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Copper-Catalyzed Alkene Aminoazidation as a Rapid Entry to 1,2-Diamines and Installation of an Azide Reporter onto Azaheterocycles

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Abstract

A copper-catalyzed aminoazidation of unactivated alkenes is achieved for the synthesis of versatile unsymmetrical 1,2-diamine derivatives. This transformation offers an effective approach to installing an amide and an azide from two different amino precursors onto both terminal and internal alkenes, with remarkable regio- and stereoselectivity. Mechanistic studies show that this diamination reaction proceeds via a nucleophilic amino cyclization followed by an intermolecular C–N bond formation using electrophilic azidoiodinane. This pathway differs from previous azidoiodinane-initiated alkene functionalization, suggesting new reactivity of azidoiodinane. Furthermore, this aminoazidation reaction provides an efficient strategy to introduce azide, one of the most useful chemical reporters, onto a broad range of bioactive azaheterocycles, offering new opportunities in bioorthogonal chemistry and biological studies. Rapid syntheses of 5-HT_{2C} agonist, (–)-enduracididine and azidocholesterol derivatives demonstrate broad applications of this method in organic synthesis, medicinal chemistry, and chemical biology.

Graphical abstract

INTRODUCTION

Vicinal 1,2-diamines are essential skeletons ubiquitously found in natural products and widely used in catalysts, ligands, agrochemicals, and pharmaceuticals (Figure 1).¹ Alkene diamination reactions, a straightforward and valuable route to 1,2-diamines by installing two amino groups directly onto readily available alkenes, therefore have received great interest in organic chemistry.² For example, recent development in metal-catalyzed diamination has

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Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data for all compounds.

Crystallographic data for compounds **3w-triazole**, **3z-triazole**, **7-amide**, and **9-amide** (CIF).

Notes

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significantly advanced the preparation of 1,2-diamines.³ Yet, in most cases, two amino groups are tethered in the same precursors in order to achieve the second amination step effectively. Diamination of internal alkenes is especially difficult, because the common alkyl-metal intermediates tend to undergo undesired side reactions of protonation and β -hydride elimination rather than desired second C–N bond formation (Scheme 1, A). A series of elegant diamination reactions have been reported under metal-free oxidative condition,⁴ including diamination reactions of internal alkenes.^{4c–i,4m} Yet most reactions need to use two identical amino groups or two amino groups tethered in the same precursors, due to the poor chemoselectivity between two different nitrogen nucleophiles. Therefore, developing a modular diamination reaction that can install two different amino groups across both terminal and internal alkenes is highly desired for accessing diversely substituted unsymmetrical diamines, which are the most common diamine derivatives (Figure 1).

Here we report a copper-catalyzed alkene diamination that enables installation of two different amino groups onto both terminal and internal alkenes selectively (Scheme 1, B). With our interests in developing electrophilic amination-based alkene difunctionalization,^{3w,5} we envisioned that the use of azidoiodinane as a highly reactive amino precursor would allow for an accelerated intermolecular amination in the second amination step, thus overcoming the problematic competing protonation and β -hydride elimination pathways. Mechanistic studies reveal that azidoiodinane contributes to the second C–N bond formation as a trapping reagent in our transformation, which is different from its role as an electrophilic source to initiate alkene functionalization in previous work.⁶ The impact of this work, in addition to a modular access to diverse diamines, is further highlighted by the great value of the azide group in organic chemistry and chemical biology. The azide group is one of the most useful building blocks in organic synthesis for constructing diverse nitrogen-containing molecules and one of the most valuable chemical reporters in bioorthogonal conjugation such as in Huisgen ‘click’ cycloaddition⁷ and the Staudinger ligation.⁸ Overall, this alkene diamination reaction not only offers a rapid entry to diverse diamines but also a facile approach to installing an azide onto privileged azaheterocycles to facilitate biological studies including target identification and imaging.

