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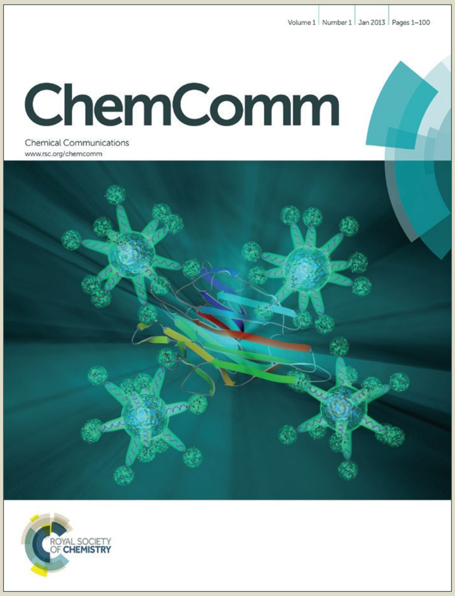

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ARTICLE TYPE

A Sustainable and Simple Catalytic System for Direct Alkynylation of C(sp^2)–H Bond with Low Nickel Loadings

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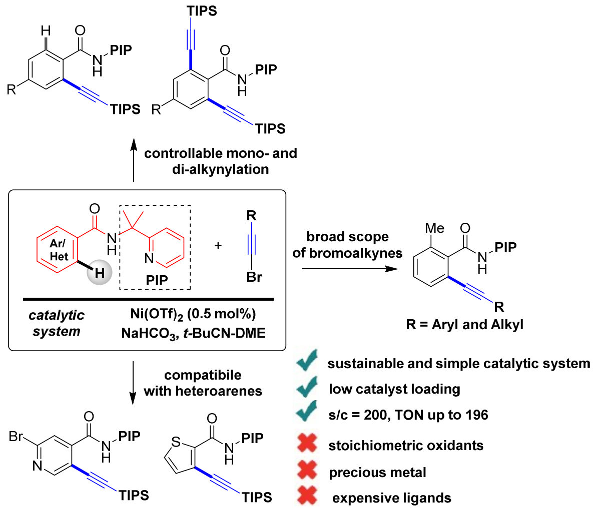
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A sustainable and simple catalytic system for the atom-economical alkynylation of benzamides with low nickel loadings is described. No organic or metallic oxidants and expensive ligands are required. A broad range of benzamides and bromoalkynes bearing various synthetically useful functional groups are compatible with this reaction. The versatility of this operationally simple protocol has been further demonstrated by the controllable mono- and di-alkynylation. Importantly, substrate/catalyst ratios of up to 200, and a turnover number of 196 were achieved, highlighting the potential of this protocol for synthetic applications.

The discovery of novel transformations that are cost-effective and sustainable to the construction of complex organic molecules is the long-standing goal of synthetic chemists in both academia and industry. Therefore, transition-metal-catalyzed direct functionalization of C-H bonds represents one of the most promising transformations.[1] This strategy obviates the need to prefunctionalize the starting materials and reduces the production of undesired wastes, thus rendering synthetic routes more step- and atom-economical. Despite these advantages, the inherent limitations and challenges of C-H functionalization reactions compared to traditional cross-coupling reactions cannot be overlooked, such as the use of high catalyst loadings and complicated catalytic systems with excess of additives or metallic oxidants.[1,2] Accordingly, the development of more effective and simple catalytic systems for the direct functionalization of C-H bonds at low catalyst loadings would be a considerable advantage for industrial applications and for sustainable consideration.

The prevalence of alkynes in natural products, medicinal targets, and functional materials has motivated tremendous efforts directed toward the synthesis of these fundamental building blocks.[3] Recently, the emerged "inverse Sonogashira coupling" involving the direct alkynylation of unactivated aryl C-H bonds with alkynyl halides or pseudohalides has attracted much attention.[4,5] Palladium- and ruthenium-catalyzed alkynylation of unactivated C-H bonds with (triisopropylsilyl)ethynyl bromide (**2a**) was achieved by the Chatani and Yu groups with the assistance of different kind of auxiliaries.[6] Chang reported a Pd-catalyzed alkynylation of N-aryl-2-aminopyridine with (triisopropylsilyl)acetylene.[7] In 2014, Loh,[8] Li[9a] and Glorius[9b] have reported Rh-catalyzed alkynylation of C(sp^2)-H bonds with hypervalent alkynyl iodine reagents. However, these methods rely on the use of high loading of precious metal catalysts (4-10 mol% Pd or Rh) with the best TON of 25.[10] Moreover, these reactions employ complicated catalytic systems, and require a sterically bulky group (usually a triisopropylsilyl group)[11] to prevent the coordinating of the alkyne unit with metal center. More recently, the Yu and Dai group[12] and our group[13] have independently developed copper-mediated alkynylation of arenes with terminal alkynes. A broad range of terminal alkynes have been used by Yu and Dai, however, only moderate yields have been achieved and a stoichiometric amount of copper salt was used as catalyst. Therefore, more sustainable catalytic system, employing significantly low loading of cheap metal catalyst, for the coupling of a wide array of diversely substituted arenes with bromoalkynes are highly desirable.

