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Construction of Bisbenzopyrone via *N*-Heterocyclic Carbene Catalyzed Intramolecular Hydroacylation−Stetter Reaction Cascade

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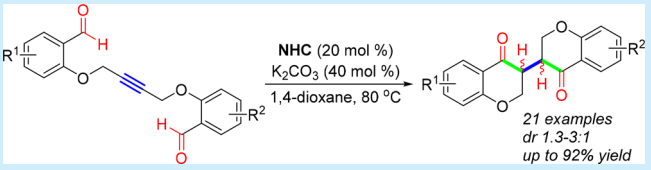
Supporting Information

ABSTRACT: An efficient synthesis of bisbenzopyrones by a *N*-heterocyclic carbene (NHC)-catalyzed intramolecular hydroacylation−Stetter reaction cascade has been developed. A series of symmetrical and unsymmetrical bisbenzopyrones were obtained with good to excellent yields. Bisbenzopyran-4-ol was synthesized efficiently.



Bisbenzopyrone and bisbenzopyran are important scaffolds in natural products such as chamaejasmine and bisbenzopyran-4-ol (Figure 1).[1] These molecules display a wide range of biological and medicinal activities in plant growth, development, self-defense, and the treatment of wounds, burns, asthma, and ulcers.[2] Many remarkable endeavors have been made to synthesize these natural products. The key step is how to construct the bisbenzopyrone or bisbenzopyran core. Only a few examples utilizing Ullmann-type coupling/reduction or radical dimerization have been reported, although a long reaction route or low yield was encountered (Scheme 1, eqs 1, 2).[3] Therefore, the development of direct and efficient synthetic methods to synthesize these molecules using simple starting materials is highly desirable.

In recent decades, the NHC-catalyzed reaction has emerged as a powerful strategy to assemble relatively complex molecules.[4] Among them, NHC-catalyzed intramolecular Stetter reactions of aldehydes with various Michael acceptors have been extensively studied.[5] Remarkable advances have been recorded in the NHC-catalyzed hydroacylation of unactivated alkenes.[6] Meanwhile, the NHC-catalyzed hydroacylation of alkynes has also been developed.[7] Recently, we have developed several unconventional NHC-catalyzed reactions.[8] To continue our research interest in the development and application of NHC-catalyzed reactions, herein, we report the first NHC-catalyzed intramolecular hydroacylation−Stetter reaction cascade,[9] which leads to the formation of bisbenzopyrones efficiently.

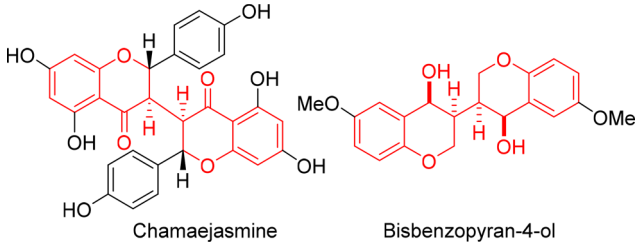
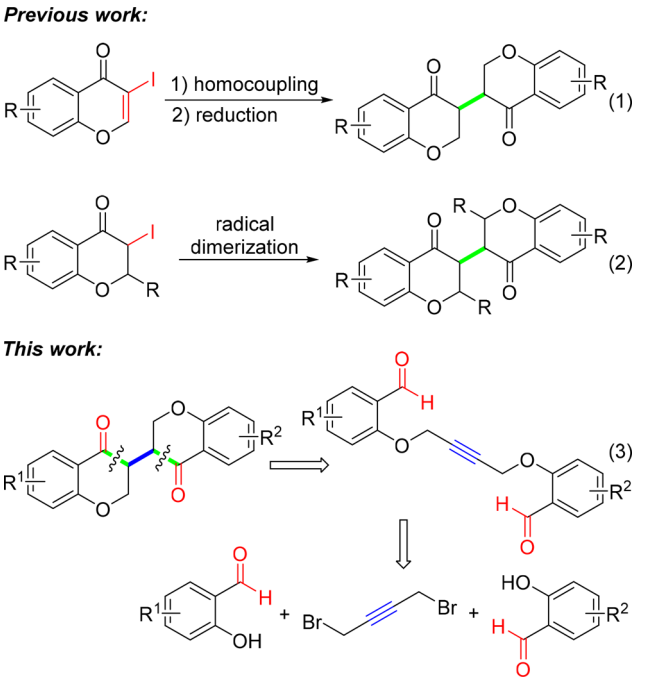


Figure 1. Selected bisbenzopyrone and bisbenzopyran natural products.

