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To be cited as: *ChemCatChem* 10.1002/cctc.201600868

Link to VoR: http://dx.doi.org/10.1002/cctc.201600868

A Journal of
ChemPubSoc Europe

WILEY-VCH

www.chemcatchem.org

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Sequential functionalization of alkynes and alkenes catalyzed by Au(I)- and Pd(II)-NHC complexes

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Received:((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. The iodination of terminal alkynes for the synthesis of 1-iodoalkynes using *N*-iodosuccinimide in the presence of a Au(I)-NHC catalyst is reported. A series of aromatic alkynes was successfully transformed into the corresponding 1-iodoalkynes in good to excellent yields using mild reaction conditions. The further use of these compounds as organic building blocks and the advantageous choice of metal-NHC complexes as catalysts for alkyne functionalization were further demonstrated by performing selective Au(I)-catalyzed hydrofluorination to yield (*Z*)-2-fluoro-1-iodoalkenes, followed by a Suzuki-Miyaura cross-coupling with aryl boronic acids catalyzed by a Pd(II)-NHC complex to access tri-substituted (*Z*)-fluoroalkenes. All methodologies can be performed sequentially w only minor variations in the optimized individual reacti conditions, maintaining high efficiency and selectivity all cases, therefore providing straightforward access valuable fluorinated alkenes from commercially availat terminal alkynes.

Keywords: Alkynes; iodination; hydrofluorination; cros coupling; gold; palladium; *N*-heterocyclic carbe bifluoride

Introduction

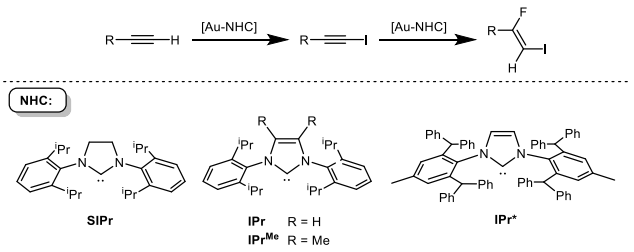
1-Iodoalkynes are extremely useful organic compounds, with industrial applications as fungicides[1] or antimicrobials,[2] but mainly as building blocks in coupling chemistry[3] and alkyne addition reactions.[4] Within the general synthetic possibilities of 1-haloalkynes,[5] this iodinated derivative has been shown to be a key intermediate in the preparation of a plethora of molecules.[6] This fact has attracted much attention in the synthetic chemistry community for some decades, further highlighting the interest in developing robust methodologies for its synthesis.

Despite the widespread use of the traditional reaction between an organic acetylide and an electrophilic iodide source for the iodination of terminal alkynes,[7] the need for stoichiometric amounts of base and the use of restrictive reaction conditions (*e.g.,* low temperatures and moisture-free systems) have evidenced a lack of efficiency for more complex systems. In response to this, the use of end-capped alkyne derivatives as reactive equivalents of terminal alkynes represents one of the attempts to circumvent these inconveniences. Species such as trimethylsilylacetylenes,[8] alkynyltrifluoroborate or propiolic acids,[10] among others,[11] have been us as suitable substrates for iodination chemistry un less forcing conditions. On the other hand, the use these derivatives still presents some limitations, su as a shorter library of commercially availa substrates and only moderate atom economy of processes, which reaffirms the interest in improv the synthetic routes involving simple alkynes. Al various "I$^+$" sources (including iodide,[12] iodoni salts,[6n,13] iodinated ionic liquids,[14] iodoalkanes, iodinated cyclic nitronates,[16] *N*-iodomorphol hydroiodide,[6c,6i,6k,6r] or *N*-iodosuccinimide)[17] ha been developed and used for the iodination terminal alkynes. However, the lack of reactivity of some alkyne systems remains a significant concern. The need to overcome these difficulties is nowadays attracting much attention.

The use of transition metals as catalysts for alkyne functionalization has been extensively reviewed.[18] In that context, the generation of metal acetylides under basic conditions has been exploited in-depth, and some examples of metal-catalyzed electrophilic iodination of terminal alkynes are available in the literature. The use of copper[19] or silver[4f,4h,20] salts as catalysts has afforded the conversion of a wide range

of alkynes into the corresponding 1-iodoalkynes with good results. However, since an excess of base is required for the copper-catalyzed system, and due to the fairly high catalyst loading of $AgNO_3$ (10-20 mol%) and high sensitivity and toxicity of the latter, the search for a better catalytic system for alkyne iodination is still ongoing. More recently, a cationic Au(I)-phosphine complex has been shown as an alternative.[21]

During the development of transition metal catalysts supported by NHC ligands (NHC = *N*-heterocyclic carbene), we envisaged that these catalysts could also activate terminal alkynes for the synthesis of 1-iodoalkynes through electrophilic iodination (Scheme 1).



Scheme 1. Initial strategy for the one-pot iodination/hydrofluorination of terminal alkynes using gold-NHC bifluoride catalysts.

Since 1-iodoalkynes are considered important organic building blocks, subsequent one-pot functionalization reactions were considered in an attempt to validate the need for robust NHC-based metal systems. Among different possibilities, the hydrofluorination of the newly formed iodinated alkynes to yield 2-fluoro-1-iodoalkenes was selected (Scheme 1). The main interest of this transformation resides in the preparation of fluorine-containing olefins,[22] which are of great interest in biological systems and are also widely present in the structure of pharmaceuticals.[23] This strategy would allow the difunctionalization of alkynes by simultaneously setting up both fluorine and iodine moieties on the same molecule. The difunctionalization of alkynes has been exploited successfully,[24] including the formation of C-X bonds (X = Cl, Br).[25] Nonetheless, very few functionalities have been introduced onto alkynes with concomitant C-F bond formation.[24i,24k,25c,26] Recently, and with precedents in the 2007 work of Sadighi,[27] Nolan and co-workers have developed the hydrofluorination of internal alkynes using Au(I)-NHC bifluoride catalysts.[28] Encouraged by their successful conversion of (chloroethynyl)benzene into its corresponding (*Z*)-2-fluoro-1-chloroalkene, we opted to use the same bifluoride catalysts. These hydrofluorination catalysts bear a triethylamine moiety that can be used as an internal base to form gold acetylides and, in that manner, allow the electrophilic iodination of terminal alkynes. For these reasons, gold-NHC bifluorides were chosen as initial catalysts to perform both transformations.

