SHORT COMMUNICATION

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Solvent-Free Ball-Milling Biginelli Reaction by Subcomponent Synthesis

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We report here an understanding of systems chemistry on small molecules through covalent mechanochemistry. As a proof-of-concept, the multicomponent Biginelli reaction by subcomponent synthesis was considered as a model system. Reactions were performed under solvent-free, metal-free, mechanochemical (ball milling) and ambient laboratory conditions. Br^+-catalyzed oxidation of benzyl alcohols led to the product benzaldehydes and byproduct H^+ which were further promoted as component and catalyst, respectively, for a cascade transformation to dihydropyrimidones within the same reaction pot. Remarkably, in solution, the reaction system could not be reproduced at room temperature even after 24 h.

Introduction

Many cascading chemical reactions are involved in the process of haemostasis[1] which causes bleeding to stop. These kinds of biological processes are examples of self-sorting methodologies[2] in systems biology.[3] However, the study of systems chemistry[4] offers a primary understanding into the self-sorting principles[5] of molecular networks that eventually assist us to gain new systems[6] with functions and properties unlike any conventional materials.[7] Also, a subcomponent self-assembly approach[8] under systems chemistry, is a synthetic method in which ligands of metallo-supramolecular complexes are produced in situ from their subcomponents. This systems chemistry method has been established to be a promising technique for the synthesis of high-purity metal complexes from complex mixtures of reactants with a minimum number of reaction steps[9] and possibly unexplored in organic synthesis.

With rising public concern over alternative energy and global warming, it is important to decrease the usage of chemicals in routine chemical synthesis. Essentially, developing recyclable methodology and eliminating waste are important aspects for doing reactions in a greener fashion.[10] Recently, ball-milling mechanochemistry,[11] as a solvent-free method for synthetic transformations has become an area of research interest due to its benefits over solution-based methods.[12] Many advantages are associated during synthesis by mechanochemistry.[11d] This method has huge importance for green processes due to time efficiency, environmentally friendliness and inexpensive synthesis. High yielding reactions, fewer byproducts and minimum purification add extra significance to this method in organic synthesis.[13] Organic synthesis of small molecules by mechanochemistry has been considerably explored,[13a] including multistep synthesis, olefin metathesis,[14] amongst others. In addition, we have also recently explored the research area under mechanochemistry.[9b,10,15] Therefore, we anticipated that ball-milling methodology could possibly be used for the supply of mechanical energy and reactions might be done in environmentally benign way.

Considering these aspects, we are demonstrating here a unique example of a covalent (metal-free) approach in systems chemistry in which subcomponent and catalyst were

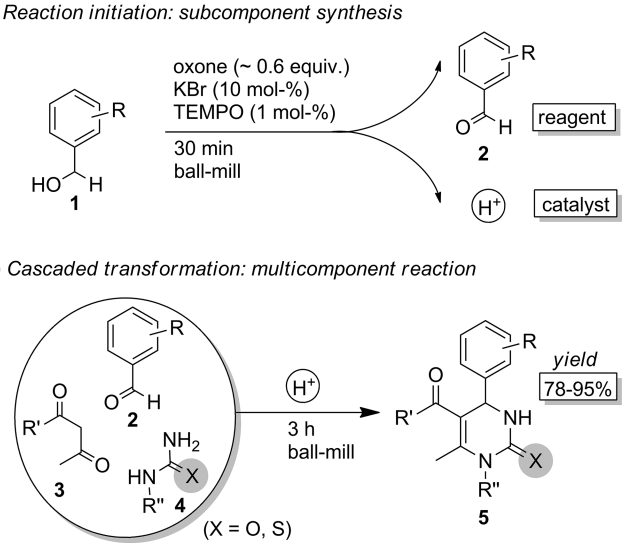

Figure 1. System chemistry model. a) Subcomponent synthesis and b) multicomponent transformation.

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synthesized and used for cascade post-synthetic transformations for the multicomponent Biginelli reaction (Figure 1) within a single ball-milling pot. Thus, under mechanochemical conditions, we establish here a paradigm to make a link between metal-free subcomponent synthesis and a multicomponent transformation to understand systems chemistry in small molecules of thermodynamically stable systems.

