ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Exploiting amphiphilicity: facile metal free access to thianthrenes and related sulphur heterocycles†

Martin Pawliczek,[ab] Lennart K. B. Garve[a] and Daniel B. Werz*[a]

Cite this: *Chem. Commun.*, 2015, **51**, 9165

Received 28th February 2015,
Accepted 28th April 2015

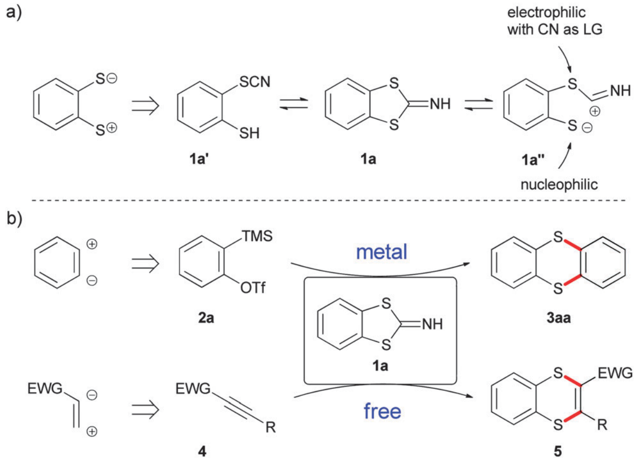
DOI: 10.1039/c5cc01757b

www.rsc.org/chemcomm

Benzodithioloimines are reacted with arynes or alkynes substituted with electron-withdrawing groups to afford the corresponding thianthrene or benzo[*b*][1,4]dithiine derivatives. The transformation takes place under mild reaction conditions without any transition metal. Furthermore, the reaction mode could be expanded to 2-thiocyanatopyrroles yielding pyrrolothiazoles.

In the last decades sulphur-containing molecules have received great attention because of their interesting biological properties[1] and their unique application in material science.[2] For that purpose, the development of new methodologies dealing with the formation of carbon–sulphur bonds has become a major topic in modern organic synthesis.[3] Traditional methods which take advantage of the high nucleophilicity of sulphur require harsh reaction conditions to form arene–sulphur bonds. Therefore, elevated temperatures, strong bases or a specific substitution pattern at the arene are needed making them unattractive for numerous target molecules.[4] These drawbacks could be bypassed utilising metal catalysed cross-coupling reactions for C–S bond formation.[5] Nevertheless, applications in material science require highly pure compounds without any extraneous metal impurities. Thus, transition metal free protocols for the formation of C–S bonds under mild reaction conditions are of considerable interest.[6]

Regarding the reaction properties of thiophenols, sulphur reacts as a nucleophile. However, its philicity can be reversed by converting thiophenol into the corresponding sulfenyl chloride or thiocyanate. In this shape, sulphur acts as electrophile suitable for substitution by nucleophiles (*e.g.* lithium or Grignard reagents).[7] For the facile synthesis of heterocycles containing two sulphur atoms, 1,2-thiophenol derivatives equipped with both abilities are of utmost importance (Scheme 1a). This means one sulphur atom should act as nucleophile, the other one as electrophile. 2-Thiocyanatobenzenethiol (**1a′**) which exists in its closed form **1a** was chosen as target substrate.[8] Providing the required abilities easily visualised by its open form **1a″**, compound **1a** should be able to react with other easily polarisable or polarised substrates such as arynes[9] or alkynes substituted with electron-withdrawing (EWG) groups.[10] As products, the corresponding dithiaheterocycles **3aa** and **5**, respectively, should be formed (Scheme 1b).



Scheme 1 (a) Reaction mode of mononitrile-substituted 1,2-dithiophenol. (b) Possible reaction partners and desired products.

