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Lewis-Base-Catalysed Selective Reductions of Ynones with Mild Hydride Donor

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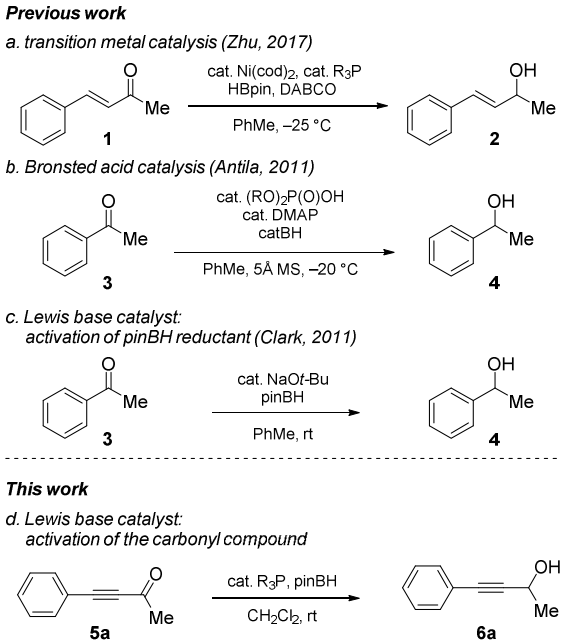
Ynones are efficiently reduced with a mild hydride donor in presence of catalytic amount of nucleophilic phosphines. The reactions are selective 1,2-reductions that give propargyl alcohols in yields of up to 96%. It is proposed that success in these reactions depends on activation of ynone by a Lewis base catalyst. Protic additive plays a key role in suppressing the undesired reaction pathways and accelerating the 1,2-reductions.

Propargylic alcohols are a common moiety in natural products and biologically active molecules,[1] and they serve as versatile intermediates in organic synthesis.[2] Secondary propargylic alcohols can be prepared via 1,2-reduction of ynones that are easily accessible, i.e. via addition of alkynyl nucleophiles to various carbonyl compounds.[3] Reductions of carbonyl compounds, including ynones, and chemoselectivity of these reactions have been the subject of investigation for many decades.[4] Recent efforts have focused on the use of mild reducing agents, mild hydride donors with overall goal of developing more selective transformations.[5]

Easy to handle, mild hydride donors such as pinacolborane (pinBH) is an ideal reductant for applications in small scale preparation of compound libraries where scope and generality are of high importance. The low reactivity of pinBH prevents its direct use as a reducing agent and enables its use in catalytic processes.[6] The common strategies to increase the reactivity of such mild hydride donors, illustrated in Scheme 1, are to rely on transition metal mediated activation,[7] Brønsted or Lewis acid activation of the substrate,[8] and/or activation of the borane with a suitable Lewis base.[9] Inspired by reductions catalysed by frustrated Lewis pairs,[10] and the surge of interest in metal-free catalysts for reductions,[8,11] we speculated that (i) a suitable Lewis base may be used to activate the carbonyl substrate, instead of activating the borane, and increase its reactivity towards mild hydride donors such as pinBH (Scheme 1d), and that (ii) different carbonyl compounds could be chemoselectively reduced based on their contrasting reactivities with Lewis bases.



Scheme 1 Catalytic reduction of carbonyl compounds with mild-hydride-donor boranes.

To test both of our hypotheses, we focused on reactions of pinBH with ynone **5a** and simple ketones (acetophenone and cyclohexanone) in presence of a Lewis base catalyst. The choice of catalyst and reaction solvent in the initial experiments was governed by the intent to activate the carbonyl compound while avoiding activation of borane through creation of a Lewis adduct. Simple nucleophilic phosphines were chosen as catalysts because they don't form stable adducts with pinBH.[12] Dichloromethane, 1,2-dichloroethane or toluene were used as solvents to avoid

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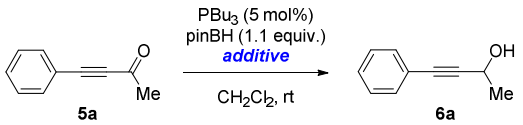
activation of pinBH through formation of Lewis adduct with solvent molecules. In the presence of catalytic amounts of tributylphosphine (20 mol%), ynone **5a** readily reacted with pinBH while acetophenone and cyclohexanone remained unaffected after prolonged exposure to the reaction conditions. In absence of phosphine catalyst, pinBH does not reduce the ynone **5a**. These experiments seemingly corroborated the initial hypotheses showing (i) the effectiveness of phosphine catalysts in reductions of ynones with pinBH and (ii) that phosphines do not promote reduction of ketones which opened the door for development of chemoselective catalytic reactions.

