

Chiral Phosphoric Acid Catalyzed Inverse-Electron-Demand Aza-Diels–Alder Reaction of Isoeugenol Derivatives

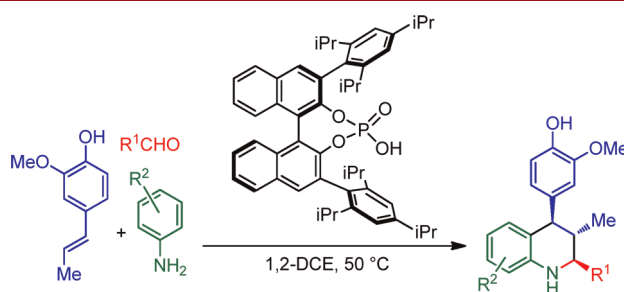
Long He, Mathieu Bekkaye, Pascal Retailleau, and Géraldine Masson*

Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, ICSN, CNRS,
91198 Gif-sur-Yvette Cedex, France

masson@icsn.cnrs-gif.fr

Received May 7, 2012

ABSTRACT



Highly enantio- and diastereoselective three-component inverse electron-demand aza-Diels–Alder reaction of aldehydes, anilines, and isoeugenol derivatives catalyzed by a chiral phosphoric acid catalyst are reported. A wide variety of 2,3,4-trisubstituted tetrahydroquinolines containing an aryl group at the 4-position were obtained in a one-pot process with good to high yields and excellent stereoselectivities (>95:5 dr and up to >99% ee).

The inverse electron-demand aza-Diels–Alder reaction (IEDDA reaction) is an important acid-catalyzed cycloaddition allowing access to 2,3,4-trisubstituted tetrahydroquinolines from *N*-aryl imines and electron-rich alkenes.^{1,2} The development of a catalytic enantioselective version of

this so-called Povarov reaction has recently received considerable attention due to the prevalence of these structural motifs in many natural products and pharmaceutically promising compounds.³ Therefore, a wide variety of dienophiles such as enol ethers, enecarbamates, and cyclopentadienes have been successfully used in an enantioselective IEDDA reaction.⁴ Despite recent developments, the use of simple acyclic alkenes as dienophiles for the enantioselective formation of tetrahydroquinolines has met with limited success. Ricci et al.^{5a} reported the first two-component Povarov reaction using vinylindoles as alkene dienophiles catalyzed by a chiral phosphoric acid.⁵ Very recently, Feng et al.^{5b} have disclosed that a chiral *N*, *N*-dioxide-Sc(OTf)₃ complex catalyzed an enantioselective IEDDA reaction employing α -alkyl styrenes as dienophiles and *N*-arylimines derived from *ortho*-hydroxyanilines as dienes. Despite the aforementioned advances, no example of an IEDDA reaction using unsymmetrically

(1) (a) Povarov, L. S.; Mikhailov, B. M. *Izv. Akad. Nauk SSR, Ser. Khim.* **1963**, 953. (b) Povarov, L. S. *Russ. Chem. Rev.* **1967**, 36, 656.

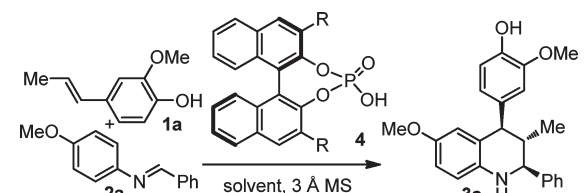
(2) For a general review of inverse-electron-demand aza-Diels–Alder reactions, see: (a) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, 57, 6099. (b) Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2008**, 77, 137. (c) Kouznetsov, V. V. *Tetrahedron* **2009**, 65, 2721.

(3) For an overview on the preparation and biological activity of 1,2,3,4-tetrahydroquinolines, see: (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, 52, 15031. (b) Isambert, N.; Lavilla, R. *Chem.—Eur. J.* **2008**, 14, 8444. (c) Sridharan, V.; Suryavanshi, P. A.; Carlos Menéndez, J. *Chem. Rev.* **2011**, 111, 7157.

(4) (a) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, 37, 7357. (b) Sundararajan, G.; Prabakaran, N.; Varghese, B. *Org. Lett.* **2001**, 3, 1973. (c) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, 128, 13070. (d) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, 131, 4598. (e) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. *Org. Lett.* **2010**, 21, 2266. (f) Xie, M.-S.; Chen, X.-H.; Zhu, Y.; Gao, B.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2010**, 49, 3799. (g) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, 327, 986. (h) Bernardi, L.; Comes-Franchini, M.; Fochi, M.; Leo, V.; Mazzanti, A.; Ricci, A. *Adv. Synth. Catal.* **2010**, 352, 3399. (i) Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc.* **2011**, 133, 14804.

