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Asymmetric Synthesis of 3,4-Dihydrocoumarin Motif with an All-Carbon Quaternary Stereocenter *via* a Michael−Acetalization Sequence with Bifunctional Amine-thiourea Organocatalysts

Bor-Cherng Hong,*,† Prakash Kotame,† and Gene-Hsiang Lee‡

Department of Chemistry and Biochemistry, National Chung Cheng University, Chia-Yi, 621, Taiwan, R.O.C., and Instrumentation Center, National Taiwan University, Taipei, 106, Taiwan, R.O.C.

chebch@ccu.edu.tw

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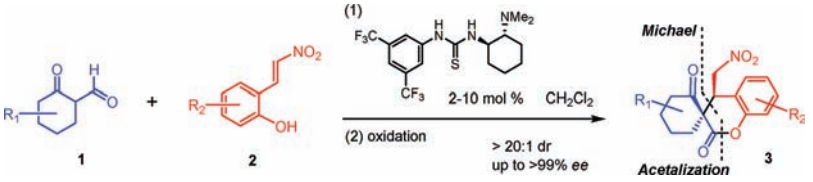
ABSTRACT



Asymmetric domino Michael−acetalization reactions of 2-hydroxynitrostyrene and 2-oxocyclohexanecarbaldehyde with a bifunctional thiourea-tertiary-amine organocatalyst, e.g., the Takemoto catalyst, followed by oxidation providing the 1′,3-spiro-2′-oxocyclohexan-3,4-dihydrocoumarin having one all-carbon quaternary stereocenter with excellent diastereo- and enantioselectivities (up to >99% *ee*), are described. The structures and absolute configurations of the products were confirmed by X-ray analysis.

Recent advances in cascade and sequential organocatalysis have provided a new approach for efficient stereoselective production of a wide spectrum of cyclic molecules. Among them, organocatalytic annulations, e.g., the [4 + 2],[1] [3 + 3],[2] [3 + 2],[3] [4 + 3],[4] [1 + 2 + 3],[5] [1 + 2 + 2],[6] [2 + 2 + 2][7] annulations, represent the most intriguing and efficient protocols since multiple bonds and contiguous stereocenters can be constructed in a one-pot operation. Coumarins and dihydrocoumarin derivatives are prevalent in nature, and many of the derivatives exhibit diverse

† National Chung Cheng University.
‡ National Taiwan University.

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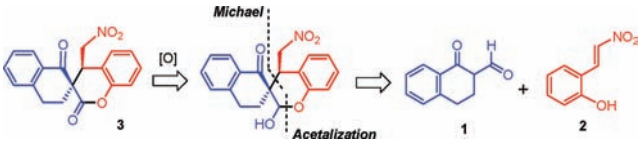
biological activities, including antineoplastic activity,[8] antiherpetic activity,[9] and inhibition of protein kinases,[10] aldose reductase,[11] and HIV-1 reverse transcriptase.[12] Consequently, extensive synthetic studies of this skeleton have been reported, including the synthesis of 3,4-disubstituted dihydrocoumarins,[13] 3,4-dihydro-4-alkyl-2*H*-chromen-2-ol,[14] and tetrahydro-6*H*-benzo[*c*]chromen-6-ones were.[15] However, few examples have concerned the preparation of 3,3-dialkylchroman-2-ones,[16] a unique skeleton possessing pharmacologic activities.[17] Considering the above background in the context of organocatalytic asymmetric reactions,[18] we envisioned an approach to this system via a domino Michael–acetalization reaction[19] of 2-hydroxynitrostyrene[20] and 2-oxocyclohexanecarbaldehyde,[21] followed by an oxidation (Scheme 1). Herein, we describe the examples of enantioselective organocatalytic domino Michael–acetalization reactions of 2-hydroxynitrostyrene (**2**) and 2-oxocyclohexanecarbaldehyde (**1**). This methodology permits production of 1′,3-spiro-2′-oxo-cyclohexan-3,4-dihydrocoumarin, with an all-carbon quaternary stereocenter[22] and the spirane system,[23] and provides the product in excellent yields and stereoselectivities with up to a >20:1 diastereomeric ratio (dr) and 99% enantiomeric excess (*ee*).

