

Ruthenium-Catalyzed Oxidative Synthesis of 2-Pyridones through C–H/N–H Bond Functionalizations

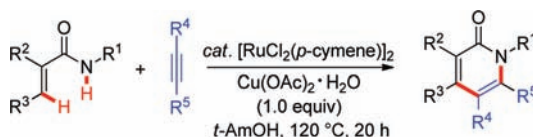
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ABSTRACT



An inexpensive ruthenium catalyst enabled oxidative annulations of alkynes by acrylamides with ample scope, which allowed for the preparation of 2-pyridones employing various electron-rich and electron-deficient acrylamides as well as (di)aryl- and (di)alkyl-substituted alkynes.

Pyridones are key structural motifs in compounds with important activities of relevance to biology.¹ As a result, different methods for the selective preparation of these heterocycles were devised,¹ among which transition-metal-catalyzed transformations have received significant recent attention.² Particularly, catalyzed direct functionalizations of C–H bonds have emerged as economically and ecologically benign tools for the synthesis of substituted heterocycles.³ Thus, cross-dehydrogenative reactions have proven valuable, since they avoid the use of prefunctionalized starting materials and thereby allow for a streamlining of organic synthesis.^{3,4} Based on pioneering reports on rhodium-catalyzed oxidative annulation reactions by the research groups of Miura and Satoh⁵ as well as Fagnou,^{6–8} Li and co-workers recently disclosed a useful rhodium-catalyzed

synthesis of 2-pyridones through oxidative couplings between acrylamides and alkynes.⁹ While this report represented remarkable progress, the rhodium catalyst

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unfortunately displayed significant limitations. For instance, (i) dialkyl-substituted alkynes gave complicated reaction mixtures, (ii) superstoichiometric amounts (2.2 equiv) of the terminal oxidant $\text{Cu}(\text{OAc})_2$ proved mandatory, and (iii) the use of acrylamides bearing electron-deficient *N*-substituents resulted in unsatisfactory selectivities. Based on mechanistic studies on carboxylate assistance in ruthenium-catalyzed C–H bond transformations,^{10,11} we recently devised a first ruthenium-catalyzed¹² oxidative^{13,14} annulation process through C–H bond cleavages.¹⁵ Since inexpensive¹⁶ ruthenium complexes have thus far been underexplored for oxidative annulation processes, we became interested in probing their use for an oxidative synthesis of 2-pyridones through cleavages of C–H and N–H bonds, on which we wish to report herein. Importantly, the inexpensive ruthenium catalyst displayed a significantly improved substrate scope as compared to

the previously reported rhodium⁹ complex, which *inter alia* set the stage for high-yielding 2-pyridone syntheses with dialkyl-substituted alkynes and acrylamides with electron-deficient *N*-substituents.

At the outset of our studies, we optimized reaction conditions for the oxidative annulation of alkyne **2a** by acrylamide **1a** for the synthesis of 2-pyridone **3aa**. Optimal reaction conditions involved the use of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the terminal oxidant in *t*-AmOH as the solvent. Other sacrificial oxidants, such as benzoquinone (0%), air (5%), or AgOAc (65%), provided less satisfactory results. Representative alternative solvents, including DME (< 5%) or MeOH (44%), gave inferior yields of the desired product **3aa**. Notably, 1 equiv of the terminal oxidant $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ turned out to be sufficient, which compares favorably with a rhodium-catalyzed⁹ process that required superstoichiometric amounts of the oxidant (2.2 equiv).

With optimized reaction conditions in hand, we explored the scope of the ruthenium-catalyzed pyridone

