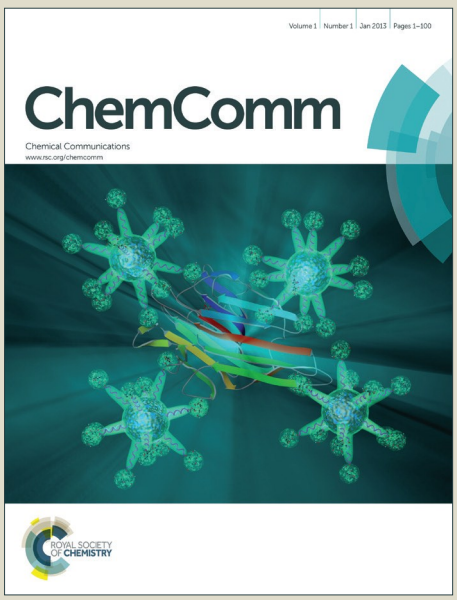
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Chem. Commun.

COMMUNICATION

Enantioselective synthesis of 4*H*-pyranonaphthoquinones *via* sequential squaramide and silver catalysis†

Uğur Kaya,[a] Pankaj Chauhan,[a] Daniel Hack,[a] Kristina Deckers,[a] Rakesh Puttreddy,[b] Kari Rissanen,[b] Dieter Enders[a*]

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

DOI: 10.1039/x0xx00000x
ww.rsc.org/

An enantioselective one-pot Michael addition/hydroalkoxylation reaction between 2-hydroxy-1,4-naphthoquinones and alkyne-tethered nitroalkenes catalyzed by a cinchona-derived squaramide and a silver(I) salt has been developed. The sequential protocol provides a direct access to 4*H*-pyranonaphthoquinones in moderate to very good yields and good to excellent enantioselectivities at a very low catalyst loading (0.5 mol%) of the squaramide.

Natural products bearing a 1,4-naphthoquinone skeleton are distributed widely throughout the plant kingdom. Among these, the pyranonaphthoquinones show a plethora of biological activities including anticancer[1], anticoccidial[2] or antibiotic[3] properities. The naturally occurring pyranonaphthoquinones **I** and **II** (α-lapachones) exhibit anti-tumor property[4,5], whereas the pyranokunthone A (**III**) and B (**IV**) show strong antimalarial activity.[6] Due to their interesting bioactivities much effort has been devoted to the development of efficient synthetic methods for the asymmetric synthesis of naphthoquinone derivatives.[7]

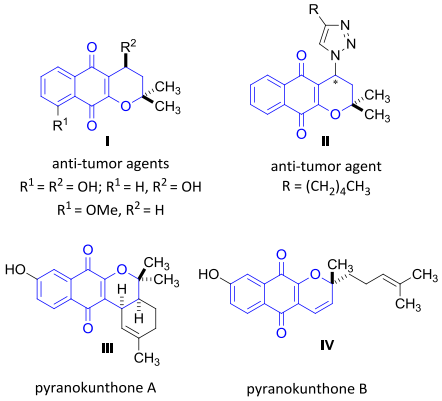
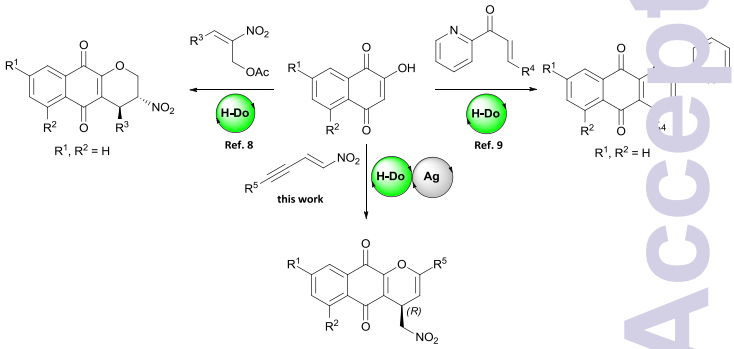


Fig. 1 Bioactive compounds containing pyranonaphthoquinone scaffolds

Recently, Namboothiri and da Silva Júnior have reported an asymmetric synthesis of pyranonaphthoquinones u[sing] Morita-Baylis-Hillman acetates of nitroolefins.[8] Furthermore Singh *et al*. published an asymmetric synthesis [of] pyranonaphthoquinones catalyzed by a bifunctional bis-squaramide catalyst (Scheme 1).[9] To the best of o[ur] knowledge, there is no report on the asymmetric synthesis [of] pyranonaphthoquinones by merging organo- and met[al] catalysis.



