

Iron-Catalyzed Reactions of 2-Pyridone Derivatives: 1,6-Addition and Formal Ring Opening/Cross Coupling

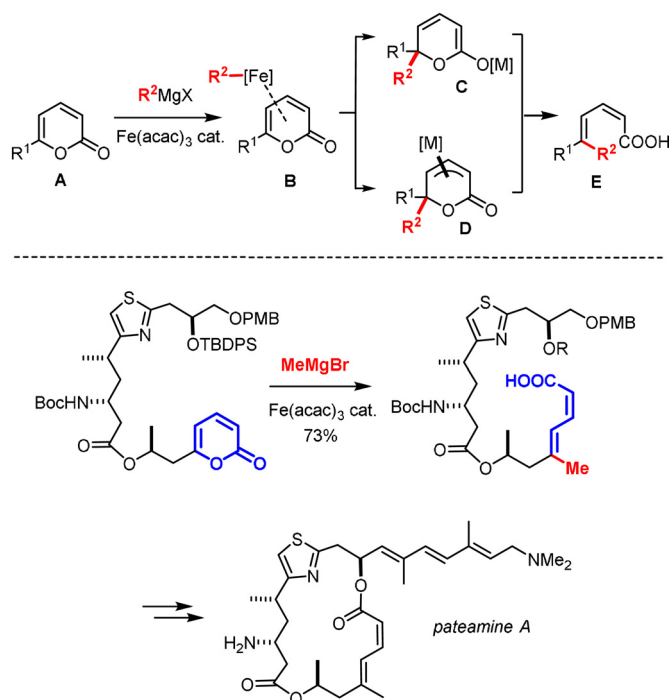
Lin Huang, Yiting Gu, and Alois Fürstner*^[a]

Dedicated to Prof. Henry N. C. Wong on the occasion of his 70th birthday

Abstract: In the presence of simple iron salts, 2-pyridone derivatives react with Grignard reagents under mild conditions to give the corresponding 1,6-addition products; if the reaction medium is supplemented with an aprotic dipolar cosolvent after the actual addition step, the intermediates primarily formed succumb to ring opening, giving rise to non-thermodynamic *Z,E*-configured dienoic acid amide derivatives which are difficult to make otherwise. Control experiments as well as the isolation and crystallographic characterization of a (tricarbonyl)iron pyridone complex suggest that the active iron catalyst generated in situ exhibits high affinity to the polarized diene system embedded into the heterocyclic ring system of the substrates, which likely serves as the actual recognition element.

Introduction

During our investigations into cross coupling, cycloaddition and cycloisomerization reactions using cheap, practical, non-toxic and benign iron catalysts,^[1–4] we discovered that 2-pyrones **A** undergo an unusual transformation when treated with Grignard reagents in the presence of catalytic Fe(acac)₃ at low temperature (Scheme 1). These substrates swiftly convert into dienoic acid derivatives **E** by what appears to be a ring opening/cross coupling reaction, in which the enol ester subunit of the heterocyclic ring formally gains the role of a leaving group that is replaced by the incoming nucleophile with retention of configuration.^[5] Uncatalyzed attack of the organomagnesium reagent on the lactone carbonyl group of **A** is too slow to be competitive^[6] and the non-thermodynamic *Z,E*-configured 1,3-diene motif of the resulting product **E** usually persists under the mild conditions.^[7] Moreover, the low-valent iron catalyst



Scheme 1. Iron-catalyzed formal ring opening/cross coupling of pyrones.

generated in situ proved compatible with numerous functional groups, including heteroatom donor sites that interfere with more traditional cross coupling. For its favorable profile and the ready availability of differently substituted pyrone derivatives,^[8,9] this unorthodox transformation laid the ground for concise approaches to the marine natural product pateamine **A** and its almost equipotent analog DMDA-Pat **A**, in that it allowed the very sensitive but critically important dienoate subunit of these highly cytotoxic agents to be unveiled at a late stage from a robust heterocyclic precursor.^[10,11]

Indirect evidence, however, suggested that the net outcome of the reaction is probably not the result of a true cross coupling manifold; rather, the reaction is thought to proceed via an initial 1,6-addition followed by ring opening of the resulting intermediate of type **C** or **D**.^[5,10,12] This latter step could proceed in an electrocyclic or ionic fashion; in any case, it must be fast and facile even at low temperature, because the proposed intermediates defied all attempts at characterization. Provided that this mechanistic hypothesis is valid, it should be possible to engage other heterocyclic compounds containing a polarized diene entity into similar transformations.

[a] Dr. L. Huang, Y. Gu, Prof. A. Fürstner
Max-Planck-Institut für Kohlenforschung
45470 Mülheim/Ruhr (Germany)
E-mail: fuerstner@kofo.mpg.de

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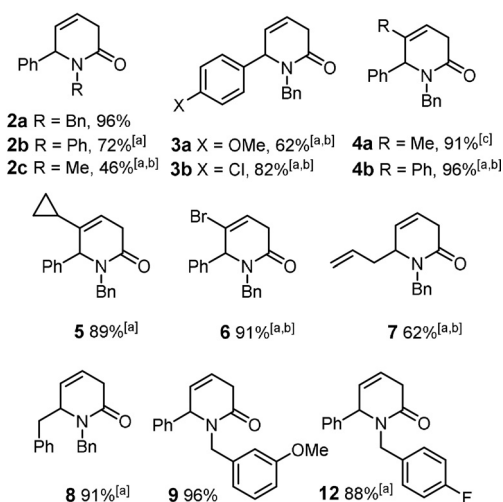
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Results and Discussion

