JOC Article
pubs.acs.org/joc

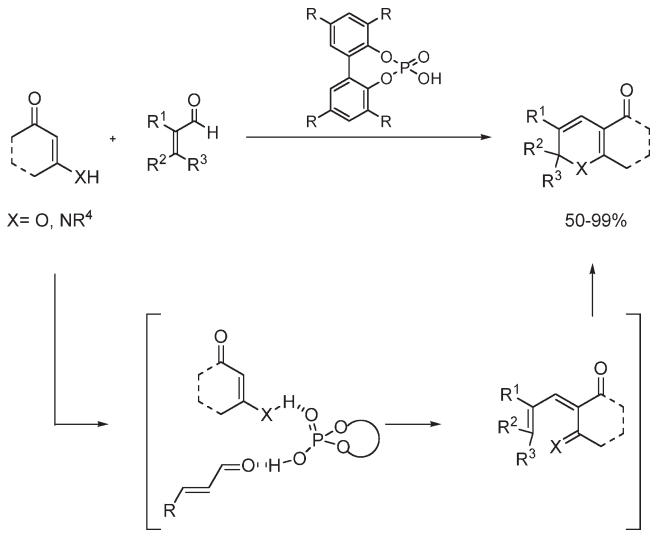
Metal-Free Brønsted Acid Catalyzed Formal [3 + 3] Annulation. Straightforward Synthesis of Dihydro-2*H*-Chromenones, Pyranones, and Tetrahydroquinolinones

Julie Moreau,[†] Claudie Hubert,[†] Jessika Batany,[†] Loic Toupet,[‡] Thierry Roisnel,[§] Jean-Pierre Hurvois,[†] and Jean-Luc Renaud*,[⊥]

[†]*Sciences Chimiques de Rennes, Catalyse et Organométalliques, UMR 6226,* [‡]*Institut de Physique de Rennes, Groupe Matière Condensée et Matériaux, UMR 6626,* [§]*Sciences Chimiques de Rennes, Diffraction Rayons-X, UMR 6226, CNRS-Université de Rennes 1, Campus de Beaulieu-35042 Rennes Cedex, France, and* [⊥]*Laboratoire de Chimie Moléculaire et Thioorganique, UMR 6507, INC3M, FR 3038, ENSICAEN-Université de Caen, 14050 Caen, France*

jean-luc.renaud@ensicaen.fr

Received June 17, 2009



Brønsted acids catalyze the addition of enolizable β-diketones, β-ketoesters, and vinylogous amides to α,β-unsaturated aldehydes to lead to substituted chromenones, pyranones, and tetrahydroquinolinones in good yields under mild reaction conditions via a formal [3 + 3] cycloaddition.

Introduction

Oxadecalins, chromanes, and pyranocoumarins contain a tetrahydropyran or a pyran core in which the pyranyl moiety is fused to a six-membered ring. These fundamental structural moieties represent a dominant heterocycle core for several organic transformations and are embedded in several natural products,[1] such as arisugacins[2] and pyripyropenes[3] which contain a chromanone subunit, cordipyridones,[4] hongoquercins,[5] forskolin,[6] and rhododaurichromanic acids[7] (Figure 1). Elegant approaches to these intermediates and their use in synthesis have already

*To whom correspondence should be addressed. Fax: 33(0)231452877. Phone: 33(0)231452842.

(1) For recent reviews, see: (a) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683. (b) Tang, Y.; Oppenheimer, J.; Song, Z.; You, L.; Zhang, X.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10785.

(2) For isolation and biological activities of arisugacin, see: (a) Ōmura, S.; Kuno, F.; Otoguro, K.; Sunazuka, T.; Shiomi, K.; Masuma, R.; Iwai, Y. *J. Antibiot*. **1995**, *48*, 745. (b) Kuno, F.; Otoguro, K.; Shiomi, K.; Iwai, Y.; Ōmura, S. *J. Antibiot*. **1996**, *49*, 742. (c) Kuno, F.; Shiomi, K.; Otoguro, K.; Sunazuka, T.; Ōmura, S. *J. Antibiot*. **1996**, *49*, 748. (d) Otoguro, K.; Kuno, F.; Omura, S. *Pharmacol. Ther*. **1997**, *76*, 45. For C−H, see: (e) Otoguro, K.; Shiomi, K.; Yamaguchi, Y.; Arai, N.; Sunazuka, T.; Masuma, R.; Iwai, Y.; Ōmura, S. *J. Antibiot*. **2000**, *53*, 50.

(4) Isaka, M.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Org. Chem*. **2001**, *66*, 4803.

(5) Roll, D. M.; Manning, J. K.; Carter, G. T. *J. Antibiot*. **1998**, *51*, 635.

(6) (a) Bhat, S. V; Bajwa, B. S.; Dornauer, H.; de Souza, N. J.; Fehlhaber, H.-W. *Tetrahedron Lett*. **1977**, *18*, 1669. (b) Bhat, S. V; Bajwa, B. S.; Dornauer, H.; de Souza, N. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 767.

(7) Kashiwada, Y.; Yamzaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioko, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.

DOI: 10.1021/jo901238y Published on Web 11/12/2009

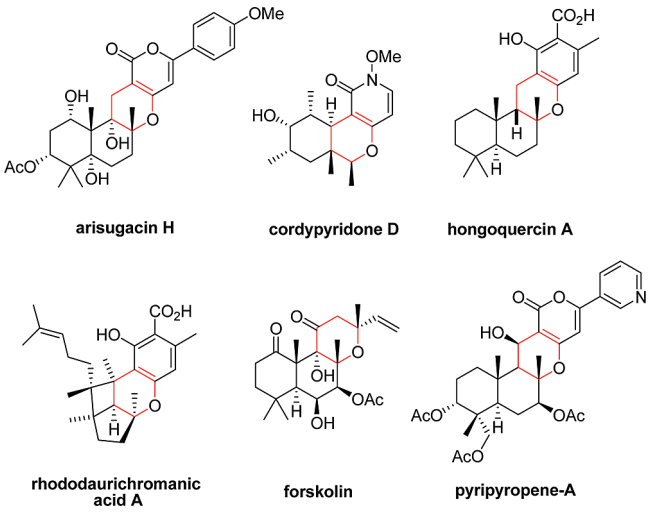
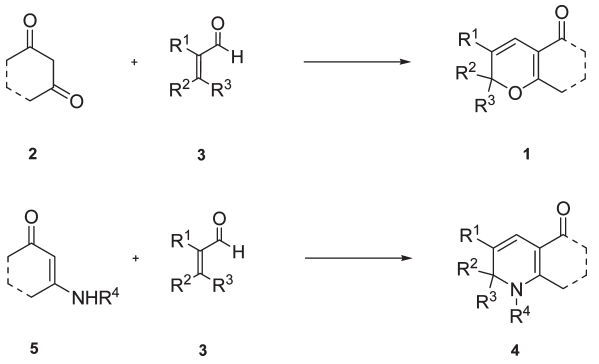


FIGURE 1. Natural compounds containing a pyran core.

been described by several groups using either α,β-unsaturated iminium salts as activated electrophiles,[8] Lewis acids as catalysts,[9] or a tandem Stille-oxo-electrocyclization reaction.[10−13]

1,3-Dicarbonyl derivatives constitute important synthetic intermediates as they incorporate electrophilic and nucleophilic functionalities.[14] These derivatives can be condensed to α,β-unsaturated aldehydes to form a 2*H*-pyran motif via a formal [3 + 3] cycloaddition (Scheme 1).[15] From a synthetic point of view, this type of approach allows the formation of multiple bonds, rings, and new stereogenic centers. Cycloadditions and related reactions are commonly promoted by heat, light, high pressure, sonication, or by the use of transition metal and Lewis acids as catalysts.[16] More recently, activation by small organic molecules has emerged as an important tool in catalysis, and a large number of

SCHEME 1. General Brønsted Acid Catalyzed Synthesis of 7,8-Dihydro-2*H*-Chromen-5(6*H*)-ones, Pyrano[3,2-*c*]chromen-5(2*H*)-ones, and 1,2,7,8-Tetrahydroquinolin-5(6*H*)-ones



reactions have been described using such organocatalysts.[17,18] These catalysts do not contain any metals; they are stable under a large set of reaction conditions and are moisture insensitive. Among the known carbonyl activators, Brønsted acids have appeared as catalysts of choice in a large variety of synthetically useful reactions in organic chemistry.

Several groups have already described the synthesis of 2*H*-pyran-containing derivatives from cyclic β-diketones and α,β-unsaturated aldehydes in the presence of Lewis acids. In 2002, Lee et al. reported the use of $InCl_3$ (50 mol%) as the best Lewis acid. The condensation was carried out in refluxing acetonitrile, and yields ranged from 40 to 70%.[19] Later, Hsung et al. reported a similar reaction in dichloromethane at room temperature, in the presence of 1 equiv of $BF_3 \cdot Et_2O$,[20] affording the expected heterocycles in moderate to high yields. In a complementary approach, the same group developed a catalyst-free addition of 1,3-dicarbonyl compounds on α,β-unsaturated iminium salts.[21] These iminium salts reacted in sealed tubes with 1,3-diketones at temperatures ranging from 80 to 150 °C and provided the desired 2*H*-chromenones in moderate to good yields. Although successful, this approach suffered from several drawbacks such as the use of moisture sensitive iminium salts and harsh reaction conditions.

Organocatalyzed approaches were also reported in the literature. Following the pioneering work of Hua et al. devoted to proline-mediated pyran synthesis,[22] several groups introduced ethylenediamine diacetate as organocatalyst for the synthesis of tetrahydropyrans.[23] Thus, Lee and collaborators described the synthesis of one chromenone derivative catalyzed by ethylenediamine diacetate.[24] They also reported the reaction of α,β-unsaturated aldehydes with

(8) (a) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L.-L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729. (b) Cole, K. P.; Hsung, R. P. *Chem. Commun.* **2005**, 5784. (c) Cravotto, G.; Nano, G. M.; Tagliapietra, S. *Synthesis* **2001**, *1*, 49.

