Organic LETTERS

Letter

pubs.acs.org/OrgLett

Organocatalytic Enantioselective Michael–Michael–Michael–Aldol Condensation Reactions: Control of Five Stereocenters in a Quadruple-Cascade Asymmetric Synthesis of Highly Functionalized Hexahydrophenanthrenes

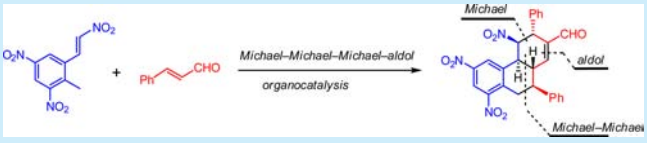
Arun Raja,[†] Bor-Cherng Hong,*[,†] and Gene-Hsiang Lee[‡]

[†]Department of Chemistry and Biochemistry, National Chung Cheng University, Chia-Yi, 621, Taiwan, R.O.C.

[‡]Instrumentation Center, National Taiwan University, Taipei, 106, Taiwan, R.O.C.

Supporting Information

ABSTRACT: A cascade organocatalysis has been developed for the enantioselective synthesis of a highly functionalized hexahydrophenanthrene-2-carbaldehyde containing five contiguous stereogenic centers with high diastereoselectivity and high enantioselectivity (>99% *ee*). The one-pot method comprises a cascade of organocatalytic Michael–Michael–Michael–aldol reactions of 2-methyl-1,5-dinitro-3-((*E*)-2-nitrovinyl)benzene and α,β-unsaturated aldehydes (e.g., cinnamaldehyde). The structure and absolute configuration of a product were confirmed by X-ray analysis of an appropriate derivative.



Cascade/domino organocatalysis reactions have attracted much attention during the past decade in the contexts of green chemistry and chemical efficiency;[1] consequently, this method has emerged as a pivotal strategy in contemporary organic synthesis.[2] Particularly, the ability to construct complex molecular architectures can be easily accessed via transformations beyond double cascade reactions. The pioneering *tour de force* involving triple cascade organocatalysis was introduced by Enders et al.[3] However, fewer examples have been reported that involve quadruple cascade reactions that construct four new C–C bonds and that generate multiple stereocenters.[4,5] Among those examples, the reactions were frequently triggered by a hetero-Michael or enol alkylation reaction. In addition, many double or triple cascade reactions have been initiated by oxa-Michael,[6] sulfa-Michael,[7] and aza-Michael[8] reactions.[9] The method of cascade organocatalysis initiated by a carbo-Michael reaction, especially with a benzylic nucleophile, toward an enal is rare and challenging, as compared to their heterocycle counterparts.[10] Therefore, the development of exquisite higher-order cascade reactions in the construction of the aforementioned polycarbocycles is highly attractive and in great demand by synthetic chemists. Notably, hexahydrophenanthrene constitutes the basic skeleton of many naturally occurring and synthetic compounds possessing a number of interesting biological properties, and the hexahydrophenanthrene derivatives have received much attention in synthetic endeavors (Figure 1).

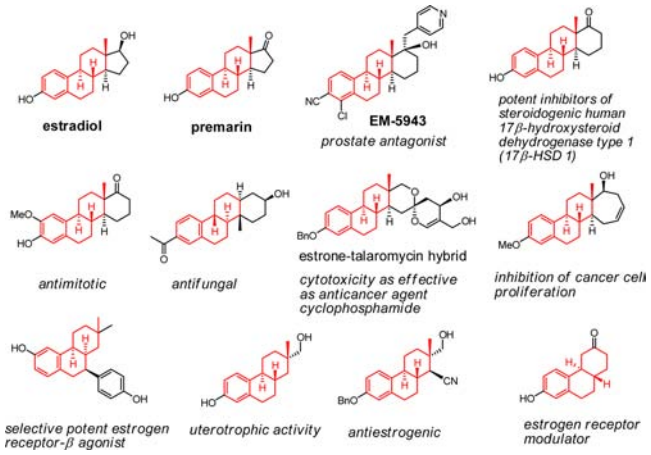
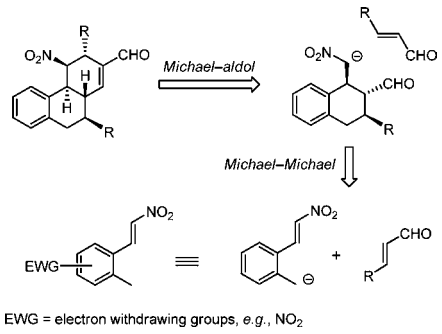


Figure 1. Selected examples of biologically active natural or synthetic compounds with the hexahydrophenanthrene core.

