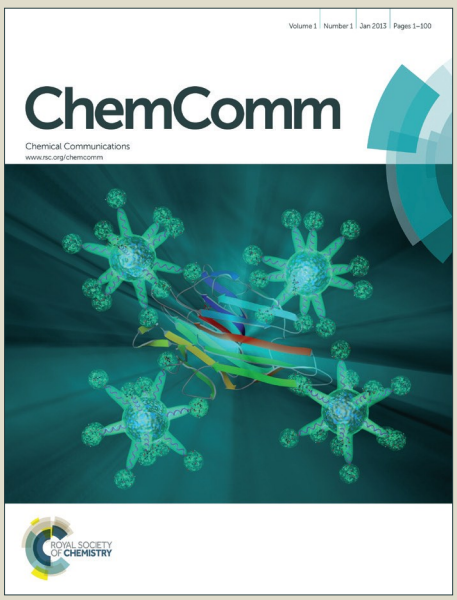
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: V. Dwivedi, H. Madala, R. Kant and S. R. Maddi, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC06251A.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

View Article Online
DOI: 10.1039/C5CC06251A

Journal Name

COMMUNICATION

N-Substitution Dependent Stereoselectivity Switch in Palladium Catalyzed Hydroalkynylation of Ynamides: A Regio and Stereoselective Synthesis of Ynenamides‡

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

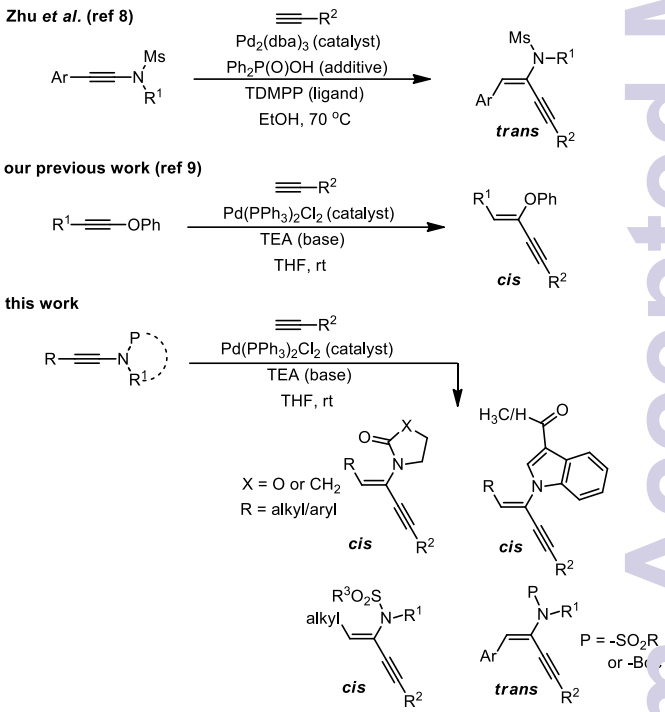
DOI: 10.1039/x0xx00000x

www.rsc.org/

Vikas Dwivedi,[a]† Madala Hari Babu,[a]† Ruchir Kant[b] and Maddi Sridhar Reddy[a,c*]

A highly general palladium catalysed regioselective hydroalkynylation of ynamides for versatile building blocks enamides with alkyne tether is achieved with an *N*-substitution dependent stereoselectivity switch under very mild reaction conditions.

