Published in final edited form as:

Org Lett. 2010 May 7; 12(9): 1960–1963. doi:10.1021/ol100378t.

Chiral Phosphoric Acid-Catalyzed Addition of Dihydropyrans to *N*-Acyl Imines: Stereocontrolled Access to Enantioenriched Spirocyclic Oxazoletetrahydropyrans with Three Contiguous Stereocenters

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Abstract

Dihydropyran derivatives readily undergo addition to *N*-acyl imines in the presence of chiral Phosphoric acids. This addition process yields an attractive product that is capable of a tandem oxidative-cyclization via an epoxide intermediate.

Chiral Brønsted acids have been shown as highly effective catalysts for stereocontrolled additions to imines.¹ The use of *N*-acyl imines, in particular, has been a very successful substrate for activation by chiral phosphoric acid (PA) based catalysis.² As part of our ongoing efforts in the chiral PA activation of *N*-acyl electrophiles,³ we have been continually interested in establishing new stereocontrolled C-C bond forming reactions. During the course of our investigation into the use of dihydropyran (DHP) as a substrate for aza-Diels-Alder⁴ chemistry, a report by Mead and coworkers⁵ described the achiral Mannich-type addition of DHP and derivatives to *N*-acyl imines catalyzed by trifluoroacetic acid or BF₃·OEt₂. Concurrent with the Mead study, we observed that the chiral PA-catalyzed reaction of DHP with *N*-acyl imine **1** also provided the direct Mannich product, rather than the [4+2] adduct (Scheme 1). We were excited because the addition, if rendered highly enantioselective, would have the following unique features: a) it is a relatively novel carbon-carbon bond forming reaction, which could provide synthetically useful chiral allyl amines (or amides); b) functionalized chiral dihydropyran derivatives, are found in numerous bioactive natural products and compounds with medicinal interest.⁶ We report herein, to the best of our knowledge, the first catalytic

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Supporting Information Available Experimental procedures, characterization, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

asymmetric addition of DHP derivatives to *N*-acyl imines, together with interesting examples of the potential synthetic utilization of this reaction.

We initiated our studies with VAPOL phosphoric acid^{3a} (5 mol % catalyst loading) as the catalyst, and toluene as the solvent. The reaction was run at room temperature and yielded the addition product in 45% yield and 37% ee. This result encouraged us to further explore the reaction conditions. Catalyst screening showed that (*R*)-TRIP-PA⁷ gave the best result in terms of enantioselectivity and yield. Therefore, (*R*)-TRIP-PA was used to evaluate the effect of solvent on the reaction. As shown in Table 1, coordinating solvents such as THF and ether (entries 3 and 5) gave poor results. Chloroform provided the best yield at 85% and ee at 71% (entry 8).

Decreasing the temperature lowered the yield and ee dramatically (entry 9). Increasing the temperature to 50°C afforded a lower yield of the major product, due in part to the formation of more side products, while providing only modest ee. We then turned our attention to the effect of different substituents on the phenyl ring of the benzoyl group. As shown in Table 1, introduction of a methoxy or methyl group in the ortho or meta positions of the phenyl ring did not induce a positive effect (entries 11–12). However, to our delight, the same substituent groups in the para position gave significant improvement on yield and ee (entries 13–14; 83% ee and 85% ee, respectively). In addition, the catalyst loading could be decreased to 2 mol %, providing an even higher yield (98%) without compromising the enantioselectivity (entry 15). Furthermore, a *N,N*-dimethylamino substituted *N*-acyl imine substrate provided the highest enantioselectivity, up to 89% (entry 17), presumably due to increased steric hindrance at the para- position. The *N,N*-dimethylamino substituted *N*-acyl group has been removed, as demonstrated by Terada et. al.⁸

Once the optimized conditions were established, the substrate scope of the asymmetric addition of DHP to *N*-acyl imine derivatives was studied. This reaction is tolerant of a variety of *N*-acyl imines (**1a–1h**). For example, the addition of imines bearing electron-withdrawing groups (*p*-chloro, **1b**; entry 2; *p*-bromo, **1c**; entry 3) gave very high yield and excellent enantioselectivity, up to 90%. An example of an *N*-acylimine with an electron-donating group, such as *para*-methyl, also allowed for a good yield and 90% ee (entry 5). However, a strong electron-donating substituent had a negative effect on the ee (78% ee, entry 6). Additionally, the imines with methoxy (76% ee, entry 6) and fluoro (91% ee, entry 7) substituents on the *meta* position provided similar results in comparison to their *para* counterparts. We were pleased to find the reaction general for various DHP derivatives.

As shown in Table 2, the reaction of DHP derivative **2b**, bearing an *n*-propyl group, afforded up to 92% yield and 92% ee. The DHP derivatives with larger steric hindrance and longer alkyl chain groups, such as reactants **2c** and **2d**, also gave high enantioselectivities (90% and 89%, entries 10 and 11, respectively). Finally, the DHP derivative with methoxyethyl substitution produced a lower ee (81%, entry 13), presumably due to the possible coordination of the ether to the phosphoric acid catalyst.