(9) (a) Kurdyumov, A. V.; Lin, N.; Hsung, R. P.; Gullickson, G. C.; Cole, K. P.; Sydorenko, N.; Swidorski, J. J. *Org. Lett.* **2006**, *8*, 191. (b) Lee, Y. R.; Kim, D. H.; Shim, J.-J.; Kim, S. K.; Park, J. H.; Cha, J. S.; Lee, C.-S. *Bull. Korean Chem. Soc.* **2002**, *23*, 998. (c) Appendino, G.; Cravotto, G.; Giovenzana, G. B.; Palmisano, G. *J. Nat. Prod.* **1999**, *62*, 1627.

(10) Tambar, U. K.; Kano, T.; Zepernick, J. F.; Stoltz, B. M. *Tetrahedron Lett.* **2007**, *48*, 345.

(11) (a) Li, C.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 10484. (b) Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095.

(12) Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y *Angew. Chem., Int. Ed.* **2002**, *41*, 3192.

(13) (a) Malerich, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2003**, *125*, 9554. (b) Malerich, J. P.; Maimone, T. J.; Elliott, G. I.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 6276.

(14) For recent reviews on the reactivity of 1,3-dicarbonyl compounds, see: (a) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957. (b) Rodriguez, J. *Synlett* **1999**, 505. (c) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27.

(15) For a recent review, see: Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23.

(16) For reviews on cycloaddition, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

(17) (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. (c) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575. (d) List, B. *Chem. Rev.* **2007**, *107*, 5413. (e) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187.

(18) For a review on organocatalyzed cycloadditions, see: Shen, J.; Tan, C.-H. *Org. Biomol. Chem.* **2007**, 3229.

(19) Lee, Y. R.; Kim, D. H.; Shim, J.-J.; Kim, S. K.; Park, J. H.; Cha, J. S.; Lee, C.-S. *Bull. Korean Chem. Soc.* **2002**, *23*, 998.

(20) Kurdyumov, A. V.; Lin, N.; Hsung, R. P.; Gullickson, G. C.; Cole, K. P.; Sydorenko, N; Swidorski, J. J. *Org. Lett.* **2006**, *8*, 191.

(21) (a) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690. (b) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L.-L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1733.

(22) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888.

(23) (a) Huang, C.-N.; Kuo, P.-Y.; Lin, C.-H.; Yang, D.-Y. *Tetrahedron* **2007**, *63*, 10025. (b) Hu, H.; Harrison, T. J.; Wilson, P. D. *J. Org. Chem.* **2004**, *69*, 3782. (c) Tietze, L. F.; Kiedrowski, G. V.; Berger, B. *Synthesis* **1982**, 683.

(24) Lee, Y. R.; Kim, D. H. *Synthesis* **2006**, 603.

resorcinol derivatives[25] or with 4-hydroxy-2-quinolones[26] catalyzed by this diammonium salt. More recently, Rueping et al. showed that the condensation of β-diketones with α,β-unsaturated aldehydes, in the presence of diarylproline derivatives as catalysts, yielded the unexpected 2-hydroxy-4-substituted chromane derivatives. The latter may come from a 1,4-addition of the keto-enolic functions to the in situ generated iminium salts.[27] Interestingly, in the presence of L-proline, the catalytic process followed another pathway and provided, as major product, the conjugated dienone resulting from a Knoevenagel condensation between the unsaturated aldehyde and the diketone.[28]

When we started our studies,[29,30] little was known on the activation of unsaturated carbonyl compounds by phosphoric acid derivatives and no general studies on the synthesis of pyran-containing derivatives were proposed in the literature.[31,32] We report here our contribution to the synthesis of several 7,8-dihydro-2*H*-chromen-5(6*H*)-one and pyrano-[3,2-*c*]chromen-5(2*H*)-one derivatives from β-diketones and conjugated enals in the presence of a catalytic amount of Brønsted acid under mild reaction conditions (Scheme 1). This new methodology is then extended further to the synthesis of some substituted 1,2,7,8-tetrahydroquinolin-5(6*H*)-ones and octahydrochromanones.

Results and Discussion

We have recently reported a simple and efficient preparation of several 1,4-dihydropyridines **8** from the enaminoesters **9** and α,β-unsaturated aldehydes **3**, catalyzed by the phosphoric acids **6** and **7** (Scheme 2).[29] These catalysts activated the unsaturated aldehydes and allowed the addition of the enaminoesters **9**. We were also pleased to find that the same organocatalysts opened a rapid access to some 7,8-dihydro-2*H*-chromen-5(6*H*)-ones **1**.[30]

Synthesis of 7,8-Dihydro-2*H*-Chromen-5(6*H*)-ones 1. As a model reaction, we chose the reaction between **2a** and the enal **3a**. Only starting materials were isolated from the reaction mixture when a blank reaction was carried out (entry 1, Table 1). As shown in Table 1, several Brønsted acids were investigated. The addition of 5 mol% of **6** in the reaction medium promoted the formation of 7,8-dihydro-2*H*-chromen-5(6*H*)-one **1a**, which was then isolated in 70% yield (entry 2, Table 1). It is worth mentioning that the use of ethylenediamine diacetate as catalyst led to **1a** in a comparable yield.[24] Nevertheless, in this work, the scope and limitations of this synthetic transformation were not outlined. The use of the bulkier catalyst **7** had a slight effect on the reactivity (entry 3, Table 1). A higher catalyst loading (15 mol%) was required with Brønsted acids such as HBF_4, PTSA, or PPTS to ensure a complete conversion. Then, in these conditions, **1a** was isolated in yields ranging from 59 to 70% (entries 4−6, Table 1). In view of these preliminary results, the study has been carried on with **7** as catalyst.

SCHEME 2. Synthesis of 1,4-Dihydropyridines Catalyzed by Phosphoric Acid 6 or 7

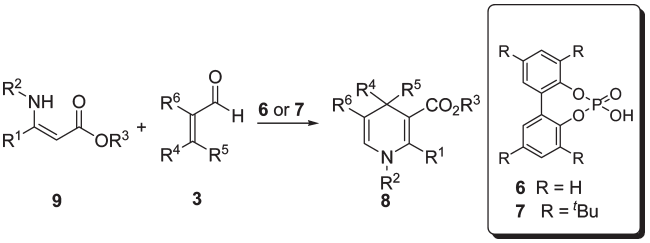
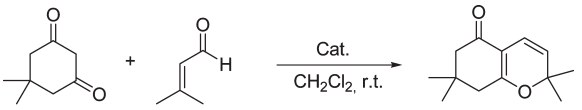


TABLE 1. Brønsted Acids Comparison for the Synthesis of 7,8-Dihydro-2*H*-Chromen-5(6*H*)-one 1a[a]



entry	catalyst	conversion (%)[c]	yield (%)[d]
1	−	0	0
2	**6**	100	70
3	**7**	96	73
4	HBF_4[b]	96	70
5	PTSA[b]	97	66
6	PPTS[b]	60	59

[a]With 0.5 mmol of β-diketone **2a**, 0.75 mmol of α,β-unsaturated aldehyde **3a**, 0.025 mmol of catalyst (5 mol%), 5 mL of CH_2Cl_2, 150 mg of Na_2SO_4 (1.05 mmol). [b]Reaction was performed with 15 mol% of catalyst. [c]As determined by ^1H NMR spectroscopy. [d]Isolated yield after purification on silica gel.

To extend the scope of the reaction, the condensation of various α,β-unsaturated aldehydes **3** with the β-diketone **2a** was investigated (Table 2). Reactive aldehydes such as 2-methylbutenal **3a**, 3-methylbutenal **3b**, and citral **3c** led to the corresponding chromenone derivatives **1a**−**c** in high yields (entries 1−3, Table 2). This is an exceedingly mild method for such an annulation reaction. Aldehydes such as crotonaldehyde **3d** and pentenal **3e** led to the expected adducts **1d** and **1e** but in lower yields (16 and 15%, respectively). To improve the yields and the reaction rates, several experimental conditions were evaluated. High conversions and yields were then obtained by heating at 60 °C in toluene. Compounds **1d** and **1e** were isolated in 78 and 81% yields, respectively (entries 8 and 10, Table 2). With aromatic aldehydes such as cinnamaldehyde **3f** and *p*-nitrocinnamaldehyde **3g**, a catalyst loading of 15 mol % was necessary to ensure the completion of the reaction in dichloromethane at room temperature. The chromenone derivatives **1f**,**g** were then obtained in 72 and 61% yields, respectively (entries 11 and 12, Table 2).

Under these optimized reaction conditions, several analogues were synthesized starting from **2b** and aldehydes **3a**−**e**

(25) (a) Lee, Y. R.; Choi, J. H.; Yoon, S. H. *Tetrahedron Lett.* **2005**, *46*, 7539. (b) Lee, Y. R.; Xia, L. *Synthesis* **2007**, 3240. (c) Lee, Y. R.; Kim, J. H. *Synlett* **2007**, 2232. (d) Lee, Y. R.; Xia, L. *Tetrahedron Lett.* **2008**, *49*, 3283. (e) Park, B. H.; Lee, Y. R.; Lyoo, W. S. *Synthesis* **2009**, 2146.

(26) Lee, Y. R.; Choi, J. H.; Trinh, D. T. L.; Kim, N. W. *Synthesis* **2005**, 3026.

