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An efficient alkynylation of 4-thiazolidinone with terminal alkyne under C–H functionalisation†

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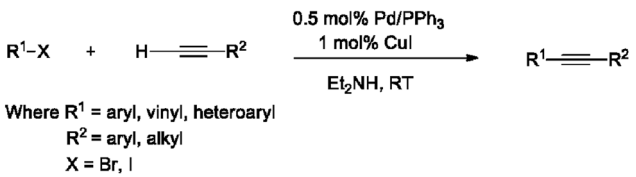
A method of palladium catalysed efficient alkynylation through the cross coupling reaction of terminal alkynes with the slightly more acidic C–H bonds of 4-thiazolidinone has been developed. This method allows the direct introduction of an ethynyl group into the 4-thiazolidinone moiety. Mild reaction conditions involving aerial oxidation and one pot synthesis make this reaction more efficient for the formation of sp^3(C)–sp(C) bond.

Introduction

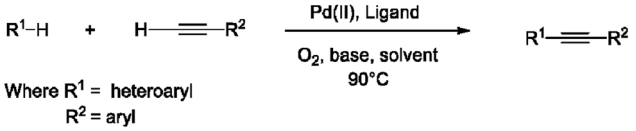
The development of transition metal catalysed reactions that facilitate the activation of unreactive C–H bonds has achieved considerable growth during the last two to three decades.[1–7] A major advantage of C–H functionalisation over traditional organometallic reactions is that the C–H activation strategy not only facilitates the synthesis of complex heterocycles in fewer steps but also needs cheaper precursors than are typically found in the case of traditional coupling *i.e.*, that require halogenated precursors. Based on these facts, direct functionalisation of unreactive C–H bonds of heterocycles provides an interesting approach in the world of synthetic chemistry. Conjugated enynes are found to be excellent building blocks, mostly useful as intermediates in natural products, optical materials, pharmaceuticals, agrochemicals, *etc.* Furthermore, the excellent reactivity of alkyne functionality toward metathesis, cycloaddition, addition reactions, *etc.*,[8–10] encourages many researchers to work in the direction of forming sp^3–sp carbon–carbon bonds. The generation of substituted alkyne functionality from classical cross-coupling or homo-coupling reactions generally requires a reaction between a nucleophile and an electrophile in the presence of a transition metal catalyst. Typical organometallic reagents that are required as nucleophiles are B, Sn, Zn, Mg, Si, *etc.*[11] among which some are either expensive or toxic. Moreover, preparation of such organometallic reagents involves air sensitive and multistep reactions. Substituted enynes can also be synthesised by the Stephens–Castro reaction,[12] Sonogashira coupling,[13] Heck alkynylation,[14] Heck–Sonogashira–Cassar coupling,[15] *etc.* All these reactions require either a co-catalyst in addition to palladium or organometallic precursors. Sonogashira–Hagihara coupling[16] was also developed, but it also requires halogenated precursor. From the above discussion it is concluded that straightforward introduction of the alkyne group generally requires functionalised reactant material such as unsaturation or halides. Hence efforts have been diverted toward cross-coupling reactions involving activation of unreactive C–H bonds under palladium catalysis, as this procedure requires mild reaction conditions as well as a cheap, readily available substrate and catalyst.[17]

Besides the problem discussed above regarding traditional coupling, if acidic C–H bonds could be alkynylated directly, then it would provide an excellent method with good potential value.[18–20] Based on the above concept, herein we report the straightforward alkynylation of slightly more acidic C–H bonds of 4-thiazolidinone with terminal acetylene using a palladium catalyst without the need for any pre-functionalisation of the substrate. Up to now this kind of work has mostly been carried out *via* nucleophile–electrophile coupling pathways, but here we are reporting the reaction that proceeds through a nucleophile–nucleophile coupling strategy. In order to carry out the desired coupling, substrate 4-thiazolidinone was synthesised

