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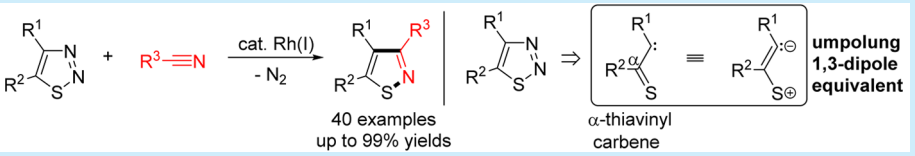
Synthesis of Isothiazole via the Rhodium-Catalyzed Transannulation of 1,2,3-Thiadiazoles with Nitriles

Boram Seo, Ya Gob Kim, and Phil Ho Lee*

Department of Chemistry, Kangwon National University, Chuncheon 24341, Republic of Korea

Supporting Information

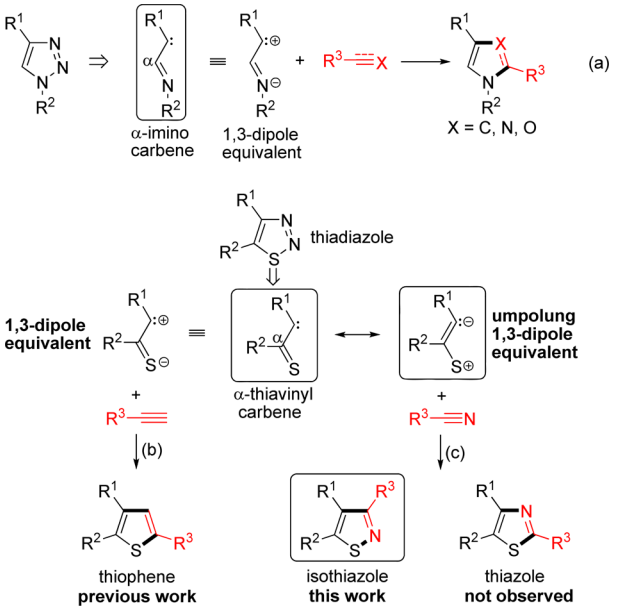


ABSTRACT: A synthetic method for obtaining a wide variety of isothiazoles by the Rh-catalyzed transannulation of 1,2,3-thiadiazoles with alkyl, aryl, and heteroaryl nitriles, which proceeds via an α-thiavinyl Rh-carbenoid intermediate, was developed. The results suggest that during its reaction with nitriles, the α-thiavinyl carbene acts as an umpolung 1,3-dipole equivalent, in contrast to its behavior during its reaction with alkynes. The developed method was successfully employed to synthesize pentaoligomeric arylene compounds consisting of three benzene and two isothiazole rings.

Because isothiazoles are valuable structural motifs found in many natural products, pharmaceutical compounds, and functional materials,[1] streamlined methods for their synthesis from readily available compounds must be developed.[2] Recently, *N*-sulfonyl-1,2,3-triazoles were easily prepared from 1-alkynes and *N*-sulfonyl azides and employed as convenient α-imino carbene precursors.[3] This study demonstrated that the α-imino carbene acts as a 1,3-dipole equivalent in transannulation reactions with unsaturated compounds. Thus, the transannulation of *N*-sulfonyl-1,2,3-triazoles has become a valuable approach for synthesizing a wide variety of five-membered heterocycles (Scheme 1a).[4] More recently, the Rh-catalyzed transannulation of 1,2,3-thiadiazoles with alkynes was reported to give thiophenes with high regioselectivity via an α-thiavinyl carbene (Scheme 1b).[5] These results indicate that the carbene carbon in the generated complex is electrophilic and the α-thiavinyl sulfur is nucleophilic. Accordingly, it was hypothesized that a Rh catalyst could be used in the transannulation of thiadiazoles with nitriles to obtain thiazoles. However, no thiazoles were observed, and isothiazoles were unexpectedly produced instead, indicating that the carbene carbon is nucleophilic and the α-thiavinyl sulfur is electrophilic. These results suggest that the α-thiavinyl carbene acts as an umpolung 1,3-dipole equivalent when reacting with a nitrile, in contrast to its reaction with an alkyne. Herein, we report for the first time new 1,3-dipole equivalents generated from thiadiazoles in the presence of a Rh catalyst and a method for synthesizing a wide variety of isothiazoles by the Rh-catalyzed transannulation of 1,2,3-thiadiazoles with alkyl, aryl, and heteroaryl nitriles via an α-thiavinyl Rh-carbenoid intermediate (Scheme 1c).

