Organic LETTERS

Letter

pubs.acs.org/OrgLett

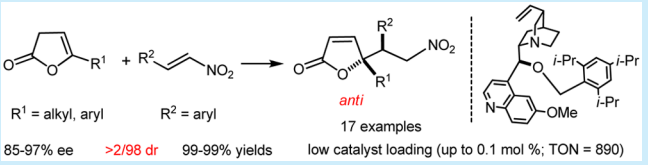
Anti-Selective Asymmetric Nitro-Michael Reaction of Furanones: Diastereocontrol by Catalyst

Tohru Sekikawa,* Takayuki Kitaguchi, Hayato Kitaura, Tatsuya Minami, and Yasuo Hatanaka*

Department of Applied Chemistry, Graduate School of Engineering, Osaka City University, Sumiyoshi, Osaka 558-8585, Japan

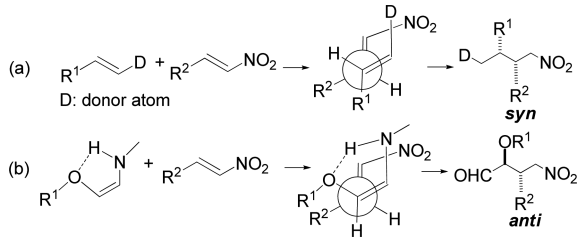
Supporting Information

ABSTRACT: Catalyst-controlled switching of diastereoselectivity from high *syn*-selectivity (>98/2 dr, *syn*) to *anti*-selectivity (up to 96/4 dr, *anti*) of the asymmetric nitro-Michael reaction of furanones is described. *Anti*-diastereoselectivity of the nitro-Michael reaction is very rare. With 0.1−5 mol % loadings of an *epi*-quinine catalyst, the reaction of 5-substituted 2(3*H*)-furanones with nitroalkenes smoothly proceeded to give the *anti*-Michael adducts in good yields (up to 95%) with excellent diastereo- and enantioselectivities (up to 96/4 dr, *anti*; up to 99% ee). DFT calculations support a model that accounts the high *anti*-diastereoselectivity.



Among the large variety of asymmetric Michael reactions developed so far, nitroalkenes have been one of the most widely used Michael acceptors because of the synthetic importance of chiral nitroalkanes, which undergo facile β-alkylation reactions and interconversions to important organic functional groups.[1] Although a large number of nitro-Michael reactions catalyzed by enamine catalysts and bifunctional hydrogen-bonding catalysts have been reported, these reactions exclusively exhibit *syn*-selectivity.[2] The predominant *syn*-selectivity of the nitro-Michael reaction is explained by the transition-state model proposed by Seebach, in which donor atoms and acceptor atoms are situated close to each other (Scheme 1a).[3] The first example of an *anti*-selective nitro-

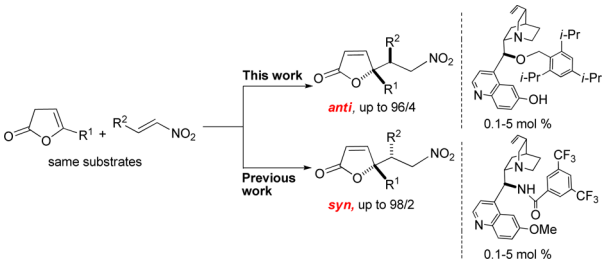
Scheme 1. Nitro-Michael Reaction via Seebach's Transition-State Model



Michael reaction of aldehydes promoted by an enamine catalyst was reported by Barbas and co-workers.[4] They achieved high *anti*-selectivity in the nitro-Michael reaction by introducing an alkoxy group at the β-carbon of aldehydes. The reaction of β-alkoxyaldehydes with enamine catalysts predominantly leads to (*Z*)-enamines that are stabilized by intramolecular H-bonding, which then give the *anti*-Michael adduct via Seebach's transition-state model (Scheme 1b). Their strategy is a substrate-controlled diastereoselectivity, which is a typical synthetic protocol.[5]

