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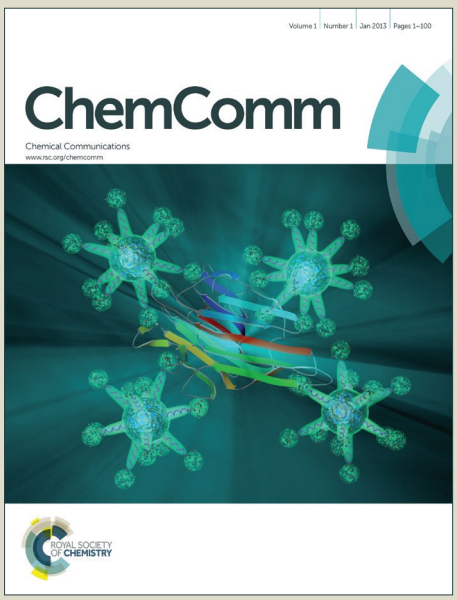

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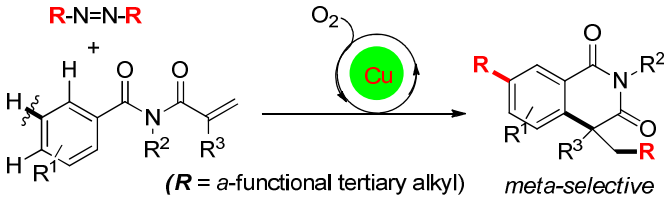

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Aerobic oxidative cyclization of benzamides via *meta*-selective C-H *tert*-alkylation: Rapid entry to 7-alkylated isoquinolinediones†

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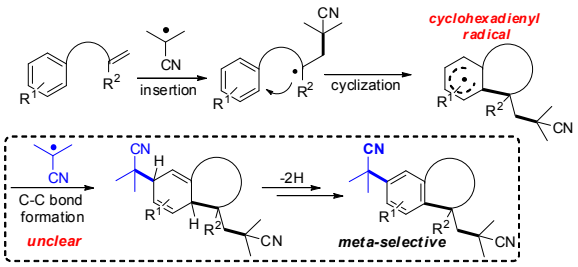
A novel copper-catalyzed aerobic oxidative cyclization of benzamides via *meta*-selective C-H *tert*-alkylation using AIBN and analogues as radical precursors was described. This strategy provides an elusive and rapid means to 7-*tert*-alkylated isoquinolinediones, as well as the construction of tertiary alkyl-aryl C(sp^3)-C(sp^2) bonds in positional selectivity.

Elegant construction of tertiary alkyl-aryl C(sp^3)-C(sp^2) bonds in positional selectivity, leading to quaternary carbon centers naturally occurred in pharmaceuticals, is a perennial topic of interest for organic chemists.[1] In this context, the past years have witnessed substantial progresses on remote *site*-selective C-H functionalization of electronically unbiased arenes by using these strategies including steric control,[2] template approach,[3] transient mediator,[4] and others,[5] while the *meta*-selective C-H *tert*-alkylation for constructing tertiary alkyl-aryl C(sp^3)-C(sp^2) bonds remains scarce.[6,7] In general these examples on remote C-H *tert*-alkylation of aromatic rings involve a radical process with tertiary halides as tertiary radical precursors.[1c,7] Notably, competitive elimination and rearrangement usually complicate the preparation of structurally complex tertiary halides.[8] Thus, increasing the diversity of tertiary radical precursors applied in C-H *tert*-alkylation is still in high demand by synthetic chemists. AIBN (azodiisobutyronitrile) and analogues serve as important tertiary radical source and generate free radicals under mild conditions. Thereby, extending the application of such azo reagents in the construction of quaternary centers is arguably of high interest.[9]

