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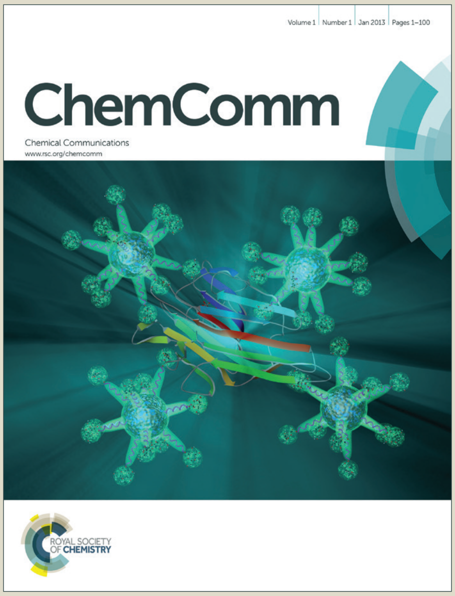

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Carbonylative Coupling of Allylic Acetates with Arylboronic Acids

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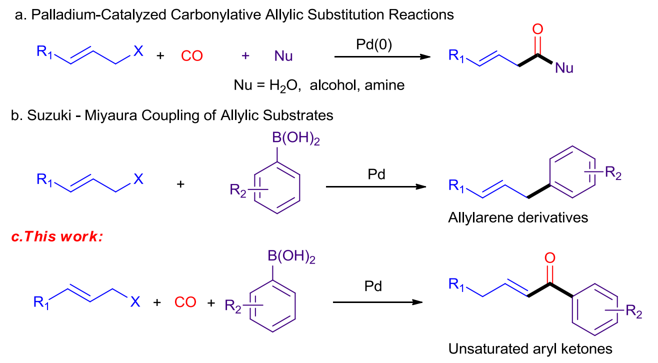
The first allylic carbonylation reaction of allylic acetates with aryl boronic acids under carbon monoxide has been developed. Using Pd-PCy$_3$ as catalyst, a wide spectrum of allylic acetates was carbonylated in the presence of various aryl boronic acids, affording β,γ-unsaturated aryl ketones in good to excellent yields. Preliminary studies indicate that carbon monoxide always inserts at the least substituted terminal allylic carbon and the resulting α,β-unsaturated aryl ketones generally isomerise to the ketones obtained.

Palladium-catalyzed Tsuji-Trost reaction is one of the most used C-C bond formation reactions for synthetic chemists, attracting broad interest in the past decades.[1] Among various palladium-catalyzed allylic substitution reactions, the carbonylative allylic substitution reactions have been extensively studied, which are favoured in the synthesis of unsaturated carbonyl compounds.[2, 3] In these carbonylation reactions, allylic acetates,[4] carbonates,[5] chlorides,[6] ethers,[7] amines,[8] phosphates[5b, 9] and alcohols[6a, 10] have been used as the electrophilic coupling partners. The most common nucleophilic partners are water, alcohols, and amines, which allow for the access of β,γ-unsaturated carboxylic acids, esters or amides (Scheme 1, a). To the best of our knowledge, however, no aryl boronic acids have been used as coupling partners in such carbonylative allylic substitution reactions. This is somewhat surprising, because aryl boronic acids, which are air and moisture stable, have been widely used as arylating reagents in organic synthesis,[11] and particularly, they have been demonstrated to be effective nucleophiles in allylic substitution reactions (Scheme 1, b).[12] In addition, it is noted that the carbonylation of arylboronic acids in the presence of alcohols,[13] alkenes[14], alkynes[15] and aryl halides[16] has been well documented.