Initially, the transition metal-catalyzed transannulation of ethyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate (**1a**) with benzonitrile (**2a**) was examined (Table 1). When **1a** was reacted with **2a** in the presence of $[Ir(COD)Cl]_2$ (2 mol %) and DPPF (5 mol %) in chlorobenzene at 130 °C for 1 h, the transannulation

Scheme 1. 1,3-Dipole Equivalents Generated from Triazoles and Thiadiazoles



product was not detected (entry 1). $Rh_2(esp)_2$ was also unable to catalyze the transannulation reaction (entry 2). However, $Rh(PPh_3)_3Cl$ and the $[Rh(COD)Cl]_2$ (2 mol %) and DPPF (5 mol %) system gave the transannulation product in 66% (entry 3) and 80% (entry 4) yields, respectively. Lower yields were achieved with the Ph_3P, DPPE, XantPhos, and DPEPhos ligands than with DPPF (entries 5−8). The highest trans-

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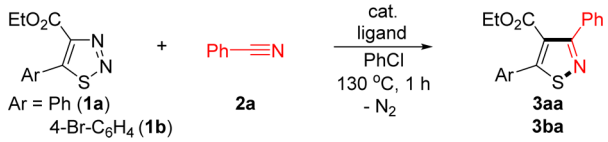
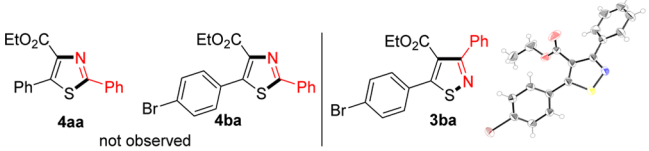
Table 1. Reaction Optimization[a]



entry	1	cat. (mol %)	ligand (mol %)		yield[b] (%)
1	**1a**	$[Ir(COD)Cl]_2$ (2)	DPPF (5)		0
2	**1a**	$Rh_2(esp)_2$ (2)	DPPF (5)		0
3	**1a**	$Rh(PPh_3)_3Cl$ (2)	DPPF (5)	**3aa**	66
4	**1a**	$[Rh(COD)Cl]_2$ (2)	DPPF (5)	**3aa**	80
5	**1a**	$[Rh(COD)Cl]_2$ (2)	PPh_3 (10)		0
6	**1a**	$[Rh(COD)Cl]_2$ (2)	DPPE (5)		0
7	**1a**	$[Rh(COD)Cl]_2$ (2)	XantPhos (5)		0
8	**1a**	$[Rh(COD)Cl]_2$ (2)	DPEPhos (5)	**3aa**	14
9	**1a**	$[Rh(COD)Cl]_2$ (5)	DPPF (12)	**3aa**	99 (99)[c]
10	**1b**	$[Rh(COD)Cl]_2$ (5)	DPPF (12)	**3ba**	90 (89)[c]

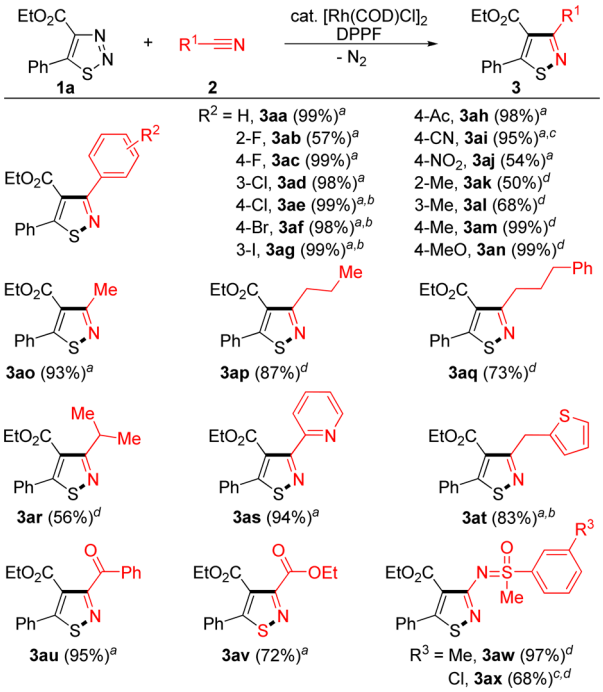
[a]Reaction conditions: **1** (0.2 mmol), **2a** (2 mmol), the catalyst (2−5 mol %) and the ligand (5−12 mol %) were reacted at 130 °C for 1 h in chlorobenzene under N_2. [b]NMR yield using CH_2Br_2 as an internal standard. [c]Isolated yields.