(5) (a) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, 46, 327. (b) Xie, M.; Liu, X.; Zhu, Y.; Zhao, X.; Xia, Y.; Lin, L.; Feng, X.-M. *Chem.—Eur. J.* **2011**, 17, 13800. Also see: (c) Dickmeiss, G.; Jensen, K. L.; Worgull, D.; Franke, P. T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, 50, 1580.

Table 1. Chiral Phosphoric Acid Catalyzed IEDDA Reaction between Isoeugenols **1a** and Imine **2a**^a



entry	R	temp	2a/1a ratio	solvent	yield (%) ^b	ee (%) ^c
1	C ₆ H ₅ (4a)	25	1:1.5	CH ₂ Cl ₂	16	37
2	2-naphthyl (4b)	25	1:1.5	CH ₂ Cl ₂	16	47
3	1-naphthyl (4c)	25	1:1.5	CH ₂ Cl ₂	21	87
4	9-anthracenyl (4d)	25	1:1.5	CH ₂ Cl ₂	13	79
5	4-ClC ₆ H ₄ (4e)	25	1:1.5	CH ₂ Cl ₂	15	33
6	4-FC ₆ H ₄ (4f)	25	1:1.5	CH ₂ Cl ₂	27	59
7	2,4,6-(ⁱ Pr) ₃ C ₆ H ₅ (4g)	25	1:1.5	CH ₂ Cl ₂	35	93
8	4g	25	1:10	CH ₂ Cl ₂	50	93
9	4g	50	1:10	CHCl ₃	51	85
10	4g	50	1:10	1,2-DCE	80	95
11	4g	50	1:10	toluene	43	86
12	4g	70	1:10	1,2-DCE	80	95

^a General conditions: (*E*)-Isoeugenol **1a**, imine **2a** (0.10 mmol), catalyst **4** (0.01 mmol) in solvent (1.0 mL) with 3 Å MS (50 mg) for 48 to 96 h. ^b Yields referred to chromatographically pure 2,3- and 3,4-*trans*-isomer **3a**. In each case, the ratio of “all *trans*”/“all *cis*” stereoisomers was higher than 95/5 by ¹H NMR. ^c *Ee* was determined by chiral HPLC analysis.

β-substituted alkenes for the preparation of optically active tetrahydroquinolines with three contiguous stereocenters has been reported yet.

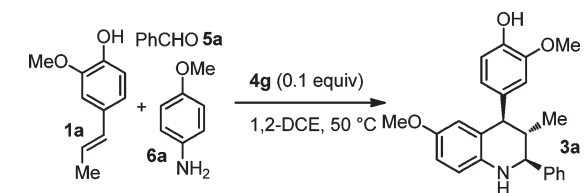
The past decade has witnessed the emergence of chiral phosphoric acids, pioneered by Akiyama and Terada's groups,⁶ as efficient catalysts for numerous enantioselective

(6) For first reports on the use of binol-derived phosphoric acids in enantioselective transformations, 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.

(7) For recent reviews on Brønsted acid catalysis, see: (a) Yamamoto, H.; Payette, N. In *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, 2009; p 73. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Yu, X.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516. (d) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. For recent reviews on chiral phosphoric acid catalysis, see: (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (f) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (g) Terada, M. *Chem. Commun.* **2008**, 4097. (h) Terada, M. *Synthesis* **2010**, 1929. (i) Terada, M. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101. (j) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (k) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227. (l) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539.

(8) For selected racemic examples with isoeugenols as dienophiles, see: (a) Kouznetsov, V. V.; Romero Bohórquez, A. R.; Stashenko, E. E. *Tetrahedron Lett.* **2007**, *48*, 8855. (b) Kouznetsov, V. V.; Merchan Arenas, D. R.; Romero Bohórquez, A. R. *Tetrahedron Lett.* **2008**, *49*, 3097. (c) Kouznetsov, V. V.; Bello Forero, J. S.; Amado Torres, D. F. *Tetrahedron Lett.* **2008**, *49*, 5855. (d) Kouznetsov, V. V.; Merchan Arenas, D. R.; Arvelo, F.; Bello Forero, J. S.; Sojo, F.; Muñoz, A. *Lett. Drug Des. Discovery* **2010**, *7*, 632. (e) Romero Bohórquez, A. R.; Kouznetsov, V. V. *Synlett* **2010**, 970. (f) Merchan Arenas, D. R.; Rojas Ruiz, F. A.; Kouznetsov, V. V. *Tetrahedron Lett.* **2011**, *52*, 1388.

