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Ligand-Accelerated Gold-Catalyzed Addition of in Situ Generated Hydrazoic Acid to Alkynes under Neat Conditions

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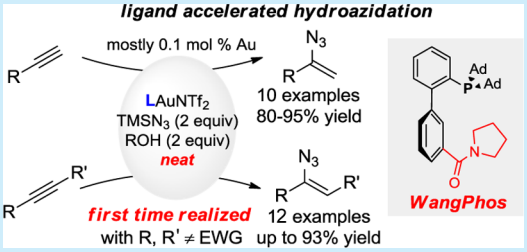
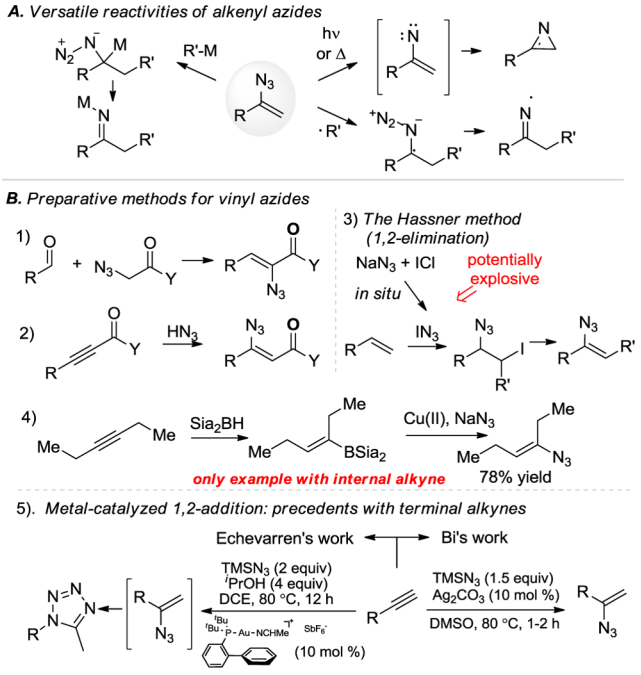
Supporting Information

ABSTRACT: The direct addition of in situ generated hydrazoic acid to alkynes is realized without solvent by using a gold catalyst derived from a recently designed remotely functionalized biaryl-2-ylphosphine ligand (i.e., WangPhos). With terminal alkynes, the additions are mostly realized with 0.1 mol% catalyst loadings and at 40 °C. With more challenging internal alkynes devoid of direct EWG substitution, the one-step transformation is realized for the first time with generally high efficiency at ambient temperature.



Vinyl azides are versatile intermediates in the synthesis of bioactive alkaloids and/or *N*-heterocycles[1] and serve as precursors to reactive vinyl nitrene and synthetically exceptionally valuable 2*H*-azirines (Scheme 1A).[2] They can also react readily with organometallic reagents to generate metalloimine with newly formed C−C bonds and with a radical to access an imino radical.[1i] Their synthesis[1d,e,3] can be mostly achieved via condensation of aldehydes with α-azido esters/ketones, 1,4-additions to electron-deficient π systems, 1,2-eliminations, hydroboration/oxidative azidation,[4] and 1,2-additions of HN_3[5] (Scheme 1B). Whereas the first two approaches afford the electronically deficient subtypes, the last three strategies are suitable for the preparation of those of electronically neutral or rich, but are still limited especially in the cases of internal vinyl azides. For the 1,2-elimination approach, the method developed by Hassner,[3a,6] whereas an iodoazidation of alkenes using iodine azide is followed by a base-promoted elimination of HI, is often employed due to its succinct nature (Scheme 1B-3). However, this method is not ideal as IN_3, despite in situ generated, is still a safety concern due to its explosive nature, the strongly oxidative/electrophilic nature of the conditions including the use of ICl significantly limits the scope of tolerable functional groups,[7] and with internal alkene substrates regioselectivity can be an issue. For the hydroboration/oxidative azidation approach,[4] the reaction requires excess of Cu(II) salt, uses unstable and freshly prepared Sia_2BH, and leads to formally anti-Markovnikov syn addion of HN_3, and the symmetric case shown in Scheme 1B-4 is the only reported internal alkyne example.

