Asymmetric Catalysis

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Enantioselective Synthesis of α-Secondary and α-Tertiary Piperazin-2-ones and Piperazines by Catalytic Asymmetric Allylic Alkylation**

*Katerina M. Korch, Christian Eidamshaus, Douglas C. Behenna, Sangkil Nam, David Horne, and Brian M. Stoltz**

Abstract: *The asymmetric palladium-catalyzed decarboxylative allylic alkylation of differentially N-protected piperazin-2-ones allows the synthesis of a variety of highly enantioenriched tertiary piperazine-2-ones. Deprotection and reduction affords the corresponding tertiary piperazines, which can be employed for the synthesis of medicinally important analogues. The introduction of these chiral tertiary piperazines resulted in imatinib analogues which exhibited comparable antiproliferative activity to that of their corresponding imatinib counterparts.*

Piperazine is a common structural motif in pharmaceuticals and is considered to be a privileged scaffold in medicinal chemistry.[1] Piperazine itself has been used as an anthelmintic and notable piperazine-containing, small-molecule pharmaceuticals include imatinib (**1**; a kinase-inhibiting anticancer agent),[2] ciprofloxacin (**2**; a potent fluoroquinolone antibiotic),[3] piribedil (**3**; an antiparkinsonian agent),[4] and indinavir (**4**; an HIV protease inhibitor, Figure 1 a).[5] Common methods for the selective asymmetric preparation of substituted piperazines[6] include enantioselective hydrogenation,[7] enzyme-mediated chiral resolution,[8] α-lithiation mediated by (−)-sparteine and other chiral diamines,[9] palladium-catalyzed cyclizations,[10] or synthesis from amino acids or other members of the chiral pool.[11] One of the most straightforward methods for the synthesis of chiral piperazines is the reduction of the corresponding chiral keto- or diketopiperazine. However, methods for the asymmetric preparation of these piperazine precursors are currently limited.

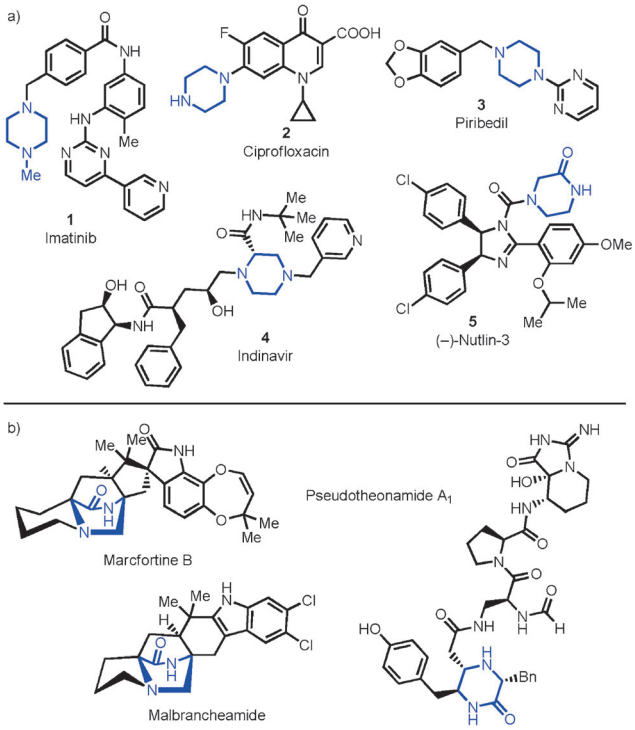

Figure 1. a) Representative piperazine and piperazin-2-one containing pharmaceuticals. b) Representative bioactive natural products possessing piperazin-2-one core structures.

Piperazin-2-ones possess an additional functionality (i.e., the carbonyl) which allows the synthesis of more highly substituted piperazine-2-ones, and, upon reduction, yield substituted piperazine derivatives. Although piperazin-2-ones are employed infrequently in medicinal chemistry, they can be found in some pharmaceutical agents including the p53/MDM2 inhibitor (−)-nutlin-3 (**5**; Figure 1 a),[12] and in several naturally occurring bioactive compounds including the marcfortines,[13] pseudotheonamides,[14] and malbrancheamides (Figure 1 b).[15] Piperazin-2-ones also play a crucial role as conformationally constrained peptidomimetics. These piperazin-2-ones mimic inverse γ-turns in peptides, which play crucial roles in the secondary structures of proteins.[16] Chiral piperazin-2-ones[17] can be prepared from amino acids or other members of the chiral pool[18] or by chiral-auxiliary-