Sonogashira-Tohda-Hagihara reaction



Our work



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routinely. The slightly more acidic proton of the synthesised 4-thiazolidinone moiety was chosen for functionalisation with terminal acetylene by employing palladium catalysis. However, the same reaction also might be applicable to the other substrate with an acidic C–H bond, but here we choose the 4-thiazolidinone molecule because of its well reported excellent biological profile and also because synthesis of this molecule requires a cheap and easily available substrate.[21–24]

Experimental section

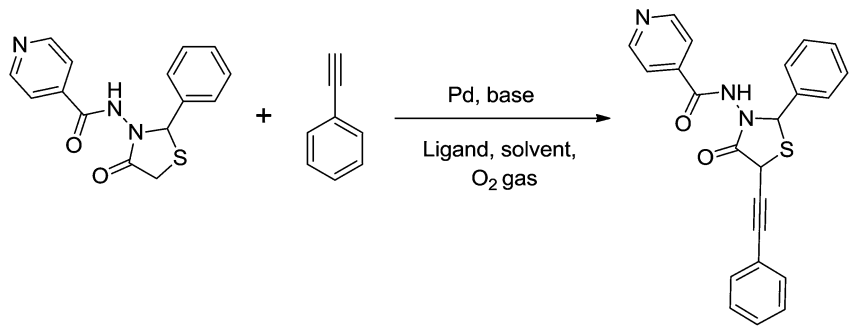
1. Reagents and materials

All reactions except the coupling reaction were carried out under nitrogen atmosphere. 1,4-Dioxane and toluene were dried over Na with benzophenone-ketyl intermediate as an indicator. Solutions and solvents that are moisture and air sensitive were transferred through a stainless-steel cannula or syringe. All chemicals were received from appropriate suppliers. Analytical grade solvents were used. Reactions were monitored routinely by TLC. Aluminium-backed silica gel was used for TLC (silica gel 60 F254 grade, Merck DC) and spots were visualised by UV light. Column chromatography was performed on silica gel LC 60A (70–200 micron).

2. Instrumental

All synthesised compounds were characterised by ^{1}H NMR, ^{13}C NMR, mass spectroscopy as well as by elemental analysis. A Veego electronic apparatus VMP-D (Veego Instruments Corporation, Mumbai, India) was used for checking the melting point in open capillaries and the results are uncorrected. Varian Gemini 200 MHz and Avans 300 MHz model spectrometers were used for ^{1}H NMR and ^{13}C NMR spectra, respectively. DMSO-d_6 was used as the solvent and TMS as the internal standard with 200 MHz and 300 MHz resonant frequencies of ^{1}H NMR and ^{13}C NMR, respectively. Chemical shifts were recorded as parts per million (ppm) downfield from TMS for ^{1}H NMR and ^{13}C NMR. Splitting patterns are designated as follows: d, doublet, s, singlet, t, triplet, dd, double doublet, m, multiplet. A Heraeus CarloErba 1180 CHN analyser (Hanau, Germany) was used for elemental analysis.

Table 1 Reaction optimization[a]



