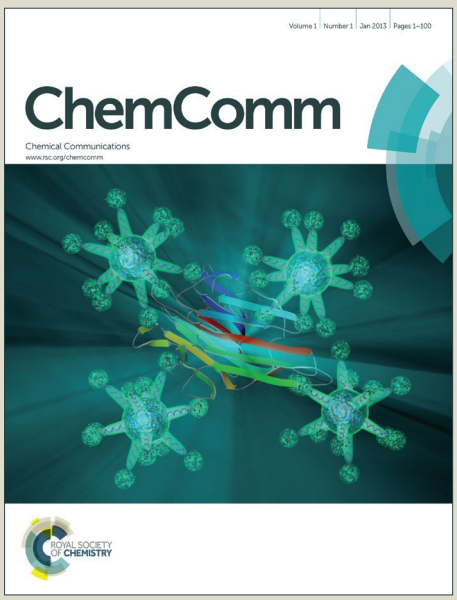
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: N. T. Patil, M. O. Akram and S. Bera, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC07119H.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

ChemComm

View Article Online
DOI: 10.1039/C6CC07119H

COMMUNICATION

A Facile Strategy for Accessing 3-Alkynylchromones through Gold-Catalyzed Alkynylation/Cyclization of *o*-Hydroxyarylenaminones

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

DOI: 10.1039/x0xx00000x

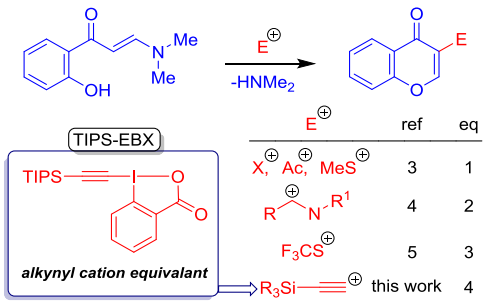
www.rsc.org/

Manjur O. Akram,[ac] Saibal Bera[bc] and Nitin T. Patil[ac]*

A strategy based on tandem alkynylation of *o*-hydroxyarylenaminones followed by intramolecular cyclization has been developed to generate a diverse array of 3-alkynyl chromones. The functionality embedded in these key intermediates enables their facile elaboration into more diverse structures by a variety of functionalizations and ring-forming processes.

Chromones are a group of naturally occurring compounds that are ubiquitous in nature, especially in plants.[1] Over the years, this molecular scaffold has emerged as privileged structure for the drug discovery and development.[2] Traditionally, chromones moieties are synthesized from *o*-hydroxy-acetophenones by the tandem cyclization process by the Baker-Venkataraman, Claisen-Schmidt or Vilsmeier-Haack reactions. Generally these approaches lead to 3-functionalized chromones but often utilize harsh reaction conditions. Alternative method to synthesize 3-substituted chromones involves the electrophile triggerd cyclization reaction of *o*-hydroxyarylenaminones (Scheme 1, eq 1). However, traditionally, these reactions are limited to the electrophiles such as halogens, acyl and -SMe groups.[3]

In 2009, Pan *et al*. elegantly developed a route to 3-aminomethyl chromones through a three component assembly of *o*-hydroxyarylenaminones, aldehydes and urea in the presence of stoichiometric amount of TMSCl (Scheme 1, eq 2).[4] Recently, Yang and co-workers, developed a method to synthesize 3-[(trifluoromethyl)thio]-4*H*-chromen-4-one using stoichiometric amounts of $AgSCF_3$ and trichloroisocyanuric acid (TCCA) (eq 3).[5] Mechanistically, active trifluoromethanesulfanyl cation, generated in situ from TCCA and $AgSCF_3$, was responsible for the cyclization to occur. Very recently, the research group of Suffert and Blond realized the importance Yang's approach for the synthesis of 3-alkyl chromones utilizing 5 equiv alkyl iodides and stoichiometric amounts of AgOTf.[6] To the best of our knowledge, there is no report on the cyclization of *o*-hydroxyarylenaminones triggered by an alkynyl cation equivalent (eq 4). Since the alkyne moieties, especially terminal ones, are versatile functional handle for many organic transformations, the development of a *truly catalytic and practical method* is highly desirable to synthesize 3-alkynyl chromones.[7] Realization of such a method would not only offer structurally diverse chromones but would also provide valuable synthons which found diverse application in the synthesis of heterocyclic scaffolds.[8] Be noted that such a kind of 3-alkyl chromones are accessed from 3-iodochromones through sonogashira reactions.[8o]



