Carbenes

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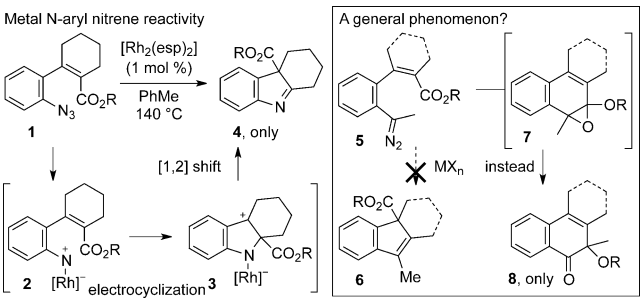
Copper-Catalyzed Formation of α-Alkoxycycloalkenones from *N*-Tosylhydrazones

*Naijing Su, Juliana A. Theorell, Donald J. Wink, and Tom G. Driver**

Abstract: *The combination of 20 mol % of copper iodide and lithium tert-butoxide triggers the formation of a broad range of substituted, functionalized α-alkoxy 2H-naphthalenones from readily available N-tosylhydrazones. The data suggests that this transformation occurs through cycloaddition of a copper carbenoid with an ester, followed by a Lewis acid-catalyzed [1,2] alkyl shift of the in situ generated alkoxyepoxide intermediate.*

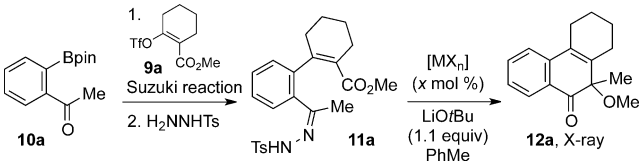
The reactivity of transition-metal carbene complexes has spurred significant innovation which dramatically simplifies the synthesis of complex, functionalized molecules.[1,2] These divalent reactive intermediates have been widely exploited in cyclopropanation,[3] cycloaddition,[4] annulation,[5] metathesis,[6] and C–H bond functionalization processes.[7] In contrast, the use of these reactive intermediates to trigger cascade processes has lagged behind the established transformations.[8] Our group has pursued the synthesis of N-heterocycles from aryl azides by using transition-metal catalysts to generate and control metal N-aryl nitrenes in C–H bond-amination reactions.[9] Our mechanistic experiments suggested that C(sp^2)–H functionalization occurred through a tandem reaction in which C–N bond formation preceded C–H bond cleavage,[10] and we exploited this mechanism by substituting the hydrogen with other migrating groups to achieve the formation of functionalized 3*H*-indoles, such as **4**, from trisubstituted styryl azides (**1**) through an electrocyclization-[1,2] carboxylate rearrangement (Scheme 1).[11] During the course of our investigations, we were curious if this reactivity pattern was unique to rhodium N-aryl nitrenes or if it was general to other divalent catalytic intermediates, such as metal aryl carbenes. While metal carbenes are established to react with ketones and aldehydes to afford epoxides,[12,13] esters coordinate with the electrophilic carbenes to produce a dipole which can be captured through a dipolar cycloaddition reaction.[4] In the absence of a dipolarophile, we anticipated that an electrocyclization/migration sequence might occur to afford the indene **6**. Alternatively, a [2+1] cycloaddition, unprecedented with an ester, could occur to produce the alkoxy-substituted epoxide **7**, which might rearrange under the reaction conditions because it is well-established that enol-ester-derived epoxides undergo acyloxy migrations to produce α-acyloxy ketones.[14,15] Herein, we report the copper-catalyzed transformation of *N*-tosylhydrazones into α-alkoxy ketones through a [1,2] alkyl-shift of an in situ generated alkoxy-substituted epoxide.[16]



Scheme 1. Divergent reactivity of metal divalent catalytic intermediates. esp = α,α,α′,α′-tetramethyl-1,3-benzene-diproprionate.

To determine if related reactivity patterns are embedded in metal carbenoids, the reactivity of the *N*-tosylhydrazone **11a** was investigated (Table 1). *N*-Tosylhydrazones were chosen as the carbene precursor because they are well-established as a safe and nontoxic source of alkyl diazo compounds,[17,18] and the requisite substrate is rapidly accessible from a Suzuki cross-coupling reaction between the aryl boronate **10** and vinyl triflate **9**. To our delight, exposure of

Table 1: Development of the optimized reaction conditions for 2*H*-naphthalenone.