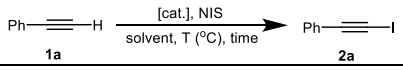
Results and Discussion

The iodination and hydrofluorination reactions were first conducted separately to allow the determination of optimal conditions for both, and later on, to merge the two in a one-pot procedure. In the case of the iodination, phenylacetylene (**1a**) was selected as a readily available and simple model substrate for optimization, while *N*-iodosuccinimide (NIS) was chosen as a convenient electrophilic iod source. The initial blank test revealed that reaction of **1a** with two equivalents of NIS in tolue at 65ºC afforded a 6% conversion (iodoethynyl)benzene (**2a**) after 24 h (Table 1, en 1). The use of 5 mol% of the Au(I) bifluoride catal with the formula $[Au(IPr^{Me})(NEt_3)][HF_2]$ (IPr^{Me} *N,N'*-bis-[2,6-(di-*iso*-propyl)phenyl]-4,5-dimethylimidazol-2-ylidene), greatly enhanced t reactivity under the same conditions, leading to 5 conversion (Table 1, entry 2). Satisfyingly, by sim decreasing the reaction temperature to 50ºC, f conversion towards **2a** was observed (Table 1, en 4). Further variation of the temperature resulted i significant decrease in the conversion rate (Table entries 3 and 5). The stoichiometry of NIS for reaction at 50 ºC proved to be crucial for an optir performance, since the use of 1.5 equivalents un the previous conditions substantially decreased amount of **2a** (Table 1, entry 6). A comparison w the use of polar solvents was carried out, and a lov performance was evidenced when dichlorometha was used (Table 1, entry 7), therefore maintain toluene as a suitable solvent. It should be mentior that the subsequent hydrofluorination reaction, t we previously reported,[28] was only compatible w toluene and dichloromethane, hence only these t solvents were tested. Under these conditions, decrease in the catalyst loading was not possi without eroding the reaction conversion (Table entry 8); however, by testing other Au(I)-NI bifluoride complexes (Table 1, entries 9-10), amount of [Au] could be reduced to 3 mol% wh using $[Au(SIPr)(NEt_3)][HF_2]$ (SIPr = *N,N'*-bis-[2 (di-*iso*-propyl)phenyl]imidazolin-2-ylidene) catalyst (Table 1, entry 10). With this system, reaction time was reduced to 15 h, maintaining f conversion of the starting alkyne and obtaining 8 isolated yield of **2a** (Table 1, entry 11).

The reactivity of other terminal alkynes under these optimal conditions was next explored, and the experimental results are summarized in Scheme 2. No significant difference in the reactivity of aromatic alkynes bearing either electron-donating or electron-withdrawing groups was observed, obtaining in all cases the corresponding 1-iodoalkynes **2a-2j** in good to excellent yields. The general procedure could also be applied to aromatic dialkynes, and by simply increasing the amount of Au to 6 mol%, the double

iodination product **2k** was successfully prepared in an 84% yield. *Ortho*-substituted substrates proved to be less compatible, as shown by the low isolated yield (40%) of the iodinated alkyne **2d**, presumably due to steric hindrance closer to the Au center. The latter phenomenon has been previously observed in similar gold-catalyzed additions to alkynes.[18n,29]

Table 1. Optimization of the Au(I)-catalyzed iodination of phenylacetylene[a]

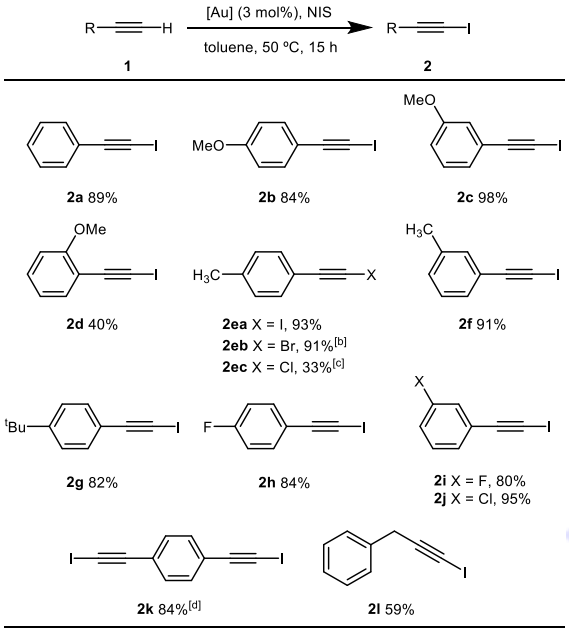


Entry	[Cat.] (mol%)	T(ºC)	Conversion (%)[b]
1	---	65	6
2	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	65	55
3	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	80	37
4	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	50	>99
5	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	30	38
6[c]	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	50	35
7[d]	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (5)	50	36
8	[Au(IPr^{Me})(NEt$_3$)][HF$_2$] (3)	50	43
9	[Au(IPr*)(NEt$_3$)][HF$_2$] (3)	50	76
10	[Au(SIPr)(NEt$_3$)][HF$_2$] (3)	50	>99
11[e]	[Au(SIPr)(NEt$_3$)][HF$_2$] (3)	50	>99 (89)[f]

[a]Reaction conditions: alkyne (0.25 mmol), NIS (2 equiv.), [Au], toluene (0.5 mL), 24 h. [b]Determined by ^{1}H NMR. [c] NIS (1.5 equiv.). [d] CH_2Cl_2. [e]15 h.[f] Isolated yield. IPr* = *N*,*N'*-bis-[2,6-bis-(diphenylmethyl)-4-methylphenyl]imidazol-2-ylidene.

Although aliphatic alkynes were not suitable substrates for straightforward iodination (displaying <30% conversion of the starting material when 1-heptyne or 1-ethynylcyclohexene were tested), the use of 3-phenyl-1-propyne as substrate afforded better results by providing the iodinated product **2n** in 59% isolated yield. The reduced performance observed for this type of substrates is most probably due to the lower acidity of aliphatic terminal alkynes when compared to aromatic ones, therefore limiting the deprotonation-iodination rate under the presented optimal conditions.

The versatility of the iodination procedure was further demonstrated using other *N*-halosuccinimides in an attempt to access the corresponding 1-bromo- and 1-chloroalkynes. To our delight, an increase of the reaction time to 24 h allowed for the conversion of 4-ethynyltoluene (**1e**) to the corresponding 1-bromoalkyne (**2eb**) in a 91% isolated yield. Under these conditions, only 33% isolated yield of the related 1-chloroalkyne (**2ec**) was obtained, as expected by the marked decrease in reactivity of the related succinimide.



[a] Reaction conditions: alkyne (0.50 mmol), NIS (1.0 mmol), [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), toluene (1 mL), 50 °C, 15 h. Isolated yields. [b] NBS instead of NIS, 24 h. [c] NCS instead of NIS, 24 h. [d] [Au] 6 mol%

Scheme 2. Scope of the Au(I)-catalyzed halogenation terminal alkynes[a]

Next, the separate optimization of hydrofluorination reaction was conducted. Us iodophenylacetylene (**2a**) as a model substrate, a after minor optimization, it was found that t conversion to (*Z*)-2-fluoro-1-iodo-3-phenylethe (**3a**) could be obtained after 2 h at 50 ºC, by usin mol% of the same Au(I) catal [Au(SIPr)(NEt$_3$)][HF$_2$], as used in the iodinat step.[30] Only one product was observed and la isolated in 88% yield by column chromatography. traces of any other stereo- or regioisomer w detected, with all spectroscopic data matching wit vicinal *cis* distribution of the halogen atoms.