Scheme 1. Construction of Bisbenzopyrone Skeleton



Inspired by NHC-catalyzed addition reactions, it was anticipated that bisbenzopyrone skeletons could be generated via the NHC-catalyzed intramolecular hydroacylation−Stetter reaction cascade of the corresponding alkynl bisbenzaldehydes, which could be prepared easily from commercially available 1,4-dibromobut-2-yne and 2-hydroxybenzaldehydes (Scheme 1, eq 3). Furthermore, unsymmetric bisbenzopyrones will be obtained conveniently starting from different hydroxy-

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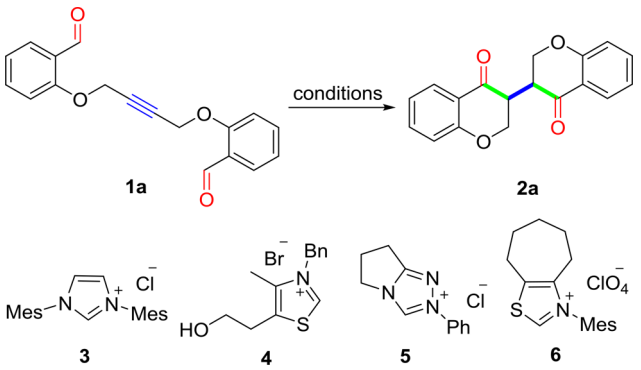
Table 1. Optimization of the Reaction Conditions[a]



entry	NHC	base	solvent	temp (°C)	time (h)	yield (%)[b]
1	**3**	K_2CO_3	THF	70	5	0
2	**4**	K_2CO_3	THF	70	5	0
3	**5**	K_2CO_3	THF	70	5	0
4	**6**	K_2CO_3	THF	70	5	51
5	**6**	Cs_2CO_3	THF	70	5	0
6	**6**	^{t}BuOK	THF	70	5	0
7	**6**	DBU	THF	70	5	16
8	**6**	^{i}Pr$_2$NEt	THF	70	5	0
9	**6**	K_2CO_3	THF	80	2	66
10	**6**	K_2CO_3	toluene	80	2	0
11	**6**	K_2CO_3	CH_3CN	80	2	21
12	**6**	K_2CO_3	DMF	80	2	trace
13	**6**	K_2CO_3	1,4-dioxane	80	2	82
14	**6**	K_2CO_3	1,4-dioxane	90	2	81
15[c]	**6**	K_2CO_3	1,4-dioxane	80	2	82
16[d]	**6**	K_2CO_3	1,4-dioxane	80	2	46

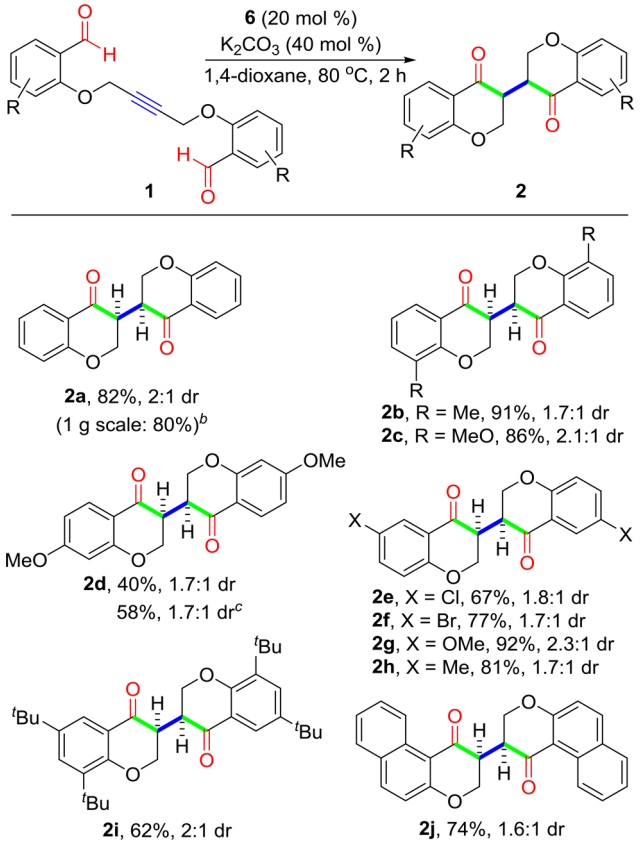
[a]Reactions were carried out with **1a** (0.10 mmol), NHC·HX (0.02 mmol), and base (0.04 mmol) in solvent (1.0 mL) under N_2. [b]Isolated yield. [c]1.0 equiv of K_2CO_3 was used. [d]**6** (0.01 mmol), K_2CO_3 (0.02 mmol).

benzaldehydes ($R^1 \neq R^2$), which are difficult to obtain from those dimerization strategies.

