



Hydrogen peroxide mediated formation of heteroaryl ethers from pyridotriazol-1-yloxy heterocycles and arylboronic acids

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ARTICLE INFO

Article history:

Received 6 July 2009

Revised 24 July 2009

Accepted 27 July 2009

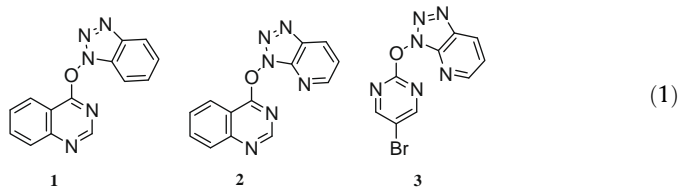
Available online 6 August 2009

ABSTRACT

Pyridotriazol-1-yloxy pyrimidine **3** reacts with arylboronic acids under palladium-free, Cs₂CO₃, (0.8%) H₂O₂, and DME conditions to produce heteroaryl ethers **4–16** in good yields comparable to the oxidative palladium-catalyzed reaction. The yields of aryl ethers **17–19** from quinazoline **2** with (0.8%) H₂O₂ were modest. Hydrogen peroxide is superior to dioxygen as an oxidant in these reactions.

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Recently, we have reported on the synthetic versatility of phosphonium-mediated S_NAr reactions of biologically important heterocycles^{1,2} using BOP reagents.^{3,4} Mechanistic studies regarding the nature of the intermediates in these reactions using ³¹P NMR and ESI MS techniques are consistent with a pathway involving stepwise formation of heterocyclic benzotriazol-yloxy adducts from the phosphonium intermediates.⁵ In this regard, benzotriazol-yloxy quinazoline **1** and other thienopyrimidine heterocycles readily reacted with various nucleophiles in S_NAr fashion.⁵ Moreover, since the benzotriazol-yloxy and pyridotriazol-1-yloxy (OPT) adducts are more stable than the corresponding phosphonium intermediates, further investigations of the reactions of **2** and **3** (Eq. 1) under oxidative palladium-catalyzed conditions (Pd(PPh₃)₄, O₂, Cs₂CO₃, and DME–H₂O) with arylboronic acids led to the unexpected formation of heteroaryl ethers.^{6,7} This transformation is synthetically valuable especially in cases where phenols are not readily available for S_NAr type reactions and is unique compared to the homocoupling reactions in metal-catalyzed reactions in that unsymmetrical ether compounds are obtained instead of biaryls.^{8,9}

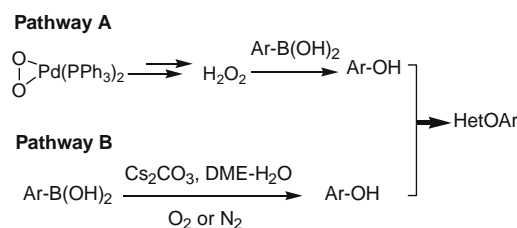


Mechanistic studies on the oxidative palladium-catalyzed reaction of **2** using labeled dioxygen (¹⁸O₂) led to the conclusion that the ether oxygen is derived from phenols which are generated from two sources: oxidative Pd catalyzed pathway A (H₂O₂ via

O₂) and a non-palladium-mediated pathway B involving Cs₂CO₃ and arylboronic acid (Scheme 1). While the contribution of each pathway to the formation of phenols and eventually heteroaryl ethers was not explored, the latter pathway was unexpected and does not seem to depend solely on dioxygen.

The roles of the Pd(0) catalyst and dioxygen in pathway A were conceived to provide a source of H₂O₂ in situ, which in turn forms phenols in situ. Assuming that quinazolines⁶ and pyrimidines⁷ OPT adducts react similarly in the oxidative palladium reaction, we explored further the transformation of OPT adducts **2** and **3** to heteroaryl ethers using arylboronic acids and (0.6–1%) H₂O₂ as an oxidant without Pd(0) catalyst. Conceptually, this seemed as an attractive strategy to probe further the synthetic utility of this transformation and its possible mechanistic implications. In this Letter, we report our results on the reaction of **2** and **3** with arylboronic acids mediated by H₂O₂ as an oxidant.

