JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Remote Control of Axial Chirality: Aminocatalytic Desymmetrization of *N*-Arylmaleimides via Vinylogous Michael Addition

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Supporting Information

ABSTRACT: Remote control of the axial chirality of *N*-(2-*t*-butylphenyl)succinimides was realized via the vinylogous Michael addition of 3-substituted cyclohexenones to *N*-(2-*t*-butylphenyl)maleimides. 9-Amino(9-deoxy)*epi*-quinine promoted the enantioselective desymmetrization, leading to atropisomeric succinimides with two adjacent stereocenters.

Organocatalysis is a powerful strategy that can exploit the catalytic ability of organic molecules in specific reaction pathways for the synthesis of enantioenriched compounds. Organocatalysts have become a versatile and powerful tool in chemists' hands, finding applications in many of the most important organic transformations.[1] Among these organic transformations, those organocatalysts that control the formation of remote stereocenters through the generation of a conjugated π-system, namely dienamine, trienamine, tetraenamine, and vinylogous iminium ion catalysts, have opened new frontiers in the area of amino and Brønsted base catalysis.[2] Recently, organocatalysis has been applied to the enantioselective synthesis of atropisomeric compounds.[3] Atropisomerism is a property of molecules with important biological activities or employed as ligands or catalysts.[4] However, organocatalytic syntheses in which the axial chirality of compounds is controlled are still rare. After the first example of the enantioselective synthesis of atropisomeric amides by dynamic resolution was reported by Clayden,[5] only a few papers have been published on this topic. Most of them focus on the preparation of enantioenriched biaryls,[6] tertiary amides,[7] anilides,[8] allenes,[9] and aminonaphthols[10] using various catalytic strategies.[11]

Herein, we report the remote control[12] of the axial chirality of atropisomeric succinimides[13] via an aminocatalytic vinylogous Michael addition[14]/desymmetrization[15] sequence of *N*-(2-*t*-butylphenyl)maleimides (Figure 1). The key feature of our methodology is the ability of a cinchona alkaloid primary amine catalyst[16] to transfer its stereochemical information to both a prochiral center several bonds away[2e−g,r,s] and a more distant prochiral axis by directing the addition of the dienamine to either carbon atom $\mathbf{C_A}$ or $\mathbf{C_B}$ from the side not shielded by the *t*-butyl group. Through this mechanism, the following two simultaneous stereochemical events are realized: the generation of two contiguous stereocenters and the remote control of an axial chirality far from the reaction site.

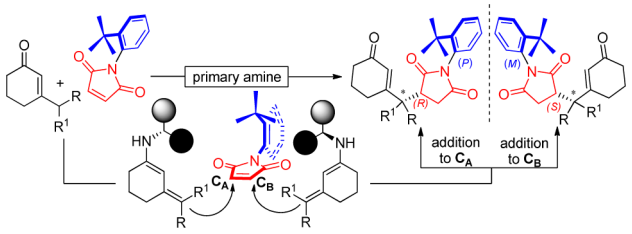


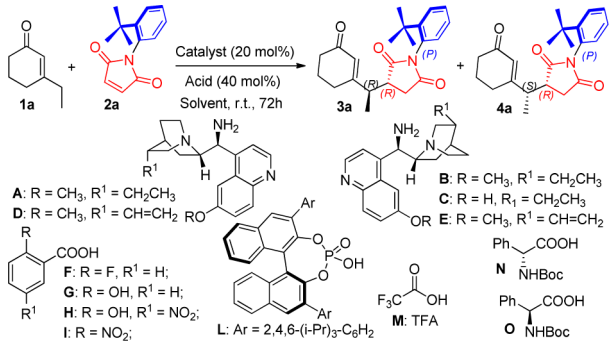
Figure 1. Remote control of axial chirality via the vinylogous Michael addition/desymmetrization of rotationally constrained *N*-(2-*t*-butylphenyl)maleimide.

