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

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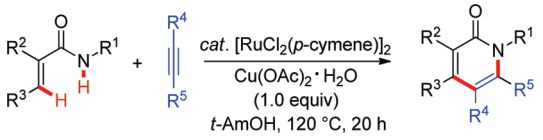
ABSTRACT



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 Satoh[5] 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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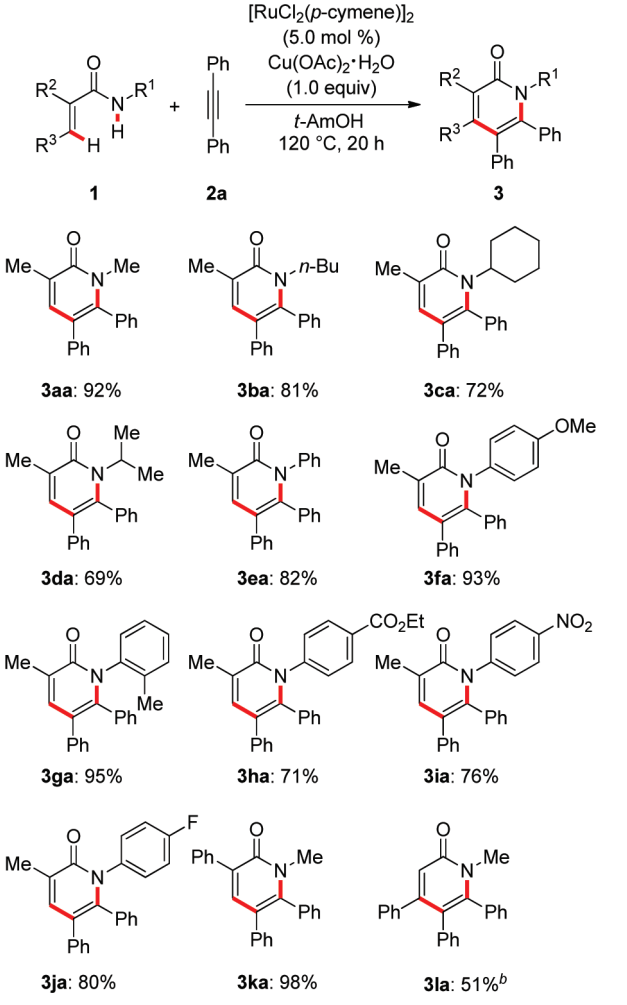
unfortunately displayed significant limitations. For instance, (i) dialkyl-substituted alkynes gave complicated reaction mixtures, (ii) superstoichiometric amounts (2.2 equiv) of the terminal oxidant $Cu(OAc)_2$ proved mandatory, and (iii) the use of acrylamides bearing electron-deficient *N*-substituents 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-catalyzed[12] oxidative[13,14] annulation process through C−H bond cleavages.[15] Since inexpensive[16] 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 rhodium[9] 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 $Cu(OAc)_2•H_2O$ 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 $Cu(OAc)_2•H_2O$ turned out to be sufficient, which compares favorably with a rhodium-catalyzed[9] 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

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



[a] Reaction conditions: **1** (1.0 mmol), **2a** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2•H_2O$ (0.5 mmol), *t*-AmOH (2.0 mL), 120 °C, 20 h; isolated yields. [b] $Cu(OAc)_2•H_2O$ (1.0 mmol), 100 °C, 48 h.

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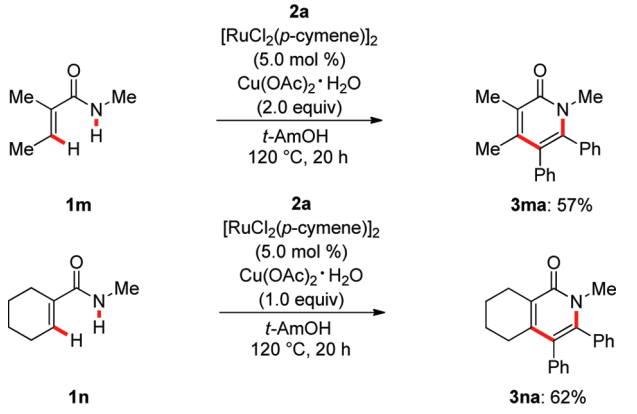
(16) $[Cp^*RhCl_2]_2$: 2545 € versus $[RuCl_2(p\text{-cymene})]_2$: 257 € (5.0 g, Sigma-Aldrich, 2011).

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-catalyzed[9] 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 tolane (**2a**) but also enabled the efficient conversion of functionalized diaryl-substituted alkynes **2b**−**2g** (Scheme 3).

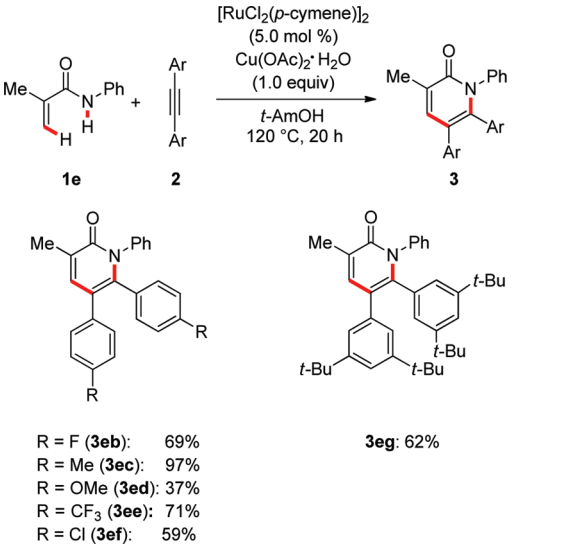
Likewise, unsymmetrically substituted alkynes **2** proved to be viable substrates (Scheme 4). Importantly, the oxidative annulations with alkynes **2h** and **2i** occurred with remarkably high regioselectivity, which set the stage for the preparation of 2-pyridones **3lh** and **3li**.

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

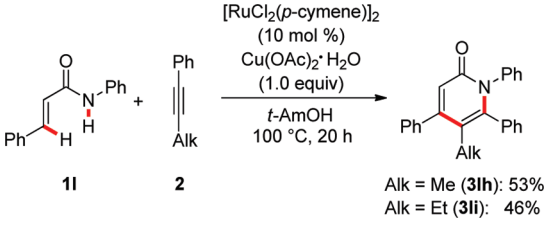
(17) Products stemming from hydroarylations of alkyne **2a** were isolated here as a minor byproduct. For detailed information, see the Supporting Information.

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

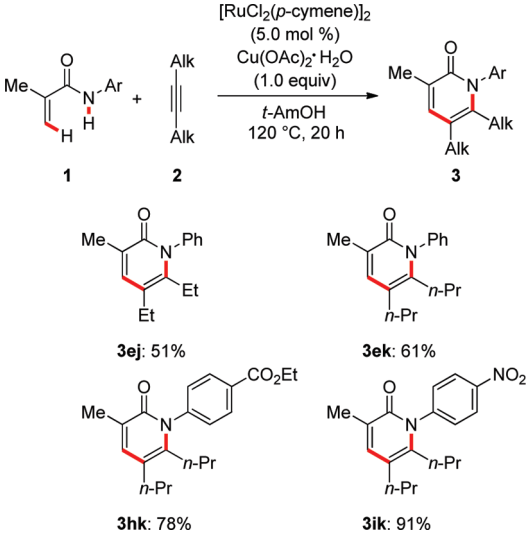
Scheme 3. Annulation with Diaryl-Substituted Alkynes **2b**−**2g**



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 studies[15] indicate a reaction manifold involving initial intermolecular carboruthenation 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 ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.