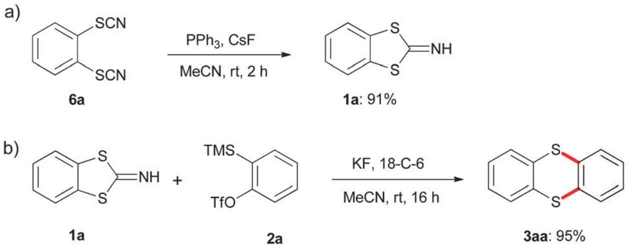
At the beginning of our investigations, we intended to establish a fast and efficient access to key compound **1a** since the methods described in the literature proved to be tedious.[8] We discovered, when treating aromatic 1,2-dithiocyanatobenzene **6a** with PPh_3 in the presence of base in acetonitrile, **1a** is formed in up to 91% yield within 1 h at room temperature (Scheme 2a). With compound **1a** in hand, we proved the amphiphilic behaviour of the two sulphur atoms. Based on our previous considerations, we chose a common aryne precursor for the desired metal free transformation which would provide a novel entry to the thianthrene scaffold.[11] To our delight, common

---

[a] *Technische Universität Braunschweig, Institut für Organische Chemie, Hagenring 30, 38106 Braunschweig, Germany. E-mail: d.werz@tu-braunschweig.de*

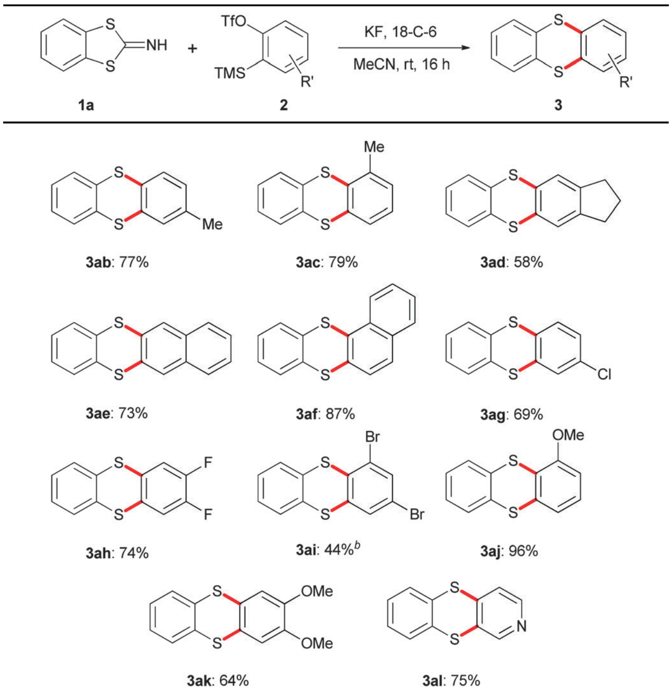
[b] *Georg-August-Universität Göttingen, Institut für Organische und Biomolekulare Chemie, Tammannstraße 2, 37077 Göttingen, Germany*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5cc01757b



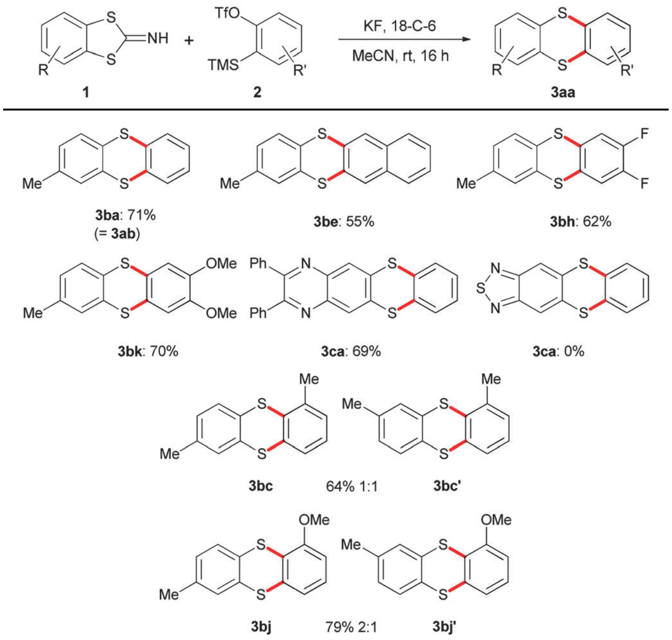
Scheme 2 (a) Synthesis of **1a**. (b) Reaction of **1a** with aryne precursor **2a**.