Scheme 1. Reactivities of Alkenyl Azides and Their Synthesis



Metal-catalyzed 1,2-additions of HN_3, i.e., hydrazoic acid, to alkynes could offer a straightforward, one-step, atom-economic alternative. Echavarren and co-workers[8] reported a synthesis of tetrazoles from terminal alkynes and in situ generated HN_3 in the presence of JohnPhosAu(NCMe)$^+$ SbF_6^- (Scheme 1B-5). The vinyl azide **1**, a Markovnikov adduct, is the likely reaction intermediate but is apparently susceptible to further reaction under the requisite thermo conditions (i.e., 80 °C) except in one case. A corresponding silver catalysis implicated by the work of Jiao[9] and later developed by Bi[5] is again conducted with terminal alkynes at 80 °C, and vinyl azides are formed in good yields at short duration but could react further after extended heating to eventually afford nitriles.[9] While in these studies the hazardous nature of hydrazoic acid is mitigated by

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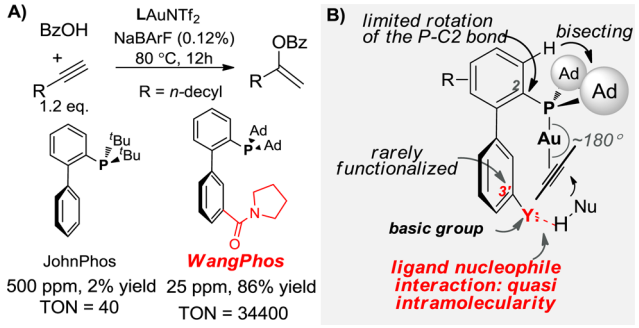
its in situ generation via the reaction between commercially available $TMSN_3$ and an alcohol, the reactions are limited to terminal alkynes, and the requisite elevated temperature appears to diminish the reaction yield. For internal alkynes leading to internal vinylazides, they are implicated as intermediates in an Au/Ag catalysis but not detected.[10]

Recently we[11] reported that by functionalizing the privileged biphenyl-2-ylphosphine framework with an amide group at the C3′ position the resulting bifunctional phosphine ligand, i.e., WangPhos, enables exceptionally expedient acid additions to alkynes, thereby permitting ppm-level gold catalysis (Scheme 2A). Comparing with JohnPhos, which is sterically and

Scheme 2. (a) WangPhos and Its Application in Gold-Catalyzed Acid Addition to Alkyne; and (b) the General Design of Remotely Functionalized Biphenyl-2-ylphosphine Specifically Accommodating Au(I) Catalysis

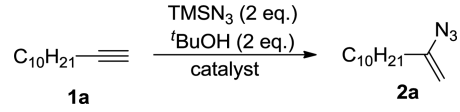


electronically comparable but lack of the remote amide group, this novel ligand accelerates the reaction by estimated 860 times. The design, shown in Scheme 2B and supported by DFT calculations, entails the positioning of the remote amide group near the incoming nucleophile by relying on the rather unique and robust linear structure of L-Au-substrate, thereby enabling a general base catalysis by the amide group and a quasi intramolecular nucleophilic attack at the alkyne.

In our attempt to expand the synthetic utility of this novel ligand and explore the applicability of the design to valuable nucleophiles beyond carboxylic acids, H_2O and aniline,[11] we decided to examine in situ generated HN_3, which, however, is structurally distinctive from our reported nucleophiles due to its linear azido moiety and could be challenging. Nevertheless, potential rate acceleration of HN_3 addition to alkynes by WangPhos would offer advantages of high synthetic values, including (a) low reaction temperatures, which could avoid product decomposition, (b) low catalyst loadings, (c) a broad reaction scope including previously unsuitable internal alkynes, and/or (d) synthetically useful regioselectivity.

