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Highly Regio- and Stereoselective Synthesis of Tetrasubstituted Olefins by the Three-Component Tandem Reaction of Allylzinc Bromide, Acetylenic Sulfone, and Halohydrocarbon

Meihua Xie,* Jialiang Wang, Xiaoxia Gu, Ying Sun, and Shaowu Wang*

Anhui Key Laboratory of Functional Molecular Solids, Institute of Organic Chemistry, School of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui 241000, China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

gxmeihua@yahoo.com.cn; swwang@mail.ahnu.edu.cn

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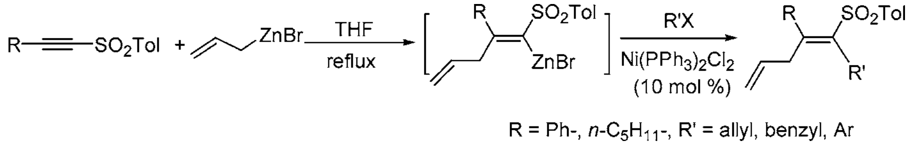
ABSTRACT



Tetrasubstituted olefins containing a 1,4-diene structural unit can be regio- and stereoselectively constructed in one pot by the allylzincation of acetylenic sulfones, followed by Negishi cross-coupling with halohydrocarbons in the presence of catalytic $Ni(PPh_3)_2Cl_2$.

Polysubstituted olefins are present in many naturally occurring biologically active compounds such as terpenoids, pheromones, etc. They are also key intermediates in a number of transformations leading to natural products and have remained an active area of research for organic chemists.[1] On the other hand, the sulfone group both activates the adjacent multiple carbon−carbon bonds and provides a useful functional group for further transformation by various desulfonylation methods.[2] Therefore stereodefined vinyl sulfones are important synthetic intermediates due to the presence of the carbon−carbon double bonds and the carbon−sulfur bonds. The synthesis of vinyl sulfones has been studied extensively.[3] However, reports on the synthesis of vinyl sulfones by carbometalation reaction are limited.[4]

Organozinc compounds are very useful and versatile reagents because of their high functional group compatibility and their excellent reactivity in the presence of an appropriate transition metal catalyst.[5,6c] Recently, nickel compounds used as catalysts for Negishi cross-coupling of the organozinc reagents with both unactivated secondary alkyl halides and aryl halides have attracted much attention since they are inexpensive and commercially available materials, but limited works mainly cover Ni(0) or Ni(II)/Zn catalytic systems.[6] Fu et al. recently reported Ni(II)-catalyzed enantioselective

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* Address correspondence to this author at Anhui Normal University.

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Negishi reactions of racemic secondary benzylic halides and secondary α-bromo amides with organozinc reagents.[7] However, reports on the Negishi cross-coupling of the vinyl zinc bromides with unactivated aryl halides catalyzed by Ni(II) complexes are rare. Considering the importance of organozinc reagents in organic synthesis, we studied the allylzincation of acetylenic sulfones and their further reaction with halohydrocarbons catalyzed by $Ni(PPh_3)_2Cl_2$. Herein, we wish to report the regio- and stereoselective synthesis of tetrasubstituted olefins containing a 1,4-diene structural unit by allylzincation of acetylenic sulfones, followed by Negishi coupling of the *situ*-produced vinyl zinc bromide with halohydrocarbons including both activated allyl bromide and unactivated aryl halides in the presence of catalytic $Ni(PPh_3)_2Cl_2$.

First, we examined the allylzincation reaction of acetylenic sulfones as shown in Scheme 1 and Table 1. Addition of 1-phenyl-2-(*p*-tolylsulfonyl)ethyne to the solution of allylzinc bromide (prepared in situ from allyl bromide and activated zinc) in THF smoothly produced the α-sulfonyl vinyl zinc reagent **2a**, which upon hydrolysis with saturated NH_4Cl afforded the sole geometric isomer (*Z*)-2-phenyl-1-(*p*-tolylsulfonyl)-1,4-pentadiene **3a** in high yield (up to 96%).[8] From Table 1, we can see that the best reaction condition is that acetylenic sulfone reacted with 0.5 mol/L of allylzinc bromide at reflux temperature for 2 h (entry 5, Table 1).