We report a catalyst-controlled switching from normal *syn*-selectivity of the asymmetric nitro-Michael reaction of furanones to *anti*-selectivity (Scheme 2). Catalyst control of the diastereoselectivity of an organic reaction is more practical and

Scheme 2. Catalyst-Controlled Switching of Diastereoselectivity



expedient than substrate control because the need to modify the substrate to achieve high diastereoselectivity severely limits the substrate scope. To the best of our knowledge, a successful organocatalyst-controlled diastereoselectivity of the nitro-Michael reaction is very rare.[1] Moreover, catalyst-controlled switching from high *syn*-selectivity (>90 dr) to high *anti*-selectivity (>90 dr) of an asymmetric reaction using the same substrates seems to be seldom.[4d]

Recently, we reported the asymmetric nitro-Michael reaction of 2(3*H*)-furanones to give chiral β-butenolides catalyzed by *epi*-quinine-derived 3,5-bis(CF_3)benzamide, which exclusively exhibits high *syn*-selectivity (>98/2 dr) and excellent enantioselectivity (>90% ee) (Scheme 2).[6] The extremely high *syn*-selectivity of this reaction affords a perfect opportunity to investigate the catalyst-controlled switching of the diastereoselectivity.

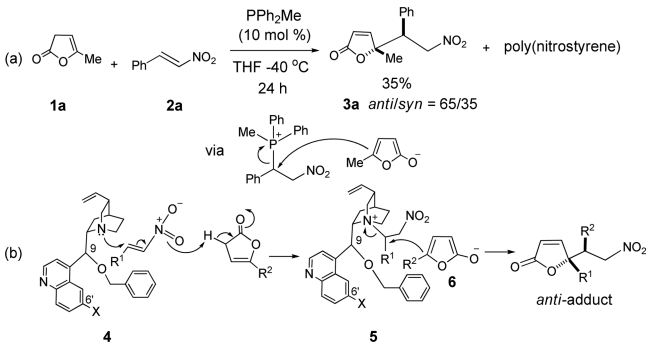
We have found that a 10 mol % loading of PPh_2Me catalyzes the nitro-Michael reaction of angelica lactone **1a** with nitro-

Received: December 14, 2015

DOI: 10.1021/acs.orglett.5b03539
Org. Lett. XXXX, XXX, XXX−XXX

styrene **2a** in THF at −40 °C, giving the corresponding adduct **3a** (Scheme 3a). The reaction mechanism likely involves conjugate

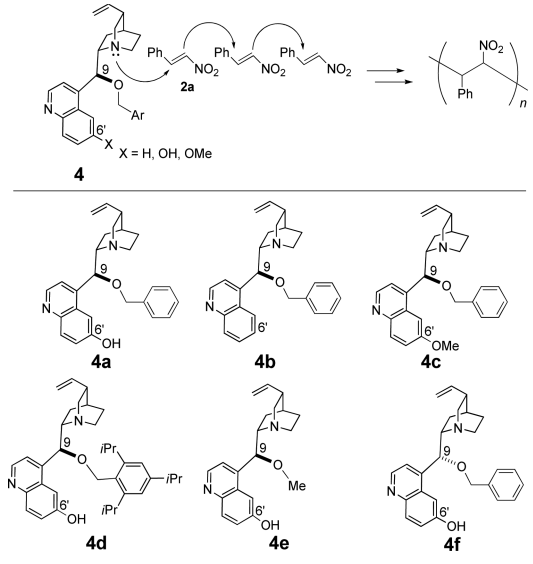
Scheme 3. *Anti*-Selective Nitro-Michael Reaction



addition of PPh_2Me to **2a**.[7] The crucial aspect of the reaction is the moderate *anti*-selectivity (*anti*/*syn* = 65/35). Based on this result, we have made an assumption that the quinuclidine nitrogen of quinine catalysts **4** would undergo conjugate addition to nitroalkenes, giving nitroammonium intermediate **5** (Scheme 3b).[8] Analogously to the PPh_2Me-catalyzed nitro-Michael reaction, the nucleophilic substitution of **5** with dienolate **6** is expected to afford an *anti*-adduct.