Scheme 1. Retrosynthetic Analysis



Initially, **1a** and **2a** were treated with Jørgensen–Hayashi catalyst **I**–HOAc (20 mol %). No desired Michael–acetalization hemiacetal product (**3a**) was observed, but

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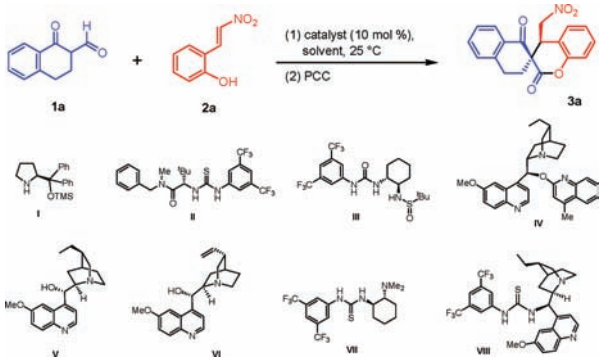
(25) Unfortunately, the parasitical dead-end product intermediate **4a** of the cascade reaction was quite stable with respect to a variety of acid and moisture conditions, and several attempts to modify the reaction conditions to regenerate the active catalyst **I** from **4a** in the reaction sequence were in vain (Scheme 2).

Table 1. Screening of Catalysts and Optimization of Conditions for the Domino Michael–Acetalization Reaction of **1a** and **2a**[a]



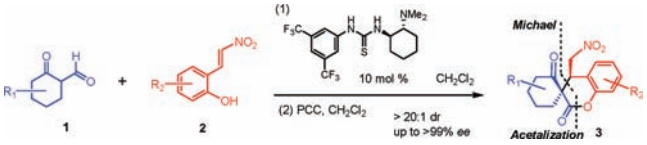
entry	catalyst	solvent	time[b] (h)	yield (%)[c]	*ee* (%)[d]
1	**I**[e]	CH_2Cl_2	24	~0	na
2	**II**	CH_2Cl_2	48	~0	na
3	**III**	CH_2Cl_2	48	~0	na
4	**IV**	CH_2Cl_2	22	33	12
5	**V**	CH_2Cl_2	12	28	−40
6	**VI**	CH_2Cl_2	12	26	−42
7	NEt_3	CH_2Cl_2	20	21	0
8	**VII**	CH_2Cl_2	0.33	67	97
9	**VIII**	CH_2Cl_2	1	52	97
10	**VII**	CH_2Cl_2[f]	38	57	87[g]
11	**VII**	toluene	0.33	65[h]	97
12	**VII**	THF	48	59[h]	nd

[a] Unless otherwise noted, the reactions were performed in the presence of 10 mol % catalyst and in 0.11 M of **1a** with a 1/1 ratio of **1a**/**2a** at ca. 25 °C. [b] Reaction time for Michael–acetalization. [c] Isolated yields of the adducts **3a**. [d] Enantiomeric excess (*ee*) determined by chiral column chromatography (Chiralpack IA). [e] 20 mol % of **I** was used along with 20 mol % of HOAc as additive. [f] 2 mol % catalyst was used. [g] Determined by chiral column chromatography (Chiralpack IC). [h] Solvent was changed to CH_2Cl_2 prior to the subsequent PCC oxidation.

instead an enamine intermediate **4a** was obtained (Table 1, entry 1) (Scheme 2).[24,25]