Scheme 1

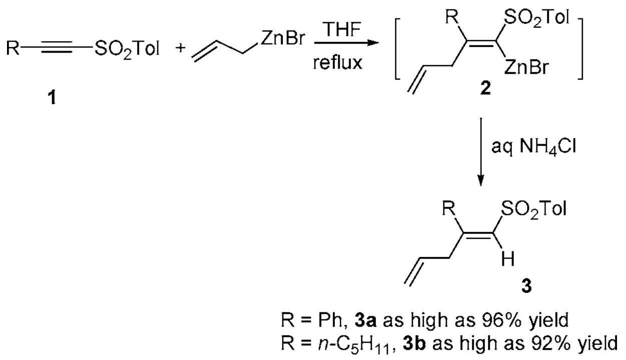


Table 1. Reaction of Allylzinc Bromide with Acetylenic Sulfones

entry	R	allyl zinc bromide/**1** ratio	concn (M)	*T* (°C)	time (h)	yield (%)[a]
1	Ph−	1.0	0.5	50	3	54
2	Ph−	1.2	0.5	50	5	83
3	Ph−	1.5	0.5	50	3	91
4	Ph−	1.5	0.5	30	7	48
5	Ph−	1.5	0.5	reflux	2	96
6	Ph−	1.5	0.1	reflux	5	80
7	Ph−	1.5	0.25	reflux	2	91
8	Ph−	1.5	1.0	reflux	2	90
9	Ph−	2.0	0.5	reflux	1	89
10	n-C_5H_{11}−	1.5	0.5	reflux	1.5	92
11	n-C_5H_{11}−	1.2	0.5	reflux	2	90

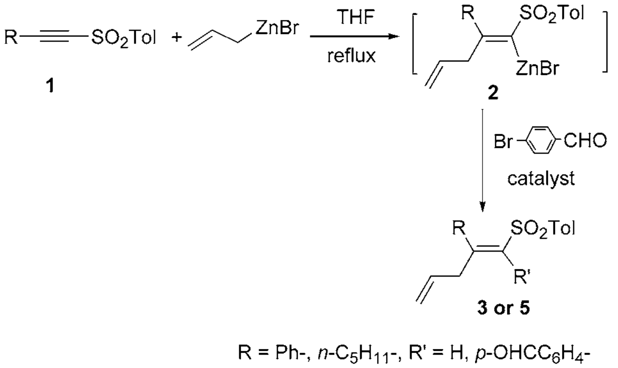
[a] Isolated yields based on **1**.

In the case of the allylzincation reaction of 1-(*p*-tolylsulfonyl)-1-heptyne, (*E*)-1-(*p*-tolylsulfonyl)-2-(*n*-pentyl)-1,4-pentadiene **3b** was obtained exclusively in 92% yield (entry 10, Table 1).

The configurations of **3a** and **3b** were verified by the NOESY spectra. The NOESY spectra show that there are strong correlations between the vinyl proton and the allylic protons of the allyl group, suggesting that the vinyl proton is cis oriented with the allyl group. So the stereochemistry of allylzincation of either phenyl or n-C_5H_{11} group functionalized acetylenic sulfones is pure *syn*-addition.

Although reports on the carbozincation of alkynes are well-known, trapping of the vinyl zinc intermediate formed by carbozincation of alkynes with an electrophile other than a proton is rare.[5a,b] To extend the application of allylzincation of acetylenic sulfones, we studied the Negishi coupling reaction of the halohydrocarbons, especially unactivated aryl halides, with α-sulfonyl vinyl zinc reagent **2** obtained by the allylzincation of acetylenic sulfones. *p*-Bromobenzaldehyde was chosen to optimize the reaction conditions (Scheme 2) and several reaction conditions were examined (Table 2). Table 2 showed different Ni(II) catalysts (10 mol % based on 1-phenyl-2-(*p*-tolylsulfonyl)ethyne) and the catalyst loadings that were examined for their ability to catalyze the Negishi coupling reactions. The coupling reactions of α-sulfonyl vinyl zinc reagent **2** with halo-