Entry	Catalyst	mol %	*T* [°C]	Yield [%][a]
1	CuI	20	90	98
2	CuBr	20	90	68
3	CuCl	20	90	30
4	$(CuOTf)_2$·PhMe	20	90	43
5	$Cu(OTf)_2$	20	90	20
6	$CuBr_2$	20	90	36
7	$[Rh_2(O_2CMe)_4]$	5	90	dec.
8	$AlCl_3$	5	90	dec.
9	none	n.a.	90	10
10	CuI	10	90	76
11	CuI	20	50	20

[a] Determined using ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard. DME = dimethoxyethane, OTf = trifluoromethylsulfonate, Ts = 4-methyltoluenesulfonate.

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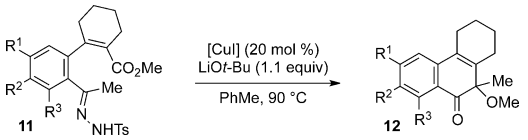
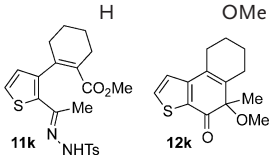
11a to LiO*t*Bu (1.1 equiv) and 20 mol % of CuI produced a single product in 98 % (entry 1), and it was established to be the α-methoxy-2*H*-naphthalenone **12a** by X-ray crystallography. The expected indene was not observed. The identity of the copper catalyst proved critical to obtaining the indene in good yield (entries 2–6). In comparison to CuI, lower reaction yields were obtained with CuBr, CuCl, and $(CuOTf)_2{\cdot}PhMe$ as well as copper(II) salts. $[Rh_2(OAc)_4]$ as well as Lewis acids, such as $AlCl_3$, were also examined as potential catalysts but only decomposition was observed (entries 7 and 8).[19] In the absence of a metal salt, **12a** was observed in only 10 % (entry 9). Lowering the catalyst loading of CuI to 10 mol % or reducing the reaction temperature to 50 °C also led to diminished **12a** formation (entries 10 and 11). Changing the solvent or the counterion of the alkoxide base also had a deleterious effect on 2*H*-naphthalenone formation.[19]

By using the optimal reaction conditions, the scope of this transformation was interrogated by adding substituents to the aryl portion of the hydrazone (Table 2). The electronic nature of the substrate was modified through substituting the 4-position with a range of different functional groups (entries 1–6). This reaction appears insensitive to the electronic nature of the R^1 group, thus resulting in good conversions with electron-donating groups as well as electron-withdrawing groups. This reaction also tolerates substitution at the 5-position of **11** without attenuation of the yield of the 2*H*-naphthalenone (entries 7–9). While the reaction is insensitive to changes to the electronic nature of the substrate, increasing the steric environment, by adding a second *ortho* substituent, attenuated the yield of the reaction (entry 10). Because 2,6-disubstituted aryl hydrazones are competent substrates in carbene and carbenoid reactions,[17b,d] we attribute this adverse effect to the destabilizing steric interactions that might occur in a co-planar transition state specific to the reaction. The thiophene *N*-tosylhydrazone **11k** was also found to be competent in this transformation to enable access to the heterocycle **12k** (entry 11).

Next, the identity of the *ortho*-substituent of the aryl hydrazone was varied to further survey the scope of this new reaction (Table 3). The effect on changing the steric environment around the reaction center was investigated first (entries 1 and 2). As expected from Table 2, we found an inverse correlation between the reaction yield and the size of

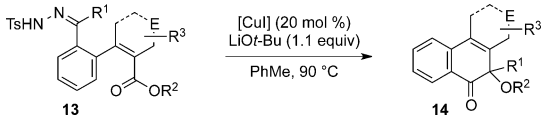
Table 2: Examination of the scope and limitations of the tandem reaction.



Entry	11	R^1	R^2	R^3	Yield [%][a]
1	**11a**	H	H	H	93
2	**11b**	MeO	H	H	60
3	**11c**	Ph	H	H	72
4	**11d**	F	H	H	67
5	**11e**	Cl	H	H	87
6	**11f**	F_3C	H	H	68
7	**11g**	H	OMe	H	64
8	**11h**	H	Me	H	77
9	**11i**	H	Cl	H	87
10	**11j**	H	H	OMe	25
11	**11k**				53

[a] Yield of **12** isolated after neutral alumina chromatography, only product obtained.

Table 3: Effect of the *o*-alkenyl substituent identity on 2*H*-naphthalenone formation.