(27) (a) Rueping, M.; Sugiono, E.; Merino, E. *Chem.—Eur. J.* **2008**, *14*, 6329. (b) Rueping, M.; Merino, E.; Sugiono, E. *Adv. Synth. Catal.* **2008**, *350*, 2127.

(28) Goswami, P; Das, B. *Tetrahedron Lett.* **2009**, *50*, 897.

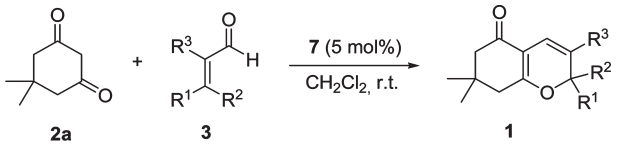
(29) Moreau, J.; Duboc, A.; Hubert, C.; Hurvois, J.-P.; Renaud, J.-L. *Tetrahedron Lett.* **2007**, *48*, 8647.

(30) Hubert, C.; Moreau, J.; Batany, J.; Duboc, A.; Hurvois, J.-P.; Renaud, J.-L. *Adv. Synth. Catal.* **2008**, *350*, 40.

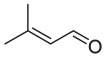
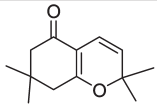
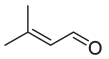
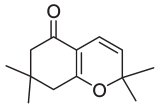
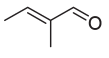
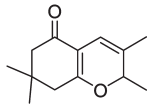
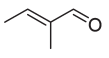
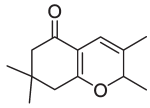
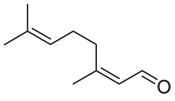
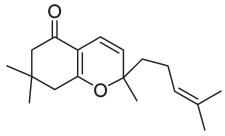
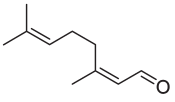
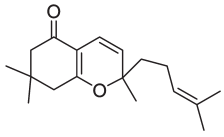
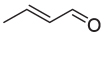
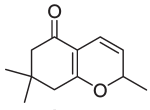
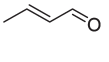
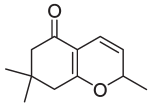
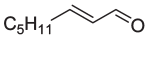
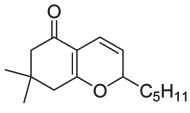
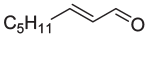
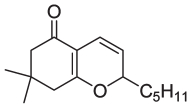
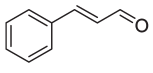
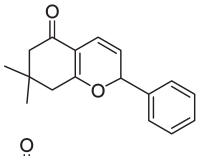
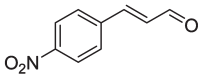
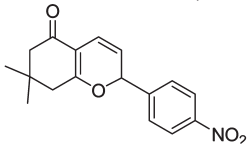
(31) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097.

(32) For recent works, see: (a) Rueping, M.; Nachtsheim, B. J.; Moreth, S. M.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593. (b) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 5836. (c) Rueping, M.; Ieawsuwan, W. *Adv. Synth. Catal.* **2009**, *351*, 78.

TABLE 2. Synthesis of 7,8-Dihydro-2*H*-Chromen-5(6*H*)-ones 1a−g[a]

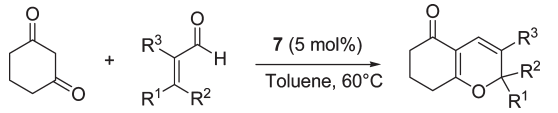


2a **3** **1**

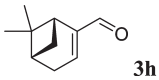
Entry	Aldehydes **3**		Compounds **1**		Yield (%)[b]
1		**3a**		**1a**	73
2		**3a**		**1a**	88[c]
3		**3b**		**1b**	73
4		**3b**		**1b**	79[c]
5		**3c**		**1c**	95
6		**3c**		**1c**	99[c]
7		**3d**		**1d**	16
8		**3d**		**1d**	78[b]
9		**3e**		**1e**	15
10		**3e**		**1e**	81[c]
11		**3f**[d]		**1f**	72
12		**3g**[d]		**1g**	61

[a]With 0.5 mmol of β-diketone **2a**, 0.75 mmol of α,β-unsaturated aldehyde, 0.025 mmol of **7** (5 mol%), 5 mL of CH_2Cl_2, 150 mg of Na_2SO_4 (1.05 mmol). [b]Isolated yield after purification on silica gel. [c]Toluene, 60 °C. [d]Reaction was performed with 15 mol% of catalyst.

TABLE 3. Synthesis of Compounds 10a−f[a]



2b 3 10

Entry	Aldehyde **3**	Compound **10**	Yield (%)[b]
1	**3a**	**10a**	74
2	**3b**	**10b**	20
3	**3c**	**10c**	90
4	**3d**	**10d**	48
5	**3e**	**10e**	77
6	 **3h**	**10f**	50 (d.e.= 96%)

[a]With 0.5 mmol of β-diketone **2b**, 0.75 mmol of α,β-unsaturated aldehyde, 0.025 mmol of **7** (5 mol%), 5 mL of toluene, 60 °C, 150 mg of Na_2SO_4 (1.05 mmol). [b]Isolated yield after purification on silica gel.

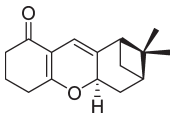
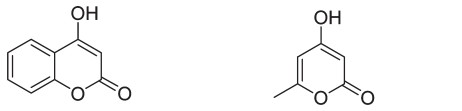


FIGURE 2. *2H*-Chromenones **10f** (see Table 1 in the Supporting Information for an ORTEP drawing).



2c **2d**

FIGURE 3. β-Diketones **2c** and **2d**.

(Table 3). Compared with **2a**, the reactivity was lower. For example, aldehydes **3b** and **3d** furnished the corresponding products **10b** and **10d** in low to moderate yields (entries 2 and 4, Table 3). All other yields were good, and the 2-substituted 7,8-dihydro-2*H*-chromen-5(6*H*)-ones **10** were isolated in up to 90% yield.

10f was isolated in 50% yield and in high diastereoselectivity (de = 96%) from the optically active (−)-myrtenal **3h** and the β-diketone **2b**. A slow crystallization of **10f** in ether allowed the formation of suitable crystals for X-ray analysis. The structure showed the relative configuration of the newly formed stereogenic center C-10 (Figure 2).

Thus, this protocol proved to be general for the preparation of several 2-substituted 7,8-dihydro-2*H*-chromen-5(6*H*)-ones. It is worth mentioning that the use of Brønsted acid **7** led to the same 2*H*-chromenones obtained with iminium salts[8] and Lewis acids,[9] *but in milder reaction conditions* (*lower catalyst loading, lower temperature*).

Synthesis of Pyrano[3,2-*c*]chromen-5(2*H*)-ones 11 and 7-Methyl Pyrano[4,3-*b*]pyran-5(2*H*)-ones 12. Having established the scope of this reaction with cyclic β-diketones, we extended it to more sterically hindered β-ketolactones such as 4-hydroxycoumarin **2c** and 6-methyl-4-hydroxy-2-pyrone **2d** (Figure 3).

In the optimized reaction conditions (toluene, 60 °C, 5 mol % of catalyst **7**), we were pleased to note that the reactivity of these β-ketolactones was excellent and led cleanly to the corresponding heterocycles. Except with the aromatic aldehyde **3f**, yields greater than 88% were obtained from the aldehydes **3a−e** and **3i** (entries 1−5, Table 4). Starting from the methyl pyrone **2d**, almost all compounds were obtained in quantitative yields (entries 8−15, Table 4). Whereas most of these substrates were isolated as oils, **11a** crystallized in diethyl ether. An X-ray structure of one crystal confirmed the regioselectivity of this reaction (Figure 4).

The reaction of **2d** with (−)-myrtenal **3h** afforded the corresponding tricyclic compound in a moderate 52% yield (entry 14, Table 4), but with a gratifying diastereoisomeric excess of 88% (as determined by NMR analysis). A nuclear Overhauser effect analysis provided us the relative configuration of compound **12g** as shown in Table 4 (entry 14). The proton of the newly formed stereogenic center and the methylene bridge of the myrtenal moiety are in a *syn* configuration.

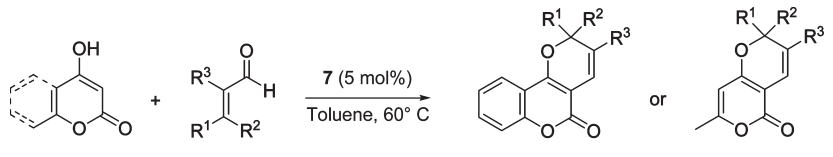
Synthesis of Tetrahydroquinolinones 14. Tetrahydroquinolinones **14** could also be prepared from vinylogous amide **13** via this phosphoric acid catalyzed formal [3 + 3] cycloaddition (Scheme 3).

Following our ongoing work on Lewis acid catalyzed synthesis of functionalized β-enaminoesters and β-enaminones,[33] we were able to isolate at room temperature in dichloromethane the *N*-benzylamide **13** in 75% yield (Scheme 4).