2-Pyridones are obvious and relevant candidates.^[13–15] the enamide embedded in their ring system is certainly not a privileged subunit for classical cross coupling via oxidative insertion/reductive elimination, whereas an iron catalyzed 1,6-addition is feasible since acyclic $\alpha,\beta,\gamma,\delta$ -unsaturated amides have previously been shown to react with aryl-Grignard reagents in the presence of catalytic amounts of FeCl_2 with high selectivity.^[16,17] Indeed, the *N*-benzylated substrate **1**, on treatment with PhMgBr and $\text{Fe}(\text{acac})_3$ (5 mol%), gave product **2a** in which the heterocyclic ring is intact (Table 1); under optimized conditions (THF, -45°C), the yield was almost quantitative (entry 6). $\text{Fe}(\text{acac})_3$, $\text{Fe}(\text{acac})_2$ and FeCl_3 work almost equally well,^[18] whereas the reaction did not proceed with FeF_3 or in the absence of an iron precatalyst.^[19]

As evident from the examples shown in Scheme 2, the reaction is tolerant of different polar and apolar functionalities in the substrate as well as in the Grignard reagent. The arguably most notable case is product **6** derived from 1-benzyl-5-bro-



Scheme 2. Scope of the iron-catalyzed 1,6-addition reaction to 2-pyridones; unless stated otherwise, all reaction were performed with RMgBr (1.5 equiv), $\text{Fe}(\text{acac})_3$ (5 mol%) in THF at -45°C ; [a] with 3 equiv of RMgX ; [b] at -20°C ; [c] at -45°C to RT.

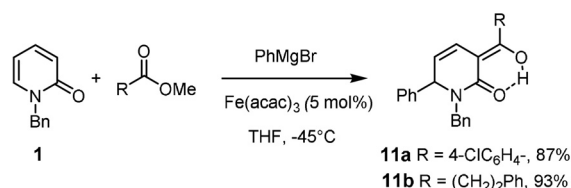
Table 1. Reaction optimization and gathering of mechanistically relevant information (entries 10–15, see below).^[a]

| Entry | FeX_n | Solvent | T [$^\circ\text{C}$] | 2 ^[b] |
|-------|-------------------------------------------------------------------------|-----------------------|-----------------------------|------------------------|
| 1 | $\text{Fe}(\text{acac})_3$ | Et_2O | -78 | 19 |
| 2 | $\text{Fe}(\text{acac})_3$ | Et_2O | -45 | 69 |
| 3 | $\text{Fe}(\text{acac})_3$ | Et_2O | -20 | 46 ^[c] |
| 4 | $\text{Fe}(\text{acac})_3$ | toluene | -45 | 78 |
| 5 | $\text{Fe}(\text{acac})_3$ | THF | -45 | 94 (83) ^[d] |
| 6 | $\text{Fe}(\text{acac})_3$ | THF | -45 | 96 ^[e,f] |
| 7 | FeCl_3 | THF | -45 | 93 |
| 8 | FeF_3 | THF | -45 | n.r. |
| 9 | $\text{Fe}(\text{acac})_2$ | THF | -45 | 89 |
| 10 | $[(\text{Me}_4\text{Fe})\cdot(\text{MeLi})][\text{Li}(\text{OEt}_2)_2]$ | THF | $-45 \rightarrow \text{RT}$ | 78 |
| 11 | $\text{Fe}(\text{CO})_5$ $(\text{CO})_3\text{Fe}$ | THF | $-45 \rightarrow \text{RT}$ | 78 |
| 12 | | THF | $-45 \rightarrow \text{RT}$ | 65 |
| 13 | | THF | $-45 \rightarrow \text{RT}$ | 99 |
| 14 | | THF | $-45 \rightarrow \text{RT}$ | 45 |
| 15 | | THF | $-45 \rightarrow \text{RT}$ | 75 |

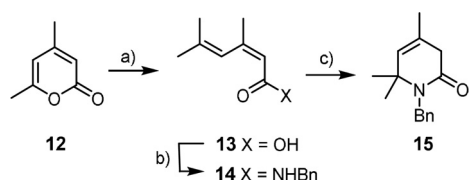
[a] unless stated otherwise, all reactions were carried out using PhMgBr (3 equiv); [b] determined by NMR, unless stated otherwise; [c] small amounts of unidentified byproducts were detected in the crude mixture; [d] using PhMgCl ; [e] isolated yield; [f] using only 1.5 equivalents of PhMgBr .

mopyridin-2(1*H*)-one: the fact that the bromide substituent persists under the chosen reaction conditions implies that the iron catalyzed addition reaction to the heterocyclic ring is even faster than a regular iron catalyzed cross coupling, although the latter process is known to proceed very rapidly at low temperatures,^[20–23] such stunning “inverse” chemoselectivity is exceedingly rare.^[24] Since spontaneous ring opening did not occur, it was also possible to intercept the enolate primarily formed by 1,6-addition with an appropriate electrophilic partner (Scheme 3). The high yielding preparation of compounds **11a,b** illustrates this point (for the structure of compound **11a** in the solid state, see the SI). Once again it is remarkable that the iron catalyzed 1,6-addition to the 2-pyridone outcompetes the uncatalyzed reaction of the Grignard reagent with the (aromatic or aliphatic) ester present in the mixture; likewise, the reaction is faster than cross coupling with the chloride substituent of methyl chlorobenzoate used to make **11a**, which is known to be an excellent substrate otherwise.^[25–27]

These results are consistent with a 1,6-addition reaction as the actual iron catalyzed event; it remained to be clarified, however, why this step is followed by instantaneous ring opening in the pyrone series but not with 2-pyridones such as **1**. To this end, we transformed the pyrone-derived dienonic acid **13** into the corresponding amide **14** (Scheme 4); on deprotonation with LiHMDS and warming of the resulting mixture, **14** cyclized to the corresponding dihydropyridin-2-one **15**. Since this control experiment suggested that the cyclic form is thermo-



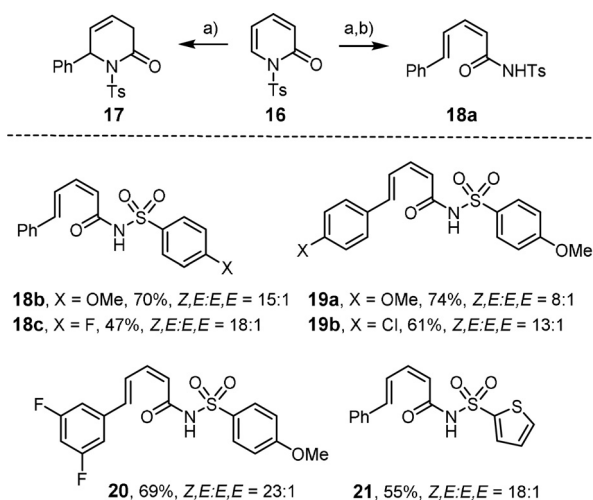
Scheme 3. Iron-catalyzed three component coupling reactions.