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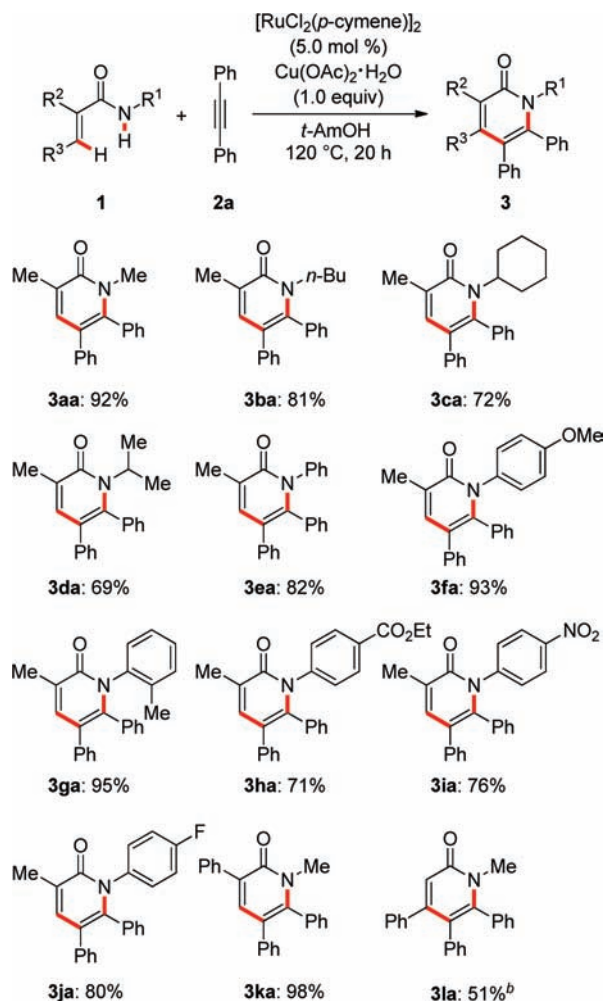
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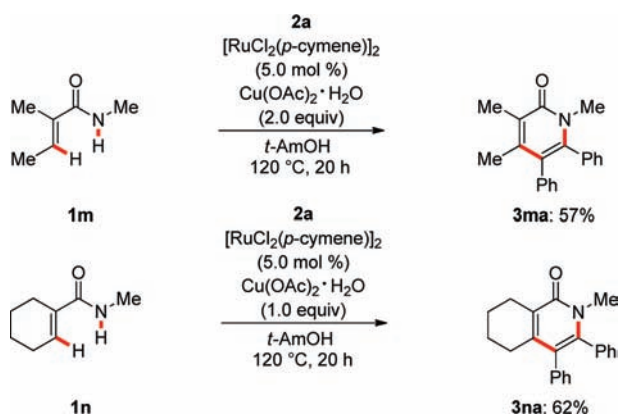
(16) $[\text{Cp}^*\text{RhCl}_2]_2$: 2545 € versus $[\text{RuCl}_2(p\text{-cymene})]_2$: 257 € (5.0 g, Sigma-Aldrich, 2011).

Scheme 1. Scope of the Ruthenium-Catalyzed Oxidative Annulation of Alkyne **2a**^a



synthesis using alkyne **2a** (Scheme 1). We were delighted to observe that the catalytic system turned out to be broadly applicable. Hence, acrylamides **1** bearing various *N*-alkyl or *N*-aryl substituents were efficiently converted to 2-pyridones **3aa–3da** and **3ea–3ja**, respectively. It is particularly noteworthy that amides **1** bearing electron-withdrawing *N*-substituents chemoselectively delivered products **3ha–3ja**, a notable difference compared to a rhodium-catalyzed⁹ transformation in which a mixture of products was obtained. Moreover, acrylamides **1** bearing different substituents in the α - or β -position could be employed in the ruthenium-catalyzed oxidative annulation. Interestingly, β -phenyl substituted acrylamide **1l** proved also to be a viable substrate, while no coupling product could be detected when using this starting material in the rhodium-catalyzed oxidative coupling.⁹

Scheme 2. Ruthenium-Catalyzed Oxidative Annulations with α,β -Disubstituted Amides **1m** and **1n**



Furthermore, our new ruthenium-based annulation method allowed for the first use of α,β -disubstituted acrylamides in oxidative 2-pyridone syntheses, which provided direct access to products **3ma** and **3na** (Scheme 2).¹⁷

The inexpensive ruthenium catalyst was not limited to the oxidative annulation of toluene (**2a**) but also enabled the efficient conversion of functionalized diaryl-substituted alkynes **2b–2g** (Scheme 3).