The optimized conditions were applied to vari 1-iodoalkynes (Scheme 3). The procedure v successful for all tested substrates, maintaining h reactivity at fairly short reaction times. Interestin the challenging substrate **2k** afforded corresponding symmetrical compound (**3k**) as single product through double hydrofluorinat using 6 mol% of the gold catalyst after only 4 h a in an 86% isolated yield.The 1-bromoalkyne **2eb** v also converted into its related 1-bromo fluoroalkene (**3eb**) in good isolated yield, thus extending the applicability of this method to both bromo- and iodoalkynes.

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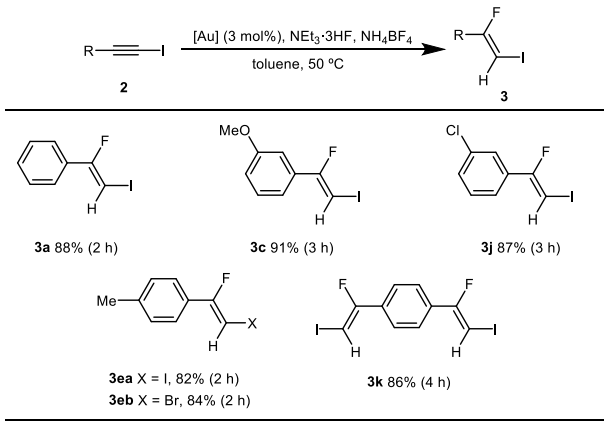
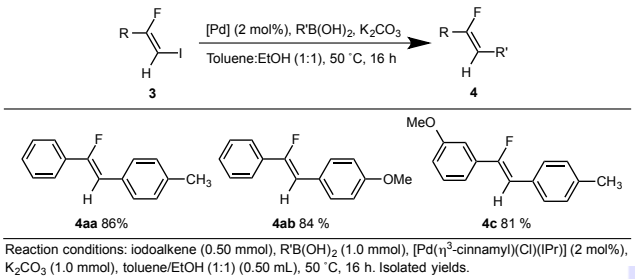


Reaction conditions: alkyne (0.50 mmol), NEt_3·3HF (1.5 mmol), NH_4BF_4 (0.75 mmol), [Au(SIPr)(NEt_3)][HF_2] (3 mol%), toluene (1 mL), 50 ºC. Isolated yields.

Scheme 3. Scope of the Au(I)-catalyzed hydrofluorination of 1-iodoalkynes.

Encouraged by the performance of metal-NHC systems for the reactions optimized above, the presence of a reactive C-I bond was next capitalized on. Therefore, it was decided to expand the one-pot procedure to a third functionalization reaction. Cross-coupling chemistry was chosen as an interesting method which could provide access to stereo- and regio-controlled trisubstituted fluoroalkenes, which still represents a great challenge for modern synthetic methods, and would therefore be regarded as a very useful tool for synthesis. The Suzuki-Miyaura cross-coupling reaction was selected for testing purposes. A similar idea has been conceived by Hara and co-workers, who have shown the efficiency of cross-coupling for the functionalization of fluoroalkene derivatives using a variety of Pd sources as catalysts.[26a,31] However, despite the intense study of NHC-based systems for cross-coupling,[32] no reports are available involving fluoroiodoalkenes; as a result, this field, dominated by the use of Pd-phosphine species,[33] could benefit from the development of an alternative catalytic system for the preparation of these highly valuable fluoroalkenes.

To that end, **3a** was selected as a model substrate for the coupling reaction with *p*-tolylboronic acid. Two well-defined Pd(II)-NHC complexes, [Pd(η^3-cinnamyl)(Cl)(IPr)] (IPr = *N,N'*-bis-[2,6-(di-iso-propyl)phenyl]imidazol-2-ylidene) and [Pd(μ-Cl)Cl(IPr)]$_2$, were selected as they represent late generation catalysts for Pd-mediated reactions.[34,35] A slight modification of previously reported conditions[34d] afforded a robust methodology for the complete conversion of **3a** into the respective trisubstituted alkene (**4a**) after 16 h at 50 ºC, using 2 mol% of [Pd(η^3-cinnamyl)(Cl)(IPr)] in the presence of two equivalents of boronic acid and two equivalents of K_2CO_3.[36]Although ethanol on its own also gave full conversion, the presence of toluene in the iodination and hydrofluorination reactions meant that a toluene/ethanol mixture was better suited for a one-pot sequential procedure. Under these conditions, **4a** was isolated in 86% yield. Substituents in either the boronic acid or the iodoalkene are also tolerated, maintaining a good overall performance and selectivity of the catalytic system (Scheme 4).



Reaction conditions: iodoalkene (0.50 mmol), R'B(OH)$_2$ (1.0 mmol), [Pd(η^3-cinnamyl)(Cl)(IPr)] (2 mol%), K_2CO_3 (1.0 mmol), toluene/EtOH (1:1) (0.50 mL), 50 ˚C, 16 h. Isolated yields.

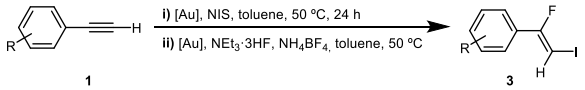
Scheme 4. Scope of the Pd-catalyzed Suzuki-Miya cross-coupling of fluoroiodoalkenes with arylboronic ac

Avoiding the tedious isolation of the involv intermediates could undoubtedly result in a v straightforward two- or even three-step ra functionalization of terminal alkynes. The number similar alternatives to such procedures is very limi such as the one-pot forr bromination/hydrofluorination of terminal alky reported by Jiang and co-workers in 2012;[37] t methodology, however, did not afford gc selectivity for the synthesis of the related iodoalke To that end, combining all three reactions in a o pot sequential procedure was then attempted.

Upon initial testing, we found vari incompatibilities for a one-pot sequence in all tes reactions, leading to little conversion towards expected compounds. Thus, additional modificati were necessary to reach the desired goal.

The sequential iodination/hydrofluorination v first optimized and we quickly realized that excess NIS presented a major problem for hydrofluorination step. By decreasing the amount NIS to 1.3 equivalents and increasing the react time of the iodination step to 24 h, followed simple filtration through cotton wool, hydrofluorination reaction proceeded smoothly afford the desired products **3** (Table 2).[38] Howev due to that filtration, the gold catalyst had to reintroduced into the mixture for the second step proceed in a reliable manner. The efficiency of t sequential procedure was remarkable, obtaining gc yields in all cases (Table 2, entries 1-3). Th reactions proved comparable with the overall yie obtained in the stepwise functionalization; example, the sequential procedure provides **3a** starting from **1a** with 82% yield, as opposed to a 78% yield over two individual steps. In addition, the sequential reaction was scaled up to 5 mmol (starting from **1a**), while maintaining a good performance after only increasing the time of the hydrofluorination step to 4 h (88%, Table 2, entry 1).

