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Direct Conversion of Internal Alkynes into α-Iodoenones: One-Step Collaborative Iodination and Oxidation

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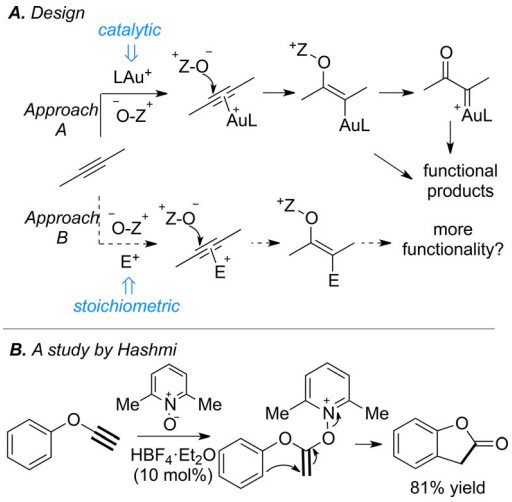
Abstract: The reaction of an internal alkyne with 2,6-dichloropyridine *N*-oxide, a nucleophilic oxidant, and electrophilic *N*-iodosuccinimide (NIS) simultaneously enables the direct access to versatile α-iodoenones. Electronically biased internal alkynes undergo the one-step transformation with excellent regioselectivities and with practical *Z*/*E* ratios. In comparison to the related oxidative gold catalysis using pyridine *N*-oxides, this reaction employs NIS as the stoichiometric ynophile instead of the soft acidic noble metal catalyst and affords products featuring an additional versatile C–I bond. Similar strategies for replacing ynophilic cationic gold(I) complexes in oxidative gold catalysis with likewise ynophilic stoichiometric electrophiles would enable the development of new synthetic methods.

Keywords: alkynes; enones; iodination; oxidation; pyridine *N*-oxides

α-Iodoenones possess an electrophilic enone moiety susceptible to either 1,4- or 1,2-addition and a versatile C–I bond for transition metal catalysis. As such, they are valuable structures in organic synthesis. Their syntheses have been achieved mostly *via* iodination of functional substrates such as enones,[1] α-silyl/stannyl-α,β-unsaturated ketones,[2] propargylic alcohols[3] and their ester counterparts,[4] and occasionally *via* oxidation of iodinated allylic alcohols.[5] There is seldom an approach that accomplishes both oxidation and iodination in a collaborative fashion in one step from substrates with lesser degrees of oxidation/functionalization.[6] Herein, we report an implementation of this approach using minimally functionalized internal alkyne substrates.

For the past several years our group[7] and others[8] have reported the applications of an oxidative gold catalysis strategy in the development of versatile synthetic methods. As shown in Approach A of Scheme 1A, the coordination of a soft Lewis acidic gold catalyst to a C≡C triple bond triggers the attack of a nucleophilic oxidant at its π bond. The initial adduct can undergo fragmentation of the inherently weak O–Z bond to offer expedient access to versatile α-oxo gold carbenes; alternatively, it may proceed to functionalized products without the carbene intermediacy in the presence of a more facile reaction pathway. Due to the catalytic nature of this chemistry, the *in situ* generated Au–C bond in this class of reactions



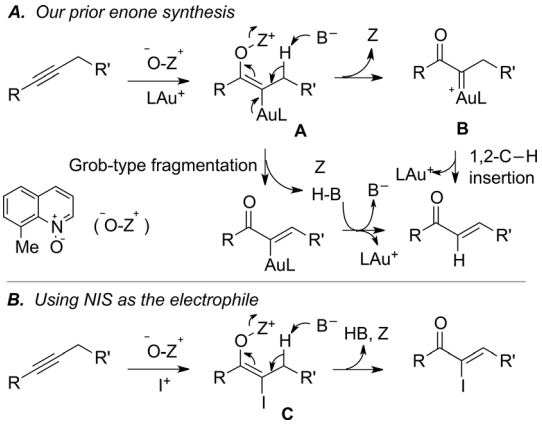
Scheme 1. Replacing gold catalysts with stoichiometric electrophiles in the oxidation of alkynes by nucleophilic oxidants.

are invariably converted into H–C or C–C bonds upon catalyst regeneration.