Table 1 Scope of thianthrenes with respect to aryne[a]



[a] Reaction conditions: **1a** (50 μmol), **2** (75 μmol), KF (150 μmol), 18-C-6 (150 μmol), MeCN (2 mL), rt, 16 h. [b] 200 μmol of **2** were used.

Table 2 Scope of thianthrenes with respect to dithioloimine and aryne[a]



[a] Reaction conditions: **1** (50 μmol), **2** (75 μmol), KF (150 μmol), 18-C-6 (150 μmol), MeCN (2 mL), rt, 16 h.

conditions using KF and 18-crown-6 in acetonitrile at ambient temperature yielded the desired thianthrene **3aa** in excellent 95% yield (Scheme 2b).

Exposition of **1a** to various aryne precursors under the above-mentioned reaction conditions yielded the corresponding thianthrenes (Table 1). Alkyl-substituted arynes and such with extended π-systems were successfully converted to their thianthrene counterparts **3ab–3af** in 58–87% yield. Chloro-, fluoro-, and bromo-substituted thianthrenes **3ag**, **3ah**, and **3ai** were obtained in yields ranging from 44 to 74%. In the case of the dibromo derivative **3ai** higher loadings of aryne precursor were required. Thianthrenes equipped with one or two methoxy substituents **3aj** and **3ak** were accessed in 64% and 96% yield, respectively. Furthermore, also a pyridine-based aryne precursor was able to undergo the transformation to azathianthrene **3al** in 75% yield.

Similarly, variations with respect to the dithioloimine bearing core are possible (Table 2). Methyl-substituted **1b** in combination with the unfunctionalised aryne precursor was exposed to the reaction conditions yielding **3ba** in 71%. Naphthyl-based **3be**, difluoro- **3bh** and dimethyoxy-substituted systems **3bk** were obtained in yields ranging from 55 to 70%. Because of their high electronegativity the latter two substituents render the important in-plane π orbital of the aryne highly electron-deficient. Further, benzodithioloimines containing pyrazine or thiadiazole heterocyclic cores were also applied. Pyrazine derivative **3ca** could be obtained in 69% yield, whereas the formation of **3ca** stayed out.

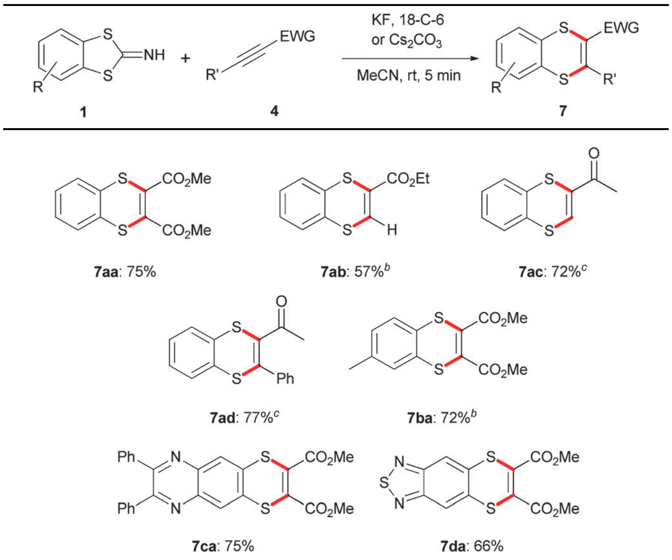
Finally, **1b** was exposed to unsymmetrical aryne precursors substituted with a methyl or a methoxy group. As result, inseparable mixtures of **3bc**/**3bc′** (64%, ratio of 1 : 1) and **3bj**/**3bj′** (79%, ratio of 2 : 1) were obtained, respectively. This observation demonstrates that even the methoxy-substituted aryne, known for its high distortion and hence its high regioselectivity in aryne chemistry, does not achieve a satisfying ratio of regioisomers.[12]

In addition, we also tried a one-step procedure applying 1,2-dithiocyanatobenzene **6a** by addition of PPh$_3$ to the aryne reaction. Unfortunately, the resulting yields were lower with 65% as the best result. A further drawback was the separation of PPh$_3$ from the product by column chromatography wherefore the two-step procedure proved to be the method of choice.

