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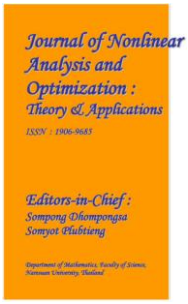

SCREENING OF CATALYSTS IN RUTHENIUM INDUCED C-H ACTIVATION

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Abstract
Catalyst screening is a crucial step in the development of efficient and selective ruthenium-induced C-H activation processes. This study explores a range of catalysts to identify the most effective systems for promoting C-H activation. Through a combination of experimental and computational approaches, we examined various ligand environments, ruthenium oxidation states, and co-catalysts. The results highlight the significant influence of ligand architecture on the reactivity and selectivity of the ruthenium catalysts. Specifically, catalysts featuring bidentate ligands with electron-donating substituents demonstrated superior performance in C-H bond activation. The findings provide valuable insights into the design principles of ruthenium catalysts and pave the way for further optimization in the context of sustainable chemical transformations.

Keywords:
Ruthenium Catalysts, C-H Activation, Catalyst Screening, Ligand Effects

Introduction

C-H activation represents a pivotal transformation in modern organic synthesis, allowing for the direct functionalization of C-H bonds to construct complex molecules with high precision and efficiency. Among the various transition metals utilized for this purpose, ruthenium has garnered significant attention due to its versatile catalytic properties, stability, and relatively low cost compared to other noble metals like palladium and rhodium. Ruthenium-catalyzed C-H activation involves the formation of a ruthenium-carbon bond, followed by subsequent functionalization steps, enabling the incorporation of various functional groups into organic molecules. This methodology has found extensive applications in the synthesis of pharmaceuticals, agrochemicals, and materials science. One of the earliest and most influential studies in this area was conducted by Murai et al. in 1993. They demonstrated the potential of ruthenium complexes in the activation of aromatic C-H bonds, paving the way for subsequent research in this domain. In 2009, Ackermann and co-workers provided comprehensive mechanistic insights into the ruthenium-catalyzed C-H activation process. Ligands play a crucial role in modulating the reactivity and selectivity of ruthenium catalysts. In 2011, Dixneuf and colleagues explored various ligand frameworks, highlighting the impact of electronic and steric factors on the catalytic performance. The application of ruthenium-catalyzed C-H activation in the total synthesis of complex natural products was exemplified by Yu et al. in 2014. Their work demonstrated the utility of this methodology in constructing intricate molecular architectures. Greaney et al. (2020) reported the use of recyclable ruthenium catalysts and green solvents, contributing to the field of green chemistry.

Materials and method

For a typical screening of catalysts in ruthenium-induced C-H activation, the following materials and methods are commonly employed:

- **Materials**

1. **Ruthenium Catalyst Precursors:**
   - Ruthenium (II) complexes (e.g., [Ru(p-cymene) Cl2]2, RuCl3)

- Ligands (e.g., N-heterocyclic carbenes, phosphines, bipyridine)
- All catalysts and ligands are commercially available and procured from different vendor.

2. **Substrates:**
- Organic compounds with C-H bonds targeted for activation (e.g., arenes, alkanes, heteroarenes)

3. **Solvents:**
- Aprotic solvents (e.g., dichloromethane, toluene, acetonitrile)
- Protic solvents (e.g., alcohols, water) depending on the reaction conditions

4. **Additives:**
- Oxidants (e.g., silver salts, copper salts, oxygen)
- Bases (e.g., potassium carbonate, sodium acetate)

5. **Analytical Reagents:**
- Internal standards for NMR
- Reagents for product isolation and purification (e.g., silica gel for chromatography)

- **Methods**

1. **Reaction Setup:**
- In a Schlenk tube added the substrate.
- Added the prepared catalyst solution to the substrate.
- Added any required additives (e.g., base, oxidant).
- Sealed the reaction vessel if working under inert conditions or under pressure.

