Organocatalysis Hot Paper

International Edition: DOI: 10.1002/anie.201610203
German Edition: DOI: 10.1002/ange.201610203

NHC-Organocatalyzed C_{Ar}–O Bond Cleavage: Mild Access to 2-Hydroxybenzophenones

*Daniel Janssen-Müller[+], Santanu Singha[+], Fabian Lied, Karin Gottschalk, and Frank Glorius**

Dedicated to Professor Ronald Breslow on the occasion of his 85th birthday

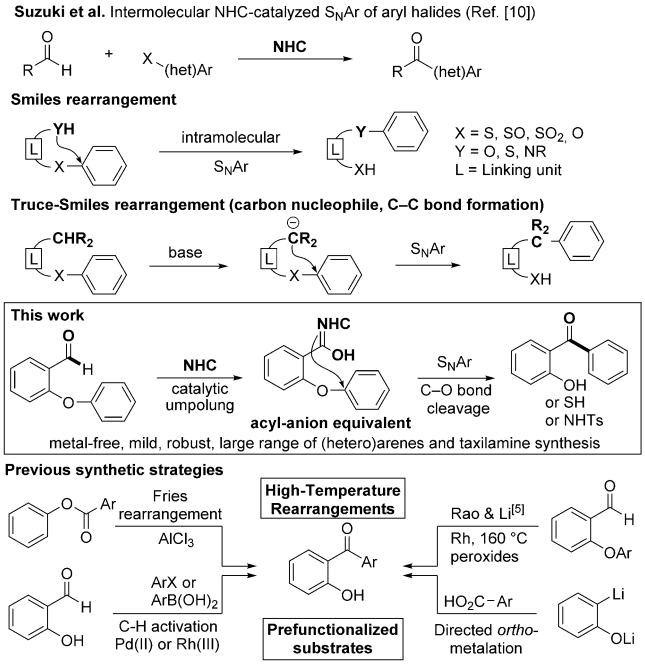
Abstract: *A Truce–Smiles rearrangement of acyl-anion equivalents generated by N-heterocyclic carbene (NHC) catalysis has been achieved. The developed method includes C_{Ar}–O, C_{Ar}–S, or C_{Ar}–N bond cleavage for the formation of a C_{Ar}–C bond and enables access to 2-hydroxybenzophenones, an important structural motif that is present in several bioactive natural products. By utilizing this procedure, the alkaloid taxilamine was synthesized in three steps. DFT calculations and control experiments support a classical S_NAr mechanism with a catalyst-bound Meisenheimer-type intermediate. The method features mild reaction conditions, excellent functional-group tolerance, and a broad substrate scope, including various classes of (hetero)arenes.*

Catalytic C_{Ar}–O bond cleavage represents a difficult, but emerging field that has a great impact on the sustainable use of renewable chemical feedstocks, since these are rich in hydroxy, ether, or ester groups. The field is dominated by homogeneous nickel(0) catalysis for oxidative addition to a range of C_{Ar}–O bonds,[1] which has enabled several coupling reactions to be developed and is especially useful with unactivated, easily accessible substrates such as phenyl esters and anisoles.[2]

An interesting, but underdeveloped example of an S_NAr reaction capable of cleaving C_{Ar}–O bonds is the Truce–Smiles rearrangement, a variation of the more general Smiles rearrangement. The intramolecular substitution of a C_{Ar}–heteroatom bond (such as C_{Ar}–O) by a tethered carbanion nucleophile (Scheme 1) has been known since the initial report by Truce et al. in 1958,[3] but stayed rather unexplored until recently, when it caught the attention of some researchers and resulted in different applications with variations in nucleophiles, linkers, and electrophiles.[4]

