OH-Directed Alkynylation of 2-Vinylphenols with Ethynyl Benziodoxolones: A Fast Access to Terminal 1,3-Enynes**

Peter Finkbeiner, Ulrich Kloeckner, and Boris J. Nachtsheim*

Abstract: The first direct alkynylation of 2-vinylphenols was developed. The rationally optimized hypervalent iodine reagent TIPS-EBX* in combination with $[(Cp*RhCl_2)_2]$ as a C-H-activating transition metal catalyst enables the construction of a variety of highly substituted 1,3-enynes in high yields of up to 98%. This novel C-H activation method shows excellent chemoselectivity and exclusive (Z)-stereoselectivity, and it is also remarkably mild and tolerates a variety of functional groups. Furthermore, synthetic modifications of the resulting 1,3-enynes were demonstrated. To our knowledge, this is the first example for an OH-directed C-H alkynylation with hypervalent iodine reagents.

Transition-metal-catalyzed C-H activation is an efficient approach for the construction of molecular complexity from barely substituted precursors.^[1] The direct alkynylation of (hetero)aryl and olefinic C-H bonds is of particular interest because the resulting (hetero)aryl alkynes and 1,3-enynes are privileged structural motifs in a variety of biological active compounds and single-emitting components.^[2-4] Furthermore, they are valuable precursors for the synthesis of a variety of carbo- and heterocycles.^[5-7] Key to success for an efficient C-H bond activation is the existence of a metal-coordinating directing group, under the guidance of which only one particular C-H bond is activated in a highly regioselective manner.^[8] For direct C-H alkynylation reactions, this has led to efficient protocols for the chemoselective synthesis of 2alkynyl substituted heteroarenes.^[9] For the direct alkynylation of aromatic carbocycles or alkenes, additional nitrogencontaining directing groups such as amides, pyridines, pyrazoles, oxazolines, or N-oxides have frequently been used.^[10] In general, a free hydroxyl functionality as part of a phenol or naphthol ring is unsuitable as a directing group in alkynylations. The OH group can act as a nucleophile and directly react with the electrophilic alkyne reagent or further react in a cyclization cascade after initial C-H alkynylation to give oxygen-containing hetero- or spirocycles.[11,12] In a seminal study, Yamaguchi and co-workers developed the first, and so far only, protocol for the direct ortho-alkynylation of elec-

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tron-rich phenols by using $GaCl_3$ as the catalyst and triethylsilylchloroethyne as the electrophilic alkyne transfer reagent (Scheme 1 a).^[13] However, despite its importance, this method has major drawbacks, such as limited substrate scope

a) Yamaguchi and co-workers, 2002



Scheme 1. Phenol alkynylations. DIPEA = N, N-diisopropylethylamine, TIPS = triisopropylsilyl.

and very harsh reaction conditions (160 °C, *n*BuLi as a base). Furthermore, this reaction must be seen as a Lewis acid mediated addition/elimination cascade rather than a true OH-directed alkynylation reaction with terminal alkynes under C–H-activating conditions. To the best of our knowledge such a reaction has not been described so far.

Hypervalent alkynyl iodine compounds are versatile electrophilic reagents that have recently been applied in a variety of alkyne transfer reactions.^[14] In particular, 1silylethynyl-1,2-benziodoxol-3(1H)-ones (silyl-EBX) have been utilized in such transformations owing to their fast and reliable synthesis and a well-balanced stability/reactivity ratio.^[15] Very recently, there have been reports of their use in direct alkynylation reactions under C-H-activating conditions with transition metal catalysts, in particular Rh^{III}.^[16] Herein, we report their application in a rhodium(III)-catalyzed direct C-H alkynylation of 2-vinylphenols with perfect stereo- and chemoselectivity (Scheme 1b). This reaction affords fast and efficient access to highly substituted 1,3envnes and,^[17] to the best of our knowledge, is a very rare example of an OH-directed alkynylation under C-H-activating conditions.

