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Catalytic Asymmetric Intramolecular Hydroarylations of ω-Aryloxy- and Arylamino-Tethered α,β-Unsaturated Aldehydes

Hai-Hua Lu, Hui Liu, Wei Wu, Xu-Fan Wang, Liang-Qiu Lu, and Wen-Jing Xiao*[a]

Phenols, anilines, and their derivatives are chemicals manufactured in large quantities by modern chemical industries and serve as important feedstocks in the synthesis of pharmaceuticals, agro-, and fine chemicals.[1] The development of direct and catalytic synthetic transformations of these simple substrates to valuable compounds has therefore remained a focal point for extensive research effort in both industrial and academic settings. Historically, these transformations are carried out by Friedel–Crafts reactions with acyl or alkyl halides in the presence of Lewis acids.[2] Over the past 20 years, there has been a considerable effort to achieve direct C–H functionalization of these electron-rich arenes by C–H activation mediated by transition-metal complexes.[3] Among them, direct intramolecular hydroarylation represents one of the most powerful transformations for the rapid construction of fused aromatic heterocycles, a common synthon found in natural products and medicinal agents.[4] Despite advances, increasing the diversity of possible substrates and the stereoselectivity of the reaction remain challenges. While a variety of protocols have been described for the intramolecular hydroarylation of the more electron-rich indoles and pyrroles,[5] to our knowledge, only a handful of examples are known for the analogous phenol- and aniline-derived reactants.[6] In particular, there are only a couple of examples known to date on the enantioselective intramolecular hydroarylation of benzene derivatives with reasonable enantioselectivity.[6a,b] For instance, Bergman, Ellman, and co-workers developed an intramolecular *ortho*-alkylation of *meta*-isobutenyl-substituted aromatic imines catalyzed by a chiral rhodium complex, for which 22–90% *ee* was observed.[6a,b] This methodology has been limited to specific substrate classes, and the olefin isomerization in the substrate would be problematic in the presence of metal complexes.[6d] Thus, efficient catalytic systems for asymmetric intramolecular hydroarylation are highly desirable.

Complementing organometallic catalysis, enantioselective organocatalysis has recently emerged as the preeminent strategy for asymmetric synthesis.[7] While organocatalyzed enantioselective intermolecular hydroarylations of electron-rich arenes have been extensively investigated,[8] it is surprising that no example is available for the intramolecular version of this reaction type that employs readily available phenols and anilines as starting materials. Herein, we demonstrate that organocatalysis has been exploited to achieve the first asymmetric intramolecular arylation of ω-aryloxy- and arylamino-tethered α, β-unsaturated aldehydes by using a chiral secondary amine catalyst. Notably, this new transformation allows the production of functionalized chromans[9] and tetrahydroquinolines[10] in high enantiopurity [Eq. (1)].

Starting from phenols or anilines, the substrates **1** for this study were successfully synthesized by using cross metathesis reactions of the corresponding phenyl homoallyl ethers or amines with crotonaldehyde as the key step in the presence of Hoveyda–Grubbs' second-generation catalyst **5**.[5f] The seminal work of MacMillan and co-workers[11] has established the concept of iminium catalysis that enables the LUMO-lowering activation of α, β-unsaturated aldehydes. With this activation model in mind, we hypothesized that an iminium catalysis protocol might be susceptible to the asymmetric intramolecular hydroarylation. Mechanistically, unsaturated aldehyde **1** should be activated by chiral secondary amine **4** via the reversible formation of iminium ion **6**,[12] in which the *Si* face is shielded by the bulky group of the catalyst. As a result, we expected that the electron-rich benzene framework would attack from the *Re* face of the activated alkene, thereby generating the bicyclic system **7**. Subsequent hydrolysis of the enamine moiety would afford the requisite

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Homepage: http://chem-xiao.ccnu.edu.cn/default.aspx

