ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 4069

Received 15th January 2014,
Accepted 17th February 2014

DOI: 10.1039/c4cc00345d

www.rsc.org/chemcomm

Stereospecific hydrodehalogenation of alkenyl bromides: a new approach to the synthesis of (*E*)-alkenes†

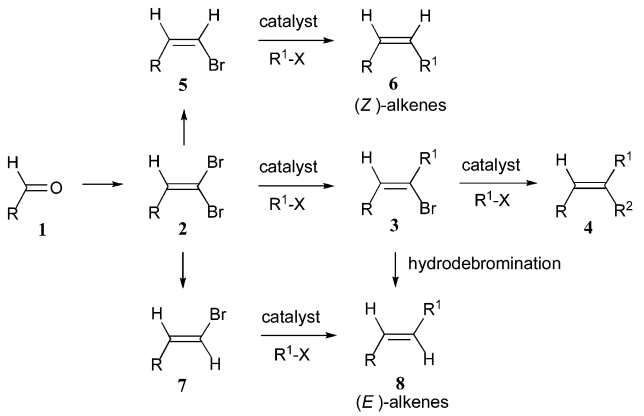
Giorgio Chelucci

The pair $NaBH_4$–TMEDA and catalytic $PdCl_2(PPh_3)_2$ in THF at room temperature is a mild and efficient system for the hydrodebromination of alkenyl bromides, providing a facile reduction procedure that allows completing the process advantageously, leading from aldehydes to (*E*)-alkenes.

To prepare geometrically pure 1,2-disubstituted alkenes, metal-catalyzed cross-coupling reactions between stereodefined 1-bromo-1-alkenes and a variety of organometallic reagents have proven to be reliable (**5** to **6** and **7** to **8**, Scheme 1).[1] Consequently, geometrically pure (*Z*)- or (*E*)-alkenyl halides are required. The 1,1-dibromovinyl functionality **2** is an attractive and versatile bidentate electrophile for organometallic chemistry, making their metal-catalyzed cross-couplings with a variety of organometallic reagents (**2** to **3**, Scheme 1) facile and selective.[2] Moreover, the 1,1-dibromo-1-alkene moiety is a valuable source of 1-bromoalkenes (**2** to **5** or **7**, Scheme 1). In fact, the palladium-catalysed hydrodehalogenation of 1,1-dibromoalkenes with Bu_3SnH is a well-recognized procedure to obtain (*Z*)-vinyl bromides (**2** to **5**, Scheme 1).[2,3] On the other hand, methodologies for the efficient synthesis of (*E*)-vinyl bromides from 1,1-dibromo-1-alkenes give satisfactory results only in a few favorable cases (**2** to **7**, Scheme 1).[2,4]

Based on this background we cogitated that the successful stereospecific hydrodebromination of the (*Z*)-alkenyl bromide, formed after initial *trans*-selective monosubstitution of the 1,1-dibromovinyl group, would offer a simple and convenient way for converting aldehydes to (*E*)-1,2-disubstituted alkenes (**1** → **2** → **3** → **8**, Scheme 1).

The hydrodehalogenation of 1,2-disubstituted-1-halo-1-alkenes to the related alkenes has been pursued using catalyzed[5,6] and non-catalyzed approaches.[7–9] Two examples of stereoselective catalyzed methods have been described. The system *n*-Bu_3SnH and $Pd(PPh_3)_4$ at 25 °C afforded the related alkenes stereoselectively, but worked well only with alkenyl iodides.[5] The second case concerns the stereospecific hydrodebromination of bromofluoroalkenes with HCOOH–*n*-Bu_3N and $PdCl_2(PPh_3)_2$ in DMF at 35–60 °C.[6]



Scheme 1

In this communication we wish to report that the couple sodium borohydride/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine ($NaBH_4$–TMEDA) under palladium catalysis is an efficient and stereospecific system for the hydrodebromination of (*Z*)-1,2-disubstituted-1-bromo-1-alkenes.

To confirm previous results we initially examined the reduction of the model substrate (*Z*)-1-(2-bromo-2-phenylvinyl)-4-methoxybenzene **1a** by using *n*-$Bu_3SnH/Pd(PPh_3)_4$ in toluene at 25 °C[5] (Table 1). Under these reaction conditions no conversion was observed within 48 h. It was also ineffective carry out the reaction at 50 °C or use other Pd-catalysts such as $Pd(OAc)_2$–PPh_3, $Pd_2(dba)_3$–TFP and $PdCl_2(PPh_3)_2$. On the other hand, when the reducing system HCOOH–*n*-Bu_3N and $PdCl_2(PPh_3)_2$ in DMF at 60 °C was employed,[6] total conversion of **1a** was obtained after 16 h, affording the product **2a** in 66% yield.

