

Fe-Catalyzed Regiodivergent [1,2]-Shift of α -Aryl Aldehydes

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S Supporting Information

ABSTRACT: An Fe-catalyzed conversion of aldehydes to ketones via [1,2]-shift has been developed. This skeletal rearrangement shows a wide substrate scope and chemo-selectivity profile while exhibiting an excellent [1,2]-aryl or [1,2]-alkyl shift selectivity that is easily switched by electronic effects.

Carbonyl compounds rank among the most versatile synthons in organic synthesis.¹ Despite the robustness of classical protocols for their synthesis,¹ the search for alternatives, particularly in a catalytic fashion, still represents a formidable challenge.² Among all available scenarios, the means for catalytically interconverting carbonyl compounds with total control of selectivity would be highly desirable, hence increasing molecular complexity while following the principles of both atom³ and step economy.⁴ Indeed, aldehydes are known to undergo skeletal rearrangements en route to ketone derivatives via [1,2]-shift.^{5,6} However, the need for stoichiometric amounts of highly reactive Brønsted⁵ or Lewis acids⁶ and the harsh reaction conditions required^{5b} reduce the potential application profile of these rather appealing events.⁷ In 2005, a remarkable contribution by Chatani showed that GaCl₃ nicely promoted the skeletal rearrangement of aldehydes.⁸ Unfortunately, large amounts of GaCl₃ were required (typically 50–200 mol%), and low selectivities were found for [1,2]-alkyl shifts.⁸

The ability to prepare highly functionalized backbones rationally, predictably, and in a catalytic fashion from a common precursor is central in organic synthesis.⁹ Recently, our research group described an intriguing ligand-controlled selectivity in C–H functionalization reactions in which benzocyclobutenones or styrenes were selectively prepared from common α -aryl aldehyde precursors¹⁰ utilizing rather electron-rich palladium complexes (Scheme 1, top pathways).¹¹ We envisioned that orthogonal reactivity could be achieved via [1,2]-shift using a more Lewis acidic catalyst (routes c and d).^{12,13} Herein, we describe our investigations on the regiodivergent catalytic skeletal rearrangement via [1,2]-shift of α -aryl aldehydes using simple, abundant, and nontoxic iron salts as catalysts (routes c and d).¹⁴ The method is characterized by its wide scope, simplicity, and divergence in product selectivity that can be easily switched by electronic effects.

We initiated our investigation with **1a** as the model substrate, and the effects of several Lewis acids, solvents, and temperatures were systematically examined (Table 1).¹⁵ Among all Lewis acids analyzed, we found that the best reactivity was

Scheme 1. Catalytic Pathways for α -Aryl Aldehydes

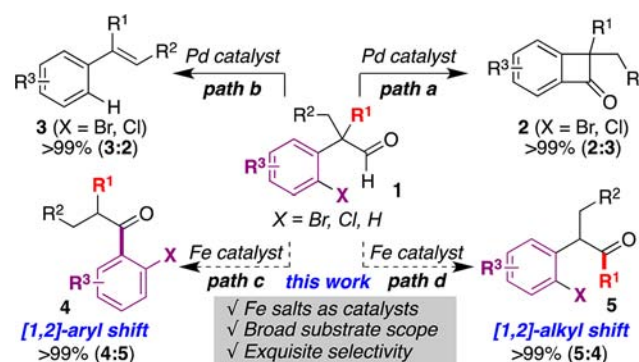


Table 1. Optimization of Reaction Conditions^a

Entry	Fe catalyst	Solvent	Ligand	Yield (%) ^b
1	FeCl ₃ ·6H ₂ O	Toluene	-	12
2	FeCl ₃	Toluene	-	22
3	FeF ₃	Toluene	-	0
4	FeBr₃	Toluene	-	94^{c,d}
5	Fe(OTf) ₃	Toluene	-	11
6	Fe(acac) ₃	Toluene	-	3
7	FeBr ₂	Toluene	-	0
8	FeBr ₃	o-xylene	-	90
9	FeBr ₃	DCE	-	42
10	FeBr ₃	Dioxane	-	0
11	FeBr ₃	DMF	-	0
12	FeBr ₃	tBuOH	-	0
13	FeBr ₃	Toluene	L1	0
14	FeBr ₃	Toluene	L2	0
15	FeBr ₃	Toluene	L3	0
16	GaCl ₃	Toluene	-	0, 84 ^e

1a $\xrightarrow[\text{Solvent, 80 } ^\circ\text{C}]{\text{Fe cat (5 mol%)}}$ **4a** + **4aa**
Not detected

L1

L2

L3

^aConditions: **1a** (0.5 mmol), Fe catalyst (5 mol%), solvent (2 mL), ligand (if any, 5 mol%), 14 h. ^bGC yield using dodecane as internal standard. ^cIsolated yield. ^dWith 4 Å MS. ^eConditions reported in ref 8 (50 mol% GaCl₃), additionally obtaining **4aa** in a 9% yield.