Scheme 1 Synthesis of 3-substiuted chromones: known and present work

Over the last few years, TIPS-EBX reagent has emerged as a powerful alkynylating agent.[9] The use of this reagent was first introduced by Waser and co-workers in the metal catalyzed alkynylation of indoles, pyrroles, thiophenes and anilines.[10] Leveraging the ability of TIPS-EBX to deliver alkynyl moieties in an electrophilic manner, other researchers also applied this reagent for various organic transformations.[11] Recently, we reported an interesting example of regio-divergent site-selective C–H alkynylation of isoquinolones with TIPS-EBX catalyzed by gold and rhodium catalysts.[12] Similarly, we reported a route to access alkynylated quinalizinones via gold(I)-catalyzed aminoalkynylation of alkynes with TIPS-EBX as a source of alkynyl cation equivalent.[13]

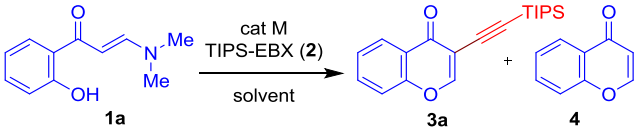
As a part of our ongoing interest in gold/TIPS-EBX chemistry, we envisaged that *o*-hydroxyarylenaminones would undergo metal catalyzed alkynylation with TIPS-EBX followed by subsequent intramolecular cyclization to produce 3-alkynyl chromones (Scheme 1, eq 4). Though there are reports on the alkynylation of electron-rich (hetero)aromatics,10[a-g] the report on alkynylation of acyclic

[a] Division of Organic Chemistry, CSIR - National Chemical Laboratory, Dr. Homi Bhabha Road, Pune - 411 008, India, E-mail: n.patil@ncl.res.in.
[b] Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune - 411 008, India.
[c] Academy of Scientific and Innovative Research (AcSIR), New Delhi - 110 025, India.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

enamines are scarce. There exists only one report wherein Huang et al. has reported α-vinylidenation and the α-vinylidenation/γ-alkynylation cascade of aldehydes involving alkynylation of acyclic enamices as a transient step.[14] Therefore, the validity of the proposal lies in the successful alkynylation reactions of *o*-hydroxyarylenaminones with TIPS-EBX reagent. Herein, we report the realization of the concept. To the best of our knowledge, this is one of the rarest examples of metal catalyzed synthesis of alkynylated heterocycles using TIPSEBX-alkyne chemistry.13,[15]

Our initial investigation was focused on the reaction of (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-ones **1a** with TIPS-EBX (**2**) (Table 1). At the outset of our study, catalyst screening was performed with gold catalysts as they are known to be the best for the alkynylation of electron rich species.10 To our delight, when **1a** was treated with TIPS-EBX (**2**) in presence of 10 mol% AuCl in toluene at room temperature, the desired product **3a** was obtained in 79% yield (entry 1). However, the reaction was accompanied with 15% of undesired 4*H*-chromen-4-one (**4**). When $AuCl_3$ was employed as a catalyst, the desired product **3a** was obtained only in 32% yield and undesired **4** was obtained in 44% yield. Next, phosphine ligated gold complexes were examined; however, they found to be inert; the starting material was recovered in quantitative amounts in both the cases (entries 3 and 4). Similarly, silver(I) salts were unable to promote the reactions (entries 5 and 6). After detailed solvent screening, DCE was found to be the solvent of choice and in this case product **3a** was obtained in 87% yield (entry 7). When slight excess of TIPS-EBX (1.2 equiv) was used, the yield was improved up to 94% (entry 9). Lowering the catalyst loading (5 mol%) did not hamper the yield of reaction (entry 9). However, further lowering of the catalyst loading resulted in the poor conversion (entry 10).