With the purpose of evaluating the nucleophilicity of the quinuclidine nitrogen, we carried out the polymerization of (*E*)-*β*-nitrostyrene **2a** promoted by *epi*-quinines at 10 mol % loadings of *epi*-quinines in THF at the room temperature (Scheme 4).

Scheme 4. Quinine Derivative-Promoted Polymerization of Nitrostyrene



4a, **4d**, and **4e** promote the polymerization of nitrostyrene **2a**

The reaction furnished poly(nitrostyrene) as an insoluble material, whose structure was determined by elemental analysis. We observed that bifunctional *epi*-quinine-derived catalysts **4a**, **4d**, and **4e** are capable of promoting the polymerization of **2a** to give a polymer in quantitative yield. The rate of polymerization strongly depends on the structures of the catalysts. The *epi*-quinine-derived **4d** bearing a 6′-OH and sterically demanding 9-OCH_2[2,4,6-(*i*-Pr)$_3C_6H_2$] substituent exhibited a reaction rate for the polymerization of **2a** lower than that for **4a** and **4e**, which completed the polymerization within 10 min. In contrast, the replacement of 6′-OH of **4a** with 6′-H (**4b**) and the replacement of 6′-OH of **4a** with 6′-OMe (**4c**)[9a] profoundly depresses the activity of *epi*-quinine-derived catalysts for the polymerization reaction. Quinine-derived **4f**[9b] bearing 6′-OH (diastereomer of **4a**) failed to promote the polymerization. These results conclusively reveal that the 6′-OH of *epi*-quinine derivatives is essential for the nucleophilic activation of **2a**. The ^{13}C NMR spectra of the mixture of **4a** and **2a** (**4a**/**2a** = 1:2, C_6D_6) indicated that δ (^{13}C) of the *β*-carbon of **2a** did not shift upon the addition of **4a**, revealing a very weak interaction between the quinuclidine N and **2a**. To reveal the role of the 6′-OH group of *epi*-quinine-derived catalysts **4a**, **4d**, and **4e**, we carried out theoretical calculations (Figure 1). Simplified structures of the Michael

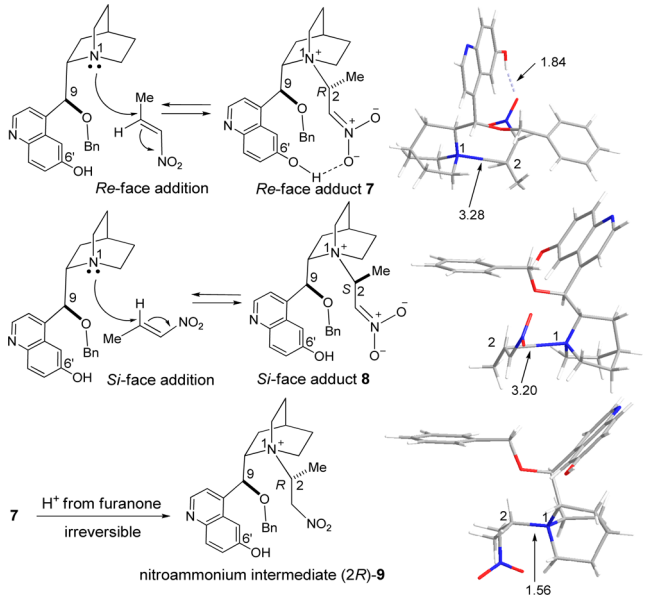


Figure 1. Simplified models of *re*-face and *si*-face adducts optimized at B3LYP/6-31G(d). Atomic distances in angstroms.

