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Augmentation of enantioselectivity by spatial tuning of aminocatalyst: Synthesis of 2-alkyl/aryl-3-nitro-2*H*-chromenes by tandem oxa-Michael Henry reaction

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ABSTRACT: Asymmetric oxa-Michael addition of salicylaldehyde to conjugated nitroalkenes often suffers from poor reactivity, selectivity and long reaction time. Because of formation of an iminium ion with aminocatalyst, the nucleophilicity of the phenolic hydroxy group in salicylaldehyde reduces further to make the oxa-Michael reaction

reversible. Here we report a structurally simple and easily accessible L-proline derived aminocatalyst, phenyl L-prolinamide for asymmetric tandem oxa-Michael Henry reaction of salicylaldehyde with conjugated nitroalkene to give 2-alkyl/aryl-3-nitro-2*H*-chromenes in excellent enantioselectivity within a short reaction time.

KEYWORDS: *Phenyl L-prolinamide, salicylaldehyde, nitroalkene, asymmetric 1,4-addition, tandem oxa-Michael-Henry, 2-alkyl/aryl-3-nitro-2H-chromenes*

Introduction

Asymmetric synthesis of enantiomerically pure compounds has experienced phenomenal growth due their applications in electronic and optical devices, polymers and, more importantly, as drug and biological probe. Since absolute purity of single enantiomer dictates the efficacy and specificity of a drug, asymmetric synthesis always strives for cent percent enantioselectivity, which is easier said than done. The factors such as structural complexity, accessibility and cost of the catalysts, catalyst loading, and the

reaction conditions often become secondary in the quest of achieving optimum enantioselectivity. Recently, small molecule organocatalysis has shown great promise in asymmetric synthesis after discovery of L-proline as an efficient organocatalyst by List et al.[1] But, there are only a handful of asymmetric aminocatalysts[1-3] which are structurally simple, easily accessible, cost-effective, and yet efficient. Given its application of asymmetric synthesis in drug development, pharmaceutical companies require catalytic methods which are cost effective, easy to handle, and give highly optically purity. Therefore, development of new asymmetric methodology, improvement of existing method by either modifying the existing processes or employing structurally simpler catalyst to achieve greater enantioselectivity are very important dimensions of asymmetric synthesis.

Asymmetric oxa-Michael addition reaction is considered as one of the most difficult reactions in organic chemistry due to poor nucleophilicity of oxygen and reversible nature of the reaction.[4] Due to delocalization of the oxygen lone pair in the aryl ring, phenolic -OH behaves as a very poor nucleophile for oxa-Michael reaction. Among the phenols, the

nucleophilicity of salicylaldehyde is one of the worsts; it is an extremely poor and hard oxygen nucleophile. Therefore, nucleophilic 1,4-additions of salicylaldehyde to conjugated aldehyde or nitroalkene are often challenging and their asymmetric versions are extremely limited.[4-9] In the aminocatalytic addition of salicylaldehyde to conjugated aldehyde, the poor nucleophilicity of salicylaldehyde is compensated by activation of the aldehyde *via* formation of a more electrophilic and hard conjugated iminium ion that facilitates the addition of the 'hard' phenolic oxygen (Figure 1). Whereas, in case of addition to conjugated nitroalkene, the reaction of salicylaldehyde with the catalyst forms an iminium ion to reduce the nucleophilicity further. As a result, addition of salicylaldehyde to α,β-unsaturated nitroalkene is extremely difficult leading to poor enantioselectivity, and longer reaction time.

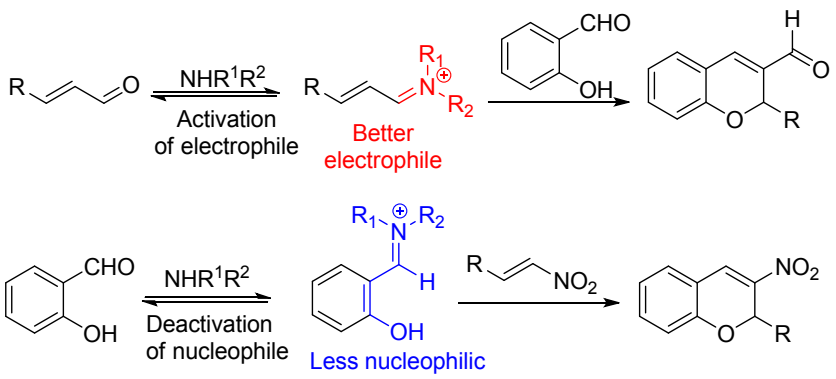


Figure 1. 1,4-Addition of salicylaldehyde

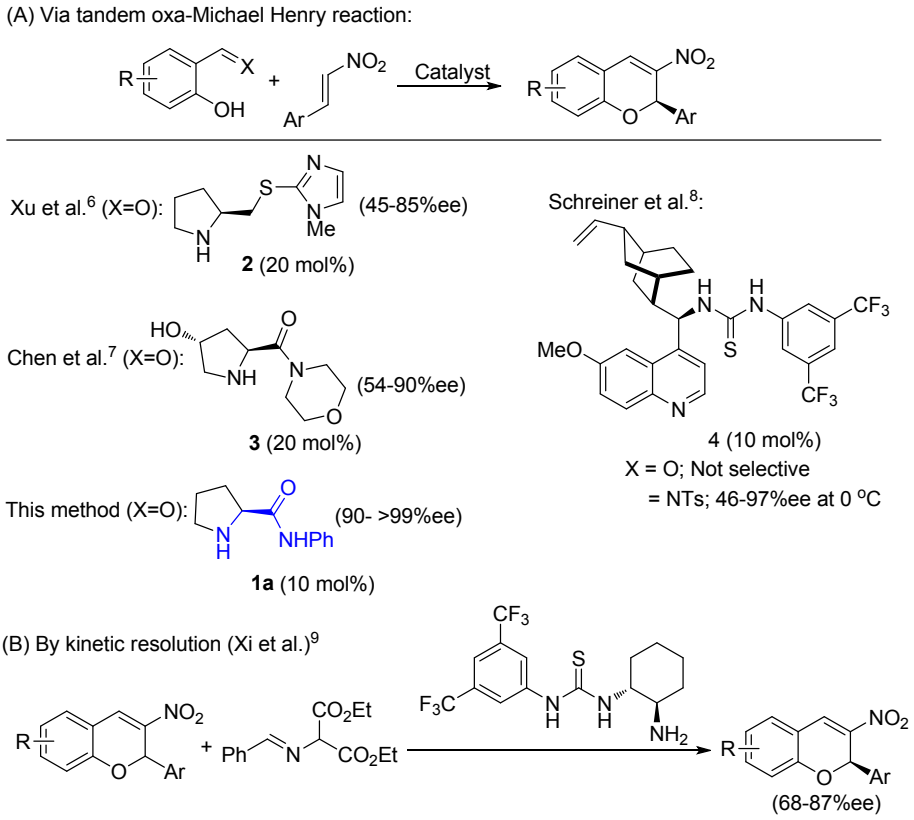
One of the major applications of asymmetric oxa-Michael addition of phenols to α,β-unsaturated olefins is the synthesis of chromenes or benzo-pyrans.[4-13] They are useful building blocks for synthesis of many biologically active heterocyclic compounds having antitumor, antiviral, antimicrobial, anti-anaphylactic, antidiabetic, anticoagulant, and diuretic properties.[14-22] Among the 2*H*-chromenes, 3-nitro-2*H*-chromenes have attracted attention from synthetic chemist due to their diverse applications.[23] 3-Nitro-2*H*-chromenes have shown second harmonic generation for potential application as nonlinear optical materials.[24] It also acts as precursors to a variety of medicinally important 2*H*-benzopyran derivatives such as flavonols,[25] and amines.[26] Moreover, the scope of manipulating the nitroalkene moieties for the synthesis of important target molecules,[27] and the extent of difficulty to achieve good enantioselectivity in their asymmetric synthesis have unleashed an opportunity and a challenge.