Hydroalkynylation of alkyne (alkyne-alkyne cross dimerization)[1-3] is a remarkably straightforward, simple and atom economical means for the construction of enyne, a linchpin subunit in many natural products[4] and a useful intermediate for the construction of larger molecules.[5] As a result, there has been a deep search for both homodimerization and cross dimerization of two different alkynes. Although a great attention was given for homo dimerization,[1] and cross addition of terminal alkynes to acceptor alkynes,[2] the addition to neutral internal alkynes[3] and to electron rich alkynes are yet to be studied and standardized. On the other hand, enamines/enamides are equally highly sought after scaffolds because of their significance in both medicinal and synthetic chemistries, and due to their presence in various natural products.[6] Hence, an enormous effort was made for their selective synthesis.[7] The synthesis of hybrid of these two intriguing subunits (i.e. enynes and enamides), namely ynenamides (or enynamides), may pave the way for the synthesis of new class of molecules with new therapeutic indexes. In this direction, Zhu *et al*. recently reported an elegant Pd-catalyzed *trans* addition of terminal alkynes to aryl ynamides to achieve selectively α, β-disubstituted enamides [Scheme 1 (a)].[8] As part of our on-going program to explore the new reactivities of activated alkynes,[9-10] we previously reported a regioselective *syn* addition of acetylenes to ynol ethers under very mild conditions [Scheme 1 (**b**)].[9] We herein describe a regioselective syn addition of acetylenes to ynamides [Scheme 1 (c)]. Incidentally, with the ynamides bearing non cyclic substitution on nitrogen, we observed a strange but interesting stereoselectivity switch depending on aryl or alkyl substitution at the C-terminal.

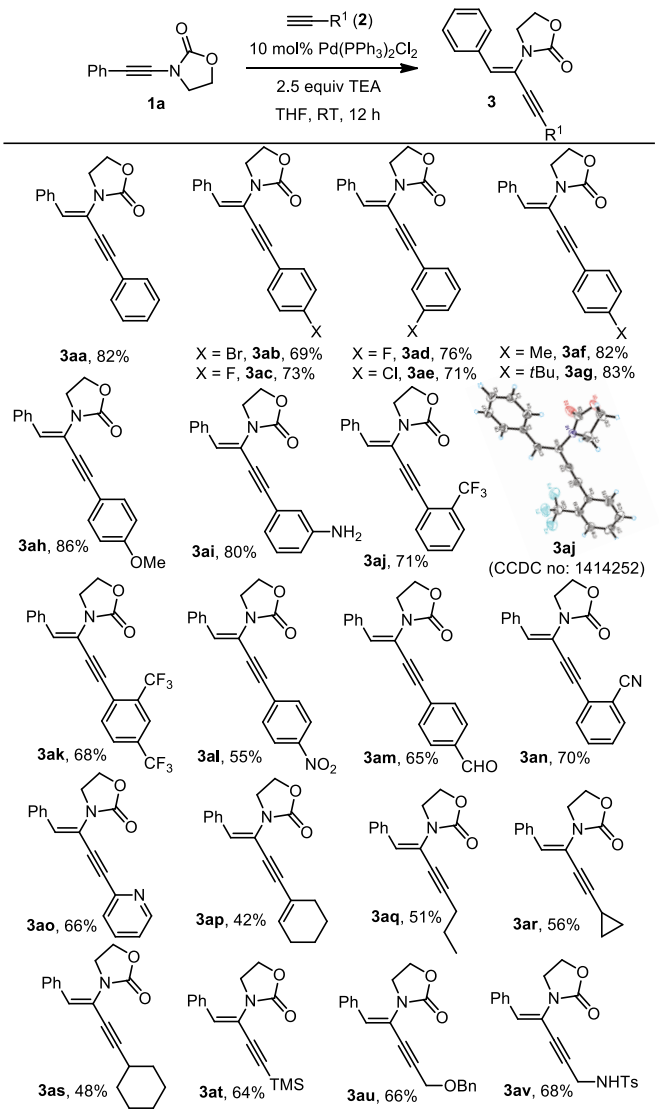


Scheme 1. Cross dimerization of acetylenes and electron rich alkynes.