Results and Discussion

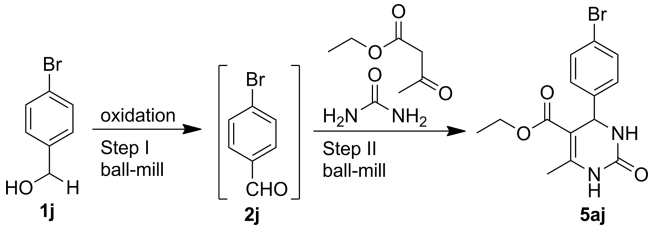
Metal-free oxidation reactions are common in pharmaceutical industries to avoid toxic metal contamination in drugs.[16] Like hypervalent iodine,[17] Br^+-catalyzed reactions with oxone–TBAB[18] or NBS[19] (TBAB = tetrabutylammonium bromide; NBS = *N*-bromosuccinimde) are also popular as the metal-free oxidant. In Figure 1a, Br^+-catalyzed, green and solvent-free mechanochemical oxidation of alcohols to aldehydes is described. Reactions were carried out by using a combination of a catalytic amount of potassium bromide (KBr), oxone and TEMPO [$(2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4)$-2,2,6,6-tetramethylpiperidin-1-yl-oxy radical].[20]

Aldehydes obtained from the first step were used as a component, and the byproduct H^+ was the catalyst for the following Biginelli reaction (Figure 1b). The first step of the reaction was conceived as a covalent type of subcomponent synthesis. However, the second step may be an example of self-sorting in which dihydropyrimidones (DHPMs) were obtained with benzaldehydes, 1,3-dicarbonyls (ethyl acetoacetate or acetyl acetone) and urea (or thiourea) as components. Both steps were carried out in one pot and the total system can be considered as an example of systems chemistry under the area of covalent mechanochemistry.[21]

Table 1 represents the optimization of the reaction conditions. During optimization, the progress of the reactions was checked by TLC or ^{1}H NMR spectroscopy. In a typical run, milling apparatus was stopped and a small portion of sample was collected from the reaction vessel and examined. Once the reaction was finished, solid mass was taken in a flask, washed with appropriate solvents and filtered off. The most appropriate conditions (entry 5) were identified in which both reaction steps cooperatively led to the final products in reasonable yields. Generally, the multicomponent Biginelli reaction works in the presence of a catalyst that could be either acid or base. On the contrary, in this methodology, no catalyst was required to be added externally.

Togo and co-workers reported the KBr–oxone–TEMPO mediated oxidation of benzyl alcohols for 24 h in different solvents, such as CH_3CN–water, dichloromethane or ethyl acetate.[20] Over oxidation could not be controlled and a significant amount of benzoic acid formation was reported in several cases. These kinds of shortcomings are very common in solution-phase oxidation chemistry. However, using this methodology, under solvent free ball-milling conditions

Table 1. Optimization of reaction conditions for the synthesis of **5aj**.



Entry	Step I (conditions)	Yield of **2j** [%][a]	Step II	Yield of **5aj** [%]
1	IBX[b] (1.1 equiv.) 1 h	94	> 4 h	no reaction
2	NBS (1.5 equiv.) 30 min	> 98	> 4 h	Trace (< 3)
3	oxone (1 equiv.) TBAB[c] (10 mol-%) TEMPO (10 mol-%) 30 min	> 98	3.5 h	81
4	oxone (1 equiv.) KBr (10 mol-%) TEMPO (10 mol-%) 30 min	> 98	3.5 h	91
5	Oxone (≈ 0.6 equiv.) KBr (10 mol-%) TEMPO (1 mol-%) 30 min	> 98	3.5 h	95

[a] Yields were determined by ^{1}H NMR analysis. [b] IBX = 2-iodoxybenzoic acid. [c] TBAB = tetrabutylammonium bromide.

the oxidation was achieved by using 1 mol-% of TEMPO in 30 min in near quantitative conversion. In general, it is expected that in a constrained system the maximum possible concentration of reacting partners is reached, which puts the system under high stress and hence could lead to uncontrollable oxidation of newly formed aldehydes to the corresponding acids. In contrast, the described methodology for alcohol oxidation (Figure 1a) might serve as an important example in which a solution-based oxidation reaction was achieved under solvent-free ball-milling conditions, in higher efficiency, with better yields and no over-oxidized products. Furthermore, this methodology was unsuccessful in ethyl acetate.[20]

The efficiency of this two-step mechanochemical methodology for the synthesis of DHPMs looks highly promising. Products were isolated in very good to excellent yields at relatively shorter reaction times (Figure 2). This methodology works for a wide range of electron-rich (**5ae**, **5af**, **5ah** and **5ai**), electron-deficient (**5ag**) aromatic and thiophenyl aldehydes (**5al**).