Isoquinolinediones are important structural motifs present in natural products and pharmaceutical compounds with certain biological functions.[10] Developing convenient synthetic routes of them has attracted remarkable attention from medicinal and synthetic chemists. Recently, several examples leading to functionalized isoquinolinediones via cyclization of alkenes being distal to an aromatic ring have been disclosed.[11] Analysis of these catalytic cycles toward isoquinolinediones generally involves a cyclohexadienyl radical intermediate, which might be scavenged by another robust radical (e.g., tertiary radical) thereby arousing a chance to incorporate some functionalized motifs onto the aromatic ring. Thus, we hypothesized that the cyclization of methacryloyl benzamides leading to 7-*tert*-alkyated isoquinolinediones via cascade radical addition/cyclization/C-C bond formation using AIBN as radical source is possible (Scheme 1).[12] However, despite difunctionalization of alkenes via cascade radical addition/cyclization for the synthesis of *N*-containing heterocycles (especially oxindoles) was extensively explored in the past years,[13] such a strategy involving an additional *tert*-alkylation of a proximal aromatic ring in a site-selective manner remains unclear to date. With our ongoing studies on the synthesis of isoquinolinediones,[11d] we herein disclose an oxidative cyclization via *meta*-selective *tert*-alkylation using AIBN and analogues as tertiary radical sources by Cu catalysis, thereby allowing for the "green" synthesis of 7-*tert*-alkylated isoquinolinediones.



Scheme 1. Proposed strategy for the synthesis of 7-*tert*-alkyated isoquinolinediones

At the outset of our studies, the reaction of *N*-butyl-*N*-methacryloyl benzamide **1a** with AIBN was attempted under different conditions (Table 1). First, the catalytic combination of CuI/DTBP used in our previous reactions was examined.

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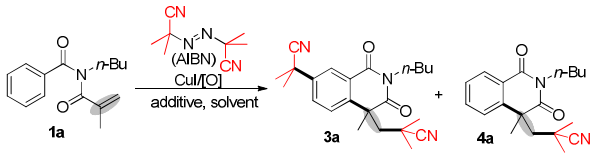
Unfortunately, this reaction was observed to be messy and only a trace amount of the desired product **3a** was detected by GC-MS along with side-product **4a** aroused by an expected cascade radical addition/cyclization (entry 1).[9] In addition, the oxidant TBHP also gave inferior results (entry 2). Further screenings revealed that replacement of DTBP with mild oxidant air seemed to make the reaction more efficient. Additionally, the studies from our lab and others disclosed that the use of a base was beneficial for the cyclization of alkenes toward isoquinolinediones.[11] Thereby, both the base and air were next employed in the reactions to explore the optimal conditions. Remarkably, we found that the solvent has dramatic impact on the cyclization, using DMF as a solvent led to **4a** in a yield of 75%, while 1,4-dioxane redirected the cyclization to give **3a** in 58% yield as the main product (entries 3-6). Notably, the oxidant switch from air to O_2 leads to a similar yield (entry 6). However, the absence of air or O_2 hampered the reaction, and decreased the yield of **3a** to 21% (entry 8). Next, we were happy to find that the use of KF has positive effect on the formation of **3a,** and further improved the yield to 73% (entry 9). But other fluoride salts such as NaF, CaF_2 and CsF led to lower yield (entries 10-12). Further screening of bases revealed that the K_3PO_4 remained as the best choice (entries 13-15), which is consistent with the observations that the potassium salts as bases or additives (eg., KF) were, comparing with other metal salts (eg., NaF), more beneficial for the cyclization.[11d] In addition, reducing the amount of AIBN to 2 equiv. would retard the formation of **3a** (entry 16)**.** Notably, further investigation revealed that other metal catalysts such as CuBr, $FeBr_2$, AgOAc, $Mn(OAc)_2$, etc. did not afford better results than CuI (for details see SI).

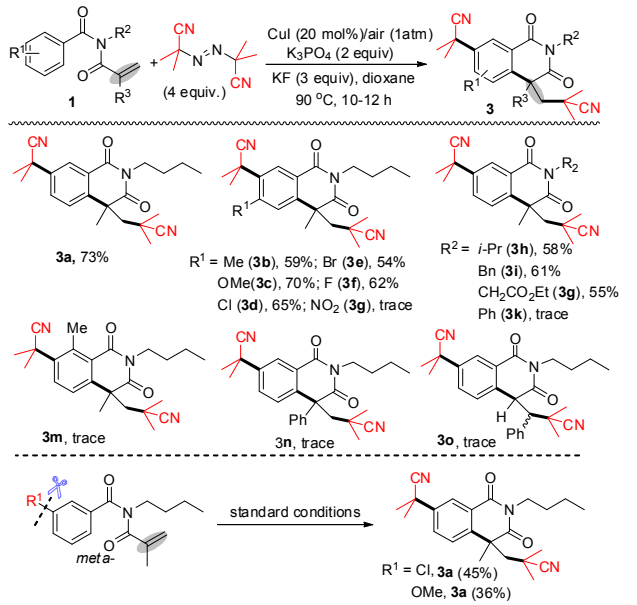
Table 1 Optimization of reaction conditions[a]