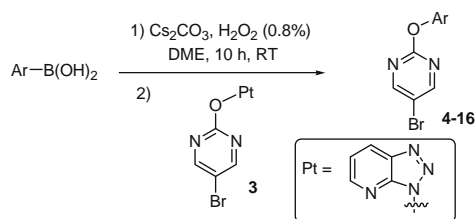
The reaction of arylboronic acids with pyrimidine **3** under Cs₂CO₃, (0.8%) H₂O₂, and DME conditions led to aryl ethers in variable yields (Table 1). Aryl ethers generated from arylboronic acids in entries 4, 6, and 11 are formed in substantially lower yields than those from the oxidative palladium-catalyzed reaction⁷ while aryl ether **10** was formed in higher yields under the palladium-free conditions. The isolated yields obtained with arylboronic acids in



Scheme 1.

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Table 1
Synthesis of aryl ethers **4–16** from **3**



Entry	Boronic acid	Yield ^{a,b} (%)
1		4 ; 58, 62
2		5 ; 82, 85
3		6 ; 25, 28
4		7 ; 56, 83
5		8 ; 75, 70
6		9 ; 19, 63
7		10 ; 61, 33
8		11 ; 53, 48
9		12 ; 17, 34
10		13 ; 84, 87
11		14 ; 34, 95
12		15 ; 41, 55
13		16 ; 23, 44

^a Based on isolated products, average of 2–3 experiments Cs₂CO₃, (0.8%) H₂O₂, and DME.

^b Pd(PPh₃)₄, O₂, Cs₂CO₃, and DME–H₂O).

entries 1, 2, 5, 8, 10, and 12 are comparable to those obtained by the oxidative palladium-catalyzed reaction employing the same arylboronic acids⁷ and attest to the synthetic potential of this

transformation. Although the yields for aryl ethers in entries 3, 9, and 13 are relatively low, they are however, comparable to those obtained by the oxidative palladium conditions.

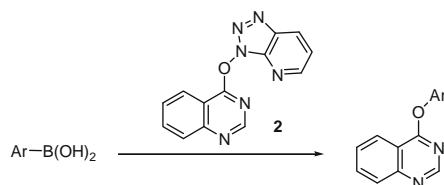
Therefore, in the case of pyrimidine **3** and in reference to the mechanistic proposal outlined in Scheme 1, the formation of aryl ethers under Cs₂CO₃, (0.8%) H₂O₂, and DME conditions in entries 1–3, 5, 7–10, 12, and 13 competes well with the oxidative palladium-catalyzed reaction.⁷ This finding suggests an attractive synthesis of heteroaryl ethers under palladium-free conditions.

Quinazoline **2** which was previously shown to furnish aryl ethers under Pd(0) conditions, led to the formation of aryl ethers **17–19** with 5-pyrimidinyl, *p*-methoxyphenyl, and phenylboronic acids, respectively under the new H₂O₂ conditions (Table 2). The lower yields of ethers **17–19** compared to those obtained by the oxidative palladium-catalyzed reaction suggest that the latter transformation⁶ is a superior method for forming quinazoline heteroaryl ethers compared to the palladium-free H₂O₂ conditions.

Having established a differential in reactivity between **2** and **3** under the palladium-free conditions, it became necessary to evaluate the extent of pathway B (Scheme 1) contributions in the oxidative palladium-catalyzed reaction. To compliment our earlier mechanistic studies,⁶ quinazoline **2** was reacted with 5-pyrimidinylboronic acid under Cs₂CO₃, ¹⁸O₂, and DME–H₂O conditions without the Pd(0) catalyst and the ratio of incorporation of ¹⁸O into the ether product **17** was monitored with time using ESI/MS techniques. After 24 h, the conversion to the ether product amounted to <10% with a ratio of ¹⁶O:¹⁸O being 44:56 (Scheme 2). The low conversion is also consistent with that obtained using dioxygen and suggests that pathway B is minor relative to pathway A in the oxidative palladium-catalyzed reaction. Similarly, the preparation of aryl ethers **4**, **7**, and **14** (Table 1 entries 1, 4, and 11) from **3** proceeds in low yields (10–27%) under Cs₂CO₃, O₂, and DME–H₂O conditions.

To account for differences between the palladium-free H₂O₂ conditions and oxidative palladium-catalyzed conditions,⁶ it would seem plausible to suggest that the choice of arylboronic acid plays a significant role in the formation of phenols from H₂O₂ as in the palladium-free conditions or pathway A in the oxidative palladium reaction⁶ since the hydrolysis of ArPdOOB(OH)₂(PPh₃)₂ produces

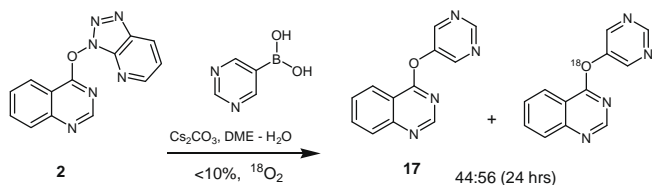
Table 2
Synthesis of aryl ethers from **2**



Entry	Boronic acid	Yield ^a (%)	Yield ^b (%)
1		17 ; 20	78
2		18 ; 34	66
3		19 ; 30	80

^a Based on isolated products, average of 2–3 experiments Cs₂CO₃, (0.8%) H₂O₂, and DME.