Prompted by the aforementioned background and in an effort to expand our exploration on organocatalyzed annulations,[11,12] we envisioned that a quadruple cascade organocatalysis[13] could afford a highly functionalized polycarbocyclic system with five contiguous stereogenic centers (Scheme 1). For example, retrosynthetic disconnection of hexahydrophenanthrene-2-carbaldehyde via aldol and Michael transforms led to the 1-(nitromethyl)naphthalene-2-carbaldehyde and enal (Scheme 1). A subsequent double Michael transform of the adduct would yield the 1-methyl-2-((*E*)-2-nitrovinyl)benzene and enal. The methyl group on the toluenyl moiety can be activated by introducing electron-withdrawing groups, e.g., NO_2,[14] on the aromatic ring. Therefore, the toluene derivative would be able to be deprotonated by a weak base and serve as an effective phenylogous nucleophile for the conjugate addition. Herein, we report the details of such an approach and the method that permitted enantioselective synthesis of a hexahydrophenan-

Received: September 24, 2014
Published: October 22, 2014

Scheme 1. Retrosynthetic Analysis



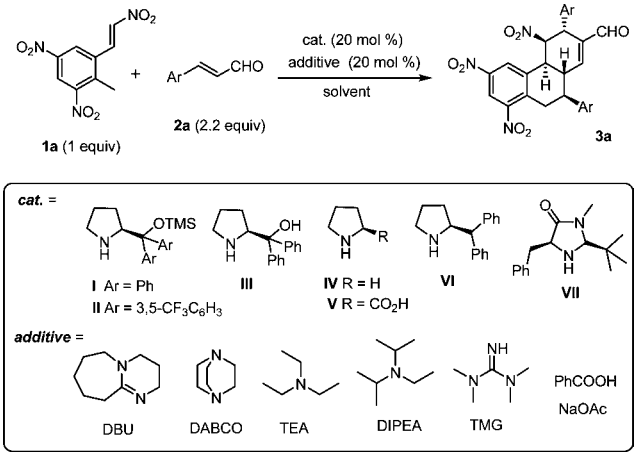
threne-2-carbaldehyde with five contiguous centers by domino carbo-Michael–Michael–Michael–aldol condensation.

At the outset of the study, the cascade reaction of (*E*)-2-methyl-1,5-dinitro-3-(2-nitrovinyl)benzene (**1a**)[15] and cinnamaldehyde (**2a**) was performed with 20 mol % of Jørgensen–Hayashi catalyst (**I**)[16] in $ClCH_2CH_2Cl$ at ambient temperature for 5 days; this process only yielded a trace amount of the product (Table 1, entry 1). The same reaction conditions with the addition of benzoic acid and catalyst **I** also gave a similar result (Table 1, entry 2). In order to trigger the reaction of **1a**, the additive was replaced by a base, e.g., DBU, and to our delight, the reaction proceeded and gave 12% yield of hexahydrophenanthrene-2-carbaldehyde **3a** as the only observable diastereomer (Table 1, entry 3). Accordingly, the reaction was screened with a variety of base additives and catalyst **I** to obtain the optimum yield of adduct **3a** (Table 1, entries 4–7). With strong bases employed, e.g., DBU, DABCO, the reactions are readily reversible with quantitative recovery of the starting materials and polar residues. The best result was obtained in the reaction with the combination of diisopropylethyl amine (DIPEA, Hünig base) and catalyst **I** in $ClCH_2CH_2Cl$ at ambient temperature for 60 h, affording a 25% yield of the adduct **3a** as the only observable diastereomer (Table 1, entry 7).

The same reaction in various solvents was screened for optimization with *cat.* **I**–DIPEA (20 mol %), e.g., toluene, CH_2Cl_2, $CHCl_3$, CH_3CN, EtOH, and THF (Table 1, entries 8–13). Apparently, the reaction in toluene provided the highest yield of product **3a**, 54%, along with the enantioselectivity >99% *ee* (Table 1, entry 8). On the other hand, the reaction with a strong base, 1,1,3,3-tetramethylguanidine (TMG), in THF only yielded a trace amount of the product **3a** (Table 1, entry 14). The reaction with an excess amount of additive DIPEA (100 mol %) and **I** (20 mol %) in toluene did not improve the yield but afforded less yield, 38% (Table 1, entry 15). The reaction was further scrutinized with a variety of organocatalysts (**II**–**VII**) along with DIPEA; however, none of those attempts gave promising results (Table 1, entries 16–21).

