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Copper/Nafion-Catalyzed Hydroarylation Process Involving Ketenimine Intermediates: A Novel and Synthetic Approach to 4-Sulfonamidoquinoline-2-ones and Derivatives Thereof

Benedikt Reichart,[a] Gema Guedes de la Cruz,[a] Klaus Zangger,[a] C. Oliver Kappe,[a] and Toma Glasnov[a,*]

[a] Christian Doppler Laboratory for Flow Chemistry and Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, 8010 Graz, Austria
Fax: (+43)-316-380-9840; phone: (+43)-316-380-8690; e-mail: toma.glasnov@uni-graz.at

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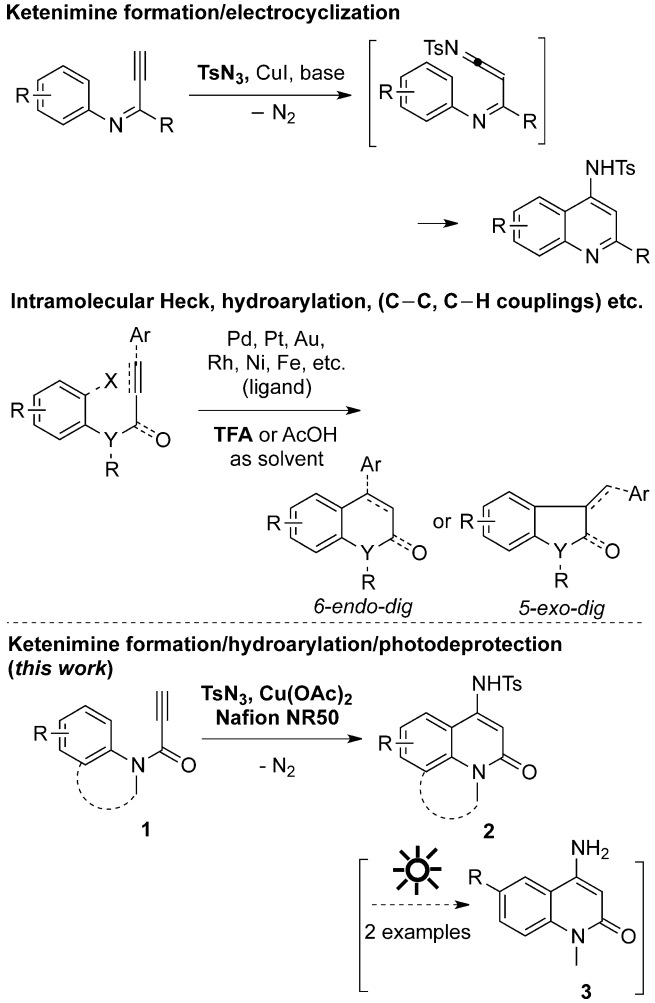
Abstract: A copper(II)/NafionNR50-catalyzed cascade is demonstrated, wherein *in situ* keteneimine formation and hydroarylation processes are involved. Various substituted 4-sulfonamidoquinolin-2-ones and various derivatives thereof were obtained. The robust toluenesulfonamide protecting group can be removed on demand in a mild light-promoted process to provide access to otherwise difficult to obtain 4-aminoquinolin-2-ones.

Keywords: catalysis; copper; cyclization; heterocycles; microwave and continuous flow chemistry

Ketenimines, originally reported by Staudinger in 1920 as nitrogen analogues of ketenes,[1] are important reactive species and useful synthetic intermediates. In the past few years various practical and versatile approaches to ketenimines have been developed, leading to an extensive implementation of ketenimine chemistry in a variety of highly efficient reactions.[2] In 2005, an elegant *in situ* generation of ketenimines *via* a copper-catalyzed azide-alkyne "click" reaction was reported by Chang et al.[3] As outlined in Scheme 1, in the presence of a Cu(I) catalyst, the [3+2] cycloaddition between toluenesulfonyl azide (TsN_3) and a terminal alkyne occurs, followed by a ring opening, extrusion of molecular nitrogen and hetero-Wolff rearrangement to provide N-tosyl ketenimines.[2f] As reactive intermediates the generated N-sulfonyl ketenimines have an additional N-substitution site, and therefore offer wider reactivity which is in direct dependence on the nature of the N-substitution. Importantly, the reactivity of the N-sulfonyl ketenimines is mainly characterized by initial nucleophilic attack on the C- atom adjacent to the nitrogen[4] as, for example, in the recent synthesis of quinolines *via* electrocyclization (Scheme 1).[4i] Quinolones have provoked a lot of interest due to their various applications as novel therapeutic agents, dyes etc. and have triggered the development of many general and efficient methods for their preparation.[5] On the other hand, 4-substituted quinolin-2-ones or coumarin-2-ones (Scheme 1) have been so far prepared using various (mostly precious) metal catalysts (Au, Pt, Pd, Rh, Ni, Bi, Fe etc.) or bimetallic systems (Pd/Cu, Au/Ag, etc.) in an *endo-dig* hydroarylation processes as a powerful strategy for constructing carbo- and heterocycles (Scheme 1).[6,7]