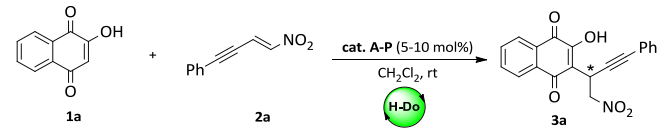
Scheme 1 Recent approaches for the asymmetric synthesis of pyranonaphthoquinones

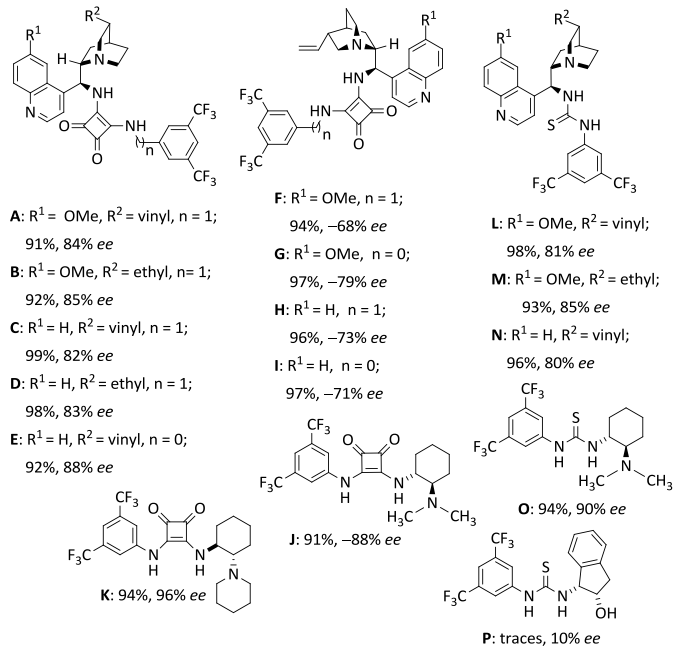
The combination of transition metal catalysis an[d] organocatalysis became an interesting and important area o[f] research.[10] The merger of two catalytic systems has led to powerf[ul] strategies for the development of desirable transformations, whi[ch] are not possible by using an organocatalyst or metal catalyst independently. This merger led to the development of new an[d] previously inaccessible reactions in a one-pot procedure with th[e] advantages of step-, redox-, and pot-economy and reduced c[os]ts and time. The main challenge of this approach is to ensure that [the] catalysts, substrates, intermediates or solvents are compatible during the whole reaction sequence.[10d] Predominantly expensiv[e] gold or palladium complexes were used in combination wi[th] organocatalysts, whereas the sequential merger of silver- and organocatalysis has been less explored.[11,12] Recently our group h[as] observed that silver is a suitable candidate for π-activation providing better catalyst compatibility and lower catalyst costs [as] compared to the Au(I) catalysts.[13]

[a] *Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany. E-mail: enders@rwth-aachen.de*
[b] *Department of Chemistry, University of Jyväskylä, 40014 Jyväskylä, Finland.*
† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data (HPLC, NMR, MS, IR). See DOI: 10.1039/x0xx00000x

Owing to the interesting biological activities associated with the naphthoquinone derivatives and knowing the catalytic power of the squaramide and silver catalysts, we herein report on the enantioselective synthesis of 4*H*-pyranonaphthoquinones using alkyne-tethered nitroolefins **2** and 2-hydroxy-1,4-naphthoquinones **1** in the presence of a cinchona-derived squaramide and AgOTf as catalysts.

Our initial exploration focused on the Michael addition of 2-hydroxy-1,4-naphthoquinone (**1a**) to the alkyne-tethered nitroolefin **2a**. The reaction of **1a** with **2a** in CH_2Cl_2 at room temperature in the presence of 10 mol% of the bifunctional squaramide **A** gave the desired product **3a** in 91% yield and 84% *ee* (Scheme 2). Fortunately, all cinchona-derived squaramides as well as the thiourea catalysts afforded the Michael adduct in very good yields and enantioselectivities with the exception of the thiourea catalyst **P** (Scheme 2). This suggests that the presence of a tertiary amine is pivotal for the catalytic efficiency. The best result was obtained with the squaramide **K** which gave 94% yield and 96% *ee* of **3a**. Hence, we decided to use **K** for further optimization studies.