After securing the optimal reaction conditions (Table 1, entry 8), we next scrutinized the scope and limitations of the quadruple cascade organocatalysis reaction with variants of nitroalkene **1** and enal **2**. The reaction appeared quite general with respect to the substrates tested, providing the corresponding adducts with excellent stereoselectivities and in good yields (Table 2, entries 1–10). Usually, the reactions were completed within 3 days, but a longer reaction time was required in the case with chlorosubstituted nitroalkene **1** (Table 2, entries 9 and 10). Moreover, an additional amount of DIPEA (50 mol %) was needed to complete the reaction with **1i** and **1j**. It is noteworthy that although the cascade reaction providing product **3a** would

Table 1. Screening of the Catalysts, Additives, Solvents, and Reaction Conditions for the Cascade Reactions[a]



entry	cat.–additive	solvent	time (h)	yield[b] (%)	ee[d] (%)
1	**I**–	$ClCH_2CH_2Cl$	120	<5[c]	nd
2	**I**–PhCOOH	$ClCH_2CH_2Cl$	120	<5[c]	nd
3	**I**–DBU	$ClCH_2CH_2Cl$	120	12	nd
4	**I**–DABCO	$ClCH_2CH_2Cl$	168	10	nd
5	**I**–TEA	$ClCH_2CH_2Cl$	48	23	>99
6	**I**–NaOAc	$ClCH_2CH_2Cl$	120	<5[c]	nd
7	**I**–DIPEA	$ClCH_2CH_2Cl$	60	25	nd
8	**I**–DIPEA	toluene	65	54	>99
9	**I**–DIPEA	CH_2Cl_2	72	24	>99
10	**I**–DIPEA	$CHCl_3$	96	21	>99
11	**I**–DIPEA	CH_3CN	72	nr[c]	nd
12	**I**–DIPEA	EtOH	72	nr[c]	nd
13	**I**–DIPEA	THF	96	34	99
14	**I**–TMG	THF	96	<5[c]	nd
15	**I**–DIPEA[e]	toluene	120	38	nd
16	**II**–DIPEA	toluene	168	<5[c]	nd
17	**III**–DIPEA	toluene	168	nr[c]	nd
18	**IV**–DIPEA	toluene	96	<5[c]	0
19	**V**–DIPEA	toluene	168	nr[c]	na
20	**VI**–DIPEA	toluene	96	22	>99
21	**VII**–DIPEA	toluene	120	nr[c]	na

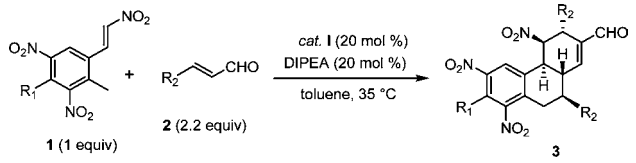
[a]Unless otherwise noted, the reactions were performed with catalyst–additive (20 mol %) in 0.2 M of **1** with a ratio of 1/2.2 of **1a** and **2a** at ambient temperature. [b]Isolated yields of **3a**; dr >20:1. [c]Recovered most starting materials (**1a** and **2a**). [d]Determined by HPLC with a chiral column (Chiralpak IC). [e]1.0 equiv of DIPEA (100 mol %) was added. nr = no reaction. nd = not determined. na = not available.

generate five new chiral centers, leading to a maximum of 32 possible stereoisomers, only one enantiomer was observed in this reaction. In addition, the overall yields of these quadruple cascade organocatalyses were ca. 50%, which is an average 85% yield for each C–C bond formation reaction. Moreover, except for the polar residues, the reactions are rather clean according to TLC and the crude ^1H NMR spectrum. Adduct **3** is the only isolable product in these reactions. The other side product (isomer or intermediate), if any, occurred in <5% yield.