However, in a hydroarylation process both ends of the double or triple bond can react, thus resulting in the formation of either *exo*- or *endo*-cyclization products. Whereas often one pathway is preferred,[8] control and switching of the cyclization modes is generally a significant challenge and requires precious metal catalysts in combination with "designer" ligands.[9] Furthermore, the so far explored processes cover alkynes, alkenes and allenes but not ketenimines derived from alkynyl amides.[7] Despite the significant recent advances in ketenimine chemistry we reasoned that there is further reactivity to explore.

Herein we report a novel reaction model featuring an intramolecular ketenimine generation/capture involving a $Cu(OAc)_2$-NafionNR50-catalyzed hydroarylation process to efficiently provide functionalized 4-amino-substituted quinolin-2-ones and derivatives thereof. The toluenesulfonyl group can be removed on demand in a mild but effective visible light-driven flow deprotection step. For our purpose, broadly substituted alkynyl amides **1** (Scheme 1) were easily prepared *via* a microwave-assisted coupling protocol from the corresponding anilines[10] (for synthetic pro-



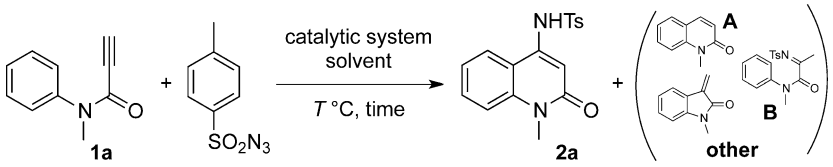
Scheme 1. Synthetic route to 4-tosylamidoquinolin-2-ones *via* ketenimine formation/hydroarylation process.

cedure see the Supporting Information) and could be isolated in sufficiently high purity and yield for the envisaged transformations. With the starting materials at hand, **1a** was chosen as our model substrate (Table 1) having an unbiased *p*-position occupied only by an H-atom. Following the synthetic protocol demonstrated by Cui,[4i] we initially evaluated the system of CuI/K_2CO_3 in dichloromethane (DCM) as solvent at 100 °C and 60 min reaction time, disappointingly delivering only traces of the expected product and mainly resulting in a complex mixture of side products with **B** being the major one (Table 1, entry 1).

Increasing the temperature and/or reaction time did not improve the outcome of the reaction (data not shown). Thus, we could exclude this catalytic system as being not suitable for our studies and turned our attention to exploring catalytic systems, previously reported in hydroarylation processes (Table 1, entries 2–6).[6,7] Several metals such as Pd(II), Pt(II) and an Au/Ag system, known to undergo electrophilic metallation of aromatic C–H bonds, were tested. Although all the catalytic systems were active, none could drive the reaction selectively towards the desired 4-sulfonamidoquinolin-2-one **2a**. The most active and selective catalyst – $PtCl_2$ – provided exclusively **A** – 4-unsubstituted *N*-methylquinolin-2-one – as the sole product of a hydroarylation reaction without involving the TsN_3 present in the reaction mixture (Table 1, entry 3). The same reaction outcome was observed when TsN_3 was omitted (Table 1, entry 4). $Pd(OAc)_2$ in combination with trifluoroacetic acid (TFA) showed similar results, although being slightly less reactive (Table 1, entry 5). Interestingly though, when using a catalytic system containing $Pd(OAc)_2$ and $Cu(OTf)_2$, we could observe a minor increase in the selectivity towards the desired product **2a**. This motivated an experiment where only $Cu(OAc)_2$ in place of $Pd(OAc)_2$ was used in a combination with 1 equiv. of TFA. To our satisfaction, the Cu(II) salt simultaneously promoted both the ketenimine formation and the hydroarylation process to deliver somewhat lower conversion (55%), however in a nearly 2:1 ratio in favour of the desired product **2a** (Table 1, entry 7). Rapid screening with several additional acids led surprisingly to selectivity of >99% towards the desired product in the case when NafionNR50, a solid super acid,[11] was used (Table 1, entry 10). Further optimization of temperature, reaction time, solvent, amount of NafionNR50 and catalyst resulted in the final conditions, providing selectively **2a** in 94% isolated yield (Table 1, entry 17). It is worth mentioning that higher concentrations (10 mol%) of $Cu(OAc)_2$ were beneficial for faster and complete reaction. Mechanistically we consider a Cu(II/III)-redox system,[12] involving highly electrophilic cationic copper species formed *in situ* with NafionNR50, to be in operation, and being able to undergo electrophilic metallation of the aromatic C–H bond in the *o*-position with respect to the amide functionality in the alkynyl amides **1** (Scheme 2).[6b,c]

