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N-Heterocyclic Carbene-Catalyzed Stereoselective Cascade Reaction: Synthesis of Functionalized Tetrahydroquinolines

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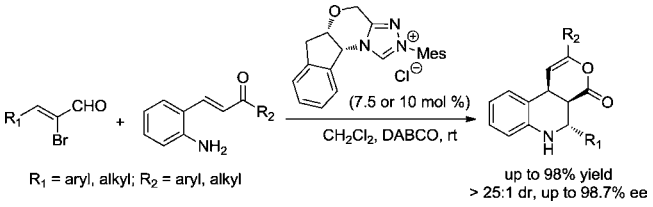
ABSTRACT



The first *N*-heterocyclic carbene-catalyzed stereoselective aza-Michael−Michael−lactonization cascade reaction of 2′-aminophenylenones and 2-bromoenals for the construction of chiral functionalized tetrahydroquinolines with three consecutive stereogenic centers has been achieved in high yields (up to 98%) with excellent diastereo- (>25:1) and enantioselectivities (up to 98.7% *ee*).

The tetrahydroquinolines are very attractive targets because of their biological activities. This structural motif naturally occurs in several biologically active natural products and pharmaceutics. In recent years, interest in the synthesis of chiral tetrahydroquinolines has increased dramatically.[1] Until now, many synthetic methods for accessing such compounds have been developed, such as enantioselective hydrogenation of quinolines,[2] aza-Diels−Alder reactions,[3] Reissert-type reactions,[4] NHC-catalyzed intramolecular aldehyde−ketone benzoin reactions,[5] etc.

N-Heterocyclic carbene (NHC)-catalyzed umpolung reactions have received great attention and contributed tremendously to progress in recent decades.[6,7] Since Glorius et al.[8a] and Bode et al.[8b] independently reported the NHC-catalyzed reaction of enals, all kinds of 2-functionalized aldehydes[9−14] have been explored in a large number of umpolung reactions. However, the value of NHC-catalyzed cascade reactions has only received growing

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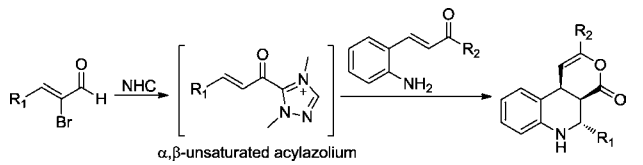
Scheme 1. NHC-Catalyed Stereoselective Cascade Reaction



attention in the past four years.[15] α,β-Unsaturated acylazolium intermediates, which are efficient 1,3-(bis)-electrophiles used for 1,4- or 1,2-addition reactions, can be formed from α,β-unsaturated acyl fluorides,[16] ynals,[10] enals with an oxidant,[17] and 2-haloenals.[18] However, only the carbonyl and β-carbon atoms of the 1,3-(bis)-electrophile are used. In addition, little effort has been focused on the use of the α,β-unsaturated acylazolium intermediate in enantioselective cascade reactions.[16d] In continuation of our investigations into enantioselective reactions, we designed an efficient stereoselective aza-Michael−Michael−lactonization cascade reaction of 2-bromoenals and 2′-aminophenylenones catalyzed by NHC for the synthesis of chiral functionalized tetrahydroquinolines (Scheme 1). This strategy allows three new bonds and three stereocenters to be constructed in a single cascade sequence.

