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ARTICLE TYPE

Freedom: A copper-free, oxidant-free and solvent-free palladium catalysed homocoupling reaction.

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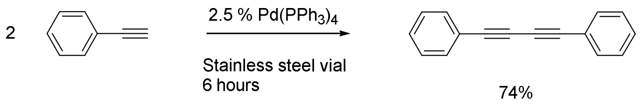
Herein, we describe a copper-free, oxidant-free, solvent-free homocoupling reaction using a palladium catalyst under mechanochemical conditions. We extended the methodology to palladium catalyst on solid support which showed a different reactivity and different product ratios from the non-supported catalyst. We were able to recycle the polymer supported catalyst for 5 cycles.

Over the past decade there has been an increased focus on the novel field of mechanochemistry.[1-3] Mechanochemical reactions are of particular interest in organic chemistry due to the reduced need of solvent for reactions under these unique conditions.[4-6] One specific area that has garnered a lot of interest is mechanochemically driven metal catalysed reactions. Metal catalysed reactions such as Suzuki,[7-10] Heck[11, 12] and Sonogashira[13, 14] have been shown to be successful under solvent-free mechanochemical conditions. Recently, Stolle, and co-workers reported on the coupling of terminal alkynes for the synthesis of 1,3 diynes under these unique conditions.[15, 16] Using traditional copper catalysts they reported that a wide variety of terminal alkynes undergo Glaser coupling to give 1,3 diynes in high yields. More recently there has been a push to incorporate palladium as a co-catalyst in the coupling reactions of terminal alkynes. Palladium catalysts are typically used with low catalytic loading, can be recycled and palladium catalysed reactions are overall better understood than copper catalysed reactions.[17-23] Further depending on the palladium catalyst used, the head to head and the head to tail enyne product can also be formed.[21, 24] To this end, we wanted to develop a palladium catalysed homocoupling reaction using solvent-free mechanochemical conditions.

It has been previously shown that copper or an additional oxidant is needed to carry out palladium catalysed homo couplings of terminal alkynes.[18,25] Because we have previously demonstrated that a copper ball, and copper vial can be used in lieu of a copper catalyst, we conducted the reaction in a copper milling vial with a copper ball.[13, 26] After milling phenyl acetylene, potassium carbonate and tetrakistriphenylphosphinepalladium in a copper vial for 6 hours, we observed an 80% yield of the desired 1,4 diphenyl 1,3-butadiyne. As a control, we conducted the same reaction in the copper vial with a copper ball in the absence of the palladium catalyst. To our surprise, we did not observe any of the expected 1,4-diphenyl buta-1,3-diyne product, even after milling for 16 hours. This suggests that under these conditions copper was not involved in the mechanism of the coupling reaction.

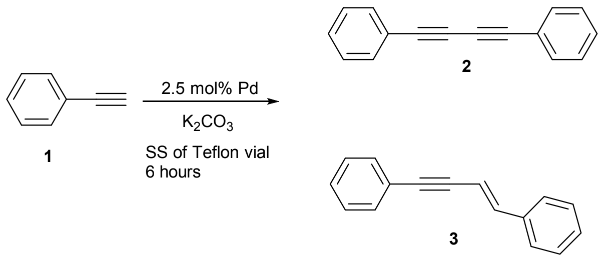


Scheme 1. Homocoupling of phenyl acetylene under solvent-free ball milling

In order to further explore the necessity of copper or any additional metal, we performed the coupling reaction in a stainless steel milling vial and in a Teflon® milling vial. In both cases we observed similar product yields to what was observed in the copper vial suggesting that copper was not a necessary co-catalyst (scheme 1). Additionally, we conducted the reaction in a Teflon® vial in an inert atmosphere and observed no change in yield or product ratio. This suggests that an additional oxidant is not needed under these novel conditions. In solution, it is well known that different palladium catalysts can give different coupling products. Tetrakistriphenylphosphinepalladium gives high yields of the 1,4-diphenyl buta-1,3-diyne (i.e, head to head coupling), while bis(triphenylphosphine)palladium dichloride in the absence of excess triphenylphosphine gives high yields of enynes.[20, 27] Milling phenylacetylene in the presence of bis(triphenylphosphine)palladium dichloride instead of tetrakistriphenylphosphinepalladium gave (E)-1,4-diphenylbut-1-en-3-yne (i.e., enyne coupling product) in high yield. A diasteromeric mixture is typically formed when bis(triphenylphosphine)palladium dichloride is used as the catalyst in solution, however under our mechanochemical conditions the reaction was shown to be completely diastereospecific, giving rise only to the E isomer.