Table 2. Catalytic Enantioselective Three-Component IEDDA Reaction^a



entry	1a/6a ratio	3 Å MS	yield (%) ^b	ee (%) ^{c,d}
1	10:1	50 mg	80	95
2	10:1	no	80	96
3	2:1	no	72	96
4	3:1	no	75	94
5	4:1	no	81	96
6	4:1	no	trace ^e	ND ^f

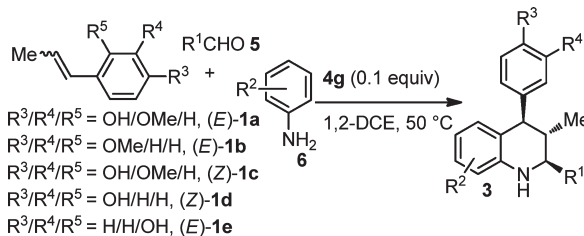
^a General conditions: (*E*)-Isoeugenol **1a**, benzaldehyde (**5a**) (0.12 mmol), 4-anisidine **6a** (0.10 mmol), catalyst **4g** (0.01 mmol) in 1,2-DCE (1.0 mL) for 24 to 72 h. ^b Yields referred to chromatographically pure 2,3- and 3,4-*trans*-isomer **3a**. ^c *Ee* was determined by chiral HPLC analysis. ^d Dr (> 95:5) was determined by ¹H NMR analysis. ^e Catalyst [**4g**]₂Ca (10 mol %) used. ^f Not determined.

transformations using imines as electrophiles.⁷ These bi-functional catalysts are generally known to cooperatively activate both the electrophilic imine and the nucleophile *via* H-bonding to ensure high enantioselectivities.⁷ Based on this, we hypothesized that an alkene with a H-bond donor would be a suitable dienophilic partner for an enantioselective catalytic IEDDA reaction.⁸ Accordingly, we selected isoeugenol derivatives bearing a free phenol functional group as dienophiles. In addition, this approach would result in the efficient synthesis of optically enriched trisubstituted 4-aryltetrahydroquinoline derivatives possessing potential antiparasitic and anticancer activities.^{3,8d,9} Herein, we present a highly diastereo- and enantioselective one-pot, three-component catalytic route to the synthesis of tetrahydroquinolines having an aryl group at the 4-position.

We initiated our investigations using (*E*)-isoeugenol (**1a**), preformed arylimine **2a**, and 10 mol % of chiral phosphoric acid derived from (*R*)-BINOL **4** in CH₂Cl₂ at rt in the presence of 3 Å molecular sieves (Table 1). All catalysts tested afforded high diastereoselectivity (95:5) in favor of 2,3- and 3,4-*trans* tetrahydroquinoline **3a**. Catalyst **4g**, with a bulky 2,4,6-triisopropyl phenyl group in the 3,3'-position of (*R*)-BINOL,¹⁰ furnished the cycloadduct with the highest enantioselectivity but with a low yield. To further optimize the procedure, this IEDDA reaction was chosen for a survey of different solvents and temperatures.

(9) (a) Gerlach, M.; Przewosny, M.; Englberger, W.; Reissmueller, E.; Bloms-Funke, P.; Maul, C.; Jagusch, U.-P. U.S. Patent 0087926 A1, 2003. (b) Gómez-Barrio, A.; Montero-Pereira, D.; Nogal-Ruiz, J. J.; Escario, J. A.; Muelas-Serrano, S.; Kouznetsov, V. V.; Vargas Méndez, L. Y.; Urbina Gonzáles, J. M.; Ochoa, C. *Acta Parasitol.* **2006**, *51*, 73.

(10) (*R*)-TRIP catalyst **4g** was easily prepared from (*R*)-BINOL; see: (a) Akiyama, T. U.S. Patent 0276329 A1, Dec 7, 2006. (b) Klusmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, 2189.