Table 1 Optimization studies[a]

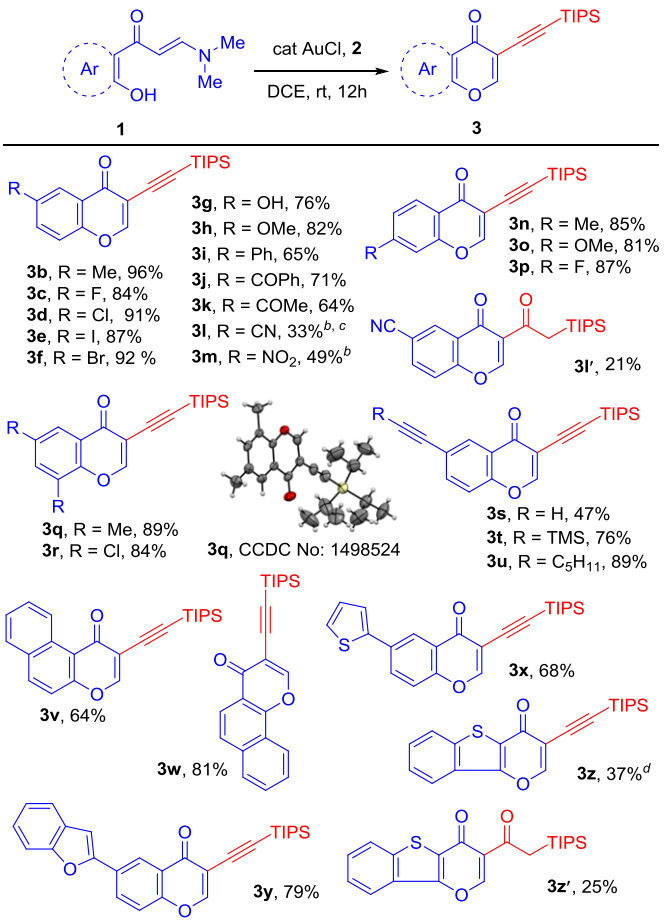


entry	cat M	solvent	time(h)	yields (%)[b]	
				3a	**4**
1	AuCl	toluene	12	79	15
2	$AuCl_3$	toluene	12	32	44
3	PPh_3AuOTf[c]	toluene	12	-	-
4	PPh_3AuNTf_2[d]	toluene	12	-	-
5	AgOTf	toluene	12	-	-
6	$AgNTf_2$	toluene	12	-	-
7	AuCl	DCE	12	87	-
8	AuCl	DCE	12	94[e]	-
9	**AuCl**	**DCE**	**12**	**93**[e,f]	**-**
10	AuCl	DCE	24	49[g]	-

[a] Reaction conditions: 0.20 mmol **1a**, 0.20 mmol **2**, 10 mol% metal cat, solvent (2 mL), rt, 12h. [b] Isolated yields. [c] Generated in situ by mixing 10 mol% PPh_3AuCl and 10 mol% AgOTf. [d] Generated in situ by mixing 10 mol% PPh_3AuCl and 10 mol% $AgNTf_2$. [e] 1.2 Equiv of TIPS-EBX. [f] 5 mol% AuCl was used. [g] 2 mol% AuCl was used.

With the optimized reaction conditions in hand, the scope of the reaction was examined with various *o*-hydroxyarylenaminones. As shown in Table 2, alkynylated chromones were obtained in moderate to excellent yields, irrespective of substitution patterns on the phenyl ring. For instance, the substituents such as -Me, -Ph, -F, -Cl, -Br, -I, -OH, -OMe were well tolerated to afford corresponding products **3b-3i** in 65-96% yields. Electron-withdrawing substituents, such as benzoyl and acetyl group, also well tolerated giving the desired alkynylated products **3j** and **3k** in 71 and 64% yields, respectively.

Table 2 Gold catalyzed C-3 alkynylation of chromones[a]

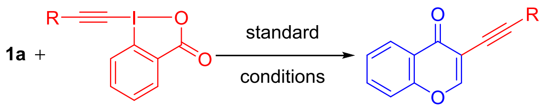


[a] Reaction conditions: 0.20 mmol **1**, 0.24 mmol **2**, 5 mol% AuCl, DCE (2 mL), rt, 12h. [b] Reaction was stirred for 6h. [c] Hydration product **3l′** was obtained alongside in 21% yield. [d] Hydration product **3z′** was obtained alongside in 25% yield.

