NJC

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

rsc.li/njc

View Article Online
DOI: 10.1039/C7NJ01803G

Journal Name

ARTICLE

Ytterbium(III)-Catalyzed Three-Component Reactions: Synthesis of 4-Organoselenium-quinolines and Application in Copper-free Sonogashira Cross-coupling Reactions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Isadora M. de Oliveira,[a] Stanley S. N. Vasconcelos,[b] Cristiane S. Barbeiro,[b] Thiago C. Correra,[a] Anwar Shamim,[a] Daniel C. Pimenta,[c] Ignez Caracelli,[d] Julio Zukerman-Schpector,[e] Hélio A. Stefani,[b]* Flávia Manarin[f]*

4-organoselenium-quinolines were synthesized via model multi-component Povarov (MCR) reactions between p-anisidine, ethyl glyoxylate and ethynyl(phenyl)selane, catalyzed by the Lewis acid Yb(OTf)3, with yields ranging from moderate to good. This method is advantageous in that there is no requirement for an oxidant and that the reaction has a wide scope. These 4-organoselenium-quinolines allowed access to 4-alkynyl-quinolines, which were synthesized via copper free Sonogashira cross-coupling reactions catalyzed by a new palladium catalyst that employs an oxazoline derivative as a ligand. A plausible mechanism was proposed based on HRMS studies.

The quinoline ring system is present in a wide array of natural compounds,[1] and materials[2]. These natural quinoline-bearing compounds and materials have been reported to exhibit a large range of biological properties such as neuroprotective[3], anti-tuberculosis[4], anti-trypanosomal,[5] anti-cancer[6] and anti-toxoplasmosis effects.[7]

Based on their versatility in multi-disciplinary fields, the development of new synthetic strategies for the preparation of quinoline derivatives has attracted great attention in the field of organic synthesis.

Several methods have been reported for the synthesis of quinoline rings; the classical methodologies that date from 1880 usually involve harsh reaction conditions and show various limitations for diversity-oriented synthesis.[11] However, the Povarov reaction is one of the most straightforward multi-component strategies for the synthesis of functionalized quinolines.[12] This protocol is an inverse electron-demand aza-Diels-Alder reaction between aryl imines (formed *in situ*) and terminal alkynes. The classical Povarov reaction employed electron-rich olefins; however, alkynes can also be used as dienophiles in the Povarov reaction.

There are several Povarov methodologies in the literature based on Lewis acid catalysis,[13] Bronsted acid[3] and even catalyst-free[14] conditions to obtain 2,4-disubstituted quinoline derivatives. However, similar approaches of multi-component Povarov reactions involving chalcogen atoms as substituents in the quinoline ring nucleus, which is a privileged structure, have been unexplored.

Selenium-containing compounds have found great utility in biology and chemistry due to their highly promising properties.[15] Unsaturated organoselenides can be used as versatile synthetic intermediates as an alternative to organohalides in cross-coupling reactions.[16] In the pharmacology field, a series of selenium-containing clioquinol derivatives were evaluated as multi-functional anti-Alzheimer´s disease (AD) agents. These compounds notably exhibited inhibition of metal-induced Aβ aggregation.[17]

In this paper, we report a synthetic route to access novel 2,4-dissubstituted selenium-quinoline derivatives via multi-component (MCR) Povarov reactions and their subsequent use as intermediates in copper-free Sonogashira cross-coupling reactions.

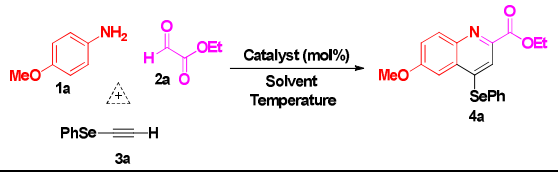
The unique structural features and potential bioactivity of quinolines prompted us to investigate this cycloaddition reaction under various conditions. Initially, screening of reaction parameters, including catalyst, solvent, temperature and reaction time, was conducted using a model multi-component (MCR) Povarov reaction between *p*-anisidine **1a**, ethyl glyoxylate **2a** and ethynyl(phenyl)selane **3a** (Table 1).