Table 3. Chiral Brønsted Acid Catalyzed IEDDA Reaction^a


$R^3/R^4/R^5 = \text{OH/OMe/H, (E)-1a}$
 $R^3/R^4/R^5 = \text{OMe/H/H, (E)-1b}$
 $R^3/R^4/R^5 = \text{OH/OMe/H, (Z)-1c}$
 $R^3/R^4/R^5 = \text{OH/H/H, (Z)-1d}$
 $R^3/R^4/R^5 = \text{H/H/OH, (E)-1e}$

entry	R ¹	R ²	1	3	yield (%) ^b	ee (%) ^c
1	4-BrC ₆ H ₄	4-OMe	1a	3b	79 ^d	97
2	4-NO ₂ C ₆ H ₄	4-OMe	1a	3c	92	98
3	4-CNC ₆ H ₄	4-OMe	1a	3d	70	96
4	4-FC ₆ H ₄	4-OMe	1a	3e	66	94
5	3-FC ₆ H ₄	4-OMe	1a	3f	86	96
6	3-ClC ₆ H ₄	4-OMe	1a	3g	71	96
7	3-NO ₂ C ₆ H ₄	4-OMe	1a	3h	93	96
8	3-BrC ₆ H ₄	4-OMe	1a	3i	83	96
9	2-FC ₆ H ₄	4-OMe	1a	3j	74	96
10	2-BrC ₆ H ₄	4-OMe	1a	3k	93	96
11	4- <i>i</i> PrC ₆ H ₄	4-OMe	1a	3l	65	94
12	Cyclohexyl-	4-OMe	1a	3m	61 ^e	90
13	3-CF ₃ C ₆ H ₄	4-Cl	1a	3n	73	91
14	1-naphthyl	4-Cl	1a	3o	70	94
15	4-PhC ₆ H ₄	4-Cl	1a	3p	79	>99
16	4-ClC ₆ H ₄	4-Cl	1a	3q	72	93
17	4-CH ₃ C ₆ H ₄	4-Cl	1a	3r	79	96
18	4-CF ₃ C ₆ H ₄	4-Cl	1a	3s	89	96
19	C ₆ H ₅	4-Cl	1a	3t	81	96
20	C ₆ H ₅	4-Br	1a	3u	74	96
21	C ₆ H ₅	4-NO ₂	1a	3v	82	97
22	C ₆ H ₅	4-CF ₃	1a	3w	75	95
23	C ₆ H ₅	4-F	1a	3x	77	95
24	C ₆ H ₅	3-Cl	1a	3y	91	96
25	C ₆ H ₅	H	1a	3z	75	94
26	C ₆ H ₅	4-CH ₃	1a	3aa	78	97
27 ^f	C ₆ H ₅	4-OMe	1b	3ab	<10	91
28	C ₆ H ₅	H	1c	3z	11	85 ^g
29	C ₆ H ₅	4-OMe	1d	3ac	61	73
30	C ₆ H ₅	4-OMe	1e	3ad	53	45 ^h

^a General conditions: Isoeugenol derivatives **1** (0.40 mmol), aldehyde **5** (0.12 mmol), arylamine **6** (0.10 mmol), catalyst **4g** (0.01 mmol) in 1,2-DCE (1.0 mL) for 24 to 96 h. ^b Yields referred to chromatographically pure product, and the ratio of “all trans”/“all cis” stereoisomers was higher than 95/5 unless indicated otherwise. ^c Ee was determined by chiral HPLC analysis. ^d 15/1 dr. ^e 10/1 dr. ^f Reaction at 70 °C. ^g 2/1 dr in favor of “all cis-isomer”. ^h 7/1 dr.

To our delight, when the reaction was carried out at 50 °C in 1,2-dichloroethane (1,2-DCE), the desired tetrahydroquinoline **3a** was isolated in 80% yield and with 95% ee

(11) (a) Seayad, J.; List, B. *Catalytic Asymmetric Multicomponent Reactions*. In *Multicomponent Reaction*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; p 227. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (c) Enders, D.; Grondal, C.; Hüttel, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (d) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. (e) Gong, L.-Z.; Chen, X.-H.; Xu, X.-Y. *Chem.—Eur. J.* **2007**, *13*, 8920. (f) Dandapani, S.; Marcaurelle, L. A. *Curr. Opin. Chem. Biol.* **2010**, *14*, 362. (g) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156.

(entry 10). When higher temperatures were used, however, no improvement in the final yield was observed (entry 12).

