Synthesis of di-substituted alkynes *via* palladium-catalyzed decarboxylative coupling and C-H activation

Alberto Gómez-Herrera,[a] Fady Nahra,[b] Jiufeng Wu,[a] Frédéric Izquierdo,[a] Marcel Brill,[a] Catherine S. J. Cazin,[b] and Steven P. Nolan*[b][c]

***Abstract**: A straightforward methodology for the decarboxylative cross-coupling of aryl bromides and phenylpropiolic acid using a Pd(II)-NHC catalyst has been developed. Various aryl bromides have been successfully transformed into the corresponding di-substituted alkynes using environmentally benign conditions (weak base and ethanol as solvent). This efficient catalytic system also proved useful for the copper-free Sonogashira coupling of aryl and alkenyl bromides with various terminal alkynes. The synthetic utility of these methodologies was highlighted in the synthesis of a polyaromatic compound and various fluoroenynes.*

Introduction

The use of palladium-based catalytic systems for the formation of C-C bonds is a common and increasingly important strategy in organic synthesis.[1] Among these systems, the preparation of internal alkynes has proved to be a highly useful methodology. Traditional strategies to prepare these compounds consist of reacting acetylides (obtained from terminal alkynes in the presence of an appropriate base) with aryl or alkenyl halides. This method presents significant restrictions (long synthetic routes, inconvenient use of strong bases, low functional group tolerance and air-sensitivity). To this end, the Sonogashira reaction has been shown to be a more convenient approach, allowing for easy access to internal alkynes starting from a wide range of terminal alkynes and organic halides using a Pd(II)/Cu(I) catalytic system.[2] This procedure is nowadays commonly utilized for the synthesis of various symmetrical and unsymmetrical alkynes, owing mainly to its milder reaction conditions and broader substrate tolerance compared to traditional methodologies. However, this reaction usually requires a large excess of an amine base, and it also produces inconvenient stoichiometric amounts of Cu(I)-salts as waste.

The use of alkynyl carboxylic acid derivatives as terminal alkyne surrogates in the palladium-catalyzed decarboxylative coupling has also gained some attention (Scheme 1). While useful for the formation of various types of C-C bonds,[3] it was not until 2008 that the first representative example of C(*sp*)-C(*sp*^{2}) intermolecular decarboxylative coupling was reported. Lee and co-workers presented a straightforward palladium-catalyzed procedure which allowed for the synthesis of internal alkynes, using a C-H activation/decarboxylative coupling sequence.[4] The two-step one-pot procedure employed propiolic acid and aryl iodides for the C-H activation reaction (1st step) affording aryl propiolic acid derivatives; these species were then used as substrates in combination with aryl bromides for the decarboxylative coupling (2nd step) using [$Pd_2(dba)_3$] as catalyst for both reactions. While good overall performance was obtained, the requirement for multiple synthetic steps, as well as the moisture sensitivity and cost of the employed reagents (tetrabutylammonium fluoride, P^tBu_3) have precluded a much wider application of this method. In subsequent studies, the same group improved upon this catalytic system,[5-6] as propiolic acid was replaced with substituted analogues, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as base and P^tBu_3 was replaced by 1,4-bis(diphenylphosphino)butane (dppb) as ligand.

In 2010, the first example using the more commercially available aryl chlorides as coupling partners was presented by Li and co-workers, with $Pd(OAc)_2$ as catalyst and a bulky monodentate Buchwald-type phosphine (XPhos).[7] The wider applicability of this protocol has inspired the most recent work in the field. Wu and co-workers reported the coupling of aryl chlorides and propiolic acid derivatives using a ferrocene-based palladacycle in the presence of XPhos and K_2CO_3.[8a-b] Lee and co-workers recently followed up on this procedure and reported the use of $Pd(OAc)_2$ in combination with a Josiphos-type ligand for the coupling of propiolic acid derivatives and aryl chlorides.[8c] It should be noted that the use of Cu(I)[9] and other metal additives[10] or co-catalysts[11] was also shown to be active in this transformation; however, these protocols remain limited, exhibiting low functional group tolerance and relying on high temperatures to proceed efficiently.

