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Utilization of Copper-Catalyzed Carboarylation−Ring Closure for the Synthesis of New Oxazoline Derivatives

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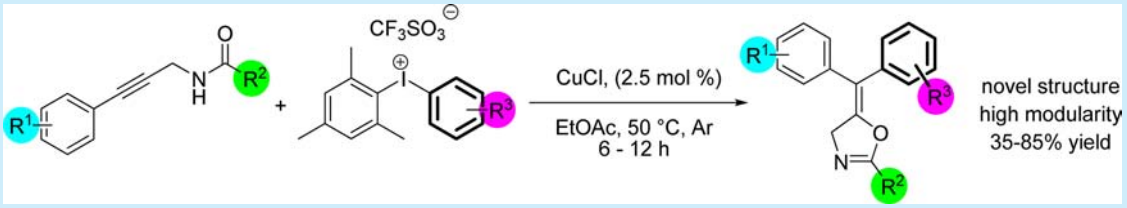
Supporting Information



ABSTRACT: A copper-catalyzed carboarylation−ring-closure strategy was used for the modular synthesis of oxazolines via the reaction of 1-aryl- and 1-alkylpropargylamides and diaryliodonium salts. The novel approach enables the efficient, modular synthesis of oxazoline derivatives bearing fully substituted exo double bonds.

Transition metal-catalyzed ring closures of alkyne derivatives are powerful tools for the construction of heterocyclic molecules.[1] With the utilization of hypervalent iodonium salts,[2] the cyclization step can be extended with an additional C−C bond formation using an in situ electrophilic arylcopper(III) species.[3] In our laboratory, we developed an arylation−ring closure strategy which enables the formation of new carbacyclic and heterocyclic molecules via *endo-dig* cyclization, providing easy access to fully substituted exo double bonds. With the exploitation of the synthetic opportunities of this catalytic approach we synthesized novel benzoxazine derivatives from *o*-ethynylanilides[4] and *o*-acetamidobenzonitriles[5] (Scheme 1). The utilization of diaryliodonium salts in this transformation ensures the high modularity of the method.

In continuation of our research devoted to the study of copper-catalyzed cyclization−arylations with hypervalent reagents, we aimed to extend our synthetic strategy to the construction of five-membered heterocycles such as oxazolines equipped with fully substituted exo double bonds. To achieve this goal, we aimed to use propargylic amides as substrates (Scheme 1). The electrophile-mediated or transition-metal-catalyzed cyclizations of propargylic amides to the corresponding oxazolines and oxazoles are important synthetic tools for the access of a heterocyclic core[6] with significant pharmaceutical interest.[7]

Although the existing catalytic transformations enable the cyclization of both terminal and internal propargylic amides,[6] there is no synthetic methodology to the access of oxazolines equipped with fully substituted exo double bonds.

The optimization study of the transformation was performed with *N*-(3-phenylprop-2-ynyl)pivalamide (**1a**). This model substrate was treated with mesityl(phenyl)iodonium triflate (**2a**) in the presence of different copper catalysts in various solvents under argon at 50 °C (Table 1). The solvent screening