The product mixture isolated in reaction of ynone **5a** highlighted the issues with reaction regioselectivity. The well-established modes of reactivity including 1,2- and 1,4-reduction with possible overreduction pathways, alkyne hydroboration, and dimerization or oligomerization of ynones could easily lead to formation of a variety of different products. The major products in the reduction of ynone **5a**, however, were the products of 1,2- and 1,4-reduction, **6a** and **1**. Products of overreduction (allylic alcohol derived from **1**) and ynone dimerization were observed in minor quantities.

Table 1 Effects of additives on reaction selectivity and isolated yield of the 1,2-reduction product.



5a **6a**

Entry	Additive (1.5 eq.)	Time	Yield of 6a (%)[a]
1	AcOH	120 min	(trace)
2	DABCO	16 h	0
3	NEt_3	16 h	(18)
4	*t*-BuOK	10 min	(trace)
5	H_2O	10 min	86 (86)
6	MeOH	60 min	61
7	EtOH	60 min	64
8	*i*-PrOH	10 min	94
9	*t*-BuOH	10 min	87 (89)

[a] Isolated yield of **6a**. Numbers in brackets designate yield determined ^{1}H NMR spectroscopy of crude product mixtures after quench designated time point using triphenylmethane as standard.

Further optimization of the reaction conditions revealed that protic additives suppress the major side reactions: 1,4-reduction and dimerization/oligomerization of ynone. The increase in selectivity and isolated yields of propargylic alcohol **6a** correlates to the increased amount of *tert*-butanol in the reaction milieu (Table 1, ESI document). When 1.5 equivalents of *tert*-butanol were present in the mixture, products of 1,4-reduction and dimerization/oligomerization were not observed and the propargylic alcohol **6a** was the only product isolated upon aqueous work up. Furthermore, in presence of *tert*-butanol additive, catalyst loading could be reduced to as low as 1 mol% for tributylphosphine without effecting the yield. Only 1.1 equivalents of pinBH were sufficient to effect complete consumption of the starting ynone. In absence of phosphine, *tert*-butanol doesn't catalyse the 1,2-reduction reaction: reduction product **6a** was not observed after 6 hours in presence of 2 equiv. of pinBH and 2 equiv. of alcohol.

A set of commercially available and easy to handle alkyl- and arylphosphines was tested as Lewis base catalysts in the reductions of ynones (for detailed results see Table 2, ESI document). Triphenylphosphine and diphenylmethylphosphine provided the desired product in acceptable yields but required longer reaction times and failed to drive complete consumption of ynone after 24 hours. Trialkylphosphines proved to be more efficient catalysts with tributyl- and trimethylphosphine both effecting full conversion of ynone within 10 minutes with desired products isolated in high yield. In contrast, bulky trialkylphosphines, tri-*t*-butylphosphine and tricyclohexylphosphine, showed decreased activity which highlighted the importance of nucleophilicity of the phosphine catalyst for successful reaction outcome.

Upon optimizing the reaction conditions for reduction of **5a**, substrate scope for the 1,2-reductions of ynones was evaluated with special attention to the identity of the α' and γ substituents in the ynones. Urgency to evaluate various combinations of alkyl and aryl substituents was brought on by the previous reports which map an extremely divergent reactivity network in phosphine catalysed reaction of ynones or ynoates under similar reactions conditions.[13]

Gratifyingly, substrates with either alkyl and aryl groups in α' and γ positions were equally reactive as **5a**, all providing the products of 1,2-reductions in good yields (Scheme 2, compounds **6a**, **6b**, **6d**, **6e** and **6f**). Similar reactivity was observed even when a tertiary carbon centre was present in α' or γ positions of the ynone. However, quaternary carbon centres in these positions significantly decrease the rates of the reduction reactions making them less practical (Scheme 2, compounds **6c** and **6g**).