In the first stage of the study, we investigated the stereoselective aza-Michael−Michael−lactonization cascade reaction of 2-bromoenal **1a** and 2′-aminophenylenone **2a** catalyzed by chiral *N*-heterocyclic carbene **3a** (10 mol %) in toluene at rt. The NHC-catalyst **3a** provided the product **4a** in moderate yield and enantioselectivity (Table 1, entry 1). The Morita−Baylis−Hillman reaction did not proceed under these conditions probably due to the increased degree of conjugation of 2′-aminophenylenones which did not favor conjugate addition of the DABCO to the Michael acceptor. Furthermore, a series of chiral NHC-catalysts **3b**−**3g** were tested in the cascade reaction and the results showed that NHC-catalyst **3d** was the best catalyst for this transformation (entry 4). When chiral NHC-catalysts **3e**−**3g** were used, compound **5** was provided instead of the desired product **4a**. A screen of bases revealed DABCO to be the preferred base (entry 4). Other solvents were also investigated, and dichloromethane was found to be the best reaction solvent (entry 10). To increase the yield of this cascade reaction, the ratio of 2-bromoenal **1a** and 2′-aminophenylenone **2a** was optimized (entries 12−14). To our delight, the product **4a** was obtained with 98% yield, >25:1 dr, and 97% ee when 1.5 equiv of the 2-bromoenal was used (entry 13). When the amount of NHC-catalyst **3d** was reduced to 7.5 mol %, a high yield, excellent diastereo- and enantioselectivity, and a fast reaction rate were maintained (entry 15). Upon further reduction to 5 and 3 mol %, slightly lower yields and enantioselectivities were obtained, respectively (entries 16−17). When 2-chloro-3-phenylacrylaldehyde (**1a′**) was used, the product **4a** was isolated in 91% yield and 93% ee (entry 18).

To demonstrate the generality of the NHC-catalyst **3d** promoted stereoselective aza-Michael−Michael−lactonization cascade reaction, a variety of 2-bromoenals and 2′-aminophenylenones were explored (Table 2). When the cascade reaction of 2-bromoenals **1a**−**1f** and 2′-aminophenylenone **2a** were examined under the optimized conditions, products **4a**−**4f** were obtained in high yield

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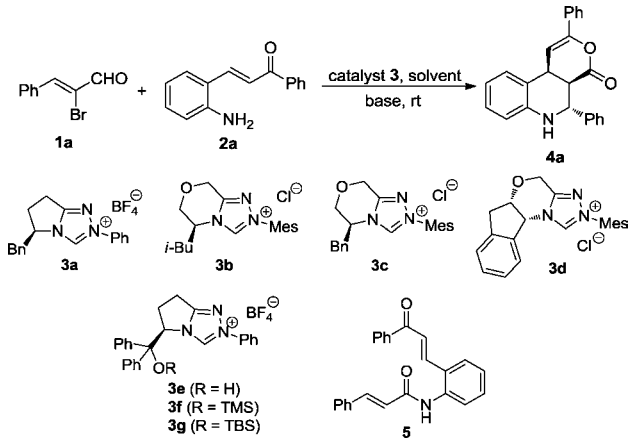
Table 1. Optimization of Reaction Conditions[a]



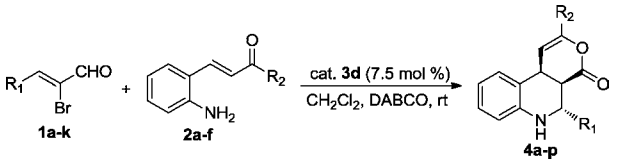
entry	catalyst (mol %)	base	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**3a** (10)	DABCO	toluene	7	62	>25:1	73
2	**3b** (10)	DABCO	toluene	3	65	>25:1	93
3	**3c** (10)	DABCO	toluene	3	65	>25:1	94
4	**3d** (10)	DABCO	toluene	3	76	>25:1	94
5	**3d** (10)	Cs_2CO_3	toluene	3	63	>25:1	96
6	**3d** (10)	K_2CO_3	toluene	3	53	>25:1	98
7	**3d** (10)	DBU	toluene	3	46	>25:1	94
8	**3d** (10)	Et_3N	toluene	3	70	>25:1	97
9	**3d** (10)	DABCO	THF	3	62	>25:1	94
10	**3d** (10)	DABCO	CH_2Cl_2	3	79	>25:1	97
11	**3d** (10)	DABCO	CH_3CO_2Et	3	48	>25:1	97
12[e]	**3d** (10)	DABCO	CH_2Cl_2	3.5	94	>25:1	97
13[f]	**3d** (10)	DABCO	CH_2Cl_2	3.5	98	>25:1	97
14[g]	**3d** (10)	DABCO	CH_2Cl_2	3.5	98	>25:1	94
15[f]	**3d** (7.5)	DABCO	CH_2Cl_2	3.5	98	>25:1	97
16[f]	**3d** (5)	DABCO	CH_2Cl_2	4.5	97	>25:1	96
17[f]	**3d** (3)	DABCO	CH_2Cl_2	9	93	>25:1	95
18[f,h]	**3d** (3)	DABCO	CH_2Cl_2	3.5	91	>25:1	93

