies the experimental error.

(39) When $(Et_3O)PF_6$ is used to synthesize **2a**, no detectable amount of **3a** is observed by NMR spectroscopy, probably because Et_3O^+ reacts with traces of water to give Et_2OH^+.

(40) The ^{31}P NMR spectrum of the reaction solution shows the signals of **2a** (85% of total), **3a** (7%), and of diaqua complex $[Ru(OH_2)_2(PNNP)]^{2+}$ (8%). The formation of the latter sets free **4a**, which probably deprotonates **2a** to **3a**.

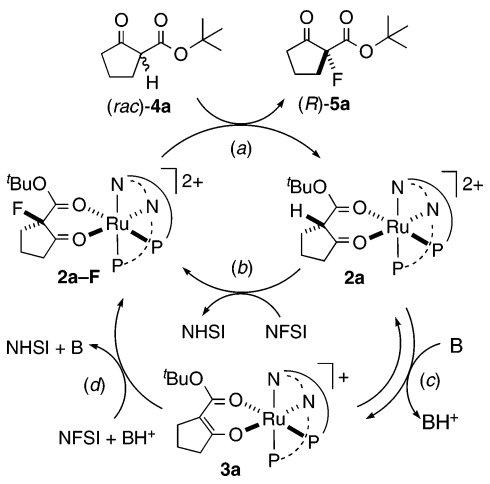
(41) Bonaccorsi, C.; Santoro, F.; Gischig, S.; Mezzetti, A. *Organometallics* **2006**, *25*, 2002.

(42) A tentative explanation of this fact is that the non-fluorinated β-keto ester **4a** is present in part in the enolic form, which is less basic than the keto form. In the fluorinated β-keto ester, the oxygen lone pairs are not delocalized because of the quaternary α-C atom, and this apparently enhances the basicity slightly.

(43) The accumulation of NHSI during catalysis cannot be responsible for this effect, as NHSI does not affect the enantioselectivity of the catalytic reaction (Table 4, run 3).

(44) Blanco, C. A.; Hynes, M. J. *Can. J. Chem.* **1991**, *70*, 2285.

Scheme 4



concentration of **3a** by acting as the base B in step *c*. As **3a** undergoes fluorine transfer with higher enantioselectivity than its dicationic keto analogue **2a**, the enantiomeric excess of **5a** increases with increasing conversion of **4a**.[46] Oxygen-containing molecules (Et_2O, **4**, or **5**) are pivotal as weak proton acceptors (B) in several steps. They accelerate the catalytic reaction by assisting the proton transfer in the equilibrium between **2a** and **3a**, which is slow in pure dichloromethane. Additionally, BH^+ protonates $(PhSO_2)_2N^-$ formed from NFSI and prevents its coordination to ruthenium. When **3a** is used as catalyst, the proton is missing, and the reaction of $(PhSO_2)_2N^-$ with **2a**−**F**, in which **5a** is weakly bound, interferes with the ligand exchange step (*a*).

A final problem concerns the detailed mechanism of fluorine transfer to **2a**. This step obviously implies C−H bond breaking but without forming **3a**, since otherwise one would expect the same enantioselection in the stoichiometric fluorination of **2a** and **3a**, which is not the case. We have encountered a similar problem in the Michael addition of **4a** catalyzed by **2a**. In that case, the keto complex **2a** reacts with methyl vinyl ketone to give the Michael product, whereas the enolato complex **3a** is completely unreactive even in the presence of a weak acid such as Et_3NH^+.[23] We are considering the possible involvement of a tautomeric form of **2a** that features a coordinated enol form of **4a**.

Conclusion

The complexes of general type $[Ru(O{-}O)(PNNP)]^{2+}$ (O−O = β-keto ester) in their nondeprotonated form are versatile Lewis acidic catalysts for electrophilic additions to β-keto esters, such as electrophilic fluorination and Michael reactions. The reactivity of these complexes is modulated by the acid−base reaction between the dicationic complexes of type **2**, which contain the 1,3-dicarbonyl compound in the diketo form, and their enolato analogues **3**. Additional lines of evidence suggest that proton-transfer processes play a pivotal role in both reaction classes. In the case of fluorination, we suggest that the effect of oxygen-containing molecules (be it solvent, substrate, or product) on the activity and the enantioselectivity results from a combination of thermodynamic and kinetic effects concerning the acid−base equilibrium between complexes **2** and **3**.

