JOC Article

Fe(0)-Mediated Synthesis of Tri- and Tetra-Substituted Olefins from Carbonyls: An Environmentally Friendly Alternative to Cr(II)

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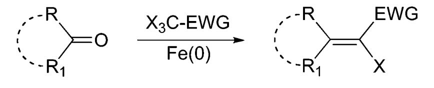

X = F, Cl, Br, OMe, H EWG = CO_2H, CO_2Me, CN

Fe(0) was investigated as a cost-effective, environmentally friendly alternative to Cr(II) for the olefination of carbonyls by activated polyhalides. In many instances, Fe(0) was equivalent or superior to Cr(II). Notably, Fe(0), but not Cr(II), proved compatible with a wide range of functionality, inter alia, unprotected phenol, aryl nitro, carboxylic acid, and alkyl nitrile. A surprising reversal of stereoselectivity for aldehydes versus ketones was observed using both metals. The resultant α-halo-α,β-unsaturated or α,β-unsaturated carboxylic acids, esters, and nitriles are common structural elements in numerous compounds of interest as well as key intermediates in the preparation of other functionality.

Introduction

Recent publications from these[1] and other laboratories[2] have elucidated the rich mechanistic and synthetic versatility of organochromium reagents. The efficacy of these transformations and, in many cases, their unprecedented stereo- and/or chemoselectivities have accordingly attracted wide attention from the chemical community. However, restrictions upon the use of toxic heavy metals for organic synthesis have highlighted the urgent need for wide-ranging surveys of the reactivity and stereoselectivity of more benign metals and eco-friendly protocols.[3] Since iron and its derivatives satisfy many of the desired criteria, inter alia, minimal toxicity, ease of handling, good stability, commercial availability in various forms, and relatively low costs, it was singled out for further evaluation. While the utility of polyvalent and complexed zerovalent iron for C−C coupling has been cogently demonstrated,[4,5] surprisingly few studies have exploited iron in its elemental (solid) form. Herein, we describe a comparative study of elemental Fe(0)- versus Cr(II)-driven condensations of activated polyhalides (Scheme 1) and the surprising reversal of stereoselectivity for aldehydes versus ketones. The resultant α-halo-α,β-unsaturated or α,β-unsaturated carboxylic acids, esters, and nitriles are common structural elements in numerous compounds of interest as well as key intermediates in the preparation of other functionality.[6,7]

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(1) (a) Bejot, R.; Tisserand, S.; Reddy, L. M.; Barma, D. K.; Baati, R.; Falck, J. R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2008. (b) Falck, J. R.; Bandyopadhyay, A.; Barma, D. K.; Shin, D. S.; Kundu, A.; Kishore, R. V. K. *Tetrahedron Lett.* **2004**, *45*, 3039. (c) Barma, D. K.; Kundu, A.; Bandyopadhyay, A.; Kundu, A.; Sangras, B.; Briot, A.; Mioskowski, C.; Falck, J. R. *Tetrahedron Lett.* **2004**, *45*, 5917. (d) Barma, D. K.; Kundu, A.; Zhang, H. M.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218. (e) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 2183. (f) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 2179. (g) Falck, J. R.; Barma, D. K.; Venkataraman, S. K.; Baati, R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 963. (h) Baati, R.; Barma, D. K.; Krishna, U. M.; Mioskowski, C.; Falck, J. R. *Tetrahedron Lett.* **2002**, *43*, 959.

(2) Recent examples: (a) Nakagawa, M.; Saito, A.; Soga, A.; Yamamoto, N.; Taguchi, T. *Tetrahedron Lett.* **2005**, *46*, 5257. (b) Concellon, J. M.; Bernad, P. L.; Mejica, C. *Tetrahedron Lett.* **2005**, *46*, 569. (c) Takenaka, N.; Xia, G. Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198. (d) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031. (e) Halterman, R. L.; Crow, L. D. *Tetrahedron Lett.* **2003**, *44*, 2907. (f) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schroder, M.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 1032.