RESULTS AND DISCUSSION

Reaction Condition

We chose *N*-methoxy amide **1a** as the model substrate toward developing alkene aminoazidation with azidoiodinane **2** (Table 1). Note that our previous studies have demonstrated that the alkoxy protecting group on amides can effectively promote the desired amination pathway for the proposed alkyl-metal intermediates, while other protecting groups gave no or trace amounts of amination products.^{3w,9} Encouragingly, when the reaction was run in MeOH in the presence of a copper catalyst, the desired aminoazidation product **3a** was observed (entries 1–9). Particularly effective catalysts are CuOAc, Cu(OAc)₂ and Cu(acac)₂. Using Cu(acac)₂ as the catalyst, we examined different solvents (entries 10–16), among which MeCN proved the best in this transformation. Further comparison among Cu(acac)₂, Cu(OAc)₂ and CuOAc with a 10 mol % loading (entries 17–19) revealed CuOAc most effective, which was chosen as our standard aminoazidation conditions (entry 19). In

the absence of a copper catalyst (entry 20), **1** was fully recovered and no desired product was observed, suggesting essential role of copper catalyst in this reaction.

Scope of Alkene Aminoazidation

With established aminoazidation conditions, we examined the generality of this transformation on different alkenes (Table 2). Starting with terminal alkenes, we first confirmed 5-membered aminoazidation product **3b** smoothly formed in 89% yield, in an analogous manner to the 6-membered product **3a**. Non-aromatic alkenes were also effective substrates, and different substitutions on the backbone of unsaturated amides were all tolerated in this transformation, as evidenced by the successful formation of **3c–3j**. Besides mono-substituted alkenes, 1,1-disubstituted alkenes also readily gave products **3k–3l**. Notably, the aminoazidation protocol tolerates basic nitrogens well. For example, heteroarene-containing alkenes **1m–1n** that were problematic substrates in our previous diamination work^{3w} effectively formed desired aminoazidation products **3m–3n**, suggesting the greater compatibility of this aminoazidation transformation. Besides the formation of lactams, the oxazolidinone **3p** and imidazolidinones **3q–3r** were also formed in the diamination reactions. Note that the dia-stereoselectivity of this transformation may be influenced by the substitution of the backbone, as observed in the formation of **3h**, **3j**, **3o**, and **3r**. Furthermore, the remarkable generality and efficacy of this transformation were demonstrated on a range of internal alkenes. Under standard conditions, 1,2-substituted alkenes were effective to afford aminoazidation products, such as **3s** and **3t**, in 73% and 52% yield, respectively. Cyclic internal alkenes readily underwent aminoazidation, affording fused-ring containing products **3u–3w** and the bridged lactam-containing products **3x–3z** with only one diastereoisomer observed by ¹H-NMR (dr >20:1). To clarify the stereochemistry resulted from this aminoazidation reaction, we obtained the triazole derivatives of **3w** and **3z**, upon the cycloaddition reaction with phenylacetylene, and confirmed the *anti*-relationship of two amino functional groups (see X-ray), which was consistent among the stereochemical outcome of aminoazidation products **3u–3z** from the cyclic alkenes.

Mechanistic Studies

In order to understand the reaction pathways involved in this aminoazidation reaction, we conducted a series of control experiments (Scheme 2). First, the aminoazidation reaction of alkene **1d** in the presence of radical scavenger TEMPO led to a quantitative formation of amino-oxygenation product **4** with no observation of aminoazidation product **3d**. This outcome suggests an intramolecular amino-cyclization pathway and the involvement of an alkyl radical, which can be effectively trapped by TEMPO. Consistent with a process occurring through a radical intermediate, the reaction of *trans*-*D*-substituted **D-1d** led to a 1:1 mixture of *D*-substituted **D-3d** (Scheme 2, A).

When (*E*)- and (*Z*)-stereoisomers of **5** were subjected to standard aminoazidation conditions, both led to the formation of a mixture of **7** in the same diastereomeric ratio as well as byproduct **8**. Likewise, the aminoazidation reactions of (*E*)- and (*Z*)-stereoisomers of **6** also led to the formation of a mixture of **9** with a same diastereomeric ratio. The loss of stereochemistry in both cases further indicates the involvement of radical intermediates in

the reaction (Scheme 2, B). Simultaneously, in the reaction of alkene **10**, 5-*exo* product **11** was not observed while 6-*endo* lactam product **11'** formed in 87% yield, which was different from the selective formation of 5-*exo* product **31** in the reaction of analogous methyl-substituted alkene **11** (Scheme 2, C). Overall, the results of these control experiments all suggest that the involvement of radical intermediates contribute to the re-gio- and stereoselective outcomes in this aminoazidation reaction. The *anti*-stereoselectivity observed on the bicyclic products are probably due to the radical trapping from the less sterically hindered side.