We screened various primary amines and acidic cocatalysts in a model reaction between 3-ethylcyclohex-2-en-1-one **1a** and *N*-(2-*t*-butylphenyl)maleimide **2a** (Table 1). The first reaction was performed with 9-amino(9-deoxy)*epi*-hydroquinine **A** (20 mol %) and *o*-fluorobenzoic acid **H** (40 mol %) and afforded a 70:30 mixture of only two diastereoisomers,[17] **3a** (major) and **4a** (minor) in 43% yield and >99% enantiomeric excess (ee) for each diastereoisomer (entry 1). NOE NMR experiments on **3a** and **4a** confirmed that the dienamine approached **2a** from the side opposite the *t*-butyl group.[17] 9-Amino(9-deoxy)*epi*-hydroquinidine **B** allowed the opposite enantiomers to be obtained with high enantiocontrol but in lower yield (entry 2), and catalyst **C** (6′-hydroxy-9-amino(9-deoxy)*epi*-hydroquinidine) or counteranions with coordinating hydroxyl groups did not affect the yields and diastereomeric ratio (d.r.) (entries 3−6). Stronger acids suppressed the reaction (entries 7−8), and with 2 equiv of **1a**, the overall yield increased to 58% (entry 9). We then tested the effect of *N*-Boc-D-phenylglycine **N** and *N*-Boc-L-phenylglycine **O** as chiral cocatalysts with quinines **A** or **D** and quinidines **B** or **E** primary amines (entries 10−17).[18] With catalyst **A**, yields comparable to those with achiral acid **F** were obtained, although they showed lower d.r. (entries 10−11), whereas 9-amino(9-deoxy)*epi*-quinine **D** resulted in a reasonable increase in the yields (entries 12−13). Low reactivities were observed when 9-amino(9-deoxy)*epi*-quinidine **E** and **B** were used (entries 14−17). With 10 mol % of **D**, the reaction was too slow, and the role of the acidic species was crucial to obtain the desired product (entries 18−19).

Received: June 4, 2014
Published: July 9, 2014

   dx.doi.org/10.1021/ja505610k | *J. Am. Chem. Soc.* 2014, 136, 10250−10253

Table 1. Screening of the Reaction Conditions[a]

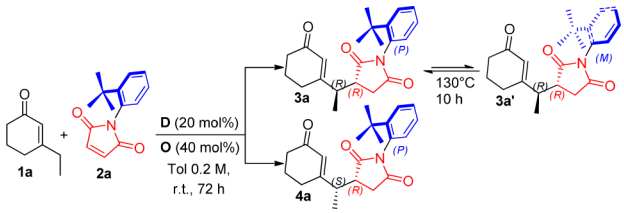


entry	catalyst	acid	yield (%)[b] 3a + 4a	d.r.[c] 3a:4a	ee (%)[d] 3a/4a
1	A	F	43	70:30	>99/>99
2	B	F	30	70:30	> −99/> −99
3	C	F	33	70:30	> −99/> −99
4	A	G	30	70:30	>99/>99
5	A	H	25	70:30	>99/>99
6	A	I	42	70:30	>99/>99
7	A	L	–	–	–
8	A	M	–	–	–
9[e]	A	F	58	67:33	>99/>99
10[e]	A	N	51	65:35	>99/>99
11[e]	A	O	60	65:35	>99/>99
12[e]	D	N	70	70:30	>99/>99
13[e]	D	O	75	70:30	>99/>99
14[e]	E	N	43	70:30	> −99/> −99
15[e]	E	O	35	70:30	> −99/> −99
16[e]	B	N	40	65:35	> −99/> −99
17[e]	B	O	33	65:35	> −99/> −99
18[e]	D	O	40	65:35	>99/>99
19[e]	D	–	<10	42:58	n.d.

[a]Reactions performed with **1a** (0.2 mmol) and **2a** (0.2 mmol) in 1 mL of toluene. [b]Sum of diastereoisomers. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by chiral HPLC analysis. [e]Performed using 2 equiv of **1a**.