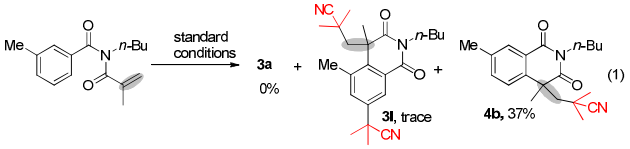
entry	[O]	base/additive	solvent	yield **3a** (%)[b]	yield **4a** (%)[b]
1	DTBP	none	DMF	trace	13
2	TBHP	none	DMF	trace	9
3	air	K_3PO_4	DMF	11	75
4	air	K_3PO_4	DMSO	13	62
5	air	K_3PO_4	dioxane	58	11
6	air	K_3PO_4	CH_3CN	27	23
7	O_2	K_3PO_4	dioxane	54	15
8[c]	—	K_3PO_4	dioxane	21	10
9	***air***	***K_3PO_4/KF***	***dioxane***	***73***	***13***
10	air	K_3PO_4/NaF	dioxane	61	15
11	air	K_3PO_4/CaF_2	dioxane	36	9
12	air	K_3PO_4/CsF	dioxane	53	14
13	air	K_2CO_3/KF	dioxane	19	12
14	air	K_2HPO_4/KF	dioxane	35	10
15	air	Cs_2CO_3/KF	dioxane	18	13
16[d]	air	K_3PO_4/KF	dioxane	22	8

[a] Reaction conditions: **1a** (0.3 mmol), AIBN (4 equiv.), CuI (20 mol %), oxidant (2 equiv.) or O_2/air (1 atm.), base (2 equiv.), additive (3 equiv.) and solvent (2 mL) at 90 °C for 10 h. DTBP = Di-*tert*-butyl peroxide, TBHP = *tert*-Butyl hydroperoxide, DMF = Dimethyl formamide, DMSO = Dimethyl sulfoxide. [b] Yield of the isolated product. [c] Under N_2 atmosphere. [d] Reducing the amount of AIBN to 2 equiv.

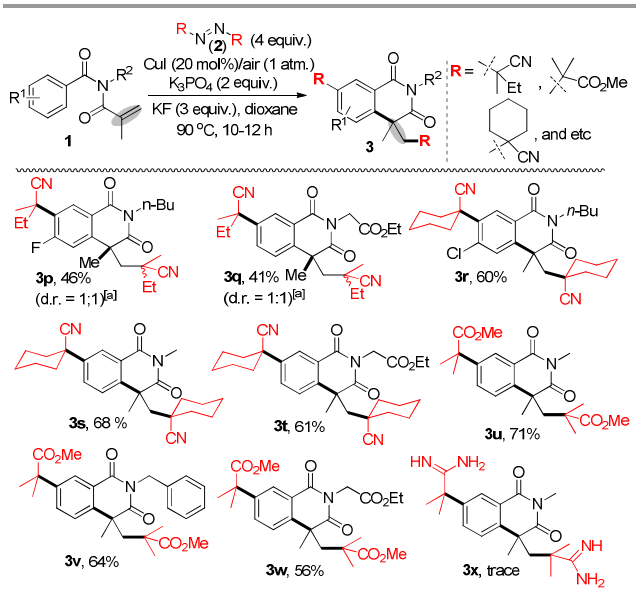
With the optimal conditions in hand, the scope of methacryloyl benzamides was next investigated (Scheme 2). Gratefully, a series of substituents (e.g., Me, OMe, F, Cl and Br) on the *para*-position of the aromatic ring were observed to be well compatible with the optimal conditions (**3b**-**f**). However, the NO_2 group was inefficient for the cyclization possibly due to its strong electron-withdrawing effect (**3g**). Various groups such as *i*-Pr, Bn and CH_2CO_2Et on the N-atom were well tolerated under the reaction conditions and afforded the corresponding isoquinolinediones in moderate to good yield (**3h**-**g**). However, the phenyl group on the *N*-atom was inefficient for the cyclization and substantial demethacryloylation leading to *N*-phenylbenzamide was observed. Consistent with the previous reports,[11c,d] the reaction appears to be sensitive to steric effect of substituent, and the annulation of *o*-methyl substrate was completely suppressed (**3m**). In addition, olefins bearing both *alpha*- and *beta*-substituted phenyl groups were also inefficient for the cascade process (**3n** and **3o**)**.** Interestingly, methacryloyl benzamides bearing activated *meta*-substituents (e.g., Cl and OMe) underwent the cascade process to give product **3a** specifically *via* the cleavage of *meta*-substituted groups. In contrast to above results, the reaction of *meta*-methyl benzamide provided the **4b** in 37% yield as the main product, but failed to lead to both **3a** and **3l** possibly due to the difficulty of inert C-C bond cleavage and steric effect (eqn (1)).