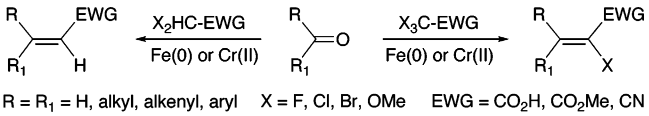
(3) Bagchi, D.; Stohs, S. J.; Downs, B. W.; Bagchi, M.; Preuss, H. G. *Toxicology* **2002**, *180*, 5.

(4) For recent examples of the application of iron derivatives in the formation of C−C bonds, see: (a) Fürstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc.* **2005**, *127*, 12236. (b) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (c) Bolm, C.; Legros, J.; LePaih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(5) For recent C−C couplings using Fe(0) complexes, see: (a) Terent'ev, A. B.; Vasil'eva, T. T.; Kuz'mina, N. A.; Mysova, N. E.; Chakhovskaya, O. V. *Russ. J. Org. Chem.* **2001**, *37*, 1273. (b) Terentiev, A. B.; Vasilieva, T. T.; Kuz'mina, N. A.; Chakhovskaya, O. V.; Brodsky, E. S.; Belokon, Y. N. *Russ. Chem. Bull.* **2000**, *49*, 722.

10.1021/jo061445u CCC: $33.50

SCHEME 1



Results and Discussion

It was anticipated that Cr(II) and Fe(0) would mediate many of the same transformations since they have similar reduction potentials (−0.41 and −0.45 V vs SHE, respectively).[8] On the other hand, the disparities (e.g., geometry, aggregation, and Lewis acidity) manifested by organoiron reagents[9] and comparable organochromium species[8] augured for useful variances in stereoselectivity and/or functional group compatibility.

The former prediction was confirmed during condensations of benzaldehyde **1** and 4-dimethylaminobenzaldehyde **4** with methyl trichloroacetate **2** in THF using Fe powder at 23−60 °C overnight or, as previously reported,[1d] using $CrCl_2$ at room temperature for 1−2 h. The yields and *Z*-stereoselectivities for α-chloroacrylates **3** and **5** were outstanding and essentially equivalent for both reagents (Table 1, entries 1 and 2, respectively). As expected, Rieke iron exhibited higher reactivity than commercial Fe(0) powder.[10,11] All of the starting materials were consumed after just 1 h at room temperature, but complex product mixtures of α-chloroacrylate, dehalogenated acrylate, dichlorohydrin, and uncharacterized compounds were obtained.

A determination of the scope of the condensation also revealed some significant differences between the metal reductants. Under the influence of Fe(0) powder, phenol **6** and nitro **8** afforded **7** (entry 3) and **9** (entry 4), respectively, in good yields and stereocontrol (*Z*/*E* > 99:1). The lack of competitive aryl nitro reduction under these conditions is noteworthy.[12] In contrast, **6** and **8** did not react with $CrCl_2$, even under forcing conditions (refluxing THF, 12 h), and could be recovered unchanged. Heterocyclic aldehydes were well tolerated as seen in the smooth conversions of indole **10**, furan **12**, and thiophene **14** into the corresponding adducts **11** (entry 5),[1d] **13** (entry 6), and **15** (entry 7). In this series, chromium displayed the superior *Z*-stereoselectivity, whereas iron gave somewhat better yields, except with indole **10**. Conjugated and aliphatic aldehydes behaved analogously, for example, **16**→**17** (entry 8) and **18**→**19** (entry 9), with $CrCl_2$ providing nominally better yields and conspicuously better *Z/E* ratios. Interestingly, the presence of catalytic $CrCl_2$ (20 mol %) under the usual Fe(0) reaction conditions [Fe(0) (8 equiv), THF, 55 °C, 14 h] was sufficient to impart chromium's stereoselectivity,[13] for instance, **16**→**17** (86%, *Z*/*E* > 99:1).

The range of suitable polyhalogenated substrates encompassed ethyl dichlorofluoroacetate **20**, methyl tribromoacetate **22**, tribromoacetic acid **24**, ethyl dibromoacetate **26**, trichloroacetonitrile **28**, and methyl 2,2-dichloro-2-methoxyacetate **31**. These provided access to (*Z*)-α-fluoroacrylate **21** (entry 10), (*Z*)-α-bromoacrylate **23** (entry 11),[14] (*Z*)-α-bromoacrylic acid **25** (entry 12), (*E*)-acrylate **27** (entry 13),[15] α-chloro-α,*β*-unsaturated nitriles **29**/**30** (entries 14 and 15), and (*Z*)-α-methoxyacrylate **32** (entry 16) in good to excellent yields. While the yields and stereoselectivities were broadly similar, the superior functional group compatibility of Fe(0) is patently evident in entries 12 and 15; only in entry 16 was the result with Fe(0) unsatisfactory.

