Copper-catalyzed direct transformation of simple alkanes to alkenyl nitriles via aerobic oxidative N-incorporation†

Xiaoqiang Huang,a Xinyao Lia and Ning Jiao*a,b

A novel direct transformation of aliphatic terminal alkanes to alkenyl nitriles through the incorporation of a nitrogen atom into the simple hydrocarbons has been reported. The usage of inexpensive copper catalyst, O₂ as the sole oxidant, broad substrate scope as well as feasibility for "late-stage modification" make this protocol very promising. Mechanistic studies including DFT calculation demonstrate a novel 1,2-hydride shift process for this novel nitrogenation reaction.

Introduction

Direct transformation of simple and readily available hydrocarbons into complex and high value-added compounds is a long-standing topic in organic synthesis.1 Aliphatic alkanes, which are very common and easily accessible building blocks, provide chemists with a fertile testing ground for the construction of complex organic molecules.2-9 Many useful reactions of these simple hydrocarbons have been disclosed on the basis of the C=C triple bond transformation, such as coupling,10 addition,11 cyclization,12 and metathesis reactions.13 However, the transformation of simple aliphatic terminal alkanes involving the cleavage of the propargylic C(sp³)–H bond is still limited.14,9

Recently, novel transformation of simple alkanes has been disclosed through the assistance of transition metals. Yamamoto's group significantly developed palladium/acid catalyzed alkylation and hydrometallation reaction of internal alkanes with nucleophiles (Scheme 1, A).10 By using a Rh(i)/phosphine ligand/benzoic acid catalyst system, Breit and co-workers pioneeringly achieved the intermolecular coupling of aliphatic terminal alkanes with carboxylic acids and sulfonyl hydrazides under redox-neutral conditions (Scheme 1, B).11 Despite these breakthroughs, new catalytic systems and new strategies are highly desirable to disclose novel transformations of aliphatic terminal alkanes.

Herein, we report a novel Cu-catalyzed aerobic oxidative transformation of simple terminal alkanes to alkenyl nitriles (Scheme 1, C). In this present chemistry: (1) a very simple hydrocarbon is successfully converted into an N-containing compound through the incorporation of a nitrogen atom into the substrate; (2) inexpensive Cu-catalyst, the green molecular oxygen oxidant, as well as the broad substrate scope make this protocol very attractive and low-cost; (3) a novel propargylic C(sp³)–H bond cleavage through 1,2-H shift mechanism is proved. (4) DFT calculation reasonably explains the mechanism and the stereoselectivity of products.

Results and discussion

We commenced this research by choosing commercially available 5-phenyl-1-pentyne 1a as the model substrate. To our delight, the nitrogenation product 2a was obtained with azidotrimethylsilane (TMSN₃) as nitrogen source under copper-catalyzed aerobic conditions (Table 1). A detailed screening of different reaction parameters (see ESI† for more...
information), the direct functionalization of 1a gave 2a in 78% yield with a slight Z-selectivity (Z : E = 65 : 35) under the optimized conditions: TMSN₃ (2.0 equiv.), CuBr (20 mol%), pyridine (2.0 equiv.) and NaOAc (1.0 equiv.), in PhCl at 90 °C under O₂ (1.0 atm) for 48 h (entry 1, Table 1). As expected, only trace amount of 2a could be obtained under an argon atmosphere (entry 2). Copper catalyst is essential in this transformation, as no 2a was formed without copper salt or with other common metal salts (such as [Ag], [Fe], [Co], [Mn], see ESI†). Other copper salts showed lower efficiencies than CuBr (entries 4–5). Further studies indicated that the reaction did not work in the absence of pyridine (entry 7). DMEDA and l-proline led to no reaction (entries 8–9). Catalytic amount of pyridine only delivered 2a in 26% yield (entry 10). It is noteworthy that NaOAc, a very weak base, is the most effective additive while not indispensable for product formation (entries 11–13). However, great efforts to improve the Z : E ratio of the product did not reach a satisfying result (see ESI† for more information).