Regioselectivity[22] for the synthesis of DHPMs by using *N*-methyl urea was also established (Figure 3).[23] The reactions are controlled by steric effects and that leads to the formation of a single regioisomer in all cases. In comparison, **5bd** was obtained in 88% yield after two steps, however, using aluminium-planted mesoporous silica catalyst the reported yield was 86%.[24]

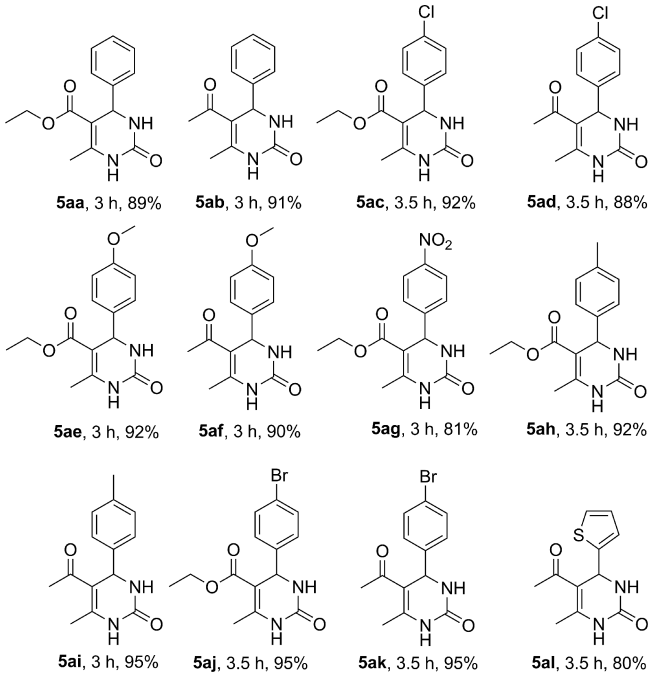


Figure 2. The overall (two-step) yields of DHPMs, reaction time for the second step (with an additional 30 min for the first step) and compound identification numbers are shown here.

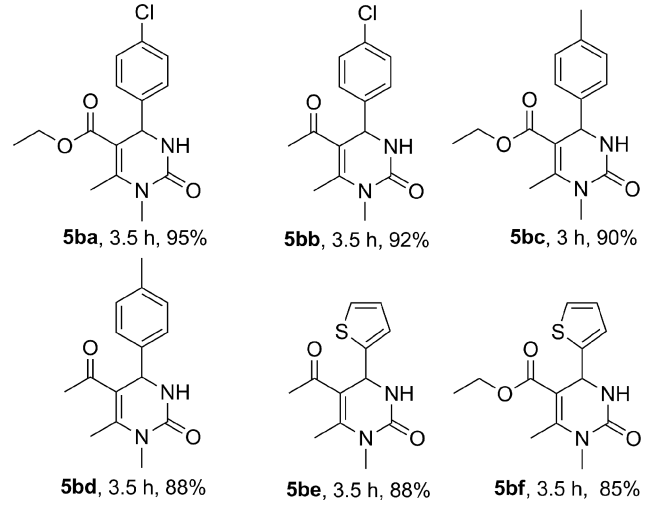


Figure 3. Regioselective synthesis of DHPMs by using *N*-methyl urea.

Furthermore, the reactions with thiourea also resulted in DHPMs with good yield (Figure 4).

The systems chemistry approach under mechanochemistry described here, is a collection of two consecutive thermodynamically stable reaction systems of small molecules. Complete success for two steps (DHPM synthesis) is dependent upon active participation of products (aldehydes) and byproducts (H^+) of the first step. As shown in Table 1, mechano-milling oxidation of alcohols to aldehydes was successful with 2-iodoxybenzoic acid (IBX, entry 1),[10] *N*-bromosuccinimide (NBS, entry 2) and oxone–KBr–TEMPO (entry 3). As representative examples in Figure 5

