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Substrates as Electron-Donor Precursors: Synthesis of Naphtho-Fused Oxindoles via Benzannulation of 2-Halobenzaldehydes and Indolin-2-ones

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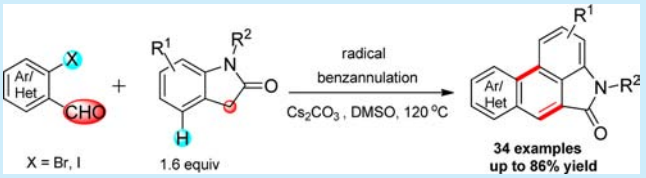
Supporting Information

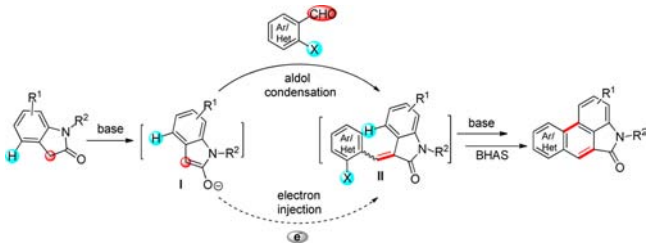
ABSTRACT: An unusual benzannulation reaction has been realized by integrating intermolecular adol condensation with subsequent intramolercular base-promoted homolytic aromatic substitution. This novel cascade reaction provides a straightforward approach toward various naphtho-fused oxindoles from 2-halobenzaldehydes and indolin-2-ones in the presence of Cs_2CO_3 in DMSO. The enolates of indolin-2-ones as new and internal electron donors have been demonstrated to initiate intramolecular radical dehalogenative coupling.



Organopromoted dehalogenative coupling between haloarenes and arenes is perceived as an extremely attractive means to construct aryl−aryl bonds since the publication of some pioneering examples demonstrated by Itami, Shi, Shirakawa/Hayashi, and Kwong/Lei.[1] In the following years, continuous attention has been mainly focused on exploring new organic molecules for these inter-/intramolecular couplings.[2,3] These reactions are mediated by a base (typically KOtBu) and an organic additive and commonly use the benzene series as solvent. Although the general reaction profile summarized by Studer and Curran features base-promoted homolytic aromatic substitution, the precise role of various organocatalysts in the radical initiation step remain ambiguous.[4] Recently, pivotal progress was made by Tuttle, Murphy, and co-workers, who proposed a unifying mechanism where various organic molecules served as precursors of electron donors that transfer an electron to halobenzene, leading to the formation of the initial aryl radicals after release of a halide anion.[5] We noticed that enolates of simple esters, ketones, and cyclic amides could act as electron donors for the coupling of iodoarenes to arenes.[5b] On the basis of the structure−property relationship, we predicted that indolin-2-ones might initiate this type of C−C coupling reaction. Herein, a novel and fascinating cascade reaction related to indolin-2-ones and 2-halobenzaldehydes was conceived in which indolin-2-ones acted as both the substrate and electron donor precursors. In our hypothesis, deprotonation of indolin-2-ones would afford electron-rich enolates **I** in the presence of base. Most enolates could condense with 2-halobenzaldehydes to give intermediate **II**, which would undergo base-promoted homolytic aromatic substitution with the assistance of electrons released from the rest of the enolates, forging aryl−aryl bonds to deliver naphtho-fused oxindoles (Scheme 1).

Polycyclic compounds containing an oxindole framework are widely found in naturally occurring alkaloids such as aristolactams (**1**),[6] sauristolactam (**2**),[6] anhydrohapaloxindole A (**3**),[7] prioline (**4**),[8] and cyclopiamides (**5**)[9] (Figure 1). A broad array of biological properties, including antitumor,[10] anti-inflammatory,[11] and antiplatelet[12] activities, have been investigated for some of these 3,4-fused oxindole alkaloids. Although naphthoxindoles are structural analogues of the aforementioned alkaloids, the lack of research about their pharmacological activities may be attributed to the rare synthetic examples[13] for

Scheme 1. Reaction Design: In Situ Generated Enolate Anions of Indolin-2-ones Play Dual Roles in the Cascade Process for the Construction of Naphtho-Fused Oxindoles



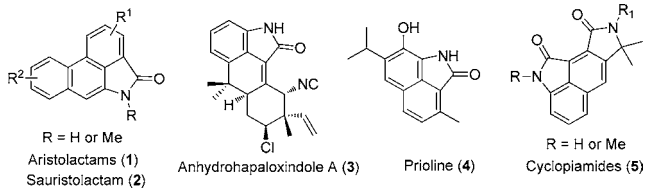


Figure 1. Selected polycyclic alkaloids containing the oxindole framework.