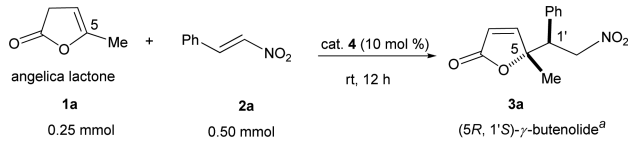
adducts formed by the conjugate addition of quinuclidine N(1) to the *re*- and *si*-face of nitroalkene were optimized at B3LYP/6-31G(d). The results of the calculations are surprising. The structure of the optimized *re*-face adduct **7** discloses a very weak interaction between quinuclidine N(1) and nitroalkene, as indicated by the very long N(1)−C(2) bond length (3.28 Å), and an intramolecular H-bonding between 6′-OH and nitronate oxygen effectively stabilized **7**. The long N(1)−C(2) bond length can be ascribed to the strong electrostatic repulsion between the nitronate moiety and N(1), which bears a considerable negative charge (−0.3868; Mulliken). The formal positive charge on N(1) can be neutralized by electron release from five neighboring hydrogen atoms in the geminal positions relative to N(1).[10] In contrast, the *si*-face adduct **8** cannot engage in intramolecular H-bonding between 6′-OH and the nitronate oxygen. Consequently, **8** dissociates into the catalyst and the nitroalkene due to the electrostatic repulsion between the negatively charged N(1) and the nitronate moiety. The N(1)−C(2) bond length of **8** (3.20 Å) is roughly comparable to the sum of van der Waals radii of N and C (3.25 Å).[11] Electrostatic repulsion between N(1) and C(2) of **7** is reduced when **7** is protonated by furanone (Figure 1). The resulting nitroammonium intermediate (2*R*)-**9** is considered to be thermodynamically stable; the N(1)−C(2) bond length of 1.56 Å is normal

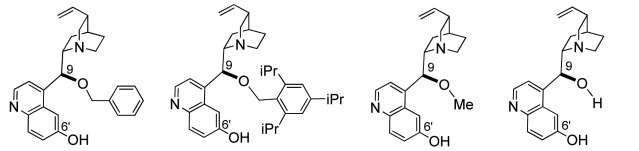
DOI: 10.1021/acs.orglett.5b03539
Org. Lett. XXXX, XXX, XXX−XXX

as a N−C covalent bond.[12] DFT calculations strongly suggested that the conjugate addition of quinuclidine N(1) to the nitroalkene would occur predominantly at the *re*-face of the nitroalkene, affording the nitroammonium intermediate (2*R*)-**9**.

As expected from the *anti*-selectivity of the PPh_2Me-catalyzed nitro-Michael reaction, *epi*-quinine derivatives are capable of catayzing the conjugate addition of **1a** to **2a** with *anti*-selectivity (Table 1). For example, with 10 mol % loading of **4a**, the Michael

Table 1. Catalytic Nitro-Michael Addition of 1a to 2a





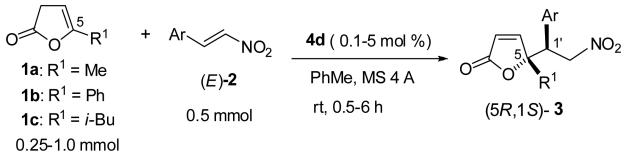
entry[b]	catalyst	solvent	yield (%)[c]	*anti*/*syn*[d]	ee [%] (*anti*)[e]
1	**4a**	THF	35	93/7	93
2	**4g**	THF	51	69/31	87
3	**4h**	THF	56	70/30	71
4	**4d**	THF	66	78/22	86
5	**4d**	Et_2O	69	88/12	94
6	**4d**	CH_2Cl_2	74	81/19	94
7	**4d**	*i*-PrOH	58	79/21	38
8	**4d**	MePh	75	88/12	96
9[f]	**4d**	MePh	69	94/6	97

[a]Absolute configuration was assigned by analogy with compound **3ah** (Table 2, entry 7). [b]Reaction of 0.25 mmol of furanones **1** and 0.5 mmol of nitrostyrene **2** with 10 mol % loading of catalyst **4** at room temperature unless otherwise noted. [c]Isolated yield. [d]Diastereomer ratio was determined by ^{1}H NMR analysis of crude product. [e]Obtained by chiral HPLC analysis. [f]Reaction was conducted in the presence of 4 Å MS (50 mg) with 5 mol % loading of **4d**.

