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Catalytic Alkyne Arylation Using Traceless Directing Groups

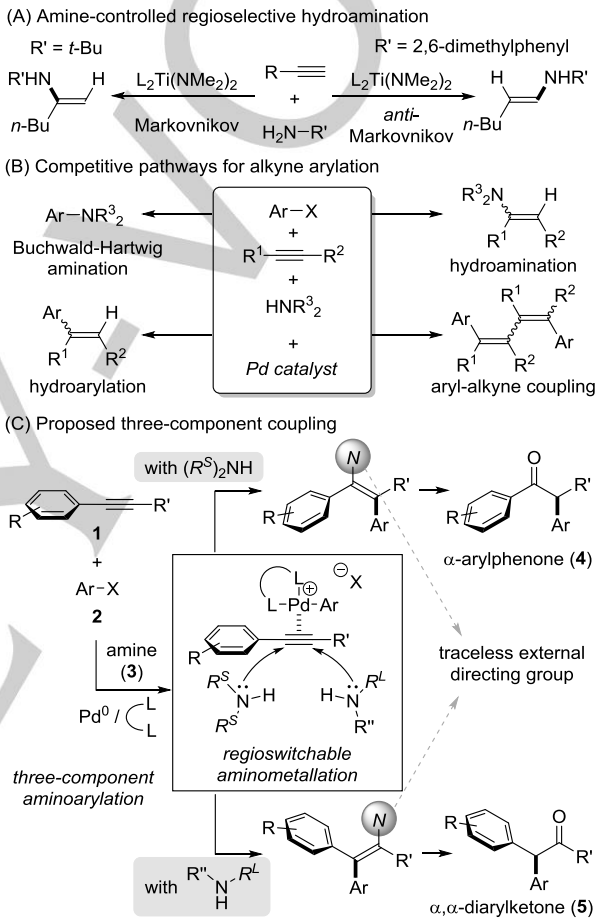
Jung-Woo Park,*[a,b] Bubwoong Kang[a] and Vy M. Dong*[a]

Abstract: Using Pd(0)/Mandyphos, we achieve a three-component aminoarylation of alkynes to generate enamines, which hydrolyze to either *α*-arylphenones or *α*,*α*-diarylketones. This Pd-catalyzed method overcomes established pathways to enable the use of amines as traceless directing groups for C–C bond formation.

In nature, regiocontrol results from the selective binding of substrates in an enzymatic pocket, while synthetic chemists devise strategies that include tuning of reagents, catalysts, and directing groups. Hydroamination is an attractive way to functionalize alkynes, whereby both *anti*-Markovnikov and Markovnikov selective variants have been demonstrated.[1,2] In these studies, regioselectivity for the aminopalladation step[3] depends on the amine, where bulky amines add to the less hindered position of a terminal alkyne (Scheme 1A).[2a] Inspired by these findings, we hypothesized that amines could be used as directing groups for C–C bond formation in the related, but less explored, carboamination of alkynes.[4-6] Herein, we report a three-component carboamination of alkynes that upon hydrolysis affords access to either *α*-arylphenone **4** or *α*,*α*-diarylketone **5**, depending on choice of the amine (Scheme 1B). This Pd-catalyzed strategy occurs by a distinct mechanism and offers complementary scope to emerging hydrative arylation of alkynes and *α*-arylation of ketones.[7,8] Moreover, we showcase the use of amines as traceless directing groups for alkyne functionalization.[9]

Pioneering aminoarylation of alkynes include intramolecular variants[4a-c] and annulative examples.[4a,d,e] To date, only one intermolecular, two-component aminoarylation has been demonstrated. In this case, enamines are generated from Michael acceptors, such as alkyl- or aryl-propynoic esters.[6] We imagined developing a three-component coupling between an amine, unactivated alkyne, and aryl-electrophile by Pd-catalysis (Scheme 1B). As part of our design, we proposed that aryl-electrophile **2** would undergo oxidative addition to Pd(0) to generate a *π*-acidic complex, which would bind the alkyne. This *π*-complex can undergo addition with an amine to form two possible regioisomers.

