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Preparation of conjugated 1,3-enynes by Rh(III)-catalysed alkynylation of alkenes *via* C–H activation†

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An experimentally simple additive-free Rh(III)-catalysed direct alkynylation of alkenes has been developed. This protocol employs commercially available TIPS-EBX as the alkyne source, giving access to conjugated terminal enynes following a simple silyl-deprotection. This method has also been applied to arenes.

Alkynes are arguably one of the most versatile functionalities in synthetic chemistry, transformable into a multitude of functional groups, or readily incorporated into the structural backbone of organic molecules.[1] The privileged nature of alkynes in click chemistry further highlights their value.[2] Furthermore, conjugated and non-conjugated enynes have been widely exploited in organic synthesis.[3]

Over the past decade, the impact of transition metal-mediated C–H activation on the preparation of organic molecules has developed considerably.[4] The direct functionalisation of C–H bonds, obviating the need for pre-functionalisation is of particular interest when considering the increasing demands for efficiency in chemical synthesis. Whilst C–H activation strategies have been employed to mediate the alkynylation of (hetero)arenes and sp^3-carbon atoms by Pd[5] or Ru[6] catalysis, methods employing Rh catalysis are yet to be developed.[7]

The hypervalent iodine reagent 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **1**) introduced by Zhdankin[8] has recently risen to prominence as an efficient alkynylating reagent. The Waser research group has reported several beautiful examples[9] of the direct alkynylation of heterocycles, enolates and, most recently thiols using **1** and either by gold or palladium catalysis, under typically very mild conditions. Encouraged by the recent use of hypervalent iodonium reagents in combination with Rh(III) as demonstrated in elegant work by Li,[10] we proposed to develop a Rh(III) alkynylation protocol employing **1** as the alkyne source, and in particular to develop a novel approach to obtain synthetically valuable 1,3-enynes[3] *via* C–H activation.

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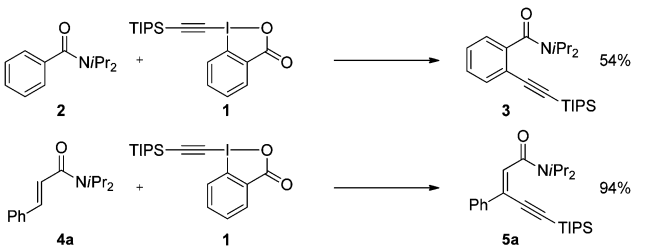

Scheme 1 Initial results of Rh(III) alkynylation. Conditions: **2** or **4** (0.200 mmol), **1** (2.0 eq.), $RhCp^*(MeCN)_3(SbF_6)_2$ (10 mol%), CH_2Cl_2 (1.5 mL), 80 °C, 16 h.

We initially investigated the direct alkynylation of arene **2** using a diisopropylbenzamide directing group, and were pleased to find that following a short optimisation, the reaction proceeded in the absence of any additives to give **3** in a moderate 54% yield, using 10 mol% of the cationic $RhCp^*(MeCN)_3(SbF_6)_2$ complex (Scheme 1).[11] Catalyst loading, reaction temperature, reaction stoichiometry and concentration were all shown to be critical (see ESI†). Upon changing the substrate to investigate the preparation of enynes, we were startled to find that using the same directing group, substrate **4a** gave **5a** in an excellent 94% isolated yield.

The reaction proceeded in the absence of any additives, and under an atmosphere of air, with no special precautions taken to exclude moisture. Control reactions excluded the role of atmospheric oxygen as an oxidant, and confirmed the requirement of the catalyst. The reaction was also shown to proceed in 91% yield using 5 mol% $[RhCp^*Cl_2]_2$ and 20 mol% $AgSbF_6$. Whilst we were able to reduce the reaction temperature and catalyst loading for the preparation of **5a**, we found that these conditions were unsuitable for alternate substrates (see ESI†).

We subsequently explored the scope with regard to substitutions on the aryl ring (Fig. 1), and were pleased to find that substitution at the *o*-, *m*-, and *p*-positions with a range of electron-withdrawing and electron-rich groups was tolerated. The preparation of **5a** on a 2 mmol scale with excellent yield demonstrated the scalability of this reaction.

