

SUMMARY OF THE DISSERTATION DONE

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**Ruthenium(II)-Catalyzed C–H Bond Activation and
Functionalization**

FROM

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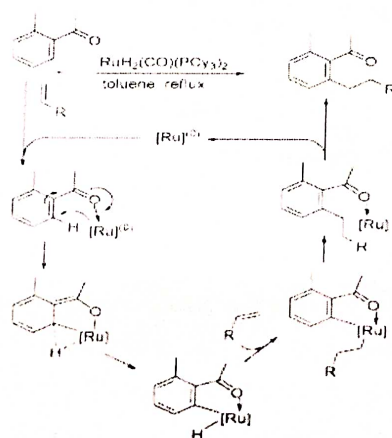
1. INTRODUCTION

The catalytic functionalization of unreactive C–H bonds has recently brought a revolution in synthetic methodologies for the production of pharmaceuticals and natural products and for opening new routes to molecular materials and polymers. The regioselective direct conversion of C–H bonds into C–C bonds offers the challenge to replace several classical catalytic cross-coupling reactions involving the coupling of organohalides with an organometallic intermediate RM (M = Li, MgX, ZnX, BR₂, SnR₃, SiR₃, etc.) or with a functional alkene as in the Heck reaction. Transition metal catalysts initially based on palladium or rhodium complexes^{1,2} have been found to promote C–C bond formation via direct C–H bond activation under mild conditions. A large variety of metal catalysts³ and especially the cheaper ruthenium catalysts^{4,5} are now useful for the efficient catalytic conversion of C–H bonds.

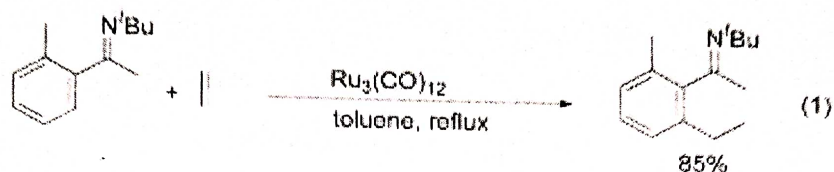
2. RUTHENIUM(0) CATALYSTS AND sp² C–H BOND FUNCTIONALIZATION

One of the first significant results in ruthenium-catalyzed sp²C–H bond activation consisted of the ortho-alkylation of phenol by ethylene in the presence of catalytic amounts of potassium phenoxide and the tetraphosphite complex Ru(II)- (P(OPh)₃)(P(OPh₂)(OC₆H₄))((PhO)₂POC₆H₃OP(OPh)₂) featuring two ortho-metalated ligands.⁶ However, the pioneering work in ortho-directed C–H bond activation/functionalization with ruthenium(0) catalysts was initiated by Murai with Chatani and Kakiuchi.⁷ This was the first example of chelation-assisted and directed regioselective catalytic alkylation of aromatic ketones with alkenes in the presence of RuH₂(CO)-(PPh₃)₃, a stable precursor of Ru(0) catalyst.⁴ On the basis of DFT calculations, it was proposed that in this catalytic reaction the metal precursor is first reduced into a ruthenium(0) species simply by H₂ elimination on heating and the C–H bond cleavage proceeds on oxidative addition via directed nucleophilic attack of the ruthenium(0) onto the ortho-carbon atom of the aromatic ketone, followed by migration of the hydrogen to the ruthenium center (Scheme 1).⁸ The hydrogen is more efficiently trapped with vinylsilane to generate the Ru(0) species.^{8c}

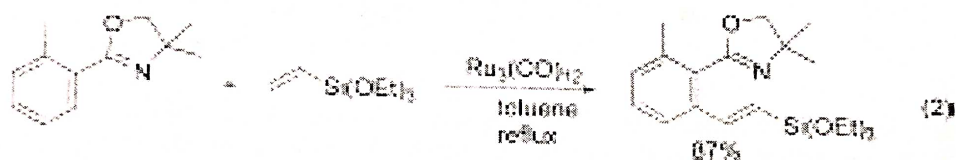
Scheme 1. Ruthenium(0) C–H Bond-Activation Mechanism



This reaction involving aromatic or vinylic sp^2C-H bond activation by low-valent ruthenium catalysts and formal insertion of a double bond into a carbon-hydrogen bond leading to alkylated products with atom economy are now described under the general name of Murai reaction. The scope of this reaction involves a wide range of alkenes including ethylene, vinylsilanes, and styrenes and could be applied to a variety of aromatic aldehydes, ketones, and esters.⁴ The reaction was extended to heterocycles such as pyrroles, furans, and thiophenes substituted by an acyl group in 2- or 3-position, which led to 3- or 2-alkylated products, respectively, in almost quantitative yields. Aldimines, ketimines, and nitriles also exhibited efficient directing effects (eq 1).⁹