Direct access to chiral spirocyclic compounds with a quaternary stereogenic center represents a significant challenge in organic synthesis.⁹ The carbon-carbon double bond of the functionalized chiral **3** provides a useful handle for further synthetic transformations. We envisioned that epoxidation of the double bond, followed by a tandem in situ intramolecular ring opening could occur to form a chiral polycyclic tetrahydropyran. As shown in Scheme 2, treating chiral compound **3ba** with an excess of *m*-CPBA, followed by aqueous NaHSO₃ afforded the spirocyclic oxazoletetrahydropyran **4ba** in 84% yield and 90% ee.¹⁰ Under similar reaction conditions, both **3ca** and **3ea** also provided the corresponding spirocyclic compounds **4ca** and **4ea** with 92% ee and 90% ee, respectively. It is noteworthy that the overall reaction

sequence generates three chiral centers, including one quaternary chiral center. The absolute configuration of the spirocyclic oxazoletetrahydropyran was revealed to be (*S*)-C10, (*R*)-C11 and (*S*)-C12 by single crystal X-ray diffraction of compound **4ca**.

The exact mechanism for this tandem reaction sequence has not been precisely determined, however, it is reasonable that the high stereoselectivity is induced by the vicinal chiral amide group via hydrogen bonding interactions with *m*-CPBA through a six-membered ring transition state **I** (Figure 2). Directed by the amide, *m*-CPBA reacts with the enol ether from the *Re*-face to stereoselectively form the epoxide. This is followed by an intramolecular S_N2 reaction (**II**) to provide the chiral spirocyclic tetrahydropyran **4**.

In conclusion, we have reported the first catalytic asymmetric addition of DHP derivatives to *N*-acyl imines. This reaction has been shown to provide potentially useful chiral DHP derivatives in high yields and enantioselectivities. By using the chiral DHP addition products as the starting material, structurally unique spirocyclic oxazoletetrahydropyrans could be synthesized stereoselectively via a tandem epoxidation/ring-opening reaction sequence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (NIH GM-082935) and the National Science Foundation (NSF-0847108) for financial support. We also thank Dr. Wenhua Zheng (USF) for the preparation of TRIP-PA.

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Figure 1.
ORTEP representation of the X-ray structure of **4ca** with displacement ellipsoids shown at a 50% probability level

Figure 2.
A plausible mechanism for the tandem cyclization leading to the spirocyclic skeleton

Scheme 1.

DHP addition to imine resulting in a Mannich type product

Scheme 2.

Highly selective preparation of chiral spirocyclic oxazoletetrahydropyrans

Table 1

Optimization of Reaction Conditions

entry ^a	R	solvent	PA, mol%	temp, °C	time, h	yield, % ^b	ee, % ^c
1	Ph	toluene	5	rt	20	61	64
2	Ph	DCM	5	rt	20	64	33
3	Ph	THF	5	rt	20	nd	na
4	Ph	EtOAc	5	rt	20	24	54
5	Ph	ether	5	rt	20	nd	na
6	Ph	DCE	5	rt	20	48	28
7	Ph	hexane	5	rt	20	79	60
8	Ph	CHCl ₃	5	rt	24	85	71
9	Ph	CHCl ₃	5	-20	48	<10	40
10	Ph	CHCl ₃	5	50	18	31	64
11	3,5-MeOC ₆ H ₃	CHCl ₃	5	rt	26	80	72
12	2-MeC ₆ H ₄	CHCl ₃	5	rt	21	73	72
13	4-MeC ₆ H ₄	CHCl ₃	5	rt	21	90	83
14	4-MeOC ₆ H ₄	CHCl ₃	5	rt	21	82	85
15	4-MeOC ₆ H ₄	CHCl ₃	2	rt	24	98	85
16	4-MeOC ₆ H ₄	CHCl ₃	1	rt	24	78	81
17	4-Me ₂ NC ₆ H ₄	CHCl ₃	2	rt	24	76	89

^a Molar ratio of 1/2 = 1.0/1.0 equiv;^b 4 Å MS were added in entries 8, 11–17;^c Isolated yields;^d ee determined by chiral HPLC.

Table 2

Substrate Scope

entry ^a	R ¹ (1)	R ² (2)	time, h	product (3)	yield, % ^b	ee, % ^c
1 ^d	Ph (1a)	H (2a)	21	3aa	76	89
2	<i>p</i> -ClC ₆ H ₄ (1b)	H (2a)	24	3ba	90	90
3	<i>p</i> -BrC ₆ H ₄ (1c)	H (2a)	39	3ca	94	90(5) ^e
4	<i>p</i> -FC ₆ H ₄ (1d)	H (2a)	25	3da	88	89
5	<i>p</i> -CH ₃ C ₆ H ₄ (1e)	H (2a)	21	3ea	80	90
6	<i>p</i> -CH ₃ OC ₆ H ₄ (1f)	H (2a)	25	3fa	79	78
7	<i>m</i> -CH ₃ OC ₆ H ₄ (1g)	H (2a)	20	3ga	95	76
8	<i>m</i> -FC ₆ H ₄ (1h)	H (2a)	24	3ha	86	91
9	<i>p</i> -ClC ₆ H ₄ (1b)	<i>n</i> -Pr (2b)	15	3bb	92	92
10	<i>p</i> -ClC ₆ H ₄ (1b)	<i>i</i> -butyl (2c)	18	3bc	72	90
11	<i>p</i> -ClC ₆ H ₄ (1b)	<i>i</i> -pentyl (2d)	23	3bd	92	89
12	<i>p</i> -ClC ₆ H ₄ (1b)	<i>n</i> -C ₆ H ₁₃ (2e)	19	3be	92	88
13	<i>p</i> -ClC ₆ H ₄ (1b)	(CH ₃) ₂ OCH ₃ (2f)	25	3bf	95	81

^aMolar ratio of 1/2 = 1.5/1.0 equiv;^bIsolated yield;^cee determined by chiral HPLC;^d1/2 = 1.0/1.0 equiv;^eAbsolute configuration was determined from X-ray diffraction of compound 4ca.