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Catalytic Asymmetric Aza-Michael−Michael Addition Cascade: Enantioselective Synthesis of Polysubstituted 4-Aminobenzopyrans

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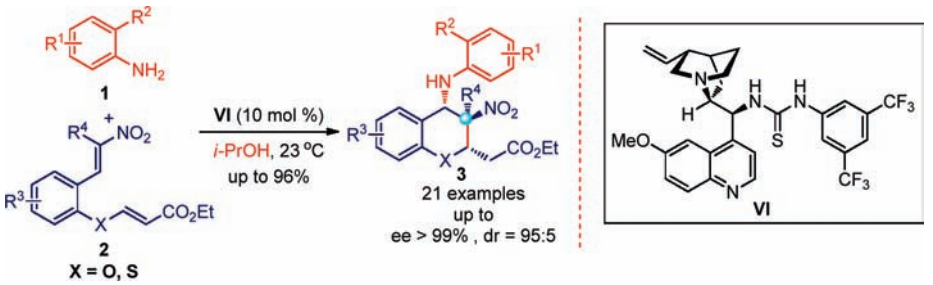
ABSTRACT



A catalytic asymmetric aza-Michael−Michael addition cascade of anilines to nitroolefin enoates in the presence of chiral bifunctional thiourea catalysts has been disclosed. This reaction provides a mild and efficient approach to polysubstituted chiral 4-aminobenzopyrans bearing three consecutive stereocenters in high yields with excellent stereoselectivities.

Densely functionalized complex molecules bearing a heterocycle architecture are featured in many naturally occurring products and medicinally relevant compounds that display a diverse range of biological activities.[1] In this context, benzopyrans and in particular their 4-amino derivatives are of great importance due to a number of drugs containing this ubiquitous motif.[2] For instance, they can function as modulators of calcium and potassium channels for influencing the activity of the heart and blood

(1) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH GmbH & Co. KGaA: New York, 2004.

(2) (a) Schweizer, E. E.; Meeder-Nycz, O. *Chromenes, Chromansses, and Chromones*; Wiley-Interscience: New York, 1977. (b) Keay, B. A. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, UK, 1996; Vol. 2, p 395. (c) Hepworth, J. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon; Oxford, UK, 1984; Vol. 3, p 11. For reviews of benzopyrans, see: (d) Shen, H. C. *Tetrahedron* **2009**, *65*, 3931. (e) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (f) Buckle, D. R.; Arch, J. R. S.; Fenwick, A. E.; Hough-Frydrych, C. S. V.; Pinto, I. L.; Smith, D. G.; Taylor, S. G.; Tedder, J. M. *J. Med. Chem.* **1990**, *33*, 3028. (g) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Showell, G. A. *J. Med. Chem.* **1984**, *27*, 1127.

(3) (a) Rovnyak, G. C.; Ahmed, S. Z.; Ding, C. Z.; Dzwonczyk, S.; Ferrara, F. N.; Humphreys, W. G.; Grover, G. J.; Santafianos, D.; Atwal, K. S.; Baird, A. J.; McLaughlin, L. G.; Normandin, D. E.; Sleph, P. G.; Traeger, S. C. *J. Med. Chem.* **1997**, *40*, 24. (b) Evans, J. M.; Fake, C. S.; Hamilton, T. C.; Poyser, R. H.; Watts, E. A. *J. Med. Chem.* **1983**, *26*, 1582.

(4) (a) Wang, J.; Xu, F.-X.; Lin, X.-F.; Wang, Y.-G. *Tetrahedron Lett.* **2008**, *49*, 5208. (b) Kumar, R. S.; Nagarajan, R.; Perumal, P. T. *Synthesis* **2004**, 949. (c) Anniyappan, M.; Muralidharan, D.; Perumal, P. T.; Vittal, J. J. *Tetrahedron* **2004**, *60*, 2965. (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, P. N. *Chem. Lett.* **2004**, 1436. (e) Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Tetrahedron* **2002**, *58*, 10301. (f) Yadav, J. S.; Reddy, B. V. S.; Madhuri, C.; Sabitha, G.; Jagannadh, B.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 6381. (g) Yadav, J. S.; Reddy, B. V. S.; Sekhar, K. C.; Geetha, V. *Tetrahedron Lett.* **2001**, *42*, 4405.

