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Cascade Access to Carboline Carboxylates from Indolyl Ketoximes and Acrylates via Palladium-Catalyzed C–H Bond Alkenylation/Annulation

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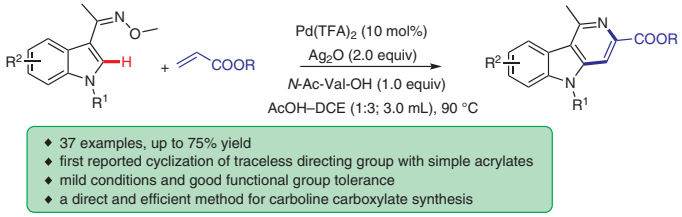

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Abstract An efficient palladium-catalyzed C–H bond alkenylation/annulation strategy to access carboline carboxylates from indolyl ketoximes and acrylates through C–C/C–N bond formation is reported. Indolyl ketoximes not only direct *ortho*-olefination with acrylates, but also undergo an intramolecular N–O bond cleavage/traceless annulation to construct carboline carboxylates straightforwardly in this concise method.

Key words carboline carboxylates, alkenylation, annulation, indolyl ketoximes, C–H activation, palladium catalysis

Carboline carboxylates are outstanding structural motifs in a variety of natural products, pharmaceuticals, and drug-like scaffolds (Figure 1).[1] Over the past decades, classical methods have been reported for the syntheses of these type of compounds, including the Pictet–Spengler reaction and the Bischler–Napieralski reaction.[2] However, these transformations usually require high temperatures or an excess of oxidants.[3] Therefore, the search for efficient and environmentally friendly methods for synthesizing carboline carboxylates has attracted much attention.

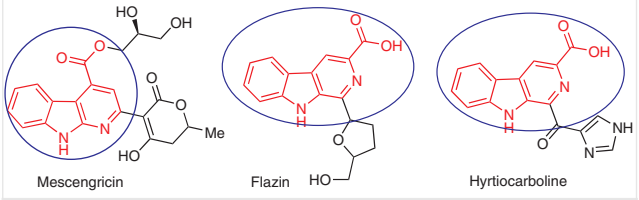

Figure 1 Some bioactive carbolines containing a carboxy group

In recent years, directing-group-assisted C–H bond functionalization with transition-metal catalysts has emerged as a powerful tool for generating C–C and C–X bonds with high site selectivity in atom- and step-economic modes.[4] In particular, a variety of directing groups such as ester,[5] amide,[6] carboxy,[7] pyridyl,[8] and others[9] have been successfully applied to *ortho*-olefination. In addition, the groups of Sanford,[10a,b,d] Che,[10c] Yu,[10e] and Shi[10f] have described oxime ethers that have excellent directing abilities to assist in C–H functionalizations. Given the remarkable properties of oxime ethers in the *ortho*-C(sp^2)–H alkenylations reported by Ellman,[11a] Sun,[11b] and Jeganmohan[11c] and their respective co-workers, an ingenious strategy has been developed involving the design of oxime ethers to act as traceless directing groups in building blocks for fused heterocycles.[12]

In 2019, we reported a benzothienyl methyloxime-directed tandem approach to benzothienopyridines from substituted styrenes through Pd catalysis.[13a] Later, a similar cascade formation of C–C and C–N bonds was reported for substituted carbolines (Scheme 1A).[13b] However, these methods were limited in that only intermolecular alkenylation products were isolated when acrylates were used. Here, we reported a cascade access to carboline carboxylates from indolyl ketoximes and acrylates, in which acrylates were successfully employed as the coupling partners to implement C–H bond olefination and annulation (Scheme 1B).

