JOC Note
pubs.acs.org/joc

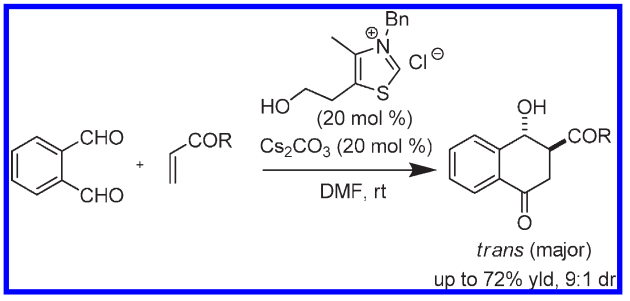
Diastereoselective Synthesis of 4-Hydroxytetralones via a Cascade Stetter−Aldol Reaction Catalyzed by *N*-Heterocyclic Carbenes

Fang-Gang Sun, Xue-Liang Huang, and Song Ye*

Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

songye@iccas.ac.cn

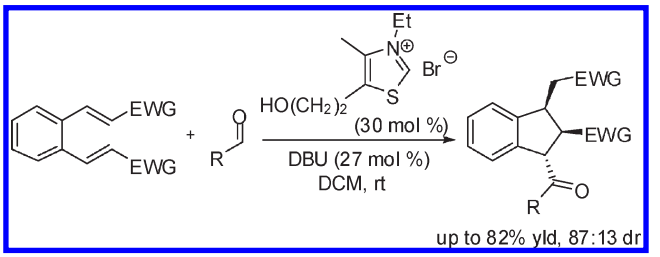
Received November 6, 2009



A cascade Stetter−aldol reaction of phthalaldehyde and Michael acceptors catalyzed by *N*-heterocyclic carbenes was developed. The corresponding 3-substituted-4-hydroxytetralones were obtained in moderate to good yields with good *trans*-selectivities. On the contrary, the separated Stetter reaction followed by aldol reaction gave 3-substituted-4-hydroxytetralones with good *cis*-selectivity. Oxidation or dehydration of the resulted 4-hydroxytetralone gave the corresponding naphthalenediol or naphthol derivative, respectively, in good yield.

Cascade reactions, which allow two or more reactions to occur consecutively in one pot, are of great interest in modern synthesis.[1] Generally, two requirements for a cascade reaction are that (1) a reactive intermediate is formed in the former reaction that can further react in the latter reaction and (2) the conditions for the consecutive reactions are compatible. The Stetter reaction is the addition of aldehydes to Michael acceptors catalyzed by *N*-heterocyclic carbenes (NHCs).[2,3] Although an enolate, which is a very useful reactive intermediate in organic synthesis, is generated in the Stetter reaction, the cascade reactions involving this enolate have rarely been reported.

SCHEME 1. Gravel's Cascade Stetter−Michael Reaction



During the preparation of this manuscript, Gravel et al. reported a NHC-catalyzed cascade Stetter−Michael reaction for the synthesis of indanes (Scheme 1).[4] In this manuscript, we wish to report a NHC-catalyzed cascade Stetter−aldol reaction for the diastereoselective synthesis of 4-hydroxytetralones.[5]

4-Hydroxytetralones and their derivatives are useful intermediates in organic synthesis and present as the key motif in several natural products and biological active compounds, such as isocatalponol, isoshinanolone, and plumbagin.[6] However, to the best of our knowledge, there are only limited examples for the synthesis of this motif.[7] We envisioned that the enolate **5**, generated from phthalaldehyde **1** and Michael acceptor **2** via a NHC-catalyzed Stetter reaction, may further undergo intramolecular aldol reaction to afford 4-hydroxytetralones **3** (Figure 1).

Initial experiment revealed that the reaction of phthalaldehyde and ethyl(vinyl)ketone **2a** catalyzed by NHC **6a′**, generated from thiazolium salt **6a** in the presence of the base Cs_2CO_3, gave 4-hydroxytetralone **3a** in 45% yield with a 1:1 ratio of *trans*- and *cis*-isomers (Table 1, entry 1). It should be noted that only slight epimerization of *cis*- to *trans*-isomer or *trans*- to *cis*-isomer was observed in the presence of 20 mol % Cs_2CO_3 or DBU.[8]

After ruling out the in situ isomerization of the *trans*/*cis*-isomers, the optimization of reaction conditions was then carried out to improve the diastereoselectivity and yield. It

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006.

