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Double Diastereocontrol in Bifunctional Thiourea Organocatalysis: Iterative Michael–Michael–Henry Sequence Regulated by the Configuration of Chiral Catalysts

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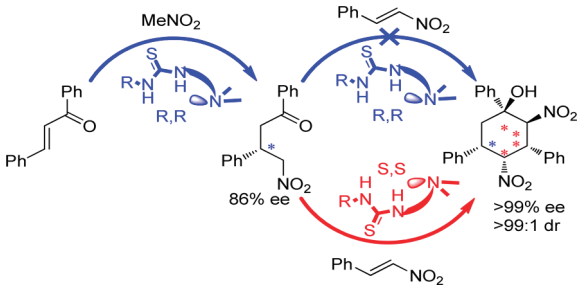
ABSTRACT



The importance and reactivity consequences of the double diastereocontrol in noncovalent bifunctional organocatalysis were studied. The results suggest that the bifunctional thioureas can have synthetic limitations in multicomponent domino or autotandem catalysis. Nevertheless, we provided a means to exploit this behavior and used the configuration of the chiral catalyst as a control element in organo-sequential reactions.

As a frontier discipline, asymmetric organocatalysis has contributed greatly to the past decade's advances in synthetic organic chemistry.[1] One of its impressive and current applications is the construction of complex molecules via domino or cascade reactions.[2,3] To date, the majority of organo-cascade procedures rests upon primary amine,[4] secondary amine,[5] or Brønsted acid[6] catalysis. The bifunctional thioureas, contrary to their commanding organocatalytic performance, have seen much less utilization in multicomponent reactions.[7] Thus,

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(1) (a) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007. (c) *Hydrogen Bonding in Organic Synthesis*; Pihko, P., Ed.; Wiley-VCH: Weinheim, Germany, 2009. (d) A special issue on asymmetric organocatalysis: *Chem. Rev.* 2007, *107*, 5413. (e) Melchiorre, P.; Margio, M.; Armando, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (f) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229.

(2) (a) Excellent review on tandem catalysis with taxonomy: Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. (b) Recent review: Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.

(3) Pioneering works on organo-cascade reactions: (a) Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* **2000**, *41*, 6951. (b) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272. (c) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (d) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (e) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (f) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861.

(4) Selected organo-cascade reactions with primary amine catalysts: (a) Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7196. (b) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (c) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892.

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it would be of interest to know whether a mechanistic reason exists behind this apparent disparity. In this paper, we report our synthetic studies which aimed to explore the capabilities of bifunctional thioureas in a Michael-type organo-cascade reaction. As a result, an interesting regulatory mechanism for the catalytic cycle was noticed: the chiral product of the first Michael step inhibited its own further reaction. Nevertheless, this seemingly restrictive effect, which turned out to be the exaggerated form of the double diastereocontrol, was alleviated and beneficially exploited for the iterative assembly of densely functionalized cyclohexanes.

The bifunctional quinine organocatalyst **1a,b** and its pseudoenantiomer **2**[8] have became a versatile tool in organocatalysis, especially in asymmetric 1,2- and 1,4-addition reactions.[9] Despite the catalytic advantage offered by the dual activation, the application of these bifunctional catalysts (or their analogs) was scarce in multicomponent reactions. Therefore, a synthetic study was initiated to uncover any structural or mechanistic reasons which could adversely affect a cascade reaction. We envisaged a thiourea **1a** catalyzed Michael−(Michael−Henry) stepwise sequence (Figure 1) as a model of a cascade process. First, the enantioenriched *R*-**6a** was formed in an organocatalytic Michael addition of nitromethane (**4**) to chalcone **5a**.[8a,b] In the second and separate step, we probed constructing a cyclohexane derivative **8** in a catalytic Michael−Henry sequence using the same catalyst and conditions. Despite the high reactivity of nitrostyrene **7a**, however, we were unable to detect **8** or any addition products after 1 week.

