Heterocycles

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Formal Ring-Opening/Cross-Coupling Reactions of 2-Pyrones: Iron-Catalyzed Entry into Stereodefined Dienyl Carboxylates**

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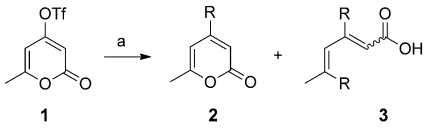
Iron-catalyzed cross-coupling reactions are distinguished by many virtues.[1–8] While the potential economic and environmental benefits of using a largely benign and very cheap base metals are obvious, specific chemical characteristics such as the ready scalability[9] and the often exceptional reaction rates even at low temperatures are also noteworthy. Moreover, bare iron catalysts allow various C–X bonds, which are considered fairly unreactive by the standards of palladium chemistry, to be activated with surprising ease. An early lead finding was the discovery that (hetero)aryl chlorides are innately better partners than their bromide or iodide counterparts.[10,11] Since then, the list of electrophiles amenable to iron-catalyzed cross-coupling has been considerably extended to encompass sulfonates, sulfamates, sulfones, sulfides, phosphonates, carbamates, and even pivalates, to name the most prominent examples.[10,12,13] Likewise, alkyl halides perform surprisingly well[1–8] and iron-catalyzed C–H bond activation has also made considerable progress.[2,14]

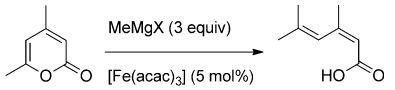
Herein we expand this list by pursuing a conceptually different type of formal cross-coupling process. The reaction is distinguished by the fact that the leaving group is an integral part of a heterocyclic ring which is opened as the new C–C bond is formed. Though potentially very useful, such transformations have surprisingly little precedent in the prolific cross-coupling arena altogether.[15,16] We became aware of this unusual reaction format while analyzing the results of the seemingly routine cross-coupling of the triflate **1** with various Grignard reagents in the presence of [Fe(acac)$_3$] (5 mol%, Scheme 1).[17,18] Although iron-catalyzed C–C bond-forming reactions of other 2-pyrone derivatives had previously met with limited success,[19] the alkylations of **1** proceeded smoothly, thus furnishing compounds **2** in appreciable yields. However, the crude reaction mixture contained small amounts of dialkylated by-products of type **3** as a mixture of isomers. Ring-opening reactions of 2-pyrones usually occur upon nucleophilic attack of a Grignard reagent onto their carbonyl group.[20] In the present case, the iron catalyst has obviously superseded this conventional reactivity mode and turned it into a rather unusual cross-coupling process, in which the lactone moiety gained a new role as a nontraditional leaving group.[21]



Scheme 1. Lead discovery showing that a new ring-opening reaction accompanies regular iron-catalyzed cross-coupling of a 2-pyronyl triflate: a) RMgCl (in THF), [Fe(acac)$_3$] (5 mol%), Et$_2$O, −78 °C; R = Me: 79% (**2a**) + 8% (**3a**); R = $C_{14}H_{29}$: 74% (**2b**) + 11% (**3b**); acac = acetylacetonato, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

Intrigued by this outcome, we focused on the optimization of this novel transformation using MeMgX as the reagent (Table 1). This choice was basically dictated by the fact that

Table 1: Solvent dependence of the iron-catalyzed formal ring-opening/cross-coupling reaction of a model pyrone.[a]



4a **5a**

Entry	Reagent	Solvent	M	T [°C]	Yield [%][b]	Z/E[d]
1	MeMgCl in THF	THF	0.1	−78	0[c]	–
2	MeMgCl in THF	THF	0.1	−30	15[c]	1:2
3	MeMgCl in THF	toluene	0.025	−30	91	4:1
4	MeMgCl in THF	Et$_2$O	0.1	−30	61[c]	10:1
5	MeMgBr in Et$_2$O	Et$_2$O	0.1	−78	81[c]	>20:1
6	MeMgBr in Et$_2$O	Et$_2$O	0.1	−30	96	>20:1
7	MeMgBr in Et$_2$O/ LiCl (6 equiv)	Et$_2$O	0.1	−30	93	>20:1
8	MeMgBr in Et$_2$O	toluene	0.025	−30	93	>20:1

