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Decarboxylative Alkynyl Termination of Palladium-Catalyzed Catellani Reaction: A Facile Synthesis of α-Alkynyl Anilines via *Ortho* C−H Amination and Alkylation

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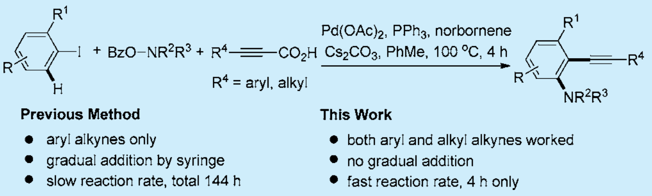
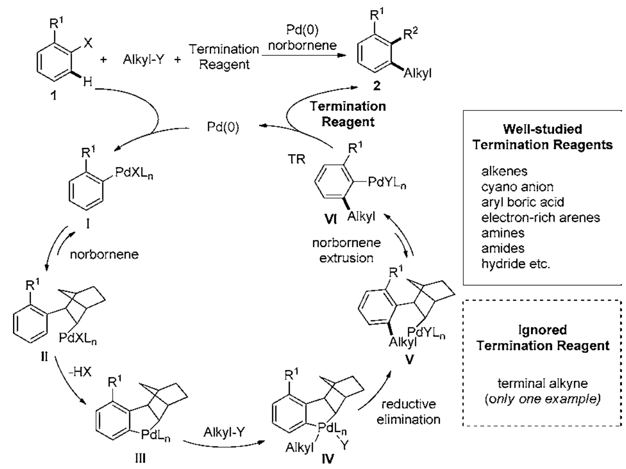
Supporting Information

ABSTRACT: A palladium-catalyzed synthesis of α-alkynyl anilines is reported. The reaction proceeds via Catellani *ortho* C−H amination followed by decarboxylative alkynylative amination. Different terminal alkyne precursors were screened, and it was found that alkynyl carboxylic acids were superior over other alkynes, which led to operationally simple reaction conditions (no gradual addition of alkynes) and broad substrate scope. The reactivity of three different components matched well; as a result, relatively higher reaction temperature could be used, greatly shortening the reaction time to 4 h from the previously reported 144 h.



Synthetic organic chemistry, as well as medicinal chemistry and material sciences, are beneficiaries of the developments in transition-metal-catalyzed transformations. Among them, special attention has been paid to palladium-catalyzed reactions due to their broad functional group tolerance and diverse reaction pathways. The Catellani reaction, which was discovered by Catellani in the 1990s[1] and further developed by the groups of Catellani and Lautens et al., is a powerful method for the synthesis of polyfunctionalized arenes.[2] As depicted in Scheme 1, it is generally believed that the key steps of the Catellani reaction are the formation of palladacycle **III** and the oxidative addition of alkyl halides to five-membered palladacycle **IV**.[3] The reductive elimination of **IV**, followed by norbornene extrusion, gives rise to arylpalladium intermediate **VI**, which subsequently undergoes classic reactions associated with Pd catalysis. Various termination reagents, including internal or external alkenes, cyanide, arylboronic acids, electron-rich arenes, amines, amides, and carbenes, etc., have been subjected to the reactions, and quite a number of useful and structurally complex molecules were synthesized using this methodology.[4] In sharp contrast to the well-studied Sonogashira coupling,[5] the Catellani reaction terminated by Sonogashira coupling is still challenging due to mismatched reactivity of terminal alkynes and other substrates. To the best of our knowledge, there was only one report described by Catellani and co-workers in 2004 in this field (Scheme 2A).[6] Because of the high reactivity of terminal alkynes, the reaction only gave 30% conversion of aryl iodides under the standard conditions (conditions A) and only afforded a complex mixture, including the expected product **3** (8%) as well as side products **4**−**6** (Scheme 2A). Moderate to good yields (66−79% brsm yields) with 82−90% conversions could be achieved after a very careful optimization (conditions B); however, the conditions still have limitations: (1) large excess of alkyl bromides were used; (2) very slow addition both of alkyl bromide and phenylacetylenes (within 72 h) via syringe pump was necessary;[7] (3) ambient reaction temperature was important to avoid side reactions, resulting the requirement for an additional 72 h of stirring to obtain a reasonable conversion. Thus, it is desirable yet still challenging to develop new practical synthetic methods to construct polysubstituted arenes bearing alkyne functionalities via the Catellani *ortho* C−H functionalization followed by Sonogashira-type termination reactions.

