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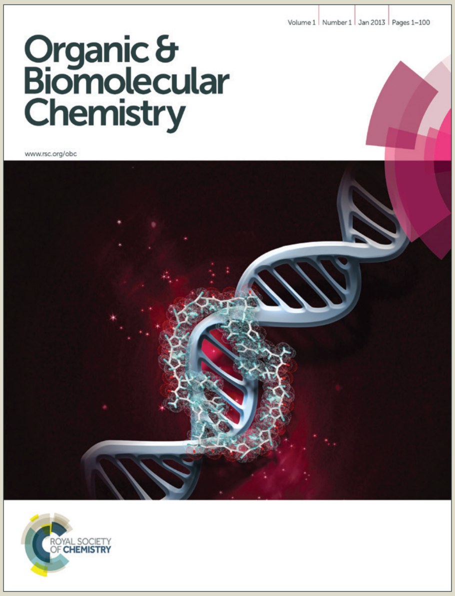

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Chemo-, Regio-, and Stereoselective Heck-Matsuda Arylation of Allylic Alcohols under Mild Conditions

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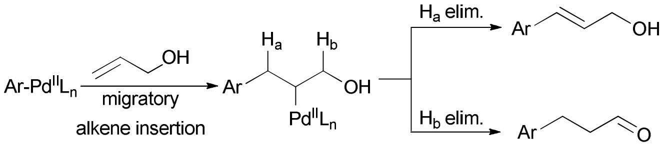
Heck arylation with allylic alcohol is extremely challenging due to chemo-, regio-, and stereoselective scrambling. Here we report a mild protocol for the alcohol selective β- and α-arylation of allylic and cinnamyl alcohols respectively with aryldiazonium salts. The steric and electronic parameters of the alkene play a prominent role in the regioselectivity.

Since its discovery, a significant effort has been dedicated to the development of highly efficient and selective Heck-Mizoroki reaction for the arylation of alkenes.[1] Consequently, it has been recognized as one of the most powerful synthetic tools for C-C bond formation.[2] The extent of research on Heck reaction over the past decades has inculcated the false notion that Heck chemistry is now a mature area. However, the mechanistic understanding of subtle changes that dictate regioselectivity and β-hydride elimination is still limited.[3] Despite its robustness and efficiency, the Heck reaction involving aryl halides and triflates is mainly limited to the activated olefins such as acrylates, styrenes etc. On the contrary, Heck arylation of electronically nonbiased olefin is still challenging due to sluggish alkene insertion and non-specific β-hydride elimination.[4] Similarly, Heck arylation of allylic alcohol is extremely challenging due to chemo-, regio-, and stereochemical scrambling and double bond isomerization (Scheme 1).[5]



Scheme 1. Chemoselectivity in Heck arylation with allylic alcohol.

Mechanistically, after oxidative addition of palladium(0)- to the aryl electrophile, a migratory β-alkene insertion occurs to generate an unstable σ-alkyl-Pd species. Subsequently, random β-hydride elimination (either H_a or H_b, Scheme 1) leads to the formation of a mixture of products, which limits its synthetic utility. Therefore, a mild reaction protocol that controls β-hydride elimination will be extremely useful in regio-, and chemoselective arylation of allylic alcohols. In general, oxidative addition to the aryl electrophiles such as aryl halides, triflates etc. is the rate limiting step, which requires high temperature, ligands, bases etc.[6] The harsh reaction conditions lead to the non-specific arylation, β- hydride elimination, and double bond isomerizations. After the first report by Matsuda and coworkers in 1977, arenediazonium salts have been exploited as reactive aryl halide surrogates in Pd-catalyzed cross-coupling reactions.[7] The Sengupta,[8] Genêt,[9] Correia,[10] Felpin[11] and other groups[12] have contributed substantially to the Heck-Matsuda arylation of olefins. Recently, the Sigman group has accomplished styrenyl selective arylation of electronically nonbiased olefins with aryl diazonium salts.[13] Due to the facile oxidative addition to the aryldiazonium salts, the cross-coupling took place under mild reaction conditions, without any additional ligand or base. Therefore, we decided to optimize Heck-Matsuda arylation of allylic alcohols with aryldiazonium salts. Although, there are few reports of Heck arylation with allyl or crotyl alcohol,[14] but most of them provides a mixture of aldehyde(or ketone) and alcohol. In addition, Heck-Matsuda arylation with β-substituted alkenes especially cinnamyl alcohols is underexplored.[15] A Heck arylation of cinnamyl alcohol with expensive aryl iodide has been reported by the Cacchi group.[16] However high reaction temperature, stoichiometric base, and longer reaction time was required to afford only a low to moderate yield of the desired products. Here we report an alcohol selective, β- and α-arylation of allyl and cinnamyl alcohols respectively using aryldiazonium salts (Scheme 2). From the systematic study, we have observed that besides steric factors, electronic parameters of the alkene also play an important role in regioselectivity.