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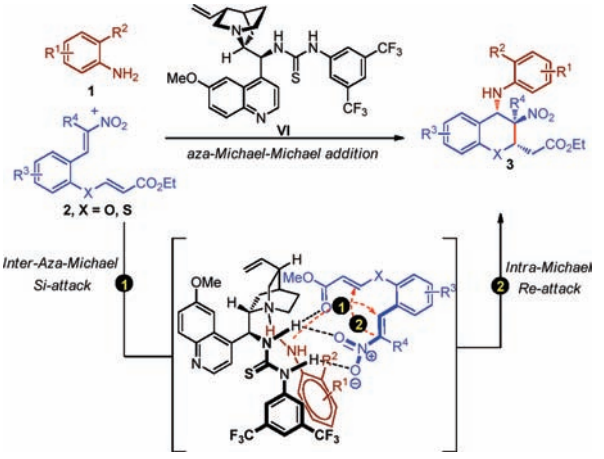
pressure.[3] The development of highly efficient, selective, and environmentally benign methods to construct this fused cyclic structure has received much attention in the chemical community.[4] Compared with many nonasymmetric procedures, however, catalytic asymmetric approaches to 4-aminobenzopyrans are relatively rare.[5] Notably, Rueping and co-workers recently reported an elegant example of enantioselective Mannich-ketalization reactions to provide 4-aminobenzopyrans in high enantioselectivities, albeit with fair diastereoselectivities.[6] Despite advances, the search for new catalytic asymmetric methods to form polysubstituted 4-aminobenzopyrans, especially with multiple consecutive stereocenters, is still highly desirable.

During the past decades, organocatalytic cascade/domino reactions have emerged as a powerful synthetic tool for the construction of multiple carbon−carbon or carbon−heteroatom bonds in a single operation.[7] In this regard, Michael addition initiated Michael−Michael addition cascade was identified as a useful strategy to make complex molecules.[8] Although there are many reports on organocatalytic asymmetric aza-Michael addition reactions, to our knowledge, enantioselective aza-Michael−Michael cascade reactions remain largely unexplored.[9] As part of our ongoing research program addressing carba- and heterocycle-oriented methodology development,[10] we herein wish to disclose a mild and efficient organocatalyzed asymmetric cascade aza-Michael−Michael addition reaction of anilines with nitroolefin enoates. This novel method allows an efficient and straightforward formation of two carbon−carbon bonds and three consecutive stereocenters (including one quaternary stereocenter) in one operation with high yields (up to 96%) and excellent stereoselectivities (up to >99% ee, mostly >95:5 dr).

Scheme 1. Proposed Reaction Pathway for the Cascade Sequence



Our designed approach to chiral 4-aminobenzopyrans is described in Scheme 1. Mechanistically, the chiral bifunctional thiourea catalyst **VI** activated nitroolefin enoates through multiple hydrogen-bonding interactions while its basic tertiary amino site activated the nucleophilic anilines.[11] The intermolecular aza-Michael reaction of nitroolefin enoates proceeded through *Si*-face attack, followed by the intramolecular Michael addition through *Re*-face attack, to form highly functionalized 4-aminobenzopyrans.

To examine the feasibility of the proposed aza-Michael−Michael addition cascade of anilines with nitroolefin enoates, the reaction was initially performed in CH_2Cl_2 at room temperature in the presence of bifunctional

(5) One example describes the conversion of chiral 4-chromanols into the corresponding amino derivatives. See: Burgard, A.; Lang, H.-J.; Gerlach, U. *Tetrahedron* **1999**, *55*, 7555.