[a] Reaction conditions: **1a**/**2a**/base = 1:1:1.1 (molar ratio). [b] Isolated yield. [c] Determined by ^{1}H NMR (400 MHz) of crude product. [d] Determined by chiral HPLC. [e] **1a**/**2a** = 1.25:1 (molar ratio). [f] **1a**/**2a** = 1.5:1 (molar ratio). [g] **1a**/**2a** = 1.75:1 (molar ratio). [h] 2-Chloro-3-phenylacrylaldehyde (**1a′**) was used.

and excellent enantioselectivity. However, when the reactions of 2′-aminophenylenone **2a** and 2-bromoenals **1g**−**1j**, which contain electron-donating or -withdrawing groups, were carried out under the optimized conditions, the products **4g**−**4j** were obtained in moderate yields and excellent enantioselectivities. It should be noted that 2-bromoenals **1j** with the CF_3− group exhibited slightly low enantioselectivity. With respect to the alkyl-substituted 2-bromoenal **1k**, product **4k** was afforded in 48% yield with 86.9% ee.

Several 2′-aminophenylenones were also examined for this reaction. In the course of the experiment, we found that both electron-withdrawing and -donating substituents on the aromatic ring of the 2′-aminophenylenones **2b**−**2e** provided the products **4l**−**4o** in high yield and excellent enantioselectivity. The reaction of alkyl substituted 2′-aminophenylenone **2f** also worked well to give product **4p** with 75% yield and 98.7% ee.

Table 2. Substrate Scope of the NHC-Catalyzed Cascade Reaction[a]



R_1 (**1**)	R_2 (**2**)	prod	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
Ph (**1a**)	Ph (**2a**)	**4a**	3.5	98	>25:1	97.2
4-FC_6H_4 (**1b**)	Ph (**2a**)	**4b**	3.5	98	>25:1	98.3
2-ClC_6H_4 (**1c**)	Ph (**2a**)	**4c**	4	98	>25:1	97.3
3-ClC_6H_4 (**1d**)	Ph (**2a**)	**4d**	3.5	98	>25:1	95.1
4-ClC_6H_4 (**1e**)	Ph (**2a**)	**4e**	3.5	98	>25:1	95.0
4-BrC_6H_4 (**1f**)	Ph (**2a**)	**4f**	3	93	>25:1	96.7
4-MeC_6H_4 (**1g**)	Ph (**2a**)	**4g**[e]	4	98	>25:1	97.6
4-$MeOC_6H_4$ (**1h**)	Ph (**2a**)	**4h**[e]	6	95	>25:1	94.0
4-$NO_2C_6H_4$ (**1i**)	Ph (**2a**)	**4i**[e]	3.5	93	>25:1	97.7
4-$CF_3C_6H_4$ (**1j**)	Ph (**2a**)	**4j**[e]	3.5	93	>25:1	89.7
Me, (**1k**)	Ph (**2a**)	**4k**[e]	8	48	>25:1	86.9
Ph (**1a**)	4-ClC_6H_4 (**2b**)	**4l**[e]	2.5	93	>25:1	97.6
Ph (**1a**)	4-BrC_6H_4 (**2c**)	**4m**[e]	2.5	95	>25:1	89.2
Ph (**1a**)	4-MeC_6H_4 (**2d**)	**4n**[e]	3.5	98	>25:1	94.8
Ph (**1a**)	4-$MeOC_6H_4$ (**2e**)	**4o**[e]	2.5	97	>25:1	98.0
Ph (**1a**)	Me (**2f**)	**4p**[e]	3.5	75	>25:1	98.7

[a] Reaction conditions: **1**/**2**/catalyst **3d**/DABCO = 1.5:1:0.075:1.65 (molar ratio). [b] Isolated yield. [c] Determined by ^{1}H NMR (400 MHz) of the crude products. [d] Determined by chiral HPLC. [e] Catalyst **3d** (10 mol %) was used.