Initially, the *O*-methyl oxime **1a** and methyl acrylate (**2a**) were chosen as starting materials for the reaction (Table 1). To our delight, 31% of the alkenylation/cyclization product **3a** was obtained by using a Pd salt as the catalyst, a

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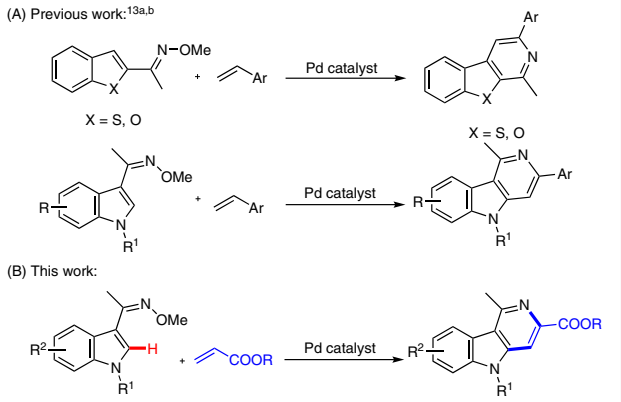


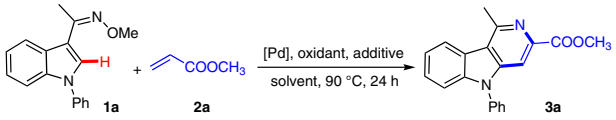
Scheme 1 Pd-catalyzed annulations of ketoximes with alkenes

Ag salt as the oxidant, an amino acid as the additive, and DCE as the solvent at 90 °C (Table 1, entry 1). Other solvents [1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), 1,4-dioxane, and AcOH] all gave unsatisfactory results (entries 2–4). When 1:3 AcOH–DCE was used as the solvent, a satisfactory yield was obtained (entry 5). AcOH not only causes C–H bond cleavage, but also plays an important role in the formation of the C–N bond, which is necessary for this annulation.[13a,14]

When other oxidants were tested, Ag_2O showed the best activity, giving the product **3a** in 57% yield (Table 1, entries 6–9). When the performance of various catalysts was examined, $Pd(TFA)_2$ was found to give the highest yield (entries 10–14). Further optimization was carried out to increase the yield of the product (entry 14). Amino acids have been reported to promote C–H activation,[13a] and, as expected, *N*-Ac-Val-OH showed a better reactivity than other additives (entries 15–20). The effect of an N_2 atmosphere was also examined (entry 21).