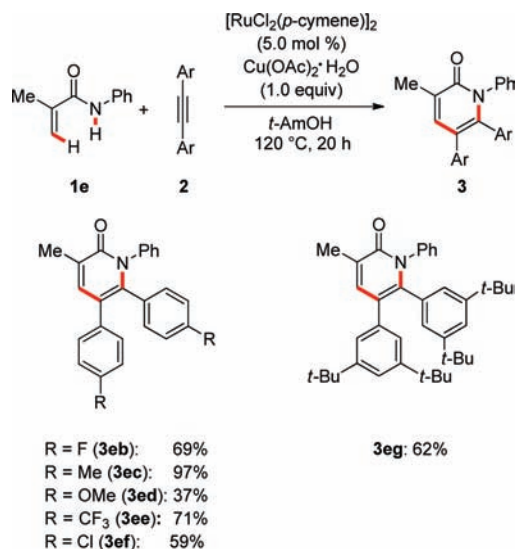
Likewise, unsymmetrically substituted alkynes **2** proved to be viable substrates (Scheme 4). Importantly, the oxidative annulations with alkynes **2h** and **2i** occurred with remarkably high regioselectivity, which set the stage for the preparation of 2-pyridones **3lh** and **3li**.

In contrast to a recently reported rhodium catalyst,⁹ the ruthenium-based protocol allowed for the use of dialkyl-substituted alkynes as well (Scheme 5).¹⁸ Notably, even the more challenging amides **1h** and **1i** displaying

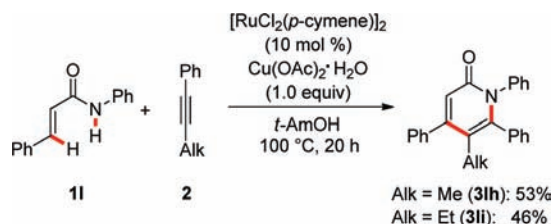
(17) Products stemming from hydroarylations of alkyne **2a** were isolated here as a minor byproduct. For detailed information, see the Supporting Information.

(18) Intermolecular competition experiments between diaryl- and dialkyl-substituted alkynes (**2a** versus **2k**, and **2b** versus **2c**) revealed that electron-deficient toluene derivatives are preferentially converted (see Supporting Information).

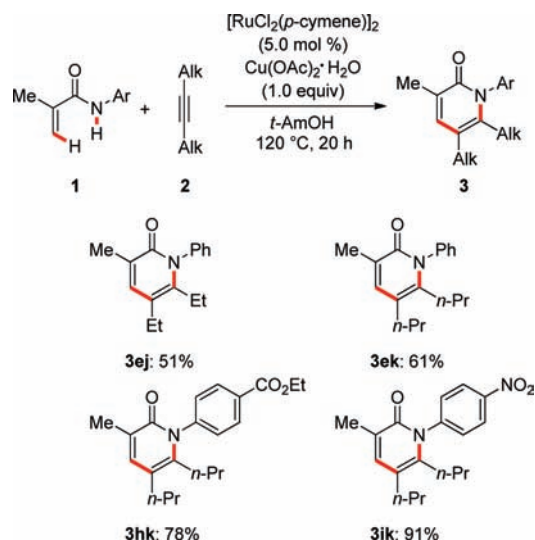
Scheme 3. Annulation with Diaryl-Substituted Alkynes **2b–2g**



Scheme 4. Ruthenium-Catalyzed Annulation with Unsymmetrically Substituted Alkynes **2h** and **2i**



Scheme 5. Oxidative Annulation with Dialkyl-Substituted Alkynes **2**



electron-deficient *N*-substituents furnished the desired products **3hk** and **3ik**, respectively, in high yields.

As to the reaction mechanism, our preliminary studies¹⁵ indicate a reaction manifold involving initial intermolecular carboration of alkyne **2**, along with a subsequent intramolecular C–N bond formation.

In summary, we have disclosed a novel ruthenium-catalyzed oxidative synthesis of 2-pyridones. Importantly, the inexpensive ruthenium catalysts displayed a notable chemo- and regioselectivity, which resulted in a significantly improved substrate scope as compared to a related rhodium-catalyzed transformation. These results clearly

illustrate the beneficial features and remarkable potential of thus far underexplored ruthenium catalysts in oxidative annulative C–H bond functionalization processes.

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Supporting Information Available. Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.