Pd/Ag-Catalyzed Direct Coupling of 1-Trimethylsilyl Alkynes with Vinyl Triflates

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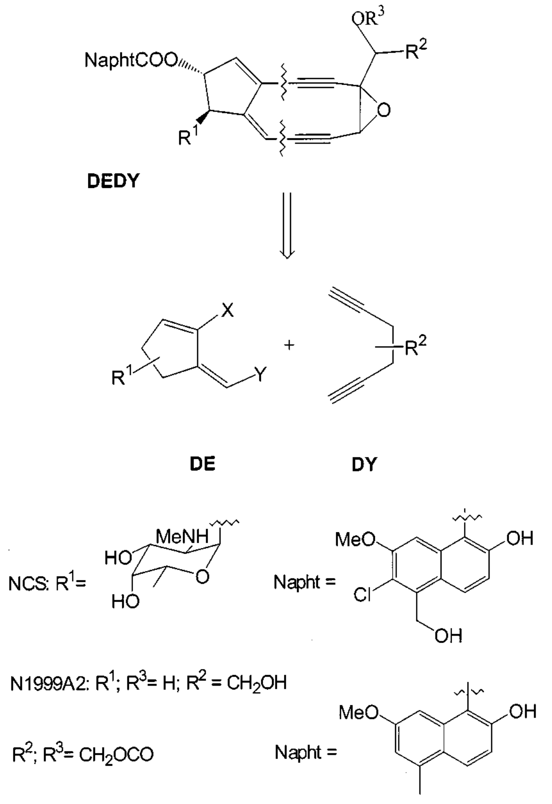
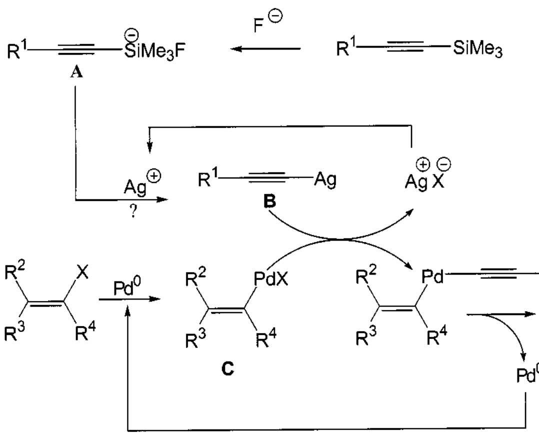
The commercially available tetrabutylammonium fluoride trihydrate is able to promote the cross-coupling of vinyl triflates with 1-trimethylsilylalkynes in the presence of a catalytic amount of tetrakis(triphenylphosphane)palladium and silver iodide.

In connection with our interest in the synthesis of enyne-containing natural products,[1,2] especially dienediynes (DEDY)[3–5] and analogs[6] (Scheme 1), we recently showed that silver iodide and tetrakis(triphenylphosphane)palladium are efficient catalysts for the coupling of sensitive vinyl triflates with alkynes.[5,6]



Scheme 1

Mechanistic investigations of this process suggested the formation of silver acetylides in situ.[7] These results and the well-known affinity of fluoride towards silicon led us to imagine a direct way for the coupling of activated alkenes with 1-trimethylsilylalkynes in the presence of a palladium catalyst. We reasoned that the fluorosilicate[8] formed in situ by the addition of fluoride to 1-trimethylsilylalkynes (**A** in Scheme 2) would be displaced by the more electropositive silver ion, the release of volatile trimethylsilylfluoride would facilitate this process. The silver acetylide thus formed (**B**) would then enter the palladium catalytic cycle through transmetallation with a vinylpalladium species (**C**) produced in situ by oxidative addition. The transmetallation step would thus free the silver ion, allowing a separate catalytic cycle to take place with silver ion (Scheme 2).



Scheme 2. Envisaged mechanism

We also surmised that since silver acetylides are efficiently prepared in protic solvents,[7,9] the fluoride source which should initiate the overall process does not necessarily need to be anhydrous. The most common and thus cheap fluoride source commercially available, i.e. tetrabutylammonium fluoride trihydrate (TBAF), would thus serve our purpose. It is worth noting that in the only two examples of coupling reactions involving 1-trimethylsilylalkynes that we are aware of,[10] an anhydrous source of fluoride (TASF) is required as well as a very dissociating solvent (HMPA) and/or harsh conditions.