Despite our extensive work in oxidative gold catalysis[7] and the works of others using ynophiles such as NIS and $B(C_6F_5)_3$ to induce non-oxidative transformations similar to gold(I),[9] we have been intrigued by the possibility that, as outlined in Approach B, the gold catalyst could be replaced by stoichiometric amounts of a non-metal ynophile/electrophile (E^+) *via* a non-carbene pathway. To this end, a non-catalytic oxidative process could be realized, affording functional products featuring the electrophile and thus displaying increased functionalization. Conceptually, this strategy avoids the use of gold and could in theory open opportunities to develop valuable counterparts to various oxidative gold catalysis.

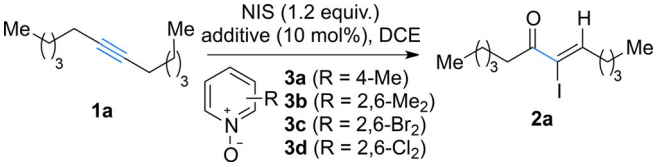
A related precedent is the synthesis of dihydrobenzofuranones by Hashmi,[10] where the stoichiometric electrophile is a proton in the form of HBF_4 etherate (Scheme 1B). Notably in this case, the alkynes are electron-rich, and products do not incorporate extra functionality.

In 2010 our group reported an Au-catalyzed oxidation of internal alkynes into enones with good to excellent regioselectivities (Scheme 2A).[7e] In the proposed reaction mechanism, the initial adduct **A** is fragmented into an α-oxo gold carbene, i.e., **B**, which undergoes 1,2-C–H insertion to render the enone product; however, it is possible that **A** might instead undergo deprotonative Grob-type fragmentation followed by protodeauration. With Approach B in Scheme 1A in mind, we anticipated that if a stoichiometric electrophile (e.g., NIS) was used *in lieu* of the gold catalyst, the initial iodinated adduct **C** could likewise undergo deprotonative fragmentation to produce α-iodoenones from internal alkynes in the presence of a base (Scheme 2B).[11]



Scheme 2. Our previous enone synthesis and a designed one-step collaborative oxidation and iodination of an internal alkyne.

Table 1. Initial reaction discovery and optimization.[a]



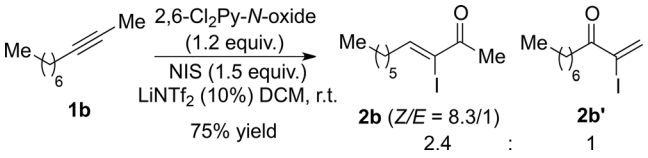
Entry	Oxidant	Additive	Temp./Time	**2a/1a**[b]	*Z/E*
1	**3a**	–	r.t./4 h, 60 °C/19 h	22%/35%	19/1
2	**3b**	–	r.t./4 h, 60 °C/19 h	41%/30%	4.6/1
3	**3c**	–	r.t./4 h, 60 °C/19 h	46%/36%	7.7/1
4	**3d**	–	r.t./4 h, 60 °C/19 h	63%/5%	7.7/1
5	**3d**	$Mg(OTf)_2$	r.t./24 h	53%/33%	7.2/1
6	**3d**	$La(OTf)_3$	r.t./24 h	67%/15%	7.1/1
7	**3d**	LiOTf	r.t./24 h	58%/32%	7.4/1
8	**3d**	$Ni(OTf)_2$	r.t./24 h	65%/9%	8.0/1
9	**3d**	$LiNTf_2$	r.t./24 h	70%/10%	6.8/1
10	**3d**	NaBARF	r.t./12 h	80%/8%	7.4/1
11[c]	**3d**	$LiNTf_2$	r.t./24 h	80%/2%	7.7/1
12[d]	**3d**	$LiNTf_2$	r.t./24 h	80%/2%	7.6/1
13[e]	**3d**	$LiNTf_2$	r.t./24 h	84%[f]/–	6.3/1

[a] Initial [**1a**] = 0.05 M.
[b] Estimated by ^{1}H NMR using the two methyl groups from 6-dodecyne as the reference.
[c] NIS (1.5 equiv.).
[d] Initial [**1a**] = 0.1 M, NIS (1.5 equiv.).
[e] DCM as solvent. Initial [**1a**] = 0.1 M, NIS (1.5 equiv.).
[f] Due to the co-elution of 2,6-dichloropyridine, **2a** was isolated as a mixture with the pyridine in a calculated yield of 79% and with a *Z/E* ratio of 23:1.