Initially we synthesized the oxazolidinone based phenyl ynamide **1** and treated it with 1.2 equivalents of phenyl acetylene **2a**, 10 mol% $Pd(PPh_3)_2Cl_2$ and 2.5 equivalents of triethylamine in THF at room temperature (the conditions identified earlier in our laboratory for the cross addition of acetylenes to ynol ethers).[9] The expected product **3aa** was cleanly formed with excellent regio- and stereoselectivity (Table 1). With this exciting result, we next turned to evaluate its generality. Initially we verified the scope of the reaction with respect to acetylenes. Similar to phenyl acetylene various halophenyl acetylenes reacted successfully despite the possibility of Sonogashira coupling. Thus, **2b-e** provided the corresponding products **3ab-ae** in 69-76% yields. As is evident from the table, the yields in case of electron rich phenyl acetylenes were higher when compared to their electron deficient counterparts.

[a] *Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram extension, Sitapur Road, Lucknow 226031, India.*
[b] *Molecular & Structural Biology Division, CSIR-CDRI, Lucknow 226031, India.*
[c] *Academy of Scientific and Innovative Research, New Delhi 110001, India.*
† Contributed equally.
‡CDRI Communication No: xxxx. Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

Table 1. Addition of acetylenes **2** to oxazolidinone ynamide **1a**.[a]

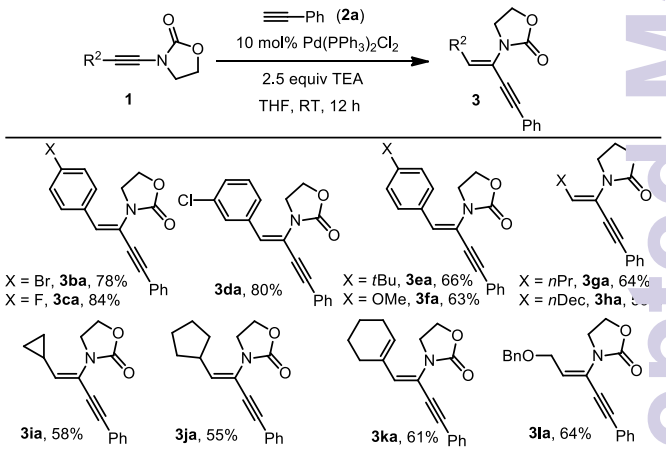


[a]Reaction conditions: **1a** (1.0 mmol), **2** (1.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.1 mmol), TEA (2.5 equiv), THF (0.5 M), RT, 12 h.

Thus, alkyl- and methoxyphenyl acetylenes **2f-h** produced the corresponding products **3af-ah** in 82-86% yields. The unprotected amino group in **2i** survived the reaction very well to produce **3ai** in 80% yield. CF_3-substituted phenyl acetylenes **2j-k** were also added smoothly to produce the expected products **3aj-ak** in 68-71% yields. The structure of **3aj** was unambiguously confirmed by X-ray crystallography. Nitrophenyl acetylene **2l** gave **3al** in a moderate yield of 55%. Incurring a high functional group tolerance to the reaction, formyl- and cyano-substituted phenyl acetylenes showed a hassle free reactivity to produce the products **3am-3an** albeit in slightly reduced yields (66-70%). Pyridylacetylene also smoothly reacted in the reaction to produce heteroaryl adduct **3ao** in 66% yield. In contrast to aromatic acetylenes, although conjugated, cyclohexenyl acetylene showed a moderate reactivity to yield **3ap** in 42%. Aliphatic acetylenes (**2q-s**) were found to be less productive (48-51% yields) compared to aromatic counterparts, whereas trimethylsilyl acetylene, and propargyl derivative **2t** and **2u** respectively reacted smoothly (66-68% yields) under standard conditions.