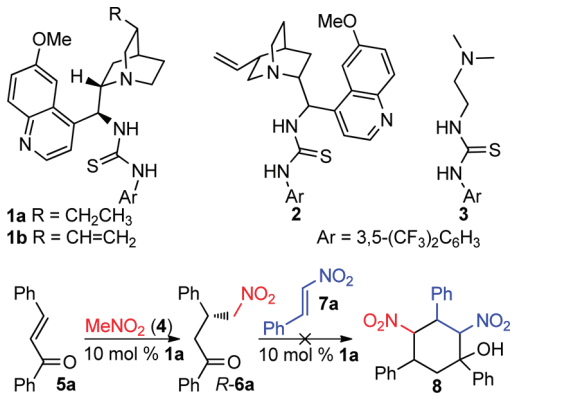


Figure 1. Bifunctional thiourea catalysts and stepwise multicomponent organocatalytic strategy to construct cyclohexane derivative **8**.

The unsuccessful initial experiment prompted us to investigate its mechanistic origin. In addition to the failure of the second step, we also attempted to find a rationale for the exclusive monoadduct formation in the first step. These two cases are analogous and seem to be mechanistically related. As a working hypothesis, we supposed that the incapacity of catalyst **1a** for the second Michael addition arose from an intriguing situation of double diastereocontrol.[10,11] Specifically, the combination of the chiral catalyst **1a** and its chiral product *R*-**6a** generates a mismatched pair with a sufficiently high barrier to the succeeding

(5) Reviews on organo-cascade reactions with secondary amine catalysts: (a) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (b) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (c) Westermann, B.; Ayaz, M.; van Berkel, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846. Selected examples:(d) Lu, M.; Zhu, D.; Lu, Y.; Hou, Y.; Tan, B.; Zhong, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187. (e) Chandler, C.; Galzerano, P.; Michrowska, A.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1978. (f) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (g) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349. (h) Jiang, H.; Elsner, P.; Jensen, K. L.; Falcicchio, A.; Marcos, V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6844. (i) Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776. (j) Enders, D.; Wang, C.; Mukanova, M.; Greb, A. *Chem. Commun.* **2010**, *46*, 2447. (k) Ma, A.; Ma, D. *Org. Lett.* **2010**, *12*, 3634.

(6) Selected examples of Brønsted acid catalyzed reactions: (a) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498. (b) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (c) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796. (d) Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4226. (e) Albert, B. J.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 2747.

(7) A successful Michael−Michael two-component cascade reaction was reported using Takemoto's bifunctional thiourea catalyst. The one-pot domino method has limited applicability, and it was generally less efficient than the two-step cyclization using TMG or KOH bases in the second step: (a) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365. A rather similar case using bifunctional cinchonas: (b) He, P.; Liu, X.; Shi, J.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 939. A Michael−Michael two-component cascade reaction with DKR interplay using thiourea catalyst **1**: (c) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177. (d) Yu, C.; Zhang, Y.; Song, A.; Ji, Y.; Wang, W. *Chem.—Eur. J.* **2011**, *17*, 770. (e) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8379. A multicomponent organo-cascade reaction, thiourea catalyst **1** and **2** (or their analogs) were applied in orthogonal tandem catalytic procedures (combined with Jørgensen−Hayashi catalyst). (f) Wang, Y.; Han, R.-G.; Zhao, Y.-L.; Yang, S.; Xu, P.-Y.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9834. (g) Wang, Y.; Yu, D.-F.; Liu, Y.-Z.; Wei, H.; Luo, Y.-C.; Dixon, D. J.; Xu, P.-Y. *Chem.—Eur. J.* **2010**, *16*, 3922. (h) Ren, Q.; Gao, Y.; Wang, J. *Chem.—Eur. J.* **2010**, *16*, 13594. (i) Gao, Y.; Ren, Q.; Wu, H.; Li, M.; Wang, J. *Chem. Commun.* **2010**, *46*, 9232. (j) Gao, Y.; Ren, Q.; Siau, W.-Y.; Wang, J. *Chem. Commun.* **2011**, *47*, 5819. (k) Corrrigendum: An exceptional Michael−Michael−Henry cascade promoted by a bifunctional thiourea catalyst. Basle, O.; Raimondi, W.; del Mar Sanchez Duque, M.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Org. Lett.* 2010, *12*, 5246−5249.

(8) Our work on bifunctional organocatalysis: (a) Vakulya, B.; Varga, Sz.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (b) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151. (c) Vakulya, B.; Varga, Sz.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475. (d) Tárkányi, G.; Király, P.; Varga, Sz.; Vakulya, B.; Soós, T. *Chem.—Eur. J.* **2008**, *14*, 6078. (e) Király, P.; Soós, T.; Varga, Sz.; Vakulya, B.; Tárkányi, G. *Magn. Reson. Chem.* **2010**, *48*, 13.