To further investigate the formation of possible radical intermediates, alkenes **12** and **13**, containing a standard radical clock cyclopropane moiety at either vinyl position, were subjected to the aminoazidation reactions. In the reaction of **12**, desired aminoazidation product **14** was not observed while **15** was formed in 73% yield, likely via the aminocyclization radical intermediate (**I**) followed by a facile ring opening to form (**II**) and the subsequent azidation (Scheme 3). Interestingly, the reaction of **13** not only formed desired aminoazidation product **16** in 52% yield, but also a 1:1 mixture of (*E*)- and (*Z*)-isomers of **17** in 28% yield, while another possible ring-opening product **18** was not detected. The formation of **17**, likely resulting from the ring opening of intermediate (**IV**) to generate intermediate (**V**) followed by the azidation reaction, indicates the involvement of 6-*endo* amino cyclization in this case and revealed the role of azidoiodinane as the aminating agent in the trapping step. On the other hand, the absence of product **18** suggests that this aminoazidation does not involve the contribution of possible radical intermediates (**VI**) or (**VII**). This outcome dismisses the probability that this reaction is initiated by the electrophilic azidation, which was commonly observed in the previous alkene azidation reactions.^{6a-6h}

Based on these mechanistic studies above, we envision two plausible pathways involved in this aminoazidation reaction (Figure 2). In the first pathway (A), the intramolecular aminocupration¹¹ of alkene **1** occurs upon alkene activation by a copper (II) catalyst via intermediate **I-A** to form alkyl-copper complex **II-A** or **II-A'**, in either *exo* or *endo* cyclization manner. The subsequent reaction with azidoiodinane **2** would afford the aminoazidation product **3** or **3'**, while the copper (II) catalyst could be regenerated by a redox process. In an alternative pathway (B), the reaction could be initiated by the oxidative addition of Cu(I) with azidoiodinane **2** to generate Cu(III) intermediate **I-B**, which would coordinate with alkene **1** to form **I'-B** subsequently. The aminocyclization of **I'-B** could occur in either *exo* or *endo* cyclization manner to form **II-B** or **II-B'** accordingly, which would give diaminated product **3** or **3'**. As suggested by the above mechanistic studies, the copper-alkyl intermediate **II** could undergo homolysis of the carbon-copper bond to form radical intermediates **III**,^{3m,3w} which would influence the regioselectivity in the aminocyclization step and consequently contribute to the formation of *exo* product **3** or *endo* product **3'**.

Synthetic Applications

With the importance of azide group as one of the most useful building blocks and the most versatile chemical reporter,^{7-8,10} this aminoazidation reaction affords great value and

potential for its application in the synthesis and study of biologically important molecules. For example, we demonstrate that this diamination reaction provides a rapid entry to diverse 1,2 amino-containing molecules, by completing a concise synthesis of 5-HT_{2c} agonist¹² (Scheme 4). Starting from aminoazidation product **3a**, SmI₂-mediated removal of OMe protecting group and the *N*-allylation provided azide **19** in 95% yield. The subsequent transformation of **19** into piperazine **20** was achieved by the ozonolysis and the treatment of Raney nickel under hydrogen, which effectively promoted the reduction of azide and the subsequent reductive amination in one step. We also developed a rapid synthesis of (–)-enduracididine, a key component of the naturally occurring macrocyclic polypeptide antibiotic enduracidin.¹³ Starting from azide **3o**, the hydrogenative reduction in the presence of Boc₂O followed by Mo(CO)₆-promoted cleavage of OMe protecting group formed Boc-protected amine **21** in 83% yield. The deprotection of both Phth and Boc groups was readily achieved to give free amine **22** in 93% yield over two steps. Finally, ester hydrolysis with NaOH of amide **22** followed by BrCN-mediated guanidine formation successfully gave (–)-enduracididine **23**.

Finally, we examined the amino azidation reaction of a cholesterol derivative **24** bearing the urea group at the C3 position (Scheme 5). Even at a gram scale, the reaction afforded product **25** selectively and efficiently in 87% yield. To illustrate the versatile synthetic utility of the azide group, **25** was transformed into primary amine **26a**, secondary amine **26b**, and amide **26c**, as well as primary amine **26d** with methoxyl protecting group cleaved in one step (Scheme 5). Furthermore, the azide **25** readily reacted with bicyclo[6.1.0]non-4-yn-9-ylmethanol **27** to form **26e** via a strain-promoted [3 + 2] copper-free cycloaddition¹⁴ as well as underwent the Huisgen cycloaddition with dimethyl acetylenedicarboxylate to form **26f**. These examples demonstrate the applicability of this aminoazidation on complex molecules and its utilities to construct richly and diversely functionalized nitrogen-containing skeletons.