Initially, we investigated the oxidative coupling of 2-(1methylvinyl)phenol **1a** with TIPS-EBX. When **1a** was treated with $[(Cp*RhCl_2)_2]$ as a C-H-activating transition metal catalyst and AgOAc, **2a** was isolated in 59% yield (Table 1,

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[a] Reactions were conducted with 0.2 mmol of **1a** and 0.24 mmol of the iodane. [b] 10 mol % AgOAc was added. [c] 1.5 equiv of base were added. [d] Reaction was performed with 1 mol % of the Rh^{III} catalyst.

[e] DCE = 1,2-dichloroethane, DMF = N,N-dimethylformamide.

entry 1). By adding DIPEA as a base, the reaction could be significantly accelerated and even performed at room temperature to give **2a** in 65% yield (Table 1, entry 2). We then realized that the reaction proceeded even in the absence of a cocatalyst to yield **2a** in 75% (Table 1, entry 3).

However, we still detected significant side-product formation by NMR analysis of the crude product. The two most abundant side products were identified as being the benzoic acid esters **3** (4% yield) and **4** (5% yield). The latter is the result of a subsequent OH alkynylation followed by hydrolysis of the triple bond (Figure 1).^[11] Neither the corresponding *ortho*-alkynylated phenol derivative nor the corresponding *E*-configured stereoisomer could be detected, which demonstrates the perfect chemo- and stereoselectivity of this chelate-assisted transformation. On performing an intense literature search for rhodium(III)-mediated C–H insertions, we found a report by Maitlis and co-workers from 1987. It describes the formation of a cyclometallated rhodium



Figure 1. Analysis of the side products.

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benzoate (5a) through an ortho C-H insertion of a (Rh^{III}Cp*) complex into benzoic acid.^[18] In our reaction, this pathway could lead to the undesired formation of 5b from 2-iodo benzoic acid, which is formed from TIPS-EBX after alkyne transfer. To prevent insertion of the Rh^{III} catalyst into the H6-C6 bond of 2-iodo benzoic acid and to sterically hinder the formation of 3, we modified the alkynyl benziodoxolone and synthesized the ortho-CH₃-substituted derivative TIPS-EBX*. Furthermore, Waser and co-workers reported TIPS-EBX* to be significantly more reactive in gold(I)-catalyzed alkynylations of indoles than TIPS-EBX.^[15b] To our delight, this change led to the formation of 2a in an excellent yield of 91% (Table 1, entry 4). Decreasing the catalyst loading to 1 mol% (Table 1, entry 5) had a negative impact on product yield (81%). Finally, a variety of solvents were investigated, however, this did not lead to further improvement of the reaction performance (Table 1, entries 6-8).

With the optimal reaction conditions in hand, we investigated the substrate scope of this transformation (Scheme 2). Electron-poor 2-(1-methylvinyl)phenols, in particular 4- and 5-halogen-substituted derivatives, as well as a 4-nitro-substituted derivative, reacted well to give products 2b-2f in excellent yield (86-93%). 4,6-Dichloro-substituted 2-(1methylvinyl)phenol showed outstanding reactivity and gave 2g in 98% yield. Electron-rich derivatives bearing a 4-methyl or a 4-methoxy substituent gave compounds 2h and 2i in 92% and 87% yield, respectively. We then changed the substitution pattern of the exocyclic double bond. When 2-vinylphenol $(R^2 = H)$ was used as the substrate, the reaction was sluggish and the desired product 2j could only be isolated in a moderate yield of 40% after 72 h. However, introducing an ethyl side chain restored reactivity to give 2k in 78% yield. A variety of 2-(1-phenylvinyl)phenols ($R^2 = Ph$) reacted well to give compounds 21-2n in 77-84% yield. Next, we varied the aryl group of the 1-arylvinyl side chain (20-2s). 4-Fluorophenyl and 3,5-bis(trifluoromethyl)phenyl substituents gave 20 and 2p in 71% and 90% yield, respectively. For 2p, the solvent was changed from acetonitrile to 1,2-dichloroethane because of solubility problems. The same change was necessary for the 4-cyanophenyl derivative, which finally gave **2q** in 78% yield. Heterocyclic substituents, such as benzo[d]-[1,3]dioxoles and 2,5-dimethyl thiophenes, gave the desired products 2r and 2s in 77% and 95% yield, respectively. When a β-alkyl substituent was introduced, no alkynylated product (2t) was observed. Finally, we showed that the 2-hydroxy functionality is crucial for reactivity. 3-(1-methylvinyl)phenol does not give the desired alkynylated product 2u. O-Methylation of 2-(1-methylvinyl)phenol also inhibits this transformation (2v) completely. In all of these cases (2t-2v), no conversion into the corresponding products was observed and significant amounts (>80%) of the starting materials were recovered.