The Truce–Smiles rearrangement transforms readily accessible C_{Ar}–O bonds into synthetically valuable C–C bonds with high atom economy, often without the need for electronic activation of the arene because of the strength of the employed carbon nucleophile. One drawback of this reaction is normally the strong base required for generation of the carbanion, such as BuLi or KO*t*Bu, which results in harsh reaction conditions. A catalytic method to generate the required carbanion without the need for a strong base would be highly desirable and could result in robust, mild, and more economic reaction procedures. Pioneering work in 2011 by Rao and Li on a rhodium-catalyzed Truce–Smiles rearrangement involves an intramolecular S_NAr reaction of an acyl-rhodium species: Unfortunately, the novel procedure requires 10 mol% of the expensive rhodium catalyst, excess peroxide oxidant, and the reported reaction temperature is 160 °C, thus making this transformation impractical.[5]

NHC organocatalysis has proven to be a reliable tool to generate carbon nucleophiles.[6] Umpolung of aldehyde substrates to provide an acyl-anion equivalent has led to several important transformations, including the benzoin condensation,[7] Stetter reaction,[8] and hydroacylation of electron-neutral and, more recently, electron-rich and heteroaromatic olefins.[9] The S_NAr reaction of the Breslow intermediate and fluoro- or chloroarenes has been studied since the seminal



Scheme 1. C_{Ar}–O bond cleavage leads to aryl migration and C–H functionalization of the parent aldehyde.

[*] D. Janssen-Müller,[+] S. Singha,[+] F. Lied, K. Gottschalk, Prof. Dr. F. Glorius
Westfälische Wilhelms-Universität Münster
Organisch-Chemisches Institut
Corrensstrasse 40, 48149 Münster (Germany)
E-mail: glorius@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/glorius/

[+] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201610203.

report by Suzuki and co-workers in 1998,[10] but, to date, this chemistry could not be extended to the cleavage of C_{Ar}–O bonds or rearrangement reactions.

Herein, we report an NHC-organocatalyzed Truce–Smiles rearrangement, which operates through an intramolecular S_NAr reaction of a catalytically generated acyl-anion equivalent under mild conditions and with high yields. The obtained 2-hydroxybenzophenone moiety is present in many highly important natural products and pharmaceuticals, including many biologically active and antibiotic compounds such as pyoluteorin,[11] acremonidin E,[12] the pyrrolomycin family,[13] the marinopyrrole family,[14] and cercophorin A (Figure 1).[15] The highly potent glucose-6-phosphate translocase inhibitor mumbaistatin[16] and the protein kinase A and C inhibitor balanol (not shown)[17] also bear the 2-hydroxybenzophenone motif.

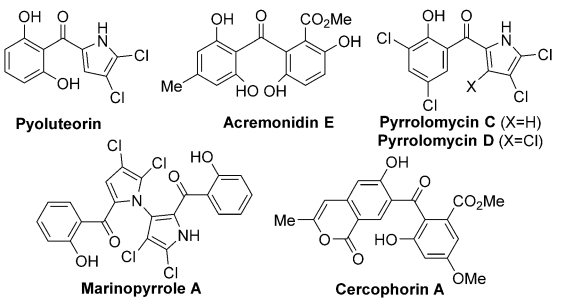
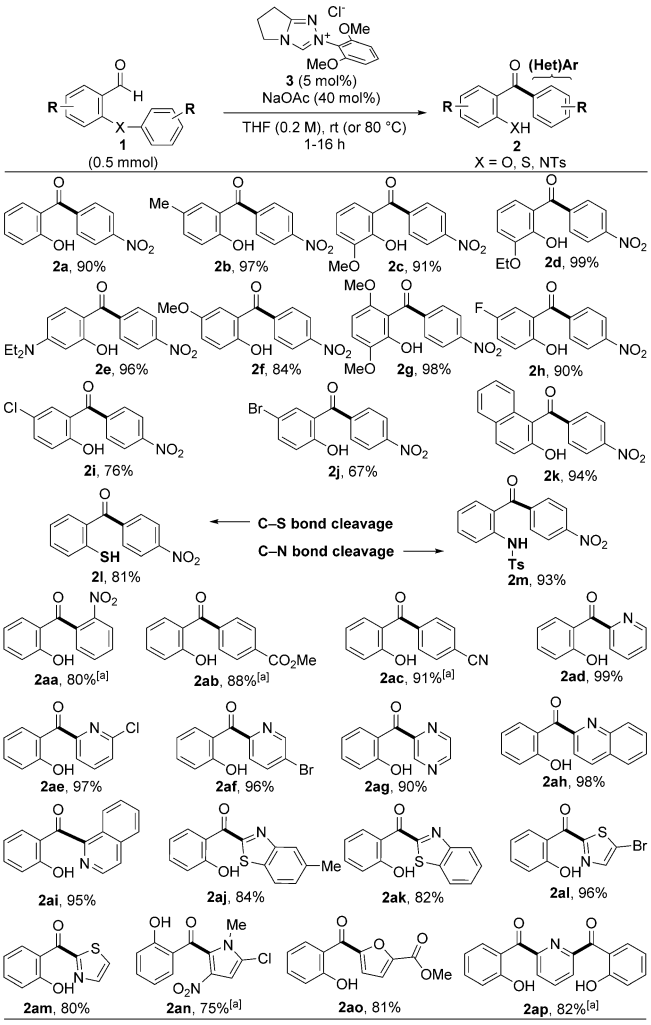