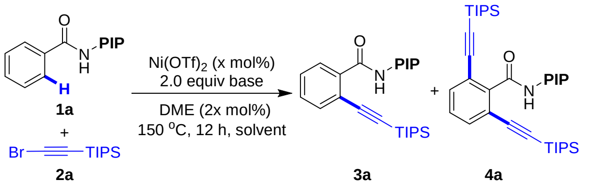


Scheme 1. Ni-Catalyzed Alkynylation of (Hetero)aryl C –H Bonds with Low Catalyst Loadings.

Herein, we disclose a versatile and efficient nickel-catalyzed alkynylation of unactivated aromatic C-H bonds with bromoalkynes (Scheme 1). The significance of this study is threefold: 1) The reaction can proceed with as little as 0.5 mol% of Ni($OTf)_2$, which equate to a substrate/catalyst (s/c) ratio of 200 and the highest turnover number (TON) up to 196. 2) The alkynylation reaction proceeds under a sustainable and simple catalytic system without the need of expensive ligands and/or metallic oxidants. 3) Chatani and coworkers have reported a nickel-catalyzed oxidative alkynylation and intramolecular annulations of arenes with internal alkynes employing a 2-pyridinylmethylamine auxiliary.[14,15] Nonetheless, nickel-catalyzed alkynylation of *unactivated* C-H bonds has not yet been realized. Therefore, this versatile system also highlights a new mode of reaction catalyzed by nickel catalyst.

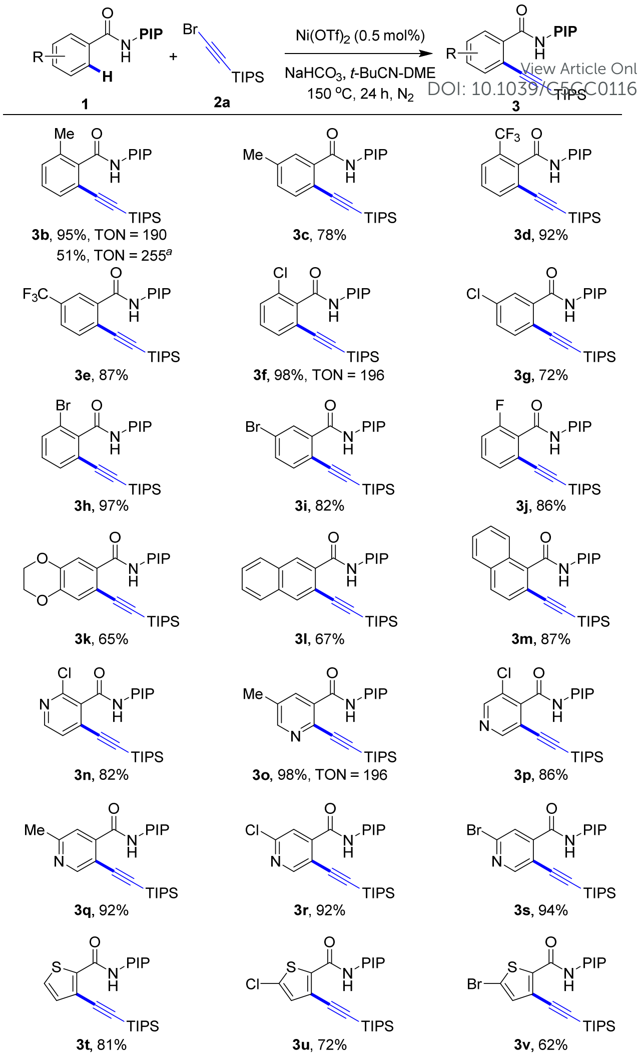
Our investigation was inspired by the elegant studies of Ni-catalyzed C-H functionalization[16-17] and recent advances on the use of our newly developed bidentate directing group derived from (pyridin-2-yl)isopropyl amine (PIP-amine) for C–H functionalization reactions.[18-20] We commenced our studies by testing the reaction of benzamide **1a** with (triisopropylsilyl)ethynyl bromide (**2a**). We were delighted to find that the desired aryl alkyne **3a** was obtained in moderate yield when $Ni(OTf)_2$ was used as catalyst and DME as ligand (Table 1, entry 1, 60% yield). A thorough screening of solvents showed that pivalonitrile can dramatically improve the yield and afforded the expected product in good yield (entry 8, 81%). The addition of $NaHCO_3$ as base improved the catalytic efficiency and gave almost quantitatively conversion of the starting material (entry 9). Gratifyingly, the catalyst loading can be reduced to 0.5 mol% under the optimized reaction conditions with an increased concentration of the reaction (entry 10, from 0.1 M to 0.8 M in pivalonitrile, **Condition A**). It is worth noting that the mono- and dialkynylation products could be selectively obtained by adjusting the stoichiometry of **1a** and bromoalkyne **2a**. Thus, when 4 equivalent of bromoalkyne **2a** was used, dialkynylated product **4a** was isolated in 92% yield (entry 11, **Condition B**); while monoalkynylation could be achieved in the presence of 2 equivalent of benzamide **1a** (entry 12, **Condition C**). We then examined the effect of various directing groups on the direct C-H alkynylation and the PIP directing group gave the best results.[21]