Experimental Section

General. Reactions with air- or moisture-sensitive materials were carried out under an argon atmosphere using Schlenk techniques. Complexes **1**[18] and **3a**[23] were prepared by published procedures. ^1H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded on Bruker AVANCE spectrometers AC 200, DPX 250, and DPX 300, respectively. Multidimensional NMR spectra were recorded on Bruker AVANCE spectrometers DPX 400 and DPX 500. ^1H and ^{13}C positive chemical shifts in ppm are downfield from tetramethylsilane. ^{19}F NMR spectra were referenced to external $CFCl_3$, and ^{31}P NMR spectra were referenced to external 85% H_3PO_4. ESI-MS measurements were performed on a Finnigan TSQ Quantum instrument by Mr. Luca Cereghetti (Prof. Peter Chen's group, ETH Zürich). The signals are given as *m*/*z* and the intensities in percentages of the base peaks (in italics). Optical rotations were measured using a Perkin-Elmer 341 polarimeter with a 1-dm cell. Elemental analyses were carried out by the Laboratory of Microelemental Analysis of the ETH Zürich.

General Procedure for Ruthenium-Catalyzed Fluorination. A solution of $[RuCl_2(PNNP)]$ (**1**) (20.0 mg, 0.024 mmol, 0.1 equiv) and $(Et_3O)PF_6$ (12.2 mg, 0.049 mmol, 0.205 equiv) in CH_2Cl_2 (2 mL; 1.5 mL for reactions in CH_2Cl_2/Et_2O (1:1)) was stirred at room temperature overnight. A color change from red to brown indicated the formation of the catalytically active complex. The substrate (0.24 mmol, 1 equiv) was added, and the mixture was diluted with CH_2Cl_2 (1 mL), or with Et_2O (1.5 mL) for reactions in CH_2Cl_2/Et_2O (1:1). After 10 min, *N*-fluorobenzenesulfonimide (NFSI, 82 mg, 0.26 mmol, 1.08 equiv) was added, and the reaction was monitored by TLC. After completion, the reaction was quenched by adding tetrabutylammonium chloride (20 mg, 0.072 mmol, 0.3 equiv) to deactivate the catalyst. The solvent was evaporated under reduced pressure, and the oily residue was subjected to flash chromatography under the conditions specified below. Analytical methods were developed with racemic products, which were prepared by the same method by using racemic **1**. Yields refer to isolated products unless otherwise stated. Conversions were determined by ^1H NMR spectroscopy as the ratio between the product and the sum of the starting material and product. Enantiomeric excesses were determined either by chiral GC on a ThermoQuest GC Trace 2000 series, a SUPELCO β-DEX 120 (30 m), or γ-DEX 120 (30 m) column, helium carrier (1.4 mL/min), split injector (42 mL/min, 200 °C), FID detector (air/H_2 350/35 mL/min, 250 °C), or by HPLC using Agilent HPLC 1100 and HPLC 1050 series systems. The retention time of the major isomer is given in italics.

2-*tert*-Butoxycarbonyl-2-fluorocyclopentanone (5a). Yield: 44 mg (91%). (In CH_2Cl_2/Et_2O (1:1): 46 mg (94%).) Analytical data are in agreement with literature values.[13] TLC (hexane/EtOAc, 10:1): R_f = 0.15 ($KMnO_4$); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.66−2.04 (m, 6 H, CH_2), 1.53 (s, 9 H, C(CH_3)$_3$); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −162.7 (dd, J = 21.0 Hz, J = 17.2 Hz); $[\alpha]^{20}_D$ +107.5 (c = 1.37, $CHCl_3$), 91% ee; GC: β-DEX column 90 °C isotherm; Retention times: 74.3 (*S*) and *75.7* min (*R*). The absolute configuration of the major enantiomer was determined to be *R* by an X-ray study of the camphanic ester **7** (see below).

2-Ethoxycarbonyl-2-fluorocyclopentanone (5b). Yield: 34.6 mg (82%). (In CH_2Cl_2/Et_2O (1:1): 35.3 mg (84%).) Analytical data are in agreement with literature values.[47] TLC (hexane/EtOAc, 10:1): R_f = 0.10 ($KMnO_4$); ^1H NMR ($CDCl_3$, 250 MHz): δ 4.32 (q,

(45) Addition of (*rac*)-**5a** (1.2 equiv) to $[Ru(OEt_2)_2(PNNP)]^{2+}$, formed from **1** and $(Et_3O)PF_6$ (2 equiv) in CD_2Cl_2, gives a mixture of **5a**-containing complexes, as indicated by five broad triplets between δ −162 and −166 in the ^{19}F NMR spectrum (the signal of free **5a** is at δ −162.7), which we attribute to different diastereomers of $[Ru(\mathbf{5a})(PNNP)]^{2+}$ (**2a-F**). β-Keto ester **4a** binds more strongly to ruthenium than its fluorinated analogue **5a**, as no change is observed in the ^{31}P or ^{19}F NMR spectra upon addition of excess **5a** (10 equiv) to **2a**.