Figure 1. Members of a large group of biologically active natural products containing the 2-hydroxybenzophenone moiety. All the compounds shown are antibiotics.

Subjecting salicylaldehyde derivative **1a** to NHC catalysis afforded the rearrangement product **2a** under a range of conditions. The reaction was systematically optimized by variation of the NHC catalyst, base, solvent, and temperature by running reactions with substrate **1a** on 0.1 mmol scale reactions, with quantification by ^{1}H NMR spectroscopy and using CH_2Br_2 as an internal standard.[18] It was found that the reaction is most efficient at room temperature in THF with a weak base (NaOAc) and the use of highly nucleophilic triazolium-NHC **3**, which bears a N-dimethoxyphenyl substituent,[19] whereas different NHC precursors with less-electron-donating N substituents or a thiazole or imidazole core performed significantly worse. Benzophenone product **2a** could be isolated from a 0.5 mmol scale reaction in excellent yield (90%) under optimized conditions.

With the optimized conditions in hand, we studied the scope of the reaction. We first varied the substitution pattern on the salicylaldehyde portion of the substrate (Scheme 2). Electron-donating functional groups, such as methyl, methoxy, ethoxy, and diethylamino (**2b**–**2g**), are tolerated, and provided the products in very high yields of up to 99%. Reactions of electron-deficient substrates also proceed in high yields (**2h**–**2j**). Changing the benzaldehyde moiety to naphthaldehyde gives the product **2k** in 94% yield.

Of particular note is that C–S and C–N bond cleavage is also possible when the substrate contains a thioether or amino



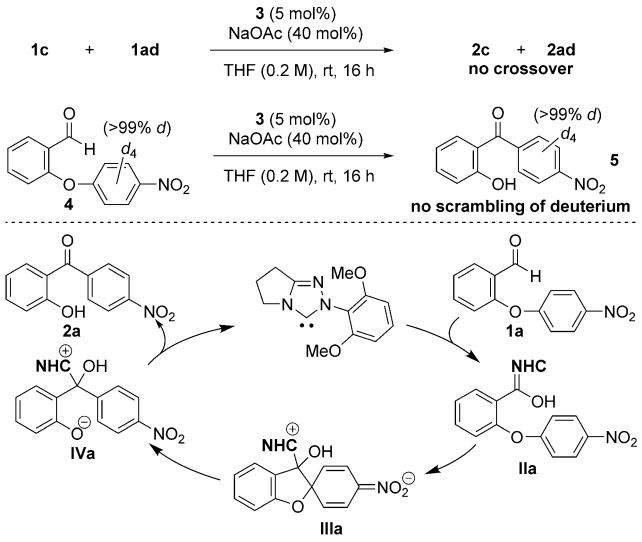
Scheme 2. Substrate scope. Yields given are for the isolated products following column chromatography. **2i** and **2an** were synthesized on a 0.3 mmol scale. [a] Reaction at 80 °C.