It is pertinent to note that asymmetric synthesis of 2-aryl-3-nitro-2*H*-chromenes via the tandem oxa-Michael Henry reaction of salicylaldehyde with β-nitrostyrenes is extremely

limited and gives only moderate enantioselectivity. Xu and coworkers employed 1-methyl-2-((pyrrolidin-2-ylmethyl) thio)-1*H*-imidazole (**2**) derived from L-proline to catalyze the reaction of salicylaldehyde with β-nitrostyrene to observe moderate enantioselectivities in most of the cases.[6] Given the ready accessibility of L-proline, they tested the catalytic activity of L-proline for the said reaction and observed poor yield with no enantioselectivity. Chen and coworker[7] employed a tertiary amide derivative of 4-hydroxy L-proline (**3**) as catalyst to achieve mostly moderate enantioselectivity. Additionally, these methods[6,7] suffer from high catalyst loading (20 mol%) and long reaction time (3-5 days). Although Schreiner and coworkers used a cinchona derived bifunctional thiourea (**4**) catalyst to synthesize chiral 2-aryl-3-nitro-2*H*-chromenes directly from the reaction of salicylaldehyde and *β*-nitrostyrene, they observed low yields along with negligible stereoinduction. By using salicyl-*N*-tosylimine in place of salicylaldehyde, they could synthesize chiral 2-aryl-3-nitro-2*H*-chromenes in moderate to good yields and enantioselectivities *via* a tandem oxa-Michael-aza-Henry-desulfonamidation pathway.[8] Since kinetic resolution is one of mainstays in asymmetric synthesis, Xi et al.[9] employed a bifunctional thiourea catalyzed kinetic resolution of racemic 3-nitro-2*H*-chromenes to

achieve optically active (*R*)-3-nitro-2*H*-chromene derivatives with moderate to good enantioselectivities (Scheme 1). Unlike the methods for usual kinetic resolution, where the synthesis of both the enantiomers remains the primary target, this reaction led to irreversible formation of moderately enantioselective multifunctional 3,4-diphenyl-3a-nitrobenzo-pyrano-[3,4-c]pyrrolidine-1,1-dicarboxylate derivatives and hence the opposite enantiomers did not form.

Scheme 1. Enantioselective synthesis of 2-aryl-3-nitro-2*H*-chromenes



Results and Discussion

The fact that asymmetric synthesis of 2-aryl-3-nitro-2*H*-chromenes suffers from poor reactivity and the reversible nature of the reaction,[28] the development of an effective catalyst that can stabilize the oxa-Michael intermediate and facilitates rapid Henry reaction in the subsequent step is critical to achieve high enantioselectivity. The efficiency of asymmetric catalysis ideally depends on spatial interactions between the reactants and catalyst. Therefore, optimization of these interactions is often dictated by position and orientation of interacting groups rather than steric congestion in the catalytic site. We proposed that a stable H-bond donor functional group nearer to the asymmetric centre of L-proline core might help in having a better asymmetric 1,4-addition of salicylaldehyde with the β-nitroalkene acceptor, which may in turn lead to better enantioselectivity in the

aforesaid tandem oxa-Michael-Henry reaction. Since L-prolinamides offer such structural features and are among the most easily accessible L-proline derivatives, we planned to employ a secondary amide derived from L-proline to catalyze the reaction of salicylaldehyde with β-nitroalkene. We reasoned that the N-H group in a conformationally rigid secondary amide might activate the β-nitroalkene *via* H-bonding to dictate the *si*-face attack by the phenolic oxygen of salicylaldehyde on the β-nitroalkene to give one enantiomer preferentially (Figure 2).

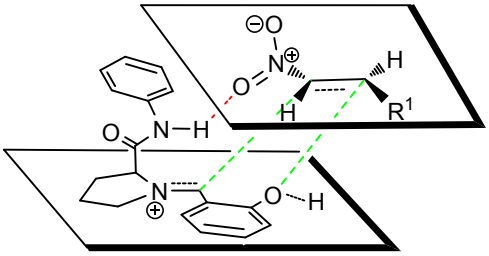


Figure 2. Mechanistic perspective on H-bonding directed oxa-Michael addition

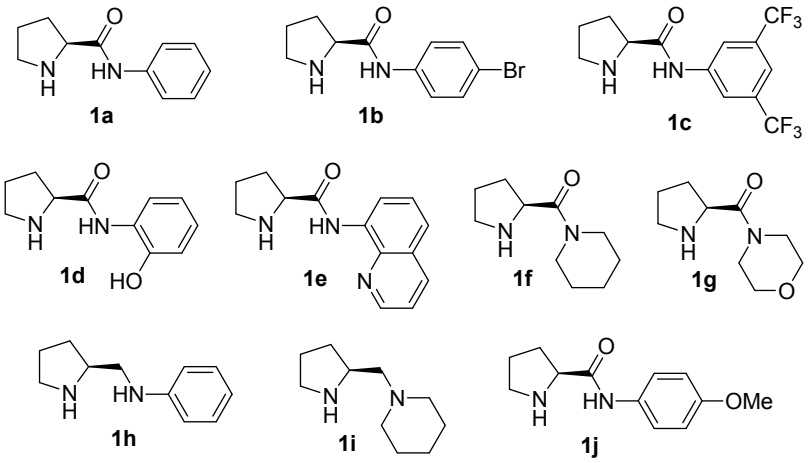
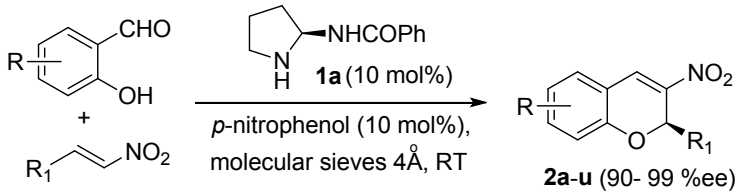


Figure 3. L-Proline derived amidoamine catalysts

Therefore, we synthesized a series of amides (Figure 3, **1a**-**g**, **1j**) starting from the reaction of Boc-L-proline and aromatic/hetero-aromatic amines following literature protocol[29,30] and tested their catalytic efficiency for asymmetric synthesis of 2-aryl-3-nitro-2*H*-chromenes. Our studies led to discovery of one of the simplest, efficient and highly enantioselective methods for the said synthesis employing a catalytic amount of phenyl L-prolinamide (Scheme 2).

Scheme 2. Synthesis of 2-aryl/furyl-3-nitro-2*H*-chromene

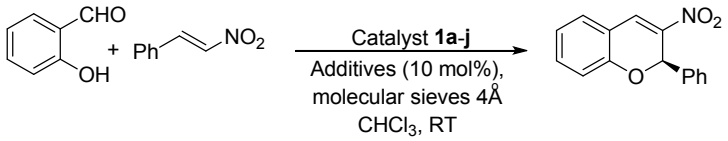


2a-**u** (90- 99 %ee)

The L-proline derived arylamides (**1a**-**e**) were employed to understand the effect of the N-H in governing the enantioselectivity of the reaction. We proposed that if a tertiary amide is used, the nitroalkene should approach the iminium salt from the opposite side of the sterically hindered amide functionality due to the absence of the NH in the tertiary amide group to generate the opposite stereoisomer. Therefore, the L-proline derived tertiary amide analogues (**1f**-**g**) were synthesized to evaluate if a tertiary amide group in the catalyst facilitates the binding of the nitroalkene with the catalyst. To evaluate the efficacy of amidoamines, a model reaction of salicylaldehyde with β-nitrostyrene was carried out in the presence of a catalytic amount of phenyl-L-prolinamide, **1a** (10 mol%) and *p*-nitrophenol (10 mol%) in chloroform (Table 1, entry 1). The reaction took almost 36 h at ambient temperature (22 ^{o}C) to undergo complete conversion. The structure of the product confirmed by IR, NMR, and MS. HPLC analysis of the compound employing Chiralcel AS-H column revealed excellent formation of (*R*)-isomer in 99% ee. To understand the role of the Bronsted acid better, we screened some other protic acids (Table 1, entries 1-7) to find that reaction rate and the extent of enantioselectivity is barely dependent on the nature of the Bronsted acid under our reaction conditions, while the

reaction time was found shortest when p-nitrophenol was used. Therefore, we screened all the other catalysts in the presence of *p*-nitrophenol as an additive. Substitution on the phenyl ring with electron withdrawing groups (**1b**-**c**) and H-bond donor (**1d**) and acceptor (**1e**) groups hardly helped in enhancing catalytic efficiency of the model reaction under similar reaction conditions.

Table 1. Screening of catalyst and additives[a-c]



Entry	catalyst	additives	t/h	%yield[d]	%ee[e]
1	**1a** (10)	*p*-nitrophenol	36	92	>99
2		PhCOOH	60	90	>99
3		TFA	60	88	>99
4		CH_3COOH	60	90	>99
5		*p*-$NO_2C_6H_4CO_2H$	60	92	99
6		*p*-TsOH	60	87	>99
7		None	60	40	92
8	**1b** (10)	*p*-nitrophenol	36	88	76

9	**1c** (10)	*p*-nitrophenol	36	90	15
10	**1d** (10)	*p*-nitrophenol	36	89	96
11	**1e** (10)	*p*-nitrophenol	36	92	24
12	**1f** (10)	*p*-nitrophenol	120	80	>99
13	**1f** (10)	None	120	25	90
14	**1g** (10)	*p*-nitrophenol	120	84	10
15	**1h** (10)	*p*-nitrophenol	120	87	20
16	**1i** (10)	*p*-nitrophenol	120	91	05
17	**1j** (10)	*p*-nitrophenol	120	79	10
18	**1a** (15)	*p*-nitrophenol	36	96	>99
19	**1a** (5)	*p*-nitrophenol	36	80	90
20	**1a** (10)	*p*-nitrophenol	120	90	92[f]

[a]Salicylaldehyde (0.5 mmol): Nitroalkene= 1:1. [b]Catalyst: Additive= 1:1. [c]50 mg of molecular sieves was used. [d]Isolated yields. [e]Stereoselectivity was determined by HPLC analysis of the crude mixture using Chiralcel AS-H column. [f]In the absence of 4Å molecular sieves.

