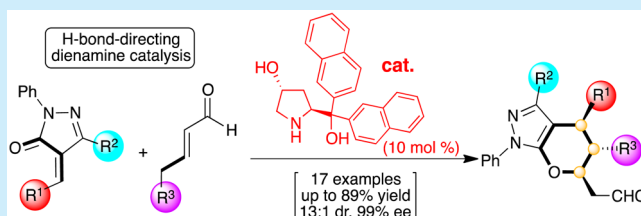


## H-Bond-Directing Organocatalyst for Enantioselective [4 + 2] Cycloadditions via Dienamine Catalysis

Shoulei Wang,<sup>†</sup> Carles Rodriguez-Esrich,<sup>†</sup> and Miquel A. Pericàs<sup>\*,†,‡</sup><sup>†</sup>Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Av. Països Catalans 16, 43007 Tarragona, Spain<sup>‡</sup>Departament de Química Orgànica, Universitat de Barcelona, 08080 Barcelona, Spain

## S Supporting Information

**ABSTRACT:** An efficient, highly regio- and stereoselective [4 + 2] cycloaddition reaction to generate tetrahydropyranopyrazole frameworks has been developed. To this end, a dienamine-based catalytic strategy that relies on the H-bond-directing effect of the hydroxy group of a dinaphthylprolinol-type aminocatalyst has been used. This enables the synthesis of multifunctionalized heterocyclic derivatives with three contiguous stereocenters in good yields and excellent enantioselectivities.



Optically active pyrazolones and their derivatives are widely occurring scaffolds that can be found in many natural products and medicinally active molecules.<sup>1</sup> As a consequence, the catalytic asymmetric synthesis of pyrazolones has been the subject of several studies,<sup>2</sup> mainly involving three different strategies: (a) the deprotonation of the relatively acidic  $\alpha$ -protons to generate a transient nucleophile;<sup>3</sup> (b) the exploitation of the inherent nucleophilicity of the pyrazole nitrogens;<sup>4</sup> and (c) the use of exocyclic alkylidene pyrazolones as Michael acceptors,<sup>5</sup> which can lead to cascade processes for the construction of spirocycles.

Tetrahydropyranopyrazoles<sup>6</sup> (THPPs) and dihydropyranopyrazolones<sup>7</sup> (DHPPOs) are formal derivatives of pyrazolones in which this heterocyclic moiety is fused to a pyran or pyranone ring, respectively. Several members of this subclass present interesting pharmaceutical and biological properties, which make them appealing synthetic targets (Figure 1). Nevertheless, the

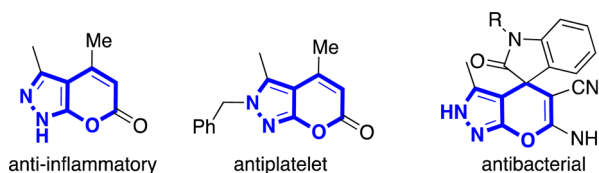
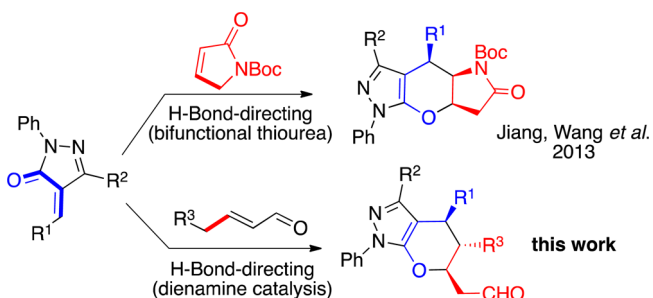


Figure 1. Some biologically active pyranopyrazol(on)es.

