

# A Highly Diastereo- and Enantioselective Synthesis of Tetrahydroquinolines: Quaternary Stereogenic Center Inversion and Functionalization

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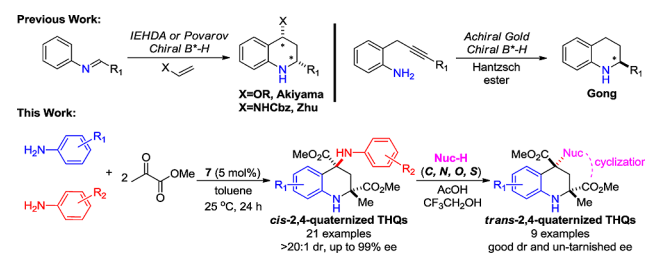
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**S** Supporting Information

**ABSTRACT:** Tetrahydroquinolines containing two quaternary stereogenic centers were synthesized with excellent ee and dr via a four-component cyclization reaction catalyzed by a chiral phosphoric acid. High chemoselectivity was achieved by differentiating anilines with similar reactivities to yield diverse “hybrid” products. The chirality of the quaternary C4 atom of the 4-amino-tetrahydroquinoline products was found to undergo highly stereoselective inversion, enabling facile functionalization using a wide range of nucleophiles (C, O, N, and S).

Tetrahydroquinolines (THQs) belong to a class of heterocycles of high pharmacological value, and they have attracted attention from medicinal and synthetic chemists because of their abundance in both natural products and drug molecules that possess various biological activities.<sup>1</sup> The rapid assembly of chiral THQs has resulted primarily from recent advances in enantioselective organocatalytic cascade reactions and cooperative catalysis (Scheme 1).<sup>2,3</sup> One particular strategy,

## Scheme 1. Representative Asymmetric Strategies for the Synthesis of Substituted THQs



developed by Gong, employs relay catalysis of a gold(I)-catalyzed hydroamination and a chiral Brønsted acid-catalyzed transfer hydrogenation to synthesize 2-substituted THQs enantioselectively in one pot.<sup>3k</sup> Chiral phosphoric acid-catalyzed enantioselective Povarov reactions and inverse-electron-demand hetero-Diels–Alder (IEHDA) reactions, developed by Akiyama, Zhu, and Masson, permit the synthesis of 2,4-disubstituted THQs.<sup>3a–j</sup> However, the substrate scope of these reactions is limited to preformed aldimines or aldehydes. In contrast, asymmetric Povarov reactions involving ketones are rare,<sup>4</sup> limiting access to THQs containing quaternary chiral centers. The multicomponent condensation of two anilines and two

enolizable ketones is potentially complicated and unclear because the rapid enamine/iminium equilibrium may lead to a number of reaction pathways and combination cascades such as aldol, Mannich, Claisen, Michael, and so on. We describe a highly diastereo- and enantioselective synthesis of THQs with two quaternary stereogenic centers and rich functionalities using pairs of anilines and pyruvates. The phenylamino-substituted C4 quaternary center of the products was found to have extraordinary synthetic versatility through an acid-catalyzed elimination and addition mechanism. The phenylamino group could be replaced by a wide range of C-, O-, N-, and S-based nucleophiles in a formal “S<sub>N</sub>2 substitution”.

Our group has been interested in developing methods that allow direct access to 4-amino-THQs because of their pharmacological relevance.<sup>5</sup> Inspired by the above-mentioned work of Akiyama, Zhu, and Masson, we challenged the chiral Brønsted acid-catalyzed Povarov reaction with pairs of pyruvates and anilines. To the best of our knowledge, no other example of an organocatalytic Povarov reaction involving enolizable ketones can be found in the literature.<sup>4</sup>