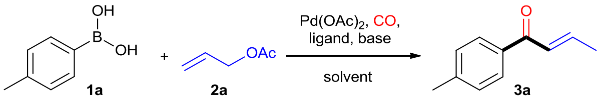
Following our continued research interest in palladium-catalyzed carbonylation reactions[17] and Heck reaction of aryl boronic acids,[18] herein we would like to describe a new palladium-catalysed carbonylative allylic substitution reaction with arylboronic acids, affording various α,β-unsaturated aryl ketones in good yields (Scheme 1, c). Such unsaturated ketones are important intermediates and versatile functional groups for organic synthesis.[19] They are generally accessed by oxidation reaction of e.g. aryl ketones[20] or olefins[21], aldol condensation[22], cross metathesis,[23] and acylation of organometallic reagents.[24] They can also be synthesized through catalytic three-component carbonylative cross-coupling reactions.[25] However, the synthesis of α,β-unsaturated ketones from allylic carbonylation with nucleophilic aryl boronic acids has received none attention.



Scheme 1 Pd-Catalyzed carbonylative substitution of allylic substrates.

Initially, the carbonylation of *p*-tolylboronic acid and allyl acetate catalyzed by palladium was investigated (Table 1). Unlike the conventional carbonylative allylic substitution reactions leading to β,γ-unsaturated carboxylic derivatives, the α,β-unsaturated aryl ketone **3a** was obtained in 15% of yield under the catalysis of Pd(OAc)$_2$ and PPh$_3$ in toluene at 120 °C for 12 h in the presence of KOH (Table 1, entry 3). The formation of the conjugated **3a**, rather than the β,γ-unsaturated analogue, suggests that an isomerisation reaction has taken place (vide infra). Different ligands were investigated and PCy$_3$ was found the most efficient ligand.[26] Amongst the solvents screened, dioxane gave the best yield (Table 1, entry 4-8). Various bases were also surveyed (Table 1, entries 9-11). Compared with inorganic bases, the organic ones gave inferior yields.[26] To our delight, a significant increase in yield was observed when the base was changed from K_3PO_4 to its hydrated form (Table 1, entries 12 vs 11). Further experiments revealed that water indeed affected the reaction (Table 1, entries 12-15); when 4 additional equivalents of water were introduced, a good yield of 72% was obtained (Table 1, entry 14). The yield further increased to 81% when a mixture of toluene and dioxane (1:1) was used as the solvent and the amount of water lowered to 2 equivalents (Table 1, entries 15).

Table 1 Optimization of reaction conditons [a]

