

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

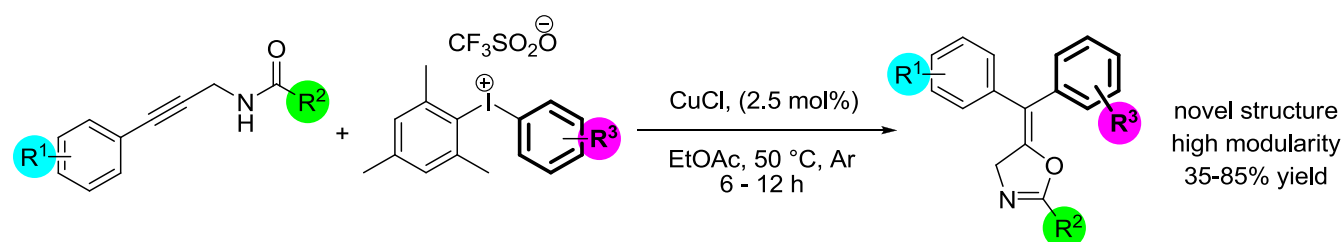
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Supporting Information Placeholder



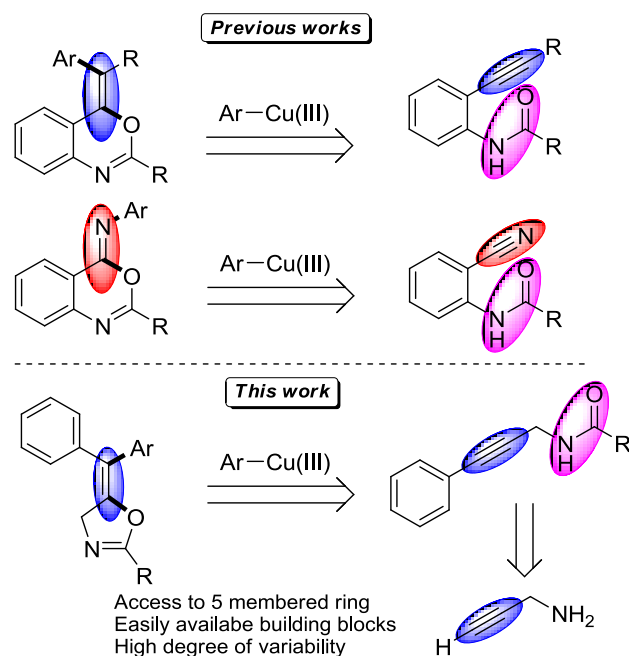
ABSTRACT: A copper-catalyzed carboarylation-ring closure strategy was used for the modular synthesis of oxazolines the reaction of 1-aryl-propargylamides and diaryliodonium salts. The novel approach enables the efficient, modular synthesis of oxazolines derivatives bearing fully substituted exo double 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 aryl-copper(III) species.³ In our laboratory, we developed an arylation-ring closure strategy enables for the formation of new carbocyclic 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 ortho-ethynylanilides⁴ and ortho-acetamidobenzonitriles⁵ (Scheme 1). The utilization of diaryliodonium salts in this transformation ensures the high modularity of the methodology.

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 core⁶ 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.

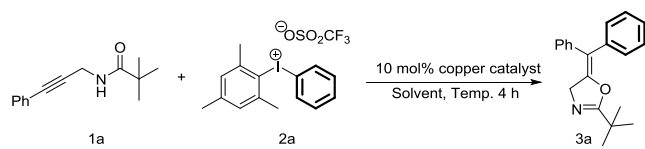
Scheme 1. Utilization of arylation-ring closure strategy



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 transition-metal catalysts in various solvents under argon. We found that the propargyla-

amide 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-(diphenylmethylene)-4,5-dihydrooxazole by NMR analysis.

