Asymmetric Catalysis

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Phosphothreonine as a Catalytic Residue in Peptide-Mediated Asymmetric Transfer Hydrogenations of 8-Aminoquinolines

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Abstract: *Phosphothreonine (pThr) was found to constitute a new class of chiral phosphoric acid (CPA) catalyst upon insertion into peptides. To demonstrate the potential of these phosphopeptides as asymmetric catalysts, enantioselective transfer hydrogenations of a previously underexplored substrate class for CPA-catalyzed reductions were carried out. pThr-containing peptides lead to the observation of enantioselectivities of up to 94:6 e.r. with 2-substituted quinolines containing C8-amino functionality. NMR studies indicate that hydrogen-bonding interactions promote strong complexation between substrates and a rigid β-turn catalyst.*

Few organocatalytic systems have been demonstrated to be as versatile in the realm of asymmetric synthesis as chiral phosphoric acids (Figure 1). Their prowess as chiral Brønsted acids and chiral counterions has been demonstrated over a remarkable range of enantioselective reactions of interest to synthetic chemists.[1] In parallel, but seemingly unrelated, the phosphorylation of proteinogenic amino acids, including threonine (**1**), has emerged as a post-translational modification of proteins with an ever-expanding list of functions of biochemical significance.[2,3] In our laboratory, we continue to study the interfaces of biochemically important building blocks and structures for their capacity to influence fundamentally interesting stereoselective reactions.[4] In this study, we report the enantioselective transfer hydrogenation of 8-aminoquinolines[5,6] mediated by phosphothreonine (pThr)-containing peptides with the NADH-like dihydropyridine reductant Hantzsch ester hydride (HEH).

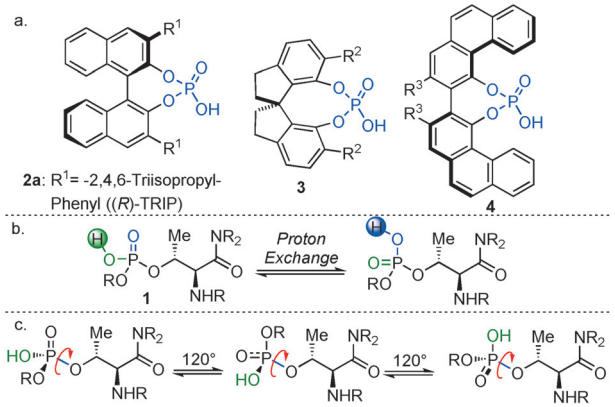
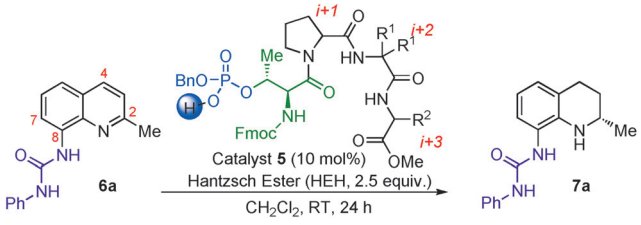


Figure 1. a) Previously developed chiral CPAs: BINOL (**2**), SPINOL (**3**), and VAPOL (**4**). b) A new pThr-based CPA (**1**). Lack of C_2-symmetry results in diastereotopic P–OH environments. c) Free rotation of the P–OR bond produces non-equivalent rotamers.