To implement this design, we chose 6-dodecyne as the substrate and *N*-iodosuccinimide (NIS) as the electrophile for initial reaction discovery and conditions optimization. As shown in Table 1, various pyridine *N*-oxides were screened. To our delight, the desired product (**2a**) was formed in 22% NMR yield when 4-picoline *N*-oxide (**3a**) was used (entry 1); however the reaction was very slow with a considerable amount of alkyne substrate remaining unreacted despite long reaction times. Under the same conditions, 2,6-lutidine *N*-oxide (**3b**), a sterically hindered and weaker oxidant, improved the yield to 41% (entry 2), 2,6-dibromopyridine *N*-oxide (**3c**), a sterically hindered and stronger oxidant, further enhanced the reaction efficiency (entry 3), and 2,6-dichloropyridine *N*-oxide (**3d**) proved to be optimal with the reaction yield increasing to 63% (entry 4). We reasoned that the slow reaction rate might be attributed to the relatively low reactivity of NIS toward C-C triple bonds. To this end, various Lewis acid additives were introduced to increase the electrophilicity of the halogenating reagent. As a consequence, as shown in entries 5–10, the reactions would now proceed at a reasonable rate at ambient temperature. From a performance perspective, NaBARF and $LiNTf_2$ were the

top two performers, with NaBARF being the best additive screened to date (entry 10); however, due to the relatively high cost of NaBARF, $LiNTf_2$ was chosen as the ideal additive to use. Using 1.5 equivalents of NIS and changing the solvent from DCE to DCM further improved the yield, and the α-iodoenone **2a** was formed in an optimal 84% yield. In all these cases, **2a** was formed as a mixture of geometric isomers, with the Z-isomer favored, and the ratio, mostly around 7–8/1, appears to be affected substantially by oxidant (*cf.* entries1–3) and to a small extent by other factors such as additive, temperature and solvent.

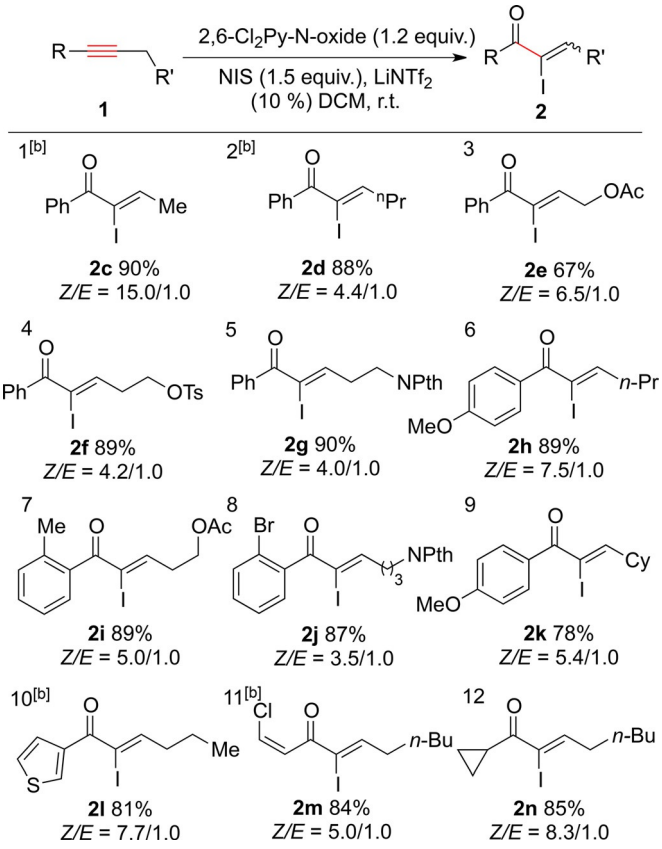
With the optimal conditions identified (Table 1, entry 13), we proceeded with examining the substrate scope of internal alkynes. Initially we probed the regioselectivity of the reaction of 2-decyne. As shown in Scheme 3, the reaction displays moderate regioselectivity and fairly good geometric selectivities, with three isomeric α-iodoenones formed in a combined 75% yield. In contrast, the optimized gold catalysis in the synthesis of the non-iodinated enone counterparts displays a good regioselectivity of 11:1 favoring the same regioisomer and a geometric selectivity of >25:1 favoring the *E*-isomer.[7e] This comparison does reveal the advantage of gold catalysis in achieving more control, albeit at the expense of lesser functionalization in the product.