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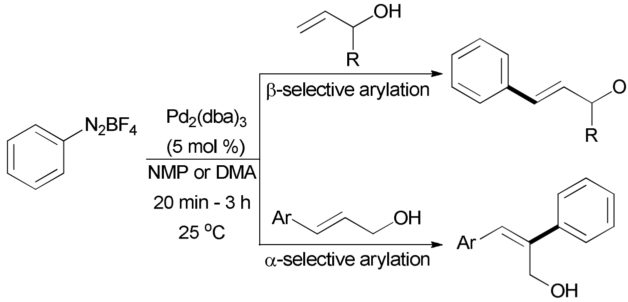
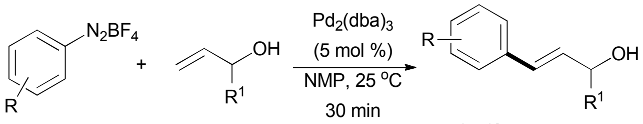
Electronic Supplementary Information (ESI) available: Full experimental details, spectral characterization and ^{1}H, and ^{13}C spectra. See DOI: 10.1039/c000000x/



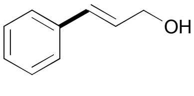
Scheme 2. Regioselective arylation with aryldiazonium salts.

To begin, we tested simple allyl alcohol and phenyldiazonium salt with a catalytic amount of Pd$_2$dba$_3$. A rapid effervescence of nitrogen was observed after the addition of the catalyst in DMF at room temperature. Unfortunately, the yield of the desired cinnamyl alcohol was low (~20 %) although, all starting material was consumed. Next, we screened several solvents which are frequently used in Heck-Matsuda reaction, e.g. MeOH, CH$_3$CN, DMA, NMP etc. It was observed that amide solvents are superior and NMP is the best solvent for this transformation. It was also found that tetrafluoroborate counterion is crucial for the reaction outcome. Presumably, in addition to the improved stability of the diazonium moiety, its non-coordinating nature imparts electrophilicity to the metal center for facile alkene insertion.[17] The amide solvent stabilizes the incipient electrophilic Pd-species which is formed through oxidative addition.[18] All of our screening with simple allyl alcohol afforded only a moderate yield of the desired product (**2a**, **2b**, **Table 1**) and a substantial amount of oligomerization was observed. However, using secondary allylic alcohols, the yield of the arylation product was increased. The arylation with 3-butene-2-ol afforded the corresponding alcohol in good to high yields (**2c-2g**, **Table 1**).

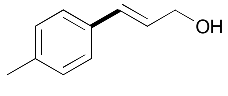
Table 1. Substrate scope with allylic alcohols[a,b]



