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Decarboxylative/Sonogashira-type cross-coupling using $PdCl_2(Cy^*Phine)_2$†

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The $PdCl_2(Cy^*Phine)_2$ precatalyst containing the *meta*-terarylphosphine ligand, Cy*Phine, can effectively mediate decarboxylative cross-coupling with a diverse range of (hetero-)aryl, aryl and alkyl chlorides including those with unprotected functionality. Using a facile and robust protocol, this process was extended to the first synthesis of symmetrical di(heteroaryl)alkynes *via* tandem Sonogashira/decarboxylative cross-coupling of heteroaryl chlorides and propiolic acid.

Introduction

Compounds with acetylenic bridges are widely found in numerous natural products,[1] pharmaceuticals[2] and materials.[3] In particular, diarylacetylenes are of special interest in the fields of electronic materials and metal–organic frameworks (MOF) due to their rigidity, linear connectivity and extended π-conjugation.[4] These complex internal alkyne (Csp–Csp^2) compounds are commonly prepared by the powerful and facile palladium-catalyzed Sonogashira reaction.

The development of highly active catalysts and broadly applicable synthetic protocols for Sonogashira coupling including the copper-free variant, has led to wide scale adoption and industrial application.[5] Some notable contributions have been reported by Buchwald,[6] Beller,[7] Hua,[8] Colacot[9] and Plenio.[10] Recently, our group advanced the scope of palladium-catalyzed copper-free Sonogashira coupling[11] to a variety of diverse, challenging and industrially relevant substrates using the Pd-Cy*Phine catalyst based on the monodentate *meta*-terarylphosphine ligand, Cy*Phine (Fig. 1). Despite its versatility, the Sonogashira reaction and its' copper-free variant tends to produce by-products, especially for the electron-rich challenging substrates.

One attractive alternative synthetic strategy to access internal alkynes that has emerged recently is the transition-metal catalyzed decarboxylative cross-coupling of aryl halides or pseudohalides with alkynyl carboxylic acids.[12–14] The reaction proceeds *via* the elimination of CO_2, avoiding the formation of homocoupled and enyne by-products that are commonly observed. Other advantages of the decarboxylative cross-coupling method include the use of stable and widely available alkynylcarboxylic acids or carboxylate salts as substrates and potentially simplified large-scale purification procedures as CO_2 is main the stoichiometric side-product.

Since the first reported palladium-catalyzed tandem Sonogashira/decarboxylative coupling of propiolic acids with aryl halides to prepare internal alkynes by Lee *et al.*,[12a] several studies thereafter have utilized a variety of palladium and/or copper catalysts to improve and expand the scope of the reaction, although methodologies are still largely limited to aryl bromides or iodides.[12,13] It was only recently that the scope of the decarboxylative cross-coupling of alkynyl carboxylic acids was extended to the more challenging aryl chlorides by employing the bulky, electron-rich biarylphosphine ligand, XPhos as a promoter in the presence of an appropriate Pd source. Using the $Pd(OAc)_2$/XPhos[14a] catalyst system in Cs_2CO_3/THF, the decarboxylative cross-coupling of electron-withdrawing aryl chloride or chlorobenzene could be achieved in high yields. With the ferrocene-type palladacycle/XPhos[14b] catalyst system, the scope of the reaction was further expanded to include variety of aryl chloride and (hetero-)aryl chloride substrates. The use of $PdCl_2$/XPhos[14c] catalyst system enabled

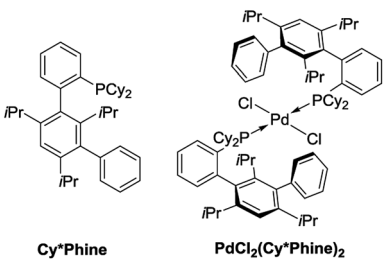

Fig. 1 Structures of Cy*Phine and $PdCl_2(Cy^*Phine)_2$ precatalyst.