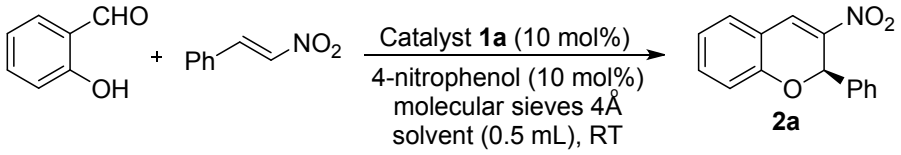
When the catalytic efficacy of the L-proline derived tertiary amides (**1f**-**g**) were screened in the model reaction keeping the other reaction parameters unchanged, surprisingly, the extent of enantioselectivity was found to be extremely good (>99%) with **1f** to give the (*R*)-isomer preferentially, despite taking longer reaction time (5 d) for completion. Since

the nitrogen of tertiary amide group is very difficult to protonate,[31] such finding is possible only when the oxygen of the amide is protonated.[32] Therefore, we concluded that the amide oxygen might have been protonated by *p*-nitrophenol to facilitate the *si*-face attack on the *β*-nitroalkene to give stereoselective oxa-Michael addition product. To reaffirm the possible role of the protonated carbonyl of the amide group in stereoinduction, we conducted the model reaction with a catalytic amount of **1f** (10 mol%) in the absence of *p*-nitrophenol keeping the other parameters unchanged (entry 13). The reaction was very slow and gave hardly 25% yield in 5 days. But we were very happy to note that, here too, the (*R*)-isomer was the major product with 90%ee. The role of the carbonyl group was further investigated by carrying out the model reaction in the presence of the diamines **1h** and **1i**. Here, the model reaction was very slow and gave poor enantioselectivities upon using **1h** and **1i** (Entries 15 and 16). These findings made it abundantly clear that the amide carbonyl has provided additional directional rigidity besides accelerating the reaction rate by getting protonated under our reaction conditions. Interestingly, when *p*-methoxyphenyl L-prolinamide (**1j**) bearing an electron-donating OMe group at the phenyl ring was tested as catalyst in the model reaction, the efficacy of the catalyst was found to

be very low (10% ee). The fact that the result was reminiscent of the reaction catalyzed by **1g** led us believe that there may be a competition of the protonated oxygen of the morpholine moiety (and *p*-methoxyphenyl) with the amide N-H of the catalyst to directs the approach of the nitroalkene. The catalyst loading was also optimized to observe that 10 mol% of catalyst loading serves the best (Entries 1, 18, 19). Our next step was to study the effect of solvent in the phenyl-L-prolinamide catalysed asymmetric synthesis of 2-aryl-3-nitro-2*H*-chromenes. All other solvents such as 1,2-dichloroethane, dichloromethane, THF, acetonitrile, and DMSO showed inferior results in terms of reaction rate, yield and enantioselectivity (Table 2). It is interesting to note that the model reaction showed very good enantioselectivity (96%) in methanol despite the solvent can potentially compete with the amide N-H to activate the nitroalkene *via* formation of H-bond. We reason that the amide group plays a dual role of activating the nitroalkene in oxa-Michael addition and subsequent Henry reaction for the formation of 3-nitro-2*H*-chromene derivatives. The fact that the oxa-Michael step is highly reversible, the formation of the 1,2-addition product is very critical to achieve a thermodynamically stable product. Even if methanol may activate the β-nitroalkene *via* H-bond to form the rapidly reversible oxa-Michael adduct, it

may not be able to bring the reacting sites close enough to facilitate the subsequent Henry reaction to generate the product. Moreover, the ambient temperature was found to be optimum to achieve good enantioselectivity and yields. While the reaction at 10 °C for 5 days gave 53% yield with >99% enantiomeric excess, the reaction at 40 °C showed the opposite effect despite reducing the reaction time considerably (Table 2).

Table 2. Screening of solvents[a]

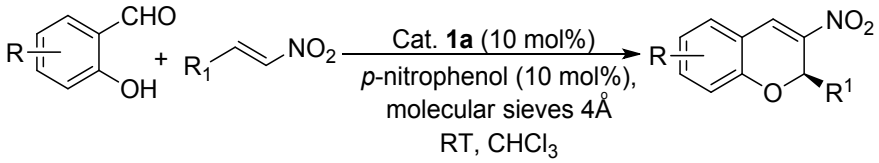


Entry	Solvent	Temp (°C)	t/h	Yield[b]	ee%[c]
1.	$C_2H_4Cl_2$	20	36	90	80
2.	CH_2Cl_2	20	36	92	96
3.	**$CHCl_3$**	**20**	**36**	**96**	**>99**
4.	THF	20	36	90	92
5.	CH_3CN	20	36	80	>99
6.	DMSO	20	36	97	42
7.	MeOH	20	36	82	96
8.	Isopropyl alcohol	20	36	84	96
9.	**$CHCl_3$**	**10**	**120**	**53**	**>99**
10.	$CHCl_3$	40	48	70	54

[a]Reactions were carried out at 0.5 mmol scale and 50 mg molecular sieves was used. [b]Isolated yields are reported. [c]Stereoselectivity was determined by HPLC analysis of the crude mixture using Chiralcel AS-H columns.

After optimizing the reaction parameters, the substrate scopes were studied to explore the versatility of our protocol (Table 3). To our pleasure, the reaction of salicylaldehyde with various *β*-nitrostyrene derivatives gave excellent yields and enantioselectivity at room temperature reaction conditions. Electron withdrawing or electron donating substituents on the phenyl ring of the *β*-nitrostyrene derivatives did not affect the yields and enantioselectivity. Some substrate and solvent specific enantioselectivity were also noted. For example, the reaction of salicylaldehyde with *p*-fluoro-*β*-nitrostyrene gave the corresponding 3-nitro-2*H*-chromene in 86%ee in chloroform (Entry 8) and 99%ee in acetonitrile medium (Entry 9). When 5-methoxy salicylaldehyde (Entries 13-19) was taken as the starting material, excellent yield and enantioselectivity were observed. Most importantly, the reaction works for highly docile nucleophile such as 5-chloro salicylaldehyde (entries 21, 22) to give excellent yield and enantioselectivity. The reaction of a *β*-nitroalkene with heterocyclic substituent, namely (*E*)-2-(2-furyl)nitroethene with salicylaldehyde under the optimized conditions gave the desired product in 99% ee (Entry 23).

Table 3. Synthesis of 2-aryl-3-nitro-2*H*-chromenes[a]



Entry	R	R^1	Product	t/h	%yield[b]	%ee[c]
1	H	Ph	**2a**	36	96	>99
2	H	4-$CH_3C_6H_4$	**2b**	36	92	84
3	H	4-$CH_3C_6H_4$	**2b**	36	94	>99[d]
4	H	4-$CH_3OC_6H_4$	**2c**	36	90	98
5	H	4-ClC_6H_4	**2d**	36	93	94
6	H	2-ClC_6H_4	**2e**	36	98	>99
7	H	3-BrC_6H_4	**2f**	36	92	>99
8	H	4-FC_6H_4	**2g**	36	94	86
9	H	4-FC_6H_4	**2g**	36	92	>99[e]
9	H	2-MeO C_6H_4	**2h**	48	97	>99
10	H	2,4-$(OCH_2O)C_6H_3$	**2i**	48	91	>99
12	H	1-naphthyl	**2j**	48	90	90
13	5-OMe	4-$CH_3C_6H_4$	**2k**	36	92	98
14	5-OMe	2-ClC_6H_4	**2l**	36	95	94
15	5-OMe	4-$CH_3OC_6H_4$	**2m**	36	90	>99
16	5-OMe	2-$CH_3OC_6H_4$	**2n**	36	94	98

17	5-OMe	4-FC_6H_4	**2o**	36	91	>99
18	5-OMe	C_6H_5	**2p**	36	95	>99
19	5-OMe	4-ClC_6H_4	**2q**	36	93	99
20	3-OMe	C_6H_5	**2r**	36	90	99
21	5-Cl	C_6H_5	**2s**	60	92	98
22	5-Cl	4-ClC_6H_4	**2t**	60	90	90
23	H	2-furyl	**2u**	60	91	99

[a]Reactions were carried out at 0.5 mmol scale and 50 mg molecular sieves was used. [b]Isolated yields are reported. [c]Stereoselectivity was determined by HPLC analysis of the crude mixture using Chiralcel AS-H columns. [d]Solvent is dichloromethane. [e]Solvent is acetonitrile

The fact that our reaction conditions work well for the reaction of salicylaldehyde with 1-nitropent-1-ene to give 2-butyl-3-nitro-2*H*-chromene (**3a**) in 90% yield with 96%ee (Scheme 3), the reaction does not depend on the nature of β-nitroalkene.