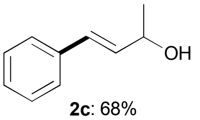
2a-2j



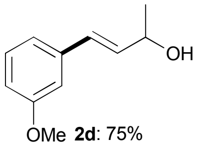
2a: 38%



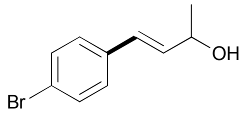
2b: 37%



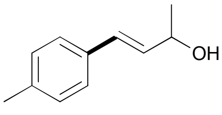
2c: 68%



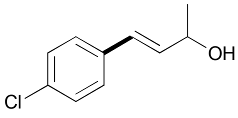
2d: 75%



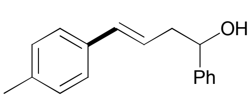
2e: 57%



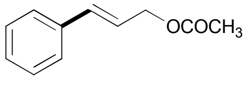
2f: 66%



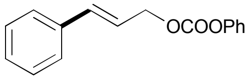
2g: 60%



2h: 42%



2i: 82%

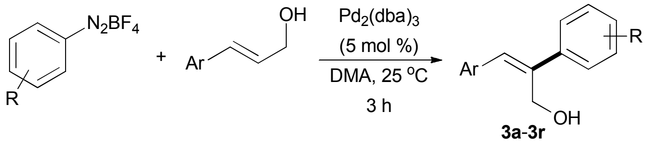


2j: 67%

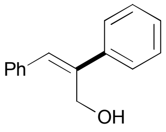
[a] The reaction was performed with 0.2 mmol scale. [b] yield refer to here is the isolated pure product.

A homoallylic alcohol also underwent the Heck-Matsuda reaction affording moderate yield of the arylation product (**2h**, **Table 1**). Interestingly, protected allyl alcohols such as allyl acetate (**2i**, **Table 1**), allyl carbonate (**2j**, **Table 1**) underwent smooth arylation providing β- arylation in high yields. In general, these substrates are unstable under Pd(0)- catalysis e.g. Tsuji-Trost conditions.[19] This demonstrates the mild nature of this reaction conditions.

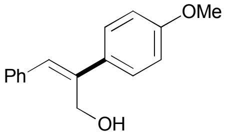
Table 2. Substrate scope with cinnamyl alcohols[a,b]