With the optimal conditions in hand, we next investigated the substrate scope of this transformation. This reaction exhibited a good functional group compatibility (Table 2). Long-chain-alkyl substituted alkynes were successfully transformed to the corresponding alkenyl nitriles in good yields (2a–2e). Notably, propargylic 3° C–H of 1f could be cleaved, giving 2f in 61% yield. To our satisfaction, terminal alkyne 1g, bearing a TBDMS protected hydroxyl group, worked well (2g, 68%). Remarkably, linkages, including ether bonds (2h–2n) and ester bonds (2o–2q), did not reduce effectiveness. Several functional groups (trifluoromethyl, chlorine, vinyl and thienyl) were well tolerated in the present catalytic system. Furthermore, reasonable yields were obtained for alkynes containing phthalimide and sulfonamide group, respectively (2r–2s). Interestingly, C–H bond adjacent to internal ethynyl group was inactive, which leads to the high regioselectivity.

Alkenyl nitriles are not only useful building blocks in synthetic chemistry but also important structure motifs commonly found in drugs. Moreover, late-stage modification is a highly valuable strategy for medicinal chemistry research. Therefore, several complex bioactive molecule derivatives were synthesized, including natural products and a class of anti-HIV agents. The full details of these applications will be published elsewhere soon.

**Table 1** Selected optimization of the reaction conditions

| Entry | Variation from standard conditions | Yieldb (%) | Z : E† |
|-------|-----------------------------------|------------|-------|
| 1     | None                              | 78         | 63 : 35 |
| 2     | Ar instead of O₂                   | Trace      | —     |
| 3     | Without CuBr                      | 0          | —     |
| 4     | Cu(OAc)₂ instead of CuBr          | 49         | 69 : 31 |
| 5     | CuBr instead of CuBr              | 62         | 67 : 33 |
| 6     | 10 mol% CuBr was employed          | 45         | 63 : 34 |
| 7     | Without pyridine                  | 0          | —     |
| 8     | DMEDA instead of pyridine         | 0          | —     |
| 9     | l-proline instead of pyridine     | 0          | —     |
| 10    | 0.4 equiv. pyridine was employed   | 26         | 69 : 31 |
| 11    | Without NaOAc                     | 48         | 64 : 36 |
| 12    | LiOAc instead of NaOAc            | 48         | 64 : 36 |
| 13    | NaOMe instead of NaOAc            | 47         | 67 : 33 |

| Entry | Variation from standard conditions | Yieldb (%) | Z : E† |
|-------|-----------------------------------|------------|-------|
| 14    | R₁ = one-naphth                   | 60         | 64 : 36 |
| 15    | R₂ = 2-naphth                     | 57         | 64 : 36 |
| 16    | R₁ = Me                          | 69         | 69 : 31 |
| 17    | R₂ = 2-CN                         | 40         | 64 : 36 |
| 18    | R₁ = TBDMS                        | 68         | 69 : 31 |
| 19    | R₂ = n-C₆H₁₄                      | 59         | 69 : 31 |
| 20    | R₁ = TBDMS                        | 61         | —     |

a Standard conditions: 1a (0.40 mmol), TMSN₃ (0.80 mmol), CuBr (0.08 mmol), pyridine (0.80 mmol) and NaOAc (0.40 mmol) in PhCl (2.0 mL) under O₂ (balloon) was stirred at 90 °C for 48 h. b Isolated yields. c Determined by ³¹H NMR measurement of the crude mixture. DMEDA = N,N-dimethyl-1,2-ethanediamine.
submitted to the optimal conditions (Table 3). Natural alcohol derivatives containing ester or ether linkages, such as menthol, borneol, nopol and cholesterol, worked well in the current transformation, generating the corresponding alkenyl nitriles in 49–73% yield (4a, 4d–f), respectively. Alkyne 3b that was prepared from antibacterial metronidazole afforded alkyl alkenyl nitrile 4b in 60% yield. Besides, terminal alkyne with a protected sugar moiety selectively underwent aerobic oxidation, giving nitration product 4e in 67% yield. These results demonstrate that the present protocol could be applied in late-stage bioactive compound modification.