[a] *Instituto de Química, Universidade de São Paulo, São Paulo, SP – Brasil.*
[b] *Departamento de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, SP – Brasil. E-mail: hstefani@usp.br*
[c] *Instituto Butantã, São Paulo, SP – Brasil.*
[d] *Departmento de Física, Universidade Federal de São Carlos, São Carlos, SP – Brasil.*
[e] *Departmento de Química, Universidade Federal de São Carlos, São Carlos, SP – Brasil.*
[f] *Centro de Engenharias e Ciências Exatas- CECE, Universidade Estadual do Oeste do Paraná, Toledo, PR – Brasil. E-mail: fgmanarin@gmail.com*

Electronic Supplementary Information (ESI) available: Experimental section, detailed experimental procedures, characterization data and copies of the ^{1}H, ^{13}C NMR e mass spectra for the mechanism. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C7NJ01803G

Table 1. Optimization of Multi-component (MCR) Povarov Reaction Conditions.



Entry	Catalyst (mol %)	Time(h)	Solvent	Yield (%)[e]
1	$Yb(OTf)_3$ (10)	4	ACN	69
2	$FeCl_3$ (10)	18	ACN	40
3	$Sc(OTf)_3$ (10)	20	ACN	60
4	Ag(OTf) (10)	19	ACN	47
5	$In(OTf)_3$ (10)	19	ACN	53
6	$SnCl_2$	20	ACN	45
7	TfOH (10)	3	ACN	35
8	I_2 (10)	22	ACN	42
9	$AuCl_3$ (10)	18	ACN	40
10	$Yb(OTf)_3$ (10)	22	ACN	65
11	$Yb(OTf)_3$ (10)	10	ACN	60[a]
12	$Yb(OTf)_3$ (10)	18	ACN	62[b]
13	$Yb(OTf)_3$ (20)	2	ACN	75
14	$Yb(OTf)_3$ (10)	20	DCM	50[c]
15	$Yb(OTf)_3$ (10)	17	Toluene	47[d]

Conditions: p-anisidine (0.5 mmol, 1.0 eq.), ethylglyoxylate (0.5 mmol, 1.0 eq.), catalyst (10 - 20 mol%), solvent (3.0 mL), ethynyl(phenyl)selane (0.6 mmol, 1.2 eq.), in N2 atmosphere. [a]TEMPO. [b]Ambient atmosphere. [c]Temperature 45 °C. [d]Temperature 100 °C. [e]Isolated yields.

When substrates **1a**, **2a**, and **3a**, in a ratio of 1:1:1.2, were reacted in the presence of $Yb(OTf)_3$ (10 mol%) in acetonitrile under reflux for 4 h, compound **4a** was isolated in 69% yield (Table 1, entry 1). Several other Lewis and Bronsted acids, such as $FeCl_3$, $SnCl_2$, TfOH, I_2 and $AuCl_3$, were also screened as catalyst, however the desired product **4a** was achieved in poor yields of (Table 1, entries 2, 6-9). Triflates have proved to be efficient Lewis acid catalysts for the synthesis of several important biologically active heterocyclic molecules due of their distinct properties such as moisture insensitivity, stability, reusability and high catalytic activity.[18] They have also been used efficiently for the synthesis of quinoline derivatives,[7,13] therefore we decided to screen the effectiveness of $Yb(OTf)_3$, $Sc(OTf)_3$, Ag(OTf) and $In(OTf)_3$ (Table 1, entries 1, 3-5). However, $Yb(OTf)_3$ was found to be the most effective when compared to all the catalysts studied.

