

Zinc-mediated CH-activation of tetrahydrofuran under mild conditions for the regioselective addition to aryl-propiolates[†]

Florian Pünner and Gerhard Hilt*

 Cite this: *Chem. Commun.*, 2014, 50, 7310

 Received 5th May 2014,
 Accepted 20th May 2014

DOI: 10.1039/c4cc03348e

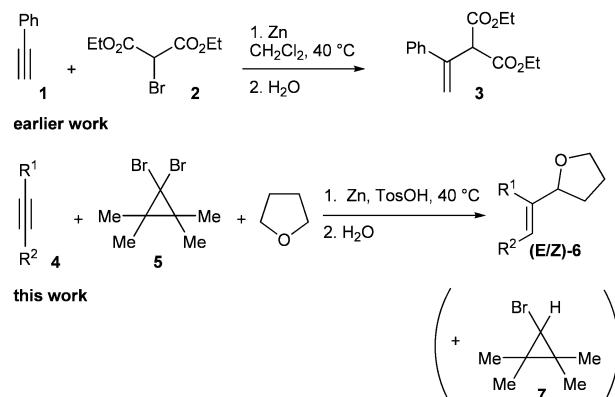
www.rsc.org/chemcomm

The CH-activation of THF is realized in a zinc-mediated process using a dibromocyclopropane as a crucial additive. The highly regioselective addition to aryl-substituted propiolates as well as the regio- and stereoselective addition to diynes are described.

The CH-activation of arenes by transition metals is a vivid research topic under intensive investigation at the present time.¹ The use of directing groups for CH-activation of arenes in the *ortho*-position is well described. The most elegant method for the CH-activation of arenes can be considered to be the *Catellani* reaction where the directing group (norbornyl substituent) is introduced *in situ* and removed later on to result in multiple substituted arene derivatives.² Besides the reports for the CH-activation of arenes in the *ortho*-position, the functionalization of the *meta*- or *para*-position has been disclosed only a few times.³ On the other hand, CH-activation of simple ethers such as tetrahydrofuran (THF) has recently received increasing attention.⁴ We herein present a method for the CH-activation of THF and its reaction with alkynes for the regioselective synthesis of tri- and tetrasubstituted alkenes.

In the course of our ongoing investigation concerning iron-catalyzed transformations of strained ring systems⁵ and the activation of carbon-bromine bonds by zinc powder,⁶ we reported the transformation of terminal alkynes (**1**) with bromomalonate (**2**) for the synthesis of β,γ -unsaturated malonates such as **3**.

When the bromo-substituted derivative was altered from the malonate **2** to the dibromocyclopropane derivative **5**, a corresponding addition reaction was not observed. Instead, the regioselective addition of the solvent (THF) to the alkyne led to the new product **6** as a mixture of the *E*- and *Z*-isomers. The proto-debrominated derivative **7** was identified as a stoichiometric side product (Scheme 1). In the formal addition of THF to alkynes, the application of zinc powder in combination with acids, such as



Scheme 1 Zinc-mediated formation of **3** compared to the formal hydro-tetrahydrofuranylation of alkynes.

conc. HBr or TosOH, was sufficient to initiate the reaction. When different charges of zinc powder were tested, the best results in terms of yield and shortened reaction time were obtained with the zinc powder of highest purity available (99.999%, ABCR) in combination with TosOH-H₂O to initiate the reaction.

Other additives, such as a cobalt based catalyst (CoBr₂/PPh₃/ZnI₂), in combination with zinc powder were also catalytically active to form the desired product, but increased amounts of the cyclo-trimerisation product of the alkyne were observed as by-products.⁷ Ruthenium based additives, such as RuCl₃ and Ru(PPh₃)₃Cl₂, were also capable to provide the product of type **6a**, but had no advantage in yield or selectivity compared to the application of zinc powder alone. Other potential catalysts, such as CoBr₂ (in the absence of phosphine ligands), MnCl₂, CuI, CuBr₂, and Pd(PPh₃)₂Cl₂ were unreactive and prohibited the reaction completely.

