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Copper-catalyzed stereoselective alkylhydrazination of alkynes†

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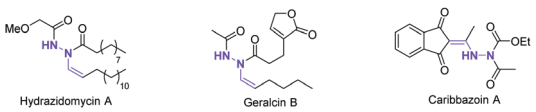
An unprecedented Cu-catalyzed stereoselective alkylhydrazination reaction involving terminal alkynes, azocarboxylic esters as a nitrogen source, and dimethyl 2,2′-azobis(2-methylpropionate) and its analogues as a carbon source is presented here. This protocol provides direct access to tri-substituted (*E*)-alkenyl-hydrazines with good regio- and stereoselectivity under mild conditions. The transformation proceeds without an external oxidant or additives and shows good functional group tolerance. The alkenylhydrazine products could be easily converted into valuable 1,4-dicarbonyl and allyl carboxylic derivatives.

Hydrazines are versatile structures in organic chemistry that can participate in the synthesis of N-containing heterocycles, such as indoles, pyrazoles, and cinnolines;[1] be transformed into amines through N–N bond cleavage;[2] or be converted into other functional groups. Hence, many protocols for the synthesis of organic hydrazines, especially alkyl-, aryl- and acyl-substituted ones, have been documented.[3–5] However, alkenyl-substituted hydrazines have been reported less frequently. It is worth noting that some natural alkenylhydrazines possess diverse bioactivities (Scheme 1), such as hydrazidomycin A (antiproliferative activity), geralcin B (antineoplastic activity), and caribbazoin A (hypotensive activity in rats).[6] Previous protocols for the preparation of alkenylhydrazines mainly include ketone-type Mitsunobu reactions,[7a–c] addition of allenes or enamides to azodicarboxylates,[7d–f] and aza-Baylis–Hillman reactions from alkyl vinyl ketones and azodicarboxylates.[7g,h] In addition, the synthesis of alkenylhydrazines from alkynes is a promising route because of the availability and flexibility of alkynes, which can be divided into two paths (Scheme 2, route A). One path is the transformation of alkynes to stereo-fixed alkenyl halides or boronic acids, which then react with substituted hydrazines *via* Pd- or Cu-catalyzed cross-coupling reactions.[8] Examples include nucleophilic alkenyl metal species derived from the reaction of stoichiometric metal reagents (*e.g.*, Al and Ni) with alkynes, which then react with electrophilic azocarboxylic esters.[9] Therefore, a new synthetic method for the synthesis of alkenylhydrazines starting from simple alkynes in a 'one-pot', regio-/stereoselective, and catalytic manner is highly required.

On the other hand, with the development of transition metal catalysis, difunctionalization of C–C triple bonds has drawn considerable attention for its efficient construction of complex molecules from simple, commercially available compounds.[10] Among them, tremendous progress in the incorporation of alkyl moieties into triple bonds has been achieved. A major synthetic target for such transformations, including hydroalkylation,[11] haloalkylation,[12] oxyalkylation[13] and carboalkylation,[14] is the incorporation of an alkyl radical across the C–C triple bonds to build useful multi-substituted alkenes or ketones. However, alkylamination of alkynes is still challenging. This is probably due to the vinyl radical intermediate, which is reactive and unstable, readily undergoes H-atom abstraction rather than be captured by the nitrogen source.[15] To solve this problem, electron-withdrawing group radicals were incorporated into the alkynes to stabilize the formed vinyl radicals. Liu, Liang and Bao developed three-component carboazidation of alkynes using $TMSN_3$ as an amine source with further transformation to achieve fluoroalkyl substituted azirines.[16] A variety of fluoroalkyl radical sources have been reported in the literature. However, the reaction was sluggish when alkyl iodine was used as the radical source.[16c] Hence, the spread of these protocols to more common alkyl radicals is significantly urgent. With this in mind, we



Scheme 1 Biologically active compounds containing alkenylhydrazine moieties.