1a **2a** **3a**

Entry	Catalyst	Ligand	Base	Solvent	Yield[b]
1	$Pd_2(dba)_3$	Brettphos	KOAc	1,4-Dioxane	Trace
2	$Pd_2(dba)_3$	Xphos	Cs_2CO_3	1,4-Dioxane	Trace
3	$Pd(dppf)Cl_2$	Xphos	Cs_2CO_3	1,4-Dioxane	34%
4	$Pd(PPh_3)_2Cl_2$	Xphos	Cs_2CO_3	1,4-Dioxane	45%
5	$PdCl_2$	Xphos	Cs_2CO_3	1,4-Dioxane	40%
6	**$Pd(OAc)_2$**	**Xphos**	**Cs_2CO_3**	**1,4-Dioxane**	**60%**
7	$Pd(OAc)_2$	Brettphos	Cs_2CO_3	1,4-Dioxane	37%
8	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	1,4-Dioxane	20%
9	$Pd(OAc)_2$	*t*-Bu brettphos	Cs_2CO_3	1,4-Dioxane	31%
10	$Pd(OAc)_2$	Dppf	Cs_2CO_3	1,4-Dioxane	21%
11	$Pd(OAc)_2$	Josiphos	Cs_2CO_3	1,4-Dioxane	48%
12	$Pd(OAc)_2$	Sphos	Cs_2CO_3	1,4-Dioxane	56%
13	**$Pd(OAc)_2$**	—	**Cs_2CO_3**	**1,4-Dioxane**	**16%**
14	$Pd(OAc)_2$	Xphos	K_2CO_3	1,4-Dioxane	14%
15	$Pd(OAc)_2$	Xphos	KOAc	1,4-Dioxane	Trace
16	$Pd(OAc)_2$	Xphos	LiO^tBu	1,4-Dioxane	28%
17	$Pd(OAc)_2$	Xphos	KO^tBu	1,4-Dioxane	15%
18	$Pd(OAc)_2$	Xphos	Cs_2CO_3	Toluene	45%
19	$Pd(OAc)_2$	Xphos	Cs_2CO_3	DMF	20%
20	$Pd(OAc)_2$	Xphos	Cs_2CO_3	THF	18%

[a] Catalyst: 1.5 mol%, ligand: 3 mol%, 4-thiazolidinone 1.0 mmol, terminal acetylene: 1.0 mmol, base: 2.5 mmol, solvent: 5 ml per mmol, 1 atm. O_2.
[b] Isolated yields.

3. Preparation of Schiff base substrates

The corresponding hydrazide (isonicotinic acid hydrazide or nicotinic acid hydrazide) or aryl amine with different aryl aldehydes was reacted at reflux temperature using ethanol as a solvent according to the literature without any modification.[25,26] The progress of the reaction was continuously monitored using TLC. After completion of the reaction, the reaction mixture was poured into cold water so that solid precipitates of Schiff base came out. Other Schiff base derivatives were prepared from the corresponding aryl amine and aryl aldehyde. The yield of the reaction is 80–85%.

4. General procedure for the synthesis of 4-thiazolidinone

An oven dried flat-bottomed flask previously equipped with a magnetic stir bar was charged with Schiff base (0.01 mol) and thioglycolic acid (0.01 mol) in dry toluene as solvent.[27,28] The system was modified by using a Dean–Stark apparatus in order to remove the water molecules formed azeotropically during the reaction. The reaction mixture was heated at refluxing temperature. After the completion of the reaction, the mixture was poured into a cold aqueous sodium bicarbonate solution in order to remove unreactive thioglycolic acid. The crude product was filtered, washed with distilled water and purified by crystallisation. The reaction gives a yield of 80–85%.

5. Typical procedure for palladium catalysed coupling of 4-thiazolidinone with terminal alkyne

4-Thiazolidinone (1.0 mmol), ligand (2.0 mol%), base (2.5 mmol) and a palladium catalyst (1.0 mol%) in 1,4-dioxane were stirred in an oven dried flat-bottom flask which was equipped with a condenser under nitrogen atmosphere. After stirring for 30 minutes at room temperature, the flask was vacuumed and refilled with O_2. Then the flow of O_2 was maintained at 1 ml min^{-1}. Terminal acetylene 2a (1.0 mmol) dissolved in 1,4-dioxane (2.0 ml) was slowly added using a syringe pump at 60 °C. The temperature was then raised to 90 °C. After completion of the reaction, the reaction mixture was poured into cold aqueous sodium bicarbonate solution and then filtered through a pad of celite, eluting with dichloromethane. The filtrate was concentrated and the residue was purified by using column chromatography in order to get the desired product.[29] The yield was 55–60%.