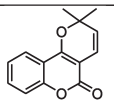
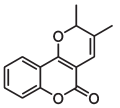
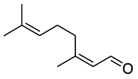
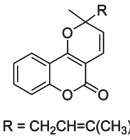
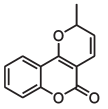
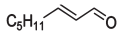
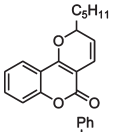
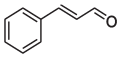
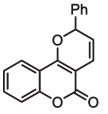
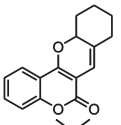
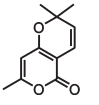
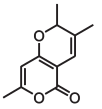
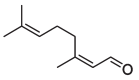
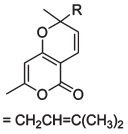
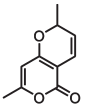
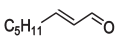
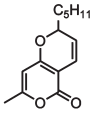
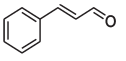
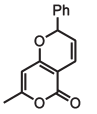
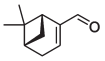
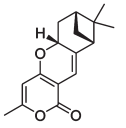
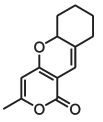
At room temperature, in the presence of 5 mol% of phosphoric acid **7**, no reaction occurred between **13** and **3j** (entry 1, Table 5). An increase of the temperature led to an improvement of the reactivity. At 60 °C, the catalytic formal [3 + 3] cycloaddition between **13** and pentenal **3j** provided not only the desired compound **14a** in a moderate conversion of 50% but also numerous side products. However, at 90 °C, the tetrahydroquinolinone **14a** was isolated cleanly as a

(33) (a) Kaur Vohra, R.; Renaud, J.-L.; Bruneau, C. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1943. (b) Kaur Vohra, R.; Renaud, J.-L.; Bruneau, C. *Synthesis* **2007**, 731. (c) Hebbache, H.; Hank, Z.; Boutamine, S.; Meklati, M.; Bruneau, C.; Renaud, J.-L. *C. R. Chimie* **2008**, 612.

TABLE 4. Synthesis of 2*H*-Pyrans 11 and 12[a]



2c-d 3 11a-g 12a-h

Entry	Aldehydes 3		Compounds 11		Yield (%)[c]
1		**3a**		**11a**	94
2		**3b**		**11b**	88
3		**3c**	 R = $CH_2CH{=}C(CH_3)_2$	**11c**	99
4		**3d**		**11d**	94
5		**3e**		**11e**	99
6		**3f**		**11f**	0
7		**3i**		**11h**	89
8		**3a**		**12a**	99
9		**3b**		**12b**	99
10		**3c**	 R = $CH_2CH{=}C(CH_3)_2$	**12c**	99
11		**3d**		**12d**	99
12		**3e**		**12e**	99
13		**3f**		**12f**	25
14		**3h**		**12g**	52 (d.e. = 88%)
15		**3i**		**12h**	99

[a]With 0.5 mmol of β-diketone **2c** or **2d**, 0.75 mmol of a α,β-unsaturated aldehyde, 0.025 mmol of **7** (5 mol%), 5 mL of toluene, 60 °C, 150 mg of Na_2SO_4 (1.05 mmol). [b]Isolated yield after purification on silica gel.

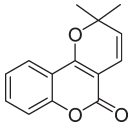
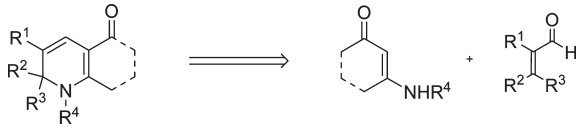


FIGURE 4. Compound **11a** (see Table 1 in the Supporting Information for an ORTEP drawing).

single regioisomer in a gratifying yield of 70%. More polar solvent such as ethanol or dimethylformamide seems to inhibit the reaction as no tetrahydroquinolinone was isolated. The use of such cyclic vinylogous amide **13** in a formal [3 + 3] cycloaddition had already been described by Hsung et al.,[34] but the reaction conditions were here again more harsh (150 °C in a sealed tube) and moisture sensitive α,β-unsaturated imminium salts have to be handled. As a consequence, this new procedure opens an easy access to a variety of substituted tetrahydroquinolinones.

SCHEME 3



Having defined the best reaction conditions, various aldehydes were engaged with compound **13**. With citral **3c**, the corresponding tetrahydroquinolinone was obtained in 81% yield (compound **14b**, Figure 5). Moreover, the formal [3 + 3] cycloaddition in the presence of cinnamaldehyde and

(34) (a) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *3*, 509. (b) Wei, L.-L.; Hsung, R. P.; Sklenicka, H. M.; Gerasyuto, A. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 1517.

SCHEME 4. Preparation of the Vinylogous Amide 13

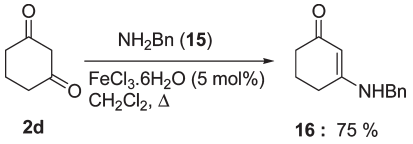
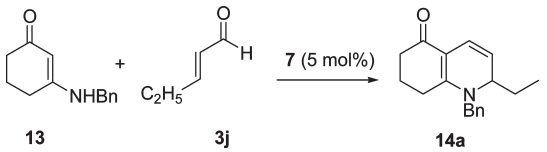


TABLE 5. Solvent and Temperature Studies for the Synthesis of 14a[a]



entry	solvent	temperature	yield (%)[b]
1	toluene	rt	nr
2	toluene	60	50
3	toluene	90	70
4	ethanol	90	nr[c]
5	DMF	90	nr[c]

[a]With 0.5 mmol of **13**, 0.75 mmol of α,β-unsaturated aldehyde **3j**, 5 mol% of catalyst **7**, 150 mg of Na_2SO_4 (1.05 mmol), 5 mL of toluene. [b]Isolated yield after purification on silica gel. [c]No reaction.

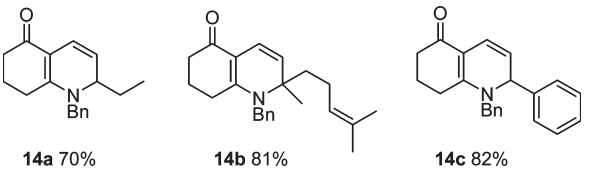


FIGURE 5. Extension to different tetrahydroquinolinones.

13 gave rise to the tetrahydroquinolinone **14c** in a very good yield (82%).

A recently emerging direction for organocatalysis has resulted from the independent initial discoveries by Akiyama[35] and Terada[36] that chiral phosphoric acids can provide excellent enantioselectivities for a broad range of highly enantioselective addition reactions on imines which involve chiral contact ion pairs generated in situ.[37] As we have already shown that these chiral phosphoric acids, derived from the optically active (*S*)-(−)-binaphthol (Figure 6), could promote the synthesis of enantioenriched 1,4-dihydropyridines,[29] we anticipated that the same chiral catalysts could furnish the desired optically enriched chromenones.

In a first set of experiments, reactions were carried out between the 4-hydroxycoumarin **2c** and crotonaldehyde **3d** at 40 °C in toluene. Whatever the catalyst used, the yields were high but the enantioselectivities were poor (below 10%, Table 6). We attempted to improve these results by decreasing the temperature. At room temperature, a low conversion was obtained even after a long reaction time, and no

(35) For recent reviews, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
(36) For a recent review, see: Terada, M. *Chem. Commun.* **2008**, 4097.
(37) For recent reviews, see: (a) Suzuki, K.; Seno, A.; Tanabe, H.; Ueno, K. *Synth. Met.* **2004**, *14*, 89. (b) You, S.-L. *Chem. Asian J.* **2007**, *2*, 820. (c) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758.

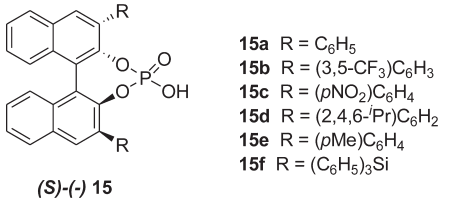


FIGURE 6. Chiral phosphoric acid catalysts **15**.

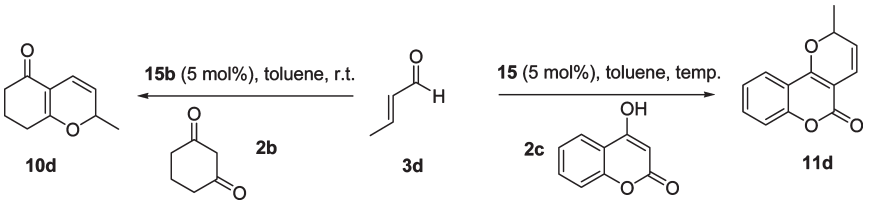
enhancement of the enantioselectivity was noticed (entry 6, Table 6). The use of cyclohexanedione **2b** instead of 4-hydroxycoumarin **2d** led to **10d** in high yield at room temperature but without any enantioselectivity (entry 7, Table 6).

Starting from the vinylogous amide **13** and cinnamaldehyde **3f**, a rapid screening of reaction conditions revealed that the tetrahydroquinolinone **14c** could be obtained in high yields at 90 °C in toluene but always as a racemic mixture, whatever the catalyst used (Scheme 5). As far as we know, no enantioselective reaction of 1,3-diketones or related derivatives with α,β-unsaturated aldehydes catalyzed by phosphoric acids has been described in the literature. Similar approach was indeed described by Rueping, using diarylprolinol ether as catalyst.[5] However, as already mentioned, this catalysis led to the 4-substituted 2*H*-pyrans and not to the 2-substituted 2*H*-pyrans. In our reaction conditions, the absence of enantioselectivity might be due to the reaction pathway (vide infra).

Synthesis of 3,4,7,8-Tetrahydro-2*H*-chromen-5(6*H*)-one 16 and Octahydrochromen-5-one 17. The first approach toward modification of the pyran core was the hydrogenation of alkenes to produce either the corresponding 3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-ones or the octahydrochromen-5-ones. Hydrogenation of the C_3-C_4 double bound of **10a** has successfully been carried out in acetic acid, in the presence of 10 mol % of Pd/C, under 10 psi of hydrogen. **16** was produced in 70% yield. In these conditions, the C_5-C_6 double bound was not reduced (Scheme 6). An increase of the pressure to 100 psi allowed the reduction of both alkenes. The chromanone **17** was then isolated in 52% yield (Scheme 6). According to the ^1H and ^{13}C NMR data, only one diastereoisomer was obtained. Unfortunately, we have not been able to crystallize this derivative and cannot assign the relative and absolute stereochemistry of the new stereocenters.