So far, the use of phosphines as ligands has dominated this area of research, and the application of NHC-based (NHC = *N*-heterocyclic carbenes) palladium complexes in these types of reactions has remained scarce.[12] Recent reports, have mainly described the use of Pd(II)-NHC complexes as efficient catalysts in the copper-free Sonogashira coupling. Considering their success in cross-coupling reactions under mild and greener conditions,[13] we envisaged similar protocols could be applied to both the copper-free Sonogashira reaction and the decarboxylative coupling using our previously reported Pd(II)-NHC precatalysts.[13-14] The ease of handling of the latter and their high reactivity and performance at low catalyst loadings, could certainly be a great advantage in the synthesis of internal alkynes through both reactions. In this context, we present herein the application of Pd(II)-NHC pre-catalysts, of the formula

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[a] Dr. Alberto Gómez-Herrera, Dr. Frédéric Izquierdo, Dr. Marcel Brill, Jiufeng Wu
School of Chemistry
University of St Andrews
St Andrews, KY16 9ST, UK.
[b] Prof. Dr. Steven P. Nolan, Prof. Dr. Catherine S. J. Cazin, Dr. Fady Nahra
Department of Chemistry and Centre for Sustainable Chemistry
Ghent University
Krijgslaan 281 - S3, 9000 Gent, Belgium.
E-mail: Steven.Nolan@UGent.be.
[c] Chemistry Department
College of Science, King Saud university
PO Box 2455, Riyadh, 11451, Saudi Arabia

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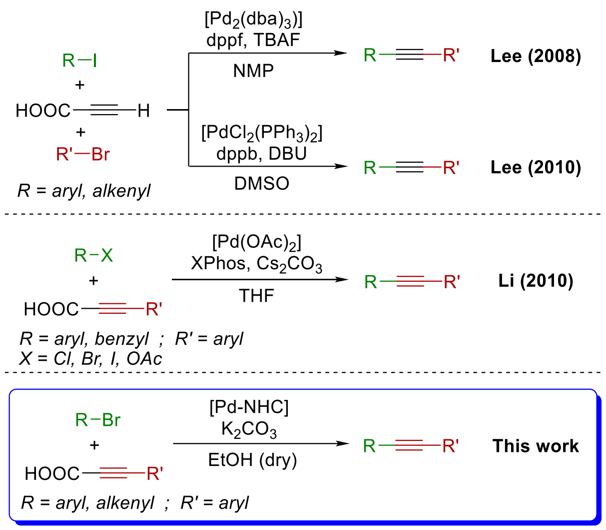
[Pd(η^3-cin)Cl(NHC)], in the decarboxylative coupling of aryl bromides and propiolic acid under mild conditions. The C-H activation reaction (Copper-free Sonogashira coupling) is also fully investigated using these readily available pre-catalysts.



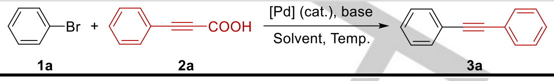
Scheme 1. Decarboxylative coupling of propiolic acid derivatives with organic halides catalyzed by palladium complexes.

Results and Discussion

[Pd(η^3-cin)Cl(IPr)] (IPr = *N,N'*-bis-[2,6-(di*iso*propyl) phenyl]imidazol-2-ylidene; cin = cinnamyl)[15] was chosen as the initial catalyst for investigating the decarboxylative coupling between bromobenzene (**1a**) and phenylpropiolic acid (**2a**). This complex is currently one of the most advantageous catalysts for cross-coupling,[13c-d,16,17] due to its high versatility in C-C bond formation, stability in air and ease of activation.[18] Preliminary tests were conducted using a 1:1 ratio of an EtOH/H_2O mixture at 80°C in the presence of 1.3 equiv. of Cs_2CO_3 as base (Table 1). Under these conditions, an 81% conversion to the desired product **3a** was observed (Table 1, entry 1). Reducing the equivalents of **2a** and the base to 1.1 equiv. each had a detrimental effect on the conversion (Table 1, entry 2). The use of NEt_3 as base had a similar effect, reducing the conversion to 70% (Table 1, entry 3). When Cs_2CO_3 was replaced by the less expensive K_2CO_3, an equally good conversion was obtained (82%; Table 1, entry 4); therefore, all subsequent optimization reactions were conducted using K_2CO_3. Increasing the catalyst loading to 5 mol% improved the observed conversion (89%; Table 1, entry 5). Interestingly, when a sealed reaction vessel was used, a much lower conversion towards **3a** was observed (Table 1, entry 5 vs entry 6). This is attributed to the escape and removal of the generated CO_2, favoring the decarboxylation process.

