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Regiodivergent Synthesis of Oxadiazocines *via* Dirhodium-Catalyzed Reactivity of Oxazolidines and α-Imino Carbenes

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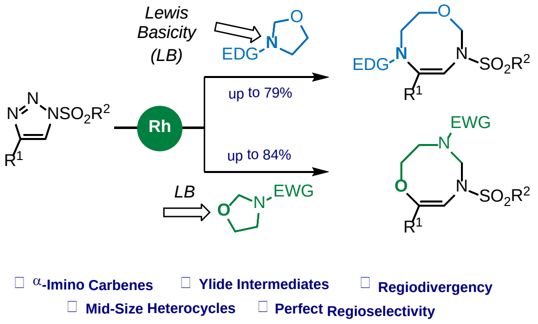
Dedicated to Prof. Masahiro Murakami on the occasion of his 65th birthday



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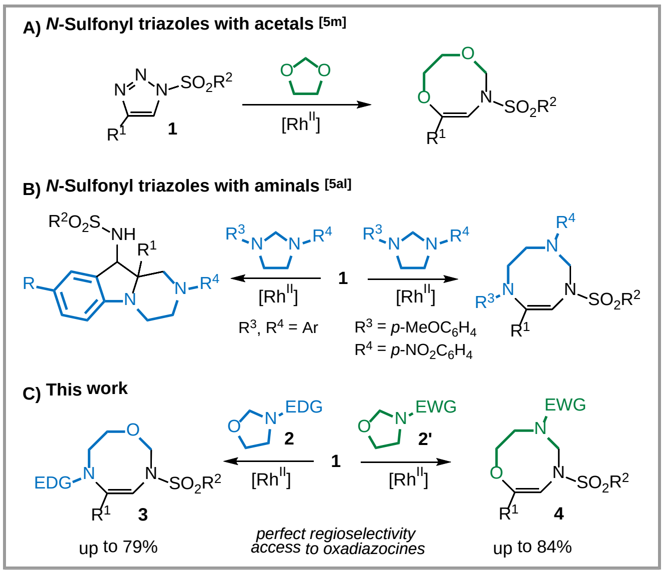
Abstract Using electron-rich or electron-poor *N*-substituted oxazolidines as substrates, selective formation of either ammonium or oxonium ylides is possible in the presence of α-imino carbenes. As such, treatment of 5-membered oxazolidine precursors with *N*-sulfonyl-*1,2,3*-triazoles under dirhodium catalysis (2 mol%) affords the regiodivergent synthesis of either 8-membered 1,3,6- or 1,4,6-oxadiazocines upon the initial N- or O-reactivity with the carbene.

Key words Carbenes; diazaoxa heterocycles; 8-Membered rings; Regiodivergency; Rh(II)-catalysis; Triazoles; Ylides

N-Sulfonyl-1,2,3-triazoles **1**, made readily through Cu(I)-catalyzed azide alkyne cycloadditions (CuAACs)[1] are prime building blocks in biological, medicinal and synthetic chemistry.[2] For the purpose of this study, under metal-catalyzed conditions, they decompose to afford α-imino carbenes.[3,4] These electrophilic unsaturated intermediates have received much attention, as many synthetically useful and original processes can be afforded, from migrations to ylide-forming reactions and subsequent transformations.[5] Of importance for the current study, α-imino carbenes react equally well with oxygen[5n] and nitrogen[5ad] atoms to afford the corresponding oxonium or ammonium ylide intermediates. A large panel of reactions is then afforded by these processes occurring at single reactive sites. With substrates or functional groups containing both heteroatoms, competition between the two types of *Lewis*-bases can then formally occur leading possibly to mixtures of products.[5a] Herein, in a new development, the intermolecular reactivity of *N*-sulfonyl-1,2,3-triazoles **1** with oxazolidines **2** is reported (Scheme 1C). Under dirhodium catalysis (2 mol%), either 1,3,6-oxadiazocines **3** or 1,4,6-oxadiazocines **4** are afforded depending on the substitution of the nitrogen-atom (yields up to 84%). Mechanistically, after the initial formation of α-imino carbenes, regiodivergent addition to oxazolidines of type **2** or **2'** occurs on either the N- or O-atoms to form the subsequent ammonium or oxonium ylide intermediates. Then, ring opening and trapping of the resulting iminium or oxycarbenium ions generates a fully divergent formation of 8-membered ring oxadiazocines **3** or **4** with regioisomeric ratios (r.r.) above 25:1.