[a] The reactions were invariably stopped after 20 min. [b] Yield of isolated product. [c] The substrate was either not or not completely converted after 20 min. [d] Determined by ^{1}H NMR spectroscopy.

the resulting di-unsaturated acid derivatives are of immediate relevance for target-oriented synthesis since many natural products comprise stereodefined methyl-branched dienyl carboxylate or methyl-branched dienyl carbinol subunits.[22] When working at ≤ -30 °C in Et$_2$O, toluene, or mixtures thereof, the acid **5a** was obtained from the pyrone **4a** and MeMgBr in high yield after only 20 minutes and virtually as a single isomer (>20:1). Its non-thermodynamic 2*Z*,4*E* configuration was confirmed by X-ray diffraction (see the Supporting Information). It is of note, however, that even small amounts of THF in the mixture led to substantial

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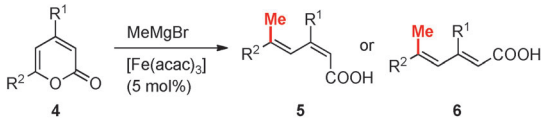
scrambling of the double bond geometry; therefore it is important that the Grignard reagent itself be prepared in an Et_2O solution.

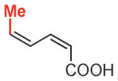
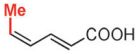
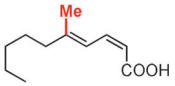
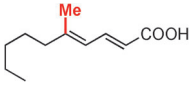
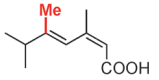
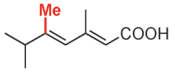
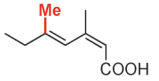
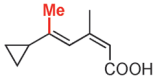
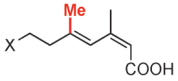
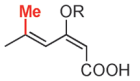
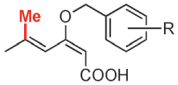
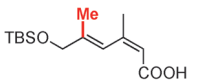
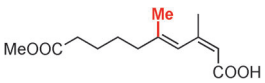
Products comprising a disubstituted (rather than trisubstituted) alkene in conjugation to the acid are even more isomerization prone (Table 2). Yet, even such dienyl carboxylates could be secured with respectable selectivity in favor of the 2*Z*,4*E* isomer, provided that the reactions were performed and quenched at −60 °C. Interestingly though, almost complete isomerization with formation of the thermodynamically more stable 2*E*,4*E*-configured acids **6** was observed when the mixtures were allowed to reach ambient temperature prior to work-up (Table 2, entries 1–6). The data in Table 2 also illustrates the structural scope of the method. Good to excellent yields were attained in all cases investigated and the selectivity was invariably high. As expected from our previous experiences in the field of iron catalysis,[10–12,23] the reaction turned out to be compatible with a variety of functional groups, including primary alkyl iodides and chlorides, esters, ethers, silyl ethers, enol ethers, acetals, aryl fluorides, and even cyclopropyl rings adjacent to the reacting site.

Higher-alkyl Grignard reagents can also be used for the pyrone ring-opening/cross-coupling when the reaction is performed in Et_2O/toluene (1:1; Scheme 2). Since slightly longer reaction times are needed, the corresponding 2*E* isomers were selectively formed. Likewise, the consecutive introduction of two different alkyl groups is feasible starting from hydroxypyrone triflate derivatives such as **1** (Scheme 2).

Table 2: Iron-catalyzed reactions of 2-pyrone derivatives with MeMgBr.