^b Pd(PPh₃)₄, O₂, Cs₂CO₃, and DME–H₂O).



Scheme 2.

H₂O₂ and ArPd(OH)(PPh₃)₂.^{6,10} Excess arylboronic acid can, however, be consumed in the palladium-catalyzed reaction by transmetalation of ArPd(OH)(PPh₃)₂ leading to Ar₂Pd(PPh₃)₂ and its reductive elimination to the homocoupling product Ar-Ar.¹⁰

Although the conversion of arylboronic acids to phenols has been previously reported to proceed with 30% H₂O₂¹¹ or other oxidants such as perborate,¹² hydroxylamine,¹³ and oxone,^{14,15} limitations of these methods have been reported.^{10,16,17} Experimentally, we aimed at using a low concentration of hydrogen peroxide (<1%) for comparative purposes with the oxidative palladium-catalyzed reaction^{5–7} since in this case higher concentrations were inhibitory to the formation of heteroaryl ethers.^{6,7} The experimental procedure adopted under the palladium-free conditions is a one-pot, two-step sequence involving oxidation of arylboronic acids with (0.8–1%) hydrogen peroxide followed by the addition of the OPT heterocycle **2** or **3**.

In conclusion, the reaction of arylboronic acids with OPT heterocycles **2** and **3** under Cs₂CO₃, (0.8%) H₂O₂, and DME conditions produces heteroaryl ethers in good synthetic yields and is superior to that involving Cs₂CO₃, O₂, and DME–H₂O conditions. Comparative studies between quinazoline **2** and pyrimidine **3** indicate that the palladium-free Cs₂CO₃, (0.8%) H₂O₂, and DME conditions produce heteroaryl ethers **4–16** in yields comparable to that of the palladium-catalyzed conditions (Pd(PPh₃)₄, O₂, Cs₂CO₃, and DME–H₂O) in the case of **3**. However, for quinazoline **2** the palladium-catalyzed process is more efficient.

This new transformation complements the direct S_NAr with phenols^{5,18,19} and competes well with the oxidative palladium-catalyzed reaction.^{6,7} The relative simplicity in eliminating palladium metal and dioxygen and employing H₂O₂ as an oxidant makes it an attractive consideration for the synthesis of heteroaryl ethers. This reaction strongly highlights on the complexity in understanding the reaction pathways in these oxidative transformations.²⁰

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.135.

