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COMMUNICATION

Investigating *N*-methoxy-*N′*-aryl ureas in oxidative C–H olefination reactions: an unexpected oxidation behaviour†

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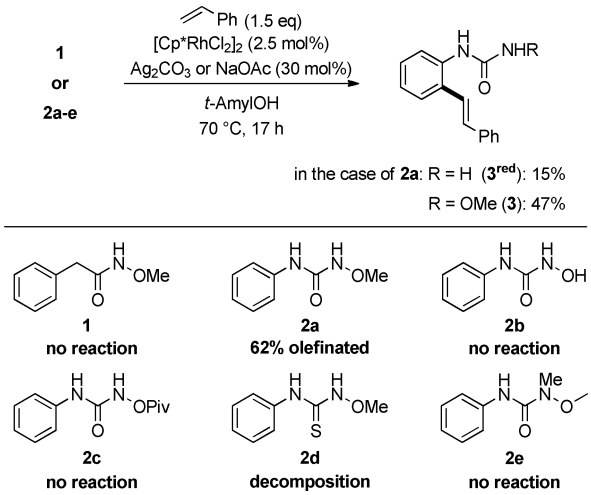
Herein, we report a urea derived directing group for mild and highly selective oxidative C–H bond olefination. Subsequent intramolecular Michael addition affords dihydroquinazolinones in good yields. The N–O bond of the urea substrate exhibits superior oxidative behaviour compared to a variety of other external oxidants.

Over the past decades, transition-metal catalyzed activation of traditionally unreactive carbon–hydrogen bonds has attracted considerable attention. C–H bond activation has since become a unique strategy to access complex structural motifs by efficient C–C bond forming reactions.[1] With the first report by Fujiwara and Moritani dating back to 1967,[2] a variety of oxidative Heck-coupling reactions[3] through C–H bond activation have been investigated. Several transition metals, such as Pd,[4] Rh[5] and Ru,[6] are known to effect this transformation.

The general drawback in these reports is the need for an external, mostly metallic, oxidant which leads to undesired waste production and usually necessitates high reaction temperatures, which limits the scope of these transformations. Oxidants pre-installed in the substrates[7] have been the subject of pioneering investigations by the groups of Cui and Wu,[8] Hartwig,[9] Yu,[10] Chiba[11] and Fagnou[12] to overcome these limitations. By allowing the reaction to proceed under milder conditions, internal oxidants generally allow for a much broader scope of substrates. Recently, Fagnou *et al.*[12] and our group[13] reported on the use of *N*-methoxybenzamides[14] as an oxidizing directing group (DG^{ox}) for C–H bond alkynylation and olefination reactions.

Continuing our studies on the use of N–O bonds as internal oxidants, we set out to explore how structural changes affect the activity of the DG^{ox}. The *N*-methoxy amide unit was located to be one atom away from the aromatic ring. Formal insertion of a CH_2-unit (**1**) did not lead to the desired olefinated product under our standard Rh(III)-catalyzed reaction conditions in the presence of styrene (Scheme 1). This is presumably due to the rotational freedom around the C–C bond which allows the directing group to access a conformation which is out of the plane of the aromatic ring. Based on this hypothesis, we were delighted to see that limiting this rotational freedom by replacing the CH_2-unit with an NH led to significantly enhanced reactivity. Thus, urea[15] **2a** afforded the olefinated product with styrene as the coupling partner, $[Cp^*RhCl_2]_2$ as the catalyst and Ag_2CO_3 as the base in *t*-AmylOH at 70 °C, although as a separable mixture of the reduced urea $\mathbf{3}^{red}$, the *N*-methoxy urea **3** and the reduced substrate (*N*-phenyl urea). These initial results indicated that the oxidation is not exclusively internal, in contrast to our findings with *N*-methoxybenzamides.[13] Further modifications on the DG^{ox} unfortunately did not affect the selectivity. No olefinated products were observed with the modified substrates **2b–2e**, even with weakened (**2c**) or sterically more accessible (**2b**) N–O bonds.



Scheme 1 Directing group/oxidant modifications.

To overcome the observed selectivity issue of internal *versus* external oxidation, we chose to continue our study by using Michael acceptors as coupling partners. We believed that after the initial olefination step, a 6-*exo* aza-Michael addition could take place to afford dihydroquinazolinones.[16,17] Indeed, using ethyl acrylate instead of styrene led to the isolation of **4aa** in 60% yield. Oxidation did not occur from the product **4aa**, probably as a consequence of steric hindrance of the now tertiary urea-nitrogen. After optimization,[18] we were able to isolate **4aa** in 75% yield,[19a] using 2.5 mol% $[Cp^*RhCl_2]_2$ and 30 mol% NaOAc in *t*-butyl alcohol (eqn (1)), with a second equivalent of **2a** as the external organic oxidant.[19]