Scheme 4. a) MeMgBr, Fe(acac)₃ (5 mol%), Et₂O, -30 °C, 93%; b) BnNH₂, HOBT, EDC-HCl, Et₃N, CH₂Cl₂, DMF, 92%; c) LiHMDS, DMF, 100 °C, 67%; EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBT = 1-hydroxybenzotriazole; LiHMDS = lithium hexamethyldisilazide.

dynamically more stable in this case, attempts were made to change the tip in favor of the ring opened product by altering the *N*-substituent. Based on literature precedent,^[28] the *N*-tosyl derivative **16** was deemed adequate (the structure of **16** in the solid state is contained in the SI) (Scheme 5): initially, however, only the 1,6-adduct **17** was attained on reaction with PhMgBr and catalytic Fe(acac)₃. Under standard conditions, the conversion remained incomplete, but the outcome could be improved in the presence of PPh₃ (10 mol%) in Et₂O as the solvent. Although the dihydropyridone ring of **17** is hardly puckered, the phenyl substituent is axially oriented to avoid eclipsing with the adjacent *N*-Ts group (Figure 1).^[29] Interestingly, addition of DMF to the crude mixture and raising the temperature from -30 °C to -10 °C entailed the expected ring opening with formation of amide **18a** in respectable yield and excellent geometrical purity in favor of the non-thermodynamic *Z,E*-diene isomer,^[30] this stereochemical assignment was confirmed by single crystal X-ray diffraction (Figure 2). The additional examples compiled in Scheme 5 show that this method has a reasonable scope and provides access to products that are difficult to make otherwise.

The data outlined above leave little doubt that the observed ring opening/cross coupling of 2-pyrone and 2-pyridone derivatives is the net outcome of two consecutive steps: of them,



Scheme 5. a) PhMgBr, Fe(acac)₃ (5 mol%), Ph₃P (10 mol%), Et₂O, -30 °C, 62%; b) DMF, -30 °C → -10 °C, 60% (over both steps), *Z,E,E,E* ≥ 15:1.

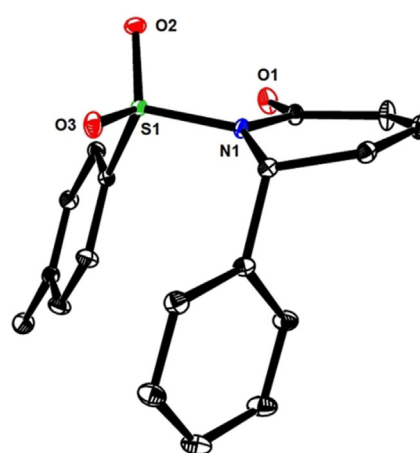


Figure 1. Structure of compound **17** in the solid state; H-atoms are omitted for clarity.

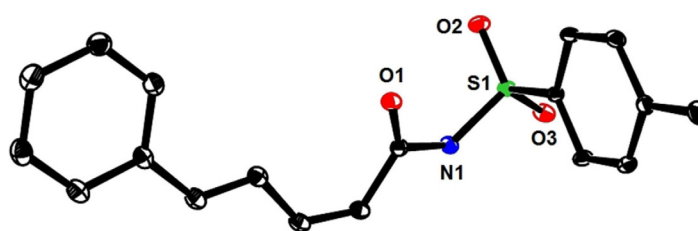
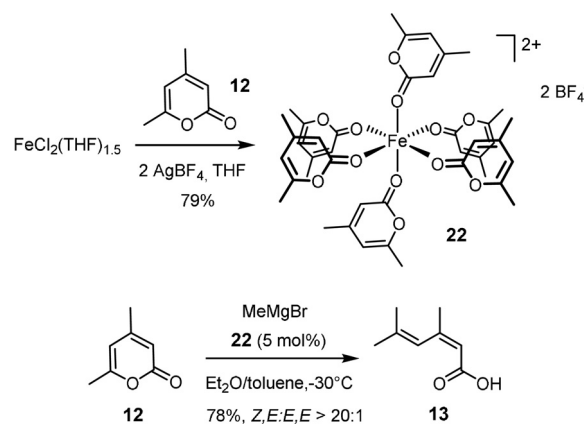


Figure 2. Structure of compound **18a** in the solid state; H-atoms are omitted for clarity.

only the initial 1,6-addition is thought to proceed under the aegis of an iron catalyst, whereas the actual ring cleavage is most likely an uncatalyzed event, which is much more facile for 2-pyrones than for *N*-tosylated 2-pyridones.^[30] To gain further insights, we studied the interaction of such substrates with various iron sources. The Fe(+2) or Fe(+3) precatalyst is supposed to act as a simple Lewis acid that binds to the more accessible lone pair of the carbonyl group: using an ionized Fe(+2) salt, we managed to obtain a homoleptic adduct that is stable enough to be isolated and catalytically competent (Scheme 6). The structure of complex **22** in the solid state



Scheme 6. Preparation of the homoleptic iron pyrone complex **22** and ex-amination of its catalytic competence; in the solid state, the unit cell of **22** contains an additional but unbound molecule of **12**.