Further inspection of the substrate scope has shown that both electron rich and electron poor ynones are efficiently reduced under the optimized conditions (**6h**, **6i**, **6j** and **6k**). A selection of substrates containing various heterocycles such as furan, thiophene, both protected and non-protected indole and protected aniline all tolerated the mild reaction conditions well and produced the corresponding propargyl alcohols in good yields (Scheme 2, compounds **6j**-**6o**). It is worth noting that under optimized conditions, acetophenone (**3**) and cyclohexanone (**8**) do not react even after longer periods of time similar to our initial experiments. Other reducible groups are also not affected under optimized conditions as illustrated by substrates **6h**, **6j**, **6k**, **6o**, **6p** and **6q** which contain nitro, carbamate, amide, ester and nitrile groups respectively.

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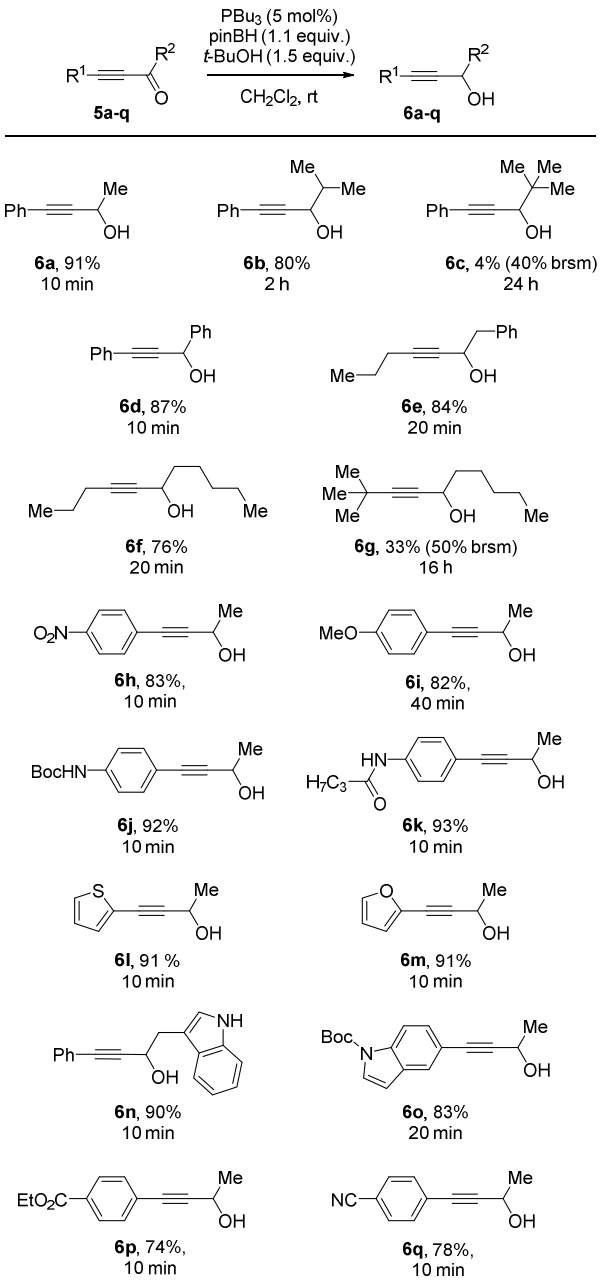
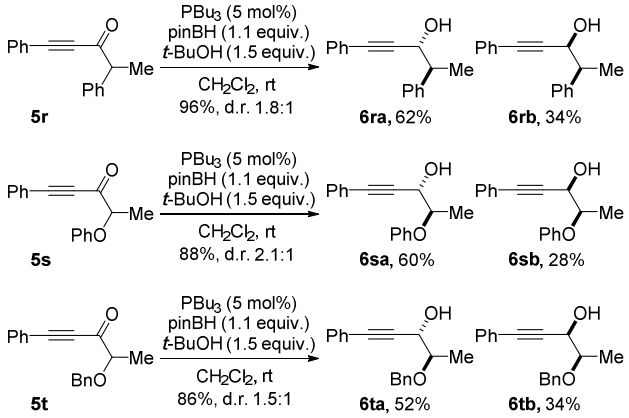


Scheme 2 Reaction scope for the phosphine catalysed ynone reduction with pinacolborane.