The structure and the absolute configuration of the products were assigned based on X-ray analysis of (+)-**4i** (Figure 2), prepared from the reduction of **3i** (DIBAL-H, CH_2Cl_2, 0 °C, 1 h) and the subsequent esterification (4-Cl-C_6H_4COCl, Et_3N, *cat.* DMAP, CH_2Cl_2, 0 °C to rt, 2 h; 55% overall yield for two steps).

dx.doi.org/10.1021/ol502821e | *Org. Lett.* 2014, 16, 5756–5759

Table 2. Scope of the Asymmetric Quadruple Cascade Reaction of 1 and 2[a]



entry	R_1, R_2	time (h)	yield[b] (%)	ee[c] (%)
1	**3a** R_1 = H; R_2 = C_6H_5	65	54	>99
2	**3b** R_1 = H; R_2 = 4-BrC_6H_4	80	50	>99
3	**3c** R_1 = H; R_2 = 4-MeC_6H_4	60	61	>99
4	**3d** R_1 = H; R_2 = 4-$OMeC_6H_4$	84	48	>99
5	**3e** R_1 = H; R_2 = 4-ClC_6H_4	65	53	>99
6	**3f** R_1 = H; R_2 = 4-FC_6H_4	72	52	>99
7	**3g** R_1 = H; R_2 = 3-MeC_6H_4	72	42	>99
8	**3h** R_1 = H; R_2 = 4-EtC_6H_4	60	56	>99
9[d]	**3i** R_1 = 4-Cl; R_2 = C_6H_5	120	40	>99
10[d]	**3j** R_1 = 4-Cl; R_2 = 4-MeC_6H_4	144	42	>99

[a]Unless otherwise noted, the reactions were performed with catalyst **I**–additive (20 mol %) in 0.2 M of **1** with a ratio of 1/2.2 of **1a** and **2a** at 35 °C. [b]Isolated yields of **3a**. [c]Determined by HPLC with a chiral column (Chiralpak IC). [d]0.5 equiv of DIPEA was added.

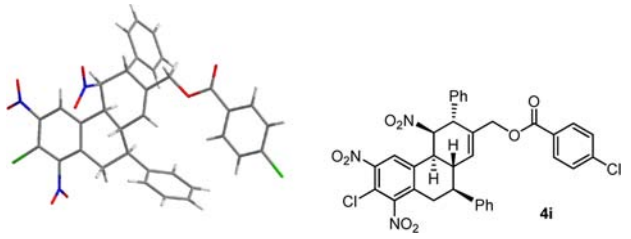
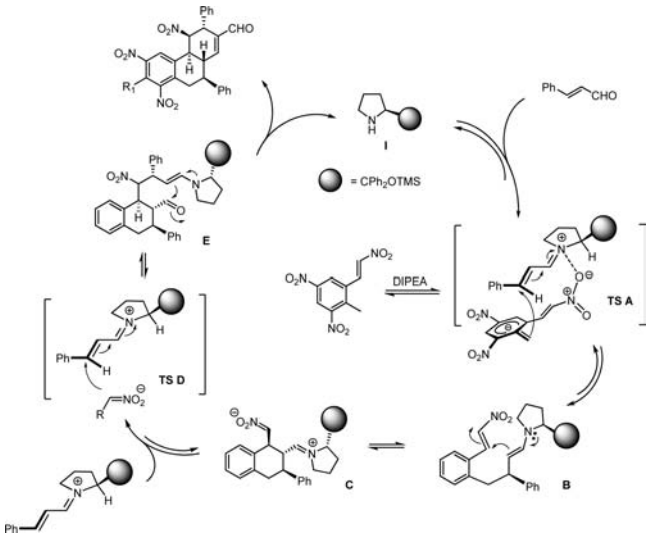


Figure 2. Stereoplots of the X-ray crystal structures of (+)-**4i**: C, gray; O, red; N, blue; Cl, green.

To account for the stereoselectivity of this transformation, we propose a plausible mechanism, as depicted in Scheme 2. Initial nucleophilic attack of a benzylic anion, generated *in situ* from **1a** with DIPEA,[17] on the iminium-activated cinnamaldehyde **2a** from the *Re* face under the control of the catalyst (**TS A**) gives intermediate enamine **B**, which cyclizes to iminium **C** and subsequently reacts with another iminium-activated cinnamaldehyde **2a** from the *Re* face under the control of the catalyst (**TS D**) to afford intermediate **E**. Consequently, the intramolecular aldol condensation of the intermediate provides **3a** and regenerates the catalyst. The intriguing and excellent stereoselectivity of the cascade reaction may arise from synergistic effects: (1) the severe steric hindrance conferred by the bulky substituent at the catalyst, which hampers the reaction at the *Si* face (**TS A**); (2) the positive charge of the iminium ion on the pyrrolidinium to interact with the negative charge of the nitro substituent in **1a**, acting as an "electron sink".[18] This dual effect directs the first-step Michael addition of the phenylogous dinitro toluene toward the iminium-activated **2a** as depicted in Scheme 2 to afford excellent stereoselectivity.