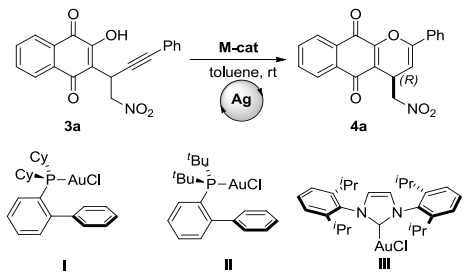


Scheme 2 Catalyst screening for the asymmetric Michael addition of **1a** and **2a**

Further investigations were carried out by screening different solvents. In all solvents the reactions resulted in very good yields of **3a** and performing the reaction in CH_2Cl_2 provided a good enantiomeric excess of **3a** within 30 minutes. Decreasing the catalyst loading slightly improved the yield and the enantioselectivity. Studies on the effect of the catalyst loading and of the temperature showed that the reduction of the catalyst loading to 0.5 mol% afforded the Michael adduct in 95% yield and 96% *ee* at room temperature (see supporting information).

Next, we focused on the hydroalkoxylation through the π-activation of the alkyne **3a** by late transition metal complexes. The Michael adduct was transformed selectively to the 6-*endo*-dig-product in the presence of 10 mol% of the Au(I) catalyst in 95% yield (Table 1, entry 1). The Au(I) catalysts **II** and **III** also afforded the 4*H*-pyranonaphthoquinones in satisfactory yields (entry 2-3), while the yield in the case of PPh_3AuCl was only moderate (entry 4). Ag(I) salts also provided the desired product **4a** in moderate yields (entry 9-11).

Table 1 Optimization studies for the hydroalkoxylation reaction[a]



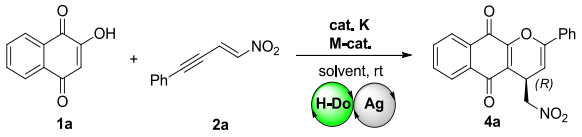
Entry	Catalyst	Time (h)	Yield (%)[b]
1	**I**/$AgNTf_2$	5	95
2	**II**/$AgNTf_2$	5	90
3	**III**/$AgNTf_2$	24	95
4	PPh_3AuCl/$AgNTf_2$	24	77
5	$PtCl_2$	24	n.d.
6	CuI	24	n.d.
7	$AgCO_3$	24	n.d.
8	$AgNO_3$	24	n.d.
9	AgOTf	24	74
10	$AgNTf_2$	24	68
11	$AgBF_4$	24	71

[a]Reaction conditions: Michael adduct **3a** (0.2 mmol), **M-cat** (10 mol%) and toluene (2 mL, 0.1 M). [b]Yield of **4a** after flash chromatography.

Pt(II) and Cu(I) were not able to promote the desired hydroalkoxylation although those metals have found wide application as carbophilic π-acids.

For the desired one-pot protocol we investigated the combination of both catalytic reactions. First, we studied the reaction using squaramide **K** and Au(I) catalyst **I** under relay catalytic conditions. Unfortunately, only traces of **4a** could be isolated (Table 2, entry 1). The same reaction was conducted under sequential catalytic conditions. We could observe by TLC that the Michael reaction was not working well and the annulated product was obtained in only 7% yield and 96% *ee* (Table 2, entry 2). Afterwards, the reaction of **1a** with **2a** by combining the squaramide **K** and AgOTf was investigated. Again the reaction afforded only traces of the product under relay catalytic conditions, maybe due to the disturbance of the catalyst-substrate interaction in the Michael addition step.

