One-step Access to *N*-Enoxyimides by Gold-catalysed Addition of *N*-Hydroxyimides to Terminal Alkynes

Received 00th January 20xx,
Accepted 00th January 20xx

Coralie Duchemin,^a Nicolai Cramer^{*a}

DOI: 10.1039/x0xx00000x

www.rsc.org/

Abstract: *N*-enoxyimides have become attractive substrates for novel catalytic transformations, yet their tedious multi-step synthesis hamper full exploitation of their synthetic potential. We report a gold(I)-catalyzed protocol to access *N*-enoxyimides from simple and widely available terminal alkynes and the corresponding *N*-hydroxyimides in a single step. The transformation proceed with aryl-, alkenyl- and alkyl alkynes, facilitating further studies of this substrate class in C-H functionalizations and photocatalysis.

Hydroxylamine derivatives are not only important motifs in pharmaceuticals and agrochemicals¹ but as well valuable substrates for a variety of complexity-building transformations.² For instance, hydroxylamine derivatives have been extensively used as directing groups in catalytic C-H functionalizations and concomitant cleavage of the oxygen-nitrogen bond allowed reoxidation of the catalyst (Scheme 1).³ In this context, phenoxyamides were established as efficient internal oxidants for Rh(III)-catalyzed aryl C(sp²)-H functionalizations.⁴ Rovis disclosed related Rh(III)-catalyzed vinylic C(sp²)-H functionalizations using related the enoxyphthalimide motif as the oxidative directing group.⁵ Subsequent trapping reactions with Michael acceptors were used to selectively form *trans*-^{5a} or *cis*-cyclopropanes,^{5c} as well as to trigger carboaminations^{5b} Moreover, the ability of oxyamides to engage in radical processes has been exploited in the decarboxylative functionalization of redox active esters triggered either photocatalytically⁶ or by nickel complexes.⁷ Along the same lines, Feng reported a photo-catalyzed process for the carboamination of alkenes with *N*-enoxyphthalimides.⁸

Exploitation of the weak N-O bond in catalysis

Scheme 1. Synthetic versatility of hydroxylamine derivatives for catalysis.

Despite this steeply increasing synthetic versatility, the efficient access to the *N*-enoxyimide structural motif is still very cumbersome and represents an unsolved problem. Except the straight Michael-addition of *N*-hydroxyimides to acetylene dicarboxylates,⁹ the only general reported route involves preparation of the vinylboronic acid in three steps from the corresponding alkene (Scheme 2).^{5a} In turn, the vinylboronic acid is subjected to a copper(I)-mediated coupling with *N*-hydroxyphthalimide.¹⁰ Besides the drawbacks of the low synthetic efficiency of a three-step procedure and the use of copper-mediated reactions, this protocol is only suited for *N*-hydroxy-phthalimides. Related substrates like *N*-hydroxysuccinimide or *N*-hydroxycarbamate do not engage in the transformation.^{10b}

Gold(I)-catalyzed additions of oxygen nucleophiles to terminal alkynes have become an efficient method for the synthesis of a variety of *O*-vinyl derivatives.¹¹ For instance, the addition of HOBt to alkynes was reported by Hammond and Xu.¹² Zhang disclosed the synthesis of indoles by the addition of aryl hydroxamic acids and *N*-aryl-*N*-hydroxycarbamates to alkynes forming labile vinyl ether intermediates which readily rearranged in analogy to the Fischer indole synthesis.¹³ Moreover, the addition of pyridine *N*-oxides to alkynes is used

^a Laboratory of Asymmetric Catalysis and Synthesis, EPFL SB ISIC LCSA, BCH 4305
CH-1015 Lausanne (Switzerland). E-mail: nicolai.cramer@epfl.ch
Electronic Supplementary Information (ESI) available: Experimental procedures
and characterization of all new compounds. See DOI: 10.1039/x0xx00000x

for enolate umpolung reactivities.¹⁴ Notably, hydroxylamine derivatives with two electron-withdrawing substituents on the nitrogen atom such as *N*-hydroxylimides have not investigated as suitable nucleophiles. Given the need for and efficient synthetic access and inspired by these reports, we explored the feasibility of a gold(I)-catalyzed efficient single step synthesis of *N*-enoxyimides by the addition of *N*-hydroxyimides to widely accessible terminal alkynes (Scheme 2).

Reported route for enoxyphthalimides^{5a}

This work: direct catalytic access to *N*-enoxyimides

Scheme 2. Streamlined synthetic access to *N*-enoxyimides.