catalytic enantioselective transformation of pyrazolone derivatives into functionalized THPPs has received scant attention. In 2012, Enders disclosed an aminocatalytic 3-component reaction that provides THPPs with two stereocenters.<sup>8</sup> One year later, Wang and co-workers reported the bifunctional thiourea-catalyzed asymmetric [4 + 2] cycloaddition of  $\alpha,\beta$ -unsaturated  $\gamma$ -butyrolactams with exocyclic alkylidene pyrazolones (Scheme 1, top).<sup>9</sup> As for the related DHPPOs, the Ye and Biju groups

## Scheme 1. [4 + 2] Cycloaddition with Alkylidene Pyrazolones



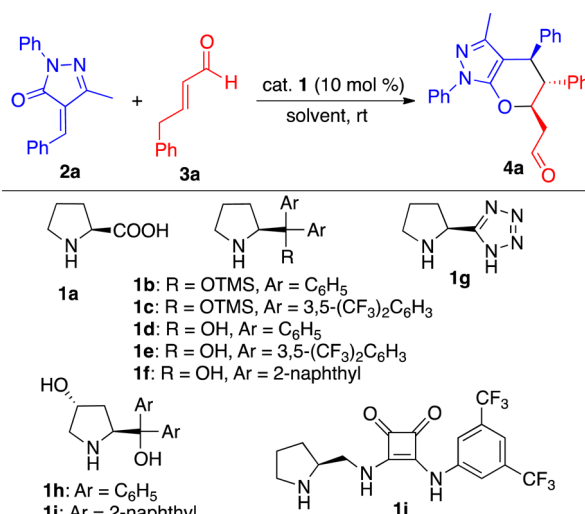
independently reported NHC-catalyzed enantioselective annulations for the synthesis of these scaffolds.<sup>10</sup> However, the catalytic enantioselective construction of THPP scaffolds bearing three contiguous stereocenters is still a challenging endeavor.

Cycloadditions play a pivotal role in the construction of diverse heterocyclic skeletons.<sup>11</sup> Of special interest is the application of aminocatalytic [4 + 2] processes that involve dienamine intermediates. These can play a dual role as dienes or dienophiles,<sup>12</sup> and their nucleophilicity allows inverse-electron-demand hetero-Diels–Alder (IEDHDA) reactions to be carried out when they are combined with Michael acceptors. In 2012, Jørgensen et al. pioneered the H-bond-directing dienamine strategy in an excellent report showing a distal regio- and stereoselective IEDHDA reaction.<sup>13</sup> More recently, the Chen group developed a [4 + 2] cycloaddition reaction of 1-aza-1,3-butadienes with  $\alpha,\beta$ -unsaturated aldehydes by employing dienamine catalysis.<sup>14</sup> Inspired by previous works on H-bond-directing dienamine-mediated strategies,<sup>13,15</sup> we report herein an

Received: December 18, 2015

IEDHDA reaction between enals and alkylidene pyrazolones (Scheme 1, bottom). This dienamine-mediated process gives rise to THPPs with three contiguous stereocenters in excellent stereoselectivities. We began to study this reaction with pyrrolidine-derived aminocatalysts, given their success in dienamine-mediated processes.<sup>16</sup> Alkylidene pyrazolone **2a** and  $\alpha,\beta$ -unsaturated aldehyde **3a** were chosen as model substrates, and a range of solvents were screened at room temperature (Table 1).

Table 1. Optimization of Reaction Conditions<sup>a</sup>



**1a**: R = OH, Ar = C<sub>6</sub>H<sub>5</sub>  
**1b**: R = OTMS, Ar = C<sub>6</sub>H<sub>5</sub>  
**1c**: R = OTMS, Ar = 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>  
**1d**: R = OH, Ar = C<sub>6</sub>H<sub>5</sub>  
**1e**: R = OH, Ar = 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>  
**1f**: R = OH, Ar = 2-naphthyl  
**1g**: R = N<sub>3</sub>, Ar = C<sub>6</sub>H<sub>5</sub>  
**1h**: R = OH, Ar = C<sub>6</sub>H<sub>5</sub>  
**1i**: R = OH, Ar = 2-naphthyl  
**1j**: R = OH, Ar = 2-naphthyl