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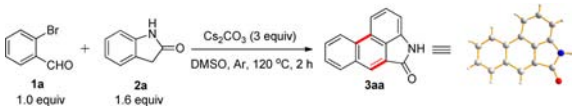
preparing diverse candidates for drug screening. Herein, we present an unusual benzannulation reaction for the direct construction of diverse naphtho-fused oxindoles; its advantages include the use of readily available starting materials, simple reaction conditions, and good functional group compatibility.

We commenced our studies by exploring the cascade reaction between 2-bromobenzaldehyde (**1a**) with indolin-2-one (**2a**) to optimize the reaction conditions. After extensive screening of various reaction parameters, treatment of **1a** (1 equiv) with **2a** (1.6 equiv) and Cs_2CO_3 (3 equiv) under Ar atmosphere at 120 °C for 2 h gave the highest yield of the desired naphtho[3,2,1-*cd*]indol-5(4*H*)-one (**3aa**), which was identified by X-ray crystallographic analysis (Table 1). Among

Table 1. Screening of Optimal Reaction Conditions[a]



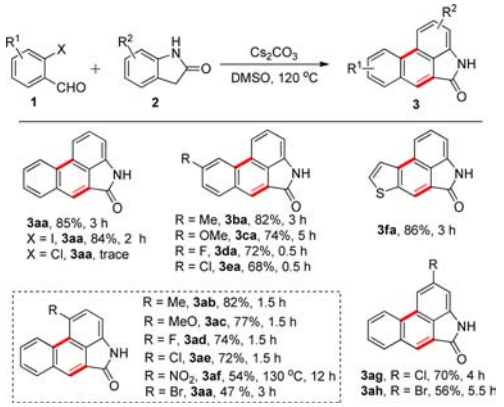
entry	variation from the standard conditions	yield[b] (%)
1	none	84
2	K_2CO_3 instead of Cs_2CO_3	72
3	K_3PO_4 instead of Cs_2CO_3	75
4	KOH instead of Cs_2CO_3	76
5	DBU instead of Cs_2CO_3	12
6	piperidine instead of Cs_2CO_3	trace
7	KOtBu instead of Cs_2CO_3	81
8	under air or O_2	trace
9	1 equiv of H_2O was used	80
10	5 mmol of **1a** was used, 12 h	76

[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.48 mmol), Cs_2CO_3 (0.9 mmol), and DMSO (4 mL) under Ar atmosphere at 120 °C for 2 h. [b]Isolated yield.

various inorganic or organic bases, Cs_2CO_3 proved to be excellent, although KOtBu worked almost equally as well (entry 1 versus entries 2−7). Several solvents, including DMF, toluene, and 1,4-dioxane, were subsequently examined, and DMSO proved to be the most effective solvent (entry 1 versus Table S1, entries 1−3). Increasing or decreasing the temperature of the reaction did not lead to any further improvements in the yield (Table S1, entries 4 and 5). For the amounts of indolin-2-one (**2a**) used, we found that 1.6 equiv of **2a** was preferred for the benzannulation reaction (entry 1 versus Table S1, entries 6−9). Increasing the amount of Cs_2CO_3 had no effect on the reaction (Table S1, entry 10), but decreasing the amount of Cs_2CO_3 had a negative effect (Table S1, entry 11). The poor reactivity observed in the presence of air or O_2 is consonant with a radical mechanism (entry 8). Notably, the standard conditions were well compatible with water and show capacity for the gram-scale synthesis of **3aa** in 76% yield (entries 9 and 10).