(6) Rueping, M.; Lin, M.-Y. *Chem.—Eur. J.* **2010**, *16*, 4169. During the preparation of this work, Ricci and co-workers reported a catalytic asymmetric inverse-electron-demand [4 + 2] cycloaddition of salicyladimines with electron-rich alkenes to synthesize the 4-aminobenzopyran derivatives. See: Bernardi, L.; Comes-Franchini, M.; Fochi, M.; Leo, V.; Mazzanti, A.; Ricci, A. *Adv. Synth. Catal.* 2010, *362*, 3399.

(7) (a) Tietze, L. F.; Gordon, B.; Kersten, G. M., Eds. *Domino Reactions in Organic Synthesis*: Wiley-VCH, Weinheim, Germany, 2006. For selected reviews on cascade (domino) reactions, see: (b) Hussian, M. M.; Patrick, J. W. *Acc. Chem. Res.* **2008**, *41*, 883. (c) Li, Z.-G.; Chad, B.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (e) Guo, H.; Ma, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (f) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (g) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (h) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967.

(8) For an excellent review of cacade Michael/Michael reaction, see: (a) Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed.* **1993**, *32*, 1010. For selected examples of organocatalytic cascade Michael−Michael reactions, see:(b) 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. (c) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177. (d) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928. (e) Sun, X.; Sengupta, S.; Petersen, J. L.; Wang, H.; Lewis, J. P.; Shi, X.-D. *Org. Lett.* **2007**, *9*, 4495. (f) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732. (g) Li, H.; Zu, L. S.; Xie, H. X.; Wang, J.; Jiang, W.; Wang., W. *Org. Lett.* **2007**, *9*, 1833. (h) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365.

(9) For a review on organocatalytic aza-Michael additions, see: (a) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058. There is only one example of organocatalytic asymmetric aza-Michael−Michael addition reactions, see:(b) Li, H.; Zu, L.-S.; Xie, H.-X.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636.

(10) (a) Lu, L.-Q.; Zhang, J.-J.; Li, F.; Cheng, Y.; An, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4495. (b) Wang, X.-F.; Chen, J.-R.; Cao, Y.-J.; Cheng, H.-G.; Xiao, W.-J. *Org. Lett.* **2010**, *12*, 1140. (c) Lu, L.-Q.; Li, F.; An, J.; Zhang, J.-J.; An, X.-L.; Hua, Q.-L.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9542. (d) Chen, C.-B.; Wang, X.-F.; Cao, Y.-J.; Cheng, H.-G.; Xiao, W.-J. *J. Org. Chem.* **2009**, *74*, 3532. (e) Lu, L.-Q.; Cao, Y.-J.; Liu, X.-P.; An, J.; Yao, C.-J.; Ming, Z.-H.; Xiao, W.-J. *J. Am. Chem. Soc.* **2008**, *130*, 6946. (f) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489. (g) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 1847.

(11) Reviews on bifunctional Cinchona alkaloid amino thiourea catalysis: (a) Connon, S. J. *Chem. Commun.* **2008**, 2499. (b) Marcelli, T.; Maarseveen, J. H.; Van; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. For selected examples, see:(c) Liu, X.-Q.; Lu, Y.-X. *Org. Lett.* **2010**, *12*, 5592. (d) Liu, X.-Q.; Lu, Y.-X. *Org. Biomol. Chem.* **2010**, *8*, 4063. (e) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236. (f) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (g) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830. (h) Zu, L.-S.; Wang, J.; Li, H.; Xie, H.-X.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (i) Zu, L.; Xie, H.; Li, H.; Wang, J.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1882. (j) Wang, Y.; Liu, X.-F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (k) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (l) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796.