Scheme 1. Utilization of Arylation−Ring-Closure Strategy

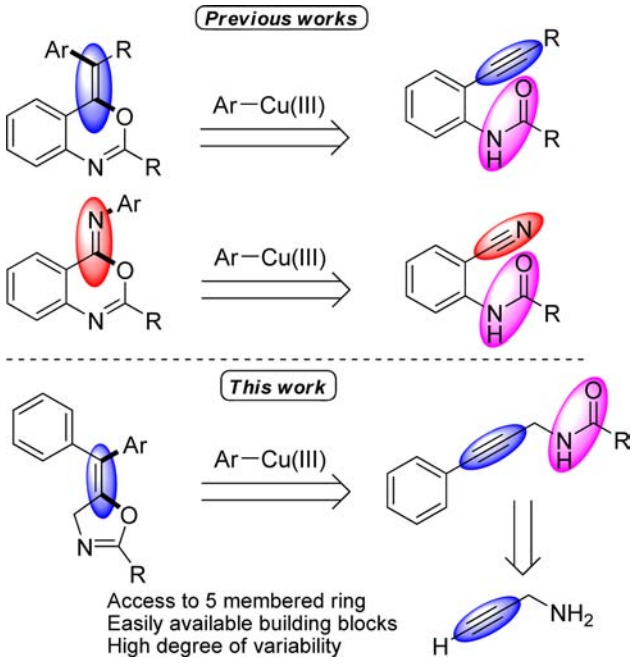


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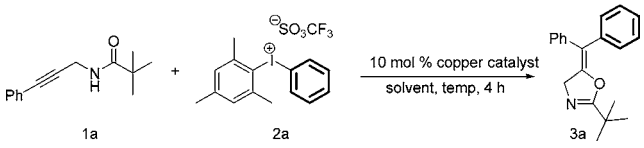
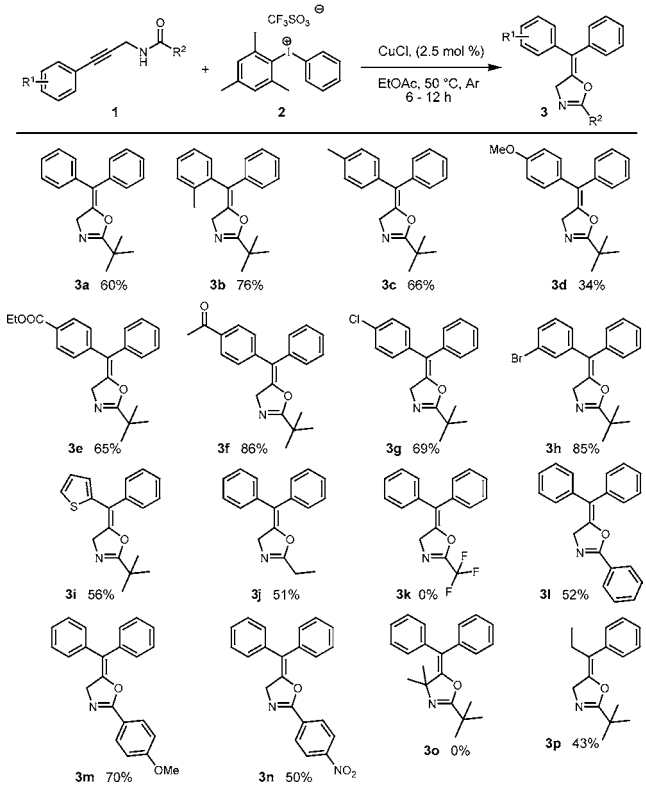
Table 1. Optimization Studies[a]



entry	catalyst	solvent	temp (°C)	conv[b] (%)
1	$Cu(OTf)_2$	DCE	50	11
2	$Cu(OTf)_2$	CH_2Cl_2	50	31
3	$Cu(OTf)_2$	toluene	50	5
4	$Cu(OTf)_2$	THF	50	59
5	$Cu(OTf)_2$	EtOH	50	0
6	$Cu(OTf)_2$	EtOAc	50	100
7	Cu(II)acac	EtOAc	50	0
8	$CuSO_4$	EtOAc	50	0
9	$Cu(MeCN)_4OTf$	EtOAc	50	100
10	CuO	EtOAc	50	0
11	CuI	EtOAc	50	0
12	CuBr	EtOAc	50	76
13	CuCl	EtOAc	50	100
14	CuCl	EtOAc	25	0
15	5 mol % CuCl	EtOAc	50	100[c]
16	2.5 mol % CuCl	EtOAc	50	100[c]

[a]Catalyst (0.01 mmol, 0.10 equiv), *N*-(3-phenylprop-2-yn-1-yl)-pivalamide (0.1 mmol, 1.0 equiv), mesitylphenyliodonium triflate (0.12 mmol, 1.2 equiv), solvent (1.0 mL), Ar. [b]Percent conversions of *N*-(3-phenylprop-2-yn-1-yl)pivalamide were determined by GC−MS. [c]*N*-(3-Phenylprop-2-yn-1-yl)pivalamide (0.5 mmol, 1.0 equiv), mesitylphenyliodonium triflate (0.6 mmol, 1.2 equiv), EtOAc (5.0 mL), Ar, 50 °C.