With the optimal reactions in hand, we investigated the generality of the benzannulation reaction with respect to 2-halobenzaldehydes and free N−H indolin-2-ones (Scheme 2). The electronic effects exerted by the substituents at the C4 position of 2-bromobenzaldehydes are weak and the corresponding free N−H naphthoxindoles **3aa**−**ea** were obtained in moderate to good yields. Reactions involving electron-deficient 2-bromobenzaldehydes are faster than those using electron-donating or electron-neutral ones (compared **3da**−**ea** to **3aa**−**ca**). 3-Bromothiophene-2-carbaldehyde was suitable for this

Scheme 2. Substrate Scope of 2-Halobenzaldehydes and Free N−H Indolin-2-ones[a,b]



[a]Reaction conditions: **1a**−**f** (0.5 mmol, 1 equiv), **2a**−**h** (0.8 mmol, 1.6 equiv), Cs_2CO_3 (1.5 mmol, 3 equiv), 4 mL DMSO, 120 °C, under Ar. [b]Isolated yields. For the crystal structure of compound **3aa**, see the Supporting Information.

benzannulation transformation (**3fa**, 86%). The reaction conditions were well compatible with various substitutions at the C5 position of indolin-2-ones regardless of the electronic properties, and the target products were obtained in satisfactory yields (72−82%, **3ab**−**ae**). A prolonged time and elevated temperature were required to accomplish the conversion of 5-nitroindolin-2-one and 2-bromobenzaldehyde, albeit in lower yield (54%, **3af**). Indolin-2-ones bearing halogen groups (Cl and Br) at the C6 position also showed moderate reactivities and afforded the corresponding products, which could undergo further synthetic modification (70% and 56%, **3ag** and **3ah**). The dehalogenated product (**3aa**) was obtained in 47% isolated yield when 5-bromoindolin-2-one and 2-bromobenzaldehyde were used as substrates.[14] 2-Iodobenzaldehyde also exhibited good reactivity under the optimized conditions; however, 2-chlorobenzaldehyde reacted sluggishly with **1a** to afford the condensation products.

Various 2-bromobenzaldehydes and N-substituted indolin-2-ones were then examined to broaden the substrate scope. As shown in Scheme 3, when 1-methylindolin-2-one (**2i**) was treated with 2-bromobenzaldehydes bearing various substituents (H, −Me, −OMe, −F, and −Cl) at the 4-position of the aromatic ring, products **3ai**−**ei** were obtained in 64−74% yield. Heteroaryl aldehydes were suitable substrates and afforded the two novel scaffords **3fi** and **3gi** in 77% and 75% yield, respectively. Interestingly, when 2-bromobenzaldehydes with substituents at the 5-position of phenyl were reacted with 1-methylindolin-2-one (**2i**), the cascade provided the separable regioisomers in moderate combined yield (**3hi**−**ji** and **3hi′**−**ji′**).[15] 2-Bromobenzaldehyde (**1a**) with 1-methylindolin-2-ones with electron-rich substituents (5-Me and 5-OMe) were smoothly converted into the desired products in good yields (74% and 65%, **3aj** and **3ak**). Halogen atoms at the 5-, 6-, and 7- positions of 1-methylindolin-2-ones were all tolerated and gave the corresponding products in moderate to good yields (46−72%, **3al**−**ao**). Indolin-2-ones with two substituents on the nitrogen atom were tested and delivered the desired products in good yields (78% and 76%, **3op** and **3oq**).

Having established the scope of our new cascade reaction, we turned our attention to evaluating the reaction mechanism as postulated in the design plan. Initially, the reactions of 2-