Table 2. Sequential Au(I)-catalyzed iodination/hydrofluorination of terminal arylalkynes.[a]

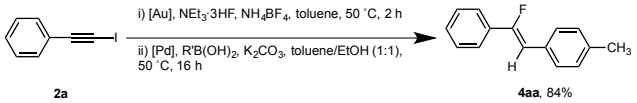


1 3

Entry	R	Product	Time (Step ii)	Yield (%)[b]
1	H	3a	3 h (4 h)[c]	82 (88%)[c]
2	m-OMe	3c	4 h	88
3	m-Cl	3j	4 h	78

[a]Reaction conditions: i) alkyne (0.50 mmol), NIS (0.65 mmol), [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), toluene (1 mL); ii) [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), NH_4BF_4 (0.75 mmol), NEt$_3$·3HF (1.5 mmol).[b] Isolated yields. [c] 5 mmol scale.

Next we focused on the hydrofluorination/cross-coupling sequential reaction. The formation of a biphasic system after the hydrofluorination step prevented the smooth carry over to the cross-coupling reaction. Therefore, it was necessary to recover the top layer (containing the hydrofluorination product **3a**) and neutralize the excess acid with K_2CO_3 before adding the remaining reagents and the palladium catalyst.[38] With this procedure, we were able to isolate **4aa** in 84% yield (Scheme 5). It should be mentioned that this yield is better than the overall isolated yield of **4aa** (76%), obtained *via* the two separate reactions, which highlights the efficiency of such a sequential procedure.

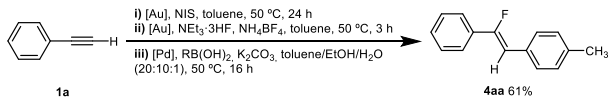


2a 4aa, 84%

Reaction conditions: i) IC≡CPh (0.50 mmol), [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), NEt$_3$·3HF (1.5 mmol), NH_4BF_4 (0.75 mmol), toluene (1 mL); ii) [Pd(η^3-cinnamyl)(Cl)(IPr)] (2 mol%), *p*-tolylboronic acid (1.0 mmol), K_2CO_3 (1.0 mmol). Isolated yield.

Scheme 5. Sequential Au/Pd-catalyzed iodination/hydrofluorination/cross-coupling reaction of **1a.**

Finally, we attempted to combine both sequential procedures into one, in order to obtain **4aa** starting directly from **1a** (Scheme 6). Under the new optimized conditions, we performed all three reactions sequentially starting from **1a** and these experiments afforded the desired product **4aa** in 61% yield (compared to an overall yield of 67% obtained *via* all three reactions carried out separately).[39] With only one purification step to afford the end-product, this sequential reaction is highly practical. It is to be noted that no decrease in the selectivity was witnessed in any of the performed sequences, which highlights the robustness of the catalytic methods for the presented reactions.



1a **4aa** 61%

Reaction conditions: i) PhC≡CH (0.50 mmol), [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), NIS (0.65 mmol), toluene (1.0 mL). ii) [Au(SIPr)(NEt$_3$)][HF$_2$] (3 mol%), NEt$_3$·3HF (1.5 mmol), NH_4BF_4 (0.75 mmol). iii) [Pd(η^3-cinnamyl)(Cl)(IPr)] (2 mol%), *p*-tolylboronic acid (1.0 mmol), K_2CO_3 (1.0 mmol). Isolated yield.

Scheme 6. Sequential Au/Pd-catalyzed iodination/hydrofluorination/cross-coupling reaction of **1a.**

Conclusion

In conclusion, we have developed an efficient and straightforward methodology for the synthesis of iodoalkynes using a gold-NHC bifluoride catalyst a *N*-iodosuccinimide as electrophilic iodine source. range of substrates is well tolerated and gives acc to the corresponding iodinated products in good excellent yields. The versatility of the prepared iodoalkynes as building blocks was furt highlighted by performing a gold-catalyz hydrofluorination that afforded (Z)-2-fluoro iodoalkenes in good yields. The reactive C-I bond these molecules was used to further increase molecular complexity by means of a palladiu catalyzed cross-coupling with boronic acids to aff trisubstituted (Z)-fluoroalkenes in good yields. In presented reactions, a variety of functionalities w tolerated, which allowed for the preparation o library of alkynes and alkenes of great use in orga synthesis. The robustness of the three descrit methods was further demonstrated by the possibil to perform these reactions sequentially, with o minor changes and handling being required. T rapid functionalization protocol can be perform without tedious intermediate isolation or reduction performance, and therefore should be of gr practical use to the synthetic community.

Experimental Section

Gold-catalyzed iodination of terminal alkynes

A screw-cap vial equipped with a stirring bar charged with [Au(SIPr)(NEt$_3$)][HF$_2$] (10.9 mg, 0.0 mmol, 3 mol%), *N*-iodosuccinimide (225 mg, 1 mmol equiv.), toluene (1 mL) and the alkyne (0.5 mmol). T vial was closed under N_2 atmosphere, and the react mixture was stirred at 50 ºC for 16 h. The crude mixt was purified by column chromatography (SiO_2) to obt the title compound.

Gold-catalyzed hydrofluorination of 1-iodoalkynes

A plastic screw-cap vial equipped with a stirring bar was charged with the 1-iodoalkyne (0.5 mmol), [Au(SIPr)(NEt$_3$)}(HF$_2$)] (10.9 mg, 0.015 mmol, 3 mol%), NH_4BF_4 (81.0 mg, 0.75 mmol, 1.5 equiv.) and toluene (1 mL). NEt$_3$·3HF (0.25 mL, 1.5 mmol, 3 equiv.) was added dropwise while stirring. The vial was closed under N_2 atmosphere and the reaction mixture was stirred at 50 °C for the corresponding time. The conversion was determined by ^{1}H NMR ($CDCl_3$). After full conversion of

the starting material, the crude mixture was purified by column chromatography (SiO_2) to obtain the title compound.

Palladium-catalyzed cross-coupling of 2-fluoro-1-haloalkenes

A screwcap vial equipped with a stirring bar was charged with fluoroalkene (0.5 mmol), *p*-tolylboronic acid (140.2 mg, 1 mmol, 2 equiv.), K_2CO_3 (138.2 mg, 1 mmol, 2 equiv.), [Pd(η^3-cinnamyl)(Cl)(IPr)] (6.5 mg, 0.01 mmol, 2 mol%), toluene (0.25 mL) and EtOH (0.25 mL), in air. The reaction mixture was stirred at 50 °C for 16 h. The solvents were evaporated under reduced pressure, and the obtained residue was purified by column chromatography (SiO_2) to yield the title compound.

