ORGANIC LETTERS

2010
Vol. 12, No. 21
4948−4951

"One-Pot" Access to 4*H*-Chromenes with Formation of a Chiral Quaternary Stereogenic Center by a Highly Enantioselective Iminium-allenamine Involved Oxa-Michael−Aldol Cascade

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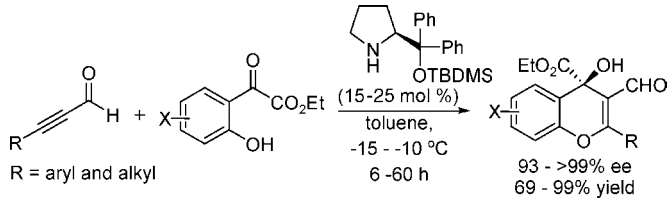
Received September 2, 2010

ABSTRACT



An unprecedented organocatalytic highly enantioselective cascade Michael−aldol reaction has been developed in high yields under mild reaction conditions. The "one-pot" process affords an efficient approach to the synthetically and biologically important chiral 4*H*-chromenes bearing a quaternary stereogenic center. The study significantly expands the scope of less explored organocatalytic iminium-allenamine chemistry.

Despite the fact that 4*H*-chromenes are an important class of core structures featured in a number of naturally occurring and biologically active molecules,[1,2] asymmetric methods allowing rapid access to this molecular architecture are extremely rare.[3,4] The ability to access the complex members of the chiral 4*H*-chromene family in an enantioselective manner allows chemists to explore their potential biological properties. Therefore, the development of catalytic asymmetric strategies for the efficient construction of structurally diverse chiral 4*H*-chromenes is quite valuable to the fields of organic synthesis and chemical biology/medicinal chemistry.

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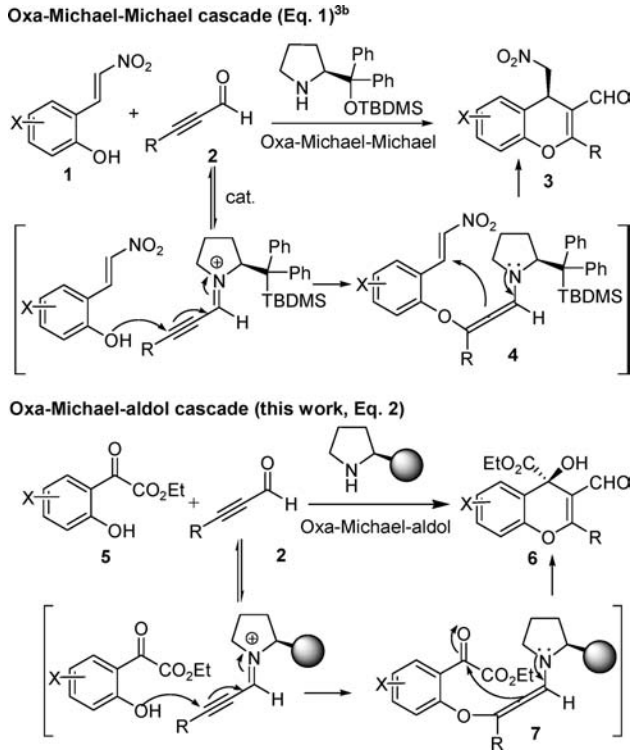
10.1021/ol102096s
Published on Web 10/11/2010

Toward this end, our group has recently reported the first enantioselective cascade oxa-Michael−Michael reactions of ynals involving an unprecedented iminium-allenamine activation mode (Scheme 1, eq 1).[3b] Despite the extensively

Scheme 1. Alkynals Participating in Enantioselective Cascade Oxa-Michael−Michael and −Aldol Reactions Promoted by a Chiral Secondary Amine Involving a Novel Iminium-allenamine Activation Mode



investigated iminium-enamine strategy with cascade sequences,[5] the respective iminium-allenamine chemistry is much less appreciated. Expanding the scope of the chemistry will not only add a new domain in organocatalysis but also, more importantly, afford new potentially useful platforms for the facile assembly of important molecular scaffolds. We questioned whether the conceptually novel tactic could be extended to an oxa-Michael−aldol cascade sequence, which would generate the structurally diverse 4*H*-chromenes with installation of new functionalities. Herein, we wish to report the results which have led to an asymmetric iminium-allenamine approach to chiral 4*H*-chromenes bearing chiral α-hydroxy carboxylate functionality in high yields (84−99%) and with excellent enantioselectivities (93−>99% ee) for a wide range of substrates (eq 2). A powerful "one-pot" oxa-Michael−aldol cascade reaction between (2-hydroxy-phenyl)-2-oxoacetates and ynals is realized for the first time. Furthermore, a quaternary stereogenic center involving formation of versatile α-hydroxy carboxylate motif, a still synthetically unmet issue in organic synthesis,[6] is created highly enantioselectively.

