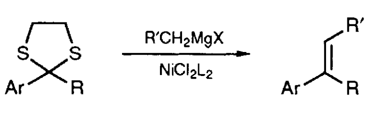
In situ Activation of C_{sp^3}–S Bond by Tandem Nickel-catalysed Alkenation of 1-Aryl-1,3-bis(dithioacetals) with Me_3SiCH_2MgCl

Ken-Tsung Wong and Tien-Yau Luh*

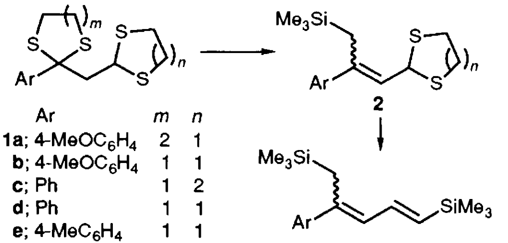
Department of Chemistry, National Taiwan University, Taipei, Taiwan 10764, Republic of China

The aliphatic C–S bond is activated by the *in situ* generation of a double bond *via* tandem nickel-catalysed alkenation of 1-aryl-1,3-bisdithioacetals with Me_3SiCH_2MgCl.

Although transition metal-catalysed cross coupling reactions are highly versatile in carbon–carbon bond formation,[1] the applications of the corresponding process with the unactivated C_{sp^3}–X bond are limited.[2] It is noted that only neopentyl iodides undergo coupling reactions with aromatic Grignard reagents in the presence of a palladium catalyst.[2c] The major impediment is the low reactivity of the C_{sp^3}–X bond towards oxidative addition with transition metals, and occasionally side reactions such as reduction, β-elimination, as well as homocoupling becoming predominant.[2b–d] One possible way to solve this problem is to design a substrate which could, under the reaction conditions, *in situ* generate a double bond so that the originally unreactive C_{sp^3}–X moiety becomes an allylic one. Consequently, further coupling with the Grignard reagent could take place. Our recent discovery on the nickel-catalysed alkenation of benzylic or allylic dithioacetals



(1)



(2)

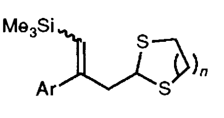
	Ar	m	n
1a;	$4\text{-MeOC}_6\text{H}_4$	2	1
b;	$4\text{-MeOC}_6\text{H}_4$	1	1
c;	Ph	1	2
d;	Ph	1	1
e;	$4\text{-MeC}_6\text{H}_4$	1	1
f;	$4\text{-PhC}_6\text{H}_4$	1	1

	Ar
3a;	$4\text{-MeOC}_6\text{H}_4$
b;	Ph
c;	$4\text{-MeC}_6\text{H}_4$
d;	$4\text{-PhC}_6\text{H}_4$

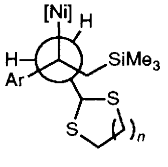
with Grignard reagents [eqn. (1)][3] provides a useful model to test this viewpoint; the strategy is outlined in eqn. (2). Bis(dithioacetal) **1** contains one benzylic dithioacetal moiety and one aliphatic dithioacetal group located at the C-3 position relative to the benzylic dithioacetal functionality. In the presence of the nickel catalyst, the benzylic dithioacetal group would be expected to react first with the Grignard reagent generating intermediate **2** which continuously reacts with the Grignard reagent under the reaction conditions leading to diene **3**.

We have shown previously that the nickel-catalysed cross coupling reaction of the dithioacetals occurs *via* the first formation of the carbon–carbon bond followed by a formal elimination step.[3] Thus, **4** may also be formed in addition to **2** depending on the orientation of β-elimination. In order to activate the aliphatic dithioacetal moiety in **1**, the first coupling reaction would require the formation of the double bond regioselectively; and only allylic dithioacetal **2** can further couple with the Grignard reagent, **4** being unreactive.

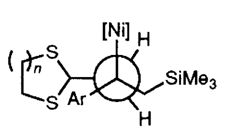
Bis(dithioacetals) were conveniently prepared according to modified literature procedures.[4] At the beginning of this work, **1a** was treated with 6 equiv. of Me_3SiCH_2MgCl in the presence of 5 mol% of $NiCl_2(PPh_3)_2$ in refluxing benzene–diethyl ether for 16 h to afford a 35 : 65 ratio of **3a**† ($E:Z$ = 20 : 80) and **4a** ($E:Z$ = 60 : 40) in 87% yield. On the other hand, the reaction of **1b** afforded in 88% yield a 63 : 37 mixture of **3a** ($E:Z$ = 14 : 86) and **4a** ($E:Z$ = 40 : 60). These results are compatible with our earlier findings where allylsilane is obtained predominantly when five-membered dithiolane is employed, and vinylsilane becomes the major product using six-membered dithiane as the substrate.[5] The ring size of the nonbenzylic dithioacetal moiety in **1**, however, had no effect on the product distribution. Thus, the reactions of **1c** and **d** gave similar ratios of **3b** and **4b**.