With this procedure for thianthrenes in hand, we tried to expand the scope to other heterocyclic scaffolds. Therefore, alkynes **4** bearing an electron-withdrawing group were utilised resulting in benzo[*b*][1,4]dithiines.[13] Slight adjustments of the reaction conditions were necessary to obtain the desired products, but in all cases much faster transformations were observed using these polarised alkynes.[14]

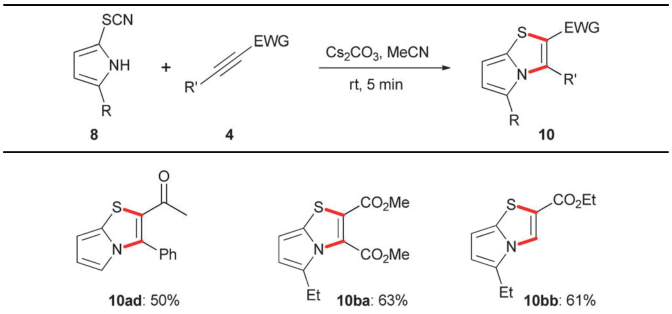
Consequently, dimethylester **7aa** and mono-methylester **7ab** were reached in 75% and 57% yields, respectively (Table 3).

Table 3 Scope of dithioloimines with EWG-substituted alkynes[a]

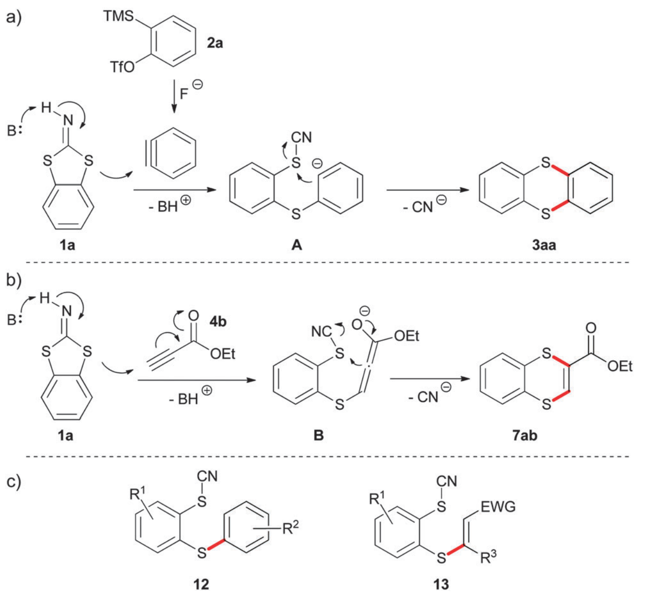


[a] Reaction conditions: **1a** (200 μmol), **4** (300 μmol), KF (600 μmol), 18-C-6 (600 μmol), MeCN (2 mL), rt, 5 h. [b] Reaction conditions: **1** (500 μmol), **4** (750 μmol), KF (1.50 mmol), 18-C-6 (1.50 mmol), MeCN (5 mL), rt, 5 h. [c] Cs_2CO_3 (600 μmol) instead of KF and 18-C-6.

Table 4 Reaction of **8** with EWG-substituted alkynes **4** to afford **10**[a]



[a] Reaction conditions: **8** (200 μmol), **4** (4.00 mmol), Cs_2CO_3 (300 μmol), MeCN (3 mL), rt, 5 min.



Scheme 4 Proposed mechanistic scenario: (a) for the reaction with arynes; (b) for the reaction with Michael acceptors; (c) observed side products.