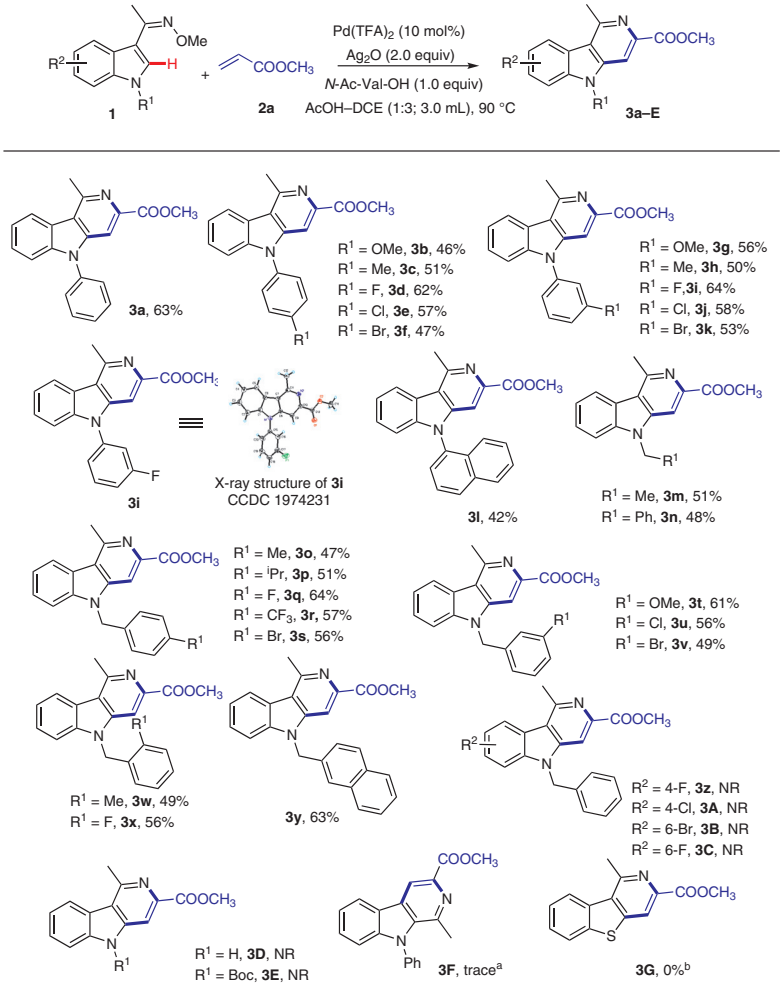
With the optimized conditions in hand, we examined the scope of various substituents on the reactants oximes **1** (Scheme 2). A variety of electron-donating groups (**3b**, **3c**, **3g**, and **3h**) or electron-withdrawing groups (**3d**, **3e**, **3f**, and **3i–k**) were all transformed into the corresponding carboline derivatives in moderate yields, generally accompanied by byproducts from intermolecular alkenylation. Notably, the *N*-(1-naphthyl) substrate also afforded the desired product **3l** in a good yield. It is worth mentioning that an *N*-ethyl-protected indolyl *O*-methyloxime also reacted well to deliver the cyclization product **3m** in 51% yield. Additionally, *N*-benzyl-protected substrates also underwent the reaction to provide the corresponding products **3n–x**. *N*-Benzyl substituents carrying a variety of functional groups (OMe, Me, *i*-Pr, F, Cl, Br, and CF_3) were all well tolerated, as was an *N*-(2-naphthylmethyl) group (**3y**). However, with F, Cl, and Br substituents on the benzene ring of the indole, no reaction occurred (**3z** and **3A–C**). We also tested the N-unprotected and *N*-Boc-protected *O*-methyl oxime indoles, but no products were obtained under the standard conditions (**3D** and **3E**). When a 2-acetylindole *O*-methyl oxime and a benzothieno *O*-methyl oxime reacted with methyl acrylate, excellent yields of the corresponding intermolecular alkenylation products **3F′** and **3G′** were obtained instead of the cycloaddition product **3F** and **3G**. It is possible that the Pd(0) species cannot insert into the oxime ether due to oxidative addition failure, which keeps the reaction in the intermolecular alkenylation stage.[13a]

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Oxidant	Additive	Yield[b] (%)
1[c]	$Pd(OAc)_2$	AgTFA	*N*-Ac-Val-OH	31
2[d]	$Pd(OAc)_2$	AgTFA	*N*-Ac-Val-OH	NR
3[e]	$Pd(OAc)_2$	AgTFA	*N*-Ac-Val-OH	NR
4[f]	$Pd(OAc)_2$	AgTFA	*N*-Ac-Val-OH	30
5	$Pd(OAc)_2$	AgTFA	*N*-Ac-Val-OH	47 (41[g], 21[h])
6	$Pd(OAc)_2$	AgOAc	*N*-Ac-Val-OH	49
7	$Pd(OAc)_2$	Ag_2CO_3	*N*-Ac-Val-OH	37
8	$Pd(OAc)_2$	Ag_2O	*N*-Ac-Val-OH	57
9	$Pd(TFA)_2$	Ag_3PO_4	*N*-Ac-Val-OH	32
10	$[Cp^*RhCl_2]_2$	Ag_2O	*N*-Ac-Val-OH	NR
11	$PdCl_2$	Ag_2O	*N*-Ac-Val-OH	39
12	$Pd(PPh_3)_2Cl_2$	Ag_2O	*N*-Ac-Val-OH	54
13	$Pd(MeCN)_2Cl_2$	Ag_2O	*N*-Ac-Val-OH	57
14	**$Pd(TFA)_2$**	**Ag_2O**	***N*-Ac-Val-OH**	**63** (54,[i] 60[j])
15	$Pd(TFA)_2$	Ag_2O	–	trace
16	$Pd(TFA)_2$	Ag_2O	*N*-Ac-Gly	42
17	$Pd(TFA)_2$	Ag_2O	glycine	trace
18	$Pd(TFA)_2$	Ag_2O	py	<10
19	$Pd(TFA)_2$	Ag_2O	$Cu(OAc)_2$	48
20	$Pd(TFA)_2$	Ag_2O	PivOH	37
21	$Pd(TFA)_2$	Ag_2O	*N*-Ac-Val-OH	46[k]