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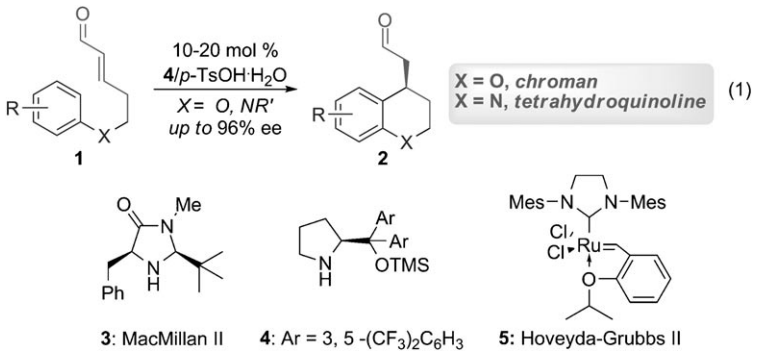
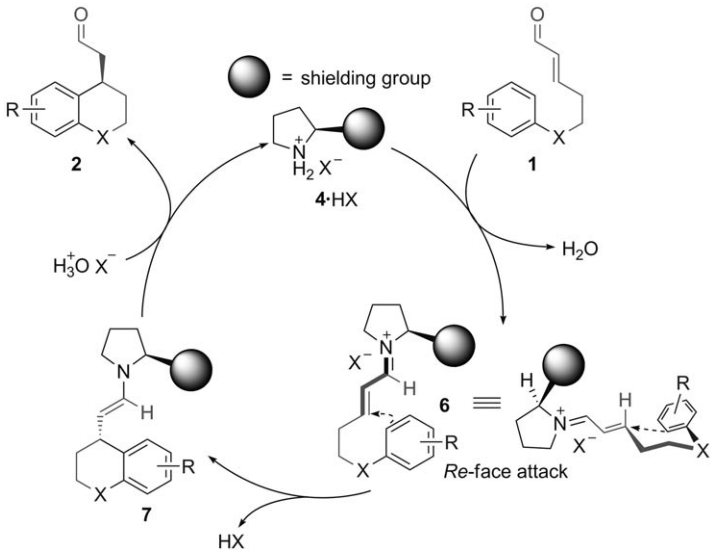


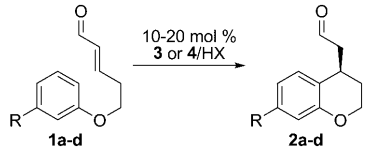
benzene-fused heterocycle **2** and regenerate the amine catalyst **4** (Scheme 1).



Scheme 1. Organocatalytic enantioselective intramolecular hydroarylation.

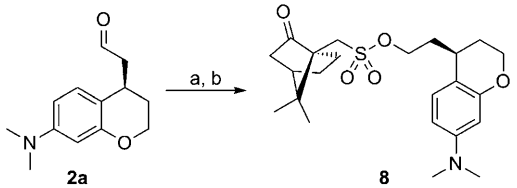
To our delight, exposure of (*E*)-5-[3-(dimethylamino)phenoxy]pent-2-enal (**1a**) to 20 mol% of imidazolidinone catalyst **3** in the presence of 20 mol% of 3,5-dinitrobenzoic acid in diethyl ether at room temperature did indeed provide the desired chroman derivative **2a** with enantioinduction and good levels of reaction efficiency (Table 1, entry 1, 77% yield, 90% *ee*). As revealed in Table 1, the reaction appears quite general with respect to the nature of the nitrogen substituents (R = NMe_2, pyrrolidino, piperidino, morpholino, entries 1–4) in the benzene ring without substantial loss in yield or enantiocontrol (59–77% yield, 87–90% *ee*). The catalyst screening indicated that a higher yield (83%) and comparable enantiomeric excess (88% *ee*) could be obtained in a shorter reaction time when chiral secondary amine **4** was employed as the reaction catalyst (entry 1 versus entry 5, Table 1).[12,13] Further optimization revealed that the combination of amine **4** and *p*-TsOH·H_2O exhibited optimal conversion and enantiocontrol in solvents such as diethyl ether or methyl *tert*-butyl ether (MTBE) (entries 6–11, Table 1). An enantioselectivity/temperature profile discloses that the enantioselectivity of the reaction can be further improved to 96% *ee* by lowering the temperature to −25°C (entry 8, Table 1). To determine the absolute configuration of the product, the bicyclic product **2a** with excellent enantiomeric excess was then converted into its (1*S*)-(+)-10-camphorsulfonate derivative **8** in two steps (Scheme 2). The absolute configuration was unambiguously determined to be *R* by X-ray crystallographic analysis (Figure 1).[14] This result supports our proposed stereochemi-

