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Enantioselective Synthesis of Dihydrocoumarins *via* N-Heterocyclic Carbene-Catalyzed Cycloaddition of Ketenes and *o*-Quinone Methides

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This paper is dedicated to Professor Li-Xin Dai on the occasion of his 85th birthday.

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Abstract: Chiral N-heterocyclic carbenes were found to be efficient catalysts for the formal [4+2]cycloaddition reaction of alky(aryl)ketenes and *o*-quinone methides to give the corresponding 3,3,4-trisubstituted 3,4-dihydrocoumarins in good yields with good diastereoselectivities and excellent enantioselectivities.

Keywords: asymmetric catalysis; cycloadditions; dihydrocoumarins; ketenes; N-heterocyclic carbenes

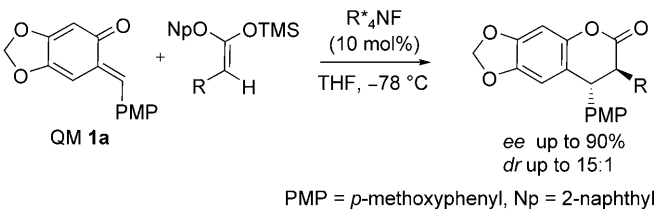
3,4-Dihydrocoumarin derivatives are widely distributed in nature and are present as important active ingredients in many traditional Chinese herbal medicines.[1] Biological studies reveal that 3,4-dihydrocoumarins show versatile activities such as aldose reductase inhibition, antiherpitic and HIV replication inhibition, thus making them attractive candidates as lead compounds in drug discovery.[2]

Great efforts have been devoted to the synthesis of dihydrocoumarins and many approaches have been developed. Beside the hydrogenation of coumarins, hydroarylation of cinnamic acids and their derivatives is an efficient method to construct dihydrocoumarins.[3] Metal-mediated or metal-catalyzed reactions, such as reaction of chromium Fishcer carbenes with ketene acetals,[4] palladium-catalyzed cyclocarbonylation of *o*-isopropenylphenols,[5] rhodium-catalyzed reaction of 3-(2-hydroxyphenyl)cyclobutanones,[6] were also developed. In addition, several interesting approaches have been reported recently, including the $AlCl_3$-mediated reactions of α-hydroxyketene *S*,*S*-acetals with arenes,[7] isocyanide-based four-component reactions,[8] intramolecular redox lactonization of *o*-hydroxycinnamaldehydes,[9] and domino Michael addition/acyaltion of aryloxyacetaldydes.[10]

However, the catalytic asymmetric synthesis of 3,4-dihydrocoumarins is still rare,[7,8,11] and the enantioselective synthesis of highly substituted 3,4-dihydrocoumarins remains a challenge.

Recently, Lectka et al. reported the pioneering enantioselective cycloadditions of the *o*-quinone methide (QM) **1a** and silylketene acetals to give 3,4-disubstituted 3,4-dihydrocoumarins in good yields with highly enantioselectivities (Scheme 1).[11,12] It is interesting that this reaction works for enolates generated from silylketene acetals with chiral ammonium fluoride, but not for enolates generated from butyryl chloride, thermodynamic Hünig's base and kinetic base of the chiral catalyst benzoylquinidine.

N-Heterocyclic carbenes (NHCs) have been demonstrated as useful reagents for the synthesis of heterocyclic compounds,[13] excellent ligands for organometallic compounds,[14] and versatile organocatalysts for varied reactions.[15,16] In this context, Smith et al. and our group independently found that enolates generated from ketenes and catalytic chiral NHCs are versatile reagents for several formal [2+2] and [4+2]cycloaddition reactions.[17] In this communi-



Scheme 1. Lectka's synthesis of dihydrocoumarins.

cation, we report the preliminary results of the NHC-catalyzed formal [4+2]cycloaddition of ketenes and *o*-quinone methides **1** to give the highly substituted dihydrocoumarins.