[*] K. M. Korch, Dr. C. Eidamshaus, Dr. D. C. Behenna, Prof. Dr. B. M. Stoltz
The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology
1200 E. California Blvd, MC 101-20, Pasadena, CA 91125 (USA)
E-mail: stoltz@caltech.edu
Dr. S. Nam, Prof. Dr. D. Horne
Molecular Medicine, Beckman Research Institute
City of Hope Comprehensive Cancer Center
1500 East Duarte Road, Duarte, CA 91010 (USA)

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mediated alkylations[19] or dynamic resolutions.[20] However, most of the available methods are not capable of generating chiral α-tertiary piperazin-2-ones (**6**; Figure 2) and there are no previous examples for preparation of this motif by catalytic enantioselective methods. Thus, there is an unaddressed absence of catalytic asymmetric synthesis strategies to these valuable compounds.

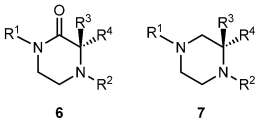


Figure 2. α-Tertiary piperazin-2-one and α-tertiary piperazine.

Our research group has had a longstanding interest in the construction of α-tetrasubstituted carbonyl compounds including quaternary centers using transition-metal catalysis and has developed reaction conditions for the asymmetric allylic alkylation of lactams to furnish α-quaternary lactam products.[21] Morpholin-3-ones were also identified as viable substrates under the same reaction conditions, thus generating an α-tertiary stereocenter.[22] We sought to extend this catalyst system to enantioselectively generate α-tertiary piperazin-2-ones (**6**), which, upon subsequent reduction, would generate chiral tertiary piperazines (**7**). α-Tertiary piperazine species are not well precedented in the literature presumably because of the difficulties associated with their preparation, and no general methods exist for their asymmetric synthesis, let alone catalytic asymmetric synthesis. A direct, catalytic asymmetric synthesis of tertiary piperazin-2-ones and their subsequent reduction to the piperazines would provide access to an invaluable scaffold, thus enabling the exploration of unprecedented chemical space (Figure 3).

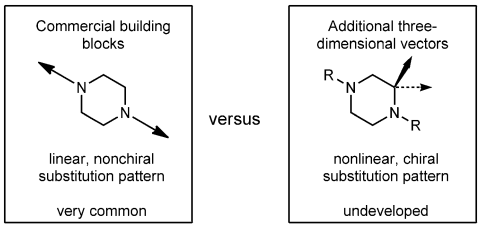
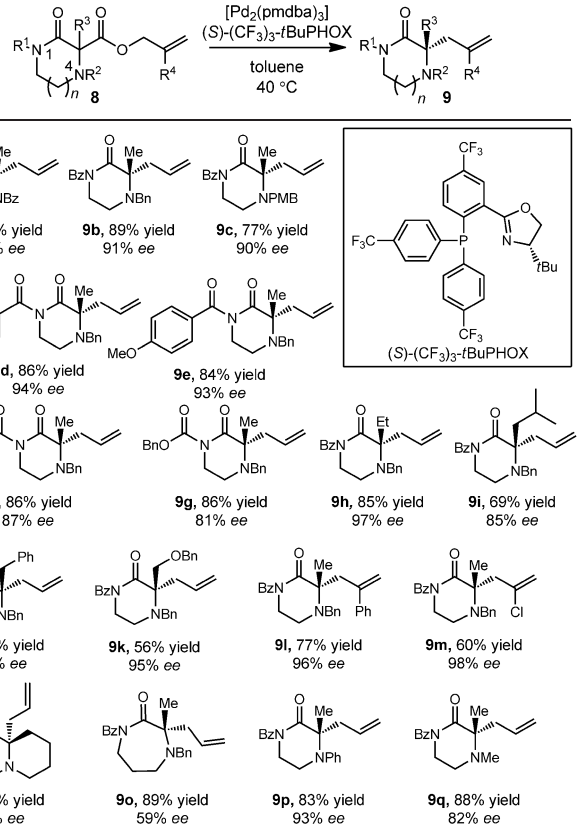


Figure 3. Entry into largely unexploited chemical space.

