

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7176

www.rsc.org/obc

PAPER

Rhodium-catalyzed C–H activation and conjugate addition under mild conditions†

Luo Yang,‡ Camille A. Correia and Chao-Jun Li*

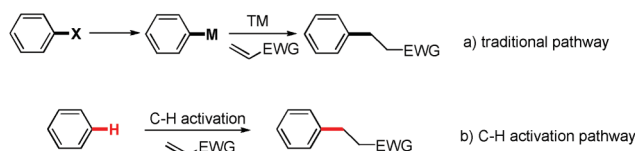
Received 6th May 2011, Accepted 24th June 2011

DOI: 10.1039/c1ob05993a

An efficient rhodium^{III}-catalyzed C–H activation and subsequent conjugate addition was achieved under mild conditions. The reaction utilized inert arenes to replace stoichiometric organometallic reagents and can tolerate various functional groups as well as air and water.

Introduction

The conjugate addition of organometallic reagents to α,β -unsaturated carbonyl compounds is one of the most useful methods for the formation of C–C bonds.¹ It generally requires the pre-generation of organometallic reagents from stoichiometric aryl halides,² which lowers the synthetic efficiency and produces tremendous waste at the same time (Scheme 1, route a). With the recent great advances in catalytic arene C–H activations,³ the generation of organometallic reagents *in situ* from C–H activation and subsequent conjugate addition with α,β -unsaturated carbonyl compounds would be an ideal pathway (Scheme 1, route b). Pioneered by Murai's research,⁴ low valent transition metal-catalyzed hydroarylation of alkenes has been developed into an efficient strategy for alkylarene synthesis;⁵ however, relatively high temperatures (above 120 °C) are necessary and only terminal alkenes can be applied. Recently, Zhao and co-workers reported the rhodium(I)-catalyzed activation of electron-deficient perfluoroarenes and its application to conjugate addition without an *ortho* directing group.⁶ *Herein we report an unprecedented rhodium(III)-catalyzed directed arene C–H activation and subsequent conjugate addition under very mild reaction conditions.*



Scheme 1 Traditional pathway vs. C–H activation pathway in the conjugate addition.

Rhodium-catalyzed conjugate addition reactions of organoboron, zinc, tin, silicon, bismuth, lead, titanium

Department of Chemistry, McGill University, Montreal, QC, Canada H3A 2K6. E-mail: cj.li@mcgill.ca; Fax: +01-514-398-8457; Tel: +01-514-398-3797

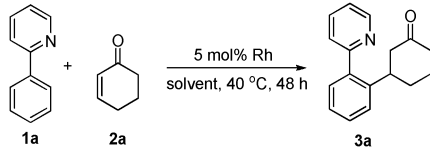
† Electronic supplementary information (ESI) available: Experimental details and spectral data. See DOI: 10.1039/c1ob05993a

‡ Present address: College of Chemistry, Xiangtan University, Xiangtan, 411105, China.

and zirconium reagents with α,β -unsaturated carbonyl compounds proceeded under mild conditions with high regio- and stereoselectivities.^{1,9} In these reactions, the reactive organorhodium species are generated by the transmetalation from the organoboron (and organometallic) reagents.^{1b,7} Instead of using organometallic reagents, we envisioned that this active organorhodium species could also be generated directly from the inert C–H bonds. While relatively high temperature was required to realize the *ortho* group-directed oxidative addition of a low valent transition metal to the aromatic C–H bonds in the Murai reaction,^{4,5} much milder conditions are expected by generation of organorhodium species through electrophilic substitution of a high valent rhodium catalyst.⁸

