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

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · AUGUST 2013

Impact Factor: 12.11 · DOI: 10.1021/ja4068707 · Source: PubMed

3 AUTHORS, INCLUDING:

Alvaro Gutierrez Bonet
ICIQ Institute of Chemical Research of Catalonia
2 PUBLICATIONS **24** CITATIONS
SEE PROFILE

Areli Flores-Gaspar
Universidad Antonio Nariño
11 PUBLICATIONS **158** CITATIONS
SEE PROFILE

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

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

Álvaro Gutiérrez-Bonet,[†] Areli Flores-Gaspar,[†] and Ruben Martin*[,‡]

[†]Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain
[‡]Catalan Institution for Research and Advanced Studies (ICREA), Passeig Lluïs Companys, 23, 08010, Barcelona, Spain

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 chemoselectivity 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 atom[3] 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 Brønsted[5] or Lewis acids[6] 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 $GaCl_3$ nicely promoted the skeletal rearrangement of aldehydes.[8] Unfortunately, large amounts of $GaCl_3$ 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 precursors[10] 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

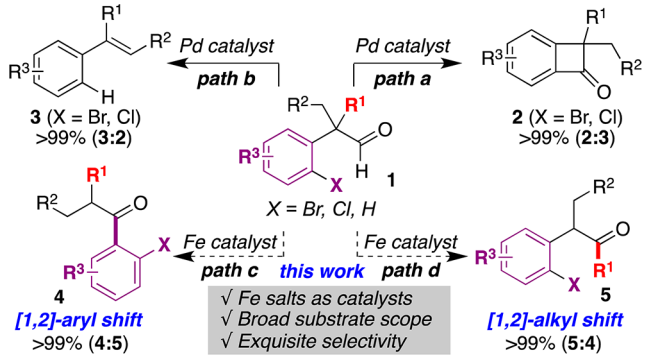
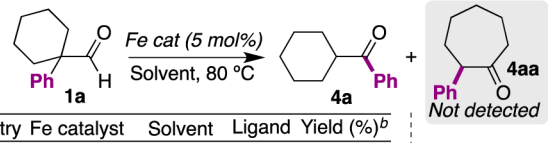
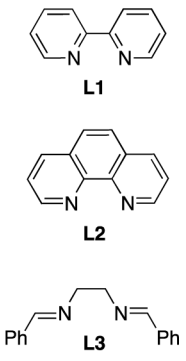


Table 1. Optimization of Reaction Conditions[a]



Entry	Fe catalyst	Solvent	Ligand	Yield (%)[b]
1	$FeCl_3·6H_2O$	Toluene	-	12
2	$FeCl_3$	Toluene	-	22
3	FeF_3	Toluene	-	0
4	***$FeBr_3$***	***Toluene***	**-**	***94***[c],0[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	$FeBr_3$	*t*BuOH	-	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]



[a]Conditions: **1a** (0.5 mmol), Fe catalyst (5 mol%), solvent (2 mL), ligand (if any, 5 mol%), 14 h. [b]GC yield using dodecane as internal standard. [c]Isolated yield. [d]With 4 Å MS. [e]Conditions reported in ref 8 (50 mol% $GaCl_3$), 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 $FeBr_3$ providing excellent results (entry 4).[16,17] In line with known literature data employing Lewis acids as catalysts,[12] while coordinating

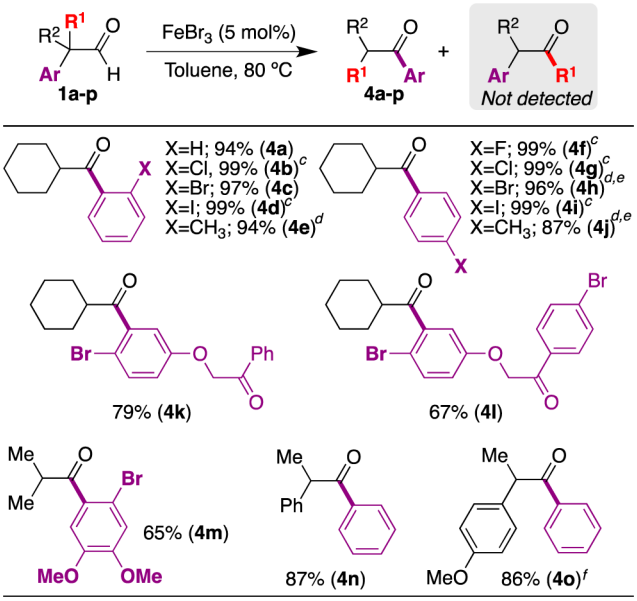
Received: July 5, 2013
Published: August 8, 2013

   dx.doi.org/10.1021/ja4068707 | J. Am. Chem. Soc. 2013, 135, 12576−12579

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 $FeBr_3$ as the catalyst (entry 4). To put these results in perspective, we found no reaction of **1a** with $GaCl_3$ (5 mol%) and non-negligible amounts of **4aa** under Chatani's conditions (50 mol% $GaCl_3$, 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 preparative scope of this reaction (Table 2). As