CONCLUSION

In summary, we developed a copper-catalyzed alkene diamination that enables the selective incorporation of two different amino groups using two different amino precursors. The success of this diamination reaction rests in the use of highly electrophilic azidoiodinane for an effective intermolecular amination, which overcomes the undesirable side reactions. Mechanistic studies reveal the contribution of azidoiodinane to the second C–N bond formation in this reaction, distinct from its role of initiating alkene functionalization in previous studies, suggesting its new reactivity and utility in amination reactions. With the versatile value of the azide group in organic synthesis and bioorthogonal chemistry, this alkene diamination reaction not only offers a rapid entry to diversely functionalized diamine-containing molecules, but also a facile approach to installing an azide chemical reporter onto complex nitrogen-containing skeletons to facilitate their studies and applications in biomedical and material research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Lucet D, Le Gall T, Mioskowski C. *Angew Chem Int Ed.* 1998; 37:2581.(b) Kotti SRSS, Timmons C, Li GG. *Chem Biol Drug Des.* 2006; 67:101. [PubMed: 16492158]
2. Recent reviews:(a) Cardona F, Goti A. *Nat Chem.* 2009; 1:269. [PubMed: 21378869] (b) de Figueiredo RM. *Angew Chem Int Ed.* 2009; 48:1190.(c) De Jong S, Nosal DG, Wardrop DJ. *Tetrahedron.* 2012; 68:4067. [PubMed: 22888177] (d) Muñiz K, Martínez C. *J Org Chem.* 2013; 78:2168. [PubMed: 23437968] (e) Zhu YG, Cornwall RG, Du HF, Zhao BG, Shi Y. *Acc Chem Res.* 2014; 47:3665. [PubMed: 25402963]
3. (a) Backvall JE. *Tetrahedron Lett.* 1978; 163(b) Bar GLJ, Lloyd-Jones GC, Booker-Milburn KI. *J Am Chem Soc.* 2005; 127:7308. [PubMed: 15898768] (c) Streuff J, Hövelmann CH, Nieger M, Muñiz K. *J Am Chem Soc.* 2005; 127:14586. [PubMed: 16231907] (d) Du HF, Yuan WC, Zhao BG, Shi Y. *J Am Chem Soc.* 2007; 129:7496. [PubMed: 17521192] (e) Muniz K. *J Am Chem Soc.* 2007; 129:14542. [PubMed: 17985900] (f) Zhao BG, Yuan WC, Du HF, Shi YA. *Org Lett.* 2007; 9:4943. [PubMed: 17973481] (g) Du HF, Zhao BG, Shi Y. *J Am Chem Soc.* 2008; 130:8590. [PubMed: 18549207] (h) Hovelmann CH, Streuff J, Brelot L, Muniz K. *Chem Commun.* 2008:2334.(i) Li H, Widenhofer RA. *Org Lett.* 2009; 11:2671. [PubMed: 19514795] (j) Sibbald PA, Michael FE. *Org Lett.* 2009; 11:1147. [PubMed: 19203248] (k) Sibbald PA, Rosewall CF, Swartz RD, Michael FE. *J Am Chem Soc.* 2009; 131:15945. [PubMed: 19824646] (l) Iglesias A, Perez EG, Muniz K. *Angew Chem Int Ed.* 2010; 49:8109.