annulation product yield, which was quantitative, was obtained with $[Rh(COD)Cl]_2$ (5 mol %) and DPPF (12 mol %) in chlorobenzene at 130 °C for 1 h (entry 9). The product was initially expected to be the thiazole **4aa**. However, after **1b** was reacted with **2a** in the presence of $[Rh(COD)Cl]_2$ (5 mol %) and DPPF (12 mol %), X-ray crystallography revealed that the product was the isothiazole **3ba** (89%). The catalyst, solvent, and stoichiometry of the reaction of **1a** with **2a** were optimized as shown in the Supporting Information.

Next, ethyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate (**1a**) was reacted with several aromatic and aliphatic nitriles (**2**) to demonstrate the scope and efficiency of this Rh-catalyzed transannulation reaction (Scheme 2). Although 2-fluorobenzonitrile (**2b**) was transannulated to **3ab** in only 57% yield due to steric hindrance, 4-fluorobenzonitrile (**2c**) was smoothly converted to the corresponding isothiazole (**3ac**) in quantitative yield. Transannulation with 3- and 4-chlorobenzonitriles (**2d** and **2e**, respectively) was also possible, leading to the corresponding isothiazoles (**3ad** and **3ae**, respectively) in excellent yields. Cyclization with 4-bromobenzonitrile (**2f**) and 3-iodobenzonitrile (**2g**) gave the isothiazoles **3af** and **3ag**, respectively, in quantitative yields. Transannulation with a benzonitrile (**2h**) bearing a labile acetyl group proceeded smoothly to afford **3ah** in 98% yield. The monoisothiazole **3ai** was selectively obtained in 95% yield from 1,4-dicyanobenzene (**2i**) under the optimized reaction conditions. The benzonitrile (**2j**) with the strongly electron-withdrawing 4-nitro group gave the desired product **3aj** in moderate yield. However, because benzonitriles with electron-donating groups, such as methyl and methoxy groups, are less reactive, the reaction conditions were slightly modified. Although 3-methylbenzonitrile (**2l**) reacted with **1a** to produce the desired isothiazole **3al** in 54% yield under the optimized conditions, modifying the reaction conditions (adding the Rh catalyst (2.5 mol %) and DPPF

Scheme 2. Nitrile Substrate Scope[a]



[a]**1a** (0.2 mmol), **2** (2 mmol), $[Rh(COD)Cl]_2$ (5 mol %), and DPPF (12 mol %) were reacted at 130 °C for 1 h. [b]0.4 mmol of **2**. [c]1 mmol of **2**. [d]After **1a** (0.2 mmol) was reacted with **2** (2 mmol) in the presence of $[Rh(COD)Cl]_2$ (2.5 mol %) and DPPF (6 mol %) at 130 °C for 1 h, more $[Rh(COD)Cl]_2$ (2.5 mol %) and DPPF (6 mol %) were added to the reaction mixture, which was then stirred at 130 °C for 1 h.