Scheme 2



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[8] General procedure for the reaction of allylzinc bromide with acetylenic. Synthesis of **3**: The Schlenk flask with a condenser was charged with THF (1.4 mL), activated zinc dust (46 mg, 0.7 mmol), and allyl bromide (0.06 mL, 0.7 mmol) under argon atmosphere. The mixture was stirred at 0 °C until the zinc disappeared (about 1 h). To the mixture was added the acetylenic sulfone (0.47 mmol). The reaction mixture was stirred at reflux temperature until the reaction reached completion (monitored by TLC). The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate (3 × 10.0 mL). The organic layer was combined and dried over $MgSO_4$. After filtration and removal of solvent in vacuo, the crude product was purified with flash chromatography (silica/hexanes−ethyl acetate 8:1 for **3a** and 20:1 for **3b** v/v) to give the desired product **3** in high yield.

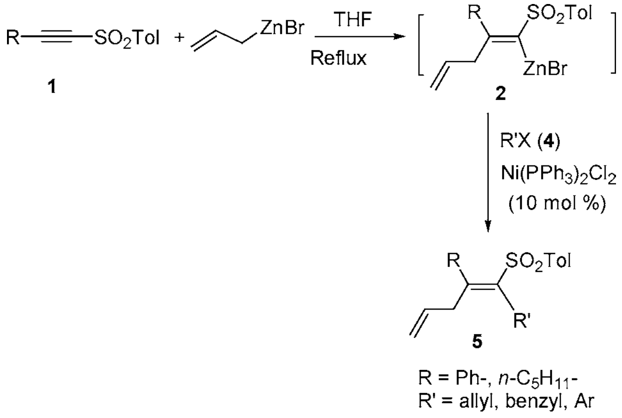
Table 2. The Screening of Catalysts for the Negishi Coupling Reaction of α-Sulfonyl Vinyl Zinc Reagent **2** and *p*-Bromobenzaldehyde

entry	R	catalyst	product (yield,%)[a]
1	C_6H_5-		**3a** (90)
2	C_6H_5-	$Ni(PPh_3)_2Cl_2$ (10 mol %)	**5j** (63)
3	C_6H_5-	$Ni(acac)_2$ (10 mol %)	**3a** (71) + **5j** (trace)
4	C_6H_5-	$Ni(dppe)Cl_2$ (10 mol %)	**3a** (73) + **5j**(trace)
5	C_6H_5-	$Ni(PPh_3)_2Cl_2$ (1 mol %)	**3a** (70) + **5j** (12%)
6	C_6H_5-	$Ni(PPh_3)_2Cl_2$ (5 mol %)	**3a** (15) + **5j** (52%)
7	C_6H_5-	$Ni(PPh_3)_2Cl_2$ (20 mol %)	**5j** (68)
8	*n*-$C_5H_{11}-$	$Ni(PPh_3)_2Cl_2$ (10 mol %)	**5s** (60)
9	*n*-$C_5H_{11}-$	$Ni(acac)_2$ (10 mol %)	**3b** (74) + **5s** (trace)
10	*n*-$C_5H_{11}-$	$Ni(dppe)Cl_2$ (10 mol %)	**3b** (73) + **5s** (trace)

[a] Isolated yields based on **1**.

hydrocarbons cannot happen in the absence of Ni(II) catalysts (entry 1, Table 2). Among the catalysts examined, $Ni(PPh_3)_2Cl_2$ was the most effective (entry 2, Table 2). Increasing the amount of $Ni(PPh_3)_2Cl_2$ in the reaction (1−20 mol %) led to an increased yield of the desired coupling products (Table 2). So, 10 mol % of $Ni(PPh_3)_2Cl_2$ was used to catalyze the coupling reactions to avoid a large amount of catalyst loading.