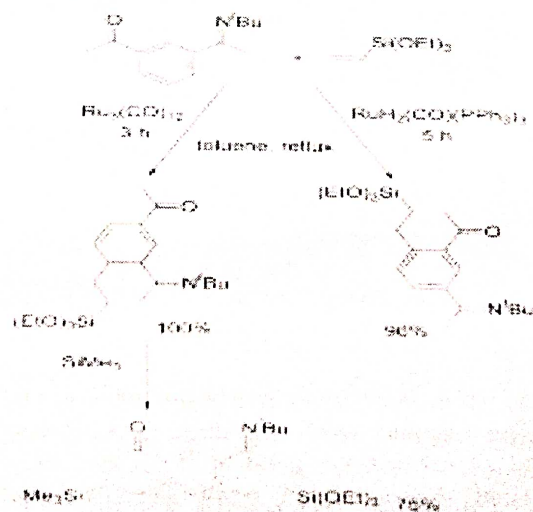


By contrast, under the same conditions, the reaction of aryloxazoline with triethoxyvinylsilane led to formal ortho-vinylation Scheme 1. Ruthenium(0) C-H Bond-Activation Mechanism of the arene ring. This product was assumed to be produced via insertion of the olefin into the ruthenium-carbon bond (carbometalation) followed by β -H elimination (eq 2).¹⁰



When the substrate contained both acetyl and imine directing groups, the nature of the formed product depended on the catalyst nature, and different olefins could be involved in sequential transformations. Thus, $Ru_3(CO)_{12}$ revealed the imine directing group efficiency, whereas $RuH_2(CO)(PPh_3)_3$ catalytic alkylation was directed by the ketone group (Scheme 2).¹¹

Scheme 2. Ru(0) Catalysts Selecting Their Preferred Directing Group

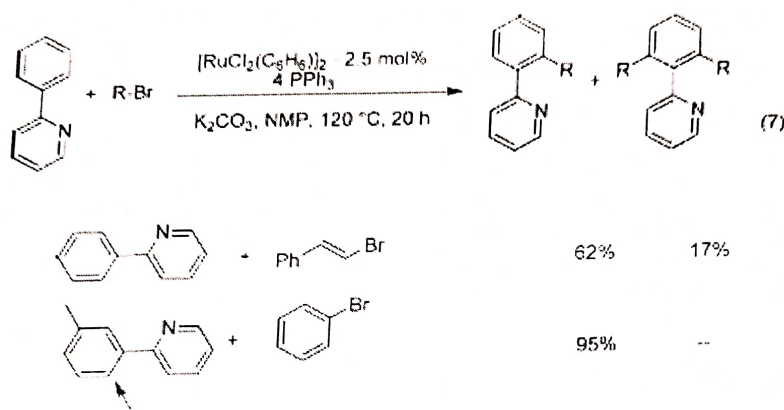


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3. RUTHENIUM(II)-CATALYZED sp^2C-H BOND ACTIVATION/FUNCTIONALIZATION

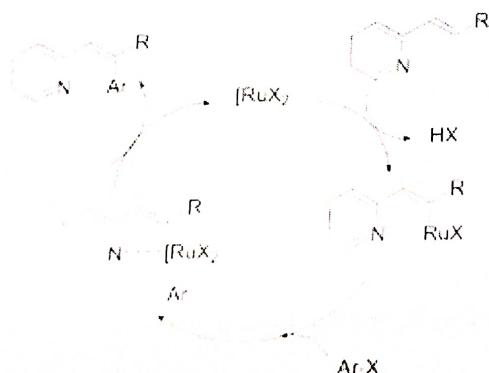
Catalytic Arylation Reactions of (Hetero)arenes and Alkenes with Aryl and Heteroarylhalides

The monoarylation of several substituted 2-pyridylarenes was selectively obtained in good yields for which the substituents, likely for steric reasons, inhibited diarylation. One example of monoalkenylation of phenylpyridine with E-PhCH=CHBr was obtained (62%) along with 17% of dialkenylation product (eq 7). This new arylation and alkenylation reactions showed that the 2-pyridyl group was an efficient directing group for functionalization of sp^2C-H bonds at the neighboring ortho position.⁷



The reaction was proposed to occur via initial oxidative addition of the arylhalide to Ru(II), followed by β -cis-ruthenation of the olefinic moiety and reductive elimination. However, on the basis of more recent mechanistic studies,¹² the other proposed option seems more realistic via β -cis-ruthenation assisted by carbonate taking place first, followed by Ar-X oxidative addition (Scheme 4).

Scheme 4. Proposed Mechanism of Arylation of Functional Alkenes



4. Conclusion

Simple ruthenium(II) catalysts can now be considered as essential in the catalytic activation of sp^2C-H bonds for a variety of C-C bond-forming reactions. These catalysts are relatively inexpensive with respect to other efficient metal catalysts for C-H bond transformations, and some of them are rather stable to air, usual oxidants, and water. The direct arylations with (hetero)arylhalides of arenes and

alkenes containing a directing group have been discovered first with the association of Ru(II)-PPh₃ catalytic systems. They appear now more efficiently performed by the combination of carboxylate-ruthenium(II) catalytic systems that effectively favor diarylation. The success recently obtained with ruthenium(II) catalysts, the activity of which is strongly modified by the addition of very simple cocatalysts or oxidant or by creating halide-free ruthenium(II) catalysts, will probably motivate the synthesis of new efficient ruthenium catalysts for C-H bond activation, as the ruthenium(II) catalysts used presently are most of the time derived from [RuCl₂(arene)]₂. There are still many challenges to overcome, such as the control of regioselectivity at other C-H sites than at the ortho position of functional groups or the efficiency of new directing groups. Whereas the sp²C-H bond activation has been successfully transferred into C-C bond formation, the activation of sp³C-H bond with ruthenium(II) catalysts is certainly attractive. Although there is already much evidence for stoichiometric sp³C-H bond activation with ruthenium complexes, only a few catalytic sp³C-H bond functionalizations are appearing. The use of ruthenium(II) catalysts for sp³C-H bonds remains a challenge for this decade.

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