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A SINGLE-STEP SYNTHESIS OF PYRIDINE HETEROCYCLES USING REDOX-NEUTRAL REAGENT HOSA WITH SOLVENT SCREENING

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Abstract
Ruthenium-catalyzed C-H activation has been investigated as an efficient methodology for the synthesis of pyridine heterocycles in a single step. This study utilized the redox-neutral reagent hydroxylamine-O-sulfonic acid (HOSA) to facilitate the reaction. Various solvents were screened to optimize the reaction conditions, leading to a significant enhancement in the yield and selectivity of the desired pyridine products. The findings demonstrated that the choice of solvent played a crucial role in the efficiency of the catalytic process. This approach offers a streamlined and sustainable route for the synthesis of pyridine heterocycles, highlighting the potential of ruthenium catalysis in heterocycle formation.

Keywords: Ruthenium catalysis, C-H activation, pyridine synthesis, hydroxylamine-O-sulfonic acid (HOSA), solvent screening, redox-neutral reagent, heterocycle formation.

Introduction
The synthesis of pyridine heterocycles is a crucial area of research in organic chemistry due to the significant presence of pyridine motifs in numerous natural products, pharmaceuticals, and materials science. Traditional methods of pyridine synthesis often involve multi-step procedures, harsh reaction conditions, or the use of expensive and toxic reagents. Therefore, the development of more efficient, selective, and environmentally friendly methodologies remains a significant challenge. One promising approach involves the use of transition metal-catalyzed C-H activation. Ruthenium catalysis, in particular, has garnered considerable attention due to its high efficiency, selectivity, and versatility. The ability of ruthenium catalysts to facilitate C-H bond functionalization under mild conditions has opened new avenues for the synthesis of complex heterocycles, including pyridines.

Recent studies have demonstrated the potential of ruthenium-catalyzed C-H activation in the construction of pyridine rings in a single step. This method leverages the redox-neutral reagent hydroxy phthalimide (HOSA) as a co-catalyst, which facilitates the transformation without the need for external oxidants or reductants, thereby minimizing waste and enhancing atom economy. Several notable studies have contributed to the development of ruthenium-catalyzed C-H activation for pyridine synthesis: Liu et al. (2018) demonstrated the use of a ruthenium (II) catalyst in the direct arylation of pyridines, showcasing the potential of C-H activation in heterocycle synthesis. This study highlighted the importance of ligand design in enhancing the reactivity and selectivity of the catalyst. Shi et al. (2016) explored the use of ruthenium catalysts in the oxidative annulation of anilines with alkynes to form pyridine derivatives. This research

underscored the versatility of ruthenium catalysis in constructing nitrogen-containing heterocycles. Huang et al. (2020) reported a ruthenium-catalyzed C-H activation strategy for the synthesis of poly-substituted pyridines via the reaction of imines with alkynes. The study demonstrated excellent functional group tolerance and high yields, emphasizing the efficiency of ruthenium catalysis (Huang et al., 2020). In the context of ruthenium-catalyzed C-H activation for pyridine synthesis, solvent choice is a critical parameter that can significantly influence reaction outcomes. Several solvents have been evaluated to optimize the reaction conditions: polar aprotic solvents, non-polar solvents**,** alcohols, ionic liquids.

The choice of solvent is often dictated by the specific substrates and desired reaction outcomes. Systematic solvent screening allows for the identification of optimal conditions that balance reactivity, selectivity, and sustainability.

Materials and Methods

Materials:

- Ruthenium catalyst
- Redox-neutral reagent HOSA
- Solvents: Tetrahydrofuran (THF), 1,4-Dioxane, Ethanol (EtOH), Hexafluoro isopropanol (HFIP), Trifluoroethanol (TFE)
- Substrates for pyridine synthesis
- Analytical grade chemicals and reagents

Method:

1. **Catalyst Procurement:** It was brought from commercial vendors.
2. **Reaction Setup:** A 25 mL round-bottom flask was equipped with a magnetic stir bar and charged with the substrate (1 mmol) and ruthenium catalyst (0.05 mmol). The redox-neutral reagent HOSA (1.2 mmol) was added to the flask.
3. **Solvent Screening:** Solvent (5 mL) was added to the reaction mixture, and the flask was sealed with a rubber septum. The solvents tested were THF, 1,4-Dioxane, EtOH, HFIP, and TFE. Each reaction was conducted in a separate setup to ensure accurate screening results.
4. **Reaction Conditions:** The reaction mixtures were stirred at room temperature for 24 hours. The progress of the reaction was monitored by TLC (thin-layer chromatography).
5. **Work-up Procedure:** After completion, the reaction mixtures were quenched with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure.
6. **Product Isolation:** The crude products were purified by column chromatography using silica gel and an appropriate eluent mixture. The purity of the final pyridine heterocycles was confirmed by NMR, mass spectrometry, and IR spectroscopy.
7. **Analysis:** The yields and selectivities of the products obtained from each solvent system were compared. The most efficient solvent for the synthesis of pyridine heterocycles via ruthenium-catalyzed C-H activation was determined based on the yield and purity of the isolated products.