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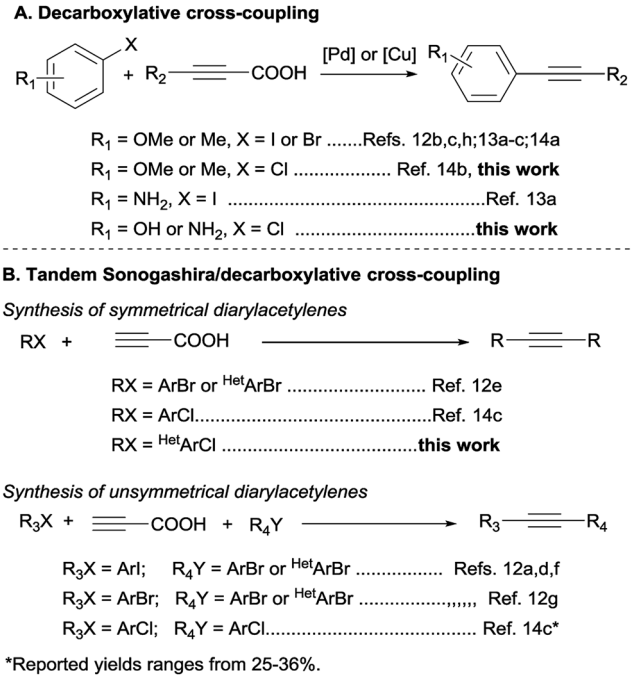


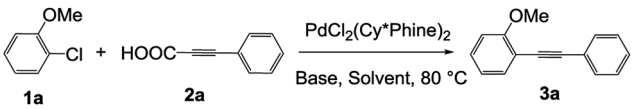
Scheme 1 A comparison of the state of the art: (A) decarboxylative cross-coupling of challenging aryl halides and arylpropolic acids, (B) synthesis of diarylacetylenes and di(hetero)arylacetylenes by tandem Sonogashira/decarboxylative cross coupling of propolic acid and aryl- or heteroaryl-halides.

the assembly of diarylalkynes from aryl chlorides and propiolic acid in a one-pot manner, avoiding the need to use or prepare terminal acetylene partners. Despite this improved synthetic applicability of the decarboxylative cross-coupling, several challenges still remain. Unprotected functional groups, such as phenols and anilines, are generally not well tolerated and the assembly of di(hetero)arylacetylenes from the corresponding heteroaryl chlorides are still problematic. Herein, we report the expansion of the scope of the decarboxylative cross-coupling to more challenging (hetero-)aryl chlorides substrates and greater functional group tolerance using the $PdCl_2(Cy^*Phine)_2$ catalyst system (Scheme 1). This process also enabled the first assembly of symmetrical di(hetero)aryl alkynes *via* the tandem Sonogashira/decarboxylative coupling of heteroaryl chlorides with propiolic acid.

Results and discussion

Using the electron-rich 2-chloroanisole (**1a**) and 3-phenylpropiolic acid (**2a**) as the model substrates, moderate to good yields of 1-methoxy-2-(phenylethynyl)benzene (**3a**) in 44 and 85% could be obtained using 1 mol% of $PdCl_2(Cy^*Phine)_2$, K_3PO_4 as the base at 80 °C in CH_3CN (Table 1, entry 1) or Cs_2CO_3 in CH_3CN (Table 1, entry 2) respectively, after 1.5 h. With the better performing Cs_2CO_3 as the base, a range of solvents with various polarities were evaluated (Table 1, entries 3–7). Of which, two solvents stand out: the combination of Cs_2CO_3/dioxane was able to improve the yield of **3a** to 98% (Table 1, entry 6) whereas the use of Cs_2CO_3/THF was able to give quantitative yield of **3a** (Table 1, entry 7). We then examine the effect of various inorganic bases (*e.g.*, K_2CO_3, Na_2CO_3, K_3PO_4, NaO*t*Bu, LiHMDS) or organic bases (*e.g.*, NEt_3 and piperidine) in THF (Table 1, entries 8–14). Interestingly, while Cs_2CO_3 remained the better choice amongst the bases tested, K_3PO_4 in THF gave an improved result of 80% (Table 1, entry 10), highlighting the synergistic effect of solvent and base.

