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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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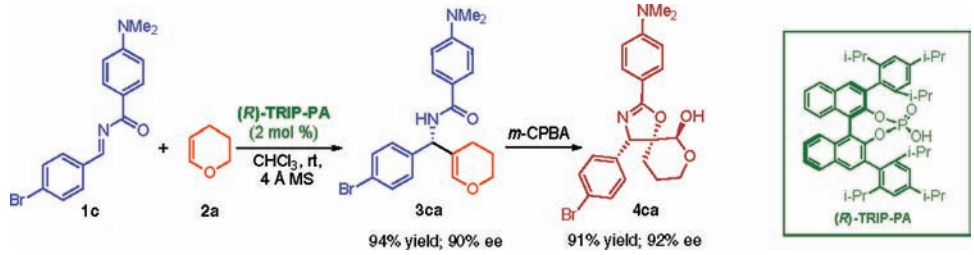
ABSTRACT



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 very successful 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−Alder[4] chemistry, a report by Mead and co-workers[5] described the achiral Mannich-type addition of DHP and derivatives to *N*-acyl imines catalyzed by trifluoroacetic acid or BF_3−OEt_2. 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,

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(1) For reviews, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Terada, M. *Chem. Commun.* **2008**, 4097.

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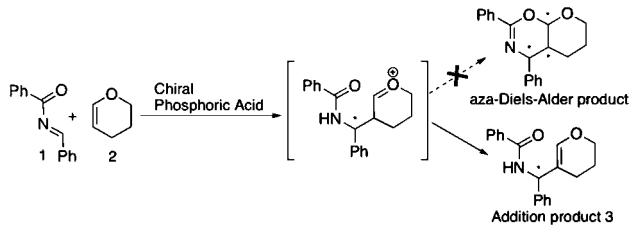
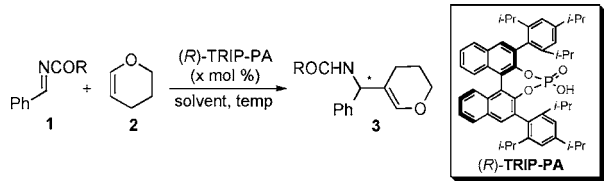
Scheme 1. DHP Addition to Imine Resulting in a Mannich-Type Product



the first catalytic 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-PA[7] 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

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-$MeOC_6H_3$	$CHCl_3$	5	rt	26	80	72
12	2-MeC_6H_4	$CHCl_3$	5	rt	21	73	72
13	4-MeC_6H_4	$CHCl_3$	5	rt	21	90	83
14	4-$MeOC_6H_4$	$CHCl_3$	5	rt	21	82	85
15	4-$MeOC_6H_4$	$CHCl_3$	2	rt	24	98	85
16	4-$MeOC_6H_4$	$CHCl_3$	1	rt	24	78	81
17	4-$Me_2NC_6H_4$	$CHCl_3$	2	rt	24	76	89

[a] Molar ratio of **1**/**2** = 1.0/1.0 equiv. [b] With 4 Å MS added in entries 8 and 11−17. [c] Isolated yields. [d] Enantiomeric excess determined by chiral HPLC.

solvents such as THF and ether (entries 3 and 5) gave poor results. Chloroform provided the best yield at 85% and 71% ee (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 and 12). However, to our delight, the same substituent groups in the para position gave significant improvement on yield and ee (entries 13 and 14; 83 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*-acyl imine 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

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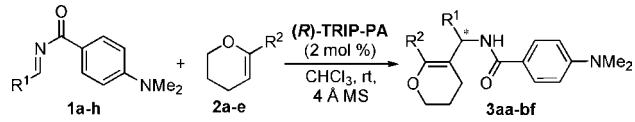
(7) TRIP-PA was first prepared and used by List et al. See: Hoffmann, S.; Seayad, A.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424.

(8) It has been shown that the *N*,*N*-dimethylamino *N*-acyl protecting group can be removed in a two-step reaction sequence. Please see: Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360.