Results and discussion

With the above analysis in mind, we first examined the reaction of 2-phenylpyridine (**1a**) and 2-cyclohexenone (**2a**) catalyzed by [CODRhCl]₂ and [Cp*RhCl]₂ (Table 1, entry 1) based on our early work on rhodium-catalyzed conjugate additions with organometallic compounds in air and water;⁹ however, the expected conjugate addition product (**3a**) was not detected either by crude ¹H NMR or GC-MS analysis. To increase the activity of the rhodium catalyst, different silver salts were tested as the chloride abstractor for [Cp*RhCl]₂ (entries 2–4). The yield increased dramatically to 90% on addition of AgOTf. While AgPF₆ was also effective, AgSbF₆ was found to be the best, and the NMR yield of the conjugate addition product **3a** was increased to 94%. These positive results further prompted us to use the pre-purified (CH₃CN)₃Cp*Rh(SbF₆)₂ (Rh*, Cp* = pentamethylcyclopentadienyl) as the catalyst directly, leading to almost quantitative formation of product **3a** (entry 5). This C–H activation and conjugate addition can be performed not only in lower polarity solvent such as CH₂Cl₂, DCE, toluene and chlorobenzene but also in much more polar THF and even a protic solvent, *tert*-butanol (entries 5–10). It is worth noting that this reaction can also be performed at room temperature with comparable yields after a longer reaction time (entry 11). Furthermore, the reaction was not sensitive to either water or O₂, and a similar yield was

Table 1 Optimization of the C–H activation and conjugate addition^a


Entry	Rh (mol%)	Additive	Solvent	Yield ^b (%)
1	[Cp*RhCl ₂] ₂ (2.5)	—	CH ₂ Cl ₂	0
2	[Cp*RhCl ₂] ₂ (2.5)	AgOTf	CH ₂ Cl ₂	90
3	[Cp*RhCl ₂] ₂ (2.5)	AgPF ₆	CH ₂ Cl ₂	70
4	[Cp*RhCl ₂] ₂ (2.5)	AgSbF ₆	CH ₂ Cl ₂	94
5	(CH ₃ CN) ₃ Cp*Rh(SbF ₆) ₂ (5)	—	CH ₂ Cl ₂	97
6	(CH ₃ CN) ₃ Cp*Rh(SbF ₆) ₂ (5)	—	DCE	96
7	(CH ₃ CN) ₃ Cp*Rh(SbF ₆) ₂ (5)	—	Toluene	66
8	(CH ₃ CN) ₃ Cp*Rh(SbF ₆) ₂ (5)	—	PhCl	83
9	(CH ₃ CN) ₃ Cp*Rh(SbF ₆) ₂ (5)	—	THF	89 ^c
10	(CH ₃ CN) ₃ Cp*Rh(SbF ₆) ₂ (5)	—	^t BuOH	63
11	(CH ₃ CN) ₃ Cp*Rh(SbF ₆) ₂ (5)	—	CH ₂ Cl ₂	93 ^d
12	(CH ₃ CN) ₃ Cp*Rh(SbF ₆) ₂ (5)	H ₂ O (20 μL)	CH ₂ Cl ₂	92 ^e
13	[Cp*RuCl ₂] ₂ (2.5)	AgSbF ₆	CH ₂ Cl ₂	0
14	Pd(TFA) ₂ (5.0)	—	CH ₂ Cl ₂	0
15	Cu(OTf) ₂ (5.0)	—	CH ₂ Cl ₂	0
16	In(OTf) ₃ (5.0)	—	CH ₂ Cl ₂	0

^a Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Rh], additives (10 mol%), CH₂Cl₂ (0.5 mL), reacted for 48 h at 40 °C under argon, unless otherwise noted.^b ¹H NMR yields. ^c Reacted for 24 h. ^d Reacted at r.t. for 10 days. ^e Reacted for 72 h under air.

obtained when the reaction was performed in the presence of water and under air atmosphere (entry 12). Under similar conditions, [Cp*RuCl₂]₂/AgSbF₆, Pd(TFA)₂, Cu(OTf)₂ and In(OTf)₃ were all found to be ineffective catalysts, which differentiated this C–H activation and conjugate addition from the normal Lewis acid-promoted Friedel–Crafts reaction. The Rh* catalyst played a unique role in the activation of both the inert C–H bonds and 2-cyclohexenone (**2a**).

Under the optimized conditions, the substrate scope of this novel C–H activation and conjugate addition was explored. As shown by the results in Table 2, all the 2-phenylpyridine analogs tested (**1a–1i**) reacted with 2-cyclohexenone (**2a**) smoothly to produce the corresponding conjugate addition product efficiently, regardless of the electronic nature of the substituents. The influence of substituents at different positions of the phenyl ring was also examined. The *ortho*-methyl substrate **1c** reacted with 2-cyclohexenone in high yield. 2-β-Naphthylpyridine **1f** was also applicable to this reaction and only the less hindered C–H bond was activated to give the corresponding conjugate addition product. Substituted by an electron withdrawing acetyl group, the substrate **1i** was also reactive, which further differentiates this reaction from the classical Friedel–Crafts reaction. However, the C–H activation and conjugate addition process cannot stop at the mono-alkylation step and almost a quantitative yield of the corresponding *di*-alkylation product **3i** was obtained.