Our preliminary studies revealed that activated ketones (i.e., pyruvates) are viable substrates for direct condensation with equal amounts of anilines to generate THQ products with 2,4-substituted carbon centers. This transformation was racemically catalyzed by Mg(ClO<sub>4</sub>)<sub>2</sub> at room temperature in quantitative yield with a poor dr (cis/trans = 1:2). Various chiral phosphoric acids<sup>6</sup> were then examined to improve the dr and induce facial discrimination (Table 1). Although nonsubstituted BINOL-derived phosphoric acid **4a** failed to promote this reaction, its 3,3'-disubstituted analogues significantly enhanced the catalytic activity. Both the dr and ee increased proportionally with the size of these substituents. Helical VAPOL-derived phosphoric acid **5**<sup>7</sup> was less effective and enantioselective, although the dr remained high. The more acidic triflyl-substituted phosphoramidate **6a**<sup>8</sup> promoted an interesting racemic reaction favoring the trans isomer. The corresponding magnesium and calcium phosphate salts did not catalyze this reaction, ruling out the previously documented metal-contamination effects.<sup>9</sup> As with other chiral phosphoric acid-catalyzed processes, the enantioselectivity of the reaction was strongly influenced by the polarity of the solvent. Less polar solvents led to improved ee by attenuating the solvation of the hydrogen-bonded catalyst–substrate complex.

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Table 1. Catalyst Screening and Reaction Optimization<sup>a</sup>

4a: Ar = H  
4b: Ar = 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>  
4c: Ar = 3,4,5-F<sub>3</sub>C<sub>6</sub>H<sub>2</sub>  
4d: Ar = 9-anthracenyl

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6a: Ar = 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>  
OM = NHTf  
6b: Ar = 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>  
M = Mg<sub>12</sub>

7: Ar = 9-anthracenyl

entry	cat	solvent	product	conv (%) <sup>b</sup>	cis/trans <sup>b</sup>	ee (%) <sup>c</sup>
1	4a	PhMe	3a	4	3.5:1	11
2	4b	PhMe	3a	81	1:1.2	60
3	4c	PhMe	3a	75	4.6:1	57
4	4d	PhMe	3a	66	>20:1	85
5	5	PhMe	3a	38	>20:1	46
6	6a	PhMe	3a	83	1:2.7	4
7	6b	PhMe	3a	<5	—	—
8	4d	dioxane	3a	82	>20:1	77
9	4d	MeCN	3a	83	1:2.6	10
10	4d	DCM	3a	86	>20:1	70
11	4d	IPAC <sup>d</sup>	3a	79	>20:1	78
12	7	PhMe	3a	85	>20:1	89
13	7	PhMe	3b	88	>20:1	95

<sup>a</sup>The reactions were performed with 0.2 mmol of **1** and 0.2 mmol of **2** in 1 mL of solvent at 25 °C for 24 h. <sup>b</sup>Determined via <sup>1</sup>H NMR analysis of the crude mixture. <sup>c</sup>Determined via chiral HPLC. <sup>d</sup>IPAC = isopropyl acetate.

Both the dr and ee were further enhanced by switching to the corresponding H<sub>8</sub>-BINOL-based phosphoric acids,<sup>10</sup> which have slightly larger dihedral angles than their BINOL counterparts.<sup>11</sup> Catalyst **7**, with two bulky 9-anthracenyl groups, afforded 88% conversion to the single cis product **3b** with 95% ee for the unsubstituted aniline substrate.

The substrate scope was then examined (Table 2). Both electron-rich and electron-poor anilines were tolerated, although

Table 2. Substrate Scope for the Enantioselective Synthesis of Cis-2,4-Diquaternized THQs<sup>a</sup>

15 examples  
7 (5 mol%)  
toluene  
25 °C, 24 h

3a: R = Me, 84%, 89% ee, >20:1 dr  
3b: R = H, 90%, 95% ee, >20:1 dr  
3c: R = OMe, 65%, 99% ee, >20:1 dr  
3d: R = Br, 81%, 95% ee, >20:1 dr  
3e: R = CF<sub>3</sub>, 73%, 97% ee, >20:1 dr  
3f: R = Cl, 78%, 94% ee, >20:1 dr  
3g: R = I, 78%, 95% ee, >20:1 dr  
3h: R = OEt, 64%, 91% ee, >20:1 dr  
3i: R = SMe, 82%, 91% ee, >20:1 dr

3j, 71%, 98% ee, >20:1 dr  
3k, 81%, 87% ee, >20:1 dr  
3l, 79%, 96% ee, >20:1 dr  
3m, R = CO<sub>2</sub>Me, 93%, 95% ee, >20:1 dr  
3n, 68%, 95% ee, >20:1 dr  
3o, R = CO<sub>2</sub>Me, 72%, 95% ee, >20:1 dr