To gain mechanistic insight into this transformation, some control experiments were conducted under the standard conditions. Allene 5, which could be generated from alkyne 1a, failed to afford nitriles under the present conditions (eqn (1)), indicating a novel mechanism different from Breit's works. In addition, propargylic azide 6 or allylic azide 7 could not furnish alkenyl nitriles either (eqn (2) and (3)). These results ruled out the possibility of 6 and 7 as intermediates of the transformation.

Considering that the current nitration reaction could only be catalyzed by copper salt, and the Glaser–Hay homocoupling product could be detected in some cases, we postulated that copper acetylide might be an intermediate of this reaction. Although, no product was formed employing copper(I)-acetylide 8 as a substrate (eqn (4)), which might due to the aggregation of 8, 2c could be obtained in comparative yield when 8 was used as a catalyst (eqn (5)). When C(sp)–H bond deuterated alkenes 1a-1-d1 was subjected to the reaction, no deuterium was detected in the product, which is in accordance with the existence of copper acetylide species (eqn (6)).

Furthermore, labeling experiment with propargylic C–H bond deuterated 1a-3,3-d2 was performed. To our surprise, nearly 100% incorporation of deuterium at both α and β positions of the nitrile was observed (eqn (7)). Hence, the cleavage of propargylic C–H bond might proceed via a 1,2-hydride shift. Then, an intermolecular kinetic isotopic experiment was conducted giving the result of k_H/k_D = 2.2 (eqn (8)).

On the basis of all these results and previous reports, a proposed mechanism is depicted in Scheme 2. The reasonable first step is the formation of copper(I)-acetylide intermediate A. Then, copper triazolide B formed via Cu-catalyzed azide–alkyne cycloaddition (CuAAC) undergoes ring-opening reaction affording cuprated diazoimine C. The oxidation of C

---

**Table 3** The late-stage modification

| R | Standard conditions | R’CN |
|---|-------------------|------|
| Ph | 2a, 0% | |
| Ph | 2a, 0% | |
| Ph | 3 | |

| 4a | 49%, b 65:35 | menthol derivative |
| 4b | 60%, 68:32 | metronidazole derivative |
| 4c | 67%, 67:33 | glucosamine derivative |
| 4d | 73%, 65:35 | borneol derivative |
| 4e | 52%, 63:37 | nopol derivative |
| 4f | 50%, 68:32 | cholesterol derivative |

a Standard conditions: see entry 1, Table 1. b Isolated yields. c Determined by 1H NMR measurement of the crude mixture.
under aerobic conditions with assistance of pyridine gives α-diazonitrile D and regenerates the copper(i) catalyst.23 Subsequently, upon loss of dinitrogen D would afford carbene E or copper carbene F.21 Finally, 1,2-hydride shift of the carbene species generates the alkynyl nitrile.17 Alternatively, a mechanism with ethynyl azide could also be possible. Cu-catalyzed aerobic oxidative cross-coupling of terminal alkynes with TMSN₃ might generate ethynyl azide G,38 which is known to liberate dinitrogen leading to the formation of cyanocarbene species E.24

To further explore the stereoselectivity of the reaction, density functional theory (DFT) calculation investigation was carried out (Fig. 1).25 After the sequential CuAAC19 and ring-opening process,20,21 the α-diazonitrile INT1 is generated (see ESI† for details). The pyrolysis of INT1 has two pathways. In pathway A, the thermal induced release of N₂ through TS1 requires an activation free energy of 22.3 kcal mol⁻¹ to give cyanocarbene carbene INT2. Alternatively, INT2 generated from ethynyl azide could not be excluded.24 The subsequent 1,2-hydride shift process57 via Z-TS2 and E-TS2 almost barrierlessly delivers Z-2 and E-2, respectively. It is noteworthy that the energy barrier gap between Z-TS2 and E-TS2 is insignificant (only 0.3 kcal mol⁻¹), which might be due to the similar steric hindrance between hydrogen and cyano group. The calculated Z : E ratio of 2 via pathway A is predicted to be 64 : 36, which is qualitatively consistent with the experimentally observed 66 : 34 Z : E ratio for this reaction.