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- 5-Bromo-2-phenoxy-pyrimidine (**4**): Phenyl boronic acid (50 mg, 0.41 mmol) and Cs₂CO₃ (443 mg, 1.36 mmol) were dissolved in DME (5 mL) at rt. Aqueous H₂O₂ (0.04 mL, 0.8%) was added to the reaction mixture and purged with O₂. The reaction mixture was stirred for 6 h. 3-(5-Bromo-pyrimidin-2-yloxy)-3H-[1,2,3] triazolo [4,5-b]pyridine (36 mg, 0.12 mmol) was then added at rt and the reaction mixture was stirred for a further 10 h. The crude reaction mixture was then directly purified by flash chromatography to afford a white solid (49 mg, 58%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.56 (s, 2H), 7.45 (m, 2H), 7.29 (m, 1H), HRMS (ES-MS) [(M+H)⁺]: for C₁₀H₇BrN₅O 250.9814, found 250.9817.
- 5-Bromo-2-(2-methoxyphenoxy)-pyrimidine (**5**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.54 (s, 2H), 7.17 (m, 2H), 7.03 (m, 2H), 3.75 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₁H₉BrN₂O₂ 280.9920, found 280.9918.
- 5-Bromo-2-(3-methoxyphenoxy)-pyrimidine (**6**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.57 (s, 2H), 7.33 (m, 1H), 6.83 (m, 3H), 3.81 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₁H₉BrN₂O₂ 280.9926, found 280.9919.
- 5-Bromo-2-(4-methoxyphenoxy)-pyrimidine (**7**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.56 (s, 2H), 7.12 (d, 2H, J = 9.3 Hz), 6.96 (d, 2H, J = 9.0 Hz), 3.82 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₁H₉BrN₂O₂ 280.9920, found 280.9919.
- 5-Bromo-2-(4-methylsulfanyl-phenoxy)-pyrimidine (**8**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.57 (s, 2H), 7.33 (d, 2H, J = 6.6 Hz), 7.13 (d, 1H, J = 6.9 Hz), 2.50 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₁H₉BrN₂OS 296.9692, found 296.9688.
- 2-(5-Bromo-pyrimidin-2-yloxy)-benzoic acid methyl ester (**9**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.54 (s, 2H), 8.08 (dd, 1H, J = 1.6 Hz, J = 7.8 Hz), 7.63 (dt, 1H, J = 1.5 Hz, J = 7.5 Hz), 7.37 (dt, 1H, J = 0.9 Hz, J = 7.8 Hz), 7.24 (dd, 1H, J = 0.9 Hz, J = 8.1 Hz), 3.72 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₂H₉BrN₂O₃ 308.9869, found 308.9871.
- 3-(5-Bromo-pyrimidin-2-yloxy)-benzoic acid methyl ester (**10**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.58 (s, 2H), 7.98 (m, 1H), 7.86 (t, 1H, J = 2.4 Hz), 7.53 (t, 1H, J = 7.8 Hz), 7.39 (m, 1H), 3.92 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₂H₉BrN₂O₃ 308.9869, found 308.9875.
- 4-(5-Bromo-pyrimidin-2-yloxy)-benzoic acid methyl ester (**11**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.59 (s, 2H), 8.14 (d, 2H, J = 9.2 Hz), 7.24 (d, 2H, J = 8.4 Hz), 3.93 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₂H₉BrN₂O₃ 308.9869, found 308.9870.
- 1-[2-(5-Bromo-pyrimidin-2-yloxy)-phenyl]-ethanone (**12**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.55 (s, 2H), 7.89 (dd, 1H, J = 1.8 Hz, J = 7.8 Hz), 7.60 (td, 1H, J = 1.8 Hz, J = 7.5 Hz), 7.38 (td, 1H, J = 0.9 Hz, J = 7.8 Hz), 7.23 (dd, 1H, J = 0.9 Hz, J = 7.5 Hz), 2.52 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₂H₉BrN₂O₂ 292.9920, found 292.9919.
- 1-[3-(5-Bromo-pyrimidin-2-yloxy)-phenyl]-ethanone (**13**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.58 (s, 2H), 7.55 (m, 1H), 7.34 (t, 1H, J = 7.8 Hz), 7.13 (m, 1H), 6.79 (s, 1H), 2.62 (s, 3H). HRMS (ES-MS) [(M+Na)⁺]: for C₁₂H₉BrN₂O₂ 314.9740, found 314.9735.
- 1-[4-(5-Bromo-pyrimidin-2-yloxy)-phenyl]-ethanone (**14**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.59 (s, 2H), 8.06 (d, 2H, J = 9.2 Hz), 7.29 (d, 2H, J = 8.8 Hz), 2.62 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₂H₉BrN₂O₂ 292.9919, found 292.9918.
- 5-Bromo-2-(pyrimidin-5-yloxy)-pyrimidine (**15**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 9.13 (s, 2H), 8.73 (s, 2H), 8.62 (s, 2H). HRMS (ESI-MS) [(M+H)⁺]: for C₈H₆BrN₄O 252.972, found 252.9719.
- 5-Bromo-2-(pyrimidin-5-yloxy)-pyrimidine (**16**): ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.91 (d, 2H, J = 5.1 Hz), 8.77 (s, 2H), 6.51 (d, 2H, J = 5.1 Hz). MS (ESI-MS) [(M+H)⁺]: for C₉H₆BrN₃O 252.06, found 252.06.

Aryl ethers **4**, **7**, **14** from **3**, Cs₂CO₃ and dioxygen in DME:

5-Bromo-2-phenoxypyrimidine (4): This compound was synthesized from 3-(5-bromo-pyrimidin-2-yloxy)-3H-[1,2,3] triazolo [4,5-*b*] pyridine (10 mg, 0.03 mmol), phenyl boronic acid (12 mg, 0.10 mmol), and Cs₂CO₃ (44 mg, 0.14 mmol) in DME (1 mL). The reaction mixture was purged with dioxygen and stirred at rt for 10 h. The crude reaction mixture was then directly purified by flash chromatography to afford a white solid (2 mg, 27%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.56 (s, 2H), 7.45 (m, 2H), 7.29 (m, 1H), 7.19 (d, 2H, *J* = 4.2 Hz). HRMS (ES-MS) [(M+H)⁺]: for C₁₀H₇BrN₂O 250.9814, found 250.9817.