Scheme 1. Proposed Catalytic Cycle



Following our ongoing interests in the study of the Catellani reaction for the synthesis of multisubstituted arenes and related complex natural products,[2d,4e] we found it was critical to match

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Scheme 2. Catellani Reactions Terminated with Sonogashira-Type Coupling

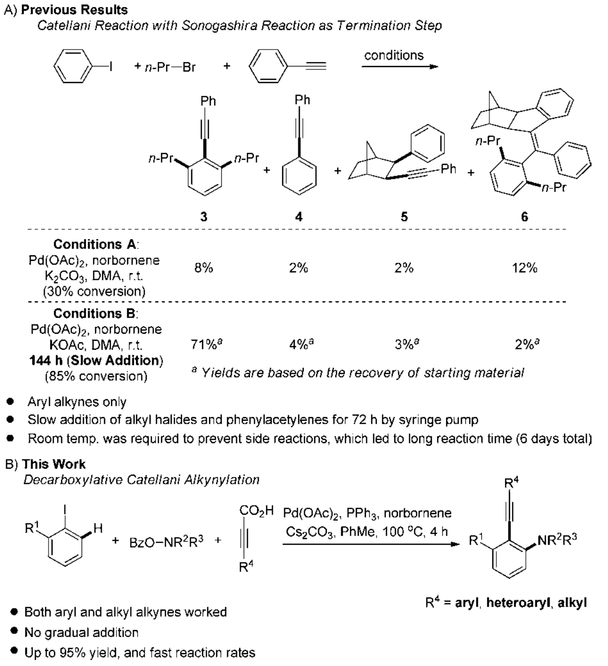
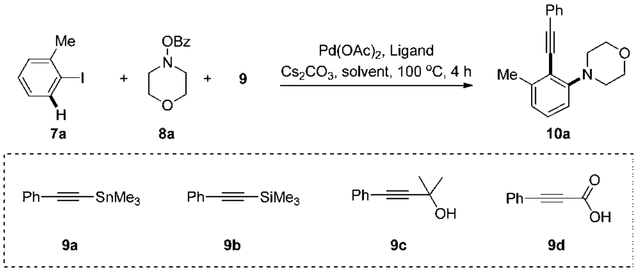


Table 1. Reaction Conditions: Optimization[a]



entry	alkyne	ligand	solvent	yield of **10a**[b] (%)
1	**9a**	PPh_3	toluene	5
2	**9b**	PPh_3	toluene	6
3	**9c**	PPh_3	toluene	60
4	**9d**	PPh_3	toluene	87
5	**9d**	$P(2\text{-furyl})_3$	toluene	65
6	**9d**	$P(o\text{-tolyl})_3$	toluene	8
7	**9d**	$P(p\text{-tolyl})_3$	toluene	79
8	**9d**	PPh_3	toluene	12[c]
9	**9d**	PPh_3	toluene	17[d]
10	**9d**	PPh_3	CH_3CN	34
11	**9d**	PPh_3	dioxane	55
12	**9d**	PPh_3	$(CH_2Cl)_2$	67
13	**9d**	PPh_3	DMF	39

[a] The reaction was conducted on 0.20 mmol of **7a**, 0.24 mmol of **8a**, 0.30 mmol of **9**, 1.20 mmol of norbornene, 0.60 mmol of Cs_2CO_3, 5 mol % of $Pd(OAc)_2$, and 12.5 mol % of phosphine. [b] Isolated yields. [c] K_3PO_4 was used. [d] K_2CO_3 was used.