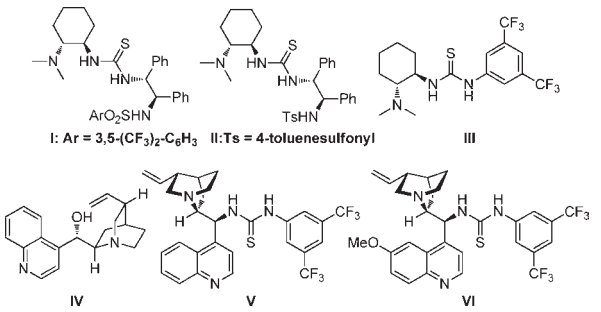
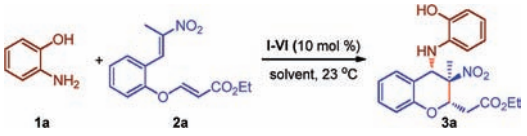


Figure 1. Screened organocatalysts.

organocatalyst **I** (10 mol %) (Figure 1 and Table 1). To our delight, the reaction proceeded smoothly to provide the desired chroman **3a** in moderate yield (67%) with good enantioselectivity (86% ee) and excellent diastereoselectivity (97:3) (Table 1, entry 1). On this basis, several commonly used bifunctional organocatalysts (Figure 1) were screened to further improve the reaction efficiency and stereoselectivities. Among them, cinchona alkaloid amino thiourea **VI** (10 mol %) was found to be the best one for this cascade process (Table 1, entry 6, 70% yield, 96% ee and 97:3 dr). We also investigated the effects of the reaction medium on this cascade reaction. As revealed in Table 1, the solvents had a dramatic influence on the reaction.

Table 1. Asymmetric Aza-Michael−Michael Addition Reaction of Aniline **1a** with Nitroolefin Enoate **2a** under Various Conditions[a]

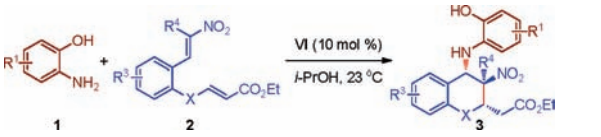


entry	solvent	catalyst	time (h)	yield (%)[b]	ee (%)[c]	dr[c]
1	CH_2Cl_2	**I**	48	67	−86	97:3
2	CH_2Cl_2	**II**	48	69	−86	91:9
3	CH_2Cl_2	**III**	48	56	−71	96:4
4	CH_2Cl_2	**IV**	48	43	−31	65:35
5	CH_2Cl_2	**V**	48	75	88	98:2
6	CH_2Cl_2	**VI**	48	70	96	97:3
7	DCE	**VI**	72	73	93	>95:5
8	Et_2O	**VI**	20	82	90	>95:5
9	THF	**VI**	24	77	88	>95:5
10	CH_3CN	**VI**	12	86	92	>95:5
11	toluene	**VI**	48	65	97	>95:5
12	CH_3OH	**VI**	8	83	94	>95:5
13	EtOH	**VI**	4	95	95	>95:5
14	^{i}PrOH	**VI**	2	96	96	>95:5
15	^{t}BuOH	**VI**	2	95	96	>95:5
16[d]	^{i}PrOH	**VI**	11	92	96	>95:5
17[e]	^{i}PrOH	**VI**	24	95	89	>95:5

[a] Unless noted, reactions were carried out with **1a** (0.75 mmol), **2a** (0.30 mmol), and **I**−**VI** (10 mol %) in 2.0 mL of solvent at 23 °C. [b] Isolated yield. [c] Determined by chiral HPLC. [d] 2 mol % **VI** was used. [e] The reaction was performed at 0 °C. DCE = 1,2-dichloroethane.

Although excellent levels of stereoselectivities were observed, longer reaction times were needed for nonpolar, aprotic solvents (Table 1, entries 6−11). Suprisingly and interestingly, polar and protic solvents, which were usually deemed to disrupt the hydrogen-bonding interactions between the catalyst and substrates,[10f] gave the most encouraging results (Table 1, entries 12−15) for the reaction of **1a** and **2a**. When the catalyst loading was decreased to 2 mol %, the reaction gave comparable results albeit with somewhat prolonged reaction times (Table 1, entry 16). Lowering the temperature to 0 °C, the reaction gave the product in 95% yield and 95:5 dr. But much longer reaction time was needed, and the enantioselectivity was decreased to 89% (Table 1, entry 17). The best results can be obtained with the use of 2-propanol as the solvent at room temperature in the presence of 10 mol % of catalyst **VI** (Table 1, entry 14, 2 h, 96% yield, 96% ee and >95:5 dr).