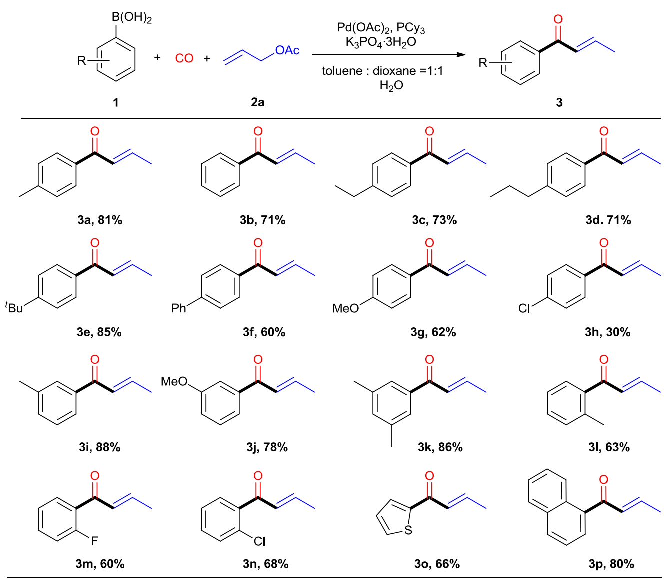


Entry	Cat.	Ligand	Base	solvent	Yield
1	None	None	KOH	$PhCH_3$	None
2	$Pd(OAc)_2$	None	KOH	$PhCH_3$	None
3	$Pd(OAc)_2$	PPh_3	KOH	$PhCH_3$	15%
4	$Pd(OAc)_2$	PCy_3	KOH	$PhCH_3$	30%
5	$Pd(OAc)_2$	PCy_3	KOH	THF	trace
6	$Pd(OAc)_2$	PCy_3	KOH	CH_3CN	trace
7	$Pd(OAc)_2$	PCy_3	KOH	CH_2Cl_2	None
8	$Pd(OAc)_2$	PCy_3	KOH	dioxane	36%
9	$Pd(OAc)_2$	PCy_3	KF $2H_2O$	$PhCH_3$	23%
10	$Pd(OAc)_2$	PCy_3	NaOH	$PhCH_3$	35%
11	$Pd(OAc)_2$	PCy_3	K_3PO_4	$PhCH_3$	30%
12	$Pd(OAc)_2$	PCy_3	K_3PO_4 $3H_2O$	$PhCH_3$	60%
13[b]	$Pd(OAc)_2$	PCy_3	K_3PO_4 $3H_2O$	$PhCH_3$	64 %
14[c]	$Pd(OAc)_2$	PCy_3	K_3PO_4 $3H_2O$	$PhCH_3$	72 %
15[b]	$Pd(OAc)_2$	PCy_3	K_3PO_4 $3H_2O$	$PhCH_3$ / dioxane	81%

[a] Reaction conditions: **1a** (0.5 mmol, 1 equiv), **2a** (1.0 mmol, 2 equiv), base (1 equiv), catalyst (4 mol %) and ligand (10 mol %) in solvent (3 mL) under CO (5 bar) at 120 ℃ for 12 h. [b] 2 equivalents of water were added. [c] 4 equivalents water were added.

Water may play a role in hydrolysing the boronic acid anhydride (i.e. boroxine), present in the substrate or formed during the reaction. In fact, our investigation[26] revealed that the actual reacting species was the boronic acid, whereas the corresponding boroxine displayed an inferior reactivity.[26,27] Due to the commercial aryl boronic acids containing various levels of boroxine, the aryl boronic acids used in this study were recrystallized from CH_3CN and water and dried in air as described in the literature.[26] This procedure afforded "wet" boronic acids and was used directly.

With the optimized reaction conditions in hands, the scope of the carbonylation reaction was then explored. Firstly, various aryl boronic acids were examined for coupling with allyl acetate under CO (5 bar) by using $Pd(OAc)_2/PCy_3$ as catalyst and K_3PO_4 $3H_2O$ as base in the presence of 2 equivlents of water. As summarized in Scheme 2, all the aryl boronic acids examined were successfully converted to the corresponding α,β-unsaturated aryl ketones. However, those bearing electron-donating substituents appear generally to be more reactive than those having electron-withdrawing groups. Furthermore, a hetero aromatic boronic acid was shown to be viable, affording the corresponding α,β-unsaturated aryl ketone **3o** in 66% yield. In addition, naphthalen-2-ylboronic acid and allyl acetate also underwent the carobonylative coupling, giving the α,β-unsaturated ketone **3p** in high yield (Scheme 2).



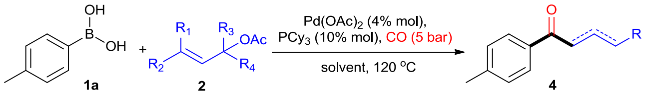
Scheme 2 Carbonylative allylic substitution with aryl boronic acids (see ESI for details).

