Enantioselective Fluorination

DOI: 10.1002/anie.201205383

A Doubly Axially Chiral Phosphoric Acid Catalyst for the Asymmetric Tandem Oxyfluorination of Enamides**

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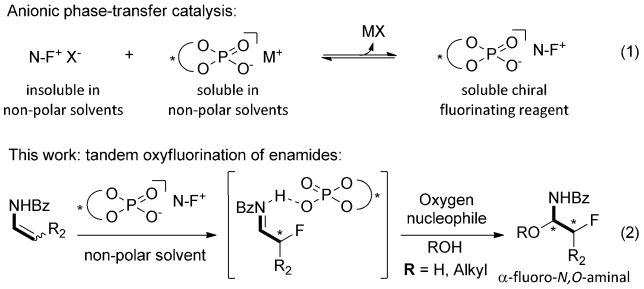
The selective construction of carbon–fluorine bonds is of great interest to medicinal chemists because the replacement of a carbon–hydrogen bond with a carbon–fluorine bond continues to be an effective approach to the development of biologically active molecules with improved physical and metabolic profiles and biological activities.[1] To this end, a number of impressive examples of catalytic enantioselective fluorination have been reported over the last decade.[2,3] Our laboratory has recently introduced a novel strategy for asymmetric fluorination based on phase-transfer catalysis using chiral anionic catalysts based on BINOL-derived phosphates [Eq. (1)].[4,5] Motivated by the importance of the



β-fluoroamine motif in medicinal chemistry we employed this strategy to develop a highly asymmetric fluorination of cyclic enamides, allowing us to isolate stable but highly versatile enantioenriched α-fluoro-*N*-acylimines.[4b] Given the proven ability of BINOL phosphoric acid catalysts to control addition to imines,[6] we posited that aldehyde-derived enamides should be of particular interest as our protocol, upon enamide fluorination, would generate in the first instance a protonated *N*-acyliminium ion [Eq. (2)]. This intermediate should exhibit hydrogen-bonding interactions with the chiral phosphate anion, allowing catalyst-controlled addition of an external oxygen nucleophile, constituting an oxyfluorination of enamides.[7] The resulting stereodefined α-fluoro-*N*,*O*-aminal would be of particular interest as chiral *N*,*O*-aminals are prevalent in natural products and the effect of fluorine introduction on this motif remains, to the best of our knowledge, thus far unexplored.[8] With regard to existing asymmetric *N*,*O*-aminal synthesis, Antilla and co-workers have reported the phosphoric acid-catalyzed addition of alcohols[9] and hydroperoxides[10] to *N*-acylimines, although examples delivering high enantioselectivity were restricted to aromatic imines and in no cases could simple water be used as nucleophile in order to obtain a hemiaminal.

We were aware that our aim of utilizing a single catalyst to carry out two consecutive enantioselective transformations presented complications. Not only must the catalyst be capable of promoting both reactions, but the inherent diastereocontrol from the initially installed stereocenter could be matched or mismatched with the catalyst control for formation of the second stereocenter.

However, this same effect might enable the effect of double stereodifferentiation to be exploited, potentially leading to extremely high stereocontrol in certain cases. Furthermore, observations during our previous studies suggested that, despite drying at 80 °C under vacuum, the Selectfluor employed in our fluorination contains intrinsic moisture that we hypothesized may be sufficient to enable in situ formation of the hemiaminal.