(2) (a) Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 81. (b) Stetter, H. *Angew. Chem., Int. Ed.* **1976**, *15*, 639.

(3) For recent reviews on NHC-catalyzed reactions, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606 and references therein. (b) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (c) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.

(4) Sánchez-Larios, E.; Gravel, M. *J. Org. Chem.* **2009**, *74*, 7536.

(5) For our recent publications on NHC catalysis, see: (a) He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466. (b) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. (c) Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192.

(6) (a) Inoue, K.; Inouye, H.; Taga, T.; Fujita, R.; Osaki, K.; Kuriyama, K. *Chem. Pharm. Bull.* **1980**, *28*, 1224. (b) Anh, N. H.; Ripperger, H.; Porzel, A.; Sung, T. V.; Adam, G. *Phytochemistry* **1997**, *44*, 549. (c) Tokunaga, T.; Takada, N.; Ueda, M. *Tetrahedron Lett.* **2004**, *45*, 7115. (d) Nyangulu, J. M.; Nelson, K. M.; rose, P. A.; Gai, Y.; Loewen, M.; Lougheed, B.; Quail, J. W.; Cutler, A. J.; Abrams, S. R. *Org. Biomol. Chem.* **2006**, *4*, 1400.

(7) (a) Joly, S.; Nair, M. S. *Tetrahedron: Asymmetry* **2001**, *12*, 2283. (b) Gopishetty, S. R.; Heinemann, J.; Deshpande, M.; Rosazza, J. P. N. *Enzyme Microb. Technol.* **2007**, *40*, 1622. (c) Allen, J. G.; Henntemann, M. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 571. (d) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725. (e) Dohi, T.; Takenaga, N.; Goto, A.; Fujioka, H.; Kita, Y. *J. Org. Chem.* **2008**, *73*, 7365. (f) Nakanishi, M.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 861.

(8) See Supporting Information for details.

DOI: 10.1021/jo902376t Published on Web 12/07/2009

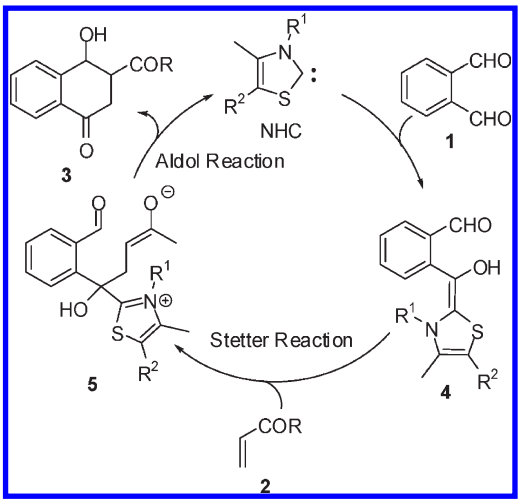
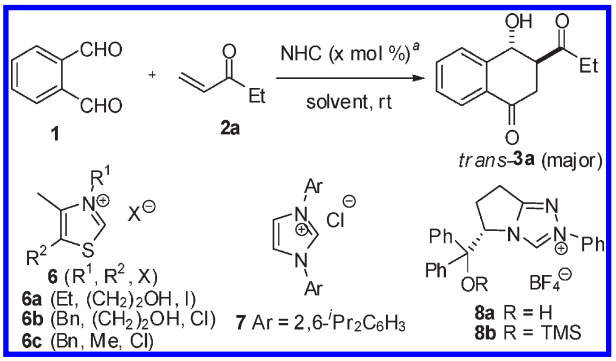


FIGURE 1. Proposed cascade Stetter−aldol reaction catalyzed by NHC.