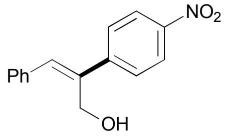
3a-3r



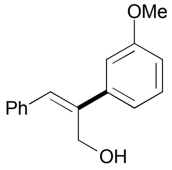
3a: 62%



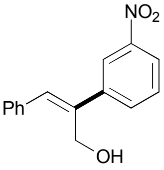
3b: 65%



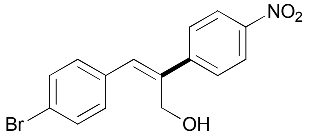
3c: 71%



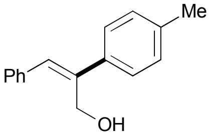
3d: 64%



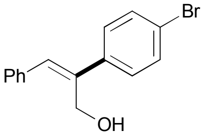
3e: 64%



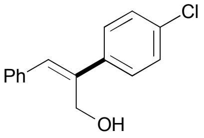
3f: 76%



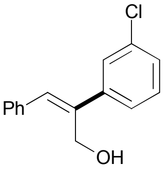
3g: 64%



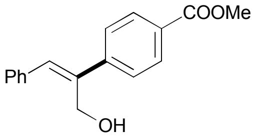
3h: 58%



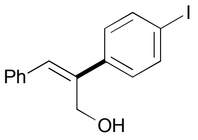
3i: 52%



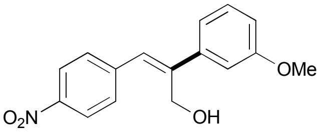
3j: 50%



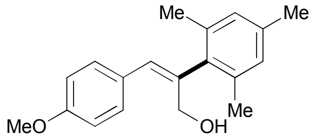
3k: 73%



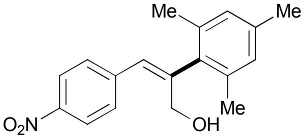
3l: 40%



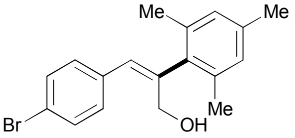
3m: 65%



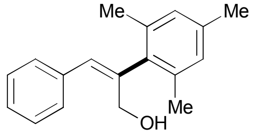
3n: 85%



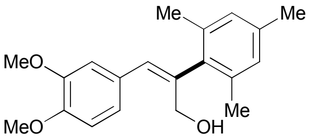
3o: 92%



3p: 90%



3q: 70%

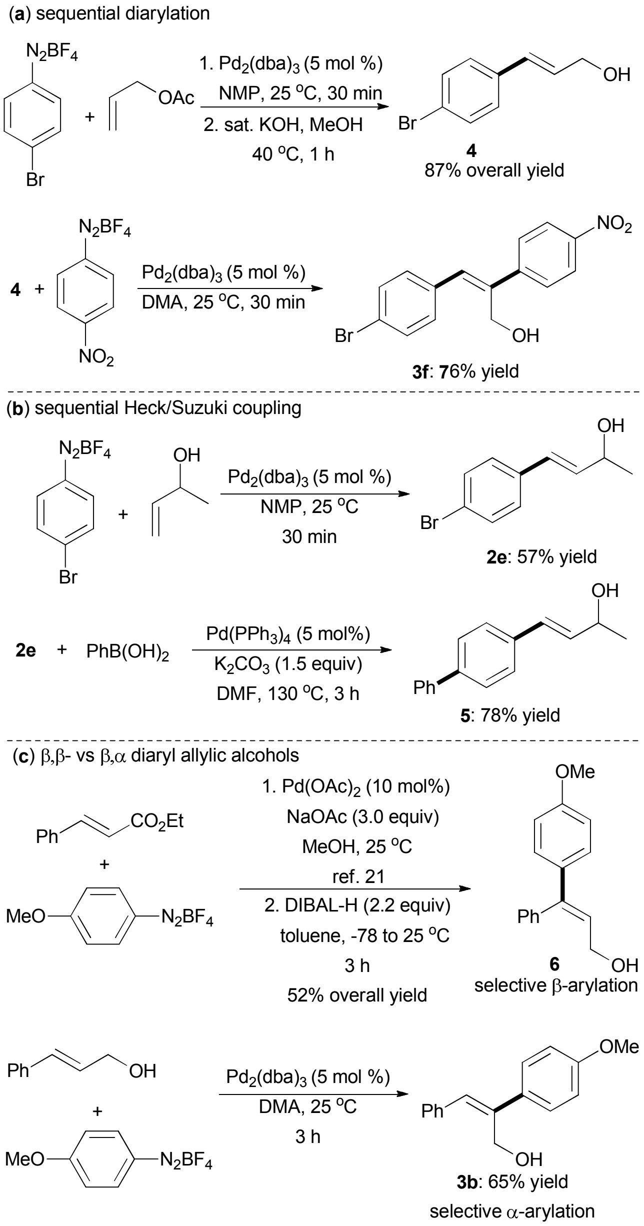


3r: 90%

[a] The reaction was performed with 0.2 mmol scale. [b] yield refer to here is the isolated pure product.

Next we turned our attention to the arylation of cinnamyl alcohol derivatives. From our previous experience with allyl alcohol we realized that cinnamyl alcohol may lead to the selective α- arylation due to steric hindrance with the terminal phenyl group. That said, we investigated analogous Heck-Matsuda reaction with cinnamyl alcohol and arenediazonium tetrafluoroborate. Gratifyingly, a good yield of the arylation product was obtained simply by changing the solvent to DMA. As anticipated, the α- arylation was obtained exclusively to afford (*Z*)-2-3-diarylallylic alcohol. The stereochemistry of the arylation product was assigned by NOESY experiment and comparing with the literature report (see the Supporting Information).[20] A number of cinnamyl alcohol derivatives and arenediazonium salts were examined for the coupling reaction, and a wide range of functional groups such as methoxy (**3b**, **3d, Table 2**), nitro (**3c**, **3e**, **3f, Table 2**), ester (**3k, Table 2**), bromo (**3h, Table 2**), chloro (**3i**, **3j**, **Table 2**), even iodo (**3l, Table 2**), were compatible under the reaction conditions. However, reaction with *p*-iodophenyldiazonium (**3l**) also gave ~10% of the corresponding aldehyde via double bond isomerization. These halogen substituents are useful for further cross-couplings. Gratifyingly, a sterically hindered mesitylenediazonium salt provided excellent yield of the arylation product (**3n-3r, Table 2**). Interestingly, no arylation was observed with cinnamyl acetate which indicates that besides steric effects the free hydroxyl group also may have role in regioselectivity through coordination with the metal center.