Medicinal chemistry has long utilized linearly substituted, nonchiral piperazines and has also, although less frequently, utilized chiral α-secondary piperazines, as in indinavir (**4**).[22] Access to enantiopure α-tertiary piperazines would provide a unique opportunity to explore these three-dimensionally elaborated piperazines in drug discovery.

Given that secondary and tertiary nitrogen atoms may exhibit undesired reactivity in palladium-catalyzed reactions, it is necessary to protect both nitrogen atoms of the ketopiperazine ring. Taking into consideration our prior results, in which N-benzoyl-protected lactams reacted with high enantioselectivities in the decarboxylative asymmetric

Table 1: Catalytic enantioselective piperazin-2-one decarboxylative allylic alkylation. Scope of protecting-group tolerance and scope of α-substituents.[a]



[a] Conditions: piperazin-2-one **8** (1.0 equiv), $[Pd_2(pmdba)_3]$ (5 mol%), (*S*)-$(CF_3)_3$-*t*BuPHOX (12.5 mol%) in toluene (0.014 M) at 40°C for 12–48 h. All reported yields are those for the isolated products. The *ee* values were determined by SFC using a chiral stationary phase. Bz = benzoyl, PMB = *para*-methoxybenzyl.

allylic alkylation,[21e] we began our studies with the 1,4-bis(benzoyl)ated piperazin-2-one **8a** (Table 1). When utilizing tris(4,4′-methoxydibenzylideneacetone)dipalladium(0) ($[Pd_2(pmdba)_3]$) at a 5 mol% loading and the (*S*)-$(CF_3)_3$-*t*BuPHOX ligand at 12.5 mol% loading in a 0.014 M solution of toluene, the bis(N-benzoyl)ated α-allylated product **9a** was formed in high yield but with a modest *ee* value. It was reasoned that the sp^2-hybridized nature of the N4 position was detrimental to the enantioselectivity of the reaction because of its ability to stabilize the enolate intermediate.[23] Taking into consideration the need for an alkyl-protecting group at the N4 position, we next examined the 4-benzylpiperazin-2-one **8b** (R^1 = Bz, R^2 = Bn, R^3 = Me, R^4 = H). Under our standard reaction conditions, the N-benzyl-protected α-allylated compound **9b** was obtained in good yield and *ee* value. Additional N4-protecting groups were investigated for the chemoselective deprotection of N4. The *para*-methoxybenzyl-protecting group, which can be removed by acidic or oxidative conditions, would allow orthogonal deprotection. The 4-methoxybenzylpiperazin-2-one **9c** was also obtained with a good *ee* value but with slightly lower yield than that of **9b**. Given the slightly higher yield, the 4-

benzyl-protecting group was selected for further optimization.

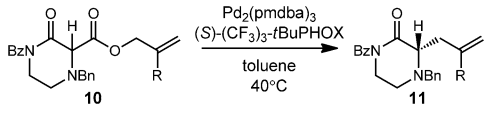
In efforts to increase the *ee* value of the allylic alkylated products, additional protecting groups at N1 were examined. Considering that benzoylated compounds provided the best results in the lactam case,[21e] we examined additional acyl-protecting groups (Table 1). The *para*-fluoro and *para*-methoxy benzoyl compounds **9d** and **9e**, respectively, were obtained with nearly identical *ee* values and just slightly lower yields, thus demonstrating that substantial electronic changes of the N1 substituent do not have a strong influence on the reaction efficiency or selectivity. However, the reaction is somewhat sensitive toward *ortho* substitution at the N1-benzoyl group as **9f** was obtained in a significantly lower enantiomeric excess compared to that of **9d** and **9e**. Additionally, the 1-carboxybenzyl ketopiperazine **9g** was also prepared in high yield, albeit with moderate *ee* value. Given these data, the unsubstituted benzoyl group was selected as the optimal choice for an N1-protecting group, and the benzyl group was selected as the optimal N4 group.