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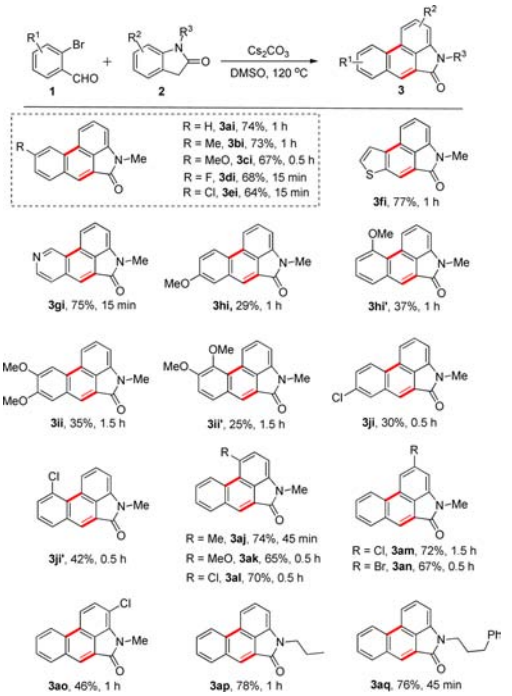
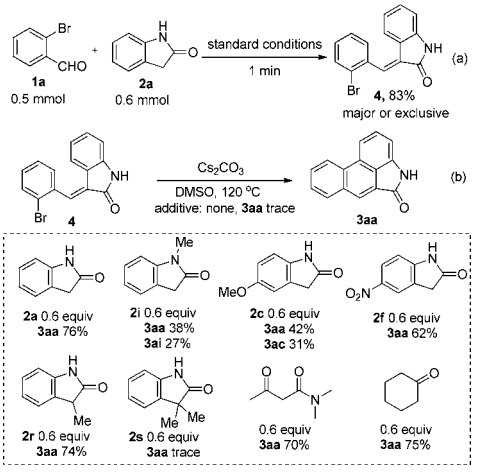
Scheme 3. Substrate Scope of 2-Bromobenzaldehydes and N-Substituted Indolin-2-ones[a,b]



[a]Reaction conditions: **1a–j** (0.5 mmol, 1equiv), **2i–q** (0.8 mmol, 1.6 equiv), Cs_2CO_3 (1.5 mmol, 3 equiv), 4 mL of DMSO, 120 °C, under Ar. [b]Isolated yields. For the crystal structures of compound 3bi, 3ci, and 3ii′ see the Supporting Information.

bromobenzaldehyde (**1a**) and indolin-2-one (**2a**) were conducted under the standard conditions for 1 min, and only (*E*)-3-(2-bromobenzylidene)indolin-2-one (**4**) was isolated in 83% yield (Scheme 4a). Various organic additives were then

Scheme 4. Control Experiments

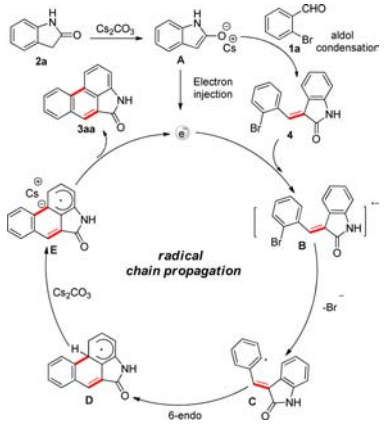


added to convert (*E*)-3-(2-bromobenzylidene)indolin-2-one **4** into the target product (**3aa**). The desired product **3aa** was not formed in the absence of **2a**, but the use of 0.6 equiv of **2a** gave **3aa** in 76% yield. To further elucidate the role of indolin-2-ones in the benannulation process, **4** was treated with other indolin-2-ones (0.6 equiv) bearing varying substituents under the optimized conditions. The desired products **3aa** were obtained in 38% and 42% yield along with two new products (**3ai** and **3ac**) in the presence of 0.6 equiv of **2i** or **2c**, while sole **3aa** was formed in 62% yield with **2f** as the organic additive.[16] These results suggest that various indolin-2-ones could promote the coupling reaction of intermediate **4**.

To investigate the effect of blocking the benzylic position of indolin-2-ones, 3-methylindolin-2-one (**2r**) and 3,3-dimethylindolin-2-one (**2s**) were tested under the reaction conditions, and 3-methylindolin-2-one (**2r**) turned out to be an efficient additive to facilitate the C–H arylation, whereas 3,3-dimethylindolin-2-one (**2s**) did not promote the formation of the intramolecular aryl–aryl bond. These results indicated that benzylic C–H deprotonation of indolin-2-ones is the major pathway for the electron-donor formation. Other organic molecules with active methylene such as *N*,*N*-dimethyl-3-oxobutanamide and cyclohexanone were found to be effective initiators for the intramolecular BHAS reaction, which further demonstrated that the enolate anions play crucial roles in the radical initiation step. Taken together, these control experiments indicated that the enolates of indolin-2-ones serve as organic donors to initiate the intramolecular radical dehalogenative coupling (Scheme 4b).

