Cascade Reactions

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Iminium–Allenamine Cascade Catalysis: One-Pot Access to Chiral 4*H*-Chromenes by a Highly Enantioselective Michael–Michael Sequence**

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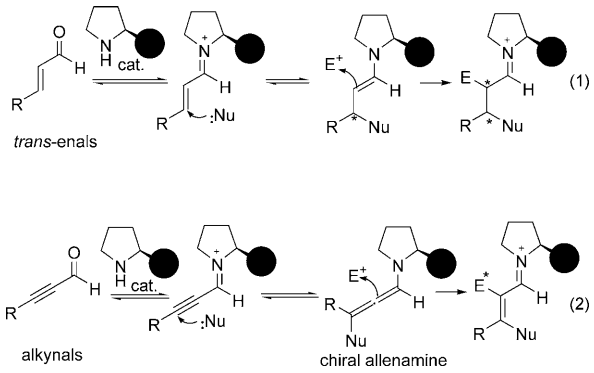
Iminium catalysis has been utilized with great success in highly efficient enantioselective cascade reactions for the facile construction of complex molecular architectures.[1] The chemistry relies on a combined iminium–enamine activation strategy to control the enantioselectivity at the β-carbon atom on the α,β-unsaturated aldehyde [Scheme 1, Eq. (1)].[1]



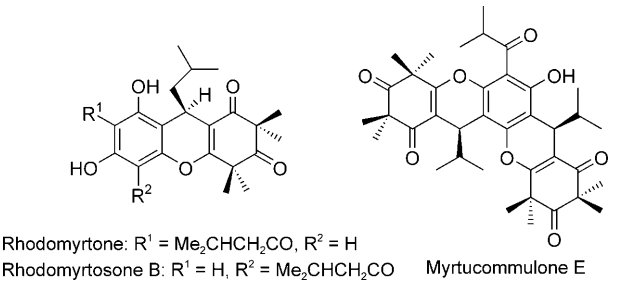
Scheme 1. Conventional (1) and iminium–allenamine (2) catalytic enantioselective iminium-initiated cascade reactions.

Importantly, the geometry of the *trans* enals controls the Michael-initiated cascade reactions to afford high enantio- and/or diastereoselectivity. In contrast to these widely reported iminium catalyzed systems, the organocatalytic cascade transformation involving asymmetric conjugate addition to an alkynal has not yet been reported, presumably owing to the fact that the alkynal substrates possess no prochiral center at the β-carbon atom. This chemistry remains largely unexplored, even in single-step conjugate addition reactions.[2] Recently, MacMillan and co-workers reported the use of propynal as the dienophile in an efficient iminium activated [4+2] cycloaddition reaction.[2h]

To perform an enantioselective cascade reaction on an alkynal substrate, we envision that their use instead of an enal in the initial Michael addition to an iminium ion formed in situ would afford an unprecedented chiral allenamine intermediate [Eq. (2)].[3–6] The allenamine formed would then act as the nucleophile in a subsequent enantioselective reaction with an electrophile to produce a new stereogenic center.

This organocatalytic iminium–allenamine strategy faces two important concerns. First, alkynals are known to be a challenging class of electrophiles in asymmetric synthesis,[2] and it is expected that they would behave differently to the well-established enals in terms of reactivity and stereocontrol, because they adopt different structures and geometry (linear sp hybridized alkynes versus *trans* sp^2 hybridized olefins). Second, the stereochemistry is governed by a poorly understood chiral allenamine[4–6] that is formed in situ in the second step of the cascade reaction, whilst in the classic iminium–enamine cascade processes, the enantioselectivity is generally controlled by the initial conjugate addition step.

4*H*-Chromenes are a core structural feature of an array of fascinating natural products that have intriguing biological activities (Scheme 2). For example, rhodomyrtone and rhodomyrtosone B show potent antibiotic activities,[7] whereas the dimeric 4*H*-chromene acylphloroglucinol, myrtucommulone E, serves as a promising α-glucosidase inhibitor with antibacterial activity.[8] These frameworks have become attractive targets in organic synthesis,[9,10] and, despite significant advances having been made, asymmetric methods for their construction are still extremely rare.[11]



Scheme 2. Examples of 4*H*-chromenes as substructures in biologically interesting natural products.