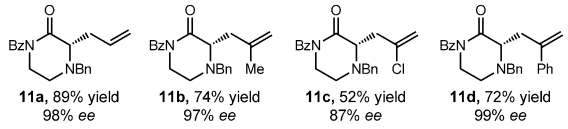
With protecting groups for both nitrogen atoms investigated, the scope of the reaction with regard to the α-substituent was examined. Piperazin-2-ones bearing alkyl (**9h, 9i**) and benzyl (**9j**) groups were prepared, as was the benzyl ether **9k**, which provides an additional handle for further functionalization (Table 1). Additionally, the bicyclic product **9n**, which is reminiscent of the marcfortine core, was obtained in good yield in the reaction. The effect of expanding ring size was also examined. The 1,4-diazepan-2-one **9o** was formed with only moderate enantiomeric excess, a result that suggests that the reaction is sensitive to ring size, contrary to the lactam examples.[21e]

Common piperazine pharmacophores include N-aryl-piperazines and N-methylpiperazines,[24] and we sought to determine if 4-aryl ketopiperazines and 4-methyl ketopiperazines were also competent substrates in this chemistry. The low *ee* values observed for **9a** suggests that an sp^2-hybridized N4 would prove detrimental to the enantioselectivity of the reaction. Despite this, the 4-phenyl compound **9p**, with its partial sp^2 character of the aniline nitrogen atom, could be obtained in good yield and with excellent enantiomeric excess (Table 1). The 4-methylketopiperazine **9q** could also be prepared in good yield but with slightly diminished *ee* value.

Contrary to results with the piperdinone substrates, we were delighted to find that even the unsubstituted α-secondary ketopiperazine **11a** could be obtained in excellent yield and enantioselectivity (Table 2). Previous attempts to generate trisubstituted stereocenters by our asymmetric allylic alkylation of lactam and ketone substrates were unsuccessful. Such experiments have generally resulted in mixtures of mono-, di-, and unallylated products, and the desired trisubstituted product was formed in poor yield and with only moderate *ee* value. We were delighted to find that in the case at hand, the unsubstituted α-secondary ketopiperazine **11a** could be obtained with no detectable amounts of di- or unallylated byproducts. It is likely that the low acidity of the α-hydrogen atom of the monosubstituted piperazin-2-one substrate and product is key to obtaining a high yield of the monoallylated product. Given this exciting result, additional

Table 2: Scope of allyl substituents for α-secondary piperazin-2-ones.[a]

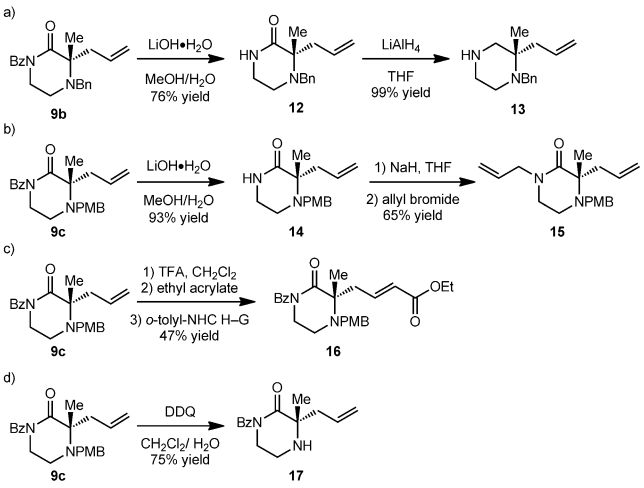




[a] Conditions: piperazin-2-one **8** (1.0 equiv), $[Pd_2(pmdba)_3]$ (5 mol%), (S)-$(CF_3)_3$-*t*BuPHOX (12.5 mol%) in toluene (0.014 M) at 40°C for 12–48 h. All reported yields are those for the isolated products. The *ee* values were determined by SFC using a chiral stationary phase.

allyl substrates were tested. Numerous allyl groups are compatible, including the methallyl **11b**, chloroallyl **11c**, and phenylallyl **11d** which were all obtained in fair to excellent yield and high enantioselectivity.

The ketopiperazine products can be converted into the related piperazines in two steps, hydrolysis of the benzoyl group to thepiperazine-2-one **12** and subsequent reduction of the amide to the piperazine **13** (Scheme 1 a). The deprotected



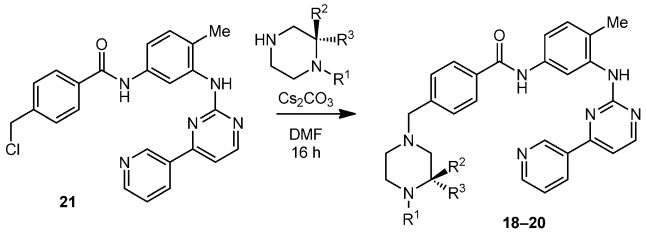
Scheme 1. a) Protecting-group removal and reduction to yield the piperazine **13**. b) Protecting-group removal and alkylation to yield the piperazin-2-one **15.** c) Cross-metathesis with ethyl acrylate. d) Oxidative cleavage of PMB-protecting group. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, NHC = N-heterocyclic carbene, H–G = Hoveyda–Grubbs catalyst, TFA = trifluoromethanesulfonyl, THF = tetrahydrofuran.