This interesting result prompted us to assess other reducing systems that were effective in the hydrodehalogenation of halogenated heterocycles (Table 1).[10]

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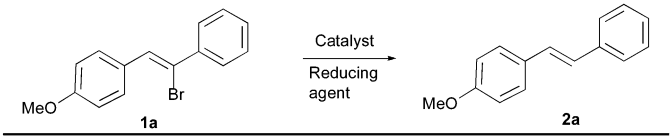
† Electronic supplementary information (ESI) available: General experimental procedures along with copies of the ^1H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c4cc00345d

Table 1 Hydrodebromination of (*Z*)-1-(2-bromo-2-phenylvinyl)-4-methoxybenzene[a]



Catalyst	Reducing agent	Solvent	Temp. (°C)	Time (h)	Conv. (**2a**/**1a**)[b]	Yield[c] (%)
$Pd(PPh_3)_4$	*n*-Bu_3SnH	DMF	60	48	0 : 100	—
$PdCl_2(PPh_3)_2$	HCOOH/*n*-Bu_3N	DMF	60	16	100 : 0	66
$Pd(PPh_3)_4$	HCOONa	DMF	60	14	100 : 0	80
$PdCl_2(PPh_3)_2$	$HCOONH_4$	MeOH	60	48	33 : 67	nd
$Pd(PPh_3)_4$	NaOMe	DMF	60	36	100 : 0	33
$PdCl_2(PPh_3)_2$	Et_3SiH	MeCN	60	24	100 : 0	0
$Pd(OAc)_2/PPh_3$	$NaBH_4$/TMEDA	THF	25	20	100 : 0	88
$PdCl_2(PPh_3)_2$	$NaBH_4$/TMEDA	THF	25	20	100 : 0	92

[a] For experimental details see ESI. [b] Determined by ^1H NMR. [c] Isolated yields.

Interestingly, HCOONa and $Pd(PPh_3)_4$ in DMF at 60 °C afforded **2a** in 80% yield, while $HCOONH_4$–$PdCl_2(PPh_3)_2$ in MeOH at 60 °C, NaOMe–$Pd(PPh_3)_4$ in DMF at 60 °C, and Et_3SiH–$PdCl_2(PPh_3)_2$ in MeCN at 60 °C provided unsatisfactory yields. Finally, when **1a** was treated with the couple $NaBH_4$–TMEDA as the hydride source in the presence of $Pd(OAc)_2$ and PPh_3 in THF at room temperature,[11] **2a** was obtained in 88% yield after 20 h. The proton NMR spectrum of the crude reaction mixture indicated for **2a** a coupling constant of 16.3 Hz due to the *trans* arrangement of the olefin protons, and excluded the presence of the corresponding *Z*-isomer. Gratified by this result we tried to increase the efficiency of this reducing procedure by examining other catalysts, $Pd(PPh_3)_4$, $PdCl_2/PPh_3$, $Pd_2(dba)_3$, $Pd_2(dba)_3$–PPh_3, $Pd_2(dba)_3$–TFP, $PdCl_2(PPh_3)_2$ and $PdCl_2$(dppf). Among them $PdCl_2(PPh_3)_2$ was the best performing one, increasing the yield of **2a** up to 92% (Table 1).

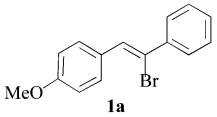
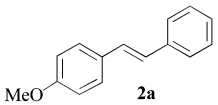
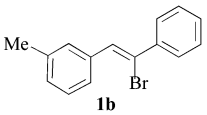
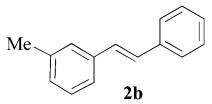
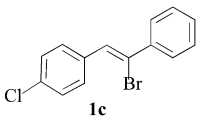
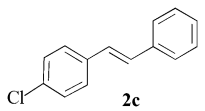
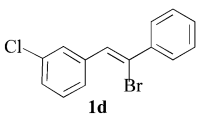
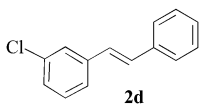
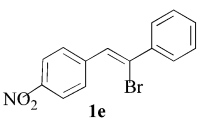
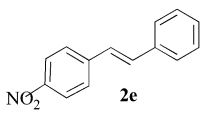
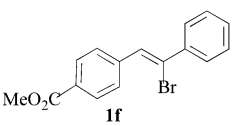
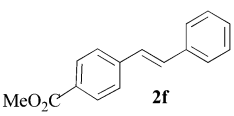
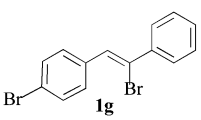
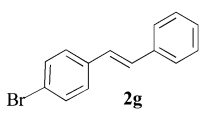
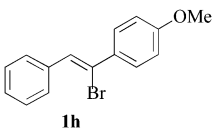
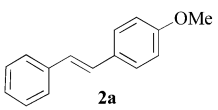
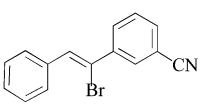
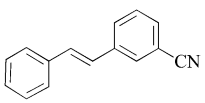
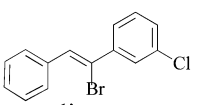
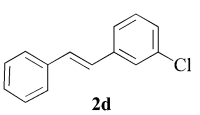
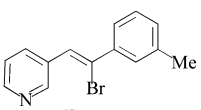
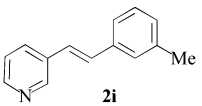
The scope of the reaction was then explored by using a variety of (*Z*)-1,2-disubstituted-1-bromo-1-alkenes. The starting alkenyl bromides were obtained by C-1 homologation of the related aldehydes under standard Corey–Fuchs conditions, followed by stereoselective Suzuki–Miyaura cross-coupling of the initially formed 1,1-dibromo-1-alkenes,[2] with the exception of the bromo enyne **1p** that was prepared by Negishi cross-coupling.[2]