Table 2 One-pot Michael addition/hydroalkoxylation reaction[a]



Entry	M-Catalyst	Solvent	Time (h)	Yield (%)[e]	*ee* (%)[f]
1[b]	**I** (10 mol%)/$AgNTf_2$	DCM/ toluene	24	traces	n.d.
2[c]	**I** (10 mol%)/$AgNTf_2$	DCM/ toluene	24	7	96
3	AgOTf (10 mol%)	DCM	4.5	83	98
4[d]	AgOTf (15 mol%)	DCM	3.5	93	98
5[d]	AgOTf (20 mol%)	DCM	5	83	98

[a]Reaction conditions: 1,4-naphthoquinone **1a** (0.25 mmol), nitroalkene **2a** (1.1 eq.), **cat. K** (1 mol%), solvent (2.5 mL, 0.1 M). [b]Relay catalytic condition. [c]Sequential catalytic condition: after full conversion of 1,4-naphthoquinone **1a**, **M-cat** was added to the reaction. [d]The Reaction was carried out with **cat. K** (0.5 mol%). [e]Yield of **4a** after flash chromatography. [f]The enantiomeric excess was determined by HPLC on a chiral stationary phase.

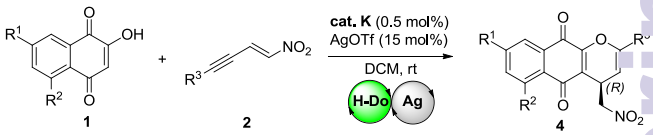
Fortunately, changing to sequential catalytic conditions provided the product with 83% yield and 98% *ee* (Table2, entry 3). Increasing the catalyst loading of Ag(I) gave **4a** in 93% yield and 98% *ee* (Table 2, entry 4).

With the optimized conditions in hand, the substrate scope of the reaction was investigated by changing the substituents on the nitroalkenes **2** and 2-hydroxy-1,4-naphthoquinones **1** (Table 3). The electron neutral 1-naphthyl and 2-naphthyl nitroalkenes reacted efficiently with **1a** and afforded the desired products **4b** and **4c** in high yields and excellent enantioselectivities. The nitroalkenes bearing electron-withdrawing groups also worked well under this sequential reaction protocol and provided promising results in terms of product yield and enantioselectivity, except for the 4-$CF_3C_6H_4$ group which gave a high *ee*, but a low yield of 25% (**4f**). The electron-rich nitroalkenes also led to the formation of the desired products **4g**-**j** in good to high yields and high enantioselectivities. However, heteroaryl substituted nitroalkenes are not suitable substrates for the transformation and alkyl substituted nitroalkenes led to poor product yield, albeit with excellent enantioselectivities (**4k**-**n**). The variation of the substituents on the naphthoquinone substrate **1** is also possible with electron- releasing and electron-withdrawing substituents leading to good yields and high *ee*'s, except for **4s** which gave 89% *ee*.

The proposed structure including the absolute configuration was determined by X-ray crystal structure analysis of compound (*R*)-**4e**. For all other pyranonaphthoquinones the absolute configuration was assigned by analogy to (*R*)-**4e** (Figure 2).

A plausible reaction mechanism, which is based on the experimental results described above, is given in Scheme 3. The proposed mechanism contains two different catalytic cycles.

Table 3 Substrate scope for the Michael addition/ hydroalkoxylation reaction[a]



4	R^1	R^2	R^3	Yield (%)[b]	*ee* (%)[c]
a	H	H	Ph	93	98
b	H	H	1-naphthyl	94	96
c	H	H	2-naphthyl	88	97
d	H	H	2-ClC_6H_4	81	95
e	H	H	2-BrC_6H_4	83	96
f	H	H	4-$CF_3C_6H_4$	25	96
g	H	H	3-$MeOC_6H_4$	77	96
h	H	H	3-MeC_6H_4	91	96
i	H	H	2-MeC_6H_4	93	95
j	H	H	3,4(-OCH_2O-)C_6H_3	91	92
k	H	H	2-furanyl	traces	-
l	H	H	2-thienyl	23	99
m	H	H	*n*-butyl	50	95
n	H	H	cyclopentyl	19	97
o	MeO	H	Ph	84	97
p	Me	Me	Ph	86	96
q	MeO	H	3-MeC_6H_4	70	97
r	MeO	H	1-naphthyl	84	97
s	Me	Me	3,4(-OCH_2O-)C_6H_3	76	89
t	F	H	Ph	70	97

[a]Reaction conditions: 1,4-naphthoquinone **1** (0.25 mmol), nitroalkene **2** (1.1 eq.), **cat. K** (0.5 mol%), solvent (2.5 mL, 0.1 M). After full conversion of the 1,4-naphthoquinone **1**, AgOTf (15 mol%) was added to the reaction. [b]Yield of **4** after flash chromatography. [c]The enantiomeric excess was determined by HPLC on a chiral stationary phase.