Result and discussion

To reach the desired goal, we first checked the feasibility of our experimental result using phenyl acetylene 1a and *N*-(4-oxo-2-phenylthiazolidin-3-yl) isonicotinamide (INH) 2a as model reactants to gain a preliminary understanding so that we could optimize the reaction conditions for a more efficient synthetic route under mild conditions. Our preliminary inspection was carried out with the catalyst $Pd(OAc)_2$, with dppf as ligand, Cs_2CO_3 as base and 1,4-dioxane as solvent at 90° using O_2 as oxidant. However, the result we got was an inadequate yield of the desired product with the concomitant formation of other byproducts. Hence, to achieve satisfactory formation of 3a we screened a series of ligands, catalysts, bases and solvents to ensure the viability of the proposed coupling phenomenon. The optimum results are summarized in Table 1. Consequently, through several different experiments, it was observed that in the presence of $Pd(OAc)_2$, the cross-coupling of 1a and 2a could produce the desired product 3a at 65% yield, whereas other palladium catalysts were less effective compared with $Pd(OAc)_2$. Replacement of $Pd(OAc)_2$ by $Pd(dppf)Cl_2$ and $Pd(Ph_3P)_2Cl_2$ provides a considerable yield compared to the use of $Pd(OAc)_2$. Moreover, the results obtained by employing $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ catalysts were considered to show them to be inappropriate as Pd precursors. In addition, to prevent homo

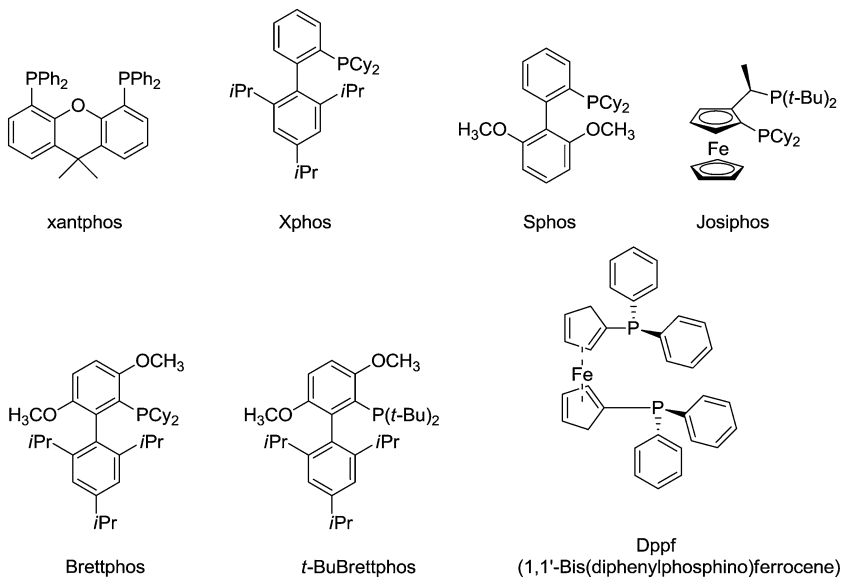
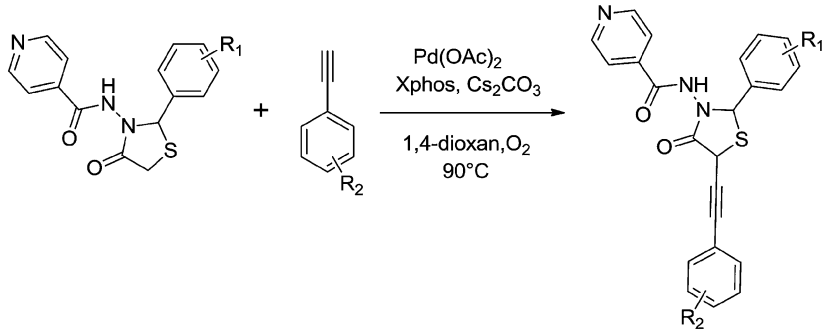


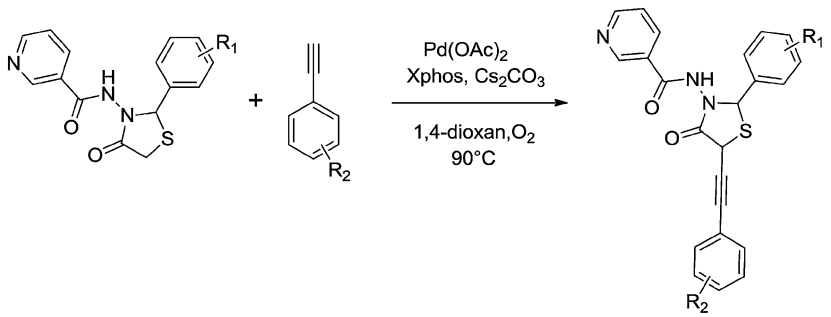
Fig. 1 Phosphine ligands.