Table 2. Asymmetric Aza-Michael−Michael Addition of Anilines **1** to Nitroolefin Enoates **2** in the Presence of 10 mol % of Organocatalyst **VI**[a]



entry	R^1	R^3	R^4	X	yield (%)[b]	ee (%)[c]	dr[c]
1	H	H	Me	O	96 (**3a**)	96	>95:5
2	H	4-F	Me	O	71 (**3b**)	>99	>95:5
3	H	4-Cl	Me	O	92 (**3c**)	94	>95:5
4	H	4-Br	Me	O	84 (**3d**)	94	>95:5
5	H	4-Me	Me	O	92 (**3e**)	94	>95:5
6	H	4-MeO	Me	O	94 (**3f**)	94	95:5
7	4-Me	5-MeO	Me	O	83 (**3g**)	96	>95:5
8	4-Me	4-Br	Me	O	82 (**3h**)	94	>95:5
9	5-Me	4-Br	Me	O	85 (**3i**)	93	>95:5
10	6-Me	H	Me	O	94 (**3j**)	93	>95:5
11	6-Me	5-MeO	Me	O	81 (**3k**)	94	>95:5
12	4-Me	H	Me	O	94 (**3l**)	96	>95:5
13[d]	4-Br	H	Me	O	94 (**3m**)	>99	>95:5
14	4-Cl	H	Me	O	89 (**3n**)	93	>95:5
15	4-^{t}Bu	H	Me	O	91 (**3o**)	94	>95:5
16	H	H	Et	O	91 (**3p**)	96	>95:5
17	H	H	Bn	O	89 (**3q**)	93	>95:5
18	H	H	Me	S	95 (**3r**)	91	65:35
19[e]	H	H	Me	S	93 (**3s**)	94	95:5

[a] Unless noted, reactions were carried out with **1** (**1a**−**h**) (0.75 mmol), **2** (**2a**−**k**) (0.30 mmol), and **VI** (10 mol %) in 2.0 mL of ^{i}PrOH at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The absolute configuration of **3m** was determined by X-ray analysis. [e] The cofiguration of α,β-unsaturated ester on the nitroolefin enoate is *Z* type.

Having established the optimal reaction conditions, we next examined the scope of the aza-Michael−Michael addition cascade by employing a variety of anilines and nitroolefin enoates. As highlighted in Table 2, this transformation has a broad scope of both substrates. Variation in the electronic or steric contribution of anilines (**1**) and nitroolefin enoates (**2**) can be tolerated in the reaction. For

example, nitroolefin enoates (**2**), bearing electron-withdrawing or electron-donating groups on the aromatic ring at the para- and/or meta-positions to the oxygen atom, generally afforded the products without loss in reaction efficiency (71% to 96% yield) or stereoselective outcomes (94% to >99% ee, ≥95:5 dr, entries 1−7 in Table 2). The ethyl or benzyl group in the α position of nitroolefin enoates could also be accommodated in this cascade procedure, providing the corresponding products **3p** and **3q** with 91% yield, 96% ee, >95:5 dr and 89% yield, 93% ee, >95:5 dr (Table 2, entries 16 and 17), respectively. Furthermore, structural variation in anilines **1** was also tolerated in this aza-Michael−Michael addition cascade. The aromatic ring bearing methyl group at the para, meta, or ortho position of the aniline could undergo the desired cascade reaction efficiently (Table 2, entries 7−11). For instance, anilines with electron-rich (Table 2, entries 12 and 15) or electron-deficient groups (Table 2, entries 13 and 14) proceeded smoothly with excellent results. As for sulfur-containing nitroolefin enoates, both *Z* and *E* configuration substrates could be successfully used in this cascade sequence. It is worth noting that substrate **2** with *Z* configuration gave a slightly better result (Table 2, entry 19, 93% yield, 94% ee, 95:5 dr) than the one with *E* configuration (Table 2, entry 18, 95% yield, 91% ee, 65:35 dr). The relative and absolute configuration of the product was unambiguously determined to be 2*S*, 3*R*, 4*S* by using X-ray crystallographic analysis of **3m** (Figure 2).[12]