Next, the use of various nitrogen-containing heterocyclic substituents as directing groups was investigated (Table 3). Pyridinyl groups with a methyl substituent at C-3 (**1j**, **1k**) or C-4 (**1l**) showed good reactivity. It is worth noting that the 2-phenylpyridine analog **1k** bearing a free hydroxyl group reacted with 2-cyclohexenone to afford **3k** in 88% yield. Besides the pyridinyl group, other nitrogen-containing heterocyclic substituents such as quinolinyl, pyrimidinyl and pyrazolyl can also act as the directing group; the

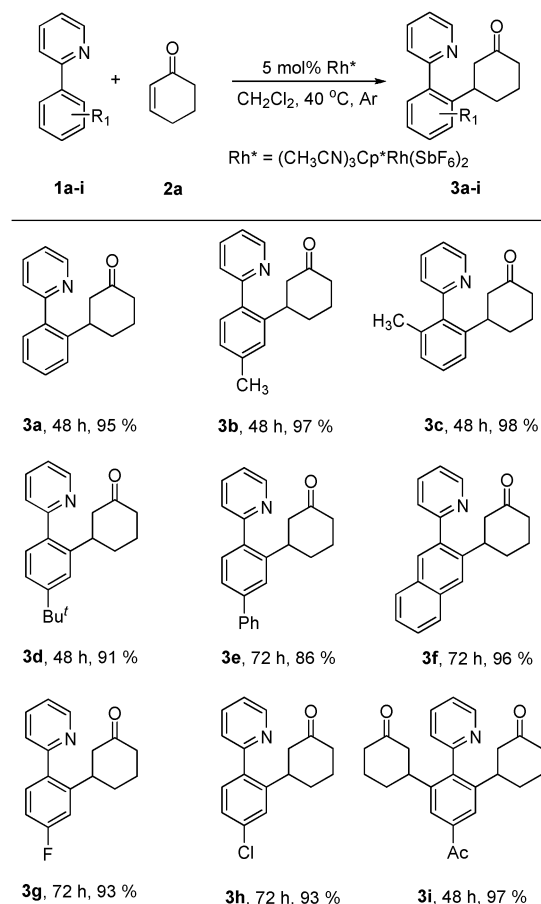
corresponding conjugate addition products **3m–3o** were obtained in medium to high yields when reacted at a slightly higher temperature.

Then, we explored the substrate scope of the Michael acceptor in this C–H activation and conjugate addition process (Table 4). Besides 2-cyclohexenone (**2a**), the reaction of 2-phenylpyridine with 2-cyclopentenone (**2b**) and *trans*-4-hexen-3-one (**2c**) proceeded smoothly to afford **3p** and **3q**, respectively, in good yields. α,β-Unsaturated aldehydes such as *trans*-2-pentenal (**2d**) and cinnaldehyde derivatives (**2e–2h**) were found to be good substrates in this reaction. When the cinnaldehyde was substituted by an electron withdrawing nitro or ethoxyl carbonyl group (**2g–h**), a higher yield was obtained due to their stronger electrophilicity.

A tentative mechanism to rationalize this novel rhodium-catalyzed C–H activation and subsequent conjugate addition is illustrated in Scheme 2. First, the coordination of rhodium catalyst (Rh*) to 2-phenylpyridine and subsequent electrophilic substitution⁸ generates the arylrhodium complex **5**, releasing one equivalent of proton at the same time. Then, the carbon–carbon double bond of 2-cyclohexenone (**2a**) coordinates to the arylrhodium complex **5** to produce arylrhodium complex **6**, which is followed by the 1,4-conjugate addition of the arylrhodium species to the activated double bond to yield the rhodium-oxa-π-allyl species **7**.^{1b,7} Protonolysis of **7** releases the conjugate addition product and regenerates the rhodium catalyst (Rh*).