	Ar
4a;	$4\text{-MeOC}_6\text{H}_4$
b;	Ph
c;	$4\text{-MeC}_6\text{H}_4$
d;	$4\text{-PhC}_6\text{H}_4$



5a



5b

Table 1 $NiCl_2(PPh_3)_2$-catalysed reaction of **1** with Me_3SiCH_2MgCl

	Product			
1	**3**	Yield (%) ($E:Z$)	**4**	Yield (%) ($E:Z$)
a	**a**	30 (20 : 80)	**a**	57 (60 : 40)
b	**a**	55 (14 : 86)	**a**	33 (60 : 40)
c	**b**	53 (10 : 90)	**b**	22 (68 : 32)
d	**b**	54 (10 : 90)	**b**	21 (60 : 40)
e	**c**	57 (12 : 88)	**c**	35 (60 : 40)
f	**d**	46 (14 : 86)	**d**	40 (60 : 40)

Table 1 summarizes representative examples of the nickel-catalysed reactions of **1** with Me_3SiCH_2MgCl. Dienes **3** containing both vinyl- and allyl-silane functionalities were obtained in moderate yields.[6] Separation of **3** from **4** was readily achieved by column chromatography on silica gel. The stereochemistry of these products was determined by nuclear Overhauser effect (NOE) experiments.† The stereoselectivity of **3** can be understood within the framework of steric requirements of the β-elimination process, the intermediate **5a** being more stable than its conformer **5b**.

In summary, these results have demonstrated the first example of the *in situ* generation of a double bond to activate an aliphatic C–S bond. The application of this tandem reaction has illustrated a novel approach leading to diene synthesis. Although, at this stage, we cannot avoid obtaining **4** as the side product, the method does provide a convenient synthesis of dienes **3** in moderate yields.

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† The E and Z isomers were readily separated by HPLC. ^{1}H NMR data ($CDCl_3$, 200 MHz): 1E,3Z-**3a**: δ −0.08 (s, 9 H), 0.15 (s, 9 H), 2.11 (s, 2 H), 3.78 (s, 3 H), 5.86 (d, J 18 Hz, 1 H), 6.28 (d, J 11 Hz, 1 H), 6.82 (dd, J 11, 18 Hz, 1 H), 6.85 (d, J 11 Hz, 2 H), 7.38 (d, J 11 Hz, 2 H); 1E,3E-**3a**: δ −0.19 (s, 9 H), 0.00 (s, 9 H), 1.91 (s, 2 H), 3.81 (s, 3 H), 5.68 (d, J 18 Hz, 1 H), 5.96 (d, J 11 Hz, 1 H), 6.60 (dd, J 11, 18 Hz, 1 H), 6.83 (d, J 11 Hz, 2 H), 7.15 (d, J 11 Hz, 2 H); 1E,3Z-**3b**: δ −0.12 (s, 9 H), 0.99 (s, 9 H), 2.19 (s, 2 H), 5.87 (d, J 18 Hz, 1 H), 6.26 (d, J 11 Hz, 1 H), 6.79 (dd, J 11, 18 Hz, 1 H), 7.20–7.40 (m, 5 H); 1E,3E-**3b**: δ −0.03 (s, 9 H), 0.18 (s, 9 H), 1.96 (s, 2 H), 5.68 (d, J 18 Hz, 1 H), 5.98 (d, J 11 Hz, 1 H), 6.58 (dd, J 11, 18 Hz, 1 H, 25% NOE enhancement upon irradiation at δ 2.19), 7.18–7.36 (m, 5 H); 1E,3Z-**3c**: δ −0.10 (s, 9 H), 0.09 (s, 9 H), 2.17 (s, 2 H), 2.31 (s, 3 H), 5.84 (d, J 18 Hz, 1 H), 6.25 (d, J 11 Hz, 1 H), 6.78 (dd, J 11, 18 Hz, 1 H), 7.08 (d, J 8 Hz, 2 H), 7.27 (d, J 8 Hz, 2 H); 1E,3E-**3c**: δ −0.17 (s, 9 H), −0.04 (s, 9 H), 1.92 (s, 2 H), 2.33 (s, 3 H), 5.68 (d, J 18 Hz, 1 H), 5.96 (d, J 11 Hz, 1 H), 6.60 (dd, J 11, 18 Hz, 1 H), 7.07 (d, J 8 Hz, 2 H), 7.30 (d, J 8 Hz, 2 H); 1E,3Z-**3d**: −0.08 (s, 9 H), 0.12 (s, 9 H), 2.22 (s, 2 H), 5.89 (d, J 18 Hz, 1 H), 6.34 (d, J 11 Hz, 1 H), 6.82 (dd, J 11, 18 Hz, 1 H), 7.31–7.62 (m, 9 H); 1E,3E-**3d**: δ −0.13 (s, 9 H), 0.01 (s, 9 H), 1.98 (s, 2 H), 5.74 (d, J 18 Hz, 1 H), 6.03 (d, J 11 Hz, 1 H), 6.65 (dd, J 11, 18 Hz, 1 H), 7.29–7.65 (m, 9 H).

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