At the outset, we studied the hydroazidation by using the more reactive terminal alkyne 1-dodecyne as substrate. As shown in Table 1, entry 1, the reaction performed with in situ generated WangPhosAuNTf$_2$ (1 mol%) as catalyst, ^{t}BuOH as the proton source and in DCM indeed occurred at ambient temperature, but did not complete even after 18 h. Nevertheless, WangPhos performed much better than JohnPhos (entry 2), indicating that the ligand remote amide group engages accelerating interaction with HN_3. After substantial effort of condition optimization, we discovered that the reaction was at best run neat. To this end, the vinyl azide **2a** was formed in an outstanding 95% yield in 2 h (entry 3). Counteranion screening (entries 4−6) reveals that $BARF^-$ performed slightly

Table 1. Reaction Optimization



entry	catalyst (mol%)	conditions	time (h)	yield[a,b] (%)
1	WangPhosAuCl/AgNTf$_2$ (1)	DCM (0.1M), rt	18	58
2	JohnPhosAuCl/AgNTf$_2$ (1)	DCM (0.1M), rt	18	3
3	WangPhosAuCl/AgNTf$_2$ (1)	neat, rt	2	95
4	WangPhosAuCl/AgOTf (1)	neat, rt	2	82
5	WangPhosAuCl/AgSbF$_6$ (1)	neat, rt	2	92
6	WangPhosAuCl/NaBARF (1)	neat, rt	2	96
7	WangPhosAuCl (0.1) NaBARF (1)	neat, rt	10	91
8	WangPhosAuCl (0.1) NaBARF (1)	neat, 40 °C	2	93[c]
9	JohnPhosAuCl (0.1) NaBARF (1)	neat, 40 °C	24	62
10	IPrAuCl (0.1)/NaBARF (1)	neat, 40 °C	24	25
11	Ph$_3$PAuCl (0.1)/NaBARF (1)	neat, 40 °C	24	trace
12	(2,6-^{t}Bu$_2$C$_6$H$_3$)O]$_3$PAuCl (0.1) NaBARF (1)	neat, 40 °C	24	11
13	BrettPhosAuCl (0.1) NaBARF (1)	neat, 40 °C	24 h	63

[a]Determined by ^{1}H NMR using the terminal methyl group as reference. [b]The remaining **1a** and its hydration product account for the mass balance. [c]87% isolated yield.

better than NTf_2^-. With an order of magnitude lower gold loading, i.e., 0.1 mol%, the relatively long reaction time in entry 7 was cut down to 2 h by slightly raising the temperature to 40 °C, and the reaction was highly efficient (entry 8). In comparison, with JohnPhos as ligand, the reaction was substantially slower, and the yield was only 62% after 24 h (entry 9). Other often used gold ligands were also examined, but most were much inferior to JohnPhos (entries 10−12), with the exception of BrettPhos, which is comparable to JohnPhos (entry 13).

The reaction scope with terminal alkynes was then examined. As shown in Table 2, both cyclohexylacetylene (entry 1) and cyclohex-1-en-1-ylacetylene (entry 2) participate the reaction smoothly. Alcoholic substrates **1d**−**1h** with different protecting groups are readily allowed (entries 3−7). For **1g** and **1h** of increased steric hindrance and less reactive C−C triple bond, the catalyst loading is a higher 0.5 mol%. For the sulfonamide alkyne substrate **1i**, an even higher 2 mol% is needed (entry 8). The reaction with phenylacetylene was uneventful. Notably, these reactions are all highly efficient, with yields ranging from 80 to 95%.

With the success with terminal alkynes, we then turned our attention to less reactive and hence challenging internal alkynes lacking direct EWG substitution, which have so far not been succumbed to metal-catalyzed hydroazidation reactions. Indeed, their reactions are in general much slower and best run with 5 mol% catalyst loading, by using more reactive ^{i}PrOH as the proton donor and at ambient termperature. Nevertheless, the desired vinyl azides can be obtained in fair to excellent