To test this hypothesis, 2,2′-(but-2-yne-1,4-diylbis(oxy))-dibenzaldehyde (**1a**) was prepared as the model substrate. As shown in Table 1, a screening of different NHC catalysts (**3**–**6**) was first carried out (entries 1–4). To our delight, the desired cascade reaction product bisbenzopyrone **2a** was obtained in 51% yield as a diastereomeric mixture (*syn*/*anti* = 2:1) when catalyst **6** was used in the presence of 40 mol % K_2CO_3 in THF at 70 °C for 5 h (entry 4). The diastereomeric ratio (dr) was determined by ^{1}H NMR and HPLC using a chiral column, in which three peaks were detected as a mixture of racemate and *meso* isomers.[10] Next, other bases such as Cs_2CO_3, ^{t}BuOK, DBU, and ^{i}Pr$_2$NEt were evaluated (entries 5–8); K_2CO_3 was the optimal base for this cascade reaction. Increasing the reaction temperature returned a measurable increase in yield (entry 9). Then, various solvents were screened, and 1,4-dioxane gave the best results (entry 13). Additionally, further increasing the reaction temperature or the loading of K_2CO_3 had no obvious influence on the reaction (entries 14 and 15). Lowering the catalyst loading to 10 mol % resulted in a lower yield (entry 16). Unfortunately, attempts to optimize the stereoselectivity were met with limited success.[10]

With the optimized reaction conditions in hand, we examined this synthetic method with a range of substrates with different substitution patterns of the aromatic ring

Scheme 2. Scope of Symmetric Substituted Aromatic Aldehydes[a]



[a]Reactions were carried out with **1** (0.10 mmol), **6** (0.02 mmol), and K_2CO_3 (0.04 mmol) in 1,4-dioxane (1.0 mL) under N_2 at 80 °C for 2 h. Yields of isolated products are reported. The dr value was determined by ^{1}H NMR or HPLC analysis; the major isomer is shown. [b]Reaction time is 4.0 h. [c]0.04 mmol **6** was used.

(Scheme 2). In general, a variety of symmetrical bisbenzopyrones were successfully prepared via this cascade reaction. Substrates with a methy or methoxyl substituent at the 3-position of the phenyl ring resulted in the desired bisbenzopyrones with high yields (**2b**, **2c**). However, the methoxyl substituted substrate at the 4-position resulted in a lower yield (**2d**). The negative effects of the electron-donating substitution at the *para* position on the yield may be attributed to the low reactivity of the aldehyde with the NHC catalyst. Substitutions of the phenyl ring at the 5-position worked well (**2e**–**2h**); both electron-withdrawing and -donating substituents gave the corresponding products in good to excellent yields. Moreover, the di-*tert*-butyl substituted substrate and the 1-naphthaldehyde substrate were also well tolerated (**2i**, **2j**). Satisfactorily, the reaction was readily scalable without losing any efficiency (Scheme 2, **2a**). The structure of *syn*-**2a** (major isomer) was confirmed by X-ray analysis.[10]

Then, we turned our attention to the construction of unsymmetrical bisbenzopyrones. As shown in Scheme 3, installing various unsymmetrial substituents on the phenyl ring had little influence on the reaction outcomes, and the corresponding products were also formed in good to excellent yields. Monomethoxyl substituted substrate **1k** returned the desired unsymmetrical bisbenzopyrone product **2k** with 87% yield. Substrates with different substituents at the 5-position of