Among the myriad of reported asymmetric chiral phosphoric acid (CPA) catalysts, the pioneering C_2-symmetric BINOL-derived catalytic scaffold (**2**), independently reported by Akiyama and Terada in 2004, has dominated the field.[7] Important variations on this substructure (**3**–**4**) complement this impressive record (Figure 1a),[8] but C_2-symmetry is a pervasive feature. Indeed, a radical departure from these established design principles has remained elusive. A catalyst framework that is not limited to C_2-symmetry could be particularly important, especially if catalysts in this family are to be applied to the selective derivatization of complex molecules.[9]

In constructing a novel pThr-containing CPA, we faced two primary challenges. First, the lack of C_2-symmetry of pThr precludes the equivalency of the two free P–O bonds, between which the acidic proton can rapidly tautomerize (Figure 1b). Second, without the two phenolic hydroxy groups tied into a BINOL-like ring, free rotation about the pThr P–O bond is enabled (Figure 1c). Both of these factors can produce numerous chemically distinct acid catalyst conformations, each exhibiting different intrinsic reaction selectivities. Nonetheless, we wondered whether pThr embedded within a well-defined peptide framework might lead to the observation of selective reactions, perhaps through bifunctional catalysis.[10]

We chose to test these concepts with pThr-containing peptides (**5**, Scheme 1) as catalysts for the transfer hydrogenation of quinolines, since CPAs have been shown to mediate the reduction of variously functionalized quinolines with high yields and selectivity.[5] Initial reaction development commenced with 2-substituted quinolines with C8-amino functionality owing to 1) their underexplored nature in the field of asymmetric heterocycle reduction,[6] 2) their presence in many bioactive agents,[11] and 3) our previously observed



Scheme 1. pThr-containing peptides (**5**) as catalysts for the reduction of **6a** to **7a**.

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results wherein appropriately functionalized amines often lead to effective catalyst–substrate interactions in peptide-mediated asymmetric reactions.[12]

The synthesis of catalysts of type **5** followed conventional peptide synthesis techniques, with a notable BOP-mediated coupling of the free side-chain monobasic phosphoric acid (Fmoc-pThr(Bn)-OH) to peptide sequences of interest.[13] As shown in Table 1, a variety of pThr-containing peptides were found to catalyze the reduction of **6a** to **7a** with high conversion and good enantiomeric ratio (e.r.). Starting with a β-turn-promoting sequence of L- or D-Pro-Aib-XXX-OMe,[14] we were intrigued to find that catalysts with either L-Pro (**5a**) or D-Pro (**5b**) at the $i+1$ position produced the same enantiomer of **7a**, albeit with higher selectivity for D-Pro (Table 1, entries 1 and 2).[15] We next turned to the $i+2$ position, where we observed that utilization of 1-amino-cyclopropane carboxylic acid (Acpc; **5c**) resulted in an increase in enantioselectivity (79:21 e.r.; Table 1, entry 3), which could potentially be the result of Acpc affecting the overall conformation or rigidity of the β-turn scaffold.[16] Exchanging the C-terminal methyl ester for a dimethyl amide (**5d**) led to a drop in e.r. (70:30 e.r.; Table 1, entry 4). While extensive variation of the the $i+3$ residue did not drastically affect selectivity, it did reveal that Met (**5e**) was the most effective, resulting in 82:18 e.r. (Table 1, entry 5). The sulfur atom of Met is not critical since the carbon isostere of Met, norleucine (Nle), was synthesized (**5f**) and behaves similarly to **5e** (80:20 e.r.; Table 1, entry 6). The stereochemistry of the $i+3$ residue exerts a small effect on selectivity since catalyst **5g** (with D-Leu in place of L-Leu at $i+3$) leads to the formation of product with 82:18 e.r. (Table 1, entry 7), although this effect was not explored further. Critically, the phosphoric acid itself is essential for mediating the reduction since exchanging pThr for Thr(Bn) abolishes catalysis (**5h**; Table 1, entry 8). Similarly, a study of truncated peptides revealed that the full tetrameric sequence was essential for the highest selectivity with this series of catalysts (Table 1, entries 9–11).