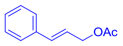
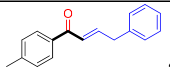
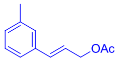
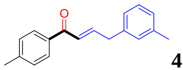
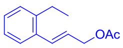
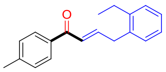
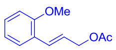
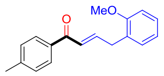
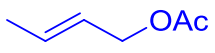
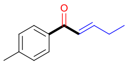
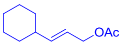
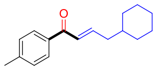
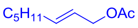
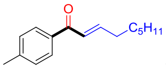
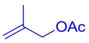
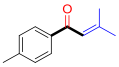
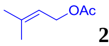
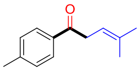
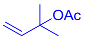
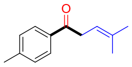
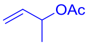
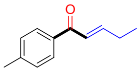
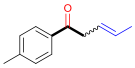
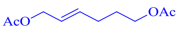
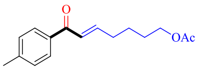
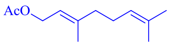
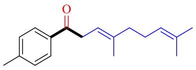
We next extended the reaction to other allyl acetates. Table 2 shows the results of their coupling with *p*-tolylboronic acids under CO. As can be seen, a wide range of unsaturated aryl ketones were obtained in moderate to excellent yields. Insertion of carbon monoxide always occurred at the least substituted terminal allylic carbon to give linear unsaturated aryl ketones rather than branched variants. In comparison with the coupling of **2a**, substituents at the γ-position of allyl acetate rendered the reaction slower, resulting in moderate yields for the α,β-unsaturated ketones **4b-4h**. Allyl acetate with substitute at the β-position was also tolerated and the desired ketone was formed with good yield (entry 8, 84%). It is interesting to note that the α and γ-disubstituted allyl acetates led to the same β,γ-unsaturated aryl ketone **4j** (entries 9 and 10), showing again that the CO insertion prefers the lest substituted allyl carbon. Bifunctional allyl acetates were also studied, and the desired products were obtained in good isolated yields (entry 12 and 13), demonstrating the high chemoselectivity, functional group tolerance and potential application of this allylic carbonylation reaction in the synthesis of complex molecules.[28]

These carbonylative coupling reactions are likely to proceed via the well-known Pd(II)-π-allyl intermediates, followed by reaction with CO and the boronic acids, with the conjugated ketones resulting from a subsequent isomerisation. However, *β,γ*-unsaturated ketones were observed when a terminal carbon of the allyl unit is doubly substituted (Table 2, entries 9, 10 and 13). This suggests that these substituents inhibit the isomerisation.

To gain insight into the reaction mechanism, we attempted to observe possible intemediates. As showed in Scheme 3, when the carbonylative coupling was stoped after 1 h, the *β,γ*-unsaturated ketones were dominant and only a small amount of

Table 2 Carbonylative arylation of allyl acetates with *p*-tolylboronic acid[a]

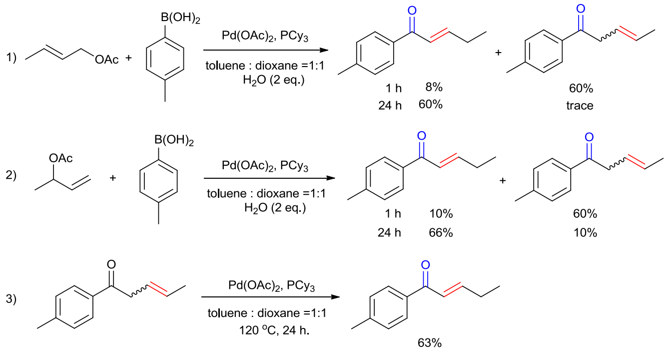


Entry	Substrate	Product	Yield (%)
1[b]	 2b	 4b	55
2[b]	 2c	 4c	56
3[b]	 2d	 4d	45
4[b]	 2e	 4e	65
5[c]	 2f	 4f	60
6[c]	 2g	 4g	56
7[c]	 2h	 4h	43
8[c,d]	 2i	 4i	84
9[c,d]	 2j	 4j	91
10[c,d]	 2k	 4j	84
11[c]	 2l	 4f  4f-a	45 10
12[c]	 2m	 4k	52
13[c]	 2n	 4l	40