Scheme 2. Scope of methacryloyl benzamides.

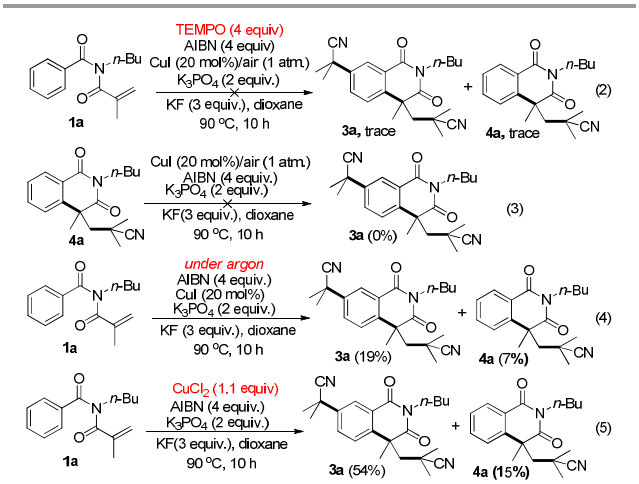


Subsequently, we also investigated the performance of AIBN analogues in the reactions (Scheme 3). To our delight, a series of azo compounds bearing *a*-functionalized tertiary alkyl groups (e.g. Et(Me)(NC)C, NC(C_6H_{10})C and $EtO_2C(Me)_2C$) were also compatible with optimal conditions, thereafter leading to a series of 7-*tert*-alkylated isoquinolinediones in moderate to good yield (**3p-w**). However, the reaction with 2,2'-(diazene-1,2-diyl)bis(2-methylpropanimidamide).2HCl failed to yield the corresponding product **3x**.



Scheme 3. Scope of azo compounds. [a] Diastereomeric ratios (d.r.) was determined by ^{1}H NMR.

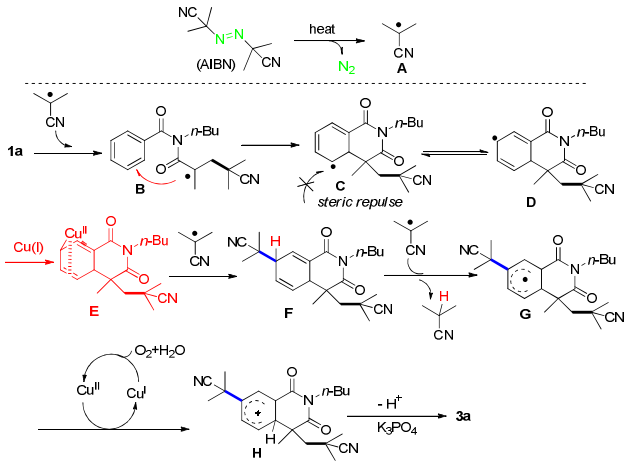
To insight into the mechanism, several control experiments were designed and performed (Scheme 4). First, by using the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl), the cyclization was completely suppressed, thus suggesting that the present reactions might involve a radical-mediated process (eqn (2), Scheme 4). Next, the reaction using side-product **4a** as the starting material cannot