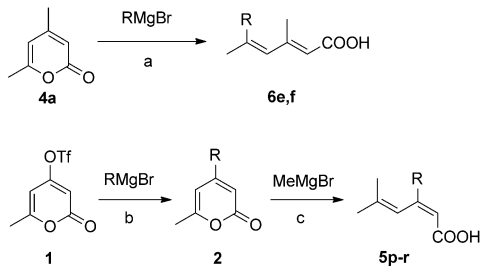
4 **5** **6**

Entry	Product		Cond.[a]	Yield [%]	2*Z*/2*E*[b]
1		**5b**	A[c]	86	7:1
2		**6b**	B	88	1:8
3		**5c**	A[c]	94	>10:1
4		**6c**	B	92	1:10
5		**5d**	C	92	>20:1
6		**6d**	B[d]	82	1:8
7		**5e**	C	93	>20:1
8		**5f**	C	90	>20:1
9		**5g**	C	90 (X=Cl)	>20:1
10		**5h**	C	68 (X=I)	>20:1
11		**5i**	A	72 (R=Me)	>20:1
12		**5j**	A	80 (R=CH_2OMe)	>20:1
13		**5k**	A	88 (R=H)	>20:1
14		**5l**	A	85 (R=3-OMe)	>20:1
15		**5m**	A	86 (R=4-F)	>20:1
16		**5n**	A	78	>20:1
17		**5o**	A	72	>20:1

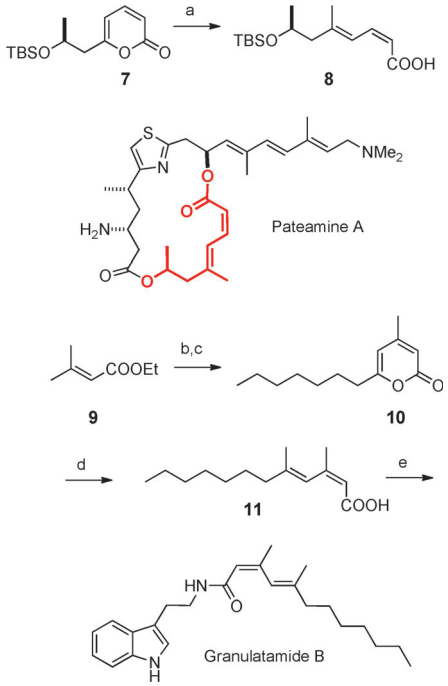
[a] Conditions A: MeMgBr in Et_2O, [Fe(acac)$_3$] (5 mol%), Et_2O/toluene (1:1, 0.025 M), −30 °C, 20 min; Conditions B: MeMgBr in Et_2O, [Fe(acac)$_3$] (5 mol%), Et_2O/toluene (1:1, 0.025 M), −30 °C→RT, 40 min; Conditions C: MeMgBr in Et_2O, [Fe(acac)$_3$] (5 mol%), Et_2O (0.05 M), −30 °C, 20 min. [b] Determined by ^{1}H NMR spectroscopy. [c] Performed at −60 °C for 40 min. [d] Performed in THF at 0 °C→RT (0.025 M). TBS = *tert*-butyldimethylsilyl.

Many applications of this new methodology can be perceived, not least because of the ready availability of 2-pyrone derivatives by a host of different methods.[20,24] Our first foray concerned the marine metabolite pateamine A which embodies a non-thermodynamic *Z*,*E*-configured diene carboxylate in its macrodiolide frame (Scheme 3).[25] This sensitive segment was prepared in excellent isomeric purity by the iron-catalyzed formal ring-opening/cross-coupling of the simple pyrone derivative **7**. Pateamine A is a potent inhibitor of eukaryotic translation initiation,[26] exhibits considerable immunosuppressive activity,[25] and was recently found to prevent cachexia-induced muscle wasting in mice.[27] Cachexia is a potentially lethal syndrome affecting many cancer and AIDS patents, and pateamine A is the first small molecule that was reported to exert an appreciable therapeutic effect on this severe disease in animal models.