At this point, two other [Pd(η^3-cin)Cl(NHC)] catalysts were screened using 3 mol% catalyst loading; [Pd(η^3-cin)Cl(IPr*)] (IPr* = (*N,N'*-1,3-bis[2,6-bis(diphenylmethyl)-4-methylphenyl] imidazol-2-ylidene) and [Pd(η^3-cin)Cl(IPr^{Cl})] (IPr^{Cl} = *N,N'*-bis-[2,6-(di*iso*propyl)phenyl]-4,5-dichloro-imidazol-2-ylidene) were shown to be less efficient than their IPr counterpart (50% and 64% conversion, respectively; Table 1, entries 7-8). The effect of the solvent was next examined. Several solvents were tested; however, no significant improvement was achieved (see Supporting Information). Increasing the water ratio from 1:1 to 1:2 seemed promising (Table 1, entries 9-10); however, when only EtOH was used as solvent, full conversion to **3a** was attained (Table 1, entry 11). Under these conditions, **3a** was isolated in 74% yield. Upon further drying of the solvent and 3 mol% of catalyst loading,[19] full conversion was maintained, (80%; Table 1, entry 12). The use of dry ethanol is not judged necessary, rendering the method more user-friendly. A decrease in the reaction temperature was attempted; however, this led to lower isolated yields of **3a** (Table 1, entries 13-14).

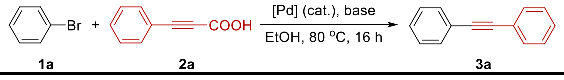
Table 1. Optimization of the Pd-catalyzed decarboxylative coupling of bromobenzene (**1a**) and phenylpropiolic acid (**2a**).[a]



Entry	Base (equiv.)	Solvent	T (°C)	Conversion (%)[b]
1	Cs_2CO_3 (1.3)	EtOH/H_2O (1:1)	80	81
2[c]	Cs_2CO_3 (1.1)	EtOH/H_2O (1:1)	80	77
3[c]	NEt_3 (1.1)	EtOH/H_2O (1:1)	80	70
4	**K_2CO_3 (1.3)**	**EtOH/H_2O (1:1)**	**80**	**82**
5[d]	**K_2CO_3 (1.3)**	**EtOH/H_2O (1:1)**	**80**	**89**
6[d][e]	K_2CO_3 (1.3)	EtOH/H_2O (1:1)	80	67
7[f]	K_2CO_3 (1.3)	EtOH/H_2O (1:1)	80	50
8[g]	K_2CO_3 (1.3)	EtOH/H_2O (1:1)	80	64
9	K_2CO_3 (1.3)	EtOH/H_2O (1:2)	80	91
10	K_2CO_3 (1.3)	EtOH/H_2O (1:3)	80	88
11	K_2CO_3 (1.3)	EtOH	80	> 99 (74)[h]
12	**K_2CO_3 (1.3)**	**EtOH (dry)**	**80**	**> 99 (80)[h]**
13	K_2CO_3 (1.3)	EtOH (dry)	70	(74)[h]
14	K_2CO_3 (1.3)	EtOH (dry)	60	(75)[h]

[a] Reaction conditions: **1a** (0.5 mmol, 1 equiv.), **2a** (1.3 equiv.), [Pd(η^3-cin)Cl(IPr)] (3 mol%), base (1.3 equiv.), EtOH/H_2O (1:1) (0.5 mL), 80 °C, 16 h. [b] Conversion determined by ^1H NMR relative to **1a**. [c] 1.1 equiv. of **2a** is used. [d] 5 mol% of [Pd]. [e] Sealed reaction vessel. [f] 3 mol% of [Pd(η^3-cin)Cl(IPr*)] was used. [g] 3 mol% of [Pd(η^3-cin)Cl(IPr^{Cl})] was used. [h] Isolated yield in parenthesis.