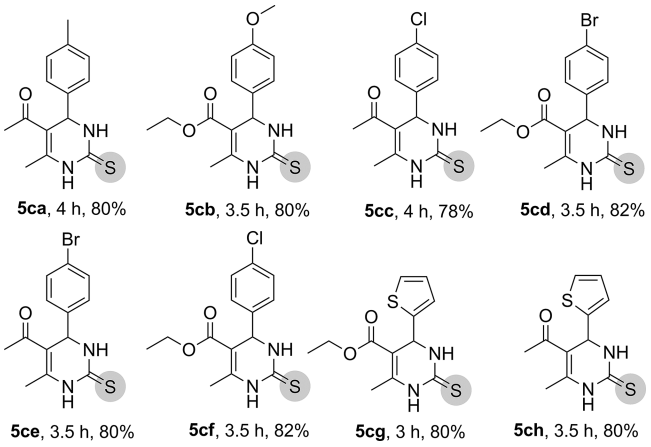


Figure 4. Synthesis of DHPMs by using thiourea.

show, analysis of the ^1H NMR spectra for NBS and oxone–KBr–TEMPO mediated oxidation reactions are clean and high yielding. Unfortunately, the second step was unsuccessful using two oxidations systems (IBX and NBS) because the byproducts were not efficient enough catalysts for the Biginelli reaction. Notably, the byproducts were 2-iodosobenzoic acid (IBA) and succinimide from reactions using IBX and NBS, respectively.

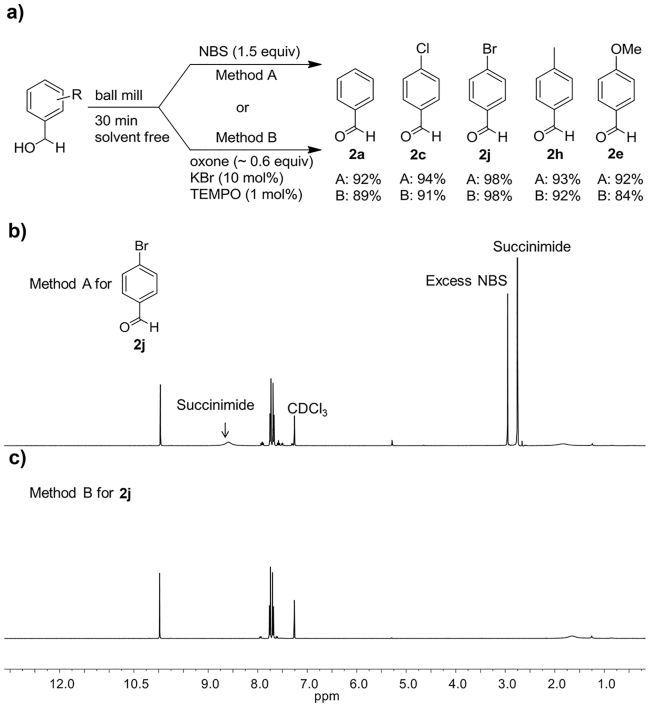


Figure 5. a) Efficiency of NBS (method A) and oxone–KBr–TEMPO (method B) mediated oxidations and b) and c) are the respective ^1H NMR spectra (in $CDCl_3$).

To the best of our knowledge solvent-free NBS-mediated oxidations of alcohols to aldehydes under the mechanochemical conditions presented herein are new. The products obtained from these reactions were sufficiently pure (Fig-

ure 4) to be used directly for synthetic transformations. This methodology is green, economical and does not use harsh conditions. We hope that this methodology will serve as an important addition to organic synthesis and industries.

In summary, we presented here a novel approach of systems chemistry for thermodynamically stable small molecules in the field of covalent mechanochemistry. This strategy represents a new level of complexity in mechanochemical reactions by using ball-milling in which subcomponents were synthesized and used for post-synthetic transformations in a multicomponent reaction within the same reaction pot. Interestingly, we have also shown for the first time that a byproduct obtained from a reaction system is used as a catalyst for another reaction. The irreproducibility of solution-based methodology for the synthesis of DHPMS also demonstrates the superiority of this mechanochemical system. We believe this environmental friendly and economical methodology will be an important addition to drug discovery and development,[25] because DHPMs are well known to have diverse biological activities[26] including anticancer properties.[27] Finally, the systems chemistry we described here for small molecules may branch out to a new field of study in covalent mechanochemistry.[21]

Experimental Section

Detailed experimental procedures are given in the Supporting Information.