Only for the application of diynes (see below), the addition of catalytic amounts of FeBr₂ (10 mol%) and triphenylphosphine (15 mol%) gave better results compared to those obtained from the reaction with the zinc powder and TosOH alone.

Other dibromocyclopropanes, such as 1,1-dibromo-2-phenylcyclopropane, also afforded products of type **6**, but **5** turned out to afford the highest yields and led to easily separable by-product **7**.

Fachbereich Chemie, Hans-Meerwein-Str., 35043 Marburg, Germany.

E-mail: Hilt@chemie.uni-marburg.de; Fax: +49 6421 2825677;

Tel: +49 6421 2825601

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc03348e



Table 1 Zinc-mediated CH-activation of THF^a

Entry	Product ^b	Yield (%)	E/Z ratio	Reaction scheme	
				Alkyne	Dibromocyclopropane
1		82	36:64		
2		75	47:53		
3		79	35:65		
4		85	32:68		
5		85	26:74		
6		89	35:65		
7		86	29:71		
8		74 ^c	44:56		
9		68 ^c	35:65		
10		58 ^c	54:46 ^d		

Table 1 (continued)

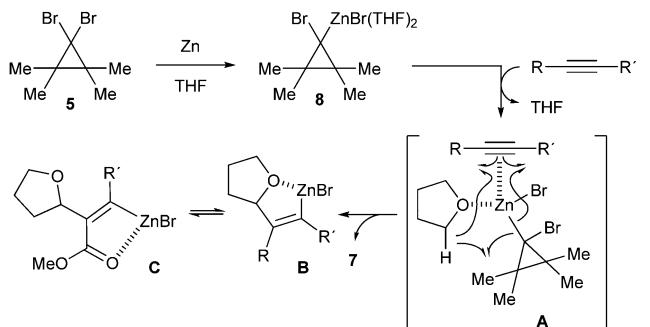
Entry	Product ^b	Yield (%)	E/Z ratio	Reaction scheme	
				Alkyne	Dibromocyclopropane
11		74	42:58		
12		24	40 ^c		
13		26 ^c (52 borsm)	>99:1		
14		28 ^c (49 borsm)	<1:99		
15		41 ^c (77 borsm)	>20:1		

^a Dibromocyclopropane 5 (2.5 eq.), zinc powder (3.0 eq.), $\text{TosOH-H}_2\text{O}$ (5.0 mol%), alkyne 4 (1.0 eq.), 4–16 h, THF (0.4 M), 40 °C. ^b The main isomer is shown. ^c Dibromocyclopropane 5 (2.0 eq.), FeBr_2 (10.0 mol%) and PPh_3 (15.0 mol%) were added. ^d For the sake of consistency the minor product is shown in this case.

Surprisingly, the reaction could not be initiated with other alkyl bromides, such as bromoethane, 1,2-dibromo-ethane, *t*BuBr, CH_2Br_2 , or CHBr_3 and the application of other reducing agents such as Fe, Mg, Mn, and Al was also unsuccessful. The application of other commonly used methods for the activation of zinc powder, such as Me_3SiCl or LiCl ,⁸ led to significantly lower yields.

The zinc-mediated CH-activation of THF could be extended to a number of aryl-substituted alkynoates. The results of these reactions are summarized in Table 1.