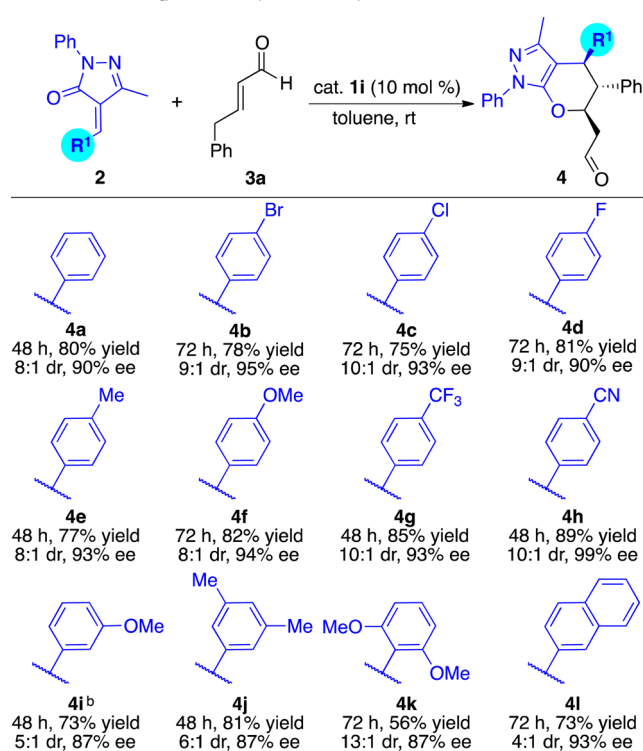
| entry | cat. | solvent                         | t (h) | yield (%) <sup>b</sup> | dr <sup>c</sup> | ee (%) <sup>d</sup> |
|-------|------|---------------------------------|-------|------------------------|-----------------|---------------------|
| 1     | 1a   | CH <sub>2</sub> Cl <sub>2</sub> | 12    | 70                     | 1:1             | 11                  |
| 2     | 1b   | CH <sub>2</sub> Cl <sub>2</sub> | 36    | 78                     | 4:1             | 24                  |
| 3     | 1c   | CH <sub>2</sub> Cl <sub>2</sub> | 48    | 76                     | 4:1             | 43                  |
| 4     | 1d   | CH <sub>2</sub> Cl <sub>2</sub> | 48    | 72                     | 6:1             | 67                  |
| 5     | 1e   | CH <sub>2</sub> Cl <sub>2</sub> | 60    | 61                     | 6:1             | 66                  |
| 6     | 1f   | CH <sub>2</sub> Cl <sub>2</sub> | 72    | 63                     | 6:1             | 74                  |
| 7     | 1g   | CH <sub>2</sub> Cl <sub>2</sub> | 6     | 77                     | 4:1             | 20                  |
| 8     | 1h   | CH <sub>2</sub> Cl <sub>2</sub> | 48    | 80                     | 7:1             | 78                  |
| 9     | 1i   | CH <sub>2</sub> Cl <sub>2</sub> | 48    | 76                     | 7:1             | 81                  |
| 10    | 1j   | CH <sub>2</sub> Cl <sub>2</sub> | 48    | 65                     | 4:1             | −38                 |
| 11    | 1i   | DCE                             | 48    | 73                     | 7:1             | 83                  |
| 12    | 1i   | CHCl <sub>3</sub>               | 48    | 72                     | 7:1             | 80                  |
| 13    | 1i   | MeCN                            | 48    | 75                     | 7:1             | 80                  |
| 14    | 1i   | Et <sub>2</sub> O               | 48    | 69                     | 6:1             | 68                  |
| 15    | 1i   | toluene                         | 48    | 80                     | 8:1             | 90                  |
| 16    | 1i   | mesitylene                      | 48    | 77                     | 8:1             | 89                  |
| 17    | 1i   | DMF                             | 48    | <10                    | nd              | nd                  |

<sup>a</sup>Reactions performed on a 0.1 mmol scale (see Supporting Information). <sup>b</sup>Isolated yield. <sup>c</sup>Determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup>Determined by chiral HPLC after reduction to the corresponding alcohol.