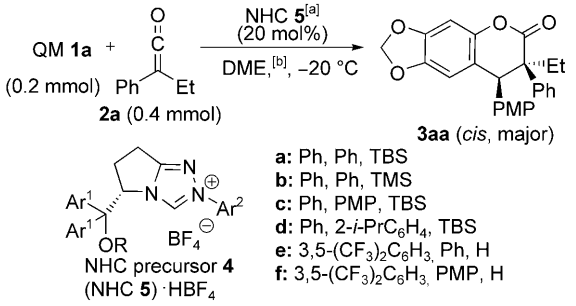
The reaction of *o*-quinone methide **1a** and phenyl-(ethyl)ketene (**2a**) was investigated under the catalysis of NHC **5**,[17b,18] which was generated freshly from NHC precursor **4** and Cs_2CO_3 as base (Table 1). We were happy to find that the corresponding 3,3,4-trisubstituted-3,4-dihydrocoumarin **3a** could be obtained in 73% with 5:1 ratio of *cis*/*trans*-isomers and 99% *ee* for *cis*-isomer and 91% *ee* for *trans*-isomer for the reaction catalyzed by NHC **5a** in THF at −20 °C (entry 1). Solvent screening revealed that DME was the solvent of choice (entries 1–9).

Several other NHCs derived from pyrogutamic acid were then tested. NHC **5b**, with a less sterically crowded TMS group, NHCs **5c** and **5d**, with *N*-(4-methoxy)phenyl and *N*-(2-isopropyl)phenyl substituents, showed similar results of diastereo- and enantioselectivties compared to NHC **5a** (entries 10–12). The NHCs **5e** and **5f**, which feature a free hydroxy group,[19] gave the dihydrocoumarin in moderate yields but with low and opposite enantioselectivities (entries 13 and 14).

Reactions at various temperatures (0, −20 and −40 °C) showed comparable results (entries 3, 15 and 16). Decreasing the loading of the NHC **5a** to 10 mol% made no notable change of the reaction, while reaction with 5 mol% catalyst led to somewhat decreased yield and diastereo- and enantioselectivities (entries 17 and 18).

When we continued with the reactions in DME, it was surprising to find that the results were varied for independent runs and very low enantioselectivity was sometimes observed. After careful investigation, we found that use of strictly purified solvent DME led to reactions with extremely low enantioselectivities (entry 1, Table 2), and that the possible impurities such as water and methanol influenced the reaction a lot (entries 2 and 3). We were satisfied to find that

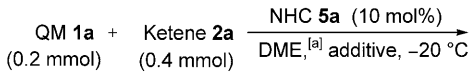
Table 1. Optimization of reaction conditions.



Entry	Varied Conditions[c]	Yield [%][d]	*cis*:*trans*[e]	*ee* [%][f,g]
1	**5a**, THF	73	5:1	99, 91
2	**5a**, ether	57	6:1	98, 54
3	**5a**, DME	77	7:1	98, 79
4	**5a**, dioxane	29	1:1	69, 6
5	**5a**, toluene	59	8:1	95, 54
6	**5a**, xylene	65	9:1	97, 49
7	**5a**, *n*-hexane	trace	–	–
8	**5a**, CH_3CN	32	3:1	6, 6
9	**5a**, DMF	trace	–	–
10	**5b**, DME	52	6:1	98, 87
11	**5c**, DME	50	7:1	99, 64
12	**5d**, DME	76	6:1	95, 85
13	**5e**, DME	42	7:1	−4, 26
14	**5f**, DME	64	6:1	−30, 64
15	**5a**, DME, 0 °C	68	7:1	97, 62
16	**5a**, DME, −40 °C	64	8:1	98, 81
17	**5a** (10 mol%), DME,	75	7:1	99, 78
18	**5a** (5 mol%), DME	61	4:1	94, 67

[a] NHC **5** was generated from its precursor **4** with the base Cs_2CO_3 (20 mol%) in the noted solvent at room temperature for 30 min and used immediately.
[b] DME in this table has not been fully purified and may contain impurities such as traces of water and methanol.
[c] The standard conditions are showed in the reaction arrow.
[d] Total isolated yield of the *cis*- and *trans*-isomers.
[e] Determined by ^1H NMR of the reaction mixture.
[f] The *ee* of the *cis*-isomer followed by that of the *trans*-isomer.
[g] The minus *ee* value indicates the opposite enantiomer was obtained as the major product.

