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## 学 位 論 文 の 要 約

博士の専攻分野の名称

博士 (工学)

氏名 ECE Hamdiye

## 学 位 論 文 題 名

Lewis Acidic Catalysis of Silyl Cyanometallates in Transformations of Phenol and Aniline Derivatives

(フェノールおよびアニリン誘導体変換反応におけるシリルシアノメタラートの Lewis 酸触媒作用)

Organosilicon compounds are generally low toxic and air and moisture stable reagents, and some of them are commercially available that have been used in many research areas such as pharmaceuticals, agrochemicals, and functionalized materials for decades. Their superiority of reactivity and availability is created interest in synthetic organic chemistry. A variety of organic transformations such as oxidation, amination, halogenation, and cross-coupling reaction, have been developed by using organosilicon reagents.

Most stable organosilicon compounds, such as tetraalkylsilanes and tetraalkoxysilanes, are neutral, and the Lewis acidity of these compounds is too weak as a catalyst for activation of the organic reagents. However, when one of the four substituents on silicon is changed to Lewis base, such as triflate (OTf) or iodide (I) ion, they become Lewis acids bearing one coordination site. The strength of Lewis acidity mainly depends on the features of the counter anions. Silyl Lewis acids (SLAs) that classified as neutral and cationic have studied for decades. They have shown many advantages for their use over other metal-centered activators and metal halides made them to be chosen as catalysts for many organic reactions like aldol-type reactions, ring constructions, and allylations.

Recently, a new approach for the preparation of cationic SLAs has been reported by Ohkuma, Yurino, and coworkers, that is, silyl cyanometallate complexes formed *in situ* from transition metal salts ( $\text{MX}_n$ ) and an excess amount of trimethylsilyl cyanide (TMSCN). The reversible property of these complexes is proposed to appropriately control the intensity of Lewis acidity. This protocol was successfully applied to allylic isocyanation using allylic phosphate as an electrophile. The ate complexes  $(\text{TMS})[\text{Pd}(\text{CN})_3]$  and/or  $(\text{TMS})_2[\text{Pd}(\text{CN})_4]$  were generated *in situ* from  $\text{Pd}(\text{OAc})_2$  and TMSCN, and these served as both Lewis acids activating allylic phosphates and *N*-nucleophiles of cyanide ( $\text{CN}^-$ ). In a similar manner, the combination of  $\text{Ag}_2\text{O}$  and TMSCN effectively catalyzed the benzylic isocyanation. In this case,  $(\text{TMS})[\text{Ag}(\text{CN})_2]$  is the active species. The author expected that the reversibly formed silyl cyanometallates show unique properties in a variety of Lewis acid-catalyzed reactions other than isocyanations, such as Friedel–Crafts-type substitutions and some oxidations.

This thesis consists of three chapters and the background of this research was described on a general introduction.

Chapter 1: The author focused on synthesis of obtusastylene (*C*-cinnamyl phenol) derivatives from phenol and anisole derivatives. Obtusastyrenes are well known for their photochemical properties, show significant bioactivities, and could be used as intermediates for construction of complex products. Allylation of aromatic compounds are reliable strategy for synthesizing obtusastyrenes. Transition metal catalyzed allylic alkylation has been reported that using an aryl metal as a nucleophile such as boronic acid species, Grignard reagent or organozinc species for formation of the *para*-substituted compounds. However, *O*-addition takes place instead of *C*-substitution of phenol without usage of aryl metals. On the other hand, Friedel–Crafts-type allylation is an outstanding strategy especially for the transformation of electron rich phenol derivatives. Lewis or Bronsted acidic catalyst accelerates the *C*-allylation of phenol without modification of aryl metal. However, control of the strategy is one of the most challenging points of Friedel–Crafts-type allylation for the *ortho*/*para* orientation. Because of this, an effective method is needed for highly regio-selective formation of these compounds in the field of synthetic organic chemistry and also biochemistry.