We began our investigations employing (*E*)-configured *N*-benzoyl enamide (*E*)-**1** (Table 1). Using **TRIP** or **C_8-TRIP** as catalysts, the desired α-fluoro-*N*,*O*-aminal **3** was isolated with excellent selectivity for the *syn*-diastereomer (entries 1 and 2).[11] However, the lack of any significant enantioselectivity was disappointing, given our previous results with cyclic enamides.[12] By using our previously reported cyclohexyl-substituted catalyst **TCYP** (**2c**),[13] promising enantioselectivity was observed in the minor diastereomer, while the major remained low but improved (entry 3). Encouragingly, 2-naphthyl-substituted catalyst **2d** gave high diastereoselectivity as well as moderate enantioselectivity (53 % *ee*), although this could not be improved upon by use of the 1-naphthyl (**2e**) or 9-anthracyl (**2f**) variants (entries 5 and 6). Intriguingly, the spirocyclic catalyst **STRIP**[14] (**2g**) delivered the hitherto disfavored *anti*-**3** as the major diastereomer with high enantiomeric excess (87 % *ee*), although diastereoselectivity (2.5:1) and yield were prohibitive (entry 7). The VAPOL-derived catalyst **2h** gave low enantioselectivity (entry 8, 32 % *ee*). Having examined three distinct chiral phosphoric acid scaffolds, including a representative range derived from the privileged BINOL architecture, we next synthesized bis-BINOL catalyst **2i**.[15] While **2i** produced disappointing results in our oxyfluorination reaction (entry 9), we hypothesized that replacing the alkoxy substitution at the 4,4′ position with phenyl (as in **2j**) might generate a more rigid and

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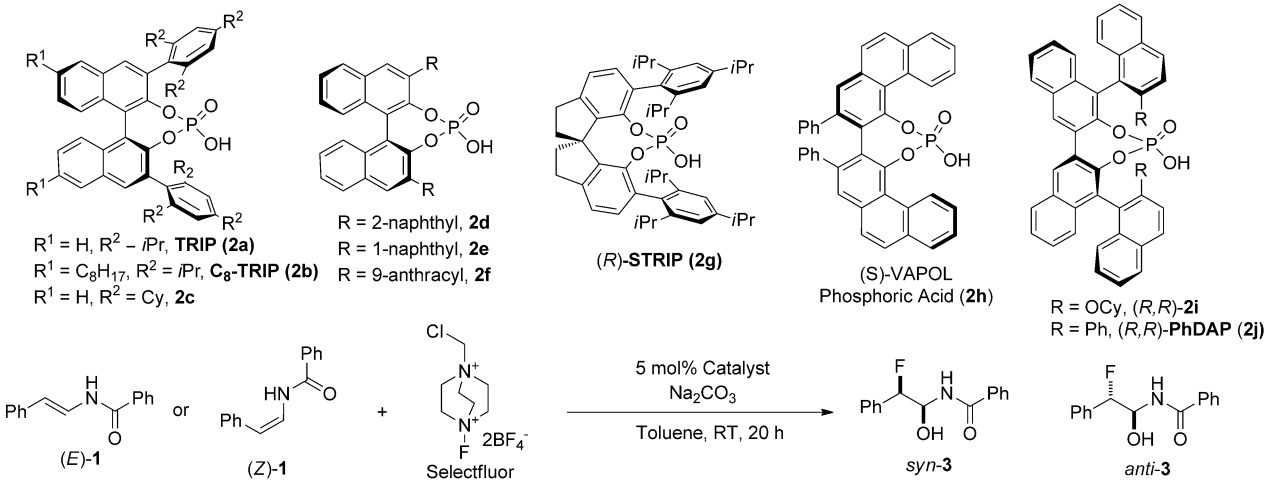
[**] We thank the University of California, Berkeley, and Amgen for financial support. T.H. gratefully acknowledges support from Mitsubishi Tanabe Pharma Corporation. R.J.P. thanks the European Commission for a Marie Curie International Outgoing Fellowship and V.R. thanks NSERC for a postdoctoral fellowship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201205383.

Table 1: Catalyst screening for fluorohydration of enamides (*E*)-**1** and (*Z*)-**1**.



