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Stereodivergent Zinc-Mediated Three-Component Synthesis of Tri- and Tetrasubstituted Alkenes

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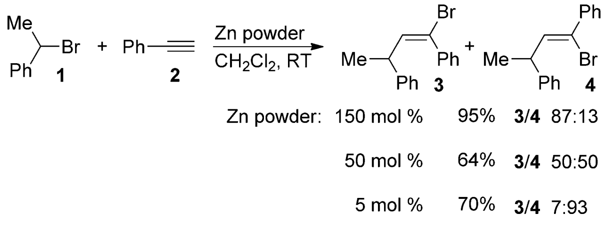
Dedicated to Karl-Heinz Dominicus on the occasion of his 70th birthday

The stereoselective synthesis of disubstituted olefins can be realized by a vast number of synthetic methods. Several named reactions for the selective synthesis of *E*- or *Z*-configured alkenes are available underlining the high synthetic value of this functional group.[1] The number of practical methods for the straightforward generation of tri- and tetrasubstituted double bonds is considerably lower. Among those transformations are several transition-metal-mediated additions of organometallic species to alkynes followed by cross-coupling reactions.[2]

Over the last couple of years, some Lewis acid catalyzed synthetic methods appeared in the literature, in which benzylic alcohols or halides were reacted with alkynes for the synthesis of halide-substituted alkenes.[3] In the course of our ongoing investigations into atom-economic transformations for the generation of carbon–carbon bonds utilizing low-valent cobalt complexes, 1-bromoethylbenzene (**1**) and phenylacetylene (**2**) were reacted under reductive conditions to regioselectively generate vinyl bromides **3** and **4**.[4] We soon realized that these products were formed even in the absence of the cobalt catalysts, and that zinc powder alone was sufficient to initiate this transformation (Scheme 1).[5,6]

Herein, we report the regiodiverse synthesis of alkenyl bromides from benzylic bromides and terminal as well as internal alkynes mediated by zinc powder and palladium-catalyzed follow-up transformations. Surprisingly, the amount of zinc powder added is closely related to the stereoselectivity of the vinyl bromide formed. The use of 150 mol % of zinc powder generated the *E*-isomer **3** as main product within 2 h reaction time, whereas utilizing catalytic amounts of zinc powder (5 mol %) led to the predominant formation of the corresponding *Z*-isomer **4** after 48 h reaction time at ambient temperature. Furthermore, we realized that under diverse conditions, utilizing varying amounts of zinc powder the *E*-isomer is the primary product (Table 1).



Scheme 1. Zinc-initiated addition of benzylic bromide to phenylacetylene.

Table 1. Time-dependent generation of *E*/*Z* vinyl bromides **3** and **4**.

Zn [mol %]	*t* [h]	Yield [%] (ratio **3**/**4**)
150	2	87 (88:12)
150	48	85 (87:13)
100	2	84 (82:18)
100	48	78 (51:49)
50	2	95 (81:19)
50	48	64 (50:50)
10	2	83 (75:25)
10	48	62 (7:93)
5	2	78 (77:23)
5	48	70 (7:93)

Even in the presence of one equivalent zinc powder, the isomerization to the *Z*-isomer **4** was observed after 48 h reaction time. However, when 150 mol % were used, this isomerization stopped, indicating that the excess zinc powder applied removed the initiator for the isomerization from the reaction mixture (see below). On the other hand, when catalytic amounts of zinc powder were applied, the isomerization to the *Z*-isomer **4** reached the maximum (7:93) and did not change when the reaction time was prolonged.

Another important parameter for the synthesis of **3** utilizing 150 mol % of zinc powder is the amount of **1** applied. The reaction of **2** with one equivalent of **1** led to **3** in only 68 %. The application of a slight excess of **1** (1.2 equiv) increased the yield already to 80 %, whereas the best results were obtained when 1.5 equivalents of **1** were used. In this case, **3** could be isolated in 95 % yield. However, larger excess of **1** did not further improve the yield. Although most reactions of organozinc species were performed in THF or other ethereal solvents, dichloromethane was identified to be the solvent of choice for the desired conversion.[7]

These findings prompted us to investigate the stereodivergent synthesis of vinyl bromides of type **6** and **7** utilizing