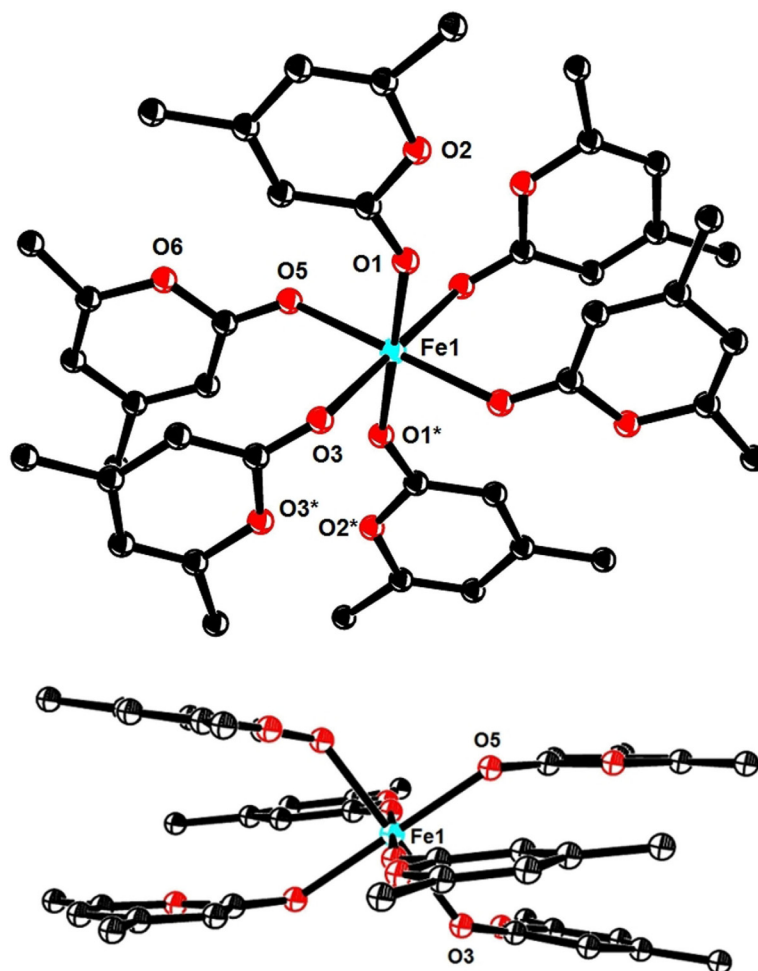


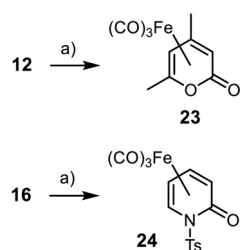
Figure 3. Structure of the Lewis acid/Lewis base adduct **22** in two different orientations; the BF_4^- counterions as well as an additional co-crystallized but unbound molecule of **12** are not shown for clarity; the full structure is contained in the SI.

(Figure 3) shows an octahedral environment comprised of six 2-pyrone ligands about the iron center.^[31] The Newman-type projection along the O1-Fe1-O1* axis reveals an interesting organization of the heterocyclic rings via π -stacking (distance between the centroids of the pyrone rings occupying the equatorial positions, 3.53 Å). All lactone carbonyl groups (for example, O1-C1 1.233(2) Å) are elongated by coordination to the Lewis-acidic cation relative to that of the parent pyrone **12** (O1-C1 1.212(1) Å; the structure of **12** in the solid state is contained in the SI).

Although such coordination to an Fe(+2) center certainly activates the carbonyl group and also enhances the vinylogous Michael acceptor properties of the pyrone, it is unlikely that this canonical Lewis acid/base interaction renders the observed 1,6-addition so astoundingly facile. Extensive screening in this laboratory showed that iron is almost uniquely capable in catalyzing this transformation.^[32] Since iron salts react instantly with polar organometallic reagents to give ate-complexes^[33–36] and/or low valent iron species,^[34,37,38] the reasons for the unusually facile addition to pyrones and pyridones are likely rooted in a more specific affinity to substrates of this kind. It is, however, exceedingly difficult to establish the nature of the

active species generated in situ, not least because low valent organometallic iron complexes are highly sensitive, often paramagnetic, and tend to “age” rapidly; moreover, the exact speciation is strongly dependent on the chosen conditions and the presence/absence of polar additives in the mixture.^[39] The mechanistic complexity of the current system is reflected in a number of control experiments, which showed that several well-defined but structurally quite distinct iron species are competent (pre)catalysts (see Table 1): thus, the intricate Fe(+2)-ate complex $[(\text{Me}_4\text{Fe})\cdot(\text{MeLi})][\text{Li}\cdot(\text{OEt}_2)]_2$ (entry 10),^[33] two different Fe⁰ olefin complexes (entries 14, 15),^[37,40] and even catalytic amounts of $\text{Fe}(\text{CO})_5$ (entry 11) or the derived pyridone complex (entry 12) worked well. In contrast to the oxophilicity of Fe(+2) and Fe(+3) salts, many low-valent iron species are inherently carbophilic; 1,3-dienes are amongst the privileged ligands which get activated toward attack by certain nucleophiles, for example, upon coordination to the $[\text{Fe}(\text{CO})_3]$ fragment.^[41–43] Therefore it seemed likely that the polarized diene motif embedded into the pyrone- or pyridone rings constitutes the critical recognition element for the active catalyst. While attempted complexation of **12** or **16** with either $[\text{CpFe}(\text{C}_2\text{H}_4)_2][\text{Li}(\text{tmeda})]$ ^[40,43] or $[\text{dipp}]\text{Fe}(\text{C}_2\text{H}_4)_2$ ^[37,43] failed to afford single

crystals suitable for X-ray diffraction, $\text{Fe}(\text{CO})_5$ served this purpose well. In this context, it is important to note that (tricarbonyl)iron complexes of 2-pyrones had previously been found susceptible to nucleophilic attack at the carbonyl group rather than at the enol ether site,^[44,45] whereas we consider them to be valid models for the reactive intermediate accountable for iron catalyzed 1,6-addition.^[10] Under this premise, 2-pyridones should be amenable to analogous π -complexation in order to explain why they react analogously; this is indeed the case



Scheme 7. a) $\text{Fe}(\text{CO})_5$, $\text{Bu}_2\text{O}/\text{THF}$ (5:1), 65°C , 19% (**23**); 21% (**24**).