Catalyst	Entry	Substrate	Yield [%][a]	*syn*:*anti*[b]	% *ee* (*syn*/*anti*)[c]	Entry	Substrate	Yield [%][a]	*syn*:*anti*[b]	% *ee* (*syn*/*anti*)[c]
(*R*)-**TRIP**	1		70	>20:1	2/–	11[d]		64	>20:1	−85/–
(*S*)-**C$_8$-TRIP**	2		37	>20:1	−5/–	12		62	>20:1	90/–
(*R*)-**2c**	3		34	10:1	21/82	13		12	5:1	−25/31
(*R*)-**2d**	4		32	>20:1	−53/–	14		30	8:1	9/65
(*R*)-**2e**	5		49	10:1	−20/9	15		39	10:1	−28/5
(*R*)-**2f**	6		27	5:1	−16/20	16		<5	–	–
(*R*)-**STRIP**	7		38	1:2.5	−17/−87	17[d]		20	1:1	45/−49
(*S*)-**2h**	8	(*E*)-**1**	32	10:1	32/−10	18	(*Z*)-**1**	9	4:1	−40/−54
(*R*,*R*)-**2i**	9		86	8:1	17/12	19		35	>20:1	−89/–
(*R*,*R*)-**PhDAP**	10		78	6:1	60/83	20		86	>20:1	−98/–

[a] Isolated yield of mixture of *syn* and *anti* diastereomers. [b] Determined by ^{19}F NMR analysis of crude reaction mixture. [c] Determined by chiral HPLC. [d] Reaction time was 65 h.

constrained pocket for the substrate, leading to higher selectivity. Satisfyingly, this proved to be the case; while diastereoselectivity was modest (6:1), phenyl-substituted doubly axially chiral phosphate **PhDAP** (**2j**) produced a clear improvement and the combined enantioselectivities were the highest obtained thus far in our investigation (entry 10, 60% and 83% *ee*). We next turned our attention to the (*Z*)-configured isomer of **1**.[16] The outcome with (*Z*)-**1** utilizing **TRIP** and **C$_8$-TRIP** was in stark contrast to the *E* isomer; these catalysts delivered high enantioselectivities while maintaining high diastereoselectivity (entries 11 and 12, 85 and 90% *ee*), although reactivity was lower with **TRIP** requiring 65 h reaction time to achieve good conversion.

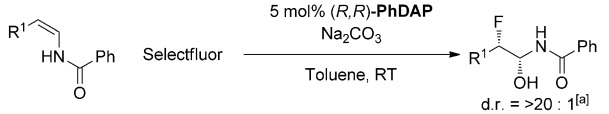
Conversely, catalysts **2c**–**2f** gave poor results, giving moderate d.r. and low enantioselectivity (entries 13–15) or no reaction at all (entry 16). **STRIP** and VAPOL-derived **2h** were mediocre; both gave poor d.r. albeit with moderate enantioselectivity (entries 17 and 18). The Du catalyst **2i** gave excellent d.r. and high enantioselectivity (entry 19, 89% *ee*), although the yield was moderate due to low conversion. Finally, the best results were obtained with **PhDAP** as a catalyst, which delivered *syn*-**3** in high isolated yield (86%), as essentially a single diastereomer and with exceptional enantioselectivity (entry 20, 98% *ee*).[17]

With optimal conditions in hand, we explored the scope of the hydroxyfluorination reaction. Both aromatic (Table 2, entries 1–3) and aliphatic (entries 4–10) substituted enamides were compatible with our tandem hydroxyfluorination process. A broad range of functional groups were tolerated under our conditions (entries 8–10), although strongly electron-donating groups on the aromatic ring reduced enantioselectivity (entry 3), Formation of undesired dimer **16**, which eroded the yield of **15**, could be reduced by use of monohydrous sodium carbonate as base, albeit with a small reduction in enantioselectivity (entries 4 and 5). Finally, in accord with the hypothesis that catalyst control is operative in the hydration of our fluorination-generated imine, substrate **12** delivered a product (**22**) chiral only at the *N*,*O*-aminal with high enantioselectivity (entry 11).

We next demonstrated that running the reaction in the presence of alcohols results in their addition being preferred over hydration, with high enantioselectivities being obtained (Scheme 1a). Furthermore, the *N*,*O*-aminal products are amenable to both oxidation (Scheme 1b), to give chiral α-fluoroimides, and reduction (Scheme 1c), to give chiral β-fluoroamines, with negligible loss of enantioselectivity at the fluorine stereocenter.