To evaluate the thermal stability with respect to epimerization of the chiral axis, **3a** was heated to 130 °C in $C_2D_2C_4$. After 10 h, an equilibrium ratio of 62:38 with a new diastereoisomer **3a′** was observed (Scheme 1). NMR analysis and a NOE experiment

Scheme 1. Thermal Stability of the Chiral Axis of 3a

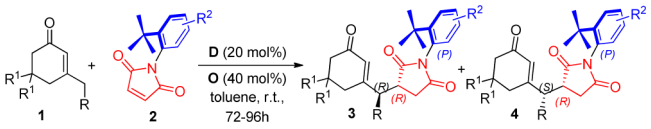


confirmed that **3a′** was not equivalent to **4a** and that it was generated by rotation of the C−N bond. The energy barrier to rotation was found to be $\Delta G^{\neq}_{epi}$ = 31.9 kcal mol^{-1}, corresponding to a $t^{25}_{1/2}$ = 1000 years.[13,17]

The substrate scope was investigated using several enones **1** and maleimides **2** (Table 2). Remarkable yields and ee values were obtained when **1a** was reacted with various maleimides.

The reaction proceeded smoothly when halogen, phenyl or methoxy substituents were present (entries 2−5). A protected

Table 2. Substrate Scope[a]



entry	R/R^1/R^2	yield (%)[b]	d.r.[c]	ee (%)[d]
1	Me/H/H	**3a** + **4a**, 75	70:30	>99/>99
2	Me/H/4-Br	**3b** + **4b**, 80	70:30	97/>99
3	Me/H/4-Cl	**3c** + **4c**, 70	72:28	>99/>99
4	Me/H/4-Ph	**3d** + **4d**, 75	70:30	96/95
5	Me/H/4-OMe	**3e** + **4e**, 80	70:30	94[e]/n.d.
6	Me/H/5-NHCbz	**3f** + **4f**, 80	75:25	98/97
7	Me/H/5-NHTs	**3g** + **4g**, 45	71:29	95[e]/n.d.
8	Me/H/5-^{t}Bu	–	–	–
9	Me/Me/H	3h + 4h, 60	70:30	96/95
10	Me/Me/4-Cl	**3i** + **4i**, 60	65:35	95/95
11[f]	Bn/H/H	**3j** + **4j**, 50	70:30	99/97
12[f]	*n*-Pr/H/H	**3k** + **4k**, 37	64:36	97/94
13[f]	Allyl/H/H	**3l** + **4l**, 36	70:30	96/96
14	*n*-Pr/H/4-Br	**3m** + **4m**, 76	70:30	99/98
15	Allyl/H/5-NHCbz	**3n** + **4n**, 63	70:30	97/97

[a]Reactions performed with **1** (0.4 mmol) and **2** (0.2 mmol) in 1 mL of toluene. [b]Sum of diastereoisomers. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by chiral HPLC analysis. [e]Determined by ^{1}H NMR using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. [f]Reaction time of 96 h.

amino group was well tolerated, and succinimides **3f,g** and **4f,g** were obtained in good yields with excellent ee values (entries 6−7). The presence of a second *t*-butyl group at position 5 of the maleimide aromatic ring resulted in only traces of products (entry 8). Maleimides with an ortho- iodo-, triethylsilyl- or phenyl groups give products whose chiral axis quickly epimerizes at 25 °C.[17] A cyclohexenone with two methyls at position 5 afforded the corresponding succinimides in high yields and enantioselectivities (entries 9−10). Enones with different substituents on the double bond[19] gave the desired products but with substantial loss of conversion, (entries 11−13) whereas with more reactive 4-Br- and 5-NHCbz-substituted maleimides, the reactivity remained reasonable (entries 14−15). The *P,R,R* absolute configuration was assigned to **3b** by X-ray diffraction,[20] and the same absolute configuration was assigned to **3a** by comparison of the ECD spectra.[17] Then we decided to check whether epimerization might be the reason for the low d.r. The catalytic salt was added to separate solutions of pure **3a** and pure **4a**, and after 24 h, we found the same 70:30 ratio of **3a** and **4a** in both mixtures (Scheme 2). Epimerization was occurring at the exocyclic stereocenter, thus allowing the assignment of the *P,R,S* absolute configuration to **4a**.[17]

We then further examined the scope by reacting different γ-disubstituted cyclohexenones (Table 3). Good yields and high ee values were obtained with isopropyl- and cyclopentyl-substituted enones (entries 1−6). Interestingly enones having two different substituents gave mixtures of diastereoisomers **6g−j** (major) and **7g−j** (minor), which had a quaternary stereocenter,[21] with increased enantioselectivity but in lower yields (entries 7−9). No epimerization from a retro-vinylogous side reaction was observed when disubstituted cyclohexenones were employed.[17]