Similar to solution, the addition of excess triphenylphosphine to the bis(triphenylphosphine)palladium dichloride catalyst favour typical head to head coupling and produces high yield of the 1,4-diphenyl buta-1,3-diyne product. Using bis(triphenylphosphine)palladium dichloride in the presence of excess

Table 1 Selectivity of different palladium catalyst under mechanochemical conditons



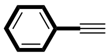
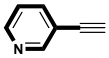
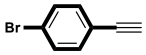
entry	catalyst	Additive	Conditions	product ratio **2**:**3**[b]	% yield[a]
1	$Pd(PPh_3)_4$	None	Stainless Steel	100:0	74%
2	$Pd(PPh_3)_4$	None	Teflon®	100:0	73%
3	$Pd(PPh_3)_4$	Bromo ethylacetate	THF/disopropyl ethyl amine	100:0	40%[c]
4	$PdCl_2(PPh_3)_2$	PPh_3	Teflon®	100:0	86%
5	$PdCl_2(PPh_3)_2$	PPh_3	Stainless Steel	100:0	90%
6	$PdCl_2(PPh_3)_2$	CuI	THF/NEt_3	NR[d]	75%[e]
7	$PdCl_2(PPh_3)_2$	None	Stainless Steel	14:86	89%
8	$PdCl_2(PPh_3)_2$	None	Teflon®	19:81	87%
9	PS-$Pd(PPh_3)_4$	None	Stainless Steel	12:88	93%
10	PS-$Pd(PPh_3)_4$	PPh_3	Stainless Steel	92:8	76%
11	$Pd(TFA)_2$	None	Teflon®	100:0	57%
12	$Pd(TFA)_2$	None	Stainless Steel	100:0	60%
13	$Pd(OAc)_2$	None	Teflon®	100:0	64%
14	$Pd(OAc)_2$	None	Stainless Steel	100:0	69%
15	$Pd(OAc)_2$	Air	THF/DABCO	100::0	58%[f]

The reactions were performed on a 2 mmol scale, using an $1/_8$" ball.
[a] Isolated yield [b] obtained via ^{1}H NMR integration.[c] Ref 21 [d] Not Reported [e] Ref 18 [f] Ref 19

Table 2. Dimerization of various alkynes using optimised conditions

$$R-\!\equiv\!-H \xrightarrow[\text{Stainless steel vial and ball}]{Pd(PPh_3)_4\ K_2CO_3} R-\!\equiv\!-\!\equiv\!-R$$

HSBM

entry	Alkyne	Catalyst	product ratio **2**:**3**[b]	% yield[a]
1		$Pd(PPh_3)_4$	100:0	74%
2		$Pd(PPh_3)_4$	100:0	71%
3		$Pd(PPh_3)_4$	100:0	82%
4		$Pd(PPh_3)_4$	100:0	62%

The reactions were performed on a 2 mmol scale, using an $1/_8$" ball.
[a] Isolated yield [b] obtained via 1H NMR integration.

triphenylphosphine gave a 90% yield of the head to head coupled product using either a Teflon® or stainless vial and ball. We extended our mechanochemical conditions to other palladium catalysts and discovered both palladium trifluoroacetate and palladium acetate gave modest yields of the head to head coupling product (Table 1.). We additionally showed the reaction can be extended beyond simply phenylacetylene (Table 2.)

Solvent-free mechanochemical conditions provides the opportunity to develop environmentally benign reactions. We wanted to explore the use of polymer supported catalysts which could be collected at the conclusion of the reaction and subsequently recycled. To our surprise, after milling phenylacetylene, potassium carbonate and polymer supported tetrakistriphenylphosphinepalladium instead of free tetrakistriphenylphosphinepalladium, we observed that the enyne product (i.e., head to head enyne) was formed in 80% yield with only a minor amount of the 1,4-diphenyl buta-1,3-diyne (i.e. head to head) product. The reaction was again diastereospecific giving rise to only the E-isomer. Previously, we reported on the milling of polymer supported reagents under mechanochemical conditions and noticed a difference in reactivity from traditional solution based conditions.[28] We were able to generate 71% yield of the 1,4-diphenyl buta-1,3-diyne with the addition of excess triphenylphosphine; we also observed similar results using polymer supported triphenylphosphine instead of free triphenylphosphine. This means that using a polymer support we can tune the reaction to either the homocoupling product (i.e, head to head coupling product) or the diasterospecific enyne product (i.e., head to head enyne coupling product). When we tested the recyclability of the polymer supported palladium catalyst we observed decreased reactivity after the first run and no reactivity after second run. We believe that after excessive milling the palladium is ultimately leached from the polymer support. The addition of excess triphenylphosphine or polymer supported triphenylphosphine helps with the recyclability of the catalyst but the reactivity of the catalyst is still diminished after the first cycle and inactive by the fifth cycle. We are currently exploring new polymer supports to increase the recyclability of the polymer catalyst.

Conclusion

In conclusion, we have developed a copper-free, solvent-free oxidant-free Glaser type coupling reaction under mechanochemical conditions. The use of tetrakistriphenylphosphinepalladium gives high yields of head to head homocoupling product while the use of bis(triphenylphosphine)palladium dichloride give high yields of only the *trans* enyne product. Unlike what has been observed in solution, under mechanochemical conditions an oxidant does not seem to be necessary but more experiments are underway better understand the mechanism of this reaction. We discovered polymer supported palladium tetrakistriphenylphosphinepalladium gives the trans enyne as the major product, showing a different reactivity than the free catalyst; the addition of free triphenylphosphine or polymer supported triphenylphosphine to the polymer supported palladium catalyst gives the head to head homocoupling product in high yields. Unfortunately, the polymer support catalyst can only be recycled twice in the absence of addition triphenylphosphine and 5 times in the presence of excess triphenylphosphine but in both cases the reactivity of the catalyst is greatly diminished. Solvent-free ball milling is a novel methodology that can provide different reactivity than observe in solution. Continuing to understand chemistry under this method will further advance chemistry and open new pathways previously unknown.

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† Electronic Supplementary Information (ESI) available: Experimental details and spectrospopic characterization of product. See DOI: 10.1039/b000000x/

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