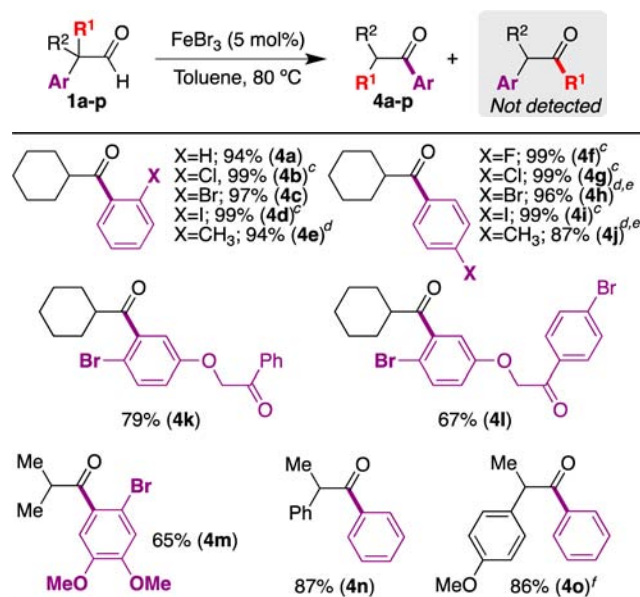
obtained when using Fe salts (5 mol%) at 80 °C. As expected, both the counterion and the oxidation state of the iron salt played critical roles for success, with FeBr₃ providing excellent results (entry 4).^{16,17} In line with known literature data employing Lewis acids as catalysts,¹² while coordinating

Received: July 5, 2013

Published: August 8, 2013

solvents gave no conversion to **4a** (entries 10–12), the use of xylene or dichloroethane (DCE) delivered the expected product (entries 8 and 9). Similarly, the inclusion of nitrogen-containing ligands had a deleterious effect on reactivity (entries 13–15). It should be noted that the ring-expansion product **4aa** via [1,2]-alkyl shift was not obtained using FeBr₃ as the catalyst (entry 4). To put these results in perspective, we found no reaction of **1a** with GaCl₃ (5 mol%) and non-negligible amounts of **4aa** under Chatani's conditions (50 mol% GaCl₃, entry 16).⁸ We believe these results nicely illustrate the excellent reactivity and selectivity of this new Fe-catalyzed protocol.¹⁸

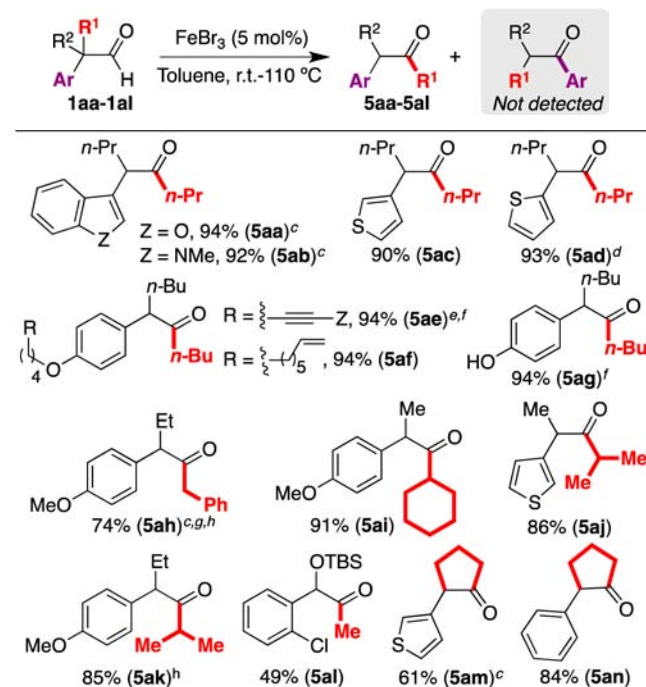
Encouraged by these findings, we turned our attention to explore the comparative scope of this reaction (Table 2). As

Table 2. Fe-Catalyzed [1,2]-Aryl Shift^{a,b}

^aAs for Table 1, entry 4. ^bIsolated yields, average of at least two independent runs. ^cFeBr₃ (15 mol%) at *T* = 130 °C. ^d*T* = 110 °C. ^eFeBr₃ (10 mol%). ^f*T* = 50 °C.

