ChemComm

This article was published as part of the

2009 'Catalysis in Organic Synthesis' web theme issue

Showcasing high quality research in organic chemistry

Please see our website (<u>http://www.rsc.org/chemcomm/organicwebtheme2009</u>) to access the other papers in this issue.

ChemComm

Direct functionalization of benzylic C–Hs with vinyl acetates via Fe-catalysis†‡

Chun-Xiao Song,^a Gui-Xin Cai,^a Thomas R. Farrell,^b Zhong-Ping Jiang,^a Hu Li,^a Liang-Bing Gan^{*a} and Zhang-Jie Shi^{*ac}

Received (in Cambridge, UK) 4th June 2009, Accepted 12th August 2009 First published as an Advance Article on the web 7th September 2009 DOI: 10.1039/b911031c

Direct cross-coupling to construct sp³ C-sp³ C bonds *via* Fe-catalyzed benzylic C-H activation with 1-aryl vinyl acetate was developed.

Transition metal-catalyzed cross-coupling reactions, such as the Heck reaction, have been well developed and become some of the most powerful methods to construct C-C bonds.1 Other developments have included coupling aliphatic halides, instead of aryl/alkenyl halides, with the functionalized olefins.² Recent advances in approaching this goal have indicated that aryl C-H bonds could be applied to C-C bond formation by coupling with functionalized alkenes via Pd(II) catalysis under oxidative conditions, avoiding the use of aryl halides.³ Undoubtedly, direct olefination of sp³ C-H bonds is more difficult due to their intrinsic properties. To the best of our knowledge, only two examples have been reported so far. Sames et al. first reported intramolecular C-C formation of the N-adjacent sp³ C-H bond of pyrroline, followed by isomerization with a tethered olefin, catalyzed by Ir complexes.⁴ The other example, reported by Li et al., showed direct olefination of sp³ C-H bonds, which was activated by both an adjacent N atom and an aryl group, presumably through an oxidation-Baylis-Hillman sequence.⁵

Compared to late transition metal-catalyzed processes, early transition metal-catalyzed transformations have unique features due to their cost effectiveness and different mechanistic insights.⁶ Among all the first row transition metals, iron draws much attention due to its high abundance, low price and low toxicity.⁷ Recently, Fe catalysis has been widely expanded,⁸ and in particular, iron catalysts have led to great advances in the direct oxidation^{8n,9} of C–H bonds, as well as in C–C bond formation.¹⁰ Herein, our developments offer a novel and useful method to construct C–C bonds *via* iron-catalyzed direct benzylic C–H transformations with functionalized olefins.

[‡] Electronic supplementary information (ESI) available: Experimental details, analytical and spectral data, and NMR spectra of compounds. See DOI: 10.1039/b911031c



Scheme 1 Original design of the cross-coupling $via \text{ sp}^3$ C–H activation with alkenes.

We originally planned to explore direct olefination through a Heck-type process via sp³ C–H activation (Scheme 1). The initial efforts were made to search for the solution of this design from diphenyl methane **1a**, which showed good activity in various transformations.¹¹ Different substituted olefins were tested in the presence of various transition metal catalysts and oxidants. Under different conditions, acrylate derivatives, which showed high reactivity in traditional Heck reactions,¹ were not efficient. Electron-rich olefins, such as 1-hexene,¹² *n*-butyl vinyl ether¹³ and 3,4-dihydropyran,¹⁴ also failed.

To our delight, when styrene was used in the presence of $FeCl_2$ as a catalyst and di-*tert*-butyl peroxide (DTBP) as an oxidant, the coupling product was observed by GC-MS and confirmed by crude ¹H NMR, accompanied by other undetermined byproducts (Scheme 2). Unfortunately, the efficiency could not be significantly improved, although various reaction parameters were screened. To our surprise, when other substituted styrenes were surveyed, the reaction was highly inhibited. Although this reaction demonstrated the first example of direct olefination of sp³ C–H bonds as a Heck-type transformation, the low efficiency and limited substrate scope hardly made this transformation applicable.