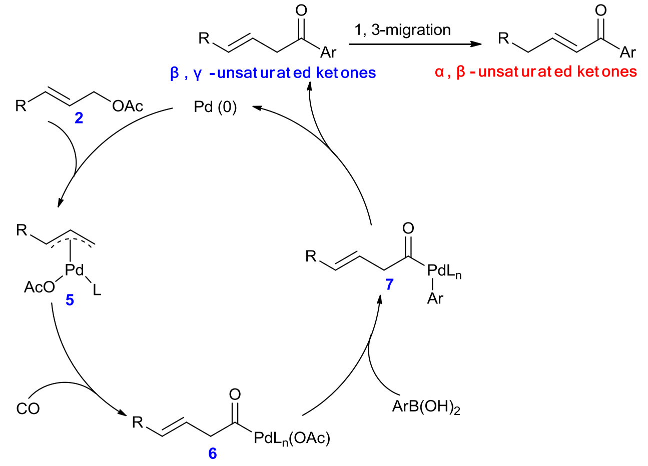
[a] Reaction conditions: **1a** (0.5 mmol, 1 equiv), **2** (1.0 mmol, 2 equiv), H_2O (2 equiv), 24 h. [b] K_3PO_4 (1 equiv) and toluene were used and no water added; [c] $K_3PO_4\ 3H_2O$ (1 equiv), toluene and dioxane (1:1) were used. [d] 12 h. See ESI for more details.

the *α,β*-isomer was formed (eqs 1 and 2). Prolonging the reaction time increased the yield of the later at the expense of the former. This is in support of the *α,β*-isomer being derived from the *β,γ*-species. Further evidence came from the isomerization of isolated **4f-a**, which afforded **4f** in 63% yield (eq 3).

On the basis of the well-known mechanism of allylic substitution and the observations above, a possible mechanism is illustrated in Scheme 4. In the first step, allyl acetate **2** reacts with a Pd(0) species generated in situ, affording a Pd(II)-π-allyl intermediate **5**. Subsequently, insertion of CO into the sterically less-congested Pd(II)-C bond in **5** results in a Pd-acyl complex **6**. Transmetalation between an aryl boronic acid and **6** produces the intermediate **7**, reductive elimination at which then leads to a β,γ-unsaturated ketone. Finally, this species undergoes isomerisation to give the conjugated product. The isomerisation is most likely catalyzed by a palladium species, as it does not take place in the absence of the palladium. When the olefin is doubly substituted at the terminal carbon, addition of palladium to the olefin is expected to be difficult, resulting in a slower isomerisation reaction.



Scheme 3 Observation and isomerisation of intermediates in the carbonylative coupling.



Scheme 4 Proposed mechanism for the carbonylative arylation of allylic acetates.

In conclusion, we have developed the first allylic carbonylation reactions between aryl boronic acids and allylic acetates. The reaction shows broad substrate scope, allowing for the carbonylative arylation of allylic acetates with aryl boronic acids to afford unsaturated aryl ketones. Whilst the preliminary studies show that insertion of CO always occurs at the least substituted terminal allylic carbon, details of the reaction mechanism remain to be delineated.

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Notes and references

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† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

1 (a) J. Tsuji, H. Takahashi and M. Morikawa, *Tetrahedron Letters*, 1965, **6**, 4387-4388; (b) B. M. Trost and T. J. Fullerton, *J. Am. Chem. Soc.*, 1973, **95**, 292-294; (c) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395-422; (d) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921-2944; (e) M. Trost, *Acc. Chem. Res.*, 1980, **13**, 385-393.

2 (a) W.-J. Xiao, G. Vasapollo and H. Alper, *J. Org. Chem.*, 2000, **65**, 4138-4144; (b) T. Satoh, M. Ikeda, Y. Kushino, M. Miura and M. Nomura, *J. Org. Chem.*,1997, **62**, 2662-2664.

3 L. Wu, X. Fang, Q. Liu, R. Jackstell, M. Beller and X.-F. Wu, *ACS Catal*, 2014, **4**, 2977-2989.

4 (a) Y. Koyasu, H. Matsuzaka, Y. Hiroe, Y. Uchida and M. Hidai, *J. Chem. Soc., Chem. Commun.*, 1987, 575-576; (b) S. I. Murahashi, Y. Imada, Y. Taniguchi and S.-y. Higashiura, *Tetrahedron Letters*, 1988, **29,** 4945-4948; (c) H. Matsuzaka, Y. Hiroe, M. Iwasaki, Y. Ishii, Y. Koyasu and M. Hidai, *J. Org. Chem.*, 1988, **53**, 3832-3838; (d) M. Iwasaki, Y. Kobayashi, J. P. Li, H. Matsuzaka, Y. Ishii and M. Hidai, *J. Org. Chem.*, 1991, **56**, 1922-1927; (e) S. Murahashi, Y. Imada, Y. Taniguchi and S. Higashiura, *J. Org. Chem.*, 1993, **58**, 1538-1545.