[a] Reaction conditions: **1a** (0.3 mmol), 2a (1.5 mmol), catalyst (10 mol %), oxidant (2.0 equiv), additive (1.0 equiv), 1:3 AcOH–DCE (1:3, 3.0 mL), 90 °C, 24 h.
[b] Isolated yield of **3a**; NR = no reaction.
[c] In DCE.
[d] In HFIP.
[e] In 1,4-dioxane.
[f] In AcOH.
[g] In 1:1 AcOH–DCE.
[h] In 1:3 AcOH–DCE.
[i] At 100 °C.
[j] At 110 °C.
[k] Under N_2.

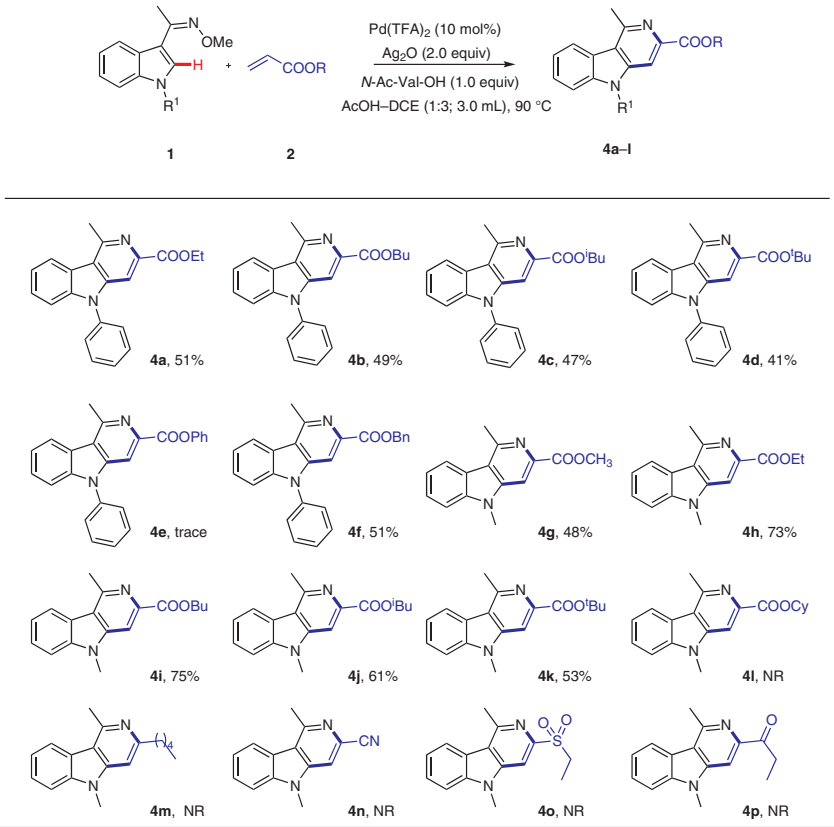


Scheme 2 Substrate scope of indole. *Reagents and conditions*: **1** (0.3 mmol), **2a** (1.5 mmol), $Pd(TFA)_2$ (10 mol%), Ag_2O (2.0 equiv), *N*-Ac-Val-OH (1.0 equiv), 1:3 AcOH–DCE (3.0 mL), 90 °C, 24 h. Isolated yields of **3** are reported (NR = no reaction). [a] The intermolecular alkenylation product **3F′** was obtained in 91% yield. [b] The intermolecular alkenylation product **3G′** was obtained in 95% yield.