On the basis of the above observations and literature reports,[4,5,17] a radical chain propagation pathway is proposed using 2-bromobenzaldehyde (**1a**) and indolin-2-one (**2a**) as examples (Scheme 5). Initially, deprotonation of the CH_2

Scheme 5. Possible Mechanism



protons within indolin-2-one (**2a**) generates the eletron-rich enolate anion (**A**) in the presence of Cs_2CO_3. Most of enolate anion **A** condenses with 2-bromobenzaldehyde, leading to the formation of **4**, and the rest acts as an eletron donor to transfer an electron to the eletron acceptor **4**. The resulting radical-anion intermediate **B** is prone to collapse to release **C** and bromide anion. A phenyl radical induced aromatic 1,6-hydrogen transfer may occur at this stage, and two regioisomers would be obtained when 5-substituted 2-bromoaldehyde is involved (see the SI). The aryl radical **C** could then form a cyclohexadienyl radical **D** via a 6-endo cyclization, followed by the second deprotonation to yield the radical anion **E**. Finally, single-electron transfer (SET) from this radical anionic species to the intermediate aryl bromide **4** gives the target product **3aa** and completes the radical-chain process. Moreover, the mechanism involving Michael addition of enolates **A** to **4** followed by intermolecular electron transfer is also possible (see the SI).

In summary, we have developed a novel cascade reaction underlining the dual roles of indolin-2-ones, in which the enolate anions of indolin-2-ones generated in situ form

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intermediates by condensation with 2-halobenzaldehydes and also act as radical initiators to complete the downstream intramolecular base-promoted homolytic aromatic substitution. This simple reaction system provides a valuable access to diverse naphtho-fused oxindoles from available starting materials with good functional group compatibility. This methodology may open an avenue to new chemistry for oxindoles. Further studies of this property of indolin-2-ones for design of new radical cascade reactions and construction of other fascinating structures containing the oxindole unit are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02515.

X-ray crystallographic data for compound **3aa** (CIF)
X-ray crystallographic data for compound **3bi** (CIF)
X-ray crystallographic data for compound **3ci** (CIF)
X-ray crystallographic data for compound **3ii′** (CIF)
Experimental procedures, product characterization, crystallographic data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673. (b) Sun, C. L.; Li, H.; Yu, D. G.; Yu, M.; Zhou, X.; Lu, X. Y.; Huang, K.; Zheng, S. F.; Li, B. J.; Shi, Z. J. *Nat. Chem.* **2010**, *2*, 1044. (c) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737. (d) Shirakawa, E.; Itoh, K. I.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537. (e) Sun, C. L.; Shi, Z. J. *Chem. Rev.* **2014**, *114*, 9219.

(2) For selected examples on organopromoted intermolecular dehalogenative couplings see: (a) Qiu, Y.; Liu, Y.; Yang, K.; Hong, W.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. *Org. Lett.* **2011**, *13*, 3556. (b) Tanimoro, K.; Ueno, M.; Takeda, K.; Kirihata, M.; Tanimori, S. *J. Org. Chem.* **2012**, *77*, 7844. (c) Liu, W.; Tian, F.; Wang, X.; Yu, H.; Bi, Y. *Chem. Commun.* **2013**, *49*, 2983. (d) Dewanji, A.; Murarka, S.; Curran, D. P.; Studer, A. *Org. Lett.* **2013**, *15*, 6102. (e) Song, Q.; Zhang, D.; Zhu, Q.; Xu, Y. *Org. Lett.* **2014**, *16*, 5272.

(3) For selected examples on organopromoted intramolecular dehalogenative couplings, see: (a) Roman, D. S.; Takahashi, Y.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3242. (b) Sun, C. L.; Gu, Y. F.; Huang, W. P.; Shi, Z. J. *Chem. Commun.* **2011**, *47*, 9813. (c) De, S.; Ghosh, S.; Bhunia, S.; Sheikh, J. A.; Bisai, A. *Org. Lett.* **2012**, *14*, 4466. (d) Wu, Y.; Wong, S. M.; Mao, F.; Chan, T. L.; Kwong, F. Y. *Org. Lett.* **2012**, *14*, 5306. (e) Bhakuni, B. S.; Kumar, A.; Balkrishna, S. J.; Sheikh, J. A.; Konar, S.; Kumar, S. *Org. Lett.* **2012**, *14*, 2838.

(4) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018.