Conducting the reaction with thiourea and urea derivatives **II** and **III** as catalysts for 48 h also provided none of the expected product **3a** (Table 1, entries 2–3). To trigger the reaction, we then turned our attention to the use of Brønsted base catalysts, e.g., **IV**, **V**, and **VI**. While these catalysts afforded the Michael–acetal adducts, the yields were low (26–33% yields of **3a** after the *in situ* PCC oxidation of Michael–acetal adducts (Table 1, entries 4–6)). Notably, the reactions with catalysts **V** and **VI** gave better enantioselectivities than those with catalyst **IV** or Et_3N (−40 and −42% *ee vs* 0% *ee*, Table 1, entries 4–7). The subtle improvement in enantioselectivity may be attributed to the multiple H-bonding effect arising from the interaction of the hydroxy group on catalysts **V** and **VI** with the nitro group during the reaction progress. This assumption was further supported by the reaction with Takemoto catalyst **VII** to afford 67% yield of **3a** and excellent enantioselectivity (97% *ee*, Table 1, entry 8). Presumably, the thiourea portion of the catalyst activated the electrophile while the amine segment activated the nucleophile. Surprisingly, with catalyst **VII** the Michael–

Table 2. Scope of the Domino Michael–Acetalization Reaction of **1a** and **2a**[a]

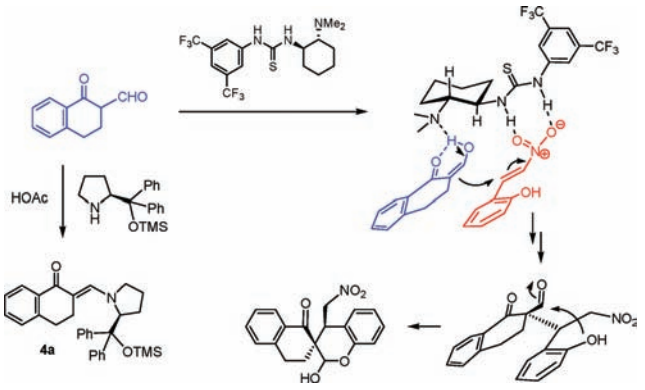


entry	time[b] (min)	3	yield (%)[c]	*ee* (%)[d]
1	20	**3a**	67	97
2	20	**3b**	51	>99
3	30	**3c**	59	98
4	30	**3d**	64	98
5	20	**3e**	56	98
6	25	**3f**	72	98
7	25	**3g**	69	97
8	30	**3h**	63	90
9	15	**3i**	59	80
10	10	**3j**	51	83
11	20	**3k**	61	98

[a] Unless otherwise noted, the reactions were performed in the presence of 10 mol % catalyst and in 0.11 M of **1a** with a 1/1 ratio of **1**/**2** at ca. 25 °C. [b] Reaction time for Michael–acetalization. [c] Isolated yields of the adducts **3**. [d] Enantiomeric excess determined by chiral column (Chiralpack IC).

acetalization step was completed in only 20 min; apparently, the bifunctional chiral double H-bonding and the Brønsted base activities not only facilitate the reaction rate but also provided a suitable asymmetric induction medium for the reaction. Replacement of Takemoto catalyst **VII** by chinchona thiourea catalyst **VIII** gave a somewhat lower yield and slower reaction (Table 1, entry 9). Moreover, performing the reaction with less catalyst loading was feasible, as only 2 mol % of **VII** was effective with a slight reduction in enantioselectivity, although a longer reaction

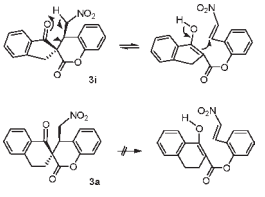
Scheme 2. Plausible Reaction Mechanism



time was required to complete the reaction (Table 1, entry 10). The same reaction proceeded smoothly in toluene but required changing the solvent to CH_2Cl_2 for the subsequent PCC oxidation (Table 1, entry 11). Conducting the reaction in THF gave a lesser yield and required a longer time for completion (Table 1, entry 12). Reactions performed in other polar solvents (e.g., CH_3CN, DMF, EtOH) were not successful and gave much lower yields.