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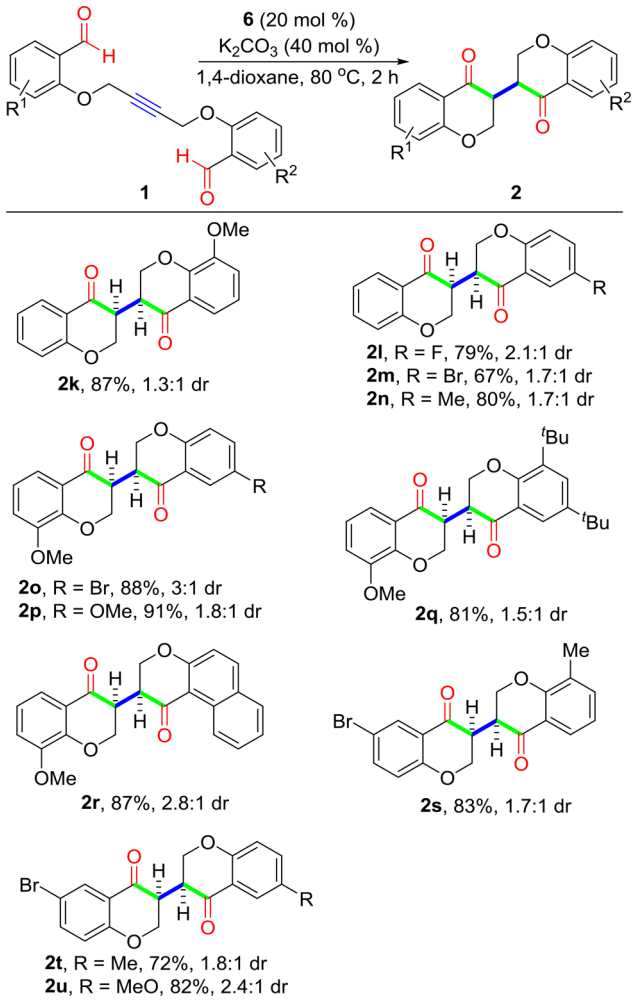
Scheme 3. Scope of Unsymmetric Substituted Aromatic Aldehydes[a]

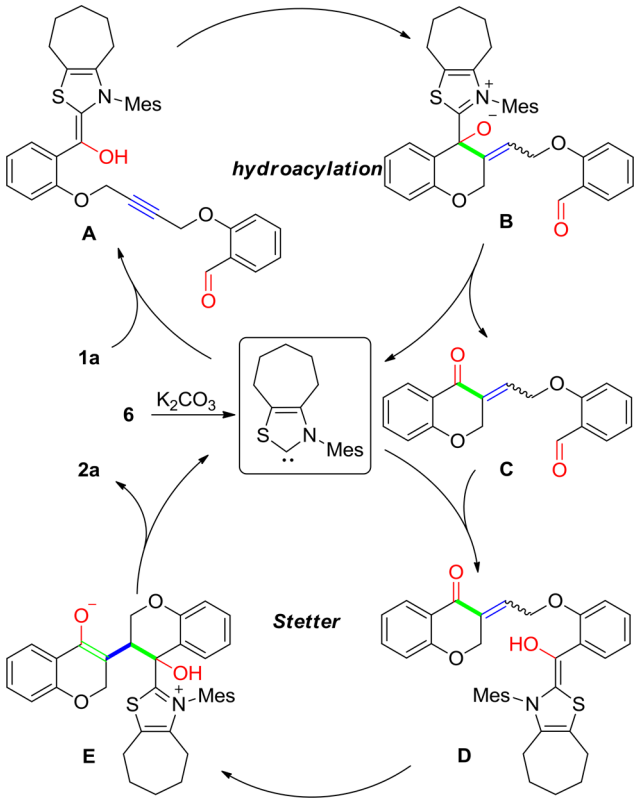


[a]Reactions were performed with compound **1** (0.10 mmol), **6** (0.02 mmol), and K_2CO_3 (0.04 mmol) at 80 °C in 1,4-dioxane (1.0 mL) under N_2 for 2 h. Yields of isolated products are reported. The dr value was determined by ^1H NMR or HPLC analysis; the major isomer is shown.

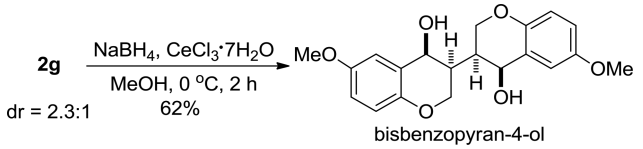
one phenyl ring all worked well in this cascade reaction (**2l**–**2n**). Substrates with a methoxyl substituent at the 3-position of one phenyl ring, and monosubstituted, disubstituted at the other phenyl ring or naphthyl ring, were well tolerated; the desired unsymmetrical bisbenzopyrone products were obtained with excellent results (**2o**–**r**). Substrates bearing substituents at the 5- and 5′-position of the phenyl rings were also converted to the products in good yields (**2t**, **2u**).