Table 2. Influence of reagent stoichiometry on reaction yield.[a]



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

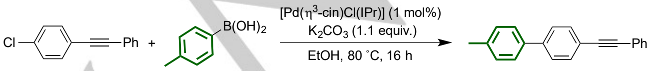
Entry	2a (equiv.)	K_2CO_3 (equiv.)	Isolated yield (%)
1	1.3	1.3	80
2	1.5	1.5	89
3	2.0	2.0	95

[a] Reaction conditions: phenylpropiolic acid (**2a**), PhBr (**1a**) (0.5 mmol, 1 equiv.), K_2CO_3, [Pd(η^3-cin)Cl(IPr)] (3 mol%), EtOH (0.5 mL), 80 °C, 16 h.

Finally, the stoichiometry reagents involved in the reaction was optimized (Table 2). Increasing the number of equivalents of both **2a** and K_2CO_3 from 1.3 to 2 equiv. afforded the desired product **3a** in 95% isolated yield (Table 2, entries 1-3).

With the optimal conditions on hand, the reaction scope was investigated (Table 3). Various electron-rich and electron-deficient aryl bromides were tolerated, maintaining good to excellent reactivity in all cases. *Para*-substituted aryl bromides (**1b-d**) bearing electron-withdrawing groups afforded excellent yields of the desired products (**3b-d**) using 3 mol% catalyst loading (Table 3, entries 2-4). Good reactivity was also achieved using the *para*-chloro-substituted bromobenzene, affording **3f** in 87% yield (Table 3, entry 6). The latter example highlights the selective coupling of C-Br over C-Cl bonds, a fact that represents a limitation and an opportunity of the present method. This selectivity is indeed a very useful synthetic tool for selective and rapid scaffold construction. We will take advantage of this selectivity shortly (*vide infra*). *Para*-substituted aryl bromides (**1e**,**g**) bearing electron-donating groups gave good yields of **3e** and **3g** (76% and 74%, respectively; Table 3, entries 5 and 7). However, in these cases, 5 mol% catalyst was needed to achieve complete conversion. *Ortho*-substitution also faired well under our optimized conditions, affording the desired products **3h-k** in good to excellent yields (Table 3, entries 8-11). Gratifyingly, the sterically hindered 2,6-dimethyl-2-bromobenzene (**1k**) was also well tolerated under these conditions, affording **3k** in 89% yield (Table 3, entry 11). Furthermore, the double cross-coupling reaction with 1,2-dibromobenzene (**1l**) also proved successful, affording the corresponding di-alkyne **3l** in 83% isolated yield (Table 3, entry 12). Unfortunately, no reactivity was observed with benzyl bromide as coupling partner (Table 3, entry 13).

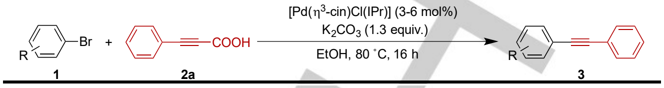
Next, the utility of the selective C-Br coupling reaction was showcased by employing **3f** as coupling substrate for the Pd-catalyzed Suzuki-Miyaura reaction with phenylboronic acid under our previously reported conditions.[17] In that manner, the polyaromatic compound **4f** was successfully isolated in 83% yield (Scheme 2).



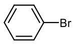
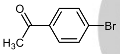
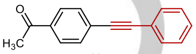
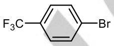
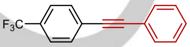
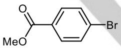
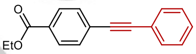
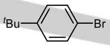
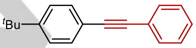
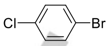
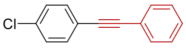
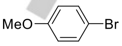
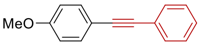
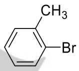
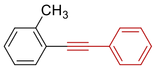
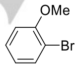
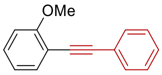
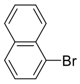
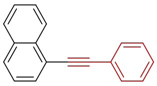
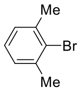
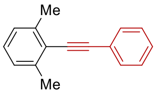
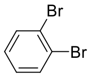
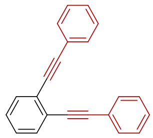
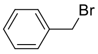
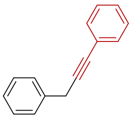
3f **4f**, 83%

Scheme 2. Pd-catalyzed Suzuki-Miyaura coupling of **3f** with arylboronic acids.