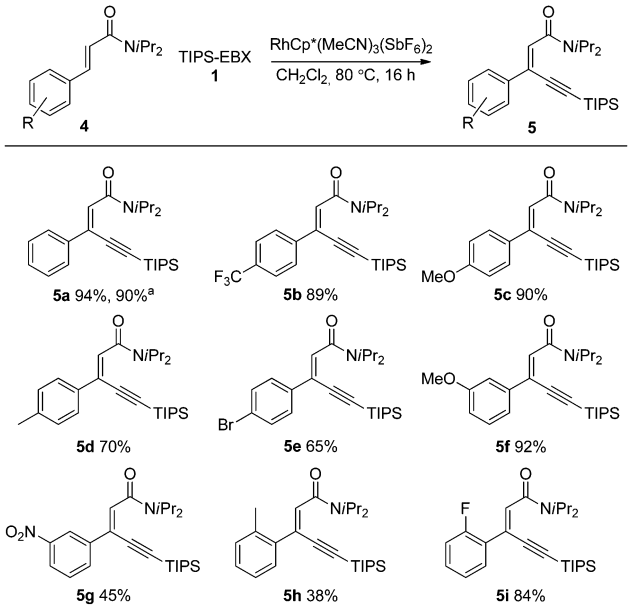

Fig. 1 Initial substrate scope. Conditions: **4** (0.200 mmol), **1** (2.0 eq.), $RhCp^*(MeCN)_3(SbF_6)_2$ (10 mol%), CH_2Cl_2 (1.5 mL), 80 °C, 16 h. Yields are reported for isolated materials. [a] 2.00 mmol scale.

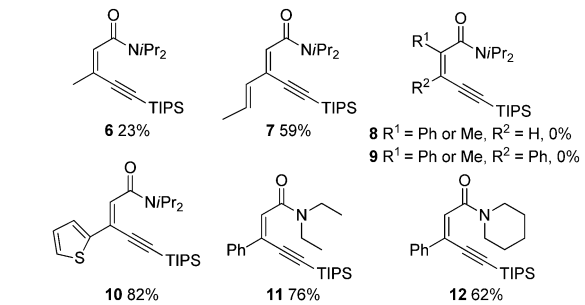

Fig. 2 Additional substrate scope for enyne formation. For reaction conditions see Fig. 1. Yields are reported for isolated materials.

Further exploration of the scope (Fig. 2) of this reaction determined that both alkyl and alkenyl substitutions were also tolerated. Unfortunately, geminal substitution of the α-carbon to the amide precluded product formation. Substitution of the phenyl ring for thiophene resulted in product formation in an excellent 82% yield. A number of alternative directing groups were also explored, with diethyl and piperidene tertiary amides giving **11** and **12** in 76% and 62% yields, respectively.

The use of different tertiary amide directing groups in the direct alkynylation of arenes has also been investigated. As discussed, the diisopropylamide directing group gave **3** in 54% yield under the reported reaction conditions. We consequently explored a number of additional tertiary amide directing groups, and were pleased to find that all reactions proceeded to give the mono-alkynylated products in high yields with the exception of the diethylamide directing group (Fig. 3). Detailed NMR analysis confirmed that the phenyl isopropyl amide directing group results in alkynylation of the benzamide aromatic ring **A**, rather than that of the acetanilide aromatic ring **B**.

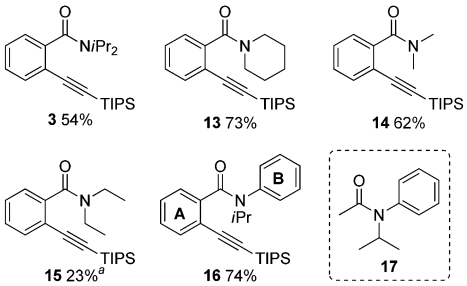

Fig. 3 Alkynylation of benzamides. For reaction conditions see Fig. 1. Yields are reported for isolated materials. [a] Reaction repeated twice giving identical yields.

The failure to identify any reaction product when employing acetanilide **17** further supports this conclusion.