(46) We disfavor an alternative explanation based on the presence of different diastereoisomers of **2a** or **3a**, as their formation is invariably completely diastereoselective.

(47) Cahard, D.; Audouard, C. Plaquevent, J. C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699.

J = 7.1 Hz, 2 H, CH_3CH_2), 2.68−2.10 (m, 6 H, CH_2), 1.34 (t, J = 7.1 Hz, 3 H, CH_3CH_2); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −164.0 (t, J = 20.5 Hz); $[\alpha]^{20}_D$ +169.0 (c = 1.53, $CHCl_3$), 99.7% ee (after separation by chiral HPLC); GC: β-DEX column 90 °C isotherm. Retention times: 58.6 (*S*) and *62.5* (*R*) min. The absolute configuration of the major enantiomer is *R* by comparison of the sign of optical rotation with the structurally related (*R*)-**5a**.

2-*tert*-Butoxycarbonyl-2-fluorocyclohexanone (5c). Yield: 33 mg (61%). Analytical data are in agreement with literature values.[16a] TLC (hexane/TBME, 9:1) (TBME is *tert*-butyl methyl ether): R_f = 0.21 (mostaine); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.88−2.39 (m, 3 H, CH_2), 2.21−1.76 (m, 5 H, CH_2), 1.55 (s, 9 H, $C(CH_3)_3$); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −159.2 (m); GC: γ-DEX column 85 °C isotherm. Retention times: 131.6 and *134.8* min.

2-Ethoxycarbonyl-2-fluorotetralone (5d). Yield: 50 mg (84%). Analytical data are in agreement with literature values.[15] TLC (hexane/TBME, 9:1): R_f = 0.10 (UV); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.12 (dd, J = 7.8 Hz, J = 1.4 Hz, 1 H, aromatic H), 7.60 (td, J = 7.6 Hz, J = 1.4 Hz, 1 H, aromatic H), 7.45−7.30 (m, 2 H, aromatic H), 4.34 (q, J = 7.2 Hz, 2 H, CH_3CH_2), 3.32−3.04 (m, 2 H, $CFCH_2$), 2.91−2.49 (m, 2 H, $CFCH_2CH_2$), 1.32 (t, J = 7.2 Hz, 3 H, CH_3CH_2); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −164.3 (dd, J = 22.4 Hz, J = 11.5 Hz); HPLC: Daicel Chiracel OB-H column; hexane/2-PrOH (85/15); 0.5 mL/min; detector: 254 nm; Retention times: *26.0* and 31.0 min.

2-Acetyl-2-fluoro-*N*-phenyl-γ-butyrolactam (5e). Yield: 53 mg (90%). Analytical data are in agreement with literature values.[10a] TLC (hexane/TBME, 7:3): R_f = 0.20 (UV). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (br d, J = 8.3 Hz, 2 H, aromatic H), 7.41 (br t, J = 7.8 Hz, 2 H, aromatic H), 7.25 (br q, J = 7.3 Hz, 1 H, aromatic H), 4.03−3.86 (m, 2 H, NCH_2), 2.91−2.79 (m, 1 H, $CFCH_2$), 2.49 (d, J = 4.9 Hz, 3 H, $C(O)CH_3$), 2.49−2.27 (m, 1 H, $CFCH_2$); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −157.2 (m); GC: β-DEX column 142 °C isotherm; Retention times: *121.7* (*R*) and 122.5 min (*S*). The absolute configuration of the major enantiomer is *R* by comparison of HPLC and GC data with literature data.[10a]

2-Acetyl-2-fluoro-*N*-benzyl-δ-valerolactam (5f). Yield: 43 mg (69%). Analytical data are in agreement with literature values.[13] TLC (hexane/EtOAc 4:1): R_f = 0.13 (UV); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.44−7.23 (m, 5 H, aromatic H), 4.69 (d, J = 14.7 Hz, 1 H, NCH_2Ph), 4.57 (d, J = 14.7 Hz, 1 H, NCH_2Ph), 3.44−3.22 (m, 2 H, NCH_2CH_2), 2.51 (d, J = 5.3 Hz, 3 H, $C(O)CH_3$), 2.50−1.88 (m, 4 H, $CFCH_2CH_2$); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −151.8 (m); GC: β-DEX column 134 °C isotherm; Retention times: *443.8* and 452.7 min.