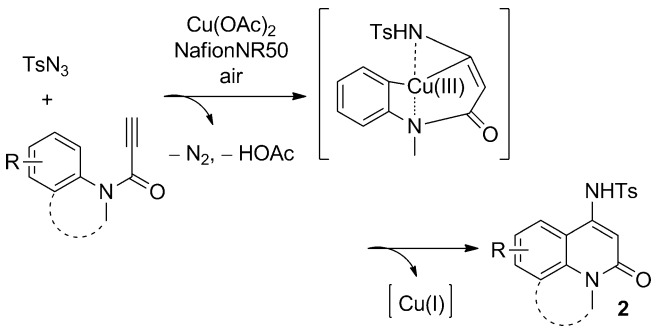
With the optimized reaction conditions in hand, we then extended the substrate scope in order to examine the general efficiency of this newly developed synthetic protocol (Table 2). The reaction tolerates various substitutions on the aromatic ring, making it compatible with, for example, halogen, ester, ether, or ketone functionality. Notably, slightly better yields were obtained with aryl substituents having electron-donating properties.[13] Furthermore, the conjugation of the ketenimine functionality with the amide group improves its acceptance properties for the aryl nucleophile at the C-2 positon adjacent to the NTs group. The catalytic system, however, could not promote a C(sp^3)–H activation process with *N*-cyclohexyl-*N*-methylpropiolamide (Table 2, **1d**). Additionally, *m*-substitution relative to the amide functionality on the aromatic ring resulted in a mixture of 5- and 7-regioisomers, as could be expected. While tertiary al-

Table 1. Catalyst screening and optimization of the ketenimine formation/hydroarylation process.[a]



Entry	Catalyst	Additive	Solvent	Temperature [°C]	Time [min]	Conversion [%][b]	**2a** Yield [%][b]
1	CuI	K_2CO_3	toluene	100	60	>99	traces
2	$AuCl_3$	AgOTf/PPh_3	toluene	80	720	77	traces
3	$PtCl_2$	–	DCE	130	60	>99	traces
4[c]	$PtCl_2$	–	DCE	130	60	>99	traces
5[d]	$Pd(OAc)_2$	TFA	DCE	80	720	97	traces
6	$Pd(OAc)_2$	$Cu(OTf)_2$	DCE	80	720	98	11
7[d]	$Cu(OAc)_2$	$BF_3{\cdot}OEt_2$	DCE	130	40	55	61
8[d]	$Cu(OAc)_2$	$MeSO_3H$	DCE	130	40	92	59
9[d]	$Cu(OAc)_2$	NafionNR50	DCE	130	40	34	±2
10[e]	$Cu(OAc)_2$	NafionNR50	DCE	130	40	>99	>99
11[e]	$Cu(OAc)_2$	NafionNR50	toluene	130	40	>95	±97
12[e]	$Cu(OAc)_2$	NafionNR50	MeCN	130	40	76	±55
13[e]	$Cu(OAc)_2$	NafionNR50	DCE	130	20	>99	>99
14[e]	Cu(0)	NafionNR50	DCE	130	20	<1	0
15[f]	$Cu(OAc)_2$	NafionNR50	DCE	130	20	>99	>99
16[g]	$Cu(OAc)_2$	NafionNR50	DCE	130	20	>87	>99
17[h]	$Cu(OAc)_2$	NafionNR50	DCE	150	10	>99	>99
18	–	NafionNR50	DCE	150	10	3	traces
19	$Cu(OAc)_2$	–	DCE	150	10	2	0
20[i]	$Cu(OAc)_2$	NafionNR50	DCE	150	30	30	traces