Finally, we investigated the principle reactivity of the obtained 1,3-enynes (Scheme 3). Compound **2a** was investigated as a model substrate. Treating **2a** with the cationic Au^I catalyst [(MeCN)AuPPh₃]SbF₆ led to 6-*exo-dig* cyclization to give 2*H*-chromene **6** in 84% yield. For further derivatization of the triple bond, protection of the free OH group was necessary. Methylation of **2a** followed by removal of the TIPS

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Scheme 2. Reactions were carried out at room temperature with 0.2 mmol 1, 0.24 mmol TIPS-EBX*, 0.30 mmol Hünig's base, and 2.5 mol% $[(Cp*RhCl_2)_2]$ in 2 mL of MeCN. Cp*= pentamethylcyclopentadiene. [b] The reaction was performed in 1,2-dichlorethane as solvent.

protecting group yielded the terminal 1,3-enyne **7** in 86% yield. Starting from this intermediate, Sonogashira coupling under standard conditions with iodobenzene gave bis-(aryl)enyne **8** in 88% yield. Copper-catalyzed Huisgen-type cycloaddition gave triazole **9** in 72% yield and reaction with the Schwartz reagent and NBS gave the corresponding diene **10** in 70% yield.

Considering mechanistic studies and proposals by other groups working in the field of rhodium(III)-catalyzed C–H bond activation, we propose a mechanism for the underlying



Scheme 3. Derivatization of model compound **2a**. TBAF = tetra-*n*-butyl-ammonium fluoride, NBS = *N*-bromosuccinimide.

reaction as shown in Scheme 4.^[12a,b,16a,d] Base-assisted ligand exchange with **1a** followed by C–H bond activation through an addition/elimination cascade leads to the formation of rhodacycle **A**. Insertion of the triple bond adjacent to the hypervalent iodine of TIPS-EBX* gives rhodacycle **B**, which undergoes elimination of 2-iodo-6-methylbenzoate to give the rhodium vinylidene complex **C**. 1,2-Migration of the vinylic moiety followed by a ligand exchange finally releases the desired product **2a** and regenerates the rhodium(III) catalyst.

In summary, we have developed a mild and highly effective method for the electrophilic alkynylation of 2vinylphenols by using modified TIPS-EBX* under rhodium-(III) catalysis. This reaction merges an OH-directed reaction with an electrophilic alkyne transfer reagent and is characterized by mild reaction conditions and ease of preparation. The corresponding products are obtained in excellent yields



Scheme 4. Proposed reaction mechanism.

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> of up to 98% and with perfect (Z)-stereoselectivity. Moreover, products of an undesired second alkynylation of the alkene or aromatic moiety were not observed. Finally, modification of the resulting valuable 1,3-enynes was successfully demonstrated in a variety of commonly applied reactions, thus demonstrating the synthetic value of this newly found reaction.