We reasoned that choice of the amine could control regioselectivity in the nucleopalladation step, whereby bulkier amines favor addition to the less hindered position. However, a number of transformations could compete,[10] including Buchwald-Hartwig amination,[11] hydroarylation,[12] hydroamination,[1] and aryl-alkyne coupling (Figure 1C).[13] Overcoming these established pathways would result in the first alkyne aminoarylation to occur by three-component coupling. Hydrolysis of the resulting enamines furnish the α-arylphenone **4** and α,α-diarylketone **5**, two useful building blocks for natural products and pharmaceuticals.[14]



Scheme 1. Three-component aminoarylation

To begin our studies, we chose 1-phenyl-1-propyne (**1a**), 3-methoxyphenyl triflate (**2a**), and morpholine (**3a**) as model substrates (Table 1). Treatment of **1a**, **2a** and **3a** with Pd and a variety of bisphosphine ligands gave no desired aminoarylation.[15] For example, with a Pd/DPPF catalyst, aryl triflate **2a** reacts with alkyne **1a** to form polyenes, with no amine incorporated. We observed a breakthrough by using a P–N ligand; specifically, the Fc-PHOX ligand provided aminoarylation in a 23% yield (**4aa**:**5aa** = 3:1), but starting material **2a** remained. We examined other ligands that bear P–N and P–P moieties and found Knochel's Mandyphos[16] **L1** promising. In tuning the aryl-substituents, we found that **L3** gave the best results (85% yield, 4:1 *rr*). Polyene mixtures from aryl triflate-alkyne coupling was prevented by use of high concentration (c > 0.8 M with amine **3a**). Weak bases

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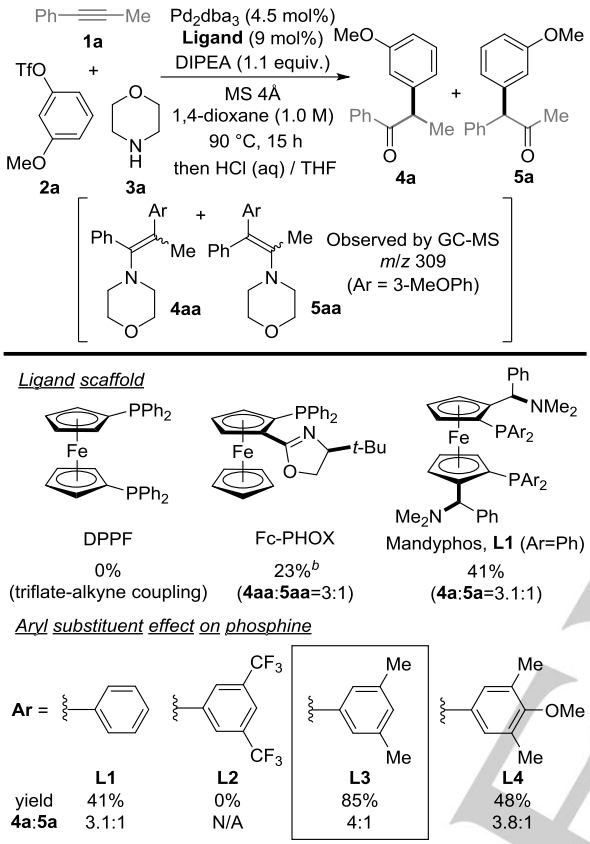
suppress the amination of aryl triflates, while use of lithium *tert*-butoxide (*t*-BuOLi) base led to Buchwald-Hartwig product, *N*-arylmorpholine.[17,] Thus, the choice of base and ligand were both critical.

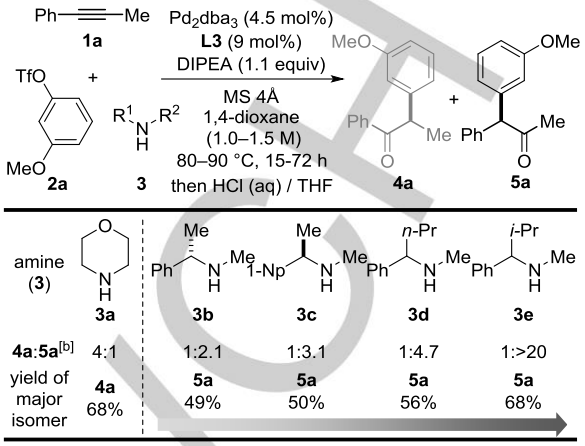
Table 1. Ligand effects on alkyne aminoarylation.[a]



[a] **1** (0.1 mmol), **2** (1.25 equiv), **3** (1.7 equiv), and MS 4A (25 mg / 0.1 mmol) were applied to the reactions. Yields and regioisomeric ratio (*rr*) determined by ^{1}H NMR using triphenylmethane as an internal standard. [b] Determined by GC-FID and GC-MS. DIPEA=*N*,*N*'-diisopropylethylamine, MS=molecular sieves, THF: tetrahydrofuran, OTf=trifluoromethanesulfonyl, DPPF=1,1'-diphenylphosphinoferrocene.