<sup>a</sup>The reactions were performed with 0.2 mmol of **1** and 0.2 mmol of **2** in 1 mL of solvent at 25 °C for 24 h. Isolated yields, ee's determined via chiral HPLC, and dr's determined via <sup>1</sup>H NMR analysis of the crude mixtures are shown. <sup>b</sup>The regioselectivity was determined by 2D NMR analysis (see the Supporting Information for spectra).

the rates for the latter were lower. Reactions involving anilines with strong electron-withdrawing substituents (e.g., NO<sub>2</sub>) proceeded slowly with low conversion. Para-, meta-, and disubstituted anilines achieved good yields and high selectivities in this four-component condensation reaction. As observed by Akiyama, Gong, Zhu, and Masson, ortho-substituted anilines were ineffective except for *o*-hydroxy analogues, where the substituent provided an additional hydrogen bond.<sup>3a–c</sup> Under these conditions, the cis isomer was consistently the only product. The relative and absolute stereochemistries were unambiguously assigned using single-crystal X-ray diffraction.<sup>12</sup> Other activated enolizable ketones were examined. The reaction was messy for 2,3-butadione and acetyl cyanide. Ethyl pyruvate led to a diastereomeric mixture at C3.

In recognizing the discrepancies in the reactivities for the different anilines, we were encouraged to examine whether a “hybrid” product could be obtained with two different anilines. As expected, high chemoselectivity was achieved for a number of aniline pairs (Table 3). Detailed studies of the various aniline

Table 3. “Hybrid” Reactions Using Two Anilines<sup>a</sup>

6 examples  
7 (5 mol%)  
toluene  
25 °C, 24 h

8a, 70%, 95% ee, >20:1 dr  
8b, 61%, 90% ee, >20:1 dr  
8c, R = CO<sub>2</sub>Me, 57%, 97% ee, >20:1 dr  
8d, 52%, 99% ee, >20:1 dr  
8e, R = CO<sub>2</sub>Me, 74%, 93% ee, >20:1 dr  
8f, R = CO<sub>2</sub>Me, 72%, 94% ee, >20:1 dr

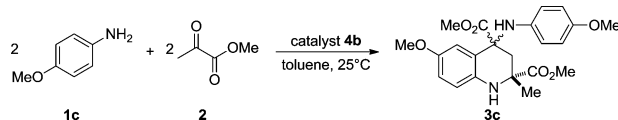
Reaction with 1c, 2, and 2' (7 (5 mol%), toluene, 24h) yields 8g<sup>b</sup> (90%, 72% ee).

<sup>a</sup>The reactions were performed by mixing **1**, **1'**, and **2** in a 1:1:2 ratio. Isolated yields, ee's determined via chiral HPLC, and dr's determined via <sup>1</sup>H NMR analysis of the crude mixtures are shown. <sup>b</sup>This reaction was performed by mixing aniline **1c**, **2**, and **2'** in a 2:1:1 ratio. PMP = *p*-methoxyphenyl.

combinations revealed that “hybrid” reactions could be achieved using aniline pairs with moderate differences in reactivity considering both steric and electronic influence. The ortho substituted anilines were tolerated in these reactions. Interestingly, for a reaction between two different carbonyl components (i.e., methyl pyruvate and *tert*-butyl glyoxylate),  $\gamma$ -lactam product **8g** was obtained in 90% yield with 72% ee.

During our preliminary catalyst screening, we observed that the dr and ee of the products changed over time (Table 4). This time-dependent cis/trans isomerization was particularly facile for electron-rich aniline substrates when less sterically hindered chiral phosphoric acids were used. Electron-deficient aniline substrates did not isomerize at room temperature. With catalyst **4b**, the reaction between **1c** and **2** yielded a cis/trans ratio of 5.2/1 after 5 h. The ee of the minor isomer *trans*-**3c** was poor (34%). In contrast, the major isomer *cis*-**3c** exhibited a high ee (98%). Over time, the dr of the products slowly changed to 1:1.4, favoring *trans*-**3c**. The ee for the accumulating trans product steadily increased (95% after 4 days), accompanied by a small loss in the optical purity of the cis product (98% to 92%).