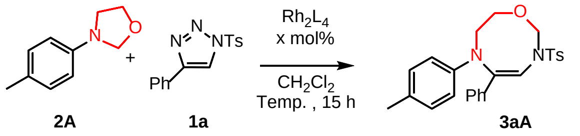


Scheme 1 Reactivity of the *N*-Sulfonyl-1,2,3-triazoles **1** with activated 5-membered heterocycles.

Previously, our group has shown that 5-membered dioxolanes and imidazolidines react readily with α-imino carbenes to yield the corresponding ylides and subsequent products (Schemes 1A and 1B). While reactions with dioxolanes generate 8-membered dioxazocines exclusively (Scheme 1A),[5m] treatment of imidazolidines leads predominantly to [1,2]-Stevens and further Friedel-Crafts pathways to yield fused indolines piperazines (Scheme 1B, left).[5al] Only with certain unsymmetrical imidazolidines, 8-membered ring formation of hexahydro-1,3,6-

triazocines occurs nevertheless (Scheme 1B, right). With these precedents in mind, we wondered what would happen with mixed oxazolidines and whether it would be possible to control the reactivity of α-imino carbene intermediates toward either the *Lewis* basic (LB) oxygen or nitrogen atoms.

Table 1 Preliminary experiments with oxazolidine 2A



Entry	Rh_2L_4	X mol%	T (°C)	Yield [a]
1	$Rh_2(Oct)_4$	3	80	49
2	$Rh_2(TFA)_4$	3	80	0
3	Rh_2(*S*-PTTL)$_4$	3	80	0
4	Rh_2(*S*-TCPTTL)$_4$	3	80	56
5	Rh_2(*R*-DOSP)$_4$	3	80	76
6	$Rh_2(OPiv)_4$	3	80	81
7	$Rh_2(OPiv)_4$	2	80	81
8	$Rh_2(OPiv)_4$	2	60	80
9	$Rh_2(OPiv)_4$	2	40	0

[a] NMR yields (^1H, 400 MHz) calculated using 1,3,5-trimethoxybenzene as an internal standard.

Preliminary experiments were performed with *N*-Tosyl-1,2,3 triazole **1a** (1.5 equiv) and *N*-tolyl oxazolidine **2A** (0.1 mmol, 1.0 equiv) as reagent and substrate; the results are reported in Table 1 (entries 1-9). Using $Rh_2(Oct)_4$ as catalyst (3 mol%) in CH_2Cl_2 at 80 °C,[5a] clean formation of predominant product **3aA** was observed (49% NMR yield, entry 1); the regiochemistry of the oxadiazocine being determined and discussed later (*vide infra*). Several dirhodium catalysts and different reaction conditions were then utilized (Figure 1 and Table S1 in addition). The most effective were Rh_2(*R*-DOSP)$_4$ and $Rh_2(OPiv)_4$ affording **3aA** in 76% and 81% yields respectively; the later catalyst was then selected. Decreasing temperature to 60 °C and catalyst loading to 2 mol% led to similar results and the milder/economical conditions were retained for the remainder of the study (entry 8).

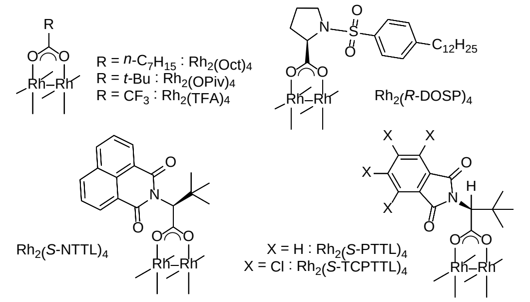


Figure 1 Dirhodium catalysts

Further temperature reduction to 40 °C led to a complete lack of reactivity (entry 9). Quantitative complexation between the *Lewis* acidic dirhodium complex and the LB oxazolidine **2** probably happens, rendering the catalyst ineffective. At 40 °C, the moderate temperature prohibits then the dissociation of the *Lewis* acid-base adduct, a step that is necessary for the decomposition of **1a**.[6]