Next, we focused on achieving regiocontrol via the amine (Table 2). We studied cyclic amines and found morpholine (**3a**) optimal for high yields and selectivity for the *α*-arylphenone **4a** (**4a**:**5a** = 4:1, 68% **4a**, entry 1).[18] We examined acyclic secondary amines and discovered that the steric bulk of the amine could switch the regioselectivity to favor *α*,*α*-diarylacetone **5a**. For example, the use of *N*-methyl-*α*-methylbenzylamine (**3b**) resulted in preference for **5a** over **4a** (2.1:1 *rr*). To improve regioselectivity, we designed and prepared *N*-methyl-*α*-isopropylbenzylamine (**3e**).[19] Increasing the size of the *α*-substituent from a methyl group to an isopropyl group resulted in an increase of 2.1:1 to greater than 20:1 *rr*.[20]

Table 2. Amine effects on regioselectivity[a]



[a] **1** (0.08-0.1 mmol), **2** (1.25 equiv), **3** (1.7 equiv), and MS 4A (25 mg / 0.1 mmol) were applied to the reactions. [b] Determined by ^{1}H NMR using triphenylmethane as an internal standard.

As shown in Table 3, we used alkynes (**1a**-**1h**) and aryl triflates (**2a**-**2h**) to prepare *α*-arylphenones **4** in 39-77% yields (4-10:1 *rr*). Heteroaromatic groups could be incorporated (**4f**-**4g**). Substitution was tolerated on the aryl triflate (**2a**-**2h**), including electron donating and withdrawing groups. Using methyl 3-phenyl-2-propyn-1-yl ether (**1i**) gave *α*-arylphenone **4m**, where the methoxymethyl group was cleaved *in situ* (48% **4m**). Thus, alkyne **1i** can be used as a masked phenylacetylene.

In addition, we accessed a natural product, *O*-desmethylangolensin (**4o**), an intestinal bacterial metabolite of daidzein (soy phytoestrogen),[14a,b] and precursors of natural neolignans **4q** and **4r**.[14c] the coupling of **1h** with aryl triflate **2g** and morpholine (**3a**) gave ketone **4n** after hydrolysis (70% **4n**, 10:1 *rr*). *O*-Desmethylangolensin (**4o**) was obtained by demethylation of **4n** using BBr_3.[21] From alkyne **1e** and triflate **2h**, we prepared ketone **4p**, a precursor for natural neolignans.