The reaction tolerates aliphatic, aromatic, silyl- and ester-substituted alkynes and diynes, proving the mildness of the transformation. Ester-, ether-, alkyl- and halogen-substituted aromatic substrates as well as a heteroaromatic substituted propiolate (entry 11) were applicable. Of considerable interest are the conversions of halide-functionalized starting materials (entries 3–5) because in no case hydrodehalogenation of the arene substituent was observed. While propiolates led to the products in short reaction times (~4 h) and in good to high yields, the E/Z-ratios of those products (entries 1–12) were not very high. In contrast, very high to excellent regio- and stereoselectivities for

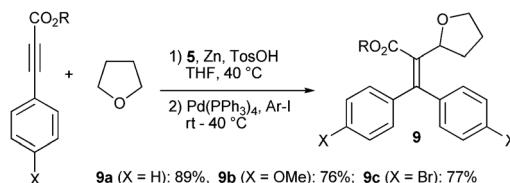


Scheme 2 Proposed reaction mechanism of the zinc-mediated CH-activation of THF.

the *syn*-addition for several symmetrical 1,3-dynes (entries 13–15) were obtained. However, the isolated yields for these products are lower due to incomplete conversions, but based on the amounts of unconsumed and recovered starting materials, the yields are still acceptable. Interestingly, when symmetrical diynes were used only one of the alkyne moieties (entries 13–15) was converted to the product in a highly regio- and stereoselective fashion. In contrast, the application of symmetric alkynes like diphenylacetylene or dimethyl acetylenedicarboxylate did not lead to the desired products, indicating that polarised triple bonds are necessary to be accepted as starting materials. This effect can be seen in the case of the alkyl-substituted alkyne (entry 12) where the regiochemistry of the THF-addition was inverted. Aryl substituents in the *para*-position did not influence the yield and stereoselectivity of the reaction to a great extent, but the reactions were significantly faster and led to slightly higher yields and selectivities, when an electron-deficient aryl propiolate was applied (entries 1–3). The highest yields and selectivities were obtained when a substituent was located in the *ortho*-position (entries 4–7). The regioselectivities were very high to excellent in all cases and only trace amounts (<3%) of other isomers were observed in GC/MS analysis of the crude reaction mixture. Taking all observations into account, we propose the reaction mechanism which is outlined in Scheme 2.

The oxidative insertion of zinc into a carbon–bromine bond generates the organo-zinc species **8** *in situ* with THF as the coordinating solvent. One of the THF molecules is replaced by the alkyne to form intermediate **A**. From the control experiments with other brominated compounds, only the carbeneoid zinc species **A** led to the formation of the proto-debrominated derivative **7** and the addition of the THF fragment to the alkyne. Based on the affinity of the zinc(II) species to alkynes and the reactivity of carbeneoids, it is likely that these processes could take place in an intramolecular fashion as outlined in structure **A**. Thereby, the *cis*-addition intermediate **B** was formed which was then quenched with water to yield the products observed when 1,3-dynes were used. In the case of the propiolates the isomerisation to the zinc-species **C** seems to be reasonable so that a mixture of the *E*- and the *Z*-isomers of **6** was generated after quenching with water.⁹

The regiochemistry of the THF-addition to propiolates and diynes indicates that the formation of an organo-zinc nucleophile from THF is unlikely. Also, the generation of a cationic



Scheme 3 *In situ* Negishi coupling of the vinyl-zinc intermediates of type **B** (**9a**: R = Et; **9b/9c**: R = Me).

oxonium-type species from THF utilizing **8** as a formal base can be excluded because such a species would also react with electron-rich arenes. When 1,2,3-trimethoxybenzene was present in the reaction, only the products of type **6** were formed and no trace of a Friedel–Crafts-type product could be detected. However, the reaction could be efficiently inhibited when TEMPO, hydroquinone and other radical reaction inhibitors were present. This indicates that the CH-activation of THF is not strictly concerted and that radical intermediates can be trapped to inhibit the reaction.

To prove that the intermediately formed organo-zinc species **B** was present, the intermediate was quenched with iodine and the corresponding *E*- and *Z*-vinyl-iodide species could be isolated (see ESI†). Also an *in situ* Negishi coupling of the organo-zinc species **B** with an aryl halide was performed. For this purpose, the intermediates of type **B** generated from the substrates **4a**, **4b** and **4c** were treated with the corresponding aryl iodide (Ar-I) in the presence of a Pd(0)-catalyst. After complete conversion of the alkyne, the alkenes **9a**, **9b** and **9c** were formed (Scheme 3) and in all three cases the yields of the products of type **9** were in the same range as those obtained after a work-up of the reaction mixture without the second step (compare to Table 1).