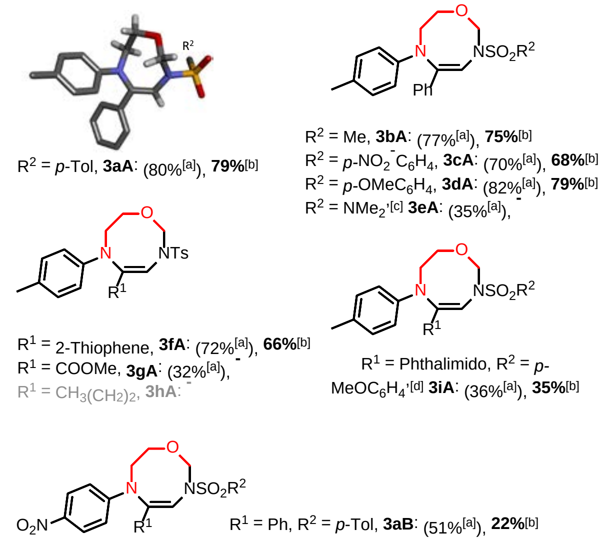
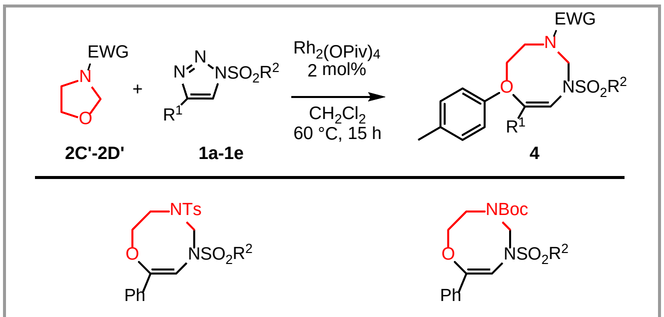


Figure 2 Formation of 1,3,6 oxadiazocine regioisomers **3**. [a] ^1H-NMR yield using 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yields. [c] Reaction performed at 100 °C during 72 h. [d] Reaction performed without metal catalyst.

With the optimized conditions in hand, triazoles **1b** to **1d** were reacted with *p*-tolyl oxazolidine **2A** to afford targeted products **3bA** to **3dA** in moderate to good isolated yields (68-79%), quite independent on the nature of the N-sulfonyl protecting group. With dimethylsulfamoyl **1e**,[7] the decomposition was sluggish and compound **3eA** was observed in the crude reaction mixture with a low yield (35% ^1H NMR); clean isolation of **3eA** could not be achieved unfortunately. While the phenyl group of **1a** could be substituted by thiophene (**1f**) or methyl ester (**1g**) residues to afford the corresponding oxadiazocines **3fA** and **3gA** in the crude reaction mixtures (72% and 32% NMR yields), only compound **3fA** could be isolated cleanly (66% yield). n-Propyl substituted triazole **1h** was also utilized,[8] a reagent providing often products with lower efficiency that aryl substituted analogs; formation of the corresponding **3hA** could not be evidenced in this case. With Davies' *N*-sulfonyl-4-phthalimido triazole **1i**,[9] product **3iA** was formed under thermal activation, albeit in only 35% yield.

At this stage, care was taken to demonstrate the regioselectivity of the oxadiazocine formation. In fact, two outcome were possible as oxazolidine of type **2** can be viewed as bifunctional reagents possessing both O- and N-atoms susceptible to compete for electrophilic carbene intermediates. In our hands and others', nitrogen atoms present often a higher nucleophilicity leading to a preferred formation of the ammonium ylides.[5a, 5ag] Also, *N*-aryl protected nitrogen atoms react readily with electrophilic carbenes to generate products of 1,2-Stevens rearrangement;[10] the aryl moiety being usually an electron-rich substituent. It was thus likely that an ammonium ylide formation would occur predominantly with substrate **2A** and lead to 1,3,6-oxadiazocines **3** over its 1,4,6-regioisomer (*vide infra*, Figure 3 and Scheme 2).