These results emphasize the efficient control exerted by the catalytic system in the desymmetrization of maleimides. The absolute configuration of compound **6h** was determined to be *P,R,S*.[17] A transition state for the formation of **6h** can be

dx.doi.org/10.1021/ja505610k | J. Am. Chem. Soc. 2014, 136, 10250−10253

Scheme 2. Exocyclic Chiral Center Epimerization

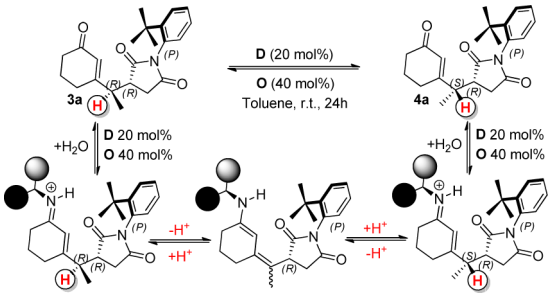
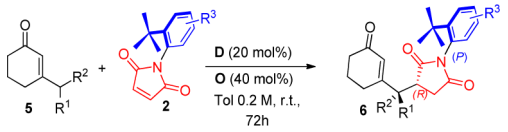


Table 3. Extension of the Substrate Scope[a]



entry	$R^1/R^2/R^3$	yield (%)[b]	d.r.[c]	ee (%)[d]
1	Me/Me/H	**6a**, 83	–	96
2	Me/Me/4-Cl	**6b**, 75	–	99
3	Me/Me/4-Ph	**6c**, 68	–	97
4	Me/Me/4-OMe	**6d**, 74	–	98
5	Me/Me/5-NHCbz	**6e**, 81	–	97
6	-(CH2)4-/H	**6f**, 80	–	97
7	Me/Et/H	**6g** + **7g**, 30	75:25	97/95
8	Me/Et/4-Br	**6h** + **7h**, 35	73:27	98/96
9	Me/Bn/H	**6j** + **7j**, 51	83:17	>99/n.d.

[a]Reactions performed with **5** (0.4 mmol) and **2** (0.2 mmol) in 1 mL of toluene. [b]Isolated yield after chromatography. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by chiral HPLC analysis.

proposed (Figure 2). The *Re* face of the γ-carbon of **5h** approaches the "bottom" face of the C_A carbon of **2b**, which is activated and held in place by a hydrogen bond from the protonated quinuclidine moiety to one of the carbonyl groups.

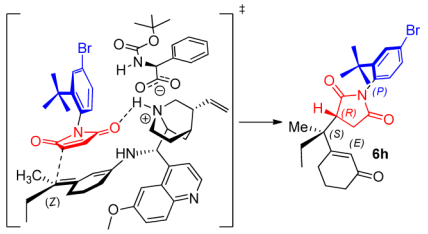


Figure 2. Proposed transition state for the formation of **6h**.

In conclusion, we developed a method for the atroposelective synthesis of succinimides using a new vinylogous Michael addition of enones to maleimides. Primary amine catalysis was fundamental for the enantioselective desymmetrization to occur with simultaneous and exclusive remote control of the chiral axis and the newly formed stereocenters. Further experiments and calculations are in progress to elucidate the reaction mechanism and the observed stereochemistry.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures; mechanistic considerations; NMR, HPLC and ECD data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The University of Bologna is gratefully acknowledged. This work is dedicated to Prof. Giuseppe Bartoli. The authors are grateful to Dr. Luca Bernardi for fruitful discussions.

■ REFERENCES

(1) (a) Mahalau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518. (b) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (f) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (g) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (h) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 659. (i) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659. (j) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6216. (k) Muller, C.; Bauer, A.; Bach, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 6640. (l) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (m) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Haston, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (n) List, B.; Čorić, I.; Grygorenko, O. O.; Kaib, P. S. J.; Komarov, I.; Lee, A.; Leutzsch, M.; Pan, S. C.; Tymtsunik, A. V.; van Gemmeren, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 282. (o) Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750.