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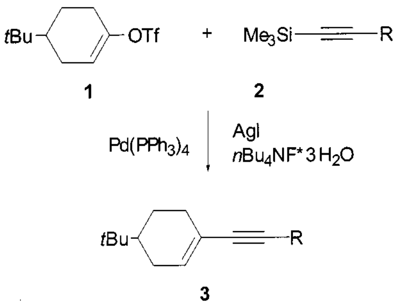
In order to check the above-mentioned assumptions, various representative trimethylsilylated alkynes **2a−d** were prepared by conventional methods[11] and submitted to TBAF in the presence of *tert*-butylcyclohexenyl triflate (**1**),[12] used as a model, and a catalytic amount of silver iodide and tetrakis(triphenylphosphane)palladium (Scheme 3).[13]



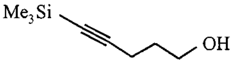
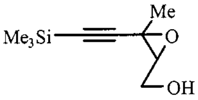
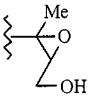
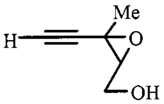
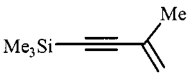
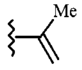
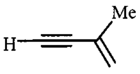
Scheme 3

Since the two related examples of coupling reaction proceeded without the need for a cocatalyst,[10] we compared the reaction with and without silver iodide. For further comparison, the corresponding free acetylenes were used in a related reaction using our described conditions.[6] These results are collected in Table 1.

In the conditions mentioned above [TBAF·$3H_2O$, $Pd(PPh_3)_4$, room temp. in DMF with or without AgI], we were delighted to observe the formation of the expected coupling products **3a−d** in good to excellent yields.

In the case of 1-trimethylsilyl-1-hexyne (**2a**), both reactions ran equally well, the reaction with silver iodide being slightly more rapid and effective than the one without (entry 1 vs. 2). With the corresponding free 1-hexyne (**4**), a comparison with our previously described conditions showed a slight but significant improvement in the presence of TBAF (entry 1 vs. 3). The efficiency of these new conditions proved to be even better with an alkyne bearing a free hydroxyl group. A quantitative coupling was achieved with 5-trimethylsilyl-4-pentynol (**2b**) in the presence of silver iodide (entry 4); without the latter, the coupling was slightly less than quantitative (entry 4 vs. 5). As in the preceding case (entries 1−2 vs. 3), the coupling of the trimethylsilylated acetylene was more efficient than the coupling of the corresponding free acetylene (entries 4−5 vs. 6) but now with a significant improvement. With an epoxidic acetylene, the differences were even more marked. The sensitive *cis*-2,3-epoxy-3-methyl-5-trimethylsilylpent-4-ynol (**2c**) gave the corresponding epoxyenyne **3c** cleanly with a better yield than the one achieved using the conditions set up for this kind of acetylenes (entry 7 vs. 9). However, in this case, the presence of silver iodide is critical since the same reaction

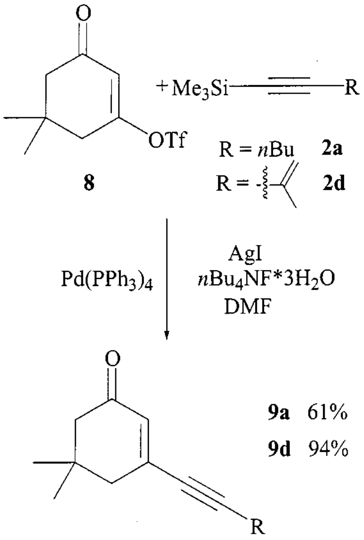
Table 1. Comparison of the direct coupling of 1-TMS-alkynes in the presence of TBAF·$3H_2O$, $Pd(PPh_3)_4$ and AgI with the coupling of the corresponding free alkynes in the presence of DIPEA, $Pd(PPh_3)_4$ and AgI