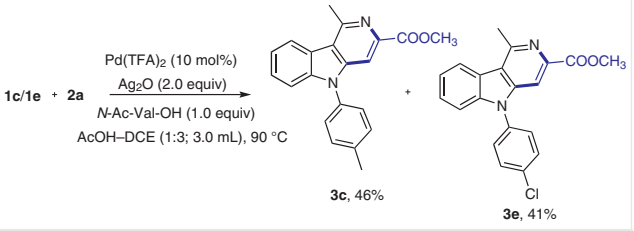
Next, we tested the substrate scope of the acrylate in the process (Scheme 3). When ethyl, butyl, isobutyl, *tert*-butyl, and benzyl acrylates were subjected to reaction with *O*-methyl oxime **1a**, the corresponding cyclization products **4a–f** were obtained in moderate yields. With phenyl acrylate as the reaction partner, disappointingly only a trace of the desired product **4e** was detected. The reactions of various acrylates with the methyl-protected indole *O*-methyloxime fortunately gave the desired annulation products **4g–k**. None of the desired product was detected when we used nonactivated alkenes such as cyclohexyl acrylate, hept-1-ene, or acrylonitrile (**4l–n**), possibly because Pd intermediates cannot interchange with these alkenes. Moreover, when ethyl vinyl sulfone and ethyl vinyl ketone were examined as reactants, disappointedly the desired products **4o** and **4p** were not obtained, possibly because of electronic effects on the alkenylation process.

Next, a series of control experiments were performed. First, an intermolecular competition experiment in which methyl acrylate (**2a**) was treated with substrates with an electron-rich (**1c**) and an electron-deficient (**1e**) substituent revealed that the latter was kinetically favored (Scheme 4). Furthermore, the scalability of the protocol was successfully tested by performing a gram-scale reaction (Scheme 5).

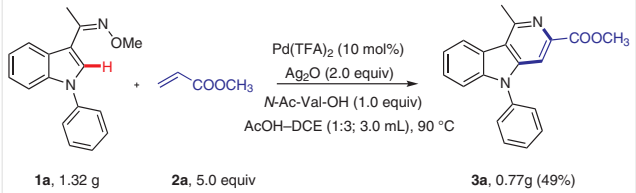
To obtain some further mechanistic insights, experiments with isotopically labeled solvents[15] and some control experiments were conducted (Scheme 6). A deuterium-incorporation study with AcOD showed that C–H activation is the first step and is reversible;[10,13,15] incorporation of deuterium in the methyl group of **3a** probably occurs after the first step of the reaction.[13] In addition, the 3-acetylindole oxime **1a** failed to react with either electron-rich methyl acrylate (**2m**) or with electron-deficient acrylonitrile (**2n**)



Scheme 3 Substrate scope of acrylate. *Reagents and conditions*: **1** (0.3 mmol), **2** (1.5 mmol), $Pd(TFA)_2$ (10 mol %), Ag_2O (2.0 equiv), *N*-Ac-Val-OH (1.0 equiv), 1:3 AcOH–DCE (3.0 mL), 90 °C, 24 h. Isolated yields of **4** are reported (NR = no reaction).



