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COMMUNICATION

Iron-Catalyzed Carbonylative Cyclization of γ,δ-Unsaturated Aromatic Oxime Esters Toward Functionalized Pyrrolines

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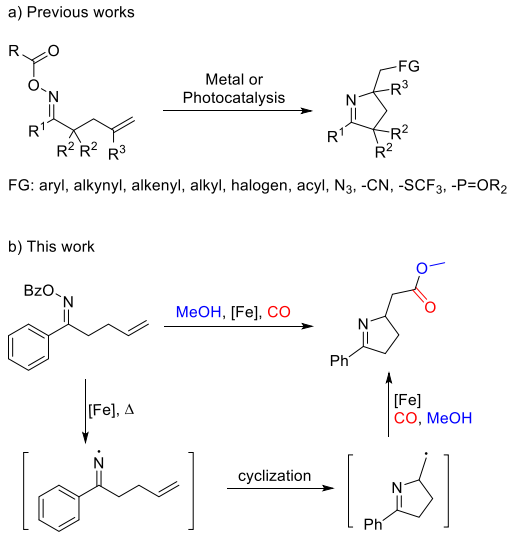
Herein, a new method on iron-catalyzed carbonylative cyclization of *γ,δ*-unsaturated aromatic oxime esters to functionalized pyrrolines has been developed. By using readily available substrates, 32 examples of functionalized pyrrolines were prepared in moderate to good yields. Notably, examples on reduction and cycloaddition reactions of the obtained product were given as well.

Intramolecular amination of alkenes is a valuable and powerful synthetic tool for preparing nitrogen-containing heterocycles such as piperazine, pyrroline, oxazolidin-2-one, pyridine, indoline, oxindole and lactam derivatives.[1] Among these heterocyclic units, pyrrolines are important heterocyclic motifs in the fields of naturally occurring products and bioactive compounds,[2] such as the special applications of *β*-homoprolines in biology and pharmacology.[3] In this regard, unsaturated oxime esters as a class of readily available and highly reactive substrates have been successfully employed in constructing a series of functionalized pyrrolines in the presence of metal or photocatalyst under mild reaction conditions (Scheme 1a).[4] Notably, Bower and co-workers reported their detailed studies on palladium-catalyzed cyclization of unsaturated oxime esters in 2015.[4a] The desired 1,2-carboamination products were produced in good yields with alcohols and organometallic reagents as the coupling partners. By performing the reaction under CO atmosphere (1 bar), the corresponding carbonylation products can be produced in an effective manner as well. Several alternative synthetic procedures relied on specific substrates, stoichiometric strong oxidants, or precious transition-metal catalyst have been established as well.[5-7]

On the other hand, carbonylation is known as one of the most effective methods to introduce carbonyl functional group into the target molecules.[8] Recently, our group has developed a series of iminyl radical-mediated carbonylation reactions of oxime esters.[9] In the carbonylative reaction of *N*-fluoro-sulfonamides, we found the sulfonamide group was not possible to remove from the obtained products.[10] This disadvantage will definitely limit the further applications of this procedure, besides the drawbacks from the substrates. Hence, a new methodology from readily available starting materials without the above discussed weaknesses is highly demanded.



Scheme 1. Functionalized pyrrolidines synthesis from oxime esters.

Considering the intramolecular amination of alkenes and the carbonylation of radicals,[11] we become interested in exploring a new method for the synthesize of functionalized pyrrolines from *γ, δ*-unsaturated oxime esters. This strategy may be achieved through transition-metal catalyzed O-N bond activation of oxime esters to generate iminyl radicals,[4,12] followed by an intramolecular cyclization to obtain new carbon radicals, which subsequently captured by CO and

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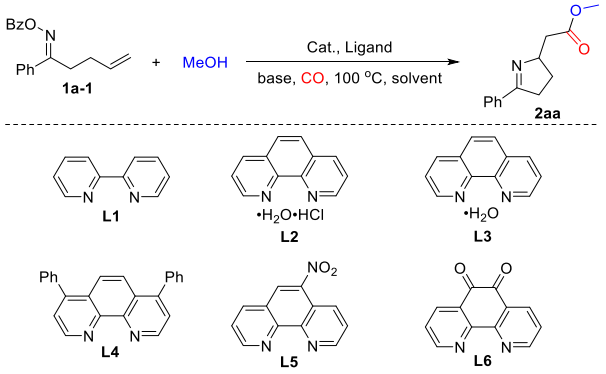
finally been converted into the corresponding products (Scheme 1b).