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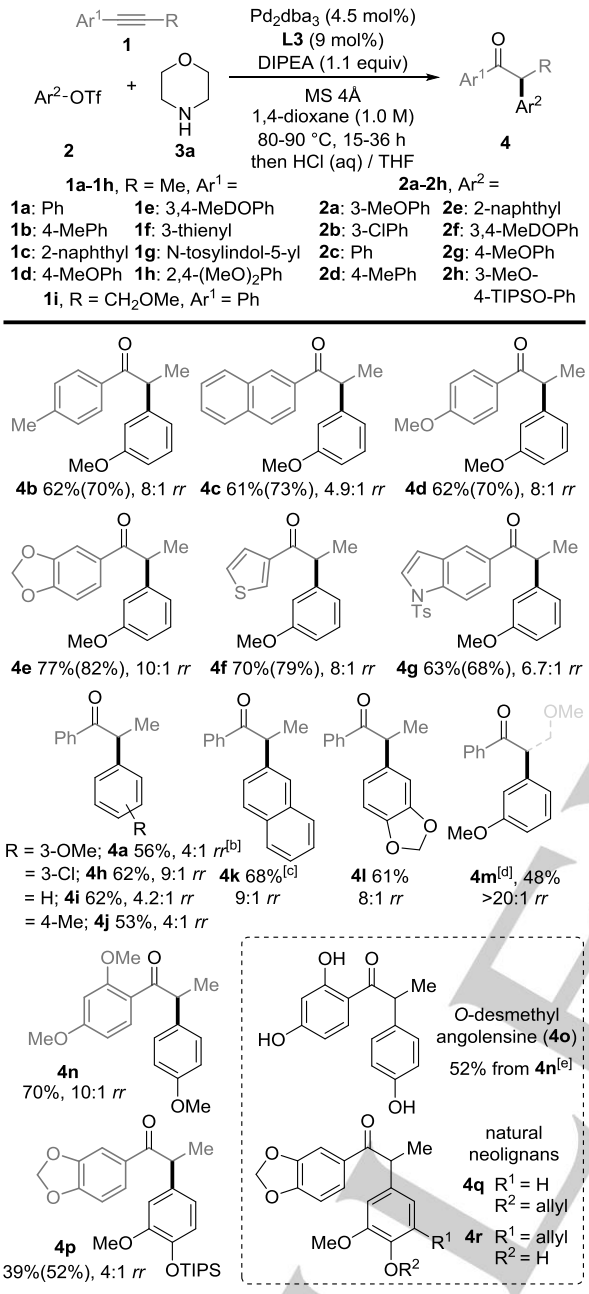
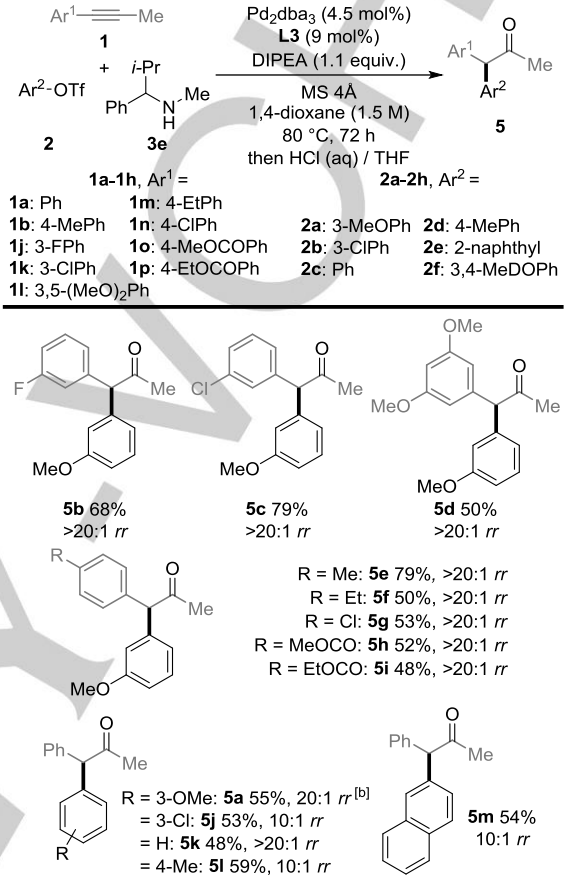
Table 3. Preparation of α-arylphenone **4** using morpholine (**3a**)[a]



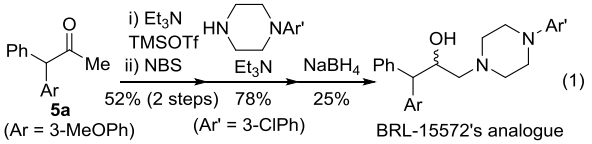
[a] **1** (0.08-0.1 mmol), **2** (1.25 equiv), **3** (1.7 equiv), and MS 4A (25 mg / 0.1 mmol) were applied to the reactions. See SI for detailed reaction conditions. Yields and regioisomeric ratio (*rr*) determined by 1H NMR using triphenylmethane as an internal standard. ^{1}H NMR yield of the major isomer **4** are in parenthesis. [b] 0.25 mmol **1a** was used. [c] 0.5 mmol **1a** was used. [d] Methyl 3-phenyl-2-propyn-1-yl ether (**1i**) was used. [e] Reaction condition: BBr_3 (10 equiv), DCM, rt, 12 h. MeDO: methylenedioxy, TIPS: triisopropylsilyl.