Table 1. Optimization studies^a



Entry	Catalyst	Solvent	Temp.	Conv. ^b %
1	-	DCE	50 °C	0
2	Cu(OTf) ₂	DCE	50 °C	11
3	Cu(OTf) ₂	CH ₂ Cl ₂	50 °C	31
4	Cu(OTf) ₂	toluene	50 °C	5
5	Cu(OTf) ₂	THF	50 °C	59
6	Cu(OTf) ₂	EtOH	50 °C	0
7	Cu(OTf) ₂	EtOAc	50 °C	100
8	Cu(II)acac	EtOAc	50 °C	0
9	CuSO ₄	EtOAc	50 °C	0
10	Cu(MeCN) ₄ OTf	EtOAc	50 °C	100
11	CuO	EtOAc	50 °C	0
12	CuI	EtOAc	50 °C	0
13	CuBr	EtOAc	50 °C	76
14	CuCl	EtOAc	50 °C	100
15	CuCl	EtOAc	25 °C	0
16	5 mol% CuCl	EtOAc	50 °C	100 ^c
17	2.5 mol% CuCl	EtOAc	50 °C	100 ^c

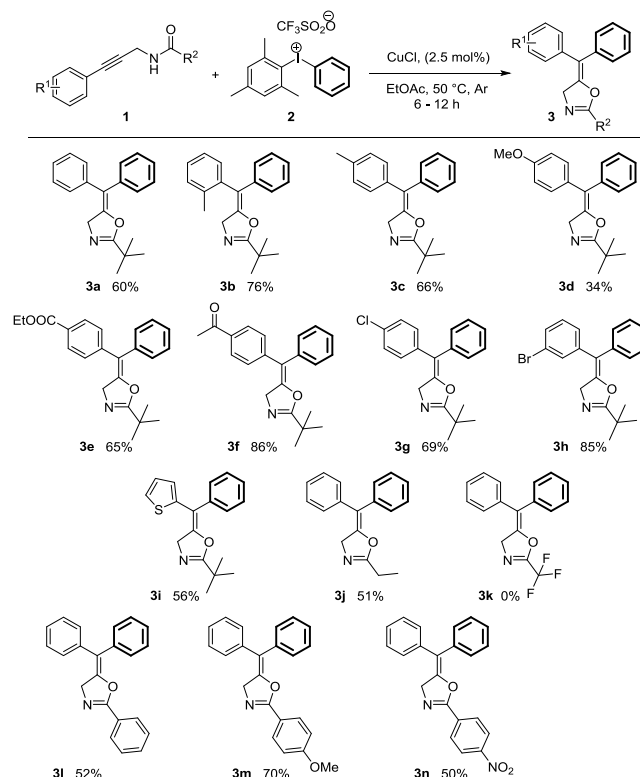
^a Catalyst (0.01 mmol, 0.10 equiv.), N-(3-phenylprop-2-yn-1-yl)pivalamide (0.1 mmol, 1.0 equiv.), mesitylphenyliodonium triflate (0.12 mmol, 1.2 equiv.), solvent (1.0 mL), Ar. ^b % conversions of N-(3-phenylprop-2-yn-1-yl)pivalamide were determined by GC-MS. ^c N-(3-phenylprop-2-yn-1-yl)pivalamide (0.5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

For the implementation of the syntheses we choose 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 applying the optimized reaction conditions (Scheme 2.). It was found that the presence of methyl group in 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 strong electron donating methoxy group was present on the phenyl group, the appropriate product **3d** was

obtained only in lower yield (34%). 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 to thiophenyl group the reaction afforded the desired product (**3i**) in 56% yield. In cases where nonsymmetrical substituted (arylphenylmethylene)-dihydrooxazoles are formed. NMR measurements confirmed the selective formation of the isomer where the oxygen and the phenyl group transferred from the iodonium salt are oriented *cis* to one another.