Scheme 2. Synthesis of Dihydrooxazoles 1[a]



[a]CuCl (0.0125 mmol, 0.025 equiv), 3-arylpropargylamide (0.5 mmol, 1.0 equiv), arylmesitiyliodonium triflate (0.6 mmol, 1.2 equiv), EtOAc (5.0 mL), Ar, 50 °C, % isolated yield.

showed that the reaction works efficiently only in EtOAc in the presence of 10 mol % of $Cu(OTf)_2$ (entries 1−6). Among the tested copper catalysts, CuCl and $Cu(MeCN)_4OTf$ also proved to be applicable in addition to $Cu(OTf)_2$ (entries 7−13). Although the reaction did not proceed at 25 °C, we were able to reduce the catalyst loading to 2.5 mol % (entries 14−16). We found that the propargylamide was transformed with full conversion in the presence of 2.5 mol % of CuCl in ethyl acetate at 50 °C. The major reaction product **3a** was isolated in 60% yield and determined to be 2-*tert*-butyl-5-(diphenyl-methylene)-4,5-dihydrooxazole by NMR analysis.

For the implementation of the syntheses we chose simple propargylamine as a readily available building block, which can be functionalized through the N-acylation of the amine function and via Sonogashira chemistry at the alkyne moiety providing versatile substrate pool.

To examine the scope and limitation of this novel transformation, different *N*-(3-arylprop-2-ynyl)pivalamides were treated with mesitylphenyliodonium triflate utilizing the most easily available CuCl as catalyst under the optimized reaction conditions (Scheme 2). It was found that the presence of a methyl group in the ortho and para positions caused a slight increase in isolated yields compared to the phenyl-propynylamide derivative **3a**. The desired compounds (**3b** and **3c**) were obtained in 76% and 66% yields, respectively. Surprisingly, when a strong electron-donating methoxy group was present on the phenyl group, the appropriate product **3d** was obtained only in lower yield (34%). The presence of ester and acetyl groups in the aromatic ring was tolerated by the system, and the appropriate dihydrooxazoles (**3e** and **3f**) were obtained in 65% and 86% yields. Arylpropynylpivalamides substituted with halogens (Cl, Br) were transformed to the appropriate dihydrooxazoles (**3g** and **3h**) in 69% and 85% yields. When the aryl group was exchanged for a thiophene-yl group, the reaction afforded the desired product (**3i**) in 56% yield.

Next, we investigated the effect of the amide functionality on the reaction. Although the presence of the ethyl group tolerated the reaction conditions and the 2-ethyloxazoline (**3j**) was isolated in 51% yield, we were not able to isolate product (**3k**) from the trifluoroacetamide. Besides alkyl amides, several aryl amides were subjected to ring closure under the developed copper-catalyzed conditions. As a result, we successfully isolated the phenyl (**3l**), *p*-methoxyphenyl (**3m**), and *p*-nitrophenyl (**3n**) derivatives in 52%, 70%, and 50% yield, respectively. The presence of two methyl groups on the propargylic part had a deleterious effect on the transformation; thus, the formation of the desired product was not observed. When 1-ethylpropynylpivalamide was treated with diphenyliodonium triflate under the optimized catalytic conditions, we successfully isolated the appropriate oxazoline derivative (**3p**) in 43% yield. With this example, we demonstrated that the procedure is applicable for the transformation of alkyl-substituted propargylic amides.