The author successfully applied Lewis acidic catalysis of silyl cyanometallates to the Friedel–Crafts-type allylation of allylic phosphates as electrophiles and phenol derivatives as nucleophiles. The *in situ* formed silyl cyanometallates from combined system of AgTFA/TMSCN and Pd(OAc)<sub>2</sub>/TMSCN were afforded regioselectively *C*-allylated products in high yield. It was found that AgTFA/TMSCN combination is suitable active catalytic system for formation of *para*-allylated anisoles. The combination of Pd(OAc)<sub>2</sub> and TMSCN worked sufficiently for the *para*-substitution of phenols. Reactivity of the allylation was affected by the electronic properties of both nucleophile and electrophile. The chemo- and regio-selective reaction of the allylic phosphates produced a series of useful cinnamyl-substituted compounds.

Chapter 2: The combination of Pd(OAc)<sub>2</sub>/TMSCN successfully applied to generation of oxindoles from diethylphosphates derived from *N*-arylmandelamides through Friedel–Crafts-type cyclization. Oxindole derivatives are shown outstanding bioactivities, and have been used as key components in medicinal chemistry. Several strategies have been reported for the synthesis of the aryl indoles. However, all previous procedures have disadvantages such as high catalyst loading, usage of strong base, and preparation of modified compound before use. A facile and reliable procedure is needed for the synthesis of oxindole derivatives.

The author successfully employed the method to broad range of the 3-aryloxindole products in high yield. Substitution of methyl, isopropyl, *tert*-butyl, and phenyl groups on the nitrogen was allowed with little influence on the product yield. *N*-Allyl and *N*-benzyl substituents were not injured by the Pd complexes. Methyl, methoxy, and halide groups were successfully introduced on the mandelic as well as the aniline phenyl rings of substrates. The mandelic phenyl ring could be replaced with naphthyl and thienyl groups, affording the cyclized products quantitatively. When the reaction was conducted with *N,N*-dibenzylmandelamide as a substrate, the benzo-fused  $\delta$ -lactam was obtained in a quantitative yield. Application of the oxindole product to the *C*3-substitution reactions afforded the 3,3-diaryloxindoles with two different aromatic rings. Furthermore, a gram-scale reaction was carried out without loss of the yield under

optimal conditions.

Chapter 3: *N*-alkylanilines were undergone oxidative cyanomethylation catalyzed by silyl cyanoargentate in the presence of TMSCN and nitromethane mediated by benzotrifluoride to generate  $\alpha$ -amino nitriles. *N*-Alkyl-*N*-cyanomethylaniline derivatives are important intermediates for several organic compounds such as 1,2-diamines,  $\alpha$ -amino ketones, and  $\alpha$ -amino aldehydes. They can be found in pharmaceuticals, agrochemicals, and catalysts. They successfully synthesized from tertiary arylamines by using transition metal catalysts, but rarely synthesized from secondary amines. The reported methods have many drawbacks. For instance, the oxidative condensation of amines, primary alcohol and TMSCN is an outstanding method, but high catalyst loading was required, and the yield was medium. The other strategy for generation of cyanomethylated compounds uses a Cu-catalyst in the presence of dimethylformamide as a methylene source. However, this method also required high (10 mol%) catalyst loading. Therefore, a novel catalytic method is desirable in the synthetic organic chemistry.

The author efficiently applied the optimized conditions to formation of the *N*-alkyl-*N*-cyanomethylaniline under air. Notably, the reaction was not proceeded smoothly in the absence of benzotrifluoride. This observation is suggested that the oxidation is promoted by benzotrifluoride. The method was not possible to form cyanomethylated products from *N*-alkyl anilines, and that was the main limitation of the procedure. Desired product was not obtained in the presence of acetonitrile instead of nitromethane as a solvent, indicating that nitromethane is the source of methylene as well as a solvent. No target product was obtained, when *N,N*-dimethylaniline was employed. This result suggested that the oxidative cyanomethylation did not proceed from *in situ* formed *N*-methylaniline and nitromethane.

This research revealed that the newly devised silyl cyanometallates act as efficient catalysts for inter- and intramolecular Friedel–Crafts-type reactions. These catalysts also achieved a novel synthetic strategy of *N*-cyanomethylation of aniline derivatives under air.