Table 2. Investigation of additives.



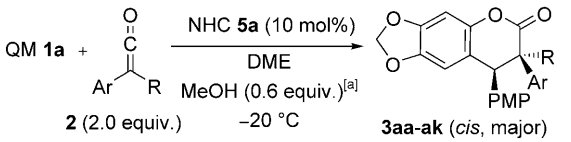
Entry	Additive	Yield [%][b]	*cis*:*trans*[c]	*ee* [%][d]
1	None	39	5:1	0, 0
2	H_2O (0.5 equiv.)	trace	–	–
3	MeOH (0.6 equiv.)	96	7:1	99, 96
4	$PhCH_2OH$ (0.5 equiv.)	53	4:1	84, 99
5	Ph_2CHOH (0.5 equiv.)	38	3;1	10, 28
6	$Sc(OTf)_3$ (0.1 equiv.)	37	2:1	1, 2
7	$Cu(OTf)_3$ (0.1 equiv.)	trace	–	–
8	pyrrole	35	3:1	29, 17
9	MeOH (0.25 equiv.)	81	5:1	98, 86
10	MeOH (0.12 equiv.)	77	5:1	97, 88

[a] The DME employed in this table was purified by double distillation from sodium/benzophenone.
[b] Total isolated yield of the *cis*- and *trans*-isomers.
[c] Determined by ^1H NMR of the reaction mixture.
[d] The *ee* of the *cis*-isomer followed by that of the *trans*-isomer.

the reactions with methanol (0.6 equiv.) as an additive led to a stable result of 96% yield as well as good diastereo- and excellent enantioselectivity (entry 3). However, some esterification of the ketene with methanol was observed when methanol was added as additive.[20] Thus, sterically hindered alcohols, which react very slowly with ketenes,[21] were employed (entries 4 and 5). Lewis acids and the base pyrrole were also tested as the additives, but no desired result was obtained (entries 6–8). The loadings of the additive methanol were also investigated (entries 3, 9 and 10).

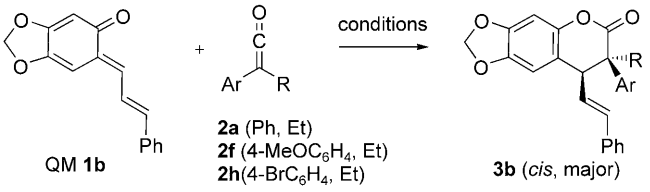
With the optimized reaction conditions in hand, a series of other aryl(alkyl)ketenes were then employed (Table 3). While phenyl(methyl)ketene offered the corresponding dihydrocoumarin in high yield but with low diastereo- and moderate enantioselectivity (entry 2), phenyl(*n*-propyl)ketene and phenyl(*n*-butyl)ketene gave the desired products in good yields with good diastereo- and high enantioselectivities (entries 3 and 4). Both ketenes with electron-donating and electron-withdrawing substituents worked very well (entries 5–8). However, the reaction of sterically crowed ketenes, such as (2-naphthyl)ethyl ketene and (2-chlorophenyl)ethylketene, were sluggish (entries 9 and 10). The reaction of diphenylketene gave the corresponding dihydrocumarin in 33% yield without enantioselectivity (entry 11).

Table 3. Catalytic enantioselective synthesis of 3,3,4-trisubstituted 3,4-dihydrocoumarins.