Closer inspection of the substrate scope clearly matched the expectations arising from our initial hypothesis. The substrates with electron withdrawing substituents, that should render the ynone more electrophilic were reduced significantly faster than the corresponding substrates that carry electron donor groups. (i.e. compound **6h** vs. **6a** vs. **6i**, Scheme 2). These observations are consistent with simple hydride delivery to carbonyl. Knowing that phosphine does not react with *tert*-butanol or pinBH,[12] we propose that the observed rate acceleration is also a consequence of higher rate of 1,4-addition of the phosphine catalyst to ynones. In presence of protic additives, resulting zwitterionic intermediate would get protonated to produce the corresponding vinylphosphonium salts.[14] Quenching of the enolate intermediate initially produced by conjugate addition of phosphine is believed to play a key role in suppressing the oligomerization of ynones which happens rapidly in absence of the additive or borane and suppressing the 1,4-reduction pathways.

After establishing that a tertiary carbon centre in α' position does not deter the reactivity of ynones (Scheme 2, entries **6b** and **6d**), diastereoselectivity of the reductions was briefly examined with ynones **5r**, **5s** and **5t** (Scheme 3).[15] The reactions of **5r** produced the 1:1.8 mixture of diastereomers **6ra** and **6rb** with combined yield of 96%. Diastereoselectivity in reductions of **5s** and **5t** which feature a phenyl and benzyl ether substituent in α' positions respectively, also proceeded with moderate diastereoselectivity producing a 1.5:1 mixture of **6sa** and **6sb** and a 1:2.1 mixture of **6ta** and **6tb** (*anti* diastereomer favoured in both cases). The observed low diastereoselectivity in these reactions may be a consequence of low selectivity in formation of *E* and *Z*-vinylphosphonium intermediates and suggests that coordination of borane followed by intramolecular hydride delivery is not the dominant pathway.



Scheme 3 Substrate control of diastereoselectivity in the phosphine catalysed 1,2-reductions of ynones.

Finally, the scalability of the developed transformation was tested. Reductions of **5a** on gram-scale proceed efficiently without deterioration of the isolated yield.

In conclusion, we have developed a phosphine catalysed chemoselective 1,2-reduction of ynones using pinBH as a mild hydride donor. The key control element in these reactions is the presence of protic additive, *tert*-butanol, which plays a role in suppressing 1,4-reduction and ynone dimerization pathways and increasing the reaction rates of the 1,2-reduction presumably through activation of pinBH. The efficiency of this transformation has been demonstrated on a number of