The reductions were carried out in THF with an excess of $NaBH_4$ (2.8 equiv.) and TMEDA (3.64 equiv.) in the presence of $PdCl_2(PPh_3)_2$ (5.0 mol%) at room temperature (Tables 2 and 3).

In the diaryl alkene series (**1a–1k**), the hydrodebromination of the vinyl bromide gave geometrically pure (*E*)-alkenes in good yields. Small differences in yields and reaction times were observed with alkenes having different kinds of substituents in one (**1a–1g**) or the other aryl rings (**1h–1k**). Thus, for instance, both (*Z*)-1-(2-bromo-2-phenylvinyl)-3-chlorobenzene **1d** and (*Z*)-1-(1-bromo-2-phenylvinyl)-3-chlorobenzene **1j** afforded the same reduced product, (*E*)-1-chloro-3-styrylbenzene **2d**, in 86% (20 h) and 88% yield (24 h), respectively.

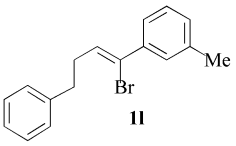
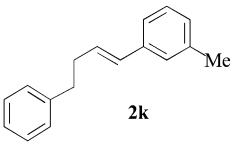
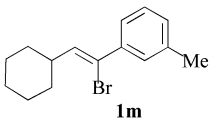
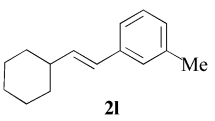
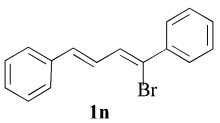
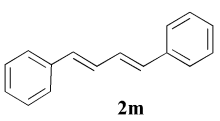
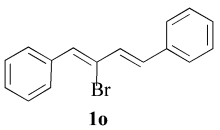
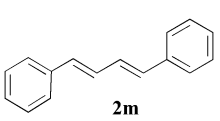
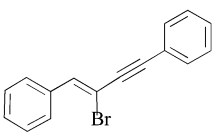
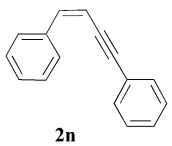
A particular comment deserves the reduction of the aryl derivatives **1e** and **1f**, bearing the nitro and methyl ester moieties, respectively. When **1e** was hydrogenolyzed under the usual reaction conditions, the target product **2e** was obtained in only 30% yield, (*E*)-4-styrylaniline being the main product, formed by consecutive reduction of the bromovinyl and nitro groups. Fortunately, by decreasing the amounts of $NaBH_4$ (1.5 equiv.) and TMEDA (2.0 equiv.) and quenching the reaction with aqueous NH_4Cl, compound **2e** was formed in 86%

Table 2 Hydrodebromination of 1,2-diaryl-1-bromo-1-alkenes[a]

Entry	Bromo alkene	Product	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	20	92
2	 **1b**	 **2b**	10	84
3	 **1c**	 **2c**	6	67
4	 **1d**	 **2d**	20	86
5	 **1e**	 **2e**	3 13	30 86[c]
6	 **1f**	 **2f**	21 30	45 72[c]
7	 **1g**	 **2g**	18	77
8	 **1h**	 **2a**	20	76
9	 **1i**	 **2h**	6	62
10	 **1j**	 **2d**	24	88
11	 **1k**	 **2i**	6	82

[a] Reaction conditions: 1-bromoalkene (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.025 mmol, 5.0 mol%), $NaBH_4$ (1.40 mmol, 2.8 equiv.) and TMEDA (1.82 mmol, 3.64 equiv.) in THF (10 mL) at rt. [b] Isolated yields. [c] $NaBH_4$ (0.75 mmol, 1.5 equiv.) and TMEDA (1.0 mmol, 2.0 equiv.).