In order to establish the catalyst system, we used 1-phenylpent-4-en-1-one *O*-benzoyl oxime **1a-1**, MeOH (50 uL) as the model substrate and nucleophile, respectively. Initially, the reaction was performed with FePC (Iron(II) phthalocyanine) as the catalyst in DCE under 50 bar of CO at 100 °C. The desired product **2aa** was produced in 67% (Table 1, entry 1). However, only trace amount of **2aa** could be detected when $Fe(OTf)_3$ or $Cu(OTf)_2$ with 1,10-Phen·HCl·H_2O was tested as the catalytic system (Table 1, entry 2). FeF_3 as an iron precursor was tested as well, 38% of the target product was formed (Table 1, entry 3). No desired molecule was observed in the absence of an iron catalyst (Table 1, entry 4). Satisfactorily, 80% of methyl 2-(5-phenyl-3,4-dihydro-2*H*-pyrrol-2-yl)acetate **2aa** was determined with $Fe(acac)_3$ and 1,10-Phen·HCl·H_2O as the catalytic system (Table 1, entry 5). Then some other solvents were examined, including MeCN, $PhCF_3$ and THF, no improved results were obtained (Table 1, entries 6-8). Different ligands were subsequently tested, which indicated that the ligand had a dramatic effect on this reaction, and 1,10-Phen·HCl·H_2O was found to be the best than the other tested ligands (Table 1, entries 9-11). Only traces of product **2aa** was found in the absence of ligand. As carboxylic acid might be the byproduct, 1.2 equiv. of HOAc as additives was tested and little influence was obtained (Table 1, entry 12). However, adding 1.2 equiv. of pyridine led to the yield of **2aa** diminished to 46% (Table 1, entry 13). And no desired product could be detected when other organic base (Et_3N) or inorganic base (Na_2CO_3) was added (Table 1, entry 14). Finally, lowing the temperature to 80 °C, the pressure of CO to 40 bar or the loading of ligand to 5 mol% lead to a slightly decreased yield of the final product (Table 1, entries 15-17).

Table 1. Optimization of reaction conditions.[a]

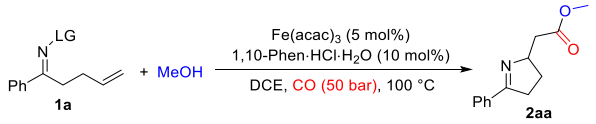


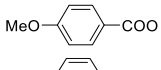
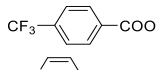
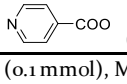
entry	variations from the standard conditions	yield[b] (%)
1	FePC instead of $Fe(acac)_3$ and ligand	67
2	$Fe(OTf)_3$ or Cu(OTf)2 instead of $Fe(acac)_3$	trace
3	FeF_3 instead of $Fe(acac)_3$	38
4	no $Fe(acac)_3$	n.d.
5	-	80 (72)[c]
6	MeCN instead of DCE	66
7	$PhCF_3$ instead of DCE	75
8	THF instead of DCE	49
9	no ligand, L1 or L4 instead of L2	trace
10	L3 or L5 instead of L2	n.d.
11	L6 instead of L2	38
12	added 1.2 equiv. HOAc	81
13	added 1.2 equiv. pyridine	46
14	added 1.2 equiv. Et_3N or Na2CO3	n.d.
15	80 °C instead of 100 °C	74
16	CO 40 bar instead of 50 bar	73
17	L2 5 mol% instead of 10 mol%	75

[a]Reaction conditions: **1a-1** (0.1 mmol), MeOH (50 uL), catalysts (5 mol%), ligands (10 mol%) in solvent (1 mL) at 100 °C for 20 h under CO (50 bar). [b]Yields were determined by GC-FID analysis using n-hexadecane as internal standard. [c]Isolated yield (**1a-1** 0.2 mmol scale). n.d.= no detection. FePC = iron(II) phthalocyanine. THF = tetrahydrofuran. DCE = 1,2-dichloroethane.