Benzyl 2-Fluoro-2-methyl-3-oxobutanoate (5 g). Yield: 46 mg (82%). Analytical data are in agreement with literature values.[10c] TLC (hexane/TBME 9:1): R_f = 0.25 (UV); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.46−7.32 (m, 5 H, aromatic H), 5.27 (s, 2 H, OCH_2), 2.31 (d, J = 4.8 Hz, 3 H, $C(O)CH_3$), 1.73 (d, J = 22.0 Hz, 3 H, CH_3CF); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −157.0 (qq, J = 22.2 Hz, J = 4.5 Hz); GC: β-DEX column 110 °C isotherm. Retention times: *96.7* and 99.1 min.

Ethyl 2-Fluoro-2-methyl-3-oxobutanoate (5h). The product was not isolated. The conversion (91%) determined by NMR spectroscopy. Analytical data are in agreement with literature values.[48] TLC (hexane/EtOAc, 8:1): R_f = 0.23 ($KMnO_4$); ^{1}H NMR (CD_2Cl_2, 250 MHz): δ 4.24 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 2.32 (d, J = 4.3 Hz, 3 H, $C(O)CH_3$), 1.69 (d, J = 22.3 Hz, 3 H, $CFCH_3$); 1.30 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); ^{19}F NMR (CD_2Cl_2, 188.3 MHz): δ −157.7 (qq, J = 22.6 Hz, J = 4.5 Hz); GC: β-DEX column 70 °C isotherm. Retention times: *16.2* (*R*) and 17.2 min (*S*). The absolute configuration is *R* (by correlation with reported data).[48,49]

Phenyl 2-Fluoro-2-methyl-3-oxopentanoate (5i). Yield: 19 mg (34%). Analytical data are in agreement with literature values.[49] TLC (hexane/TBME, 85:15): R_f = 0.38 (UV); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45−7.37 (m, 2 H, aromatic H), 7.32−7.26 (m, 1 H, aromatic H), 7.15−7.10 (m, 2 H, aromatic H), 2.84 (qd, J = 7.2 Hz, J = 3.0 Hz, 2 H, CH_3CH_2), 1.85 (d, J = 22.2 Hz, 3 H, CH_3CF), 1.17 (t, J = 7.2 Hz, 3 H, CH_3CH_2); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −159.1 (br q, J = 21.8 Hz); GC: β-DEX column 120 °C isotherm. Retention times: *40.7* (*R*) and 41.8 min (*S*). The absolute configuration is *R* (by correlation with reported data).[10c,48,49]

Ethyl 2-Fluoro-2-benzyl-3-oxobutanoate (5j). Yield: 47 mg (79%). Analytical data are in agreement with literature values.[50] TLC (hexane/TBME 9:1): R_f = 0.30 (UV); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.34−7.24 (m, 5 H, aromatic H), 4.26 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.51 (br s, 1 H, CHH′CF), 3.38 (d, J = 1.8 Hz, 1 H, CHH′CF), 2.17 (d, J = 5.0 Hz, 3 H, $C(O)CH_3$), 1.29 (t, J = 7.2 Hz, 3 H, CH_3CH_2); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −164.6 (tq, J = 25.9 Hz, J = 5.2 Hz); HPLC: Daicel Chiracel OJ column (250 × 4.6 mm); hexane/*2-PrOH* (95/5); 1 mL/min; detector: 210.8 nm. Retention times: 11.1 and *14.3* min.

Ethyl 2-Methyl-2-fluoro-3-oxo-3-phenylpropanoate (5k). Yield: 26 mg (48%). (In CH_2Cl_2/Et_2O (1:1): 36 mg (65%)). Analytical data are in agreement with literature values.[7] TLC (hexane/EtOAc, 10:1): R_f = 0.27 ($KMnO_4$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09−8.05 (m, 2 H, aromatic H), 7.64−7.58 (m, 1 H, aromatic H), 7.51−7.46 (m, 2 H, aromatic H), 4.27 (qd, J = 7.2 Hz, J = 1.0 Hz, 2 H, CH_3CH_2), 1.89 (d, J = 22.5 Hz, 3 H, CH_3CF), 1.22 (t, J = 7.0 Hz, 3 H, CH_3CH_2); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −151.8 (br q, J = 22.4 Hz); GC: β-DEX column 110 °C isotherm; Retention times: *88.2* and 89.5 min.

