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Silver Salts as New Catalyst for Coupling Reactions; Synthesis of Epoxyenynes

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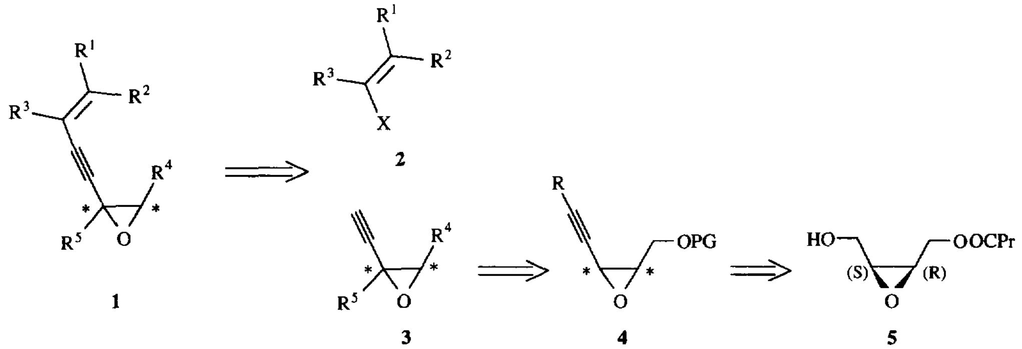
Abstract: *The coupling of ethynyloxiranes with alkenyl triflates have been achieved by treatment with the following association of catalysts: silver salt and tetrakis(triphenylphosphine) palladium. This new set of catalysts allowed for the direct formation of epoxyenynes in rather good yields.*

For a program in connection with our interest in the chemistry of ethynyl oxiranes[1-4] and devoted to the total synthesis of several natural products,[5-7] we required a mild access to chiral epoxyenynes (**1** in Scheme 1). We have recently shown that protected derivatives of (2*S*, 3*R*)-4-butyryloxy-2,3-epoxybutan-1-ol (**5** in Scheme 1), obtained by enzymatic hydrolysis of *cis*-1,4-bis(butyryloxy)-2,3-epoxybutane[8] are suitable enantiomerically pure starting materials for the asymmetric synthesis of ethynyl oxiranes (**4** in Scheme 1).[4,5] This led us to envisage the use of ethynyl oxiranes (**3** in Scheme 1) as optically pure key building-blocks for the synthesis of natural products containing an epoxyenyne moiety (**1** in Scheme 1).

The most convenient access to this class of compounds relies on the convergent strategy based on coupling reactions between a terminal acetylene and an activated alkene.[9] The literature offers numbers of methods for such couplings.[9-10] Among those, the coupling of vinyl triflates with terminal acetylenes in the presence of palladium complexes are the most convenient and therefore the most widely used.[9,11-12] However, to the best of our knowledge, the coupling of a terminal acetylene bearing an epoxy group (**3** in Scheme 1) with an activated alkene (**2** in Scheme 1) has never been reported in the literature.



Scheme 1

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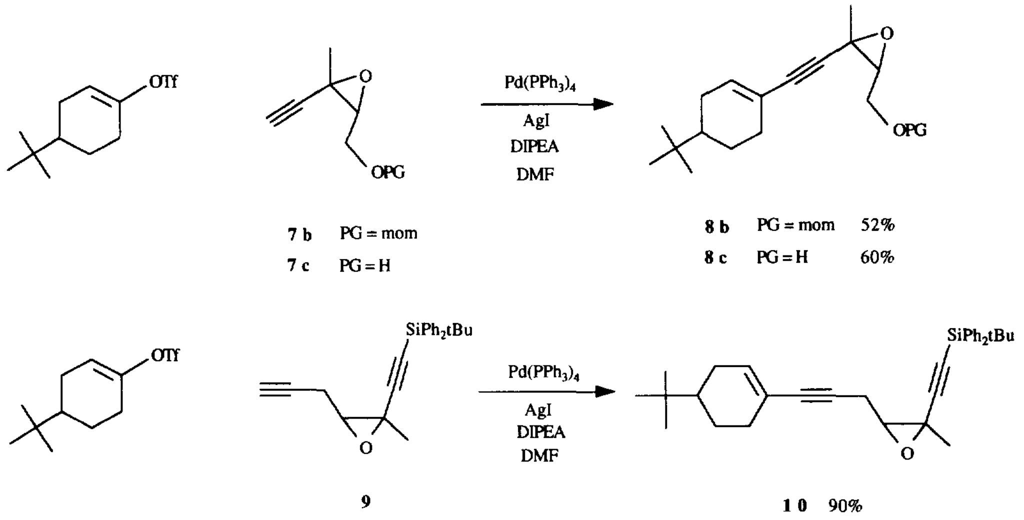
When exposed to the conditions described with cuprous iodide but with silver iodide instead as a cocatalyst , the starting materials **6** and **7** were slowly consumed in a very clean reaction and the expected product were isolated with a yield modest (Table 1, entry 5) but comparable to the best one obtained with cuprous iodide (Table 1, entry 4). We found in this case that modifications of the relative proportions of the reagents improved the yield of recovered coupling product and the best conditions are the one described in entry 6.

Other silver salts such as silver nitrate and silver carbonate proved to be also efficient catalysts in this coupling reaction but both were slightly less effective than silver iodide (Table 1, entries 7-10 vs 5-6). In order to minimize any counter-ion effect, silver triflate was also experimented. Although it was also effective as a catalyst, this salt was probably too electrophilic for use with the sensitive epoxyenyne unit and some decomposition occurred (Table 1, entry 11).