(6.0 mol %) to the reaction mixture twice; see the Supporting Information) increased the **3al** yield to 68%. Likewise, although it was sterically hindered, 2-methylbenzonitrile (**2k**) reacted with **1a** under the modified conditions to give the desired isothiazole **3ak** in 50% yield. 4-Methylbenzonitrile (**2m**) and 4-methoxybenzonitrile (**2n**) were smoothly converted to **3am** and **3an**, respectively, in quantitative yields. To examine the scope and limitations of this method, the transannulation of **1a** with aliphatic nitriles was performed under the optimized conditions. Transannulation with acetonitrile (**2o**), butyronitrile (**2p**), and 4-phenylbutyronitrile (**2q**) led to the corresponding products **3ao**, **3ap**, and **3aq**, respectively, in good to excellent yields (73−93%). However, isobutyronitrile (**2r**) was less reactive due to steric effects. Remarkably, heterocyclic nitriles, such as 2-cyanopyridine and 2-thiopheneacetonitrile, reacted with **1a** to give **3as** in 94% yield and **3at** in 83% yield, respectively. Furthermore, benzoyl cyanide and ethyl cyanoformate were converted to the desired products **3au** (95%) and **3av** (72%), respectively, via the Rh-catalyzed transannulation reaction. Cyanosulfoximines with 3-methyl and 3-chloro substituents on the phenyl ring (**2w** and **2x**, respectively) were transannulated to afford the desired isothiazoles **3aw** (97%) and **3ax** (68%), respectively. To demonstrate the feasibility of applying this method on a larger scale, 1.0 g (4.3 mmol) of ethyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate (**1a**) was reacted with benzonitrile (**2a**) under the optimized conditions to give the desired isothiazole **3aa** (1.2 g, 3.8 mmol) in 88% yield, which is comparable to that obtained in the small-scale experiment.

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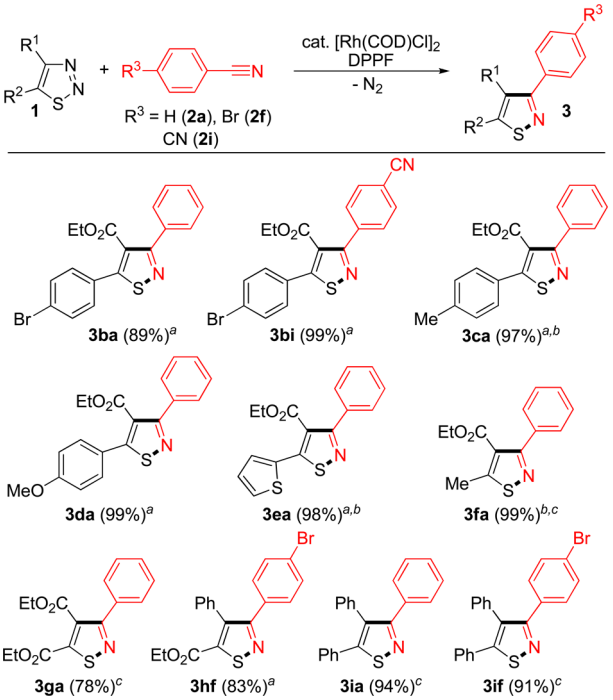
Based on these results, a wide range of thiadiazoles (**1**) were transannulated with benzonitrile (**2a**), 4-bromobenzonitrile (**2f**), and 1,4-dicyanobenzene (**2i**) (Scheme 3). Ethyl 5-aryl-

Scheme 3. Thiadiazole Substrate Scope[a]

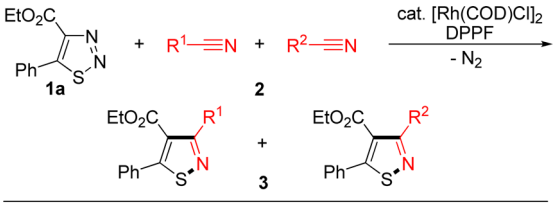


[a]**1** (0.2 mmol), **2** (2 mmol), $[Rh(COD)Cl]_2$ (5 mol %), and DPPF (12 mol %) were reacted at 130 °C for 1 h. [b]1 mmol of **2**. [c]After **1** (0.2 mmol) was reacted with **2** (2 mmol) in the presence of $[Rh(COD)Cl]_2$ (2.5 mol %) and DPPF (6 mol %) at 130 °C for 1 h, more $[Rh(COD)Cl]_2$ (2.5 mol %) and DPPF (6 mol %) were added to the reaction mixture, which was then stirred at 130 °C for 1 h.