3-Benzoyl-3-fluorodihydrofuran-2-one (5l). Yield: 31 mg (60%). Analytical data are in agreement with literature values.[10d] TLC (hexane/ TBME, 4:1): R_f = 0.17 (UV); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.20 (m, 2 H, aromatic H), 7.67 (tt, J = 7.6 Hz, J = 1.2 Hz, 1 H, aromatic H), 7.53 (tt, J = 7.7 Hz, J = 1.6 Hz, 2 H, aromatic H), 4.63−4.49 (m, 2 H, OCH_2), 3.20−3.10 (m, 1 H, CFCHH′); 2.86−2.67 (m, 1 H, CFCHH′); ^{19}F NMR ($CDCl_3$, 188.3 MHz): δ −156.8 (ddd, J = 23.9 Hz, J = 7.9 Hz, J = 1.5 Hz); HPLC: Daicel Chiracel OD-H column; hexane/2-PrOH (99.5/0.5); 0.5 mL/min; detector: 210.8 nm. Retention times: *64.0* and 70.6 min.

(1*R*,2*R*)-2-*tert*-Butoxycarbonyl-2-fluorocyclopentanol (6). (*R*,*R*)-[Ru(TsDPEN)(*p*-cymene)] (23 mg, 38 μmol, 1.8 mol %) was added to a solution of (*R*)-2-*tert*-butoxycarbonyl-2-fluorocyclopentanone **5a** (430 mg, 2.12 mmol, 88% ee) in ^{i}PrOH (18 mL). After stirring the resulting solution for 21 h at room temperature, ether (15 mL) was added, and stirring was continued for additional 3 h. Evaporation of the solvents gave the crude product, which was purified by column chromatography on SiO_2 with hexane/TBME (5:1) as eluents to give **6** as a light-yellow liquid (327 mg, 1.60 mmol, 75%). TLC (hexane/TBME, 5:1): R_f = 0.12 (mostaine). ^{1}H NMR (300 MHz, $CDCl_3$,): δ 4.33 (ddd, 1 H, J = 13.8, 8.6, 4.0 Hz, CHOH), 2.94 (d, 1H, J = 3.8 Hz, OH), 2.5−1.7 (m, 6H, CH_2), 1.51 (s, 9H, ^{t}Bu). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −156.1 (ddd, 1F, J = 36.0, 23.0, 13.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.0 (d, J = 25.1 Hz), 102.4 (d, J = 191.1 Hz), 83.2, 78.6 (d, J = 29.5 Hz), 33.4 (d, J = 23.1 Hz), 32.5 (d, J = 1.9 Hz), 28.0, 20.5. $[\alpha]^{20}_D$ −13.9 (c = 1.06, $CHCl_3$). EA: Calcd for $C_{10}H_{17}FO_3$ (204.24): C, 58.81; H, 8.39; found: C, 58.54; H, 8.41.

(1*S*)-(−)-Camphanic Acid (1*R*,2*R*)-2-*tert*-Butoxycarbonyl-2-fluorocyclopentyl Ester (7). (1*S*)-(−)-Camphanic acid chloride (430 mg, 1.98 mmol, 2.3 equiv) was added to a solution of **6** (177 mg, 0.87 mmol, 1 equiv) in pyridine (10 mL). TLC (hexane/ethyl acetate, 4:1) indicated complete conversion after stirring for 3 h at room temperature. The reaction mixture was then poured into