After examining the applicability of different 1-substituted propynylamides, we studied the reactivity of different substituted arylmesitiyliodonium triflates in the cyclization reaction with propynyl-pivalamide derivatives (Scheme 3). The presence of substituents in the ortho position on the aromatic ring of the iodonium salt had a deleterious effect on the reaction, and the appropriate oxazolines (**3q−s**) did not

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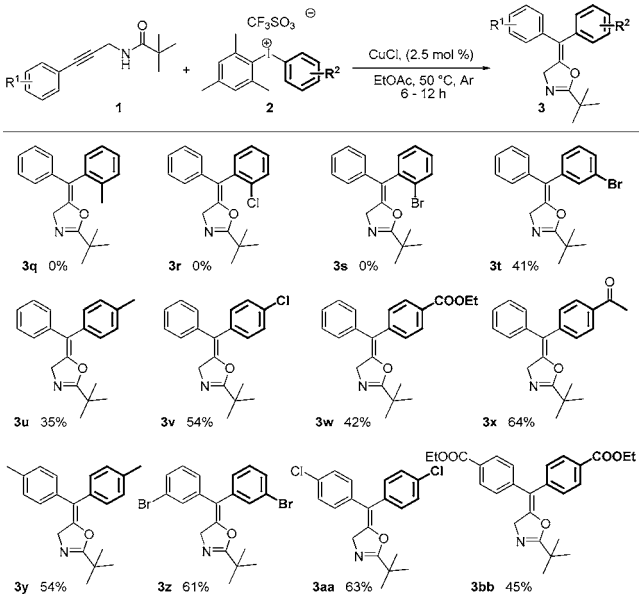
Scheme 3. Synthesis of Dihydrooxazoles 2[a]



[a]CuCl (0.0125 mmol, 0.025 equiv), 3-arylpropargyl amide (0.5 mmol, 1.0 equiv), arylmesityliodonium triflate (0.6 mmol, 1.2 equiv), EtOAc (5.0 mL), Ar, 50 °C, % isolated yield.

form. The transformation is compatible with various substituents in the meta and para positions on the phenyl group of the iodonium salt (Me, Cl, Br, Ac, COOEt), and the desired oxazolines (**3t−x**) were isolated in 40−64% yield.

Finally, reactions were performed with propynylamides and iodonium triflates bearing substituents (Me, Br, Cl, COOEt) on both aryl groups of the reactants. The expected dihydrooxazoles (**3y−bb**) with a symmetrically substituted double bond were isolated in 54%, 61%, 63%, and 45% yield, respectively.

The geometries of some obtained nonsymmetrically substituted heterocyclic alkene products (**3b,f,h,t,x**) were determined by NMR studies, and it was found in each case that the incoming aryl group originated from the iodonium salt was in a position *cis* to the oxygen of the oxazolines ring. The geometry of the exo double bound on the oxazoline ring was also established by X-ray crystallography in the case of compound **3c** (Figure 1).

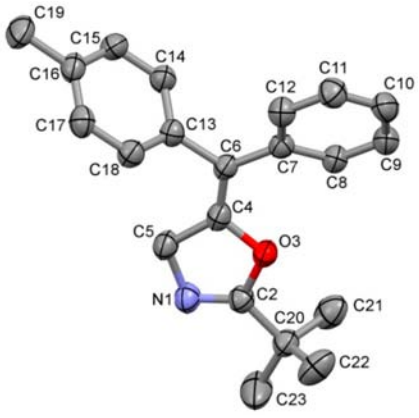
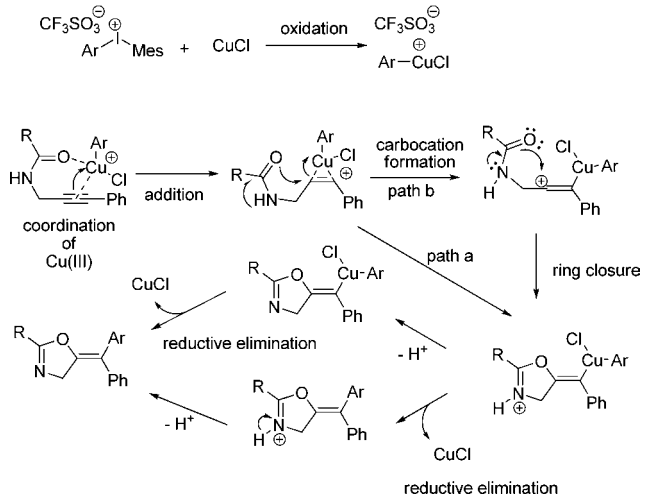