The total synthesis of the cytotoxic tryptamine derivative granulatamide B, isolated from the gorgonian *Eunicella granulate*, further illustrates the power of the new methodology (Scheme 3).[28] Multigram amounts of the required pyrone substrate **10** were obtained by condensation of the cheap 3-methyl-crotonate **9** and octanoyl



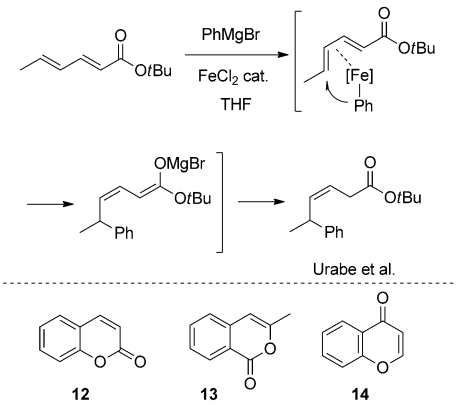
Scheme 2. a) RMgBr, [Fe(acac)$_3$] (5 mol%), Et$_2$O/toluene (1:1, 0.025 M), −30°C, 1 h, 84% (R = hexyl, d.r. > 10:1), 82% (R = -(CH$_2$)$_3$Ph, d.r. > 10:1); b) RMgX, [Fe(acac)$_3$] (5 mol%), THF/NMP (10:1), −78°C, 78% (R = *i*Pr), 74% (R = isobutyl), 60% (R = -(CH$_2$)$_3$Ph); c) MeMgBr in Et$_2$O, [Fe(acac)$_3$] (5 mol%), Et$_2$O/toluene (1:1, 0.025 M), −30°C, 20 min, 68% (R = *i*Pr, 2*Z*/2*E* > 20:1), 84% (R = isobutyl, 2*Z*/2*E* > 20:1), 73% (R = -(CH$_2$)$_3$Ph, 2*Z*/2*E* > 20:1). NMP = 1-methyl-2-pyrrolidinone.



Scheme 3. a) MeMgBr (in Et$_2$O), [Fe(acac)$_3$] (5 mol%), Et$_2$O/toluene (1:1, 0.025 M), −60°C, 80% (2*Z*/2*E* > 10:1); b) octanoyl chloride, AlCl$_3$, CH$_2$Cl$_2$, reflux; c) H$_2$SO$_4$, HOAc, 40°C, 87% (over both steps); d) MeMgBr (in Et$_2$O), [Fe(acac)$_3$] (5 mol%), Et$_2$O/toluene (1:1, 0.05 M), −30°C, 83% (2*Z*/2*E* > 20:1); e) tryptamine, HOBt, EDC·HCl, Et$_3$N, CH$_2$Cl$_2$/DMF, 82%. EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethyl-carbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole, TBS = *tert*-butyldimethylsilyl.

chloride.[24] Subsequent ring-opening/cross-coupling proceeded smoothly under the standard reaction conditions to give the acid **11** as a single isomer (83%, 2.5 mmol scale), which was condensed with tryptamine to furnish granulatamide B. Our sample was identical in all regards with the isolated natural product.[28]

Although the mechanism of this formal ring-opening/cross-coupling reaction is still under investigation, our preliminary data render a standard redox cycle involving oxidative addition/reductive elimination unlikely. Otherwise

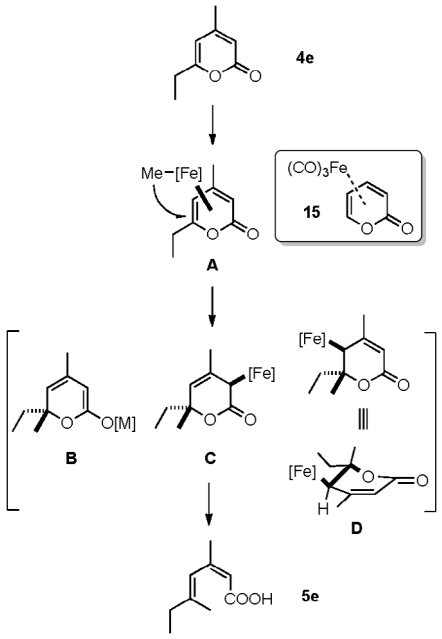


Scheme 4. Proposed mechanism of the iron-catalyzed 1,6-additon reaction developed by Urabe and co-workers (Ref. [30]). Substrates that were found not to participate in the iron-catalyzed formal ring-opening/cross-coupling.