When product **6a** was treated with iodobenzene and Pd(PPh₃)₄ as a catalyst, no conversion was observed, thereby excluding a Heck-type reaction and verifying the presence of the proposed organo-zinc intermediate **B**.

In conclusion, we have presented a very mild method for the CH-activation of tetrahydrofuran and the regioselective addition to alkynes. While ester functionalised alkynes led to *E/Z*-isomerisation, the application of 1,3-dynes generated the desired adducts with excellent stereoselectivity. The application of an *in situ* Negishi coupling generated the tetrasubstituted alkenes in overall good yields and proved the existence of organo-zinc intermediates.

Notes and references

- For selected recent reviews, see: (a) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (b) J. J. Mousseau and A. B. Charette, *Acc. Chem. Res.*, 2013, **46**, 412; (c) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886.
- (a) X. Sui, R. Zhu and Z. Gu, *Synlett*, 2013, 2023. See also: (b) M. Catellani, E. Motti and N. Della Cá, *Acc. Chem. Res.*, 2008, **41**, 1512; (c) H. Liu, M. El-Salfiti, D. I. Chai, J. Auffret and M. Lautens, *Org. Lett.*, 2012, **14**, 3648; (d) H. Liu, M. El-Salfiti and M. Lautens, *Angew. Chem., Int. Ed.*, 2012, **51**, 9846.
- (a) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Kohn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc.*, 2011, **133**, 19298; (b) N. Hofmann and L. Ackermann, *J. Am. Chem. Soc.*, 2013, **135**, 5877; (c) F. Juliá-Hernández, M. Simonetti and I. Larrosa, *Angew. Chem., Int. Ed.*, 2013, **52**, 11458; (d) C.-L. Ciana,



R. J. Phipps, J. R. Brandt, F.-M. Meyer and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 458; (e) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 463; (f) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **329**, 1593.

4 (a) J. Zhao, W. Zhou, J. Han, G. Li and Y. Pan, *Tetrahedron Lett.*, 2013, **54**, 6507; (b) D. Liu, C. Liu, H. Li and A. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 4453; (c) P. Pal Singh, S. Gudup, S. Ambala, U. Singh, S. Dadhwal, B. Singh, S. D. Sawant and R. A. Vishwakarma, *Chem. Commun.*, 2011, 5852; (d) G. S. Kumar, B. Pieber, K. R. Reddy and C. O. Kappe, *Chem. – Eur. J.*, 2012, **18**, 6124.

5 (a) G. Hilt, P. Bolze and K. Harms, *Chem. – Eur. J.*, 2007, **13**, 4312; (b) G. Hilt, P. Bolze, M. Heitbaum, K. Hasse, K. Harms and W. Massa, *Adv. Synth. Catal.*, 2007, **349**, 2018; (c) F. Pünner and G. Hilt, *Eur. J. Org. Chem.*, 2013, 5580.

6 (a) A. Miersch, K. Harms and G. Hilt, *Chem. Commun.*, 2014, **50**, 542; (b) A. Miersch, C. Kohlmeyer and G. Hilt, *Synthesis*, 2013, 3228; (c) A. Miersch and G. Hilt, *Chem. – Eur. J.*, 2012, **18**, 9798.

7 (a) G. Hilt, C. Hengst and W. Hess, *Eur. J. Org. Chem.*, 2008, 2293; (b) G. Hilt, W. Hess, T. Vogler and C. Hengst, *J. Organomet. Chem.*, 2005, **690**, 5170.

8 A. Krasovskiy, V. Malakhov, A. Gavryushin and P. Knochel, *Angew. Chem., Int. Ed.*, 2006, **45**, 6040.

9 The role of the iron additive for the increased yield of the products **6l–6o** remains unclear.