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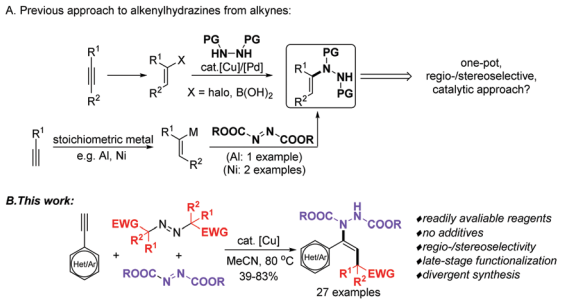
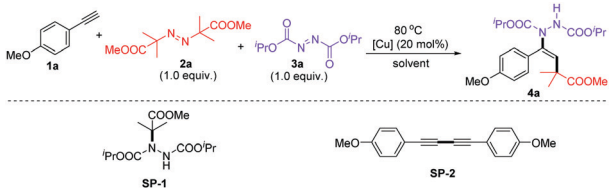


Scheme 2 Strategies for the synthesis of alkenylhydrazines.

consider whether vinyl radicals created by the addition of alkyl radicals to simple alkynes could add to azocarboxylic esters, an amine source and a readily available radical trap,[3b,c,17] to generate alkenylhydrazines. Herein, we report a novel Cu-catalyzed stereoselective alkylhydrazination of terminal alkynes with azocarboxylic esters and dimethyl 2,2′-azobis(2-methylpropionate) (AIBME) to afford trisubstituted *E*-alkenylhydrazines.

At the onset of our investigation, we chose 4-ethynylanisole (**1a**), AIBME (**2a**), and diisopropyl azodicarboxylate (DIAD) (**3a**) as model reagents to survey the reaction conditions. All of these compounds are commercially available. As shown in Table 1, in the absence of a Cu catalyst, the reaction affords the desired alkylhydrazine product in only 43% yield using MeCN as the solvent at 80 °C. Side products **SP-1** and **SP-2** were detected. These side products resulted from the intermolecular radical coupling between **2a** and **3a** or the self-coupling of substrate **1a**. Adding CuBr (20 mol%) to the reaction mixture increased the yield of **4a** to 89%. Other Cu catalysts did not show better reactivity (entries 3–7). It is worth noting that using $CuBr_2$ also worked well for this transformation (entry 6). The solvent has a significant influence on the reaction. Replacement of the solvent with DMSO, toluene, $CHCl_3$ or MeOH led to a lower reaction yield (entries 8–11). The by-product of the reaction of AIBME and DIAD reminds us to increase the concentration of alkynes. Although a 95% yield can be obtained by increasing the alkyne equivalent to 4-fold, excess alkyne resulted in only a 6% increase in the yield. We still choose 3 equiv. alkyne as the standard condition. Overall, the optimum conditions consist of heating a solution of **1a** in MeCN in the presence of CuBr (20 mol%), AIBME (1.0 equiv.), and DIAD (1.0 equiv.) at 80 °C. Under optimal conditions, **4a** was isolated in 77% yield.

Table 1 Optimization of the reaction conditions[a]

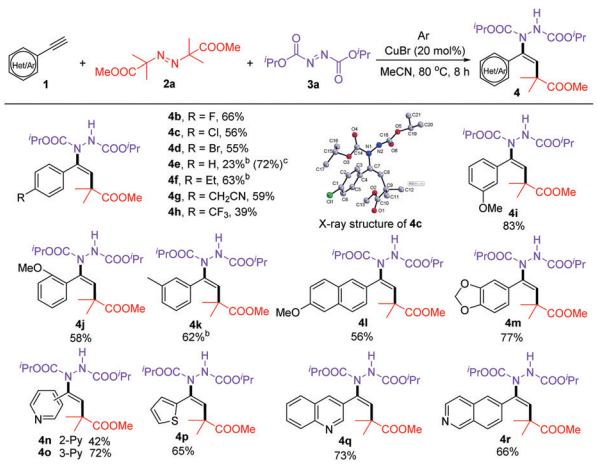


Run	Equiv. of **1a**	Catalyst	Solvent	Yield[b,c] (%)
1	3.0	—	MeCN	43
2	3.0	CuBr	MeCN	89 (77)
3	3.0	$Cu(TFA)_2$	MeCN	81
4	3.0	$Cu(NO_3)_2$	MeCN	79
5	3.0	CuI	MeCN	80
6	3.0	$CuBr_2$	MeCN	86
7	3.0	Cu_2O	MeCN	48
8	3.0	CuBr	DMSO	Trace
9	3.0	CuBr	MeOH	nd
10	3.0	CuBr	Toluene	26
11	3.0	CuBr	$CHCl_3$	36
12	4.0	CuBr	MeCN	95