(Scheme 7). Figures 4 and 5 illustrate that adduct formation entails massive distortions in both series. Back-bonding from the low-valent metal center into the π^* orbitals of the η^4 -bound heterocyclic ligand is manifest in the massive elongation of the C4–C5 bond (1.418(5) Å in pyrone complex **23** versus 1.340(1) Å in unbound pyrone **12**; the effect is even stronger in the pyridone complex **24** (C4–C5 1.436(2) Å in versus 1.343(2) Å in free **16**). As expected, the C3–C4 bond is somewhat contracted (1.403(5) Å in

23 versus 1.427(1) Å in the **12**; 1.397(2) Å in **24** versus 1.420(3) Å in **16**). Since neither 2-pyrones nor 2-pyridones show significant aromatic character, these heterocycles are torsionally flexible. In fact, the lactone (lactam) moiety is forced out of co-planarity with the olefinic π -system; as a result, orbital overlap is disrupted and the enol ether (enamido) character lost, at least in part. The incipient carbenoid nature of C5, which carries a carbon-metal bond and a leaving group, is unmistakable in the structures of complexes **23**, **24** and related complexes^[10,45] in the solid state. Delivery of an R-group from a putative loaded iron center to the C5 position becomes not only feasible but likely facile,^[46] very much in line with our experimental findings. The concomitant formation of an (iron) enolate enhances the regiochemical course of the reaction and provides an additional driving force; this enolate formation is also “precast” in the structures of **23** or **24**, because the C2–C3

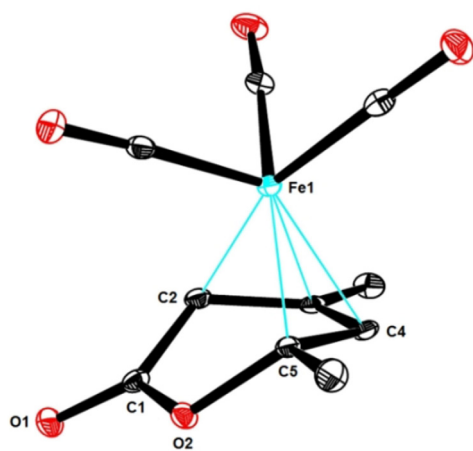


Figure 4. Structure of the pyrone tricarbonyliron complex **23** in the solid state.

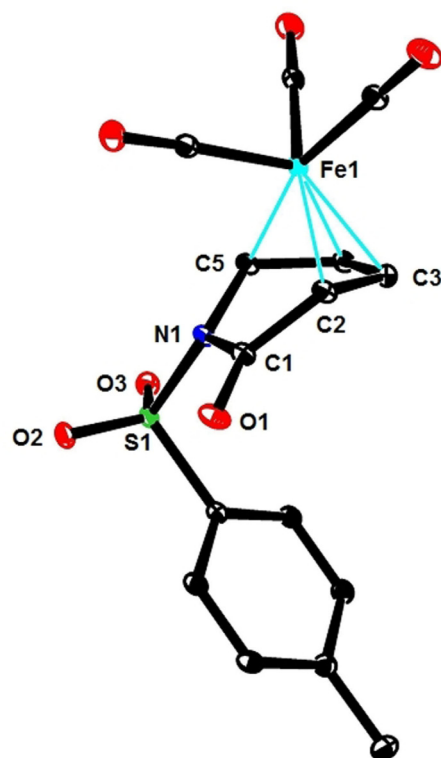
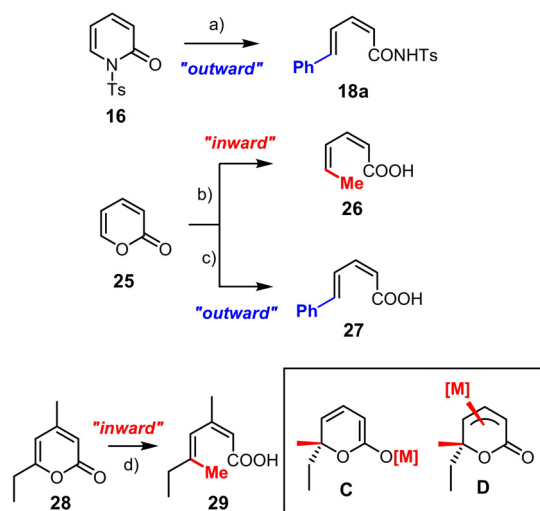


Figure 5. Structure of the pyridone tricarbonyliron complex **24** in the solid state.

bond of the pyrone (pyridone) ligand has already lost much of its former double bond character (1.435(6) Å in **23** versus 1.358(1) Å in **12**; 1.438(2) in **24** versus 1.351(3) Å in **16**) and a carbon-metal bond is also looming. Hence, adducts of this type seem to be ideally set up for regioselective transfer of a hydrocarbonyl residue from a loaded iron center to the heterocyclic ligand framework.

