Ruthenium-Catalyzed C–H/N–O Bond Functionalization: Green Isoquinolone Syntheses in Water

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ABSTRACT

Ruthenium-catalyzed isoquinolone syntheses with ample scope were accomplished through carboxylate assistance in environmentally benign water as a reaction medium. The high chemoselectivity of the ruthenium(II) carboxylate complex also set the stage for the direct use of free hydroxamic acids for annulations of alkynes.


for the reoxidation of rhodium(I) intermediates, thereby preventing the use of additional external oxidants.

Water is a nonflammable, nontoxic, green solvent, which has attracted considerable recent attention as a reaction medium for sustainable C–H bond functionalizations. Given our interest in employing water as a user-friendly solvent for catalyzed C–H bond transformations, we thus became attracted by devising first metal-catalyzed direct annulations of alkynes by benzamides in water, on which we report herein. Intriguingly, the remarkable chemoselectivity of the optimized ruthenium(II) carboxylate catalyst allowed for the use of N-methoxybenzamides as well as more atom-economical free hydroxamic acids for syntheses of isoquinolones, indispensable structural motifs in bioactive compounds of importance to medicinal chemistry.

At the outset of our studies, we probed the effect of a set of cocatalytic additives for the envisioned coupling of N-methoxybenzamide (1a) with alkyne 2a in water as green solvent (Table 1). Unfortunately, the use of KPF6 did not provide a satisfactory rate acceleration (entries 1 and 2). Yet, among different carboxylate additives, sterically hindered KO2CMes provided optimal yields of the desired product 3aa (entries 3–7). Furthermore, it is noteworthy that water compared favorably with respect to representative organic solvents (entries 7–12).

With optimized reaction conditions in hand, we explored the scope of the ruthenium-catalyzed annulation of alkynes 2 by differently substituted N-methoxybenzamides 1 with water as a reaction medium (Scheme 1).

Notably, the catalytic system proved broadly applicable, thus enabling the efficient conversion of both electron-rich arenes 1b–1d as well as electron-deficient derivatives 1e–1h displaying valuable functionalities, such as nitro or halo-substituents.

Moreover, alkyl-substituted alkynes 2 were converted with high catalytic efficacy as well (Scheme 2), while


(11) During the preparation of our manuscript a ruthenium-catalyzed annulation with hydroxamic acid esters in MeOH as the solvent was reported: Li, B.; Feng, H.; Xu, S.; Wang, B. Chem—Eur. J. 2011, 17, DOI: 10.1002/chem.201102445.


unsymmetrical alkynes 2d–2f provided the desired products 3ad–3af with excellent regioselectivities.

Table 1. Optimization of Isoquinolone Synthesis

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>H2O</td>
<td>17%</td>
</tr>
<tr>
<td>2</td>
<td>KPF6</td>
<td>H2O</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>KOAc</td>
<td>H2O</td>
<td>11%</td>
</tr>
<tr>
<td>4</td>
<td>NaOAc</td>
<td>H2O</td>
<td>17%</td>
</tr>
<tr>
<td>5</td>
<td>CsOAc</td>
<td>H2O</td>
<td>46%</td>
</tr>
<tr>
<td>6</td>
<td>KOPiv</td>
<td>H2O</td>
<td>58%</td>
</tr>
<tr>
<td>7</td>
<td>KO2CMes</td>
<td>H2O</td>
<td>81%</td>
</tr>
<tr>
<td>8</td>
<td>KO2CMes</td>
<td>t-AmOH</td>
<td>19%</td>
</tr>
<tr>
<td>9</td>
<td>KO2CMes</td>
<td>MeOH</td>
<td>65%</td>
</tr>
<tr>
<td>10</td>
<td>KO2CMes</td>
<td>DMF</td>
<td>3%</td>
</tr>
<tr>
<td>11</td>
<td>KO2CMes</td>
<td>PhMe</td>
<td>28%</td>
</tr>
<tr>
<td>12</td>
<td>KO2CMes</td>
<td>H2O</td>
<td>70%</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (0.5 mmol), 2a (1.0 mmol), [RuCl2(p-cymene)]; (2.5 mol %), additive (30 mol %), solvent (2.0 mL), 16 h; isolated yields. GC-conversion.*
As to the catalyst’s working mode it is noteworthy that well-defined ruthenium(II) carboxylate complex 4 displayed an efficacy comparable to the one observed when using the in situ generated catalytic system (Scheme 3).

Intramolecular competition experiments with substrates 1i and 1j bearing heteroatom-containing substituents in the meta-position occurred with a significantly altered site selectivity (Scheme 4) as compared to a meta-methylsubstituted N-methoxybenzamide (1d) (3da, Scheme 1). This observation can be rationalized with the key cyclo-ruthenation step depending on the kinetic C–H bond acidity.14

Additionally, intermolecular competition experiments indicated electron-deficient arenes to be preferentially functionalized (Scheme 5), hence rendering an electrophilic activation manifold less likely to be operative.

Intermolecular competition experiments between differently substituted alkynes 2a and 2c revealed tolane (2a) to be predominantly reacted (Scheme 6).

Further, annulations with differently substituted diarylalkynes highlighted electron-deficient derivatives to be converted with higher relative reaction rates.15

Experiments with isotopically labeled solvent and substrate [D3]-1a were suggestive of an irreversible C–H bond metatation (Scheme 7), which constitutes a notable difference to rhodium-catalyzed C–H bond functionalizations with N-methoxybenzamides.5b Moreover, the kinetic isotope effect (KIE) was determined to be \( k_{H}/k_{D} \approx 3.0 \) which can be rationalized with a working mode involving carboxylate-assisted ruthenation as the rate-limiting step.

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(15) See the Supporting Information for further details.
Finally, we were intrigued by the possibility of directly using significantly more atom-economical free hydroxamic acids 5 for ruthenium-catalyzed annulations of alkynes by C–H/N–O bond cleavages. Thus, we were pleased to observe that isoquinolones 3 were efficiently accessible from user-friendly acids 5 in water (Scheme 8), thereby further illustrating the remarkable robustness of the inexpensive ruthenium catalyst.

In summary, we have reported on first catalyzed annulations of alkynes by benzamides through C–H bond cleavages with water as a green reaction medium. Thus, carboxylate assistance set the stage for a broadly applicable ruthenium-catalyzed isoquinolone synthesis from N-methoxybenzamides. Moreover, the extraordinary robustness and chemoselectivity of the ruthenium(II) carboxylate catalyst allowed for the direct use of free hydroxamic acids in annulations of alkynes. Further applications of inexpensive ruthenium complexes to catalyzed oxidative C–H bond functionalizations are ongoing in our laboratories and will be reported in due course.

Acknowledgment. Support by the DFG is gratefully acknowledged.

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.