Table 3. Scope of the Pd-catalyzed decarboxylative coupling of phenylpropiolic acid and bromoarenes.[a]



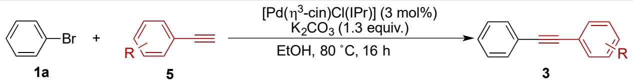
1 **2a** **3**

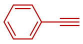
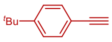
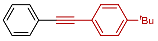
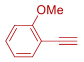
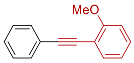
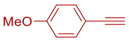
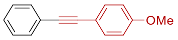
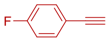
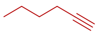
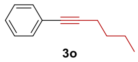
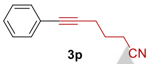
Entry	Ar-Br	Product	Isolated yield (%)
1	 **1a**	 **3a**	95
2	 **1b**	 **3b**	99
3	 **1c**	 **3c**	99
4	 **1d**	 **3d**	80
5[b]	 **1e**	 **3e**	76
6	 **1f**	 **3f**	87
7[b]	 **1g**	 **3g**	74
8[b]	 **1h**	 **3h**	97
9[b]	 **1i**	 **3i**	78
10[b]	 **1j**	 **3j**	99
11[b]	 **1k**	 **3k**	89
12[c]	 **1l**	 **3l**	83
13	 **1m**	 **3m**	0

[a] Reaction conditions: phenylpropiolic acid (2 equiv.), bromobenzene (0.5 mmol, 1 equiv.), K_2CO_3 (2 equiv.), [Pd(η^3-cin)Cl(IPr)] (3 mol%), dry EtOH (0.5 mL), 80 °C, 16 h. [b] 5 mol% [Pd(η^3-cin)Cl(IPr)]. [c] 6 mol% [Pd(η^3-cin)Cl(IPr)].

After these satisfying results, the efficiency of the catalytic system was next examined in the copper-free Sonogashira coupling of bromobenzene with various terminal alkynes. This reaction would enable an even broader reaction scope due to the wide availability of terminal alkynes compared to propiolic acid derivatives. Gratifyingly, when the optimized reaction conditions were applied to the coupling of **1a** with phenylacetylene (**5a**), **3a** could be successfully prepared in 87% isolated yield (Table 4, entry 1). Similarly, other *ortho-* and *para-*substituted electron-rich aromatic alkynes were used as coupling partners, providing good results (Table 4, entries 2-4). The coupling of 4-fluoro-phenylacetylene with bromobenzene also proceeded efficiently to provide the desired product **3n** in 94% yield (Table 4, entry 5). Interestingly, 1-hexyne and 5-hexynenitrile were successfully tolerated under our reaction conditions, affording excellent yields of **3o** and **3p** (97% and 94%, respectively; Table 4, entry 6-7). This clearly highlights the versatility of using terminal alkynes as coupling partners, especially for the preparation of unsymmetrical alkyl-substituted alkynes for which the corresponding propiolic acid derivative is not readily available.

Table 4. Scope of the copper-free Sonogashira coupling of terminal alkynes and bromobenzene.[a]



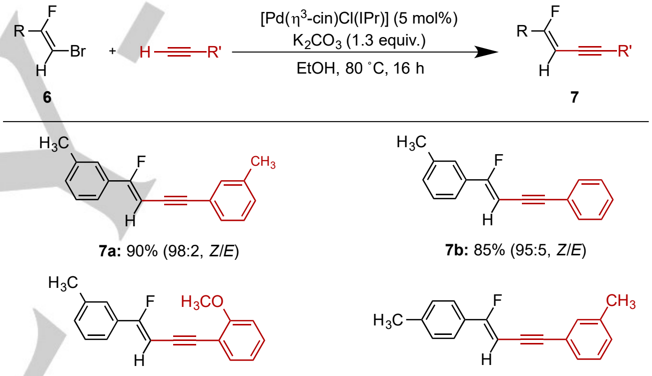
Entry	alkyne	Product	Isolated yield (%)
1[b]	 **5a**	 **3a**	87
2	 **5b**	 **3e**	87
3	 **5c**	 **3i**	74
4	 **5d**	 **3g**	79
5[c]	 **5e**	 **3n**	94
6[c]	 **5f**	 **3o**	97
7[c]	 **5g**	 **3p**	94