Initial efforts on the proposed organocatalytic enantioselective oxa-Michael−aldol cascade reaction of simple salicylaldehyde or -ketone with phenyl ynal in the presence of 20 mol % (*S*)-diphenylpyrrolinol TMS ether **I**[7] in toluene were frustrated by the failure of delivering the desired products as a result of very poor reaction yield. These studies underscored the completely different reaction behavior between ynals and enals since we have shown that enals can efficiently engage in the Michael−aldol cascade process with salicylaldehydes.[4b] We turned our attention to the more reactive ketone ester **2a** (Figure 1 and Table 1).[8] To our delight, the oxa-Michael−aldol cascade sequence proceeded smoothly to give the desired product **3a** in an excellent yield (97%) and with excellent enantiomeric excess (ee) (97%) under the same reaction conditions in toluene at rt in the presence of 20 mol % catalyst **I** within 3 h (entry 1), albeit the highly steric ketoester substrate employed. Notably, the process provides an efficient entry to useful chiral α-hydroxy carboxylates with formation of a quaternary stereogenic center in a cascade fashion. The screening of other diarylprolinol silyl ether analogues **II**−**III** revealed that the bulky

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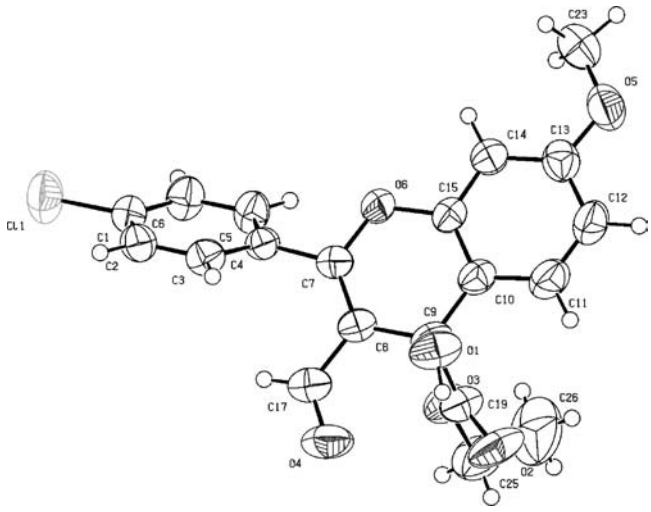
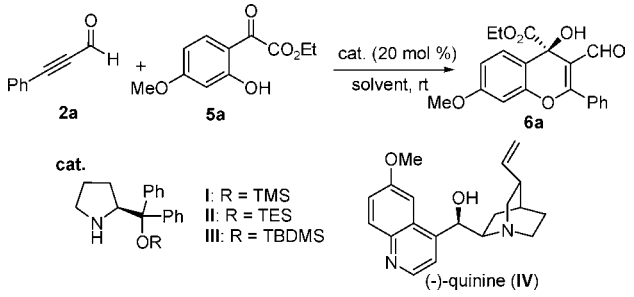


Figure 1. X-ray structure of **6h**.

Table 1. Development and Optimization of Reaction Conditions of an Organocatalytic Enantioselective Cascade Oxa-Michael−Aldol Cascade Reaction[a]



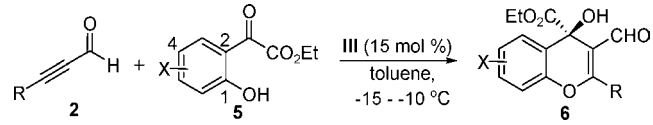
entry	cat.	solvent	t (h)	% yield[b]	% ee[c]
1	**I**	toluene	3	97	97
2	**II**	toluene	3	98	98
3	**III**	toluene	3	98	98
4	**IV**	THF	2	<5	ND[d]
5	**III**	xylene	3	96	98
6	**III**	CH_2Cl_2	3	99	97
7	**III**	$Cl(CH_2)_2Cl$	3	94	96
8e	**III**	toluene	6	98	99

[a] Reaction conditions: unless specified, a mixture of phenyl-propynal **2a** (0.080 mmol), ethyl 2-(2-hydroxy-4-methoxyphenyl)-2-oxoacetate **5a** (0.080 mmol), and catalyst (0.016 mmol) in solvent (0.5 mL) was stirred at rt for a specified time. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel AD). [d] Not determined. [e] Performed at −15∼−10 °C, and 15 mol % of catalyst **III** was applied.

TBDMS catalyst **III** gave a slightly higher enantioselectivity (Table 1, entries 2−3). Quinine alone was not effective for this transformation (entry 4). Therefore, the catalyst **III** was defined as the optimal promoter for this process. A survey of solvents led to choose toluene as the reaction medium for the process (entries 5−7). Better ee (99%) was observed when decreasing the reaction temperature to −15∼−10 °C and lowering the catalyst loading to 15 mol % (Table 1, entry 8).