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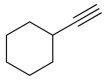
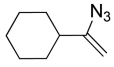
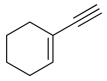
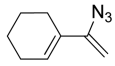
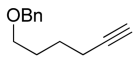
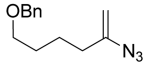
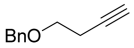
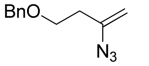
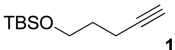
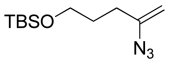
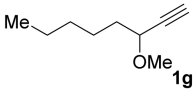
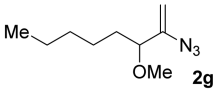
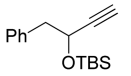
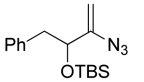
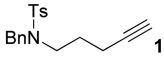
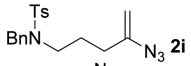
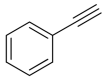
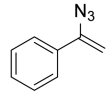
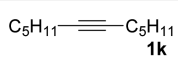
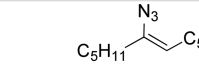
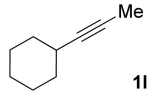
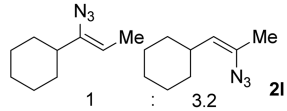
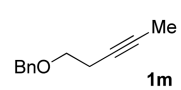
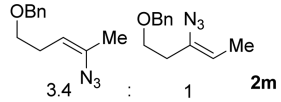
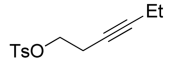
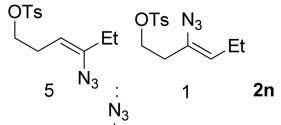
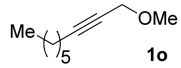
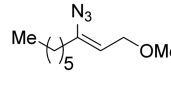
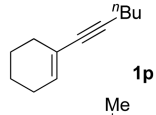
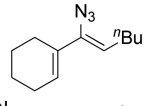
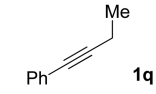
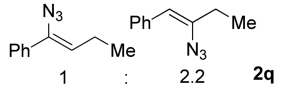
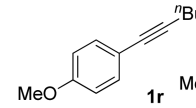
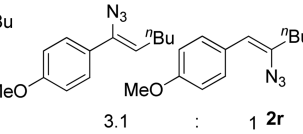
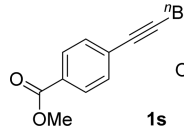
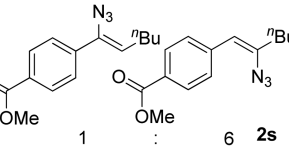
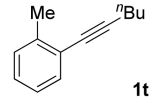
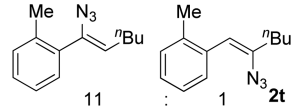
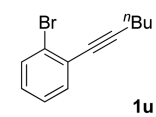
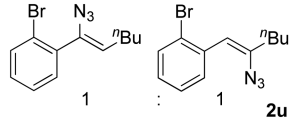
Table 2. Reaction Scope with Terminal Alkyne Substrates[a]

entry	terminal alkyne 1	alkenyl azide 2	time (h)	yield[b] (%)
1	 1b	 2b	4	95
2	 1c	 2c	4	90
3	 1d	 2d	5	80
4	 1e	 2e	7	90
5	 1f	 2f	7	81
6[b]	 1g	 2g	9	81
7[b]	 1h	 2h	9	84
8[c]	 1i	 2i	4	83
9	 1j	 2j	2	93

[a]Reaction conditions: $TMSN_3$ (2 equiv), ^{t}BuOH (2 equiv), WangPhosAuCl (0.1 mol%), NaBARF (1 mol%), neat, N_2, 40 °C. [b]0.5 mol% of WangPhosAuCl used. [c]2 mol% of WangPhosAuCl and 2 mol% of NaBARF used.