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

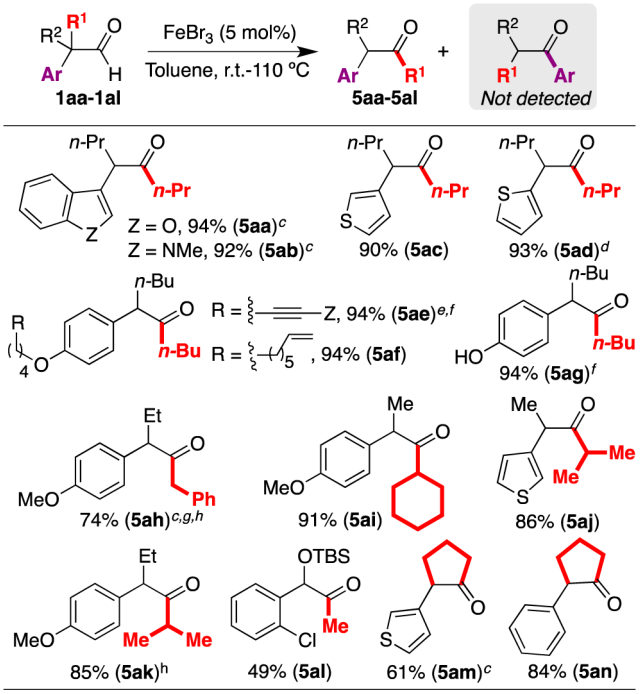


[a]As for Table 1, entry 4. [b]Isolated yields, average of at least two independent runs. [c]$FeBr_3$ (15 mol%) at T = 130 °C. [d]T = 110 °C. [e]$FeBr_3$ (10 mol%). [f]T = 50 °C.

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]



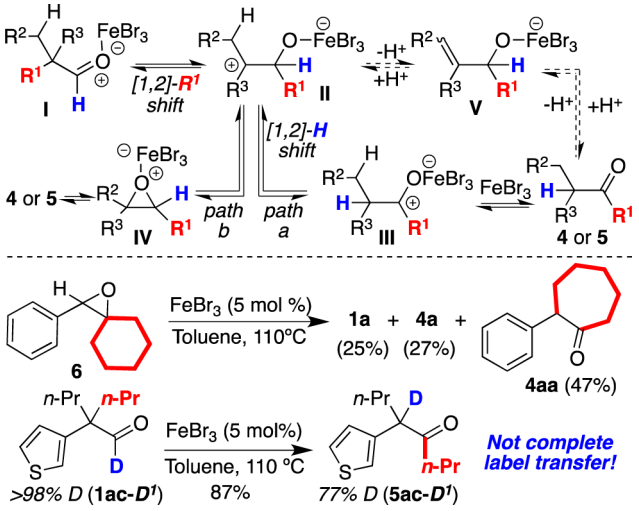
[a]As for Table 1, entry 4 (110 °C). [b]Isolated yields, average of at least two independent runs. [c]T = 50 °C. [d]1.0 g scale. [e]Z = p-$CF_3(C_6H_4)$. [f]T = 25 °C. [g]5:1 regioisomeric mixture of [1,2]-Bn vs [1,2]-Et migration. [h]$FeBr_3$ (10 mol%).

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 particular 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]

dx.doi.org/10.1021/ja4068707 | J. Am. Chem. Soc. 2013, 135, 12576−12579

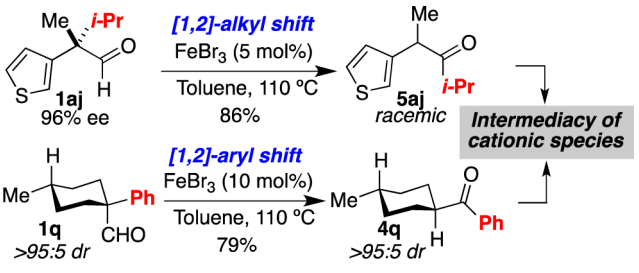
At present, we believe the reaction is initiated by activation of the aldehyde through coordination of $FeBr_3$ (**I**) that triggers a Wagner–Meerwein [1,2]-shift of the α substituent en route to **II** (Scheme 2, top).[31] In principle, two mechanistic scenarios

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.

■ AUTHOR INFORMATION

Corresponding Author

rmartinromo@iciq.es

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.

■ REFERENCES

(1) Bew, S. P. In *Comprehensive Organic Functional Groups Transformation III*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005; pp 1–380.

(2) *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

(3) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259.

(4) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.

(5) For selected references: (a) Prakash, G. K. S.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Rasul, G.; Olah, G. A. *J. Org. Chem.* **2006**, *71*, 3952. (b) van de Water, L. G. A.; van der Waal, J. C.; Jansen, J. C.; Maschmeyer, T. *J. Catal.* **2004**, *223*, 170. (c) Olah, G. A.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Etzkkorn, M.; Rasul, G.; Prakash, G. K. S. *J. Am. Chem. Soc.* **2001**, *123*, 11556.