Figure 1. Molecular structure of compound **3c**.[8] Displacement ellipsoids are drawn at the 30% probability level.[9]

On the basis of the previously reported mechanistic proposals of related transformations and the obtained geometry of the oxazolines, we propose the following mechanistic picture for the transformation (Scheme 4). Recent reports have shown

Scheme 4. Proposed Mechanistic Picture of the Transformation



that the reaction of copper salts and diaryliodonium salts generate aryl−Cu(III) species.[3] These copper(III) species are generally highly electrophilic and can easily react with electron rich π-systems. Thus, we propose that the catalytic cycle starts with the oxidation of CuCl by the iodonium salt which leads to the formation of a highly electrophilic Ar−CuCl(OTf) intermediate.

We suppose that this Cu(III) species can coordinate both to the triple bond and the lone pair of the carbonyl oxygen from the inner sphere. The electrophilic metal species activates the triple bond, forming a copper−acetylene π complex, after which the formation of the carbocationic species is also possible. The lone pair of the amide nitrogen serves as the electron source, and the oxygen of the amide moiety attacks the activated π complex (path a) or the carbocationic center (path b) which results in a 5-*exo-dig* cyclization. However, considering the geometry of the products the formation of carbocationic intermediate via path b supposedly is not favorable. The formed alkenyl(aryl)copper intermediate is able to undergo reductive elimination−deprotonation sequence in two supposed order providing the CuCl catalyst and the oxazoline product.

In summary, we demonstrated that the copper-catalyzed ring closure−carboarylation strategy can be extended to substrates bearing alkyne and amide groups. We successfully achieved the synthesis of novel oxazoline derivatives equipped with fully substituted exo double bonds in the reaction of arylpropargylicamides and diaryliodonium salts. The versatile and readily available starting materials ensure high modularity for the transformation, and the optimized reaction conditions enable the efficient synthesis of the target compounds. Further exploitation of the cyclization-arylation strategy for other alkyne derivatives functionalized with different nucleophilic part is underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01860.

X-ray crustallographic data for **3c** (CIF)

Experimental procedures, characterization data, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875−2911. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644−4680. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873−2920. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2309. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198. (f) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395−3442.

(2) (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123−1178. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523−2584. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299−5358. (d) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052−9070. (e) Zhdankin, V. V. *Hypervalent Iodine Chemistry*; Wiley: Chichester, 2014. (f) Collette, J.; McGreer, D.; Crawford, R.; Chubb, F.; Sandin, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3819−3820. (g) Koser, G. F.; Wettach, R. H.; Smith, C. S. *J. Org. Chem.* **1980**, *45*, 1543−1544. (h) Stang, P. J.; Zhdankin, V. V.; Tykwinski, R.; Zefirov, N. S. *Tetrahedron Lett.* **1992**, *33*, 1419−1422. (i) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052−9070. (j) Bouma, J. M.; Olofsson, B. *Chem. - Eur. J.* **2012**, *18*, 14242−14245. (k) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, *25*, 2521−2523. (l) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOC* **2011**, 370−409. (m) Silva, L. F., Jr.; Olofsson, B. *Nat. Prod. Rep.* **2011**, *28*, 1722−1754. (n) Tinnis, F.; Stridfeldt, E.; Lundberg, H.; Adolfsson, H.; Olofsson, B. *Org. Lett.* **2015**, *17*, 2688−2691. (o) Ghosh, R.; Stridfeldt, E.; Olofsson, B. *Chem. - Eur. J.* **2014**, *20*, 8888−8892.