linker, with the products **2l** and **2m** obtained in yields of 81% and 93%, respectively. We next investigated the scope of the migrating aryl group. The 4-nitro group, which activates the arene toward S_NAr reactions, is also tolerated in the 2-position (**2aa**). In addition to this, other electron-withdrawing groups, such as nitriles and esters, were tolerated in the reaction with no drop in yield (88% and 91%), however, these less electron-poor substrates required the reaction be heated to 80 °C.

Next, various heteroarenes were tested in this reaction. Pyridine derivatives (**2ad**–**2af**), as well as pyrazine (**2ag**), quinoline (**2ah**), and isoquinoline (**2ai**) were all tolerated, with yields above 90%. Substrates containing benzothiazoles (**2aj** and **2ak**) and thiazoles (**2al** and **2am**) were tolerated as well, with excellent yields obtained. Even pyrrole and furan derivatives, normally highly nucleophilic arenes, could be employed in this reaction when activated with electron-withdrawing groups (**2an** and **2ao**). Double C_{Ar}–O bond cleavage in a pyridine derivative was also achieved, which afforded **2ap** in 82% yield.

To evaluate the reaction mechanism we performed DFT calculations, which support the expected S_NAr mechanism proposed for the classical Truce–Smiles rearrangement. Repeating the calculations with less-activated ester substrate **1ab** provided the same mechanism, but with a notably higher activation energy for the S_NAr part of the mechanism (in line with the need for a higher reaction temperature for the formation of **2ab**).[18]

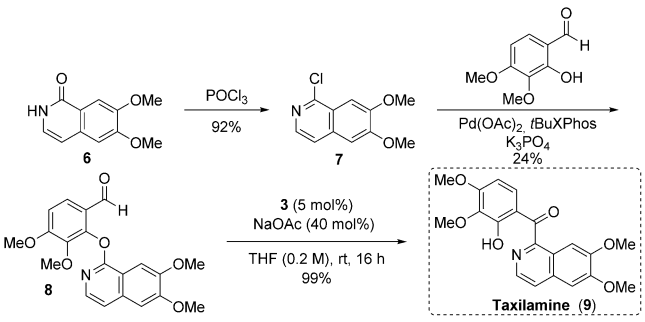
A cross-over experiment was performed with substrates **1c** and **1ad** to investigate if the reaction could be proceeding in an intermolecular fashion, but no cross-over products were detected. To test if a benzyne S_NAr mechanism or a NHC-catalyzed hydroacylation/elimination mechanism is at work, a deuterated substrate **4** was prepared. The deuteration on the arene did not change over the course of the reaction, thereby ruling out these two unlikely pathways (Scheme 3).



Scheme 3. Top: The cross-over experiment suggests a truly intramolecular mechanism. The use of deuterated substrate **4** rules out a hydroacylation or benzyne mechanism. Bottom: Simplified catalytic cycle.[18]

From the results of these mechanistic experiments and DFT calculations[18] we propose the expected catalytic cycle: The aldehyde substrate **1** forms the Breslow intermediate **II**, which, after nucleophilic attack on the arene, forms Meisenheimer type complex **III**. Elimination of the oxygen linker to give **IV**, followed by proton transfer, enables product formation and regeneration of the NHC.

To demonstrate the synthetic utility of this reaction, we synthesized the natural product taxilamine (Scheme 4), a pseudobenzylisoquinoline alkaloid found in the Chinese herb *Berberis aristata*, which is used in traditional and modern medicine.[20] Taxilamine represents a tetramethoxy derivative of our rearrangement product **2ai** and, to the best of our knowledge, a total synthesis of taxilamine has not yet been reported. Substrate **8** could be synthesized in two steps from commercially available 6,7-dimethoxy-1(2*H*)-isoquinolone (**6**) and 3,4-dimethoxysalicylaldehyde, and gave the desired alkaloid (**9**) in 99% yield.