Table 2 Scope for the reaction of 4-thiazolidinone with different terminal alkynes[a]



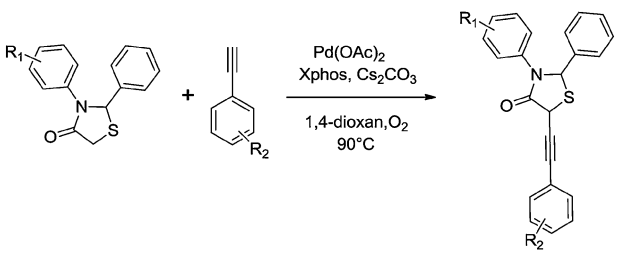
1(a-g) **2(a-g)** **3 (a-g)**

Entry	Product	R_1	R_2	Yield[b]
1	3a	–H	–H	60%
2	3b	2-CH_3	2-CH_3	65%
3	3c	4-CH_3	4-CH_3	65%
4	3d	2-NO_2	2-NO_2	67%
5	3e	2-NO_2	2-OCH_3	67%
6	3f	2-OCH_3	2-OCH_3	67%
7	3g	3-NO_2	4-$N(CH_3)_2$	70%



1(h-k) **2(h-k)** **3 (h-k)**

Entry	Product	R_1	R_2	Yield[b]
8	3h	–H	–H	60%
9	3i	2-CH_3	2-CH_3	65%
10	3j	4-CH_3	4-CH_3	65%
11	3k	4-OCH_3	4-OCH_3	70%



1(l-n) **2(l-n)** **3 (l-n)**

Entry	Product	R_1	R_2	Yield[b]
12	3l	2-NO_2	–H	62%
13	3m	4-NO_2	–H	65%
14	3n	2-CH_3	2-CH_3	67%

[a] Reaction condition: $Pd(OAc)_2$: 1.0 mol%, xphos: 2.0 mol%, Cs_2CO_3: 2.5 mmol, 4-thiazolidinone: 1.0 mmol, phenyl acetylene: 1.0 mmol. 1,4-dioxane: 5 ml per mmol, 1 atm. O_2. [b] Isolated yield.

coupling of phenyl acetylene, phenyl acetylene dissolved in 1,4-dioxane was added slowly using a syringe pump.

Screening studies regarding a ligand revealed that the phosphine ligand is most suitable in the event of this transformation. As shown in Table 1, the yield decreased when we used a bidentate ligand such as xantphos, dppf. Thus, to obtain a better result we subsequently shifted our attention toward sterically hindered monodentate phosphine ligands like xphos, josiphos, sphos, brettphos, and *t*-bu brettphos, as mentioned in Table 1. The effect of these ligands on the reaction was examined under the same reaction conditions in order to check the potential of each of these ligands. From these studies we found that sphos and josiphos provide decent yield, while brettphos and *t*-bu brettphos offer moderate yields, whereas xphos gives a better yield under the same reaction condition. From these attempts, we conclude that by employing a xphos ligand with $Pd(OAc)_2$ in 1,4-dioxane at 90 °C, an excellent yield could be obtained from among all the possibilities (Fig. 1).

As discussed in Table 1, the base has played a critical role in this reaction. Among the screened bases, Cs_2CO_3 was found to be most fruitful base among the other bases that were examined under similar reaction conditions. Replacement of Cs_2CO_3 by K_2CO_3 provided a poor yield, whereas an alkoxide base such as LiO^tBu gives a moderate yield, but when LiO^tBu was replaced with another alkoxy base such as KO^tBu the yield obtained was poor. Also, a literature survey revealed the fact that utilization of Cs_2CO_3 tolerates the functional group more widely than other bases in this kind of transformation.