adduct **3a** was obtained with high diastereo- and enantioselectivity (93/7 = *anti*/*syn*, 93% ee), although the yield was very low (35%) (entry 1). Catalysts **4g** and **4h** showed no improvement in the diastereoselectivity (entries 2 and 3). Although the diastereo- and enantioselectivity dropped considerably (78/22 dr, *anti* major; 86% ee), **4d** effectively suppressed the polymerization of **2a**, increasing the yield of **3a** (66%) (entry 4). This is apparently due to the inhibition of the polymerization by the sterically demanding 9-OCH_2[2,4,6-(*i*-Pr)$_3$$C_6H_2$] substituent. The screening of solvents showed toluene to be the solvent of choice (entries 4−8). To our delight, addition of 4 Å MS into the reaction mixture considerably improved the diastereoselectivity without affecting the high enantioselectivity (96/4 dr, *anti* major; 97% ee) (entry 9). Furthermore, catalyst loading as low as 5 mol % can be achieved.

We then turned our attention to the substrate scope of the *anti*-selective nitro-Michael reaction promoted by novel catalyst **4d**. Table 2 shows that 0.1−5 mol % loadings of **4d** allowed complete conversion of the substrates in toluene at room temperature, giving the corresponding *anti*-Michael adducts in good yields (60−95%) with a high level of diastereo- and enantioselectivities (8/12 to 97/3 dr; 84−99% ee).[13] *β*-Arylnitroalkenes **2** bearing electron-withdrawing and electron-

Table 2. Nitro-Michael Addition Catalyzed by 4d[a,b]



entry	furanone	Ar	product	yield (%)[c]	*anti*/*syn*[d]	ee (%)[e]
1	**1a**	**2b**: 4-ClPh	**3ab**	74	94/6	97
2	**1a**	**2c**: 3-ClPh	**3ac**	82	90/10	96
3	**1a**	**2d**: 2-ClPh	**3ad**	82	96/4	98
4	**1a**	**2e**: 4-MeOPh	**3ae**	78	96/4	94
5	**1a**	**2f**: 4-MePh	**3af**	84	97/3	98
6	**1a**	**2g**: 1-naph	**3ag**	68	95/5	98
7	**1a**	**2h**: 2-naph	**3ah**[f]	62	97/3	97
8	**1a**	**2i**: 2-furyl	**3ai**	63	94/6	99
9	**1b**	**2b**: 4-ClPh	**3bb**	95	90/10	94
10	**1b**	**2f**: 4-MePh	**3bf**	74	92/8	99
11	**1b**	**2i**: 2-furyl	**3bi**	60	95/5	84
12	**1b**	**2k**: 4-MeO_2CPh	**3bk**	82	90/10	88
13	**1c**	**2a**: Ph	**3ca**	70	92/8	94
14	**1c**	**2h**: 2-naph	**3ch**	60	90/10	98
15	**1c**	**2l**: 2-thienyl	**3cl**	60	88/12	99
16[g]	**1a**	**2d**: 2-ClPh	**3ad**	89	96/4	97

[a]Absolute configuration was assigned by analogy with compound **3ah** (entry 7). [b]Reaction was conducted in the presence of 4 Å MS (50 mg) with 5 mol % loading of **4d** at room temperature unless otherwise noted. [c]Isolated yield. [d]Diastereomer ratio was determined by ^{1}H NMR analysis. [e]Obtained by chiral HPLC analysis. [f]Absolute configuration of **3ah** was determined by X-ray crystallographic analysis. [g]Large-scale reaction of **2d** (7 mmol) with **1a** (10.5 mmol) was conducted with 0.1 mol % loading of **4d** in the presence of 4 Å MS.

