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Authors: Antonio M. Echavarren, Eric Tan, and Margherita Zanini

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Iridium-Catalyzed β-Alkynylation of Aliphatic Oximes as Masked Carbonyl Compounds and Alcohols

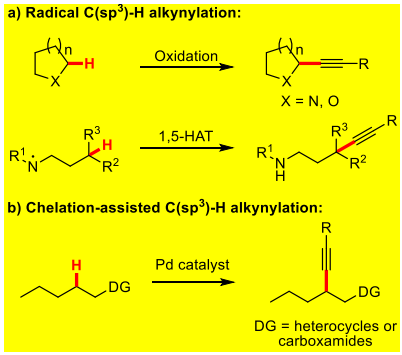
*Eric Tan,[†] Margherita Zanini,[†] and Antonio M. Echavarren**

Dedicated to the memory of our colleague and friend Prof. Dr. Kilian Muñiz

***Abstract*:** *The Ir-catalyzed C(sp³)–H alkynylation of aliphatic ketones, aldehydes, and alcohols has be performed in a general manner through their corresponding oxime derivatives in the presence of a Ir(III) catalyst. The reaction is selective towards primary C(sp³)–H bonds and can be used for the late-stage C-H alkynylation of complex molecules.*

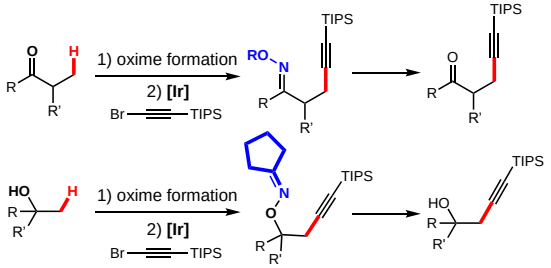
Alkynes are ubiquitous functional groups of high synthetic versatility,[1] which are also present as part of drugs,[2] natural products,[3] and organic materials.[4] The chemistry of alkynes has gained particular momentum in recent years due to the development of catalysts based on gold(I), platinum(II) and other electrophilic metals that trigger a wide variety of highly selective transformations in complex molecular settings.[5] Therefore, the development of methods for the selective introduction of alkynes in organic molecules is of the highest interest. To this end, classical cross coupling approaches require the pre-functionalization of the starting material with halides, pseudoaldehydes[6] or unsaturated bonds. In recent years, the so-called inverse-Sonogashira reaction emerged for the direct alkynylation of activated [7] and unactivated C(sp²)–H bonds[8] C–H bonds using transition-metal catalysts.

In contrast, the direct alkynylation of more challenging C(sp³)–H bonds remains underdeveloped. C(sp³-H) alkynylation can proceed via a radical pathway (Scheme 1, a), which requires either activation *via* 1,5-HAT from nitrogen in gamma position to the reactive center[9] or the presence of a heteroatom alpha to the C-H bond to achieve good reagioselectivty[10,11]. Alternatively, C(sp³-H) alkynylation through a C-H activation pathway requires the presence of a β-chelating carboxylic acid derivative or heterocycle (Scheme 1, b),[12] .



Scheme 1. Strategies in metal-catalyzed C(sp³)–H alkynylation.

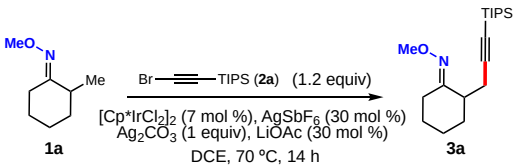
Ketoximes have been used as directing group in C(sp³)–H functionalization in the context of C–H oxygenation,[13] amidation,[14] amination,[15] arylation,[16] and iodination[17] with different transition metals as catalysts. We envisioned that the alkynylation of oximes derived from aldehydes, ketones, or alcohols[18] could significantly broaden the scope of the functionalization of C(sp³)–H bonds. With this aim, we have developed an iridium-catalyzed alkynylation directed by oximes, which in contrast to previous examples occurs exclusively at primary C(sp³)–H (Scheme 2). We also report examples of a similar process in which *N*-heterocycles are used as directing groups.



Scheme 2: Ir-catalyzed C(sp³)–H alkynylation of oximes derived from ketones, aldehydes, and alcohols.