We first examined the [4 + 2] cycloaddition reaction catalyzed by proline, which gave the desired product in excellent regioselectivity and yield, but with poor dr and ee (Table 1, entry 1). When  $\alpha,\alpha$ -diarylprolinol silyl ethers were employed, both dr and ee increased slightly (entries 2 and 3). Subsequently, screening of various  $\alpha,\alpha$ -diarylprolinols, gave a remarkable increase in stereoselectivity (entries 4–6). We tentatively attribute this to the H-bonding ability of the free hydroxy group. Notably, we found that tetrazole **1g** could enhance the reactivity dramatically (6 h) but without any improvement in ee

(entry 7). Pleasingly, compared to **1d**, catalyst **1h** (bearing an extra hydroxy group in C<sub>4</sub><sup>17</sup>) allowed to improve the yield with much higher ee and dr (entry 8). Based on this, we first prepared the more hindered 4-hydroxydinaphthylprolinol catalyst **1i**, which proved beneficial in terms of ee (entry 9). Pyrrolidine-squaramide catalyst **1j** failed to improve the catalytic activity and stereoselectivity (entry 10). Solvent screening (entries 11–17) indicated that toluene was the best option: in these conditions, using catalyst **1i**, the THPP **4a** could be isolated in 80% yield, 90% ee and 8:1 dr (entry 15). With the optimized conditions, the substrate scope of the asymmetric cycloaddition reaction was undertaken and a series of chiral THPPs were synthesized (Scheme 2).

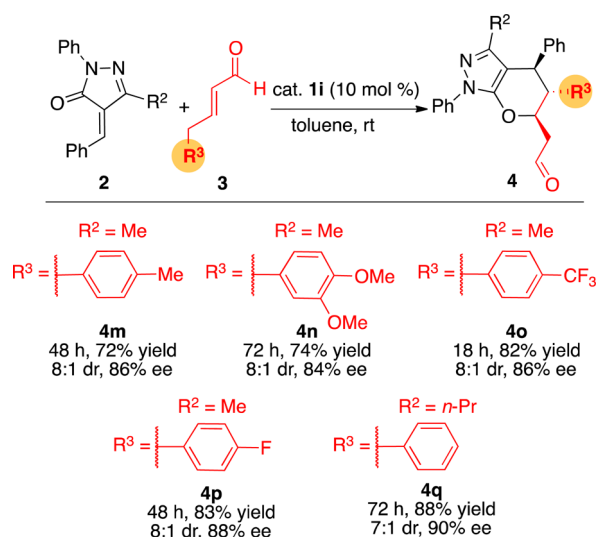
Scheme 2. Scope of Alkylidene Pyrazolones<sup>a</sup>



<sup>a</sup>Reactions performed on a 0.15 mmol scale (see the Supporting Information). <sup>b</sup>Performed at 0 °C.

In general, alkylidene pyrazolones bearing different electron-withdrawing and electron-donating substituents were well tolerated. Specifically, all of the para-substituted substrates (**4b–4h**) were obtained in good yields (75–89%), high diastereoselectivities (8:1–10:1 dr), and excellent enantioselectivities (90–99% ee). In contrast to these, the meta-substituted **4i** and **4j** gave a little decrease in the diastereo- and enantioselectivity, while maintaining the high yields. Importantly, the system also admitted introduction of double substitution on the ortho–ortho' position, providing **4k** in excellent diastereoselectivity (13:1 dr), comparable enantioselectivity (87% ee), and slightly lower yield. Furthermore, **4l** bearing a bulkier 2-naphthyl group was formed in moderate diastereoselectivity (4:1 dr) but with good yield (73%) and excellent enantioselectivity (93% ee).