Sequential iodination/hydrofluorination of terminal alkynes

A glass screw-cap vial equipped with a stirring bar was charged with [Au(SIPr)(NEt_3)][HF_2] (10.9 mg, 0.015 mmol, 3 mol%), *N*-iodosuccinimide (146.3 mg, 0.65 mmol, 1.3 equiv.), toluene (1 mL) and the alkyne (0.5 mmol). The mixture was stirred at 50 °C for 24 h. The crude mixture was filtered through a plug of cotton, into a plastic screwcap vial containing [Au(SIPr)(NEt_3)][HF_2](10.9 mg, 0.015 mmol, 3 mol%) and NH_4BF_4 (81.0 mg, 0.75 mmol, 1.5 equiv.). The cotton plug was further washed with toluene (0.4 mL) for complete recovery of the halogenated intermediate. $NEt_3 \cdot 3HF$ (0.25 mL, 1.5 mmol, 3 equiv.) was then added dropwise. The reaction mixture was further stirred at 50 °C for 16 h. The solvents were evaporated under reduced pressure, and the obtained residue was purified by column chromatography (SiO_2) to yield the title compound.

Sequential hydrofluorination/cross-coupling of 1-iodoalkynes

A plastic screw-cap vial equipped with a stirring bar was charged with 1a (0.5 mmol), [Au(SIPr)(NEt_3)][HF_2] (10.9 mg, 0.015 mmol, 3 mol%), NH_4BF_4 (81.0 mg, 0.75 mmol, 1.5 equiv.) and toluene (0.8 mL). $NEt_3 \cdot 3HF$ (0.25 mL, 1.5 mmol, 3 equiv.) was added dropwise while stirring. The vial was closed under N_2 atmosphere and the reaction mixture was stirred at 50 °C for 3 h. The crude mixture was allowed to cool down to room temperature, and the top layer from the two-phase system was recovered in a screwcap vial. While stirring, EtOH (same amount as recovered organic phase) and K_2CO_3 (345 mg, 2.5 mmol, 5 equiv., added in small portions) were added, and the mixture was stirred at 20 °C for 30 minutes. To the stirred sample, *p*-tolylboronic acid (140.2 mg, 1 mmol, 2 equiv.), K_2CO_3 (138.2 mg, 1 mmol, 2 equiv.) and [Pd(η^3-cinnamyl)(Cl)(IPr)] (6.5 mg, 2 mol%) were added, in air. The reaction mixture was stirred at 50 °C for 16 h. The solvents were evaporated under reduced pressure, and the obtained residue was purified by column chromatography (SiO_2, pentane) to yield 4aa as a white solid in 84% isolated yield.

Sequential iodination/hydrofluorination/cross-coupling of terminal alkynes

A glass screw-cap vial equipped with a stirring bar was charged with [Au(SIPr)(NEt_3)][HF_2] (10.9 mg, 0.015 mmol, 3 mol%), *N*-iodosuccinimide (146.3 mg, 0.65 mmol, 1.3 equiv.), toluene (1 mL) and 1a (0.5 mmol). The mixture was stirred at 50 °C for 24 h. The crude mixture was filtered through a plug of cotton, into a plastic screwcap vial containing [Au(SIPr)(NEt_3)][HF_2] (10.9 mg, 0.015 mmol, 3 mol%) and NH_4BF_4 (81.0 mg, 0.75 mmol, 1.5 equiv.). The cotton plug was further washed with toluene (0.4 mL) for complete recovery of the halogenated intermediate. $NEt_3 \cdot 3HF$ (0.25 mL, 1.5 mmol, 3 equiv.) was then added dropwise. The reaction mixture was furt stirred at 50 °C for 3 h. The crude mixture was allowec cool down to room temperature, and water (0.5 mL) v added. The organic layer was recovered and dropped i screw-cap vial with a stirring bar. While stirring, Et (1.5 mL), water (0.15 mL) and K_2CO_3 (345 mg, 2.5 mn 5 equiv., small portions) were added, and the mixture v stirred at 20 °C for 30 minutes. To the stirred sample, tolylboronic acid (140.2 mg, 1 mmol, 2 equiv.), K_2C (138.2 mg, 1 mmol, 2 equiv.) and [Pd(cinnamyl)(Cl)(IPr)] (6.5 mg, 2 mol%) were added, in The reaction mixture was stirred at 50 °C for 16 h. mixture was passed through a small plug of MgS washed with AcOEt (2x3 mL) and the gathered fracti were concentrated under reduced pressure. The cr mixture was purified by column chromatography (Si pentane) to yield 4aa as a white solid in 61% isolated yi

Acknowledgements

The authors gratefully acknowledge the Royal Society (Univer Research Fellowship to C.S.J.C.), Syngenta (studentship to A King Saud University (SPN) and the EPSRC (EP/K503162/1) funding. We are also grateful to Umicore for the loan of complexes and to the EPSRC National Mass Spectrom Service Centre at Swansea University for HRMS analyses. T publication is based upon work supported by the King Abdu University of Science and Technology (KAUST) Office Sponsored Research (OSR) under Award No. OSR-2015-C 1974-03.

References

[1] For selected examples, see: a) G. Jaeger, W. Paul H. Genth (A. G. Bayer), *Ger. Offen.* *3122263,1982* (Chem. Abstr. **1983**, *98*, 197757); b Jaeger, W. Brandes, P. E. Frohberger (A. G. Bay *Eur. Pat. Appl. EP 66771*, 1982 (Chem. Abstr. **19** *98*, 197764); c) W. Singer, C. C. Versfelt (Troy Chemical Corp.), *Brit. Pat. Appl. GB 2138292*, 1984 (Chem. Abstr. **1985**, *102*, 057826); d) B. F. Rose (Chevron Research Co.), *U.S. Pat. US 4639460*, 1987 (Chem. Abstr. **1987**, *106*, 156456).

[2] For selected examples, see: a) W. Gerhardt, R. Lehmann (K. Henkel), *Ger. Offen. DE 3216895*, 1983 (Chem. Abstr. **1984**,100, 51107); b) W. Gerhardt, R. Lehmann (K. Henkel), *Ger. Offen. DE 3224504*, 1984 (Chem. Abstr.**1984**, 100, 209179); c) G. Schade, W.

Paulus, H. G. Schmitt (A. G. Bayer), *Ger. Offen. DE 3526789*, 1987 (Chem. Abstr. **1987**, *106*, 98104).