A plausible catalytic cycle is depicted in Scheme 4. The catalytic cycle starts with the addition of the NHC catalyst to aldehyde **1a** to generate Breslow intermediate **A**.[11] The nucleophilic Breslow intermediate **A** subsequently participates in an intramolecular hydroacylation of unactivated alkyne to give intermediate **B**, which affords the α,β-unsaturated ketone **C** and liberation of the NHC catalyst. The configuration of **C** remains unclear, and an attempt to trap **C** failed due to the next Stetter reaction, which may be faster than the first step. Then, the nucleophilic Breslow intermediate is formed again through the addition of the NHC catalyst to **C**, which undergoes an intramolecular Stetter reaction to give the desired bisbenzopyr-

Scheme 4. Proposed Catalytic Cycle



Scheme 5. Synthesis of Bisbenzopyran-4-ol



one **2a** and release of the NHC catalyst to complete the catalytic cycle. The stereochemistry could arise from an intramolecular proton transfer event from the enolate intermediate **E**, in which the NHC moiety is too far away to control the stereoselectivity.

In summary, we have developed an efficient strategy for the synthesis of bisbenzopyrones by an NHC-catalyzed intramolecular hydroacylation–Stetter reaction cascade. This reaction involves the construction of two benzopyrones through two carbon–carbon bond formations. A variety of symmetrical and unsymmetrical bisbenzopyrones were obtained with good to excellent yields, and the obtained bisbenzopyrone **2g** could be transformed into the natural product bisbenzopyran-4-ol by simple reduction (Scheme 5). Further investigations on the mechanism and other NHC-catalyzed cascade reactions are underway 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.8b00882.

Experimental procedures, characterization data for all new compounds, and copies of ^1H, ^{13}C NMR spectra (PDF)

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Accession Codes

CCDC 1830600 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Saleem, R.; Faizi, S.; Deeba, F.; Siddiqui, B. S.; Qazi, M. H. *Planta Med.* **1997**, *63*, 454. (b) Huang, W.-K.; Zhang, Z.-J. *Kexue Tongbao* **1979**, *24*, 24; *Chem. Abstr.* **1979**, *90*, 135086m.

(2) (a) Geiger, H.; Quinn, C. In *The Flavonoids: Advances in Research*; Harborne, J. B., Mabry, T. J., Eds.; Chapman & Hall: London, 1982; Chapter 9, pp 505−534. (b) Plant Flavonoids in Biology and Medicine I: Biochemical, Pharmacological and Structure-Activity Relationships. *Progress in Clinical and Biological Research*; Cody, V., Middleton, E., Jr., Harborne, J. B., Eds.; Alan R. Liss, Inc.: New York, 1986; Vol. *213*. (c) Plant Flavonoids in Biology and Medicine II: Biochemical, Cellular, and Medicinal Properties. *Progress in Clinical and Biological Research*; Cody, V., Middleton, E., Jr., Harborne, J. B., Beretz, A., Eds.; Alan R. Liss, Inc.: New York, 1988; Vol. *280*. (d) Yuan, A. X. *Zhongguo Zhongyao Zazhi* **1993**, *18*, 609. (e) Park, M. K.; Park, J. H.; Shin, Y. G.; Kim, W. Y.; Lee, J. H.; Kim, K. H. *Planta Med.* **1996**, *62*, 363.

(3) (a) Lin, G.-q.; Hong, R. *J. Org. Chem.* **2001**, *66*, 2877. (b) Hong, R.; Feng, J.; Hoen, R.; Lin, G.-q. *Tetrahedron* **2001**, *57*, 8685. (c) Li, W.-D. Z.; Ma, B.-C. *Org. Lett.* **2005**, *7*, 271.