As mentioned earlier, this preferred regiochemistry could be established unambiguously by X-ray structural analysis of **3aA** (Figure 2). ^{13}C NMR spectroscopic analysis of compounds **3aA**, **3bA**, **3cA**, **3dA, 3iA** and **3aB** ($CDCl_3$, 126 MHz) further indicated a well-conserved chemical shift value of δ +75.8 ± 0.4 ppm for methylene groups positioned between the N and O atoms (carbinolamine center). Of interest, compound **3aB** (Figure 2) made in 22% isolated yield from oxazolidine **2B** carrying a *p*-nitrophenyl residue, presents also an analogous δ value (+75.7) for this CH_2 group. This is an excellent indication that compound **3aB** also presents a 1,3,6-oxadiazocine scaffold despite the presence of NO_2 on the N-aryl group. Clearly, this substituent is sufficiently electron-withdrawing to reduce the nucleophilicity of the N-atom,[11] but not enough to provoke a shift toward the formation of an oxonium ylide intermediate instead.



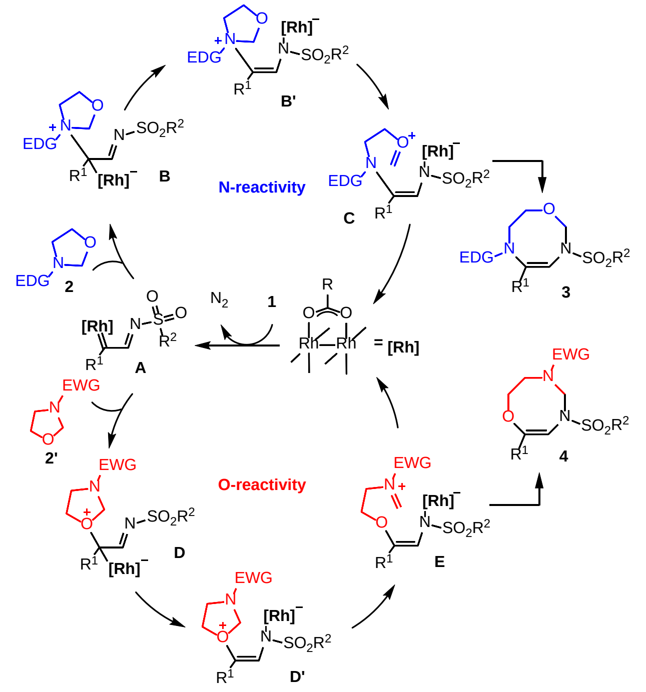
R^2 = Tol[c], **4aC'**: (94%[a]), **70%**[b]
R^2 = Me[c], **4bC'**: (94%[a]), **65%**[b]
R^2 = *p*-$NO_2C_6H_4$[c], **4cC'**: (99%[a]), **40%**[b]
R^2 = *p*-$OMeC_6H_4$[c], **4dC'**: (87%[a])
R^2 = NMe_2[c,d], **4eC'**: (14%[a])

R^2 = Tol, **4aD'**: **84%**[b]
R^2 = *p*-$NO_2C_6H_4$, **4cD'**: **79%**[b]

Figure 3 Formation of 1,4,6 oxadiazocine regioisomers **4**. [a] ^1H-NMR yield using 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yields. [c] After 6h, 1.5 equiv of triazoles **1** was added. [d] Reaction performed at 100 °C during 72 h.