shown, a wide variety of α -aryl aldehydes could be employed, affording in all cases the expected products resulting from an exclusive [1,2]-aryl shift.¹⁸ It is worth noting that both cyclic (**4a–l**) and acyclic α -alkyl substituents (**4m–o**) gave comparable yields. The reaction proceeded smoothly in the presence of aryl halides (**4b–d,f–i,k–m**), thus leaving ample opportunities for further functionalization via conventional cross-coupling reactions.² Notably, *ortho*-alkyl substitution in the aromatic motif did not hinder the reaction (**4e**). As expected, the presence of an aromatic ketone does not interfere with the formation of **4k** and **4l**. On the basis of these results, we wondered whether high selectivities could be obtained with aldehydes possessing two electronically different α -substituted aromatic groups. Interestingly, we found a single regioisomer for the skeletal rearrangement of **1o**, in which the less electron-rich aromatic ring was preferentially migrated (**4o**).^{19,20}

We hypothesized that aryl groups that could significantly stabilize a neighboring carbocation would cause a selectivity switch,²¹ thus setting the stage for a [1,2]-alkyl shift event.^{22,23} As shown in Table 3, this was indeed the case, and a host of α -aryl aldehydes could be coupled in high yields and with an excellent [1,2]-alkyl shift selectivity when utilizing electron-rich

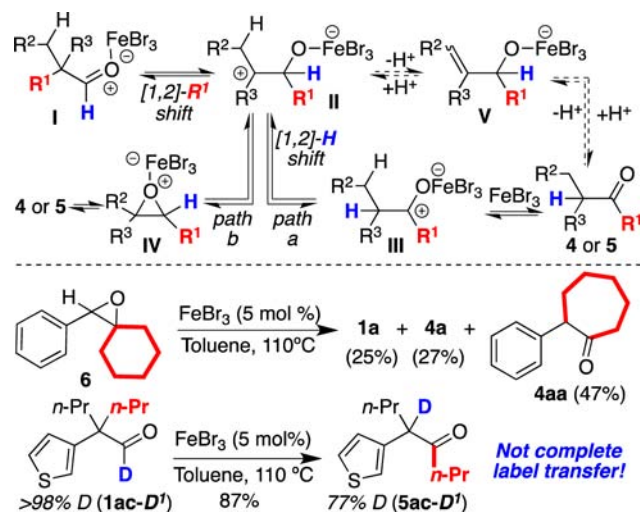
Table 3. Fe-Catalyzed [1,2]-Alkyl Shift^{a,b}

^aAs for Table 1, entry 4 (110 °C). ^bIsolated yields, average of at least two independent runs. ^c*T* = 50 °C. ^d1.0 g scale. ^eZ = *p*-CF₃(C₆H₄). ^f*T* = 25 °C. ^g5:1 regioisomeric mixture of [1,2]-Bn vs [1,2]-Et migration. ^hFeBr₃ (10 mol%).

aryl (**5ae–5ai**, **5ak**) or heteroaryl motifs (**5aa–5ad**, **5aj**, and **5am**).^{18,24} Interestingly, not even traces of [1,2]-aryl shift were detected in the crude reaction mixtures. These results are in sharp contrast with a recent Fe-catalyzed [1,2]-shift of aryl azides that selectively transfers electron-rich aromatic motifs in the presence of alkyl residues.²⁵ Importantly, the preparation of **5ad** could be easily scaled up without affecting the yield. As shown for **5aa** and **5ab**, the [1,2]-alkyl shift operated at lower temperatures than those used in Table 2, even room temperature (**5ae** and **5ag**).²⁶ Equally interesting is the fact that alkenes (**5af**) and alkynes (**5ae**) were easily accommodated as well. Surprisingly, an unprotected phenol is well tolerated (**5ag**) under the optimized reaction conditions. This is particularly noteworthy since hydroxyl groups usually inhibit reactions that employ catalytic amounts of Lewis acids.^{12,27} Although one might have speculated that a mixture of structural isomers would be formed, we found that secondary alkyl residues migrated exclusively in the presence of primary alkyl substituents (**5ai–5ak**). Likewise, high levels of selectivity were achieved for substrates possessing structurally similar α -alkyl substituents, favoring the migration of benzyl moieties (**5ah**). Particularly noteworthy is the ability to undergo an elusive [1,2]-methyl shift with α -silyloxy aldehydes (**5al**), even in the presence of non-electron-rich aromatic motifs that could trigger a [1,2]-aryl shift.^{7,28} These results clearly illustrate the potential of our protocol for rigorously controlling the migratory aptitude in [1,2]-shift events. In sharp contrast with the results in Table 2, electron-rich and even electron-neutral aromatic rings containing cyclic alkyl residues led to ring-expansion products **5am** and **5an**. At present we believe that ring strain release might be the driving force for such a migratory event.^{29,30}