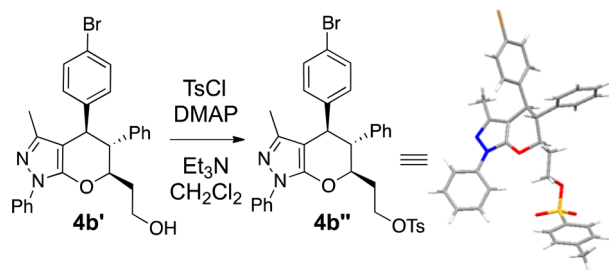
Next, we set our sights on the performance of various  $\alpha,\beta$ -unsaturated aldehydes. As presented in Scheme 3, the [4 + 2] cycloaddition reactions proceeded smoothly when enals with

Scheme 3. Scope of Various Enal Reaction Partners<sup>a</sup>

<sup>a</sup>Reactions performed on a 0.15 mmol scale (see Supporting Information).

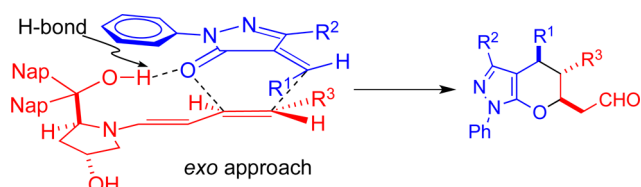
diverse electronic properties were tested. The corresponding chiral tetrahydropyranopyrazoles **4m–4p** were obtained with high enantioselectivities (84–88%), good diastereoselectivities (8:1 dr), and good yields ranging from 72 to 83%. Gratifyingly, an alkylidene pyrazolone bearing a linear aliphatic substituent afforded product **4q** in 88% yield and high stereoselectivity (7:1 dr, 90% ee). As for alkyl-substituted enals, we have only tested crotonaldehyde, which gave good yields but very poor stereoselectivities.

The absolute configuration of tosylate **4b''** (prepared from **4b'** as shown in Scheme 4) was unambiguously determined by X-ray single-crystal analysis.<sup>18</sup> The rest of the cycloadducts have been assigned by analogy to **4b**.

Scheme 4. Synthesis and X-ray Structure of **4b''**

The model we propose to account for the formation of the major product is depicted in Scheme 5. The regioselectivity of the attack can be easily inferred from the structure of the final

## Scheme 5. Model Proposed to Explain the Regio- and Stereoselectivity



product, and it also matches with the expected course of action given the polarization of the dienamine and the alkylidene pyrazolone. Regarding the stereoselectivity, whereas the pyrazolone geometry is fixed, the dienamine can adopt several conformations. However, as demonstrated by Jørgensen and co-workers on the basis of DFT calculations,<sup>16a</sup> the (*E*,*s*-*trans*,*E*)-dienamine is the most stable conformer. Thus, out of the four possible approaches (see Supporting Information for details) only the one shown in Scheme 5 leads to the major stereoisomer. The preference for such an *exo* approach is justified in terms of (a) H-bonding between the hydroxy group of the diarylprolinol and the carbonyl of the pyrazolone and (b) the repulsion between the aromatic group in the pyrazolone (slightly tilted out-of-plane) and the dienamine, which would take place in an alternative *endo* approach.

In summary, we have disclosed the first asymmetric [4 + 2] cycloaddition between alkylidene pyrazolones and enals through H-bond-directing dienamine catalysis. The reaction, promoted by a bifunctional 4-hydroxydinaphthylprolinol species, proceeds smoothly with excellent regioselectivity and high stereoselectivity (up to 89% yield, 13:1 dr, and 99% ee). Thus, we have disclosed a new and efficient protocol for the synthesis of enantioenriched, multifunctionalized tetrahydropyranopyrazole derivatives containing three contiguous stereocenters. Further application of this method and biological evaluation of the THPPs is currently underway.

## ■ ASSOCIATED CONTENT

## S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03575.

Experimental procedures, characterization data, and copies of NMR spectra and HPLC chromatograms (PDF)

Compound **4b''** (CIF)

## ■ AUTHOR INFORMATION

## Corresponding Author

\*E-mail: mapericas@iciq.es.

