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A Highly Selective Cascade Approach to Diverse Aromatic Ring Systems from Simple Aromatic Aldehydes and Propiolates

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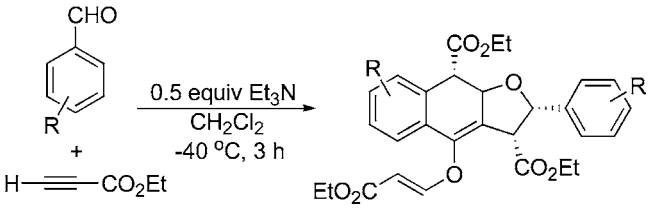
ABSTRACT



A new triethylamine-catalyzed cascade reaction of aromatic aldehydes with propiolates has been developed. This serial multi-bond-forming process furnishes diverse polycyclic aromatic hydrocarbons, including naphthalenes, phenanthrenes, benzofurans, and 2,3,9,9a-tetrahydronaphtha-[2,3-b]furans. The chemical outcome of the process depends on the reaction temperature and can be tailored selectively by an appropriate choice of experimental conditions.

Cascade reaction has emerged as a powerful tool to create molecular complexity from simple starting materials.[1,2] Unlike stepwise bond formation toward a target molecule, such process has the advantages of greatly enhanced synthetic efficiency, while generating less waste and minimizing the excessive handling. Particularly when catalytic possibility exists, this type of transformation becomes extremely valuable and an economical synthetic method for introducing chemical and structural complexity.[1] Recently, García-Tellado et al.[2] reported that a triethylamine-catalyzed cascade reaction of aliphatic aldehydes with methyl propiolate afforded either enol-protected functionalized propargylic alcohols (at 0 °C) or 1,3-dioxolanes (at −78 °C). As a part of our research program aiming at developing multicomponent cascade reactions for the synthesis of substituted aromatic compounds,[3] we herein report a new triethylamine-catalyzed cascade reaction of aromatic aldehydes with terminal conjugated acetylenes, which furnishes diverse polycyclic aromatic hydrocarbons, including naphthalenes, phenanthrenes, benzofurans, and 2,3,9,9a-tetrahydronaphtha-[2,3-b]furans. The chemical outcome of the process depends on the reaction temperature, and it can be tailored selectively by an appropriate choice of experimental conditions.

As shown in Scheme 1, benzaldehydes **1** (0.67 equiv) reacted with propiolates **2** (1.0 equiv) in the presence of a

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329−16332. (c) Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5103−5106. (d) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468−470. (e) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413−422. (f) von Wangelin, J. A.; Neumann, H.; Gördes, D.; Klaus, S.; Strübing, D.; Beller, M. *Chem.—Eur. J.* **2003**, *9*, 4286−4294. (g) Neumann, H.; von Wangelin, J. A.; Klaus, S.; Strübing, D.; Gördes, D.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4503−4507. (h) Ashfeld, B. L.; Miller, K. A.; Smith, A. J.; Tran, K.; Martin, S. F. *Org. Lett.* **2005**, *7*, 1661−1663. (i) Fedou, N. M.; Parsons, P. J.; Viseux, E. M. E.; Whittle, A. J. *Org. Lett.* **2005**, *7*, 3179−3182.

(2) (a) Tejedor, D.; García-Tellado, F.; Marrero-Tellado, J. J.; de Armas, P. *Chem.—Eur. J.* **2003**, *9*, 3122−3131. (b) de Armas, P.; García-Tellado, F.; Marrero-Tellado, J. J.; Tejedor, D.; Maestro, M. A.; Gonzalez-Platas, J. *Org. Lett.* **2001**, *3*, 1905−1908.

(3) Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866−2869.