Table 1. Organocatalytic intramolecular hydroarylation of ω-aryloxyl α,β-unsaturated aldehydes **1a–d** in the presence of catalyst **3** or **4**.[a]



Entry	Substrate (R)		Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	NMe_2	**3**	24	77	90
2	**1b**	N	**3**	16	59	88
3	**1c**	N	**3**	12	69	87
4	**1d**	N O	**3**	24	60	90
5	**1a**	NMe_2	**4**	0.5	83	88
6	**1a**	NMe_2	**4**	2.5	68	91[d]
7	**1a**	NMe_2	**4**	6	82	92[d,e]
8	**1a**	NMe_2	**4**	60	79	96[d,f]
9	**1a**	NMe_2	**4**	80	76	96[d,f,g]
10	**1a**	NMe_2	**4**	60	78	96[d,f,g,h]
11	**1a**	NMe_2	**4**	80	78	96[d,f,g,i]

[a] Unless noted, reactions were carried out with **1** (0.25 mmol), amine (**3** or **4**, 0.05 mmol), and DNBA (0.05 mmol) in Et_2O (2.5 mL, 0.1 M of **1**) at room temperature. [b] Yield of isolated product. [c] Determined by chiral HPLC after $NaBH_4$/EtOH reduction. [d] 20 mol% of *p*-TsOH·H_2O was used instead of DNBA. [e] Conducted at 0°C. [f] Conducted at −25°C. [g] 10 mol% of **4** and *p*-TsOH·H_2O were employed. [h] Et_2O (1.25 mL, 0.2 M of **1**) was used. [i] MTBE (1.25 mL, 0.2 M of **1**). DNBA = 3, 5-dinitrobenzoic acid. *p*-TsOH·H_2O = toluenesulfonic acid monohydrate. MTBE = methyl *tert*-butyl ether.



Scheme 2. Conversion of **2a** to (1*S*)-(+)-10-camphorsulfonate derivative **8**. Reagents and conditions: a) $NaBH_4$, MeOH, RT; b) (1*S*)-(+)-10-camphorsulfonyl chloride, Et_3N,·THF, 0°C to RT (37% yield, 2 steps).

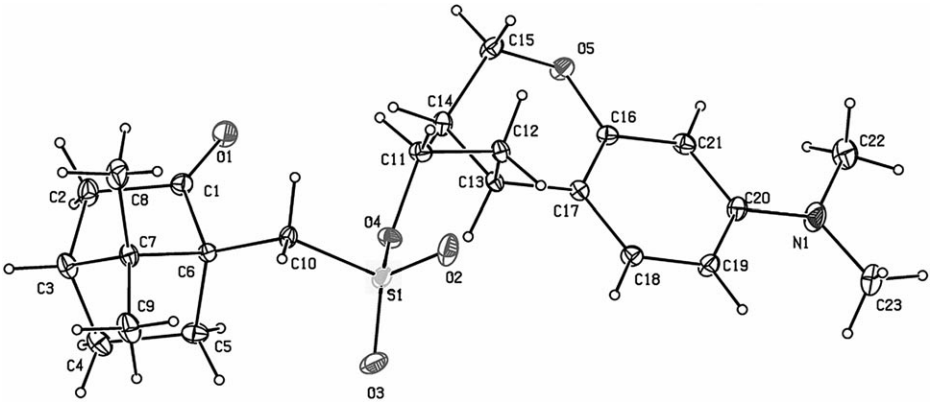
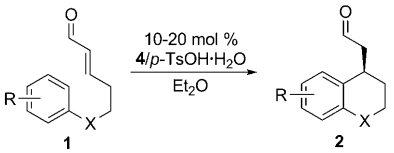