To initially investigate the transformation, we selected 4-methoxyphenyl acetylene (**1a**) and *N*-hydroxysuccinimide (**2a**) as the model substrates. The envisioned addition of **1a** to the acetylene was accomplished by (PPh₃)Au trifluoroacetate in DCE at 90 °C for 6 h. By *in situ* generation of the gold catalyst, the desired addition product **3aa** was obtained in 26 % yield (Table 1, entry 1). The yield of **3aa** was substantially increased to 65 % with a preformed (PPh₃)Au trifluoroacetate catalyst (entry 2). The observation points towards decomposition of formed product **3aa** under the reaction conditions. Conducting the reaction in strictly anhydrous conditions had no effect on the amount of **4a** (entry 3). A five-fold scale-up of the reaction increased the isolated yield of product **3aa** to 75 % (entry 4). The moderate stability of **3aa** which has the tendency to decompose under the reaction conditions to ketone **4a** requires striking a fine balance to maximize yield. The reaction outcome proved to be as well highly sensitive to several variables. Notably, replacing the trifluoroacetate anion by weaker coordinating ones such as triflate or triflimide¹⁵ was to be detrimental (entries 5, 6). In these cases, a formal hydration of **1a** was dominant yielding exclusively ketone **4a**. Subsequent variations of the ligand (IPr or Johnphos) did not substantially improve the reaction outcome (entries 7, 8). Longer reaction times caused a reduction of **3aa** and increased the ketone **4a** (entry 9), whereas lower reaction temperatures (60 °C) or lower concentrations gave largely reduced conversions (entry 10, 11). Attempts to increase the formation of **3aa** by increasing the equivalents of *N*-hydroxysuccinimide failed (entry 12). Several control experiments were conducted to gauge the relevance of the individual components of the catalyst system. In this respect, the absence of the gold catalyst completely shut down the formation of addition product **3aa** (entry 13), which excluded residual Ag(I) salts as the active catalyst.¹⁸ Omitting the addition of silver salts completely, showed that neutral (PPh₃)AuCl is not a competent catalyst and caused only unspecific degradation of

1a (entry 14). These experiments underlined the relevance of the trifluoroacetate anion in gold(I)-catalyzed transformations to modulate reactivity and selectivity.^{16,17} Moreover, trifluoroacetic acid itself did not promote the addition of succinimide at all (entry 15).

Table 1. Optimization of the *N*-enoxyimide formation^a

Entry	Catalyst	Deviations	Conv. (%) ^b	3aa (%) ^b	4a (%) ^b
1	(PPh ₃)AuCl/Ag(O ₂ CCF ₃)	-	61	26	24
2	(PPh ₃)Au(O ₂ CCF ₃)	-	95	65	10
3 ^c	(PPh ₃)Au(O ₂ CCF ₃)	-	81	54	10
4	(PPh ₃)Au(O ₂ CCF ₃)	1 mmol scale	n.d.	75 ^d	n.d.
5 ^c	(PPh ₃)Au(OTf)	-	93	0	69
6 ^c	(PPh ₃)Au(NTf ₂)	-	72	0	69
7	IPrAu(O ₂ CCF ₃)	-	100	45	12
8	CyJohnPhosAu(O ₂ CCF ₃)	-	100	75	14
9	(PPh ₃)Au(O ₂ CCF ₃)	for 14 h	81	28	27
10	(PPh ₃)Au(O ₂ CCF ₃)	at 60 °C	20	<5	<5
11	(PPh ₃)Au(O ₂ CCF ₃)	at 0.1 M	50	9	13
12	(PPh ₃)Au(O ₂ CCF ₃)	2 equiv. 2a	79	30	20
13	Ag(O ₂ CCF ₃)	-	31	0	8
14	(PPh ₃)AuCl	-	82	0	<5
15	CF ₃ CO ₂ H	-	0	-	-

^a 0.2 mmol **1a**, 0.22 mmol **2a**, 2.5 μmol **cat**, 0.2 M in DCE at 90 °C for 6 h; ^b determined by ¹H-NMR with an internal standard; ^c carried under strict N₂ atmosphere in anhydrous solvent; ^d isolated yield; n.d.=not determined.