In case of strong electron withdrawing group such as -CN, product (**3l**) was obtained only in 33% yields along with the alkyne hydration product in 21% yield.16 In the case of $-NO_2$ group,product **3m** was isolated in 49% yield and no hydration product was observed. The *o*-hydroxyarylenaminones possessing substituent at the *para*-position of the keto group gave the desired products (**3n-3p**) in yields ranging from 81 to 87%. Disubstitution on the aromatic ring was also tolerated giving access to **3q** and **3r** in 89 and 84% yields, respectively. The X-ray crystallography data for **3q** has been obtained which unequivocally confirms the structure.[16] Very interestingly, substrate bearing alkynyl substituents such as -H, -TMS and $-C_5H_{11}$ were also found to be compatible with the reaction giving 3-alkynylated chromones **3s**, **3t** and **3u** respectively in good yields (47-89%). When benzene backbone is replaced with naphthalene backbone, the desired products **3v** and **3w** were

obtained in 64 and 81% yields, respectively. Next, we became curious to explore substrates bearing electron rich heteroaromatics such as benzofuran, pyrrole, benzothiophene etc., as these scaffolds are known to undergo alkynylation.10 Interestingly, only desired products **3x** and **3y** were obtained in 68 and 79% yields, when respective *o*-hydroxyarylenaminones are subjected to gold catalysis under the standard reaction conditions. No di-alkynylation products were observed even when excess amount of TIPS-EBX was employed. Lastly, benzothiophene based substrate was examined which gave anticipated product **3z** in 37% yield alongwith alkyne hydration product in 25% yield.16

The scope of the reaction was also investigated for various EBX analogues (Scheme 2). The alkynylated products **5a** and **5b** were obtained in 76 and 68% yield, respectively when treated with TBDMS-EBX (**2a**) and TBDPS-EBX (**2b**) under the standard reaction conditions. However, the reaction failed to provide expected product when Ph-EBX (**2c**) was used as an alkynylating agent.

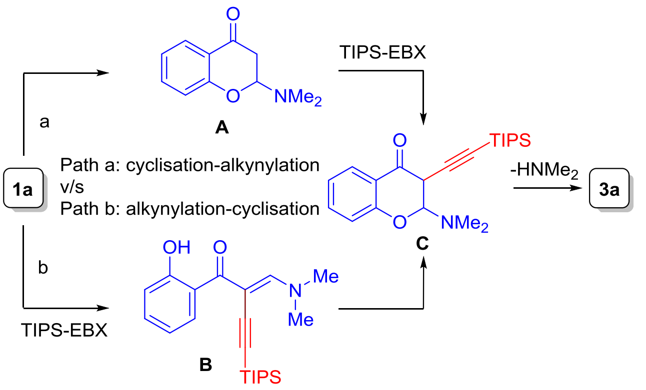


2a, R = TBDMS
2b, R = TBDPS
2c, R = Ph

5a, R = TBDMS, 76%
5b, R = TBDPS, 68%
5c, R = Ph, -%

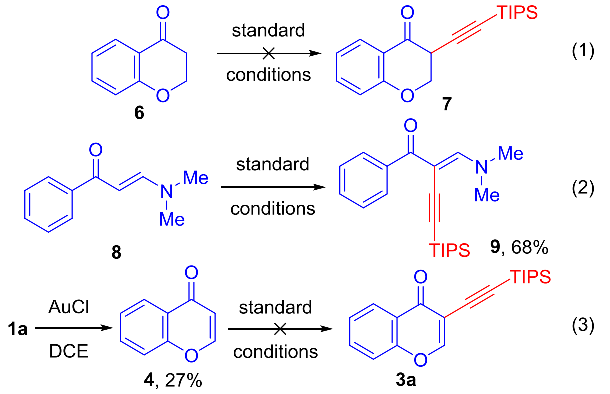
Scheme 2 Scope with various ethynylbenziodoxoles

As outlined in Scheme 3, we envisioned two plausible mechanistic pathways. An intramolecular Michael addition/cyclization of *o*-hydroxyarylenaminone **1a** would occur to produce intermediate A whose enol form would further react with TIPS-EBX to form intermediate **C** (path a). Alternatively, enaminone **1a** would undergo alkynylation[10,12] to produce intermediate **B** which after intramolecular cyclization would afford intermediate **C** (path B). Finally, the spontaneous loss of *N*,*N*-dimethylamine would take place to generate 3-alkynylchromone **3a**.