It was also gratifying to discover that a wide variety of ketones were suitable condensation partners for trichloroacetates (Table 2).[16] Tetra-substituted olefins were generated in good yields from aryl ketones **33** and **35** (entries 1 and 2), conjugated ketones **37**, **39**, and **41** (entries 3, 4 and 5), and aliphatic methyl ketones **43** and **45** (entries 6 and 7). Despite reports that benzyl ethers are cleaved under some circumstances by iron and chromium salts,[17] we observed no evidence of this during the reactions of **35**.[18] One should also note that while Cr(II)-mediated condensations typically gave somewhat better yields, for the sensitive cyclic ketone **41**, Fe(0) was more efficacious (entry 5). As might be anticipated, the *E*/*Z* ratio of the products varied in accordance with the steric differential of the opposing ketone appendages. The most noteworthy and unexpected result was the moderate to high *E*-selectivity observed for all of the Fe(0) reactions and all but one of the Cr(II) reactions. This is in stark contrast to the *Z*-stereoselectivity characteristic of aldehydes (Table 1).[19,20] Furthermore, inspection of the data in Table 2 reveals Fe(0) was consistently more stereoselective than Cr(II).

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(6) (a) Mironiuk-Puchalska, E.; Kolaczkowska, E.; Sas, W. *Tetrahedron Lett.* **2002**, *43*, 8351. (b) Dollt, H.; Zabel, V. *Aust. J. Chem.* **1999**, *52*, 259. (c) Kakehi, A.; Ito, S. *J. Org. Chem.* **1974**, *39*, 1542. (d) Marvel, C. S.; Weil, E. D.; Wakefield, L. B.; Fairbanks, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 2326.

(7) Stille: (a) Tanaka, K.; Katsumura, S. *Org. Lett.* **2000**, *2*, 373. Sonogashira: (b) Dai, W. M.; Wu, J. L.; Fong, K. C.; Lee, M. Y. H.; Lau, C. W. *J. Org. Chem.* **1999**, *64*, 5062. Suzuki: (c) Zhou, S. M.; Yan, Y. L.; Deng, M. Z. *Synlett* **1998**, 198. (d) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135. (e) Zhang, X. G.; Qing, F. L.; Yu, Y. H. *J. Org. Chem.* **2000**, *65*, 7075. (f) Qing, F. L.; Zhang, X. G. *Tetrahedron Lett.* **2001**, *42*, 5929.

(8) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1.

(9) Rosenblum, M. *Acc. Chem. Res.* **1974**, *7*, 122.

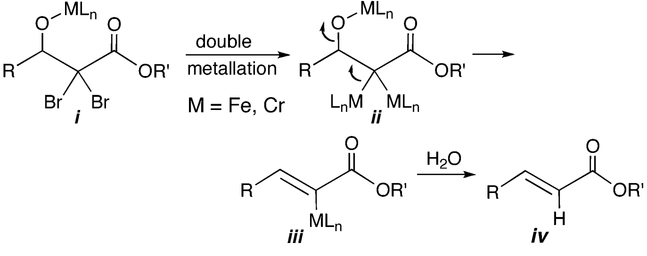
(10) Rieke, R. D. *Science* **1989**, *246*, 1260.

(11) Fe(0) powder (<10 *μ*m, 99.9%) was purchased from Aldrich and Alfa Aeser and stored/handled under an inert atmosphere to minimize formation of an oxide coating.

(12) Wang, L.; Li, P. H.; Wu, Z. T.; Yan, J. C.; Wang, M.; Ding, Y. B. *Synthesis* **2003**, 2001.

(13) $CrCl_3$/Fe(0) redox systems have been described: Hu, C. M.; Chen, J. *J. Chem. Soc., Chem. Commun.* **1993**, 72.