Recently, Sakhujaet al. reported the importance of $Yb(OTf)_3$ as a useful Lewis acid that has attracted attention in organic synthesis. It is probably one of the most effective of the lanthanide triflates, owing to its position near the end of the lanthanide series. With a larger number of protons in its nucleus, Yb^{3+} is one of the smallest lanthanides and the hardest acid of the series. Therefore, the high Lewis acidity of Yb^{3+} may be attributed to its small ionic radius. The incomplete number of electrons in the 4f orbital of Yb^{3+} results in a high tendency for this orbital to become filled. Reaction conditions using this catalyst are generally mild and often only room temperature and/or low-boiling solvents are required. The catalyst is readily recovered from the reaction mixtures and can be reused with equivalent catalytic capacity.[19]

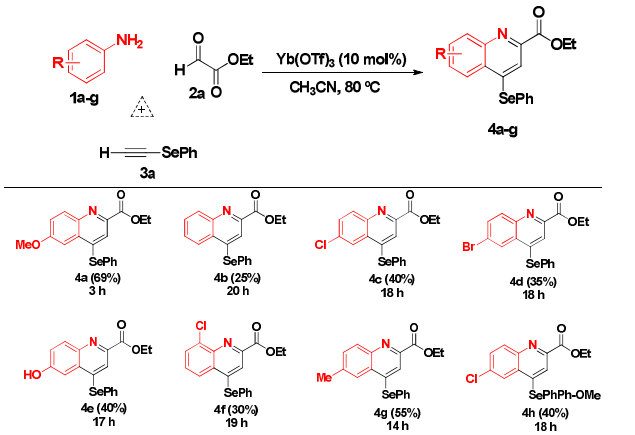
In relation to the optimization of the reaction conditions, we found that prolonging the reaction time did not improve the yields. The effect of a nitrogen atmosphere was evaluated, however there were no major changes in yield (Table 1, entry 12).

Therefore, we supposed that the yield of this reaction might be improved by using an additive, such as TEMPO, to act as an oxidant to produce quinolines from di- and tetrahydroquinolines. However, we did not observe any change in the yield when we used TEMPO as an oxidant (Table 1, entry 11). However, increasing the catalyst loading to 20 mol%, increased the yield of 4a to 75% (Table 1, entry 13). We next investigated different solvents (acetonitrile, dichloromethane and toluene) for the Yb(OTf)3 catalyzed reaction, however acetonitrile proved most suitable (Table 1, entries 1, 14 and 15).

Among the various conditions tried, the best result was obtained with $Yb(OTf)_3$ (10 mol%) as catalyst and acetonitrile as solvent at 80 ºC, providing the cyclization product in 69% (Table 1, entry 1). Confirmation of the NMR spectroscopic results was accomplished by the X-ray crystal structure of compound **4a** (See SI).

We next explored the generality of the multi-component (MCR) Povarov reaction for the synthesis of selenium-quinoline derivatives, using a variety of substituted anilines (Table 2). The results indicated that both electron-poor and electron-rich aryl substituents were tolerated. For example, *p*-Cl, *p*-Br and *o*-Cl susbtituted anilines afforded the corresponding products **4c**, **4d** and **4f** in yields ranging from 30-40%. *p*-OMe, *p*-OH and *p*-Me substituted anilines provided the corresponding products **4a**, **4e** and **4g** in moderate to good yields of 40-69%. When *p*-NO_2 substituted aniline was used, the formation of the imine intermediate was not observed. Substituent position on the anilines also exerted a noticable effect, namely the yields of reactions with *ortho*-substituted anilines were comparitively lower than the yields of reactions with *para*-substituted anilines (**4f** and **4h**).