In order to expand the scope of the reaction, other epoxyalkynes was also engaged in coupling reactions with our model triflate **6** using the optimized conditions set above. Representative examples are collected in Scheme 2. Even a non-protected acetylenic epoxyalcohol **7c** was able to be coupled, but in this case, the epoxyenyne **8c**[15] was isolated with a yield lower than the one observed with the corresponding silylated compound (**7a-8a**, see Table 1, entry 6). Another decrease in yield was also observed when a chelating group - a mom group - was present in the coupling partner : **7b** gave the epoxyenyne **8b**[15] with a 52% yield. However, with an epoxydiyne, **9**,[17] an almost quantitative yield of coupling product **10**[15] was obtained but a slight decomposition occurred during chromatography.



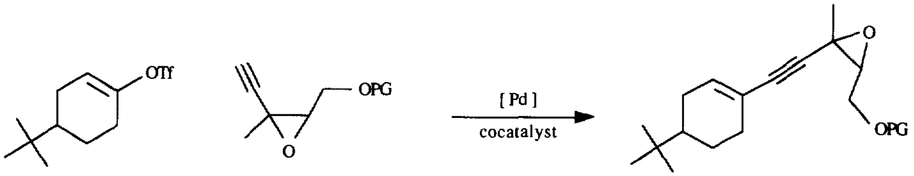
Scheme 2

These examples showed that this new set of catalysts can be used for various couplings and seems to accomodate different functional groups.

We thus needed to investigate the coupling of epoxyacetylenes as a prelude to the total synthesis of epoxyenyne natural products. In order to explore this reaction, we used two rather simple achiral compounds as models:

- a vinyl triflate, **6**, which was derived from 4-*tert* butylcyclohexanone using standard triflation;[13-14]

- the epoxyacetylene **7**, readily obtained from the commercially available 3-methyl pent-4-yn-2-en-1-ol.[2] In this communication, we present our preliminary results on the coupling of these compounds. Our results are collected in Table 1.



6 **7a-c** **8a-c**

Table 1: Coupling Reactions using **7a** (PG = $Si\ Ph_2tBu$)

entry	Pd %		Cocatal %		Base		Solvent	T°C	Time	Yields[a]
1	$Pd(OAc)_2(PPh_3)_2$	10%	-	-	NaOAc	4 éq	DMF	80°	2 h	40%
2	$Pd(OAc)_2(PPh_3)_2$	2%	-	-	nBu_3N	10 éq	DMF	85°	1 h	45%
3	$Pd(PPh_3)_4$	5%	CuI	10%	R_3N	2 éq	DMF	rt	30-60mn	20-25% [b]
4	$Pd(PPh_3)_4$	5%	CuI	10%	R_3N	2 éq	DMF	rt	30-60mn	44-54% [c]
5	$Pd(PPh_3)_4$	5%	AgI	10%	DIPEA	1.5 éq	DMF	rt	±24h	51%
6	$Pd(PPh_3)_4$	10%	AgI	20%	DIPEA	1.25 éq	DMF	rt	20 h	78%
7	$Pd(PPh_3)_4$	5%	$AgNO_3$	10%	DIPEA	1.5 éq	DMF	rt	4h	60%
8	$Pd(PPh_3)_4$	10%	$AgNO_3$	20%	DIPEA	1.25 éq	DMF	rt	15 h	52%
9	$Pd(PPh_3)_4$	5%	Ag_2CO_3	5%	DIPEA	1.5 éq	DMF	rt	4h	56%
10	$Pd(PPh_3)_4$	10%	Ag_2CO_3	20%	DIPEA	1.25 éq	DMF	rt	15 h	61%
11	$Pd(PPh_3)_4$	10%	AgOTf	20%	DIPEA	1.25 éq	DMF	rt	15 h	40%[d]

a) yields of isolated product; b) degradation of the epoxide **2** was observed but the triflate **1** was recovered; c) the epoxide was slowly added after addition of all the reagents; b, c) higher yields were obtained using DIPEA as base; d) degradation occurred.

The reported methods proved to be quite inefficient when applied to these starting materials. The Cacchi's procedure[11] gave a complex mixture from which the expected product **3**[15] could be isolated (Table 1, entries 1-2). The Sonogoshira-Linstrumelle reaction[9,12] gave even poorer results (Table 1, entries 3-4). In these conditions -tetrakis(triphenylphosphine)palladium, copper iodide and base- a rapid decomposition was observed and the expected product could only be isolated with a low yield (entry 3). In each case, increasing the substitution of the base slightly improved the formation of the coupling product **8**.

These observations and related[5] results indicated that copper salts have a deleterious effect on the epoxyyne fragment. An alternative catalyst was therefore required for an efficient coupling between vinyl triflates and epoxyacetylenes. Due to the analogy in their electronic structure and some of their chemical properties,[16] we reasoned that silver salts might be used instead of copper salts. Various silver salts were thus experimented and selected results are collected in Table 1, entries 5-11.

In summary, we have shown that epoxyenynes can easily be generated by coupling a terminal acetylene and a vinyl triflate using a new set of catalysts based on palladium complexes and silver salts. The results we presented here showed that silver salts can now be used as efficient catalysts and as an alternative to copper salts in coupling reactions. Further developments are now under current investigations in our laboratory and will be reported in due course.

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