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- Selected reviews: a) N. Kuhl, N. Schröder, F. Glorius, Adv. Synth. Catal. 2014, 356, 1443; b) D. Y. K. Chen, S. W. Youn, Chem. Eur. J. 2012, 18, 9452; c) D. A. Colby, A. S. Tsai, R. G. Bergman, J. A. Ellman, Acc. Chem. Res. 2012, 45, 814; d) G. Song, F. Wang, X. Li, Chem. Soc. Rev. 2012, 41, 3651; e) L. Ackermann, Chem. Rev. 2011, 111, 1315; f) K. Hirano, M. Miura, Synlett 2011, 294; g) D. A. Colby, R. G. Bergman, J. A. Ellman, Chem. Rev. 2010, 110, 624; h) T. W. Lyons, M. S. Sanford, Chem. Rev. 2010, 110, 1147.
- [2] A review: a) M. El-Shazly, B. D. Barve, M. Korinek, J. R. Liou, D. W. Chuang, Y. B. Cheng, M. F. Hou, J. J. Wang, Y. C. Wu, F. R. Chang, *Curr. Top. Med. Chem.* **2014**, *14*, 1076.
- [3] Recent examples of 1,3-enynes as core structural motifs in biological active compounds: a) S. C. N. Queiroz, C. L. Cantrell, S. O. Duke, D. E. Wedge, V. K. Nandula, R. M. Moraes, A. L. Cerdeira, J. Agric. Food Chem. 2012, 60, 5893; b) Y.-H. Hsieh, F.-H. Chu, Y.-S. Wang, S.-C. Chien, S.-T. Chang, J.-F. Shaw, C.-Y. Chen, W.-W. Hsiao, Y.-H. Kuo, S.-Y. Wang, J. Agric. Food Chem. 2010, 58, 3153; c) H. M. Sheldrake, C. Jamieson, S. I. Pascu, J. W. Burton, Org. Biomol. Chem. 2009, 7, 238; d) S. F. Wnuk, E. Lewandowska, P. R. Sacasa, L. N. Crain, J. Zhang, R. T. Borchardt, E. De Clercq, J. Med. Chem. 2004, 47, 5251; e) N. El-Jaber, A. Estévez-Braun, A. G. Ravelo, O. Muñoz-Muñoz, A. Rodríguez-Afonso, J. R. Murguia, J. Nat. Prod. 2003, 66, 722; f) A. Fontana, G. d'Ippolito, L. D'Souza, E. Mollo, P. S. Parameswaram, G. Cimino, J. Nat. Prod. 2000, 64, 131.
- [4] Recent examples of 1,3-enynes in optoelectronic devices:
 a) O. S. Morozov, A. F. Asachenko, D. V. Antonov, V. S. Kochurov, D. Y. Paraschuk, M. S. Nechaev, *Adv. Synth. Catal.* 2014, 356, 2671; b) Y. Liu, M. Nishiura, Y. Wang, Z. Hou, *J. Am. Chem. Soc.* 2006, 128, 5592.
- [5] V. Michelet, P. Y. Toullec, J. P. Genêt, Angew. Chem. Int. Ed. 2008, 47, 4268; Angew. Chem. 2008, 120, 4338.
- [6] a) A. Nishimura, E. Tamai, M. Ohashi, S. Ogoshi, *Chem. Eur. J.* 2014, 20, 6613; b) Z. J. Yang, B. L. Hu, C. L. Deng, X. G. Zhang, *Adv. Synth. Catal.* 2014, 356, 1962; c) P. Y. Tseng, S. C. Chuang, *Adv. Synth. Catal.* 2013, 355, 2165; d) D. Kang, J. Kim, S. Oh, P. H. Lee, *Org. Lett.* 2012, 14, 5636; e) J. Xu, Y. Wang, D. J. Burton, *Org. Lett.* 2006, 8, 2555; f) Y. Wang, J. Xu, D. J. Burton,