Having established the optimal reaction conditions (Table 1, entry 8), we next examined the scope and limitations of the above system with variants of **1** and **2**. The reaction appears quite general with respect to the substrates tested, providing the desired adducts with excellent *ee* values and dr (>20:1) in good yields (Table 2). All of the Michael−acetal reactions were completed in <0.5 h. Most of the reactions of tetrahydro-1-oxonaphthalene-2-carbaldehydes afforded the adduct in excellent enantioselectivities, while the same conditions for 2,3-dihydro-1-oxo-1*H*-indene-2-carbaldehyde and 2-oxocyclopentanecarbaldehyde gave somewhat lower enantioselectivities (Table 2, entries 9−10).[26] The structures and absolute configurations of the products were assigned based on the X-ray analysis of (+)-**3a** and (+)-**3b** (Figure 1). To explain the stereochemistry of this transformation, a plausible mechanism was proposed, as shown in Scheme 2. Activation of the nitrostyrene was achieved by intermolecular H-bonding of the thiourea moiety on the Takemoto catalyst; simultaneously, the tertiary amine portion of the catalyst, acting as the Brønsted base, assisted in the

(26) Unlike other products, **3i** and **3j** were somewhat less stable at room temperature, and a certain extent of racemization as well as decomposition was observed during the isolation and purification. These phenomena may be related to the conformation adopted by **3i** and **3j**, wherein the spiro 5,6-ring system enforced a vicinal alignment of the ketone and the CH_2NO_2 group, estimated to be 2.2 Å by Spartan '10, MMFF, such that the combination with the intrinsic strain creates a situation where the ring-opening-closing equilibrium is attained.



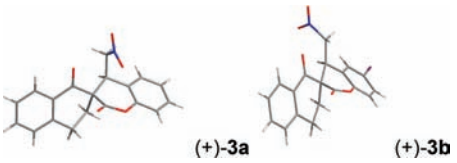


Figure 1. Stereo plots of the X-ray crystal structures of (+)-**3a** and (+)-**3b**: C, gray; N, blue; O, red; Br, purple.

enolization of the ketoaldehyde and triggered the Michael addition to the nitrostyrene from the *Re* face, as depicted in Scheme 2. Any other chelating orientation of the two reactants would cause serious steric hindrance during the attack, or alternatively, the reactants would be too far apart for effective approach. The resulting intermediate subsequently underwent acetal formation to give the Michael−acetal adduct.[27,28]

In summary, we have realized an asymmetric domino Michael−acetalization reaction of 2-hydroxynitrostyrene and 2-oxocyclohexanecarbaldehyde with a Takemoto catalyst followed by an oxidation to provide the 1′,3-spiro-2′-oxocyclohexan-3,4-dihydrocoumarin having an all-carbon quaternary stereocenter with excellent diastereo- (>20:1) and enantioselectivities (up to $>99\%$ ee). The reaction not only adds to the limited repertoire of examples of organocatalysis of 1,3-ketoaldehydes and the asymmetric construction of quaternary carbons but also demonstrates a proof of principle of the synchronous action of a Brønsted base and a H-bonding mode of catalysis. The methodology has achieved asymmetric reactions that cannot be otherwise catalyzed by enamine catalysts, e.g., a Jorgensen−Hayashi catalyst. The low catalyst loading and the facile Michael−acetalization reaction further demonstrate the merit of this model. The structures and absolute configurations of the products were confirmed by X-ray analysis of the appropriate adducts. Further work is underway to explore the synthetic applications of this procedure.

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Supporting Information Available. Experimental procedures and characterization data for the new compounds; X-ray crystallographic data for (+)-**3a** and (+)-**3b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(27) For similar topicity previously observed in other reactions, see: (a) Ayaz, M.; Westermann, B. *Synlett* **2010**, *10*, 1489. (b) See ref 22e. (c) Oino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

(28) In an alternative reaction pathway, proposed by Takemoto et al., the nitrostyrene interacts with the positively charged N-H group of the protonated amine and provides the same enantioselectivity. For a related study whereby two mechanisms afford the same enantioselectivity, see: (a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125. (b) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160.