The available experimental evidence is less clear with regard to the subsequent ring opening step. Yet, two pieces of evidence seem to advocate for an ionic rather than electrocyclic mechanism: as outlined above, the addition of DMF is necessary to entail ring cleavage in the pyridone series; pericyclic processes in general, however, are not expected to show such a strong solvent dependence.^[47,48] A perhaps more stringent argument can be seen in the stereochemical course of the reactions (Scheme 8): the outward rotation of the phenyl groups during the opening of **16** and **25** to give **18a** and **27**, respectively, would be in line with the torquoselective preference of this substituent, but the exclusive inward orientation of the methyl group in **26** violates the established selectivity rules of electrocyclic processes;^[49] the selective formation of **18a** and **27** is hence more likely thermodynamic in origin (the structure of **27** in the solid state is contained in the SI). Product **29**, the double bond geometry of which mirrors the stereostructure of the substrate, is arguably an even more stringent case.^[5] An electrocyclic opening of an intermediate of type **C** would hardly entail formation of a single stereoisomer since the two relevant substituents (Me versus Et) have the same electronic character and are similar in size. Rather, this outcome suggests



Scheme 8. a) PhMgBr, Fe(acac)₃ (5 mol %), Ph₃P (10 mol %), Et₂O, -30 °C, then DMF -30 °C → RT, 60%; b) MeMgBr, Fe(acac)₃ (5 mol %), Et₂O, -30 °C, 86%; c) PhMgBr, Fe(acac)₃ (5 mol %), Et₂O, -30 °C, 44%; d) MeMgBr, Fe(acac)₃ (5 mol %), Et₂O/toluene (1:1), -30 °C, 93%.

that some stereochemical communication between the breaking C–O bond and the metal center is operative in the stereo-determining step, as tentatively drawn in **D**. We appreciate, however, that further experimental and computational scrutiny is needed to either confirm or disprove this view.

Conclusions

The present study extends the structural space covered by iron catalyzed C–C-bond formation in general and the rather unconventional formal ring opening/cross coupling in particular. Although not all mechanistic questions could be answered in full detail, the available data suggest that the high affinity of low-valent iron catalysts to (polarized) dienes constitutes a formidable driving force which can likely be exploited in different context too. Further efforts at leveraging this and other as yet untapped opportunities of homogeneous iron catalysis for organic synthesis are underway and will be reported in due course.^[50]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,6-addition · cross coupling · dienes · heterocycles · iron catalysis · ring cleavage

- [1] A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778–789.
- [2] a) A. Fürstner, *Org. Synth.* **2019**, *96*, 1–15; b) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500–1511; c) A. Fürstner, *Angew. Chem. Int. Ed.* **2009**, *48*, 1364–1367; *Angew. Chem.* **2009**, *121*, 1390–1393; d) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624–629.
- [3] a) A. Piontek, E. Bisz, M. Szostak, *Angew. Chem. Int. Ed.* **2018**, *57*, 11116–11128; *Angew. Chem.* **2018**, *130*, 11284–11297; b) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387; c) G. Cahiez, A. Moyeux, J. Cossy, *Adv. Synth. Catal.* **2015**, *357*, 1983–1989; d) E. Nakamura, T. Hatakeyama, S. Ito, K. Ishizuka, L. Ilies, M. Nakamura, *Org. React.* **2014**, *83*, 1–209; e) W. M. Czaplik, M. Mayer, J. Cvengroš, A. Jacobi von Wangelin, *ChemSusChem* **2009**, *2*, 396–417.
- [4] a) *Iron Catalysis. Fundamentals and Applications* (Topics in Organometallic Chemistry, Vol. 33) (Ed.: B. Plietker), Springer, Heidelberg, **2011**; b) *Iron Catalysis II* (Topics in Organometallic Chemistry, Vol. 50) (Ed.: E. B. Bauer), Springer International Publishing, Cham, CH, **2015**.
- [5] C.-L. Sun, A. Fürstner, *Angew. Chem. Int. Ed.* **2013**, *52*, 13071–13075; *Angew. Chem.* **2013**, *125*, 13309–13313.
- [6] Addition to the lactone group of 2-pyrone proceeds readily otherwise, see: a) R. Gompper, O. Christmann, *Chem. Ber.* **1961**, *94*, 1784–1794; b) R. Gompper, O. Christmann, *Chem. Ber.* **1961**, *94*, 1795–1799.
- [7] Scrambling does occur upon warm-up or in the presence of nucleophilic additives or solvents; therefore the proper choice of the reaction medium is critically important, see ref. 5,10.
- [8] A. Fürstner, *Angew. Chem. Int. Ed.* **2018**, *57*, 4215–4233; *Angew. Chem.* **2018**, *130*, 4289–4308.
- [9] For the synthesis of complex pyrone targets by our group, see: a) W. Chaladaj, M. Corbet, A. Fürstner, *Angew. Chem. Int. Ed.* **2012**, *51*, 6929–6933; *Angew. Chem.* **2012**, *124*, 7035–7039; b) L. Hoffmeister, T. Fukuda, G. Pototschnig, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 4529–4533; c) J. Preindl, K. Jouvin, D. Laurich, G. Seidel, A. Fürstner, *Chem. Eur. J.* **2016**, *22*, 237–247; d) J. Preindl, S. Schulthoff, C. Wirtz, J. Lingnau, A. Fürstner, *Angew. Chem. Int. Ed.* **2017**, *56*, 7525–7530; *Angew. Chem.* **2017**, *129*, 7633–7638.
- [10] C.-X. Zhuo, A. Fürstner, *J. Am. Chem. Soc.* **2018**, *140*, 10514–10523.
- [11] C.-X. Zhuo, A. Fürstner, *Angew. Chem. Int. Ed.* **2016**, *55*, 6051–6056; *Angew. Chem.* **2016**, *128*, 6155–6160.
- [12] Certain stabilized carbanions such as cyanide react with 2-pyrone via 1,6-addition/ring opening, although the substrate scope is exceedingly narrow and the stereoselectivity strongly dependent on the chosen conditions, see: a) G. Vogel, *J. Org. Chem.* **1965**, *30*, 203–207; b) A. R. Frisbee, M. H. Nantz, G. W. Kramer, P. L. Fuchs, *J. Am. Chem. Soc.* **1984**, *106*, 7143–7145; likewise, some scattered reports on reductive openings with NaBH₄/KOH are known, see: c) Z. H. Israili, E. E. Smismann, *J. Org. Chem.* **1976**, *41*, 4070–4074; d) M. J. Aurell, L. Ceita, R. Mestres, M. Parra, A. Tortajada, *Tetrahedron* **1995**, *51*, 3915–3928.
- [13] W. S. Hamama, M. Waly, I. El-Hawary, H. H. Zoorob, *Synth. Commun.* **2014**, *44*, 1730–1759.
- [14] For a review on the functionalization of 2-pyridones, see: K. Hirano, M. Miura, *Chem. Sci.* **2018**, *9*, 22–32.
- [15] For previous work on 2-pyridones from this laboratory, see: a) A. Fürstner, F. Feyen, H. Prinz, H. Waldmann, *Angew. Chem. Int. Ed.* **2003**, *42*, 5361–5364; *Angew. Chem.* **2003**, *115*, 5519–5522; b) A. Fürstner, F. Feyen, H. Prinz, H. Waldmann, *Tetrahedron* **2004**, *60*, 9543–9558.
- [16] a) S. Okada, K. Arayama, R. Murayama, T. Ishizuka, K. Hara, N. Hirone, T. Hata, H. Urabe, *Angew. Chem. Int. Ed.* **2008**, *47*, 6860–6864; *Angew. Chem.* **2008**, *120*, 6966–6970; b) G. Sugano, K. Kawada, M. Shigeta, T. Hata, H. Urabe, *Tetrahedron Lett.* **2019**, *60*, 885–890.
- [17] See also: a) K. Fukuhara, H. Urabe, *Tetrahedron Lett.* **2005**, *46*, 603–606; b) T. Hata, T. Nakada, Y. T. Oh, N. Hirone, H. Urabe, *Adv. Synth. Catal.* **2013**, *355*, 1736–1740.
- [18] Fe(acac)₃ (99.9+ % purity) is the pre-catalyst of choice because it is cheap, non-hygroscopic and commercially available. It is unlikely that trace impurities of copper in Fe(acac)₃ are the actual catalyst because control experiments with various copper salts did not lead to product formation; see also ref. 32.