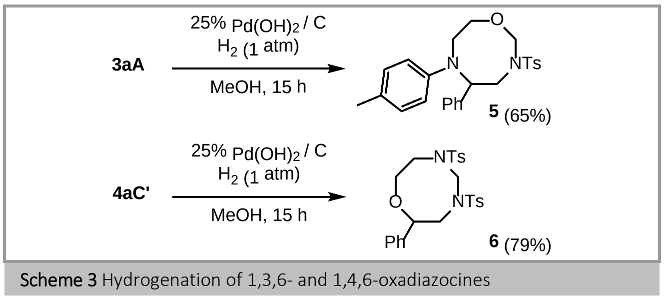
With the goal of achieving exclusive formation of the O-ylide, it was then clear that stronger electron-withdrawing groups (EWGs) were needed on the N-atom, to shield the nitrogen reactivity. Based on previous results with morpholines,[5ag] oxazolidine of type **2'**carrying either tosylate or carbamate (BOC) EWGs were selected and prepared. Validation of this approach was immediate in the reaction of *N*-Tosyl oxazolidine **2C'** with triazoles **1a** to **1d** to afford 1,4,6-oxadiazocines **4aC'** to **4dC'** in effective yields (87-99%, NMR, Figure 3). In the *N*-tosyl series, by-products of triazole decomposition were found to co-elute on column or thin-layer chromatography with targeted derivatives **4**. Clean isolation required then additional purification by either trituration or recrystallization reducing consequently the isolated yields (40-70%). This issue was not observed with *N*-Boc oxazolidine **2D'**, which afforded 1,4,6-oxadiazocines **4aD'** and **4cD'** in good isolated yields (79-84%). Of note, for compounds **4** carrying a Boc protecting group, regiochemistry could be readily determined by HMBC (Heteronuclear Multiple Bond Correlation) NMR experiments. In fact, for **4aD'** and **4cD'**, ^3J coupling can be observed between the protons of the aminal CH_2 group and the carboxyle carbon of the carbamate (N**C**(O)O^{t}Bu), which is only possible with a 1,4,6-oxadiazocine scaffold.

To rationalize the above divergence toward either 1,3,6- or 1,4,6-oxadiazocine products, a mechanistic rationale can be proposed; some of the steps being inspired from previous theoretical studies of the group.[5al] From complex **A**, C—N bond formation occurs between the carbene complex and oxazolidines **2** carrying aryl substituents, achieving the nitrogen ylide intermediate **B** (blue cycle). Most likely, the system rapidly evolves to **B'** by switching the Rh catalyst from the C to the N atom of the former α-imino carbene. In this disposition, aminal opening occurs leading to the oxycarbenium intermediate **C** that ought to be quite stable compared to the initial reactants.[5al] At this stage, intermediate **C** evolves exclusively towards N-cyclizations and interesting mid-size 8-membered heterocycles of type **3**; C-cyclization towards 1,4-morpholine adducts being totally absent in this study. When oxazolidines **2'** containing electron-withdrawing groups are used, C—O bond formation occurs with the carbene complex instead (red cycle) and leading to oxygen ylide intermediate **D**. Subsequent steps then follow an analogous pathway as detailed for the N-series via isomerized **D'**, ring-opened iminium **E** and finally 1,4,6-oxadiazocine **4** upon N-cyclization.



Scheme 2 Mechanism proposal

With heterocycles **3aA** and **4aC'** in hand, hydrogenation could be further achieved by addition of H_2 (1 atm) under $Pd(OH)_2$ over charcoal (Pearlman's catalyst) to afford 8-membered ring derivatives **5** and **6** in 65% and 79% yields respectively (Scheme 3); the carbinolamine or aminal groups remaining intact during H_2 addition. Not surprisingly, these saturated compounds presented a much higher shelf-life stability than the oxadiazocine precursors.



Scheme 3 Hydrogenation of 1,3,6- and 1,4,6-oxadiazocines

In summary, novel 1,3,6-oxadiazocine **3** and 1,4,6-oxadiazocine **4** were prepared in a single step from *N*-sulfonyl triazoles **1** and oxazolidines **2**. Under dirhodium catalysis, α-imino carbenes were generated and led to the formation of either ammonium or oxonium ylide intermediates, depending upon the substituent on the N-atom. Then, after subsequent ring openings of the activated carbinolamine or aminal functional groups, intramolecular ring closures afforded 8-membered derivatives **3** and **4** exclusively.[12] Mechanistically, this regio-divergence could be engineered by the "simple" choice of aryls group or EWGs (Ts, Boc) on the nitrogen. Finally, with **3** and **4** in hand, saturated 1,3,6- **5** and 1,4,6-oxadiazocane **6** were prepared efficiently upon hydrogenation. This methodology could open the door to the preparation of derivatives of type **7** and **8** that are potential antimicrobial agents or HIV integrase inhibitors (Figure 4).[13]