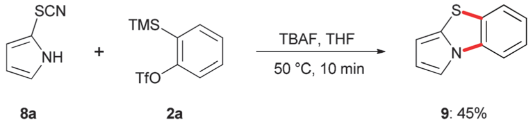
Michael acceptors based on ketones could be converted in yields of 72% for **7ac** and 77% for **7ad**. Modifications regarding the dithioloimine core were performed as well. Methyl-substituted dimethylester derivative **7ba** could be achieved in 72% yield. Also, other heterocyclic systems could be introduced resulting in pyrazine **7ca** and thiadiazol **7da** and in 75% and 66% yield. In addition, the application of Michael acceptors based on double bonds was unsuccessful. We assume that in such a case the retro-Michael reaction in contrast to the ring closure is the preferred mode of action.[15]

Encouraged by these results, we investigated whether also nitrogen might play the nucleophilic role. Changing the aromatic core to 2-thiocyanatopyrrole the endocyclic nitrogen should be prone to act as nucleophile. As result, the analogous transformation under modified reaction conditions yielded the desired benzo[*d*]pyrrolo[2,1-*b*]thiazole[16] (**9**) in 45% yield (Scheme 3).

Further, also Michael acceptors were shown to be suitable substrates to afford the corresponding pyrrolo[2,1-*b*]thiazole[17] derivatives **10ad**, **10ba** and **10bb** in 50–63% yield (Table 4). Because of the high reactivity and amphiphilic character of **8**, it rather tends to undergo a homocoupling than a 1,4-addition. This problem was partially counteracted by applying higher loadings of Michael acceptor.

We propose the following plausible reaction mechanisms being responsible for product formation (Scheme 4). Precursor **2a** is transformed into the reactive aryne. Deprotonation of benzodithioloimine favours the nucleophilic attack on the aryne leading to intermediate **A** (Scheme 4a). This species undergoes a concomitant nucleophilic substitution on sulphur, whereby nitrile acts as leaving group to form product **3aa**. The pivotal reaction steps for alkynes substituted with electron-withdrawing groups are similar (Scheme 4b). Nevertheless, in this case the formation of the reactive triple bond is not necessary resulting in shorter reaction times in comparison with the previous transformation. The proposed reaction mechanisms are supported by side products **12** and **13** which are formed if ring-closure stays out because of protonation of intermediate **A** or **B** (Scheme 4c).

In conclusion, we developed a broadly applicable transition metal free method for the synthesis of thianthrenes and benzodithiines. For this purpose, amphiphilic dithioloimines containing negatively and positively polarised sulphur were reacted with arynes and alkynes substituted with electron-withdrawing groups. Additionally, the concept of two differently polarised heteroatoms was transferred to a nitrogen–sulphur combination.



Scheme 3 Reaction of **8a** with aryne precursor **2a**.

The use of 2-thiocyanatopyrroles paves the way for a novel, fast and efficient entry to benzo[*d*]pyrrolo[2,1-*b*]thiazoles and pyrrolo[2,1-*b*]thiazoles, respectively. Further studies to expand this methodology to other heterocyclic scaffolds are ongoing.

This research was supported by the German Research Foundation (DFG, Emmy Noether and Heisenberg Fellowships to D.B.W.) and by the Fonds der Chemischen Industrie (PhD Fellowship to M.P. and Dozentenstipendium to D.B.W.). L.K.B.G. thanks the Studienstiftung des deutschen Volkes for a PhD Fellowship.

Notes and references

1 (*a*) B. Stumpf, C. Eberle, M. Kaiser, R. Brun, R. L. Krauth-Siegel and F. Diederich, *Org. Biomol. Chem.*, 2008, **6**, 3935; (*b*) A. Gangjee, Y. Zeng, T. Talreja, J. J. McGuire, R. L. Kisliuk and S. F. Queener, *J. Med. Chem.*, 2007, **50**, 3046; (*c*) S. F. Nielsen, E. Ø. Nielsen, G. M. Olsen, T. Liljefors and D. Peters, *J. Med. Chem.*, 2000, **43**, 2217.