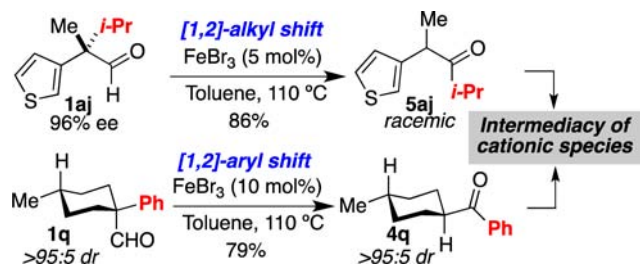
At present, we believe the reaction is initiated by activation of the aldehyde through coordination of FeBr_3 (I) that triggers a Wagner–Meerwein [1,2]-shift of the α substituent en route to II (Scheme 2, top).³¹ In principle, two mechanistic scenarios

Scheme 2. Mechanistic Proposal



are conceivable from II: [1,2]-hydride shift (III, path a)^{6a} or Meinwald-type rearrangement via the intermediacy of IV (path b).³² To lend support for path b, we independently prepared **6** and studied its reactivity under our reaction conditions (Scheme 2, bottom).¹⁵ As shown, a statistical mixture of **1a**³³ and **4a** as well as **4aa**, probably formed via [1,2]-alkyl shift, was obtained. At present, we believe that a Meinwald-type rearrangement through IV is highly unlikely since we did not detect even traces of **4aa** in our screening studies (Table 1). Additionally, we did not observe a quantitative deuterium transfer from **1ac-D**¹ to **5ac-D**¹, suggesting that the [1,2]-hydride shift does not come exclusively from the aldehydic C–H bond but also from other vicinal C–H bonds (V). In line with the notion that cationic intermediates come into play, we found that **1aj** (96% ee) led to racemic **5aj** (Scheme 3, top). A

Scheme 3. Cationic vs Concerted Mechanism



similar observation was made for the reaction of **1q** (Scheme 3, bottom). In this case, we found that **1q**, unambiguously characterized by X-ray crystallography,¹⁵ was converted to **4q**, illustrating that a concerted [1,2]-shift does not operate under these conditions and that the selectivity is controlled by the conformational preference of the substituents on the cyclohexyl ring.³⁴

In summary, we have developed an Fe-catalyzed skeletal rearrangement of aldehydes to ketones via [1,2]-shift in which the selectivity of the migratory event is controlled by electronic

effects.³⁵ The wide scope and the selectivity profile suggest that our protocol could be a powerful alternative en route to ketone derivatives from available precursors without requiring stoichiometric amounts of metal complexes. The asymmetric version is currently under study in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank ICIQ Foundation, the European Research Council (ERC-277883), and MICINN (CTQ2012-34054) for financial support. Johnson Matthey, Umicore, and Nippon Chemical Industrial are acknowledged for a gift of metal and ligand sources. We sincerely thank MS and HPLC units at ICIQ and Antonio de la Torre at URV for further assistance. R.M. and A.F.-G. thank MICINN for a RyC and FPU fellowship. This paper is dedicated to Prof. Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

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(17) FeBr₃ (98% purity, Sigma Aldrich) was utilized. Identical reactivity was found with other FeBr₃ sources from Strem (99% purity) and Alfa Aesar (98% purity). Atomic absorption spectroscopic analysis showed that no significant traces of other transition metals were present (ppm). The most abundant of these elements, however, were tested in our screening, and we did not find any remarkable catalytic behavior. See Supporting Information for details.

(18) No reaction took place in the absence of catalyst at 80, 110, or even 150 °C.

(19) This result is in sharp contrast with the ability of other catalytic [1,2]-aryl shifts in which electron-rich aromatic motifs are preferentially migrated. See for example: Sun, K.; Liu, S.; Bec, P. M.; Driver, T. G. *Angew. Chem., Int. Ed.* **2011**, 50, 1702.

(20) It is worth noting that the use of α -aryl acid chlorides or α -aryl Weinreb amides as substrates led to decomposition. In any case, we observed even traces of a migratory event.

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(26) We observed that the [1,2]-alkyl shift (Table 3) was significantly faster than the [1,2]-aryl shift (Table 2). Such observation is in line with the Hammond postulate that suggests a preferential carbon–carbon bond cleavage for the most stable carbocation intermediate.

(27) Related substrates possessing a dimethylamino or a piperidine substituent in the *para* position resulted in recovered starting material.

(28) The low yields of **5al–m** are attributed to the decomposition found when subjecting **1al–m** to our optimized conditions.

(29) The reaction of an α -cyclopropyl or a α -cyclopentyl aryl aldehyde led to decomposition.

(30) Interesting, **5an** was not obtained upon exposure of cyclobutyl phenyl ketone under our Fe-catalyzed protocol. This result suggests that the skeletal rearrangement of **1an** does not proceed via an initial [1,2]-aryl shift followed by ring-expansion, but rather via [1,2]-alkyl shift.

(31) Control experiments in the presence of HBr, TfOH, *p*TsOH·H₂O, and TFA showed very low or no conversion of **1a** to **4a**, thus indicating that the reaction is not mediated by traces of Brønsted acid. See Supporting Information for details.

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