Entry	**3aa–ak** (Ar, R)	Yield [%][b]	*cis*:*trans*[c]	*ee* [%][d,e]
1	**aa**: Ph, Et	96	7:1	99, 96
2	**ab**: Ph, Me	92	2:1	51, FS
3	**ac**: Ph, *n*-Pr	90	9:1	98, 85
4	**ad**: Ph, *n*-Bu	67	4:1	97, 96
5	**ae**: 4-MeC$_6$H$_4$, Et	94	6:1	98, 86
6	**af**: 4-MeOC$_6$H$_4$, Et	80	4:1	96, FS
7	**ag**: 4-ClC$_6$H$_4$, Et	90	7:1	99, FS
8	**ah**: 4-BrC$_6$H$_4$, Et	96	7:1	99, FS
9	**ai**: 2-naphthyl, Et	30	3:1	58, FS
10	**aj**: 2-ClC$_6$H$_4$, Et	trace	–	–
11	**ak**: Ph, Ph	33	–	0

[a] The esterification of ketenes with methanol is the observed side reaction with a ratio of **3** to ester of about 3:1.
[b] Total yields of the *cis*- and *trans*-isomers.
[c] Determined by ^{1}H NMR of the reaction mixture.
[d] Determined by chiral HPLC.
[e] The *ee* of the *cis*-isomer followed by that of the *trans*-isomer. FS = failed to separate the two enantiomers in Daicel Chiralpak columns.



Conditions: NHC **5a** (10 mol%), DME, MeOH (0.6 equiv.), –20 °C

3ba: 93%, *cis*:*trans* = 3:1, 98% *ee* (*cis*), 95% *ee* (*trans*)
3bf: 95%, *cis*:*trans* = 3:1, 93% *ee* (*cis*), 93% *ee* (*trans*)
3bh: 92%, *cis*:*trans* = 2:1, 90% *ee* (*cis*), 97% *ee* (*trans*)

Scheme 2. Reactions of *o*-quinone methide **1b**.

The reaction of *o*-quinone methide **1b** with a cinnamyl substituent also gave dihydrocoumarins in very good yields with moderate diastereo- and excellent enantioselectivities for both diastereomers (Scheme 2).

The proposed catalytic cycle is depicted in Figure 1. The addition of NHC to ketenes gives enolates **6**, which react with *o*-quinone methides **1** *via* an inverse electron demand [4+2]cycloaddition to give adduct **7**, followed by fragmentation to furnish the final product **3** and regenerate the NHC.

The absolute stereochemistry of compound **3ag** was determined by X-ray analysis to be (*3R,4S*),[22] and other dihydrocoumarins prepared from QM **1a**[23] were assigned the same configuration based on the direction of their specific optical rotations. This stereochemical outcome is consistent with our previously reported planar transition mode (Figure 2).[17d] Both less sterically crowded conformations are adapted for the C(NHC)–C(enolate) single bond and the C=C double bond of the enolate in the proposed model.

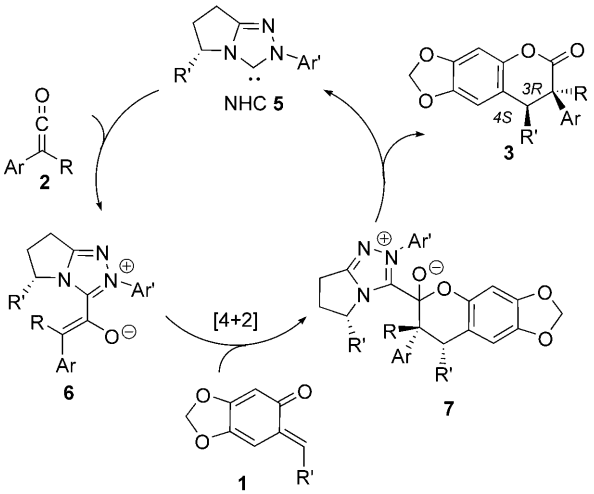


Figure 1. Proposed catalytic cycle.

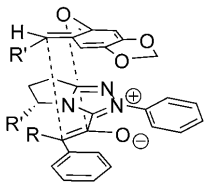


Figure 2. Possible stereochemical model.