In the first cycle the squaramide **K** acts as a bifunctional catalyst. The plausible transition state (**TS**) involves the synergistic activation of the nitroolefin **2a** by the squaramide moiety and the deprotonation of the 2-hydroxy-1,4-naphthoquinone (**1a**) by the tertiary amine to facilitate the Michael addition. Concurrently, the deprotonated **1a** attacks the fixed nitroolefin **2a** from the *Re*-face to provide the Michael adduct **3a**. In the second catalytic cycle the silver catalyzes the electrophilic activation of the alkyne to facilitate the hydroalkoxylation in a 6-*endo*-dig fashion selectively resulting in the vinylsilver intermediate, which undergoes protodeargentation to provide the desired pyranonaphthoquinone **4a**.

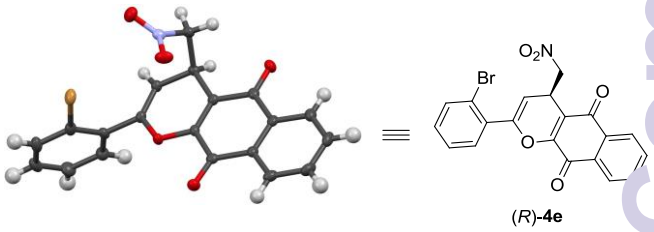
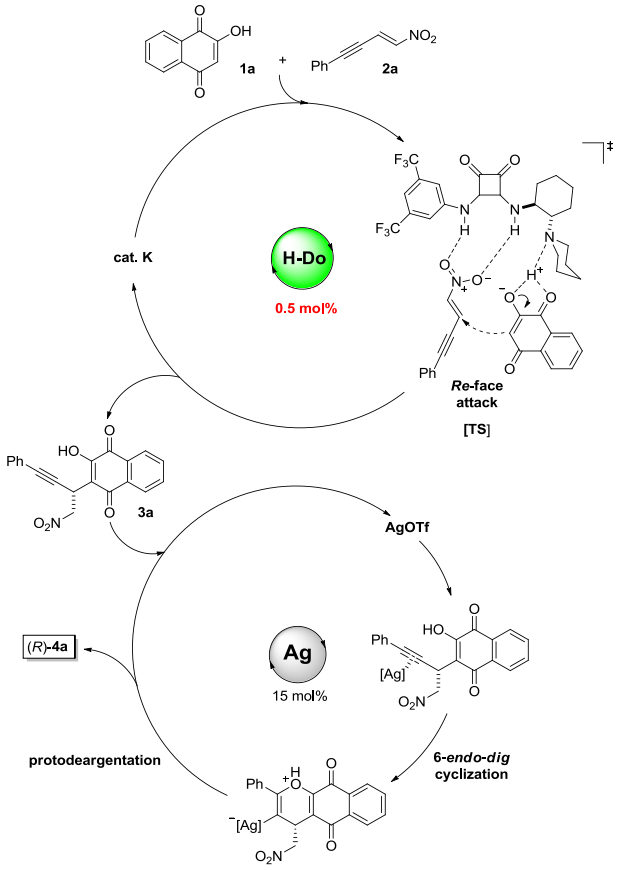


Fig. 2 X-ray crystal structure of (*R*)-**4e**[14]

In conclusion, we have developed an enantioselective one-pot sequential Michael addition/hydroalkoxylation reaction by combining hydrogen-bonding catalysis and π-activation. This merger provided substituted 4*H*-pyranonaphthoquinones in moderate to very good yields and excellent enantioselectivities by using a low cat-



Scheme 3 Proposed catalytic cycles of the Michael addition/hydroalkoxylation reaction

alyst loading of the squaramide. Further studies on the combination of squaramide with transition metal catalysis are ongoing in our laboratories.

Financial support from the European Research Council (ERC Advanced Grant 320493 "DOMINOCAT") is gratefully acknowledged.