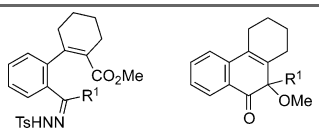
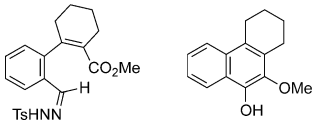
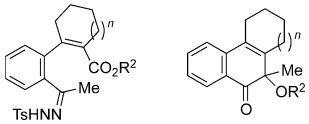
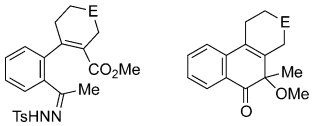
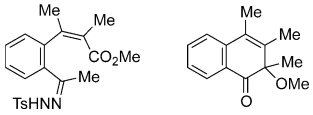
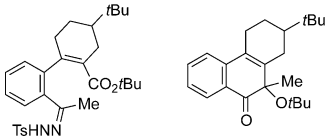
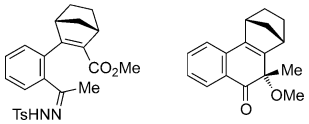
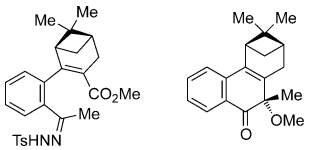
Entry	13	*N*-tosylhydrazone	2*H*-naphthalenone	Yield [%][a]
1	**13a**			58, R^1 = Et
2	**13b**			30, R^1 = *i*Pr
3	**13c**			61
4	**13d**			60, *n* = 0, R^2 = Et
5	**13e**			65, *n* = 2, R^2 = Me
6	**13f**			78, *n* = 3, R^2 = Me[b]
7	**13g**			50, E = O
8	**13h**			50, E = NBoc
9	**13i**			55, E = NTs
10	**13j**			35
11	**13k**			82 d.r. = 60:40[c]
12	**13l**			40 d.r. ≥ 95:5[d,e]
13	**13m**			71 d.r. ≥ 95:5[d,e]

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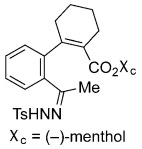
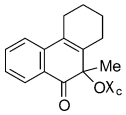
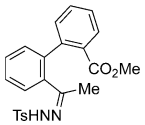
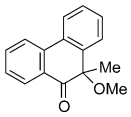
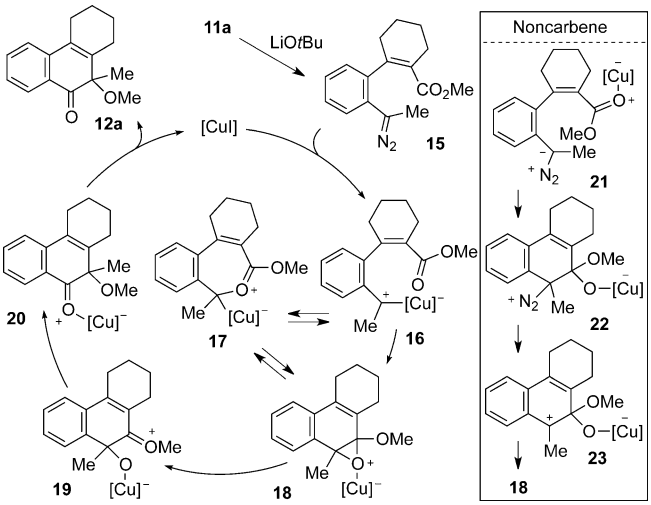
Table 3: (Continued)

Entry	13	*N*-tosylhydrazone	2*H*-naphthalenone	Yield [%][a]
14	**13n**			quant. d.r. 55:45[d]
15	**13o**			40[f]

[a] Yield of **14** isolated after neutral alumina chromatography, only product obtained. [b] Reaction performed in PhH. [c] Determined using ^{1}H NMR spectroscopy. [d] Determined using SFC-MS. [e] Identity of the major diastereomer determined by nOe spectroscopic experiments. [f] Styrene elimination product formed in 23%. Ac = acetyl, Boc = *tert*-butyloxycarbonyl.

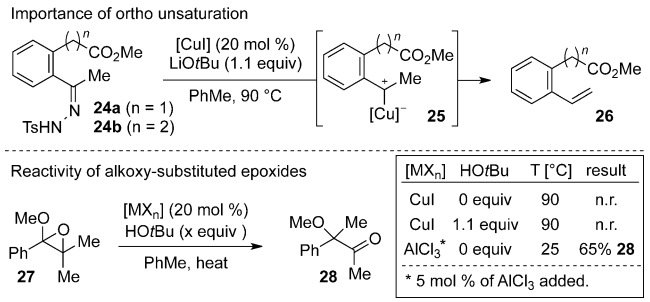


Scheme 2. Possible mechanisms for 2*H*-naphthalenone formation.