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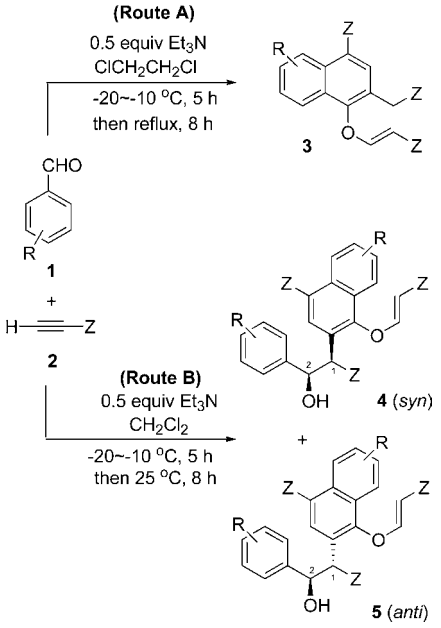
Scheme 1



catalytic amount of triethylamine (0.5 equiv) to give a naphthalene derivative **3** in 45−66% yield when the reaction was carried out in $ClCH_2CH_2Cl$ at −20 to −10 °C for 5 h and then at reflux for 8 h (Route A) (Table 1). When the reaction was performed in CH_2Cl_2 at −20 to −10 °C for 5 h and then at 25 °C for 8 h, products **4** and **5** instead of **3** were isolated in 56−71% total yields (Route B) (Table 2). In all cases, no *Z*-isomers of the products were detected. The *syn* and *anti* configurations of the products **4** and **5** were assigned from NMR evidence, namely, J_{H1-H2}.[4] Trioctylamine was also found to be able to promote this reaction (see the Supporting Information).

Table 1. Triethylamine-Catalyzed Synthesis of Polysubstituted Naphthalenes **3**

entry	R	Z	product	yield (%)[a]
1	H (**1a**)	CO_2Et (**2a**)	**3a**	45
2	2-Me (**1b**)	CO_2Me (**2b**)	**3b**	53
3	4-Me (**1c**)	**2a**	**3c**	66
4	4-Et (**1d**)	**2b**	**3d**	65
5	4-Ph (**1e**)	**2a**	**3e**	63
6	4-MeO (**1f**)	**2b**	**3f**	60
7	4-$PhCH_2O$ (**1g**)	**2a**	**3g**	56
8	4-TsO (**1h**)	**2a**	**3h**	56
9	3,4-dimethyl (**1i**)	**2a**	**3i**	52
10	3,4-OCH_2O− (**1j**)	**2a**	**3j**	57

[a] Isolated yield refers to propiolate.

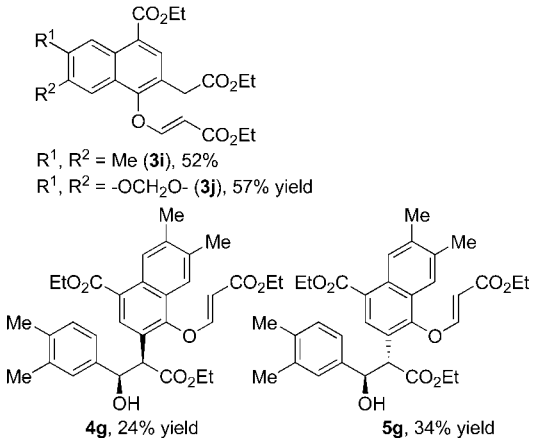
It is noteworthy that presumably because of steric reasons asymmetric benzaldehydes **1i** and **1j** furnished only the less crowded naphthalenes **3i** and **3j** (Route A) or **4g** and **5g** (Route B), as structurally shown in Scheme 2. It was also found that 1-naphthaldehyde (**1k**) afforded a phenanthrene derivative **3k** in 58% yield (Scheme 3), and furan-2-carbaldehyde (**1l**) gave a benzofuran derivative **3l** (53% yield) (Scheme 4, Route A) or **4h** (30% yield) and **5h** (21% yield) (Scheme 4, Route B), respectively.