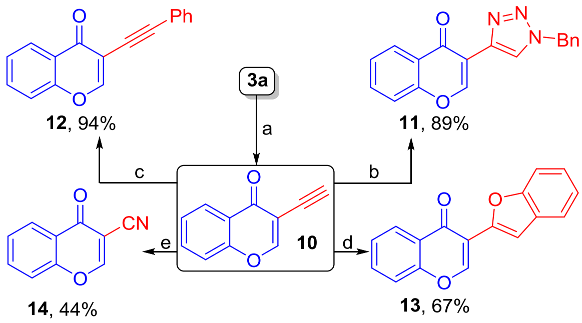
Scheme 3 Plausible paths of alkynylation

To understand the precise reaction mechanism, a few experiments have been conducted (Scheme 4). The reaction of chroman-4-one (**6**) with TIPS-EBX was performed under the standard reaction conditions (eq 1). However, the desired product **7** was not obtained at all, clearly ruling out path a (Scheme 3). On the contrary, reaction of phenylenaminone **8** under standard reaction conditions afforded alkynylation product **9** in 68% isolated yields (eq 2). This experiment clearly supports path b (Scheme 3). It is also possible that 4*H*-chromen-4-one (**4**) would be generated first which would undergo alkynylation with TIPS-EBX in the presence of gold catalyst. However, the failure of reaction of **4** under standard reaction conditions (eq 3) unequivocally ruled out this possibility.



Scheme 4 Control experiments

Further transformations of the products would require deprotection of -TIPS group (Scheme 5). Initially, the attempts to remove -TIPS group in **3a** under conventional reaction conditions were all failed.16 Later, we found that the smooth deprotection of -TIPS group occurred providing 3-ethynylchromone **10** in 79% yield when the combination of TBAF and camphor sulphonic acid (CSA) was employed (path a). Next, 3-ethynylchromone **10** was subjected to copper catalyzed azide-alkyne cyclo-addition reaction and Sonogashira reaction to afford corresponding triazole **11** and internal alkyne **12** in 89 and 94% yields, respectively (path b and c). Further, 3-(benzofuran-2-yl)-chromone **13** was synthesized via Sonogashira reaction/intramolecular hydroalkoxylation relay process (path d). Next, 3-cyanochromone **14** was accessed in 44% yield using ^{t}BuONO as nitrogenating agent and 2-picoline-*N*-oxide as an oxidant (path e).[17]



[a] Reaction conditions: (a) CSA, TBAF, THF, 0 °C - rt, 2h. (b) BnN_3, $CuSO_4.5H_2O$, sodium ascorbate, $^{t}BuOH/H_2O$ (1:1), rt, 1h. (c) PhI, $Pd(PPh_3)_2Cl_2$, CuI, THF:NEt_3 (5:1), rt, 2h. (d) 2-Iodophenol, $Pd(PPh_3)_2Cl_2$, CuI, THF:NEt_3 (5:1), 60 °C, 12h. (e) ^{t}Butyl nitrite, 2-picoline-*N*-oxide, THF, N_2, 70 °C, 24h.

Scheme 5 Synthetic utility of the product[a]

In conclusion, we have developed a facile catalytic alkynylation/cyclization reactions of *o*-hydroxyarylenaminones that led to the formation of 3-alkynyl chromones. The cascade involves the gold-catalyzed alkynylation of the enaminone moiety with TIPS-EBX followed by subsequent intramolecular cyclization. The

usefulness of the method has been demonstrated by de-silylation and its transformation into various functionalised chromones. The alkynylation of acyclic enamines reported herein should be of particular importance because one can access several other heterocyclic scaffolds using this chemistry.

Generous financial support by the Department of Science and Technology (DST), New Delhi (grant number SB/S1/OC-17/2013)and the Council of Scientific and Industrial Research (CSIR), New Delhi (grant number CSC0108 and CSC0130) is gratefully acknowledged. We thank Dr. Rahul Banerjee for assistance with X-ray crystallography. M. O. A. thanks CSIR for the award of Junior Research Fellowship.

Notes and reference+

1 (a) S. Khadem, R. J. Marles, *Molecules* 2012, **17**, 191-206; (b) K. S. Sharma, S. Kumar, K. Chand, A. Kathuria, A. Gupta, R. Jain, *Curr. Med. Chem.* 2011, **18**, 3825-3852; (c) G. P. Ellis, In Chromenes, Chromanones, and Chromones: The Chemistry of Heterocyclic Compounds; Ellis, G. P., Ed.; John Wiley & Sons, Inc.: New York, 1977; Vol. **31**, pp 455-480.