5 (a) J. Tsuji, K. Sato and H. Okumoto, *J. Org. Chem.*, 1984, **49**, 1341-1344; (b) T.-a. Mitsudo, N. Suzuki, T. Kondo and Y. Watanabe, *J. Org. Chem.*, 1994, **59**, 7759-7765.

6 (a) J. Tsuji, J. Kiji, S. Imamura and M. Morikawa, *J. Am. Chem. Soc.*, 1964, **86**, 4350-4353; (b) T. Okano, N. Okabe and J. Kiji, *B Chem Soc Jpn*, 1992, **65**, 2589-2593; (c) A. Yamamoto, *Bull. Chem Soc Jpn*, 1995, **68**, 433-446; (d) J. Kiji, T. Okano, Y. Higashimae and Y. Fukui, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1029-1031; (e) S. Tommasi, S. Perrone, F. Rosato, A. Salomone and L. Troisi, *Synthesis*, 2012, **3**, 423-430.

7 D. Neibecker, J. Poirier and I. Tkatchenko, *J. Org. Chem.*, 1989, **54**, 2459-2462.

8 S.-I. Murahashi, Y. Imada and K. Nishimura, *Tetrahedron*, 1994, **50**, 453-464.

9 R. Takeuchi and Y. Akiyama, *J. Organomet. Chem.*, 2002, **651**, 137-145.

10 (a) J. F. Knifton, *J. Organomet. Chem.*, 1980, **188**, 223-236; (b) R. Naigre and H. Alper, *J. Mol. Catal. A: Chem.*, 1996, **111**, 11-15; (c) Q. Liu, L. Wu, H. Jiao, X. Fang, R. Jackstell and M. Beller, *Angew. Chem. Int. Ed.*, 2013, **52**, 8064-8068.

11 (a) A. Suzuki, *Acc. Chem. Res.*, 1982, **15**, 178-184; (b) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457-2483

12 For reactions catalyzed by Pd: (a) H. Ohmiya, Y. Makida, T. Tanaka and M. Sawamura, *J. Am. Chem. Soc.*, 2008, **130**, 17276-17277; (b) T. Nishikata and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2009, **131**, 12103-12105; (c) H. Ohmiya, Y. Makida, D. Li, M. Tanabe and M. Sawamura, *J. Am. Chem. Soc.*, 2009, **132**, 879-889; reactions catalyzed by Au: (d) M. D. Levin and F. D. Toste, *Angew. Chem. Int. Ed.*, 2014, **53**, 6211-6215; for reactions catalyzed by Cu: (e) H. Ohmiya, N. Yokokawa and M. Sawamura, *Org. Lett.*, 2010, **12**, 2438-2440; for catalyst-free reactions: (f) A. Scrivanti, V. Beghetto, M. Bertoldini and U. Matteoli, *Eur. J. Org. Chem.*, 2012, 264-268.

13 C. Sik Cho, T. Ohe and S. Uemura, *J. Organomet. Chem.*, 1995, **496**, 221-226.

14 (a) C.-M. Yu, J.-H. Kweon, P.-S. Ho, S.-C. Kang and G. Y. Lee, *Synlett*, 2005, 2631-2634; (b) X.-F. Wu, H. Neumann and M. Beller, *Chem. Asian J.*, 2012, **7**, 282-285.

15 (a) Q. Liu, H. Zhang and A. Lei, *Angew. Chem. Int. Ed.*, 2011, **50**, 10788-10799; (b) (b) X.-F. Wu, H. Neumann and M. Beller, *ChemSusChem*, 2013, **6**, 229-241.

