

Metal-Catalyzed Tandem C-Heteroatom and C-C Bond Forming Reactions : New Synthesis of Isoquinolines and Related Compounds

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URL	http://hdl.handle.net/10097/39352

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学位の種類	博士(理学)
学位記番号	理博第2293号
学位授与年月日	平成18年9月15日
学位授与の要件	学位規則第4条第1項該当
研究科, 専攻	東北大学大学院理学研究科(博士課程) 化学専攻
学位論文題目	Metal-Catalyzed Tandem C-Heteroatom and C-C Bond Forming Reactions: New Synthesis of Isoquinolines and Related Compounds (金属触媒を用いたタンデム型炭素 - ヘテロ元素及び炭素 - 炭素結合形成反応: イソキノリン及び関連化合物の新合成法)
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Chapter 1: The Lewis acid and/or transition metal-catalyzed addition of carbon nucleophiles to imines is one of the most important methods for the preparation of nitrogen-containing compounds. In particular, the direct addition of carbon pronucleophiles to imines in the presence of catalysts is highly desirable as it represents an atom economical approach. Previously Yamamoto reported the first example of metal-catalyzed direct addition of malononitrile derivatives and simple ketones, such as acetone, to activated imines. This transformation is useful for synthesizing amines and amino acid derivatives. However activated imines that bear an electron withdrawing group on the imine nitrogen atom have to be used as a substrate to induce the addition of pronucleophiles. Although direct Mannich-type reactions of activated ketone and malonate and direct nitro-Mannich (aza-Henry) reaction catalyzed by metals and Bronsted acids were also reported recently, activated imines were also required in these cases. In this chapter, the synthetic method of the functionalized

1,2-dihydroisoquinoline skeletons through the direct addition of various carbon pronucleophiles to ortho-

alkenylaryl aldimines is reported. Without using the ordinary activated imines bearing an electron-withdrawing group, the addition to imine proceeded well probably due to the in situ formation of the reactive isoquinolinium intermediate. In general the construction of 1,2-dihydroisoquinoline framework can be achieved by the nucleophilic addition to the isoquinolinium salt, which are derived from the corresponding isoquinolines using acylating or alkylating agents. Obviously, the present reaction proceeded without such activation and the current transformation provides an alternative method for the construction of 1,2-dihydroisoquinolines.

Chapter 2: Since tetrahydroisoquinolines, 1,2-dihydroisoquinolines and their derivatives are compounds of great interest due to their biological and pharmaceutical properties, development of efficient synthetic methods of these compounds has been the subject of great interest. The preparation of tetrahydroisoquinoline can be performed in many ways, but ultimately the majority of the methods involve reaction of classical method like Pictet-Spengler, Bischler-Napieralski, and Pomeran-Fritsch reactions. For ring closure, they normally require strong acidic condition and/or some activation through an introduction of electron-donating groups in benzene ring, such as an alkoxy group. Although the cyclization of ortho-alkenyl-benzylamines is also known as a preparation method of tetrahydroisoquinoline, the reaction should be conducted under severe basic condition. Besides the formation of tetrahydroisoquinoline skeleton, an efficient method for introduction of carbon unit at the C-1 position has recently been explored since many of useful isoquinolines have substituents at that position. Alkylation or acetylation of nitrogen atom of 3,4-dihydroisoquinoline and isoquinoline compounds, followed by nucleophilic attack of certain nucleophiles to the resulting iminium part is well known. In this chapter, the development of new synthetic method for multisubstituted tetrahydroisoquinoline derivatives by using transition metal catalysts, such as $\text{RhCl}(\text{PPh}_3)_3$ and $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, via the tandem C-N and C-C bond formation using ortho-alkenylaryl aldimines and pronucleophiles is reported. Any strong acids or bases are not required and the reaction proceeds under nearly neutral condition. The current transformation provides an alternative method for the construction of tetrahydroisoquinoline, which can be used as building blocks of bioactive tetrahydroisoquinoline alkaloids.

Chapter 3: Ring expansion is one of the most useful methodologies for the synthesis of medium sized rings, which are commonly found in many natural products. It is well known that the cycloaddition of electron rich olefins, such as enamines and enol ethers, with dimethyl acetylenedicarboxylate gives cyclobutene intermediates, which undergo electrocyclic ring opening to afford medium sized rings. In this chapter, the synthetic method of the pyran derivatives, fused with medium and large rings (7-10 and 14), via the palladium catalyzed reaction of enynals with dimethyl acetylenedicarboxylate is reported. The reaction proceeds through the cycloaddition of dimethyl acetylenedicarboxylate to an electron rich olefin, derived from the intramolecular cyclization of enynals, and subsequent ring expansion. It was found that the combination of $\text{Pd}(\text{OAc})_2$ and cyclooctadiene is a suitable catalytic system for the present reaction.

Chapter 4: The imino-ene reaction is a powerful synthetic method of functionalized amine compounds in organic synthesis. Although Lewis acids have been often used as activating agents, it was essential to use stoichiometric amounts of Lewis acids and there is no report of the Lewis acid-catalyzed reaction. It was known that reactions were catalyzed by transition metal complexes. However, it was necessary to use activated imines, having electron-withdrawing groups on the nitrogen atom. In this chapter, it is reported that the palladium-catalyzed intramolecular imino-ene reaction with unactivated imine compounds takes place. When ortho-alkenylarylaldehydes were treated with a catalytic amount of $\text{Pd}_2(\text{allyl})_2\text{Cl}_2$ in 1,4-dioxane at 100 °C, the intramolecular imino-ene reaction proceeded to give amino indene derivatives in good to high yields. Analogous palladium-catalyzed ene reaction of ortho-alkenylbenzaldehydes also proceeded to give indenols in good to high yields.

論文審査の結果の要旨

Sal Prima Yudha S. 氏は、有機金属触媒を用いた新規変換反応の開発を目的として研究を行い、様々な優れた分子変換プロセスの開拓に成功した。第一章と第二章では、有用な生理活性を示す天然物の基本骨格であるジヒドロイソキノリンおよびテトラヒドロイソキノリン骨格の新規合成法の開発について研究を行った。その結果、オルトアルキニルアルジミンまたはオルトアルケニルアルジミンとプロ求核剤とから、銀触媒とロジウム触媒を用いたタンDEM型付加環化反応を開発し、それぞれ目的物を一挙に合成できることを示した。本反応はニトロメタンなどのプロ求核剤を直接用いることができるダイレクト型付加反応で進行するために、原子効率の高い環境調和型の反応である。同時にこれらの結果は、炭素親和性ルイス酸触媒が有機合成反応に極めて有効であることを示している。これまでルイス酸触媒は、主にカルボニル基などのヘテロ原子を含む官能基の活性化剤として有機合成に用いられてきた。これに対し本反応は、アセチレン結合やオレフィン結合に対し高い親和性を示す銀触媒やロジウム触媒を炭素親和性ルイス酸触媒として用いることにより達成された反応であり、概念的にも極めて独創性の高い反応である。第三章では新しい環拡大型反応の開発を、第四章ではパラジウム触媒をルイス酸触媒として用いた、触媒的イミノエン反応の開発であり、どちらの反応も触媒の特徴をうまく引き出した優れた変換反応である。これらの研究成果は、Sal Prima Yudha S. 氏の有機合成化学に対する尽きることのない興味関心と、日々のたゆまない試行錯誤の繰り返しから生まれたものであり、博士論文として適している。以上の結果は、同氏が自立して研究活動を行うに必要な高度の研究能力と学識を有することを示している。したがって、Sal Prima Yudha S.氏提出の博士論文は、博士（理学）の学位論文として合格と認める。