Scheme 4. Total synthesis of taxilamine in three steps.

In conclusion, we have developed a procedure for the rearrangement of *O*-aryl salicylaldehydes to yield 2-hydroxybenzophenones. The reaction has a very broad substrate scope, including various classes of (hetero)arenes, works under mild conditions, and has enabled the three-step total synthesis of taxilamine. Mechanistic experiments and DFT calculations both support the same expected S_NAr mechanism.

Acknowledgements

Generous financial support by the Deutsche Forschungsgemeinschaft (IRTG2027 Münster-Toronto, Leibniz Award) is gratefully acknowledged. We thank Dr. Lisa Candish and Dr. Chang Guo (WWU) for helpful discussions.

Conflict of interest

The authors declare no conflict of interest.

Keywords: aromatic substitution · carbenes · natural products · organocatalysis · rearrangement

[1] For selected reviews on catalytic cleavage of C_{Ar}–O bonds, see a) J. Cornella, C. Zarate, R. Martin, *Chem. Soc. Rev.* **2014**, *43*, 8081; b) M. Tobisu, N. Chatani, *Acc. Chem. Res.* **2015**, *48*, 1717; c) M. Tobisu, N. Chatani, *Top. Curr. Chem.* **2016**, *41*, 374; d) C. Zarate, M. van Gemmeren, R. J. Somerville, R. Martin, *Appl. Organometal. Chem.* **2016**, DOI: 10.1016/bs.adomc.2016.07.001.

[2] For catalytic C_{Ar}–O cleavage of anisole, see a) J. W. Dankwardt, *Angew. Chem. Int. Ed.* **2004**, *43*, 2428; *Angew. Chem.* **2004**, *116*, 2482; b) M. Tobisu, T. Shimasaki, N. Chatani, *Angew. Chem. Int. Ed.* **2008**, *47*, 4866; *Angew. Chem.* **2008**, *120*, 4944; c) M. Tobisu, A. Yasutome, K. Yamakawa, T. Shimasaki, N. Chatani, *Tetrahedron* **2012**, *68*, 5157.

[3] W. E. Truce, W. J. Ray, Jr., O. L. Norman, D. B. Eickemeyer, *J. Am. Chem. Soc.* **1958**, *80*, 3625.

[4] For reviews on the Truce–Smiles rearrangement, see a) T. J. Snape, *Chem. Soc. Rev.* **2008**, *37*, 2452; b) K. Plesniak, A. Zarecki, J. Wicha, *Top. Curr. Chem.* **2007**, *275*, 163; for recent examples see c) D. Ameen, T. J. Snape, *Eur. J. Org. Chem.* **2014**, 1925; d) T. J. Snape, *Synlett* **2008**, 2689; e) K. Okuda, M.

Yoshida, T. Hirota, K. Sasaki, *Chem. Pharm. Bull.* **2010**, *58*, 363; f) M. Getlik, B. J. Wilson, M. M. Morshed, I. D. G. Watson, D. Tang, P. Subramanian, R. Al-awar, *J. Org. Chem.* **2013**, *78*, 5705; g) Y. Liu, X. Zhang, Y. Ma, C. Ma, *Tetrahedron Lett.* **2013**, *54*, 402; h) A. D. Alorati, A. D. Gibb, P. R. Mullens, G. W. Stewart, *Org. Process Res. Dev.* **2012**, *16*, 1947; i) C. Dey, D. Katayev, K. E. O. Ylijoki, E. P. Kündig, *Chem. Commun.* **2012**, *48*, 10957; j) J. P. Gonález, M. Edgar, M. R. J. Elsegood, G. W. Weaver, *Org. Biomol. Chem.* **2011**, *9*, 2294; k) L. El Kaim, L. Grimaud, X. F. Le Goff, A. Schiltz, *Org. Lett.* **2011**, *13*, 534; l) C. M. Holden, S. M. A. Sohel, M. F. Greaney, *Angew. Chem. Int. Ed.* **2016**, *55*, 2450; *Angew. Chem.* **2016**, *128*, 2496; m) K. Okuda, N. Watanabe, T. Hirota, K. Sasaki, *Tetrahedron Lett.* **2010**, *51*, 903.