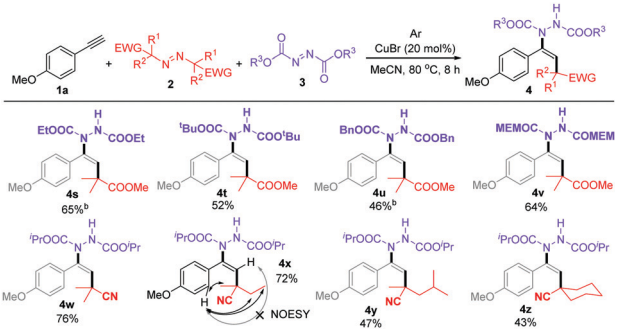
[a] Reaction conditions: alkyne (**1a**), AIBME (**2a**, 0.2 mmol, 1.0 equiv.), DIAD (**3a**, 0.2 mmol, 1.0 equiv.), catalyst (20 mol%), solvent (2.5 mL), 80 °C, 8 h, under Ar. [b] Yield of **4a** was determined by crude ^{1}H NMR with 4-nitroacetophenone as an internal standard. [c] Isolated yield in parentheses. nd = not detected.

With the optimal reaction conditions in hand, we set to examine the alkyne substrate scope for the three-component alkylhydrazination reactions. As shown in Scheme 3, aryl alkynes substituted with MeO, alkyl, halides, $NCCH_2$, and F_3C functional groups are tolerated under the optimized conditions, with modest to good yields. The structure of **4c** (CCDC 1948643†) was confirmed by a single-crystal X-ray diffraction experiment, and the stereochemistry of the trisubstituted alkenylhydrazine is the *E* configuration. Electron-donating aryl groups resulted in better yields than the electron-withdrawing examples. *ortho*-Substituents on phenyl led to lower efficiency (**4a** *vs.* **4j**). 2-Ethyl-6-methoxynaphthalene and 5-ethynyl-benzo[1,3]dioxole afforded the corresponding products **4l** and **4m** in 56% and 77% yield, respectively. Heteroaromatics such as pyridine, thiophene, and (iso)quinoline were highly compatible with the reaction conditions. Unfortunately, aliphatic alkynes failed to react under our standard conditions.

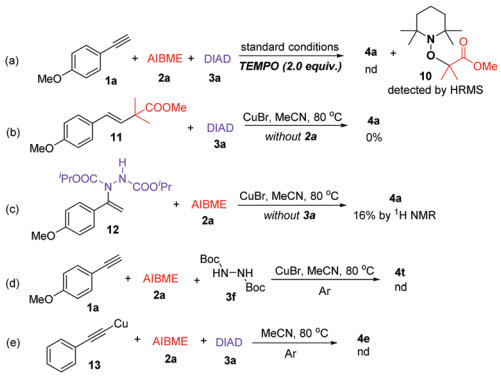
Next, we examined the substrate scope for other azocarboxylic esters and AIBME analogues under these reaction conditions. In addition to DIAD, other azocarboxylic esters, such as diethyl azodicarboxylate (DEAD) **3b**, di-*tert*-butyl azodicarboxylate (DBAD) **3c**, dibenzyl azodicarboxylate **3d**, and di-2-methoxyethyl azodicarboxylate **3e**, were also compatible with standard conditions, leading to modest yield (**4s**–**4v**). Replacement



Scheme 3 Scope of aryl alkynes.[a] Isolated yield. [b] Preparative thin-layer chromatography was conducted to remove **SP-1** from the products owing to their very similar polarities. [c] Yield in parentheses was determined by ^{1}H NMR using an internal standard.



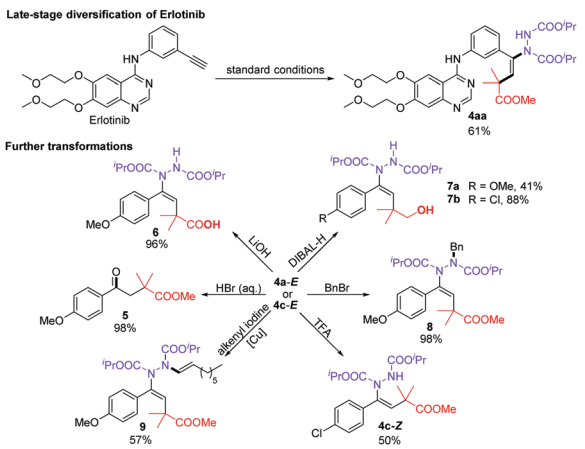
Scheme 4 Scope of azocarboxylic esters and AIBN analogues, [a] isolated yield. [b] Preparative thin-layer chromatography was conducted.