After inspection of the effect of the base's role, the effect of solvent was studied in great detail. Based on various parameters, an appropriate solvent was chosen. We had subsequently screened 1,4-dioxane, THF, DMF and toluene as solvents and examined their effects on the resultant yield. However, we found that among all the mentioned solvents 1,4-dioxane offered the highest yield. Our results suggest that on increasing the polarity of the solvent, *e.g.* when THF and DMF were used instead of 1,4-dioxane, a lower yield was obtained, and when a nonpolar solvent such as toluene was used instead of 1,4-dioxane, a lower yield was acquired.

After completion of the effective examination of the various parameters of the desired reaction, we turned our attention to checking the possibility of the same reaction with other substrates (*e.g.*, various 4-thiazolidinone derivatives as well as various terminal alkynes) producing a viable catalytic system based on optimized conditions (Table 2).

The results obtained indicated that the examined catalytic system was suitable for a wide range of substrates. Moreover, this catalytic system tolerates a wide range of functional groups, including $-OCH_3$, $-CH_3$, $-CONH$, $-N(CH_3)_2$ and $-NO_2$. Furthermore, this catalyst system failed when the substrate contains –X (halogen) and $-NH_2$ groups because if any halogen or $-NH_2$ group were there, the palladium catalyst would react with it first instead of reacting with the acidic $-CH_2$ group. In such a situation we further need to include some additives to improve the employed catalytic system, with the anticipation of getting the desired product.

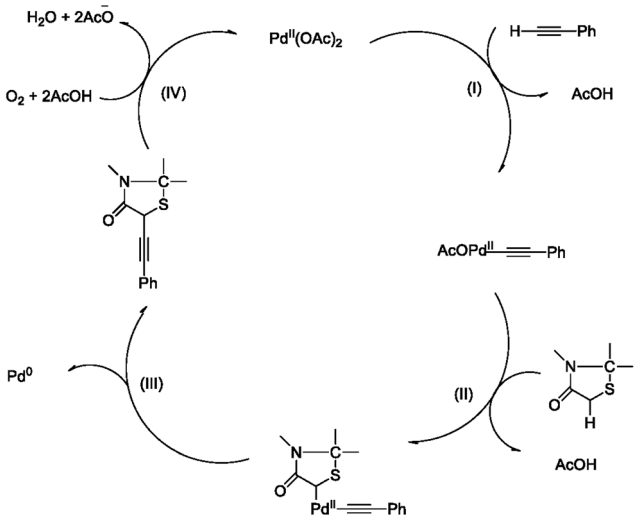


Fig. 2 Plausible mechanism.

Based on a study of the cross-coupling reaction and a literature survey, the plausible mechanism was suggested in following scheme (Fig. 2).

The mechanism consists of (I) removal of the AcOH molecule on the reaction between the terminal alkyne with the base, producing a palladium acetate complex (II). Again removal of the AcOH molecule takes place when the palladium complex reacts with the 4-thiazolidinone moiety, forming a new palladium complex (III). Elimination of palladium due to transmetallation gives Pd^0 along with the desired product (IV). The reaction between oxygen and the eliminated AcOH yields an AcO^- ion which further reacts with Pd^0 to give $Pd(OAc)_2$.

Conclusion

In conclusion, herein we have demonstrated a feasible, effective and extensive method for a palladium catalysed cross-coupling reaction to generate a new C–C bond between sp^3 (C–H) and sp (C–H) by using the acidic C–H bond of 4-thiazolidinone and the C–H bond of a terminal alkyne group. The significance of the proposed reaction is that this kind of cross-coupling reaction has hitherto not been reported. However, a similar type of coupling can be carried out by using cross-dehydrogenative coupling. Furthermore, the proposed catalytic system is capable of tolerating various functional groups, which makes this method more feasible for academic as well as industrial research.

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