Next, the scope of the reaction was investigated with optimized conditions (Scheme 3). The electronic nature of the aryl substituent of the alkyne was found to have an influence on the reactivity. The reaction works best with alkynes having electron-rich aryl groups and somewhat less efficient for those with electron-deficient aryl or sterically-hindered substituents. Nevertheless, the obtained yield of the single step transformation is still largely competitive with the reported 4-step sequence which is not described for *N*-hydroxysuccinimides. Pleasingly, alkenyl- and alkyl-substituted alkynes are particularly well suited for the gold-catalysed addition. Noteworthy, no synthesis for this substitution pattern is reported. For example, 1-ethynylcyclohex-1-ene (**1g**) provided dienoxyl derivative **3ga** in 62 % yield. Besides simple alkyl moieties (**3ha**, **3na**), a variety of functionalized alkyl groups having potentially reactive groups in proximity to the

alkyne moiety were submitted to the addition conditions. Esters (**3ia**), ethers (**3la**), phthalimido groups (**3ka**) as well as a chloride (**3ja**) and a cyclopropyl group (**3ma**) did not disturb the addition reaction of *N*-hydroxysuccinimide. Finally, the *N*-hydroxyimide portion can be varied as well. In this respect, the enoxyphthalimide **3hb** was formed in 65 % yield. Enoxymaleimide **3hc** proved to be more sensitive and was isolated in moderate yield. Internal alkynes were not suitable substrates with the current catalyst system.

Scheme 3. Scope of gold-catalyzed addition. Conditions: 1.0 mmol **1**, 1.1 mmol **2**, 0.05 mmol (PPh₃)Au(O₂CCF₃), 0.2 M in DCE at 90 °C for 6 h. ^b with 10 mol% (PPh₃)Au(O₂CCF₃); ^c at 0.5 M.

To briefly illustrate the utility of the transformation and the synthetic potential of the enoxyimides, **3ba** was used as substrate in two very recently reported state-of-the-art catalytic transformations. For instance, exposure of *N*-enoxy-succinimide **3ba** to conditions reported by Rovis,^{5a} [Cp*RhCl₂]₂ in the presence of cesium acetate and ethyl acrylate, provided cyclopropane **5** in 72 % yield as 61:39 *cis/trans* ratio (Scheme 4). The switch from the original phthalimide group to the succinimide group resulted in a substrate induced *cis*-dominance. A catalyst-induced *cis*-selectivity could be obtained for enoxyphthalimide fine-tuning of the catalyst.^{5c} Combined with catalyst engineering, the outlined succinimide-type substrate might become useful to boost *cis*-selectivity for refractory substrates or to serve as suitable platform to develop catalytic enantioselective cyclopropanation reactions with chiral cyclopentadienyl complexes.¹⁹ Moreover, *N*-enoxy-succinimide **3ba** successfully participated in an iridium-photo-catalyzed carboamination of olefins in analogy to recently

disclosed work by Feng.⁸ For instance, irradiation of a mixture of **3ba** ethylvinylether in the presence of an iridium photocatalyst, triggered smooth carboamination and formed ketone **6** in 52 % yield. To the best of our knowledge, this represents a rare example of an *N*-oxysuccinimide moiety in a visible light photoinduced radical process.²⁰

Scheme 4. Exemplary applications of enoxysuccinimide **3ba** in state-of-the-art catalysis.

Conclusion

In summary, we reported a gold(I)-catalyzed addition of *N*-hydroxyimides to terminal alkynes. Formal alkyne hydration presumably by decomposition of the desired *N*-enoxyimide product was mitigated by using trifluoroacetate counterion on the gold(I) complex. The process accommodates several *N*-hydroxyimides and a range aryl, alkenyl and alkyl alkynes decorated with a variety of functional groups including halogens, phthalimides, esters and ethers. *N*-Enoxysuccinimides were shown to be suitable substrates for Rh(III)-catalyzed cyclopropanations and photo-redox carboaminations. We expect that the reported efficient *N*-enoxyimide preparation will further enable exploitation of their untapped synthetic potential.

Conflicts of interest

The authors declare no competing financial interests.

Notes and references

- (a) Y. Ashani, I. Silman in *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*, Part 1 (Eds.: Z. Rappoport, J. F. Liebman), Wiley, Chichester, 2009, pp. 609-651; (b) N. Chen and J. Xie, *Organic & Biomolecular Chemistry*, 2016, **14**, 11028-11047; (c) S. Jeanmart, A. J. F. Edmunds, C. Lamberth and M. Pouliot, *Biorg. Med. Chem.*, 2016, **24**, 317-341.
- (a) M. Manuela, A. Pereira, P. P. Santos in *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*, Part 1 (Eds.: Z. Rappoport, J. F. Liebman), Wiley, Chichester, 2009, pp. 343-498; (b) A. A. Tabolin and S. L. Ioffe, *Chem. Rev.*, 2014, **114**, 5426-5476.
- For selected reviews on oxidizing directing groups, see: (a) F. W. Patureau and F. Glorius, *Angew. Chem. Int. Ed.*, 2011, **50**, 1977-1979; (b) H. Huang, X. Ji, W. Wu and H. Jiang, *Chem. Soc. Rev.*, 2015, **44**, 1155-1171; (c) J. Mo, L. Wang, Y. Liu and