(2) (a) Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1. For dienamine catalysis: (b) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. (c) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878. (d) Curti, C.; Rassu, G.; Zambrano, V.; Pinna, L.; Pelosi, G.; Sartori, A.; Battistini, L.; Zanardi, F.; Casiraghi, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 6200. (e) Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20642. (f) Bastida, D.; Liu, Y.; Tian, X.; Escudero-Adán, E.; Melchiorre, P. *Org. Lett.* **2013**, *15*, 220. (g) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685. (h) Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543. (i) Zhu, B.; Zhang, W.; Lee, R.; Han, Z.; Yang, W.; Tan, D.; Huang, K.-W.; Jiang, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 6666. (j) Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y.-L. *J. Am. Chem. Soc.* **2009**, *131*, 14626. (k) Yin, X.; Zheng, Y.; Feng, X.; Jiang, K.; Wei, X.-Z.; Gao, N.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2014**, *53*, 6245. For trienamine catalysis: (l) Halskov, K. S.; Johansen, T. K.; Davis, R. L.; Steurer, M.; Jensen, F.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 12943. (m) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053. (n) Xiong, X.-F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2012**, *51*, 4401. (o) Zhou, Z.; Feng, X.; Yin, X.; Chen, Y.-C. *Org. Lett.* **2014**, *16*, 2370. For vinylogous iminium ion catalysis: (p) Silvi, M.; Chatterjee, I.; Liu, Y.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 10780. (q) Dell'Amico, L.; Albrecht, Ł.; Naicker, T.; Poulsen, P. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 8063. (r) Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 6439. (s) Tian, X.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 5360. (t) Tian, X.; Hofmann, N.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2997. For tetraenamine catalysis: (u) Stiller, J.; Poulsen, P. H.; Cruz Cruz, D.; Dourado, J.; Davis, R. L.; Jørgensen, K. A. *Chem. Sci.* **2014**, *5*, 2052.

(3) (a) Christie, G. H.; Kenner, J. H. *J. Chem. Soc.* **1922**, *121*, 614. (b) Tetrahedron Symposium: Atropisomerism; Clayden, J., Ed. *Tetrahedron* **2004**, *60*, 4325. (c) Cozzi, P. G.; Emer, E.; Gualandi, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 3847.

(4) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, *6*, 503. (c) Clayden, J.; Fletcher, S. P.; McDouall, J. J. W.; Rowbottom, S. J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5331. (d) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem. Int. Ed* **2009**, *48*, 6398. (e) LaPlante, S. R.; Edwards, P. J.; Fader, L. D.; Jakalian, A.; Hucke, O. *ChemMedChem.* **2011**, *6*, 505. (f) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed* **2005**, *44*, 5384. (g) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563. (h) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193. (i) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539. (j) Nicolaou, K. C.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888. (k) Clayden, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 949. (l) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033.

(5) (a) Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 2556. (b) Clayden, J.; Lai, L. W. *Tetrahedron Lett.* **2001**, *42*, 3163. For metal catalyzed examples: (c) Terauchi, J.; Curran, D. P. *Tetrahedron: Asymmetry* **2003**, *14*, 587. (d) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676. (e) Kitagawa, O.; Kohriyama, M.; Taguchi, T. *J. Org. Chem.* **2002**, *67*, 8682. (f) Suda, T.; Noguchi, K.; Hirano, M.; Tanaka, K. *Chem.—Eur. J.* **2008**, *14*, 6593. (g) Ototake, N.; Morimoto, Y.; Mokuya, A.; Fukaya, H.; Shida, Y.; Kitagawa, O. *Chem.—Eur. J.* **2010**, *16*, 6752. (h) Koidea, H.; Uemura, M. *Chem. Commun.* **1998**, 2483. (i) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923.

(6) (a) Gustafson, J. L.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251. (b) Li, G.-Q.; Gao, H.; Keene, C.; Devonas, M.; Ess, D. H.; Kurti, L. *J. Am. Chem. Soc.* **2013**, *135*, 7414. (c) De, C. K.; Pesciaioli, F.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 9293. (d) Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3964. (e) Link, A.; Sparr, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5458.

(7) (a) Rios, R.; Jimeno, C.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10272. (b) Barrett, K. T.; Miller, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 2963. (c) Chan, V.; Kim, J. G.; Jimeno, C.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2004**, *6*, 2051.

(8) Shirakawa, S.; Liu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 916.