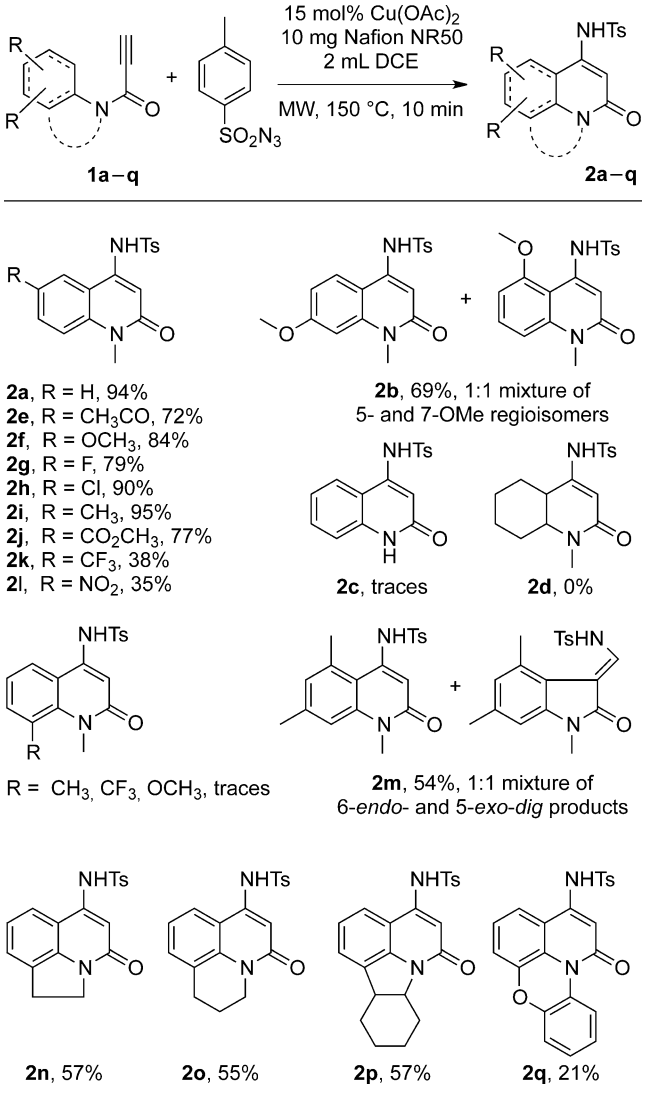
[a] *General conditions:* 0.8 mL solvent, 0.12 mmol **1a**, 10 mol% catalyst, 1.02 equiv. TsN_3 (270 µL 11–15% w/w solution in toluene); conventional heating at 80 °C and 100 °C; microwave heating at temperatures above 100 °C.
[b] Determined by HPLC at 254 nm.
[c] Without addition of TsN_3.
[d] 1 equiv. of additive.
[e] 100 mg NafionNR50.
[f] 30 mg NafionNR50.
[g] 5 mol% $Cu(OAc)_2$.
[h] 10 mg NafionNR50.
[i] Without addition of TsN_3 – the main product here resulted from a Glaser–Hay coupling.



Scheme 2. Considered mechanistic pathway – ligands are omitted for clarity.

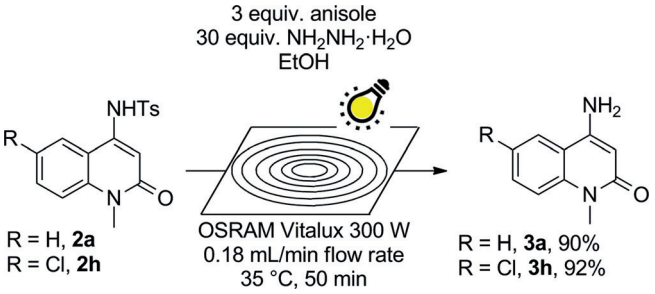
kynyl amides **1a**, **b** and **1e–l** as well as **1p–t** were successfully utilized in the reaction, the secondary alkynyl amide **1c** provided only traces of the cyclized product, due to either complexation with the copper catalyst or protonation by NafionNR50 thus disturbing the aromatic C–H activation. Interestingly, *ortho*-substitution of the starting alkynyl amides in **1m–o** hindered the reaction and only traces of the cyclized products **2m–o** were found in the reaction mixture. Extending the reaction time or increasing the reaction temperature as well as the catalyst amount did not help the reaction to proceed in the latter cases. We could rationalize that steric hindrance is the most probable reason for this observation. When using 3,5-disubstituted alkynyl amide **1m** a strong cumulative activation in the *ortho*-postion of the aromatic ring led to the formation of a 1:1 mixture of 6-*endo*- and 5-*exo-dig* products (Table 2, **2m**). The same result was observed with the corresponding alkynyl amide derived from 3,4,5-trimethylaniline (data not shown).