To facilitate the application of this method, we were keen to establish a fuller picture of the functional group tolerance of this reaction and consequently we undertook a robustness screen as recently reported by Collins and Glorius.[12] The screen demonstrated that the reaction was tolerant of aromatic chlorides, nitriles, esters and tertiary amides, with these functionalities showing high stability under reaction conditions. Alkyl chlorides and a terminal olefin were amenable to the reaction conditions. Aliphatic and aromatic amines, a primary alcohol and a terminal alkyne were all shown to inhibit the reaction. Of the heterocycles screened, azacycles were typically detrimental to the reaction or unstable under the reaction conditions with the exception of 2-chloroquinoline. Pleasingly though, biologically relevant thiophenes and benzofurans were well tolerated, and proved to be stable under the reaction conditions. The full data are reported in the ESI.†

We have demonstrated TBAF mediated-deprotection of catalysis products to give terminal enynes and have also demonstrated a one-pot desilylation-Sonogashira coupling reaction to give **20** in 50% yield. The alkynylation of the natural product piperine **21** has also been demonstrated (Fig. 4).

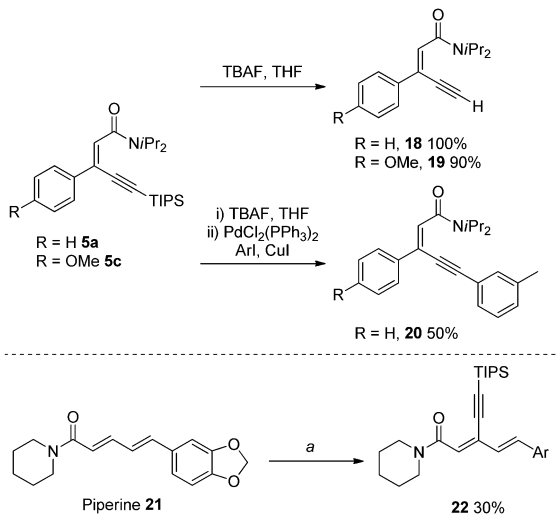

Fig. 4 Derivatisation of reaction products and application to a natural product. *a* **21** (0.200 mmol), **1** (2.0 eq.), $RhCp^*(MeCN)_3(SbF_6)_2$ (10 mol%), CH_2Cl_2 (1.5 mL), 80 °C, 16 h. Yields are reported for isolated materials.

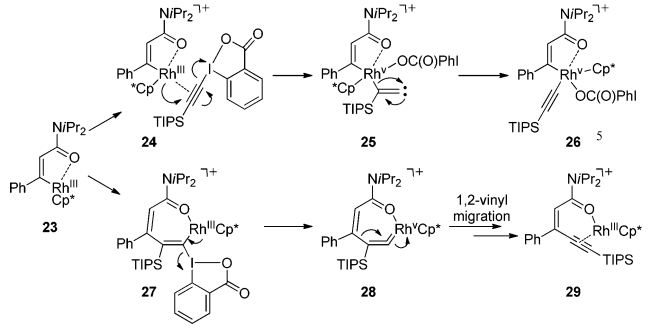

Fig. 5 Proposed mechanistic pathways.

We present two feasible mechanistic scenarios following amide-directed C–H activation of **5** to give rhodacycle **23** (Fig. 5):

(1) Following coordination of the alkyne, addition of rhodium, expelling 2-iodobenzoic acid would give rise to carbene **25**.[8g,13,14] Carbene rearrangement to give Rh(v) species **26** would enable formation of **5** following reductive elimination. Direct oxidative-addition of **1** to give **26** could also be considered.

(2) In accord with the strongly polarised nature of **1**, regio-selective carborhodation generating alkenyl-rhodacycle **27**, followed by α-elimination of 2-iodobenzoic acid would give rise to rhodium vinylidene species **28**. A concerted or stepwise vinyl-migration[8a] and elimination sequence would subsequently give rise to target **5** and regenerate a catalytically active Rh(III) species: the proposed migration is supported by labelling studies undertaken by Loh.[7] Carborhodation of the alkyne with the reverse selectivity seems to be unlikely due to potential steric clashes between the Cp* ligand and the triisopropylsilyl group, as well as the electronic polarisation of **1**.

In summary we have presented for the first time the preparation of enynes *via* a C–H activation protocol. This process introduces an electronically inverted retrosynthetic disconnection of enynes when compared to the classical Sonogashira coupling. This protocol has also been applied to the alkynylation of benzamides and further validates the potential applications of TIPS-EBX **1** by use of rhodium catalysis.

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