(m) Sequeira FC, Turnpenny BW, Chemler SR. *Angew Chem Int Ed.* 2010; 49:6365.(n) Zhao BG, Peng XG, Cui SL, Shi YA. *J Am Chem Soc.* 2010; 132:11009. [PubMed: 20698659] (o) MacDonald MJ, Schipper DJ, Ng PJ, Moran J, Beauchemin AM. *J Am Chem Soc.* 2011; 133:20100. [PubMed: 22098595] (p) Wang YF, Zhu X, Chiba S. *J Am Chem Soc.* 2012; 134:3679. [PubMed: 22296256] (q) Ingalls EL, Sibbald PA, Kaminsky W, Michael FE. *J Am Chem Soc.* 2013; 135:8854. [PubMed: 23734771] (r) Olson DE, Su JY, Roberts DA, Du Bois J. *J Am Chem Soc.* 2014; 136:13506. [PubMed: 25233140] (s) Turnpenny BW, Chemler SR. *Chem Sci.* 2014; 5:1786. [PubMed: 24932404] (t) Zhang B, Studer A. *Org Lett.* 2014; 16:1790. [PubMed: 24588747] (u) Zhu YG, Shi YA. *Chem Eur J.* 2014; 20:13901. [PubMed: 25213994] (v) Fu SM, Yang HH, Li GQ, Deng YF, Jiang HF, Zeng W. *Org Lett.* 2015; 17:1018. [PubMed: 25668749] (w) Shen K, Wang Q. *Chem Sci.* 2015; 6:4279.(x) Yuan YA, Lu DF, Chen YR, Xu H. *Angew Chem Int Ed.* 2016; 55:534.(y) Liu RH, Wei D, Han B, Yu W. *ACS Catal.* 2016; 6:6525.(z) Martinez C, Perez EG, Iglesias A, Escudero-Adan EC, Muniz K. *Org Lett.* 2016; 18:2998. [PubMed: 27266654]
- 4.(a). Roben C, Souto JA, Gonzalez Y, Lishchynskiy A, Muniz K. *Angew Chem Int Ed.* 2011; 50:9478. (b) Kong AD, Blakey SB. *Synthesis.* 2012; 44:1190.(c) Chavez P, Kirsch J, Hovelmann CH, Streuff J, Martinez-Belmonte M, Escudero-Adan EC, Martin E, Muniz K. *Chem Sci.* 2012; 3:2375.(d) Kim HJ, Cho SH, Chang S. *Org Lett.* 2012; 14:1424. [PubMed: 22364422] (e) Muller CH, Frohlich R, Daniliuc CG, Hennecke U. *Org Lett.* 2012; 14:5944. [PubMed: 23181768] (f) Souto JA, González Y, Iglesias A, Zian D, Lishchynskiy A, Muñiz K. *Chem Asian J.* 2012; 7:1103. [PubMed: 22383364] (g) Souto JA, Martínez C, Velilla I, Muñiz K. *Angew Chem Int Ed.* 2013; 52:1324.(h) Ortiz GX Jr, Kang B, Wang Q. *J Org Chem.* 2014; 79:571. [PubMed: 24359462] (i) Chen H, Kaga A, Chiba S. *Org Lett.* 2014:6136–6139. [PubMed: 25422848] (j) Hong KB, Johnston JN. *Org Lett.* 2014; 16:3804. [PubMed: 24981419] (k) Danneman MW, Hong KB, Johnston JN. *Org Lett.* 2015; 17:2558. [PubMed: 25942322] (l) Mailyan AK, Young K, Chen JL, Reid BT, Zakarian A. *Org Lett.* 2016; 18:5532. [PubMed: 27778502] (m) Muniz K, Barreiro L, Romero RM, Martinez C. *J Am Chem Soc.* 2017; 139:4354. [PubMed: 28277652]
- 5(a). Hemric BN, Shen K, Wang Q. *J Am Chem Soc.* 2016; 138:5813. [PubMed: 27114046] (b) Hemric BN, Wang Q. *Beil J Org Chem.* 2016; 12:22.
- 6(a). Zhang B, Studer A. *Org Lett.* 2013; 15:4548. [PubMed: 23930944] (b) Kong WQ, Merino E, Nevado C. *Angew Chem Int Ed.* 2014; 53:5078.(c) Yin H, Wang T, Jiao N. *Org Lett.* 2014;