(14) Control experiments indicate that **23** and **25** are stable under the reaction conditions. We speculate the minor amounts of debrominated byproducts arise via double metalation of the initial Reformatsky-type adduct ***i*** to give ***ii***. We and others have previously invoked the generation of *gem*-dichromium intermediates: Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *J. Am. Chem. Soc.* **2001**, *123*, 9196. The greater reactivity of bromides makes this process partially competitive with the pathway in Figure 1.



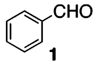
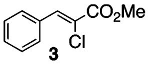
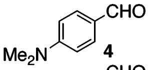
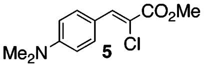
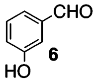
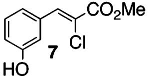
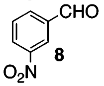
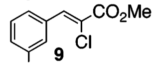
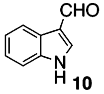
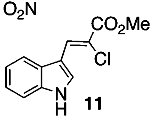
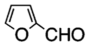
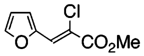
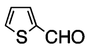
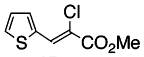
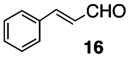
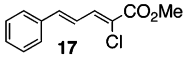
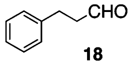
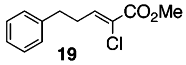
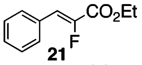
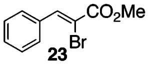
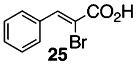
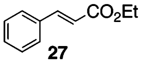
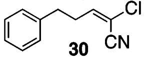
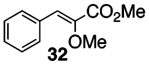
(15) For a mechanistically related, stereoselective synthesis of (*E*)-α,*β*-unsaturated esters using SmI_2, see: Concellon, J. M.; Concellon, C.; Mejica, C. *J. Org. Chem.* **2005**, *70*, 6111.

(16) In sharp contrast, reactions of methyl tribromoacetate with ketones afforded complex product mixtures. This may reflect its greater steric profile and/or the proclivity of the more reactive bromides toward undesired side reactions.

(17) (a) Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477. (b) Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823.

(18) Considering standard reduction potentials of Fe(II)/Fe (−0.45 V), Fe(III)/Fe (−0.04 V), and Fe(III)/Fe(II) (+0.77 V) compared to Cr(III)/Cr(II) (−0.41 V), we postulate the formation of Fe(II) salts in the tandem Reformatsky elimination reaction.

TABLE 1. Fe(0)- versus Cr(II)-Mediated α-Halo-olefination of Aldehydes

entry	aldehyde	polyhalide	adduct	Fe(0)[a] yield[c] (Z/E)	Cr(II)[b] yield[c] (Z/E)
1	 **1**	Cl_3CCO_2Me **2**	 **3**	99 (>99/1)	99 (>99/1)
2	 **4**	**2**	 **5**	99 (>99/1)	98 (>99/1)
3	 **6**	**2**	 **7**	89[d] (>99/1)	0[e]
4	 **8**	**2**	 **9**	79 (>99/1)	0[e]
5	 **10**	**2**	 **11**	65[f] (>99/1)	91[g] (>99/1)
6	 **12**	**2**	 **13**	90 (5/1)	71 (20/1)
7	 **14**	**2**	 **15**	99 (5.6/1)	68 (20/1)
8	 **16**	**2**	 **17**	89 (6/1)	99 (>99/1)
9	 **18**	**2**	 **19**	95 (15/1)	99 (>99/1)
10	**1**	Cl_2FCCO_2Et **20**	 **21**	79 (>99/1)	99 (>99/1)
11	**1**	Br_3CCO_2Me **22**	 **23**	79[h,i] (8/1)	99 (30/1)
12	**1**	Br_3CCO_2H **24**	 **25**	80[j] (>99/1)	0[e]
13	**1**	Br_2HCCO_2Et **26**	 **27**	82[k] (1/30)	83 (1/99)
14	**1**	Cl_3CCN **28**	 **29**	77[h,l] (1/3.2)	70 (1/1)
15	**18**	**28**	 **30**	89[g,l] (1/1.5)	0
16	**1**	$Cl_2(MeO)CCO_2Me$ **31**	 **32**	25 (30/1)	92 (30/1)

[a] Fe powder (10 equiv), THF, 55−60 °C, 14 h. [b] $CrCl_2$ (6 equiv), THF, 23 °C, 1−2 h. [c] Isolated yield after SiO_2 chromatographic purification. Z/E ratio determined by ^1H NMR and/or GC. [d] 23 °C, 4 h. [e] Warmed to reflux. [f] 35% of **10** recovered. [g] Required 8 equiv of $CrCl_2$ and 1.5 equiv of **2**. [h] 23 °C. [i] 15% dehalogenated adduct isolated. [j] 20% dehalogenated adduct isolated. [k] 90 °C. [l] Stereochemistry determined by nOe.