(9) (a) Hashimoto, T.; Sakata, K.; Tamakuni, F.; Dutton, M. J.; Maruoka, K. *Nat. Chem.* **2013**, *5*, 240. (b) Liiu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212. (c) Liu, H.; Feng, W.; Kee, C.-W.; Leow, D.; Loh, W.-T.; Tan, C.-H. *Adv. Synth. Catal.* **2010**, *352*, 3373.

(10) (a) Brandes, S.; Bella, M.; Kjœrsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1147.

(11) (a) Gramigna, L.; Duce, S.; Filippini, G.; Fochi, M.; Comes Franchini, M.; Bernardi, L. *Synlett* **2011**, *18*, 2745. (b) Barret, K. T.; Metrano, A. J.; Rablen, P. R.; Miller, S. J. *Nature* **2014**, *509*, 71.

(12) (a) Clayden, J.; Lund, A.; Vallverdú, L.; Helliwell, M. *Nature* **2004**, *431*, 966. (b) Clayden, J. *Chem. Soc. Rev.* **2009**, *38*, 817. (c) Jiang, H.; Albrecht, Ł.; K. A. Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287. (d) Brown, R. A.; Diemer, V.; Webb, S. J.; Clayden, J. *Nat. Chem.* **2013**, *5*, 853. (e) Li, J.-L.; Yue, C.-Z.; Chen, P.-Q.; Xiao, Y.-C.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2014**, *53*, 5449.

(13) (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131. (b) Duan, W.-L.; Imazaki, Y.; Shintani, R.; Hayashi, T. *Tetrahedron* **2007**, 8529. (c) Bennet, D. J.; Pickering, P. L.; Simpkins, N. S. *Chem. Commun.* **2004**, 1392. (d) Li, S.; Leow, D.; Huang, K.-W.; Tan, C.-H. *Chem. Asian. J.* **2009**, *4*, 1741.

(14) For reviews on the use of maleimides as Michael acceptors see: (a) Chauhan, P.; Kaur, J.; Chimni, S. S. *Chem.—Asian J.* **2013**, *8*, 328. For examples see: (b) Zhao, G.-L.; Xu, Y.; Sundén, H.; Eriksson, L.; Sayah, M.; Córdova, A. *Chem. Commun.* **2007**, 734. (c) Xue, F.; Liu, L.; Zhang, S.; Duan, W.; Wang, W. *Chem.—Eur. J.* **2010**, *16*, 7979. (d) Yu, F.; Sun, X.; Jin, Z.; Wen, S.; Liang, X.; Ye, J. *Chem. Commun.* **2010**, 4589. (e) Wang, J.; Zhang, M.-M.; Zhang, S.; Xu, Z.-A.; Li, H.; Yu, X.-H.; Wang, W. *Synlett* **2011**, 473. For vinylogous examples see: (f) Manna, M. S.; Mukherjee, S. *Chem.—Eur. J.* **2012**, *18*, 15277. (g) Guo, Y.-L.; Jia, L.-N.; Peng, L.; Qi, L.-W.; Zhou, J.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *RSC Adv.* **2013**, *3*, 16973. (h) Lu, J.; Zhou, W.-J.; Liu, F.; Loh, T.-P. *Adv. Synth. Catal.* **2008**, *350*, 1796.

(15) For desymmetrization of five-membered ring compounds see: K. Aikawa, T.; Okamoto, K.; Mikami. *J. Am. Chem. Soc.* **2012**, *134*, 10329 and references therein.

(16) (a) Cassani, C.; Rapún, R. M.; Arceo, E.; Bravo, F.; Melchiorre, P. *Nat. Protoc.* **2013**, *8*, 325. (b) Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748.

(17) See Supporting Information for details.

(18) (a) Carlone, A.; Bartoli, G.; Bosco, M.; Pesciaioli, F.; Ricci, P.; Sambri, L.; Melchiorre, P. *Eur. J. Org. Chem.* **2007**, 33, 5492. (b) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49. (c) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (d) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6216.

(19) With 3-methyl-2-cyclohexen-1-one, 3-ethyl-2-cyclopenten-1-one, and non-3-en-2-one no reaction was observed.

(20) CCDC 977351 for **3b**, see Supporting Information for details.

(21) Bella, M.; Gasperi, T. *Synthesis* **2009**, *10*, 1583.