Scheme 2. Synthesis of dihydrooxazoles 1.^a



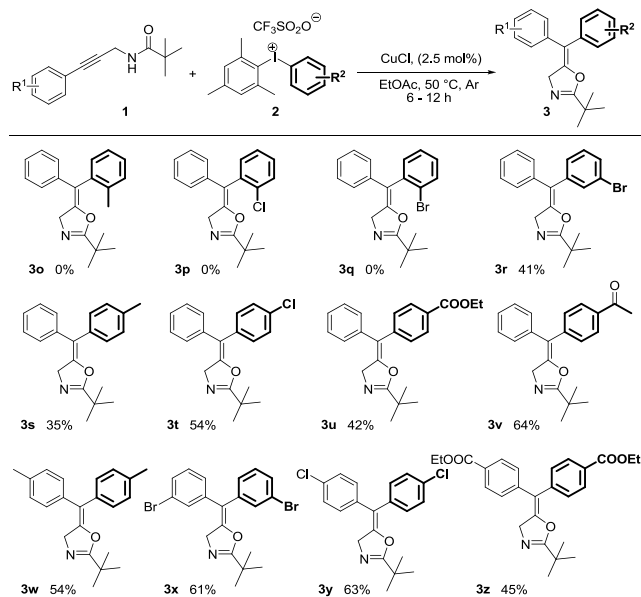
^a CuCl (0.0125 mmol, 0.025 equiv.), 3-arylpropargyl amide (0.5 mmol, 1.0 equiv.), arylmesityliodonium triflate (0.6 mmol, 1.2 equiv.), EtOAc (5.0 mL), Ar, 50 °C, % isolated yield

Next we investigated the effect of the amide functionality on the reaction. Although, the presence of 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.

After examining the applicability of different arylpropynyl anilides we studied the reactivity of different substituted arylmesityliodonium 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 deleterious effect on the reaction, and the

appropriate oxazolines (**3o-3q**) did not form. The transformation is compatible with various substituents in meta- and para positions on the phenyl group of the iodonium salt (Me, Cl, Br, Ac, COOEt) and the desired oxazolines (**3r-3v**) were isolated in 40-64% yield.

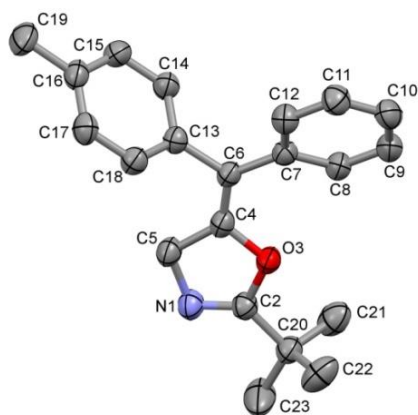
Scheme 3. Synthesis of dihydrooxazoles 2.^a



^a CuCl (0.0125 mmol, 0.025 equiv.), 3-arypropargyl amide (0.5 mmol, 1.0 equiv.), arylmesityliodonium triflate (0.6 mmol, 1.2 equiv.), EtOAc (5.0 mL), Ar, 50 °C, % isolated 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 (**3w-3z**) with symmetrical substituted double bond were isolated in 54%, 61%, 63%, and 45% yield respectively.

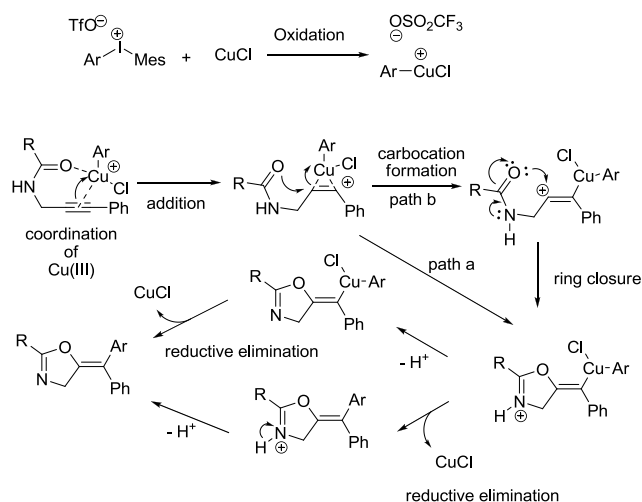
Figure 1. Molecular structure of compound 3c.⁸ Displacement ellipsoids are drawn at the 30% probability level.⁹



The geometries of the obtained non-symmetrically substituted heterocyclic alkene products (**3r-3v**) were determined by NMR studies and it was found that the incoming aryl group originated from the iodonium salt was in *cis* position to the oxygen of the oxazolines ring. The geometry of the exo double bond on the oxazoline ring was also established by X-ray crystallography in case of compound **3c** (Figure 1.).