We recently found that the combination of a Cp*Rh(III) catalyst and bromo-alkyne is a highly active system for the alkynylation of a broad-range of aromatic and olefinic C(sp²)–H bonds.[19] However, our attempt to extend these procedures to aliphatic C(sp³)–H bonds in oxime **1a** proved unsuccessful (Table 1, entry 1). The solution was found by using Cp*Ir(III) catalyst and TIPS-protected bromo alkyne **2a** (Table 1, entry 2), with $AgSbF_6$, Ag_2CO_3 and LiOAc as additives in 1,2-dichloroethane (DCE) as solvent. Under this condition, product **3a** resulting from the alkynylation at the methyl group was obtained in 78% yield. Control experiments showed the essential role of all reaction components (Table 1, entries 3-4). Other metal catalysts used in C–H functionalization were inactive (Table 1, entry 5).[20] The use of other silver salts (Table 1, entry 6), lower catalyst loading (Table 1, entry 7), lower or higher temperature (Table 1, entry 8) or other solvents (Table 1, entries 9-11) gave **3a** in lower yields. No conversion was observed with bromo- or iodo-alkynes **2b-d** (Table 1, entry 12).

Table 1. Ir-catalyzed C(sp³)–H alkynylation of **1a** with **2a**.[a]



entry	**Deviation** from optimized condition	yield **3a** (%)[a]
1	[Cp*RhCl₂] instead of [Cp*IrCl₂]	0

[*] E. Tan, M. Zanini, Prof. A. M. Echavarren
Institute of Chemical Research of Catalonia (ICIQ), Barcelona Institute of Science and Technology
Av. Països Catalans 16, 43007 Tarragona (Spain)
Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/ Marcel·li Domingo s/n, 43007 Tarragona (Spain)
E-mail: aechavarren@iciq.es
[†] These authors contributed equally to this work.
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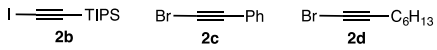
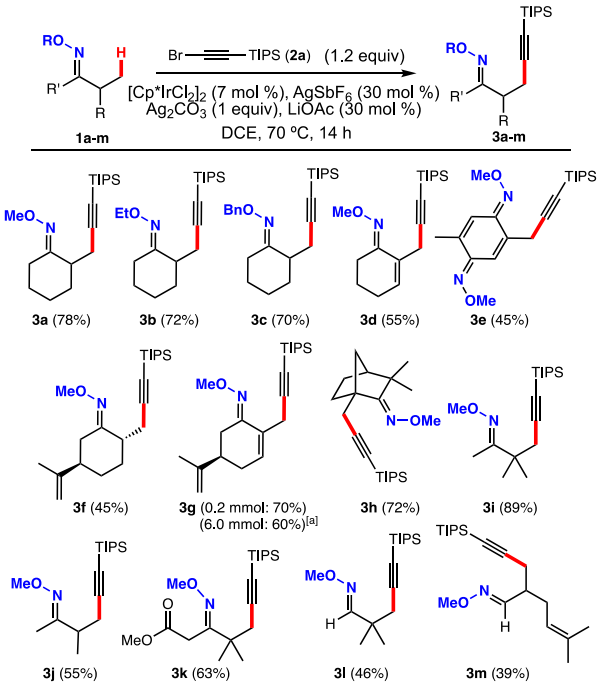
2	None	80 (78)[b]
3	Without [Cp*IrCl$_2$]	0
4	Without Ag_2CO_3, LiOAc, or $AgSbF_6$	0
5	With $MnBr(CO)_5$, Cp*Co(CO)I$_2$, Pd(OAc)$_2$, or [RuCl$_2$(*p*-cymene)]$_2$ instead of [Cp*IrCl$_2$]	0
6	With $AgNO_3$ or Ag_2O instead of Ag_2CO_3	0
7	With 3 or 5 mol % of catalyst instead of 7 mol %	25 or 50
8	At 25 ºC or 80 ºC	60
9	With THF instead of DCE	50
10	With *tert*-amyl alcohol instead of DCE	20
11	With DCE/TFE (1/1) or DCE/HFIP (1/1) instead of DCE	50 or 40
12	With **2b**-**d**	0

[a] Yield determined by ^{1}H NMR with biphenyl as internal standard. [b] Isolated yields in parentheses.