2 (a) A. Gaspar, M. J. Matos, J. Garrido, E. Uriarte, F. Borges, *Chem. Rev.* 2014, **114**, 4960-4992; (b) R. S. Keri, S. Budagumpi, R. K. Pai, R. G. Balakrishna, *Eur. J. Med. Chem.* 2014, **78**, 340-374.

3 (a) A. Bornadiego, J. Díaz, C. F. Marcos, *Adv. Synth. Catal.* 2014, **356**, 718-722; (b) D. A. Vasselin, A. D. Westwell, C. S. Matthews, T. D. Bradshaw, M. F. G. Stevens, *J. Med. Chem.* 2006, **49**, 3973-3981; (c) J. Bólos, S. Gubert, L. Anglada, J. M. Planas, C. Burgarolas, J. M. Castelló, A. Sacristán, J. A. Ortiz, *J. Med. Chem.* 1996, **39**, 2962-2970; (d) I. Yokoe, K. Maruyama, Y. Sugita, T. Harashida, Y. Shirataki, *Chem. Pharm. Bull.* 1994, **42**, 1697-1699; (e) R. B. Gammill, *Synthesis* 1979, 901-903.

4 J.-P. Wan, Y.-J. Pan, *Chem. Commun.* 2009, 2768-2770.

5 H. Xiang, C. Yang, *Org. Lett.* 2014, **16**, 5686-5689.

6 J. Joussot, A. Schoenfelder, L. Larquetoux, M. Nicolas, J. Suffert, G. Blond, *Synthesis* 2016, **48**, 3364-3372.

7 For previous reports on catalytic approaches to chromones, see: (a) J. Yang, N. Yoshikai, *Angew. Chem., Int. Ed.* 2016, **55**, 2870-2874; (b) S. Vedachalam, Q.-L. Wong, B. Maji, J. Zeng, J. Ma, X.-W. Liu, *Adv. Synth. Catal.* 2011, **353**, 219-225; (c) J. Renault, Z. Qian, P. Uriac, N. Gouault, *Tetrahedron Lett.* 2011, **52**, 2476-2479; (d) S. Vedachalam, J. Zeng, B. K. Gorityala, M. Antonio, X.-W. Liu, *Org. Lett.* 2010, **12**, 352-355; (e) Q. Yang, H. Alper, *J. Org. Chem.* 2010, **75**, 948-950; (f) E. Awuah, A. Capretta, *Org. Lett.* 2009, **11**, 3210-3213; (g) M. Shimizu, H. Tsurugi, T. Satoh, M. Miura, *Chem. Asian J.* 2008, **3**, 881-886; (h) C. Zhou, A. V. Dubrovsky, R. C. Larock, *J. Org. Chem.* 2006, **71**, 1626-1632; (i) B. Liang, M. Huang, Z. You, Z. Xiong, K. Lu, R. Fathi, J. Chen, Z. Yang, *J. Org. Chem.* 2005, **70**, 6097-6100; (j) G. W. Kabalka, A. R. Mereddy, *Tetrahedron Lett.* 2005, **46**, 6315-6317.

8 (a) Y. Liu, S. Jin, L. Huang, Y. Hu, *Org. Lett.* 2015, **17**, 2134-2137; (b) G. Cheng, Y. Hu, *Org. Lett.* 2012, **14**, 3206-3209; (c) F. Xie, X. Pan, S. Lin, Y. Hu, *Org. Biomol. Chem.* 2010, **8**, 1378-1381; (d) Y. Xiao, J. Zhang, *Chem. Commun.* 2010, **46**, 752-754; (e) Y. Liu, L. Huang, F. Xie, Y. Hu, *J. Org. Chem.* 2010, **75**, 6304-6307; (f) X. Yu, B. Du, K. Wang, J. Zhang, *Org. Lett.* 2010, **12**, 1876-1879; (g) R. Liu, J. Zhang, *Chem. Eur. J.* 2009, **15**, 9303-9306; (h) G. Cheng, Y. Hu, *J. Org. Chem.* 2008, **73**, 4732-4735; (i) L. Zhao, G. Cheng, Y. Hu, *Tetrahedron Lett.* 2008, **49**, 7364-7367; (j) G. Cheng, Y. Hu, *Chem. Commun.* 2007, 3285-3287; (k) X. Liu, Z. Pan, X. Shu, X. Duan, Y. Liang, *Synlett* 2006, **12**, 1962-1964; (l) C. H. Oh, V. R. Reddy, A. Kim, C. Y. Rhim, *Tetrahedron Lett.* 2006, **47**, 5307-5310; (m) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* 2005, **70**, 4531-4534; (n) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* 2005, **70**, 7679-7685; (o) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* 2004, **126**, 11164-11165.