Scheme 3



A series of halohydrocarbons were subjected to the above optimal reaction conditions (Scheme 3). The results are summarized in Table 3. From Table 3, we can see that the scope of halohydrocarbons is very broad. The halohydrocarbon can be allyl bromide, aryl chlorides, aryl bromides, and aryl iodides. The bromides and iodides are more reactive than the chlorides, which can be seen from the results of reactions of 2-chloro-5-iodopyridine or 1-bromo-4-chlorobenzene with **2** producing the chloro-containing products (entries 16, 17, and 24, Table 3). The coupling reaction of vinyl zinc reagent with halohydrocarbon in the presence of $Ni(PPh_3)_2Cl_2$ is also functional group compatible. The ester (entries 15 and 20, Table 3), nitrile (entries 14 and 23, Table 3), ketone (entries 13 and 22, Table 3), aldehyde (entries 11, 12, and 21, Table 3), and amine (entry 10, Table 3) are tolerated in the coupling reaction. The *p*- or *m*-bromotoluene can couple with reagent **2** smoothly to give the corresponding products **5** in moderate yields (entries 5 and 6, Table 3); however, in the case of the *o*-bromotoluene compound **3a** was isolated instead of the desired product (entry 7, Table 3), which may be attributed to the steric effect.

Table 3. One-Pot Three-Component Reactions of Allylzinc Bromide, Acetylenic Sulfone, and Halohydrocarbons

entry	R	R′X	product (yield, %)[a]
1	C_6H_5-	allyl bromide	**5a** (83)
2	C_6H_5-	$C_6H_5CH_2Br$	**5b** (40)
3	C_6H_5-	*p*- $BrC_6H_4CH_2Br$	**5c** (41)
4	C_6H_5-	C_6H_5Br	**5d** (47)
5	C_6H_5-	*p*- $BrC_6H_4CH_3$	**5e** (60)
6	C_6H_5-	*m*- $BrC_6H_4CH_3$	**5f** (57)
7	C_6H_5-	*o*- $BrC_6H_4CH_3$	**3a** (93)
8	C_6H_5-	*p*- $BrC_6H_4C_2H_5$	**5g** (43)
9	C_6H_5-	*p*- $CH_3OC_6H_4I$	**5h** (55)
10	C_6H_5-	*p*-$BrC_6H_4N(CH_3)_2$	**5i** (63)
11	C_6H_5-	*p*-BrC_6H_4CHO	**5j** (63)
12	C_6H_5-	*p*-ClC_6H_4CHO	**5j** (55)
13	C_6H_5-	*p*-$IC_6H_4COCH_3$	**5k** (61)
14	C_6H_5-	*p*-BrC_6H_4CN	**5*l*** (57)
15	C_6H_5-	*p*-$CH_3OCOC_6H_4I$	**5m** (40)
16	C_6H_5-	2-chloro-5-iodopyridine	**5n** (51)
17	C_6H_5-	*p*-ClC_6H_4Br	**5o** (54)
18	*n*-$C_5H_{11}-$	allyl bromide	**5p** (74)
19	*n*-$C_5H_{11}-$	*p*- $CH_3OC_6H_4I$	**5q** (45)
20	*n*-$C_5H_{11}-$	*p*-$CH_3OCOC_6H_4I$	**5r** (43)
21	*n*-$C_5H_{11}-$	*p*-BrC_6H_4CHO	**5s** (60)
22	*n*-$C_5H_{11}-$	*p*-$IC_6H_4COCH_3$	**5t** (51)
23	*n*-$C_5H_{11}-$	*p*-BrC_6H_4CN	**5u** (57)
24	*n*-$C_5H_{11}-$	2-chloro-5-iodopyridine	**5v** (65)

[a] Isolated yields based on **1**.

The reaction could be performed very easily as follows. To a freshly prepared solution of allylzinc bromide in THF was added acetylenic sulfone at 0 °C and the reaction mixture was refluxed for 2 h. After the allylzincation was complete, halohydrocarbons and $Ni(PPh_3)_2Cl_2$ were added successively and stirred at 50 °C for 2−12 h to obtain the expected products.[9]

The stereoselectivity of the one-pot three-component allylzincation of acetylenic sulfones/Negishi cross-coupling