Conclusions

In summary, we have developed an efficient rhodium-catalyzed C–H activation and subsequent conjugate addition under mild conditions. Unlike the previous rhodium catalyzed conjugate addition, the current process does not require pre-generation of a stoichiometric quantity of organometallic reagents. The reaction

Table 2 The reaction of 2-phenylpyridine analogs with 2-cyclohexenone^a

^a Conditions: **1a-i** (0.2 mmol), **2a** (0.4 mmol), $(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (Rh^* , 5 mol%, 0.01 mmol), CH_2Cl_2 (1.0 mL), reacted at 40 °C under argon, unless otherwise noted. The yield of isolated product is reported.

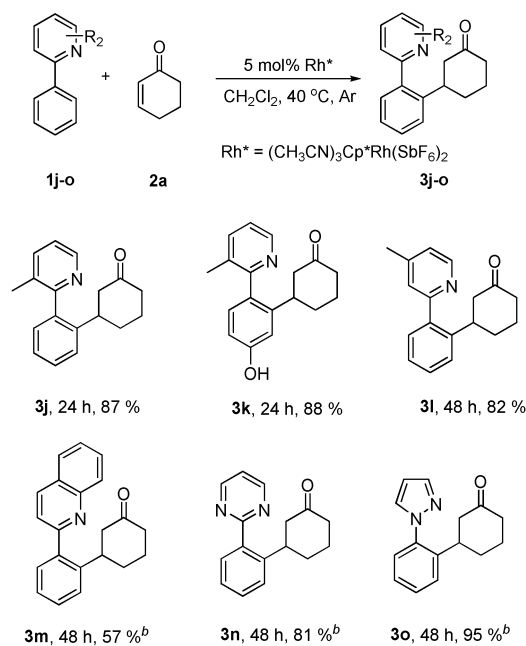
can tolerate a wide range of functional groups such as ketones, esters, halide, nitro, and unprotected hydroxyl groups as well as air and water. The scope, mechanism, application and asymmetric introduction of this novel reaction are under investigation.

Experimental section

General experimental procedure

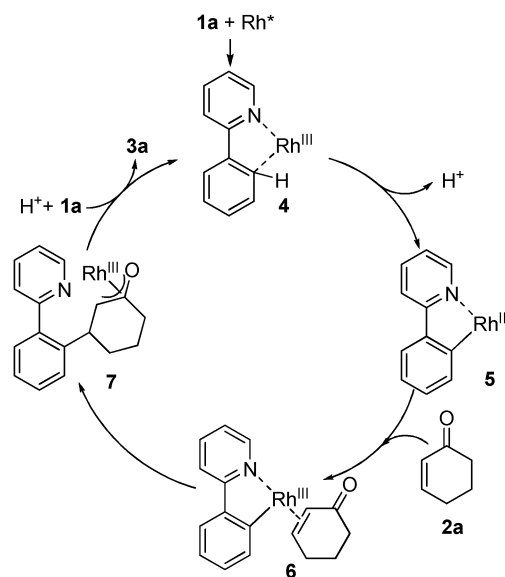
A general experimental procedure is described as following: an oven-dried reaction vessel was charged with $(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (Rh^* , 8.4 mg, 5 mol%, 0.01 mmol), CH_2Cl_2 (1 mL, dried by CaH_2), 2-phenylpyridine (**1a**, 31 mg, 0.2 mmol) and 2-cyclohexenone (**2a**, 0.4 mmol, 38.4 mg, 40.2 μ L) under argon. The vessel was sealed and heated at 40 °C (oil bath temperature) for 48 h. The resulting mixture was cooled to room temperature, filtered through a short silica gel pad, transferred to silica gel column directly and eluted with hexanes and ethyl acetate (2:1) to give products **3a** (47.6 mg, 95% yield) as a light yellow solid.