1,2,3-thiadiazole-4-carboxylates with an electron-withdrawing bromo group or electron-donating methyl or methoxy group on the aryl ring efficiently reacted with **2a**, providing the desired isothiazoles **3ba**, **3ca**, and **3da**, respectively, in good to excellent yields (89−99%) under the optimized conditions. The transannulation of the thiadiazole **1b** with 1,4-dicyanobenzene (**2i**) produced the corresponding isothiazole **3bi** in quantitative yield. The thiadiazoles with a 2-thienyl and methyl group at R^2 were also converted to the desired isothiazoles **3ea** and **3fa** in excellent yields. Diethyl 1,2,3-thiadiazole-4,5-dicarboxylate (**1g**) was also transannulated by the developed reaction to afford the isothiazole **3ga** in 78% yield. When the thiadiazole **1h** was employed in the reaction with 4-bromobenzonitrile (**2f**), the corresponding isothiazole **3hf** was obtained in 83% yield. When 4,5-diphenyl-1,2,3-thiadiazole (**1i**) was reacted with **2a** and **2f**, the corresponding isothiazoles **3ia** and **3if** were obtained in 94% and 91% yields, respectively.

Competition experiments between various aryl and alkyl nitriles were also performed (Scheme 4). Ethyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate (**1a**) was simultaneously reacted with 4-methoxybenzonitrile and 4-chlorobenzonitrile (2 equiv each), which resulted in the formation of the isothiazoles **3ae** as the major product, indicating that the electron-deficient aryl nitrile is more reactive than the electron-rich aryl nitrile. Similarly, simultaneous transannulation with 4-methoxybenzonitrile and 4-bromobenzonitrile (2 equiv each) resulted in the selective

Scheme 4. Competition Experiments between Various Benzonitriles[a]



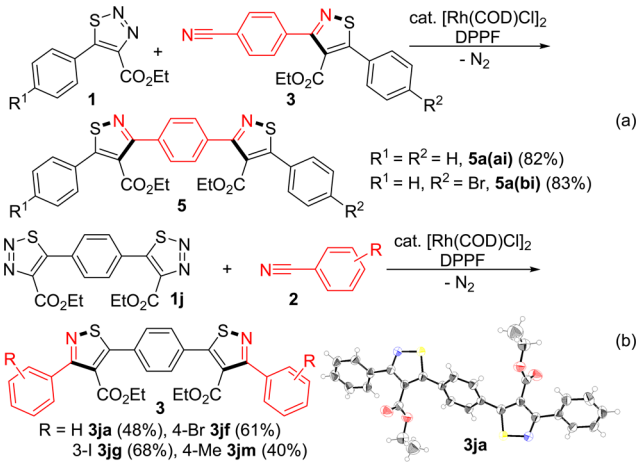
entry	R^1	R^2	yield (%)[b]	
1	4-MeO-C_6H_4 (**2n**)	4-Cl-C_6H_4 (**2e**)	**3an** (20)	**3ae** (80)
2	4-MeO-C_6H_4 (**2n**)	4-Br-C_6H_4 (**2f**)	**3an** (0)	**3af** (99)
3	Ph (**2a**)	*n*-Pr (**2p**)	**3aa** (62)	**3ap** (38)

[a]**1** (0.2 mmol), **2** (nitrile, 0.4 mmol each), $[Rh(COD)Cl]_2$ (5 mol %), and DPPF (12 mol %) were reacted at 130 °C for 1 h. [b]NMR yield using CH_2Br_2 as an internal standard.

production of the isothiazoles **3af** in quantitative yield. In the benzonitrile and butyronitrile competition experiment, the isothiazole **3aa** produced by transannulation with benzonitrile was the major product (entry 3).