N1 can be further alkylated to form, for instance, the diallyl piperazin-2-one **15** (Scheme 1 b). Cross-metathesis can also be performed (Scheme 1 c). Additionally, the 4-methoxybenzyl group can be selectively cleaved under oxidative conditions to form the piperazine-2-one **17** (Scheme 1 d).

Finally, we have demonstrated that these tertiary piperazines can successfully be incorporated into known piperazine-containing pharmaceuticals, thus leading to novel analogues with comparable bioactivities in preliminary testing. Substitution on the piperazine ring has been shown to

modulate bioactivity and, in some cases, result in more specific and stronger enzyme binding.[25] We considered imatinib (**1**), an antiproliferative agent developed for the treatment of several cancers, notably including Philadelphia chromosome-positive chronic myelogenous leukemia (CML),[2] to be an ideal candidate for proof of concept. Imatinib targets the Abl tyrosine kinase domain of the Bcr-Abl fusion protein, and it is known that genetic point mutations can render imatinib ineffective because it is no longer able to bind to the enzyme.[26] The piperazine moiety of the molecule forms two key hydrogen bonds to two amino acid residues, and thus plays a crucial role in binding.[27]

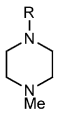
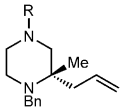
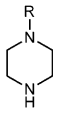
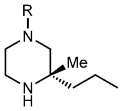
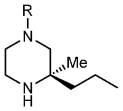
Given that the piperazine is so crucial to the binding of imatinib, we wanted to explore whether highly substituted and congested piperazine analogues would disrupt these interactions. The enantiomerically pure, benzylated analogue **18** (Scheme 2) was assessed for its antiproliferative activity



Scheme 2. Synthesis of imatinib analogues from the precursor **19**. DMF = *N*,*N*-dimethylformamide.

against the human K562 CML cell line. The N-substituted analogue **18** was found to have significantly less antiproliferative activity than imatinib (**1**; Table 3), thus signifying that too much bulk around N4 might perturb key interactions. We

Table 3: Antiproliferative activity of imatinib and imatinib analogues.[a]

N-substituted compounds		Free N–H analogues		
				
1 Imatinib	**18**	**19** desmethyl imatinib	(*S*)-**20**	(*R*)-**20**
197 ± 9	> 100 000	684 ± 27	571 ± 21	428 ± 29

[a] IC_{50} values [nM] are those for K562 CML cells and are reported ± standard deviation.

also synthesized two novel desmethyl tertiary piperazine-containing imatinib analogues (Scheme 2). These analogues, (*S*)-**20** and (*R*)-**20**, were assayed for their antiproliferative activity and were found to have activities slightly greater than that of the N-desmethyl imatinib (CGP 74588) **19**, the main bioactive metabolite of imatinib. The *R*-enantiomer is slightly more potent [(*R*)-**20**, Table 3]. These results point to the potential utility of stereochemically rich piperazines as important building blocks for medicinal chemistry. Additionally, these novel substructures will likely open up new chemical space around a privileged scaffold in drug discovery.

In summary, we have developed the first catalytic enantioselective synthesis of α-tertiary piperazin-2-ones. These important molecules can be easily converted into novel α-tertiary piperazines. This method utilizes palladium catalysts derived from $[Pd_2(pmdba)_3]$ and electron-deficient PHOX ligands to deliver α-tertiary piperazin-2-ones in good to excellent yields and enantioselectivities. This method also allows the synthesis of α-secondary piperazin-2-ones in modest to excellent yields and good to excellent enantioselectivities. In addition to being tolerant of a variety of N-substitutions, this reaction is also tolerant of substitution at the stereocenter including fused bicycles such as those found in piperazine-2-one-containing natural products. We have further demonstrated that these chiral piperazin-2-ones can be reduced to the corresponding chiral piperazines, and these chiral α-tertiary piperazines can successfully be incorporated into known piperazine-containing pharmaceuticals. Specifically, these piperazines can be incorporated into the imatinib framework without major perturbation of the drug's antiproliferative activity against the human K562 CML cell line, thus indicating the enormous potential that these novel three-dimensionally elaborated chiral piperazines have in drug discovery.

