Organic LETTERS

Letter

pubs.acs.org/OrgLett

Fe-Catalyzed Direct α C–H Amination of Carbonyl Compounds

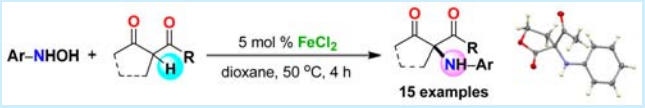
Siva Murru,*[,†] Charles Seth Lott,[†] Frank R. Fronczek,[‡] and Radhey S. Srivastava*[,†]

[†]Department of Chemistry, University of Louisiana at Lafayette, Lafayette, Louisiana 70504, United States

[‡]Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, United States

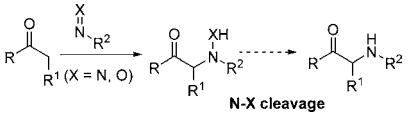
Supporting Information

ABSTRACT: A direct Fe-catalyzed α-amination of 1,3-dicarbonyl compounds has been accomplished using arylhydroxylamines as aminating agents. This novel protocol allows convenient access to α-amino carbonyl derivatives without the need for any postreaction manipulations. This is an operationally simple procedure that works at low temperatures in shorter reaction times and produces high yields with excellent N-selectivity.



Carbonyl compounds bearing α-amino substitution are widely represented among pharmaceutically active compounds, peptides and proteins, and complex natural products.[1] Development of a direct synthetic strategy toward this high-value synthon is a longstanding goal in organic synthesis, with many research groups greatly contributing to α-amination. Transition metal catalyzed α-aminations, through the reactions of suitable nucleophiles and their electrophilic partners, have been reported.[2] For instance, the catalytic α-amination of enolate derivatives such as ketones, β-ketoesters, and aldehydes often involves the use of 2π-electrophile aza-substrates to deliver α-hydrazinyl or α-hydroxy-amino products, two structural classes that must undergo drastic reductive conditions to cleave N–N and N–O bonds in order to access the corresponding amines[3] (Scheme 1).

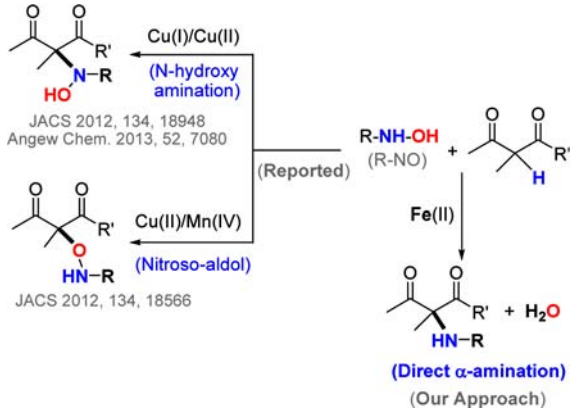
Scheme 1. Postreaction Modifications (N–X Bond Cleavage) To Make α-Amino Carbonyl Compounds



Similarly, the direct coupling of carbonyls and nucleophilic amines is appealing and a more straightforward strategy for the synthesis of α-amino carbonyls. Mechanistically, such a coupling of two nucleophiles would require high temperatures and judicious selection of oxidative conditions using a terminal oxidant. Recently, MacMillan et al. reported a direct α-amination reaction with nucleophilic amines under aerobic conditions in which an electrophilic α-bromocarbonyl was generated in situ through an aerobic oxidation-coupled process.[4] However, the method is only good for strong nucleophilic secondary amines.