3a. 1H NMR (500 MHz, $CDCl_3$, TMS) δ 8.67 (ddd, J = 1.0, 2.0, 5.0 Hz, 1H), 7.76 (td, J = 2.0, 8.0 Hz, 1H), 7.40–7.44 (m, 2H),

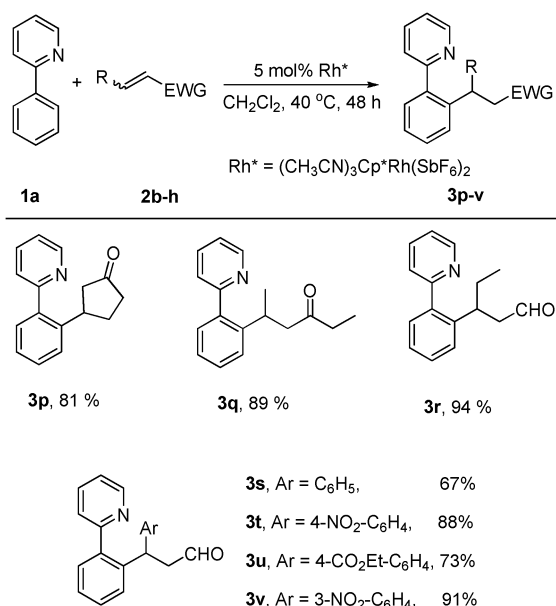
Table 3 Pyridine analogs as the directing groups in the C–H activation and conjugate addition^a

^a Conditions: **1j-o** (0.2 mmol), **2a** (0.4 mmol), $(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (Rh^* , 5 mol%, 0.01 mmol), CH_2Cl_2 (1.0 mL), reacted at 40 °C under argon, unless otherwise noted. The yield of isolated product is reported.

^b Reacted at 50 °C.

**Scheme 2** Tentative mechanism for the C–H activation and subsequent conjugate addition.

7.26–7.36 (m, 4H), 3.27–3.33 (m, 1H), 2.53 (d, J = 8.5 Hz, 2H), 2.30–2.39 (m, 2H), 2.04–2.09 (m, 2H), 1.79–1.87 (m, 1H), 1.53–1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS) δ 211.4, 159.8, 149.2, 142.4, 140.0, 136.8, 130.4, 129.0, 126.6, 126.3, 124.4, 122.2, 49.1, 41.4, 40.3, 33.0, 25.7. HRMS (ESI) m/z : $[M + H]^+$ calc'd for $C_{17}H_{18}ON$, 252.1383; found: 252.1376.

Table 4 The substrate scope of the Michael acceptor in the C–H activation and conjugate addition^a

^a Conditions: **1j-o** (0.2 mmol), **2a** (0.4 mmol), (CH₃CN)₃Cp^{*}Rh(SbF₆)₂ (Rh^{*}, 5 mol%, 0.01 mmol), CH₂Cl₂ (1.0 mL), reacted at 40 °C for 48 h under argon, unless otherwise noted. The yield of isolated product is reported.

Acknowledgements

We are grateful to the Canada Research Chair (Tier I) and E. B. Eddy Foundations (to CJL), CFI, NSERC and the FQRNT Center for Green Chemistry and Catalysis for partial support of our research.