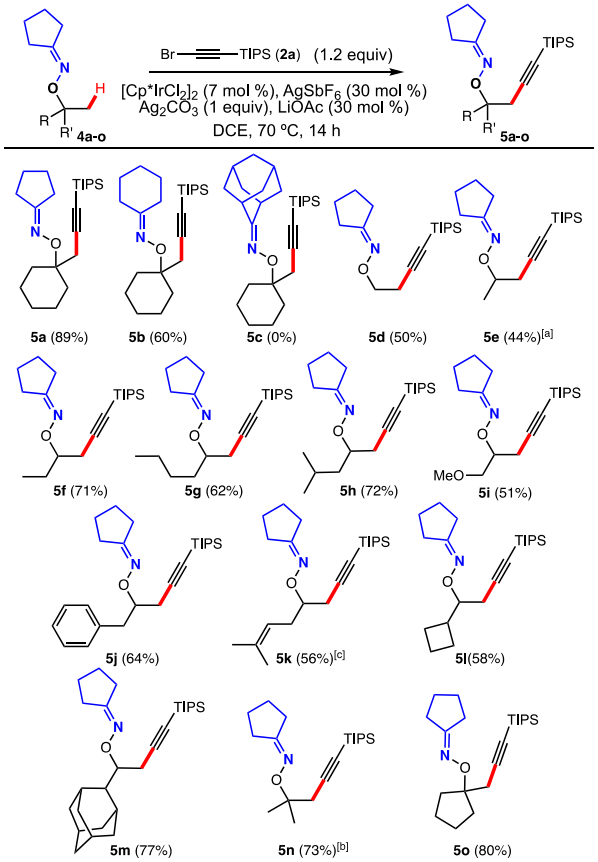


Under the optimized conditions, oxime ethers **1a**-**c** led to **3a**-**c** in similar yields (70-78%) (Scheme 3), whereas the free oxime, the acetoxime and the *O*-allyl oxime of 2-methylcyclohexanone failed to provide the β-alkynylated products. In the case of **1b**, no alkynylation at the methyl of the ethoxy group of the oxime was observed. The methoximes of 2-methyl-2-cycloxanone (**1d**), 2,5-dimethylbenzoquinone (**1e**), and (+)-*trans*-dihydrocarvone (**1f**) gave **3d-f** in moderate yields. The alkynylation of the methoxime of (*R*)-carvone (**1g**) afforded **3g** in good yield in a 6 mmol scale. Interestingly, (L)-fenchone derivative **1h** leads to **3h** by selective alkynylation at the bridgehead methyl group.[21] Methoximes of acyclic ketones and aldehydes **1i**-**m** also provided the corresponding alkynylated products **3i**-**m**.



Scheme 3. Ir-catalyzed C(sp^3)–H alkynylation of oximes derived from ketones and aldehydes. Yields are for isolated products. [a] Reaction performed with 6 mmol (1.1 g, 6 mmol) of methyl oxime under standard conditions.

Oximes derived from alcohols could also be alkynylated in the presence of iridium catalyst under identical conditions (Scheme 4). Among the different alcohol derivatives tested with 1-methylcyclohexanol, the oxime derived from cyclopentanone **4a** gave the highest yield of alkynylated derivative **5a** (89%). Products derived from primary (**5d**), secondary (**5e**-**m**), and tertiary (**5n**-**o**) alcohols could be alkynylated in 44-80% yield. All the reactions display an exquisite selectivity towards the activation of the C–H bond that would form the 5-membered iridacycle as demonstrated in the formation of **5f** in which the methyl in α-position to the alcohol is selectively alkynylated over the one in β-position. Interestingly, this selectivity is maintained in presence of C(sp^2)–H bond in β-position (**5k**). The presence of an ether (**5i**), aromatic ring (**5j**), or bulky adamantyl group (**5m**) does not erode the selectivity of the transformation.



Scheme 4. Ir-catalyzed C(sp^3)–H alkynylation of oximes derived from alcohols. Yields are for isolated products. [a] Dialkynylated product also isolated in 21% yield. [b] Obtained as a mixture 3:1 of mono:di-alkynylated peoducts. [c] Yield corrected for conversion (57%).

Substrates bearing functional groups such as a carboxylic acid, ester, ketone, amide, amine or *O*-thiocarbamate β to a primary C(sp^3)–H bond did not react under our standard conditions.[22] However, nitrogen heterocycles such as pyridines **6a-c**, pyrazole **6d** or pyrazine **6e** led to C–H alkynylation products **7a**-**e** at 120 °C in good yields (Scheme 5).

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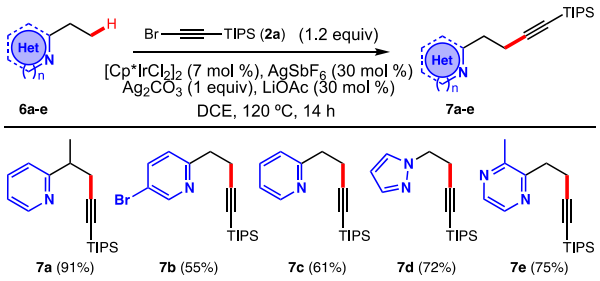
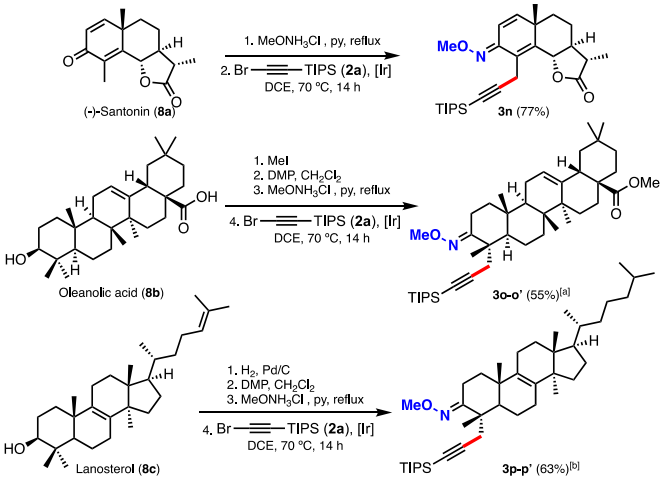