Scheme 3. Synthesis of 2-butyl-3-nitro-2*H*-chromenes

We conducted an experiment to ^{1}HNMR experiment by mixing the catalyst **1a** with β-nitrostyrene in $CDCl_3$ to understand their nature of interaction between them. We have noted significant downfield shift in δ value of the amide proton upon addition of the β-nitrostyrene to suggest that the nitro group of the nitroalkene might be forming H-bond with amide proton (Figure 4).

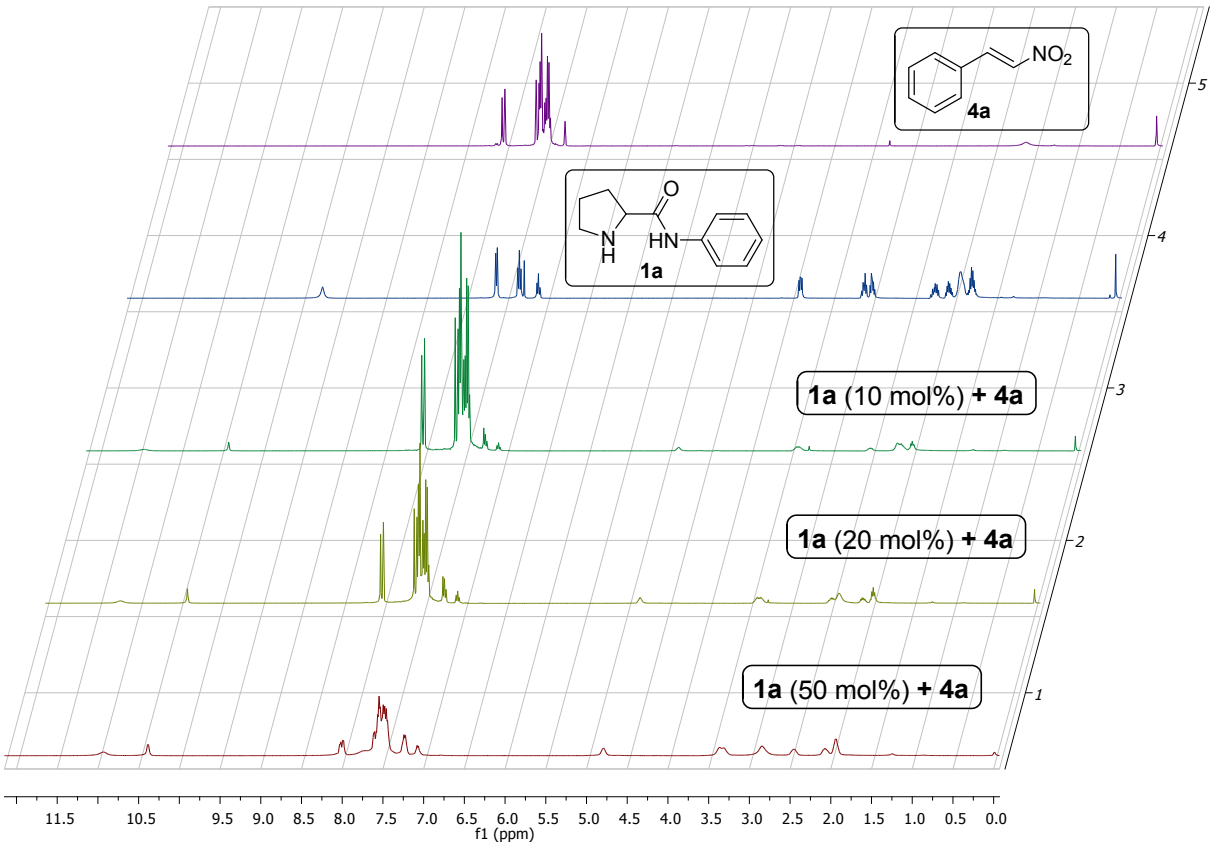


Figure 4. H-bonding interaction of the catalyst **1a** with β-nitrostyrene

Conclusion

In summary, the catalyst efficiency of an asymmetric organocatalyst can be improved by tuning the position and spatial orientation of the interacting functional groups. Here, a highly enantioselective asymmetric oxa-Michael addition of salicyaldehyde to β-nitroalkene to synthesize biologically important 2-alkyl/aryl/furyl-3-nitro-2*H*-chromenes was achieved by employing a simpler and readily accessible phenyl L-prolinamide. Poor reactivity of oxygen nucleophile towards 1,4-addition and low stereoselectivity due to the reversible nature of the oxa-Michael step of the reaction could be circumvented by employing a secondary amide bearing L-prolinamide derivative. The N-H of the conformationally rigid amide group might have played a profound role on the extent of enantioselective induction and the reaction rate in the asymmetric tandem oxa-Michael Henry reaction of salicylaldehyde with β-nitroalkenes. Given the difficulty attached to oxa-Michael reaction, achieving more than 99 %ee for many 2-aryl-3-nitro-2*H*-chromenes is an extremely good result. The reaction worked equally with 5-cholorosalicylaldehyde

which is extremely significant. Structural simplicity of the catalyst and its easy accessibility, wide substrate scope, low catalyst loading, short reaction time and excellent enantioselectivity are some of the salient features of this reaction.

Experimental Section

General Information. Unless otherwise mentioned, all chemicals and solvents were purchased from commercial suppliers and were used as received. Benzaldehyde was distilled before use. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer using TMS as internal reference with $CDCl_3$ as solvent, while the ^{13}CNMR spectra were recorded at 100 MHz. Mass spectra were obtained from Waters ZQ 4000 mass spectrometer by the ESI method, while the elemental analyses of the complexes were performed on a Perkin–Elmer-2400 CHN/S analyzer. Analytical HPLC was performed on a WATERS Series instrument using chiral stationary phase CHIRALPAK AS. Silica gel G and Silica gel 230-400 Mesh (E. Merck) was used for thin-layer chromatography (TLC) and flash column chromatography respectively. TLC plates were visualized by UV or

iodine or by immersion in anisaldehyde stain (by volume: 95% ethanol, 3.5% sulfuric acid, 1% acetic acid and 2.5 % anisaldehyde) followed by heating. All the nitroolefins were prepared freshly using reported procedure.[33] The catalysts **1a**-**e**[29,30,34], **1f**-**g**[7] and **1j**[35] were synthesized by following literature protocols. Racemic compounds were prepared by using DABCO as catalyst.[36] (S)-*N*-(pyrrolidin-2-ylmethyl)aniline and (S)-1-(pyrrolidin-2-ylmethyl)piperidine were purchased from Sigma-Aldrich.

Analytical data of the catalysts

***N*-Phenylpyrrolidine-2-carboxamide (1a).**[34] White solid. Yield 85%. M.p. 74-76 °C. $[\alpha]_D^{22}$= −74.2 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{20}$= −77.0 (c, 1.0, $CHCl_3$)].[6] IR (KBr cm^{-1}): ν 3266, 3134, 3057, 2969, 2871, 1670, 1599, 1525, 1443, 1384. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.73-1.82 (m, 2H), 1.91 (br s, 1H), 2.01-2.09 (m, 1H), 2.18-2.27 (m, 1H), 2.96-3.02 (m, 1H), 3.06-3.12 (m, 1H), 3.87 (dd, *J* = 5.2, 9.2 Hz, 1H), 7.07-7.11 (m, 1H), 7.30-7.34 (m, 2H), 7.60 (dd, *J* = 1.2, 8.8Hz, 2H), 9.74 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 26.1, 30.6, 47.2, 60.8, 119.3, 123.9, 128.9, 137.7, 173.0 ppm. Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.42; H, 7.36; N, 14.86.