Table 3. Reaction Scope with Internal Alkyne Substrates[a]

entry	internal alkyne 1	alkenyl azide 2[b]	time (h)	yield[b] (%)
1	 1k	 2k	12	79[c]
2	 1l	 1 : 3.2 2l	12	52[d] (89)[e]
3	 1m	 3.4 : 1 2m	12	85
4	 1n	 5 : 1 2n	12	80
5	 1o	 2o	5	83
6	 1p	 2p	6	56[d] (87)[e]
7	 1q	 1 : 2.2 2q	12	93
8	 1r	 3.1 : 1 2r	12	82
9	 1s	 1 : 6 2s	20	83
10	 1t	 11 : 1 2t	12	78[f]
11	 1u	 1 : 1 2u	12	93
12	1v	2v	12	90

[a]Reaction conditions: $TMSN_3$ (2 equiv), ^{i}PrOH (2 equiv), WangPhosAuNTf$_2$ (5 mol%), NaBARF (5 mol%), neat, N_2, rt. [b]Regioisomer ratios determined by ^{1}H NMR. [c]2 mol% of WangPhosAuNTf$_2$ and NaBARF used. [d]The remaining substrate accounts mostly for the mass balance. [e]The NMR yield based on substrate conversion. [f]Only the major isomer was isolated.

yields (Table 3). For example, hydroazidation of the symmetric 6-dodecyne affords (*Z*)-6-azido-6-dodecene in 79% yield (entry 1). With the sterically biased cyclohexyl methyl acetylene **1l**, the reaction was sluggish, affording the vinyl azide **2l** as a regioisomeric mixture in a moderate 52% yield and in >90% yield based on substrate consumption (entry 2). This observed preference of the azido group attacking the less sterically demanding alkyne end is consistent with our prior oxidation chemistry.[12] Aliphatic alkynes with protected/functionalized hydroxyl groups were also examined. A moderate regioselectivity was observed in the case of **1m** (entry 3), and the major isomer of the product **2m** is favored by sterics and inductive effect. The inductive effect is enhanced with **1n** featuring a more electron-withdrawing tosyloxy β to the C−C triple bond and largely responsible for the synthetically useful 5:1 ratio (entry 4). In the case of an α-EWG, even a MeO group is inductive enough to dictate a complete regioselectivity (entry 5). With enyne **1p** where the C−C triple bond is conjugated to an alkene, the reaction turned out to be highly regioselective, despite a moderate yield due to sluggish conversion (entry 6). We then studied various arylalkynes **1q**−**1v** and interrogated the impact of arene substituents on reaction regioselectivity. Somewhat surprisingly, for the phenyl substrate **1q**, the hydroazidation is only moderately selective; moreover, the 2-azido isomer of **2q** is slightly favored over the 1-azido one, suggesting the phenyl group is a bulky group and possibly also behaves more of an inductive electron-withdrawing group than a resonance stabilizer (entry 7). With a 4-MeO group, the 1-azido isomer is favored in a ratio of 3.1/1 over the 2-azido product (entry 8). As expected, an electron-withdrawing ester group at the same position enhances the preference for the 2-azido isomer (entry 9). To our surprise, an ortho-Me group leads to a good regioselectivity (11:1) favoring the 1-azido product (entry 10). An *ortho*-Br, however, results in no selectivity (entry 11). Finally, diphenylacetylene reacted smoothly to afford the azidostilbene **2v** in an excellent yield (entry 12). Importantly, these reactions are mostly good to

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high yielding, and should be synthetically useful despite the moderate regioselectivities in some cases.

In summary, we have applied our designed, remotely functionalized biaryl-2-ylphosphine ligand, i.e., WangPhos, to a gold-catalyzed direct addition of in situ generated hydrazoic acid to alkynes. With terminal alkynes, the reactions are mostly realized with 0.1 mol% catalyst, in the absence of solvent and under mild heating (40 °C). With internal alkyne substrates, this one-step transformation to synthetically valuable internal vinyl azides is realized for the first time with generally high efficiency due to the exceedingly mild reaction conditions. Moreover, some of the reactions exhibit synthetically valuable regioselectivities. Comparing to electronically and sterically similar JohnPhos, the significant rate acceleration by WangPhos is consistent with that the ligand 3′-amide group behaves as a general base catalyst in promoting HN_3 attack of alkyne, despite the distinctive linear structure of the azido moiety. This successful accommodation of valuable and structurally diverse nucleophiles beyond previously studied carboxylic acid, H_2O, and aniline suggests the general utility of WangPhos in substantially accelerating and improving gold catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01359.

Experimental procedures and compound characterization and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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