Figure 1. X-ray crystal structure of (1*S*)-(+)-10-camphorsulfonate derivative **8.**

cal outcome, and the stereochemistry of other products could be tentatively assigned by assuming an analogous enantioinduction (Scheme 1).

Having established the optimal conditions for the intramolecular hydroarylation, we next examined the scope of substrates in this organocatalytic reaction with the use of catalyst **4**/*p*-TsOH·H_2O in diethyl ether. As highlighted in Table 2, significant structural variation in the benzene architecture can be realized. Introduction of a methyl substituent at the *ortho*- or *para*-position to the oxygen atom is well tolerated, and excellent enantioselectivities can be achieved in both cases (entries 2 and 3, Table 2, 96 and 89% *ee*, respectively). The *N*,*N*-dimethyl group can be easily removed by direct deamination[8e] or readily converted to other functional groups by Ni-catalyzed Suzuki cross-couplings,[15] and in doing so diverse and structurally complex chromans can be generated. Moreover, the aryl framework can be successfully extended to aniline systems (entries 4–12, Table 2). Variation in the *N*-protecting group (X = NBoc, NCbz, NTs, NMe, NBn, entries 4–9, Table 2) is possible with *N*-electron-withdrawing groups having better enantiocontrol. Incorporation of a piperidino group instead of the *N*,*N*-dimethyl group at the

Table 2. Organocatalyzed intramolecular hydroarylation of phenol- and aniline-derived enals.[a]



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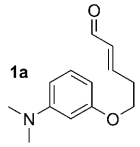
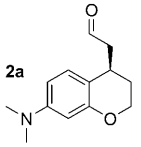
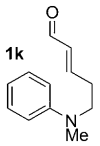
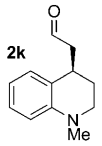
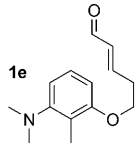
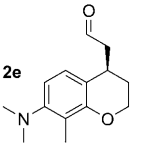
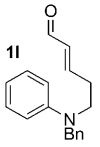
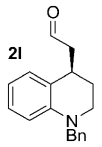
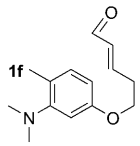
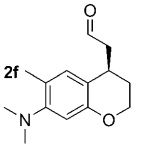
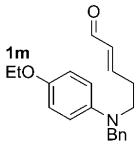
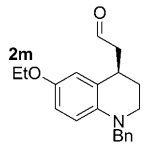
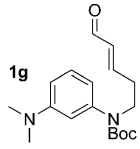
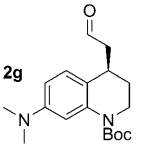
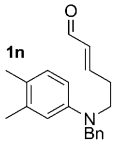
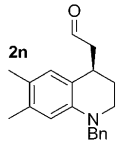
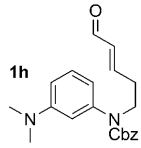
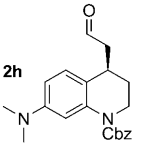
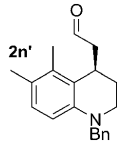
1			78	96	8			61	70[d]
2			72	96	9			65	76[d]
3			50	89	10			80	74[d]
4			70	87	11			98 (71: 29)	92(**2n**)[e]
5			68	87					