The structures of all compounds were assigned on the basis of ^1H NMR, ^{13}C NMR, and mass spectra analysis. The X-ray diffraction structures of compounds **11a** and **10f** (see Supporting Information, Table 1) and NMR analysis (^1H, ^{13}C, HMBC, and HMQC) revealed without any ambiguity the formation of the 2-substituted isomers. Two different mechanism pathways might explain the formation of this regioisomer. On one hand, according to route A (Scheme 7), a direct Michael addition of the enol to the unsaturated aldehyde (both activated by the phosphoric acid) might lead to the intermediate **18**. A subsequent aldolization/dehydratation sequence might liberate the expected heterocyclic derivatives **1**, **10**−**12**, or 2-substituted 2*H*-dihydropyridine type **14**. On the other hand, a Knoevenagel condensation between the enol derivative of the β-diketone or the vinylogous amide and the electrophilic carbonyl of the enal might

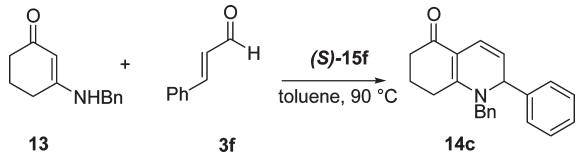
TABLE 6. Attempts at the Enantioselective Synthesis of 11d or 14c[a]



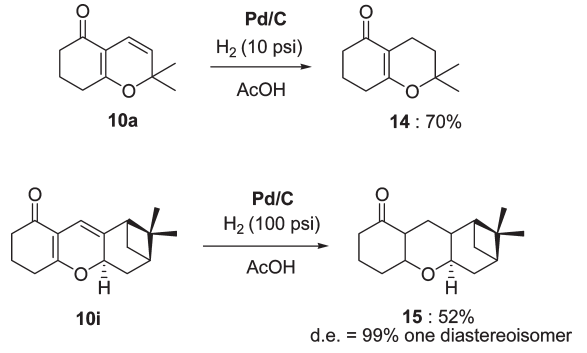
entry	catalyst	compound	yield (%)[b]	ee (%)[c]
1	**15a**	**11d**	99	7
2	**15b**	**11d**	99	8
3	**15c**	**11d**	99	6
4	**15d**	**11d**	99	7
5	**15e**	**11d**	99	7
6	**15b**	**11d**	15[d]	6
7	**15b**	**10d**	70[d]	0

[a]With 0.5 mmol of β-diketone **10d** or **11d**, 0.75 mmol of α,β-unsaturated aldehyde, 5 mol% of catalyst **15**, 150 mg of Na_2SO_4 (1.05 mmol), 5 mL of toluene, 40 °C. [b]Isolated yield after purification on silica gel. [c]Enantiomeric excesses were measured by chiral HPLC analysis. [d]Reaction was run at room temperature for 8 days.

SCHEME 5. Enantioselective Attempts for the Synthesis of 14c



SCHEME 6. Selective Hydrogenation of 10a and 10f



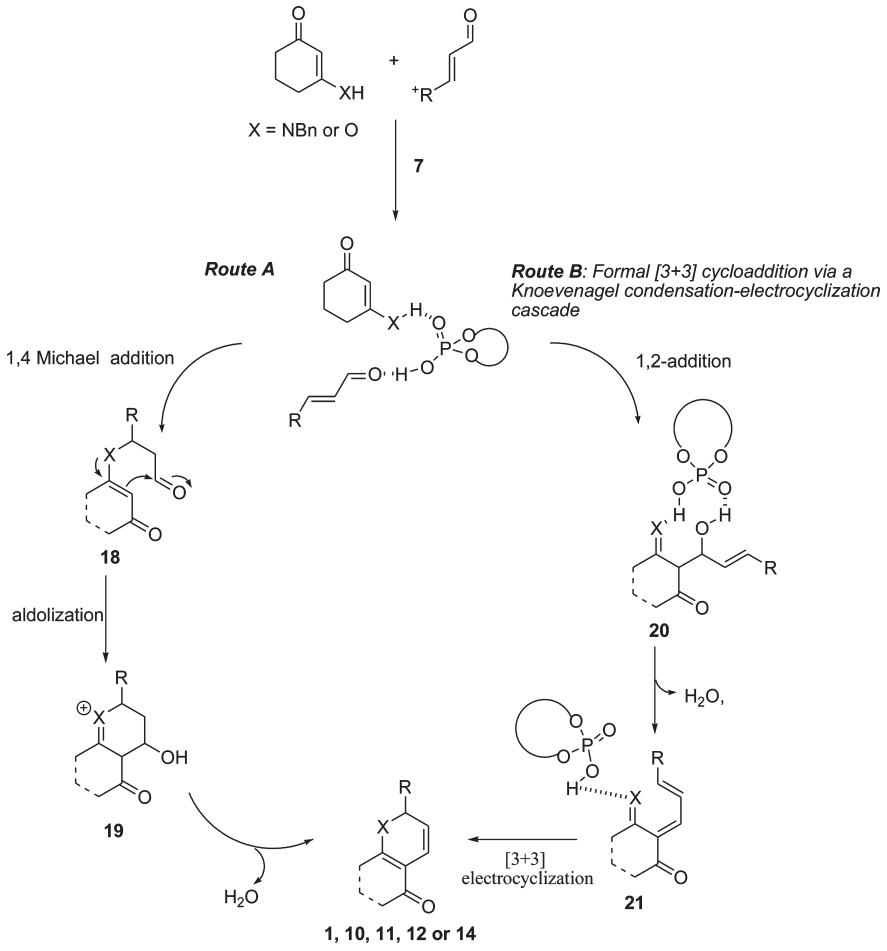
furnish the oxa- or azatriene intermediate **21**, which might undergo a [3 + 3] electrocyclization to form the heterocyclic compounds (route B, Scheme 7). This condensation/electrocyclization might also occur through a double activation of the catalyst, *which can play both the role of a Brønsted acid* (*to activate the aldehydes via hydrogen bonding*) *and the role of Lewis base* (*to activate the enol form of the diketone or the vinylogous amide*). Then, the activation of both partners of this reaction by the same catalyst might explain the greater reactivity all along the catalytic process. Furthermore, the almost absence of enantioselectivities, whatever the catalyst used for the cycloaddition, seems to be a direct consequence of the electrocyclization approach and might be explained according to this mechanism. Indeed, even if a phosphoric acid catalyst is necessary to promote the oxa- or azatriene synthesis, either the [3 + 3] electrocyclization does not require any acid activation to occur or, as depicted in Scheme 7, the catalyst is not tightly bonded to the triene intermediate. Then, the chiral part of the catalyst cannot have any influence on the new formed stereogenic center.

This route B of the proposed mechanism was also previously favored by Hsung[21b] and Yang,[23a] who underlined the presence of different oxatrienes. In our hands, as mentioned above, when aromatic aldehydes and dicarbonyl derivatives **2c** and **2d** were engaged in the catalytic process, we observed by NMR analysis unsaturated compounds and not the expected cycloadduct (see Supporting Information). Several attempts to purify them were, however, unsuccessful. In the nitrogen series, during the optimization studies, triene compounds were also isolated (in low yields, $< 15\%$) when the reaction was run at 60 °C. Such triene intermediates can also be obtained as major compounds at room temperature, but a simple heating at 90 °C led to the cycloadducts. Then, all of these results/observations provided some clues to favor route B in this phosphoric acid catalysis.

Conclusion

We have developed the first phosphoric acid catalyzed formal [3 + 3] cycloaddition allowing the synthesis of a variety of substituted chromenones, pyranones, and tetrahydroquinolinones from cyclic β-diketones, β-ketolactones, or vinylogous amides and α,β-unsaturated aldehydes. These reactions proceeded in mild conditions via carbonyl activation. Very good yields were obtained in the optimized reaction conditions, and β-ketolactones offered the awaited products in quantitative yields with almost all aldehydes. Syntheses involving optically pure aldehydes showed good diastereoisomeric excesses, and hydrogenation tests highlight the possibility to obtain 1-oxadecalin-type motives with also a very high level of diastereoselectivity. Oxatriene compounds, observed by NMR analysis, were proposed as intermediates of the catalytic cycle. These clues supported a mechanism involving a sequential Knoevenagel condensation and a 6π-electron electrocyclization. The low or absence of enantioselectivity was explained either by too weak interactions between the chiral phosphoric acids and the heterotrienes or by noncatalyzed electrocyclization.

SCHEME 7. Two Likely Mechanisms for the Formation of 2*H*-Pyrans and 1,2-Dihydropyridines



Experimental Section

General: Purifications by column chromatography were performed with 70−230 mesh silica gel. TLC analysis was carried out on alumina sheets precoated with silica gel (60 F254) and visualized with UV light; NMR spectra were recorded with a Bruker Avance DRX 500 FT spectrometer [200.13 MHz (^{1}H) and 50.33 MHz (^{13}C)] or a Bruker AH 300 FT spectrometer [300.13 MHz (^{1}H) and 75.45 MHz (^{13}C)]. Chemical shifts are expressed in parts per million downfield from TMS. High-resolution mass spectra were obtained with a Varian Mat 311 double focusing instrument at the CRMPO "Centre de Mesures Physiques de l'Ouest" with a source temperature of 170 °C. An ion accelerating potential of 3 kV and ionizing electrons of 70 eV were used. All commercially available reagents were used as supplied. Solvents were freshly distilled and kept under argon flush. Enantioselective excesses were determined by chiral HPLC analysis using a Chiralpak AD column (eluent: hexane/^{i}-PrOH 99/1, UV = 254 nm, flow rate = 0.5 mL/min). **6** and **7** were prepared according to Vogt and collaborators.[38] Catalysts **15a−f** were synthesized according to known procedures.[39]

General Procedure for the Synthesis of 2*H*-Chromenones 1, 10, 11, and 12: To previously dried sodium sulfate (150 mg) were successively added under argon phosphoric acid **6** or **7** (5 mol %), toluene (5 mL), the β-diketone or β-ketoester (0.5 mmol), and the appropriate unsaturated aldehyde (0.6 mmol). The mixture was stirred at 60 °C until completion by TLC analysis. The solution was then filtered on a plug of Celite and concentrated under vacuum. The crude oil was purified on silica gel by flash chromatography (eluent: petroleum ether/diethyl ether, 9/1).