Notes and references

1 A. M. Heapy, A. V. Patterson, J. B. Smaill, S. M. F. Jamieson, C. P. Guise, J. Sperry, P. A. Hume, K. Rathwell and M. A. Brimble, *Bioorg. Med. Chem.*, 2013, **21**, 7971.

2 J. T. Fitzgerald, P. P. Henrich, C. O'Brien, M. Krause, E. H. Ekland, C. Mattheis, J. M. Sa, D. Fidock and C. Khosla, *J. Antibiot.*, 2011, **64**, 799.

3 (a) S. Ōmura, H. Tanaka, Y. Okada and H. Marumo, *J. Chem. Soc. Chem. Commun.*, 1976, 320; (b) H. Imai, K. Suzuki, S. Kadota, M. Iwanami and T. Saito, *J. Antibiot.*, 1989, **42**, 1186.

4 A. Fujiwara, T. Mori, A. Lida, S. Ueda, Y. Hano, T. Nomura, H. Tokuda and H. Nishino, *J. Nat. Prod.*, 1998, **61**, 629.

5 E. H. G. da Cruz, C. M. B. Hussene, G. G. Dias, E. B. T. Diogo, I. M. M. de Melo, B. L. Rodrigues, M. G. da Silva, W. O. Valenca, C. A. Camara, R. N. de Oliveira, Y. G. de Paiva, M. O. F. Goulart, B. C. Cavalcanti, C. Pessoa and E. N. da Silva Júnior, *Bioorg. Med. Chem.*, 2014, **22**, 1608.

6 B. Onegi, C. Kraft, I. Kohler, M. Freund, K. Jenett-Siems, K. Siems, G. Beyer, M. F. Melzig, U. Bienzle and E. Eich, *Phytochemistry*, 2002, **60**, 39.

7 For selected examples, see: a) W.-M. Zhou, H. Liu and D.-M. Du, *Org. Lett.*, 2008, **10**, 2817; (b) Y.-F. Wang, W. Zhang, S.-P. Luo, G.-C. Zhang, A.-B. Xia, X.-S. Xu and D.-Q. Xu, *Eur. J. Org. Chem.*, 2010, **4981**; (c) A. D. Wadsworth, J. Sperry and M. A. Brimble, *Synthesis*, 2010, **15**, 2604; (d) W. Yang and D. Du, *Adv. Synth. Catal.*, 2011, **353**, 1241; (e) P. A. Hume, J. Sperry and M. A. Brimble, *Org. Biomol. Chem.*, 2011, **9**, 542; (f) C. D. Donner and M. I. Casana, *Tetrahedron Lett.*, 2012, **53**, 1105; (g) R. A. Fernandes, V. P. Chavan, S. V. Mulay, A. Manchoju, *J. Org. Chem.*, 2012, **77**, 10455; (h) A. Pillay, L. Rousseau, M. A. Fernandes and C. B. de Koning, *Org. Biomol. Chem.*, 2012, **10**, 7809; (i) B. D. Bala, S. M. Rajes and S. Perumal, *Green Chem.*, 2012, **14**, 2484; (j) J. H. Le and D. Y. Kim, *Bull. Korean Chem. Soc.*, 2013, **34**, 1619; (k) J. J. Duffy, J. Garcia-Torres, R. C. F. Jones, M. R. J. Elsegood and S. M. Allin, *Synlett*, 2013, **24**, 185-188; (l) C. D. Donner, *Tetrahedron*, *2013*, **69**, 377; (m) A. M. Heapy, A. V. Patterson, J. B. Smaill, S. M. F. Jamieson, C. P. Guise, J. Sperry, P. A. Hume, K. Rathwell and M. A. Brimble, *Bioorg. Med. Chem* 2013, **21**, 7971; (n) M. A. Brimble, N. P. S. Hassan, B. Naysmith and J. Sperry, *J. Org. Chem.*, 2014, **79**, 7169; (o) A. D. Thi, T. H. V. Thi, H. T. Phuong, T. H. Nguyen, C. P. The, V. Duc, Y. Depetter, T. V. Nguyen and M. D'hooghe, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 3355; (p) J. Bian, X. Qian, N. Wang, T. Mu, X. Li, H. Sun, L. Zhang, Q. You and X. Zha *Org. Lett.*, 2015, **17**, 3410; (q) T. A. D. Thi, Y. Depetter, K. Mollet, H. T. Phuong, D. V. Ngoc, C. P. The, H. T. Nguyen, H. H. N. Thi, H. H. Nguyen, M. D'hooghe and T. V. Nguyen, *Tetrahedron Lett.*, 2015, **56**, 2422.