Scheme 6 Preliminary mechanistic studies.

of AIBME with other azo compounds with various α-cyano tertiary alkyl groups (*e.g.*, 2,2-azobis(2-methylpropionitrile) (AIBN) **2b**, 2,2-azodi(2-methylbutyro-nitrile) (AMBN) **2c**, 2,2′-azobis(2,4-dimethyl)-valeronitrile **2d** and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) **2e**) resulted in smooth reactions under the standard conditions to give allylic cyano-substituted alkenylhydrazines (**4w–4z**) in 43–76% yield. To confirm the stereochemistry of products with α-cyano tertiary alkyl groups, **4x** was selected for the NOESY experiment, and the configuration is as drawn (Scheme 4).

In the following, we hope that more complex molecules can be modified with this protocol. Erlotinib, a tyrosine kinase inhibitor, was chosen in the late-stage diversification experiment. As expected, the desired product **4aa** was isolated in 61% yield under standard conditions. Moreover, alkenylhydrazine product **4a** contains multiple functionalities, including ester, alkene, and hydrazine, which could be transformed into useful molecules. For example, site-selective hydrolysis of **4a** into 1,4-dicarbonyl compound **5** or alkenylhydrazine **6** with an allyl carboxyl could be realized under acidic or basic hydrolysis conditions. Reduction of esters to primary alcohols **7** using DIBAL-H, installation of alkyl-/alkenyl- onto nitrogen to afford **8** and **9** under mild conditions, and acid promoted isomerization of **4c-*E*** to **4c-*Z*** could also be furnished in modest to good yields (Scheme 5, see the ESI† for more details).

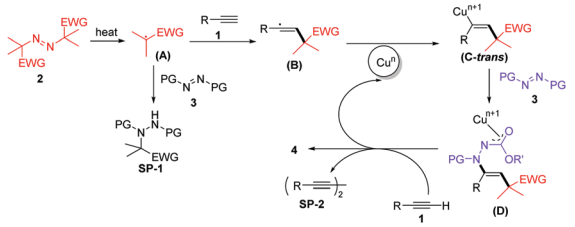


Scheme 5 The application of the alkylhydrazination reaction and further transformation of products.

To explore the reaction mechanism of the alkylhydrazination process, several control experiments were designed under optimized conditions (Scheme 6). First, the reaction was completely suppressed when the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction system, and no product was detected by ^{1}H NMR. The alkylated TEMPO product **10** could be observed by HRMS analysis. These results indicated that the reaction involves a radical-mediated pathway. Second, when possible intermediate **11** was used as the starting material in the absence of **2a**, no desired **4a** was observed. Next, when alkenylhydrazine **12** reacted with AIBME in the presence of CuBr, **4a** with 16% yield was detected by NMR. **12** was reported to show activity towards phosphorus-centred radicals to give β-ketophosphine oxides in the presence of cat. Cu and oxygen as stoichiometric oxidants.[18] However, we did not detect **12** under the standard reaction conditions. It is unlikely that **12** was the possible intermediate. Replacement of **3c** with commercially available bis-Boc-hydrazine **3f** leads to no **4t**, which suggests that the N=N bond is necessary for alkylhydrazination reactions. Finally, using phenylethynyl copper **13** as the starting material, target **4e** was not detected under standard conditions, which means that ethynylcopper species are not likely to be involved.

Based on the above mechanistic experimental results and previous reports,[4d,11b,19] a plausible mechanism is proposed involving the decomposition of AIBME by heating to generate an α-ester tertiary radical, which adds to aryl alkynes to afford the corresponding vinyl radical **B**. Further oxidation by Cu^n to vinyl–Cu^{n+1} species occurs (***C-trans***). The *E* configuration of the newly formed alkene is probably due to the steric hindrance of vinyl Cu with an α-ester tertiary alkyl group.[12b,14a] In the following, addition of **3** gave rise to Cu^{n+1} species **D**.[4d,11b,c] Afterward, reduction of Cu^{n+1} by excess alkynes provided an alkenyl-hydrazine product and regenerated the Cu^n catalyst.[11b] **SP-1** was also isolated in the reaction system, which was derived from the trap of radical **A** by **3** (Scheme 7).

In summary, we have developed an unprecedented copper-catalyzed stereoselective alkylhydrazination of alkynes with commercially available carbon and nitrogen sources, providing the desired *E*-alkenylhydrazines in modest to good yields. This methodology possibly involves a radical pathway without



Scheme 7 Plausible mechanism.

external oxidants or additives. Note that this reaction enhances the chemistry of azocarboxylic esters towards vinyl radicals, which may arise from various radical sources. Further investigations into the application of this strategy are still underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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