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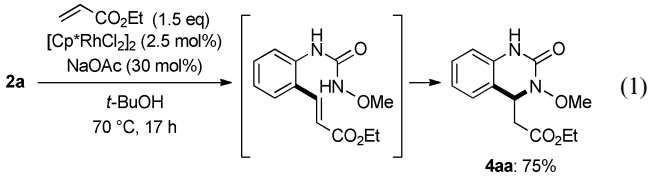
† Electronic supplementary information (ESI) available: Detailed experimental procedures, full characterization data and ^1H and ^{13}C spectra of all synthesized compounds. See DOI: 10.1039/c1ob05636k



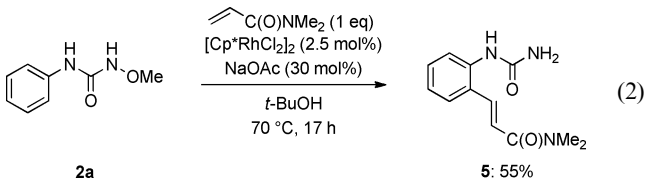
(1)

We then studied a variety of external oxidants under our optimized reaction conditions. Intriguingly, both metallic (Table 1, entries 2 to 8) and organic oxidants (entries 9 to 20) proved to be less effective, either inhibiting the reaction or leading to reduced yields. Only in the case of NMO was a significant amount of the reduced oxidant detected. Based on our observation of this unique oxidation behaviour, we synthesized compounds **2f** to **2i**, which possess the same urea oxidizing group, but would not undergo directed C–H activation under the reaction conditions. Even with these compounds as oxidants, major oxidation occurred from the substrate. Although **2h** exhibited oxidative behaviour competitive with the parent substrate **2a**, compound **2a** appeared to be the superior oxidant in all cases.

Because of the superior oxidation behaviour of **2a**, we decided to use two equivalents of **2a** in our reaction. One half serves as the substrate, whereas the other half is used as an organic oxidant. In all of the following reactions, the alkene was used as the limiting component.

We then explored a range of olefin coupling partners. The reaction proceeded smoothly with a variety of acrylates (Table 2, entries 1–4) and the desired dihydroquinazolinones were obtained in good yields. Intriguingly, even rather unreactive olefins like acrylonitrile (entry 5), methyl vinyl ketone (entry 6) and heteroatom-substituted olefins such as phosphonates and sulfonates (entries 7, 8) underwent the desired reaction in moderate to good yields.

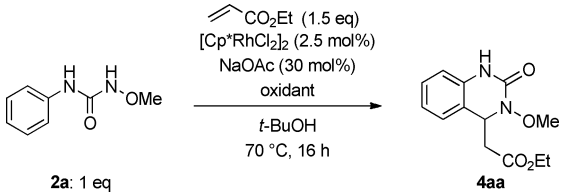
Surprisingly, the use of *N*,*N*-dimethyl acrylamide (eqn (2)) as the coupling partner led only to a trace amount of the corresponding dihydroquinazolinone. Instead, 55% of the reduced Heck-product **5** was isolated as the major product. Two factors could potentially have contributed to this outcome. First, the reduced electrophilicity of the amide moiety disfavors intramolecular Michael addition. Second, coordination of the *N*,*N*-dimethyl urea motif to the intermediate Rh(I) species may be more favourable due to the increased Lewis basicity, which precludes the reduction of **2a**.

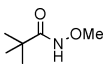
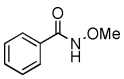
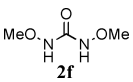
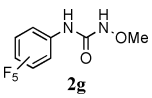
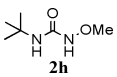
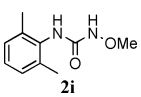


(2)

To probe the electronic effects on both the C–H bond activation as well as the oxidation event, we subjected *N*-methoxy-*N*′-aryl ureas (**2j–2t**) to our optimized conditions. We were delighted to see that the reaction proceeded similarly well with mesomerically (Table 3, entries 1–2) as well as inductively electron-withdrawing functional groups (entry 3). For the electron-rich aromatic system **2n** (entry 5), in which the substituent is in conjugation with the directing group, a higher reaction temperature was required. Independent of their electronic nature, substituents in the *meta*-position afforded the desired cyclised products in high regioisomeric ratios (13 : 1 to >24 : 1) favouring activation of the less hindered C–H bond[20] to give **4ob–4qa** in good yields. Steric bulk at the *ortho*-position, which could potentially force the urea directing group out of planarity and therefore hamper C–H abstraction,[15a] was also tolerated in the reaction (entries 9–10). Even the more challenging naphthyl derived urea (**2t**, entry 11) reacted with *n*-butyl acrylate in the presence of the Rh^{III} catalyst to give **4tb**. It is noteworthy that all tested halogen substituents (Br, Cl, F) on the aromatic ring are well-tolerated. In