The possible mechanism for this cascade reaction is illustrated in Figure 1. Addition of the *N*-heterocyclic carbene, generated by deprotonation of precursor **3d**, to the 2-bromoenal **1** forms the Breslow intermediate **A**. Intermediate **A** is transformed into **C** through tautomerization and debromination. The aza-Michael addition of 2′-aminophenylenone **2** to **C** provides enolate **D**. Enolate **D** can itself undergo intramolecular Michael addition to give **E**, which can participate in intramolecular lactonization to furnish the desired product **4** and regenerate the *N*-heterocyclic carbene catalyst.

The structures of the products **4a**−**4p** were characterized by spectroscopic data, and the absolute configuration of the product was determined to be as in (4*R*,5*R*,10*S*)-**4f** by X-ray crystal analysis (Figure 2).[19] The absolute configuration of the other products was assigned tentatively by analogy.

The synthetic versatility of the adducts in this stereoselective cascade reaction was illustrated by a further transformation. The adduct **4a** could be easily ring opened by benzylamine to the tetrahydroquinoline derivative **6** in 96% yield and 95.5% ee (Scheme 2).

In conclusion, we have developed an efficient NHC-catalyzed stereoselective aza-Michael−Michael−lactonization

(19) CCDC 950181 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

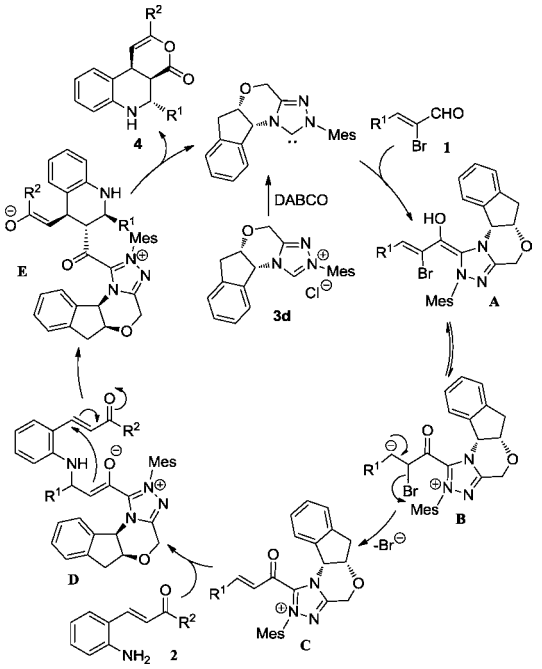


Figure 1. Possible catalytic cycle.

cascade reaction of 2′-aminophenylenones and 2-bromoenals. Functionalized tetrahydroquinolines with three consecutive stereogenic centers were obtained in high yield with excellent diastereo- and enantioselectivities. This approach is attractive due to the mild reaction conditions and the potential utilization value of the products in molecular biology and pharmacy. In addition, this strategy extends the scope of NHC-catalysis and provides a simple protocol for the NHC-catalyzed cascade reaction.

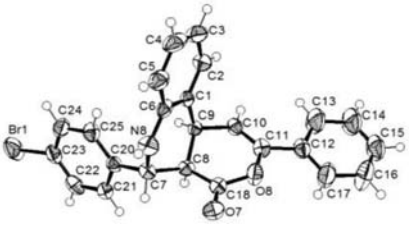
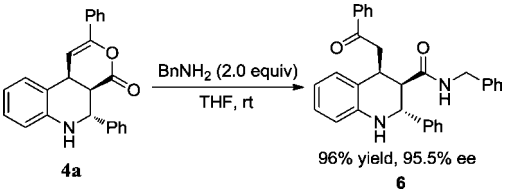


Figure 2. X-ray crystallography of compound **4f**.

Scheme 2. Transformation of Compound **4a**



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Supporting Information Available. Experimental procedure, characterization data for the products, crystallographic data of compound **4f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.