Further tests opened a new channel to approach our original design. Interestingly, when 1-phenyl vinyl acetate **2a** was submitted to the aforementioned conditions, a new product **3aa** was observed. To optimize this transformation, different conditions were screened (ESI, Table S1‡) and we found that in the absence of either FeCl₂ or DTPE, the reaction was terminated. The results also indicated that other common metal salts, such as Co, Cu, Mn and Pd, were not suitable for this transformation. Due to its availability, low price, catalytic efficiency and tolerance of environments, FeCl₂ was determined to be the most effective catalyst. DTPE was found as the best oxidant and the desired product was isolated in 74% yield (ESI, Table S1, entry 7‡). Other peroxides, such as TBHP and

Scheme 2 Direct olefination of benzylic C-H bonds with styrene.

^a Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Peking University, Beijing, China. E-mail: zshi@pku.edu.cn; Fax: +86 010-62760890; Tel: +86 010-62760890

^b Department of Chemistry, University of Rochester, Rochester, NY 14627, USA

^c State Key Laboratory of Organometallic Chemistry Chinese Academy of Sciences, Shanghai 200032, China

[†] This article is part of a ChemComm 'Catalysis in Organic Synthesis' web-theme issue showcasing high quality research in organic chemistry. Please see our website (http://www.rsc.org/chemcomm/ organicwebtheme2009) to access the other papers in this issue. ‡ Electronic supplementary information (ESI) available: Experimental

Table 1 C-C formation via FeCl2-catalyzed benzylic sp³ C-H activation^a

	Ar^{1} R $+$ Ph $2a$ $-$	FeCl ₂ (10 m DTBP (1.2 e N ₂ , 100 °C,	aquiv) 24 h	Ph R ₃ O
Entry	Ar^1	R	1	Yield (%)
1	$Ar^1 = R = I$	Ph	1a	3aa (74)
2	$Ar^1 = R = 4$	-FPh	1b	3ba (62)
3	4-FPh	Ph	1c	3ca (73)
4	4-CIPh	Ph	1d	3da (63)
5	4-PhPh	Ph	1e	3ea (77)
6	4-MeOPh	Ph	1f	3fa (45)
7	2-MeOPh	Ph	1g	3ga (13)
8	2-Nap	Ph	1ที่	3ha (69)
9		\bigcirc	1i	3ia (77)
10	\sim	$\mathbf{\hat{\mathbf{A}}}$	1j	3ja (59)

^{*a*} The reaction was carried out in 4.0 mmol of **1** and 0.5 mmol of **2a**, in the presence of 0.6 mmol of DTBP and 0.05 mmol of FeCl₂ under N₂ at 100 °C for 24 h and isolated yields were obtained after column chromatography if without further note.

¹BuOOCOPh could also promote the reaction, but with lower efficiencies. Notably, stable poly-*tert*-butylperoxylated fullerene was first observed to show partial reactivity.¹⁵

Different benzylic substrates were explored (Table 1), and we found that various derivatives of diphenylmethane were suitable. Electronic effects seemingly played an important role. Electronwithdrawing groups partially promoted the yields (entries 2–4), but in contrast, electron-donating groups decreased the efficiency. For example, the presence of a methoxyl group on the phenyl ring decreased the yield obviously (entry 6). Steric effects in *ortho*-substituted substrate **1g** also dramatically lowered the yield (entry 7). Aside from substituted phenyls, naphthyl and seven-membered cyclic diphenyl methane derivatives were suitable substrates, and the desired products were isolated in good yields (entries 5, 8 and 9). The reaction could be extended to the isochroman and the desired product **3ja** was obtained in 59% yield, with functionalization at the highly reactive benzylic position adjacent to the O-atom (entry 10).

