Asymmetric Synthesis of Polysubstituted 4-Amino- and 3,4-Diaminochromanes with a Chiral Multifunctional Organocatalyst

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A series of multifunctional catalysts with two chiral diaminocyclohexane units were developed and successfully applied in the asymmetric oxa-Michael—aza-Henry cascade reaction of salicylaldimines with nitroolefins. This approach provides a simple and efficient entry to polysubstituted chiral 4-aminobenzopyrans with three consecutive stereocenters and in high yield (up to 97%) with excellent stereoselectivity (up to 98% ee and >99:1 dr). Facile access to the nonsymmetric optically pure 3,4-diaminochromanes was also obtained.

4-Aminochromanes are ubiquitous in biologically active compounds,¹ as subunits in antihypertensive² and anti-ischemic drugs,³ and as modulators of calcium and potassium channels to control cardiac activity and blood pressure.⁴ Recent research has shown that 4-amino-chromane-substituted 2-alkylimidazopyridine derivatives

10.1021/ol300798t © 2012 American Chemical Society Published on Web 04/12/2012 could be used as selective acid pump antagonists for the treatment of gastresophageal reflux disease.⁵ Because of the importance of the 4-aminochromane framework, synthesis⁶ and, in particular, catalytic asymmetric preparation of 4-aminochromanes have attracted considerable attention. The existing syntheses for 4-aminochromane and its analogues mainly involve reactions of salicylaldimines with electron-rich alkenes,⁷ alkynals,⁸ azalactones,⁹ or allenic esters.¹⁰ Xiao and co-workers designed complex nitroolefin-tethered enoates as substrates and used the catalytic asymmetric aza-Michael–Michael cascade reaction triggered by anilines to obtain a series of 4-aminobenzopyrans derivatives with functional acetate substituents at the 2-position in high yields and with excellent stereoselectivities.¹¹

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Scheme 1. Asymmetric Synthesis of 4-Aminochromane Using a Tandem Oxa-Michael–Aza-Henry Reaction Strategy



Very recently, Schreiner and co-workers¹² reported an asymmetric oxa-Michael-aza-Henry domino reaction of salicyl-N-tosylimine 1 with nitrostyrenes 2 catalyzed by quinine thiourea and achieved only product 3 with one chiral center (Scheme 1), which was thought to be produced by desulfonamidation-elimination from the oxa-Michael-aza-Henry addition intermediate 4. If the subsequent desulfonamidation reaction could be suppressed, the optically active 4-aminochromane 4 bearing three chiral centers could be obtained as the main product. Further reduction of the nitro group of 4 would provide direct access to the nonsymmetric diamine compounds 5. Chiral diamines play an important role in pharmaceuticals¹³ and show potential application in catalytic asymmetric synthesis as auxiliaries^{13a,14} and organocatalysts¹⁵ and as ligands in metal catalysis.¹⁶ Therefore, we investigated development of a facile catalytic methodology to synthesize enantiomeric pure 4-aminochromanes 4 and their derivatives. Herein, we describe the use of multifunctional catalysts VIII in an efficient asymmetric oxa-Michael-aza-Henry cascade reaction with high product yields (up to 97%) and excellent stereoselectivities (up to 98% ee and > 99:1 dr).



Figure 1. Screened organocatalysts.