(6) For selected references: (a) Domingo, L. R.; Arnó, M.; Sáez, J. A. *J. Org. Chem.* **2009**, *74*, 5934. (b) Nilson, M. G.; Funk, R. L. *J. Am. Chem. Soc.* **2011**, *133*, 12451. (c) Davies, H. M. L.; Dai, X. *J. Am. Chem. Soc.* **2004**, *126*, 2692. (d) Aungst, R. A.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3553.

(7) For an elegant related reaction using α-siloxy aldehydes that proceeds via silyl transfer, see: (a) Ooi, T.; Ohmatsu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 2410. (b) Ohmatsu, K.; Tanaka, T.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5203. (c) Ohmatsu, K.; Tanaka, T.; Ooi, T.; Maruoka, K. *Tetrahedron* **2009**, *65*, 7516.

(8) Oshita, M.; Okazaki, T.; Ohe, K.; Chatani, N. *Org. Lett.* **2005**, *7*, 331.

(9) For a review, see: Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10954.

(10) For selected α-arylation of aldehyde derivatives: (a) Nareddy, P.; Mantilli, L.; Guénée, L.; Mazet, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 3826. (b) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127. (c) Martin, R.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 4561. (d) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236.

(11) (a) Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466. (b) Flores-Gaspar, A.; Gutiérrez-Bonet, Á.; Martin, R. *Org. Lett.* **2012**, *14*, 5234. (c) Flores-Gaspar, A.;

Martin, R. *Adv. Synth. Catal.* **2011**, *353*, 1223. (d) Flores-Gaspar, A.; Martin, R. *Org. Synth.* **2012**, *89*, 159.
(12) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2006.
(13) For a review dealing with skeletal rearrangements via [1,2]-carbon-carbon shift, see: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, Chapter 4, pp 705−1014.
(14) For reviews on Fe-catalyzed reactions, see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Correa, A.; García-Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (c) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (d) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624.
(15) See Supporting Information for details.
(16) For a selection of catalytic transformations utilizing $FeBr_3$, see: (a) Zhang, T.; Bao, W. *J. Org. Chem.* **2013**, *78*, 1317. (b) Xu, T.; Yang, Q.; Li, D.; Dong, J.; Yu, Z.; Li, Y. *Chem.—Eur. J.* **2010**, *16*, 9264. (c) Marcos, R.; Rodriguez-Escrich, C.; Herrerías, C. I.; Pericàs, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 16838. (d) Giraud, A.; PRovot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron* **2006**, *62*, 7667. (e) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15050. (f) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387 and references therein.
(17) $FeBr_3$ (98% purity, Sigma Aldrich) was utilized. Identical reactivity was found with other $FeBr_3$ 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.
(21) For selectivity control in migratory events, see: (a) Gerrand, W.; Hudson, H. R. *Chem. Rev.* **1965**, *65*, 697. (b) Crone, B.; Kirsch, S. F. *Chem.—Eur. J.* **2008**, *14*, 3514. (c) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143.
(22) McKenzie, A.; Dennler, W. S. *J. Chem. Soc.* **1926**, 1596.
(23) Aryl groups typically have a better migratory aptitude in Wagner−Meerwein-type rearrangements due to the delocalization of the positive charge into the aromatic ring. However, steric and electronic effects might have an influence on the migration event. See for example: (a) Brown, H. C.; Kim, C. J. *J. Am. Chem. Soc.* **1968**, *90*, 2082. (b) Winstein, S.; Morse, B. K.; Grunwald, E.; Schreiber, K. C.; Corse, J. *J. Am. Chem. Soc.* **1952**, *74*, 1113. (c) Nakamura, K.; Osamura, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9112. (d) Nakamura, K.; Osamura, Y. *Tetrahedron Lett.* **1990**, *31*, 251.
(24) For recent procedures invoking a switch of migratory aptitude, see: (a) Ref 7b. (b) Suda, K.; Kikkawa, T.; Nakajima, S.-I.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554 and references therein.
(25) Nguyen, Q.; Nguyen, T.; Driver, T. G. *J. Am. Chem. Soc.* **2013**, *135*, 620.
(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 a 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·H_2O, 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.
(32) (a) Suda, K.; Baba, K.; Nakajima, S.-I.; Takanami, T. *Chem. Commun.* **2002**, 2570. (b) Gudla, V.; Balamurugan, R. *Tetrahedron Lett.* **2012**, *53*, 5243. (c) Vyas, D. J.; Larionov, E.; Besnard, C.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2013**, *135*, 6177. (d) Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582.
(33) For Fe-catalyzed conversion of epoxides to aldehydes, see: (a) Picione, J.; Mahmood, S. J.; Gill, A.; Hilliard, M.; Hossain, M. *Tetrahedron Lett.* **1998**, *39*, 2681. (b) Ertürk, E.; Göllü, M.; Demir, A. S. *Tetrahedron* **2010**, *66*, 2373.
(34) For additional mechanistic studies, see Supporting Information .
(35) For other regiodivergent metal-catalyzed [1,2]-shifts via cycloisomerization processes, see: (a) Dudnik, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645. (b) Davies, P. W.; Martin, N. *Org. Lett.* **2009**, *11*, 2293. (c) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440. (d) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195.