[3] For selected examples about coupling reactions using 1-iodoalkynes, see: a) P. L. Southwick, J. R. Kirchner, *J. Org. Chem.* **1962**, *27*, 3305-3308; b) K. Takai, T. Kuroda, S. Nakatsukasa, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1985**, *26*, 5585-5588; c) R. Takeuchi, Y. Tsuji, M. Fujita, T. Kondo, Y. Watanabe, *J. Org. Chem.* **1989**, *54*, 1831-1836; d) J. Barluenga, J. M. González, I. Llorente, P. J. Campos, *Angew. Chem.* **1993**, *105*, 928-929; *Angew. Chem. Int. Ed.* **1993**, *32*, 893-894; e) M. H. Nantz, D. K. Moss, J. D. Spence, M. M. Olmstead, *Angew. Chem.* **1998**, *110*, 476-479; *Angew .Chem. Int. Ed.* **1998**, *37*, 470-473; f) S. Yamanoi, T. Matsumoto, K. Suzuki, *Tetrahedron Lett.***1999**, *40*, 2793-2796; g) M. Kunishima, D. Nakata, S. Tanaka, K. Hioki, S. Tani, *Tetrahedron*, **2000**, *56*, 9927-9935; h) M. V. Russo, C. Lo Sterzo, P. Franceschini, G. Biagini, A. Furlani, *J. Organomet. Chem.* **2001**, *619*, 49-61; i) Y. Y. Ku, T. Grieme, P. Sharma, Y.-M. Pu, P. Raje, H. Morton, S. King, *Org. Lett.* **2001**, *3*, 4185-4187; j) S. V. Damle, D. Seomoon, P. H. Lee, *J. Org. Chem.* **2003**, *68*, 7085-7087; k) A. S. K. Hashmi, R. Döpp, C. Lothschütz, M. Rudolph, D. Riedel, F. Rominger, *Adv. Synth. Catal.* **2010**, *352*, 1307-1314; l) D. L. Usanov, H. Yamamoto, *J. Am. Chem. Soc.* **2011**, *133*, 1286-1289; m) H. Liu, C. Chen, L. Wang, X. Tong, *Org. Lett.* **2011**, *13*, 5072-5075; n) M. Zhu, M. Ning, W. Fu, C. Xu, G. Zou, *Bull. Korean. Chem. Soc.* **2012**, *33*, 1325-1328; o) S. Mader, L. Molinari, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2015**, *21*, 3910-3913.

[4] For selected examples about alkyne addition reactions using 1-iodoalkynes, see: a) G. Zweifel, H. Arzoumanian, *J. Am. Chem. Soc.* **1967**, *89*, 5086-5088; b) W. Xu, W.-Y. Chen, *J. Org. Chem.* **2002**, *67*, 9421-9427; c) J. E. Hein, J. C. Tripp, L. B. Krasnova, B. Sharpless, V. V. Fokin, *Angew. Chem.* **2009**, *121*, 8162-8165; *Angew. Chem. Int. Ed.* **2009**, *48*, 8018-8021; d) C. Recsei, C. S. P. McErlean, *Tetrahedron: Asymmetry,* **2010**, *21*, 149-152; e) J. A. Crossley, D. L. Browne, *J. Org. Chem.* **2010**, *75*, 5414-5416; f) M. Juríček, K. Stout, P. H. J. Kouwer, A. E. Rowan, *Org. Lett.* **2011**, *13*, 3494-3497; g) D. Fu, J. Zhang, S. Cao, *J. Fluorine Chem.* **2013**, *156*, 170-176; h) Y. Gao, M. Yin, W. Wu, H. Huang, H. Jiang, *Adv. Synth. Catal.* **2013**, *355*, 2263-2273; i) A. H. Banday, V. J. Hruby, *Synlett*, **2014**, *25*, 2463-2466.

[5] W. Wu, H. Jiang, *Acc. Chem. Res.* **2014**, *47*, 2483-2504.

[6] For some examples of the synthesis of useful chemicals using 1-iodoalkynes as intermediates, see: a) C. Burgess, G. Cooley, P. Feather, V. Petrow, *Tetrahedron*, **1967**, *23*, 4111-4116; b) D. W. Knight, G. Pattenden, *J. Chem. Soc. Perkin Trans.* **1975**, 641-644; c) C. Lüthy, P. Konstantin, K. G. Untch, *J. Am. Chem. Soc.* **1978**, *100*, 6211-6217; d) R. Rossi, A. Carpita, *Tetrahedron*, **1983**, *39*, 287-290; e) S. Nishida, M. Murakami, T. Mizuno, T. Tsuji, H. Oda, N. Shimizu, *J. Org. Chem.* **1984**, *49*, 3429-3432; f) R. H. Boutin, H. Rapoport, *J. Org. Chem.* **1986**, *51*, 5320-5327; g) T. D. Aicher, Y. Kishi, *Tetrahedron Lett.* **1987**, *28*, 3463-3466; h) Y. Kishi, *Pure Appl. Chem.* **1992**, *64*, 343-350; i) K. C. Nicolaou, A. Liu, Z. Zeng, S. McComb, *J. Am. Chem. Soc.* **1992**, *114*, 9279-9282; j) T. Mandai, T. Matsumoto, M. Kawada, J. Tsuji, *J. Org. Chem.* **1992**, *57*, 6090-6092; k) J. B. Nerenberg, D. T. Hung, P. K. Somers, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 12621-12622; l) L. M. Antunes, M. G. Organ, *Tetrahedron Lett.* **2003**, *44*, 6805-6808; m) J. Picard, N. Lubin-Germain, J. Uziel, J. Augé, *Synthesis*, **2006**, *6*, 979-982; n) N. Joubert, F. Amblard, K. L. Rapp, R. F. Schinazi, L. Agrofoglio, *Tetrahedron,* **2008**, *64*, 4444-4452; o) Dei, T. Shimogaki, A. Matsumoto, *Macromolecu* **2008**, *41*, 6055-6065; p) D. A. Barancelli, A. Mantovani, C. Jesse, C. W. Nogueira, G. Zeni, *J. M Prod.* **2009**, *72*, 857-860; q) R. C. Hoye, G. Anderson, S. G. Brown, E. E. Schultz, *J. Org. Ch* **2010**, *75*, 7400-7403; r) K. Mori, *Tetrahedron,* **20** *68*, 1936-1946; s) M. Ruetz, R. Salchner, K. Wurs Fedosov, B. Kräutler, *Angew. Chem.* **2013**, *1* 11617-11620; *Angew.Chem. Int. Ed.* **2013**, 11406-11409; t) K. Okamoto, M. Watanabe, Sakata, M. Murai, K. Ohe, *Org. Lett.* **2013**, *15*, 58 5813.

[7] For some examples using this traditional approa see: a) T. H. Vaughn, J. A. Nieuwland, *J. Am. Ch Soc.* **1932**, *54*, 787-791; b) T. H. Vaughn, J. Nieuwland, *J. Am. Chem. Soc.* **1933**, *55*, 2150-21 c) A. F. Kluge, K. G. Untch, J. H. Fried, *J. Am. Ch Soc.* **1972**, *94*, 9256-9258; d) M. Bassetti, B. Floris Illuminati, *Organometallics*, **1985**, *4,* 617-623; e) Camici, P. Dembech, A. Ricci, G. Seconi, M. Tad *Tetrahedron,* **1988**, *44*, 4197-4206; f) J. E. A. Luitl J. Pietruszka, *Eur. J. Org. Chem.* **2000**, 2557-2562 H. A. Stefani, R. Cella, F. A. Dörr, C.M. de Pereira P. Gomes, G. Zeni, *Tetrahedron Lett.* **2005**, *46*, 20 2003; h) G.-W. He, F.-W. Liu, X.-H. Xu, *Chin Org. Chem.* **2007**, *27*, 663-665; i) L.-G. Meng, P Cai, Q.-X. Guo, S. Xue, *Synth. Commun.* **2008**, 225-231.

[8] T. Nishikawa, S. Shibaya, S. Hosokowa, M. Iso *Synlett,* **1994**, 485-486.