Additionally, different leaving groups (LG) of the oxime esters **1a** substrates were also examined (Table 2). The yield of **2aa** dramatical decreased when OAc was used as the leaving group instead of OBz. Other aryl or heterocyclic substituted leaving groups were checked and no better results were obtained under the optimal reaction conditions.

Table 2. Optimization of oxime ester leaving groups.[a]



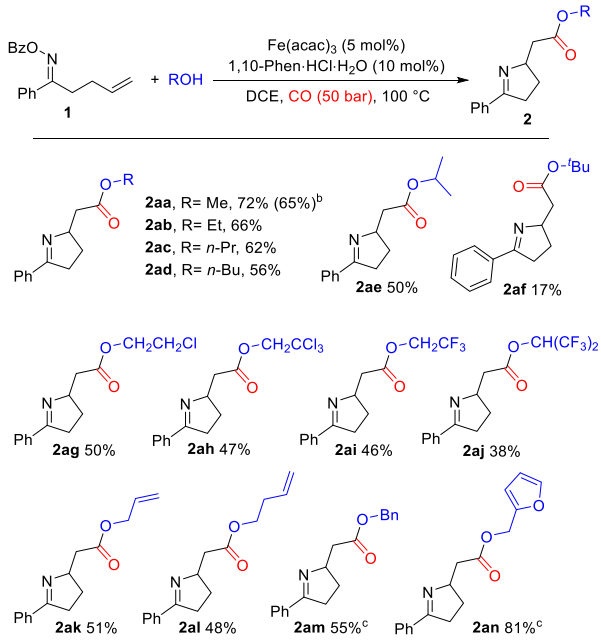
entry	LG	yield[b] (%)
1	OBz (1a-1)	80
2	OAc (1a-2)	12
3	OBz^{5F} (1a-3)	78
4	 (1a-4)	46
5	 (1a-5)	72
6	 (1a-6)	68

[a]Reaction conditions: **1a** (0.1 mmol), MeOH (50 uL), $Fe(acac)_3$ (5 mol%), 1,10-Phen·HCl·H_2O (10 mol%) in DCE (1 mL) at 100 °C for 20 h under CO (50 bar). [b]Yields were determined by GC-FID analysis using n-hexadecane as internal standard.

Having established the optimized reaction conditions, we started to explore the substrate scope of this reaction with different alcohols and unsaturated aromatic oxime esters. Firstly, a series of alcohols were reacted with oxime esters **1a-1** (Scheme 2). Some low boiling point primary alkyl alcohols like methanol, ethanol, propanol, and n-butanol were all reacted well with oxime esters **1a-1** to form the desired products **2aa-2ad** in 56%-72% yields. Even isopropanol as secondary alcohol and *t*-butanol as sterically hindered tertiary alcohol were also smoothly converted into the target

products **2ae** and **2af** in 50% and 17% yields, respectively. Additionally, a series of halogen-substituted aliphatic alcohols can be applied as well and gave the corresponding products **2ag**-**2aj** in moderate yields. Furthermore, alcohols with a terminal alkenyl unit were also tolerated, affording the desired products **2ak** and **2al** in 51% and 48% yields, respectively. Notably, benzylalkohol and furfurylalkohol as high boiling point alcohols can also be applied, the desired carbonylation products **2am** and **2an** were provided in moderate to good yields. To further explore the synthetic value of this protocol, a 1.0 mmol scale reaction of **1a-1** with methanol was carried out under the best reaction conditions, the corresponding product **2aa** was delivered in 65% isolated yield.