After many isothiazoles **3** were efficiently synthesized in this study, oligomeric arylene compounds consisting of benzene and isothiazole rings were prepared using the developed reaction. For example, the isothiazole **3ai** produced by the transannulation of ethyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate (**1a**) with 1,4-dicyanobenzene (**1i**) was further reacted with **1a** to give the (benzene/isothiazole) pentaoligomer **5a(ai)** in 82% yield under the modified optimum conditions (Scheme 5a). Pentaoligomers with a different connectivity of nitrogen

Scheme 5. Synthesis of Pentaoligomeric Arylene Compounds



and sulfur bond in two isothiazole rings were also synthesized (Scheme 5b). When 1,4-di(thiadiazolyl)benzene **1j** was reacted with 3-iodobenzonitrile (**2g**), the desired penta(arylene) **3jg** consisting of three benzene and two isothiazole rings was obtained in 68% yield. The structures of **3ja** and **3jf** were confirmed by X-ray crystallography (see the Supporting Information).

A possible reaction mechanism for the transannulation of thiadiazole **1** with nitrile **2** is proposed in Scheme 6. First, a reversible ring−chain tautomerization of thiadiazole **1** affords the α-diazo thiocarbonyl **A**. The α-thiavinyl Rh-carbenoid **B** is subsequently generated from the denitrogenation of **A** with

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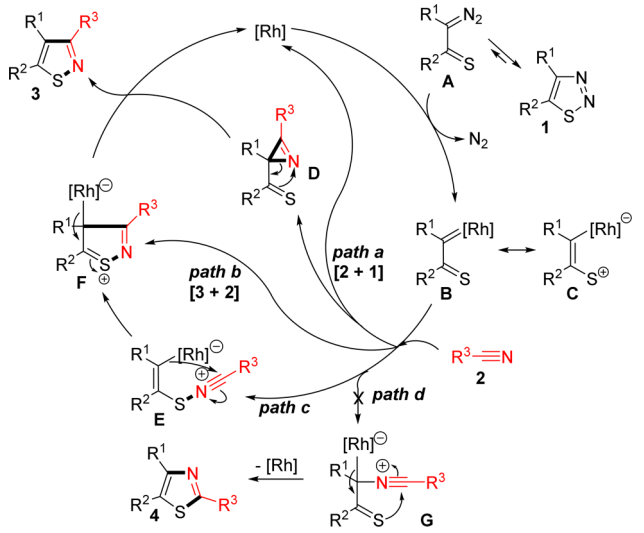
Scheme 6. Possible Mechanism



Rh(I).[5,6] The [2 + 1] cycloaddition of **B** to nitrile **2** yields the thiocarbonyl azirine intermediate **D**, which then cycloisomerizes to isothiazole **3** (path a).[7] On the other hand, the sulfenium intermediate **C**, which is a resonance structure of **B**, might undergo a nucleophilic attack by nitrile **2** (path c) to produce the nitrilium cation **E**, which then cyclizes to give the zwitterionic intermediate **F**. Finally, **F** releases the Rh catalyst to afford isothiazole **3**. Alternatively, the zwitterionic intermediate **F** can be generated through a direct [3 + 2] cycloaddition of nitrile **2** to the α-thiavinyl Rh-carbenoid **B** (path b). Based on the observed selective isothiazole formation, the thiocarbonyl azirine intermediate **D** is ruled out in the catalytic cycle. Also, because expected thiazole **4** was not produced, **G** is ruled out in the catalytic cycle (path d). On the other hand, the observed higher reactivity of electron-deficient nitriles indicates that path c is less likely. Undoubtedly, more detailed investigations are needed to elucidate the exact mechanism for this transformation.

In summary, a method for synthesizing a wide range of isothiazoles by a Rh-catalyzed transannulation of 1,2,3-thiadiazoles with alkyl, aryl, and heteroaryl nitriles via a Rh α-thiavinyl carbenoid intermediate was developed. The results suggest that the α-thiavinyl carbene acts as an umpolung 1,3-dipole equivalent in its reaction with nitriles, in contrast to its transannulation with alkynes. This method was employed to efficiently synthesize pentaoligomeric arylene compounds consisting of three benzene and two isothiazole rings.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02499.

Experimental procedures, characterization data, X-ray crystallography data (**3ba**, **3ja**, and **3jf**) (PDF)
Crystallography data for **3ja** (CIF)
Crystallography data for **3jf** (CIF)
Crystallography data for **3ba** (CIF)
NMR spectra of all the products (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: phlee@kangwon.ac.kr.

Notes

The authors declare no competing financial interest.

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