***N*-(4-Bromophenyl) pyrrolidine-2-carboxamide (1b).**[34] Brown gum. Yield 84%. $[\alpha]_D^{22}$= −27.3 (c, 0.3, $CHCl_3$) [Lit. $[\alpha]_D^{20}$= −20.0 (c, 0.59, MeOH)].[7] IR (KBr, cm^{-1}): ν 3257, 3104, 3043, 2973, 1676, 1590, 1517, 1395. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.72-1.78 (m, 2H), 1.98-2.06 (m, 1H), 2.14 (br, 1H), 2.18-2.26 (m, 1H), 2.94-3.00 (m, 1H), 3.05-3.11 (m, 1H), 3.83-3.86 (dd, *J* = 4.8, 8.8 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 9.81 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 26.0, 30.5, 47.1, 60.7, 116.6, 121.0, 131.8, 136.8, 172.1 ppm. Anal. Calcd for $C_{11}H_{13}BrN_2O$: C, 49.09; H, 4.87; N, 10.41. Found: C, 48.99; H, 4.80; N, 10.44.

***N*-(3,5-Bis(trifluoromethyl)phenyl) pyrrolidine-2-carboxamide (1c).**[34] Colourless gum. Yield 80%. $[\alpha]_D^{22}$= −42.1 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{20}$= −37.0 (c, 0.05, $CHCl_3$)].[8] IR (KBr, cm^{-1}): ν 3246, 2977, 1693, 1531, 1473, 1441, 1383. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.76-1.82 (m, 2H), 2.01-2.09 (m, 1H), 2.21-2.3 (m, 1H), 2.55 (br, 1H), 2.99-3.05 (m, 1H), 3.10-3.16 (m, 1H), 3.92 (dd, *J* = 5.2, 8.8 Hz, 1H), 7.57 (s, 1H), 8.13 (s, 2H), 10.26 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 26.2, 30.6, 47.3, 60.8, 116.9-117.0 (unresolved),

118.8-118.9 (unresolved), 121.7, 124.4, 127.2, 131.6-132.6, 139.2, 174.3 ppm. Anal. Calcd for $C_{13}H_{12}F_6N_2O$: C, 47.86; H, 3.71; N, 8.59. Found: C, 47.91; H, 3.78; N, 8.58.

***N*-(2-Hydroxyphenyl) pyrrolidine-2-carboxamide (1d).**[34] Brown solid. Yield 84%. M.p. 164-166 °C. $[\alpha]_D^{22}$= −41.9 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{20}$= −45.6 (c, 1.0, CH_2Cl_2)].[9] IR (KBr, cm^{-1}): ν 3354, 3225, 3065, 2971, 2871, 1640, 1586, 1537, 1455, 1384. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76-1.83 (m, 2H), 2.02-2.10 (m, 1H), 2.18-2.3 (m, 1H), 2.99-3.05 (m, 1H), 3.10-3.15 (m, 1H), 3.94 (dd, *J* = 4.8, 9.6 Hz, 1H), 6.84 (dt, *J* = 1.6, 7.2 Hz, 1H), 6.91 (dd, *J* = 1.6, 8 Hz, 1H), 7.01 (dd, *J* = 1.6, 8 Hz, 1H), 7.09-7.14 (m, 1H), 9.99 (s, 1H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 25.9, 30.6, 47.0, 60.4, 117.1, 119.5, 120.7, 125.1, 125.4, 147.5, 174.4 ppm. MS (ESI) calcd for $C_{11}H_{14}N_2O_2$ 207.1, found *m/z* 207.05 $[M+H]^+$. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.97; H, 6.78; N, 13.61.

***N*-(Quinolin-8-yl) pyrrolidine-2-carboxamide (1e).**[34] Beige solid. Yield 88%. M.p. 145-147 °C. $[\alpha]_D^{22}$= +24.4 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{20}$= +18.6 (c, 1.0, $CHCl_3$)].[8] IR (KBr cm^{-1}): ν 3400, 3302, 2972, 2868, 1677, 1528, 1486, 1424, 1384. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.72-1.89 (m, 2H), 2.08-2.14 (m, 1H), 2.23-2.32 (m, 2H), 3.11-3.2 (m, 2H), 4.01 (dd, *J* = 5.2,

9.2 Hz, 1H), 7.43 (dd, *J* = 4, 8 Hz, 1H), 7.48-7.55 (m, 2H), 8.13 (dd, *J* = 1.6, 8 Hz, 1H), 8.83 (dd, *J* = 1.6, 7.2 Hz, 1H), 8.87 (dd, *J* = 1.6, 4.4 Hz, 1H), 11.60 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 26.0, 31.0, 47.4, 61.8, 116.3, 121.3, 121.6, 127.1, 128.0, 134.3, 136.1, 139.0, 148.5, 174.2 ppm. MS (ESI) calcd for $C_{14}H_{15}N_3O$ 241.1, found *m/z* 242.0 $[M+H]^+$. Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.57; H, 6.21; N, 17.45.

Piperidin-1-yl(pyrrolidin-2-yl)methanone (1f).[7] Yellow gum. Yield 80 %. $[\alpha]_D^{22}$= -47.2 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{20}$= -53.0 (c, 0.54, MeOH)].[10] IR (KBr cm^{-1}): ν 3445, 2948, 2866, 1642, 1482, 1449, 1418. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.6-1.69 (m, 6H), 1.88-1.96 (m, 1H), 1.99-2.08 (m, 1H), 2.10-2.21 (m, 1H), 2.47-2.56 (m, 1H), 3.41-3.59 (m, 7H), 4.81 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 23.9, 24.8, 25.2, 25.8, 29.7, 44.2, 46.4, 46.6, 58.1, 166.3 ppm. Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 65.86; H, 9.90; N, 15.46.

Morpholino(pyrrolidin-2-yl)methanone (1g).[7] Light brown gum. Yield 84 %. $[\alpha]_D^{22}$= -62.4 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{20}$= -59.1 (c, 2.0, MeOH)]. IR (KBr, cm^{-1}): ν 3441, 2952, 2862,

1643, 1482, 1449, 1419. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.88-1.96 (m, 1H), 2.00-2.07 (m, 1H), 2.11-2.18 (m, 1H), 2.45-2.54 (m, 1H), 3.45-3.57 (m, 6H), 3.70-3.75 (m, 5H), 4.83 (s, 1H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 24.6, 29.5, 43.1, 45.7, 46.8, 57.9, 66.0, 66.3, 167.0 ppm. Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 59.51; H, 8.68; N, 15.36.

N-(4-Methoxyphenyl)pyrrolidine-2-carboxamide.[35] Beige solid. Yield 84%. M.p. 80-81 °C. [α]D22= −27.3 (c, 0.3, $CHCl_3$) [Lit. $[\alpha]_D^{25}$= -20.2 (c, 0.92, MeOH)]. IR (KBr cm^{-1}): ν 3411, 3301, 2970, 2865, 1672, 1529, 1381. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.71-1.76 (m, 2H), 1.97-2.05 (m, 1H), 2.14-2.21 (m, 2H), 2.93-3.08 (m, 2H), 3.77 (s, 3H), 3.81-3.84 (m, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 9.62 (s, 1H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 26.2, 30.6, 47.2, 55.4, 60.8, 113.9, 120.7, 131, 155.9, 173.1 ppm. MS (ESI) calcd for $C_{12}H_{16}N_2O_2$ 220.1, found *m/z* 221.1 $[M+H]^+$. Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.41; H, 7.33; N, 12.75.

General procedure for synthesis of 2-alkyl/aryl-3-nitro-2*H*-chromenes. A 10 mL round bottom flask equipped with a stirring bar was charged with salicylaldehyde (61 mg, 0.5 mmol), catalyst **1a** (10 mg, 0.05 mmol), molecular sieves (4 Å, 0.05 g), 4-nitrophenol (7 mg, 0.05 mmol), and trans-*β*-nitroalkene (0.5 mmol) in chloroform (0.5 mL) and allowed to stir at room temperature for specified time. The reaction mixture was then directly transferred to a silica gel column and purified by using ethyl acetate in hexane as eluent to get the desired product.

Analytical data of 2-alkyl/aryl/furyl-3-nitro-2*H*-chromenes

3-Nitro-2-phenyl-2*H*-chromene (2a).[7] Yellow solid; R_f = 0.5 (1:9, ethyl acetate: hexane). Yield: 120 mg (96%). M.p. 92-93 ^oC. $[\alpha]_D^{22}$=-41 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{25}$ = -33.0 (c 0.27, ethanol)].[12] IR (KBr): ν 3071, 3032, 1648, 1605, 1544, 1511, 1325, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 6.59 (s, 1H), 6.87(d, *J* = 8 Hz, 1H), 7.01 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.31-7.35 (m, 5H), 7.37-7.40 (m, 2H), 8.07 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ*74.2, 117.2, 117.9, 122.5, 127.0, 128.8, 129.3, 129.4, 130.4, 134.3, 136.7, 141.1, 153.5 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH,

90:10, 1.0 mL min^{-1}): τ_{major} = 8.27 min (100% ee). MS (ESI) calcd for $C_{15}H_{11}NO_3$ 253.0, found *m/z* 253.1$[M]^+$. Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.10; H, 4.36; N, 5.56.