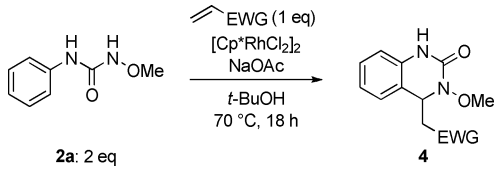
Table 1 Screening of external oxidants



Entry	Oxidant	Yield[a]
1	none	78 (75)[b]
2	$Cu(OAc)_2$	18
3	$Cu(OAc)_2$ (0.2 eq), O_2	0
4	CAN	0[c]
5	Ag_2CO_3	27
6	AgOAc	11
7	$KHSO_5$	0
8	$K_2S_2O_8$	28
9	*m*-CPBA	0[c]
10	*t*-BuOOH	28
11	benzoquinone	0[c]
12	quinoline *N*-oxide	28
13	anthraquinone	34
14	TEMPO	32
15	NMO	43
16	**2b**	0
17	**2c**	0
18	**2e**	35
19		42
20		13
21	 **2f**	25
22	 **2g**	39[d]
23	 **2h**	53[e]
24	 **2i**	37[d]

Unless otherwise stated, an approximately equal amount of *N*-phenyl urea, resulting from reduction of the substrate was observed along with the formation of the dihydroquinazolinone.[a] Yield of **4aa** was determined by ^1H NMR using CH_2Br_2 as an internal standard. [b] With 2 equivalents of **2a**. Isolated yield in parentheses. [c] Mainly decomposition was observed. [d] Only a trace amount of the reduced oxidant was detected by HRMS. [e] The amount of *N*-phenyl urea was determined to be 42%.

Table 2 Exploration of the substrate scope of the alkene

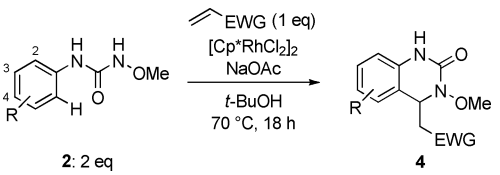


2a: 2 eq **4**

Entry	EWG	Product	Yield[a]
1	CO_2Et	**4aa**	75
2	CO_2Et	**4aa**	69[b]
3	CO_2n-Bu	**4ab**	75
4	CO_2t-Bu	**4ac**	72
5	CN	**4ad**	44[c,d]
6	C(O)Me	**4ae**	41[e]
7	$P(O)(OEt)_2$	**4af**	26[f]
8	SO_2Ph	**4ag**	69

Reaction conditions: **2a** (2 mmol), alkene (1 mmol), $[Cp^*RhCl_2]_2$ (0.025 mmol), NaOAc (0.3 mmol) in *t*-BuOH (0.1 M) at 70 °C for 18 h.[a] Isolated yields. [b] Using 1 mol% $[Cp^*RhCl_2]_2$ on a 7.5 mmol scale. [c] Additional 24 h at 90 °C. [d] 45% of **2a** was recovered. [e] The corresponding intermolecular Michael addition product was observed. [f] 25% of the reduced Heck-product was observed.

Table 3 Exploration of the substrate scope of the aromatic ring



2: 2 eq **4**

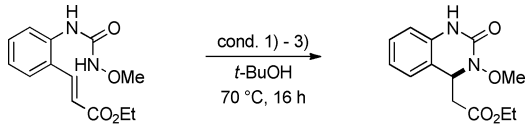
Entry	R	EWG	Product	Yield[a]
1	4-NO_2 (**2j**)	CO_2Et	**4ja**	71
2	4-Ac (**2k**)	CO_2Et	**4ka**	74[b]
3	4-F (**2l**)	CO_2Et	**4la**	66
4	4-Me (**2m**)	CO_2n-Bu	**4mb**	77
5	4-OEt (**2n**)	CO_2t-Bu	**4nc**	42[c]
6	3-Cl (**2o**)	CO_2n-Bu	**4ob**[20]	61
7	3-Me (**2p**)	CO_2Et	**4pa**[20]	67[d]
8	3-OMe (**2q**)	CO_2Et	**4qa**[20]	73[e]
9	2-Me (**2r**)	CO_2Et	**4ra**	60
10	2-Br (**2s**)	CO_2Et	**4sa**	64[c]
11	**2t**[f]	CO_2n-Bu	**4tb**	50[c]

Reaction conditions: **2a** (2 mmol), alkene (1 mmol), $[Cp^*RhCl_2]_2$ (0.025 mmol), NaOAc (0.3 mmol) in *t*-BuOH (0.1 M) at 70 °C for 18 h.[a] Isolated yields. [b] Reaction carried out on a 0.3 mmol scale. [c] Additional 24 h at 90 °C. [d] Isolated as an inseparable mixture of regioisomers (13 : 1). [e] Isolated as an inseparable mixture of regioisomers (>24 : 1). [f] **2t** = *N*-methoxy-*N*′-(1-naphthyl) urea; reaction carried out on a 0.5 mmol scale.

all cases, the corresponding Heck-product resulting from oxidative addition[21] of the C–X bond was not detected, a significant advantage of rhodium-catalyzed processes compared to those of palladium.