Scheme 4. Control experiments.

lead to 3**a** under the standard conditions, thereafter revealing that the formation of **3a** in the reaction seem to involve another process different from further C(sp^2)-H *tert*-alkylation of **4a** (eqn (3)). The reaction under argon atmosphere gave much lower yield than the one under the standard conditions (eqn (4)). In addition, the replacement of the catalytic combination of CuI/air with a stoichiometric amount of $CuCl_2$ also led to **3a** in 54 % yield, thereby suggesting this cyclization could involve the Cu(I)/Cu(II) oxidative cycle promoted by air (eqn (5)).[14]

Based on above experimental results and previously reported mechanism,[9-16] a possible mechanism was proposed as outlined in Scheme 5. First, the AIBN decomposes to give radical **A** under heat, followed by the addition of radical **A** onto the C-C double bond of **1a** generating an alkyl radical **B**. Intramolecular cyclization of intermediate **B** with the proximal aryl ring forms radical intermediate **C**, which is left intact due to the steric effect**.** Immediately, the electron rearrangement of radical **C** occurs to afford its resonance isomer **D,** and then the reaction of radical D with Cu(I) species proceeds to form Cu(II) intermediate **E**,[15] which would be captured by another radical **A** to form cyclohexa-1,4-diene derivative **F**. Subsequently, radical **A** abstracts an allyl hydrogen of intermediate **F** to yield radical intermediate **G.**[16] In addition, the cleavage of *meta*-substituted Cl and OMe groups in this step was rationalized by the formation of π-allylcopper intermediate and then σ-allylcopper intermediate,[17] which might lead to **3a** *via* the β-H elimination of the copper species (see Scheme 2). Next**,** the intermediate **G** is then oxidized by Cu(II) species to form the cyclohexadienyl cation **H** and generates Cu(I) species (path I), Notably, in the presence of air, such a Cu(I) species is oxidized to regenerate Cu(II) species.[14] Finally, the abstraction of an aryl hydrogen in intermediate **H** by base takes place to afford the desired 7-alkylated isoquinolinedione **3a**.



Scheme 5. Proposed mechanism for the formation of **3a.**

In order to further understand the hydrogen abstraction mechanism of intermediate **F** to generate radical **G**, calculations using unrestricted density functional theory (DFT) with the hybrid functional B3LYP as implemented in Gaussian

09 package were sequentially conducted (Figure 1; for details see SI).[18] The free energy barrier for this step is calculated to be accessible (14.4 kcal/mol). This step results in a **Prod** state composed of the radical **G** and an acetonitrile molecule (H-**A**). The **Prod** is much more stable than the **React** (by -14.7 kcal/mol), since the spin in the radical **G** are delocalized by a larger π-conjugated system than in the radical **A**. This implies that the reaction is irreversible, that is, the reverse hydrogen transfer from acetonitrile (H-**A**) to radical **G** is unreachable.

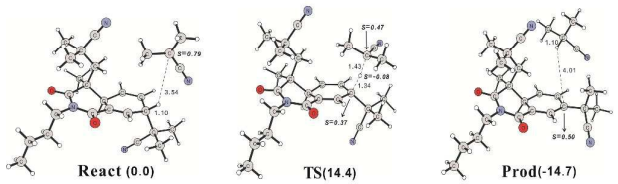


Figure 1. Optimized structures of stationary points. All distances are given in angstrom (Å). The unpaired spin populations are also shown. The free energies (in kcal/mol) are provided in parentheses with the React as the energy reference (0.0 kcal/mol).

In summary, we have discovered a novel copper-catalyzed cyclization of benzamides via *meta*-selective C(sp^2)-H *tert*-alkylation using AIBN and analogues as tertiary radical precursors for the first time. It is worthy to note that such a strategy affords an elusive and rapid entry to 7-*tert*-alkylated isoquinolinediones, as well as the construction of tertiary alkyl-aryl C(sp^3)-C(sp^2) bonds in positional selectivity. The use of readily available AIBN and analogues as tertiary radical precursors, the air as the oxidant and low cost copper as the catalyst make this protocol a "green" means to *tert*-alkylated isoquinoline-1,3(*2H*,*4H*)-dione derivatives.

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