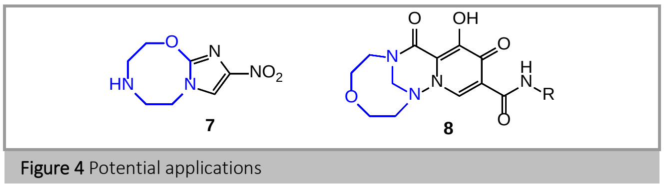


Figure 4 Potential applications

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Supporting Information

YES (this text will be updated with links prior to publication). CCDC 2241633 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Primary Data

The dataset for this article can be found at the following DOI: 10.26037/yareta:3cndx4brorddfaq4rc3oq2ggke. It will be preserved for 10 years

Conflict of Interest

The authors declare no conflict of interest.

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(6) This aspect was probed later in the manuscript with the reactivity of **1a** with oxazolidine **2C'** carrying a tosyl EWG in place of the *p*-tolyl moiety of **2A**. In the presence of this protected and thus less-*Lewis* basic N-atom, dirhodium catalysis could occur at 40 °C only to afford **4aC'** in 93% NMR yield.

(7) Triazole **1e** has been rarely used for α-imino carbene generation, and this exclusively in the context of Tröger base chemistry. See reference 5aa.

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(11) Contrary to the reactions with **2A** that present excellent conversions, crude mixture analysis indicated a large proportion of unreacted starting **2B** with a ~3:1 ratio between **3aB** and **2B**. See the supporting information.

(12) **General Procedure for ring expansion**
In a screw-cap vial containing oxazolidine **2A** (0.2 mmol, 1 equiv) and *N*-sulfonyl-1,2,3-triazole **1a** (0.3 mmol, 1.5 equiv), $Rh_2(OPiv)_4$ (0.004 mmol, 0.02 equiv) in CH_2Cl_2 (0.8 mL) were added. The reaction mixture is stirred during 15 h at 60 °C. The solvent was removed under reduced pressure and the crude residue was purified on chromatography column over SiO_2 (pentane/Et2O, 9:1 to 8:2). R_f = 0.24 (SiO_2, Pentane/Et_2O (8:2) mp 165–167 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm = 2.15 (s, 3H, -CH_3-), 2.43 (s, 3H, -CH_3-), 3.38-3.50 (m, 2H, -CH_2-), 3.66-3.78 (m, 2H, -CH_2-), 5.14 (s, 2H, -CH_2-), 6.46 (d, *J* = 8.5 Hz, 2H, -CH- aromatic), 6.74 (s, 1H, -CH vinylic), 6.89 (d, *J* = 8.2 Hz, 2H, -CH- aromatic), 7.14-7.25 (m, 2H, -CH aromatic), 7.26-7.32 (m, 3H, -CH aromatic), 7.81 (d, *J* = 8.3 Hz, 2H, -CH- aromatic) ; ^{13}C NMR (126 MHz, $CDCl_3$): δ/ppm = 20.5 (-CH_3-), 21.7 (-CH_3-), 52.1 (-CH_2-), 64.7 (-CH_2-) 75.8 (-CH_2-), 117.4 (2 -CH- aromatic), 117.6 (-CH- aromatic), 126.4 (2 -CH- aromatic), 127.6 (-CH- vinyl), 127.9 (CH aromatic), 128.5 (2 -CH- aromatic), 128.6 (C vinyl), 129.6 (2 -CH- aromatic), 130 (2 -CH- aromatic), 131.8 (C aromatic), 137 (C aromatic), 138.1 (C aromatic), 141.2 (C aromatic), 143.9 (C aromatic). IR (neat): $\tilde{\nu}$/cm^{-1} 3851, 3067, 2862, 1592, 1575, 1510, 1444, 1389, 1350, 1300, 1257, 1156, 1128,1097, 1013, 966, 932, 912, 887, 837, 800, 762, 694, 671, 636, 604, 567. HRMS (ESI): *m/z* calcd for $C_{25}H_{26}N_2O_4S^+$: 451.1687; found: 451.1681 [M+H]$^+$.

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