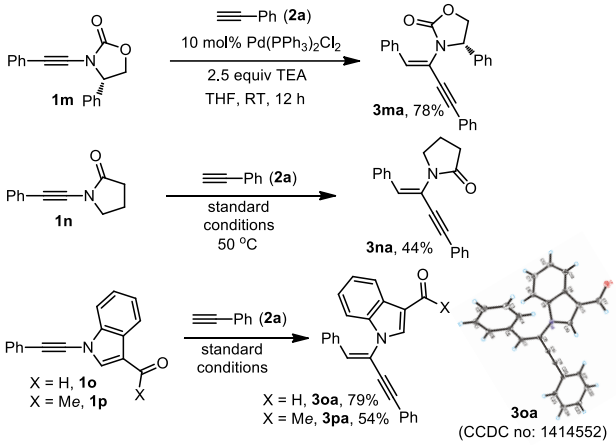
With the above encouraging results, we next aimed to evaluate reaction scope with respect to ynamides. Similar to **1a**, halophenyl ynamides **1b-d** were also added by phenyl acetylene with an excellent yielding (78-84%). In case of electron rich ynamides (**1e-j**) the yields were slightly dropped (63-66%). The reaction was not restricted to aromatic ynamides, the aliphatic substrates (**1g-j**) also effectively participated in the reaction although with relatively less yielding (55-64%). Further, cyclohexenyl ynamide **1k** yielded the desired dienynamide **3ka** in 61% yield. Propargyl alcohol based ynamide **1l** was also found to be competent reaction partner to deliver **3la** in 64% yield.

Table 2. Addition of phenyl acetylene to oxazolidinone ynamide **1**.[a]



[a]Reaction conditions: **1** (1.0 mmol), **2a** (1.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.1 mmol), TEA (2.5 equiv), THF (0.5 M), RT, 12 h.

Having successfully tested the newly found method by varying substitution on C-terminal of ynamides, we set out to unveil that how the change of substitution on nitrogen would vary the results. Pleasingly, despite the steric hindrance from closely positioned phenyl group, enantiopure chiral ynamide **1m** (prepared from commercially available enantiopure phenyl oxazolidinone) underwent the hydroalkynylation very cleanly to afford **3ma** in 78% yield (Scheme 2). Compared to oxazolidinone ynamides,

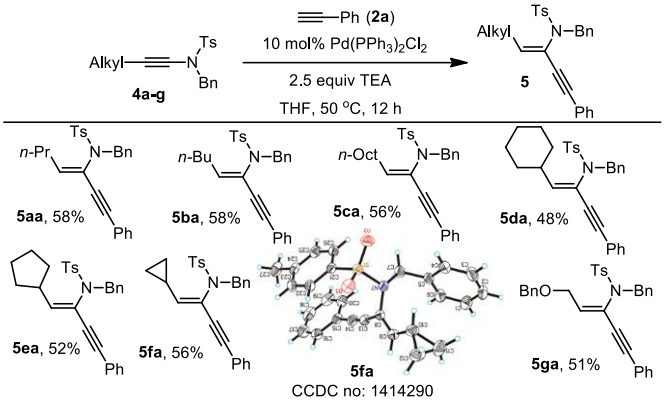


Scheme 2. Scope of reaction with various ynamides **1m-p**.

pyrrolidinone based ynamide **1n** needed slightly elevated temperature (50 °C) to furnish **3na** in moderate yield of 44%. Delightfully, indole based ynamines **1o** and **1p** were found to participate well in the reaction to produce **3oa** and **3pa** respectively in good to moderate yields (54-79%). Structure of **3oa** was confirmed by single crystal X-ray diffraction.

Our attention was next turned to explore the reactivity of *N*-protected secondary ynamides. We first chose *N*-tosyl aliphatic ynamides which were found by Zhu *et al.* to be poorly reactive (<35% conversion) to produce a mixture of isomers (79:21) with a slight predominance of *trans* addition product. Surprisingly, when subjected to our standard conditions (with an elevation of temperature to 50 °C), tosyl protected aliphatic ynamide **4a** reacted well and produced selectively the *syn* addition adduct **5aa** in 58% yield (Table 3). No *trans* isomer but an unidentified by-product (15%) was isolated. We immediately verified this contrasting result for its generality. Pleasingly, similar to **4a**, other *n*-alkyl and cycloalkyl *N*-tosyl ynamides **4b-f** produced corresponding *syn* addition adducts in 48-58% yields. Likewise, propargyl derivative **4g** also gave *syn* addition adduct **5ga** in 51% yield. Structure of **5fa** was confirmed by X-ray crystallography.