2 (*a*) P. Choto, K. Rasmussen and G. Grampp, *Phys. Chem. Chem. Phys.*, 2015, **17**, 3415; (*b*) C. C. Ferrón, M. Capdevila-Cortada, R. Balster, F. Hartl, W. Niu, M. He, J. J. Novoa, J. N. L. Navarrete, V. Hernández and M. C. R. Delgado, *Chem. – Eur. J.*, 2014, **20**, 10351; (*c*) A. M. Khenkin, G. Leitus and R. Neumann, *J. Am. Chem. Soc.*, 2010, **132**, 11446; (*d*) C. Marti, J. Irurre, A. Alvarez-Larena, J. F. Piniella, E. Brillas, L. Fajari, C. Aleman and L. Julia, *J. Org. Chem.*, 1994, **59**, 6200; (*e*) T. Sarukawa and N. Oyama, *J. Electrochem. Soc.*, 2010, **157**, F23; (*f*) G. Jones, B. Huang and S. F. Griffin, *J. Org. Chem.*, 1993, **58**, 2035.

3 (*a*) J. Mao, T. Jia, G. Frensch and P. J. Walsh, *Org. Lett.*, 2014, **16**, 5304; (*b*) L. Wang, W. He and Z. Yu, *Chem. Soc. Rev.*, 2013, **42**, 599; (*c*) R. B. N. Baig and R. S. Varma, *Chem. Commun.*, 2012, **48**, 2582; (*d*) P. Bichler and J. A. Love, *Top. Organomet. Chem.*, 2010, **31**, 39; (*e*) C.-K. Chen, Y.-W. Chen, C.-H. Lin, H.-P. Lin and C.-F. Lee, *Chem. Commun.*, 2010, **46**, 282.

4 (*a*) J. Ham, I. Yang and H. Kang, *J. Org. Chem.*, 2004, **69**, 3236; (*b*) A. V. Bierbeek and M. Gingras, *Tetrahedron Lett.*, 1998, **39**, 6283; (*c*) A. B. Pierini, M. T. Baumgartner and R. A. Rossi, *J. Org. Chem.*, 1987, **52**, 1089; (*d*) J. Lindley, *Tetrahedron*, 1984, **40**, 1433.

5 (*a*) I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2011, **111**, 1569; (*b*) H. Yang, Y. Li, M. Jiang, J. Wang and H. Fu, *Chem. – Eur. J.*, 2011, **17**, 5652; (*c*) P. Anbarasan, H. Neumann and M. Beller, *Chem. Commun.*, 2011, **47**, 3233; (*d*) F. Ke, Y. Qu, Z. Jiang, Z. Li, D. Wu and X. Zhou, *Org. Lett.*, 2011, **13**, 454; (*e*) M. A. Fernández-Rodríguez, Q. Shen and J. F. Hartwig, *Chem. – Eur. J.*, 2006, **12**, 7782.

6 (*a*) Y. Yang, Z. Chen and Y. Rao, *Chem. Commun.*, 2014, **50**, 15037; (*b*) J.-K. Qui, W.-J. Hao, D.-C. Wang, P. Wei, J. Sun, B. Jiang and S.-J. Tu, *Chem. Commun.*, 2014, **50**, 14782; (*c*) F.-L. Yang and S.-K. Tian, *Angew. Chem., Int. Ed.*, 2013, **52**, 4929; (*d*) N. Umiersky and G. Manolikakes, *Org. Lett.*, 2013, **15**, 188; (*e*) S. Liang, R. Zhang, L. Xi, S. Chen and X. Yu, *J. Org. Chem.*, 2013, **78**, 11874; (*f*) S. A. Amelichev, L. S. Konstantinova, N. V. Obruchnikova, O. A. Rakitin and C. W. Rees, *Org. Lett.*, 2006, **8**, 4529.

7 (*a*) L. Melzig, C. B. Rauhut, N. Naredi-Rainer and P. Knochel, *Chem. – Eur. J.*, 2011, **17**, 5362; (*b*) J. R. Fotsing and K. Banert, *Synthesis*, 2006, 261; (*c*) D. B. Werz, R. Gleiter and F. Rominger, *J. Org. Chem.*, 2004, **69**, 2945; (*d*) D. B. Werz and R. Gleiter, *J. Org. Chem.*, 2003, **68**, 9400; (*e*) F. D. Toste and I. W. J. Still, *Tetrahedron Lett.*, 1995, **36**, 4361; (*f*) H. Maruyama, M. Shiozaki, S. Oida and T. Hiraoka, *Tetrahedron Lett.*, 1985, **26**, 4521.