Table 3 Hydrodebromination of 1,2-disubstituted-1-bromo-1-alkenes[a]

Entry	Bromo alkene	Product	Time (h)	Yield[b] (%)
12	 **1l**	 **2k**	24	64
13	 **1m**	 **2l**	19	92[c]
14	 **1n**	 **2m**	24	75
15	 **1o**	 **2m**	5	60
16	 **1p**	 **2n**	4	88

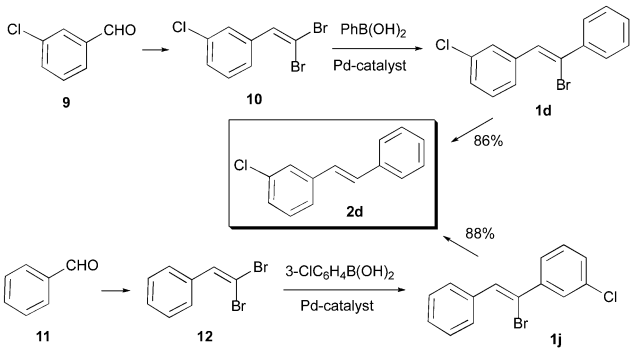
[a] Reaction conditions: 1-bromoalkene (0.5 mmol), $PdCl_2(PPh_3)_2$ (0.025 mmol, 5.0 mol%), $NaBH_4$ (1.40 mmol, 2.8 equiv.) and TMEDA (1.82 mmol, 3.64 equiv.) in THF (10 mL) at rt. [b] Isolated yields. [c] Reaction carried out at 65 °C.

yield after 13 h. Analogously, the reduction of **1f** under these reaction conditions afforded the alkene **2f** in 72% yield.

To further expand the scope of our catalytic system, we next investigated the hydrodebromination of other kinds of 1,2-disubstituted-1-bromo-1-alkenes (Table 3). Good catalytic activity at 25 °C was observed in the removal of the vinyl bromide from compound **1l** derived from the aliphatic aldehyde 3-phenylpropanal. On the other hand, the bromide in **1m** originated from the more sterically hindered cyclohexanecarbaldehyde was unreactive at room temperature, but the reduction took place at 65 °C within 19 h to give the expected alkene **2l** in excellent yield (92%).

Two types of 1,3-bromodienes were examined bearing the bromo substituent in the terminal or internal positions of the conjugate double bonds (**1n** and **1o**, respectively). Both compounds were hydrodebrominated in good yields (75% and 60%, respectively). Compound **1n** was reduced more slowly, but afforded a better yield, while **1o** afforded opposite results.

Finally, the reduction of the 1,3-enyne **1p** proceeded smoothly to afford the *cis*-alkene **2n** as the sole product in 88% yield. Partial or complete stereoinversion at the Br-bearing C=C bond in Pd-catalyzed cross-coupling reactions of 2-bromo-1,3-dienes with various types of organozinc reagents has been previously



Scheme 2 Two synthetic approaches to (*E*)-alkene **2d**.

observed.[2] However, this predictable event was not detected by us in the reduction of the bromodienes **1n** and **1o**, which in both cases afforded only the (*E,E*)-diene **2m**. On the other hand, recent studies have shown that cross-coupling reactions of (*Z*)-2-bromo-1-en-3-ynes were accompanied by significant, but partial stereoisomerization,[12] while we observed complete stereoinversion in the reduction of **1p**.

In summary, the pair $NaBH_4$–TMEDA and catalytic $PdCl_2(PPh_3)_2$ in THF at 25 °C is a mild and efficient system for the hydrodebromination of alkenyl bromide derivatives. Under these conditions a variety of (*Z*)-1,2-disubstituted-1-bromo-1-alkenes are stereospecifically converted into the related (*E*)-alkenes at room temperature in good yields. Moreover, the reducing system shows high functional group tolerance, *e.g.*, halogen, ester, alkyne, alkene, nitro and nitrile substituents.

Importantly, this efficient reduction procedure allows completing the process advantageously, leading from aldehydes to (*E*)-alkenes (aldehydes → 1,1-dibromo-1-alkenes → (*E*)-1-bromo-1-alkenes → (*E*)-alkenes) and providing an alternative way to carry out other olefination reactions by a judicious selection of the coupling partners and well-designed starting materials. Thus, for instance, the (*E*)-alkene **2d** (Scheme 2) is formed in similar yields by reduction of both **1d** and **2j**, which were in turn obtained from 3-chlorobenzaldehyde and benzaldehyde, respectively.

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