Table 2. Substrate Scope

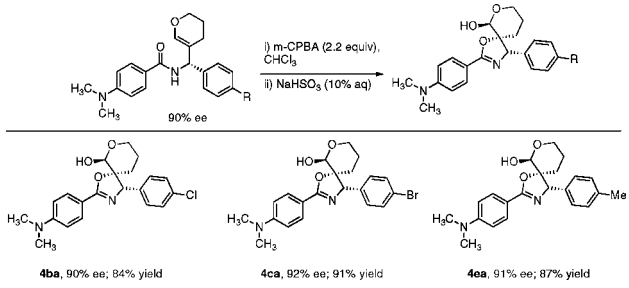


entry[a]	R^1 (**1**)	R^2 (**2**)	time, h	product (**3**)	yield, %[b]	ee, %[c]
1[d]	Ph (**1a**)	H (**2a**)	21	**3aa**	76	89
2	*p*-ClC_6H_4 (**1b**)	H (**2a**)	24	**3ba**	90	90
3	*p*-BrC_6H_4 (**1c**)	H (**2a**)	39	**3ca**	94	90(S)[e]
4	*p*-FC_6H_4 (**1d**)	H (**2a**)	25	**3da**	88	89
5	*p*-$CH_3C_6H_4$ (**1e**)	H (**2a**)	21	**3ea**	80	90
6	*p*-$CH_3OC_6H_4$ (**1f**)	H (**2a**)	25	**3fa**	79	78
7	*m*-$CH_3OC_6H_4$ (**1g**)	H (**2a**)	20	**3ga**	95	76
8	*m*-FC_6H_4 (**1h**)	H (**2a**)	24	**3ha**	86	91
9	*p*-ClC_6H_4 (**1b**)	*n*-Pr (**2b**)	15	**3bb**	92	92
10	*p*-ClC_6H_4 (**1b**)	*i*-butyl (**2c**)	18	**3bc**	72	90
11	*p*-ClC_6H_4 (**1b**)	*i*-pentyl(**2d**)	23	**3bd**	92	89
12	*p*-ClC_6H_4 (**1b**)	*n*-C_6H_{13} (**2e**)	19	**3be**	92	88
13	*p*-ClC_6H_4 (**1b**)	$(CH_2)_2OCH_3$ (**2f**)	25	**3bf**	95	81

[a] Molar ratio of **1**/**2** = 1.5/1.0 equiv. [b] Isolated yield. [c] Enantiomeric excess determined by chiral HPLC. [d] **1**/**2** = 1.0/1.0 equiv. [e] Absolute configuration was determined from X-ray diffraction of compound **4ca**.

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.

Scheme 2. Highly Selective Preparation of Chiral Spirocyclic Oxazoletetrahydropyrans



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 $NaHSO_3$, 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 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** (Figure 1).

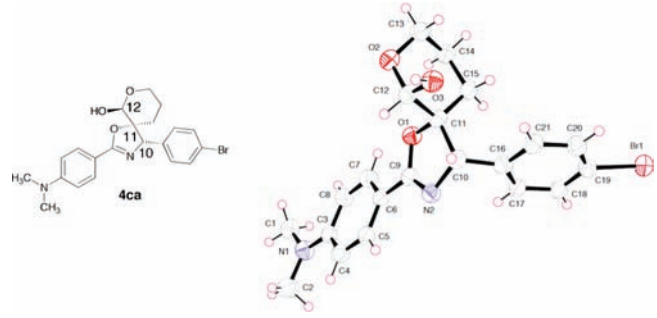


Figure 1. ORTEP representation of the X-ray structure of **4ca** with displacement ellipsoids shown at a 50% probability level.

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

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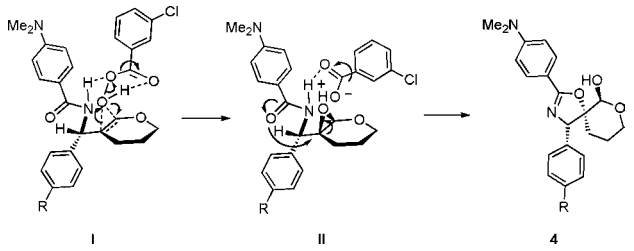

Figure 2. Plausible mechanism for the tandem cyclization leading to the spirocyclic skeleton.

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.

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Note Added after ASAP Publication. The author name Guilong was misspelled in the version of this paper published on April 2, 2010; it was corrected in the version posted on April 6, 2010.

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

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