Form 3

Abstract of Thesis

Name (Abhijit Sen)	
Title	Development of Aza-Wacker-Type Reaction Promoted by Pd–SPRIX Catalyst (Pd–SPRIX触媒を活用するaza-Wacker型反応の開発)

Abstract of Thesis

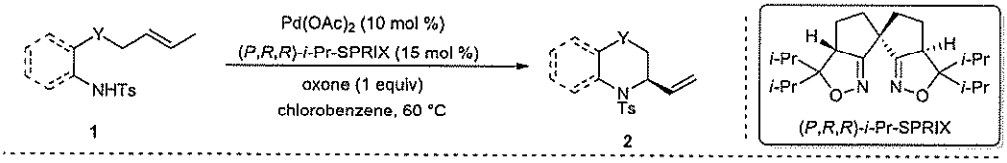
Nitrogen-containing molecules are ubiquitous in pharmaceutical and naturally occurring substrates. These molecules are also playing a significant role in material science and industrial chemistry. A database of Food and Drug Administrator of USA (FDA) approved drug suggests 84% of total small-molecule drugs contain at least one nitrogen atom and 59% of total small-molecule drugs contain at least one nitrogen heterocycles.[1] These data clearly focus the importance of nitrogen-containing molecules. As a result, several methodologies have been developed for the construction of C–N bond. Among them, oxidative amination of olefin, known as aza-Wacker-type reaction, is supposed to be a straightforward and an efficient method. Previously, our group developed a unique ligand, SPRIX, possessing isoxazoline coordination sites on a rigid spiro framework.[2] The low σ-donating ability of SPRIX preserves the Lewis acidity of palladium salts and as a result, olefin can easily coordinate to palladium. The induced electrophilicity of olefin upon the coordination may allow the nitrogen center to undergo nucleophilic addition to olefin. Herein, I developed enantioselective aza-Wacker-type cyclization of alkenyl sulfonamides **1** promoted by Pd–SPRIX catalyst (Project 1) and intermolecular aza-Wacker-type reaction between internal olefins **3** and nitrogen nucleophiles **4** to construct allylamine derivative **5** catalyzed by Pd–SPRIX complex (Project 2).

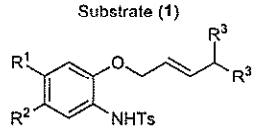
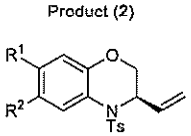
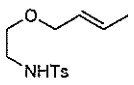
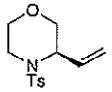
Project 1: Enantioselective Synthesis of *N*-Heterocycles *via* Aza-Wacker-Type Cyclization

A 6-membered *N*-heterocycle having a chiral center at the α-position to the nitrogen atom, especially, is observed in a variety of small molecule drugs. Palladium-catalyzed aza-Wacker-type cyclization is a very simple and easy way to construct a C–N bond for the synthesis of *N*-heterocycles. In spite of several reports of enantioselective 5-membered cyclization, the enantioselective 6-membered aza-Wacker-type cyclization has not been reported yet.

In 2012, Stahl and his coworkers published aza-Wacker-type cyclization of alkenyl sulfonamide **1** which provided *N*-heterocyclic molecules **2** in a racemic manner.[3] I conceived that the unique property of SPRIX enabled 6-membered nitrogen-heterocycles to be constructed enantioselectively. After optimization of reaction parameters, aza-Wacker-type cyclization of substrates **1a** was found to proceed efficiently in the presence of 10 mol % palladium acetate, 15 mol % (*P,R,R*)-*i*-Pr-SPRIX, and 1 equiv of oxone in chlorobenzene solvent at 60 °C to furnish 6-membered *N*-heterocycle **2a** in 84% yield with 69% ee.

Table 1. Enantioselective aza-Wacker-type cyclization of alkenyl sulfonamide **1**



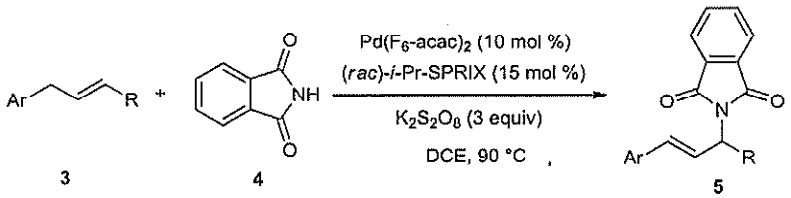
Substrate (1)	Product (2)	Yield(%), Ee (%)
		R^1 = H, R^2 = H, R^3 = H (**2a**) 84%, 69%
		R^1 = H, R^2 = OMe, R^3 = H (**2b**) 77%, 53%
		R^1 = H, R^2 = Br, R^3 = H (**2c**) 64%, 36%
		R^1 = Me, R^2 = H, R^3 = H (**2d**) 87%, 54%
		R^1 = H, R^2 = H, R^3 = CH_3 (**2e**) 79%, 80%
		Y = O (**2f**) 84%, 69%
		Y = CH_2 (**2g**) 84%, 69%
		Y = NTs (**2h**) 84%, 69%