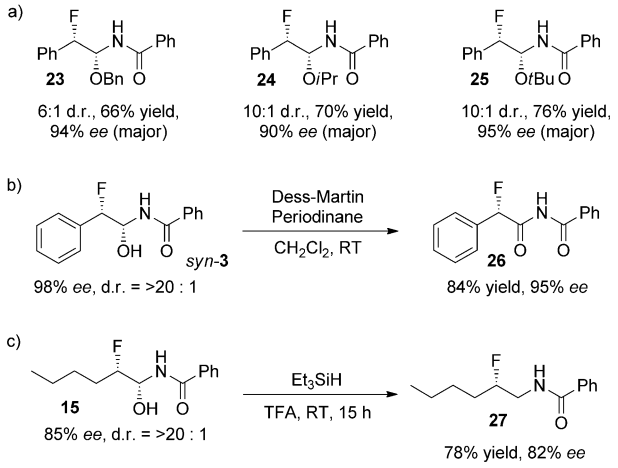
In order to test the limits of our reaction, we turned our attention to a substrate possessing a chiral quaternary fluorine stereocenter, specifically the benzoyl enamide derived from 2-phenylpropionaldehyde. This substrate is notably challenging; organocatalytic aldehyde α-fluorination processes have

Table 2: Substrate scope of fluorohydration of enamides.

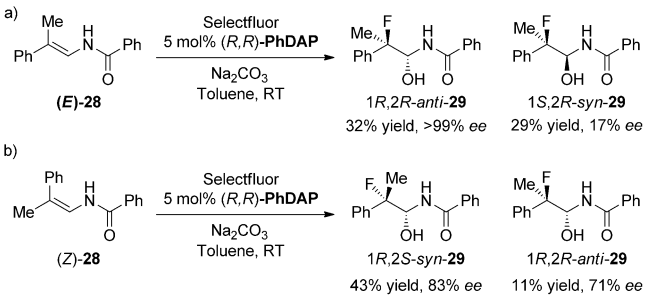


Entry	Substrate	Product	Yield[b] (*ee*)[c] (both in %)
1	R^2 = H ((*Z*)-**1**)	R^2 = H (*syn*-**3**)	86 (98)
2	R^2 = F (**4**)	R^2 = F (**13**)	63 (97)
3	R^2 = OMe (**5**)	R^2 = OMe (**14**)	59 (70)
4	**6**	**15** and **16**	**15**: 52 (92) **16**: 29, d.r. = 3:1[a]
5[d]	**6**	**15** + **16**	**15**: 80% (85) **16**: trace
6	**7**	**17**	52 (91)
7	**8**	**18**	67 (90)
8	**9**	**19**	60 (92)
9	**10**	**20**	73 (89)
10	**11**	**21**	61 (87)
11	**12**	**22**	80 (90)

[a] Determined by ^{19}F NMR analysis of crude reaction mixture. [b] Yields of isolated product. [c] Determined by chiral HPLC. Relative and absolute configuration of **17** determined by X-ray crystallography. All other products assigned by analogy. [d] $Na_2CO_3 \cdot H_2O$ was used instead of Na_2CO_3.



Scheme 1. Fluoroalkoxylation and elaboration of products. Yields refer to yields of isolated *syn* and *anti* diastereomers. See the Supporting Information for reaction conditions.



Scheme 2. Double stereodifferentiation in the formation of a quaternary fluorine stereocenter. Relative and absolute configuration of *syn*-**29** determined by X-ray crystallography (see the Supporting Information for details). All other products assigned by tentative analogy.

generally failed to give >50% *ee* on the parent aldehyde.[3k,l,18] Fluorination of (*E*)-**28** under our conditions, rather than giving a single diastereomer as with secondary enamides, instead gave a pair of readily separable diastereomers, *syn*-**29** and *anti*-**29**, in an approximately 1:1 ratio (Scheme 2a). While *syn*-**29** had low *ee* (17%), *anti*-**29** was formed with exquisite selectivity (>99% *ee*). We propose that the outcome is a result of double stereodifferentiation:[19] while our initial fluorination likely occurs with good stereocontrol, this is refined by the catalyst to excellent levels at the hydration step, albeit at the expense of final product yield, providing >99% *ee* in the matched case. By employing (*Z*)-**28**, we found that (*R*,*R*)-**PhDAP** delivered *syn*-**29** as the major diastereomer (4:1 d.r.), and although the effects of double stereodifferentation were not as pronounced in this case, synthetically useful levels of enantioselectivity in *syn*-**29** were obtained (Scheme 2b, 83% *ee*).