3-Nitro-2-(p-tolyl)-2*H*-chromene (2b).[6] Yellow solid; R_f = 0.54 (1:9, ethyl acetate: hexane). Yield: 122 mg (92%). M.p. 138- 140 °C. $[\alpha]_D^{22}$= -6.89 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{25}$ = -34.5 (c 0.35, ethanol)].[11] IR (KBr): ν 3066, 3023, 2960, 1650, 1607, 1504, 1333, 1064 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 3.1 (s, 3H), 6.54 (s, 1H), 6.84 (d, J = 8 Hz, 1H), 6.98 (dt, J = 0.8, 7.6 Hz, 1H), 7.11 (d, J = 8 Hz, 2H), 7.24-7.32 (m, 4H), 8.04 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.2, 74.1, 117.3, 118.0, 122.4, 127.0, 129.1, 129.5, 130.3, 133.8, 134.2, 139.5, 141.2, 153.5 ppm. The ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 7.41 min, τ_{minor} = 10.48 min (84% ee). The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 7.84 min, (100% ee)(CH_2Cl_2 as solvent in reaction medium). MS (ESI) calcd for $C_{16}H_{13}NO_3$ 267.0, found *m/z* 267.1$[M]^+$. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.86; H, 4.89; N, 5.25.

2-(4-Methoxyphenyl)-3-nitro-2*H*-chromene (2c).[6] Yellow solid; R_f = 0.46 (1:9, ethyl acetate: hexane). Yield: 126 mg (90%). M.p. 162-164 °C. $[\alpha]_D^{22}$= -51.1 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{25}$ = -20.0 (c 0.22, ethanol)].[11] IR (KBr): ν 3069, 3011, 2959, 2904, 2839, 1649, 1606, 1509, 1329, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H), 6.51 (s, 1H), 6.80-6.84 (m, 3H), 6.98 (t, J = 8 Hz, 1H), 7.29-7.31 (m, 4H), 8.03 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.2, 73.9, 114.1, 117.3, 118.0, 122.4, 128.5, 128.9, 129.0, 130.3, 134.2, 141.3, 153.5, 160.4 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 15.83 min, τ_{minor} = 11.31 min (98% ee). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{13}NO_4Na$ 306.0737; Found 306.0755. MS (ESI) calcd for $C_{16}H_{13}NO_4$ 283.0, found *m/z* 283.1 $[M]^+$. Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.81; H, 4.60; N, 4.91.

2-(4-Chlorophenyl)-3-nitro-2*H*-chromene (2d).[9] Yellow solid; R_f = 0.4 (1:9, ethyl acetate: hexane). Yield: 132 mg (93%). M.p. 139-140 °C. $[\alpha]_D^{22}$= -29.3 (c, 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{25}$ = -20.0 (c 0.19, ethanol)].[11] IR (KBr): ν 3081, 3010, 1644, 1608, 1510, 1333, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.54 (s, 1H), 6.86 (d, J = 12 Hz, 1H), 7.02 (dt, J = 0.8, 7.6 Hz,

1H), 7.29-7.36 (m, 6H), 8.06 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 73.4, 117.3, 117.7, 122.7, 128.4, 129.0, 129.5, 130.5, 134.5, 135.2, 135.4, 140.7, 153.2 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 10.85 min, τ_{minor} = 13.37 min (94% ee). MS (ESI) calcd for $C_{15}H_{10}ClNO_3$ 287.0, found *m/z* 287 $[M]^+$. Anal. Calcd for $C_{15}H_{10}ClNO_3$: C, 62.62; H, 3.50; N, 4.87. Found: C, 62.61; H, 3.47; N, 4.84.

2-(2-Chlorophenyl)-3-nitro-2*H*-chromene (2e). Yellow solid; R_f = 0.4 (1:9, ethyl acetate: hexane). Yield: 140 mg (98%). M.p. 137-138 °C. $[\alpha]_D^{22}$= - 9.85 (c, 1.0, $CHCl_3$). IR (KBr): ν 3074, 3012, 1642, 1601, 1508, 1322, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.83 (d, *J* = 8 Hz, 1H), 7.02 (dt, *J* = 0.8, 7.6 Hz, 1H), 7.08 (s, 1H), 7.12-7.16 (m, 1H), 7.20 (dd, *J* = 4, 8 Hz, 1H), 7.29- 7.37 (m, 3H), 7.49 (d, *J* = 0.8, 8 Hz, 1H), 8.17 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 70.7, 117.4, 117.7, 122.6, 127.1, 127.9, 130.2, 130.3, 130.6, 130.9, 133.2, 134.1, 134.4, 140.1, 153.1 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 7.79 min (100% ee).

MS (ESI) calcd for $C_{15}H_{10}ClNO_3$ 287.0, found *m/z* 287.1 $[M]^+$. Anal. Calcd for $C_{15}H_{10}ClNO_3$: C, 62.62; H, 3.50; N, 4.87. Found: C, 62.59; H, 3.52; N, 4.88.

2-(3-Bromophenyl)-3-nitro-2*H*-chromene (2f). Yellow solid; R_f = 0.4 (1:9, ethyl acetate: Hexane). Yield: 152 mg (92%). M.p. 115-117 °C. $[\alpha]_D^{22}$= -49.3 (c, 1.0, $CHCl_3$). IR (KBr): ν 3066, 3010, 1648, 1605, 1511, 1328, 1069 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.59 (s, 1H), 6.94 (d, J = 8Hz, 1H), 7.08 (t, J = 8 Hz, 1H), 7.22-7.27 (m, 1H), 7.31-7.36 (m, 1H), 7.38-7.40 (m, 2H), 7.50-7.56 (m, 2H), 8.13 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ73.3, 117.3, 117.6, 122.8, 122.9, 125.6, 129.7, 130.1, 130.4, 130.6, 132.5, 134.5, 138.9, 140.3, 153.2 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 7.88 min, τ_{minor} = 12.53 min (>99% ee). MS (ESI) calcd for $C_{15}H_{10}BrNO_3$ 330.9, found *m/z* 331.0 $[M]^+$. Anal. Calcd for $C_{15}H_{10}BrNO_3$: C, 54.24; H, 3.03; N, 4.22. Found: C, 54.25; H, 3.03; N, 4.24.

2-(4-Fluorophenyl)-3-nitro-2*H*-chromene (2g).[9] Yellow solid; R_f = 0.4 (1:9, ethyl acetate: hexane). Yield: 127 mg (94%). M.p. 93-95 °C. $[\alpha]_D^{22}$= -6.23 (c, 1.0, $CHCl_3$). IR (KBr): ν 3069, 3006, 1646, 1601, 1509, 1328, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.56 (s,

1H), 6.87 (d, *J* = 8 Hz, 1H), 6.98-7.04 (m, 3H), 7.32-7.38 (m, 4H), 8.07 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 73.4, 115.7, 115.9, 117.3, 117.8, 122.7, 128.9, 129.0, 129.3, 130.4, 132.7, 132.7, 134.4, 141.0, 153.3, 162.0, 164.5 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 8.73 min, τ_{minor} = 11.44 min (86% ee)($CHCl_3$ as solvent in reaction medium). The ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 9.57 min, (100% ee) (CH_3CN as a solvent). MS (ESI) calcd for $C_{15}H_{10}FNO_3$ 271.0, found *m/z* 271.1 $[M]^+$. Anal. Calcd for $C_{15}H_{10}FNO_3$: C, 66.42; H, 3.72; N, 5.16. Found: C, 66.46; H, 3.75; N, 5.22.

2-(2-Methoxyphenyl)-3-nitro-2*H*-chromene (2h).[8] Yellow solid; R_f = 0.54 (1:9, ethyl acetate: hexane). Yield: 136 mg (97%). M.p. 109-111 °C. IR (KBr): ν 3066, 3014, 2949, 2914, 2840, 1648, 1607, 1509, 1325, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.91 (s, 1H), 6.80 (s, 1H), 6.83 (d, *J* = 8 Hz, 1H), 6.95-7.00 (m, 2H), 7.06 (s, 1H), 7.16 (dt, *J* = 1.6, 7.6 Hz, 3H), 7.29-7.34 (m, 3H), 8.09 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.8, 68.8, 111.4, 117.2, 118.0, 120.4, 122.1, 124.3, 127.9, 129.6, 130.1, 131.0, 134.0, 140.6, 153.7, 157.2

ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 7.79 min (100% ee). MS (ESI) calcd for $C_{16}H_{13}NO_4$ 283.0, found *m/z* 283.1 $[M]^+$. Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.90; H, 4.66; N, 5.01.