- X. Cui, *Synthesis*, 2015, **47**, 439-459; (d) H. Sun and Y. Huang, *Synlett*, 2015, **26**, 2751-2762; (e) X.-G. Liu, H. Gao, S.-S. Zhang, Q. Li and H. Wang, *ACS catal.*, 2017, **7**, 5078-5086.
- 4 For selected examples, see: (a) G. Liu, Y. Shen, Z. Zhou and X. Lu, *Angew. Chem. Int. Ed.*, 2013, **52**, 6033-6037; (b) Y. Shen, G. Liu, Z. Zhou and X. Lu, *Org. Lett.*, 2013, **15**, 3366-3369; (c) F. Hu, Y. Xia, F. Ye, Z. Liu, C. Ma, Y. Zhang and J. Wang, *Angew. Chem. Int. Ed.*, 2013, **53**, 1364-1367; (d) Y. Chen, D. Wang, P. Duan, R. Ben, L. Dai, X. Shao, M. Hong, J. Zhao and Y. Huang, *Nat. Commun.*, 2014, **5**, 4610; (e) P. Duan, X. Lan, Y. Chen, S.-S. Qian, J. J. Li, L. Lu, Y. Lu, B. Chen, M. Hong and J. Zhao, *Chem. Commun.*, 2014, **50**, 12135-12138; (f) Z. Hu, X. Tong and G. Liu, *Org. Lett.*, 2016, **18**, 1702-1705. (k) Z. Zhou, G. Liu, Y. Chen and X. Lu, *Org. Lett.*, 2015, **17**, 5874-5877; (h) Q. Wu, Y. Chen, D. Yan, M. Zhang, Y. Lu, W.-Y. Sun and J. Zhao, *Chem. Sci.*, 2017, **8**, 169-173; (i) Z. Hu and G. Liu, *Adv. Synth. Catal.*, 2017, **359**, 1643-1648; (j) X. Wang, A. Lerchen, C. G. Daniliuc and F. Glorius, *Angew. Chem. Int. Ed.*, 2017, **57**, 1712-1716; (f) Y. Wang, Y. Chen, Y. Yang and B. Zhou, *Org. Chem. Front.*, 2018, **5**, 1844-1847; (g) X. Wang, Y. Li, T. Knecht, C. G. Daniliuc, K. N. Houk and F. Glorius, *Angew. Chem. Int. Ed.*, 2018, **57**, 5520-5524.
- 5 (a) T. Piou and T. Rovis, *J. Am. Chem. Soc.*, 2014, **136**, 11292-11295; (b) T. Piou and T. Rovis, *Nature*, 2015, **527**, 86; (c) T. Piou, F. Romanov-Michaëlidis, M. A. Ashley, M. Romanova-Michaëlidis and T. Rovis, *J. Am. Chem. Soc.*, 2018, **140**, 9587-9593; (d) T. Piou and T. Rovis, *Acc. Chem. Res.*, 2018, **51**, 170-180.
- 6 For selected examples, see: (a) K. Okada, K. Okamoto and M. Oda, *J. Am. Chem. Soc.*, 1988, **110**, 8736-8738; (b) G. Pratsch, G. L. Lackner and L. E. Overman, *J. Org. Chem.*, 2015, **80**, 6025-6036; (c) Y. Jin and H. Fu, *Asian J. Org. Chem.*, 2016, **6**, 368-385; (d) L. Candish, M. Teders and F. Glorius, *J. Am. Chem. Soc.*, 2017, **139**, 7440-7443; (e) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers and V. K. Aggarwal, *Science*, 2017, **357**, 283; (f) D. Hu, L. Wang and P. Li, *Org. Lett.*, 2017, **19**, 2770-2773; (g) W. Zhao, R. P. Wurz, J. C. Peters and G. C. Fu, *J. Am. Chem. Soc.*, 2017, **139**, 12153-12156.
- 7 For selected examples, see: (a) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C.-M. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2016, **138**, 2174-2177; (b) T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate and P. S. Baran, *Science*, 2016, **352**, 801; (c) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman and D. J. Weix, *J. Am. Chem. Soc.*, 2016, **138**, 5016-5019; (d) J. T. Edwards, R. R. Merchant, K. S. McClymont, K. W. Knouse, T. Qin, L. R. Malins, B. Vokits, S. A. Shaw, D.-H. Bao, F.-L. Wei, T. Zhou, M. D. Eastgate and P. S. Baran, *Nature*, 2017, **545**, 213; (e) J. M. Smith, T. Qin, R. R. Merchant, J. T. Edwards, L. R. Malins, Z. Liu, G. Che, Z. Shen, S. A. Shaw, M. D. Eastgate and P. S. Baran, *Angew. Chem. Int. Ed.*, 2017, **56**, 11906-11910; (f) L. Huang, A. M. Olivares and D. J. Weix, *Angew. Chem. Int. Ed.*, 2017, **56**, 11901-11905.