TABLE 1. Optimization of Reaction Conditions

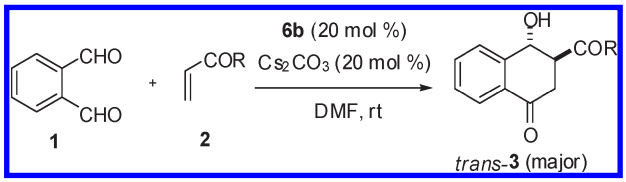


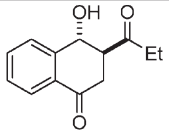
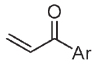
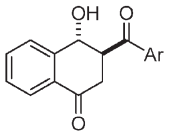
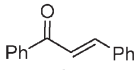
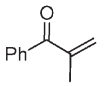
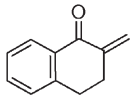
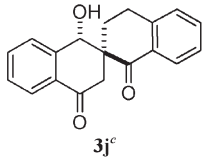
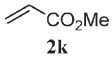
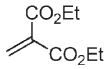
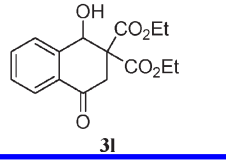
entry	NHC precursor, base (mol %)	solvent	yield (%)[b]	*trans*:*cis*[c]
1	**6a**, Cs_2CO_3 (10)	THF	45	1:1
2	**6a**, Cs_2CO_3 (10)	toluene	40	1:1
3	**6a**, Cs_2CO_3 (10)	CH_3CN	35	1:1
4	**6a**, Cs_2CO_3 (10)	DMF	62	8:1
5	**6a**, Cs_2CO_3 (10)	DMSO	39	3:1
6	**6a**, Cs_2CO_3 (10)	MeOH	trace	
7	**6a**, Cs_2CO_3 (10)	*t*-BuOH	25	1:1
8[d]	**6a**, Cs_2CO_3 (10)	DMF	53	4:1
9	**6b**, Cs_2CO_3 (10)	DMF	65	9:1
10	**6c**, Cs_2CO_3 (10)	DMF	43	5:1
11	**7**, DBU (20)	THF	trace	
12	**7′** (20)[e]	THF	trace	
13	**8a**, Cs_2CO_3 (10)	DMF	trace	
14	**8b**, DBU (20)	THF	trace	
15	**6b**, Cs_2CO_3 (20)	DMF	72	8:1
16	**6b**, K_2CO_3 (20)	DMF	33	>20:1
17	**6b**, $KOBu^t$ (20)	DMF	31	3:1
18	**6b**, DBU (20)	DMF	61	4:1
19	**6b**, DIPEA (20)	DMF	54	3:1

[a]NHCs **6′**−**8′** were generated from the NHC precursors **6**−**8** (10−20 mol %) in situ in the presence of the noted base (10−20 mol %). [b]Isolated yield of the pure *trans*-**3a** (entries 4−19), except entries 1−3 (isolated yield of *trans*/*cis* mixture). [c]Determined by ^{1}H NMR (300 MHz) of the reaction mixture. [d]The reaction was carried out at 0 °C. [e]NHC **7′** was prepared from its precursor **7** with *t*-BuOK as base and used after purification.

was found that reaction varied a lot in different solvents (Table 1, entries 1−7), and reaction in DMF gave the best yield (62%) and selectivity (*trans*:*cis* = 8:1). Low reaction

TABLE 2. Synthesis of *trans*-4-Hydroxytetralones via a Cascade Stetter−Aldol Reaction Catalyzed by NHC 6b′



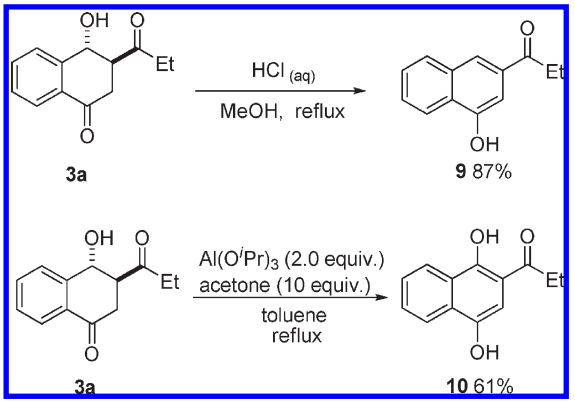
entry	2	3	yield (%)[a]	*trans*:*cis*[b]
1	 **2a**	 **3a**	72	8:1
2	 **2b**, **3b** (Ar = Ph)		53	7:1
3	**2c**, **3c** (Ar = 4-$MeOC_6H_4$)		47	6:1
4	**2d**, **3d** (Ar = 4-ClC_6H_4)		54	7:1
5	**2e**, **3e** (Ar = 2-$EtOC_6H_4$)[c]		31	7:1
6	**2f**, **3f** (Ar = β-naphthyl)		52	8:1
7	**2g**, **3g** (Ar = 2−furyl)		52	6:1
8	 **2h**	/	trace	/
9	 **2i**	/	trace	/
10	 **2j**	 **3j**[c]	70	9:1
11	 **2k**	/	trace	/
12	 **2l**	 **3l**	57	/