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support from the Institute of Chemical Research of Catalonia (ICIQ) Foundation, MINECO (grant CTQ2012-38594-C02-01 and Severo Ochoa Excellence Accreditation 2014-2018: SEV-2013-0319) and DEC Generalitat de Catalunya (Grant 2014SGR827) is acknowledged. The CELLEX Foundation is also gratefully acknowledged for financing the High-Throughput Experimentation (HTE) laboratory.

## ■ DEDICATION

Dedicated to Prof. Karl Anker Jørgensen on his 60th anniversary.

## ■ REFERENCES

- (1) (a) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984–7034. (b) Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4501–4503. (c) Bondock, S.; Rabie, R.; Etman, H. A.; Fadda, A. A. *Eur. J. Med. Chem.* **2008**, *43*, 2122–2129. (d) Kimata, A.;

- Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. *J. Med. Chem.* **2007**, *50*, 5053–5056.
- (2) For a review, see: Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Commun.* **2015**, *51*, 12890–12907.
- (3) (a) Gogoi, S.; Zhao, C.-G. *Tetrahedron Lett.* **2009**, *50*, 2252–2255. (b) Yang, Z.; Wang, Z.; Bai, S.; Liu, X.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 596–599. (c) Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2010**, *352*, 827–832. (d) Wang, Z.; Yang, Z.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 4928–4932. (e) Alba, A.-N. R.; Zea, A.; Valero, G.; Calbet, T.; Font-Bardía, M.; Mazzanti, A.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2011**, *2011*, 1318–1325. (f) Wang, Z.; Chen, Z.; Bai, S.; Li, W.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 2776–2779. (g) Mazzanti, A.; Calbet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2012**, *10*, 1645–1652. (h) Li, F.; Sun, L.; Teng, Y.; Yu, P.; Zhao, J. C.-G.; Ma, J.-A. *Chem. - Eur. J.* **2012**, *18*, 14255–14260. (i) Wang, H.; Wang, Y.; Song, H.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2013**, *2013*, 4844–4851. (j) Tao, Z.-L.; Zhang, W.-Q.; Chen, D.-F.; Adele, A.; Gong, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 9255–9258. (k) Li, J.-H.; Du, D.-M. *Org. Biomol. Chem.* **2013**, *11*, 6215–6223. (l) Li, J.-H.; Du, D.-M. *RSC Adv.* **2014**, *4*, 14538–14545. (m) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643–5647.
- (4) Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249–2252.
- (5) (a) Zea, A.; Alba, A.-N. R.; Mazzanti, A.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2011**, *9*, 6519–6523. (b) Liu, L.; Zhong, Y.; Zhang, P.; Jiang, X.; Wang, R. *J. Org. Chem.* **2012**, *77*, 10228–10234. (c) Liang, J.; Chen, Q.; Liu, L.; Jiang, X.; Wang, R. *Org. Biomol. Chem.* **2013**, *11*, 1441–1445. (d) Chen, Q.; Liang, J.; Wang, S.; Wang, D.; Wang, R. *Chem. Commun.* **2013**, *49*, 1657–1659. (e) Geng, Z.-C.; Chen, X.; Zhang, J.-X.; Li, N.; Chen, J.; Huang, X.-F.; Zhang, S.-Y.; Tao, J.-C.; Wang, X.-W. *Eur. J. Org. Chem.* **2013**, *2013*, 4738–4743. (f) Zhang, J.-X.; Li, N.-K.; Liu, Z.-M.; Huang, X.-F.; Geng, Z.-C.; Wang, X.-W. *Adv. Synth. Catal.* **2013**, *355*, 797–808. (g) Chauhan, P.; Mahajan, S.; Loh, C. C. J.; Raabe, G.; Enders, D. *Org. Lett.* **2014**, *16*, 2954–2957. (h) Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2014**, *356*, 2330–2336. (i) Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T. *Angew. Chem., Int. Ed.* **2016**, *55*, 268–272.