Table 1 Reaction conditions optimization: effects of bases and solvents[a]



1a 2a 3a

Entry	Base	Solvent	Yield[b] (%)
1	K_3PO_4	CH_3CN	44
2	Cs_2CO_3	CH_3CN	85
3	Cs_2CO_3	Toluene	70
4	Cs_2CO_3	DMSO	41
5	Cs_2CO_3	DMF	74
6	Cs_2CO_3	Dioxane	98
7	Cs_2CO_3	THF	>99(99)[c]
8	K_2CO_3	THF	83
9	Na_2CO_3	THF	35
10	K_3PO_4	THF	80
11	NaO^{t}Bu	THF	0
12	LiHMDS	THF	Trace
13	NEt_3	THF	Trace
14	Piperidine	THF	0

[a] Reaction conditions: 1 mol% $PdCl_2(Cy^*Phine)_2$, 0.5 mmol of **1a**, 0.6 mmol of **1b**, 1.2 mmol base, 2 mL of solvent, 80 °C, 1.5 h. [b] GC yield based on 0.5 mmol of **1a** using dodecane as an internal standard. [c] Isolated yield.

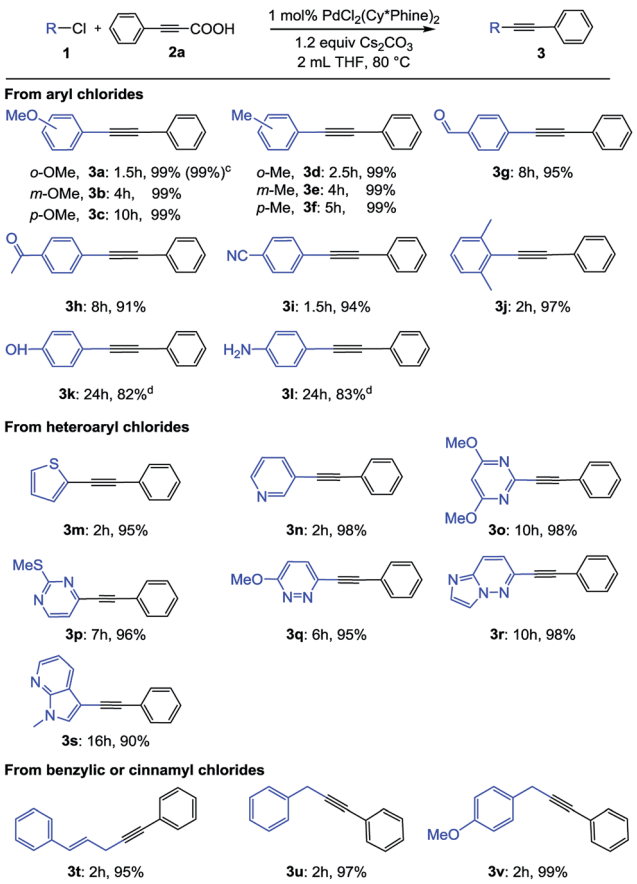
To gain insights on the productivity of the $PdCl_2(Cy^*Phine)_2$ catalyst system, the model reaction was carried out at lower temperatures and lower catalyst loadings. Lowering the reaction temperatures to 70 °C led to complete conversion after prolonged times (Table 2, entry 1) but a further decrease to 60 °C resulted in only 70% yield after 12 h (Table 2, entry 2). A catalyst loading of as low as 0.1 mol% is sufficient to achieve quantitative **3a**, albeit requiring a much longer reaction time (Table 2, entry 4) for complete conversion. No coupling occurred in the absence of the catalyst even under prolonged time (24 h), indicating the essential role of the $PdCl_2(Cy^*Phine)_2$ catalyst system in facilitating the reaction (Table 2, entry 5).