8 (*a*) P. Stanetty, G. Hattinger, M. D. Mihovilovic and K. J. Mereiter, *J. Heterocycl. Chem.*, 2000, **37**, 955; (*b*) J. Nakayama, A. Sakai, S. Tokita and M. Hoshino, *Heterocycles*, 1984, **22**, 27.

9 (*a*) J.-A. García-López, M. Çetin and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2015, **54**, 2156; (*b*) D. Giallombardo, A. C. Nevin, W. Lewis, C. C. Nawrat, R. R. A. Kitson and C. J. Moody, *Tetrahedron*, 2014, **70**, 1283; (*c*) J. Zhao and R. C. Larock, *J. Org. Chem.*, 2007, **72**, 583; (*d*) D. C. Rognessa and R. C. Larock, *Tetrahedron Lett.*, 2009, **50**, 4003; (*e*) J. Zhao and R. C. Larock, *Org. Lett.*, 2005, **7**, 4273; (*f*) D. Hong, Z. Chen, X. Lin and Y. Wang, *Org. Lett.*, 2010, **12**, 4608.

10 (*a*) C. Shao, Q. Zhang, G. Cheng, C. Cheng, X. Wang and Y. Hu, *Eur. J. Org. Chem.*, 2013, 6443; (*b*) K. Yoshimura, T. Oishi, K. Yamaguchi and N. Mizuno, *Chem. – Eur. J.*, 2011, **17**, 3827; (*c*) E. B. Castillo-Contreras and G. R. Dake, *Org. Lett.*, 2014, **16**, 1642; (*d*) M. Yoshida, K. Saito, Y. Fujino and T. Doi, *Chem. Commun.*, 2012, **48**, 11796.

11 (*a*) D. Kundu, T. Chatterjee and B. C. Ranu, *Adv. Synth. Catal.*, 2013, **355**, 2285; (*b*) K. Radhakrishnan and C.-H. Lin, *Synlett*, 2005, 2179; (*c*) P. Preedasuriyachai, P. Charoonniyomporn, O. Karoonnirun, T. Thongpanchang and Y. Thebtaranonth, *Tetrahedron Lett.*, 2004, **45**, 1343.

12 (*a*) J. M. Medina, J. L. Mackey, N. K. Garg and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 15798; (*b*) F.-L. Liu, J.-R. Chen, Y.-Q. Zou, Q. Wei and W.-J. Xiao, *Org. Lett.*, 2014, **16**, 3768; (*c*) S. S. Bhojgude, T. Kaicharla and A. T. Biju, *Org. Lett.*, 2013, **15**, 5452.

13 (*a*) G. L. Morgans, E. L. Ngidi, L. G. Madeley, S. D. Khanye, J. P. Michael, C. B. de Koning and W. A. L. van Otterlo, *Tetrahedron*, 2009, **65**, 10650; (*b*) E. M. Engler, V. V. Patel and R. R. Schumaker, *Tetrahedron Lett.*, 1981, **22**, 2035; (*c*) P. Blatcher, S. Warren, S. Ncube, A. Pelter and K. Smith, *Tetrahedron Lett.*, 1978, **26**, 2349.

14 Different bases were tested (K_2CO_3, KOH, DABCO, KOAc, CsF, Cs_2CO_3, KF/18-C-6). Cs_2CO_3 or KF/18-C-6 gave the best results in the specific cases as stated in Table 3.

15 J. Evarts, E. Torres and P. L. Fuchs, *J. Am. Chem. Soc.*, 2002, **124**, 11093.

16 (*a*) P. Zhao, H. Yin, H. Gao and C. Xi, *J. Org. Chem.*, 2013, **78**, 5001; (*b*) M. Kucukdisli and T. Opatz, *Eur. J. Org. Chem.*, 2012, 4555.

17 (*a*) D. C. Rogness, N. A. Markina, J. P. Waldo and R. C. Larock, *J. Org. Chem.*, 2012, **77**, 2743; (*b*) K. C. Majumdar and S. Nath, *Synthesis*, 2011, 1413; (*c*) Y. S. Song and K.-J. Lee, *Synthesis*, 2007, 3037.