The cis/trans isomerization was further validated by another independent experiment: stirring a solution of pure *cis*-**3c** or *trans*-**3c** in the presence of 5 equiv of HOAc at room temperature

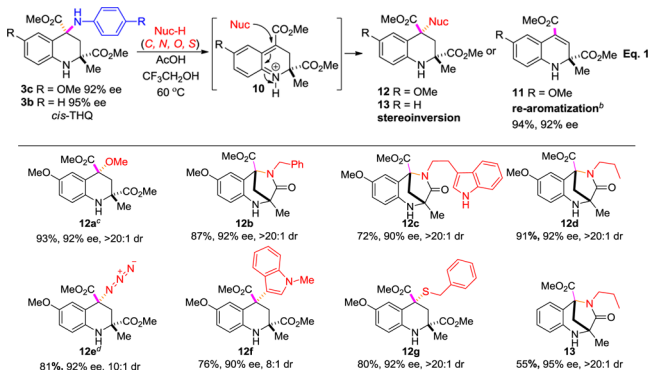
**Table 4. Correlation of Cis/Trans Isomerization and Enantiomeric Excess with Reaction Time<sup>a</sup>**


entry	time (h)	trans/cis	trans ee (%)	cis ee (%)	conv (%)
1	5	1:5.2	34	98	76
2	11	1:3.4	44	98	83
3	20	1:3.4	74	98	89
4	44	1:2.2	90	96	92
5	72	1:1.6	93	93	92
6	96	1:1.4	95	92	94

<sup>a</sup>Six parallel reactions were carried out using 0.1 mmol of **1c**, 0.1 mmol of **2**, and 0.005 mmol of **4b** in 0.5 mL of toluene at room temperature. The dr's and conversions were determined via <sup>1</sup>H NMR analysis of the crude mixtures; the ee's were determined via chiral HPLC.

led to a thermodynamic mixture of the cis and trans isomers (1:1.5) and a small quantity of a dihydroquinoline (DHQ) byproduct, **11**.<sup>13</sup> This DHQ became the dominant product when a large excess of pyruvate was used.<sup>14</sup> At 50 °C, this equilibrium favored the trans isomer only through an intramolecular lactamization to assemble a novel bridged benzodiazepine scaffold. This process can be carried out in one pot with a 50% overall yield from the aniline and methyl pyruvate, allowing the rapid biological evaluation of this class of pharmacophores.<sup>15</sup>

The cis/trans isomerization likely results from a C4 aniline elimination/readdition pathway (eq 1 in Table 5). Taking this

**Table 5. Stereogenic Center Inversion and Functionalization<sup>a</sup>**

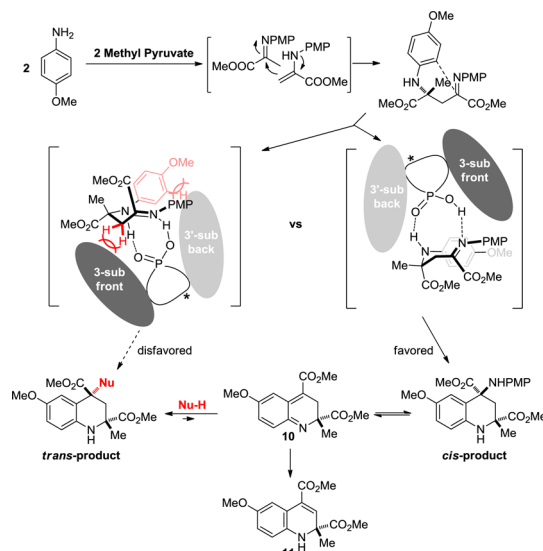
<sup>a</sup>The reaction conditions were not fully optimized. Excess nucleophile (20 equiv) was used. <sup>b</sup>MeNO<sub>2</sub> was used as the solvent in the absence of an external nucleophile. <sup>c</sup>MeOH was used as the solvent. <sup>d</sup>The nucleophile was NaN<sub>3</sub>.