(9) Review on thiourea based cinchonas: (a) Connon, S. J. *Chem. Comm* **2008**, 2499. Seminal references: (b) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C. *Synlett* **2005**, 603. (c) Reference 8a. (d) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (e) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

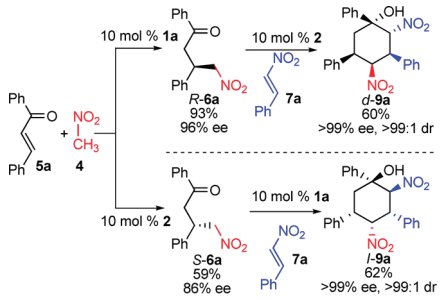
(10) For details about double diastereocontrol, see: (a) Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, CA, 2009. (b) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1. (c) Sharpless, K. B. *Chem. Scr.* **1985**, *25*, 71. (d) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Conell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.

(11) Recent organocatalytic examples of double diastereocontrol (predominant external, catalyst control): (a) Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. R. *J. Org. Chem.* **2006**, *71*, 4818. (b) Gryko, D.; Zimnicka, M.; Lipiński, R. *J. Org. Chem.* **2007**, *72*, 964. (c) Crisóstomo, F. R. P.; Lledó, A.; Shenoy, S. R.; Iwasawa, T.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2009**, *131*, 7402. (d) Peschiulli, A.; Procuranti, B.; O' Connor, C. J.; Connon, S. J. *Nat. Chem.* **2010**, *2*, 380. (e) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227. (f) Morris, K. A.; Arendt, K. M.; Oh, S. H.; Romo, D. *Org. Lett.* **2010**, *12*, 3764.

intermolecular reaction; thus, the subsequent organocatalytic step becomes kinetically unfavorable.

To test the validity of double diastereocontrol as a source of inhibition, a reaction sequence was devised having a presumably matched case for the second step (Scheme 1). Accordingly, not the thiourea catalyst **1a** but its pseudoenantiomer **2** was probed for the follow-up Michael–Henry reaction. To our delight, the enantiomerically enriched Michael adduct *R*-**6a** underwent a smooth catalytic reaction with nitroolefin **7a**. The catalyst **2** also had an influence on the stereochemical outcome of the reaction: the enantiopurity increased further (>99% ee) and near full control of diastereoselectivity was achieved (>99:1 dr). Additionally, executing this iterative startegy in a one-pot manner (adding the second catalyst and the reagent after the first Michael addition finished) has no additive advantage; the pseudoenantiomeric catalysts mutually blocked their activities, affording the expected product **9a** in a markedly lower yield (<5%).

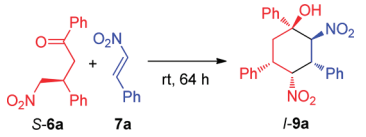
Scheme 1. Iterative Noncovalent Organocatalytic Strategy to Assemble Cyclohexane Derivatives **9a**



Interestingly, four out of the five chiral centers of cyclohexane *d*-**9a** were established in the second reaction step and not every substituent occupied the thermodynamically preferred equatorial positions. The employment of the catalysts **1a** and **2** in the reverse order led to the expected inversion of the stereochemistry in *l*-**9a**. The absolute stereochemical relationships were confirmed by X-ray single crystal structure determinations of two inclusions of *l*-**9a**.

After demonstrating the capacity of thiourea catalysts **1** and **2** in sequential reactions to construct complex molecular architectures, we proceeded to investigate the influence of further experimental parameters, such as solvent, catalyst type and load, and reagents' stoichiometry. As expected for bifunctional noncovalent organocatalysis, the reaction was more rapid and efficient in a less polar medium (Table 1, entry 4 vs 2). Additionally, the solvent polarity had no profound effect on the stereochemical efficiency. An interesting feature of the bifunctional thiourea cinchona catalysts is that the catalyst activity can be fine-tuned by modification of the remote vinyl group of the quinuclidine moiety. Probing catalyst systems **1a**–**c** showed no significant difference between their activities, although the most basic **1a** promoted the formation of *l*-**9a** with the highest conversion (entries 4–6). Since we always detected the formation of an insoluble nitrostryrene polymer in the above reactions, we used a 1 molar excess of nitrostyrene **7a** to further increase the yield of *l*-**9a**. Using the most efficient catalyst **1a**, one can reduce the catalyst load to 1 mol % without a deleterious effect on selectivity (entry 8). Additionally, no significant effect of dilution on the yield and selectivity was detected (entry 10).