[a]Isolated yield of pure *trans*-isomers. [b]Determined by ^{1}H NMR (300 MHz) of the reaction mixture. [c]The structure and *trans*-stereochemistry of **3e** and **3j** were unambiguous assigned by X-ray analysis of their crystals.

temperature gave no benefit (entry 8). Screening of NHCs showed that NHCs derived from all of the thiazolium salts **6a**−**c** worked well (entries 4, 9, and 10), whereas NHCs derived from the imidazolium **7** and triazolium salts **8a,b** did not under current reaction conditions (entries 11−14). Screening of bases revealed that although reaction using K_2CO_3 gave the best *trans*-selectivity, Cs_2CO_3 is the choice for balancing the yield and selectivity (entries 15−19). Reactions with 20 mol % catalyst loading resulted in better yield than with 10 mol % loading (entries 9 and 15).

Other Michael acceptors were then tested under the optimized reaction conditions (Table 2). All of the

SCHEME 2. Dehydration and Oxidation of 4-Hydroxytetralone 3a



aryl(vinyl)ketones **2b**−**f** worked to give the desired products in moderate to good yields with good *trans*-selectivities, except that the vinylketone **2e** with an *o*-ethoxyphenyl group led to low yield (entries 2−6). Heteroaryl(vinyl)ketone **2g** (Ar = 2-furyl) also gave good result (entry 7). Vinylketones (**2 h,i**) with an α- or *β*-substituent did not work. However, the vinylketone **2j**, featuring a "ring-closed" α-substituent, worked very well to give the spiro-product **3j** in 70% with a 9:1 dr (entry 10). Although methyl acrylate (**2k**) did not work (entry 11), the double activated α,*β*-unsaturated ester **2l** worked well (entry 12).

The resulting 4-hydroxytetralone **3a** could be transformed to the corresponding naphthol **9** and naphthalenediol **10** by dehydration and Oppenauer oxidation, respectively, in good yield (Scheme 2).

Two possible pathways from the Stetter reaction adduct **5** to final product **3** are depicted in Figure 2. In pathway A, the NHC motif leaves first to give the simple Stetter reaction product **11**, followed by aldol reaction to give **3**. In pathway B, adduct **5** undergoes the aldol reaction with NHC motif attached, followed by fragmentation to regenerate free NHC and afford final product **3**.

We envisioned that the reaction may stop before the aldol reaction if a suitable proton source were provided in the reaction. It was found that the Stetter reaction product **11a** was obtained in 55% yield when 20 mol % benzoic acid was used as an additive for the reaction, and no cascade reaction product **3a** was observed (Scheme 3). Interestingly, aldol reaction of compound **11** gave hydroxytetralone **3a** in 61% yield with *cis*-**3a** as the major diastereomer (*cis*:*trans* = 4:1).

The reversed *cis*/*trans* selectivities between the cascade Stetter−aldol reaction (*trans*-isomer as the major product) and separate Stetter reaction followed by aldol reaction (*cis*-isomer as the major product) suggest pathway B is more favored for this cascade reaction. This observation is different from the reported NHC-catalyzed cascade Stetter−Michael reaction, in which the pathway with NHC leaving before Michael addition is suggested.[4] Pathway B is more interesting than pathway A because the NHC motif is still attached for the aldol reaction in pathway B and thus makes it possible to control the stereochemistry in both Stetter and aldol steps by NHC catalysts.