1a: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.09 (s, 6H, $CH_2C(CH_3)_2$), 1.41 (s, 6H, $O(CH_3)_2$), 2.28 (d, J = 3.9 Hz, 4H, CH_2), 5.25 (d, J = 9.9 Hz, 1H, $C(CH_3)_2CH$), 6.42 (d, J = 9.9 Hz, 1H, *CH*); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 28.4, 32.3, 42.5, 50.4, 79.8, 109.6, 115.8, 122.7, 170.1, 194.6. HRMS (EI^+) calcd for $C_{13}H_{18}O_2$ 206.13068, found m/z 206.1312.

1b: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.08 (s, 6H, CH_3),1.36 (d, J = 6.4 Hz, 3H, $(O)CH(CH_3)$), 1.75 (s, 3H, CH_3), 2.28 (s, 4H, 2 × CH_2), 4.85 (q, J = 6.7 Hz, J = 8.9 Hz, 1H, $(O)CH(CH_3)$), 6.21 (s, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 18.3, 18.7, 27.1, 28.3, 31.8, 49.7, 76.7, 109.0, 110.9, 127.5, 168.1, 194.6; HRMS (EI^+) calcd for $C_{13}H_{18}O_2$ 206.13068, found m/z 206.1313.

1c: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.06 ppm (s, 6H, CH_3), 1.35 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.6−1.8 (m, 5H, CH_3 + CH_2), 1.92−2.01 (m, 2H, CH_2), 2.23 (s, 2H, CH_2), 2.25 (s, 2H, CH_2), 5.0−5.2 (m, 2H, $CH_{ethylenic}$), 6.43 (d, J = 10.1 Hz, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 16.6, 21.5, 24.6, 26.5, 26.9, 31.2, 40.7, 41.4, 49.3, 81.5, 108.0, 115.2, 120.3, 122.6, 110.8, 169.7, 192.6; HRMS (EI^+) calcd for $C_{18}H_{26}O_2$ 274.19328, found m/z 274.1934.

(38) van der Vlugt, J. I.; Hewat, A. C.; Neto, S.; Sablong, R.; Mills, A. M.; Lutz, M.; Spek, A. L.; Muller, C.; Vogt, D. *Adv. Synth. Catal.* **2004**, *346*, 993.

(39) (a) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319. (b) Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 7536. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W.C. *J. Am. Chem. Soc.* **2006**, *128*, 84.

1d: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.09 (s, 6H, CH_3), 1.42 (d, J = 6.5 Hz, 3H, CH_3) 2.26−2.30 (m, 4H, CH_2), 4.97−5.03 (m, 1H, O*CH*(CH_3)), 5.30 (dd, J = 10.1 Hz, J = 2.8 Hz, 1H, $CH_{ethylenic}$), 6.49 (d, J = 10.2 Hz, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 22.6, 27.6, 28.5, 31.0, 40.7, 49.7, 77.8, 110.6, 117.2, 126.2, 173.4, 194.6; HRMS (EI^+) calcd for $C_{12}H_{16}O_2$ 192.11503, found m/z 193.1235 (M^+H, $C_{12}H_{17}O_2$).

1e: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 0.88 (t, 3H, J = 6.0 Hz, CH_3), 1.05−1.10 (m, 6H, $2CH_3$), 1.18−1.40 (m, 6H, $3CH_2$), 1.57−1.67 (m, 2H, CH_2), 2.23−2.26 (m, 4H, $2CH_{2Cy}$), 4.86−4.89 (m, 1H, O*CH*(C_5H_{11})), 5.26 (d, 1H, J = 10.0 Hz, $CH_{ethylenic}$), 6.43 (d, 1H, J = 10.0 Hz, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 14.4, 22.9, 28.8, 32.5, 32.6, 36.1, 42.5, 50.7, 78.2, 110.7, 117.7, 117.9, 118.1, 171.6, 195; HRMS (EI^+) calcd for $C_{16}H_{24}O_2$ 248.17763, found m/z 248.1757.

1f: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.16 (s, 6H, 2 × CH_3), 2.43 (s, 2H, CH_2), 2.61 (s, 2H, CH_2), 5.04 (d, J = 2.6 Hz, 1H, (O)C*H*(Ph)), 6.42 (d, J_{AB} = 16.8 Hz, 1H, CH(Ph)-*CH*$_{ethylenic}$), 6.65 (dd, J = 4 Hz, J_{AB} = 16.8 Hz, 1H, $CH_{ethylenic}$), 7.41−7.93 (m, 5H, H_{Ar}); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 20.4, 27.4, 51.2, 52.9, 77.9, 115.4, 125.8, 126.4, 126.7, 127.6, 128.3, 126.1, 150.6, 152.7, 196.6.

1g: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.12 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 2.38 (s, 2H, CH_2), 2.56 (s, 2H, CH_2), 4.98−4.99 (m, 1H, (O)C*H*(Ph)), 6.39 (dd, J = 4 Hz, J_{AB} = 15.8 Hz, 1H, C(H)(Ph)C*H*$_{ethylenic}$), 6.89 (d, J_{AB} = 15.8 Hz, 1H, $CH_{ethylenic}$), 7.29−8.16 (m, 4H, H_{Ar}); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 27.5, 30.4, 45.1, 45.8, 76.2, 114.9, 123.5, 124.4, 126.6, 127.8, 112.0, 113.6, 112.2, 148.1, 188.4, 189.0.

10a: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.42 (s, 6H, C(*CH*$_3$)$_2$), 1.96−2.05 (m, 2H, CH_{2Cy}), 2.37−2.45 (m, 4H, CH_{2Cy}), 5.26 (d, J = 10.0 Hz, 1H, $CH_{ethylenic}$), 6.43 (d, J = 10.0 Hz, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 19.6, 27.4, 27.6, 28.7, 35.4, 78.7, 109.6, 114.8, 121.9, 170.6, 193.9; HRMS (EI^+) calcd for $C_{11}H_{14}O_2$ 178.09938, found m/z 178.1000.

10b: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.36 (d, J = 6.5 Hz, 3H, OCH(*CH*$_3$)), 1.74 (s, 3H, CH_3), 1.94−2.04 (m, 2H, CH_2), 2.36−2.45 (m, 4H, CH_2), 4.83 (q, J = 6.3 Hz, 1H, O*CH*(CH_3)), 6.21 (s, 1H, $CH_{ethylenic}$); HRMS (EI^+) calcd for $C_{11}H_{14}O_2$ 178.09938, found m/z 178.0900.

10c: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 0.26 (s, 3H, OC(*CH*$_3$)), 0.28−0.29 (m, 8H, C(*CH*$_3$)$_2$ + OC(CH_3)(*CH*$_2$)), 0.31−0.32 (m, 4H, CH_{2Cy} + CH_2), 0.35−0.36 (m, 4H, CH_{2Cy}), 5.07 (t, 1H, J = 5.8 Hz, *CH*C(CH_3)$_2$), 5.17 (d, J = 10.1 Hz, 1H, $CH_{ethylenic}$), 6.44 (d, J = 10.1 Hz, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 16.6, 19.6, 21.5, 24.7, 26.4, 27.6, 35.4, 40.7, 81.3, 109.2, 115.4, 120.6, 122.6, 130.9, 171.0, 193.8; HRMS (EI^+) calcd for $C_{16}H_{22}O_2$ 246.16198, found m/z 246.1614.

10d: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.59 (d, J = 6.4 Hz, 3H, CH_3), 1.93−2.03 (m, 2H, CH_2), 2.38−2.45 (m, 4H, CH_2), 5.01−5.04 (m, 1H, O*CH*(CH_3)), 5.30 (dd, J = 10.3 Hz, J = 2.6 Hz, 1H, $CH_{ethylenic}$), 6.49 (d, J = 9.5 Hz, 1H, $CH_{ethylenic}$); HRMS (EI^+) calcd for $C_{10}H_{12}O_2$ 164.08373, found m/z 164.0843.

10e: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 0.88 (t, J = 6.0 Hz, 3H, CH_3) 1.30−1.72 (m, 8H, CH_2), 1.92−1.98 (m, 2H, CH_{2Cy}), 2.37−2.40 (m, 4H, CH_{2Cy}), 4.86−4.90 (m, 1H, O*CH*-(C_5H_{11})), 5.27 (d, J = 9.8 Hz, 1H, $CH_{ethylenic}$), 6.44 (d, J = 10.0 Hz, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 12.9, 19.6, 21.50, 22.92, 27.29, 29.93, 30.57, 34.7, 35.4, 76.7, 116.5, 116.9,171.6,193.9; HRMS (EI^+) calcd for $C_{14}H_{20}O_2$ 220.14633, found m/z 220.1477.

10f: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 0.88−2.42 (m, 14H, CH_2), 4.92−5.00 (m, 1H, O*CH*), 6.11 (s, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 19.73, 21.70, 26.83, 27.08, 27.10, 28.02, 36.34, 79.0, 101.5, 106.9, 127.2, 176.9, 196.0; HRMS (EI^+) calcd for $C_{13}H_{16}O_2$ 204.11503, found m/z 204.1156.