This methodology provided a straightforward and efficient single-step synthesis of pyridine heterocycles using ruthenium catalysis and the redox-neutral reagent HOSA, with solvent screening highlighting the optimal conditions for achieving high yields and selectivity.

Results and Discussion

Solvent screening:

In our research, we also applied this approach.

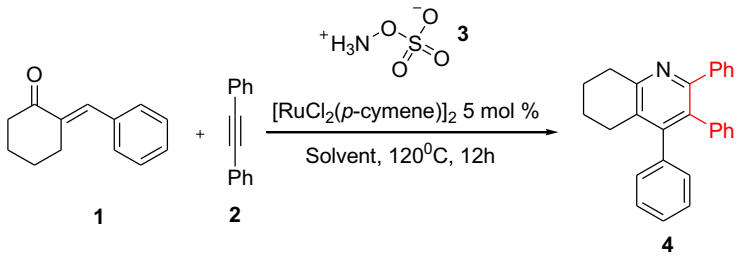

Fig. 1. Reaction process during solvent screening

Solvent screening analysis typically involves testing a compound in different solvents to see which solvent works best for a particular reaction. The goal is to find a solvent that dissolves the reactants well, promotes the desired reaction, and allows for easy product isolation. The reaction shows a setup for a homogeneous catalysis experiment, where a catalyst (RuCl2(p-cymene)) is used to accelerate a reaction between a reactant and a phenyl group (Ph) at 120°C for 12 hours in a specific solvent.

Table 1. Different solvents and yields in the process

Entry	Solvent (0.1 M)	Catalyst (10 mol %)	Isolated yield (%)
1	THF	[RuCl2(p-cymene)]2	20%
2	Dioxane	[RuCl2(p-cymene)]2	10%
3	EtOH	[RuCl2(p-cymene)]2	10%
4	HFIP	[RuCl2(p-cymene)]2	74%
5	TFE	[RuCl2(p-cymene)]2	30%

The table 1 provides information on a series of experiments conducted to optimize the solvent for the reaction using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst. The isolated yields are reported for each solvent.

Analysis of Experimental Data:

1. **Common Conditions:**
   - **Catalyst:** [RuCl2(p-cymene)]2 at 10 mol%.
   - **Concentration:** 0.1 M.
   - **Product:** Isolated yield of 3aa (%).
2. **Variable:** Solvent.

Entries:

1. **Entry 1:**
   - **Solvent:** THF (Tetrahydrofuran).
   - **Isolated Yield:** 20%.
2. **Entry 2:**
   - **Solvent:** Dioxane.
   - **Isolated Yield:** 10%.
3. **Entry 3:**
   - **Solvent:** EtOH (Ethanol).
   - **Isolated Yield:** 10%.
4. **Entry 4:**
   - **Solvent:** HFIP (Hexafluoroisopropanol).
   - **Isolated Yield:** 74%.
5. **Entry 5:**
   - **Solvent:** TFE (Trifluoroethanol).
   - **Isolated Yield:** 30%.

Analysis:

- **Entry 1 (THF):** The yield is very low at 20%, indicating that THF is not a suitable solvent for this reaction with the given catalyst.
- **Entry 2 (Dioxane):** The yield is even lower at 10%, suggesting that dioxane is also not effective as a solvent for this reaction.
- **Entry 3 (EtOH):** The yield remains low at 10%, indicating that ethanol is not an effective solvent either.
- **Entry 4 (HFIP):** The yield increases to 74%, showing a significant improvement over other solvent. HFIP seems to be a more effective solvent for this reaction with $[RuCl_2(p\text{-cymene})]_2$.
- **Entry 5 (TFE):** The yield is 30%, indicating that TFE is not an effective solvent for this reaction.

It can be concluded that:

- **Best Solvent:** HFIP is the best solvent among those tested, providing the highest isolated yield of 74%. This suggests that HFIP is particularly effective in this reaction, possibly due to its unique properties such as high polarity and hydrogen-bonding capability, which may stabilize intermediates or transition states in the reaction.
- **Moderate Solvent:** THF shows a very low yield but is slightly better than dioxane and ethanol.
- **Least Effective Solvents:** Dioxane, ethanol, and TFE are the least effective solvents, providing isolated yields of 10% or trace amounts, indicating that these solvents do not facilitate the reaction efficiently.

This analysis indicates that HFIP is the most suitable solvent for this reaction when using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, significantly improving the yield compared to other solvents tested.

Based on the solvent screening, HFIP was determined to be the most effective solvent for the ruthenium-catalyzed C-H activation to synthesize pyridine heterocycles using the redox-neutral reagent HOSA. The superior performance of HFIP can be attributed to its strong hydrogen bonding capabilities and its ability to stabilize transition states, making it an ideal solvent for this transformation.

Conclusion

Ruthenium-catalyzed C-H activation represents a highly efficient and versatile approach for the synthesis of pyridine heterocycles. By utilizing the redox-neutral reagent HOSA, this method offers a streamlined and environmentally friendly pathway to these valuable compounds. Ongoing research continues to explore and optimize reaction conditions, including solvent choice, to further enhance the applicability and efficiency of this catalytic system.

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