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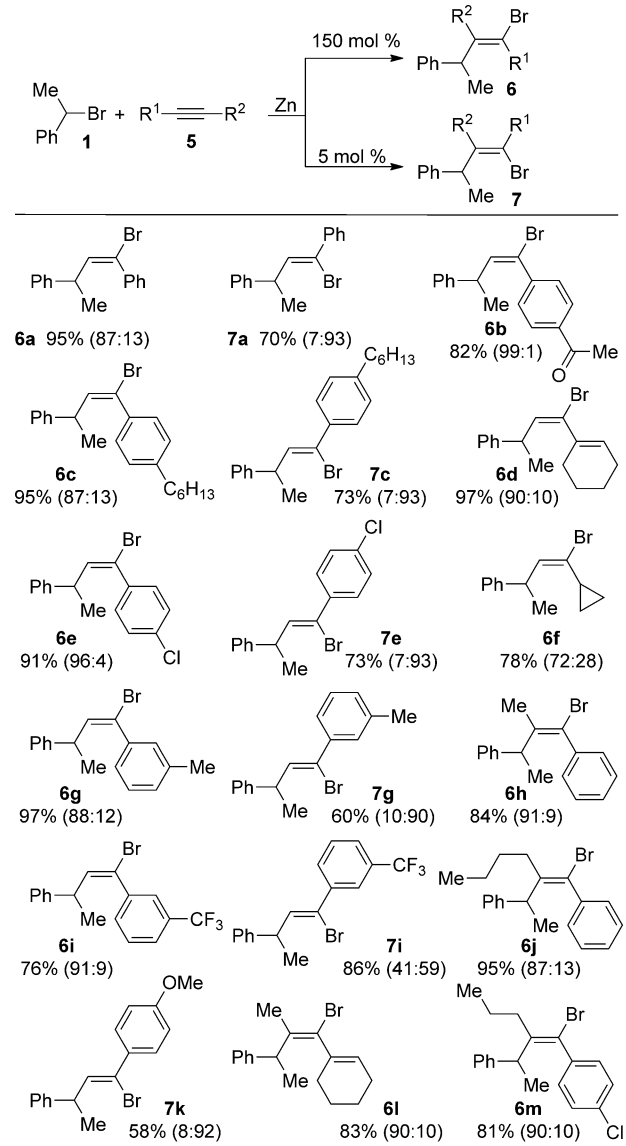
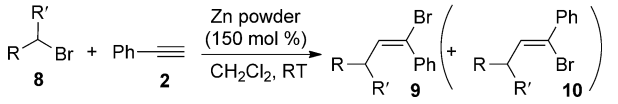
150 mol % zinc powder for the predominant formation of products of type **6** after 2 h reaction time. Complementary to these reactions, the application of catalytic amounts of zinc powder (5 mol %) led to the formation of products of type **7** after a prolonged reaction time of 48 h (Scheme 2).



Scheme 2. Zinc-initiated addition of benzylic bromide to alkynes.

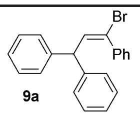
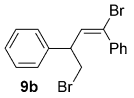
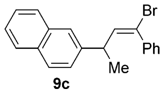
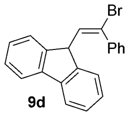
For terminal alkynes ($R^1 = H$), the complementary procedures gave good-to-excellent yields and *E*/*Z*-selectivities mostly in the range 90:10 in favor of the respective double-bond configuration. Also, a wide range of functional groups were tolerated, and electron-donating as well as electron-withdrawing groups were well accepted and gave good results. Noteworthy, internal alkynes could be applied with good success for the synthesis of products of type **6**, whereas the corresponding products of type **7** could not be obtained with comparable *Z*-selectivity as for terminal alkynes. Nevertheless, the application of internal alkynes generated the tetrasubstituted vinyl bromides **6h**,**j** and **6l**,**m** in good yields and good *E*-selectivities. Also, enynes could be applied, and the 1,3-dienyl bromides **6d** and **6l** were obtained. The application of cyclopropyl acetylene gave product **6f** in a good yield of 78 %, and more importantly, the cyclopropyl moiety serves as radical probe and remained unchanged, indicating that radical intermediates are most likely not involved in the reaction mechanism.