Table 3. *Cis* addition of **2a** to *N*-tosyl aliphatic ynamides **4**.[a]

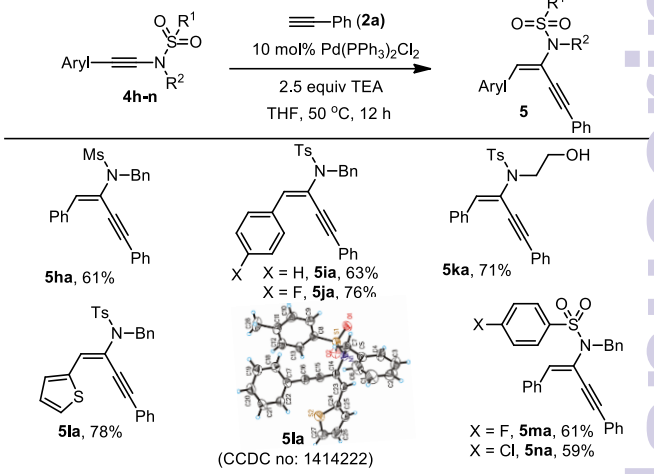


[a]Reaction conditions: **4** (1.0 mmol), **2a** (1.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.1 mmol), TEA (2.5 equiv), THF (0.5 M), 50 °C, 2-12 h.

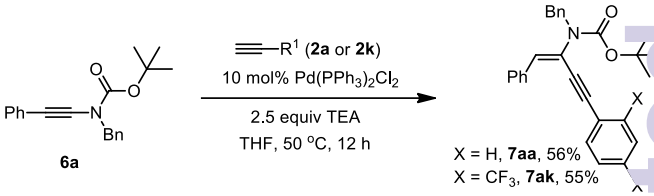
We then turned our attention toward the reactivity of *N*-sulfonyl aryl ynamides which were the substrates for *trans* addition by Zhu *et al.* Similar to their observation, and unlike in all the above cases (Tables 1-3 and Scheme 2), the addition of **2a** to **4h** led to the selective formation of *trans* adduct **5ha** in 61% yield (Table 4). Since our reaction conditions are slightly better and more convenient (no additives, non protic solvent and reduced temperature) compared to those developed by Zhu *et al.* (Scheme 1A), we wanted to pursue this *trans* addition reaction for its scope. In addition, we particularly wanted to choose the substrates other than methanesulfonamides as they were not tested in earlier finding. Thus, various *N*-arylsulfonyl arylynamides (**4i-n**) were tested under the standard conditions to obtain, pleasingly, the expected products (**5ia-na**) in good to excellent yields (59-78%).

The subsequent feedstock we chose for the reaction was *N*-Boc-aryl ynamide. Thus, when subjected to the standard conditions, **6a**

Table 4. *Trans* addition of **2a** on *N*-tosyl aryl ynamides **4**.[a]



[a]Reaction conditions: **4** (1.0 mmol), **2a** (1.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.1 mmol), TEA (2.5 equiv), THF (0.5 M), 50 °C, 2-12 h.



Scheme 3. Addition of **2a** and **2k** to Boc-protected ynamide **6a**.

afforded selectively the *trans* adducts **7aa-ak** with both phenyl- and bis(trifluoromethyl)phenyl acetylenes (Scheme 3).[11]

From these examples, i.e. aryl ynamides with non-cyclic substitution on nitrogen (Table 4 and Scheme 3), it appears that an increased bond angle between *N*-substituents is enhancing the steric hindrance between *ortho*-proton of aryl ring and *N*-substitution. Hence, the tentative enynyl palladium intermediate formed via *syn* addition (**A**, Figure 1) might have forcibly switched to sterically less hindered *trans* isomer before reductive elimination. This happened only with aryl ynamides because the aryl ring lies in plane with ynenamide system due to conjugation. Whereas with sulfonyl protected alkyl ynamides (Table 3), due to free rotation of the alkyl group, there does not exist any steric repulsion (**B**, Figure 1) from non-cyclic substituents on nitrogen and hence they underwent straight *syn* addition. However, due to less or no steric hindrance (**C-D**, Figure 1), the ynamides with *N*-cyclic substitution (Tables 1-3) uniformly incurred the *syn* addition irrespective of aryl or alkyl substitution at C-terminal.