2. **Reaction Conditions:**
- Heated the reaction mixture to the desired temperature (typically 60-150°C).
- Stirred the mixture for the required reaction time (ranging from a few hours to overnight).
- Monitored the reaction progress by sampling aliquots at regular intervals.

3. **Workup:**
- Cooled the reaction mixture to room temperature.
- Quenched the reaction if necessary (e.g., by adding water or a reducing agent).
- Extracted the organic layer if biphasic, or evaporate the solvent if homogeneous.
- Purified the product using chromatographic techniques (e.g., silica gel column chromatography).

4. **Characterization:**
- Analyzed the crude product using NMR spectroscopy to determine conversion and selectivity.
- Isolated and purified the product for further structural confirmation by NMR.

5. **Optimization:**
- Screened different ruthenium catalysts and ligands to find the most efficient system.
- Varied the solvent, temperature, and additives to optimize the reaction conditions.
- Performed control experiments to understand the mechanism and scope of the C-H activation.

- **Experimental Procedure**

1. **Catalyst Screening:**
- Weighed 0.05 mmol of [Ru(p-cymene) Cl2]2 and dissolve in 5 mL of acetonitrile.
- Added 0.1 mmol of a ligand (e.g., 1,10-phenanthroline) and stir for 30 minutes.
- In a separate Schlenk tube, added 1 mmol of the substrate (e.g., benzene).
- Added the catalyst solution to the substrate, followed by 2 mmol of an oxidant (e.g., AgOAc).
- Heated the reaction mixture to 100°C and stir for 12 hours.
- After cooling, filtered the mixture to remove any insoluble materials.
- Concentrated the filtrate and purify the product by column chromatography.

2. **Characterization:**
- Analyzed the purified product using 1H NMR spectroscopy.
- Confirmed the structure by comparing the data with known compounds or through X-ray crystallography.

3. **Optimization:**
- Repeated the procedure with different ruthenium precursors, ligands, and solvents to optimize yield and selectivity.

Result and Discussion

Catalyst screening:

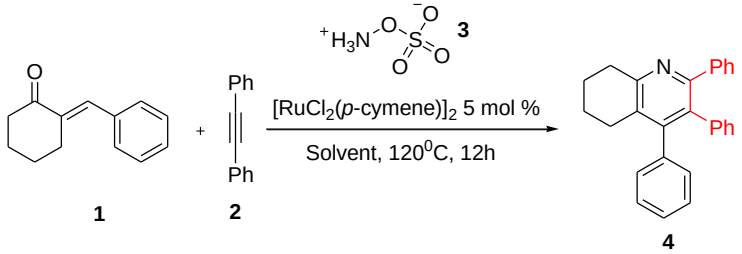

Fig. 1. Reaction process of catalyst

The Fig. 1. depicts a schematic representation of a catalyst screening experiment. While the specific catalyst is not labelled, it is likely a copper catalyst because copper catalysts are commonly used in homogeneous catalysis, which is the type of catalysis depicted in the figure.

In homogeneous catalysis, the catalyst is in the same phase as the reactants. This is in contrast to heterogeneous catalysis, where the catalyst is in a different phase from the reactants, such as a solid catalyst and liquid reactants.

The experiment involves reacting a reactant, denoted by "RuCl," with a phenyl group (Ph) in a solvent at 120°C for 12 hours. The catalyst, denoted by "RuCl(p-cymene)," is present at 5 mol%. The mol% refers to the number of moles of catalyst per 100 moles of reactant.

The experiment likely involves screening different catalysts to find the one that produces the desired product in the highest yield. The yield is the amount of product produced compared to the amount of starting material.

Table 4.1. Screening and yield of different catalysts

Entry	Solvent (0.1 M)	Catalyst	Additive 1	Temp	Isolated Yield Of %)
1	HFIP	Co(acac)2	CsOAc	120	33
2	HFIP	[cp*RhCl2]2	CsOAc	120	25
3	HFIP	[RuCl2(p-cymene)]2	CsOAc	120	68
4	HFIP	[cp*COI2]2	CsOAc	120	nd

The table 1 provides information on a series of experiments conducted to optimize the reaction conditions for the formation of the substituted phenyl-pyrrole product. Each entry varies the catalyst while keeping other conditions constant, and the isolated yields are reported.