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aqueous HCl (10%, 50 mL) and extracted twice with dichloromethane. The combined organic layers were washed twice with 0.1 M HCl and with water; then they were dried (Na_2SO_4) and concentrated. Column chromatography on SiO_2 with hexane/ethyl acetate (4:1) gave diastereomerically pure **7** as a white solid (325 mg, 0.85 mmol, 98%). TLC (hexane/EtOAc, 4:1): R_f = 0.22 (mostaine). Mp 109−113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (ddd, 1 H, J = 14.7, 5.3, 5.3 Hz, C*H*OCO), 2.50−2.20 (m, 3H, CH_2), 2.15−1.75 (m, 6H, CH_2), 1.69−1.60 (m, 1H, CH_2), 1.50 (s, 9H, ^{t}Bu), 1.09 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.94 (s, 3H, CH_3). ^{19}F NMR (188.3 MHz, $CDCl_3$): δ −155.9 (ddd, 1F, J = 29.8, 21.1, 14.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 177.8, 167.1 (d, J = 25.1 Hz), 166.2, 101.5 (d, J = 192.1 Hz), 90.8, 83.1, 80.4 (d, J = 33.4 Hz), 54.8, 54.2, 33.1 (d, J = 22.3 Hz), 30.6, 30.3 (d, J = 1.7 Hz), 28.9, 27.9, 20.3 (d, J = 1.3 Hz), 16.8, 16.7, 9.6. $[\alpha]^{20}_D$ −27.6 (c = 1.10, $CHCl_3$). EA: Calcd for $C_{20}H_{29}FO_6$ (384.44): C, 62.49; H, 7.60; found: C, 62.65; H, 7.68.

X-ray study of 7. Single crystals were grown by slow evaporation of an Et_2O solution. Crystal data for $C_{20}H_{29}FO_6$: colorless prism (0.82 mm × 0.41 mm × 0.34 mm), orthorhombic, $P2_12_12_1$, cell dimensions (293 K) a = 6.4686(11) Å , b = 13.640(2) Å, c = 23.973(4) Å, and V = 2115.1(6) Å^3 with Z = 4, D_c = 1.207 Mg/m^3, μ = 0.094 mm^{-1} (Mo Kα, graphite monochromated), λ = 0.71073°, F(000) = 824. The data were collected at 293 K on a Bruker AXS SMART APEX platform in the θ range 1.70−24.71°. The structure was solved with SHELXTL using direct methods. Of the 10915 measured reflections with index ranges $-7 \le h \le 7$, $-15 \le k \le 16$, $-23 \le l \le 28$, 3603 unique reflections were used in the refinement (full-matrix least-squares on F^2 with anisotropic displacement parameters for all non-H atoms. Hydrogen atoms were introduced at calculated positions and refined with the riding model and individual isotropic thermal parameters for each group. Final residuals were R1 = 0.0394 for 3184 reflections with $I > 2\sigma(I)$ and wR2 = 0.1101 (all data), GOF = 1.036. Max. and min. difference peaks were respectively +0.150 and −0.140 e Å^{-3}, the largest and mean Δ/σ = 0.001 and 0.000.

In Situ Preparation of 2a. Solutions of **2a** were prepared by one of the following methods. **Method *a*.** $[RuCl_2(PNNP)]$ (30 mg, 36 μmol, 1 equiv) and $(Et_3O)PF_6$ (18.3 mg, 74 μmol, 1.05 equiv) were stirred in dichloromethane (2 mL; 1.5 mL for reactions in CH_2Cl_2/Et_2O (1:1)) at room temperature for 15 h. Then, 2-*tert*-butoxycarbonylcyclopentanone (6.5 μL, 36 μmol, 1 equiv) was added, and after 6 h the solution was diluted with dichloromethane (1 mL) or with Et_2O (1.5 mL for reactions in CH_2Cl_2/Et_2O (1:1)). **Method *b*.** $TlPF_6$ (30 mg, 86 μmol, 2.4 equiv) and 2-*tert*-butoxycarbonylcyclopentanone (6.5 μL, 36 μmol, 1 equiv) were added to a solution of $[RuCl_2(PNNP)]$ (30 mg, 36 μmol, 1 equiv) in dichloromethane (2 mL; 1.5 mL for reactions in CH_2Cl_2/Et_2O (1:1)). After stirring for 15 h at room temperature, the resulting suspension was filtered to remove TlCl and excess $TlPF_6$ and then was diluted with dichloromethane (1 mL) or with Et_2O (1.5 mL for reactions in CH_2Cl_2/Et_2O (1:1)).

Stoichiometric Fluorination of 2a. To a solution of **2a** (prepared by method *a* or *b* as described above) was added NFSI (11.7 mg, 37 μmol, 1.03 equiv). After stirring for 24 h, the reaction was quenched by adding tetrabutylammonium chloride (30 mg, 108 μmol, 3 equiv) to deactivate the catalyst. The solvent was evaporated under reduced pressure and the residue purified by column chromatography on SiO_2 (hexane/ethyl acetate, 10:1), yielding **5a**. Analytical data of the product are identical to those of the standard catalytic run.