Supporting Information (see footnote on the first page of this article): The file contains the details of experimental methods, spectroscopic investigations, synthetic procedure, characterization data and spectra of the compounds.

Acknowledgments

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[1] S. Zharikov, S. Shiva, *Biochem. Soc. Trans.* **2013**, *41*, 118–123.
[2] K. L. Morris, L. Chen, J. Raeburn, O. R. Sellick, P. Cotanda, A. Paul, P. C. Griffiths, S. M. King, R. K. O'Reilly, L. C. Serpell, D. J. Adams, *Nature Commun.* **2013**, *4*, 1480.
[3] J. Snoep, H. Westerhoff, in *Systems Biology, vol. 13* (Eds.: L. Alberghina, H. V. Westerhoff), Springer Berlin Heidelberg, **2005**, pp. 13–30.
[4] a) N. Giuseppone, *Acc. Chem. Res.* **2012**, *45*, 2178–2188; b) J. R. Nitschke, *Nature* **2009**, *462*, 736–738; c) R. F. Ludlow, S. Otto, *Chem. Soc. Rev.* **2008**, *37*, 101–108.
[5] a) M. L. Saha, N. Mittal, J. W. Bats, M. Schmittel, *Chem. Commun.* **2014**, *50*, 12189–12192; b) D. Lewing, H. Koppetz, F. E. Hahn, *Inorg. Chem.* **2015**, *54*, 7653–7659; c) K. Pandurangan, J. A. Kitchen, S. Blasco, E. M. Boyle, B. Fitzpatrick, M. Feeney, P. E. Kruger, T. Gunnlaugsson, *Angew. Chem. Int. Ed.* **2015**, *54*, 4566–4570; d) J. E. Beves, J. J. Danon, D. A. Leigh, J.-F. Lemonnier, I. J. Vitorica-Yrezabal, *Angew. Chem. Int. Ed.* **2015**, *54*, 7555–7559; e) R. Chakrabarty, P. S. Mukherjee, P. J. Stang, *Chem. Rev.* **2011**, *111*, 6810–6918; f) K. Acharyya, S. Mukherjee, P. S. Mukherjee, *J. Am. Chem. Soc.* **2013**, *135*, 554–557.
[6] K. Ruiz-Mirazo, C. Briones, A. de la Escosura, *Chem. Rev.* **2014**, *114*, 285–366.
[7] a) E. R. Kay, D. A. Leigh, F. Zerbetto, *Angew. Chem. Int. Ed.* **2007**, *46*, 72–191; *Angew. Chem.* **2007**, *119*, 72; b) B. Lewandowski, G. De Bo, J. W. Ward, M. Papmeyer, S. Kuschel, M. J. Aldegunde, P. M. E. Gramlich, D. Heckmann, S. M. Goldup, D. M. D'Souza, A. E. Fernandes, D. A. Leigh, *Science* **2013**, *339*, 189–193.
[8] a) P. D. Frischmann, V. Kunz, V. Stepanenko, F. Würthner, *Chem. Eur. J.* **2015**, *21*, 2766–2769; b) A. M. Castilla, W. J. Ramsay, J. R. Nitschke, *Acc. Chem. Res.* **2014**, *47*, 2063–2073; c) H. Bunzen, Nonappa, E. Kalenius, S. Hietala, E. Kolehmainen, *Chem. Eur. J.* **2013**, *19*, 12978–12981; d) X.-P. Zhou, Y. Wu, D. Li, *J. Am. Chem. Soc.* **2013**, *135*, 16062–16065; e) D. H. Ren, D. Qiu, C. Y. Pang, Z. Li, Z. G. Gu, *Chem. Commun.* **2014**, *51*, 788–791.
[9] a) C. Giri, F. Topic, M. Cametti, K. Rissanen, *Chem. Sci.* **2015**, *6*, 5712–5718; b) C. Giri, P. K. Sahoo, R. Puttreddy, K. Rissanen, P. Mal, *Chem. Eur. J.* **2015**, *21*, 6390–6393.
[10] T. K. Achar, S. Maiti, P. Mal, *RSC Adv.* **2014**, *4*, 12834–12839.