(4) For selected reviews, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326. (c) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (e) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (f) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (g) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (h) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (i) Ryan, S.; Candish, L.; Lupton, D. W. *Synlett* **2011**, *2011*, 2275. (j) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (k) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis* **2012**, *44*, 2295. (l) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (m) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617. (n) Berkessel, A.; Yatham, V. R.; Elfert, S.; Neudörfl, J.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 11158. (o) De Sarkar, S.; Biswas, A.; Samanta, R.; Studer, A. *Chem. - Eur. J.* **2013**, *19*, 4664. (p) Ye, S.; Chen, X.-Y. *Synlett* **2013**, *24*, 1614. (q) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (r) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (s) Menon, R. S.; Biju, A. T.; Nair, V. *Chem. Soc. Rev.* **2015**, *44*, 5040. (t) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912. (u) Zhang, C.; Hooper, J. F.; Lupton, D. W. *ACS Catal.* **2017**, *7*, 2583. (v) Zhao, M.; Zhang, Y.-T.; Chen, J.; Zhou, L. *Asian J. Org. Chem.* **2018**, *7*, 54.

(5) For reviews on the Stetter reaction and selected examples of intramolecular Stetter reactions, see: (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639. (b) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632. (c) de Alaniz, J.; Rovis, T. *Synlett* **2009**, *2009*, 1189. (d) Yetra, S. R.; Patra, A.; Biju, A. T. *Synthesis* **2015**, *47*, 1357. (e) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (f) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (g) Mennen, S. M.; Blank, J. T.; Tran-Dube, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195. (h) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284. (i) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (j) McErlean, C. S. P.; Willis, A. C. *Synlett* **2009**, *2009*, 233. (k) Rong, Z.-Q.; Li, Y.; Yang, G.-Q.; You, S.-L. *Synlett* **2011**, *2011*, 1033. (l) Jia, M.-Q.; Liu, C.; You, S.-L. *J. Org. Chem.* **2012**, *77*, 10996. (m) Law, K. R.; McErlean, C. S. P. *Chem. - Eur. J.* **2013**, *19*, 15852. (n) You, S.-L.; Jia, M.-Q. *Synlett* **2013**, *24*, 1201. (o) Ema, T.; Nanjo, Y.; Shiratori, S.; Terao, Y.; Kimura, R. *Org. Lett.* **2016**, *18*, 5764. (p) Lin, Q.; Li, Y.; Das, D. K.; Zhang, G.; Zhao, Z.; Yang, S.; Fang, X. *Chem. Commun.* **2016**, *52*, 6459. (q) Rafiński, Z.; Kozakiewicz, A.; Rafińska, K. *ACS Catal.* **2014**, *4*, 1404.

(6) (a) He, J.; Tang, S.; Liu, J.; Su, Y.; Pan, X.; She, X. *Tetrahedron* **2008**, *64*, 8797. (b) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190. (c) Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4983. (d) Bugaut, X.; Liu, F.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 8130. (e) Liu, F.; Bugaut, X.; Schedler, M.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 12626. (f) Schedler, M.; Wang, D.-S.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 2585. (g) Lu, H.; Lin, J.-B.; Liu, J.-Y.; Xu, P.-F. *Chem. - Eur. J.* **2014**, *20*, 11659. (h) Janssen-Müller, D.; Schedler, M.; Fleige, M.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 12492. (i) Janssen-Müller, D.; Fleige, M.; Schlüns, D.; Wollenburg, M.; Daniliuc, C. G.; Neugebauer, J.; Glorius, F. *ACS Catal.* **2016**, *6*, 5735. (j) Wu, J.; Zhao, C.; Wang, J. *J. Am. Chem. Soc.* **2016**, *138*, 4706.

(7) (a) Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970. (b) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761. (c) Padmanaban, M.; Biju, A. T.; Glorius, F. *Org. Lett.* **2011**, *13*, 5624.

(8) (a) Zhao, M.; Yang, H.; Li, M.-M.; Chen, J.; Zhou, L. *Org. Lett.* **2014**, *16*, 2904. (b) Dong, Y.-T.; Jin, Q.; Zhou, L.; Chen, J. *Org. Lett.* **2016**, *18*, 5708. (c) Zhao, M.; Chen, J.; Yang, H.; Zhou, L. *Chem. - Eur. J.* **2017**, *23*, 2783. (d) Liu, J.-L.; Zhang, Y.-T.; Liu, H.-F.; Zhou, L.; Chen, J. *Org. Lett.* **2017**, *19*, 5272.

(9) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Schrittwieser, J. H.; Velikogne, S.; Hall, M.; Kroutil, W. *Chem. Rev.* **2018**, *118*, 270.

(10) For details, see the Supporting Information.

(11) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. (b) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699. (c) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124. (d) Berkessel, A.; Elfert, S.; Etzenbach-Effers, K.; Teles, J. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7120. (e) DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143.

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