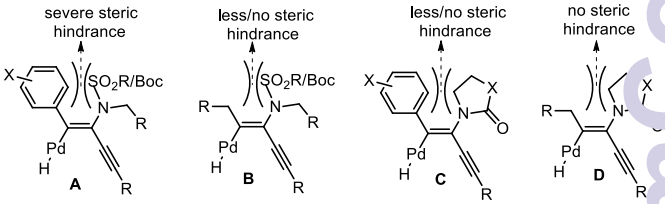
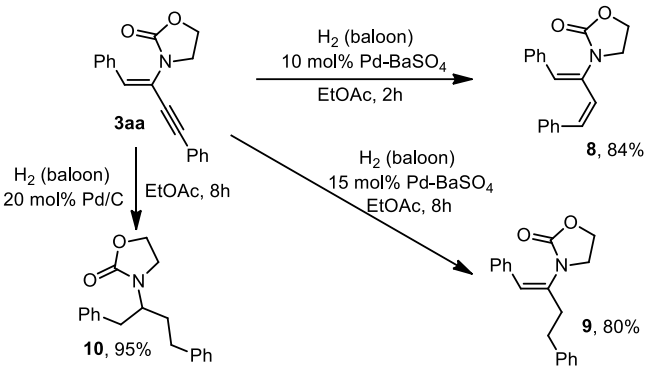


Figure 1. Steric constraints in various intermediates.

Finally, we verified whether it was possible to selectively modify the alkyne group of above ynenamides to acquire differently substituted enamides. Thus, partial *syn* reduction of **3aa** was achieved (**8** a 84%) using 10 mol% Pd-$BaSO_4$ under hydrogen atmosphere. Use of

higher amounts of catalyst (15 mol% Pd-$BaSO_4$) along with longer reaction timings (8h) cleanly led to the complete and selective reduction of alkyne group to afford **9** in 80% yield. However, use of Pd/C with hydrogen totally reduced the enyne system to afford saturated adduct **10** (95%).



Scheme 4. Reductions of ynenamide **3aa**.

In conclusion, we demonstrated the selective addition of acetylenes to ynamides under mild reaction conditions. The addition to substrates with cyclic substitution on nitrogen was always *syn* irrespective of alkyl or aryl substitution at C-terminal, whereas to substrates with noncyclic substitution (sulfonyl or Boc protected secondary ynamides), the addition was subjective depending on the steric constraints: *syn* with alkyl ynamides and *trans* with aryl ynamides. We hope that these highly and selectively functionalized/substituted subunits will find extensive applications in both synthetic and medicinal chemistries.

VD and MHB thank CSIR for the fellowships. We thank SAIF division CSIR-CDRI for the analytical support. We gratefully acknowledge the financial support by CSIR (SPLENDID, BSC 0104).

Notes and references

1 (a) B. M. Trost, C. Chan and G. Ruhter, *J. Am. Chem. Soc.*, 1987, **109**, 3486. (b) B. M. Trost, I. Hachiya and M. C. McIntosh, *Tetrahedron Lett.*, 1998, **39**, 6445. (c) C. Xu, W. Du, Y. Zeng, B. Dai and H. Guo. *Org. Lett.*, 2014, **16**, 948. (d) T. Chen, C. Guo, M. Goto and L. –B. Han, *Chem. Commun.*, 2013, 7498. (e) S. Sun, J. Kroll, Y. Luo, L. Zhang, *Synlett* 2012, 54. (f) H. M. Peng, J. Zhao and X. Li, *Adv. Synth. Catal.*, 2009, **351**, 1371. (g) M. Yoshida and R. F. Jordan, *Organometallics* 1997, **16**, 4508. (h) C. J. Pell and O. V. Ozerov, *ACS Catal.*, 2014, **4**, 3470. (i) O. V. Zatolochnaya, E. G. Gordeev, C. Jahier, V. P. Ananikov and V. Gevorgyan, *Chem. Eur. J.*, 2014, **20,** 9578.