[a] Reaction conditions: terminal alkyne **5** (2 equiv.), bromobenzene (0.5 mmol, 1 equiv.), K_2CO_3 (1.3 equiv.), [Pd(η^3-cin)Cl(IPr)] (3 mol%), EtOH (0.5 mL), 80 ºC, 16 h. [b] 1.3 equiv. of **5a** were used. [c] 5 mol% [Pd(η^3-cin)Cl(IPr)].

Next, we were keen to extend the copper-free Sonogashira coupling procedure to other coupling partners, such as alkenyl bromides. Alkenyl bromides are well known as suitable substrates for Pd-catalyzed coupling reactions.[20] A similar coupling reaction has been previously explored by Jiang and co-workers using Sonogashira-type conditions, with a conventional Pd(II)/Cu(I) catalytic system in the presence of catalytic PPh_3.[21] However, only TMS-capped fluoroenynes could be prepared using this procedure. The removal of copper as co-catalyst has also been examined for this reaction.[22] The coupling of fluorohaloalkenes using this approach has been reported by Rolando and co-workers using a [$Pd(OAc)_2$]/PPh_3/NEt_3 system for the transformation of mixtures of bromofluoroalkenes and terminal alkynes into the corresponding fluorinated enynes.[23] Based on this, we thought that revisiting this coupling reaction using Pd(II)-NHC pre-catalysts could be a worthy endeavor.

In this context, (*Z*)-1-bromo-2-fluoro-2-(3-methylphenyl)ethene was selected as suitable substrate for optimization. This alkenyl bromide was prepared according to a recent methodology published by our group, involving sequential bromination/hydrofluorination of 3-ethynyltoluene using a Au(I)-NHC bifluoride as catalyst.[24] After some optimization, using 2 equivalents of the terminal alkyne (3-ethynyltoluene) in the presence of 5 mol% of [Pd(η^3-cin)Cl(IPr)] and 1.3 equivalents of K_2CO_3 at 80 ºC for 16 h afforded full conversion of the starting material into the expected fluoroenyne (**7a**). The latter was isolated in 90% yield as an inseparable mixture of isomers (*Z*/*E* = 98:2). These optimal conditions were then tested on a representative scope of substrates (Scheme 3). Good to excellent isolated yields and good stereoselectivity were obtained in all cases, favoring (*Z*)-alkenes; however, separation of the obtained isomers was not possible by either column chromatography or crystallization.

Scheme 3. Scope of the Pd-catalyzed cross-coupling of terminal alkynes with 1-bromo-2-fluoro-2-arylalkenes.[a]



7a: 90% (98:2, *Z*/*E*)

7b: 85% (95:5, *Z*/*E*)

7c: 69% (94:6, *Z*/*E*)

7d: 91% (96:4, *Z*/*E*)

[a] Reaction conditions: **6** (0.50 mmol), alkyne (1.0 mmol), [Pd(η^3-cin)Cl(IPr)] (5 mol%), K_2CO_3 (0.65 mmol), EtOH (1 mL), 80 °C, 16 h. Isolated yields.

Conclusions

In summary, an efficient protocol for the palladium-catalyzed decarboxylative cross-coupling reaction between phenylpropiolic acid and aryl bromides has been developed using [Pd(η^3-cin)Cl(IPr)] as a conveniently commercially-available pre-catalyst. This user-friendly procedure, employing ethanol as solvent and a mild inorganic base, allowed for a wide range of differently substituted aryl bromides to be successfully transformed into the corresponding di-substituted unsymmetrical alkynes with good to excellent isolated yields. Further investigations demonstrated that terminal alkynes could be used in lieu of phenylpropiolic acid to access a broader diversity of functionalized alkynes. Other substrates containing C(sp^2)-Br bonds, such as bromofluoroalkenes, could also be used as coupling partners for the efficient and stereoselective synthesis of fluoroenynes.