Further exploration extended the substrate scope to the benzylic C–H of substituted toluene. When toluene **1k** was submitted, the desired product was obtained in a moderate yield (eqn (1), Scheme 3). The benzylic methyl group of **1l** showed excellent reactivity, which may arise from stabilization of the proposed radical intermediate (eqn (2), Scheme 3).¹⁶

Different substituted 1-aryl vinyl acetates were also explored (Table 2). We found that steric effects affected the efficiency: *ortho*-tolyl substitution lowered the yield to 52% from 65% and 68% with *para*- and *meta*-tolyl substitutions, respectively (*cf.* entry 4 with entries 2 and 3). Electronic effects similarly favored the electron withdrawing groups (*cf.* entry 5 with entries 6 and 7). It is noteworthy that C–X (X = Br or F) and ester groups tolerated the conditions well, and these groups could be transformed into different functionalities (**3af, 3ag** and **3ah**, entries 6–8). Unfortunately, 2-propenyl acetate is not suitable and only a small amount of desired product was observed by GC-MS.



Scheme 3 Fe-catalyzed direct olefination of toluene 1k and derivatives 1l with 1-phenyl vinyl acetate 2a.

Table 2 C–C formation *via* FeCl₂-catalyzed benzylic sp³ C–H activation with different vinyl esters^{*a*}

PI	H h→→Ph + 1a	R 2 -	FeCl ₂ (10 mol%) DTBP (1.2 equiv) N ₂ , 100 °C, 24 h	Ph Ph 3	¥ 0
Entry	R		3		Yield (%)
1	$\langle \rangle$	2a	Ph	Ĵ	3aa (74)
2	Me	2b	Ph O Ph	Me	3ab (65)
3	Me	 2c		Me	3ac (68)
4		e 2d	Ph H O		3ad (52)
5	MeO-	2e	Ph Ph O	ОМе	3ae (52)
6	F	2f		F	3af (69)
7	Br)	Ph Ph O	∫ ^{Br} ∫CO₂Et	3ag (70)
8	EtO ₂ C-		Ph	· ∠	3ah (59)

^{*a*} The reaction was carried out in the 4.0 mmol of **1** and 0.5 mmol of **2** in the presence of 0.6 mmol of DTBP and 0.05 mmol of FeCl₂ under N_2 at 80 °C for 24 h and isolated yields were obtained after column chromatography if without further note.

Considering the safety problem arising from the possible explosion of peroxide in the presence of transition metal species, we further experimentally modified this transformation (Scheme 4). When both vinyl acetate **2a** and DTBP was mixed and added dropwise in a half hour, **3aa** was isolated in 61% yield. To our delight, a better efficiency was obtained with the addition of only DTBP in 0.5 h. The length of the adding time to 10 h did not affect the yield significantly. Thus, this operation reduced the hazard by the decrease of the DTBP concentration.



Scheme 4 Promotion the safty of Fe-catalyzed alkylation with 1a and 2a by slow addition of DTBP and/or 2a.



Scheme 5 Proposed mechanism on direct C–C formation *via* Fe-catalyzed benzylic C–H activation *via* either radical (path A) or cationic (path B) process. I and II were observed as major byproducts.

The radical process was highly preferred to facilitate their transformations like Fenton's process.^{9g,10a,b} The chemistry demonstrated here may also go through the radical process as shown in Scheme 5, path A. The occasional observation of *tert*-butyl ether and dimerization of diphenyl methane support this hypothesis. An intermolecular isotopic competitive study ($K_{\rm H/D} = 2.4$) indicated that the proton abstraction process may be involved in the rate determining step. Another possibility for the mechanism is the cationic pathway (Scheme 5, path B). In this assumption, a radical species, generated from the first step with DTBP, might be further oxidized to a benzyl cation, which undergoes electrophilic attack to produce the desired product. However, the observed electronic feature of diarylmethane substrates does not seem to support this hypothesis.