Scheme 3. Reaction of an unsymmetrical aliphatic internal alkyne.

To avoid regioselectivity issues, we turned to electronically biased substrates, and the results are shown in Table 2. Hence, both 1-phenyl-1-propyne and 1-phenyl-1-hexyne reacted smoothly to afford the α-iodoenones **2c** (entry 1) and **2d** (entry 2), respectively, in excellent yields, with **2c** displaying a better *Z/E* ratio. Various functional substituents on the aliphatic end of the arylalkynes at different positions (entries 3–5) are allowed, affording the desired products in fair to high yields and with serviceable *Z/E* selectivities. While the lower yield of **2e** can be attributed to the inductive deactivation of the C-C triple bond by the β-acetoxy group, a more reactive TsO group γ to the alkyne moiety causes no problem (entry 4). Tolerated on the benzene ring are substituents such as MeO at the *para* position (entries 6 and 9) and Me and Br at the sterically demanding *ortho* position (entries 7 and 8). It is noteworthy that no product with

Table 2. Reaction scope.[a]

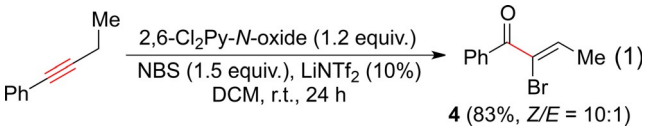


[a] Initial [**1a**] = 0.05 M. Isolated yield reported.
[b] Due to the co-elution of 2,6-dichloropyridine, the product was isolated as a mixture with the pyridine, and the calculated yield is shown.

additional iodination at the anisyl ring was observed, indicating selective alkyne activation by the electrophilic iodine reagent.

Electron-rich thiophenes were also tolerated (entry 10), with thiophen-3-yl α-iodoenone (**2l**) isolated in 81% yield. Again, no detectable ring halogenation was observed. Simple enynes gave no desired products, presumably due to the preferred reaction at the C-C double bond. However, as shown in entry 11, with the C-C double bond deactivated by a chloro group, the reaction proceeded smoothly to afford the dialkenyl ketone (**2m**) in 84% yield. Finally, a cyclopropyl group is also capable of electronically biasing the C≡C triple bond during the reaction. As such, the cyclopropyl ketone **2n** (entry 12) was formed smoothly in a very good yield.

At last, we tested whether NBS can replace NIS as the electrophilic halogen source. As shown in Eq. (1), the reaction of 1-phenyl-1-propyne proceeded smoothly under the same reaction conditions, affording the bromoenone **4** in a good yield. On the other hand, Selectfluor failed to yield the corresponding fluorinated enone.



In conclusion, a one-step conversion of an internal alkyne into a versatile α-iodoenone is realized by using a combination of 2,6-dichloropyridine *N*-oxide, a nucleophilic oxidant, and electrophilic NIS. With electronically biased internal alkyne substrates, the reactions are generally efficient and exhibit practically useful *Z*/*E* ratios. In comparison to the related oxidative gold catalysis using pyridine *N*-oxides, this reaction employs NIS as a stoichiometric ynophile instead of the noble metal catalyst and affords products featuring an additional versatile C–I bond capable of undergoing further manipulation. It is anticipated that similar strategies of replacing gold with stoichiometric ynophiles can be employed to transform other versatile oxidative gold catalysis into related non-catalyzed reactions with products possessing additional functionalities and hence increasing synthetic value.

Experimental Section

General Procedure for the Preparation of 2 from 1

2,6-Dichloropyridine *N*-oxide (1.2 equiv.), NIS (1.5 equiv.), and $LiNTf_2$ (10 mol%) were added in this particular order to a solution of the internal alkyne **1** (0.2 mmol) in dichloromethane (4 mL) in a vial at room temperature. The reaction mixture was stirred at the same temperature for 24 h. Upon completion, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired product **2**.

Acknowledgements

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