In conclusion, a highly enantioselectitive synthesis of 3,3,4-trisubstituted 3,4-dihydrocoumarins was realized by the chiral NHC-catalyzed formal [4+2]cycloaddition of aryl(alkyl)ketenes and *o*-quinone methides. It was found that the additive methanol was crucial for the high yields and enantioselectivities. The rationalization for the use of the additive methanol and expansion of the scope of substrates are underway in our laboratory.

Experimental Section

General Procedure for NHC-Catalyzed Cycloaddtion of Ketenes and *o*-Quinone Methides

To the solution of NHC **5a**, which was generated freshly from the NHC precursor **4a** (12 mg, 0.02 mmol) and Cs_2CO_3 (6.5 mg, 0.02 mmol) in DME (2 mL) at room temperature for 30 min, was added MeOH (5 μL, 0.6 equiv.) and QM **1** (51.2 mg, 0.2 mmol) at −20 °C. After stirring for 5 min, the solution of ketene **2** (0.4 mmol) in 2 mL DME was added *via* a syringe pump over 1 h. The reaction mixture was stirred at −20°C and monitored by TLC until QM **1** was fully consumed. A small portion of mixture was collected for the ^{1}H NMR spectroscopy to determine the ratio of the *cis*/*trans*-isomers. The reaction mixture was passed through a pad of silica gel and washed with ethyl acetate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to give the desired product as a mixture of *cis*/*trans*-isomers. A portion of eluent with thee pure *cis*-isomer was collected for compound characterization.

(*3R,4S*)-4-(4-Methoxyphenyl)-3-ethyl-3-phenyl-3,4-dihydro[1,3]dioxolo[4,5-*g*]coumarin (3aa): Total yield: 77.2 mg (96%) *cis*:*trans* = 7:1 [60.5 mg (75%) of pure *cis*; plus 16.7 mg (21%) of *cis*/*trans* mixture]. *cis*-**3aa:** white solid; mp 175–176 °C; R_f = 0.53 (petroleum ether/ethyl acetate = 6:1); $[\alpha]_D^{25}$: +311 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11–7.14 (m, 3H), 7.01–7.05 (m, 2H), 6.72 (s, 1H), 6.54 (d, *J* = 7.8 Hz, 2H), 6.46 (s, 1H), 6.45 (d, *J* = 7.8 Hz, 2H), 5.94 (d, *J* = 10.5 Hz, 2H), 3.88 (s, 1H), 3.68 (s, 3H), 2.25–2.40 (m, 1H), 2.10–2.15 (m, 1H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 158.5, 147.4, 144.8, 144.5, 137.0, 131.3, 129.4, 128.5, 127.6, 126.7, 118.2, 113.5, 107.8, 101.6, 98.5, 56.1, 55.3, 55.1, 28.8, 9.3; IR (KBr): ν = 1752 cm^{-1}; HR-MS (EI): *m/z* = 402.1471, calcd for $C_{25}H_{22}O_5$ $[M]^+$: 402.1467M; HPLC analysis: 99% *ee* (*cis*), 96% *ee* (*trans*), [Daicel CHIRALPAK AD-H column; 20 °C; 0.8 mL min^{-1}; solvent system: *i*-PrOH/hexanes = 2: 98; retention times: 29.6 min (*cis*-minor), 34.8 min (*trans*-major), 39.2 min (*cis*-major), 42.0 min (*cis*-minor)].

Acknowledgements

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[20] The ratio of cycloaddition product **3aa** to the esterification product, $Ph(Et)CHCO_2Me$, is about 3:1 determined by ^1H NMR of the reaction mixture. When the ester (0.6 equiv.) was used as the additive for the cycloaddition reaction, no positive effects like those of methanol were observed.

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[22] CCDC 742517 contains the supplementary crystallographic data for dihydrocoumarin **3ag** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[23] Dihydrocoumarins **3ba** and **3bf**, prepared from QM **1b**, show opposite directions of their specific rotations compared with **3aa**, but were assigned the same absolute configurations based on the identical pattern in the CD spectra (**3ba**) compared with **3aa**.