Since the pThr-containing catalysts represent a departure from C_2-symmetric CPAs, we wished to carry out a direct comparison to an established catalyst. We observed that (*R*)-TRIP (**2a**), a catalyst previously reported for 3-aminoquinoline reductions, affords **7a** with 14:86 e.r., thus revealing that a pThr-containing catalyst offers a slightly lower but still comparable e.r. in this case (entry 12).[5h] Inter-

Table 1: Optimization of the peptide sequence for transfer hydrogenation of **6a**.[a,b,e]

Entry	Cat.	*i*	*i*+1	*i*+2	*i*+3	Conv. [%][c]	e.r.[d]
1	**5a**	Fmoc-pThr(Bn)	Pro	Aib	Leu-OMe	88	60:40
2	**5b**	Fmoc-pThr(Bn)	D-Pro	Aib	Leu-OMe	83	72:28
3	**5c**	Fmoc-pThr(Bn)	D-Pro	Acpc	Leu-OMe	98	79:21
4	**5d**	Fmoc-pThr(Bn)	D-Pro	Acpc	Leu-NMe_2	92	70:30
5	***5e***	*Fmoc-pThr(Bn)*	*D-Pro*	*Acpc*	*Met-OMe*	*99*	*82:18*
6	**5f**	Fmoc-pThr(Bn)	D-Pro	Acpc	Nle-OMe	98	80:20
7	**5g**	Fmoc-pThr(Bn)	D-Pro	Acpc	D-Leu-OMe	98	82:18
8	**5h**	Fmoc-Thr(Bn)	D-Pro	Acpc	Met-OMe	0	n/a
9	**5i**	Fmoc-pThr(Bn)	D-Pro	Acpc-OMe	–	77	60:40
10	**5j**	Fmoc-pThr(Bn)	D-Pro-OMe	–	–	78	60:40
11	**5k**	Fmoc-pThr(Bn)-NMe_2	–	–	–	92	45:55
12	**2a**	–	–	–	–	99	14:86

[a] Reported results are the average of two trials. [b] Conditions: 0.06 mmol wrt **6a**, peptide **5** (10 mol%), HEH (2.5 equiv), dichloromethane (0.05 M with respect to **6a**). [c] Conversion (conv.) was determined by comparing the ^{1}H NMR integrations of the aromatic peaks of **6a** and **7a**. [d] Enantiomeric ratios were determined by HPLC using an OD-H column. [e] Abbreviations: Fmoc = fluorenylmethyloxycarbonyl; pThr(Bn) = benzylphosphothreonine; Aib = alpha-aminoisobutyric acid; Acpc = 1-aminocyclopropane carboxylic acid; Nle, norleucine (butylglycine).