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structurally diverse ynones with high yields observed for 1,2-reductions of both electron rich and electron poor ynones carrying either aryl and alkyl substituents. The reactions appear to be selective for ynones indicating that activation of the carbonyl substrate, and not the reductant, by phosphine catalyst plays a critical role. The detailed mechanistic aspects of this process will be the subject of future investigations.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1. (a) T. Shirouzu, K. Watari, M. Ono, K. Koizumi, I. Saiki, C. Tanaka, R. W. M. van Soest and T. Miyamoto, *J. Nat. Prod.*, 2013, **76**, 1337-1342; (b) D. Listunov, I. Fabing, N. Saffon-Merceron, H. Gaspard, Y. Volovenko, V. Maraval, R. Chauvin and Y. Genisson, *J. Org. Chem.*, 2015, **80**, 5386-5394; (c) D. Listunov, V. Maraval, R. Chauvin and Y. Genisson, *Nat. Prod. Rep.*, 2015, **32**, 49-75; (d) D. Listunov, S. Mazeres, Y. Volovenko, E. Joly, Y. Genisson, V. Maraval and R. Chauvin, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4652-4656.
2. (a) E. B. Bauer, *Synthesis*, 2012, **44**, 1131-1151; (b) L. Zhang, G. Fang, R. K. Kumar and X. Bi, *Synthesis*, 2015, **47**, 2317-2346; (c) Y. Zhu, L. Sun, P. Lu and Y. Wang, *ACS Catalysis*, 2014, **4**, 1911-1925; (d) B. J. Ayers and P. W. H. Chan, *Synlett*, 2015, **26**, 1305-1339.
3. (a) D. A. Alonso, C. Najera and M. C. Pacheco, *J. Org. Chem.*, 2004, **69**, 1615-1619; (b) Q. Shen, W. Huang, J. Wang and X. Zhou, *Organometallics*, 2008, **27**, 301-303; (c) C. Taylor and Y. Bolshan, *Org. Lett.*, 2014, **16**, 488-491; (d) Z. Wang, L. Li and Y. Huang, *J. Am. Chem. Soc.*, 2014, **136**, 12233-12236; (e) P.-F. Wang, Y.-S. Feng, Z.-F. Cheng, Q.-M. Wu, G.-Y. Wang, L.-L. Liu, J.-J. Dai, J. Xu and H.-J. Xu, *J. Org. Chem.*, 2015, **80**, 9314-9320; (f) R. E. Whittaker, A. Dermenci and G. Dong, *Synthesis*, 2016, **48**, 161-183; (g) S. Tang, L. Zeng, Y. Liu and A. Lei, *Angew. Chem. Int. Ed.*, 2015, **54**, 15850-15853.
4. (a) K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738-8739; (b) E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551-5553; (c) C. J. Helal, P. A. Magriotis and E. J. Corey, *J. Am. Chem. Soc.*, 1996, **118**, 10938-10939; (d) S. Eagon, C. DeLieto, W. J. McDonald, D. Haddenham, J. Saavedra, J. Kim and B. Singaram, *J. Org. Chem.*, 2010, **75**, 7717-7725; (e) V. Druais, C. Meyer and J. Cossy, *Org. Lett.*, 2012, **14**, 516-519; (f) J. S. Cha, *Bull. Korean Chem. Soc.*, 2011, **32**, 1808-1846; (g) J. Magano and J. R. Dunetz, *Org. Process Res. Dev.*, 2012, **16**, 1156-1184; (h) R. Ohta and H. Fujioka, *Chem. Pharm. Bull.*, 2017, **65**, 10-18; (i) C.-M. Yu, C. Kim and J.-H. Kweon, *Chem. Commun.*, 2004, 2494-2495.
5. (a) Z. M. Heiden and A. P. Lathem, *Organometallics*, 2015, **34**, 1818-1827; (b) C. Tsay, B. N. Livesay, S. Ruelas and J. Y. Yang, *J. Am. Chem. Soc.*, 2015, **137**, 14114-14121; (c) C. L. Pitman, K. R. Brereton and A. J. M. Miller, *J. Am. Chem. Soc.*, 2016, **138**, 2252-2260; (d) E. S. Wiedner, M. B. Chambers, C. L. Pitman, R. M. Bullock, A. J. M. Miller and A. M. Appel, *Chem. Rev.*, 2016, **116**, 8655-8692; (e) M. Horn, L. H. Schappele, G. Lang-Wittkowski, H. Mayr and A. R. Ofial, *Chem. Eur. J.*, 2013, **19**, 249-263.
6. S. Itsuno, *ACS Symp. Ser.*, 2016, **1236**, 241-274.
7. (a) C. C. Chong and R. Kinjo, *ACS Catalysis*, 2015, **5**, 3238-3259; (b) F. Chen, Y. Zhang, L. Yu and S. Zhu, *Angew. Chem. Int. Ed.*, 2017, **56**, 2022-2025; (c) V. Vasilenko, C. K. Blasius, H. Wadepohl and L. H. Gade, *Angew. Chem. Int. Ed.*, 2017, **56**, 8393-8397.