Stoichiometric Fluorination of 3a. NFSI (12 mg, 38 μmol, 1.04 equiv) was added to a solution of enolato complex **3a** (40 mg, 37 μmol, 1 equiv) in dichloromethane (1.5 mL). After stirring for 24 h at room temperature, tetrabutylammonium chloride (30 mg, 108 μmol, 2.9 equiv) was added, and the solvent was evaporated under reduced pressure. Purification by column chromatography on SiO_2 (hexane/ethyl acetate, 10:1) gave **5a** (6.0 mg, 30 μmol, 81%) with an enantioselectivity of 97% ee. Analytical data of the product are identical to those of the standard catalytic run.

Catalytic Fluorination with 3a as Catalyst. To a solution of enolato complex **3a** (26 mg, 24 μmol, 0.1 equiv) and **4a** (39 μL, 0.216 mmol, 0.9 equiv) in dichloromethane (3 mL) was added NFSI (79 mg, 0.251 mmol, 1.05 equiv vs [**3a** + **4a**]), and the mixture was stirred for 24 h at room temperature. Then, tetrabutylammonium chloride (20 mg, 72 μmol, 0.3 equiv) was added, and the solvents were evaporated. The crude product was filtered through SiO_2 with hexane/ethyl acetate (10:1), giving 44 mg of a 1.85:1 mixture of **5a** + **4a**. Conversion: 65%; enantiomeric excess of **5a**: 47% ee. Analytical data of the product are identical to those of the standard catalytic run.

Stoichiometric Fluorination of 2a in the Presence of Additives. To a solution of **2a** (prepared by method *b*) was added the appropriate additive (0.32 mmol, 9 equiv, see Table 6) and NFSI (11.7 mg, 37 μmol, 1.03 equiv). After stirring at room temperature for 24 h, the reaction was quenched with tetrabutylammonium chloride (30 mg, 108 μmol, 3 equiv), and the solvent was evaporated under reduced pressure. Purification by column chromatography on SiO_2 (hexane/ethyl acetate, 10:1) gave **5a**. Analytical data of the product are identical to those of the standard catalytic run.

Tetraphenylphosphonium Bis(benzenesulfonyl)amide ((Ph_4P)-NSI). A 0.1 M NaOH solution was added to a suspension of dibenzenesulfonimide (NHSI, 400 mg, 1.35 mmol) in deionized water (5 mL) until all NHSI was dissolved and the pH reached 7−8. This solution was added to tetraphenylphosphonium bromide (564 mg, 1.35 mmol, 1.0 equiv) dissolved in a mixture of deionized water (10 mL) and EtOH (10 mL). A white solid started to precipitate, whose crystallization was completed at 5 °C overnight. Then the solids were collected by filtration, washed twice with water/EtOH (5:1), and dried in vacuo to give the pure product as a white crystalline solid (694 mg, 1.09 mmol, 81%). Mp 178 −180 °C. ^{1}H NMR (250 MHz, CD_2Cl_2): δ 7.92 (ddd, 4 H, J = 7.7, 7.7, 1.7 Hz, *p*-H of Ph_4P^+), 7.82−7.70 (m, 12 H, aromatic H of Ph_4P^+ + NSI^-), 7.62 (dd, 8 H, J = 12.8, 7.5 Hz, aromatic H of Ph_4P^+), 7.36−7.23 (m, 6 H, aromatic H of NSI^-). ^{31}P{^{1}H} NMR (101.3 MHz, CD_2Cl_2): δ 23.3 (s, 1 P). ^{13}C{^{1}H} NMR (100.6 MHz, CD_2Cl_2): δ 147.0, 136.1 (d, 1 C, J = 3.0 Hz, Ph_4P^+), 134.8 (d, 1 C, J = 10.3 Hz, Ph_4P^+), 131.0 (d, 1 C, J = 12.9 Hz, Ph_4P^+), 130.1, 128.0, 127.0, 117.9 (d, 1 C, J = 89.7 Hz, Ph_4P^+). EA: Calcd for $C_{36}H_{30}NO_4PS_2$ (635.74): C, 68.01; H, 4.76; N, 2.20; found: C, 67.89; H, 4.61; N, 2.11.