The zinc-mediated synthesis of vinyl bromides was then applied towards other benzylic bromides (**8**) to investigate the scope of the reaction for educts of type **8** (Scheme 3). In this series of experiments, only the reaction conditions for the zinc-mediated synthesis of the *E*-isomer **9** utilizing 150 mol % of zinc powder was applied, because this protocol gave the higher yields in the previous investigation. The results for these reactions are summarized in Table 2.



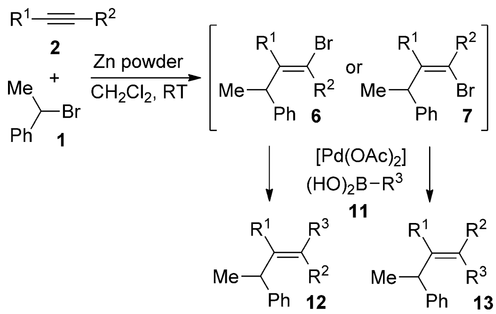
Scheme 3. Zinc-mediated synthesis of vinyl bromides **9** utilizing other benzylic bromides.

Table 2. Results of the zinc-mediated synthesis of vinyl bromides **9**.

Entry	Product	Yield [%] (**9**:**10**)
1	 **9a**	44 (96:4)
2	 **9b**	60 (90:10)
3	 **9c**	79 (74:26)
4	 **9d**	83 (56:44)

Benzyl bromide as well as benzyl iodide ($R' = H$) gave the desired products of type **9** only in a low yield, whereas a considerable amount of the Wurtz coupling product 1,2-diphenylethane was obtained. Other benzylic bromides could be applied with better success. Remarkably, the use of (1,2-dibromoethyl)benzene (Table 2, entry 2) led to the functionalization of the benzylic bromide, whereas the homobenzylic bromide stayed intact. Overall, the application of other benzylic bromides was possible, but either yields or selectivities were not as high as with **1**.

The vinyl bromides of type **6** and **7** were then applied in palladium-catalyzed Suzuki cross-coupling reactions utilizing boronic acids **11** for the formation of the tri- ($R^1 = H$) and tetrasubstituted alkenes **12** and **13** (Scheme 4). Unlike other protocols, we were interested to realize this two-step three-component reaction sequence as a one-pot procedure without isolating the intermediates of type **6** and **7**.[8]



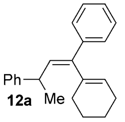
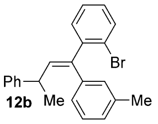
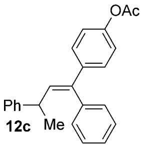
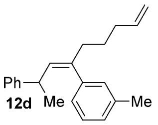
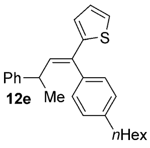
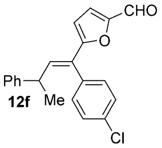
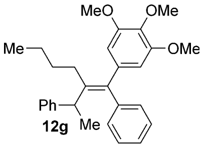
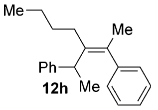
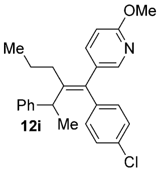
Scheme 4. Zinc-initiated three-component one-pot synthesis of tri- and tetrasubstituted alkenes.

Therefore, the intermediates were subjected to Suzuki cross-coupling conditions applying boronic acids (**11**) as third component. The results of these transformations are summarized in Table 3.

In two cases, the zinc-mediated reactions were performed with 5 mol% of zinc powder (Table 3, entries 4 and 8). In these reactions, the alternative products **13c** and **13f** were obtained in good yields and excellent *E*/*Z*-selectivities. Noteworthy, the reaction sequence could be realized in a one-pot procedure and, to our delight, the yields remained generally good-to-excellent. Many functional groups, heterocycles, and additional double bonds were tolerated enabling the synthesis of a broad variety of different molecular architectures. Eventually, the use of internal alkynes (Table 3, entries 9–11) led to the formation of tetrasubstituted alkenes. Remarkably, not only aromatic, but also aliphatic boronic acids could be applied in the Suzuki cross-coupling (Table 3, entries 5 and 10).