8. (a) Z. Zhang, P. Jain and J. C. Antilla, *Angew. Chem. Int. Ed.*, 2011, **50**, 10961-10964; (b) M. R. Adams, C.-H. Tien, B. S. N. Huchenski, M. J. Ferguson and A. W. H. Speed, *Angew. Chem. Int. Ed.*, 2017, **56**, 6268-6271; (c) A. Ford and S. Woodward, *Angew. Chem. Int. Ed.*, 1999, **38**, 335-336; (d) A. J. Blake, A. Cunningham, A. Ford, S. J. Teat and S. Woodward, *Chem. Eur. J.*, 2000, **6**, 3586-3594
9. (a) K. Revunova and G. I. Nikonov, *Chem. Eur. J.*, 2014, **20**, 839-845; (b) I. P. Query, P. A. Squier, E. M. Larson, N. A. Isley and T. B. Clark, *J. Org. Chem.*, 2011, **76**, 6452-6456. Conceptually similar activation of carbonyl compounds for addition of soft nucleophiles: (c) P. Jain, H. Wang, K. N. Houk and J. C. Antilla, *Angew. Chem. Int. Ed.*, 2012, **51**, 1391-1394.
10. (a) D. W. Stephan, *Acc. Chem. Res.*, 2015, **48**, 306-316; (b) D. W. Stephan and G. Erker, *Angew. Chem. Int. Ed.*, 2015, **54**, 6400-6441.
11. (a) C.-H. Tien, M. R. Adams, M. J. Ferguson, E. R. Johnson and A. W. H. Speed, *Org. Lett.*, 2017, **19**, 5565-5568; (b) W. Zhao, S. M. McCarthy, T. Y. Lai, H. P. Yennawar and A. T. Radosevich, *J. Am. Chem. Soc.*, 2014, **136**, 17634-17644; (c) K. D. Reichl, N. L. Dunn, N. J. Fastuca and A. T. Radosevich, *J. Am. Chem. Soc.*, 2015, **137**, 5292-5295; (d) Y.-C. Lin, E. Hatzakis, S. M. McCarthy, K. D. Reichl, T.-Y. Lai, H. P. Yennawar and A. T. Radosevich, *J. Am. Chem. Soc.*, 2017, **139**, 6008-6016; (e) C. C. Chong, H. Hirao and R. Kinjo, *Angew. Chem. Int. Ed.*, 2015, **54**, 190-194; (f) C. C. Chong, B. Rao and R. Kinjo, *ACS Catalysis*, 2017, **7**, 5814-5819; (g) S. Burck, D. Gudat, M. Nieger and W.-W. Du Mont, *J. Am. Chem. Soc.*, 2006, **128**, 3946-3955.
12. M. A. Dureen, A. Lough, T. M. Gilbert and D. W. Stephan, *Chem. Commun.*, 2008, 4303-4305. This has also been confirmed by ^{31}P and ^{11}B NMR experiments of trialkyl phosphines, pinacolborane and various mixtures of the two (for details, see ESI document).
13. (a) S. D. Rychnovsky and J. Kim, *J. Org. Chem.*, 1994, **59**, 2659-2660; (b) B. M. Trost and C.-J. Li, *J. Am. Chem. Soc.*, 1994, **116**, 10819-10820; (c) R. J. Lundgren, A. Wilsily, N. Marion, C. Ma, Y. K. Chung and G. C. Fu, *Angew. Chem. Int. Ed.*, 2013, **52**, 2525-2528; (d) D. T. Ziegler and G. C. Fu, *J. Am. Chem. Soc.*, 2016, **138**, 12069-12072; (e) K. Nagao, H. Ohmiya and M. Sawamura, *J. Am. Chem. Soc.*, 2014, **136**, 10605-10608; (f) K. Nagao, H. Ohmiya and M. Sawamura, *Org. Lett.*, 2015, **17**, 1304-1307; (g) H. Murayama, K. Nagao, H. Ohmiya and M. Sawamura, *Org. Lett.*, 2016, **18**, 1706-1709; (h) E. Mercier, B. Fonovic, C. Henry, O. Kwon and T. Dudding, *Tetrahedron Lett.*, 2007, **48**, 3617-3620; (i) G. S. Creech and O. Kwon, *Org. Lett.*, 2008, **10**, 429-432; (j) C. T. Mbofana and S. J. Miller, *ACS Catalysis*, 2014, **4**, 3671-3674.
14. Vinylphosphonium salts produced by conjugate addition of phosphines to ynones and subsequent proton quench can be isolated in presence of triflic acid as a protic additive. For caracterization of these intermediates, please see the ESI document. These intermediates are also observed by ^{1}H NMR in presence of alcohol additives.
15. (a) J. A. Marshall and M. P. Bourbeau, *Org. Lett.*, 2003, **5**, 3197-3199; (b) J. A. Marshall and K. Ellis, *Tetrahedron Lett.*, 2004, **45**, 1351-1353; (c) G. Cantagrel, C. Meyer and J. Cossy, *Synlett*, 2007, **2007**, 2983-2986; (d) M. Barbazanges, C. Meyer and J. Cossy, *Org. Lett.*, 2008, **10**, 4489-4492; (e) M. Handa, K. A. Scheidt, M. Bossart, N. Zheng and W. R. Roush, *J. Org. Chem.*, 2008, **73**, 1031-1035.