releasing substituents on the aromatic ring smoothly reacted with 5-substituted furanones **1**, affording **3** in good yields (78−82%) with high diastereo- and enantioselectivities (90/10 to 96/4 dr; 88−94% ee) (entries 4 and 12). Thus, the electronic properties of substituents on the aromatic rings of **2** have no effect on the reaction. Furthermore, the substitution pattern on the aromatic rings (entries 1−3) and the sterically demanding aromatic ring of *β*-(*E*)-arylnitroalkenes **2g** and **2h** also had no deleterious effect on the diastereo- and enantioselectivity (entries 6 and 7). Michael additions of sterically demanding 5-*iso*-butylfuranone **1c** to *β*-arylnitroalkenes **2a**, **2h**, and **2l** proceeded smoothly, giving *anti*-adducts **3ca** (94% ee), **3ch** (98% ee), and **3cl** (99% ee) in moderate to high yields (entries 13−15). To evaluate the potential of catalyst **4d**, the nitro-Michael addition of more sterically demanding 5-phenylfuranone **1b** (A-value of Ph = 3.0 kcal mol^{-1}; cf. Me = 1.70 kcal mol^{-1})[14] to *β*-arylnitroalkenes **2** was carried out, affording the *anti*-adducts with high diastereo- and enantioselectivities (>90/10 dr; 84−99% ee) (entries 9−12). Thus, the present method is especially useful for constracting the sterically congested oxygen-containing quaternary stereogenic centers adjacent to ternary stereogenic centers.[15] When the large-scale reaction of **1a** (10.5 mmol) and **2d** (7 mmol) was conducted at room temperature, we found that the catalyst loading could be reduced to only 0.1 mol % without affecting the high diastereo- and enantioselectivity as well as the high yield of the Michael adduct **3ad** (96/4 dr, *anti* major, 97% ee, 89% yield, TON = 890) (entry 16).[16]

DOI: 10.1021/acs.orglett.5b03539
Org. Lett. XXXX, XXX, XXX−XXX

The configuration of products **3** was determined to be (5*R*,1′*S*),[17] indicating that the nucleophilic attack of dienolates **6** to intermediate (2*R*)-**9** takes place from the *si*-face of **6**. Figure 2

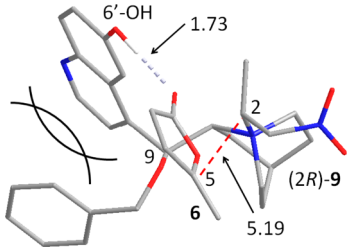


Figure 2. Simplified pre-transition-state assembly model optimized at B3LYP/6-31++G(d,p). Hydrogen atoms are omitted for clarity. Atomic distances in angstroms.

displays the simplified pre-transition-state assembly model optimized at B3LYP/6-31++G(d,p) level, which accounts for the stereochemistry of the nucleophilic attack of **6**. To avoid the steric repulsion between the substituent at the 2-position of the intermediate (2*R*)-**9** and the 5-substituent of the dienolate **6** bound to 6′-OH via H-bonding, dienolate **6** exposes the *si*-face to (2*R*)-**9**. Repulsive interaction between the sterically demanding 9-OCH_2Ar substituent and quinoline moiety directs the quinoline moiety to form a hydrogen bond between 6′-OH and **6**. The calculation adequately predicts the sense of the asymmetric induction.

In conclusion, we have developed a highly *anti*-selective nitro-Michael reaction of furanones by a catalyst-controlled switching of diastereoselectivity. Preliminary DFT calculations suggest that the *anti*-selective nitro-Michael addition of aldehydes is promising under similar conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03539.

X-ray data for (5*R*,1*S*)-naphthyl (CIF)
Experimental procedure and compound characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: sekikawa.tolu@gmail.com.
*E-mail: hatanaka@a-chem.eng.osaka-cu.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has been supported by a Grant-in-Aid for Scientific Research (C) (20550101) from JSPS.

■ REFERENCES

(1) For selected recent review of organocatalytic asymmetric nitro-Michael reactions and the application to organic synthesis, see: (a) Somanathan, R.; Chávez, D.; Servin, F. A.; Romero, J. A.; Navarrete, A.; Parra-Hake, M.; Aguirre, G.; de Parrod, C. A.; González, J. S. *Curr. Org. Chem.* **2012**, *16*, 2440. (b) Chauhan, P.; Chimni, S. S. *RSC Adv.* **2012**, *2*, 737. (c) Raimondi, W.; Bonne, D.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 40. (d) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051. (e) Xi, Y.; Shi, X. *Chem. Commun.* **2013**, *49*, 8583. (f) Roux, C.; Bressy, C. In *Comprehensive Enantioselective Organocatalysis*; Dalco, P., Ed.; Wiley-VCH: Weinheim, Germany, 2013; Vol. 3, pp 1013−1042. (g) Rios, R.; Moyano, A. In *Catalytic Asymmetric Conjugate Reaction*; Cordóva, A., Ed.; Wiley-VCH: Weinheim, Germany, 2010; pp 191−218. (h) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *2007*, 1701.