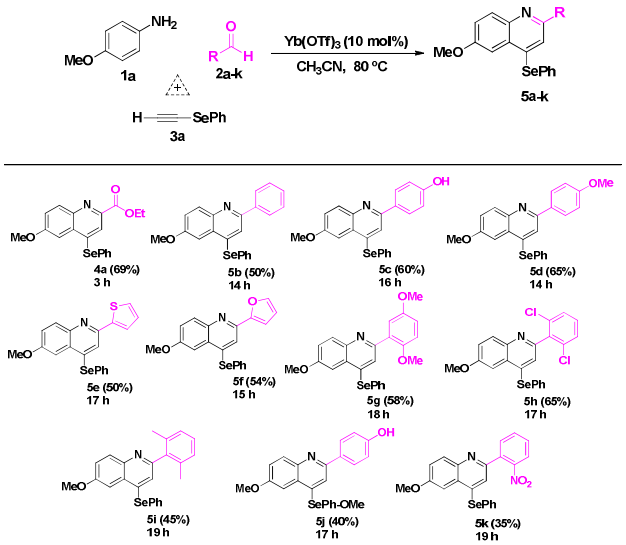
Table 2. Scope of Anilines in the Multi-component (MCR) Povarov reactions.



View Article Online
DOI: 10.1039/C7NJ01803G

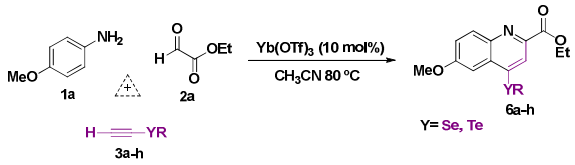
Similarly, different aldehydes were applied to make a library of selenium-substituted quinolines (Table 3). Good to moderate yields were achieved with a variety of aromatic, alkyl and heteroaromatic aldehydes.

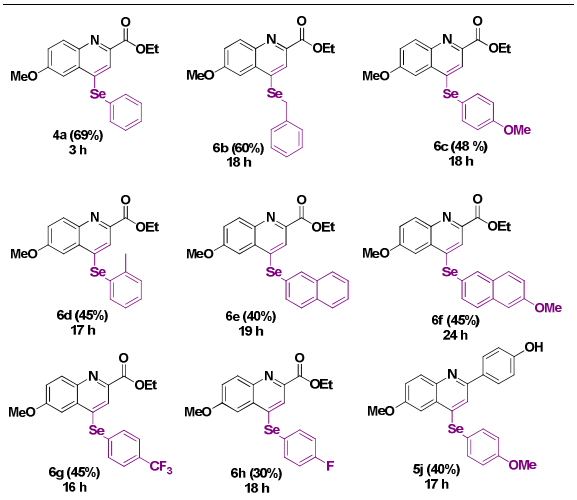
Table 3. Scope of Aldehydes in the Multi-component (MCR) Povarov reactions.



We next examined different substituted aromatic selenium acetylenes in the multi-component (MCR) Povarov reactions (Table 4). The desired products were obtained in yields ranging from 30-69%. Phenyl and benzyl alkynes were used in order to determine the influence of phenyl and benzyl groups linked to selenium. We observed that alkynes containing the phenyl group led to product formation with comparatively higher yield examples **4a** and **6b**.

Table 4. Scope of Alkynes in the Multi-component (MCR) Povarov reactions.

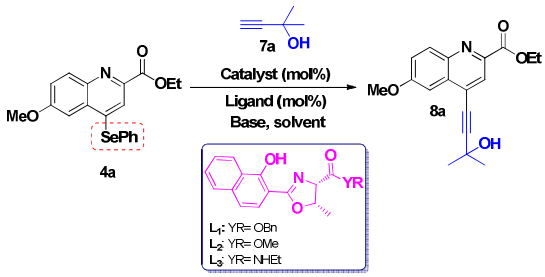




The reaction was found to tolerate both electron-withdrawing and electron-donating groups and the yields were the same for both.

To demonstrate the synthetic utility of 4-organoselenium-quinolines derivatives, compound **4a** was subjected to Sonogashira cross-coupling reactions. We tried the reactios with ethyl-6-methoxy-4-(phenylselene) quinoline-2-carboxylate **4a** and 2-methylbut-3-yn-2-ol **7a**, in the presence of various palladium catalysts, copper salts, bases, and solvents (Table 5).

Table 5. Screening of the Sonogashira cross-coupling reaction.