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[1] a) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 1–15; b) R. W. DeSimone, K. S. Currie, S. A. Mitchell, J. W. Darrow, D. A. Pippin, *Comb. Chem. High Throughput Screening* **2004**, *7*, 473–493.
[2] R. Capdeville, E. Buchdunger, J. Zimmermann, A. Matter, *Nat. Rev. Drug Discovery* **2002**, *1*, 493–502.
[3] P. C. Sharma, A. Jain, S. Jain, R. Pahwa, M. S. Yar, *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 577–589.
[4] A. Mittur, *Curr. Drug Ther.* **2011**, *6*, 17–34.
[5] B. D. Dorsey, J. P. Vacca, *Infect. Dis. Ther.* **2002**, *25*, 65–83.
[6] For a review, see: C. J. Dinsmore, D. C. Beshore, *Org. Prep. Proced. Int.* **2002**, *34*, 367–404.
[7] a) P. Kukula, R. Prins, *J. Catal.* **2002**, *208*, 404–411; b) R. Kuwano, Y. Ito, *J. Org. Chem.* **1999**, *64*, 1232–1237; c) K. Rossen, P. J. Pye, L. M. DiMichele, R. P. Volante, P. J. Reider, *Tetrahedron Lett.* **1998**, *39*, 6823–6826.
[8] a) H. Komeda, H. Harada, S. Washika, T. Sakamoto, M. Ueda, Y. Asano, *Eur. J. Biochem.* **2004**, *271*, 1580–1590; b) E. Eichhorn, J.-P. Roduit, N. Shaw, K. Heinzmann, A. Kiener, *Tetrahedron: Asymmetry* **1997**, *8*, 2533–2536.
[9] a) B. P. McDermott, A. D. Campbell, A. Ertan, *Synlett* **2008**, 875–879; b) M. Berkheij, L. van der Sluis, C. Sewing, D. J. den Boer, J. W. Terpstra, H. Hiemstra, W. I. I. Bakker, A. van den Hoogenband, J. H. van Maarseveen, *Tetrahedron Lett.* **2005**, *46*, 2369–2371; c) S. P. Robinson, N. S. Sheikh, C. A. Baxter, I. Coldham, *Tetrahedron Lett.* **2010**, *51*, 3642–3644.
[10] a) B. M. Cochran, F. E. Michael, *Org. Lett.* **2008**, *10*, 329–332; b) J. S. Nakhla, J. P. Wolfe, *Org. Lett.* **2007**, *9*, 3279–3282; c) H. Nakano, J. Yokoyama, R. Fujita, H. Hongo, *Tetrahedron Lett.* **2002**, *43*, 7761–7764; d) K. Ito, Y. Imahayashi, T. Kuroda, S. Eno, B. Saito, T. Katsuki, *Tetrahedron Lett.* **2004**, *45*, 7277–7281;

e) Y. Uozumi, A. Tanahashi, T. Hayashi, *J. Org. Chem.* **1993**, *58*, 6826 – 6832.

[11] a) S. H. Kwon, S. M. Lee, S. M. Byun, J. Chin, B. M. Kim, *Org. Lett.* **2012**, *14*, 3664 – 3667; b) S. Dekeukeleire, M. D'hooghe, M. Vanwalleghem, W. Van Brabandt, N. De Kimpe, *Tetrahedron* **2012**, *68*, 10827 – 10834; c) J. W. Mickelson, K. L. Belonga, E. J. Jacobsen, *J. Org. Chem.* **1995**, *60*, 4177 – 4183; d) S. A. Ruider, S. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2013**, *52*, 11908 – 11911; *Angew. Chem.* **2013**, *125*, 12125 – 12128; e) M. Yar, E. M. McGarrigle, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2008**, *47*, 3784 – 3786; *Angew. Chem.* **2008**, *120*, 3844 – 3846; f) V. Santes, E. Gómez, V. Zárate, R. Santillan, N. Farfán, S. Rojas-Lima, *Tetrahedron: Asymmetry* **2001**, *12*, 241 – 247; g) A. M. Warshawsky, M. V. Patel, T.-M. Chen, *J. Org. Chem.* **1997**, *62*, 6439 – 6440; h) V. Schanen, C. Riche, A. Chiaroni, J.-C. Quirion, H.-P. Husson, *Tetrahedron Lett.* **1994**, *35*, 2533 – 2536; i) L. U. Nordstrøm, R. Madsen, *Chem. Commun.* **2007**, 5034 – 5036; j) F. Crestey, M. Witt, J. W. Jaroszewski, H. Franzyk, *J. Org. Chem.* **2009**, *74*, 5652 – 5655.