9 Reviews: (a) Y. Li, D. P. Hari, M. V. Vita, J. Waser, *Angew. Chem., Int. Ed*. 2016, **55**, 4436-4454; (b) J. P. Brand, J. Waser, *Chem. Soc. Rev*. 2012, **41**, 4165-4179.

10 (a) G. L. Tolnai, S. Ganss, J. P. Brand, J. Waser, *Org. Lett*. 2013, **15**, 112-115; (b) Y. Li, J. Waser, *Beilstein J. Org. Chem.* 2013, **9**, 1763-1767; (c) J. P. Brand, J. Waser, *Org. Lett.*, 2012, **14**, 744-747; (d) J. P. Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J*. 2012, **18**, 5655-5666; (e) J. P. Brand, C. Chevalley, J. Waser, *Beilstein J. Org. Chem*. 2011, **7**, 565-569; (f) J. P. Brand, J. Waser, *Angew. Chem., Int. Ed*. 2010, **49**, 7304-7307; (g) J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem., Int. Ed*. 2009, **48**, 9346-9349. For related reports; see: (h) D. P. Hari, J. Waser, *J. Am. Chem. Soc*. 2016, **138**, 2190-2193; (i) Y. Li, J. P. Brand, J. Waser, *Angew. Chem., Int. Ed*. 2013, **52**, 6743-6747.

11 Selected reports: (a) Y. Li, F. Xie, X. Li, *J. Org. Chem*. 2016, **81**, 715-722; (b) P. Finkbeiner, U. Kloeckner, B. J. Nachtsheim, *Angew. Chem., Int. Ed*. 2015, **54**, 4949-4952; (c) H. Wang, F. Xie, Z. Qi, X. Li, *Org. Lett*. 2015, **17**, 920-923; (d) W. Ai, Y. Wu, H. Tang, X. Yang, Y. Yang, Y. Li, B. Zhou, *Chem. Commun.* 2015, **51**, 7871-7874; (e) D. Kang, S. Hong, *Org. Lett.* 2015, **17**, 1938-1941; (f) Y. Wu, Y. Yang, B. Zhou, Y. Li, *J. Org. Chem.* 2015, **80**, 1946-1951; (g) X. Zhang, Z. Qi, J. Gao, X. Li, *Org. Biomol. Chem*. 2014, **12**, 9329-9332; (h) F. Xie, Z. Qi, S. Yu, X. Li, *J. Am. Chem. Soc*. 2014, **136**, 4780-4787; (i) C. Feng, D. Feng, Y. Luo, T.-P. Loh, *Org. Lett*. 2014, **16**, 5956-5959; (j) C. Feng, D. Feng, T.-P. Loh, *Chem. Commun*. 2014, **50**, 9865-9868; (k) C. Feng, T.-P. Loh, *Angew. Chem., Int. Ed*. 2014, **53**, 2722-2726; (l) K. Collins, F. Lied, F. Glorius, *Chem. Commun*. 2014, **50**, 4459-4461.

12 A. C. Shaikh, D. R. Shinde, N. T. Patil, *Org. Lett.* 2016, **18**, 1056-1059.

13 P. S. Shinde, A. C. Shaikh, N. T. Patil, *Chem. Commun*. 2016, **52**, 8152-8155.

14 Z. Wang, X. Li, Y. Huang, *Angew. Chem., Int. Ed*. 2013, **52**, 14219-14223.

15 Y. Li, J. Waser, *Angew. Chem., Int. Ed.* 2015, **54**, 5438-5442.

16 See supporting information for details.

17 U. Dutta, D. W. Lupton, D. Maity, *Org. Lett.* 2016, **18**, 860-863.