- 16:2302. [PubMed: 24735192] (d) Zhu LP, Yu HM, Xu ZQ, Jiang XM, Lin L, Wang R. *Org Lett.* 2014; 16:1562. [PubMed: 24597742] (e) Fumagalli G, Rabet PTG, Boyd S, Greaney MF. *Angew Chem Int Ed.* 2015; 54:11481. (f) Lu MZ, Wang CQ, Loh TP. *Org Lett.* 2015; 17:6110. [PubMed: 26651361] (g) Zhu R, Buchwald SL. *J Am Chem Soc.* 2015; 137:8069. [PubMed: 26070105] (h) Qiu J, Zhang RH. *Org Biomol Chem.* 2014; 12:4329. [PubMed: 24854242] Preparation of azidoiodinane, see: (i) Zhdankin VV, Krasutsky AP, Kuehl CJ, Simonsen AJ, Woodward JK, Mismash B, Bolz JT. *J Am Chem Soc.* 1996; 118:5192.
- 7(a). Sletten EM, Bertozzi CR. *Acc Chem Res.* 2011; 44:666. [PubMed: 21838330] (b) Kolb HC, Finn MG, Sharpless KB. *Angew Chem Int Ed.* 2001; 40:2004.
- 8(a). Kohn M, Breinbauer R. *Angew Chem Int Ed.* 2004; 43:3106. (b) van Berkel SS, van Eldijk MB, van Hest JCM. *Angew Chem Int Ed.* 2011; 50:8806.
9. See the Supporting Information for aminoazidation reactions of amides bearing different protecting groups.
- 10(a). Bräse S, Gil C, Knepper K, Zimmermann V. *Angew Chem Int Ed.* 2005; 44:5188. (b) Muller T, Bräse S. *Angew Chem Int Ed.* 2011; 50:11844. (c) Hassan S, Muller TJJ. *Adv Synth Catal.* 2015; 357:617. (d) Karimov RR, Sharma A, Hartwig JF. *ACS Cent Sci.* 2016; 2:715. [PubMed: 27800554] (e) Goswami M, de Bruin B. *Eur J Org Chem.* 2017; 2017:1152.
11. Some additional examples on copper-catalyzed aminofunctionalization of olefins, see: (a) Sherman ES, Chemler SR, Tan TB, Gerlits O. *Org Lett.* 2004; 6:1573. [PubMed: 15128239] (b) Zabawa TP, Kasi D, Chemler SR. *J Am Chem Soc.* 2005; 127:11250. [PubMed: 16089447] (c) Sherman ES, Fuller PH, Kasi D. *J Org Chem.* 2007; 72:3896. [PubMed: 17428100] (d) Fuller PH, Kim JW, Chemler SR. *J Am Chem Soc.* 2008; 130:17638. [PubMed: 19049311] (e) Liwosz TW, Chemler SR. *J Am Chem Soc.* 2012; 134:2020–2023. [PubMed: 22257169] (f) Bovino MT, Chemler SR. *Angew Chem Int Ed.* 2012; 51:3923. (g) Khoder ZM, Wong CE, Chemler SR. *ACS Catal.* 2017; 7:4775.
12. Zhao GH, Kwon C, Bisaha SN, Stein PD, Rossi KA, Cao XY, Ung T, Wu G, Hung CP, Malmstrom SE, Zhang G, Qu QL, Gan JP, Keim WJ, Cullen MJ, Rohrbach KW, Devenny J, Pellemounter MA, Miller KJ, Robl JA. *Bioorg Med Chem Lett.* 2013; 23:3914. [PubMed: 23683593]
13. The original isolation of enduracididine: (a) Horii S, Kameda Y. *J Antibiot.* 1968; 21:665. [PubMed: 5716843] Previous syntheses: (b) Tsuji S, Kusumoto S, Shiba T. *Chem Lett.* 1975:1281. (c) Sanier L, Leman L, Bourguignon JJ, Dauban P, Dodd RH. *Tetrahedron.* 2004; 60:5889. ref 3r (d) Atkinson DJ, Naysmith BJ, Furkert DP, Brimble MA. *Beil J Org Chem.* 2016; 12:2325. A recent review:
- 14(a). Agard NJ, Prescher JA, Bertozzi CR. *J Am Chem Soc.* 2005; 127:11196. (b) Dommerholt J, Schmidt S, Temming R, Hendriks LJA, Rutjes FPJT, van Hest JCM, Lefebvre DJ, Friedl P, van Delft FL. *Angew Chem Int Ed.* 2010; 49:9422.