With the best Cs_2CO_3/THF conditions, a diverse range of aryl (**1a–1l**), heteroaryl (**1m–1s**), cinnamyl (**1t**), and benzyl chlorides (**1u–1v**) with 3-phenylpropiolic acid (**2a**) could be decarboxylatively coupled in good to excellent yields (82–99%) (Scheme 2). There is no electronic or steric bias of the aryl chlorides that could be coupled with **2a** to afford their corresponding internal alkynes **3a–l**. Unactivated electron-rich aryl chlorides, *e.g.*, (*o*, *m*, or, *p*)-chloroanisoles or chlorotolanes showed interesting rate trends whereby *ortho* > *meta* > *para* depending on the *o*, *m*, *p*-aryl ring substituent of the aryl

Table 2 Reaction conditions optimization: effect of catalyst loading and temperature[a]

Entry	$PdCl_2(Cy^*Phine)_2$ (mol%)	Temp. (°C)	Time (h)	Yield[b] (%)
1	1	70	10	>99
2	1	60	12	70
3	0.5	80	3	>99
4	0.1	80	36	>99
5	0	80	1.5	0

[a] Reaction conditions: $PdCl_2(Cy^*Phine)_2$, 0.5 mmol of **1a**, 0.6 mmol of **1b**, 1.2 mmol Cs_2CO_3, 2 mL of solvent. [b] GC yield based on 0.5 mmol of **1a** using dodecane as an internal standard.



Scheme 2 Decarboxylative coupling of 3-phenylpropiolic acid with organic chlorides[a,b]. [a]Reaction conditions: 1 mol% $PdCl_2(Cy^*Phine)_2$, 0.5 mmol of organic chloride **1**, 0.6 mmol of **2**, 1.2 mmol Cs_2CO_3, 2 mL of THF, 80 °C. [b]Average isolated yields of two runs. [c]8 mmol scale reaction completed within 6 h, isolated yields in parentheses. [d]3 mol% of $PdCl_2(Cy^*Phine)_2$ used instead.

chloride. It is noteworthy that whilst the protocol identified in this study is very similar to Li *et al.*,[14a] where $Pd(OAc)_2$/XPhos was used as the catalyst system, only 19% yield of the desired product could be achieved for the coupling of electron-rich 4-chloroanisole and **2a** after 10 h. Pleasingly, the facile protocol is also amenable to challenging substrates such as 4-chlorophenol (**1k**) and 4-chloroaniline (**1l**), albeit at a higher catalyst loadings (3 mol%). To demonstrate scalability, the reaction using 8 mmol of 2-chloroanisole (**1a**) and phenylpropiolic acid (**2a**) could be completed within 6 h using 1 mol% $PdCl_2(Cy^*Phine)_2$ to obtain **3a** in near quantitative yield.

In addition, the decarboxylative cross-coupling of aliphatic propiolic acids with various aryl-, heteroaryl- and benzyl chlorides including those with unprotected functionality proceeded smoothly in good to excellent yields (86–99%) using the general protocol (Table 3). Typically, the reaction for alkylpropiolic acids is slower compared to their aromatic counterparts due to their reduced reactivity and, with more challenging substrates, higher catalyst loading was found to be necessary for the reaction to reach near completion within a reasonable timeframe (Table 3, entries 3, 5, 6 and 9).

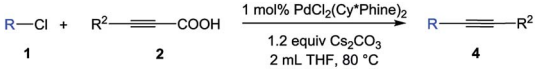
To improve the practicality of the decarboxylative cross-coupling approach for the synthesis of complex internal alkynes where the requisite coupling partners are not readily available, the development of the one-pot tandem Sonogashira/decarboxylative coupling of (hetero)aryl chlorides with propiolic acid for the preparation of symmetrical di(heteroaryl)alkynes became our next focus (Scheme 3).