[9] a) G. W. Kabalka, A. R. Mereddy, *Tetrahedron L* **2004**, *45*, 1417-1419; b) G. W. Kabalka, A. Mereddy, *J. Labelled Comp. Radiopharm.* **2005**, 359-362.

[10] a) M. J. Cohen, E. J. McNelis, *J. Org. Chem.* **1984**, *49*, 515-518; b) D. Naskar, S. Roy, *J. Org.Chem.* **1999**, *64*, 6896-6897.

[11] For other examples of alkyne derivatives, see: a) P. J. Stang, B. W. Surber, *J. Am. Chem. Soc.* **1985**, *107*, 1452-1453; b) N. Krause, D. Seebach, *Chem. Ber.* **1987**, *120*, 1845-1851; c) M. Ochiai, K. Uemura, Y. Masaki, *J. Am. Chem. Soc.* **1993**, *115*, 2528-2529; d) P. Michel, A. Rassat, *Tetrahedron Lett.* **1999**, *40*, 8579-8581; e) H. Lahrache, S. Robin, G. Rousseau, *Tetrahedron Lett.* **2005**, *46*, 1635-1637.

[12] a) L. J. Hatch, D. J. Mangold, *J. Am. Chem. Soc.* **1955**, *77*, 176-177; b) A. Ricci, M. Taddei, P. Dembech, A. Guerrini, G. Seconi, *Synthesis,* **1989**, 461-463; c) A. Casarini, P. Dembech, G. Reginato, A. Ricci, G. Seconi, *Tetrahedron Lett.* **1991**, *32*, 2169-2170; d) I. Nishiguchi, O. Kanbe, K. Itoh, H. Maekawa, *Synlett,* **2000**, *1*, 89-91; e) K. R. Reddy, M. Venkateshwar, C. U. Maheswari, P. S. Kumar, *Tetrahedron Lett.* **2010**, *51*, 2170-2173.

[13] a) J. Barluenga, J. M. Gonzalez, M. A. Rodriguez, P. G. Campos, G. Asensio, *Synthesis,* **1987**, 661-662; b) Y. Brunel, G. Rousseau, *Tetrahedron Lett.* **1995**, *36*, 2619-2622; c) H. Monenschein, G. Sourkouni-Argirusi, K. M. Schubothe, T. O'Hare, A. Kirschning, *Org. Lett.* **1999**, *1*, 2101-2104.

[14] M. Nouzarian, R. Hosseinzadeh, H. Golchoubian, *Synth. Commun.* **2013**, *43*, 2913-2925.

[15] a) Y. Sasson, O. W. Webster, *J. Chem. Soc. Chem. Commun.* **1992**, 1200-1201; b) I. J. Blackmore, A. N. Boa, E. J. Murray, M. Dennis, S. Woodward, *Tetrahedron Lett.* **1999**, *40*, 6671-6672; c) E. Abele, M. Fleisher, K. Rubina, R. Abele, E. Lukevics, *J. Mol. Catal. A: Chem.* **2001**, *165*, 121-126.

[16] A. A. Mikhaylov, A. D. Dilman, M. I. Struchkova, Y. A. Khomutova, A. A. Korlyukov, S. L. Ioffe, V. A. Tartakovsky, *Tetrahedron,* **2011**, *67*, 4584-4594.

[17] L. Bialy, H. Waldmann, *Angew. Chem.* **2008**, *120*, 1146-1149; *Angew. Chem. Int. Ed.* **2002**, *41*, 1748-1751.

[18] For selected reviews about alkyne activation with transition metals, see: a) S. Aime, L. Milone, D. Osella, *J. Chem. Soc. Chem. Commun.* **1979**, 704-705; b) S. L. Buchwald, R. B. Nielsen, *Chem. Rev.* **1988**, *88*, 1047-1058; c) N. E. Schore, *Chem. Rev.* **1988**, *88*, 1081-1119; d) P. H. Dixneuf, *Pure Appl. Chem.* **1989**, *61*, 1763-1770; e) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675-703; f) I. P. Beletskaya, C. Moberg, *Chem. Rev.* **1999**, *99*, 3435-3461; g) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079-3159; h) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795-3892; i) R. Severin, S. Doye, *Chem. Soc. Rev.* **2007**, *36*, 1407-1420; j) A. M. Lozano-Vila, S. Monsaert, A. Bajek, F. Verpoort, *Chem. Rev.* **2010**, *110*, 4865-4909; k) R. Chinchilla, C. Nájera, *Chem. Soc. Rev.* **2011**, *40*, 5084-5121; l) B. Godoi, R. F. Schumacher, G. Zeni, *Chem. Rev.* **2011**, *111*, 2937-2980; m) R. Chinchilla, C. Nájera, *Chem Rev.* **2014**, *114*, 1783-1826; n) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028-9072.

[19] T. Jeffery, *J. Chem. Soc. Chem. Commun.* **1988**, *14*, 909-910; b) J. Yan, J. Li, D. Cheng, *Synlett,* **2007**, *15*, 2442-2444; c) S.-N. Chen, T.-T. Hung, T.-C. Lin, F.-Y. Tsai, *J. Chin. Chem. Soc.* **2009**, *56*, 1078-1081; d) R. Yan, K. Sander, E. Galante, V. Rajkumar, A. Badar, M. Robson, E. El-Emir, M. F. Lythgoe, B. Pedley, E. Årstad, *J. Am. Chem. Soc.* **2013**, *135*, 703-709.

[20] a) H. Hofmeister, K. Annen, H. Laurent, R. Wiechert, *Angew. Chem.* **1984,** *96,* 720-722; *Angew. Chem. Int. Ed.* **1984**, *23*, 727-729; b) T. J. Speed, D. M. Thamattoor, *Tetrahedron Lett.* **2002**, *43*, 367-369; c) D. Lehnherr, J. M. Alzola, E. B. Lobkovsky, W. R. Dichtel, *Chem. Eur. J.* **2015**, *21*, 18122-18127.

[21] P. Starkov, F. Rota, J. M. D'Oyley, T. D. Sheppard, *Adv. Synth. Catal.* **2012**, *354*, 3217-3224.

[22] For selected examples, see: a) Filler, R.; Kobayashi, Y.; in *Biomedicinal Aspects of Fluorine Chemistry*, Elsevier: Amsterdam, **1982**; b) *Fluorine in Bioorganic Chemistry (*Eds.: J. T. Welch, S. Eswarakrishman), Wiley: New York, **1991**; *Organofluorine Chemistry: Principles a Commercial Applications* (Eds.:R. E. Banks, B. Smart, J. C. Tatlow), Plenum: New York, **1994**; d Purser, P. R. Moore, S. Swallow, V. Gouverne *Chem. Soc. Rev.* **2008**, *37*, 320-330.