Notes and references

- For reviews, see: (a) J. D. Hargrave, J. C. Allen and C. G. Frost, *Chem.-Asian J.*, 2010, **5**, 386–396; (b) K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169–196; (c) T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829–2844; (d) N. Krause and A. Hoffmann-Roder, *Synthesis*, 2001, 171–196; (e) M. P. Sibi and S. Manyem, *Tetrahedron*, 2000, **56**, 8033–8061.
- A. R. Katritzky, R. J. K. Taylor, *Comprehensive Organic Functional Group Transformations II*, Elsevier, Dordrecht, 2004, Chapter 2, pp. 561–593.
- For representative reviews, see: (a) F. Pogan and P. H. Dixneuf, *Adv. Synth. Catal.*, 2009, **351**, 1737–1743; (b) T. Naota, H. Takaya and S. I. Murahashi, *Chem. Rev.*, 1998, **98**, 2599–2660; (c) G. Dyker, *Angew. Chem.*, 1999, **111**, 1808–1822, (*Angew. Chem., Int. Ed.*, 1999, **38**, 1698–1712); (d) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633–639; (e) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731–1770; (f) R. H. Crabtree, *J. Organomet. Chem.*, 2004, **689**, 4083–4091; (g) K. Godula and D. Sames, *Science*, 2006, **312**, 67–72; (h) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (i) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318–5365; (j) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (k) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013–1025; (l) B.-J. Li, S. Yang and Z.-J. Shi, *Synlett*, 2008, 949–957; (m) M. M. Diaz-Requejo and P. J. Pérez, *Chem. Rev.*, 2008, **108**, 3379–3394; (n) X. Chen, K. M. Engle, D. H. Wang and J. Q. Yu, *Angew. Chem.*, 2009, **121**, 5196–5217, (*Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115); (o) C. Copéret, *Chem. Rev.*, 2010, **110**, 656–680; (p) I. Mkhaid, J. Barnard, T. Marder, J. Murphy and J. Hartwig, *Chem. Rev.*, 2010, **110**, 890–931; (q) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879–2932; (r) F. Kakiuchi and S. Murai, *Acc. Chem. Res.*, 2002, **35**, 826–834; (s) *Activation and Functionalization of C–H Bond*, K. I. Goldberg, A. S. Goldman, ed.; ACS Symposium Series 885, 2004.
- S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, *Nature*, 1993, **366**, 529–531.
- (a) F. Kakiuchi and S. Murai, *Acc. Chem. Res.*, 2002, **35**, 826–834; (b) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, *Pure Appl. Chem.*, 1994, **66**, 1527–1534; (c) S. Murai, F. Kakiuchi and N. Chatani, *Pure Appl. Chem.*, 1997, **69**, 589–594; (d) B. M. Trost, K. Imai and I. W. Davies, *J. Am. Chem. Soc.*, 1995, **117**, 5371–5372; (e) C.-H. Jun, J.-B. Hong, Y.-H. Kim and K.-Y. Chung, *Angew. Chem., Int. Ed.*, 2000, **39**, 3440–3442; (f) S.-G. Lim, J.-A. Alm and C.-H. Jun, *Org. Lett.*, 2004, **6**, 4687–4690.
- (a) Z.-M. Sun, J. Zhang, R. S. Manan and P. Zhao, *J. Am. Chem. Soc.*, 2010, **132**, 6936–6937; (b) Z.-M. Sun and P. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 6727–6730.
- T. Hayashi, M. Takahashi, Y. Takaya and M. Ogasawara, *J. Am. Chem. Soc.*, 2002, **124**, 5052–5058.
- (a) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908–6909; (b) D. J. Schipper, M. Hutchinson and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6910–6911; (c) A. S. Tsai, M. E. Tauchert, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 1248–1250; (d) M. P. Huestis, L. Chan, D. R. Stuart and K. Fagnou, *Angew. Chem., Int. Ed.*, 2011, **50**, 1338–1339; (e) Y. Li, W.-H. Wang, W.-P. Huang, X.-S. Zhang, K. Chen and Z.-J. Shi, *Angew. Chem.*, 2011, **123**, 2163–2167; (f) L. Yang, C. A. Correia and C.-J. Li, *Adv. Synth. Catal.*, 2011, **353**, 1269–1273.
- (a) C.-J. Li, *Acc. Chem. Res.*, 2002, **35**, 533–538; (b) S. Venkatraman and C.-J. Li, *Tetrahedron Lett.*, 2001, **42**, 781–784; (c) S. Venkatraman, Y. Meng and C.-J. Li, *Tetrahedron Lett.*, 2001, **42**, 4459–4462; (d) T. Huang, S. Venkatraman, D. Wang and C.-J. Li, *J. Am. Chem. Soc.*, 2001, **123**, 7451–7452; (e) T. Huang and C.-J. Li, *Org. Lett.*, 2001, **3**, 2037–2039; (f) T. Huang and C.-J. Li, *Chem. Commun.*, 2001, 2348–2349; (g) R. Ding, Y.-J. Chen, D. Wang and C.-J. Li, *Synlett*, 2001, 1470–1472; (h) C.-J. Li, T. S. Huang, S. Venkatraman, Y. Meng, D. Kort, R. Ding, D. Wang and T. Nguyen, *Pure Appl. Chem.*, 2001, **73**, 1315; (i) R. Ding, C.-S. Ge, Y.-J. Chen, D. Wang and C.-J. Li, *Tetrahedron Lett.*, 2002, **43**, 7789–7791; (j) W. Wu and C.-J. Li, *Lett. Org. Chem.*, 2004, **1**, 122–124.