16 (a) X.-F. Wu, H. Neumann and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 4986-5009; (b) S.Sumino, T. Ui, and I. Ryu, *Org. Lett.* 2013, **15**, 3142-3145; (c) B. M. O'Keefe, N. Simmons and S. F. Martin, *Tetrahedron*, 2011, **67**, 4344-4351; (d) H. Li, M. Yang, Y. Qi and J. Xue, *Eur. J. Org. Chem.*, 2011, 2662-2667; (e) Q. Zhou, S. Wei and W. Han, *J. Org. Chem.* 2014, **79**, 1454−1460.

17 (a) Y. Li, D. Xue, C. Wang, Z.-T. Liu and J. Xiao, *Chem. Commun.*, 2012, **48**, 1320-1322; (b) W. Lu, Y. Li, C. Wang, D. Xue, J.-G. Chen and J. Xiao, *Org. Biomol. Chem.*, 2014, **12**, 5243-5249; (c) Y. Li, W. Lu, D. Xue, C. Wang, Z.-T. Liu and J. Xiao, *Synlett*, 2014, **25**, 1097-1100.

18 J. Ruan, X. Li, O. Saidi and J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 2424-2425.

19 C. Thebtaranonth and Y. Thebtaranonth in *The Chemistry of Enones*, Vol. 29 (Eds.: S. Patai, Z. Rappoport), Wiley, New York, 1989, pp. 199-280.

20 K. C. Nicolaou, T. Montagnon, P. S. Baran and Y. L. Zhong, *J. Am. Chem. Soc.*, 2002, **124**, 2245-2258.

21 V. Weidmann and W. Maison, *Synthesis*, 2013, **45**, 2201-2221.

22 R. Mahrwald, *Modern Aldol Reactions 1,2*. Weinheim, Germany: Wiley-VCH. pp. 1218-1223.

23 K. Voigtritter, S. Ghorai and B. H. Lipshutz, *J. Org. Chem.*, 2011, **76**, 4697-4702

24 (a) Y. Obora, M. Nakanishi, M. Tokunaga and Y. Tsuji, *J. Org. Chem.*, 2002, **67**, 5835-5837; (b) Y. Hanzawa, N. Tabuchi and T. Taguchi, *Tetrahedron Lett.*, 1998, **39**, 6249-6252; (c) Y. Obora, Y. Ogawa, Y. Imai, T. Kawamura and Y. Tsuji, *J. Am. Chem. Soc.*, 2001, **123**, 10489-10493; (d) B. A. Trofimov, E. Y. Schmidt, N. V. Zorina, E. V. Ivanova and I. A. Ushakov, *J. Org. Chem.*, 2012, **77**, 6880-6886; (e) M. M. Ahire and S. B. Mhaske, *Angew. Chem. Int. Ed.*, 2014, **53**, 7038-7042.

25 (a) X.-F. Wu, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2010, **49**, 5284-5288; (b) X.-F. Wu, H. Neumann, A. Spannenberg, T. Schulz, H. Jiao and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 14596-14602; (c) J. Schranck, X.-F. Wu, H. Neumann and M. Beller, *Chem. Eur. J.*, 2012, **18**, 4827-4831; (d) X.-F. Wu, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2011, **50**, 11142-11146.

26 For details, please see the ESI.

27 (a) L. J. Gooßen and J. Paetzold, *Adv. Synth. Catal.*, 2004, **346**, 1665-1668; (b) A. Antoft-Finch, T. Blackburn and V. Snieckus, *J. Am. Chem. Soc.*, 2009, **131**, 17750-17752; (c) T. Nishikata, Y. Yamamoto and N. Miyaura, *Angew. Chem. Int. Ed.*, 2003, **42**, 2768-2770.

28 K. Asano and S. Matsubara *J. Am. Chem. Soc*. 2011, **133**, 16711-16713; (b) D. R. Li, A. Murugan and J. R. Falck, *J. Am. Chem. Soc.* 2008, **130**, 46-48