Other research groups of Yamamoto,[5a] Selig,[5b] and Alaniz[5c] have independently reported in situ generation of nitroso-carbonyls for aminoxylation (i.e., nitroso-aldol) and hydroxyamination reactions of β-ketoesters through the simultaneous use of two different catalysts: one for carbonyl activation (Lewis acid catalysis) and the other for nitroso compounds generation (Scheme 2). The most recent report by Luo et al. discloses the

Scheme 2. Previously Reported *N*-Hydroxy α-Amination and Nitroso-Aldol vs Our Direct α-Amination



preparation of *N*-hydroxy amine products using *N*-hydroxy carbamates.[5d] Maruoka et al. reported a metal-free hydroxyamination process using a combination of TEMPO and BPO as the oxidant.[6] A few other organocatalytic hydroxyamination methods were developed starting from nitrosobenzene.[7] However, the end products in all of these reactions are *N*-hydroxyl amines which require an additional reduction step to make corresponding amines. Most importantly the use of additional oxidants, precious metal catalysts, and/or other additives makes these methods more expensive. Indeed, the development of direct amination of carbonyl compounds, without the need for any postreaction manipulations, still remains challenging.

Received: March 10, 2015
Published: April 13, 2015

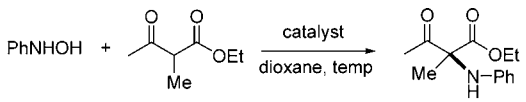
DOI: 10.1021/acs.orglett.5b00710
Org. Lett. 2015, 17, 2122–2125

Compared to other transition metals, iron is one of the most abundant in the universe, inexpensive, environmentally benign, and relatively nontoxic.[8] Over the past few decades iron catalysts have been extensively applied to various reactions, such as oxidation, epoxidation, addition, cyclization, etc.[9] However, the iron-catalyzed C−N bond-forming reactions are underdeveloped and have become an important goal for synthetic chemists. In our continuation of extensive research on catalytic amination chemistry, here we present a direct Fe-catalyzed α C−H amination process that could deliver the final products as amines utilizing hydroxylamines as aminating agents (Scheme 2). This method possesses several advantages such as (1) only a single catalyst for both electrophile generation and nucleophile activation, (2) an inexpensive and nontoxic Fe-catalyst, (3) no requirement of any oxidants or additives, (4) high *N*-selectivity, and (5) no requirement of any postreaction manipulation (reduction step).

Previously we reported transition metal catalyzed allylic C−H amination of simple olefins, 1,3-dienes, and α,β-unsaturated carbonyls using hydroxylamines as aminating agents.[10] We have isolated metal(Fe and Cu)-nitroso complexes $\{Fe[ArN(O)N(O)Ar]_3\}^{2+}2FeCl_4^-$ and $\{[Cu(ArNO)_3]^+PF_6^-\}$ and implicated them as reactive intermediates in allylic C−H amination reactions.[10b,c,f,g] The crystal structure of the Fe-azodioxide complex[10b,c] indicates the presence of both Fe(II) and Fe(III) ionic species which is an advantageous feature for bimetallic catalysis.[11] Considering these unique features, we envisioned that the Fe-catalyst would serve a dual purpose in the α-amination of 1,3-dicarbonyl compounds where Fe(II) generates active nitroso intermediates (electrophiles) and Fe(III) acts as a Lewis acid catalyst to activate the 1,3-dicarbonyl derivatives (nucleophiles).

In initial reaction development, we tested a set of known iron catalysts[12] and copper catalysts[13] for the reaction of 2-methyl ethyl acetoacetate (**a**) with phenyl hydroxylamine (**1**) in 1,4-dioxane solvent at 70 °C (Scheme 3). A few Fe-catalysts, i.e.

Scheme 3. Optimization of Conditions for the Reaction of Phenyl Hydroxylamine with 2-Methyl Ethylacetoacetate