2 (a) B. M. Trost, M. T. Sorum, C. Chan, A. E. Harms and G. Ruhter, *J. Am. Chem. Soc.*, 1997, **119**, 698. (b) Y. Shibata and K. Tanaka, *Angew. Chem., Int. Ed.*, 2011**, 50**, 10917. (c) L. Chen and C. –J. Li, *Tetrahedron Lett.*, 2004, **45**, 2771. (d) B. M. Trost, I. Hachiya and M. C. McIntosh, *Tetrahedron Lett.*, 1998, **39,** 6445. (e) C. S. Yi and N. Liu, *Organometallics* 1998, **17**, 3158. (f) T. Hirabayashi, S. Sakaguchi and Y. Ishii, *Adv. Synth. Catal.*, 2005, **347**, 872. (g) J. Ito, M. Kitase and H. Nishiyama, *Organometallics* 2007, **26**, 6412.

3 (a) T. Sakurada, Y. –K. Sugiyama and S. Okamoto, *J. Org. Chem.*, 2013, **78**, 3583. (b) N. Matsuyama, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 3576. (c) N. Matsuyama, H. Tsurugi, T. Satoh and M. Miura, *Adv. Synth. Catal.*, 2008, **350,** 2274. (d) N. Tsukada, S. Ninomiya, Aoyama and Y. Inoue, *Org. Lett.*, 2007, **9**, 2919. (e) T. Nishimura, X. –X. Guo, K. Ohnishi and T. Hayashi, *Ad. Synth. Catal.*, 2007, **349**, 2669. (f) N. Tsukada, S. Ninomiya, Y. Aoyama and Y. Inoue, *Pure Appl. Chem.*, 2008, **80**, 1[illegible]. (g) H. –D. Xu, R. –W. Zhang, X. Li, S. Huang, W. Tang an[illegible] W. –H. Hu, *Org. Lett.*, 2013, **15**, 840. (h) A. Funayama, T. Satoh and M. Miura, *J. Am. Chem. Soc.*, 2005, **127**, 15354.

4 (a) P. Nussbaumer, I. Leitner, K. Mraz, A. Stutz, *J. Med. Chem.*, 1995, ***38***, 1831. (b) L. Garlaschelli, E. Magistrali, G. Vidari and O. Zuffardi, *Tetrahedron Lett.*, 1995, **36**, 563[illegible]. (c) N. E. –Jaber, A. E. –Braun, A. G. Ravelo, O. M. –Munoz, A. R. –Afonso and J. R. Murguia, *J. Nat. Prod.*, 2003, **66**, 722. (d) T. Akiyama, K. Takada, T. Oikawa, N. Matsuura, Y. Ise, S. Okada and S. Matsunaga, *Tetrahedron* 2013, **69**, 6560

5 (a) J. B. Werness and W. Tang, *Org. Lett.*, 2011, **13**, 3664. (b) X.-L. Meng, T. Liu, Z.-W. Sun, J.-C. Wang, F.-Z. Peng and Z.-H. Shao, *Org. Lett.*, 2014, **16**, 3044. (c) W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei and W. Tang, *J. Am. Chem. Soc.*, 2010, **132**, 3664. (d) M. Rubina, M. Conley and V. Gevorgyan, *J. Am. Chem. Soc.* 2006, **128**, 5818. (e) [illegible] Rose, C. C. M. Garcia, F. Punner, K. Harms and G. Hilt, *J. Org. Chem.*, 2015, **80**, 7311. (f) E. S. Karagoz, M. Kus, G. [illegible] Akplnar, and L. Artok, *J. Org. Chem.*, 2014, **79**, 9222.