From a mechanistic point of view, the addition of the benzylic bromide to the alkyne could follow a pathway involving an organozinc species leading to the *Z*-configured product. After the *cis*-addition to the alkyne, the vinyl zinc bromide must undergo regeneration of the benzylic zinc bromide species upon reaction with **1**. Quite contrary, we observe the formation of **3** as the primary product, which suggests that the reaction proceeds through addition of benzylic cations to the alkyne as proposed by Ji and co-workers and Liu and co-workers.[3a,e] When the benzylic organozinc species underwent a Wurtz reaction, zinc bromide was formed.[9] Indeed, the reaction of **1** and **2** can also be catalyzed by commercially available $ZnBr_2$ (10 mol%). However, the reaction was less effective (66% yield), but gave the *Z*-isomer **4** in identical selectivity. Zinc bromide was also proposed to be responsible for the formation of HBr, which is causing the isomerization of the primarily formed *E*-vinyl bromide to the *Z*-vinyl bromide **4**. Indeed, HBr was detected in the gas phase and could have been formed by $ZnBr_2$-induced elimination of HBr from **1**. The HBr-induced isomerization was inhibited in control experiments, in which only the products of type **6** were obtained in the presence of NaH or cyclohexene, and no isomerization occurred. Also, when phenyl silane was added as additive, benzene could be detected by GC indicating the formation of HBr in situ.

Table 3. Results of the zinc-mediated addition/palladium-catalyzed cross-coupling reaction sequence.

Entry	R^1; R^2; R^3	Product	Yield [%] (**12**:**13**)
1	$R^1 = H$ R^2 = cyclohexenyl $R^3 = C_6H_5$		82 (91:9)
2	$R^1 = H$ R^2 = 3-MeC_6H_4 R^3 = 2-BrC_6H_4		81 (95:5)
3 4	$R^1 = H$ $R^2 = C_6H_5$ R^3 = 4-$AcOC_6H_4$		99 (98:2) 91 (5:95)
5	$R^1 = H$ R^2 = 3-MeC_6H_4 $R^3 = (CH_2)_3CH{=}CH_2$		41 (99:1)
6	$R^1 = H$ R^2 = 4-$HexC_6H_4$ R^3 = 2-C_4H_3S		80 (94:6)
7 8	$R^1 = H$ R^2 = 4-ClC_6H_4 R^3 = 5-(2-$CHOC_4H_2$)		91 (93:7) 74 (7:93)
9	R^1 = *n*Bu $R^2 = C_6H_5$ R^3 = (3,4,5-$MeO)_3C_6H_2$		62[a] (98:2)
10	R^1 = *n*Bu $R^2 = C_6H_5$ R^3 = Me		84 (87:13)
11	R^1 = *n*Pr R^2 = 4-ClC_6H_4 R^3 = 5-(2-$MeOC_5H_2N$)		96[a] (94:6)

[a] The product contains an unidentified impurity, which could not be removed by simple column chromatography.

When 150 mol% zinc powder was used, HBr was proposed to react with the excess zinc and was thereby removed from the reaction mixture, inhibiting the isomerization.

In conclusion, we have presented a zinc-mediated procedure for the synthesis of vinyl bromides, in which the stereochemistry of the double bond was dependent on the amount of zinc applied. The vinyl bromides of type **6** and **7** could then be used in a one-pot protocol for the three-component assembly of tri- and tetrasubstituted alkenes in good yields and good *E*/*Z*-selectivities utilizing a Suzuki cross-coupling of the vinyl bromides with boronic acids. The high functional-group tolerance and the flexibility of the synthetic approach are remarkable and allow the synthesis of more complex alkenes in a straightforward fashion.