[23] a) W. Zhang, W. Huang, J. Hu, *Angew. Chem.* **20** *121,* 10042-10045; *Angew. Chem. Int. Ed.* **2009**, 9858-9861; b) H. Zhang, C.-B. Zhou, Q.-Y. Chen, C. Xiao, R. Hong, *Org. Lett*. **2010**, *13*, 560-563; c) Yanai, T. Taguchi, *Eur. J. Org. Chem.* **2011**, 59 5954.

[24] For selected examples of difunctionalization terminal alkynes, see: a) A. Mizuno, H. Kusama, Iwasawa, *Angew. Chem.* **2009,** *121,* 8468-84 *Angew. Chem. Int. Ed.* **2009**, *48*, 8318-8320; b) Sha, X. Huang, *Angew. Chem.* **2009,** *121,* 3510-35 *Angew. Chem. Int. Ed.* **2009**, *48*, 3458-3461; c) L. L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **20** *132*, 3258-3259; d) B. Dutta, N. Gilboa, I. Marek *Am. Chem. Soc.* **2010**, *132*, 5588-5589; e) C. Zha N. Jiao, *J. Am. Chem. Soc.* **2010**, *132*, 28-29; f Kuang, S. Ma, *J. Am. Chem. Soc.* **2010**, *132*, 17 1787; g) Z. Chen, J. Li, H. Jiang, S. Zhu, Y. Li, C. *Org. Lett.* **2010**, *12*, 3262-3265; h) W. Wang, Jasinski, G. B. Hammond, B. Xu, *Angew. Ch* **2010,** *122,* 7405-7410; *Angew. Chem. Int. Ed.* **20** *49*, 7247-7252; i) H. Xu, S. Gu, W. Chen, D. Li Dou, *J. Org. Chem.* **2011**, *76*, 2448-2458; j) B. Xu, Wang, L.-P. Liu, J. Han, Z. Jin, G. B. Hammond *Organomet. Chem.* **2011**, *696*, 269-276; k) J. Ye, Li, B. Chen, W. Fan, J. Kuang, J. Liu, Y. Liu, Miao, B. Wan, Y. Wang, X. Xie, Q. Yu, W. Yuan Ma, *Org. Lett.* **2012**, *14*, 1346-1349; l) M. Yamagi J. Okazaki, K. Nishigai, T. Hata, H. Urabe, *Org. L* **2012**, *14*, 34-37.

[25] For some selected examples, see: a) B. M. Trost, A. J. Pinkerton, *J. Am. Chem. Soc.* **2002**, *124*, 7376-7389; b) G. W. Kabalka, Z. Wu, Y. Ju, *Org. Lett.* **2002**, *4*, 3415-3417; c) M. Schuler, F. Silva, C. Bobbio, A. Tessier, V. Gouverneur, *Angew. Chem.* **2008,** *120,* 8045-8048; *Angew. Chem. Int. Ed.* **2008**, *47*, 7927-7930; d) L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem.* **2009**, *121,* 9770-9772; *Angew. Chem. Int. Ed.* **2009**, *48*, 9592-9594; e) K. Ren, M. Wang, L. Wang, *Eur. J. Org. Chem* .**2010**, 565-571; f) Z. Chen, H. Jiang, Y. Li, C. Qi, *Chem. Commun.* **2010**, *46*, 8049-8051; g) M. Murai, R. Hatano, S. Kitabata, K.

Ohe, *Chem. Commun.* **2011**, *47*, 2375-2377; h) X. Y. Liu, P. Gao, Y. W. Shen, Y. M. Liang, *Adv. Synth. Catal.* **2011**, *353*, 3157-3160.

[26] For selected examples, see: a) M. Yoshida, A. Komata, S. Hara, *Tetrahedron,* **2006**, *62*, 8636-8645; b) T. de Haro, C. Nevado, *Adv. Synth. Catal.* **2010**, *352*, 2767-2772; c) H. Peng, G. Liu, *Org. Lett.* **2011**, *13*, 772-775; d) O. E. Okoromoba, J. Han, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2014**, *136*, 14381-14384.

[27] J. A. Akana, K. X. Bhattacharyya, P. Müller, J. P. Sadighi, *J. Am. Chem. Soc.* **2007**, *129*, 7736-7737.

[28] F. Nahra, S. R. Patrick, D. Bello, M. Brill, A. Obled, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, S. P. Nolan, *ChemCatChem.* **2015**, *7*, 240-244.

[29] L. Xie, Y. Wu, W. Yi, L. Zhu, J. Xiang, W. He, *J. Org. Chem.* **2013**, *78*, 9190-9195.

[30] For the complete optimization, see Supporting Information, Table S2.

[31] a) M. Yoshida, D. Ota, T. Fukuhara, N. Yoneda, S. Hara, *J. Chem. Soc. Perkin Trans.* 1, **2002**, 384-389; b) T. Guan, M. Yoshida, D. Ota, T. Fukuhara, S. Hara, *J. Fluorine Chem.* **2005**, *126*, 1185-1190; c) M. Sakai, T. Guan, S. Hara, *J. Fluorine Chem.* **2007**, *128*, 1444-1448.

[32] For selected reviews, see: a) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007,** *119*, 2824-2870; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768-2813; b) G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* **2011**, *40*, 5151-5169.

[33] C. Jasper, E. Montenegro, D. Pauluth, V. Reiffenrath, A. Manabe (Merck Patent Gesellschaft Mit Geschrankter Haftung), *U. S. Patent, US 2012/0267571 A1*, **2012**.

[34] For selected applications of Pd-NHC cinnamyl species as coupling catalysts, see: a). O. Navarro, N. Marion, J. Mei, S. P. Nolan, *Chem. Eur. J.* **2006**, *12*, 5142-5148; b) N. Marion, O. Navarro, J. Mei, R. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101-4111; c) A. R. Martin, A. Chartoire, A. M. Z. Slawin, S. P. Nolan, *Beilstein J. Org. Chem.* **2012**, *8*, 1637-1643; d) F. Izquierdo, M. Corpet, S. P. Nolan, *Eur. J. Org. Chem.* **2015**, 1920-1924.

[35] For selected applications of Pd-NHC dimers as coupling catalysts, see: a) M. S. Viciu, R. M. Kissling, E. D. Stevens, S. P. Nolan, *Org. Lett.* **2002**, *4*, 2229-2231; b) O. Diebolt, P. Braunstein, S. P. Nolan, C. S. J. Cazin, *Chem. Commun.* **2008**, 3190-3192; c) C. E. Hartmann, S. P. Nolan, C. S. J. Cazin, *Organometallics,* **2009**, *28*, 2915-2919.

[36] For the complete optimization, see Supporting Information, Table S3.

[37] Y. Li, X. Liu, D. Ma, B. Liu, H. Jiang, *Adv. Synth. Catal.* **2012**, *354*, 2683-2688.

[38] For more details, see Supporting Information.

[39] In step iii; the solvent mixture was reoptimized, and a mixture of toluene/EtOH/water (20:10:1) was used instead of toluene/EtOH (1:1).

10.1002/cctc.201600868

FULL PAPER

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*ChemCatChem.***2016**, *Volume*, Page – Page

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