With amine **3e**, we apply analogous conditions to make α,α-diarylacetones **5** (Table 4). Three-component coupling of arylalkynes (**1a**, **1b**, **1j**–**1p**) with substituted aryl triflates (**2a**–**2f**) yielded α,α-diarylacetones **5** in 48–79% isolated yields for the major isomer. From ketone **5a**, which was prepared by three-component aminoarylation with amine **3e**, we prepared a MeO-analogue of BRL-15572, an antidepressant from GlaxoSmithKline (eq 1).[23]

Table 4. Preparation of α,α-diarylketone **5** using amine **3e**[a]



[a] **1** (0.08-0.1 mmol), **2** (1.25 equiv), **3** (1.7 equiv), and MS 4A (25 mg / 0.1 mmol) were applied to the reactions. See SI for detailed reaction conditions. Regioisomeric ratio (*rr*) determined by ^{1}H NMR using an internal standard. Isolated yields of major isomer **5a**-**l**. [b] 0.25 mmol **1a** was used.



On the basis of our observations and literature,[3,4c] we propose the mechanism shown in Scheme 2. The Pd(0)-complex activates the aryl triflate **2** to form arylpalladium(II)-intermediate **6**. Nucleopalladation with amine **3** then occurs to afford vinylpalladium(II)-intermediate **7**. Regioselectivity for nucleopalladation depends on the sterics of the amine **3a** versus **3e**. Amines bearing small substituents (*e.g.*, **3a**) favor attack of the carbon adjacent to aryl group, while amines bearing large substituents (*e.g.,* **3e**) favor the carbon distal. Reductive elimination of vinylpalladium **7** generates enamine **8** and regenerates Pd(0).

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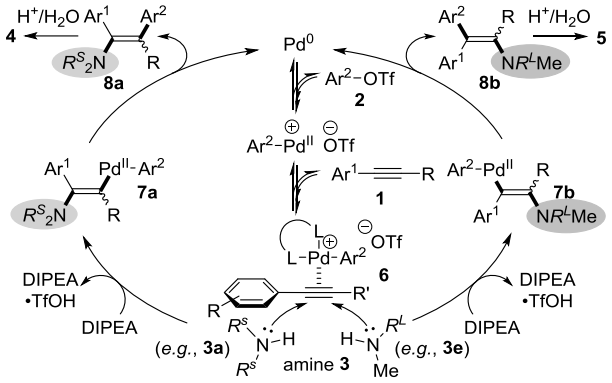

Regioswitchable aminopalladation by tuning size of amine

Scheme 2. Proposed mechanism

Future studies involve (1) designing chiral amines for stereoselective applications[23] and (2) elucidating the mechanism to guide other alkyne functionalizations.

Acknowledgements

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Keywords: alkynes • aminoarylation • multi-component coupling • palladium • regiocontrol

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[17] See SI for the detailed discussion on base effect.

[18] See SI for the results of other cyclic amines applied.

[19] The amine **3e** is prepared in one-step from isobutyrophenone with methylamine and Ti(O*i*-Pr)$_4$.

[20] With amine **3e**, concentrations higher than 1.5 M is required to suppress undesired aryl triflate-alkyne coupling reaction.

[21] The shortest reported route to **4o** is Friedel-Crafts acylation using resorcinol and *α*-methyl-(*p*-hydroxy)phenylacetic acid. See ref 14b.

[22] The commercial route is not available in literature.

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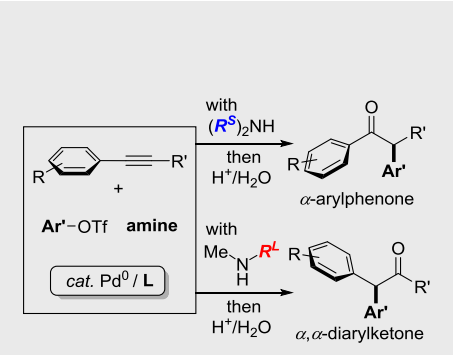
By developing a Pd(0)/Mandyphos catalyst, we have achieved a three-component aminoarylation of alkynes to generate enamines, which upon hydrolysis yield either *α*-arylphenones or *α*,*α*-diarylketones. This Pd-catalyzed method overcomes well-established pathways to enable the use of amines as traceless directing groups for C–C bond formation.



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