it would be difficult to explain why the closely related substrates **12**–**14** could not be engaged (Scheme 4). Even in the presence of an iron catalyst, MeMgCl simply added to their respective carbonyl groups. Rather, it is believed that the affinity of low-valent iron to 1,3-dienes is the key enabling feature for the new transformation described herein.[29] The reaction may therefore be related to the 1,6-additon processes described by Urabe and co-workers, who showed that α,β,γ,δ-unsaturated esters, amides, and sulfones react with aryl Grignard reagents in the presence of catalytic amounts of FeCl$_2$ to furnish *Z*-configured products exclusively (Scheme 4).[30] The striking regio- and stereoselectivity of this transformation was explained by a transient *s-cis* diene iron complex as the key reactive intermediate.

The notion that the ring-opening/cross-coupling occurs by a similar pathway is supported by the known complex **15** in which 2-pyrone serves as an η^4-bound diene ligand to an iron center (Scheme 5).[31] In the presence of alkyllithium reagents however, **15** reacts at the lactone carbonyl rather than at the enol site.[31] Therefore we propose that the critical delivery of the methyl group in our reaction occurs by an inner-sphere mechanism once a π-complex of type **A** between the pyrone substrate and an iron species carrying a methyl substituent has been formed. Previous investigations from this laboratory showed that the exhaustive methylation of Fe^{II} provides ate complexes such as [{(Me$_4$Fe)·(MeLi)}{Li·(OEt$_2$)}$_2$] (**16**) as the primary products.[32,33] Control experiments confirmed that **16** is both, an adequate stoichiometric nucleophile to effect formal ring-opening/cross-coupling of the model compound **4a**, as well as a competent catalyst for the reaction of this substrate with MeMgBr. Under its aegis (15 mol%), **5a** was formed in 82% yield with high *Z*/*E* selectivity (9:1).

Methyl transfer by formal conjugate addition to the π system of the pyrone is supposed to engender formation of an iron (or magnesium) enolate of type **B**. Subsequent electrocyclic ring-opening might account for the formation of the diene carboxylate products. This step resembles the base-mediated ring-opening of unsaturated lactones, which has ample precedent in the literature.[34] Although this pathway is suggestive, the actual mechanism of the newly



Scheme 5. Conceived mechanistic scenarios.

discovered formal ring-opening/cross-coupling reaction must be more involved. In any case, an ordinary electrocyclic opening of an enolate of type **B** hardly explains why the incoming methyl group replaces the lactone entity of the 2-pyrone ring with strict retention of configuration of the enolic double bond. Virtually no trace of the other isomer was detected even if the two substituents at the 6-position are of similar size as is the case for **5e** (Me versus Et, Scheme 5). This selectivity pattern mandates a stereochemical communication between the breaking bond and the metal center, which a flat O-metalated enolate **B** does not provide. A C-metalated species of type **C** could be invoked, for which there is some precedent in the literature.[35] Alternatively, one may speculate that the species accountable for ring opening is a carbometalation product of type **D**, which formed upon initial *syn*-selective 1,2-insertion of the π system into the Fe–Me bond. If a subsequent *trans* elimination from the most stable conformer is faster than a metallotropic rearrangement into **B**/**C**, a sequence of two stereodefined elementary steps will ensue and could explain the experimental results.

This open mechanistic aspect notwithstanding, we believe that this new methodology provides a useful entry into stereodefined dienyl carboxylates and derivatives thereof, starting from readily available 2-pyrones, and adds a valuable facet to the timely field of iron catalysis. From the conceptual viewpoint, the reaction epitomizes a largely underrepresented mode of cross-coupling based upon ring-opening of a heterocyclic scaffold. As such, the present study may inspire methodological developments in related areas of catalysis as well. Further investigations in this laboratory are underway to explore some of these possibilities.