(2) As a Michael donor, ketones often exhibit *anti*-selectivity in the nitro-Michael reaction. See: (a) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (b) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451. (c) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (d) Enders, D.; Chow, S. *Eur. J. Org. Chem.* **2006**, *2006*, 4578.

(3) (a) Seebach, D.; Goliński, J. *Helv. Chim. Acta* **1981**, *64*, 1413. (b) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 8822. (c) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 719. (d) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741.

(4) (a) Uehara, H.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2009**, *48*, 9848. (b) Uehara, H.; Imashiro, R.; Hernández-Torres, G.; Barbas, C. F., III *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 20672. (c) Imashiro, R.; Uehara, H.; Barbas, C. F., III *Org. Lett.* **2010**, *12*, 5250. (d) Hong, B. −C.; Dange, N. S.; Yen, P.-J.; Lee, G.-H.; Liao, J.-H. *Org. Lett.* **2012**, *14*, 5346.

(5) (a) Cao, L.-L.; Gao, B.-L.; Ma, S.-T.; Liu, Z.-P. *Curr. Org. Chem.* **2010**, *14*, 889. (b) Charette, A. B.; Andre, B.; Lindsay, V. *Top. Curr. Chem.* **2013**, *343*, 33. (c) Chemler, S. R.; Copeland, D. A. *Top. Heterocycl. Chem.* **2013**, *32*, 1861.

(6) (a) Sekikawa, T.; Kitaguchi, T.; Kitaura, H.; Minami, T.; Hatanaka, Y. *Org. Lett.* **2015**, *17*, 3026. (b) Manna, M. S.; Kumar, V.; Mukherjee, S. *Chem. Commun.* **2012**, *48*, 5193. (c) Terada, M.; Ando, K. *Org. Lett.* **2011**, *13*, 2026. γ-Butenolides are often subunits of natural products and biologically active compounds. For a review, see: (d) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (e) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, *1995*, 609.

(7) Lee, C.-J.; Jang, Y.-J.; Wu, Z.-Z.; Lin, W. *Org. Lett.* **2012**, *14*, 1906.

(8) Snyder, H. R.; Hamlin, W. E. *J. Am. Chem. Soc.* **1950**, *72*, 5082.

(9) (a) Mandal, T.; Zhao, C.-G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7714. (b) He, P.; Liu, X.; Shi, J.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 936.

(10) Chandra Sheker Reddy, A.; Chen, Z.; Hatanaka, T.; Minami, T.; Hatanaka, Y. *Organometallics* **2013**, *32*, 3575.

(11) Mantina, M.; Chamberlin, A. C.; Valero, R.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. A* **2009**, *113*, 5806.

(12) Pyykkö, P.; Atsumi, M. *Chem. - Eur. J.* **2009**, *15*, 186.

(13) All substrates listed in Table 2 undergo extremely high *syn*-selective nitro-Michael reaction in the presence of *epi*-quinine-derived 3,5-bis(CF_3)benzamide catalyst; see ref 6a.

(14) (a) Eliel, E. L.; Wilson, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1993; pp 696−697. (b) Eliel, E. L.; Wilson, S. H.; Doyl, M. P. *Basic Organic Chemistry*; Wiley: New York, 2001; pp 443−444.

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

(16) Most of the compounds **3** listed in Table 2 are highly crystalline materials, which can be easily recrystallized from EtOH to give the enantiomerically pure **3**.

(17) For the X-ray analysis of **3ah**, see Supporting Information.

DOI: 10.1021/acs.orglett.5b03539
Org. Lett. XXXX, XXX, XXX−XXX