In alternative pathway B, Cu(i) catalyst can induce the Cu-C bond formation on INT3 with the release of N₂ through TS3 in a stepwise manner, which requires an activation free energy of 22.3 kcal mol⁻¹ to form Cu-carbene INT4.23 The subsequent 1,2-H shift process59 via Z-TS4 and E-TS4 also barrierlessly furnishes Z-2 and E-2, respectively. Notably, Z-TS4 is also only 0.7 kcal mol⁻¹ lower in energy than E-TS4, which is corresponding to a 76 : 24 Z : E ratio of 2, in good agreement with the experimental observation.

Moreover, E-2 is only 0.3 kcal mol⁻¹ lower in energy than Z-2, indicating that the Z to E isomerization of alkynyl nitriles 2 is short of driving force thermodynamically. These results could explain why the E : Z ratio of the products is so difficult to optimize whether by dynamic or thermodynamic means.

Conclusions
In conclusion, we have developed a novel copper-catalyzed aerobic oxidative nitrogenation of simple alky lalkynes via propargylic C(sp³)–H bond cleavage. A variety of simple and easily accessible alkynes selectively undergo the transformation affording alkynyl nitriles. The late-stage modification of bioactive molecule derivatives makes this protocol very attractive. Mechanism studies indicate a 1,2-hydride shift might be the key step of this novel transformation. DFT calculation reasonably explains the stereoselectivity of products. Further studies on the mechanism and the application are ongoing in our group.

Acknowledgements
Financial support from National Basic Research Program of China (973 Program) (grant no. 2015CB856600) and National Natural Science Foundation of China (nos 21325206, 21172006), and National Young Top-notch Talent Support Program are greatly appreciated. We thank Zun Wang in this group for reproducing the results of 2d, and 2s.

Notes and references
1 (a) K. Godula and D. Sames, Science, 2006, 312, 67; (b) R. G. Bergman, Nature, 2007, 446, 391; (c) T. W. Lyons and M. S. Sanford, Chem. Rev., 2010, 110, 1147; [d] W. R. Gutekunst and P. S. Baran, Chem. Soc. Rev., 2011, 40, 1976.
2 Acetylene Chemistry: Chemistry, Biology, and Material Science, ed. F. Diederich, P. J. Stang and R. R. Tykwinski, Wiley-VCH, Weinheim, 2005.
3 For reviews on coupling reactions of terminal alkynes, see: (a) P. Siemsen, R. C. Livingston and F. Diederich, Angew. Chem., Int. Ed., 2000, 39, 2632; (b) Z. Shao and F. Peng, Angew. Chem., Int. Ed., 2010, 49, 9566; (c) R. Chinchilla and C. Najera, Chem. Soc. Rev., 2011, 40, 5084; (d) C. Zhang,
For recent C(sp)^3–H functionalizations of terminal alkynes, see: (a) T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, 130, 833; (b) L. Zhao, O. Basléd and C.-L. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, 106, 4106; (c) T. de Haro and C. Nevada, *J. Am. Chem. Soc.*, 2010, 132, 1512; (d) Y. Wei, H. Zhao, J. Kan, W. Su and M. Hong, *J. Am. Chem. Soc.*, 2010, 132, 2522; (e) M. Chen, X. Zheng, W. Li, J. He and A. Lei, *J. Am. Chem. Soc.*, 2010, 132, 4101; (f) L. Chu and F.-L. Qin, *J. Am. Chem. Soc.*, 2010, 132, 7262; (g) C.-I. Lee, J. Zhou and O. V. Ozerov, *J. Am. Chem. Soc.*, 2013, 135, 3560; (h) A. Harada, Y. Makida, T. Sato, H. Ohmiya and M. Sawamura, *J. Am. Chem. Soc.*, 2014, 136, 13932.

For nucleophilic addition to alkynes, see: (a) A. Lumbroso, N. R. Vautravers and B. Breit, *Org. Lett.*, 2010, 12, 5498; (b) B. Xu, W. Wang, L.-P. Liu, J. Han, Z. Jin and G. B. Hammond, *J. Organomet. Chem.*, 2011, 696, 269; (c) T. Mahdi and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2013, 52, 12418; (d) Z. Liu, P. Liao and X. Bi, *Org. Lett.*, 2014, 16, 3668.