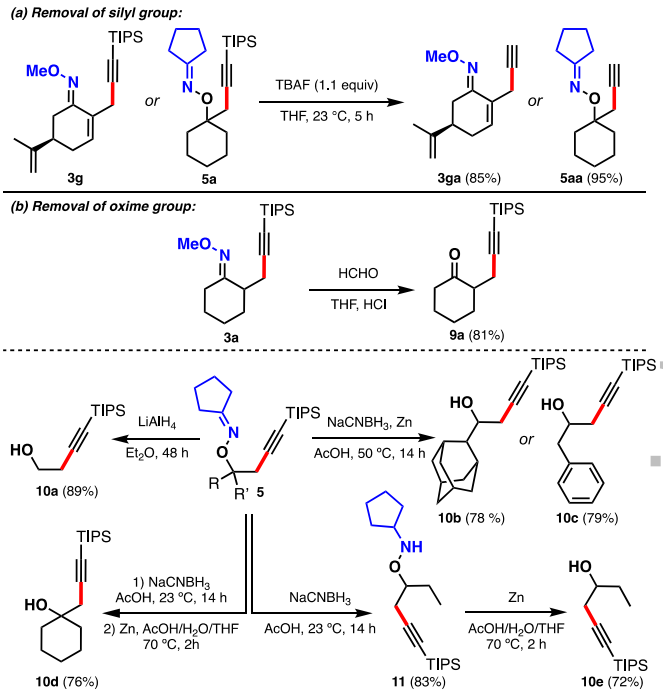
Scheme 5. Iridium-catalyzed C(sp^3)–H alkynylation directed by nitrogen heterocycles.

The reaction was applied for the late-stage functionalization of ketoximes derived from natural products **8a-c** (Scheme 6). Thus, the ketoxime derivative of (-)-santonin (**8a**) was alkynylated to form **3n** in 77 % yield. Oleanolic acid (**8b**) was converted into a separable mixture of products **3o** and **3o'** in 35% and 20%, respectively by a series of standard transformations followed by alkynylation. Similarly, lanosterol (**8c**) was transformed into **3p**, obtained as 4:1 diasteromeric mixture in 63% yield.



Scheme 6. Functionalization of santonin (**8a**), oleanolic acid, (**8b**) and lanosterol (**8c**) via their methoxime derivatives. [a] 1.7:1 mixture of diastereomers. [b] 4:1 mixture of diastereomers.

The silyl groups in **3g** and **5a** were cleanly removed with TBAF in 85% and 95% yield, respectively (Scheme 7, a). Deprotection of the methoxime **3a** to the corresponding ketone **9a** was achieved in 81% yield by treatment with formaldehyde under acidic conditions (Scheme 7, b). Oximes **5** were reduced to the alcohol either with $LiAlH_4$ (89% yield for **10a**) or $NaCNBH_3$ in presence of an excess of Zn powder (76-79% yield for **10b-d**). This procedure can be performed stepwise via hydroxylamine **11**, which was isolated in 83% yield; and then reduced in presence of Zn powder to give **10e** in 72% yield.



Scheme 7. (a) Deprotection of alkynes. (b) Cleavage of oximes. TBAF = tetrabutylammonium fluoride.

In summary, we have developped a method for the β-alkynylation of aldehydes, ketones, and alcohols using oximes as directing groups. The reaction is selective towards primary C(sp^3)-H bonds and tolerates the presence of functional groups such as ester, ether or alkenes. Cyclic and acyclic aliphatic substrates including derivatives of natural products were successful substrates. Basic heterocycles such as pyridine, pyrazole, or pyrazine could also be used as directing groups. Extension of this method for the alkynylation of other substrates is now under development in our group.

Acknowledgements

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Keywords: Iridium · C–H functionalization · Alkynylation · Oximes

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[21] In contrast, the *Z*-methoxime of (L)-fenchone is not reactive under the reaction condition and the starting material was recovered.

[22] See Supporting Information for additional details.