5-Bromo-2-(4-methoxyphenoxy)-pyrimidine (7): This compound was synthesized from 3-(5-bromo-pyrimidin-2-yloxy)-3H-[1,2,3] triazolo [4,5-*b*] pyridine (50 mg, 0.17 mmol), 4-methoxy phenyl boronic acid (78 mg, 0.51 mmol), and Cs₂CO₃ (222 mg, 0.68 mmol) in DME (2.5 mL). The reaction mixture was purged with dioxygen and stirred at rt for 10 h and was purified by flash chromatography as a white solid (10 mg, 21%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.56 (s, 2H), 7.12 (d, 2H, *J* = 9.3 Hz), 6.96 (d, 2H, *J* = 9.0 Hz), 3.82 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₁H₉BrN₂O₂ 280.9920, found 280.9919.

1-[4-(5-Bromo-pyrimidin-2-yloxy)-phenyl]-ethanone (14): This compound was synthesized from 3-(5-bromo-pyrimidin-2-yloxy)-3H-[1,2,3] triazolo [4,5-*b*] pyridine (100 mg, 0.34 mmol), 4-acetyl phenyl boronic acid (220 mg, 1.34 mmol), and Cs₂CO₃ (556 mg, 1.74 mmol) in DME (10 mL). The reaction mixture was purged with dioxygen and stirred at rt for 10 h. The crude reaction mixture was then directly purified by flash chromatography to afford a white solid (10 mg, 10%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 8.59 (s, 2H), 8.06 (d, 2H, *J* = 9.2 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 2.62 (s, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₂H₉BrN₂O₂ 292.9919, found 292.9918.

Aryl ethers **17**, **18**, **19** from **2**, Cs₂CO₃ in DME and aq H₂O₂ (0.8%).

4-(Pyrimidin-5-yloxy)quinazoline (17): This compound was synthesized from 4-(3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)quinazoline (90 mg, 0.34 mmol), Pyrimidine boronic acid (186 mg, 1.50 mmol), and Cs₂CO₃ (332 mg, 1.02 mmol) in DME (3 mL) and aq H₂O₂ (0.02 mL, 0.8%) were added to the reaction mixture and stirred for 10 h. The crude reaction mixture was purified by flash chromatography as a white solid (15 mg, 20%). ¹H NMR (CDCl₃, 400 MHz): δ (ppm) 9.06 (s, 1H), 8.41 (s, 2H), 8.77 (s, 1H), 8.39–8.37 (m, 1H), 8.06–7.96 (m, 2H), 7.76–7.73 (m, 1H). HRMS (ES-MS) [(M+H)⁺]: for C₁₂H₈N₄O₁ 225.0771, found 225.0771.

4-(4-Methoxyphenoxy)quinazoline (18): This compound was synthesized from 4-(3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)quinazoline (**2**, 64 mg, 0.25 mmol), 4-methoxy phenyl boronic acid (100 mg, 0.82 mmol), and Cs₂CO₃ (346 mg, 1.06 mmol) in DME (10 mL) and aq. H₂O₂ (0.08 mL, 0.8%) and was purified by flash chromatography as a white solid (21 mg, 34%). ¹H NMR (CDCl₃, 400 MHz): δ (ppm) 8.77 (s, 1H), 8.39–8.73 (m, 1H), 8.01 (d, *J* = 2.5 Hz, 1H), 7.94–7.90 (m, 1H), 7.68–7.64 (m, 1H), 7.20–7.17 (m, 2H), 7.01–6.99 (m, 2H). HRMS (ES-MS) [(M+H)⁺]: for C₁₅H₁₂N₂O₂ 253.0971, found 253.0964.

4-Phenoxyquinazoline (19): This compound was synthesized according to substrate **7** from 4-(3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy) quinazoline (**32** mg, 0.12 mmol), phenylboronic acid (50 mg, 0.41 mmol), and Cs₂CO₃ (173 mg, 0.53 mmol) in DME (5 mL) and aq. H₂O₂ (0.04 mL, 0.8%) and was purified by flash chromatography as a white solid (8 mg, 30%). ¹H NMR (DMSO-*d*₆, 400 MHz): δ (ppm) 8.85 (s, 1H), 8.26 (d, *J* = 8.2 Hz, 1H), 8.05–8.00 (m, 2H), 7.80 (t, *J* = 6.3 Hz, 1H), 7.68–7.66 (m, 2H), 7.56–7.54 (m, 3H). HRMS (ES-MS) [(M+H)⁺]: for C₁₄H₁₀N₂O₁ 223.0861, found 223.0862.