[12] P. Secchiero, R. Bosco, C. Celeghini, G. Zauli, *Curr. Pharm. Des.* **2011**, *17*, 569 – 577.

[13] a) J. Polonsky, M.-A. Merrien, T. Prangé, C. Pascard, S. Moreau, *J. Chem. Soc. Chem. Commun.* **1980**, 601 – 602; b) T. Prangé, M.-A. Billion, M. Vuilhorgne, C. Pascard, J. Polonsky, S. Moreau, *Tetrahedron Lett.* **1981**, *22*, 1977 – 1980.

[14] Y. Nakao, A. Masuda, S. Matsunaga, N. Fusetani, *J. Am. Chem. Soc.* **1999**, *121*, 2425 – 2431.

[15] S. Martínez-Luis, R. Rodríguez, L. Acevedo, M. C. González, A. Lira-Rocha, R. Mata, *Tetrahedron* **2006**, *62*, 1817 – 1822.

[16] a) F. Rübsam, R. Mazitschek, A. Giannis, *Tetrahedron* **2000**, *56*, 8481 – 8487; b) S. Herrero, M. T. García-López, M. Latorre, E. Cenarruzabeitia, J. Del Rio, R. Herranz, *J. Org. Chem.* **2002**, *67*, 3866 – 3873; c) M. Limbach, A. V. Lygin, V. S. Korotkov, M. Es-Sayed, A. de Meijere, *Org. Biomol. Chem.* **2009**, *7*, 3338 – 3342; d) S. Suwal, T. Kodadek, *Org. Biomol. Chem.* **2013**, *11*, 2088 – 2092; e) Z. Chen, A. S. Kende, A.-O. Colson, J. L. Mendezandino, F. H. Ebetino, R. D. Bush, X. E. Hu, *Synth. Commun.* **2006**, *36*, 473 – 479.

[17] For a review, see: C. De Risi, M. Pelà, G. P. Pollini, C. Trapella, V. Zanirato, *Tetrahedron: Asymmetry* **2010**, *21*, 255 – 274.

[18] a) J. J. Chen, T. Nguyen, D. C. D'Amico, W. Qian, J. Human, T. Aya, K. Biswas, C. Fotsch, N. Han, Q. Liu, N. Nishimura, T. A. N. Peterkin, K. Yang, J. Zhu, B. B. Riahi, R. W. Hungate, N. G. Andersen, J. T. Colyer, M. M. Faul, A. Kamassah, J. Wang, J. Jona, G. Kumar, E. Johnson, B. C. Askew, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3384 – 3389; b) M. K. Gurjar, S. Karmakar, D. K. Mohapatra, U. D. Phalgune, *Tetrahedron Lett.* **2002**, *43*, 1897 – 1900; c) G. P. Pollini, N. Baricordi, S. Benetti, C. De Risi, V. Zanirato, *Tetrahedron Lett.* **2005**, *46*, 3699 – 3701; d) S. D. Rychnovsky, T. Beauchamp, R. Vaidyanathan, T. Kwan, *J. Org. Chem.* **1998**, *63*, 6363 – 6374; e) N. A. Powell, F. L. Ciske, E. C. Clay, W. L. Cody, D. M. Downing, P. G. Blazecka, D. D. Holsworth, J. J. Edmunds, *Org. Lett.* **2004**, *6*, 4069 – 4072; f) F. Hicks, Y. Hou, M. Langston, A. McCarron, E. O'Brien, T. Ito, C. Ma, C. Matthews, C. O'Bryan, D. Provencal, Y. Zhao, J. Huang, Q. Yang, L. Heyang, M. Johnson, Y. Sitang, L. Yuqiang, *Org. Process Res. Dev.* **2013**, *17*, 829 – 837; g) Y.-Q. Fu, L.-N. Ding, L.-G. Wang, J.-C. Tao, *Synth. Commun.* **2008**, *38*, 2672 – 2683; h) G. Sudhakar, S. Bayya, K. J. Reddy, B. Sridhar, K. Sharma, S. R. Bathula, *Eur. J. Org. Chem.* **2014**, 1253 – 1265; i) L. Mata, A. Avenoza, J. H. Busto, J. M. Peregrina, *Chem. Eur. J.* **2013**, *19*, 6831 – 6839.