- [19] Certain magnesium "ate-complexes" carrying benzyl, allyl or vinyl groups, however, were previously shown to react with 2-pyridones and 2-thiopyridones in the absence of a transition metal catalyst, see: a) J. G. Sośnicki, *Tetrahedron Lett.* **2006**, *47*, 6809–6812; b) J. G. Sośnicki, *Tetrahedron* **2007**, *63*, 11862–11877; c) J. G. Sośnicki, P. Dzitkowski, L. Struk, *Eur. J. Org. Chem.* **2015**, 5189–5198; d) J. G. Sośnicki, T. Idzak, A. Borzyszkowska, E. Wroblewski, G. Maciejewska, L. Struk, *Tetrahedron* **2017**, *73*, 481–493.
- [20] M. Tamura, J. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489.
- [21] G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199–1205.
- [22] a) B. Scheiper, M. Bonnekesel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943–3949; b) A. Fürstner, A. Schleckner, C. W. Lehmann, *Chem. Commun.* **2007**, 4277–4279.
- [23] X.-L. Lu, M. Shannon, X.-S. Peng, H. N. C. Wong, *Org. Lett.* **2019**, *21*, 2546–2549.
- [24] For other cases of seemingly "inverse" selectivity under iron catalysis (coupling of an alkyl halide in the presence of an aryl or alkenyl triflate, see: a) T. Nagano, T. Hayashi, *Org. Lett.* **2004**, *6*, 1297–1300; b) T. Hatakeyama, Y. Okada, Y. Yoshimoto, M. Nakamura, *Angew. Chem. Int. Ed.* **2011**, *50*, 10973–10976; *Angew. Chem.* **2011**, *123*, 11165–11168.
- [25] a) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863; b) A. Fürstner, A. Leitner, *Angew. Chem. Int. Ed.* **2002**, *41*, 609–612; *Angew. Chem.* **2002**, *114*, 632–635.
- [26] A. Fürstner, A. Leitner, G. Seidel, *Org. Synth.* **2005**, *81*, 33–41.
- [27] See also: a) A. Fürstner, A. Leitner, *Angew. Chem. Int. Ed.* **2003**, *42*, 308–311; *Angew. Chem.* **2003**, *115*, 320–323; b) G. Seidel, D. Laurich, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3950–3952; c) B. Scheiper, F. Glorius, A. Leitner, A. Fürstner, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11960–11965.
- [28] S.-S. P. Chou, C.-J. J. Wu, *Tetrahedron* **2012**, *68*, 1185–1191.
- [29] Compare: a) P. Beak, W. K. Lee, *J. Org. Chem.* **1993**, *58*, 1109–1117; b) S. Schaubach, K. Gebauer, F. Ungeheuer, L. Hoffmeister, M. K. Ilg, C. Wirtz, A. Fürstner, *Chem. Eur. J.* **2016**, *22*, 8494–8507.
- [30] Pyridone **1** with an *N*-benzyl group failed to undergo ring opening under these conditions.
- [31] For a related dicationic complex, in which six molecules of NMP, a privileged additive in iron catalyzed cross coupling reactions, coordinate to an Fe(+2) center via their carbonyl groups, see: K. Ding, F. Zannat, J. C. Morris, W. W. Brennessel, P. L. Holland, *J. Organomet. Chem.* **2009**, *694*, 4204–4208.
- [32] A related copper catalyzed ring opening/cross coupling reaction using Grignard reagents is known for methyl 2-oxo-2*H*-pyran-5-carboxylate (methyl cumalate); however, the presence of the ester substituent on pyrone ring of this singular substrate is mandatory for the reaction to proceed, see: a) J. Agarwal, O. Bayounes, S. Thorimbert, L. Dechoux, *RSC Adv.* **2014**, *4*, 2772–2775; see also: b) K. Plevová, L. Chang, E. Martin, Q. Llopis, L. Dechoux, S. Thorimbert, *Adv. Synth. Catal.* **2016**, *358*, 3293–3297; the parent 2-pyrone undergoes copper catalyzed 1,4-addition reactions in the presence of chiral diphosphine ligands, see: B. Mao, M. Fananas-Mastral, B. Feringa, *Org. Lett.* **2013**, *15*, 286–289. Reinvestigation in our laboratory showed that each component of this system is necessary; likewise, attempted extension of this reaction beyond the parent 2-pyrone largely met with failure, Y. Gu, unpublished results.
- [33] A. Fürstner, H. Krause, C. W. Lehmann, *Angew. Chem. Int. Ed.* **2006**, *45*, 440–444; *Angew. Chem.* **2006**, *118*, 454–458.