In summary, we have described a novel method to construct sp³ C–C bonds *via* Fe-catalyzed benzylic C–H activation under mild conditions. Functionalized olefins, such as vinyl acetate and styrene, were first applied as a partner to direct coupling with C–H bonds. To the best of our knowledge, this is the first example that shows Heck-type cross coupling through sp³ C–H activation *via* a transition metal-catalyzed transformation. Further studies are under way to clearly understand the mechanistic pathway and to apply this chemistry to organic synthesis.

Notes and references

- (a) R. F. Heck, J. Am. Chem. Soc., 1968, 90, 5518; (b) T. Mizoroki,
 K. Mori and A. Ozaki, Bull. Chem. Soc. Jpn., 1971, 44, 581;
 (c) R. F. Heck and J. P. Nolley, J. Org. Chem., 1972, 37, 2320;
 (d) R. F. Heck, Palladium Reagents in Organic Synthese, Academic Press, New York, 1985.
- 2 (a) Y. Ikeda, T. Nakamura, H. Yorimitsu and K. Oshima, J. Am. Chem. Soc., 2002, 124, 6514; (b) W. Affo, H. Ohmiya, T. Fujioka, Y. Ikeda, T. Nakamura, H. Yorimitsu, K. Oshima, Y. Imamura,

T. Mizuta and K. Miyoshi, J. Am. Chem. Soc., 2006, **128**, 8068; (c) L. Firmansjah and G. C. Fu, J. Am. Chem. Soc., 2007, **129**, 11340.