For some reviews on C–C bond cleavage, see: (a) C. Köster and P. W. Davies, *Chem. Commun.*, 2005, 2307; (b) H. Villar, M. Frings and C. Bolm, *Chem. Soc. Rev.*, 2007, 36, 55; (c) C. Chen, T. Wang and N. Jiao, *Chem. Rev.*, 2014, 114, 8613.

For the intramolecular cyclization of functionalized terminal alkynes via propargylic C(sp)^3–H bond cleavage, see: (a) R. D. Grigg, J. W. Rigoli, S. D. Pearce and J. M. Schomaker, *Org. Lett.*, 2012, 14, 280; (b) H. Lebel, C. Trudel and C. Spitzen, *Chem. Commun.*, 2012, 48, 7799; (c) H. Lu, C. Li, H. Jiang, C. L. Lizardi and X. P. Zhang, *Angew. Chem., Int. Ed.*, 2014, 53, 7028.

For the propargylic oxidation of internal alkynes, see: (a) S. Sakaguchi, T. Takase, I. Iwashima and Y. Ishii, *Chem. Commun.*, 1998, 2037; (b) E. C. McLaughlin and M. P. Doyle, *J. Org. Chem.*, 2008, 73, 4317; (c) Y. Zhao, A.W. T.Ng and Y.-Y. Yeung, *Tetrahedron Lett.*, 2014, 55, 4370.

(a) I. Kadota, A. Shibuya, Y. Gyou and Y. Yamamoto, *J. Am. Chem. Soc.*, 1998, 120, 10262; (b) I. Kadota, A. Shibuya, L. M. Lutete and Y. Yamamoto, *J. Org. Chem.*, 1999, 64, 4570; (c) M. Narsireddy and Y. Yamamoto, *J. Org. Chem.*, 2008, 73, 9698.

(a) A. Lumbroso, P. Koschker, N. R. Vautravers and B. Breit, *J. Am. Chem. Soc.*, 2011, 133, 2386; (b) A. Lumbroso, N. Abermil and B. Breit, *Chem. Sci.*, 2012, 3, 789; (c) U. Gellrich, A. Meissner, A. Steffani, M. Kahny, H. J. Drexler, D. Heller, D. A. Plattner and B. Breit, *J. Am. Chem. Soc.*, 2014, 136, 1097; (d) K. Xu, V. Khakyzadeh, T. Bury and B. Breit, *J. Am. Chem. Soc.*, 2014, 136, 16124; (e) P. Koschker, M. Kähny and B. Breit, *J. Am. Chem. Soc.*, 2015, 137, 3131.

NaOAc is widely used in copper-catalyzed aerobic oxidation reactions to promote the efficiency: (a) D. Monguchi, T. Fujiwara, H. Furukawa and A. Morii, *Org. Lett.*, 2009, 11, 1607; (b) A. E. King, B. L. Ryland, T. C. Brunold and S. S. Stahl, *Organometallics*, 2012, 31, 7948.

(a) A. J. Fatiadi, in *Preparation and Synthetic Applications of Cyano Compounds*, ed. S. Patai and Z. Rappaport, Wiley, New York, 1983; (b) F. F. Fleming and Q. Wang, *Chem. Rev.*, 2003, 103, 2035; (c) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem.*, 2010, 53, 7902; (d) J. J. Schafer and W. R. Short, *Antiviral Ther.*, 2012, 17, 1495.

(a) E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker and T. Ritter, *Science*, 2011, 334, 639; (b) D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, 133, 5767; (c) X. Huang, X. Li, M. Zou, S. Song, C. Tang, Y. Yuan and N. Jiao, *J. Am. Chem. Soc.*, 2014, 136, 14858; (d) Z. Zhang and X. Jiang, *Org. Lett.*, 2014, 16, 4400.

(a) K. Banert and M. Hagedorn, *Angew. Chem., Int. Ed. Engl.*, 1989, 28, 1675, and references cited therein; (b) J. R. Fotsing and K. Banert, *Eur. J. Org. Chem.*, 2003, 3704.