10i: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 0.81 (s, 3H, CH_3),1.25−1.45 (m, 5H, CH_3 + CH_2), 1.90−2.64 (m, 10H, CH_2 + CH), 4.98 (t, 1H, J = 6.9 Hz, O*CH*), 6.05 (s, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 21.2, 22.2, 25.8, 28.0, 30.0, 33.4, 37.0, 40.5, 42.2, 48.7, 72.3, 111.2, 114.8, 133.3, 172.4, 195.8; HRMS (EI^+) calcd for $C_{16}H_{20}O_2$ 245.1542, found m/z 245.1531 (M^+H, $C_{16}H_{22}O_2$), dr 88:22.

11a: ^{1}H NMR (200.13 MHz, DMSO) δ ppm = 1.52 (s, 6H, CH_3), 5.73 (d, J = 10 Hz, 1H, $CH_{ethylenic}$), 6.38 (d, 1H, J = 10 Hz, $CH_{ethylenic}$), 7.39 (d, 2H, J = 7.7 Hz, H_{Ar}), 7.60−7.64 (m, 1H, H_{Ar}), 7.77 (d, 1H, J = 7.6 Hz, H_{Ar}); ^{13}C NMR (75.45 MHz, DMSO) δ ppm = 33.5, 86.3, 105.3, 120.4, 121.3, 122.1, 128.1, 110.0, 112.8, 118.3, 158.2, 163.6, 165.2; HRMS (EI^+) calcd for $C_{14}H_{12}O_3$ 228.07864, found m/z 228.07888.

11b: ^{1}H NMR (200.13 MHz, DMSO) δ ppm = 1.43 ppm (d, 3H, J = 6.4 Hz, CH_3), 1.86 (s, 3H, CH_3), 5.15 (q, 1H, J = 6.1 Hz, CH), 6.19 (s, 1H, $CH_{ethylenic}$), 7.40 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.55−7.7 (m, 1H, H_{Ar}), 7.77 (d, 1H, J = 7.7 Hz, H_{Ar}); HRMS (EI^+) calcd for $C_{14}H_{12}O_3$ 228.07864, found m/z 228.0799. This compound has been already described by Appendino, G., Cravotto, G.; Tagliapietra, S.; Nano, G. M.; Palmissano, G. *Helv. Chim. Acta* **1990**, *73*, 1865.

11c: ^{1}H NMR (200.13 MHz, DMSO) δ ppm = 1.09 (s, 3H, CH_3), 1.5 (s, 6H, CH_3), 1.75 (m, 2H, CH_2), 2.0−2.18 (m, 2H, CH_2), 5.0−5.15 (m, 1H, $CH_{ethylenic}$-alkyl), 5.70 (d, 1H, J = 10.1 Hz, $CH_{ethylenic}$), 6.43 (d, 1H, J = 10.1 Hz, $CH_{ethylenic}$), 7.41 (d, 2H, J = 7.6 Hz, H_{Ar}), 7.55−7.7 (m, 1H, H_{Ar}), 7.8 (d, 1H, J = 7.6 Hz, H_{Ar}); ^{13}C NMR (75.45 MHz, DMSO) δ ppm = 21.9, 26.5, 29.8, 31.4, 42.6, 87.6, 103.6, 119.1, 120.5, 120.8, 126.8, 128.1, 128.8, 130.4, 135.4, 136.9, 156.9, 162.7, 163.9; HRMS (EI^+) calcd for $C_{19}H_{20}O_3$ 296.14124, found m/z 296.1408.

11d: ^{1}H NMR (200.111 MHz, DMSO) δ ppm = 1.48 ppm (d, 3H, J = 6.5 Hz, CH_3), 5.30−5.45 (m, 1H, CH), 5.77 (dd, 1H, J = 3.0 Hz, J = 10.0 Hz, $CH_{ethylenic}$), 6.42 (d, 1H, J = 10.0 Hz, $CH_{ethylenic}$), 7.40 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.60−7.70 (m, 1H, H_{Ar}), 7.77 (d, 1H, J = 8.0 Hz, H_{Ar}); ^{13}C NMR (75.45 MHz, DMSO) δ ppm = 21.2, 75.2, 100.2, 114.6, 116.5, 116.6, 122.4, 123.6, 124.4, 132.6, 152.5, 158.5, 159.5; HRMS (EI^+) calcd for $C_{13}H_{10}O_3$ 214.06299, found m/z 214.0643.

11e: ^{1}H NMR (200.13 MHz, DMSO) δ ppm = 0.88 (t, 3H, J = 6.5 Hz, CH_3), 1.28−1.60 (m, 6H, CH_2), 1.67−1.90 (m, 2H, CH_2), 5.23 −5.30 (m, 1H, CH), 5.78 (dd, 1H, J = 10.1 Hz, J = 3.0 Hz, $CH_{ethylenic}$), 6.31 (d, 1H, J = 10.1 Hz, $CH_{ethylenic}$), 7.35−7,45 (m, 2H, H_{Ar}), 7.66−7.79 (m, 2H, H_{Ar}); ^{13}C NMR (75.45 MHz, DMSO) δ ppm = 12.9, 21.5, 22.9, 30.4, 34.7, 77.0, 99.9, 114.2, 115.6, 117.1, 120.4, 121.6, 122.9, 111.0, 152.0, 158.4, 159.7; HRMS (EI^+) calcd for $C_{17}H_{18}O_3$ 270.12559, found m/z 270.1256.

11f: ^{1}H NMR (200.13 MHz, DMSO) δ ppm = 0.50−2.30 (m, 8H, *CH*$_2$), 5.28−5.42 (m, 1H, CH_2*CH*O), 6.08 (s, 1H, *CH*$_{ethylenic}$), 7.32−7.40 (m, 2H, *H*$_{Ar}$), 7.59−7.74 (m, 2H, *H*$_{Ar}$); ^{13}C NMR (75.45 MHz, DMSO) δ ppm = 22.79, 25.32, 28.33, 79.20, 99.67, 114.12, 117.45, 115.30, 116.10, 123.10, 124.10, 110.23, 112.43, 150.99, 161.21, 163.41; HRMS (EI^+) calcd for $C_{16}H_{14}O_3$ 254.09492, found m/z 254.09429.

12a: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.46 (s, 6H, CH_3), 2.38 (s, 3H, CH_3), 5.39 (d, 1H, J = 10.0 Hz, $(CH_3)_2$C−C*H*$_{ethylenic}$), 5.80 (s, 1H, (CH_3)C(O)−C*H*$_{ethylenic}$), 6.41 (d, 1H, J = 10.1 Hz, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 19.1, 28.3, 79.1, 96.8, 99.3, 115.2, 123.8, 161.4, 163.1, 163.1; HRMS (EI^+) calcd for $C_{11}H_{12}O_3$ 192.07864, found m/z 192.0780.

12b: ^{1}H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.42 (d, 3H, J = 6.6 Hz, (O)CH(C*H*$_3$)), 2.23 (s, 3H, (O)C(C*H*$_3$)), 2.38 (s, 3H, CH_3), 4.95 (q, 1H, J = 6.6 Hz, CH), 5.82 (s, 1H, $CH_{ethylenic}$),

6.19 (s, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm =11.1, 21.7, 28.4, 76.1, 97.9, 98.9, 111.4, 128.6, 161.2, 163.3, 163.3; HRMS (EI^+) calcd for $C_{11}H_{12}O_3$ 192.07864, found *m*/*z* 192.0795.

12c: ^1H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.38 (s, 3H, (O)C(CH_3)(alkyl)), 1.55 (s, 3H, C(CH_3)$_2$), 1.63 (s, 3H, C(CH_3)$_2$), 1.76 (t, 2H, *J* = 7.7 Hz, CH_2), 2.04−2.10 (m, 2H, CH_2), 2.18 (s, 3H, CH_3), 5.10 (t, 1H, *J* = 7.1 Hz, $CH_{ethylenic}$-alkyl), 5.33 (d, 1H, *J* = 10.1 Hz, C(alkyl)−$CH_{ethylenic}$), 5.80 (s, 1H, $CH_{ethylenic}$), 6.38 (d, 1H, *J* = 10.1 Hz, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 17.6, 20.6, 22.6, 25.7, 37.5, 41.8, 82.7, 97.6, 100.2, 116.8, 123.4, 123.6, 132.2, 162.3, 162.4, 164.5; HRMS (EI^+) calcd for $C_{16}H_{20}O_3$ 260.14124, found *m*/*z* 260.1424.

12e: ^1H NMR (200.13 MHz, $CDCl_3$) δ ppm = 0.88−1.45 (m, 7H, $CH_3 + CH_2$), 2.23 (s, 3H, CH_3), 2.23−2.27 (m, 4H, $2CH_{2Cy}$), 5.80 (s, 1H, $CH_{ethylenic}$), 4.99−5.03 (m, 1H, OC*H*(C_5H_{11})), 5.43 (dd, 1H, *J* = 10.1 Hz, *J* = 3.2 Hz, $CH_{ethylenic}$), 6.46 (d, 1H, *J* = 9.8 Hz, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 14.4, 20.6, 22.9, 24.3, 31.9, 36.2, 58.0, 76.2, 91.1, 100.5, 118.3, 120.4, 163.0, 165.3; HRMS (EI^+) calcd for $[M - C_5H_{11}]^+$ $C_9H_8O_3$ − H^+ 163.03952, found *m*/*z* 163.0379.

12d: ^1H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.47 (d, 3H, *J* = 6.5 Hz, CH_3), 2.23 (s, 3H, CH_3), 5.12−5.20 (m, 1H, CH), 5.43 (dd, 1H, *J* = 10.1 Hz, *J* = 3.0 Hz, $CH_{ethylenic}$), 5.80 (s, 1H, $CH_{ethylenic}$), 6.45 (d, 1H, *J* = 9.9 Hz, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 21.6, 21.7, 73.1, 99.1, 99.3, 116.6, 119.9, 160.1, 160.3, 165.4; HRMS (EI^+) calcd for $C_{10}H_{10}O_3$ 178.06299, found *m*/*z* 178.0632.