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[1] B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500 – 1511.
[2] E. Nakamura, N. Yoshikai, *J. Org. Chem.* **2010**, *75*, 6061 – 6067.
[3] T. Hatakeyama, K. Ishizuka, M. Nakamura, *J. Synth. Org. Chem. Jpn.* **2011**, *69*, 1282 – 1298.
[4] G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199 – 1205.
[5] E. B. Bauer, *Curr. Org. Chem.* **2008**, *12*, 1341 – 1369.
[6] W. M. Czaplik, M. Mayer, J. Cvengroš, A. Jacobi von Wangelin, *ChemSusChem* **2009**, *2*, 396 – 417.
[7] K. Gopalaiah, *Chem. Rev.* **2013**, *113*, 3248 – 3296.
[8] A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624 – 629.
[9] a) C. Risatti, K. J. Natalie, Jr., Z. Shi, D. A. Conlon, *Org. Process Res. Dev.* **2013**, *17*, 257 – 264; b) A. Fürstner, A. Leitner, G. Seidel, *Org. Synth.* **2005**, *81*, 33 – 41.
[10] a) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856 – 13863; b) A. Fürstner, A. Leitner, *Angew. Chem.* **2002**, *114*, 632 – 635; *Angew. Chem. Int. Ed.* **2002**, *41*, 609 – 612.
[11] a) A. Fürstner, A. Leitner, *Angew. Chem.* **2003**, *115*, 320 – 323; *Angew. Chem. Int. Ed.* **2003**, *42*, 308 – 311; b) B. Scheiper, F. Glorius, A. Leitner, A. Fürstner, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11960 – 11965.
[12] a) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943 – 3949; b) G. Seidel, D. Laurich, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3950 – 3952; c) A. Fürstner, P. Hannen, *Chem. Eur. J.* **2006**, *12*, 3006 – 3019; d) A. Fürstner, A. Schlecker, *Chem. Eur. J.* **2008**, *14*, 9181 – 9191.
[13] For representative studies, see: a) A. L. Silberstein, S. D. Ramgren, N. K. Garg, *Org. Lett.* **2012**, *14*, 3796 – 3799; b) T. Mesganaw, N. K. Garg, *Org. Process Res. Dev.* **2013**, *17*, 29 – 39; c) T. Agarwal, S. P. Cook, *Org. Lett.* **2013**, *15*, 96 – 99; d) O. M. Kuzmina, A. K. Steib, D. Flubacher, P. Knochel, *Org. Lett.* **2012**, *14*, 4818 – 4821; e) M. C. Perry, A. N. Gillett, T. C. Law, *Tetrahedron Lett.* **2012**, *53*, 4436 – 4439; f) G. Cahiez, O. Gager, J. Buendia, C. Patinote, *Chem. Eur. J.* **2012**, *18*, 5860 – 5863; g) R. K. Shiroodi, A. S. Dudnik, V. Gevorgyan, *J. Am. Chem. Soc.* **2012**, *134*, 6928 – 6931; h) S. Gülak, A. Jacobi von Wangelin, *Angew. Chem.* **2012**, *124*, 1386 – 1390; *Angew. Chem. Int. Ed.* **2012**, *51*, 1357 – 1361; i) H. Nishikado, H. Nakatsuji, K. Ueno, R. Nagase, Y. Tanabe, *Synlett* **2010**, 2087 – 2092; j) C. M. Rao Volla, P. Vogel, *Angew. Chem.* **2008**, *120*, 1325 – 1327; *Angew. Chem. Int. Ed.* **2008**, *47*, 1305 – 1307; k) B.-J. Li, L. Xu, Z.-H. Wu, B.-T. Guan, C.-L. Sun, B.-Q. Wang, Z.-J. Shi, *J. Am. Chem. Soc.* **2009**, *131*, 14656 – 14657; l) U. S. Larsen, L. Martiny, M. Begtrup, *Tetrahedron Lett.* **2005**, *46*, 4261 – 4263; m) K. Itami, S. Higashi, M. Mineno, J. Yoshida, *Org. Lett.* **2005**, *7*, 1219 – 1222; n) N. Hayashi, M. Nakada, *Tetrahedron Lett.* **2009**, *50*, 232 – 235; o) G. Cahiez, O. Gager, V. Habiak, *Synthesis* **2008**, 2636 – 2644; p) G. Cahiez, V. Habiak, O. Gager, *Org. Lett.* **2008**, *10*, 2389 – 2392.
[14] C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293 – 1314.
[15] a) For nickel-catalyzed ring-opening/cross-coupling of cyclic enol ethers, see: E. Wenkert, E. L. Michelotti, C. S. Swindell, M. Tingoli, *J. Org. Chem.* **1984**, *49*, 4894 – 4899; b) P. J. Kocieński, M. Pritchard, S. N. Wadman, R. J. Whitby, C. L. Yeates, *J. Chem. Soc. Perkin Trans. 1* **1992**, 3419 – 3429; c) P. A. Ashworth, N. J. Dixon, P. J. Kocieński, S. N. Wadman, *J. Chem. Soc. Perkin Trans. 1* **1992**, 3431 – 3438; d) for cross-coupling/desulfurization of various sulfur-containing heterocycles, see: T.-Y. Luh, Z.-J. Ni, *Synthesis* **1990**, 89 – 103; e) M. Tiecco, M. Tingoli, E. Wenkert, *J. Org. Chem.* **1985**, *50*, 3828 – 3831; f) A. Oviedo, A. Arévalo, M. Flores-Alamo, J. J. Garcia, *Organometallics* **2012**, *31*, 4039 – 4045; g) Y.-H. Cho, A. Kina, T. Shimada, T. Hayashi, *J. Org. Chem.* **2004**, *69*, 3811 – 3823; h) for a ring opening Kumada coupling of cyclic ethers, see: J. W. Dankwardt, *Angew. Chem.*