Scheme 2. Plausible Reaction Mechanism



In summary, we have realized a concise synthesis of optically enriched and highly functionalized hexahydrophenanthrenes, containing five contiguous stereogenic centers with excellent diastereo- (>20:1) and enantioselectivities (up to >99% *ee*) by quadruple cascade organocatalysis: triple-Michael/aldol reactions. Particularly noteworthy is the one-pot operation of the quadruple cascade reaction. The method not only adds to the limited repertoire of quadruple cascade organocatalytic asymmetric reactions but also demonstrates a proof of principle of the synergistic action of a steric shielding and an electron-sink mode of catalysis and nucleophilicity. The method has achieved cascade reactions that are hardly otherwise catalyzed by enamine catalysts alone, but require the addition of DIPEA. The success in triggering the first step cascade reactions by a carbo-Michael reaction of a benzylic nucleophile toward the enal further demonstrates the merit of this model and expands the realm of their synthetic applications. The structures and the absolute configuration of the products were unambiguously confirmed by single crystal X-ray crystallographic analyses of an appropriate adduct. Further applications of this protocol in the synthesis of elaborated derivatives, e.g., steroids, are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for compound (+)-**4i**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chebch@ccu.edu.tw.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the financial support for this study from the Ministry of Science and Technology (MOST, Taiwan) and thank the instrument center of MOST for analyses of compounds.

■ REFERENCES

(1) For recent reviews: (a) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390–2431. (b) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314–325. (c) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492–8509. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (e) Lv, F.; Liu, S.; Hu, W. *Asian J. Org. Chem.*

2013, *2*, 824−836. (f) Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969−4009. (g) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237−294. (h) Aitken, L. S.; Arezki, N. R.; Dell'Isola, A.; Cobb, A. J. A. *Synthesis* **2013**, *45*, 2627−2648. (i) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278−1293. (j) Alba, A.-N.; Companyo, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1432−1474.

(2) For recent reviews, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167−178. (b) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774−793.

(3) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861−863.

(4) To our best knowledge and as described in Professor Rueping's recent review (ref 1a), the first asymmetric organocatalytic quadruple cascade reaction was introduced in 2009 from Hong's group. An efficient protocol for the synthesis of tetrahydro-6*H*-benzo[*c*]chromenes was achieved by the strategy; see: Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704−707. Accordingly, the cascade three-component organocatalysis method was applied in the enantioselective total synthesis of (+)-Conicol; see: Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776−779. For a similar extension with propargyl alcohols toward highly functionalized 10,10a-dihydro-9*H*-benzo[*c*]chromenes, see: Rueping, M.; Dufour, J.; Maji, M. S. *Chem. Commun.* **2012**, *48*, 3406−3408.

(5) For other examples of quadruple cascade organocatalysis in constructing four C−C bond reactions, see: (a) Jiang, K.; Jia, Z.-J.; Yin, X.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 2766−2769. (b) Enders, D.; Krüll, R.; Bettray, W. *Synthesis* **2010**, 567−572. (c) Erdmann, N.; Philipps, A.; Atodiresei, I.; Enders, D. *Adv. Synth. Catal.* **2013**, *355*, 847−852. (d) Enders, D.; Wang, C.; Mukanova, M.; Greb, A. *Chem. Commun.* **2010**, *46*, 2447−2449. For other examples of quadruple cascade organocatalysis in constructing three C−C bond reactions, see: (e) Rueping, M.; Haack, K. L.; Ieawsuwan, W.; Sunden, H.; Blanco, M.; Schoepke, F. R. *Chem. Commun.* **2011**, *47*, 3828−3830. (f) Zhang, F.-L.; Xu, A.-W.; Gong, Y.-F.; Wei, M.-H.; Yang, X.-L. *Chem.—Eur. J.* **2009**, *15*, 6815−6818. (g) Enders, D.; Greb, A.; Deckers, K.; Selig, P.; Merkens, C. *Chem.—Eur. J.* **2012**, *18*, 10226−10229. (h) Joie, C.; Deckers, K.; Raabe, G.; Enders, D. *Synthesis* **2014**, *46*, 1539−1546. (i) Liu, L.; Zhu, Y.; Huang, K.; Wang, B.; Chang, W.; Li, J. *Eur. J. Org. Chem.* **2014**, 4342−4350.