To simplify the process and to avoid the use of a preformed *N*-arylimine, a three-component reaction of benzaldehyde (**5a**), 4-methoxyaniline (**6a**), and isoeugenol (**1a**) was investigated next.¹¹ To our pleasure, the reaction proceeded smoothly to afford **3a** with 80% yield and 95% ee (Table 2, entry 1). In addition, the presence of molecular sieves was not essential for this cycloaddition.¹² In an attempt to reduce the amount of isoeugenol dienophile **1a**, we found that 4 equiv of **1a** gave the best result in terms of yield and enantioselectivity (entry 5). Chiral BINOL phosphate salts have proven to be the catalysts of choice for some transformations since their initial report by Ishihara et al.¹³ and later exploited by others.¹⁴ This result led us to examine the chiral calcium phosphate [**4g**]₂Ca at 50 °C in 1,2-DCE. However, only trace amounts of the desired product was isolated after 96 h (Table 2, entry 6). This showed that only metal-free chiral phosphoric acid appears able to catalyze the Povarov reaction.

With the reaction parameters for the IEDDA reaction optimized, we extended it to a selection of aldehydes, arylamines, and isoeugenol derivatives. The results of the enantioselective multicomponent IEDDA reaction are shown in Table 3. Gratefully, aromatic aldehydes with electron withdrawing substituents (entries 1–10), as well as electron donating substituents (entries 11, 14, 15, and 17) in *ortho*-, *meta*-, and *para*-positions were appropriate substrates, affording the products in good yields with excellent diastereo- and enantioselectivity (up to 99% ee). Cyclohexanecarboxaldehyde gave the three-component product **3m** in 61% yield and 90% ee (entry 12). However, a complex mixture was observed with linear aliphatic aldehydes. Both electron-rich (entries 1–12) and -deficient (entries 13–23) *para*-substituted anilines participated with good yield and enantioselectivity. Interestingly, when a substituent in the *meta*-position was present on the aniline, the cycloaddition led only to the formation of the more congested regioisomer **3y** (entry 24). The absolute configuration of **3p** was unequivocally determined to be 2*S*, 3*S*, 4*R* by single-crystal X-ray diffraction experiments (*cf.* Supporting Information (SI)).¹⁵ As the IEDDA reaction

(12) It was found that addition of MS to the Povarov reaction has an impact on the ee's of the products obtained; see ref 4b.

(13) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823.

(14) For selected examples, see: (a) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776. (b) Klusmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, 2189. (c) Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339. (d) Larson, S. E.; Li, G.; Rowland, G. B.; Junge, D.; Huang, R.; Woodcock, H. L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2188. (e) Zhang, Z.; Zheng, W.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1135. (f) Drouet, F.; Lalli, C.; Liu, H.; Masson, G.; Zhu, J. *Org. Lett.* **2011**, *13*, 94. (g) Terada, M.; Kanomata, K. *Synlett* **2011**, 1255. For examples of phosphoramidate/calcium complex, see: (h) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798. (i) Rueping, M.; Nachtsheim, B. J.; Koenigs, R. M.; Ieawsuwan, W. *Chem.—Eur. J.* **2010**, *16*, 13116. For recent reviews, see: (j) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999. (k) Rueping, M.; Koenigs, R. M.; Atodiresi, I. *Chem.—Eur. J.* **2010**, *16*, 9350. For a general review on the calcium complex in homogeneous catalysis, see: (l) Harder, S. *Chem. Rev.* **2010**, *110*, 3852.

(15) See the Supporting Information for details.

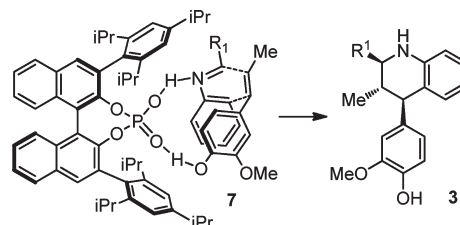
can be sensitive to dienophile geometry, we examined the reaction with a *Z*-dienophile. (*Z*)-**1c** generated the cycloadduct as a 2:1 mixture of diastereomer with only an 11% yield (entry 28). In this case, the major 2,3- and 3,4-*cis* cycloadduct was isolated as a racemic product, whereas the minor all *trans* product was obtained with 85% ee. Meanwhile, the (*Z*)-**1d** afforded the 2,3- and 3,4-*trans* product **3ac** with 73% ee (*cf.* SI).

The IEDDA reactions¹⁶ proceed through either a concerted^{4g,17} or stepwise mechanism^{4d,h,i,18,19} via a cationic intermediate according to the nature of the dienophile used. As the possibility of isomerization of *Z*-dienophiles (entries 28–29, Table 3), occurring under our experimental conditions, had been ruled out by control experiments (*cf.* SI), we thought that a stepwise mechanism could account for the nonstereoselective issue of the reaction involving *Z*-dienophiles (**1c–d**). Thus, the reaction would be viewed as a nucleophilic-type attack of isoeugenol to the *N*-arylimine with a concomitant cyclization with formation of zwitterionic intermediates.