Figure 1.
Representative vicinal diamine-containing natural products and biologically active molecules

Figure 2.

Proposed two possible mechanistic pathways involved in the alkene diamination reaction.

(A) initiated by amino-cyclization of alkene **1** and (B) initiated by oxidative addition to azidoiodinane **2**. Isolation yields shown. Substituents omitted for clarity.

(A) Current challenges in alkene diamination*internal alkenes and the installation of two different amino groups* **(B) This work: copper-catalyzed olefin aminoazidation using azidoiodinane**

- ☆ effective on both terminal and internal alkenes
- ☆ azidoiodinane as a trapping reagent in olefin functionalization
- ☆ one-step construction of azaheterocycles
- ☆ N_3 as a versatile amino precursor and a useful chemical reporter

Scheme 1.

Metal-Catalyzed Alkene Diamination Installing Two Amino Groups from Different Precursors

Scheme 2. Mechanistic Studies – Control Experiments

(A) Control experiments showing the presence of radical intermediates. (B–C) Comparison of differently substituted olefins, showing the influence of radical intermediates on the regio- and stereoselectivity in alkene diamination reactions. ^adr = diastereomeric ratio, determined by ¹H NMR of the crude mixture. Major diastereomer shown. Stereochemistry assignment based on X-ray analysis. ^bYields determined by ¹H NMR with CH₂Br₂ as an internal standard.

Scheme 3.

Radical clock experiments of cyclopropyl-substituted alkenes to capture potential radical intermediates.

Scheme 4.

Synthesis of 1,2-Diamine-containing Bioactive Compounds

Scheme 5. Synthesis of Azido-labeled and Novel Nitrogen-containing Steroid Derivatives

Reaction conditions: (a) PMe_3 , THF/ H_2O , 60 °C. (b) PMe_3 , THF/ H_2O , 60 °C; NaBH_4 , $i\text{-PrCHO}$, rt. (c) PMe_3 , THF/ H_2O , 60 °C; Ac_2O , Pyridine, rt. (d) Raney Ni, H_2 , EtOH. (e) cyclooctyne **27**, THF, rt, 2 h. (f) dimethyl acetylenedicarboxylate, toluene, reflux, 48 h.

Table 1

Diamination Condition Optimizations

entry	catalyst	equiv	solvent	Yield ^b
1	CuCN	0.2	MeOH	24%
2	CuCl	0.2	MeOH	50%
3	Cu(MeCN) ₄ PF ₆	0.2	MeOH	47%
4	CuOTf	0.2	MeOH	41%
5	CuOAc	0.2	MeOH	74%
6	CuCl ₂	0.2	MeOH	47%
7	Cu(OTf) ₂	0.2	MeOH	trace
8	Cu(OAc)₂	0.2	MeOH	74%
9	Cu(acac)₂	0.2	MeOH	74%
10	Cu(acac) ₂	0.2	DMF	57%
11	Cu(acac) ₂	0.2	toluene	48%
12	Cu(acac) ₂	0.2	DCE	59%
13	Cu(acac) ₂	0.2	THF	26%
14	Cu(acac) ₂	0.2	DME	41%
15	Cu(acac) ₂	0.2	MTBE	40%
16	Cu(acac) ₂	0.2	MeCN	90%
17	Cu(acac) ₂	0.1	MeCN	90% ^b
18	Cu(OAc) ₂	0.1	MeCN	99% ^b
19	CuOAc	0.1	MeCN	99%^b
20	–		MeCN	0% ^c

Reaction were performed with **1a** (0.1 mmol, 1 equiv), **2** (1.5 equiv), solvent (1 mL), 60 °C, unless otherwise noted.

^aYields determined by ¹H NMR with dibromomethane as an internal standard.

^bYield with **1a** (0.2 mmol, 1 equiv, 0.1 M), **2** (1.2 equiv), MeCN (2 mL).

^c**1a** was fully recovered.

Table 2

Aminoazidation of Diversely Substituted and Cyclic Alkenes.^a

terminal alkenes					
 3a (86%)	 3b (89%) ^b	 3c (59%)	 3d (98%)	 3e (100%)	 3f (94%)
 3g (66%)	 3h (70%, dr = 2.5:1)	 3i (87%)	 3j (69%, dr = 6:1)	 3k (68%)	 3l (98%)
 3m (70%)	 3n (97%)	 3o (78%, dr = 3:1)	 3p (93%)	 3q (46%)	 3r (64%, dr > 20:1)
internal alkenes					
 3s (73%, dr = 4:1)	 3t (52%)	 3u (70%, dr > 20:1)	 3v (47%, dr > 20:1)	 3w (35%, dr > 20:1)	
 3x (50%, dr > 20:1)	 3y (65%, dr > 20:1)	 3z (91%, dr > 20:1)		 3z-triazole	 3w-triazole

^a Isolated yields shown. Standard reaction conditions: **1** (0.30 mmol, 1.0 equiv), **2** (1.2 equiv), CuOAc (10 mol %) and MeCN (3.0 mL), unless otherwise noted. dr = diastereomeric ratio, determined by ¹H NMR of the crude mixture. Major diastereomer shown. Stereochemistry assignment based on NMR or X-ray analysis, details in the supporting information.

^b Run in MeOH (3.0 mL) instead of MeCN.