To gain insight into the mechanism of this transformation, we carried out a series of deuteration experiments. Treating **2m** with a catalytic amount of $[Cp^*RhCl_2]_2$ and NaOAc in *t*-BuOD at 70 °C for 16 h resulted in 89% deuterium incorporation at the *ortho*-positions (eqn (3)), indicating that the C–H bond activation step is reversible under the reaction conditions.

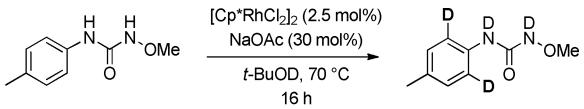
Table 4 Examination of the Michael addition step



6 **4aa**

Entry	Reaction conditions	Yield[a]
1	—	decomp.
2	$[Cp^*RhCl_2]_2$ (2.5 mol%), NaOAc (30 mol%)	95
3	NaOAc (30 mol%)	98

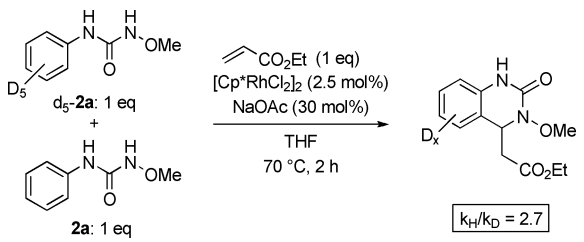
[a] Yield of **4aa** was determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard.



2m *ortho*-incorporation: 89% (^1H NMR analysis) d_x-**2m** (3)

d_0: 1%, d_1: 18%, d_2: 80% (HRMS analysis, after washing with MeOH)

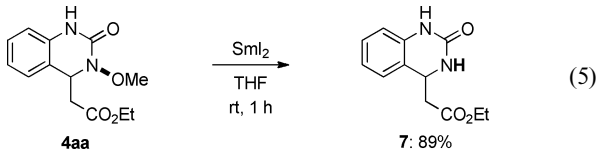
A competition experiment of d_5-**2a** with **2a** for 2 h revealed an intermolecular kinetic isotope effect (k_H/k_D) of 2.7 at low conversion (20% yield; eqn (4)). An aprotic solvent was chosen to exclude deuterium scrambling.[22,23] This result suggests that C–H bond activation is involved in the rate-determining step of the catalytic cycle. Furthermore, based on our observation that electron-poor substrates generally react faster than electron-rich urea substrates, C–H bond activation most likely occurs *via* a concerted metallation–deprotonation (CMD) mechanism as previously proposed for similar transformations.[24–26] Leaving out NaOAc completely shut down the reaction, showing the crucial role of the acetate ion in the reaction.[18]



(4)

When the olefinated Michael addition precursor **6** was subjected to the reaction conditions without rhodium and base, only decomposition of the substrate was observed (Table 4, entry 1). Quantitative cyclisation was obtained using the standard conditions (entry 2) and without the rhodium catalyst (entry 3). These results suggest a base-catalyzed process,[27] although a Rh-assisted pathway cannot be excluded.

Finally, reductive cleavage of the N–O bond[28] was readily achieved by treatment of **4aa** with SmI_2 at room-temperature, affording the free dihydroquinazolinone **7** in excellent yield (eqn (5)), expanding the synthetic utility of the reported transformation.



4aa **7**: 89% (5)

In conclusion, the reported olefination–Michael addition tandem process proceeds in a highly regioselective manner under mild conditions using an organic oxidant exhibiting a broad functional group tolerance. *N*-Methoxy-*N′*-aryl ureas were found to be superior oxidants compared to a variety of organic and metallic oxidants. Our mechanistic investigation including deuterium labelling experiments further shed light on the intermediates involved in the catalytic cycle.

Acknowledgements

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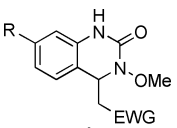
20 For *meta*-substituted substrates, C–H bond activation occurred preferably at the less hindered site to form product **4**. .



4

21 Indeed, subjecting **2s** and ethyl acrylate to Pd-catalyzed reaction conditions ($Pd(OAc)_2$, PPh_3, NEt_3) exclusively led to the formation of **4aa** in 58% ^{1}H NMR yield.

22 Around 7% of d_3-**4aa** was observed even in non-protic solvents, presumably due to quenching of the Ar-Rh species by either *in situ* generated AcOH or the NH protons of the substrate or product.

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