View Article Online
DOI: 10.1039/C7NJ01803G

Entry	Catalyst (mol%)	Base	Solvent	Yield (%)
1	$Pd(PPh_3)Cl_2$ (10)/$Cu(OAc)_2$ (20)	Et_3N	DMF	65[a]
2	$Pd(Ph_3)_4$ (10)/$Cu(OAc)_2$ (20)	Et_3N	DMF	50[a]
3	$Pd(OAc)_2$ (10)/$Cu(OAc)_2$ (20)	Et_3N	DMF	15[a]
4	$Pd(PPh_3)Cl_2$ (10)/CuI (20)	Et_3N	DMF	50[a]
5	$Pd(PPh_3)Cl_2$ (10)/$Cu(OAc)_2$ (20)	DIPA	DMF	57[a]
6	$Pd(PPh_3)Cl_2$ (5)/$Cu(OAc)_2$ (10)	Et_3N	DMF	76[a]
7	$PdCl_2$(10)/ligand 1 (20)	Et_3N	DMF	75[a]
8	$PdCl_2$(10)/ligand 2 (20)	Et_3N	DMF	10[a]
9	$PdCl_2$(10)/ligand 3 (20)	Et_3N	DMF	30[a]
10	$PdCl_2$(10)/ligand 1 (20)	Et_3N	DMF	10[c]
11	$PdCl_2$(10)/ligand 1 (20)	Et_3N	DMF	63[a,g]
12	$PdCl_2$	Et_3N	DMF	20
13	$PdCl_2$(10)/ligand 1 (20)	Cs_2CO_3	DMF	15[a]
14	$PdCl_2$(10)/ligand 1 (20)	DIPA	DMF	25[a]
15	$PdCl_2$(10)/ligand 1 (20)	Et_3N	ACN	37[a]
16	$PdCl_2$(10)/ligand 1 (20)	Et_3N	MeOH	57[d]
17	$PdCl_2$(10)/ligand 1 (20)	Et_3N	THF	27[b]
18	$PdCl_2$(10)/ligand 1 (20)	Et_3N	DMF	28[a,e,f,g]

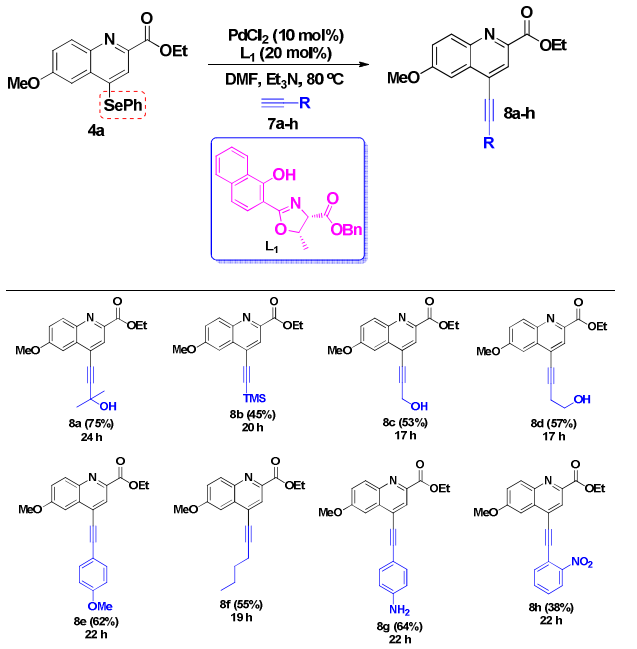
Conditions: **4a**(0.15 mmol, 1.0 eq.), **7a** (0.3 mmol, 2.0 eq.), palladium catalyst (- 10 mol%), copper catalyst (10 - 20 mol%), ligand (20 mol%), base (0.3 mmol, 2.0 eq.), solvent (1.0 mL), in N_2.[a]Temperature 80 °C. [b]Temperature 60 °C. [c]Room temperature. [d]Temperature 50 °C. [e]MW. [f]Time 1h. [g]Ambient atmosphere.