- (6) (a) Mandha, S. R.; Siliveri, S.; Alla, M.; Bommina, V. R.; Bommineni, M. R.; Balasubramanian, S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5272–5278. (b) Elfahham, H. A.; Abdel-Galil, F. M.; Ibraheem, Y. R.; Elnagdi, M. H. *J. Heterocycl. Chem.* **1983**, *20*, 667–670. (c) Khan, M. A.; Cosenza, A. G.; Ellis, G. P. *J. Heterocycl. Chem.* **1982**, *19*, 1077–1085.
- (7) (a) Azzam, S. H. S.; Pasha, M. A. *Tetrahedron Lett.* **2012**, *53*, 6834–6837. (b) Kuo, S. C.; Huang, L. J.; Nakamura, H. *J. Med. Chem.* **1984**, *27*, 539–544.
- (8) Enders, D.; Grossmann, A.; Gieraths, B.; Düzdemir, M.; Merckens, C. *Org. Lett.* **2012**, *14*, 4254–4257.
- (9) Jiang, X.; Liu, L.; Zhang, P.; Zhong, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 11329–11333.
- (10) (a) Zhang, H.-M.; Lv, H.; Ye, S. *Org. Biomol. Chem.* **2013**, *11*, 6255–6257. (b) Yetra, S. R.; Mondal, S.; Suresh, E.; Biju, A. T. *Org. Lett.* **2015**, *17*, 1417–1420.
- (11) For reviews, see: (a) Jiang, X.; Wang, R. *Chem. Rev.* **2013**, *113*, 5515–5546. (b) Pellissier, H. *Tetrahedron* **2009**, *65*, 2839–2877. (c) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558–3588. (d) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781–793.
- (12) Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287–2300.
- (13) (a) Albrecht, L.; Dickmeiss, G.; Weise, C. F.; Rodríguez-Esrich, C.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 13109–13113. (b) Weise, C. F.; Lauridsen, V. H.; Rambo, R. S.; Iversen, E. H.; Olsen, M.-L.; Jørgensen, K. A. *J. Org. Chem.* **2014**, *79*, 3537–3546.
- (14) Gu, J.; Ma, C.; Li, Q.-Z.; Du, W.; Chen, Y.-C. *Org. Lett.* **2014**, *16*, 3986–3989.
- (15) (a) Albrecht, L.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Esrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543–2546. (b) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Chem. - Eur. J.* **2014**, *20*, 358–368. (c) Qi, L.-W.; Yang, Y.; Gui, Y.-Y.; Zhang, Y.; Chen, F.; Tian, F.; Peng, L.; Wang, L.-X. *Org. Lett.* **2014**, *16*, 6436–6439.
- (16) For selected examples, see: (a) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973–12980. (b) Han, B.; He, Z.-Q.; Li, J.-L.; Li, R.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5474–5477. (c) Li, J.-L.; Kang, T.-R.; Zhou, S.-L.; Li, R.; Wu, L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6418–6420. (d) Song, A.; Zhang, X.; Song, X.; Chen, X.; Yu, C.; Huang, H.; Li, H.; Wang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 4940–4944. (e) Li, W.; Wei, J.; Jia, Q.; Du, Z.; Zhang, K.; Wang, J. *Chem. - Eur. J.* **2014**, *20*, 6592–6596. (f) Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3043–3046. For reviews, see: (g) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, *2012*, 865–887. (h) Li, J.-L.; Liu, T.-Y.; Chen, Y.-C. *Acc. Chem. Res.* **2012**, *45*, 1491–1500. (i) Jurberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869–4883.
- (17) For examples where the substitution at C<sub>4</sub> is important, see: (a) Li, Y.; Liu, X.; Yang, Y.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 288–291. (b) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854–3857. (c) Caruana, L.; Kniep, F.; Johansen, T. K.; Poulsen, P. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2014**, *136*, 15929–15932.
- (18) X-ray structure deposited under CCDC 1438957.