While the details have not been elucidated, it appears that Fe(0)-mediated condensations of aldehydes follow the same reaction pathway proposed for analogous chromium(II) olefinations,[1d,15] that is, initial one-electron transfer at the metal interface resulting in rupture of a C−X bond,[21] further reduction of the nascent 2,2-dihaloacetate radical, and generation of a metal−enolate complex. Whether the electron transfers are innersphere or outersphere is not settled. Addition of the organometallic species to the carbonyl is rapid and results in a Reformatsky-type adduct (Figure 1).[22] Subsequent reductive, anti-periplanar E_2 elimination preferentially affords the *Z*-olefin. This stereochemical outcome likely reflects the predominance of conformer **A** versus the more sterically hindered conformer **B**.

For ketones, we propose an early and crucial change in mechanism to explain the divergence in stereochemistry. Since reduction of the carbon−halogen bond of the comparatively more congested Reformatsky-type ketone adduct **47** is slower (Figure 2), electron transfer occurs through the carbonyl to generate metal enolate **48**. It is likely that chelation plays an important role in determining the conformation of **48**. Subsequent elimination occurs preferentially via conformation **C** which minimizes the steric interaction between the halide and

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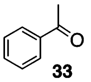
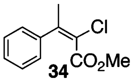
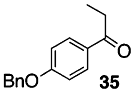
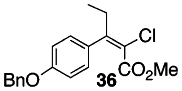
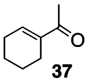
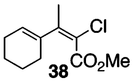
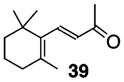
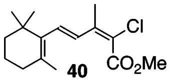
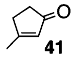
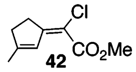
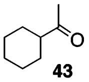
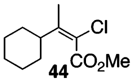
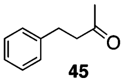
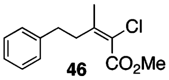
(19) The stereochemical assignments of adducts **34**, **36**, **38**, **40**, **44**, and **46** were confirmed by $LiAlH_4$ reduction (Et_2O, 0 °C, 20 min) of the ester and 2D nOe analysis of the resultant primary alcohols; comparable treatment of **42** gave an unstable product, so its stereochemistry could not be established.

(20) NB: The principal product of the $CrCl_2$-mediated condensation of **33** and **2** was previously assigned structure (*Z*)-**34**[1d] in accordance with literature data (Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698) but now must be revised as (*E*)-**34** based upon the above nOe experiments.

(21) Nuzzo, R. G.; Dubois, L. H. *J. Am. Chem. Soc.* **1986**, *108*, 2881.

(22) (a) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Elsevier: Amsterdam, 1991; Vol. 2, p 277. (b) Fürstner, A. *Synthesis* **1989**, 571.

TABLE 2. Fe(0)- versus Cr(II)-Mediated α-Chloro-olefination of Ketones

entry	ketone	polyhalide	adduct	Fe(0)[a] yield[c] (Z/E)	Cr(II)[b] yield[c] (Z/E)
1	 **33**	**2**	 **34**	80 (1/25)	90 (1/5)
2	 **35**	**2**	 **36**	82 (1/35)	80 (1/7)
3	 **37**	**2**	 **38**	77 (1/10)	95 (1/2.5)
4	 **39**	**2**	 **40**	63 (1/6)	85[d] (1/4)
5	 **41**	**2**	 **42**	95 (1/1.6)[e]	76[d] (1/1)
6	 **43**	**2**	 **44**	82 (1/18)[f]	95 (1/5)
7	 **45**	**2**	 **46**	99 (1/4)	99[d] (1/2)

[a] Fe powder (10 equiv), THF, 55−60 °C, 14 h. [b] $CrCl_2$ (6 equiv), THF, 23 °C, 1−2 h. [c] Isolated yield after SiO_2 chromatographic purification. Z/E ratio determined by ^{1}H NMR and/or GC. [d] Required 8 equiv of $CrCl_2$ and 1.5 equiv of **2**. [e] Stereochemistry unassigned. [f] 40 °C, 12 h.