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(9)) General procedure for the one-pot three-component reaction of the allylzincation/coupling reaction of vinyl zinc bromides and halohydrocarbons. Synthesis of (*Z*)-2-phenyl-1-(*p*-tolyl)-1-(*p*-tolylsulfonyl)-1,4-pentadiene (**5e**). The Schlenk flask with a condenser was charged with dry THF (1.4 mL), activated zinc dust (46 mg, 0.7 mmol), and allyl bromide (0.06 mL, 0.7 mmol) under argon atmosphere. The mixture was stirred at 0 °C until the zinc dust disappeared (about 1 h). Acetylenic sulfone (120 mg, 0.47 mmol) was added and the reaction mixture was stirred for 2 h at reflux temperature. The reaction mixture was then cooled to 50 °C, and *p*-bromotoluene (81 mg, 0.47 mmol), $NiCl_2(PPh_3)_2$ (31 mg, 10 mol %), and 3.0 mL of THF were added successively. The mixture was stirred at 50 °C for 12 h. After the reaction was complete (monitored by TLC), the mixture was quenched with a saturated NH_4Cl solution and was extracted with ethyl acetate (3 × 10.0 mL). The organic layer was combined and dried over $MgSO_4$. After filtration and removal of solvent in vacuo, the crude product was purified with flash chromatography (silica/hexanes−ethyl acetate 8:1 v/v). The desired product **5e** was obtained as a white solid (109 mg, 60%).

of vinyl zinc bromides with halohydrocarbons was verified by the X-ray diffraction analysis of compound **5e** (Figure 1).[10] Figure 1 shows that the allyl group is cis oriented with the tolyl group. The result suggests that the geometry of the double bond is reserved when the α-sulfonyl vinyl zinc reagent **2** is coupled with halohydrocarbons in the presence of $Ni(PPh_3)_2Cl_2$. No anti allylzincation−Negishi coupling products were obtained.

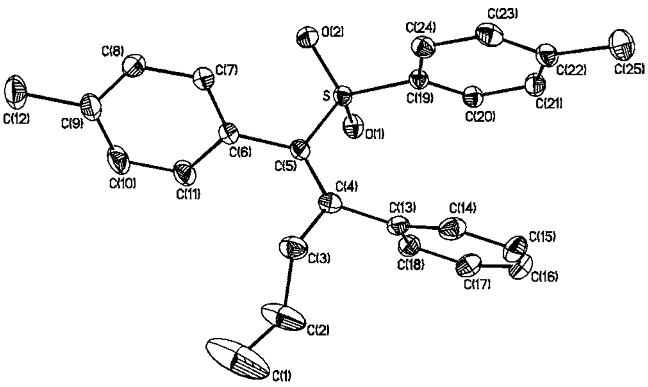

Figure 1. The molecular structure of **5e**.

In conclusion, we have found that the commercially available nickel(II) compound $Ni(PPh_3)_2Cl_2$ can catalyze the Negishi coupling of vinyl zinc bromides with a series of halohydrocarbons, especially those of unactivated aromatic halides. Thus, tetrasubstituted olefins can be conveniently, efficiently, and stereoselectively prepared by one-pot three-component reactions of allylzinc bromide, acetylenic sulfone, and halohydrocarbons. These tetrasubstituted olefins may be potential materials in the synthesis of natural products and in other synthetic transformations. Further study on the reactivity of the α-sulfonyl vinyl zinc reagent **2** with other electrophiles is now in progress in our laboratory.

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Supporting Information Available: General experimental procedures, including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10]) **Crystal data for 5e:** $C_{25}H_{24}O_2S$, MW = 388.50, triclinic, space group $P\bar{1}$, $a = 8.5858(6)$ Å, $b = 11.5065(8)$ Å, $c = 11.7576(8)$ Å; $\alpha = 72.0620(10)°$, $\beta = 82.8060(10)°$, $\gamma = 72.6040(10)°$; $V = 2446.9(3)$ Å^3, $T = 293$K, $Z = 2$, $D_c = 1.224$ g·cm^{-3}, $\mu = 0.171$ mm^{-1}, $\lambda = 0.71073$ Å, $F(000) = 412$, 5587 reflections collected, 3684 independent reflections ($R_{int} = 0.0379$). Full-matrix least-squares refinement on F^2 gives the final R indices: $R_1 = 0.0744$, $wR_2 = 0.1852$ ($I > 2\sigma(I)$) with 1.153 of goodness-of-fit (on F^2).