J. Org. Chem. 2006, 71, 7780; g) Y. Wang, D. J. Burton, Org. Lett. 2006, 8, 5295.

- [7] a) E. Li, W. Yao, X. Xie, C. Wang, Y. Shao, Y. Li, Org. Biomol. Chem. 2012, 10, 2960; b) M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, Angew. Chem. Int. Ed. 2011, 50, 1338; Angew. Chem. 2011, 123, 1374.
- [8] Reviews on directing-group-assisted C-H activation: a) F. Zhang, D. R. Spring, Chem. Soc. Rev. 2014, 43, 6906; b) S. De Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, Adv. Synth. Catal. 2014, 356, 1461; c) G. Yan, A. J. Borah, M. Yang, Adv. Synth. Catal. 2014, 356, 2375; d) L. Ackermann, Acc. Chem. Res. 2014, 47, 281; e) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, Chem. Rev. 2012, 112, 5879; f) V. Ritleng, C. Sirlin, M. Pfeffer, Chem. Rev. 2002, 102, 1731.
- [9] For a review see: A. S. Dudnik, V. Gevorgyan, Angew. Chem. Int. Ed. 2010, 49, 2096; Angew. Chem. 2010, 122, 2140.
- [10] a) Y. H. Xu, Q. C. Zhang, T. He, F. F. Meng, T. P. Loh, Adv. Synth. Catal. 2014, 356, 1539; b) Y. Ano, M. Tobisu, N. Chatani, Synlett 2012, 23, 2763; c) Y. Ano, M. Tobisu, N. Chatani, Org. Lett. 2012, 14, 354; d) M. Tobisu, Y. Ano, N. Chatani, Org. Lett. 2009, 11, 3250.
- [11] Direct alkynylation of phenols with alkynyl iodonium salts: S. Nikas, N. Rodios, A. Varvoglis, *Molecules* 2000, 5, 1182.
- [12] a) A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas, M. Gulías, J. Am. Chem. Soc. 2014, 136, 7607; b) A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas, M. Gulías, J. Am. Chem. Soc. 2014, 136, 834; c) D. J. Burns, H. W. Lam, Angew. Chem. Int. Ed. 2014, 53, 9931; Angew. Chem. 2014, 126, 10089; d) J. Nan, Z. Zuo, L. Luo, L. Bai, H. Zheng, Y. Yuan, J. Liu, X. Luan, Y. Wang, J. Am. Chem. Soc. 2013, 135, 17306; e) S. Wang, P. Li, L. Yu, L. Wang, Org. Lett. 2011, 13, 5968; f) S. Nicolai, J. Waser, Org. Lett. 2011, 13, 6324.
- [13] K. Kobayashi, M. Arisawa, M. Yamaguchi, J. Am. Chem. Soc. 2002, 124, 8528.
- [14] Reviews: a) J. P. Brand, J. Waser, *Chem. Soc. Rev.* 2012, *41*, 4165;
 b) J. P. Brand, D. F. Gonzalez, S. Nicolai, J. Waser, *Chem. Commun.* 2011, *47*, 102.
- [15] EBX salts can be used in Au- and Pd-catalyzed alkynylations of heterocycles: a) J. P. Brand, J. Waser, Org. Lett. 2012, 14, 744; b) J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, Chem. Eur. J. 2012, 18, 5655; c) J. P. Brand, J. Charpentier, J. Waser, Angew. Chem. Int. Ed. 2009, 48, 9346; Angew. Chem. 2009, 121, 9510; d) S. Nicolai, S. Erard, D. F. González, J. Waser, Org. Lett. 2010, 12, 384.
- [16] Recent examples of Rh- and Ir-catalyzed C-H alkynylations with EBX derivatives: a) C. Feng, T.-P. Loh, *Angew. Chem. Int. Ed.* **2014**, *53*, 2722; *Angew. Chem.* **2014**, *126*, 2760; b) F. Xie, Z. Qi, S. Yu, X. Li, *J. Am. Chem. Soc.* **2014**, *136*, 4780; c) C. Feng, D. Feng, T.-P. Loh, *Chem. Commun.* **2014**, *50*, 9865; d) K. D. Collins, F. Lied, F. Glorius, *Chem. Commun.* **2014**, *50*, 4459; e) J. Jeong, P. Patel, H. Hwang, S. Chang, *Org. Lett.* **2014**, *16*, 4598.
- [17] A recent review on the synthesis of enynes: R. Chinchilla, C. Nájera, *Chem. Rev.* 2014, 114, 1783.
- [18] J. M. Kisenyi, G. J. Sunley, J. A. Cabeza, A. J. Smith, H. Adams, N. J. Salt, P. M. Maitlis, J. Chem. Soc. Dalton Trans. 1987, 2459.

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C—H Activation

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OH-Directed Alkynylation of 2-Vinylphenols with Ethynyl Benziodoxolones: A Fast Access to Terminal 1,3-Enynes

TIPS and tricks for alkynylation: The first direct alkynylation of 2-vinylphenols was developed. The rationally optimized hypervalent iodine reagent TIPS-EBX* (see scheme)in combination with $[(Cp*RhCl_2)_2]$ as a C-H-activating transi-

tion metal catalyst enables the construction of a variety of highly substituted 1,3enynes in high yield under mild conditions and with excellent chemo- and stereoselectivity.