[11] a) R. S. Varma, *Green Chem.* **2014**, *16*, 2027–2041; b) G. Cravotto, E. C. Gaudino, P. Cintas, *Chem. Soc. Rev.* **2013**, *42*, 7521–7534; c) D. Braga, L. Maini, F. Grepioni, *Chem. Soc. Rev.* **2013**, *42*, 7638–7648; d) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friscic, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell, *Chem. Soc. Rev.* **2012**, *41*, 413–447; e) T. Friščić, I. Halasz, P. J. Beldon, A. M. Belenguer, F. Adams, S. A. J. Kimber, V. Honkimäki, R. E. Dinnebier, *Nature Chem.* **2013**, *5*, 66–73; f) P. Balaz, M. Achimovicova, M. Balaz, P. Billik, Z. Cherkezova-Zheleva, J. M. Criado, F. Delogu, E. Dutkova, E. Gaffet, F. J. Gotor, R. Kumar, I. Mitov, T. Rojac, M. Senna, A. Streletskii, K. Wieczorek-Ciurowa, *Chem. Soc. Rev.* **2013**, *42*, 7571–7637; g) J. G. Hernández, C. G. Avila-Ortiz, E. Juaristi, in *Comprehensive Organic Synthesis II*, 2nd ed., (Ed.: P. Knochel), Elsevier, Amsterdam, **2014**, pp. 287–314.
[12] S. Ley, M. O'Brien, R. Denton, *Synthesis* **2011**, 1157–1192.
[13] a) A. Stolle, T. Szuppa, S. E. S. Leonhardt, B. Ondruschka, *Chem. Soc. Rev.* **2011**, *40*, 2317–2329; b) G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668–7700; c) J. G. Hernández, E. Juaristi, *J. Org. Chem.* **2010**, *75*, 7107–7111.
[14] J.-L. Do, C. Mottillo, D. Tan, V. Strukil, T. Friscic, *J. Am. Chem. Soc.* **2015**, *137*, 2476–2479.
[15] a) S. Maiti, P. Mal, *Adv. Synth. Catal.* **2015**, *357*, 1416–1424; b) T. K. Achar, P. Mal, *J. Org. Chem.* **2015**, *80*, 666–672; c) S. Maiti, P. Mal, *Synth. Commun.* **2014**, *44*, 3461–3469; d) A. Bose, P. Mal, *Tetrahedron Lett.* **2014**, *55*, 2154–2156.
[16] M. Valko, H. Morris, M. T. D. Cronin, *Curr. Med. Chem.* **2005**, *12*, 1161–1208.
[17] V. V. Zhdankin, in *Hypervalent Iodine Chemistry*, John Wiley & Sons Ltd, **2013**, pp. 145–336.
[18] H. Hussain, I. R. Green, I. Ahmed, *Chem. Rev.* **2013**, *113*, 3329–3371.
[19] a) S. Adimurthy, P. U. Patoliya, *Synth. Commun.* **2007**, *37*, 1571–1577; b) J.-C. Fan, Z.-C. Shang, J. Liang, X.-H. Liu, Y. Liu, *J. Phys. Org. Chem.* **2008**, *21*, 945–953.
[20] K. Moriyama, M. Takemura, H. Togo, *J. Org. Chem.* **2014**, *79*, 6094–6104.
[21] a) J. Ribas-Arino, D. Marx, *Chem. Rev.* **2012**, *112*, 5412–5487; b) J. Ribas-Arino, M. Shiga, D. Marx, *Angew. Chem. Int. Ed.* **2009**, *48*, 4190–4193; *Angew. Chem.* **2009**, *121*, 4254; c) J. Wang, T. B. Kouznetsova, Z. Niu, M. T. Ong, H. M. Klukovich, A. L. Rheingold, T. J. Martinez, S. L. Craig, *Nature Chem.* **2015**, *7*, 323–327.
[22] C. O. Kappe, *J. Org. Chem.* **1997**, *62*, 7201–7204.

[23] Q. Chen, L.-L. Jiang, C.-N. Chen, G.-F. Yang, *J. Heterocycl. Chem.* **2009**, *46*, 139–148.
[24] H. Murata, H. Ishitani, M. Iwamoto, *Org. Biomol. Chem.* **2010**, *8*, 1202–1211.
[25] P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49.
[26] C. O. Kappe, *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052.
[27] a) M. Gartner, N. Sunder-Plassmann, J. Seiler, M. Utz, I. Vernos, T. Surrey, A. Giannis, *ChemBioChem* **2005**, *6*, 1173–1177; b) T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber, T. J. Mitchison, *Science* **1999**, *286*, 971–974.

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