We first investigated the use of bifunctional catalyst I^{17} in the model reaction of salicylaldimine 1a with nitrostyrene 2a in chlorobenzene (Cl-Ph) at -20 °C. Molecular sieves (4 Å) were added as water scavengers to prevent decomposition of the aldimine. The reaction proceeded smoothly to give the desired product 4 in good vield and diastereoselectivity, but with moderate enantioselectivity (Table 1, entry 1). In this reaction, only a small amount of the desulfonamidation product 3 was detected. Additionally, 4 was stable during workup, and no more of the desulfonamidation byproduct 3 was produced after the product was stored for several weeks at rt. Using multifunctional catalyst \mathbf{II}^{18} in the reaction increased the enantioselectivity (37% ee to 54% ee) and retained the diastereoselectivity (97:3), while the yield decreased (88% to 38%) (Table 1, entry 2). The improved enantioselectivity prompted us to design and synthesize a series of novel trifunctional catalysts III-IX, which were derived from two chiral 1, 2-diaminocyclohexane units and had tertiary amine, thiourea, and sulfonamide functional groups. The efficiencies of these catalysts were evaluated further. Using catalyst III, increases were observed in the reaction yield (38% to 78%) and enantioselectivity (54% ee to 60% ee)(Table 1, entries 2 and 3). After replacement of the methanesulfonyl subunit (catalyst III) with trifluoromethanesulfonyl (catalyst IV), the enantioselectivity increased to 67% ee, while the vield decreased to 67%(Table 1, entry 4). After the aliphatic sulfonamide moiety was changed to an aromatic sulfonamide, some promising results were observed. The enantioselectivity of the product increased when the terminal sulfonamide substituent of the catalyst was changed from 2,4,6-trimethylbenzenesulfonyl (V) (56% ee) to 4-methylbenzenesulfonyl (VI) (70% ee), 4-(trifluoromethyl)benzenesulfonyl (VII) (74% ee), or 4-nitrobenzenesulfonyl (VIII) (84% ee) (Table 1, entries 5-8). These increases may be caused by enhancement of the hydrogen bond donating ability of the sulfonamide hydrogen. The hydrogen-bond-donating ability increases with acidity and is governed by the electronic status of the aromatic substituent R. After introducing another NO₂ at the 2-position of catalyst VIII to produce catalyst IX, the enantioselectivity of the product decreased unexpectedly (Table 1, entry 9). The additional NO₂ probably disrupted the hydrogen bond interaction between the catalyst and the substrate. By comparing the results with catalysts VI and X, we can conclude that the chiral central configuration in the two diaminocyclohexane units in VI (1S, 2S, 1'S, 2'S) was a good match for

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Table 1. Asymmetric Oxa-Michael-Aza-Henry Reaction ofSalicylaldimines $1\mathbf{a}-\mathbf{c}$ with Nitrostyrenes $2\mathbf{a}$ under VariousConditions^a

	NSO ₂ Ar + NO ₂ + I-IX(11) solven 1a - c 2a - 20°C 1a: Ar = 4-MeC ₆ H ₄ - 1b: Ar = 2.4 6.(Ma)-C.Ha-	ArSO ₂ HN NO ₂ 0 mol %) A 4 Å MS C, 24 h 4aa-4ca
1c : Ar = 2,4,6- $({}^{i}Pr)_{3}C_{6}H_{2}$ -	1b : Ar = 2,4,6-(Me) ₃ C ₆ H ₂ - 1c : Ar = 2,4,6-(^{<i>i</i>} Pr) ₃ C ₆ H ₂ -	

entry	imine	cat.	solvent	yield ^{b} (%)	dr^c	$\operatorname{ee}^{c}(\%)$
1	1a	Ι	Cl-Ph	88	97:3	37
2	1a	II	Cl-Ph	38	97:3	54
3	1a	III	Cl-Ph	78	97:3	60
4	1a	IV	Cl-Ph	67	97:3	67
5	1a	\mathbf{V}	Cl-Ph	80	98:2	56
6	1a	VI	Cl-Ph	93	98:2	70
7	1a	VII	Cl-Ph	94	98:2	74
8	1a	VIII	Cl-Ph	93	99:1	84
9	1a	IX	Cl-Ph	94	97:3	74
10	1a	X	Cl-Ph	8	99:1	$^{-9}$
11	1a	VIII	F-Ph	95	97:3	80
12	1a	VIII	Me-Ph	90	98:2	76
13	1a	VIII	o-xylene	93	98:2	81
14	1a	VIII	DCM	95	97:3	78
15	1a	VIII	DCE	95	97:3	78
16	1a	VIII	CH_3CN	97	95:5	72
17	1a	VIII	THF	d		
18	1b	VIII	Cl-Ph	85	>99:1	88
19	1c	VIII	Cl-Ph	76	99:1	91
20^e	1c	VIII	Cl-Ph	79	96:4	91
21^{f}	1c	VIII	Cl-Ph	92	97:3	93
22^g	1c	VIII	Cl-Ph	93	96:4	93
23^h	1c	VIII	Cl-Ph	81	98:2	93