- 8 Y. Zhang, H. Liu, L. Tang, H.-J. Tang, L. Wang, C. Zhu and C. Feng, *J. Am. Chem. Soc.*, 2018, **140**, 10695-10699.
- 9 A. R. Kazemizadeh, A. Ramazani, B. Ganjeie *Asian J. Chem.*, 2007, **19**, 5784-5786; A. Mishra, S. Singh, M. A. Quraishi, V. Srivastava, *ChemistrySelect*, 2018, **3**, 9464-9468.
- 10 (a) H. M. Petrassi, K. B. Sharpless and J. W. Kelly, *Org. Lett.*, 2001, **3**, 139-142; (b) A. S. Patil, D.-L. Mo, H.-Y. Wang, D. S. Mueller and L. L. Anderson, *Angew. Chem. Int. Ed.*, 2012, **51**, 7799-7803.
- 11 (a) Y. Fukuda and K. Utimoto, *J. Org. Chem.*, 1991, **56**, 3729-3731; (b) J. H. Teles, S. Brode and M. Chabanas, *Angew. Chem. Int. Ed.*, 1998, **37**, 1415-1418; (c) S. Antonietti, E. Genin, V. Michelet and J.-P. Genêt, *J. Am. Chem. Soc.*, 2005, **127**, 9976-9977; (d) P. Y. Toullec, E. Genin, S. Antonietti, J.-P. Genêt and V. Michelet, *Synlett*, 2008, **2008**, 707-711; (e) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028-9072; (f) D. B. Huple, S. Ghorpade and R.-S. Liu, *Adv. Synth. Catal.*, 2016, **358**, 1348-1367.
- 12 M. Kumar, M. Scobie, M. S. Mashuta, G. B. Hammond and B. Xu, *Org. Lett.*, 2013, **15**, 724-727.
- 13 (a) Y. Wang, L. Liu and L. Zhang, *Chem. Sci.*, 2013, **4**, 739-746; (b) Y. Wang, L. Ye and L. Zhang, *Chem. Commun.*, 2011, **47**, 7815-7817.
- 14 (a) Z. Xu, H. Chen, Z. Wang, A. Ying and L. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 5515-5518; (b) Z. Xu, R. Zhai, T. Liang and L. Zhang, *Chem. Eur. J.*, 2017, **23**, 14133-14137; (c) R. L. Zhai, Y. S. Xue, T. Liang, J. J. Mi and Z. Xu, *J. Org. Chem.*, 2018, **83**, 10051-10059.
- 15 M. Jia and M. Bandini, *ACS catal.*, 2015, **5**, 1638-1652.
- 16 M. Preisenberger, A. Schier and H. Schmidbaur, *J. Chem. Soc., Dalton Trans.*, 1999, 1645-1650.
- 17 (a) Y. Yamane, N. Miwa and T. Nishikata, *ACS catal.*, 2017, **7**, 6872-6876; (b) M. Wohland and M. E. Maier, *Synlett*, 2011, **2011**, 1523-1526; (c) M. Jia, G. Cera, D. Perrotta, M. Monari and M. Bandini, *Chem. Eur. J.*, 2014, **20**, 9875-9878.
- 18 G. Fang and X. Bi, *Chem. Soc. Rev.*, 2015, **44**, 8124-8173.
- 19 (a) B. Ye and N. Cramer, *Science*, 2012, **338**, 504; (b) B. Ye and N. Cramer, *J. Am. Chem. Soc.*, 2013, **135**, 636-639; (c) B. Ye and N. Cramer, *Acc. Chem. Res.*, 2015, **48**, 1308-1318; (d) C. G. Newton, D. Kossler and N. Cramer, *J. Am. Chem. Soc.*, 2016, **138**, 3935-3941; (e) S.-G. Wang, S. H. Park and N. Cramer, *Angew. Chem. Int. Ed.*, 2018, **57**, 5459-5462.
- 20 For an example of N-oxysuccinimide substrates successfully used in a metal-catalyzed radical process, see: K. Foo, E. Sella, I. Thomé, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5279-5282.