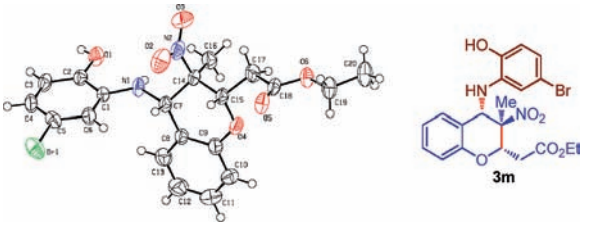


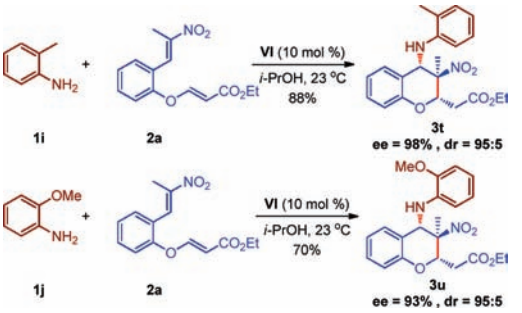
Figure 2. X-ray crystal structure of **3m**.

Perhaps more importantly, the anilines with no hydroxyl group on the aromatic ring can also participate in the present transformation. Thus, *o*-toluidine (**1i**) and 2-methoxyaniline (**1j**) underwent the aza-Michael−Michael addition reaction to afford the corresponding benzopyrans in good yield (88% and 70%, respectively), with excellent enantioselectivity (98% and 93%, respectively) and diastereoselectivity (both drs = 95:5) (Scheme 2).

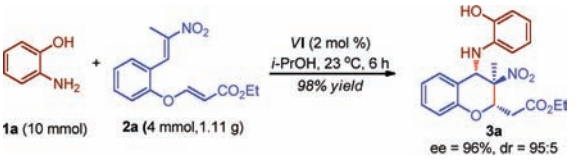
To demonstrate preparative utility of this aza-Michael−Michael addition reaction, the reaction of 2-aminophenol (**1a**) and (*E*)-ethyl 3-(2-((*E*)-2-nitroprop-1-enyl) phenoxy)acrylate (**2a**) was performed on a gram scale in the presence of only 2 mol % of catalyst **VI**. As outlined in Scheme 3, the reaction proceeded very well to afford ethyl 2-((2*S*,3*R*,4*S*)-4-(2-hydroxyphenylamino)-3-methyl-3-nitrochroman-2-yl)acetate (**3a**) in 98% isolated yield without any loss of stereoselectivities (96% ee, >95:5 dr).

(12) The configuration of **3m** was determined by X-ray crystallographic analysis. CCDC 803691 (**3m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

Scheme 2. Reaction of *o*-Toluidine **1i** and 2-Methoxyaniline **1j** with Nitroolefin Enoate **2a**



Scheme 3. The Cascade Reaction Was Performed on a Gram Scale



In summary, we have developed a mild and efficient organocatalytic aza-Michael−Michael addition cascade of anilines with nitroolefin enoates by using a readily available chiral bifunctional thiourea catalyst. This methodology provides an atom economic and straightforward approach to optically active 4-aminobenzopyrans with three consecutive stereogenic carbons including one quaternary stereocenter in excellent yields and stereoselectivities. Application of this reaction to other substrates and to the preparation of biologically relevant compounds is currently underway.

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Supporting Information Available. Experimental procedures and compound characterization data including X-ray crystal data (CIF) for **3m**. This material is available free of charge via the Internet at http://pubs.acs.org.