2-(Benzo[d][1,3]dioxol-5-yl)-3-nitro-2*H*-chromene (2i). Yellow solid; R_f = 0.3 (1:9, ethyl acetate: hexane). Yield: 134 mg (91%). M.p. 114-116 °C. IR (KBr): ν 3078, 2084, 2940, 1644, 1609, 1504, 1322, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 5.93 (s, 2H), 6.49 (s, 1H), 6.73 (d, *J* = 8 Hz, 1H), 6.85-6.87 (m, 3H), 7.01 (dt, *J* = 0.8, 7.2 Hz 1H), 7.31-7.35 (m, 2H), 8.05 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 74.1, 101.3, 107.5, 108.4, 117.3, 117.8, 121.1, 122.5, 129.1, 130.4, 130.5, 134.3, 148.0, 148.6, 153.4 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 24.69 min (100% ee). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{11}NO_5Na$ 320.0529; Found 320.0540. MS (ESI) calcd for $C_{16}H_{11}NO_5$ 297.0, found *m/z* 297.1 $[M]^+$. Anal. Calcd for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73; N, 4.71. Found: C, 64.61; H, 3.71; N, 4.75.

2-(Naphthalen-1-yl)-3-nitro-2*H*-chromene (2j).[6] Yellow solid; R_f = 0.35 (1:9, ethyl acetate: hexane). Yield: 135 mg (90%). M.p. 178-179 °C. $[\alpha]_D^{22}$= -10.08 (c, 1.0, $CHCl_3$). IR (KBr): ν 3067, 2958, 1640, 1605, 1566, 1507, 1323, 1075 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.71 (d, J = 8 Hz, 1H), 6.98 (dt, J = 0.8, 7.6 Hz, 1H), 7.21 (dt, J = 4, 8 Hz, 1H), 7.28-7.33 (m, 2H), 7.37 (dd, J = 1.6, 7.6 Hz, 1H), 7.43 (s, 1H), 7.57-7.61 (m, 1H), 7.70-7.74 (m, 1H), 7.84 (dd, J = 2, 7.2 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 8.28 (s, 1H), 8.57 (d, J = 8 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 70.6, 117.4, 118.2, 122.6, 123.8, 124.7, 124.8. 126.2, 127.0, 128.8, 130.3, 130.4, 130.5, 130.6, 131.2, 134.1, 134.2, 140.2, 153.5 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 6.77 min, τ_{minor} = 8.15 min (90% ee). MS (ESI) calcd for $C_{19}H_{13}NO_3$ 303.0, found m/z 303.1 $[M]^+$. Anal. Calcd for: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.30; H, 4.35; N, 4.65.

6-Methoxy-3-nitro-2-(p-tolyl)-2*H*-chromene (2k). Red solid; R_f = 0.4 (1:9, ethyl acetate: hexane). Yield: 136 mg (92%). M.p. 141-143 °C. $[\alpha]_D^{22}$= -31.05 (c, 1.0, $CHCl_3$). IR (KBr): ν 3001, 2964, 2920, 1645, 1612, 1546, 1505, 1330, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):

δ 2.31 (s, 3H), 3.79 (s, 3H), 6.50 (s, 1H), 6.79 (d, J = 8 Hz, 1H), 6.82 (d, J = 4 Hz, 1H), 6.88 (dd, J = 4, 8 Hz, 1H), 7.12 (d, J = 8 Hz, 2H), 7.25 (d, J = 8 Hz, 2H), 8.02 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.2, 55.7, 73.8, 113.6, 118.1, 118.4, 120.5, 126.9, 129.2, 129.4, 133.5, 139.4, 141.8, 147.4, 154.6 ppm. The % ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 7.79 min, τ_{minor} = 14.09 min (98% ee). MS (ESI) calcd for $C_{17}H_{15}NO_4$ 297.1, found m/z 297.1 $[M]^+$. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.69; H, 5.11; N, 5.10.

2-(2-Chlorophenyl)-6-methoxy-3-nitro-2*H*-chromene (2l). Red solid; R_f = 0.4 (1:9, ethyl acetate: hexane). Yield: 150 mg (95%). M.p. 148-151 °C. $[\alpha]_D^{22}$= -3.77 (c, 1.0, $CHCl_3$). IR (KBr): ν 3005, 2958, 2928, 1650, 1572, 1516, 1326, 1066 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.75 (d, J = 8 Hz, 1H), 6.85-6.88 (m, 2H), 7.01-7.02 (m, 1H), 7.09-7.16 (m, 2H), 7.25-7.29 (m, 1H), 7.47 (d, J = 8 Hz, 1H), 8.12 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.8, 70.6, 113.6, 118.2, 118.3, 120.7, 127.0, 127.9, 130.3, 130.6, 130.8, 132.9, 134.1, 140.7, 147.0, 154.8 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 7.60 min, τ_{minor} = 9.14

min (94% ee). MS (ESI) calcd for $C_{16}H_{12}ClNO_4$ 317.0, found *m/z* 317.0 $[M]^+$. Anal. Calcd for $C_{16}H_{12}ClNO_4$: C, 60.48; H, 3.81; N, 4.41. Found: C, 60.50; H, 3.81; N, 4.43.

2-(4-Methoxyphenyl)-6-methoxy-3-nitro-2*H*-chromene (2m). Red solid; R_f = 0.4 (1:9, ethyl acetate: hexane). Yield: 140 mg (90%). M.p. 147-148 °C. $[\alpha]_D^{22}$= -4.84 (c, 1.0, $CHCl_3$). IR (KBr): ν 3009, 2963, 2837, 1646, 1608, 1577, 1511, 1331, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.77 (s, 3H), 6.47 (s, 1H), 6.76-6.82 (m, 4H), 6.87 (dd, *J* = 2, 8.8 Hz, 1H), 7.27 (d, *J* = 8 Hz, 2H), 8.00 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.2, 55.7, 73.7, 113.5, 114.0, 118.1, 118.4, 120.5, 128.5, 128.6, 129.1, 141.9, 147.3, 154.6, 160.3 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 22.16 min (100% ee). MS (ESI) calcd for $C_{17}H_{15}NO_5$ 313.0, found *m/z* 313.1 $[M]^+$. Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.14; H, 4.80; N, 4.50.

2-(2-Methoxyphenyl)-6-methoxy-3-nitro-2*H*-chromene (2n). Red solid; R_f = 0.4 (1:9, ethyl acetate: hexane). Yield: 146 mg (94%). M.p. 137-139 °C. IR (KBr): ν 3001, 2958, 2840, 1644, 1608, 1581, 1512, 1331, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H),

3.93 (s, 3H), 6.75 (d, *J* = 8 Hz, 1H), 6.79-6.84 (m, 3H), 6.96 (d, *J* = 8 Hz, 1H), 7.03 (s, 1H), 7.12 (d, *J* = 8 Hz, 1H), 7.31 (t, *J* = 8 Hz, 1H), 8.06 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 55.7, 55.8, 68.4, 111.4, 113.5, 118.1, 118.5, 120.3, 120.3, 123.9, 127.7, 129.6, 131.0, 141.3, 147.5, 154.5, 157.2 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 9.40 min, τ_{minor} = 13.20 min (98% ee). MS (ESI) calcd for $C_{17}H_{15}NO_5$ 313.0, found *m/z* 313.1 $[M]^+$. Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.20; H, 4.80; N, 4.45.

2-(4-Fluorophenyl)-6-methoxy-3-nitro-2*H*-chromene (2o). Red solid; R_f = 0.35 (1:9, ethyl acetate: hexane). Yield: 136 mg (91%). M.p. 140-142 °C. $[\alpha]_D^{22}$= -34.64 (c, 1.0, $CHCl_3$). IR (KBr): ν 3076, 2960, 1643, 1604, 1574, 1507, 1323, 1068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.79 (s, 3H), 6.51 (s, 1H), 6.79-6.84 (m, 2H), 6.90 (dd, *J* = 4, 8 Hz, 1H), 7.00(t, *J* = 8 Hz, 2H), 7.33-7.36 (m, 2H), 8.03 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* 55.7, 73.2, 113.6, 115.7, 115.9, 118.1, 118.3, 120.7, 128.9, 129.0, 129.5, 132.4, 141.6, 147.1, 154.8, 161.9, 164.4 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 11.09 min (100% ee). HRMS (ESI-

TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{16}H_{12}FNO_4Na$ 324.0642; Found 324.0658. Anal. Calcd for $C_{16}H_{12}FNO_4$: C, 63.79; H, 4.01; N, 4.65. Found: C, 63.74; H, 3.99; N, 4.68.