(5) (a) Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014**, *5*, 476. (b) Zhou, S.; Doni, E.; Anderson, G. M.; Kane, R. G.; MacDougall, S. W.; Ironmonger, V. M.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 17818. (c) Barham, J. P.; Coulthard, G.; Kane, R. G.; Delgado, N.; John, M. P.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 4492.

(6) (a) Kumar, V.; Poonam; Prasad, A. K.; Parmar, V. S. *Nat. Prod. Rep.* **2003**, *20*, 565. (b) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444.

(7) Moore, R. E.; Yang, X. Q. G.; Patterson, G. M. L. *J. Org. Chem.* **1987**, *52*, 3773. (b) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, *2010*, 4527.

(8) (a) Li, M.; Zhang, J. S.; Ye, Y. M.; Fang, J. N. *J. Nat. Prod.* **2000**, *63*, 139. (b) Wu, Y. B.; Ni, Z. Y.; Shi, Q. W.; Dong, M.; Kiyota, H.; Gu, Y. C.; Cong, B. *Chem. Rev.* **2012**, *112*, 5967.

(9) Xu, X.; Zhang, X.; Nong, X.; Wei, X.; Qi, S. *Tetrahedron* **2015**, *71*, 610.

(10) (a) Choi, Y. L.; Kim, J. K.; Choi, S. U.; Min, Y. K.; Bae, M. A.; Kim, B. T.; Heo, J. N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3036. (b) Couture, A.; Deniau, E.; Grandclaudon, P.; Rybalko-Rosen, H.; Léonce, S.; Pfeiffer, B.; Renard, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557.

(11) (a) Lan, Y. H.; Chia, Y. C.; Chang, F. R.; Hwang, T. L.; Liaw, C. C.; Wu, Y. C. *Helv. Chim. Acta* **2005**, *88*, 905. (b) Zhang, Y. N.; Zhong, X. G.; Zheng, Z. P.; Hu, X. D.; Zuo, J. P.; Hu, L. H. *Bioorg. Med. Chem.* **2007**, *15*, 988.

(12) (a) Chia, Y. C.; Chang, F. R.; Teng, C. M.; Wu, Y. C. *J. Nat. Prod.* **2000**, *63*, 1160. (b) Chen, Y. C.; Chen, J. J.; Chang, Y. L.; Teng, C. M.; Lin, W. Y.; Wu, C. C.; Chen, I. S. *Planta Med.* **2004**, *70*, 174.

(13) (a) Nassar-Hardy, L.; Deraedt, C.; Fouquet, E.; Felpin, F. X. *Eur. J. Org. Chem.* **2011**, *2011*, 4616. (b) Li, J.; Wang, N.; Li, C.; Jia, X. *Org. Lett.* **2012**, *14*, 4994. (c) Park, K. Y.; Kim, B. T.; Heo, J. N. *Eur. J. Org. Chem.* **2014**, *2014*, 164.

(14) (a) Dewanji, A.; Mück-Lichtenfeld, C.; Studer, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 6749. (b) Sword, R.; O'Sullivan, S.; Murphy, J. A. *Aust. J. Chem.* **2013**, *66*, 314.

(15) (a) Karady, S.; Abramson, N. L.; Dolling, U. H.; Douglas, A. W.; McManemin, G. J.; Marcune, B. *J. Am. Chem. Soc.* **1995**, *117*, 5425. (b) Qian, X.; Cui, J.; Zhang, R. *Chem. Commun.* **2001**, 2656. (c) Karady, S.; Cummins, J. M.; Dannenberg, J. J.; del Rio, E.; Dormer, P. G.; Marcune, B. F.; Reamer, R. A.; Sordo, T. L. *Org. Lett.* **2003**, *5*, 1175.

(16) A possible dynamic equilibrium between **4** and **4′** had been proposed to explain why the mixtures of products were formed, and additional control experiments suggest that the intermediate generated from Michael addition of enolates to **4** was also a possible cyclization precursor (see the SI).

(17) (a) Yang, C.; Liu, Y.; Yang, J. D.; Li, Y. H.; Li, X.; Cheng, J. P. *Org. Lett.* **2016**, *18*, 1036. (b) Studer, A.; Curran, D. P. *Nat. Chem.* **2014**, *6*, 765. (c) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 58.

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