6 (a) D. Davyt, W. Entz, R. Fernandez, R. Mariezcurrena, A. W. Mombru, J. Saldana, L. Dominguez, J. Coll and E. Manta, *J. Nat. Prod.*, 1998, **61**, 1560. (b) J. P. Vidal, R. Escale, J. P. Girard, J. C. Rossi, J. M. Chantraine and A. Aumelas, *J. Org. Chem.*, 1992, **57**, 5857. (c) P. Alarma-Estrany, A. Guzman Aranguez, F. Huete, A. Peral, R. Plourde, T. Pelaez, B. Yerxa and J. Pintor, *J. Pharmacol. Exp. Ther.*, 2011, **337**, 703. (d) R. Matsubara and S. Kobayashi, *Acc. Chem. Res.*, 2008, **41**, 292. (e) R. Rey-Rodriguez, P. Retailleau, P. Bonnet, and S. Gillaizeau, *Chem. Eur. J.*, 2015, **21**, 3572. (f) Q. Gou, B. Deng, H. Zhang, and Jun Qin, *Org. Lett.*, 2013, **15**, 4604. (g) C. Lei, D. Wang, L. Zhao, J. Zhu and M. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 4708. (h) K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430. (i) G. [illegible] Roff, R. C. Lloyd and N. J. Turner, *J. Am. Chem. Soc.*, 2004, **126**, 4098. (j) R. Matsubara, Y. Nakamura and S. Kobayashi, *Angew. Chem. Int. Ed.* 2004, **43**, 1679.

7 (a) K. Gopalaiah and H. B. Kagan, *Chem. Rev.*, 2011, **111**, 4599. (b) D. R. Carbery, *Org. Biomol. Chem.*, 2008, **6**, 3[illegible]. (c) H. Liu, Y. Zhou, X. Yan, C. Chen, Q. Liu and C. Xi, *Org. Lett.*, 2013, **15**, 5174. (d) M. T. Herrero, J. D. de Sarralde, R. SanMartin, L. Bravo, and E. Dominguez, *Adv. Synth. Catal.* 2012, **354**, 3054. (e) W. Adam, S. G. Bosio and N. J. Turro, *J. Org. Chem.*, 2004, **69**, 1704. (f) X. Pa, Q. Cai and D. Ma, *Org. Lett.*, 2004, **6**, 1809. (g) J. Wallace, D. J. Klauber, C. Chen and R. P. Volante, *Org. Lett.*, 2003, **5**, 4749.

8 G. Liu, W. Kong, J. Che and G. Zhu, *Adv. Synth. Catal.*, 2014, **356**, 3314.

9 M. H. Babu, V. Dwivedi, R. Kant and M. S. Reddy, *Angew. Chem. Int. Ed.*, 2015, **54**, 3783.

10 (a) Y. K. Kumar, G. R. Kumar, T. J. Reddy, B. Sridhar and M. S. Reddy, *Org Lett.*, 2015, **17**, 2226. (b) N. Thirupathi, M. H. Babu, V. Dwivedi and M. S. Reddy, *Org. Lett.*, 2014, **16**, 2908. (c) Y. K. Kumar, G. R. Kumar and M. S. Reddy, *J. Org. Chem.*, 2014, **79**, 823. (d) N. Thirupathi, Y. K. Kumar, R. Kant and M. S. Reddy, *Adv. Synth. Catal.*, 2014, **356**, 1823. (e) M. S. Reddy, N. Thirupathi, M. H. Babu and S. Puri, *J. Org. Chem.*, 2013, **78**, 5878. (f) M. S. Reddy, N. Thirupathi and M. H. Babu, *Eur. J. Org. Chem.*, 2012, 5805. (g) M. S. Reddy, N. Thirupathi and Y. K. Kumar, *RSC Adv.*, 2012, **2**, 3986. (h) M. S. Reddy, Y. K. Kumar and N. Thirupathi, *Org. Lett.*, 2012, **14**, 824.

11 See Supporting Information for NOESY spectrum of **7ak**.