mechanism into account, we speculated that the transient elimination product **10** might be trapped by an external nucleophile (Nuc-H) to yield THQ analogues with diversified functionalities at C4. The success of this “S<sub>N</sub>2-like substitution” would require Nuc-H to be a better nucleophile than ArNH<sub>2</sub> and/or Nuc to be a worse leaving group than ArNH. To our delight, we were able to displace ArNH with both hard and soft nucleophiles (Table 5). Intermediate **10** was susceptible to additions by various C-, N-, O-, and S-based nucleophiles, leading to sophisticated THQ analogues that would be difficult to access using other methods. Indoles engaged in a Friedel–Crafts (FC) reaction with **10** to generate indole-substituted THQs. Treat-

ment with alcohols and azides led to 4-alkoxy- and 4-azido-substituted analogues in high yields. For primary amines, intramolecular lactamization occurred, yielding bridged benzodiazepines. Interestingly, MeNO<sub>2</sub> facilitated rearomatization to afford the corresponding DHQ product **11** in 94% yield. These reactions were not restricted to electron-rich substrates. An example using **3b** derived from nonsubstituted aniline was also effective (Table 5, product **13**). In all cases, the chirality at C2 and the newly functionalized C4 were highly enantioenriched, suggesting substrate-controlled stereospecificity.

We analyzed the mechanism of this reaction on the basis of these findings. Because of the structure of the “hybrid” aniline products, the Povarov reaction likely proceeds in a stepwise manner rather than via a concerted IEHDA mechanism, which would yield the wrong isomer. These “hybrid” THQ products from the aniline pairs are assembled via an “abnormal” Mannich reaction. The enamine derived from the more electron-deficient aniline reacts as a nucleophile, while the electrophile imine is derived from the more electron-rich aniline. The more facile FC ring closure compensates for this electronically unmatched Mannich step. In the FC step, the electron-rich aniline serves as the nucleophile to react with an imine from the more electron-deficient aniline.

This four-component condensation reaction cascade begins with an irreversible, chiral, proton-catalyzed Mannich reaction,<sup>16</sup> which establishes the C2 quaternary center with high enantioselectivity. The dr of the subsequent FC cyclization is also controlled by the catalyst. A simplified illustration is provided in Scheme 2 (the transition states for the FC cyclization

**Scheme 2. Proposed Reaction Mechanism**

are presented in brackets), in which the dark ovals represent a hindered catalyst side arm that protrudes out of the paper and the light ovals represent an identical substituent that points inward. To adopt a half-chair conformation for the FC cyclization, the substrate backbone must fold forward as dictated by the chirality at C2. The corresponding trans transition state would cause severe steric repulsion between the substrate and the catalyst flanks. However, the cis cyclization precursor is strongly favored because of its ability to dock next to the helical catalyst. The cis/trans isomerization suggests that the cis product is kinetically favored but thermodynamically less stable because of an axial–



axial dipole repulsion between the two axial ester groups, which leads to the elimination of PMPNH<sub>2</sub> under the influence of a weak Brønsted acid, yielding the unstable species **10**. This product can be further converted to the trans product (via aniline readdition), a DHQ product (via rearomatization), or various C4-functionalized THQ derivatives.