(6) For recent examples: Xia, A.-B.; Wu, C.; Wang, T.; Zhang, Y.-P.; Du, X.-H.; Zhong, A.-G.; Xu, D.-Q.; Xu, Z.-Y. *Adv. Synth. Catal.* **2014**, *356*, 1753−1760.

(7) For select examples: (a) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177−4179. (b) Du, Z.; Zhou, C.; Gao, Y.; Ren, Q.; Zhang, K.; Cheng, H.; Wang, W.; Wang, J. *Org. Biomol. Chem.* **2012**, *10*, 36−39.

(8) For recent examples: (a) Yang, W.; He, H.-X.; Gao, Y.; Du, D.-M. *Adv. Synth. Catal.* **2013**, *355*, 3670−3678. (b) Kim, S.; Kang, K.-T.; Kim, S.-G. *Tetrahedron* **2014**, *70*, 5114−5121. (c) Liu, X.; Lu, Y. *Org. Biomol. Chem.* **2010**, *8*, 4063−4065.

(9) For a recent review in the organocatalytic tandem Michael addition reactions, see: (a) Bhanja, C.; Jena, S.; SaNayak, S.; Mohapatra, S. *Beilstein J. Org. Chem.* **2012**, *8*, 1668−1694.

(10) (a) Enders, D.; Wang, C.; Bats, J. W. *Synlett* **2009**, 1777−1780. (b) Li, T.; Zhu, J.; Wu, D.; Li, X.; Wang, S.; Li, H.; Li, J.; Wang, W. *Chem.—Eur. J.* **2013**, *19*, 9147−9150. (c) Dell'Amico, L.; Companyó, X.; Naicker, T.; Bräuer, T. M.; Jørgensen, K. A. *Eur. J. Org. Chem.* **2013**, 5262−5265. (d) Li, X.; Wang, S.; Li, T.; Li, J.; Li, H.; Wang, W. *Org. Lett.* **2013**, *15*, 5634−5637.

(11) For a recent review of organocatalyzed cycloadditions, see: Hong, B.-C. In *Enantioselective Organocatalyzed Reactions II*; Mahrwald, R., Ed.; Springer: Dordrecht, 2011; Chapter 3, pp 187−224.

(12) (a) Jhuo, D.-H.; Hong, B.-C.; Chang, C.-W.; Lee, G.-H. *Org. Lett.* **2014**, *16*, 2724−2727. (b) Hong, B.-C.; Lin, C.-W.; Liao, W.-K.; Lee, G.-H. *Org. Lett.* **2013**, *15*, 6258−6261. (c) Dange, N. S.; Hong, B.-C.; Lee, C.-C.; Lee, G.-H. *Org. Lett.* **2013**, *15*, 3914−3917. (d) Hong, B.-C.; Liao, W.-K.; Dange, N. S.; Liao, J.-H. *Org. Lett.* **2013**, *15*, 468−471 and references cited therein.

(13) Hong, B.-C.; Dange, N. S. Cascade Reactions in Stereoselective Synthesis. In *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushko, N., Eds.; Wiley-Blackwell: Hoboken, NJ, 2013; Chapter 21, p 581.

(14) The nitro group, known as a "synthetic chameleon", can serve as a masked amine to be further transformed to various functionalities. Consequently, the nitro group has attracted great interest in asymmetric organocatalysis; for a recent review, see: (a) Aitken, L. S.; Arezki, N. R.; Dell'Isola, A.; Cobb, A. J. A. *Synthesis* **2013**, *45*, 2627−2648. For a recent review in naturally occurring nitro compounds, see: (b) Parry, R.; Nishino, S.; Spain, J. *Nat. Prod. Rep.* **2011**, *28*, 152−167.

(15) See Supporting Information for the preparation of nitroalkene **1a**.

(16) For recent reviews, see: Ensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248−264.

(17) The protonated *N*,*N*-diisopropylethylamine, DIPEA-H^+, can be regenerated to DIPEA during the subsequent multiple equilibrium steps.

(18) For a similar example of synergistic effects, see ref 10c.