	Alkyne		Cocat.[a]	Time	Activator[b]	Yield[c]	Product
1	$Me_3Si{-}C{\equiv}C{-}nC_4H_9$	**2a**	AgI	21 h	nBu_4NF	87 %	**3a**, R = nC_4H_9
2	”		–	24 h	nBu_4NF	85 %	”
3	$H{-}C{\equiv}C{-}nC_4H_9$	**4**	AgI	20 h	iPr_2NEt	82 %	”
4		**2b**	AgI	24 h	nBu_4NF	99 %	**3b** R = $(CH_2)_3$
5			–	24 h	nBu_4NF	97 %	
6	$H{-}C{\equiv}C{-}(CH_2)_3OH$	**5**	AgI	24 h	iPr_2NEt	73 %	”
7		**2c**	AgI	22 h	nBu_4NF	78 %	**3c** R = 
8			–	22 h	nBu_4NF	30 %	”
9		**6**	AgI	24 h	iPr_2NEt	55 %	”
10		**2d**	AgI	18 h	nBu_4NF	99 %	**3d** R = 
11			–	18 h	nBu_4NF	68 %	”
12		**7**	AgI	24 h	iPr_2NEt	90 %	”

[a] 20% was used; 10% of $Pd(PPh_3)_4$ was also used as catalyst. [b] In case of nBu_4NF, 1.5 equiv. of the trihydrate TBAF·$3H_2O$ was used without any treatment; in the case of DIPEA, 1.25 equiv. was used. [c] Yield referred to isolated pure compounds.

run without it gave only a 30% yield of coupling product (entry 8 vs. 7). This latter result clearly demonstrates the key role of silver iodide as a cocatalyst, supporting our mechanistic hypothesis.[14]

More complex vinyl triflates can also be used in this coupling. Conjugated keto vinyl triflates proved to be good partners[6b] and, as an example, 5,5-dimethyl-3-triflyloxycyclopent-2-enone (**8**) was reacted with 1-trimethylsilyl hex-1-yne (**2a**) and 1-trimethylsilyl-3-methylbut-1-yne (**2d**) providing the corresponding ketoenynes **9a** and **9d** in good to excellent yields (Scheme 4).



Scheme 4

The present investigation has demonstrated that 1-trimethylsilylalkynes can be directly coupled to vinyl triflates with commercial tetrabutylammonium fluoride in the presence of tetrakis(triphenylphosphane)palladium and silver iodide as catalysts. The use of TBAF instead of base nicely improved our original reaction.[6]

Acknowledgments

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[13] Typical experimental procedure for **1-(4-*tert*-Butylcyclohex-1-enyl)-hex-1-yne 3a:** Tetrakis(triphenylphosphane)palladium (57 mg, 0.1 equiv.), silver iodide (24 mg, 0.2 equiv.), 1-trimethylsilylhex-1-yne (**2a**; 92 mg, 1.2 equiv.) and then a solution of TBAF·3H$_2$O (236 mg, 1.5 equiv.) in DMF were successively added to a 4-*tert*-butylcyclohex-1-enyl triflate solution (**1a**; 143 mg, 0.5 mmol, 1 equiv.) in DMF kept under argon at room temperature. The resulting solution was stirred at room temperature until the starting materials disappeared (see Table 1). Ether and water were then added and the aqueous phase was extracted three times with ether. The organic phases were combined, washed three times with water, dried with magnesium sulfate, filtered and concentrated. Silica gel chromatography then yielded the pure enyne **3a** (87%). ^{1}H NMR (CDCl$_3$): δ = 0.86 (s, 9 H), 0.92 (t, J = 7.1 Hz, 3 H), 1.05−1.32 (m, 2 H), 1.34−1.58 (m, 4 H), 1.76−1.91 (m, 2 H), 2.04−2.21 (m, 3 H), 2.30 (t, J = 6.8 Hz, 2 H), 6.04 (m, 1 H). ^{13}C NMR (CDCl$_3$): δ = 13.7, 18.9, 22.0, 23.9, 27.2, 27.3, 31.0, 31.2, 32.2, 43.4, 82.0, 87.7, 120.9, 133.4. IR (neat): $\tilde{\nu}$ = 2216, 1674, 1468, 1366, 1208, 808 cm^{-1}. MS (EI): m/z (%) = 218 (100) [M$^+$], 203 (16), 175 (35), 161 (26), 147 (47). HRMS (C$_{16}$H$_{26}$): calcd. 218.2035; found 218.2039.

[14] Other mechanisms cannot be ruled out with the experiments in hand. Preliminary experiments have demonstrated that with the simplest compounds, i.e. **1** and **2a** or **4**, TBAF alone can promote the required coupling reaction, although at a lower rate. Further work is now in progress in order to delineate further the mechanisms which may compete in the present reaction.

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