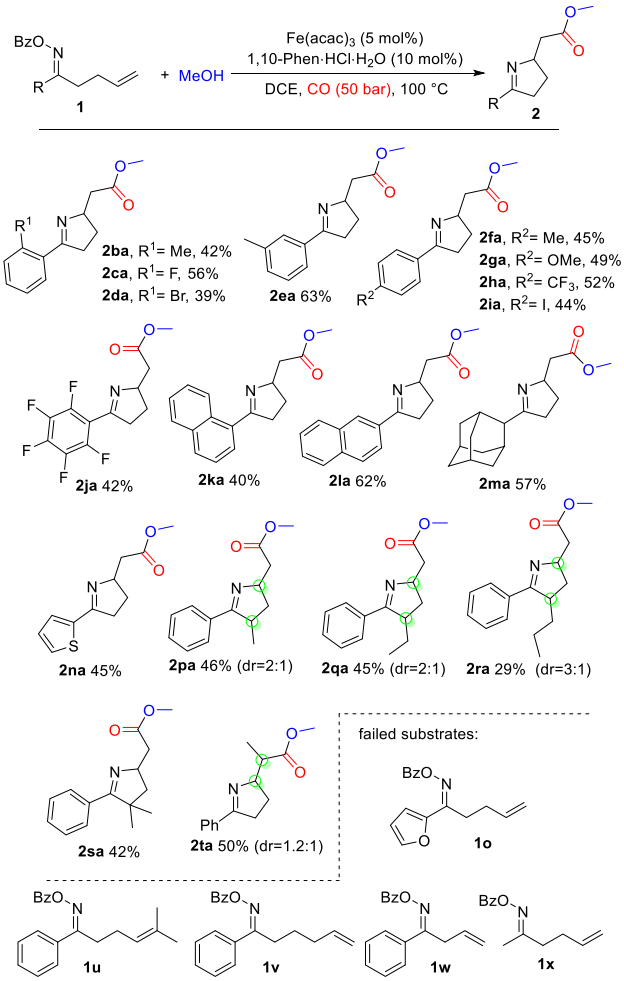
Scheme 2. Scope of alcohols.[a]



[a]Reaction conditions: **1** (0.2 mmol), ROH (0.1 mL), $Fe(acac)_3$ (5 mol%), 1,10-Phen·HCl·H_2O (10 mol%) in DCE (2 mL) at 100 °C for 20 h under CO (50 bar), isolated yield. [b]**1a-1** (1.0 mmol), MeOH (0.5 mL), DCE (7 mL). [c]ROH (2 equiv.).

Subsequently, a range of aromatic and heteroaromatic oxime esters were prepared and investigated (Scheme 3). In general, both electron-withdrawing and donating substituents on different positions of the aromatic ring were all smoothly transformed, supplying the corresponding products **2ba-2ia** in moderate yields. Perfluorinated substrate **1j** 1-(perfluorophenyl)pent-4-en-1-one *O*-benzoyl oxime was also converted into the corresponding product **2ja.** Other substrates including 1-naphthalene, 2-naphthalene and thiophene, even adamantane substituted *O*-benzoyl oximes can all be applied and gave moderate yields of the corresponding products. Moreover, a panel of substrates with different alkyl chain units on the α position of *O*-benzoyl oximes afforded the corresponding products **2pa-2sa** in moderate yields. Relatively low yield formed **2ra**, possibly due to the competitive conversion of 5-*exo*-*trig* cyclization[13] and 1,5 H-atom transfer (HAT)[14] during the reaction. To further explore the applicability of this procedure, we used substrates **1t** and **1u** to inspect the carbonylation of secondary and tertiary carbon radicals, respectively. Delightfully, 50% of methyl 2-(5-phenyl-3,4-dihydro-2*H*-pyrrol-2-yl)propanoate **2ta** can be prepared from carbonylation of the corresponding secondary radical intermediate. However, the tertiary radical intermediate was only converted into the elimination products, which were detected by GC-MS. Unfortunately, the oxime esters with furan (**1o**), different carbon chain lengths (**1v** 1-phenylhex-5-en-1-one *O*-benzoyl oxime, and **1w** 1-phenylbut-3-en-1-one *O*-benzoyl oxime) or alkyl oxime ester (**1x** hex-5-en-2-one *O*-benzoyl oxime) were failed to give the desired products.