In summary, we have presented a highly diastereoselective and enantioselective protocol to access cis-2,4-diquaternized tetrahydroquinolines using anilines, methyl pyruvates, and a chiral phosphoric acid catalyst. This method enables the use of aniline pairs to generate “hybrid” Povarov products with excellent chemoselectivity. The C4 quaternary center of the product allows for versatile synthetic manipulation using a wide range of C-, N-, O-, and S-based nucleophiles. The application of this method to the synthesis of structurally related bioactive molecules and natural products is currently underway.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Experimental procedures, characterization data, NMR spectra, HPLC traces, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) For a recent review of THQs, see: Sridharan, V.; Suryavanshi, P. A.; Menendez, J. C. *Chem. Rev.* **2011**, *111*, 7157.
- (2) (a) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (b) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (c) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278. (d) Bello, D.; Ramón, R.; Lavilla, R. *Curr. Org. Chem.* **2010**, *14*, 332. (e) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. *Chem. Soc. Rev.* **2013**, *42*, 902. (f) For a monograph, see: *Multicomponent Reactions*, 1st ed.; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (g) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633.
- (3) For recent examples of chiral organocatalytic THQ syntheses, see: (a) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (b) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (c) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804. (d) Shi, F.; Xing, G.-J.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *J. Org. Chem.* **2012**, *77*, 6970. (e) He, L.; Bekkaye, M.; Retailleau, P.; Masson, G. *Org. Lett.* **2012**, *14*, 3158. (f) Jensen, K. L.; Dickmeiss, G.; Donslund, B. S.; Poulsen, P. H.; Jørgensen, K. A. *Org. Lett.* **2011**, *13*, 3678. (g) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327. (h) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (i) Dagousset, G.; Retailleau, P.; Masson, G.; Zhu, J. *Chem.—Eur. J.* **2012**, *18*, 5869. (j) Lin, J.-H.; Zong, G.; Du, R.-B.; Xiao, J.-C.; Liu, S. *Chem. Commun.* **2012**, *48*, 7738. (k) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (l) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166. (m) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 2266. (n) Ren, L.; Lei, T.; Ye, J.-X.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 771.
- (4) Povarov reactions of ketones in the literature are restricted to nonenolizable isatins. For the only asymmetric method, see: (a) Shi, F.; Xing, G.-J.; Zhu, R.-Y.; Tan, W.; Tu, S. *Org. Lett.* **2013**, *15*, 128. For racemic Povarov reactions using isatins, see: (b) Kouznetsov, V. V.; Bello Forero, J. S.; Amado Torres, D. F. *Tetrahedron Lett.* **2008**, *49*, 5855. (c) Kouznetsov, V. V.; Merchan Arenas, D. R.; Arvelo, F.; Bello Forero, J. S.; Sojo, F.; Munoz, A. *Letts. Drug Des. Discovery* **2010**, *7*, 632.
- (5) For selected bioactive 4-amino-THQs, see: (a) Sikorski, J. A. *J. Med. Chem.* **2006**, *49*, 1. (b) Leeson, P. D.; Carling, R. W.; Moore, K. W.; Moseley, A. M.; Smith, J. D.; Stevenson, G.; Chan, T.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Hoogsteen, K. *J. Med. Chem.* **1992**, *35*, 1954.
- (6) For recent reviews of chiral phosphoric acid catalysis, see: (a) Terada, M. *Synthesis* **2010**, 1929. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Kampen, D.; Reisinger, C. M.; List, B. In *Asymmetric Organocatalysis*; List, B., Ed.; Springer: Berlin, 2010; p 395. (d) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395.
- (7) (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (b) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830. (c) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084. (d) Larson, S. E.; Baso, J. C.; Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 5186.
- (8) (a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626. (b) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411. (c) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661. (d) Vellalath, S.; Coric, I.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 9749. (e) Han, Z.-Y.; Chen, D.-F.; Wang, Y.-Y.; Guo, R.; Wang, P.-S.; Wang, C.; Gong, L.-Z. *J. Am. Chem. Soc.* **2012**, *134*, 6532.
- (9) (a) Xu, S.; Wang, Z.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880. (b) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823. (c) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798. (d) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, *14*, 2189.
- (10) (a) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802. (b) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Köckritz, A.; Pews-Davtyan, A.; Nemat, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065. (c) Pousse, G.; Le Cavalier, F.; Humphreys, L.; Rouden, J.; Blanchet, J. *Org. Lett.* **2010**, *12*, 3582. (d) Momiyama, N.; Nishimoto, H.; Terada, M. *Org. Lett.* **2011**, *13*, 2126.
- (11) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348.
- (12) See the Supporting Information for X-ray crystal structure data.
- (13) Synthesis of the racemic DHQ under strongly acidic conditions has been reported. See: (a) Waldmann, H.; Karunakar, G. V.; Kumar, K. *Org. Lett.* **2008**, *10*, 2159. (b) Hu, X.-Y.; Zhang, J.-C.; Wei, W.; Ji, J.-X. *Tetrahedron Lett.* **2011**, *52*, 2903. (c) Zhang, J.-C.; Ji, J.-X. *ACS Catal.* **2011**, *1*, 1360. (d) Zhu, Y.-W.; Qian, J.-L.; Yi, W.-B.; Cai, C. *Tetrahedron Lett.* **2013**, *54*, 638.
- (14) See the Supporting Information for experimental details.
- (15) (a) Costantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (c) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132.
- (16) For selected examples, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (c) Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun.* **2007**, 4477. (d) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254. (e) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (f) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122. (g) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6717.