Experimental Section

Representative procedure for the synthesis of **6a** and **12c** (Scheme 2, product **6a** and Table 3, entry 3): In a Schlenk tube, 1-bromoethylbenzene (**1**; 140 mg, 0.75 mmol, 1.5 equiv) and phenylacetylene (**2**; 51 mg, 0.50 mmol, 1 equiv) were dissolved under argon atmosphere in anhydrous dichloromethane (1 mL), and zinc powder (48 mg, 0.75 mmol, 150 mol %) were added. The reaction mixture was stirred for 2 h at RT and filtered over silica gel (pentane/diethyl ether 1:1). The solvent was removed and the residue was purified by column chromatography on silica gel (pentane). The product *E*-(1-bromobut-1-ene-1,3-diyl)dibenzene (**6a**) was obtained as colorless oil (137 mg, 0.48 mmol, 95 %, *E*/*Z* 87:13). ^{1}H NMR (CDCl$_3$, 300 MHz): δ=7.39–7.35 (m, 5H), 7.32–7.29 (m, 2H), 7.25–7.16 (m, 3H), 6.37 (d, J=10.7 Hz, 1H), 3.53 (dq, J=6.9, 10.8 Hz, 1H), 1.36 ppm (d, J=6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=144.6, 138.5, 128.8, 128.7, 128.6, 128.3, 126.8, 126.4, 119.8, 40.7, 22.0 ppm; IR (film): $\tilde{\nu}$=3059, 3027, 2966, 2926, 2869, 1601, 1491, 1444, 1373, 1015, 872, 764, 699, 543 cm^{-1}; MS (EI): m/z (%) 286 ([M^+], 5), 207 (83), 191 (54), 129 (100), 105 (31), 77 (27); HRMS (EI): m/z calcd for C$_{16}$H$_{15}$Br: 286.0357; found: 286.0348.

For the synthesis of **12c**, the intermediate **6a** was generated in situ as before. After complete conversion of the starting materials to **6a**, anhydrous THF (1 mL), anhydrous methanol (1 mL), potassium hydroxide (56 mg, 1.0 mmol, 2 equiv), 4-acetylphenylboronic acid (122 mg, 0.75 mmol, 1.5 equiv), triphenylphosphine (5 mg, 0.02 mmol, 4 mol %), and palladium(II) acetate (3 mg, 0.01 mmol, 2 mol %) were added. The reaction mixture was stirred for 16 h at 40 °C and then filtered over silica gel (diethyl ether). The solvent was removed, and the residue was purified by column chromatography over silica gel (pentane/diethyl ether 2:1). The product *E*-4-(1,3-diphenylbut-1-enyl)phenyl acetate (**12c**) was obtained as pale yellow oil (169 mg, 0.49 mmol, 99 %, *E*/*Z* 98:2). ^{1}H NMR (CDCl$_3$, 300 MHz): δ=7.84 (d, J=8.6 Hz, 2H), 7.45–7.37 (m, 3H), 7.30 (d, J=8.5 Hz, 4H), 7.23–7.17 (m, 5H), 6.34 (d, J=10.4 Hz, 1H), 3.63 (dq, J=6.9, 10.3 Hz, 1H), 2.57 (s, 3H), 1.41 ppm (d, J=6.9 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=197.6, 146.9, 145.7, 139.4, 139.3, 136.4, 135.6, 129.7, 128.6, 128.5, 128.2, 127.4, 127.3, 126.9, 126.2, 39.4, 26.5, 22.1 ppm; IR (film): $\tilde{\nu}$=3026, 2965, 2923, 2869, 1681, 1599, 1447, 1356, 1264, 837, 762, 699, 592 cm^{-1}; MS (EI): m/z (%) 342 ([M$^+$], 1), 326 (100), 311 (16), 283 (28), 205 (27), 165 (14); HRMS (EI): m/z calcd for C$_{24}$H$_{22}$O$_2$: 342.1620; found: 342.1611.

Keywords: alkenes · alkynes · boronic acids · palladium · zinc

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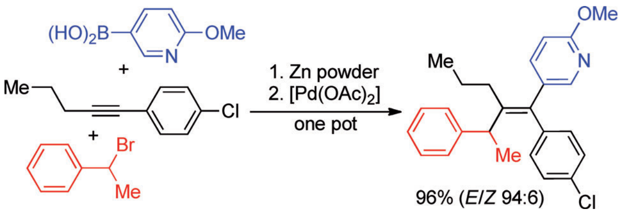

Zinc simple: The loading-dependent zinc-mediated addition of benzyl bromides to alkynes is the key step for the formation of vinyl bromides. In combination with a palladium-catalyzed Suzuki cross-coupling reaction with boronic acids tri- and tetrasubstituted alkenes were obtained in good yields and stereoselectivities in a one-pot protocol (see scheme).

Synthetic Methods

*A. Miersch, G. Hilt** .... ▮▮▮▮–▮▮▮▮

Stereodivergent Zinc-Mediated Three-Component Synthesis of Tri- and Tetrasubstituted Alkenes