Our preliminary studies focused on the reaction of ethyl-6-methoxy-4-(phenylselene)quinoline-2-carboxylate **4a** with 2-methylbut-3-yn-2-ol **7a** in the presence of 10 mol% of $Pd(PPh_3)Cl_2$ and 20 mol% of $Cu(OAc)_2$, with Et_3N as base and DMF as solvent at 80 ºC. Quinoline **8a** was isolated in 65% yield after 24 h (Table 5, entry 1). Subsequently, different palladium species such as $Pd(PPh_3)_4$, $Pd(OAc)_2$, $PdCl_2/L_1$, $PdCl_2/L_2$ and $PdCl_2/L_3$ were also tested (Table 5, entries 2, 3,7-9). $PdCl_2/L_1$ proved to be the more efficient catalyst in these reactions. Among the catalysts used, those with oxazoline ligands afford the product in higher yields with no need for the use of copper as co-catalyst. $PdCl_2$ without the oxazoline ligand gave the product in lower yields.

Other common bases that we used in this reaction, such as Et_3N, Cs_2CO_3 and DIPA, were effective too, although lower yields were obtained (Table 5, entries 12-14). This indicated that base played an important role in the reaction. The effect of the solvent was also investigated. Changing the solvent to ACN, MeOH and THF failed to improve the yield of the product **8a** (Table 5, entries 7, 15-17). Further investigation revealed that temperature was also a key factor in this reaction. When the reaction was run at room temperature, the product **8a** was obtained in only 10% yield (Table 5, entry 10). The highest yield of 75% was obtained under the optimized conditions as shown (Table 5, entry 7). The structure of compound **8a** was confirmed unequivocally by X-ray crystallographic analysis (See SI).

Using the optimized reaction conditions, the scope of this coupling reaction was evaluated using different alkynes to obtain a library of alkyne substituted quinoline derivatives, as shown in Table 6.

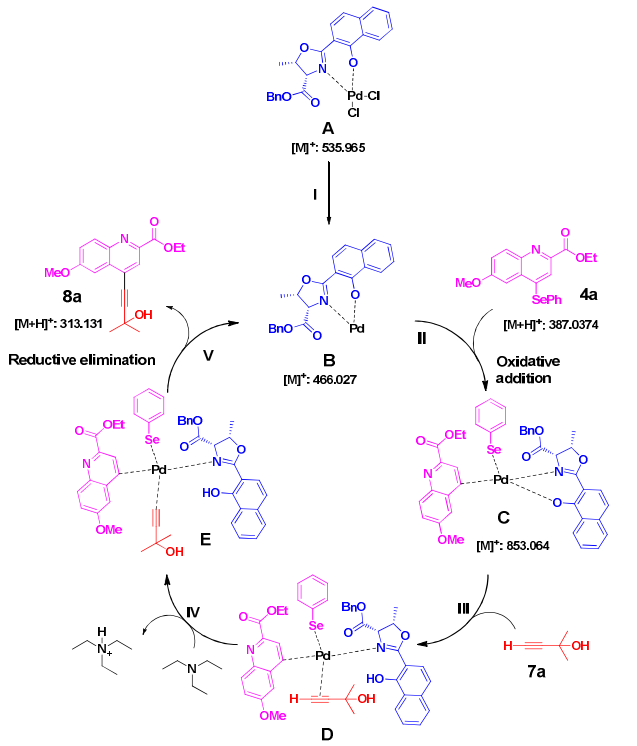
Table 6. Sonogashira Cross-coupling Reactions.



The Sonogashira cross-coupling reactions employing the oxazoline derivative as a ligand were promising, tolerating the use of different aromatic and alkyl alkynes. Alkynes with alkyl groups (**8f**) and highly electron-withdrawing groups (**8h**) gave lower yields. Alkynes with electron-donating groups gave the products **8a-e**, and **8g** in good yields.