Scheme 3. Scope of *O*-benzoyl oximes.[a]

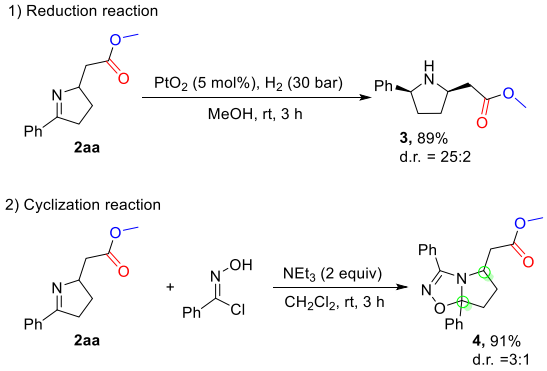


[a]Reaction conditions: **1** (0.2 mmol), ROH (0.1 mL), $Fe(acac)_3$ (5 mol%), 1,10-Phen·HCl·H_2O (10 mol%) in DCE (2 mL) at 100 °C for 20 h under CO (50 bar), isolated yield.

Moreover, the obtained product **2aa** can be easily reduced to **3** in high yield by a PtO_2-catalyzed hydrogenation reaction in MeOH under 30 bar hydrogen (Scheme 4, eq 1).[4a] Additionally, by using triethylamine as the base, a cyclization

reaction between **2aa** and *N*-hydroxybenzimidoyl chloride can occur at room temperature (Scheme 4, eq 2). The cycloaddition product **4** was formed in 91% yield.

Scheme 4. Synthetic transformations of **2aa**.



In summary, we have described an iron-catalyzed intramolecular cyclization and intermolecular carbonylation of γ,δ-unsaturated aromatic oxime esters. This method provides a new strategy for preparing various unsaturated β-homoproline esters in moderate to good yields. In addition, further synthetic transformation of the obtained product via reduction and cycloaddition were realized as well.

Conflicts of interest

There are no conflicts to declare.

Notes and references

(1) (a) A. Minatti, K. Muniz, *Chem. Soc. Rev.* 2007, **36**, 1142-1152. (b) X.-X. Guo, D.-W. Gu, Z. Wu, W. Zhang, *Chem. Rev.* 2015, **115**, 1622-1651. (c) K. Muniz, C. Martinez, *J. Org. Chem.* 2013, **78**, 2168-2174. (d) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* 2007, **107**, 5318-5365. (e) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* 2011, **111**, 2981-3019.

(2) (a) T. Fukuda, Y. Sudoh, Y. Tsuchiya, T. Okuda, Y. Igarashi, *J. Nat. Prod.* 2014, **77**, 813-817. (b) K. Lauder, A. Toscani, N. Scalacci, D. Castagnolo, *Chem. Rev.* 2017, **117**, 14091-14200. (c) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* 2014, **57**, 10257-10274. (d) N. Asano, K. Ikeda, M. Kasahara, Y. Arai, H. Kizu, *J. Nat. Prod.* 2004, **67**, 846-850. (e) H. K. Noh, J. S. Lee, Y. Kim, G. Hwang, J. H. Chang, H. Shin, D. H. Nam, K. H. Lee, *Org. Proc. Res. Dev.* 2004, **8**, 788-795.

(3) (a) F. M. Cordero, C. Vurchio, M. Lumini, A. Brandi, *Amino Acids* 2013, **44**, 769-780. (b) D. Seebach, J. Gardiner, *Acc. Chem. Res.* 2008, **41**, 1366-1375. (c) G. Cardillo, L. Gentilucci, A. R. Qasem, F. Sgarzi, S. Spampinato, *J. Med. Chem.* 2002, **45**, 2571-2578. (d) B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* 2010, **39**, 1656-1691. (e) S. Abele, K. Vögtli, D. Seebach, *Helv. Chim. Acta* 1999, **82**, 1539-1558.