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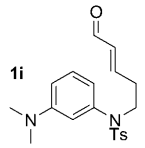
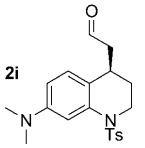
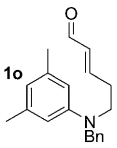
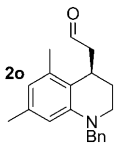
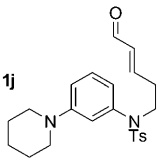
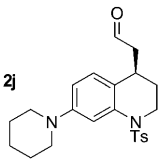
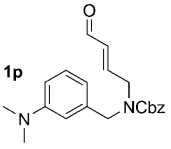
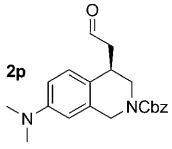
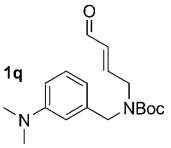
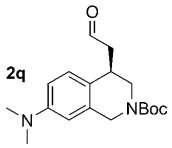
6	 **1i**	 **2i**	64	90	12	 **1o**	 **2o**	99	86[e]
7	 **1j**	 **2j**	65	90	13	 **1p**	 **2p**	80	79
					14	 **1q**	 **2q**	71	71

[a] Reactions were carried out with **1** (0.25 mmol), amine catalyst (10–20 mol%), and *p*TsOH·H_2O (10–20 mol%) in Et_2O (0.2–0.25 M of **1**) at −25-0 °C for 18–144 h. [b] Yield of isolated product. [c] Determined by chiral HPLC after $NaBH_4$/EtOH reduction. [d] CH_3CN as solvent, and hydrochloride as the additive (4.0 M HCl in dioxane). [e] CH_2Cl_2 as solvent, and hydrochloride as the additive (4.0 M HCl in dioxane).

C(3) position of the substrate gave almost identical results (entry 6 versus 7, Table 2), which implies that the modification of the *N*-substituents in the benzene ring can be accomplished. Other alkyl, dialkyl, and alkyloxyl groups can also be successfully introduced to the aryl framework (entries 10–12, Table 2); however, the reaction affords two regioisomers (**2n**/**2n′** = 71:29) in 98% total yield and 92% *ee* (major isomer **2n**) in the case of 3,4-dimethyl phenylamino-tethered enal **1n** (entry 11, Table 2). Perhaps more importantly, benzylamino-tethered enals proved to be viable reaction substrates. Thus, *N*-protected 4-[3-(dimethylamino)benzylamino]but-2-enals **1p** and **1q** were employed in the reaction and efficiently provided the corresponding tetrahydroisoquinolines[16] **2p** and **2q** in good yields and enantioselectivities (entries 13 and 14, Table 2), respectively.

In summary, we have developed the first enantioselective organocatalytic intramolecular hydroarylations of phenol- and aniline-derived enals. This methodology provides an atom economic and straightforward approach to optically active chromans and tetrahydroquinolines in good yields and high enantioselectivities (up to 96% *ee*). Application of this reaction to other substrates and to the preparation of biologically relevant compounds is currently underway.

Experimental Section

Typical procedure: A reaction vial equipped with a magnetic stirring bar was sequentially charged with catalyst **4** (15.0 mg, 10 mol%), Et_2O (1.25 mL), and *p*-TsOH·H_2O (4.8 mg, 10 mol%). The mixture was stirred at room temperature for 15 min and then cooled to −25 °C. Enal **1a** (54.8 mg, 0.25 mmol, recrystallized from Et_2O at −40 °C prior to use) was then added. After 60 h, the crude reaction mixture was directly loaded on a silica gel column, and column chromatography (petroleum ether/ethyl acetate = 4:1) afforded the pure product **2a** as a colorless oil in 78% yield with 96% *ee* (**2a** was reduced to the corresponding primary alcohol for the determination of enantiomeric excess. Chiralpak AS column, hexane/2-propanol = 90:10, 1 mL min^{-1}, 254 nm, t_{major} = 11.37 min, t_{minor} = 15.05 min).

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Keywords: asymmetric catalysis · chroman · intramolecular hydroarylation · organocatalysis · tetrahydroquinolines

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