Table 2. Triethylamine-Catalyzed Synthesis of Polysubstituted Naphthalenes **4** and **5**

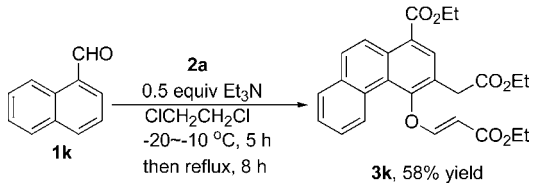
			product/yield (%)[a]			
entry	R	Z	**4**		**5**	
1	**1a**	**2a**	**4a**	21	**5a**	35
2	**1c**	**2a**	**4b**	28	**5b**	40
3	**1d**	**2b**	**4c**	29	**5c**	42
4	**1e**	**2a**	**4d**	27	**5d**	43
5	**1f**	**2b**	**4e**	26	**5e**	37
6	**1g**	**2a**	**4f**	27	**5f**	38
7	**1i**	**2a**	**4g**	24	**5g**	34

[a] Isolated yield refers to propiolate.

Scheme 2



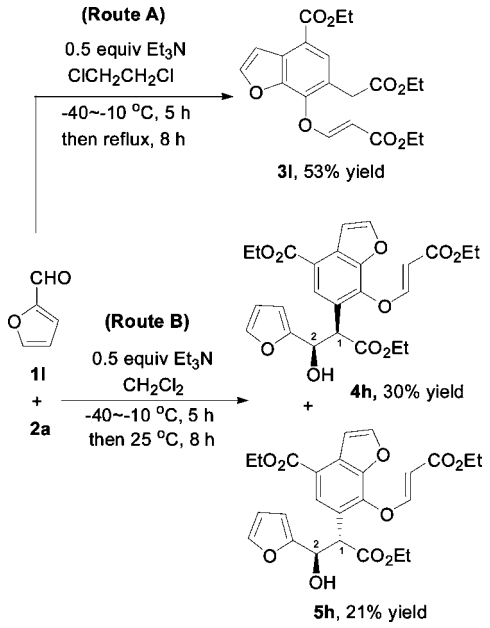
Scheme 3



We subsequently performed analogous reactions using electron-deficient benzaldehydes, such as 4-bromobenzaldehyde, and other terminal alkynes, such as 3-butyn-2-one and ethynyl *p*-tolyl sulfone, but did not observe any of the corresponding naphthalene derivatives.

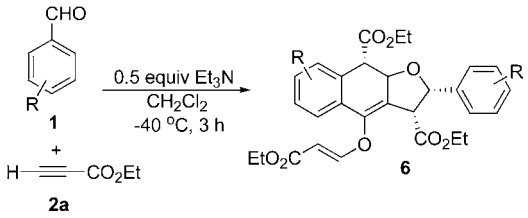
(4) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (b) Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **1995**, *60*, 7006−7009.

Scheme 4



As the next step, we obtained intermediates **6** of this cascade process by quenching the reaction with dilute acid at −40 °C (Table 3). The structure of compound **6b** was

Table 3. Triethylamine-Catalyzed Synthesis of 2,3,9,9a-Tetrahydronaphtha[2,3-b]furans **6**



entry	R	product	yield (%)[a]
1	**1a**	**6a**	63
2	**1c**	**6b**	65
3	**1d**	**6c**	66
4	4-*t*-Bu (**1m**)	**6d**	55

[a] Isolated yield refers to ethyl propiolate.

unambiguously established by X-ray crystallographic analysis (Figure 1) (see Supporting Information). Thus, triethylamine alone is able to catalyze the formation of up to five new C−C bonds and two new C−O bonds in one operation.

To understand the mechanism of our cascade process, we examined the relationships between products **3**−**6** (Scheme 5). It was found that compound **6b** could be transformed to naphthalene **3c** (90%) along with 4-methylbenzaldehyde (**1c**) by refluxing with triethylamine in $ClCH_2CH_2Cl$, while **4b** (33%) and **5b** (60%) were obtained by stirring **6b** and triethylamine in CH_2Cl_2 at room temperature (Scheme 6).