12h: ^1H NMR (200.13 MHz, $CDCl_3$) δ ppm = 1.11−2.12 (m, 8H, $4 \times CH_2$), 2.21 (s, 3H, CH_3), 5.01−5.09 (m, 1H, CH), 5.73 (s, 1H, $CH_{ethylenic}$), 6.09 (s, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 20.1, 24.5, 26.9, 33.1, 35.2, 79.7, 97.3, 99.8, 109.1, 133.1, 161.4, 162.6, 163.3; HRMS (EI^+) calcd for $C_{13}H_{14}O_3$ 218.09429, found *m*/*z* 218.0941.

12g: ^1H NMR (200.13 MHz, $CDCl_3$) δ ppm = 0.75 (s, 3H, $(CH_3)_2$), 1.26 (s, 3H, $(CH_3)_2$), 2.23 (s, 3H, CH_3), 1.62−2.62 (m, 6H, $2 \times CH_2 + 2 \times CH$), 5.11−5.15 (m, 1H, (O)C*H*(alkyl)), 5.87 (s, 1H, $CH_{ethylenic}$), 6.12 (s, 1H, $CH_{ethylenic}$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 11.1, 21.7, 28.3, 28.7, 30.7,39.1, 47.7, 70.9, 98.7, 100.6, 110.4, 134.5, 161.1, 160.7, 163.4; HRMS (EI^+) calcd for $C_{16}H_{18}O_3$ 258.12559, found *m*/*z* 258.1257; dr = 94:6.

16: ^1H NMR (300.13 MHz, $CDCl_3$) δ ppm = 1.20 (s, 6H, $2CH_3$), 1.58 (t, 2H, *J* = 6.3 Hz, $(CH_3)_2CH_2$), 1.84−1.88 (m, 2H, CH_2), 2.16 (t, 2H, *J* = 6.6 Hz, (C^1)CH_2), 2.20−2.28 (m, 4H, $C(O)CH_2 + C^4(CH_2)$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 15.6, 20.9, 26.5, 29.1, 32.1, 36.7, 53.4, 109.9, 170.4, 198.0; HRMS (EI^+) calcd for $C_{11}H_{16}O_2$ 181.1228, found *m*/*z* 181.1229 (M + H, $C_{11}H_{17}O_2$).

17: ^1H NMR (300.13 MHz, $CDCl_3$) δ ppm = 1.13 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.50−1.92 (m, 8H), 2.00−2.37 (m, 8H), 3.49−3.56 (m, 2H, $OC^1H + OC^{1'}H$); ^{13}C NMR (75.45 MHz, $CDCl_3$) δ ppm = 17.9, 21.8, 25.8, 27.9, 29.6, 31.8, 34.9, 38.5, 38.7, 40.4, 43.3, 45.4, 50.0, 68.9, 74.0, 213.9; HRMS (EI^+) calcd for $C_{16}H_{24}O_2$ 247.3605, found *m*/*z* 247.2293 (M − H, $C_{16}H_{23}O_2$); $[\alpha]^{20}_D$ +3.33 (*c* 1.08, $CHCl_3$).

Procedure for the Synthesis of 3-(Benzylamino)cyclohex-2-enone 13: One gram (8.9 mmol) of 1,3-cyclohexanedione **2b**, $FeCl_3 \cdot 6H_2O$ (5 mol%), and 100 mg of sodium sulfate were successively added in a dry Schlenk tube under argon. The solids were then dissolved in 20 mL of dichloromethane and stirred for 5 min. Benzylamine (0.96 g, 8.9 mmol) was slowly added, and the dark brown colored mixture was allowed to stir overnight. After completion, solvents were removed under vacuum and the crude oil was filtered on a plug of neutral alumina (eluent: dichloromethane/methanol, 90/10). Solvents were then removed, and **13** was obtained as a bright yellow solid.

13: ^1H NMR (400.16 MHz, $CDCl_3$) δ ppm = 1.90−1.94 (m, 2H, CH_2), 2.24 (t, 2H, *J* = 5.6 Hz, C(NH)CH_2), 2.36 (t, 2H, *J* = 5.6 Hz, C(O)CH_2), 4.18 (d, 2H, *J* = 4.4 Hz, CH_2(Ph)), 5.11 (s, 1H, $CH_{ethylenic}$), 5.54 (br d, 1H, NH), 7.22−7.30 (m, 5H, H_{Ar}); ^{13}C NMR (50.4 MHz, $CDCl_3$) δ ppm = 21.9, 29.4, 36.4, 46.9, 96.8, 127.5, 127.6, 128.7, 137.0, 165.3, 197.5; HRMS (EI^+) calcd for $C_{13}H_{15}NO$ 202.1229, found *m*/*z* 202.1232 (M + H, $C_{13}H_{16}NO$).

General Procedure for the Synthesis of Tetrahydroquinolinones 14: To previously dried sodium sulfate (150 mg) were successively added, under argon, phosphoric acid **7** (5 mol%), toluene (5 mL), **13** (0.5 mmol), and the appropriate unsaturated aldehyde (0.6 mmol). The mixture was stirred at 90 °C until completion by TLC analysis. The solution was then filtered on a plug of Celite and concentrated under vacuum. The crude oil was purified on silica gel by flash chromatography (eluent: petroleum ether/diethyl ether 50/50, then dichloromethane/methanol 90/10).

14a: ^1H NMR (200.130 MHz, $CDCl_3$) δ ppm = 0.92 (t, 3H, *J* = 7.4 Hz, CH_3), 1.69−1.97 (m, 4H, $2CH_2$), 2.29−2.50 (m, 4H, $2CH_2$), 3.94−4.00 (m, 1H, CH(ethyl)), 4.60 (AB, 2H, J_{AB} = 17.0 Hz, CH_2(Ph)), 5.2 (dd, 1H, *J* = 5.1 Hz, 9.6 Hz, $H_{ethylenic}$), 6.78 (d, 1H, *J* = 9.8 Hz, $H_{ethylenic}$), 7.21−7.42 (m, 5H, H_{Ar}); ^{13}C NMR (50.4 MHz, $CDCl_3$) δ ppm = 7.1, 20.3, 25.6, 27.0, 34.5, 51.7, 60.2, 107.4, 112.2, 120.0, 124.9, 126.6, 128.0, 135.7, 159.6, 190.7; HRMS (EI^+) calcd for $C_{18}H_{21}NO$ 266.3654 found *m*/*z* 266.2249 (M − H, $C_{18}H_{20}NO$).

14b: ^1H NMR (200.130 MHz, $CDCl_3$) δ ppm = 1.28 (s, 3H, −NC(R)(CH_3)), 1.58 (s, 3H, CH(CH_3)$_2$), 1.72 (s, 3H, CH-(CH_3)$_2$), 1.77−2.43 (m, 10H, $5CH_2$), 4.60 (AB, 2H, J_{AB} = 18.3 Hz, CH_2(Ph)), 4.93 (d, 1H, *J* = 10.0 Hz, $H_{ethylenic}$), 5.11 (t, 1H, *J* = 5.5 Hz, C*H*(CH_3)$_2$), 6.76 (d, 1H, *J* = 10.0 Hz, $H_{ethylenic}$), 7.20−7.42 (m, 5H, H_{Ar}); ^{13}C NMR (50.4 MHz, $CDCl_3$) δ ppm = 18.1, 22.0, 22.9, 26.1, 27.4, 29.7, 31.8, 35.9, 42.4, 48.2, 63.2, 107.5, 119.9, 124.1, 125.7, 127.6, 127.9, 128.0, 129.3, 132.3, 138.8, 162.6, 192.0; HRMS (EI^+) calcd for $C_{23}H_{29}NO$ 336.2320 found *m*/*z* 336.2327 (M + H, $C_{23}H_{30}NO$).

14c: ^1H NMR (200.16 MHz, $CDCl_3$) δ ppm = 1.92−1.97 (m, 2H, CH_2), 2.37 (t, 2H, *J* = 6.5 Hz, CH_2), 2.50−2.54 (m, 2H, (O)CCH_2), 4.42 (AB, 2H, J_{AB} = 16.8 Hz, CH_2(Ph)), 5.07 (d, 1H, *J* = 4.4 Hz, NCH(Ph)), 5.23 (dd, 1H, *J* = 4.6 Hz, *J* = 9.6 Hz, $H_{ethylenic}$), 6.78 (d, 1H, *J* = 9.6 Hz, $H_{ethylenic}$), 7.21−7.41 (m, 10H, H_{Ar}); ^{13}C NMR (50.4 MHz, $CDCl_3$) δ ppm = 21.7, 27.0, 35.9, 51.9, 64.7, 106.9, 115.8, 119.4, 126.5, 127.4, 128.2, 128.8, 129.4, 129.6, 136.3, 143.1, 160.6, 192.2; HRMS (EI^+) calcd for $C_{22}H_{21}NO$ 316.1692 found *m*/*z* 316.1701 (M + H, $C_{22}H_{22}NO$).

Enantioselective Approach: Enantioselective syntheses were carried out according to the general procedure, using 5 mol% of catalyst **15a**−**f**. Enantiomeric excesses were determined after purification by HPLC on a Daicel Chiralpackl AD-H chiral column (heptane/isopropanol 80/20, 1 mL/min, 285 nm).

Acknowledgment. The authors thank la Région Bretagne for a Ph.D. fellowship for J.M.

Supporting Information Available: Characterization data for all compounds and X-ray structures of **10f** and **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.