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 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, then 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 to the activated π complex (path a) or to the carbocationic center (path b) which results a 5-*exo-dig* cyclization. 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.

Scheme 4. Proposed mechanistic picture of the transformation.



Summarizing our results, in this work 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 bond 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 undergoes in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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REFERENCES

- (1) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (f) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395.
- (2) (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (d) Merritt E.A.; Olofsson B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9052. (e) V. V. Zhdankin, Hypervalent Iodine Chemistry, Wiley, Chichester **2014**. (f) J. Collette, D. McGreer, R. Crawford, F. Chubb, R. B. Sandin, *J. Am. Chem. Soc.* **1956**, *78*, 3819-3820. (g) G. F. Koser, R. H. Wettach, C. S. Smith, *J. Org. Chem.* **1980**, *45*, 1543-1544. (h) P. J. Stang, V. V. Zhdankin, R. Tykwinski, *Tetrahedron Lett.* **1992**, *33*, 1419-1422. (i) E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052-9070. (j) J. M. Bouma, B. Olofsson, *Chem. Eur. J.* **2012**, *18*, 14242-14245. (k) M. Bielawski, B. Olofsson, *Chem. Commun.* **2007**, *25*, 2521-2523. (l) M. S. Yusubov, A. V. Maskaev, V. V. Zhdankin, *ARKIVOC* **2011**, 370-409. (m) L. F. Silva, Jr., B. Olofsson, *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) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172-8174. (b) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593-1597. (c) R. J. Phipps, L. Mc Murray, S. Ritter, H. A. Duong, M. J. Gaunt, *J. Am. Chem. Soc.* **2012**, *134*, 10773-10776. (d) A. Bigot, A. E. Williamson, M. J. Gaunt, *J. Am. Chem. Soc.* **2011**, *133*, 13778-13781. (e) M. G. Suero, E. D. Bayle, B. S. L. Collins, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 5332-5335. (f) A. J. Walkinshaw, W. Xu, M. G. Suero, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 12532-12535. (g) E. Cahard, N. Bremeyer, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2013**, *52*, 9284-9288. (h) F. Zhang, S. Das, A. J. Walkinshaw, A. Casitas, M. Taylor, M. G. Suero, M. J. Gaunt, *J. Am. Chem. Soc.* **2014**, *136*, 8851-8854. (i) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260-4263. (j) J. H. Ryan, P. J. Stang, *Tetrahedron Lett.* **1997**, *38*, 5061-5064. (k) A. Casitas, X. Ribas, *Chem. Sci.* **2013**, *4*, 2301-2318. (l) Buksnaitienė, R.; Cikotienė, I.; **2015**, *26*, 479-483. (m) Peng, J.; Chen, C.; Chen, J.; Su, X.; Xi, C.; Chen, H. *Org. Lett.* **2014**, *16*, 1776-1779. (o) Cahard, E.; Male, H. P. J.; Tissot, M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2015**, DOI: 10.1021/jacs5b03937
- (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.
- (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**, 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.; Jaimes, M. B. 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.; *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**, 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.; Palchadhuri, 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.; Wood, K. W.; Claireborne, A.; Gwanlley, S. L., II; Barr, K. J.; Liu, G.; Gehke, L.; Credo, R. B.; Hua Hui, Y.; Lee, J.; Warner, R. B.; Kovar, P.; Nukkla, 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.* **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 number CCDC 1045312
- (9) C.F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Cryst.* **2006**, *39*, 453.