The electronic variation on phenylene ring by installation of OMe (**2b**), Br (**2c**) at 5-position or Me (**2d**) at 4-position had no significant effect. The introduction of a bulky *i*-Pr group at the terminal of olefin was found to be beneficial in terms of enantioinduction without loss of reactivity (**2e**). The phenylene linker was not essential for this transformation. Morpholine (**2f**), piperidine (**2g**) and piperazine (**2h**) were obtained successfully in enantioenriched form. The absolute configuration of *N*-heterocyclic product (**2c**) was determined by X-Ray crystallographic analysis.

Project 2: Efficient Construction of Allylamine Derivatives *via* Intermolecular Aza-Wacker-Type Reaction.

Allylamine derivatives are known to be versatile in modern organic synthesis as a building block for heterocyclic compounds, biologically active molecules, and pharmaceutical products.[4] The presence of allylamine core in several commercially available drugs such as naftifine, terbinafine and flunarizine proved its usefulness. Although several methodologies are available for the synthesis of allylamine derivatives, the intermolecular aza-Wacker-type reaction is expected to be a crucial one.[5] So, I envisioned that the use of internal olefin under the Pd–*i*-Pr-SPRIX catalysis might generate synthetically useful allylamine derivatives *via* aza-Wacker-type reaction. After the optimization of reaction parameters, intermolecular oxidative amination of olefin **3a** with phthalimide **4** was found to proceed smoothly in the presence of 10 mol % $Pd(F_6\text{-acac})_2$ (F_6-acac: hexafluoroacetylacetonate), 15 mol % (*rac*)-*i*-Pr-SPRIX, 3 equiv of potassium persulfate in 1,2-dichloroethane (DCE) at 90 °C to afford desired allylamine derivative **5a** in 93% yield.

Table 2. Intermolecular aza-Wacker-type reaction of **3** and **4**



3 **4** **5**

Substrate (3)	Ar	R	Product (5)	Yield (%)
3a	2-$MeOC_6H_4$	2-$MeOC_6H_4CH_2$	**5a**	93
3b	4-$MeOC_6H_4$	4-$MeOC_6H_4CH_2$	**5b**	88
3c	Ph	$PhCH_2$	**5c**	74
3d	4-$MeOC_6H_4$	Me	**5d**	88
3e	4-$CF_3C_6H_4$	Me	**5e**	77
3f	2-$MeOC_6H_4$	Me	**5f**	84

Other symmetrical substrates like **3b** and **3c** also furnished the desired product effectively. Unsymmetrical substrates underwent aza-Wacker-type reaction with excellent regioselectivity. Electron-rich (**3d**), electron-deficient (**3e**) and sterically-hindered (**3f**) substrates provided allylamine derivatives successfully.

In summary, I have successfully developed two new aza-Wacker-type reactions utilizing *i*-Pr-SPRIX ligand: Intramolecular cyclization of alkenyl sulfonamides leading to optically active 6-membered *N*-heterocycles and intermolecular amination of allylbenzene derivatives.

Reference:

1. For a review, see: Vitaku, E.; Smith, D. T.; Njardson, J., T. *J. Med. Chem.* **2014**, *57*, 10257.
2. For a review, see: Bajracharya, G. B.; Arai, M. A.; Koranne, P. S.; Suzuki, T.; Takizawa, S.; Sasai, H. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 285.
3. Lu, Z.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 1234.
4. For a review, see: Skoda, E. M.; Davis, G. C.; Wipf, P. *Org. ProcessRes. Dev.* **2012**, *16*, 26.
5. For a review, see: Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

様式 7

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本論文の著者は、光学活性なスピロ配位子を用いたパラジウム触媒反応による aza-Wacker 型反応に関する研究を行い、分子内 aza-Wacker 型反応では最高 80% ee の光学純度で収率よく目的化合物を得ることに成功している。Pd(II)活性種の発生に必要な酸化剤は、安価で安全な Oxone であり、光学活性含窒素複素環化合物の合成法として有用性が高い。また、分子間 aza-Wacker 型反応については、高い収率で目的化合物が得られることを見出しており、一般性の高い反応として今後の展開も期待できる。いずれの反応もスピロ型配位子 SPRIX を用いた場合のみ効率よく反応が進行しており、独自性、先進性も高い。反応メカニズムについて、酸化剤非存在下で化学量論量の Pd 錯体を用いた場合に触媒反応と同様な結果が得られることから Pd(II)/Pd(IV)触媒系でないことを明らかにし、速度論的同位体効果等の検討から、反応の律速段階や立体選択性発現の機構についても深い考察を行うなど、学術的にも価値のある論文である。よって、本論文は博士（理学）の学位論文として十分価値あるものと認める。