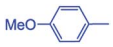
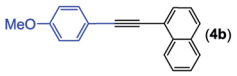
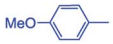
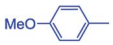
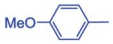
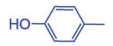
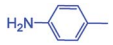
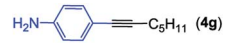
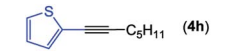
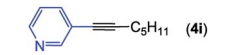
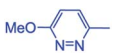
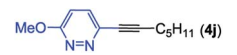
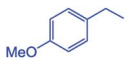
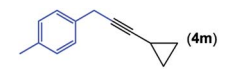
Under our standard conditions ($PdCl_2(Cy^*Phine)_2$, Cs_2CO_3, THF, 80 °C), 3-chloropyridine and propiolic acid (**5**) were chosen as the coupling partners. However, at up to 5 mol% $PdCl_2(Cy^*Phine)_2$ at 80 °C, little conversion to the desired 1,2-di(pyridin-3yl)ethyne was observed after 24 h. However, substitution of THF for the higher boiling solvent, 1,4-dioxane and repeating the reaction at 120 °C successfully afforded 1,2-di(pyridin-3-yl)ethyne (**6a**) in 55% isolated yield. Similarly, the tandem Sonogashira/decarboxylative cross-coupling of 2-chlorothiophene and 3,5-dichloropyridine yielded the desired 1,2-di(thiophen-2-yl)ethyne (**6b**) and 1,2-di(3-chloropyridin-5-yl) ethyne (**6c**) in 58% and 24% isolated yields, respectively, and together this represents the first examples of 1-pot, a tandem Sonogashira/decarboxylative cross-coupling using heteroaryl chloride substrates to yield 1,2-di(heteroaryl)alkyne products.

Conclusions

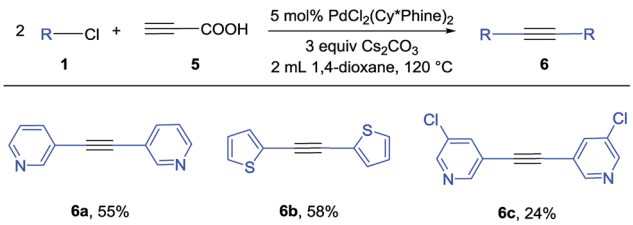
In summary, we have demonstrated the application of $PdCl_2(Cy^*Phine)_2$ in a decarboxylative cross-coupling between alkynyl carboxylic acids and a diverse array of commercially available alkyl, aryl and (hetero-)aryl chlorides with improved functional group tolerance using a facile protocol. As a complementary synthetic strategy to copper-free Sonogashira protocols using $PdCl_2(Cy^*Phine)_2$, we have also presented the first synthesis of symmetrical di(heteroaryl)alkynes *via* the tandem Sonogashira/decarboxylative cross-coupling of propiolic acid with heteroaryl chlorides. Further investigations into other tandem reaction capabilities of the $PdCl_2(Cy^*Phine)_2$ system are currently underway in our laboratories and will be reported in due course.

Table 3 Decarboxylative of organic chlorides with alkynyl carboxylic acids[a]



Entry	R	R^2	Product	Time (h)	Yield[b] (%)
1		 (2b)	 (4b)	5	98
2		(2c)	 (4c)	14	99
3[c]		(2d)	 (4d)	24	99
4		 (2e)	 (4e)	4	99
5[c]		2c	 (4f)	12	89
6[c]		2c	 (4g)	12	86
7		2c	 (4h)	12	89
8		2c	 (4i)	12	90
9[c]		2c	 (4j)	24	96
10		2e	 (4k)	5	95
11		2e	 (4l)	1	99
12		2e	 (4m)	1	98

[a] Reaction conditions: 1 mol% $PdCl_2(Cy^*Phine)_2$, 0.5 mmol of organic chloride **1**, 0.6 mmol of alkynyl carboxylic acid **2**, 1.2 mmol Cs_2CO_3, 2 mL of THF, 80 °C. [b] Average isolated yields of two runs. [c] 2 mol% of $PdCl_2(Cy^*Phine)_2$.



Scheme 3 Synthesis of symmetric di(heteroaryl)alkynes *via* tandem Sonogashira/decarboxylative cross coupling[a]. [a]Reaction conditions: 5 mol% $PdCl_2(Cy^*Phine)_2$, 1.0 mmol of R–Cl, 0.4 mmol of propiolic acid, 1.2 mmol Cs_2CO_3, 2 mL of dioxane, 120 °C, 16 h. [b]Average isolated yields of two runs.

Acknowledgements

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