Motivated by the dearth of applications of alkynals in organocatalysis (versus the widely explored enals), we recently developed a highly enantioselective catalytic double Michael addition reaction between 2-(*E*)-(2-nitrovinyl)-phenols and alkynals.[12] This one-pot process opens an efficient route to the densely functionalized, biologically interesting chiral 4*H*-chromenes. Herein, we wish to report a

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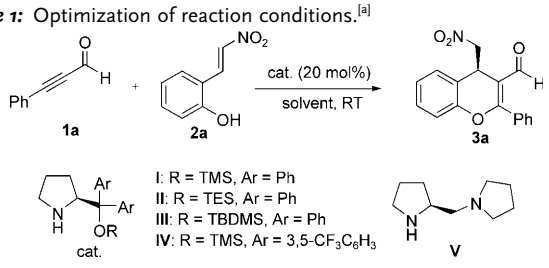
Michael–Michael sequential approach to 4*H*-chromenes using iminium–allenic enamine cascade catalysis.

To validate the feasibility of the iminium–allenamine reaction, the reaction of 3-phenyl-2-propynal **1a** with 2-(*E*)-(2-nitrovinyl)-phenol **2a** in dichloromethane was investigated at room temperature in the presence of 20 mol% organocatalyst **I** (Table 1). Chiral secondary amines, and particularly

Table 1: Optimization of reaction conditions.[a]



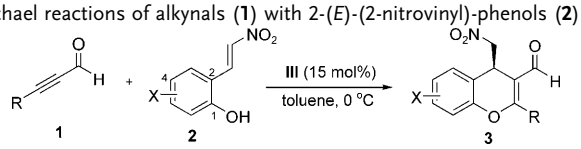
Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**I**	CH_2Cl_2	1	95	97
2	**II**	CH_2Cl_2	1	93	98
3	**III**	CH_2Cl_2	1	92	98
4	**IV**	CH_2Cl_2	1	90	96
5	**V**	CH_2Cl_2	1	91	66
6	**III**	toluene	1	94	99
7	**III**	DCE	1	92	98
8[d]	**III**	toluene	4	97	>99

[a] Unless specified, see the Experimental Section for reaction conditions. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralpak AS-H column). [d] 0°C; 15 mol% **III**. DCE = 1,2-dichloroethane, TBDMS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl.

diarylprolinol silyl ethers, are known to be capable of both iminium and enamine catalysis in enal cascade reactions.[13] Encouragingly, the reaction proceeded to completion within 1 h to yield the desired product (**3a**) in an excellent yield (95%) and in an excellent *ee* (97%) (Table 1, entry 1). This reaction shows that alkynals are more active than enals. A screen of other diarylprolinol silyl ether analogues **II**–**IV** revealed that the more bulky TBDMS catalyst **III** gave slightly higher enantioselectivities (Table 1, entries 2–4), although diamine **V**, reported by Barbas and Betancort, showed poor enantiocontrol (Table 1, entry 5).[14] Accordingly, catalyst **III** was chosen for further optimization of the reaction conditions. A survey of different reaction solvents revealed toluene to be the most suitable for this procedure (Table 1, entries 6 and 7). Lowering the reaction temperature to 0°C and the catalyst loading to 15 mol% resulted in a higher *ee* (>99%) and higher yield (97%) without considerably prolonging the reaction time (Table 1, entry 8).