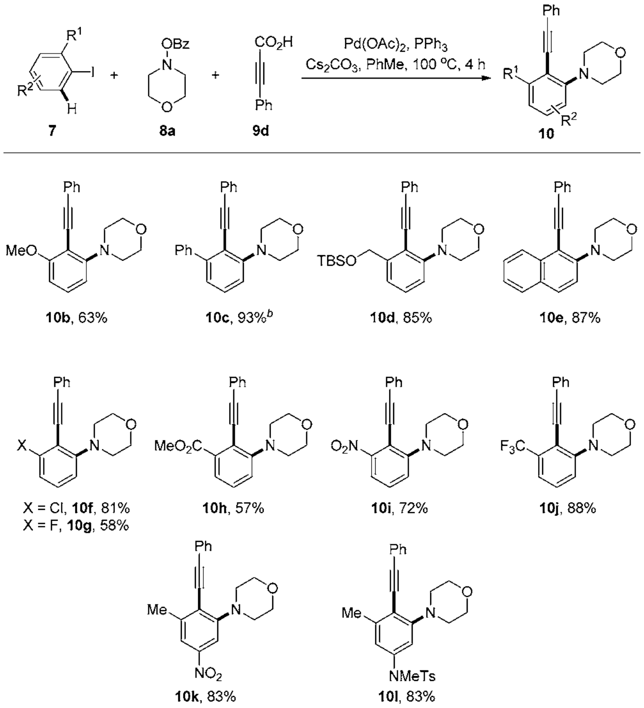
the reactivity of all three components. On the basis of the analysis of Catellani's results, it was hypothesized that the high reactivity of terminal alkynes is one of the main reasons for the formation of side products. We reasoned that compared to terminal alkynes, alkynyl analogues or precursors with relatively lower reactivity had the following advantages: (1) the insertion reaction of arylpalladium **I** with norbornene would be favored rather over the direct Sonogashira coupling, and (2) intermediate **II** would undergo C−H palladation to form palladacycle **III** instead of the formation of products like **5** through cross-coupling. As a result, no gradual addition would be required, and a relatively high temperature would be tolerable, thus significantly shortening the reaction time. Herein we report our primary results on the palladium-catalyzed Catellani reaction with a very rare alkynyl termination reaction (Scheme 2B).

Our initial examination began with the cross-coupling between alkynes, 2-methyliodobenzene and *N*-(benzoyloxy)-morpholine, which has recently been proven to be a class of efficient *ortho*-amination reagents in Catellani reaction by Dong and Chen groups (Table 1).[8] It was found that alkynylstannane (**9a**) or -silane (**9b**) were not effective reagents and the reactions delivered the desired product in very low yields, with most of the stannane and silane being unchanged (Table 1, entries 1 and 2). By the use of 2-methyl-4-phenylbut-3-yn-2-ol **9c** as the alkyne partner, the yield of **10a** was significantly improved (entry 3). Inspired by the seminal work of Goossen, Tunge, and other groups,[9,10] who disclosed transition-metal-catalyzed cross-coupling by the use of carboxylic acids via a decarboxylative process instead of organometallic reagents, 3-phenylpropiolic acid was chosen as an alkyne precursor. To our delight, when alkynyl carboxylic acid **9d** was used, the reaction afforded the desired alkynyl aniline **10a** in 87% isolated yield (entry 4). It is striking that the reaction could be conducted at 100 °C without significantly increase in the amount of the side reactions. The use of tri(2-furyl)phosphine as the ligand resulted in a relatively lower yield (entry 5). The reaction with bulky phosphine $P(o\text{-tolyl})_3$ as the ligand gave low conversion, with only 8% of **10a** being isolated (entry 6). The $Pd(OAc)_2$/$P(p\text{-tolyl})_3$ catalytic system showed similar activity in comparison with $Pd(OAc)_2$/PPh_3 (entry 7). Other bases, such K_3PO_4 and K_2CO_3, were not effective for this reaction (entries 8 and 9). Upon switching the solvent from toluene to others, it was found that no improvement in yields could be achieved (entries 10−13).

We evaluated this protocol by applying a series of *ortho*-substituted aryl iodides to synthesize different alkynyl-substituted anilines. The reaction of 2-methoxyl-, 2-phenyl-, and 2-(*O*-TBS)-hydroxymethyl iodobenzenes gave the desired products in moderate to excellent yields (Scheme 3, **10b**−**d**). The reaction of 1-iodonaphthalene also proceeded smoothly to deliver **10e** in 87% yield. 2-Chloro- and 2-fluoroiodobenzenes are also compatible substrates (**10f** and **10g**), although a relatively low yield for the 2-fluoro compound **10g** was obtained. Introducing electron-withdrawing groups at the *ortho* position gave 55−88% yields of the corresponding products (**10h**−**j**). Varying the electronic property of substituents at the *para* position of 2-methyliodobenzene had little effect on the yields (**10k**−**l**).