In conclusion, a cascade Stetter−aldol reaction of phthalaldehydes and Michael acceptors catalyzed by NHC was

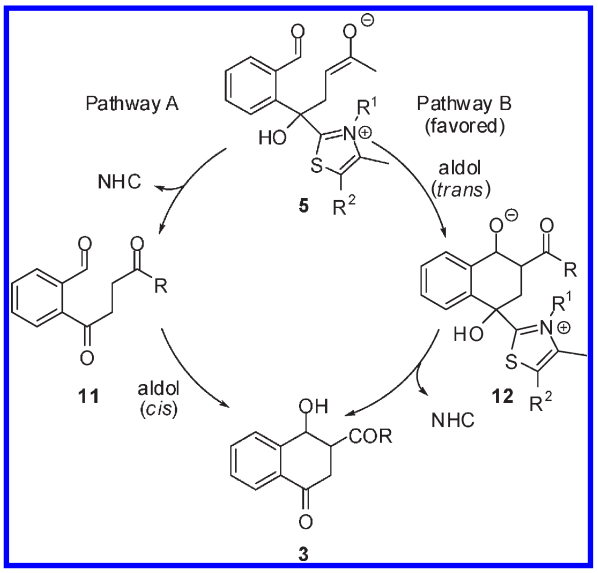
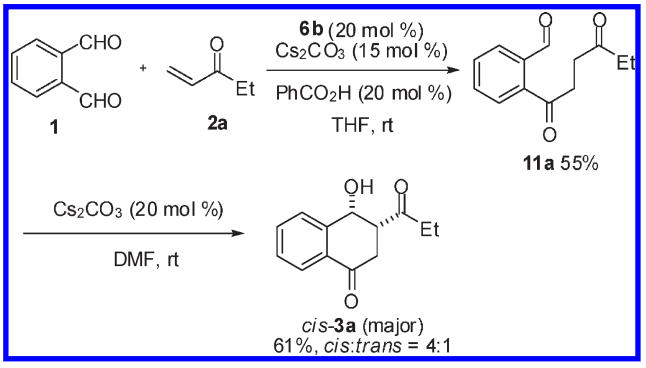


FIGURE 2. Two possible pathways from adduct **5** to product **3**.

SCHEME 3. Synthesis of *cis*-4-Hydroxytetralone 3a by Separated Stetter Reaction Followed by Aldol Reaction



developed for the diastereoselective synthesis of *trans*-3-substituted-4-hydroxytetralone. The *trans*-selectivity in the cascade reaction, which is opposite to *cis*-selectivity in separate Stetter reaction followed by aldol reaction, suggests that the aldol reaction occurs before the leaving of NHC catalyst (pathway B). Further exploration on cascade reactions catalyzed by NHCs and their asymmetric versions are underway in our laboratory.

Experimental Section

Typical Procedure for the Synthesis of *trans*-4-hydroxyltetralones via a Cascade Stetter−Aldol Reaction Catalyzed by NHC 6b′. An oven-dried 50 mL Schlenk tube equipped with a stir bar was charged with thiazolium salt (26.9 mg, 0.1 mmol) and phthalaldehyde (67 mg, 0.5 mmol). The tube was closed with a septum, evacuated, and backfilled with argon. To this mixture was added distilled solvent DMF (2.5 mL) and ethyl(vinyl)-ketone, and then the mixture was stirred for 10 min at room temperature. Cs_2CO_3 (32.6 mg, 0.1 mmol) was added to the tube. The mixture was further stirred for 3 h, then diluted with ethyl acetate, and passed through a short silica pad. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (ethyl acetate/petroleum ether) to give 78.5 mg (72%) of **3a** as a white solid, R_f = 0.26

(petroleum ether/ethyl acetate = 3:1), mp 143−144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.66−7.61 (m, 1H), 7.44−7.39 (m, 1H), 5.28 (dd, J = 4.5 Hz, 9.5 Hz, 1H), 3.35−3.26 (m, *2*H), 2.96 (dd, J = 3.9 Hz, 17.0 Hz, 1H), 2.71−2.51 (m, 3H), 1.11 (t, J = 8.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 194.6, 144.3, 134.5, 130.5, 128.0, 126.9, 126.2, 68.8, 55.2, 38.9, 35.6, 7.4; IR (KBr) v 1716, 1691, 1601, 1297, 767; EIMS m/z 218 (4.0), 161 (100); HRMS-(EI) (m/z) M^+ calcd for $C_{13}H_{14}O_3$ 218.0943, found 218.0946.

Acknowledgment. Financial support from National Science Foundation of China (20602036, 20932008), the Ministry of Science and Technology of China (2009ZX-09501-018), and the Chinese Academy of Sciences is gratefully acknowledged.

Supporting Information Available: Experimental procedures, compound characterizations, and crystal structure data of tetralone **3e** and **3j** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.