(4) (a) A. Faulkner, J. S. Scott, J. F. Bower, *J. Am. Chem. Soc.* 2015, **137**, 7224-7230. (b) C. Chen, L. Hou, M. Cheng, J. Su, X. Tong, *Angew. Chem. Int. Ed.* 2015, **54**, 3092-3096. (c) H. Su, W. Li, Z. Xuan, W. Yu, *Adv. Synth. Catal.* 2015, **357**, 64-70. (d) Y. Wang, J. Ding, J. Zhao, W. Sun, C. Lian, C. Chen, B. Zhu, *Org. Chem. Front.* 2019, **6**, 2240-2244. (e) K. Guo, H. Zhang, S. Cao, C. Gu, H. Zhou, J. Li, Y. Zhu, *Org. Lett.* 2018, **20**, 2261-2264. (f) L. Wang, C. Wang, *Org. Chem. Front.* 2018, **5**, 3476-3482. (g) H. B. Yang, N. Selander, *Chem. Eur. J.* 2017, **23**, 1779-1783. (h) C. Chen, Y. Bao, J. Zhao, B. Zhu, *Chem. Commun.* 2019, **55**, 14697-14700. (i) J. Davies, N. S. Sheikh, D. Leonori, *Angew. Chem. Int. Ed.* 2017, **56**, 13361-13365.

(5) C. Yamamoto, K. Takamatsu, K. Hirano, M. Miura, *J. Org. Chem.* 2016, **81**, 7675-7684.

(6) E. A. Wappes, S. C. Fosu, T. C. Chopko, D. A. Nagib, *Angew. Chem. Int. Ed.* 2016, **55**, 9974-9978.

(7) P. Mukherjee, R. A. Widenhoefer, *Org. Lett.* 2011, **13**, 1334-1337.

(8) (a) J.-B. Peng, F.-P. Wu, X.-F. Wu, *Chem. Rev.* 2019, **119**, 2090–2127. (b) Y. Bai, D. C. Davis, M. Dai, *J. Org. Chem.* 2017, **82**, 2319-2328. (c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* 2013, **113**, 1-35.

(9) (a) Z. Yin, Z. Zhang, Y. Zhang, P. H. Dixneuf, X.-F. Wu, *Chem. Commun.* 2019, **55**, 4655-4658. (b) Z. Yin, J. Rabeah, A. Brückner, X.-F. Wu, *ACS Catal.* 2018, **8**, 10926-10930. (c) Z. Yin, Z. Zhang, J.-F. Soulé, P. H. Dixneuf, X.-F. Wu, *J. Catal.* 2019, **372**, 272-276. (d) Z. Yin, J. Rabeah, A. Brückner, X.-F. Wu, *Org. Lett.* 2019, **21**, 1766-1769.

(10) Y. Zhang, Z. Yin, Wu, X.-F. *Org. Lett.* 2020, **22**, 1889–1893.

(11) (a) I. Ryu, *Chem. Soc. Rev.* 2001, **30**, 16-25. (b) S. Zhao, N. P. Mankad, *Catal. Sci. Technol.* 2019, **9**, 3603-3613.

(12) (a) T. Shimbayashi, D. Nakamoto, K. Okamoto, K. Ohe, *Org. Lett.* 2018, **20**, 3044-3048. (b) Y.-R. Gu, X.-H. Duan, L. Chen, Z.-Y. Ma, P. Gao, L.-N. Guo, *Org. Lett.* 2019, **21**, 917-920. (c) H. Jiang, X. An, K. Tong, T. Zheng, Y. Zhang, S. Yu, *Angew. Chem. Int. Ed.* 2015, **54**, 4055–4059. (d) H. Jiang, A. Studer, *Angew. Chem. Int. Ed.* 2017, **56**, 12273–12276.

(13) (a) J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Soc. Rev.* 2016, **45**, 2044-2056. (b) S. Z. Zard, *Chem. Soc. Rev.* 2008, **37**, 1603-1618.

(14) (a) A. R. Forrester, R. J. Napier, R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1* 1981, 984-987. (b) Y. Zhang, Z. Yin, X. F. Wu, *Adv. Synth. Catal.* 2019, **361**, 3223-3227.

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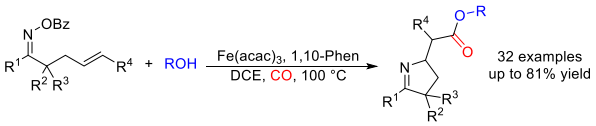

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