the hydrazone R^1 group. When the aldehyde-derived **13c** was submitted to the reaction conditions, the naphthalenol **14c** was produced (Table 3, entry 3). Next, the composition of the *ortho*-alkenyl substituent was modified (entries 4–12). While shrinking the ring-size led to an attenuated yield (entry 4), substrates containing medium-sized *o*-cycloalkenyl rings were smoothly converted into the α-methoxy-2*H*-naphthalenones **14e** and **14f** (entries 5 and 6). The reaction also tolerated *o*-heterocyclic substituents to afford **14g–i** (entries 7–9). This reaction does tolerate acyclic *o*-alkenyl groups: the hydrazone **13j** was efficiently converted into the 2*H*-naphthalenone **14j** albeit with a reduced yield (entry 10). The diastereoselectivity of the reaction was next probed (entries 11–14). While exposure of the hydrazone **13k** to the reaction conditions provided a 3:2 mixture of diastereomers, the chiral, non-racemic *o*-norbornyl **13l** afforded the 2*H*-naphthalenone product as a single diastereomer. Next, the effect of moving the one of the bridge attachments from the allylic to the homoallylic position was examined with the β-pinene-derived **13m** (entry 13). Alleviating the steric pressure around the carboxylate substituent improved the yield of the transformation without the loss of stereoselectivity to produce **14m** in 71% as a single diastereomer. In contrast, no diastereoselectivity was observed with the (−)-menthol-derived carboxylate **13n** (entry 14). This reaction could also be extended to the hydrazone **13o**, which contained an *o*-aryl group, to produce **14o** in 40% (entry 15). Elimination, however, also occurred to form the 2-substituted styrene in 23%.[19]

The conversion of the *N*-tosylhydrazones into α-methoxy-2*H*-naphthalenones is proposed to occur through the tandem cycloaddition/[1,2] rearrangement of a copper carbene (Scheme 2). The reaction of *N*-tosylhydrazone with *tert*-butoxide generates the diazo **15**,[20] which is decomposed by the copper(I) salt to produce the copper carbene **16**.[21] The epoxide **18** could be produced through either a stepwise reaction with the proximal methyl carboxylate via the ylide **17** or directly through a [2+1] cycloaddition reaction.[12] Alternatively, **18** could be formed through a noncarbene mechanism.[22] In this mechanism, the copper catalyst activates the ester for attack by **15** to produce **22**.[23] Loss of N_2 forms the benzyl cation **23**, which is attacked by the copper alkoxide to produce **18**. Ring-opening of the epoxide generates the oxocarbenium ion **19**, which triggers a [1,2] methyl shift to afford **20**.[16] Dissociation of the copper catalyst produces the product **12a**.

Several experiments were performed in an attempt to gain insight into the reactivity of the proposed catalytic intermediates.[19] First, the addition of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) to the reaction mixture did not produce any new products to indicate that radical intermediates, if formed, did not escape the solvent sheath. Attempts to trap either **17** or **19** with a dipolarophile (DMAD; dimethylacetylenedicarboxylate)[4] or an external nucleophile (Et_3SiH) did not change the reaction outcome: only the 2*H*-naphthalenone **12** was formed.[19] Next, we surveyed the reactivity of the *N*-tosylhydrazones **24** to determine if the *o*-alkenyl group was required for a successful reaction (Scheme 3). Irrespective of the potential ring formed, only β-hydride elimination was observed. Finally, to examine the potential for an alkoxy-substituted epoxide to rearrange, **27** was synthesized and its reactivity toward Lewis and Brønsted acids was tested. We found that while it remained inert toward mixtures of CuI and



Scheme 3. Experiments to elucidate the mechanism of the tandem reaction.

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tert-butanol,[22] exposure of **27** to 5 mol % of a stronger Lewis acid, $AlCl_3$, at room temperature triggered the formation of the α-methoxymethyl ketone **28**. We interpret this result to mean that epoxides, such as **18**, can rearrange provided that a strong enough Lewis acid is formed during the reaction.

In conclusion, we have discovered a new reactivity pattern for metal aryl carbenes toward pendant carboxylates to transform readily accessible aryl *N*-tosylhydrazones into functionalized α-alkoxy 2*H*-naphthalenones. Currently, we are working towards understanding the mechanism of this reaction to exploit the reactivity of these metal aryl carbenes and trigger additional tandem reactions to facilitate access to complex functionalized carbocycles.

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Keywords: carbenes · copper · cyclizations · hydrazones · synthetic methods

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[24] Exposure of the epoxide **27** to stoichiometric amounts of LiCl and *tert*-butanol produced only the hydrolyzed α-hydroxy phenyl ketone. See the Supporting Information for more details.

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