[5] H. Rao, C.-J. Li, *Angew. Chem. Int. Ed.* **2011**, *50*, 8936; *Angew. Chem.* **2011**, *123*, 9098.

[6] For recent reviews on NHC organocatalysis, see a) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336; b) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182; c) D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, *3*, 53; d) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314; *Angew. Chem.* **2012**, *124*, 320; e) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511; f) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 11686; *Angew. Chem.* **2012**, *124*, 11854; g) J. Mahatthananchai, J. W. Bode, *Chem. Sci.* **2012**, *3*, 192; h) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, 354, 1617; i) M. Fèvre, J. Pinaud, Y. Gnanou, J. Vignolle, D. Taton, *Chem. Soc. Rev.* **2013**, *42*, 2142; j) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; k) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696; l) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; m) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307; n) R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.* **2015**, *44*, 5040.

[7] R. S. Menon, A. T. Biju, V. Nair, *Beilstein J. Org. Chem.* **2016**, *12*, 444.

[8] a) T. Rovis, *Chem. Lett.* **2008**, *37*, 2; b) J. Read de Alaniz, T. Rovis, *Synlett* **2009**, 1189; c) S. R. Yetra, A. Patra, A. T. Biju, *Synthesis* **2015**, 1357.

[9] a) M. Schedler, D.-S. Wang, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 2585; *Angew. Chem.* **2013**, *125*, 2645; b) D. Janssen-Müller, M. Schedler, M. Fleige, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 12492; *Angew. Chem.* **2015**, *127*, 12671; c) J. Wu, C. Zhao, J. Wang, *J. Am. Chem. Soc.* **2016**, *138*, 4706; d) D. Janssen-Müller, M. Fleige, D. Schlüns, M. Wollenburg, C. G. Daniliuc, J. Neugebauer, F. Glorius, *ACS Catal.* **2016**, *6*, 5735.

[10] a) A. Miyashita, Y. Suzuki, K. Iwamoto, T. Higashino, *Chem. Pharm. Bull.* **1998**, *46*, 390; b) Y. Suzuki, T. Toyota, F. Imada, M. Sato, A. Miyashita, *Chem. Commun.* **2003**, 1314; c) Y. Suzuki, T. Toyota, A. Miyashita, M. Sato, *Chem. Pharm. Bull.* **2006**, *54*, 1653; d) Y. Suzuki, S. Ota, Y. Fukuta, Y. Ueda, M. Sato, *J. Org. Chem.* **2008**, *73*, 2420; e) V. P. Mehta, A. K. Sharma, S. G. Modha, S. Sharma, T. Meganathan, V. S. Parmar, E. Van der Eycken, *J. Org. Chem.* **2011**, *76*, 2920; f) Q. Y. Toh, A. McNally, S. Vera, N. Erdmann, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 3772.

[11] a) R. Takeda, *J. Am. Chem. Soc.* **1958**, *80*, 4749; b) C. R. Howell, R. D. Stipanovic, *Phytopathology* **1980**, *70*, 712; c) K. V. Rao, S. K. Chattopadhyay, G. C. Reddy, *J. Agric. Food Chem.* **1990**, *38*, 1427.

[12] H. He, R. Bigelis, E. H. Solum, M. Greenstein, G. T. Carter, *J. Antibiot.* **2003**, *56*, 923.

[13] a) N. Ezaki, M. Koyama, T. Shomura, T. Tsuruoka, S. Inouye, *J. Antibiot.* **1983**, *36*, 1263; b) M. Koyama, N. Ezaki, T. Tsuruoka, S. Inouye, *J. Antibiot.* **1983**, *36*, 1483; c) S. Cascioferro, M. V. Raimondi, M. G. Cusimano, D. Raffa, B. Maggio, G. Daidone, D. Schillaci, *Molecules* **2015**, *20*, 21658.