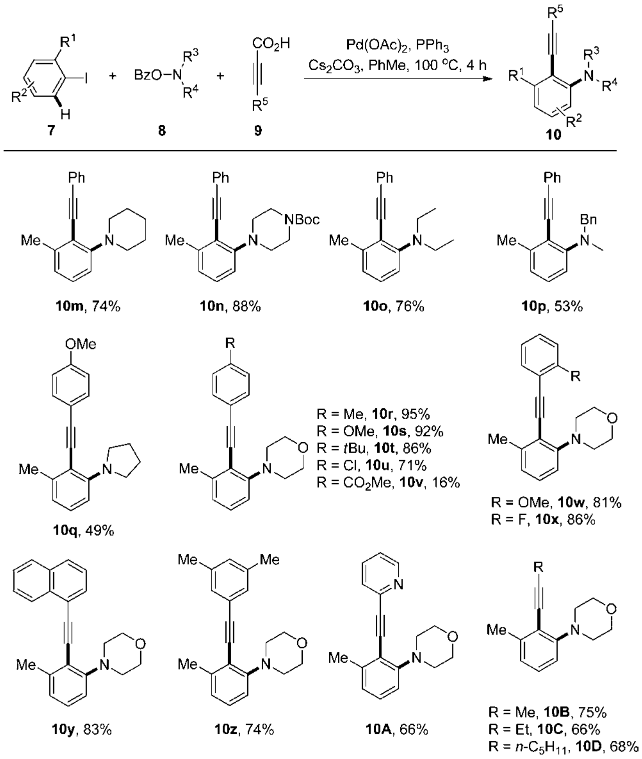
To further explore the generality of this reaction, different substituted *O*-benzoylhydroxylamines and alkynyl carboxylic acids were tested (Scheme 4). Other *N,N*-disubstituted *O*-benzoylhydroxylamines were equally compatible for this multicomponent reaction (**10n**−**q**), albeit relatively lower yields were obtained for some cases, such as pyrrolidine product **10q**. Electronic effects were investigated by varying the substituent at the *para* position of phenylpropiolic acids. With electron-donating groups at the *para* position, good to excellent yields could be achieved (**10r**−**t**). However, electron-withdrawing groups on phenylpropiolic acids were disadvantageous

Scheme 3. Substrate Scope with Various Aryl Iodides[a]



[a]The reaction was conducted on 0.20 mmol of iodides7, 1.2 equiv of **8a**, 1.5 equiv of **9d**, 6.0 equiv of norbornene, 0.60 mmol of Cs_2CO_3, 5 mol % of $Pd(OAc)_2$, and 12.5 mol % of PPh_3 in toluene at 100 °C for 4 h. [b]10 mol % of $Pd(OAc)_2$ was used.

Scheme 4. Substrate Scope[a]



[a]The reaction was conducted on 0.20 mmol of iodides **7**, 1.2 equiv of **8**, 1.5 equiv of **9**, 6.0 equiv of norbornene, 0.60 mmol of Cs_2CO_3, 5 mol % of $Pd(OAc)_2$, and 12.5 mol % of PPh_3 in toluene at 100 °C for 4 h.

for this transformation, and yields were significantly decreased, where the major side products were **5**-type bicyclo compounds (**10u** and **10v**).[11] The reactions with other substituted phenylpropiolic acids (**10w–z**), even 2-pyridinylpropiolic acid, proceeded uneventfully (**10A**). The compatibility of this reaction with aliphatic alkynes was also striking, showing significant advantages over the previous method.[12] For example, the reactions with 2-butynoic acid, 2-pentynoic acid, and 2-octynoic acid proceeded smoothly to give the corresponding products in 66–75% yields (**10B–D**).

In conclusion, we reported a palladium-catalyzed Catellani *ortho*-amination reaction, which was terminated by decarboxylative alkynylation for the efficient synthesis of substituted α-alkynyl anilines. The newly developed protocol has advantages over the previous method:[6] (1) the well-matched reactivity of alkynyl carboxylic acids with other components resulted in simple reaction conditions with easy operation, where no gradual addition was necessary; (2) in contrast to the previous methods, both aliphatic and aromatic alkynes, as well as heteroaromatic alkynes were suitable for cross-coupling; and (3) a relatively high temperature could be used, thus significantly shortening the reaction time to 4 h (previous reaction time: 144 h).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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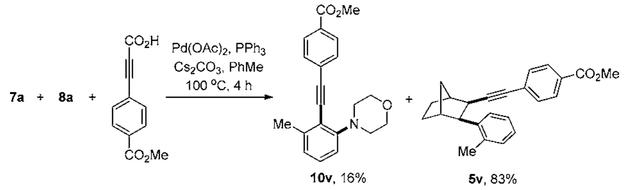
(11) Byproduct **5v** was isolated in 83% yield.



(12) According to Catellani's results, only very low conversion was achieved (18% conversion with butylacetylene) even with 72 h gradual addition; see ref 6.