8 a) D. K. Nair, R. F. S. Menna-Barreto, E. N. da Silva Júnior, M. M. Mobin and I. N. N. Namboothiri, *Chem. Commun.*, 2014, **50**, 6973; (b) G. A. M. Jardim, T. T. Guimarães, M. do Carm F. R. Pinto, B. C. Cavalcanti, K. M. de Farias, C. Pessoa, C. Gatto, D. K. Nair, I. N. N. Namboothiri and E. N. da Silva Júnior; *Med. Chem. Commun.*, 2015, **6**, 120.

9 N. Molleti and V. K. Singh, *Org. Biomol. Chem.*, 2015, **1** 5243.

10 For selected reviews on the merger of transition metal catalysis and organocatalysis, see: (a) Z. Shao and H. Zhan *Chem. Soc. Rev.*, 2009, **38**, 2745; (b) C. Zhong and X. Shi, *Eur J. Org. Chem.*, 2010, 2999; (c) C. C. J. Loh, D. Enders, *Chem Eur. J.*, 2012, **18**, 10212; (d) Z. Du and Z. Shao, *Chem. So Rev.*, 2013, **42**, 1337; (e) Y. Deng, S. Kumar and H. Wang *Chem. Commun.*, 2014, **50**, 4272.

11 For recent examples of organocatalysis and silver catalysis, see: (a) Q. Ding and J. Wu, *Org. Lett.*, 2007, **9**, 4959; (b) C Arróniz, A. Gil-González, V. Semak, C. Escolano, J. Bosch and M. Amat, *Eur. J. Org. Chem.*, 2011, 3755; (c) Q.-W. Zhang, K. Xiang, Y.-Q. Tu, S.-Y. Zhang, X.-M. Zhang, Y.-M. Zhao and T.-C. Zhang, *Chem.-Asian J.*, 2012, **7**, 894; (d) I. Ortín and D. J. Dixon, *Angew. Chem. Int. Ed.*, 2014, **53**, 3462; (e) C. Verri and P. Melchiorre, *Chem. Sci.*, 2015, **6**, 4242.

12 For recent reviews and examples of silver organic chemistr see: (a) M. Naodovic and H. Yamamoto, *Chem. Rev.*, 2008 **108**, 3132; (b) Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3199; J.-M. Weibel, A. Blanc and P. Pale, *Chem. Rev.*, 2008, **10** 3149; (d) M. Álvarez-Corral, M. Munoz-Dorado and Rodríguez-García, *Chem. Rev.*, 2008, **108**, 3174 (e) Belmont and E. Parker, *Eur. J. Org. Chem.*, 2009, 6075; (f) Harmata, *Silver in Organic Chemistry*; Wiley: Hoboken, NJ, 2010; (g) G. Abbiati and E. Rossi, *Beilstein J. Org. Che* 2014, **10**, 481; (h) S. Gujatathi and G. Zheng, *Tetrahedron*, 2015, **71**, 6183; (i) M. J. James, R. E. Clubley, K. Y. Palate, Procter, A. C. Wyton, P. O'Brien, R. K. Taylor and W. Unsworth, *Org. Lett.* 2015, **17**, 4372; (j) T. Xiao, P. Peng, Xie, Z.-Y. Wang and L. Zhou, *Org. Lett.*, 2015, **17**, 4332; (k) Fang and X. Bi, *Chem. Soc. Rev.*, 2015, **44**, 8124; (l) L. Zhang, G. Fang, R. K. Kumar and X. Bi, *Synthesis*, 2015, **47**, 2317.

13 (a) D. Hack, P. Chauhan, K. Deckers, G. N. Hermann, Mertens, G. Raabe and D. Enders, *Org. Lett.*, 2014, **16** 5188; (b) D. Hack, P. Chauhan, K. Deckers, Y. Mizutani, Raabe and D. Enders, *Chem. Commun.*, 2015, **51**, 2266.

14 CCDC 1437688