Following the initial reaction optimization, we were struck by the observation that, of the relatively diverse set of catalysts screened, the only able to provide both excellent enantioselectivities *and* diastereoselectivites with (*Z*)-**1** were the two TRIP-based catalysts (**TRIP** and **C$_8$-TRIP**) and the two doubly axially chiral catalysts (**2i** and **PhDAP**). No other was able to achieve >50% *ee* and in many cases diastereoselectivies were modest. This similarity is especially intriguing considering the fundamentally different architectures of these two classes of catalyst. We were able to obtain an X-ray crystal structure of **PhDAP** and overlaid this with that of **TRIP** (Figure 1). It can be seen that the two catalysts map

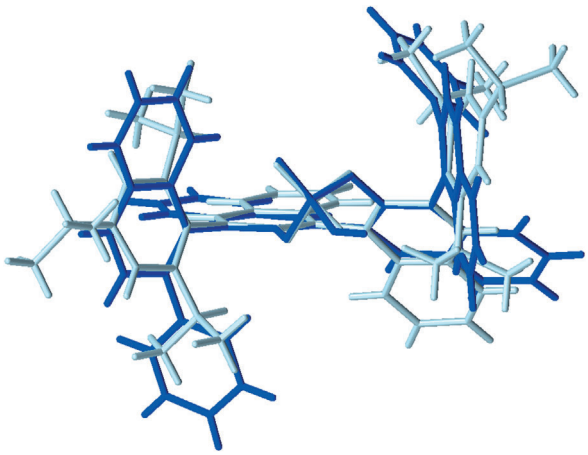
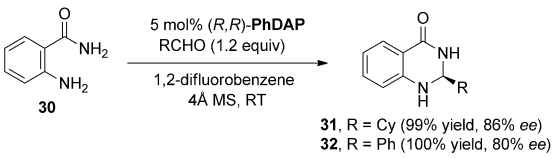


Figure 1. Overlay of X-ray crystal structures of **TRIP** (cyan) and **PhDAP** (blue).

remarkably closely onto one another, providing a compelling explanation for the observed similarities. Given the large number of enantioselective transformations reported over the last decade for which **TRIP** has been successfully employed, it may arguably be regarded as a privileged structure in asymmetric catalysis. Recent elegant progress has been disclosed with the aim of diversifying available chiral phosphoric acid scaffolds.[20] A novel catalyst architecture able to effectively emulate **TRIP**, while at the same time providing new opportunities for catalyst modification is an exciting proposition. Accordingly, we found that **PhDAP** catalyzes the formation of cyclic aminals with selectivities comparable to those reported using BINOL-derived phosphoric acids [Eq. (3)].[21] Moreover, to the best of our



(3)

knowledge, no BINOL-derived phosphoric acid catalysts have been reported bearing *ortho*-aryl substituents on the 3,3′-aromatic rings, a motif that our catalyst emulates and that provides a ready entry point for diversification.

In summary, we have developed an enantioselective tandem oxyflourination of enamides, taking advantage of the ability of a chiral phosphoric acid catalyst to control both fluorination, through our chiral anion phase-transfer strategy, as well as addition to the resulting imine, most likely through a hydrogen-bonding mechanism. In order to realize the highest enantioselectivities in this process, we have synthesized a catalyst possessing double axial chirality, the structure of which overlays remarkably with that of **TRIP**, also a competent catalyst in the process. We envisage that the structural insights presented herein will aid future informed catalyst design for related processes.

Received: July 8, 2012
Published online: August 29, 2012

Keywords: Brønsted acid catalysis · enantioselectivity · fluorination · phase-transfer catalysis · phosphoric acids

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