2004, *116*, 2482 – 2486; *Angew. Chem. Int. Ed.* **2004**, *43*, 2428 – 2432; i) for formal ring-opening/cross-coupling of cyclic enol ethers by a 1,2-metallate rearrangement, see: K. Jarowicki, P. J. Kocienski, L. Qun, *Org. Synth.* **2002**, *79*, 11 – 18.

[16] For representative studies on uncatalyzed ring-opening of pyrylium and pyridinium salts or dihydrofurans on treatment with organometallic reagents, see the following and literature cited therein: a) M. Furber, J. M. Herbert, R. J. K. Taylor, *J. Chem. Soc. Perkin Trans. 1* **1989**, 683 – 690; b) B. Feith, H.-M. Weber, G. Maas, *Chem. Ber.* **1986**, *119*, 3276 – 3296; c) T. Fujisawa, Y. Kurita, M. Kawashima, T. Sato, *Chem. Lett.* **1982**, 1641 – 1642; d) for accounts on heterocycle ring-opening by other nucleophiles, see: C. D. Vanderwal, *J. Org. Chem.* **2011**, *76*, 9555 – 9567; e) G. Piancatelli, M. D'Auria, F. D'Onofrio, *Synthesis* **1994**, 867 – 889.

[17] $[Fe(acac)_3]$ (99.9 + % purity) is the pre-catalyst of choice because it is cheap, non-hygroscopic, and commercially available. While $[(tmeda)FeI_2]$ is similarly effective, the use of $[(depe)_2FeCl_2]$ or $[(dppp)FeCl_2]$ basically halted the conversion (< 10 %, GC). No reaction was observed in the absence of an iron salt. depe = bis(diethylphosphino)-ethane; dppp = bis(diphenylphosphino)propane; tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

[18] It is unlikely that trace impurities of copper in $[Fe(acac)_3]$ are the actual catalyst because copper leads to 1,4-addition of Grignard reagents to 2-pyrones without ring opening, see: B. Mao, M. Fañanás-Mastral, B. L. Feringa, *Org. Lett.* **2013**, *15*, 286 – 289.

[19] F. Frébault, M. T. Oliveira, E. Wöstefeld, N. Maulide, *J. Org. Chem.* **2010**, *75*, 7962 – 7965.

[20] T. L. Gilchrist, *Heterocyclenchemie*, VCH, Weinheim, **1995**.

[21] For iron-catalyzed C–C bond formation under opening of a strained carbocyclic ring, see: B. D. Sherry, A. Fürstner, *Chem. Commun.* **2009**, 7116 – 7118.