Analysis of Experimental Data:

1. **Common Conditions:**
   - **Solvent:** HFIP (Hexafluoroisopropanol) at 0.1 M concentration.
   - **Additive:** CsOAc (Cesium Acetate).
   - **Temperature:** 120°C.
2. **Variable:** Catalyst.

Entries:

1. **Entry 1:**
   - **Catalyst:** $Co(acac)_2$ (Cobalt(II) acetylacetonate).
   - **Isolated Yield:** 33%.
2. **Entry 2:**
   - **Catalyst:** [Cp*RhCl2]2 (Bis(cyclopentadienyl)rhodium(III) dichloride).
   - **Isolated Yield:** 25%.

3. **Entry 3:**
   - **Catalyst:** [RuCl2(p-cymene)]2 (Bis(p-cymene)ruthenium(II) dichloride).
   - **Isolated Yield:** 68%.
4. **Entry 4:**
   - **Catalyst:** [Cp*CoI2]2 (Bis(cyclopentadienyl)cobalt(III) diiodide).
   - **Isolated Yield:** Not determined (nd).

Analysis:

- **Entry 1 ($Co(acac)_2$):** The cobalt catalyst gave a moderate yield of 33%. This shows that cobalt can catalyze the reaction but is not very efficient under these conditions.
- **Entry 2 ($[Cp^*RhCl_2]_2$):** The rhodium catalyst resulted in a lower yield of 25%, indicating that this specific rhodium complex is less effective compared to the cobalt catalyst in this reaction.
- **Entry 3 ($[RuCl_2(p\text{-cymene})]_2$):** The ruthenium catalyst provided the highest yield at 68%, demonstrating that this catalyst is significantly more efficient for this transformation compared to the cobalt and rhodium catalysts tested.

It can be concluded that:

- **Best Catalyst:** [RuCl2(p-cymene)]2 appears to be the best catalyst among those tested, providing the highest isolated yield of 68%.
- **Moderate Catalysts:** Co(acac)2 is a moderately effective catalyst with a yield of 33%.
- **Less Effective Catalysts:** [Cp*RhCl2]2 was the least effective among the catalysts with a yield of 25%.
- **Undetermined Catalyst:** The performance of [Cp*CoI2]2 remains undetermined.

This analysis indicates that ruthenium-based catalysts, specifically $[RuCl_2(p\text{-cymene})]_2$, are highly effective for this reaction, while cobalt and rhodium complexes show varying degrees of efficiency.

Although less common, Ru(III) catalysts like RuCl3 have shown promising results in certain C-H activation processes, offering different reactivity profiles compared to their Ru(II) counterparts (Jia & Kitamura, 1999). Phosphines such as PPh3 are often used to stabilize ruthenium complexes, enhancing their reactivity towards C-H bonds (Trost, 2015). N-heterocyclic carbenes provide strong σ-donation, which can increase the electron density on the ruthenium center, facilitating C-H activation (Glorius, 2007). Cyclopentadienyl ligands, such as Cp* (pentamethylcyclopentadienyl), can create a more electron-rich environment, making the ruthenium center more reactive (Gade, 2014). The choice of solvent and additives can also impact the performance of ruthenium catalysts. Polar solvents like DMSO or DMF often enhance catalyst solubility and stability, while additives such as acids or bases can modulate the reaction environment to favor C-H activation (Hartwig, 2012).

Conclusion

The screening and development of ruthenium catalysts for C-H activation have significantly advanced over the past few decades, driven by the quest for more efficient, selective, and sustainable catalytic processes. Continued research in this area promises to further expand the scope and applications of ruthenium-catalyzed C-H activation in organic synthesis.

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