Coordination of Bis(benzenesulfonyl)amide (NSI^-) to the Ru/PNNP Fragment. From $[Ru(OEt_2)_2(PNNP)]^{2+}$ and (Ph_4P)NSI. $[RuCl_2(PNNP)]$ (**1**) (20 mg, 24.1 μmol) and $(Et_3O)PF_6$ (12.3 mg, 49.6 μmol, 2.06 equiv) were dissolved in CD_2Cl_2 (0.6 mL) in an NMR tube fitted with a Young valve. The resulting solution was stirred at room temperature for 15 h, and then (Ph_4P)NSI (15.3 mg, 24.1 μmol, 1.0 equiv) was added. NMR spectroscopic analysis of the reaction mixture showed three new compounds (**8a**, **8b**, and **8c**) with AB spin patterns in the ^{31}P NMR spectrum, together with several broad unidentified signals. Selected diagnostic ^{1}H NMR signals are given below. ^{1}H NMR (300 MHz, CD_2Cl_2) **8a**: δ 9.01 (d, 1 H, J = 9.6 Hz, *H*C═N), 8.62 (s, 1 H, *H*C═N), 5.30−5.19 (m, 1 H, *H*C−N); **8b**: δ 9.08 (d, 1 H, J = 9.60 Hz, *H*C═N), 8.55 (s, 1 H, *H*C═N), 4.83−4.72 (m, 1 H, *H*C−N); **8c**: δ 9.12 (d, 1 H, J = 10.2 Hz, *H*C═N), 8.73 (s, 1 H, *H*C═N), 4.14−4.04 (m, 1 H, *H*C−N). ^{31}P{^{1}H} NMR (121.5 MHz, CD_2Cl_2): **8a**: δ 61.6 (d, 1 P, $J_{P,P'}$ = 30.1 Hz), 43.8 (d, 1 P, $J_{P,P'}$ = 30.1 Hz); **8b**: δ 62.4 (d, 1 P, $J_{P,P'}$ = 30.0 Hz), 42.1 (d, 1 P, $J_{P,P'}$ = 30.1 Hz); **8c**: δ 48.7 (d, 1 P, $J_{P,P'}$ = 27.9 Hz), 47.2 (d, 1 P, $J_{P,P'}$ = 27.8 Hz).

From Enolato Complex 3a and NFSI. *N*-Fluorobenzenesulfonimide (NFSI, 6.0 mg, 19.0 μmol, 1.04 equiv) was added to a solution of enolato complex **3a** (20 mg, 18.4 μmol) in CD_2Cl_2 (0.6 mL). The reaction mixture was analyzed by NMR spectroscopy

and by ESI MS. The NMR spectra showed quantitative conversion to the products **8a** and **8b**. The ^{1}H and ^{31}P NMR data are identical to those reported above. ^{19}F NMR (CD_2Cl_2, 188.3 MHz): δ −73.2 (d, 6 F, J = 711 Hz, PF_6^-), −162.7 (dd, 1 F, J = 21.0 Hz, J = 17.2 Hz, free **5a**). MS (ESI): *m*/*z* 1056 (M^+, *100*), 759 ([Ru(PNNP)]$^+$, *17*).

Determination of 2a/3a Exchange Rates. CD_2Cl_2 solutions of **2a** were prepared in situ by method *b*, and **4a** (8 equiv), **5a** (8 equiv), or Et_2O (CD_2Cl_2/Et_2O ratio = 6:1) were added as appropriate. The exchange rate constants of equilibrium **2a** ⇆ **3a** were determined by line width analysis of the Lorentz lines in the ^{31}P NMR spectra as described below.[51] In the slow-exchange regime, the line width $W_{\mathbf{2a}}$ for the signals of complex **2a** is:

$$W_{2a} = \frac{1}{\pi}\left(k_1 + \frac{1}{T_{2,2a}}\right)$$

By neglecting the contributions of instrumental factors to the line broadening, the above equation transforms to a simple expression for the rate constant k_1:

$$k_1 = (W_{2a} - W_{0,2a})\cdot\pi$$

where the transverse relaxation time $T_{2,\mathbf{2a}}$ is derived from the natural line width $W_{0,\mathbf{2a}}$ by $T_{2,\mathbf{2a}} = (\pi\cdot W_{0,\mathbf{2a}})^{-1}$. An analogous equation is obtained for k_{-1}. Both equations are combined into

$$k_1 - k_{-1} = (W_{2a} - W_{3a})\cdot\pi$$

under the reasonable assumption that the natural linewidths for complexes **2a** and **3a** ($W_{0,\mathbf{2a}}$ and $W_{0,\mathbf{3a}}$) are similar.

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Supporting Information Available: CIF file of (1*S*)-(−)-camphanic acid (1*R*,2*R*)-2-*tert*-butoxycarbonyl-2-fluoro-cyclopentyl ester (**7**). This material is available free of charge via the Internet at http://pubs.acs.org.

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