A mechanism was proposed based on experimental data obtained by using high resolution mass spectrometry (HRMS), as shown in Scheme 1. Initially, complex **A** forms *in situ* from the oxazoline ligand and palladium chloride, as detected by mass spectrometry [m/z 535.975]$^+$. Then, the palladium-chlorine bonds break forming complex **B** [m/z 466.010]$^+$. Oxidative addition[20] of the 4-phenylselenium-quinoline **4a** leads to the complex **C** [m/z 853.064]$^+$ (See SI) followed by coordination with the π-electrons of the alkyne **7a**. We believe that the coordination of the palladium with the alkyne (complex **D**) acidifies the terminal hydrogen, facilitating its removal after the addition of the base. Reductive elimination of complex **E** leads to the coupling product **8a** and the regeneration of catalyst **B** (for additional information and spectra see the SI).

View Article Online
DOI: 10.1039/C7NJ01803G



Scheme 1. Proposed Mechanism of the Sonogashira Cross-coupling Reactions with the Oxazoline Ligand.

Conclusions

In summary, we have developed a simple and versatile ytterbium-catalyzed *one-pot* multi-component (MCR) Povarov reaction protocol for the synthesis of structurally diverse 4-organoselenium-quinolines derivatives. Our reactions proceeded in the absence of oxidants and tolerated a wide variety of anilines, alkynes and aldehydes. Furthermore, we demonstrated the synthetic potential of 4-organoselenium-quinolines as an alternative over standard electrophilic sources in copper-free Sonogashira cross-coupling reactions.

Acknowledgements

The authors gratefully acknowledge financial support from the São Paulo Research Foundation (FAPESP grant 2012/00424-2 to HAS, 2016/04289-3 to I.M.O. and 2013/17960-7 to S.N.S.V.), São Paulo Research Foundation (FAPESP-grant 2014/15962-5, FAPESP-grant 2015-08539-1 to T.C.C.) and Coordination of Improvement of Higher Level Personnel (CAPES) for a fellowship (CAPES 23038.006960/2014-65 to T.C.C), and The National Council for Scientific and Technological Development (CNPq) for fellowships (306119–2014-5 to HAS, 308480/2016-3 to IC, 305626/2013–2 to JZ-S), The National Council for Scientific and Technological Development (CNPq) for a fellowship (459816/2014-4 F.G.M.). We thank Professor Regina H. A. Santos from IQSC-USP for the X-ray data collection.