[14] a) D. L. J. Clive, P. Cheng, *Tetrahedron* **2013**, *69*, 5067; b) C. C. Hughes, C. A. Kauffman, P. R. Jensen, W. Fenical, *J. Org. Chem.* **2010**, *75*, 3240; c) C. C. Hughes, A. Prieto-Davo, P. R. Jensen, W. Fenical, *Org. Lett.* **2008**, *10*, 629.

[15] A. C. White, J. B. Gloer, J. A. Scott, D. Malloch, *J. Nat. Prod.* **1996**, *59*, 765.

[16] a) L. Vértesy, M. Kurz, E. F. Paulus, D. Schummer, P. Hammann, *J. Antibiot.* **2001**, *54*, 354; b) L. K. Charkoudian, B. P. Farrell, C. Khosla, *MedChemComm* **2012**, *3*, 926.

[17] a) P. Kulanthaivel, Y. F. Hallock, C. Boros, S. M. Hamilton, W. P. Janzen, L. M. Ballas, C. R. Loomis, J. B. Jiang, B. Katz, J. R. Steiner, J. Clardy, *J. Am. Chem. Soc.* **1993**, *115*, 6452; b) H. Miyabe, M. Torieda, K. Inoue, K. Tajiri, T. Kiguchi, T. Naito, *J. Org. Chem.* **1998**, *63*, 4397.

[18] See the Supporting Information for more information.

[19] a) M. Schedler, R. Fröhlich, C.-G. Daniliuc, F. Glorius, *Eur. J. Org. Chem.* **2012**, 4164; b) J. Mahatthananchaia, J. W. Bode, *Chem. Sci.* **2012**, *3*, 192; c) C. J. Collett, R. S. Massey, O. R. Maguire, A. S. Batsanov, A. C. O'Donoghue, A. D. Smith, *Chem. Sci.* **2013**, *4*, 1514; d) C. J. Collett, R. S. Massey, J. A. Taylor, O. R. Maguire, A. C. O'Donoghue, A. D. Smith, *Angew. Chem. Int. Ed.* **2015**, *54*, 6887; *Angew. Chem.* **2015**, *127*, 6991; e) A. Levens, F. An, M. Breugst, H. Mayr, D. W. Lupton, *Org. Lett.* **2016**, *18*, 3566.

[20] a) G. Blaskó, M. Shamma, A. A. Ansari, Atta-ur-Rahman, *Heterocycles* **1982**, *19*, 257; b) M. P. Mitra, D. Saumya, D. Sanjita, D. M. Kumar, *J. Drug Deliv. Ther.* **2011**, *1*, 46.

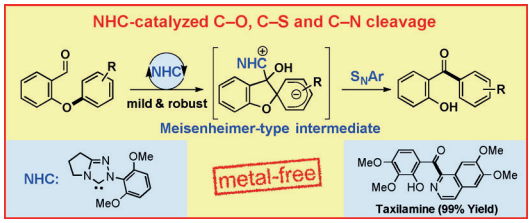
Manuscript received: October 18, 2016
Revised: January 3, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Organocatalysis

D. Janssen-Müller, S. Singha, F. Lied, K. Gottschalk, F. Glorius* ___ ■■■–■■■

NHC-Organocatalyzed C_{Ar}–O Bond Cleavage: Mild Access to 2-Hydroxybenzophenones



Catalysis with Smiles: A Truce–Smiles rearrangement of acyl-anion equivalents generated by N-heterocyclic carbene (NHC) catalysis has been achieved. The developed method includes C_{Ar}–O, C_{Ar}–S, or C_{Ar}–N bond cleavage for the formation of a C_{Ar}–C bond and enables access to 2-hydroxybenzophenones, an important structural motif present in several bioactive natural products.