^{*a*} Unless noted, reactions were carried out with **1** (0.3 mmol), **2** (0.45 mmol), 4 Å MS (85 mg) and cat. (10 mol %) in 1.0 mL of solvent at -20 °C for 24 h. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC. ^{*d*} Trace amount of product. ^{*e*} Performed at -30 °C. ^{*f*} Performed at -40 °C for 3 d. ^{*s*} 15 mol % of **VIII** was used for 70 h. ^{*h*} 5 mol % of **VIII** was used for 3 d.

achieving the stereocontrol of the product and that in catalyst X (1R, 2R, 1'S, 2'S) was a mismatch. We also screened other multifunctional catalysts (Supporting Information), but none of these performed better than catalyst VIII (Figure 1). Various solvents, including Cl-Ph, F-Ph, Me-Ph, DCM, DCE, CH₃CN, THF, and o-xylene, were screened for the reaction, and Cl-Ph performed the best (Table 1, entries 8 and 11-17). By increasing the steric hindrance of the sulfonyl groups at the N-terminal of the salicylaldimine and using 1b and 1c as substrates in the reaction, the desired products were obtained with improved stereoselectivity (88% ee and 91% ee) but decreased yield (85% and 76%) (Table 1, entries 18 and 19). Taking the enantioselectivity into consideration, 1c was selected as the substrate for further study. Lowering the reaction temperature to -30 °C increased the yield from 76% to 79% and retained enantioselectivity of 91% ee (Table 1, entries 19 and 20). With a reaction temperature of -40 °C, increases were observed in the yield (92%) and



entry	\mathbb{R}^1	\mathbb{R}^2	time (h)	${\rm yield}^b(\%)$	$\mathrm{d}\mathbf{r}^{c}$	ee^{c} (%)
1	Н	Ph	72	92 (4ca)	97:3	93
2^d	Η	$m ext{-MePh}$	24	85(4cb)	98:2	92
3^d	Η	$o\operatorname{-MePh}$	65	76(4cc)	99:1	79
4^d	Η	p-MePh	38	$72({\bf 4cd})$	95:5	89
5	Η	$m ext{-BrPh}$	66	91(4ce)	95:5	90
6	Η	m-ClPh	66	85(4cf)	96:4	90
7	Η	$m ext{-}\operatorname{FPh}$	66	91(4cg)	96:4	90
8	5-Me	Ph	53	97(4ch)	96:4	91
9	5-Me	$m ext{-BrPh}$	42	93(4ci)	95:5	92
10	5-Me	m-ClPh	42	93 (4cj)	96:4	92
11	5-Me	$m ext{-}\operatorname{FPh}$	42	91(4ck)	98:2	91
12	5-Me	$m ext{-MePh}$	42	$89\left(4cl\right)$	97:3	95
13^e	5-Me	m-MeOPh	113	72(4cl)	92:8	94
14^e	5-Me	m-NO ₂ Ph	112	$67 \left(4cn \right)$	85:15	90
15	5-Me	Pr	54	81(4co)	97:3	90
16	5-Me	ⁱ Bu	42	82 (4cp)	99:1	86
17	$5\text{-}\mathrm{Bu}^t$	$m ext{-MePh}$	42	95(4cq)	98:2	98
18	5-Br	$m ext{-MePh}$	93	73(4cr)	92:8	89
19	5-Cl	$m ext{-MePh}$	93	67 (4cs)	92:8	90
20	5-F	m-MePh	29	88 (4ct)	95:5	90
21^{f}	Н	m-BrPh	83	85 (4bb)	96:4 ^{<i>g</i>} (>99:1)	85 ^g (98)