R. Buschbeck, P. J. Low and H. Lang, *Coord. Chem. Rev.*, 2011, 255, 241; also see ref. 6c.

For selected examples of carbene and metallocarbenoid 1,2-hydride shift, see: (a) D. F. Taber, R. J. Herr, S. K. Pack and J. M. Geremia, *J. Org. Chem.*, 1996, 61, 2908; (b) N. Jiang, Z. Qu and J. Wang, *Org. Lett.*, 2001, 3, 2989; (c) V. K. Aggarwal, C. G. Sheldon, J. G. Macdonald and W. P. Martin, *J. Am. Chem. Soc.*, 2002, 124, 10300; (d) J. A. May and B. M. Stoltz, *J. Am. Chem. Soc.*, 2002, 124, 12426; (e) K. S. Graves, D. M. Thamattoor and P. R. Rablen, *J. Org. Chem.*, 2011, 76, 1584.

E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, 51, 3066.

(a) M. Ahlquist and V. V. Fokin, *Organometallics*, 2007, 26, 4389; (b) M. Meldal and C. W. Tornoe, *Chem. Rev.*, 2008, 108, 2952; (c) B. T. Worrell, J. A. Malik and V. V. Fokin, *Science*, 2013, 340, 457; also see ref. 6.

For reviews about reactions of metallocarbenes derived from 1,2,3-triazoles, see: (a) A. V. Gulevich and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2013, 52, 1371; for selected examples catalyzed by Cu-catalyst, see: (b) I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc.*, 2005, 127, 2038; (c) M. P. Cassidy, J. Rauhuel and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, 45, 3154; (d) E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless and S. Chang, *Angew. Chem., Int. Ed.*, 2007, 46, 1730; (e) H-D. Xu, Z.-H. Jia, K. Xu, M. Han, S-N. Jiang, J. Cao, J-C. Wang and M-H. Shen, *Angew. Chem., Int. Ed.*, 2014, 53, 9284; (f) V. Helan, A. Gulevich and V. Gevorgyan, *Chem. Sci.*, 2015, 6, 1928.

For selected examples on Rh-catalyzed ring expansion and rearrangement involving azavinyl carbones, see: (a) T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima and...
22. M. Murakami, J. Am. Chem. Soc., 2012, 134, 17440; (b) N. Selander, B. T. Worrell and V. V. Fokin, Angew. Chem., Int. Ed., 2012, 51, 13054; (c) T. Miura, Y. Funakoshi and M. Murakami, J. Am. Chem. Soc., 2014, 136, 2272; (d) Y. Shi, A. V. Gulevich and V. Gevorgyan, Angew. Chem., Int. Ed., 2014, 53, 14191; (e) T. Miura, T. Nakamuro, C.-J. Liang and M. Murakami, J. Am. Chem. Soc., 2014, 136, 15905.

23. For formation of copper carbenes from diazo compounds, see: (a) W. Kirmse, Angew. Chem., Int. Ed., 2003, 42, 1088; (b) Y. Liang, H. Zhou and Z.-X. Yu, J. Am. Chem. Soc., 2009, 131, 17783; (c) X. Zhao, Y. Zhang and J. Wang, Chem. Commun., 2012, 48, 10162.

24. For references about alkynyl azides, see: (a) K. Banert, M. Hagedorn, J. Wutke, P. Ecorchard, D. Schaarschmidt and H. Lang, Chem. Commun., 2010, 46, 4058; (b) I. F. D. Hyatt and M. P. Croatt, Angew. Chem., Int. Ed., 2012, 51, 7511; (c) K. Banert, R. Arnold, M. Hagedorn, P. Thoss and A. A. Auer, Angew. Chem., Int. Ed., 2012, 51, 7515.

25. All of the geometry optimizations and frequency calculations were performed at B3LYP(CPCM)/SDD-6-311+G(d,p)//B3LYP(gas)/SDD-6-31G(d) level in Gaussian 09 (M. J. Frisch, et al.). Computational details and references are given in the ESI†.