Notes and references

1 J. P. Michael, *Nat. Prod. Rep*., 2008, **25**, 166.
2 (a) H. U. Blaser, H. P. Jalett, W. Lottenbach and M. Studer, *J. Am. Chem. Soc.*, 2000, **122**, 12675. (b) A. P. Kulkarni, J. Christopher, C. J. Tonzola, A. Amit and S. A. Jenecke, *Chem. Mater*., 2004, **16**, 4556.
3 J. B. Bharate, A. Wani, S. Sharma, S. I. Reja, M. Kumar, R. A. Vishwakarma, A. Kumar and S. Bharate, *Org. Biomol. Chem*., 2014, **12**, 6267.
4 M. V. N. Souza, K. C. Pais, C. R. Kaiser, M. A. Peralta, M. Ferreira and M. C. S. Lourenço, *Bioorg. Med. Chem*., 2009, **17**, 1474.
5 O. Pietro, E. Vicente-Garcia, M. C. Taylor, D. Berenguer, E. Viayna, A. Lanzoni, I. Sola, H. Sayago, C. Riera, R. Fisa, V. Clos, B. Pérez, J. M. Kelly, R. Lavilla and D. M. Torrero, *Eur. J. Med. Chem.*, 2015, **105**, 120.
6 B. Heininger, G. Gakhar, K. Prasain, D. H. Hua and T. A. Nguyen, *Anticancer. Res.*, 2010, **30**, 3927.
7 J. McNulty, R. Vemula, C. Bordón, R. Yolken and L. Jones-Brando, *Org. Biomol. Chem.*, 2014, **12**, 255.
8 (a) K. C. Harper and M. S. Sigman, *Science*, 2011, **333**, 1875. (b) I. Abrunhosa, L. Delain-Bioton, A. C. Gaumont, M. Gulea and S. Masson, *Tetrahedron*, 2001, **60**, 9263.
9 P. Melchiorre, *Angew. Chem. Int. Ed.*, 2012, **51**, 9748.
10 E. Debroye, G. Dehaen, S. Eliseeva, S. Lauent, L. V. Elst, R. N. Muller, K. Binnemans and T. N. Parac-Vogt, *Dalton Trans.*, 2012, **41**, 10549.
11 (a) H. Skraup, *Chem. Ber.*, 1880, **13**, 2086. (b) A. Combes, *Bull. Chim. Soc. France*, 1888, **49**, 89. (c) P. Friedländer, *Chem. Ber.*, 1882, **15**, 2572. (d) W. J. Pfitzinger, *Prakt. Chem.*, 1886, **33**, 100. (e) O. Doebner and W. Von Miller, *Chem. Ber.*, 1881, **14**, 2812.
12 L. S. Povarov, *Russ. Chem. Rev.,* 1967, **36**, 656.
13 (a) K. Pericherla, A. Kumar and A. Jha, *Org. Lett.*, 2013, **15**, 4078. (b) J. McNulty, R. Vermula, C. Bordon, R. Yolken and L. J. Brando, *Org. Biomol. Chem.,* 2014, **12**, 255. (c) X. Li, Z. Mao, Y. Wang, W. Chen and X. Lin, *Tetrahedron*, 2011, **67**, 3858. (d) H. Huang, H. Jiang, K. Chen and H. Liu, *J. Org. Chem.,* 2009, **74**, 5476. (e) Y. Wang, C. Chen, J. Peng and M. Li, *Angew. Chem. Int. Ed.*, 2013, **52**, 5323. (f) C. E. Meyet and C. H. Larsen, *J. Org. Chem.*, 2014, **79**, 9835. (g) V. Gaddam, S. Ramesh and R. Nagarajan, *Tetrahedron*, 2010, **66**, 4218. (h) F. Xiao, Y. Chen, Y. Liu and J. B. Wang, *Tetrahedron*, 2008, **64**, 2755. (i) R. Rohlmann, T. Stopka, H. Richter and O. G. Mancheño, *J. Org. Chem.*, 2013, **78**, 6050.
14 M. Chen, N. Sun and Y. Liu, *Org. Lett.*, 2013, *15*, 5574.
15 (a) G. Nugesh, W. W. Du Mont and H. Sies, *Chem. Rev.*, 2001, **101**, 2125. (b) C. W. Nogueira, G. Zeni and J. B. T. Rocha, *Chem. Rev.*, 2004, **104**, 6255.
16 (a) H. A. Stefani, D. M. Leal, F. Manarin, *Tetrahedron Lett.*, 2012, **53**, 6495. (b) A. L. Stein, F. N. Bilheri and G. Zeni, *Chem. Commun.*, 2015, **51**, 15522.
17 Z. Wang, Y. Wang, W. Li, F. Mao, Y. Sun, L. Huang and X. Li, *ACS Chem. Neurosc.*, 2014, **5**, 952.
18 a) U. V. Ladziata, *Arkivoc*, 2014, **(i)**, 307. (b) S. Kobayashi, M. Sugiura, H. Kitagawa and W. W. L. Lam, *Chem. Rev.*, 2002, **102**, 2227. (c) X. Jiang and R.Wang, *Chem. Rev.*, 2013, **113**, 5515.
19 R. Sakhuja, K. Pereicherla, K. Bajaj, B. Khungar and A. Kumar, *Synthesis*, 2016, **48**, 4305.
20 A. J. Canty, M. C. Denney, J. Patel, H. Sun, B. W. Skelton, A. H. White, *Journal of Organometallic Chemistry*, 2004, **689**, 672.

Graphical Abstract

View Article Online
DOI: 10.1039/C7NJ01803G