(3) (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172−8174. (b) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593−1597. (c) Phipps, R. J.; Mc Murray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773−10776. (d) Bigot, A.; Williamson, A. E.; Gaunt, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13778−13781. (e) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332−5335. (f) Walkinshaw, A. J.; Xu, W.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 12532−12535. (g) Cahard, E.; Bremeyer, N.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9284−9288. (h) Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8851−8854. (i) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 4260−4263. (j) Ryan, J. H.; Stang, P. J. *Tetrahedron Lett.* **1997**, *38*, 5061−5064. (k) Casitas, A.; Ribas, X. *Chem. Sci.* **2013**, *4*, 2301−2318. (l) Buksnaitienė, R.; Cikotienė, I. *Synlett* **2015**, *26*, 479−483. (m) Peng, J.; Chen, C.; Chen, J.; Su, X.; Xi, C.; Chen, H. *Org. Lett.* **2014**, *16*, 3776−3779. (n) Cahard, E.; Male, H. P. J.; Tissot, M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 7986−7989.

(4) (a) Sinai, Á.; Mészáros, Á.; Gáti, T.; Kudar, V.; Palló, A.; Novák, Z. *Org. Lett.* **2013**, *15*, 5654−5657. (b) Székely, A.; Sinai, Á.; Tóth, E. B.; Novák, Z. *Synthesis* **2014**, *46*, 1871−1880.

(5) Aradi, K.; Novák, Z. *Adv. Synth. Catal.* **2015**, *357*, 371−376.

(6) (a) Hashmi, A. S. K.; Schuster, A. M.; Schmuck, M.; Rominger, F. *Eur. J. Org. Chem.* **2011**, *2011*, 4595−4602. (b) Bacchi, A.; Costa, M.; Gabriele, B.; Pelizzi, G.; Salerno, G. *J. Org. Chem.* **2002**, *67*, 4450−4457. (c) Costa, M.; Ca, N. D.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 2469−2477. (d) Hashmi, A. S. K.; Blanco Jaimes, M. C.; Schuster, A. M.; Rominger, F. *J. Org. Chem.* **2012**, *77*, 6394−6408. (e) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593−3595. (f) Chang, M.-Y.; Cheng, Y.-C.; Lu, Y.-J. *Org. Lett.* **2015**, *17*, 1264−1267. (g) Huang, H.; He, G.; Zhu, X.; Qiu, S.; Zhu, H.; Zhu, G. *J. Org. Chem.* **2015**, *80*, 3480−3487. (h) Wang, M.; Jiang, M.; Liu, J.-.T. *Org. Chem. Front.* **2015**, *2*, 542−547. (i) Senadi, G. C.; Hu, W.-P.; Hsiao, J.-S.; Vandavasi, J. K.; Chen, C.-Y.; Wang, J.-J. *Org. Lett.* **2012**, *14*, 4478−4481. (j) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501−2504. (k) Jin, C.; Burgess, J. P.; Kepler, J. A.; Cook, C. E. *Org. Lett.* **2007**, *9*, 1887−1890. (l) Weyrauch, J. P.; Hashmi, A. S. K.; Schuster, A. M.; Hengst, T.; Schetter, S.; Littmann, A.; Rudolph, M.; Hamzic, M.; Visus, J.; Rominger, F.; Frey, W.; Bats, J. W. *Chem. - Eur. J.* **2010**, *16*, 956−963.

(7) (a) Stefely, J. A.; Palchaudhuri, R.; Miller, P. A.; Peterson, R. J.; Moraski, G. C.; Hergenrother, P. J.; Miller, M. J. *J. Med. Chem.* **2010**, *53*, 3389−3395. (b) Li, Q.; Woods, K. W.; Claiborne, A.; Gwaltney, S. L., II.; Barr, K. J.; Liu, G.; Gehrke, L.; Credo, R. B.; Hui, Y. H.; Lee, J.; Warner, R. B.; Kovar, P.; Nukakla, M. A.; Zielinski, N. A.; Tahir, S. K.; Fitzgerald, M.; Kim, K. H.; Marsh, K.; Frost, D.; Ng, S.-C.; Rosenberg, S.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 465−469.

(8) Crystallographic data for the crystal structure of **3c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1045312.

(9) Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. *J. Appl. Crystallogr.* **2006**, *39*, 453−457.

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