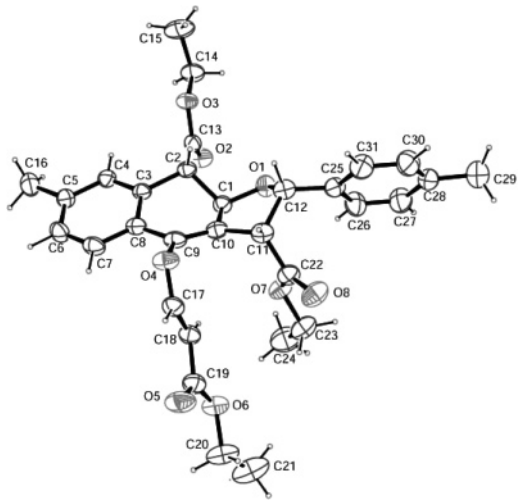
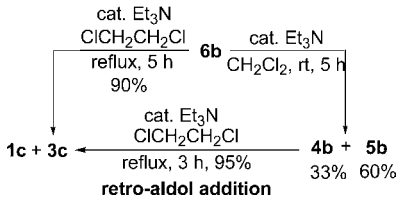


Figure 1. X-ray of compound **6b**.

On the other hand, refluxing **4b** and **5b** in the presence of triethylamine in $ClCH_2CH_2Cl$ also yielded **3c** (95%) and **1c**. In the absence of triethylamine, however, **4b**, **5b**, and **6b** are stable even at refluxing temperature. These results suggest that compound **3** was formed by a retro-aldol reaction from **4** or **5**, which in turn was generated from **6**.

Scheme 5



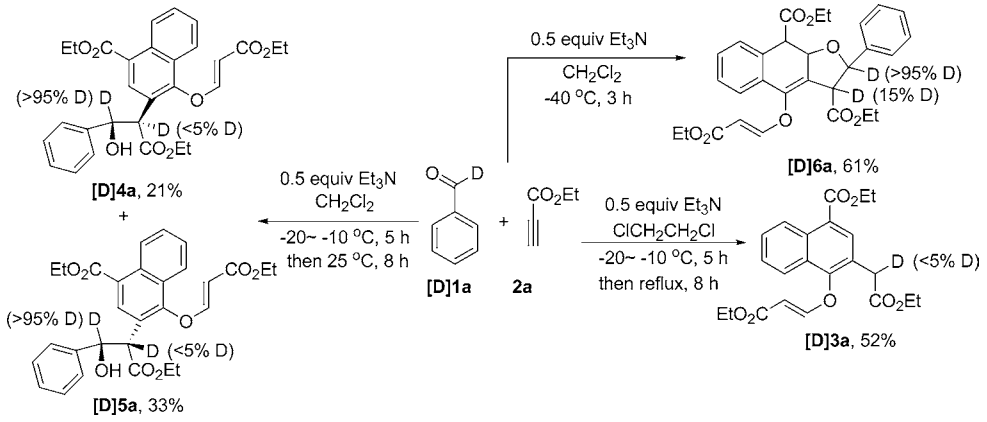
Further insight into the reaction mechanism was gained by conducting a deuterium-labeling experiment, that is, the reaction of $C_6H_5C(O)D$ (**[D]1a**) (98% D) with **1b** (Scheme 6). The deuterated products **[D]3a**, **[D]4a**, **[D]5a**, and **[D]6a** were isolated in 52, 21, 33, and 61% yields, respectively.