^{*a*} Unless noted, reactions were carried out with 1 (Ar = 2,4,6-(${}^{i}Pr$)₃-C₆H₂-, 0.3 mmol), 2 (0.45 mmol), 4 Å MS (85 mg), and VIII (10 mol %) in 1.0 mL of solvent at -40 °C. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC. ^{*d*} Performed at -20 °C. ^{*e*} Performed at -30 °C. ^{*f*} Ar = 2,4,6-(Me)₃-C₆H₂-. ^{*g*} The results in parentheses are after recrystallization.

enantioselectivity (93% ee) with a long reaction time (3 d) (Table 1, entry 21). Desulfonamidation product **3** was not detected in the reaction at -40 °C. Decreasing the catalyst load from 15 to 5 mol % resulted in no large change in the enantioselectivity or diastereoselectivity (Table 1, entries 22 and 23), but the yield decreased to 81%.

After establishing the optimized domino reaction conditions, the reaction was extended to a variety of nitroolefins and salicylaldimines. The position of the substituent on the aryl ring of nitrostyrene affected the enantioselectivity and reactivity (Table 2). Nitroolefins with metasubstituents gave better results in shorter reaction times than those with ortho- or para-substituents (Table 2, entry 2 vs entries 3 and 4). The electronic effect of the substituent on the benzene ring of the nitroolefin (Table 2, entries 5-14) or salicylaldimine had some influence on reactivity but only a small effect on the stereoselectivity (Table 2, entries 2, 12, and 17-20). The best outcome was obtained for the product of 4cg, with 95% yield and 98% ee (Table 2, entry 17). The less reactive aliphatic nitroalkenes could also be used in the reaction and gave good yields (\geq 81%), good enantioselectivities (\geq 86% ee),



Figure 2. X-ray crystal structure of 4bb.

and excellent diastereoselectivities (\geq 97:3 dr) (Table 2, entries 15 and 16). The optical purity of the product could be improved by recrystallization. For example, almost optically pure **4bb** was achieved (98% ee, >99:1 dr) after recrystallization of the initial product (85% ee, 97:3 dr) (Table 2, entry 21).

The relative and absolute configuration of the product was unambiguously determined to be 2S, 3R, 4R by X-ray crystallographic analysis of **4bb** (Figure 2).¹⁹ A transition-state model that accounts for the stereochemical outcome is shown in Figure 3.¹⁷ In this model, the protons of the thiourea and the sulfonamide simultaneously activate the nitrostyrene and the imine, respectively, through hydrogen bonds. The tertiary nitrogen deprotonates and activates the phenolic hydroxyl to attack the β -position of the nitrostyrene from the *Si*-face. This forms a negatively charged intermediate, which is involved in nucleophilic attack of the carbon of the imine from the *Re*-face successively to afford the observed products.

The oxa-Michael–aza-Henry adducts were also investigated in the synthesis of the nonsymmetric diamine compound. As outlined in Scheme 2, treatment of 4cq with Zn/ HCl at rt gave 3,4-diaminochromane 5cq in >99% yield without loss of enantiomeric purity (Scheme 2). Thus, both 4-aminochromanes and 3,4-diaminochromanes could be synthesized efficiently.

In conclusion, a series of multifunctional organocatalysts were designed and synthesized. The catalysts were successfully applied in the asymmetric oxa-Michael—aza-Henry cascade reaction of salicylaldimines with nitroolefins for the synthesis of polysubstituted 4-aminobenzopyrans with three chiral centers. This method also provides novel, facile access to the nonsymmetric 3,4-diaminochromanes compounds. Further application of these nonsymmetric diamines in catalytic asymmetric synthesis is currently underway.



Figure 3. Proposed transition-state model.

Scheme 2. Reduction of 4-Aminochromane to Produce 3,4-Diaminochromane



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Supporting Information Available. Catalysts synthesis, spectroscopic data, enantioselectivities measurement, and X-ray crystal data (CIF) for **4bb**. This material is available free of charge via the Internet at http://pubs.acs.org.

⁽¹⁹⁾ CCDC 870994 (**4bb**) 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/datarequest/cif.

The authors declare no competing financial interest.