Table 2. Ketenimine/hydroarylation cyclization process – reaction scope.[a]



[a] Isolated compounds were characterized by HR-mass, ^{1}H NMR and ^{13}C NMR spectroscopy (see the Supporting information); all yields shown are of isolated products.

Subsequently, with the desired 4-toluenesulfonamidoquinolin-2-ones **2** at hand, we sought a mild and effective method for the removal of the robust toluenesulfonyl protecting group. This would provide a direct access to substituted 4-aminoquinolin-2-ones, otherwise difficult to prepare.[14] A major limitation here are the rigorous deprotection conditions needed – predominantly harsh acidic or reductive procedures.[15] This is a major obstacle whenever working with substrates bearing sensitive functional groups. More elaborate methods dedicated to solve the problem do exist, nevertheless challenges still remain.[16] To attain the N-tosyl deprotection, we selected a photochemical process – from safety, cost, and environmental stand-



Scheme 3. Photolysis of the tosyl-protecting group under continuous-flow conditions.

points. Photoinduced S–N bond cleavage has been previously scrutinized,[17] including the photoredox cleavage with visible light from an LED source.[18] Although effective, the process relies on an expensive iridium catalyst and requires prolonged reaction times. This motivated us to employ a continuous flow approach in order to enhance the light input (better surface-to-volume ratio)[19] thus improving the overall process with the hope of shortening the reaction times. Several photolysis systems were taken into account as alternative to the reported iridium catalyst.[20] Finally, a combination of anisole and hydrazine hydrate as non-expensive donor-reductant system,[20c] provided optimal results – reaction time <1 h (50 min) and quantitative conversions (HPLC, 254 nm). After realizing the best conditions (flow rate, temperature, irradiation time, donor-reductant system; data not shown) **2a** and **2h** were selected as standard examples and subjected to continuous-flow photolysis (Scheme 3) to illustrate the usefulness of the system. Satisfyingly, even after chromatographic work-up, **3a** and **3h** were obtained in 90% and 92% yields, respectively.

Moreover, the halogen atom present in **2h** remained intact under the selected photolysis conditions, hence demonstrating the mildness of the deprotection method.

In summary, we have demonstrated an unprecedented intramolecular keteneimine–hydroarylation sequence catalyzed by the $Cu(OAc)_2$-NafionNR50 system to prepare tosylated 4-aminoquinolin-2-ones and derivatives thereof. The reaction is compatible with aromatic tertiary alkynyl amides and tolerates various substitutions on the aromatic ring. But *ortho*-substitution on the aromatic ring hinders the reaction whereas *para*-dimethyl- or 3,4,5-trimethyl-substituted aromatics provide 1:1 mixtures of 6-*endo*- (4-aminoquinolin-2-ones) and 5-*exo-dig* products. Subsequently, we could realize a mild deprotection of the sturdy tosyl-protecting group *via* a light-promoted process under continuous-flow conditions to obtain some pure 4-aminoquinoilin-2-ones.

Experimental Section

General Conditions for the Synthesis of 6-Substituted 4-Sulfonamidoquinoline-2-ones 2a, e–q under Batch Microwave Conditions

To a stirred mixture of the corresponding alkynyl amide **1a**, **e–q** (0.3 mmol) and 1.5 mL dichloroethane (DCE) in a 5-mL Pyrex microwave vial, equipped with a magnetic stir bar, $Cu(OAc)_2$ (*ca.* 6 mg, 0.03 mmol, 10 mol%, 0.1 equiv.), tosyl azide (TsN_3, 555 μL, 0.31 mmol, 1.05 equiv., 11–15% w/w solution in toluene) and powdered Nafion® NR50 (10 mg, particle size $\leq$ 250 μm, $\geq$ 0.8 mequiv./g ion exchange capacity) were added. The reaction mixture was capped with a Teflon septum, stirred for 10 s and subjected to microwave heating for 10 min (fixed hold time) at 150 °C and subsequently cooled to 50 °C. The resulting reaction mixture was concentrated under reduced pressure and the residue purified by flash chromatography ($CHCl_3$:CH_3OH = 9:1) to afford 6-substituted 4-sulfonamidoquinoline-2-ones **2a**, **e–q**.

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