Herein we propose a plausible mechanism presented in Scheme 7. Triethylamine as a nucleophile triggers the cascade sequence and forms the enol-protected propargyl alcohol **II**.[2,5] **II** then undergoes a Michael-type addition with the acetylide **I** to produce **III**, which adds to benzaldehyde. Intramolecular hydroarylation of the resulting **IV**, followed by an intramolecular Michael addition, protonation, and a triethylamine-catalyzed isomerization leads to intermediate **6**. Furan ring of **6** is opened by triethylamine to give a mixture of **4** and **5** at 25 °C. At higher temperature, further transformation into **3** by a retro-aldol reaction ensues.

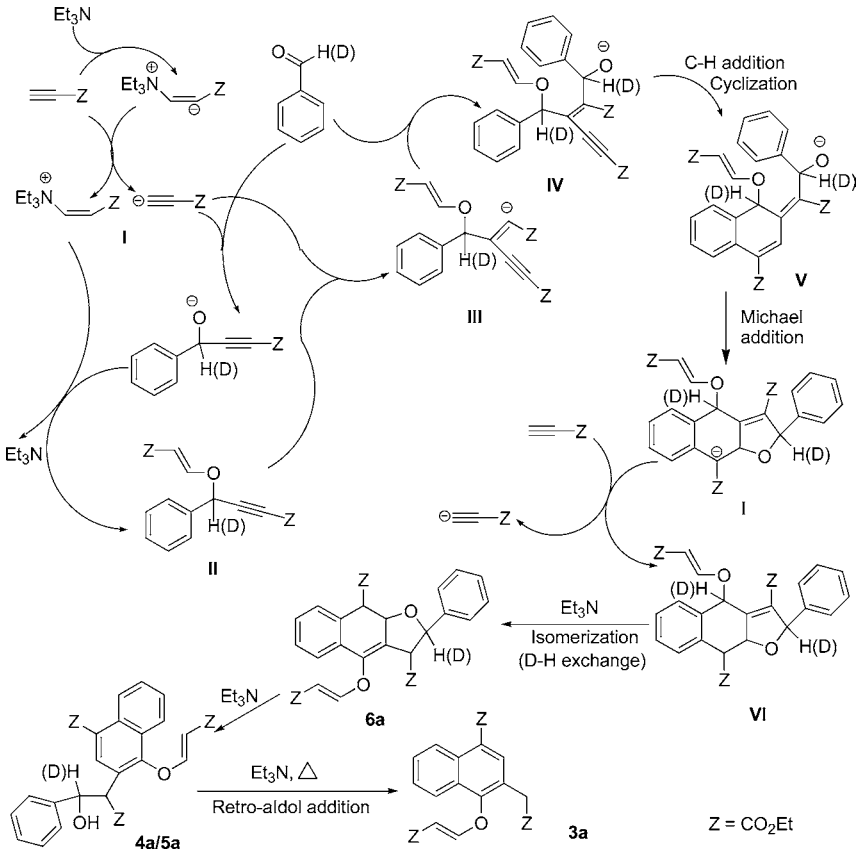
In summary, we have demonstrated that triethylamine catalyzes the condensation of aromatic aldehydes with

(5) Tejedor, D.; Santos-Expósito, A.; González-Cruz, D.; Marrero-Tellado, J. J.; García-Tellado, F. *J. Org. Chem.* **2005**, *70*, 1042−1045.

Scheme 6



Scheme 7



propiolates to furnish diverse polycyclic aromatic hydrocarbons, including naphthalenes, phenanthrenes, benzofurans, and 2,3,9,9a-tetrahydronaphtha[2,3-b]furans. The chemical outcome of this serial multi-bond-forming process depends on the reaction temperature, and it can be tailored selectively by the appropriate choice of the experimental conditions. This cascade process exhibits high bond-forming efficiency and high regioselectivity. Studies to synthesize biologically important aromatic compounds using this approach are in progress and will be reported in due course.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20272051) and the Natural Science Foundation of Zhejiang Province (R404109).

Supporting Information Available: Detailed experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all products and crystallographic information files (CIF) for compound **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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