Scheme 4 Intermolecular competition experiment

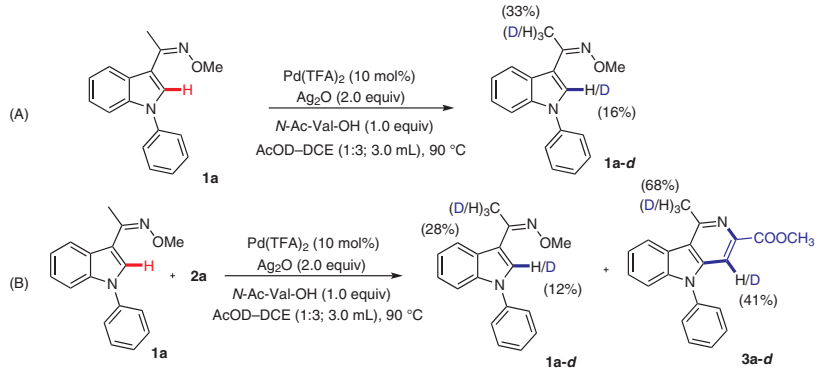


Scheme 5 Gram-scale reaction

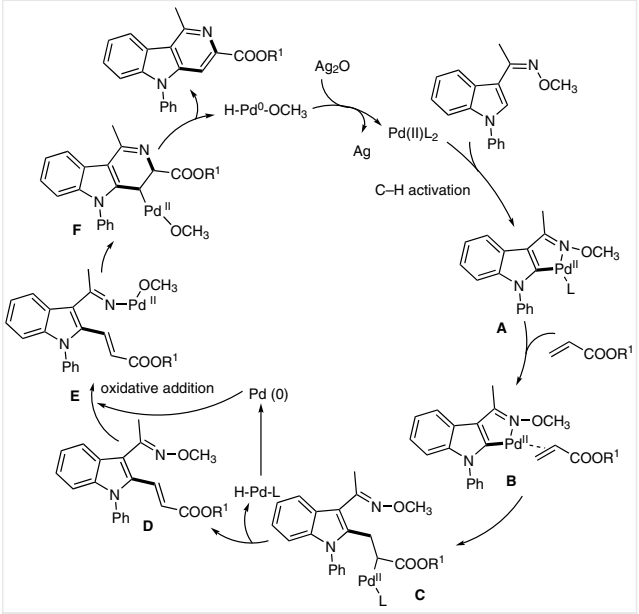
under the standard conditions, showing that appropriate electronegativity of the alkene is a key factor if it is to act as a coupling partner in the cyclization reaction.[13]

Based on these mechanistic studies and on documented reports,[11,13] a plausible mechanism for this reaction is proposed (Scheme 7). First, $Pd(TFA)_2$ coordinates with the substrate **1a** by C–H activation to form intermediate **A** reversibly, possibly through a concerted metalation–deprotonation pathway.[11b,13] The *endo*-cyclopalladated intermediate **A** then undergoes ligand exchange with the acrylate to afford intermediate **B**. Intermediate **D** and a Pd(0) species are then formed through a 1,2-migratory insertion, a β-hydride elimination, and a reductive elimination. Subsequently, oxidative addition leads to N–O bond cleavage and formation of the key alkenylpalladium(II) species **E**.[13,16] Finally, C–N bond formation and N–O bond cleavage provide intermediate **F**, which undergoes cyclization through β-hydride elimination.[17,18]

In summary, an efficient route has been developed for palladium(II)-catalyzed C–H activation/annulation of ketoximes with acrylates through C–C/C–N formation. This approach provides a direct, concise, and convenient route to a variety of carboline carboxylates that will be applied in exploring for potential drugs in the future.



Scheme 6 Deuterium-incorporation studies



Scheme 7 Plausible reaction mechanism

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707192.

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(17) CCDC 1974231 contains the supplementary crystallographic data for compound **3i**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(18) **Carboline Carboxylates 3: General Procedure**

A sealable glass tube was charged with a mixture of substrate **1** (0.3 mmol), methyl acrylate (**2a**; 1.5 mmol), $Pd(TFA)_2$ (10 mol %), Ag_2O (2.0 equiv), and *N*-Ac-Val-OH (1.0 equiv) in 1:3 AcOH–DCE (3.0 mL) and the mixture was stirred under air at 90 °C for 24 h. Upon completion of the reaction, the solution was concentrated in vacuo. H_2O (30 mL) and CH_2Cl_2 (15 mL) were added, and the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was dried ($MgSO_4$) and concentrated in vacuo to provide a crude product that was further purified by column chromatography [silica gel, PE–EtAc (10:1)].

Methyl 1-Methyl-5-phenyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylate (3a)

White solid; yield: 59.7 mg (84%); mp 191–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.0 Hz, 1 H), 8.07 (s, 1 H), 7.68 (t, *J* = 7.2 Hz, 2 H), 7.61–7.57 (m, 2 H), 7.57–7.47 (m, 4 H), 4.05 (s, 3 H), 3.34 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 153.6, 145.1, 142.5, 142.1, 135.9, 130.3 (2 C), 128.8, 127.6, 127.2 (2 C), 123.0, 121.9, 121.8, 120.3, 110.6, 106.2, 53.0, 24.1. HRMS (EI): *m/z* [M$^+$] calcd for $C_{20}H_{16}N_2O_2$: 316.1212; found: 316.1213.