Table 1. Optimization of Reaction Conditions



entry[a]	cat.	cat. load	solvent	**7a** equiv	yield[b]	ee[c]
1	**1b**	10%	CH_2Cl_2	1	46%	98%
2	**1b**	10%	CH_3CN	1	16%	96%
3	**1b**	10%	Et_2O	1	42%	98%
4	**1b**	10%	toluene	1	54%	>99%
5	**1a**	10%	toluene	1	62%	>99%
6	**1c**	10%	toluene	1	36%	>99%
7	**1a**	10%	toluene	2	73%	>99%
8	**1a**	1%	toluene	2	48%	>99%
9	**1a**	5%	toluene	2	77%	>99%
10[d]	**1a**	10%	toluene	2	76%	>99%
11[e]	**TEA**	10%	toluene	2	–	–
12	**3**	10%	toluene	2	19%	93%[f]

[a] Unless otherwise noted, all reactions were performed with *S*-**6a** (0.5 mmol), β-nitrostyrene (**7a**), and added catalyst in 1.2 mL of solvent at room temperature for 2 days. [b] Yield of the isolated product. [c] Determined by chiral HPLC analysis; the diastereomeric ratio was >99:1. [d] 2.4 mL of toluene were applied in this reaction. [e] Triethyl amine as catalyst was employed. [f] The diastereomeric ratio was slightly less than previous cases: 91:7:2.

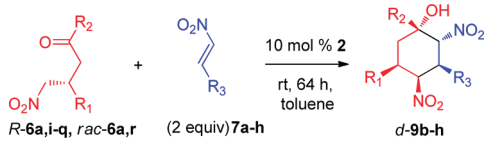
It also became apparent that a bifunctional catalyst is required to ensure the formation of the functionalized cyclohexane product *l*-**9a**, since base catalysis alone was insufficient (entry 11).[12] The achiral bifunctional analog **3**, however, was able to promote the Michael–Henry sequence. Although its catalytic efficiency is markedly less than that of **1a** (entry 7 vs 12), the astonishing feature of the reaction is the enormous level of asymmetric induction by only one stereocenter; high diastereoselectivity was achieved in the formation of four new stereocenters. Apparently, the bifunctional achiral catalyst **3** was able to restrict the conformational freedom of both substrates and created a highly rigid transition state. It seems plausible that a combination of the sterical shielding and the coordinating ability of the substituents of the controlling stereocenter was necessary for the observed high diastereoselectivity.[13] This dual action could also explain

(12) Recent example of substrate controlled organocatalytic Henry reaction affording high diastereoselectivity by an achiral base: Uehara, H.; Imashiro, R.; Hernández-Torres, G.; Barbas, C. F., III. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20672.

(13) For factors governing the stereoselectivity, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

the occurrence of the unusual form of double diastereocontrol. Finally, the above experiments indicate that the chiral substrate exerted a predominant influence on the subsequent asymmetric reaction; thus internal diastereocontrol was occurring.

Table 2. Investigation of the Scope of the Double Stereodifferentiating Michael–Henry Type Reaction