With the optimal conditions in hand, the scope of the cascade oxa-Michael−aldol reaction was investigated. Remarkably, as shown in Table 2, the cascade process exhibits

Table 2. Catalyst **III** Promoted Enantioselective Cascade Oxa-Michael−Aldol Reactions of Alkynals **2** with Ethyl 2-(2-Hydroxyphenyl)-2-oxoacetates **5**[a]



entry	R, X, **6**	t (h)	% yield[b]	% ee[c]
1	Ph, 5-MeO, **6a**	6	98	99
2	Ph, H, **6b**	8	97	99
3	Ph, 4-MeO, **6c**	8	84	96
4	Ph, 4-Me, **6d**	9	93	98
5[d]	Ph, 4-Cl, **6e**	6	99	93
6	4-$MeOC_6H_4$, 5-MeO, **6f**	6	99	99
7	4-MeC_6H_4, 5-MeO, **6g**	6	99	99
8	4-ClC_6H_4, 5-MeO, **6h**	6	97	99
9	4-BrC_6H_4, 5-MeO, **6i**	6	99	99
10	4-BrC_6H_4, 4-Me, **6j**	10	92	98
11	4-BrC_6H_4, H, **6k**	9	98	98
12	4-FC_6H_4, 5-MeO, **6l**	6	99	>99
13	3-FC_6H_4, 4-Me, **6m**	9	93	98
14	4-$NO_2C_6H_4$, 5-MeO, **6n**	6	98	99
15	3-$NO_2C_6H_4$, 5-MeO, **6o**	6	98	99
16	2-thienyl, 5-MeO, **6p**	10	92	99
17	2-furanyl, 5-MeO, **6q**	10	97	96
18	*t*-Bu, 5-MeO, **6r**	10	91	98
19[e]	$PhCH_2CH_2$, 4-Me, **6s**	60	69	97
20[e]	*n*-C_5H_{11}, 4-Me, **6t**	60	75	99

[a] Reaction conditions: unless specified, see footnote a in Table 1 and Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel AD or Chiralpak IC). [d] 15 mol % of **I** and 10 mol % of **IV** were used. [e] 25 mol % of **III** was used.

a broad substrate tolerance, and a quaternary stereogenic center is generated highly enantioselectively in all cases. A full range of aromatic ynals **2**, including electron-neutral (Table 2, entries 1−5), -donating (entries 6 and 7), and -withdrawing substituents (entries 8−15), as well as heterocyclic examples (entries 16 and 17), can participate in the cascade reactions in excellent yields (84%∼99%) and with excellent enantioselectivities (93−>99%). It is noteworthy that the substrate scope can also be expanded to highly steric demanding aliphatic alkynal, providing the desired product in 91% yield and 98% ee (entry 18). Moreover, alkyl alkynals (R = CH_2CH_2Ph and *n*-C_5H_{11}, Table 2, entries 19 and 20, respectively) were also probed for the cascade process. It was found that they efficiently participated in the reaction with excellent enantioselectivities (97 and 99% ee, respectively), although the reaction occurred slower (60 h) than aryl ones and higher catalyst loading (25 mol %) was needed as a result of their poorer reactivity. The variation in ethyl 2-(2-hydroxyphenyl)-2-oxoacetate components **5** was also possible, as demonstrated by the aromatic structures carrying electron-donating (entries 1, 3, 4, 6−10, and 12−18), -neutral

(entries 2 and 11), and -withdrawing (entry 5) groups. It is observed that with respect to substrate **5e** having electron-withdrawing Cl (entry 5) poor ee was observed. However, we found that quinine **IV** as cocatalyst was essential to ensure high enantioselectivity presumably due to its interaction with the ketone moiety in the ketoester. The absolute configuration of **6h** was determined to be *R* configuration by X-ray crystallographic analysis (Figure 1).[9]

In conclusion, we have described a new protocol for asymmetric organocatalysis through the first iminium-allenamine engaged oxa-Michael−aldol cascade reaction. In addition to the potential of this powerful "one-pot" approach to the catalytic generation of chiral 4*H*-chromenes bearing a quaternary stereogenic center, it is a rare example of a highly enantioselective cascade reaction with ynals. The operationally friendly reaction conditions and high efficiency (cascade, high yields and ee, and readily available achiral starting materials) render the process particularly attractive in the practice of organic synthesis and medicinal chemistry. Chiral 4*H*-chromene products with a versatile α-hydroxy carboxylate moiety are valuable structures for the synthesis of biologically active molecules.

(9) See Supporting Information for detail.

Acknowledgment. Financial support from the National Natural Science Foundation of China (20932003 and 90813012, R.W.) and the National S&T Major Project of China (2009ZX09503-017, R.W.) and the NSF (Chem-0704015, W.W.) is gratefully acknowledged. C.-L. Liu and X.-S. Zhang make equal contributions to this work.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR and HRMS data for products **6** and X-ray crystallographic information of **6h** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

OL102096S