Finally, we carried out a sequential Heck-Matsuda arylation to afford (*Z*)-2-3-diarylallylic alcohol. Since allyl alcohol provided low yield, we took allyl acetate for the β- arylation followed by hydrolysis to provide cinnamyl alcohol derivative, **4**. The subsequent α- arylation provided **3f** in 76% yield (**Scheme 3**, **a**). Since halogens are compatible with our reaction conditions, we have demonstrated a sequential Heck/Suzuki coupling reaction. Initially, Heck reaction was performed with 3-butene-2-ol and 4-bromo-phenyldiazonium salt to give **2e**. The product was further cross-coupled with phenyl boronic acid to yield **5** (**Scheme 3**, **b**). We have also showed that synthetically useful β, β- and β, α- diarylallylic alcohol can easily be accessed through the Heck-Matsuda reactions. The arylation of cinnamic ester occurs at the β- position selectively,[21] and the ester is reduced to the corresponding alcohol with DIBAL-H. Whereas, in this present protocol cinnamyl alcohol leads to the α- arylation product selectively (**Scheme 3**, **c**). This phenomenon demonstrates that besides steric parameters, electronic nature of the alkene also plays an important role in regioselective arylation.



Scheme 2. Synthetic manipulations of the present protocol.

Conclusions

We have developed a mild protocol for the alcohol-selective Heck-Matsuda arylation of allylic alcohols in highly regio-, and stereoselective manner. In sharp contrast to the allylic alcohols, a selective α- arylation of the cinnamyl alcohols was observed to afford (*Z*)-2-3-diarylallylic alcohol. Taking the advantage of mild reaction conditions, we have also demonstrated the sequential diarylation and Heck/Suzuki coupling. From the systematic study, we observed that besides steric factors, electronic parameters also play an important role in regioselectivity. Therefore, selective β,β- and β,α- diaryl allylic alcohols have been synthesized from cinnamic ester and cinnamyl alcohol respectively.