[22] For a different entry into these motifs starting from pyrones, see: C. Souris, F. Frébault, A. Patel, D. Audisio, K. N. Houk, N. Maulide, *Org. Lett.* **2013**, *15*, 3242 – 3245.

[23] A. Fürstner, K. Majima, R. Martín, H. Krause, E. Kattnig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992 – 2004.

[24] The ready preparation of the substrates used herein illustrates this aspect. For details, see the Supporting Information. For a particularly convenient new entry into 4-hydroxy-2-pyrones, see: W. Chaładaj, M. Corbet, A. Fürstner, *Angew. Chem.* **2012**, *124*, 7035 – 7039; *Angew. Chem. Int. Ed.* **2012**, *51*, 6929 – 6933.

[25] a) P. T. Northcote, J. W. Blunt, M. H. G. Munro, *Tetrahedron Lett.* **1991**, *32*, 6411 – 6414; b) D. Romo, R. M. Rzasa, H. A. Shea, K. Park, J. M. Langenhan, L. Sun, A. Akhiezer, J. O. Liu, *J. Am. Chem. Soc.* **1998**, *120*, 12237 – 12254; c) G. Pattenden, D. J. Critcher, M. Remuiñán, *Can. J. Chem.* **2004**, *82*, 353 – 365.

[26] W.-K. Low, Y. Dang, T. Schneider-Poetsch, Z. Shi, N. S. Choi, R. M. Rzasa, H. A. Shea, S. Li, K. Park, G. Ma, D. Romo, J. O. Liu, *Methods Enzymol.* **2007**, *431*, 303 – 324.

[27] S. Di Marco, A. Cammas, X. J. Lian, E. N. Kovacs, J. F. Ma, D. T. Hall, R. Mazroui, J. Richardson, J. Pelletier, I. E. Gallouzi, *Nat. Commun.* **2012**, *3*, 896.

[28] F. Reyes, R. Martín, R. Fernández, *J. Nat. Prod.* **2006**, *69*, 668 – 670.

[29] M. F. Semmelhack in *Organometallics in Synthesis. A Manual*, 2nd ed. (Ed.: M. Schlosser), Wiley, Chichester, pp. 1003 – 1121.

[30] a) K. Fukuhara, H. Urabe, *Tetrahedron Lett.* **2005**, *46*, 603 – 606; b) S. Okada, K. Arayama, R. Murayama, T. Ishizuka, K. Hara, N. Hirone, T. Hata, H. Urabe, *Angew. Chem.* **2008**, *120*, 6966 – 6970; *Angew. Chem. Int. Ed.* **2008**, *47*, 6860 – 6864; c) T. Hata, T. Nakada, Y. T. Oh, N. Hirone, H. Urabe, *Adv. Synth. Catal.* **2013**, *355*, 1736 – 1740.

[31] C. H. DePuy, R. L. Parton, T. Jones, *J. Am. Chem. Soc.* **1977**, *99*, 4070 – 4075.

[32] A. Fürstner, H. Krause, C. W. Lehmann, *Angew. Chem.* **2006**, *118*, 454 – 458; *Angew. Chem. Int. Ed.* **2006**, *45*, 440 – 444.

[33] A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 8773 – 8787.

[34] For a leading reference see the following and the literature cited therein: B. Schmidt, O. Kunz, *Eur. J. Org. Chem.* **2012**, 1008 – 1018.

[35] a) For structural evidence for C-metalated iron ester enolates, see: P. Laurent, S. Sabo-Etienne, A.-M. Larsonneur, H. des Abbayes, *J. Chem. Soc. Chem. Commun.* **1988**, 929 – 930; b) for O-metalated iron ketone enolates, see: S. Sabo-Etienne, H. des Abbayes, L. Toupet, *Organometallics* **1987**, *6*, 2262 – 2263; c) D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura, H. Nagashima, *Chem. Commun.* **2012**, *48*, 12231 – 12333; d) S. Kiyota, J.-I. Tamuki, N. Komine, M. Hirano, S. Komiya, *Chem. Lett.* **2005**, *34*, 498 – 499.