Table 1. Optimization of the reaction conditions[a]



entry	x (mol%)	base	solvent (M)	yield (%)[b]
1	10	Na_2CO_3	DCE (0.1)	60% (3:1)
2	10	Na_2CO_3	DME (0.1)	5%
3	10	Na_2CO_3	DMSO (0.1)	15%
4	10	Na_2CO_3	1,4-dioxane (0.1)	18%
5	10	Na_2CO_3	isobutyronitrile (0.1)	75% (4:1)
6	10	Na_2CO_3	butyronitrile (0.1)	16%
7	10	Na_2CO_3	MeCN (0.1)	trace
8	10	Na_2CO_3	pivalonitrile (0.1)	81% (3:1)
9	10	$NaHCO_3$	pivalonitrile (0.1)	99% (1:2)
10[d]	0.5	$NaHCO_3$	pivalonitrile (0.8)	99% (1:2.8)
11[e]	0.5	$NaHCO_3$	pivalonitrile (0.8)	92% (**4a**)[c]
12[f]	0.5	$NaHCO_3$	pivalonitrile (0.8)	90% (**3a**)[c]

[a]Reaction conditions: **1a** (0.1 mmol), $Ni(OTf)_2$ (x mol%), base (2 equiv), **2a** (2 equiv) and DME (2x mol%) at 150 °C for 12 h under N_2. [b]^1H NMR yield using CH_2Br_2 as the internal standard. [c] Isolated yield. [d]**1a** (0.4 mmol), 24 h. [e]**1a** (0.4 mmol), **2a** (4 equiv), 24 h. [f]**1a** (0.8 mmol), **2a** (0.4 mmol), 24 h, isolated yield based on **2a**.



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Scheme 2. The scope of benzamides. **Conditions A**: **1** (0.4 mmol), **2a** (0.8 mmol), $Ni(OTf)_2$ (0.002 mmol, 0.5 mol%), DME (0.004 mmol), $NaHCO_3$ (0.8 mmol), *t*-BuCN (0.5 mL), 150 °C, 24 h, isolated yield. [a]0.2 mol% $Ni(OTf)_2$.

Following the optimized conditions, we next tested the scope and limitation of this reaction. As shown in Scheme 2, benzamides bearing both electron-donating and electron-withdrawing groups at the *ortho* and *meta* positions of the phenyl ring reacted smoothly with bromoalkyne **2a** to give the expected monoalkynylation product selectively in good yields. When *meta*-substituted substrates was employed, the alkynylation tended to occur at the sterically more accessible position, providing the 1,2,5-trisubstituted products in high yields regioselectively (**3c**, **3e**, **3g** and **3i**). Importantly, a number of synthetically useful functional groups, such as fluoro, trifluoromethyl, chloro, bromo and methoxy, were all tolerated. Additionally, the alkynylation of 1- and 2-naphthamides also proceeded efficiently under the optimized reaction conditions (**1l** and **1m**). Alkynylation of heteroarenes, such as nicotinamides (**1n** and **1o**), isonicotinamides (**1p-1s**) and thiophene-2-carboxamides (**1t-1v**), also reacted efficiently with bromoalkyne **2a** to give the alkynylation products in high yields (**3n-3v**). Notably, halogen groups, such as chloro and bromo, were also compatible with this