Experimental Section

General procedure for the Pd-catalyzed decarboxylative coupling of phenylpropiolic acid and aryl bromides

A 4-mL screwcap vial equipped with a septum cap and a stirring bar was charged with phenylpropiolic acid (**2a**) (146 mg, 1.00 mmol, 2 equiv.), K_2CO_3 (138 mg, 1.00 mmol, 2 equiv.), [Pd(η^3-cin)Cl(IPr)] (3-5 mol%), aryl bromide (**1**) (0.50 mmol, 1 equiv.) and EtOH (0.5 mL). A needle attached to a balloon is pierced through the septum, and the reaction mixture was stirred at 80ºC for 16 h. *On a larger scale, the reaction could be refluxed using a round-bottom flask and a reflux condenser without any loss of efficiency*. The reaction mixture was diluted with CH_2Cl_2 (2 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, pentane) to afford the desired compound (**3**).

General procedure for the Pd-catalyzed copper-free Sonogashira coupling of terminal alkynes with bromobenzene

A 4-mL screwcap vial equipped with a septum cap and a stirring bar was charged with the terminal alkyne (**5**) (0.65 mmol, 1.3 equiv.), K_2CO_3 (89.8 mg, 0.65 mmol, 1.3 equiv.), [Pd(η^3-cin)Cl(IPr)] (3-5 mol%), bromobenzene (**1a**) (0.50 mmol, 1 equiv.) and EtOH (0.5 mL). A needle attached to a balloon is pierced through the septum, and the reaction mixture was stirred at 80ºC for 16 h. On a larger scale, the reaction could be refluxed using a round-bottom flask and a reflux condenser without any loss of efficiency. The reaction mixture was diluted with CH_2Cl_2 (2 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, pentane) to afford the desired compound (**3**).

General procedure for the Pd-catalyzed cross-coupling of 1-bromo-2-fluoro-2-arylalkenes and terminal alkynes

A 4-mL screwcap vial equipped with a septum cap and a stirring bar was charged with [Pd(η^3-cin)Cl(IPr)] (16.3 mg, 2.50 μmol, 5 mol%), K_2CO_3 (89.7 mg, 0.65 mmol, 1.3 equiv.), the terminal alkyne (1.00 mmol, 2 equiv.) and EtOH (0.5 mL). A solution of the bromoalkene (**6**) (0.50 mmol) in EtOH (0.5 mL) was then added. A needle attached to a balloon is pierced through the septum, and the resulting system was stirred in air at 80ºC for 16 h. On a larger scale, the reaction could be refluxed using a round-bottom flask and a reflux condenser without any loss of efficiency. The sample was diluted in CH_2Cl_2 (3 mL), dried over $MgSO_4$ and concentrated under vacuum. The resulting residue was purified by column chromatography (SiO_2) to afford the desired compound (**7**).

Acknowledgements

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Keywords: Coupling • Palladium • NHC • Aryl bromide • Decarboxylation • Internal alkyne • Fluoroenyne

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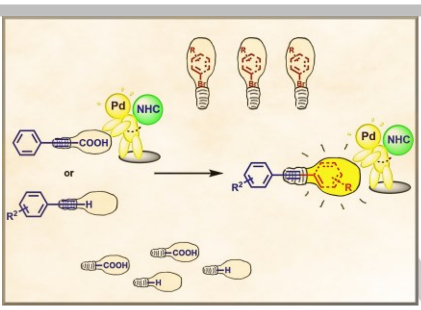
Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

A straightforward strategy for the decarboxylative cross-coupling of various aryl bromides with phenylpropiolic acid using a Pd(II)-NHC catalyst is herein described. This efficient catalytic system also proved useful for the copper-free Sonogashira coupling of aryl and alkenyl bromides with various terminal alkynes. Using this system, the synthesis of a polyaromatic compound and various fluoroenynes was successfully achieved.



*Alberto Gómez-Herrera, Fady Nahra, Jiufeng Wu, Frédéric Izquierdo, Marcel Brill, Catherine S. J. Cazin and Steven P. Nolan**

Synthesis of di-substituted alkynes via palladium-catalyzed decarboxylative coupling and C-H activation