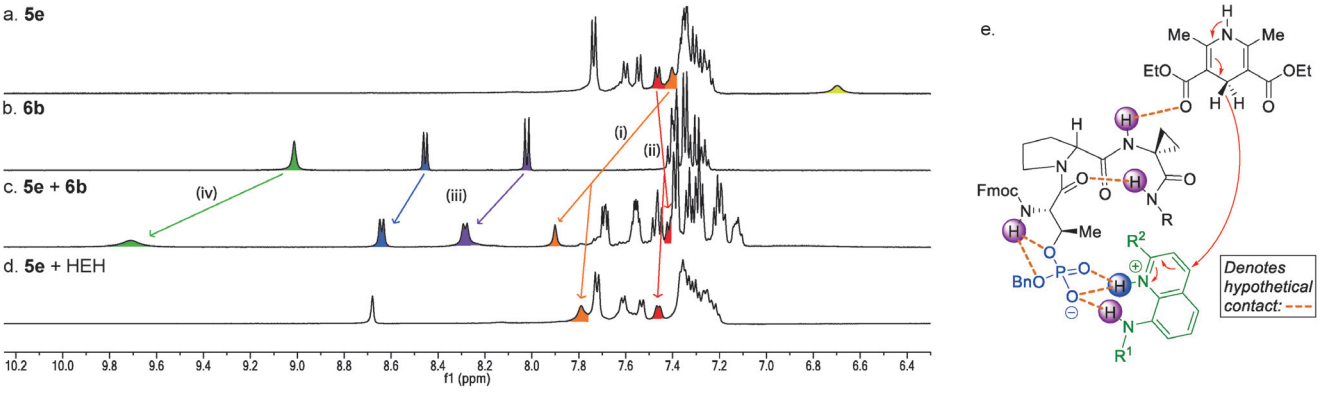


Figure 2. a) 1H NMR spectrum of **5e** in CD_2Cl_2; b) **6b** in CD_2Cl_2; and c) **5e** and 6b (1:1 stoichiometry) in CD_2Cl_2. i) For **5e**, the NH_{Acpc} signal (orange) shifts downfield and the NH_{pThr} signal (yellow) broadens into the baseline, thus suggesting the formation of H-bonds. ii) The chemical shift of the NH_{Met} signal (red) remains constant, which is characteristic of a β-turn H-bond with the pThr C=O. iii) For **6b**, large downfield shifts are observed for the C7 (blue) and C4 (purple) protons, thus suggesting the formation of a **5e**–**6b** salt. iv) A large downfield shift of the C8 N–H (green) is further evidence for the protonation of **6b**, as well as potential complexation between this N–H and **5e**. d) **5e** and HEH (1:9 stoichiometry) in CD_2Cl_2. The same trends are observed for **5e** as above.[18] e) Speculative ensemble of potential interactions between substrates and catalyst. Protons in purple are believed to be engaged in hydrogen-bonding interactions.

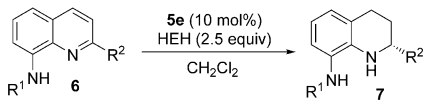
estingly, in other cases, the pThr-peptides deliver a slightly higher e.r. (substrate **6f**; see below).

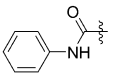
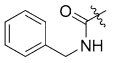
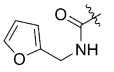
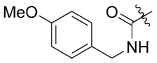
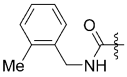
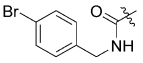
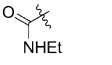
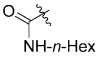
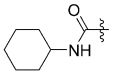
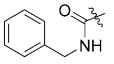
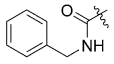
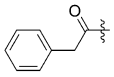
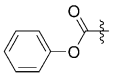
With catalyst **5e** in hand, we turned our attention to substrate scope, and the catalyst was found to function well for substrates with variations at the 8-position (Table 2). For example, benzylic ureas (**6b–6f**) led to products with up to 92:8 e.r. at RT (Table 2, entries 3, 5, 7, 9, and 11), while aliphatic ureas (**6g–6i**) are also tolerated (Table 2, entries 13, 15, 17). Lowering the temperature to 4 °C led to increases in e.r. in many cases (e.g., 94:6 e.r.; Table 2, entries 4, 6, 8, and 10), although extended reaction times were generally required. Parenthetically, in the case of **6f**, we observed that the pThr peptide delivers a slightly higher e.r. than the (*R*)-TRIP catalyst **2a** (13:87 e.r. for **6f** over 24 h). Aliphatic substitution at the quinoline C2-position (**6j-6k**) led to products with lower e.r. for reasons that are not fully understood (Table 2, entries 19–20). Finally, exchange of the urea for acetamide (**6l**) and carbamate (**6m**) resulted in slower reaction rates but similar and even higher e.r. compared to isostere **6a** (Table 2, entries 21–22).The absolute stereochemistry of the major product was determined explicitly for compound **7f** by X-ray crystallography.[17]