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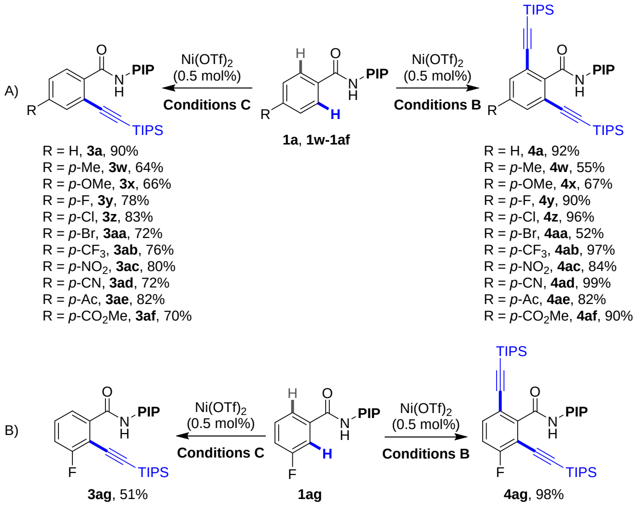
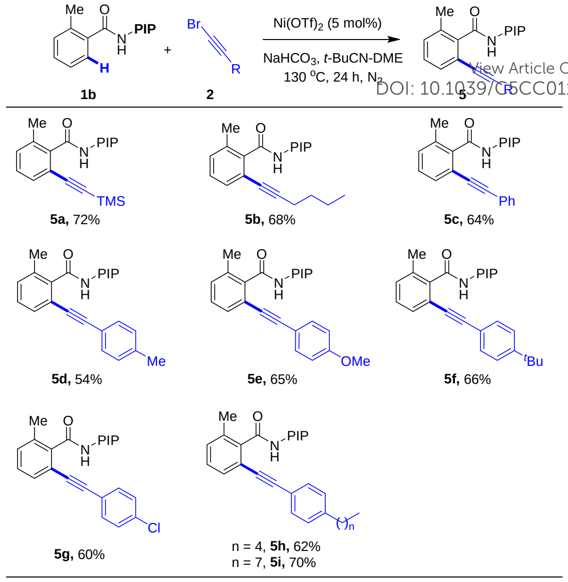
protocol, providing useful handles for further elaborations. A turnover number of 255 can be achieved with reduced yield when 0.2 mol% Ni(OTf)$_2$ was used (**3b**, 51% yield).

The controllable functionalization of sterically and electronically unbiased C-H bonds is a major challenge in nickel-catalyzed C-H functionalization reactions. To our delight, chemoselective synthesis of monoalkynylation product **3** and dialkynylation product **4** could be achieved by simply adjusting the ratio of benzamides **1** and bromoalkyne **2a** (**conditions B** and **C** in Table 1, entries 11 and 12). A wide range of functional groups, such as alkyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, nitro, cyano, acetyl and methoxycarbonyl were survived and gave the mono- and dialkynylation products respectively (Scheme 3A).[22] Notably, *meta*-Fluoro substrate **1ag** reacted predominantly at the position adjacent to fluorine under **conditions C**, perhaps due to enhanced kinetic acidity of the corresponding C–H bond (Scheme 3B). When the alkynylation reaction was conducted under **Conditions B**, dialkynylated product **4ag** was generated in high yield (98%).



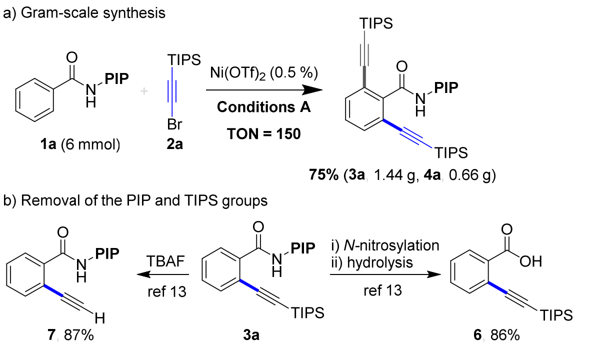
Scheme 3. Controllable Mono- and Di-alkynylation. **Conditions B**: **1** (0.4 mmol), **2a** (1.6 mmol), Ni(OTf)$_2$ (0.002 mmol), DME (0.004 mmol), NaHCO$_3$ (0.8 mmol), *t*-BuCN (0.5 mL), 150 °C, 24 h, isolated yield based on benzamide **1**. **Conditions C**: **1** (0.8 mmol), **2a** (0.4 mmol), Ni(OTf)$_2$ (0.002 mmol), DME (0.004 mmol), NaHCO$_3$ (0.8 mmol), *t*-BuCN (0.5 mL), 150 °C, 24 h, isolated yield based on bromoalkyne **2a**.