6-Methoxy-3-nitro-2-phenyl-2*H*-chromene (2p).[8] Red solid; R_f = 0.56 (1:9, ethyl acetate: hexane). Yield: 133 mg (95%). M.p. 126-127 °C. IR (KBr): ν 3069, 3031, 1646, 1601, 1544, 1510, 1324, 1068 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 6.54 (s, 1H), 6.81(d, J = 8 Hz, 1H), 6.83 (d, J = 4 Hz, 1H), 6.89 (dd, J = 4, 8 Hz, 1H), 7.33-7.36 (m, 5H), 8.03 (s, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 55.8, 74.0, 113.6, 118.1, 118.4, 120.6, 127.0, 128.8, 129.4, 136.5, 141.8, 145.4, 147.4, 154.7 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 11.09 min (>99% ee). MS (ESI) calcd for $C_{16}H_{13}NO_4$ 283.0, found *m/z* 283.1 [M]$^+$. Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.79; H, 4.62; N, 5.00.

2-(4-Chlorophenyl)-6-methoxy-3-nitro-2*H*-chromene (2q). Red solid; R_f = 0.4 (1:9, ethyl acetate: hexane). Yield: 146 mg (93%). M.p. 139-140 °C. $[\alpha]_D^{22}$= -5.89 (c, 1.0, $CHCl_3$). IR (KBr): ν 3011, 2956, 2931, 1651, 1575, 1526, 1327, 1090 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.49 (s, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H),

6.89 (dd, J = 2.8, 8.8 Hz, 1H), 7.26-7.30 (m, 4H), 8.02 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 55.7, 73.2, 113.7, 118.1, 118.2, 120.8, 128.4, 129.0, 129.6, 135.0, 135.3, 141.3, 147.1, 154.8 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 15.02 min, τ_{minor} = 22.63 min (99% ee). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{12}ClNO_4Na$ 340.0347; Found 340.0352. Anal. Calcd for $C_{16}H_{12}ClNO_4$: C, 60.48; H, 3.81; N, 4.41. Found: C, 60.53; H, 3.82; N, 4.45.

8-Methoxy-3-nitro-2-phenyl-2*H*-chromene (2r).[6,7] Red solid; R_f = 0.5 (1:9, ethyl acetate: hexane). Yield: 126 mg (90%). M.p 121-123 °C. IR (KBr) = υ 3004, 2964, 2918, 1645, 1572. 1521, 1323, 1068 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.68 (s, 1H), 6.96 (s, 3H), 7.30-7.32 (m, 3H), 7.39-7.42 (m, 2H), 8.05 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 56.3, 74.1, 116.7, 118.7, 122.1, 122.4, 127.0, 128.7, 129.3, 129.4, 136.6, 141.3, 142.7, 148.6 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 15.02 min, τ_{minor} = 22.63 min (99% ee). MS

(ESI) calcd for $C_{16}H_{13}NO_4$ 283.0, found *m/z* 283.1 $[M]^+$. Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.90; H, 4.67; N, 4.95.

6-Chloro-3-nitro-2-phenyl-2*H*-chromene (2s).[6] Yellow solid; R_f = 0.6 (1:4, ethyl acetate: hexane). Yield: 131 mg (92%). M.p. 112-114 °C. $[\alpha]_D^{22}$= (c, 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.57 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 7.24 (dd, J = 2.4, 8.8 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.33-7.34 (m, 5H), 7.97 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 74.4, 118.6, 119.2, 127.0, 127.4, 127.9, 128.9, 129.4, 129.7, 133.7, 136.1, 142.1, 151.9 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 92:08, 1.0 mL min^{-1}): τ_{major} = 7.24 min, τ_{minor} = 6.63 min (98% ee). MS (ESI) calcd for $C_{15}H_{10}ClNO_3$ 287.0, 289.0 found *m/z* 310.1 $[M+Na]^+$, 312.0 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{10}ClNO_3$: C, 62.62; H, 3.50; N, 4.87. Found: C, 62.51; H, 3.62; N, 4.95.

6-Chloro-2-(4-chlorophenyl)-3-nitro-2*H*-chromene (2t). Yellow solid; R_f = 0.5 (1:4, ethyl acetate: hexane). Yield: 144 mg (90%). M.p. 116-118 °C. $[\alpha]_D^{22}$= (c, 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.54 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.29- 7.32 (m, 6H), 7.98 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 73.6, 118.6, 119.0, 127.6, 128.1, 128.4,

129.2, 129.5, 133.9, 134.6, 135.7, 141.7, 151.6 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 92:08, 1.0 mL min^{-1}): τ_{major} = 8.90 min, τ_{minor} = 7.55 min (90% ee). MS (ESI) calcd for $C_{15}H_9Cl_2NO_3$ 320.9, 322.9, found *m/z* 321.0 $[M]^+$, 323.1 $[M]^+$. Anal. Calcd for $C_{15}H_9Cl_2NO_3$: C, 55.93; H, 2.82; N, 4.35. Found: C, 55.99; H, 2.86; N, 4.32.

2-(Furan-2-yl)-3-nitro-2*H*-chromene (2u). Yellow gum; R_f = 0.5 (1:19, ethyl acetate: hexane). Yield: 110 mg (91%). $[\alpha]_D^{22}$= (c, 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.28-6.29 (m, 1H), 6.33-6.34 (m, 1H), 6.63 (s, 1H), 6.92 (d, J = 8.8 Hz, 1H) 7.04 (t, J = 7.6 Hz, 1H), 7.34-7.38 (m, 3H), 8.05 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 67.1, 110.1, 110.6, 117.3, 118.0, 122.7, 129.9, 130.4, 134.2, 138.9, 143.9, 149.4, 153.3 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 92:08, 1.0 mL min^{-1}): τ_{major} = 12.56 min, τ_{minor} = 15.96 min (99% ee). MS (ESI) calcd for $C_{13}H_9NO_4$ 243.0, found *m/z* 244.0 $[M + H]^+$. Anal. Calcd for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.18; H, 3.3; N, 5.69.

3-Nitro-2-propyl-2*H*-chromene (3a). Red gum; R_f = 0.45 (1:19, ethyl acetate: hexane). Yield: 98 mg (90%). IR (KBr): ν 3006, 2954, 2933, 2869, 1648, 1614, 1578, 1506, 1333, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, J = 7.2, 3H), 1.44-1.54 (m, 1H), 1.58-1.63 (m, 2H), 1.79-1.88 (m, 1H), 5.53 (dd, J = 2.4, 9.6 Hz, 1H), 6.94 (d, J = 8 Hz, 1H), 7.01 (t, J = 8 Hz, 1H), 7.27 (d, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H), 7.79 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 13.5, 18.2, 34.4, 72.8, 117.3, 118.4, 122.3, 128.3, 130.3, 133.9, 142.7, 153.4 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major} = 10.47 min, τ_{minor} = 8.82 min (96% ee). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{13}NO_3H$ 220.0968; Found 220.0989.

6-Methoxy-3-nitro-2-propyl-2*H*-chromene (3b). Red solid; R_f = 0.45 (1:19, ethyl acetate: hexane). Yield: 115 mg (93%). M.p. 67-68 °C. $[\alpha]_D^{22}$= -10.46 (c, 1.0, $CHCl_3$). IR (KBr): ν 3003, 2958, 2927, 2871, 1649, 1614, 1578, 1509, 1334, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, J = 6.4 Hz, 3H), 1.42-1.54 (m, 2H), 1.81-1.88 (m, 2H), 3.80 (s, 3H), 5.49 (d, J = 8 Hz, 1H), 6.79 (s, 1H), 6.87-6.95 (m, 2H), 7.76 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 13.5, 18.3, 33.9, 55.8, 72.7, 113.6, 118.1, 118.8, 120.3, 128.2, 147.2,

154.7 ppm. The %ee was determined by HPLC using a chiralpak AS column (hexane/iPrOH, 90:10, 1.0 mL min^{-1}): τ_{major}= 10.49 min, τ_{minor} = 6.67 min (92% ee). MS (ESI) calcd for $C_{13}H_{15}NO_4$ 249.1, found *m/z* 249.1 $[M]^+$. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.67; H, 6.09; N, 5.63.

ASSOCIATED CONTENT

^1H NMR, $^{13}C\{^1H\}$NMR spectra of all the synthesized compounds and the HPLC chromatograms of the products (i.e. the 2*H*-chromene derivatives) are available free of charge *via* the Internet at http://

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The manuscript was written through contributions of both the authors. The authors have given approval to the final version of the manuscript.

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