Based on the above experimental results, a tentative transition state model **7** wherein the phosphoric acid forms H-bonds with the phenol and imine was proposed to explain the stereochemical outcome of the enantioselective IEDDA reaction (Scheme 1). Then the cycloaddition occurs to form (2*S*,3*S*,4*R*)-tetrahydroquinoline **3** exclusively. The

importance of the position of phenol on the isoeugenol derivatives was supported by the low enantioselectivity in the case of (*E*)-2-hydroxystyrene **1e** (45% ee, entry 30). In addition, a control experiment, in which (*E*)-1-methoxy-4-propenylbenzene **1b** (Table 3, entry 27) was subjected to this three-component reaction, afforded the corresponding product **3ab** in very low yield (<10%) but with good enantioselectivity (91% ee). This indicates that the free hydroxyl group in the *para*-position of the dienophile appears to be crucial for reactivity, but not for enantioselectivity.

Scheme 1. Activation Model and Possible Reaction Mechanism



In summary, we have developed an efficient enantioselective IEDDA reaction with isoeugenol derivatives as the dienophiles catalyzed by chiral phosphoric acids. This cycloaddition is applicable to a wide range of aldehydes and anilines, providing a highly diastereo- and enantioselective method to 2,3,4-trisubstituted 4-aryl-tetrahydroquinolines.^{3,8d,9} Further investigations into the mechanism of the IEDDA reaction, as well as application to the synthesis of biologically active compounds, are currently underway in our laboratory.

Acknowledgment. We thank ICSN and CNRS for financial support and ANR for postdoctoral fellowships to L.H. We also acknowledge Prof. Jieping Zhu (EPFL) for his unwavering support.

Supporting Information Available. Experimental details, characterization data, HPLC enantiomer analysis, and ¹H and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

- (16) Bello, D.; Ramón, J.; Lavilla, R. *Curr. Org. Chem.* **2010**, *14*, 332.
 (17) (a) Beifuss, U.; Ledderhose, S.; Ondrus, V. *ARKIVOC* **2005**, 147.
 (b) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *ARKIVOC* **2007**, 12. See also: (c) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330. (d) Whiting, A.; Windsor, C. M. *Tetrahedron* **1998**, *54*, 6035. (e) Crousse, B.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009. (f) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678.
 (18) (a) Lucchini, V.; Prato, M.; Scorrano, G.; Stivanello, M.; Valle, G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 259. (b) Mellor, J. M.; Merriman, G. D. *Tetrahedron* **1995**, *51*, 6115. (c) Kobayashi, S.; Ishitani, H.; Nakagawa, S. *Synthesis* **1995**, 1195. (d) Hermitage, S.; Jay, D. A.; Whiting, A. *Tetrahedron Lett.* **2002**, *43*, 9633. (e) Stevenson, P. J.; Graham, I. *ARKIVOC* **2003**, 139. (f) Carranco, I.; Díaz, J. L.; Jiménez, O.; Lavilla, R. *Tetrahedron Lett.* **2003**, *44*, 8449. (g) Sridharan, V.; Perumal, P. T.; Avendaño, C.; Carlos Menéndez, J. *Org. Biomol. Chem.* **2007**, *5*, 1351. (h) Sridharan, V.; Avendaño, C.; Carlos Menéndez, J. *Synthesis* **2008**, 1039. (i) José Alves, M.; Azoia, N. G.; Gil Fortes, A. *Tetrahedron* **2007**, *63*, 727. (j) Shindoh, N.; Tokuyama, H.; Takemoto, Y.; Takasu, K. *J. Org. Chem.* **2008**, *73*, 7451. (k) Pérez-Ruiz, R.; Domingo, L. R.; Consuelo Jiménez, M.; Miranda, M. A. *Org. Lett.* **2011**, *13*, 5116.
 (19) For examples of interrupted Povarov reaction, see: (a) Batey, R. A.; Powell, D. A.; Acton, A.; Lough, A. J. *Tetrahedron Lett.* **2001**, 42, 7935. (b) Jiménez, O.; de la Rosa, G.; Lavilla, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6521. (c) Isambert, N.; Cruz, M.; Arévalo, M. J.; Gómez, E.; Lavilla, R. *Org. Lett.* **2007**, *9*, 4199. (d) Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 5546.