- [34] A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787.
- [35] a) S. B. Muñoz, S. L. Daifuku, J. D. Sears, T. M. Baker, S. H. Carpenter, W. W. Brennessel, M. L. Neidig, *Angew. Chem. Int. Ed.* **2018**, *57*, 6496–6500; *Angew. Chem.* **2018**, *130*, 6606–6610; b) J. D. Sears, S. B. Muñoz, S. L. Daifuku, A. A. Shaps, S. H. Carpenter, W. W. Brennessel, M. L. Neidig, *Angew. Chem. Int. Ed.* **2019**, *58*, 2769–2773; *Angew. Chem.* **2019**, *131*, 2795–2799; c) S. B. Muñoz, S. L. Daifuku, W. W. Brennessel, M. L. Neidig, *J. Am. Chem. Soc.* **2016**, *138*, 7492–7495.
- [36] a) T. Parchomyk, K. Koszinowski, *Chem. Eur. J.* **2018**, *24*, 16342–16347; b) T. Parchomyk, S. Demeshko, F. Meyer, K. Koszinowski, *J. Am. Chem. Soc.* **2018**, *140*, 9709–9720; c) T. Parchomyk, K. Koszinowski, *Chem. Eur. J.* **2017**, *23*, 3213–3219; d) T. Parchomyk, K. Koszinowski, *Chem. Eur. J.* **2016**, *22*, 15609–15613.
- [37] A. Casitas, H. Krause, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 1521–1526; *Angew. Chem.* **2015**, *127*, 1541–1546.
- [38] R. B. Bedford, *Acc. Chem. Res.* **2015**, *48*, 1485–1493.
- [39] M. L. Neidig, S. H. Carpenter, D. J. Curran, J. C. DeMuth, V. E. Fleischauer, T. E. Iannuzzi, P. G. N. Neate, J. D. Sears, N. J. Wolford, *Acc. Chem. Res.* **2019**, *52*, 140–150.
- [40] A. Fürstner, K. Majima, R. Martín, H. Krause, E. Kattinig, R. Goddard, C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 1992–2004.
- [41] M. F. Semmelhack in *Organometallics in Synthesis. A Manual*, 2nd ed. (Ed.: M. Schlosser), Wiley, Chichester, pp. 1003–1121.
- [42] a) M. F. Semmelhack, J. W. Herndon, *Organometallics* **1983**, *2*, 363–372; b) M. F. Semmelhack, J. W. Herndon, J. P. Springer, *J. Am. Chem. Soc.* **1983**, *105*, 2497–2499.
- [43] A. Casitas, H. Krause, S. Lutz, R. Goddard, E. Bill, A. Fürstner, *Organometallics* **2018**, *37*, 729–739.
- [44] C. H. DePuy, R. L. Parton, T. Jones, *J. Am. Chem. Soc.* **1977**, *99*, 4070–4075.
- [45] I. J. S. Fairlamb, S. M. Syvånne, A. C. Whitwood, *Synlett* **2003**, 1693–1697.
- [46] Related iron catalyzed alkylations of metal alkylidenes account for the formation of non-terminal alkynes from lactone-derived dichloroalkenes, see: a) K. Lehr, S. Schulthoff, Y. Ueda, R. Mariz, L. Leseurre, B. Gabor, A. Fürstner, *Chem. Eur. J.* **2015**, *21*, 219–227; b) M. Fuchs, A. Fürstner, *Angew. Chem. Int. Ed.* **2015**, *54*, 3978–3982; *Angew. Chem.* **2015**, *127*, 4050–4054; c) G. Mata, B. Wölfl, A. Fürstner, *Chem. Eur. J.* **2019**, *25*, 246–254.
- [47] B. Dinda, *Essentials in Pericyclic and Photochemical Reactions*, Springer, Heidelberg, **2017**.
- [48] D. Trauner, R. Webster in *Comprehensive Organic Synthesis II* (Eds.: P. Knochel, G. A. Molander), Elsevier, Oxford, **2014**, pp. 783–825.
- [49] a) J. D. Evanseck, B. E. Thomas, D. C. Spellmeyer, K. N. Houk, *J. Org. Chem.* **1995**, *60*, 7134–7141; b) N. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1985**, *107*, 2099–2111; c) W. R. Dolbier, H. Koroniak, K. N. Houk, C. Sheu, *Acc. Chem. Res.* **1996**, *29*, 471–477.
- [50] For recent advances reported by our group, see: a) D. J. Tindall, H. Krause, A. Fürstner, *Adv. Synth. Catal.* **2016**, *358*, 2398–2403; b) P.-G. Echeverría, A. Fürstner, *Angew. Chem. Int. Ed.* **2016**, *55*, 11188–11192; *Angew. Chem.* **2016**, *128*, 11354–11358; c) A. Casitas, J. A. Rees, R. Goddard, E. Bill, S. DeBeer, A. Fürstner, *Angew. Chem. Int. Ed.* **2017**, *56*, 10108–10113; *Angew. Chem.* **2017**, *129*, 10242–10247; d) F. Gomes, P.-G. Echeverría, A. Fürstner, *Chem. Eur. J.* **2018**, *24*, 16814–16822.

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