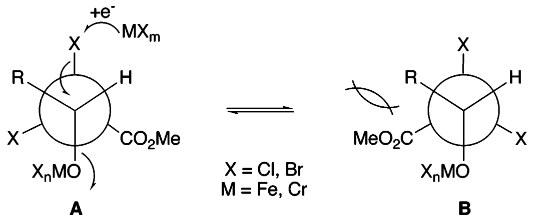


FIGURE 1. Reformatsky intermediate derived from aldehydes.

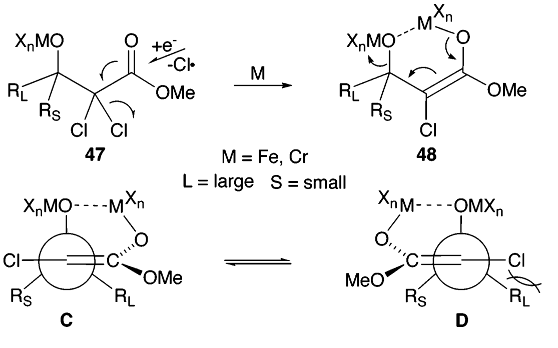
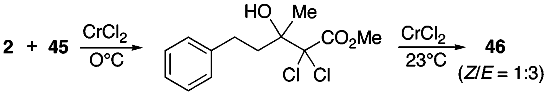


FIGURE 2. Reformatsky intermediate derived from ketones.

SCHEME 2



the R_L appendage as well as maximizes overlap of the electron-rich sp^3-hybridized oxygens (i.e., MeO^- and X_nMO^-) with the p-orbitals of the enolate C═C.

In concert with this hypothesis, the *E*-stereoselectivity observed with ketones is also realized using dichlorohydrins obtained from ketones. For example, the addition of methyl trichloroacetate **2** to benzylacetone **45** using only 2 equiv of $CrCl_2$ at 0 °C for 1.5 h or 4 equiv of Fe(0) at room temperature gave methyl 2,2-dichloro-3-hydroxy-3-methyl-5-phenylpentanoate (36−40%) and methyl 2-chloro-3-methyl-5-phenylpent-2-enoate (12−15%, $Z/E = 1:2$) (Scheme 2). Exposure of the former adduct to the chromium reaction conditions used in Table 2 led to methyl 2-chloro-3-methyl-5-phenylpent-2-enoate **46** ($Z/E = 1:3$).

Conclusion

This contribution affords new insights into organoiron chemistry. Fe(0) was found to be an effective reductant for carbonyl−polyhalide condensations giving rise to tri- and tetrasubstituted olefins. Yields and stereoselectivities are good to excellent and, in some cases, especially ketones, superior to those achieved with $CrCl_2$. Fe(0) displayed excellent compatibility with a wide range of functionality, and we anticipate that these Fe-mediated olefinations will find broad utility.

Experimental Section

Fe(0) Condensations. Polyhalide (1.1 mmol) and aldehyde or ketone (1 mmol) in anhydrous THF (2 mL) were added to a stirring, room temperature suspension of Fe powder (10 mmol; Aldrich, −325 mesh) in anhydrous THF (8 mL) under an argon atmosphere. The mixture was warmed to 23−60 °C for 4−14 h, then cooled to room temperature, quenched with water, filtered, and the filtrate was extracted three times with ether. The combined ethereal extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. Purification of the residue via SiO_2 column chromatography furnished the adduct in the indicated yield (Tables 1 and 2).

Fe(0)/Catalytic $CrCl_2$ Condensations. Conducted as described above using Fe powder (8 mmol; Aldrich, −325 mesh) and $CrCl_2$ (0.20 mmol; Strem Chemicals).

$CrCl_2$ Condensations. Conducted as described above using $CrCl_2$ (6 mmol; Strem Chemicals) at 23 °C for 1−2 h.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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