Acknowledgements

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Notes and references

1 R. F. Heck and J. P. Nolley, Jr., *J. Org. Chem.*, 1972, **37**, 2320.
2 G. T. Crisp, *Chem. Soc. Rev.*, 1998, **27**, 427; I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009; N. J. Whitcombe, K. K. Hii and S. E. Gibson, *Tetrahedron*, 2001, **57**, 7449; J. Hassan, M. Sevignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359; A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945; F. Alonso, I. P. Beletskaya and M. Yus, *Tetrahedron*, 2005, **61**, 11771; K. Koehler, S. S. Proeckl and W. Kleist, *Curr. Org. Chem.*, 2006, **10**, 1585; N. T. S. Phan, M. Van Der Sluys and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 609; A. F. Schmidt, A. Al Halaiqa and V. V. Smirnov, *Synlett*, 2006, 2861.
3 M. S. Sigman and E. W. Werner, *Acc. Chem. Res.*, 2012, **45**, 874.
4 J. H. Delcamp, A. P. Brucks and M. C. White, *J. Am. Chem. Soc.*, 2008, **130**, 11270.
5 J. Muzart, *Tetrahedron*, 2005, **61**, 4179.
6 R. Benhaddou, S. Czernecki, G. Ville and A. Zegar, *Organometallics*, 1988, **7**, 2435; P. Surawatanawong and M. B. Hall, *Organometallics*, 2008, **27**, 6222; R. Gruber and P. Fleurat-Lessard, *Organometallics*, 2014, **33**, 1996.
7 K. Kikukawa and T. Matsuda, *Chem. Lett.*, 1977, 159; K. Kikukawa, K. Nagira, F. Wada and T. Matsuda, *Tetrahedron*, 1981, **37**, 31; J. G. Taylor, A. V. Moro and C. R. D. Correia, *Eur. J. Org. Chem.*, 2011, 1403; F.-X. Felpin, L. Nassar-Hardy, F. Le Callonnec and E. Fouquet, *Tetrahedron*, 2011, **67**, 2815.
8. S. Sengupta and S. Bhattacharya, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1943; S. Sengupta and S. Bhattacharyya, *Tetrahedron Lett.*, 1995, **36**, 4475; G. Mehta and S. Sengupta, *Tetrahedron Lett.*, 1996, **37**, 8625; S. Sengupta, S. K. Sadhukhan and S. Bhattacharyya, *Tetrahedron*, 1997, **53**, 2213; S. Sengupta, S. Bhattacharyya and S. Kumar Sadhukhan, *J. Chem. Soc., Perkin Trans. 1*, 1998, 275; S. Sengupta and S. K. Sadhukhan, *Tetrahedron Lett.*, 1998, **39**, 715; S. Sengupta, S. K. Sadhukhan, S. Bhattacharyya and J. Guha, *J. Chem. Soc., Perkin Trans. 1*, 1998, 407.
9 H. Brunner, N. Le Cousturier de Courcy and J.-P. Genet, *Tetrahedron Lett.*, 1999, **40**, 4815; H. Brunner, N. Le Cousturier de Courcy and J.-P. Genêt, *Synlett*, 2000, 201; S. Darses, M. Pucheault and J.-P. Genêt, *Eur. J. Org. Chem.*, 2001, 1121.
10 E. A. Severino and C. R. D. Correia, *Org. Lett.*, 2000, **2**, 3039; C. C. Oliveira, E. A. F. dos Santos, J. H. B. Nunes and C. R. D. Correia, *J. Org. Chem.*, 2012, **77**, 8182; J. G. Taylor and C. R. D. Correia, *J. Org. Chem.*, 2012, **77**, 5220; D. A. Barancelli, A. G. Salles, J. G. Taylor and C. R. D. Correia, *Org. Lett.*, 2012, **14**, 6036; C. R. D. Correia, C. C. Oliveira, A. G. Salles and E. A. F. Santos, *Tetrahedron Lett.*, 2012, **53**, 3325; C. C. Oliveira, R. A. Angnes and C. R. D. Correia, *J. Org. Chem.*, 2013, **78**, 4373; R. A. Angnes, J. M. Oliveira, C. C. Oliveira, N. C. Martins and C. R. D. Correia, *Chem. - Eur. J.*, 2014, **20**, 13117; C. C. Oliveira, M. V. Marques, M. N. Godoi, T. Regiani, V. G. Santos, E. A. F. d. Santos, M. N. Eberlin, M. M. Sá and C. R. D. Correia, *Org. Lett.*, 2014, **16**, 5180.