We have begun to study the possible mechanism of action of the pThr-containing peptides by examining the ^{1}H NMR chemical shifts upon mixing peptide **5e** with substrate **6b** or HEH (Figure 2a–d). On the one hand, these additives have little effect on the shift of the $i+3$ NH_{Met} signal (Figure 2, red). Since this resonance is characteristic of a 10-membered ring intramolecular H-bond with the pThr C=O (a β-turn), the addition of the substrates may not perturb this key catalyst secondary structural feature. On the other hand, the NH_{pThr} signal (Figure 2, yellow) appears to broaden significantly and that of $i+2$ NH_{Acpc} (Figure 2, orange) shifts downfield in the presence of either **6b** or HEH, thus suggesting the formation of intermolecular interactions (e.g, through H-bonding) between the catalyst and substrates. Downfield shifts are also observed for the quinoline C7 (blue) and C4 (purple) proton signals, as well as for a quinoline urea N–H signal. These chemical shift perturbations are consistent with salt formation between **5e** and **6b**.[19] The downfield shift of a quinoline C8 N–H signal (Figure 2, green) could also be ascribed to an H-bond with **5e**. Further evidence for this H-bond was revealed through the reduction of 2-methylquinoline with **5e**, since the lack of directing group yields product with only 58:42 e.r.. Taken together, these observations support a reaction for which enantioselectivity derives from the formation of noncovalent interactions between **6** and the β-turn peptide catalyst **5e** (Figure 2e).

In conclusion, we report the development of pThr-containing peptides as a CPA scaffold. Strikingly, this framework, which lacks the C_2-symmetry of better known CPA scaffolds, is able to overcome the existence of both non-equivalent tautomeric states and the many rotatable bonds extant within the catalyst. It achieves this

Table 2: Substrate Scope.[a,b]



Entry	Substrate	R^1	R^2	*t* [h]	*T*	Conv.[c] [%]	Yield[d] [%]	e.r.[e]
1				24	RT	99	92	82:18
2	**6a**		Me	51	4 °C	92	86	82:18
3				24	RT	97	84	91:9
4	**6b**		Me	51	4 °C	86	82	94:6
5				24	RT	99	76	90:10
6	**6c**		Me	51	4 °C	86	79	94:6
7				24	RT	96	74	92:8
8	**6d**		Me	51	4 °C	88	81	94:6
9				24	RT	96	74	92:8
10	**6e**		Me	51	4 °C	86	79	94:6
11				24	RT	99	79	90:10
12	**6f**		Me	51	4 °C	86	70	93:7
13				30	RT	92	79	86:14
14	**6g**		Me	51	4 °C	92	86	90:10
15				36	RT	97	73	88:12
16	**6h**		Me	51	4 °C	86	70	90:10
17	**6i**		Me	30	RT	91	86	83:17
18				51	4 °C	83	74	87:13
19	**6j**		*i*Pr	24	RT	94	71	77:23
20	**6k**		Cy	24	RT	97	84	75:25[g]
21	**6l**		Me	24	RT	52	n/a[f]	89:11
22	**6m**		Me	24	RT	68	n/a[f]	79:21

[a] Reported results are the average of two trials. [b] Conditions: 0.06 mmol **6**, peptide **5e** (10 mol%), HEH (2.5 equiv), dichloromethane (0.05 M with respect to **5e**). [c] Conversion (conv.) was determined by comparing the ^{1}H NMR integrations of the quinoline aromatic peaks for the substrates and products. [d] Yield of isolated product after column chromotography. [e] Enantiomeric ratios were determined by HPLC using an OD-H column. [f] **6l** and **6n** co-eluted with oxidized Hantzsch ester pyridine (HEox) and could not be isolated. [g] Enantiomeric ratios were determined by chiral HPLC using an AD-H column.

selectivity through interactions with the substrates in the context of the peptide secondary structure. The pThr catalyst tolerates a range of functionality at the C8-urea and the C2-position of the quinoline, and is able to deliver substrates with e.r. up to 94:6 e.r.. Given the remarkable range of chemical reactions that may be catalyzed with chiral CPAs, we are hopeful that these new pThr-based catalysts will have significant utility as asymmetric catalysts, perhaps especially in the realm of chemical operations on complex substrates.

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