[19] C. L. Lencina, A. Dassonville-Klimpt, P. Sonnet, *Tetrahedron: Asymmetry* **2008**, *19*, 1689 – 1697.

[20] J. Baek, J. I. Jang, Y. S. Park, *Bull. Korean Chem. Soc.* **2011**, *32*, 4067 – 4070.

[21] a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044 – 15045; b) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2005**, *44*, 6924 – 6927; *Angew. Chem.* **2005**, *117*, 7084 – 7087; c) M. Seto, J. L. Roizen, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2008**, *47*, 6873 – 6876; *Angew. Chem.* **2008**, *120*, 6979 – 6982; d) J. Streuff, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem.* **2010**, *2*, 192 – 196; e) D. C. Behenna, Y. Liu, T. Yurino, J. Kim, D. E. White, S. C. Virgil, B. M. Stoltz, *Nat. Chem.* **2012**, *4*, 130 – 133; f) C. M. Reeves, C. Eidamshaus, J. Kim, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2013**, *52*, 6718 – 6721; *Angew. Chem.* **2013**, *125*, 6850 – 6853.

[22] A. Dömling, Y. Huang, *Synthesis* **2010**, 2859 – 2883.

[23] We have found that stabilization of the intermediate enolate likely erodes the *ee* value by forming a solvent-separated ion pair leading to an outer-sphere, non-stereoselective reaction mechanism. See: a) N. H. Sherden, D. C. Behenna, S. C. Virgil, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2009**, *48*, 6840 – 6843; *Angew. Chem.* **2009**, *121*, 6972 – 6975; b) D. C. Behenna, J. T. Mohr, N. H. Sherden, S. C. Marinescu, A. M. Harned, K. Tani, M. Seto, S. Ma, Z. Novák, M. R. Krout, R. M. McFadden, J. L. Roizen, J. A. Enquist, Jr., D. E. White, S. R. Levine, K. V. Petrova, A. Iwashita, S. C. Virgil, B. M. Stoltz, *Chem. Eur. J.* **2011**, *17*, 14199 – 14223.

[24] D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893 – 930.

[25] a) A. Rivkin, S. P. Ahearn, S. M. Chichetti, Y. R. Kim, C. Li, A. Rosenau, S. D. Kattar, J. Jung, S. Shah, B. L. Hughes, J. L. Crispino, R. E. Middleton, A. A. Szewczak, B. Munoz, M. S. Shearman, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1269 – 1271; b) Y. Hirokawa, H. Kinoshita, T. Tanaka, T. Nakamura, K. Fujimoto, S. Kahimoto, T. Kojima, S. Kato, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 175 – 179; c) J. J. Crawford, P. W. Kenny, J. Bowyer, C. R. Cook, J. E. Finlayson, C. Heyes, A. J. Highton, J. A. Hudson, A. Jestel, S. Krapp, S. Martin, P. A. Macfaul, B. P. McDermott, T. M. McGuire, A. D. Morley, J. J. Morris, K. M. Page, L. R. Ribeiro, H. Sawney, S. Steinbacher, C. Smith, A. G. Dossetter, *J. Med. Chem.* **2012**, *55*, 8827 – 8837; d) J.-M. Jimenez, C. Davis, D. Boyall, D. Fraysse, R. Knegtel, L. Settimo, S. Young, C. Bolton, P. Chiu, A. Curnock, R. Rasmussen, A. Tanner, I. Ager, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4645 – 4649.

[26] E. Weisberg, P. W. Manley, S. W. Cowan-Jacob, A. Hochhaus, J. D. Griffin, *Nat. Rev. Cancer* **2007**, *7*, 345 – 358.

[27] B. Nagar, W. G. Bornmann, P. Pellicena, T. Schindler, D. R. Veach, W. T. Miller, B. Clarkson, J. Kuriyan, *Cancer Res.* **2002**, *62*, 4236 – 4243.