11 F.-X. Felpin and E. Fouquet, *Adv. Synth. Catal.*, 2008, **350**, 863; F.-X. Felpin, E. Fouquet and C. Zakri, *Adv. Synth. Catal.*, 2008, **350**, 2559; F.-X. Felpin, E. Fouquet and C. Zakri, *Adv. Synth. Catal.*, 2008, **350**, 2559; F.-X. Felpin, K. Miqueu, J.-M. Sotiropoulos, E. Fouquet, O. Ibarguren and J. Laudien, *Chem. - Eur. J.*, 2010, **16**, 5191; F. Le Callonnec, E. Fouquet and F.-X. Felpin, *Org. Lett.*, 2011, **13**, 2646; L. Nassar-Hardy, S. Fabre, A. M. Amer, E. Fouquet and F.-X. Felpin, *Tetrahedron Lett.*, 2012, **53**, 338; C. Rossy, E. Fouquet and F.-X. Felpin, *Synthesis*, 2012, **44**, 37; N. Susperregui, K. Miqueu, J.-M. Sotiropoulos, F. Le Callonnec, E. Fouquet and F.-X. Felpin, *Chem. - Eur. J.*, 2012, **18**, 7210.
12 J. Salabert, R. M. Sebastian, A. Vallribera, A. Roglans and C. Nájera, *Tetrahedron*, 2011, **67**, 8659; R. G. Kalkhambkar and K. K. Laali, *Tetrahedron Lett.*, 2011, **52**, 1733; T. Nakano, M. Miyahara, T. Itoh and A. Kamimura, *Eur. J. Org. Chem.*, 2012, **2012**, 2161; D. S. Gaikwad and D. M. Pore, *Synlett*, 2012, **23**, 2631; I. Penafiel, I. M. Pastor and M. Yus, *Eur. J. Org. Chem.*, 2012, **2012**, 3151; J. Salabert, R. M. Sebastian, A. Vallribera, J. F. Civicos and C. Nájera, *Tetrahedron*, 2013, **69**, 2655; M. Gholinejad, *Appl. Organomet. Chem.*, 2013, **27**, 19; B. Schmidt, N. Elizarov, R. Berger and F. Hoelter, *Org. Biomol. Chem.*, 2013, **11**, 3674; B. Schmidt, N. Elizarov, R. Berger and M. H. Petersen, *Synthesis*, 2013, **45**, 1174.
13 E. W. Werner and M. S. Sigman, *J. Am. Chem. Soc.*, 2011, **133**, 9692.
14 J. B. Melpolder and R. F. Heck, *J. Org. Chem.*, 1976, **41**, 265; A. J. Chalk and S. A. Magennis, *J. Org. Chem.*, 1976, **41**, 273; T. Jeffery, *J. Chem. Soc., Chem. Commun.*, 1984, 1287; S. Bouquillon, B. Ganchegui, B. Estrine, F. Henin and J. Muzart, *J. Organomet. Chem.*, 2001, **634**, 153; J. Masllorens, S. Bouquillon, A. Roglans, F. Henin and J. Muzart, *J. Organomet. Chem.*, 2005, **690**, 3822; J. Mo, L. Xu, J. Ruan, S. Liu and J. Xiao, *Chem. Commun.*, 2006, 3591; B. Schmidt, F. Hoelter, A. Kelling and U. Schilde, *J. Org. Chem.*, 2011, **76**, 3357; P. Colbon, J. Ruan, M. Purdie, K. Mulholland and J. Xiao, *Org. Lett.*, 2011, **13**, 5456; E. W. Werner, T.-S. Mei, A. J. Burckle and M. S. Sigman, *Science*, 2012, **338**, 1455.
15 L. Bagnell, U. Kreher and C. R. Strauss, *Chem. Commun.*, 2001, 29; V. Calò, A. Nacci, A. Monopoli and V. Ferola, *J. Org. Chem.*, 2007, **72**, 2596.
16 I. Ambrogio, S. Cacchi, G. Fabrizi, A. Goggiamani and S. Sgalla, *Synlett*, 2009, 620.
17 H. von Schenck, S. Stroemberg, K. Zetterberg, M. Ludwig, B. Åkermark and M. Svensson, *Organometallics*, 2001, **20**, 2813; H. von Schenck, B. Kermark and M. Svensson, *Organometallics*, 2002, **21**, 2248; L. Xu, M. J. Hilton, X. Zhang, P.-O. Norrby, Y.-D. Wu, M. S. Sigman and O. Wiest, *J. Am. Chem. Soc.*, 2014, **136**, 1960.
18 B. B. Wayland and R. F. Schramm, *Inorg. Chem.*, 1969, **8**, 971; A. C. Bueno, A. O. de Souza and E. V. Gusevskaya, *Adv. Synth. Catal.*, 2009, **351**, 2491.
19 B. M. Trost and T. J. Fullerton, *J. Amer. Chem. Soc.*, 1973, **95**, 292; B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921.
20 J. K. F. Geirsson, B. O. Gudmundsson, J. F. Johannesdottir, J. T. Njardarson and V. G. Skulason, *Acta Chem. Scand.*, 1995, **49**, 423; J. Panteleev, R. Y. Huang, E. K. J. Lui and M. Lautens, *Org. Lett.*, 2011, **13**, 5314.
21 J. C. Pastre and C. R. D. Correia, *Adv. Synth. Catal.*, 2009, **351**, 1217.