Having established the optimal conditions for this cascade oxa-Michael–Michael reaction, we then investigated the scope of this process. As shown in Table 2, the one-pot reaction promoted by **III** serves as a general and atom-economical approach to "privileged" chiral 4*H*-chromenes, with formation of two C–C bonds, one new stereogenic center, and the incorporation of two versatile nitro and aldehyde functionalities that are available for further elaboration. Notably, in all cases, the reactions were completed in 4–5 hours, with excellent levels of enantioselectivity (98–>99% *ee*) and in high yields (92–98%). Moreover, a broad substrate scope was observed. Aromatic alkynals **1** that have electron-donating (Table 2, entries 2, 12, and 13) or electron-withdrawing substituents (Table 2, entries 3–6 and 11) were investigated, and the effects of the substituent on the reaction was found to be very limited. These reactions proceeded very smoothly, affording excellent yields (92–98%) and excellent enantioselectivities (99–>99%). A similar trend was observed with the structural variations of substrate **2** (Table 2, entries 7–9 and 11–13). Heteroaromatic alkynal thiophen-2-yl-propynal also effectively engaged in the cascade process (Table 2, entry 10). Finally, the reaction of the highly sterically hindered aliphatic alkynal also proceeded successfully, in 93% yield and 98% *ee* (Table 2, entry 14). The absolute configuration of product **3g** was determined to be *R* by using single crystal X-ray diffraction (Figure 1).[15]

Table 2: Catalyst **III** promoted enantioselective cascade oxa-Michael–Michael reactions of alkynals (**1**) with 2-(*E*)-(2-nitrovinyl)-phenols (**2**).[a]



Entry	R, X, **3**	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph, H, **3a**	4	97	>99
2	4-$MeOC_6H_4$, H, **3b**	5	93	99
3	4-ClC_6H_4, H, **3c**	4	97	99
4	4-BrC_6H_4, H, **3d**	4	95	99
5	4-$NO_2C_6H_4$, H, **3e**	4	95	99
6	3-$NO_2C_6H_4$, H, **3f**	4	93	99
7	Ph, 4-Cl, **3g**	4	92	99
8	Ph, 6-OMe, **3h**	4	95	98
9	Ph, 4-OMe, **3i**	4	97	99
10	2-thienyl, H, **3j**	4	92	99
11	4-BrC_6H_4, 4-OMe, **3k**	4	98	99
12	4-MeC_6H_4, 4-Cl, **3l**	4	94	99
13	4-$MeOC_6H_4$, 4-OMe, **3m**	4	98	99
14	*t*Bu, H, **3n**	4	93	98

[a] Unless specified, see the Experimental Section for reaction conditions. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis (Chiralpak AS-H or IC column).

In conclusion, we have developed a novel asymmetric oxa-Michael–Michael reaction involving an unprecedented

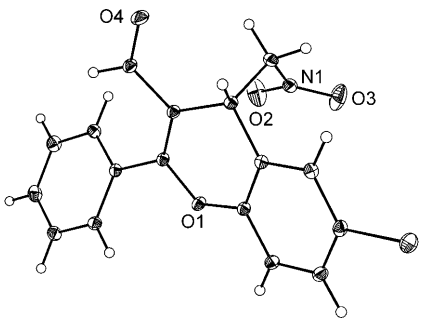


Figure 1. ORTEP of compound **3g**, with ellipsoids set at 20% probability.

chiral iminium–allenamine cascade. This process is a viable one-pot approach to synthetically and biologically significant chiral 4*H*-chromenes in high yields and with excellent enantioselectivities. A broad substrate scope has been successfully employed in this reaction, including aromatic and aliphatic alkynals as Michael acceptors, and 2-(*E*)-(2-nitrovinyl)-phenols as Michael donors/acceptors with significant structural variation. The proposed iminium–allenamine activation mode has potential applications in the development of new organocatalytic enantioselective cascade reactions. This work is currently underway within the group, including mechanistic investigation and applications of the oxa-Michael–Michael reaction in synthesis of 4*H*-chromene containing natural products and bioactive molecules.

Experimental Section

Representative procedure (see Table 2, entry 1): 2-(*E*)-(2-Nitrovinyl)-phenol **2a** (0.10 mmol) and organocatalyst **III** (5.51 mg, 0.015 mmol) were added to a solution of alkynal **1a** (0.11 mmol) in toluene (0.8 mL) at 0 °C, and the solution was stirred for 4 h. The crude reaction mixture was purified by column chromatography (hexanes/ethyl acetate) to afford the desired product, which was directly used for compound characterization and chiral HPLC analysis.

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