R-**6a,i-q**, *rac*-**6a,r** (2 equiv)**7a-h** *d*-**9b-h**

entry[a]	R_1, R_2, R_3	product	yield[b]	ee[c]	*dr*[d]
1	Ph, Ph, 2-Cl-C_6H_4	*d*-**9b**	–	–	–
2	Ph, Ph, *c*-Hex	*d*-**9c**	–	–	–
3	Ph, Ph, 3,4-$(MeO)_2$-C_6H_3	*d*-**9d**	40%	>99%	93:7
4	Ph, Ph, 2-thienyl	*d*-**9e**	47%	99%	>99:1
5	Ph, Ph, 4-Cl-C_6H_4	*d*-**9f**	53%	>99%	98:2
6	Ph, Ph, 4-NO_2-C_6H_4	*d*-**9g**	29%	>99%	>99:1
7	Ph, Ph, 4-MeO-C_6H_4	*d*-**9h**	60%	98%	94:6
8	4-Cl-C_6H_4, Ph, Ph	*d*-**9i**	45%	>99%	99:1
9	4-F-C_6H_4, Ph, Ph	*d*-**9j**	46%	>99%	94:6
10	3-Me-C_6H_4, Ph, Ph	*d*-**9k**	40%	>99%	95:5
11	Ph, 4-MeO-C_6H_4, Ph	*d*-**9l**	34%	99%	93:7
12	Ph, 4-NO_2-C_6H_4, Ph	*d*-**9m**	68%	>99%	94:6
13	Ph, 4-Cl-C_6H_4, Ph	*d*-**9n**	61%	99%	95:5
14	*c*-Hex, Ph, Ph	*d*-**9o**	–	–	–
15	$C_6H_4CH_2CH_2$, Ph, Ph	*d*-**9p**	–	–	–
16	*Z*-C_6H_4CHCH, Ph, Ph	*d*-**9q**	25%	>99%	89:11
17[e]	Ph, Ph, Ph	*d*-**9a**	22%	88%	>99:1
18[e]	Ph, Me, Ph	*d*-**9r**	35%	90%	89:11

[a] Unless otherwise noted, the reactions were performed with 0.5 mmol of Michael adducts *R*-**6a,i–q**, 1 mmol of nitroolefin (**7a–h**), and 0.05 mmol of catalyst **2** in 1.2 mL of toluene at room temperature for 64 h. [b] Combined yields of diastereoisomers. [c] Determined by chiral HPLC analysis. [d] Determined by NMR spectroscopy. [e] Reaction condition: 0.5 mmol of *rac*-**6a,r**, 0.5 mmol of *β*-nitrostyrene (**7a**), and 0.05 mmol of catalyst **2** in 1.2 mL of toluene at room temperature for 64 h.

With optimal reaction conditions established, the scope of the above iterative procedure was investigated. First, structurally different nitroolefins **7b–h** were probed as a second electrophile (Table 2). Regardless of having electron-withdrawing or -donating groups in the aryl ring's *meta* or *para* positions, nitrostyrenes **7d–h** showed similar reactivity and selectivity in the *d*-**9d–h** forming reaction (entries 3–7). Among nitrostyrenes, the sterically hindered *o*-chloro derivative **7b** failed to give any adduct (entry 1). In a similar manner, probing the aliphatic nitroolefin **7c**, somewhat surprisingly, showed no adduct formation (entry 2).

Then we continued to explore the applicability of a variety of enantiomerically enriched Michael adducts *R*-**6i–q** in the Michael–Henry sequence. As shown in Table 2, different electron-withdrawing and -donating substituents were well tolerated in the *meta* or *para* position of the aromatic rings (entries 8–13). However, no further reaction occurred when Michael adducts *R*-**6o,p** had an aliphatic substituent at the R^1 position (entries 14, 15). Nevertheless, the structurally similar olefinic derivative **6q** could be transformed to the cyclohexane product **9q** in the organocatalytic process (entry 16). These observations indicate that an additional π–π interaction might be involved in these organocatalytic reactions. Due to the unique case of double stereocontrol, we reasoned that the bifunctional thioureas could also be used for the kinetic resolution of racemic Michael adducts *rac*-**6a,r**. As expected, the matched reactions were more rapid and highly selective kinetic resolutions were achieved. Thus, the cyclohexane products **9a,r** formed with high enantio- and diastereoselectivity (entries 17, 18). Since the conversions were less than 50%, the synthetic utility of these kinetic resolutions is mediocre. Nevertheless, it is an intriguing procedure allowing access to highly enantioenriched compounds via two C–C bond forming reactions.

In conclusion, our study showed the importance and reactivity consequences of double diastereocontrol in noncovalent bifunctional organocatalysis. Our results also suggest that the bifunctional thioureas can have synthetic limitations in multicomponent domino or autotandem catalysis. Nevertheless, we provided a means to exploit this behavior and used the configuration of the chiral catalyst as a control element in organo-sequential reactions. Despite not being single-operational, the merit of this iterative method is highlighted by its efficiency to construct stereochemically dense architectures with an exquisite level of both enantio- and diastereoselectivities. As an understanding of double diastereodifferentiation in bifunctional organocatalysis emerged in our laboratory, several additional applications were identified and will be reported shortly.

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Supporting Information Available. Experimental procedures, spectral data, X-ray crystal structure, and CIFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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