- 3 (a) Y. Fujiwara, I. Moritani, S. Danno and S. Teranishi, J. Am. Chem. Soc., 1969, 91, 7166; (b) I. Moritani and Y. Fujiwara, Tetrahedron Lett., 1967, 8, 1119; (c) Y. Fujiwara, R. Asano, I. Moritani and S. Teranishi, J. Org. Chem., 1976, 41, 1681; (d) C. Jia, T. Kitamura and Y. Fujiwara, Acc. Chem. Res., 2001, 34, 633; (e) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. De Vries, P. C. J. Kamer, J. G. de Vries and P. W. N. M. van Leeuwen, J. Am. Chem. Soc., 2002, 124, 1586; (f) G. Cai, Y. Fu, Y. Li, X. Wan and Z. Shi, J. Am. Chem. Soc., 2007, 129, 7666; (g) G. Dyker, Handbook of C-H Transformations. Applications in Organic Synthesis, Wiley-VCH, Weinheim, 2005, and references therein.
- 4 B. DeBoef, S. J. Pastine and D. Sames, J. Am. Chem. Soc., 2004, 126, 6556.
- 5 Z. Li, D. S. Bohle and C. Li, Proc. Natl. Acad. Sci. U. S. A., 2006, 103, 8928.
- 6 (a) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, 97, 2879;
 (b) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, 417, 507.
- 7 (a) C. Bolm, J. Legros, J. Le Paih and L. Zani, *Chem. Rev.*, 2004, **104**, 6217; (b) A. Fürstner and R. Martin, *Chem. Lett.*, 2005, **34**, 624.
- 8 (a) T. Nagano and T. Hayashi, Org. Lett., 2004, 6, 1297; (b) A. Fürstner, A. Leitner, M. Mendez and H. Krause, J. Am. Chem. Soc., 2002, 124, 13856; (c) M. Nakamura, K. Matsuo, S. Ito and E. Nakamura, J. Am. Chem. Soc., 2004, 126, 3686; (d) I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou and P. Knochel, Angew. Chem., Int. Ed., 2005, 44, 1654; (e) K. Itami, S. Higashi, M. Mineno and J. Yoshida, Org. Lett., 2005, 7, 1219; (f) L. K. Ottesen, F. Ek and R. Olsson, Org. Lett., 2006, 8, 1771; (g) K. Bica and P. Gaertner, Org. Lett., 2006, 8, 733; (h) J. Kischel, K. Mertins, D. Michalik, A. Zapf and M. Beller, Adv. Synth. Catal., 2007, 349, 865; (i) G. Cahiez, A. Moyeux, J. Buendia and Duplais, J. Am. Chem. Soc., 2007, 129, 13788; (j) T. Hatakeyama and M. Nakamura, J. Am. Chem. Soc., 2007, 129, 9844; (k) C. Y. Li, X. B. Wang, X. L. Sun, Y. Tang, J. C. Zheng, Z. H. Xu, Y. G. Zhou and L. X. Dai, J. Am. Chem. Soc., 2007, 129, 1494; (1) A. Fürstner, K. Majima, R. Martin, H. Krause, E. Kattnig, R. Goddard and C. W. Lehmann, J. Am. Chem. Soc., 2008, 130, 1992; (m) A. Guérinot, S. Reymond and J. Cossy, Angew. Chem., Int. Ed., 2007, 46, 6521; (n) A. Correa, O. G. Mancheno and C. Bolm, Chem. Soc. Rev., 2008, 37, 1108; (o) A. Correa and C. Bolm, Angew. Chem., Int. Ed., 2007, 46, 8862; (p) O. Bistri, A. Correa and C. Bolm, Angew. Chem., Int. Ed., 2008, 47, 586; (q) A. Correa, M. Carril and C. Bolm, Angew. Chem., Int. Ed., 2008, 47, 2880; (r) M. Carril, A. Correa and C. Bolm, Angew. Chem., Int. Ed., 2008, 47, 4862
- 9 (a) P. Stavropoulos, R. Celenligil-Cetin and A. E. Tapper, Acc. Chem. Res., 2001, 34, 745; (b) C. Walling, Acc. Chem. Res., 1998, 31, 155; (c) P. A. MacFaul, D. D. M. Wayner and K. U. Ingold, Acc. Chem. Res., 1998, 31, 159; (d) M. Costas, M. P. Mehn, M. P. Jensen and L. Que Jr, Chem. Rev., 2004, 104, 939; (e) M. Christmann, Angew. Chem., Int. Ed., 2008, 47, 2740; (f) K. Suzuki, P. D. Oldenburg and L. Que Jr, Angew. Chem., Int. Ed., 2008, 47, 1887; (g) M. S. Chen and M. C. White, Science, 2007, 318, 783; (h) M. P. Sibi and M. Hasegawa, J. Am. Chem. Soc., 2007, 129, 4124.
- (a) Z. Li, L. Cao and C. Li, Angew. Chem., Int. Ed., 2007, 46, 6505;
 (b) Y. Zhang and C. Li, Eur. J. Org. Chem., 2007, 4654; (c) Z. Li,
 R. Yu and H. Li, Angew. Chem., Int. Ed., 2008, 47, 7497;
 (d) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin and S.-J. Shi, Angew. Chem., Int. Ed., 2009, 48, 3817.
- 11 (a) B. M. Choudary, A. D. Prasad, V. Bhuma and V. Swapna, J. Org. Chem., 1992, 57, 5841; (b) F. G. Bordwell, J. Cheng and J. A. Harrelson, J. Am. Chem. Soc., 1988, 110, 1229.
- 12 F. G. Bordwell and M. L. Peterson, J. Am. Chem. Soc., 1954, 76, 3952.
- 13 J. Furukawa, A. Onishi and T. Tsuruta, J. Org. Chem., 1958, 23, 672.
- 14 F. M. Menger and C. H. Chu, J. Org. Chem., 1981, 46, 5044.
- 15 L. Gan, S. Huang, X. Zhang, A. Zhang, B. Cheng, H. Cheng, X. Li and G. Shang, J. Am. Chem. Soc., 2002, 124, 13384.
- 16 C. D. Cook, J. Org. Chem., 1953, 18, 261.