Subsequently, we tested a variety of bromoalkynes and were pleased to find that this alkynylation protocol was very efficient. As shown in Scheme 4, both alkyl- and aryl-based alkynyl bromides reacted smoothly with *ortho*-methyl benzamide **1b**, furnishing **5a-5i** in generally good yields. The generality and efficiency of the alkynylation reagents rendered this Ni-catalyzed alkynylation synthetically more attractive than previously reported Pd- and Rh-catalyzed alkynylation. The TMS-protected bromoalkyne **2b** was also tolerated, affording **5a** in 72% yield. Both electron-donating and electron-withdrawing substitutents were compatible on the aryl ring of bromoalkynes (**5d-5i**).



Scheme 4. Scope of bromoalkynes. Reaction conditions: **1b** (0.2 mmol), **2** (0.4 mmol), Ni(OTf)$_2$ (0.01 mmol), DME (0.02 mmol), NaHCO$_3$ (0.4 mmol), *t*-BuCN (2 mL), 130 °C, 24 h, isolated yield.

Finally, we further demonstrated the scalability of this catalytic protocol by using **Conditions A** in Table 2 to prepare 1.44 g of **3a** and 0.66 g **4a** using only 10 mg of Ni(OTf)$_2$ (Scheme 5a). It is worth noting that the PIP auxiliary can be easily removed via a mild *N*-nitrosylation/hydrolysis sequence as we have demonstrated recently, providng an expeditious access to *ortho*-alkynylated benzoic acids (Scheme 5b).[13]



Scheme 5. Gram-scale synthesis and removal of the PIP and TIPS groups.

In conclusion, we have reported the use of a sustainable, easy to handle catalytic system that is efficient for the direct alkynylation of unactivated aryl C–H bonds employing a removable auxiliary at low nickel loadings (0.5 mol%). This reaction protocol surpasses previously reported alkynylation reactions for broad substrate scope, cheap and simple catalyst system, and high catalytic turnovers (up to 196; s/c = 200). The highly efficient and scalable catalytic reaction proceeded with excellent functional group compatibility under simple reaction

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systems, therefore representing a significant advantage in transition-metal-catalyzed C-H alkynylation reactions.

Acknowledgements

Financial support from the National Basic Research Program of China (2015CB856600), the NSFC (21422206, 21272206), the Fundamental Research Funds for the Central Universities (2014QNA3008) and Zhejiang Provincial NSFC (LZ12B02001) is gratefully acknowledged.

Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, and analytical data for all new compounds, see DOI: 10.1039/b000000x/

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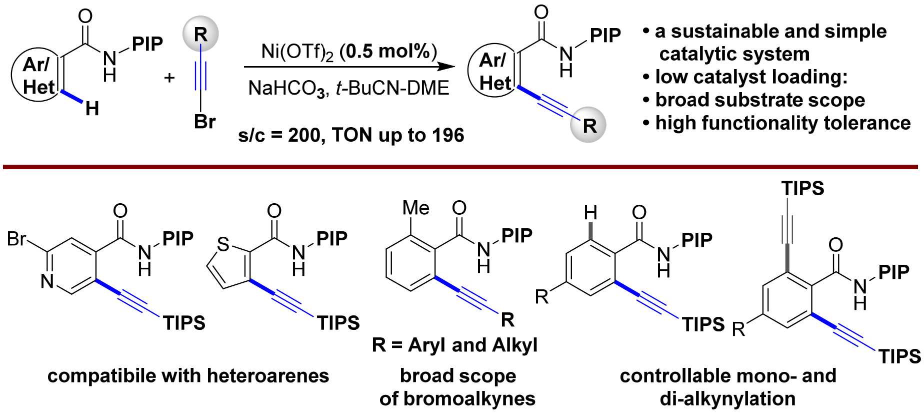

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