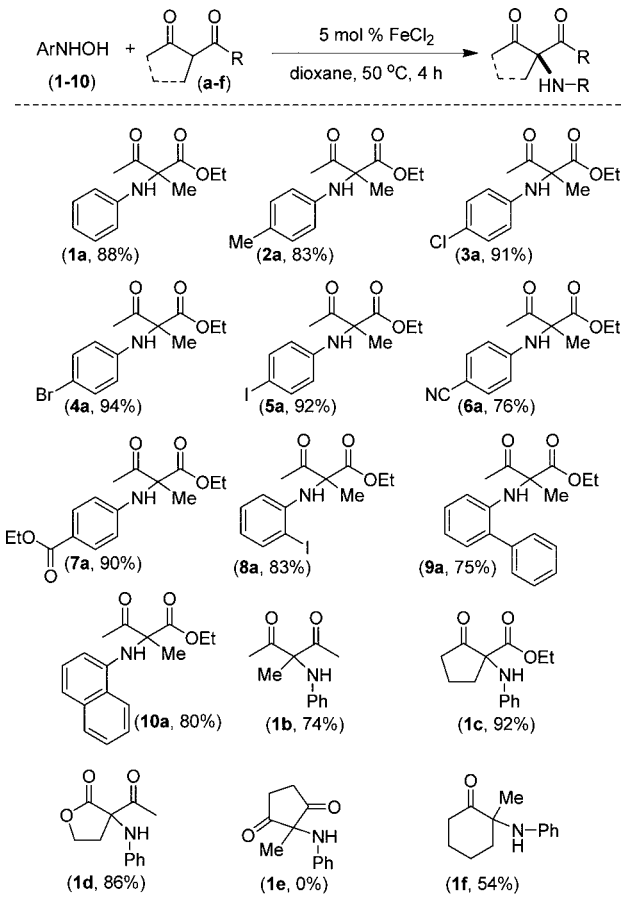


Fe-catalysts	% yield	Cu-catalysts	% yield
1. $FeCl_2.4H_2O$	81	8. $Cu(MeCN)_4PF_6$	76
2. $FeCl_3.6H_2O$	73	9. CuBr. SMe_2	trace
3. $Fe(ClO_4)_2.6H_2O$	23	10. CuCl	32
4. anh. $FeCl_2$	88	11. $CuCl_2.2H_2O$	09
5. anh. $FeCl_3$	75		
6. Fe(acac)$_3$	19		
7. Fe(Pc)	14		

anh $FeCl_2$, anh $FeCl_3$, $FeCl_2{\cdot}4H_2O$, and $FeCl_3{\cdot}6H_2O$, were found to be superior to other catalysts in terms of higher yields and shorter reaction times (3−4 h). Further screening of different solvents and a range of temperatures led us to consider *p*-dioxane as a suitable solvent and 50 °C as the optimum temperature.[14]

When a series of aryl hydroxylamines (**1**−**10**) with 2-methyl ethylacetoacetate (**a**) were subjected to optimized reaction conditions (5 mol % $FeCl_2$, p-dioxane, 50 °C), the corresponding α-amination products (**1a**−**10a**) were produced in good to excellent yields as shown in Scheme 4. p-Substituted arylhydroxylamines containing electron-withdrawing groups

Scheme 4. Direct α-Amination of 1,3-Dicarbonyl Compounds Using Phenylhydroxylamine[a,b]



[a]All reactions were performed at 50 °C with a 1:1.2 substrate ratio (PhNHOH: substrate). [b]Isolated yields.

(**3**−**7**) worked fairly well (isolated up to 95%) when compared to unsubstituted (**1**) and methyl substituted hydroxylamines (**2**). Reactions of arylhydroxylamines bearing ortho-substitutions (**8a**, **9a**) are also efficient, and the desired products were isolated in very good yields. In order to extend the reaction scope we integrated other carbonyl derivatives such as 3-methyl-2,4-pentanedione (**b**), ethyl-2-oxocyclopentanecarboxylate (**c**), and α-acetyl butyrolactone (**d**) to afford the desired amination products (**1b**−**1d**) in good yields. There appears to be no substantial steric restrictions in the case of 2-acyl cyclic carbonyl substrates **c** and **d**. Surprisingly, there was no reaction when we employed 2-methyl-1,3-cyclopentadienone (**e**) in which both the carbonyl groups are part of the strained cyclic ring. This is probably due to the steric effects of two carbonyls and the C-2 methyl group. Interestingly, 2-methyl cyclohexanone (**f**), a monocarbonyl derivative, afforded the amination product (**1f**) in relatively low yield (54%) unlike other 1,3-dicarbonyls. This observation indirectly supports the strong activation of 1,3-dicarbonyl derivatives when compared to monocarbonyl substrates.

All amination products were characterized by GC-MS, ^{1}H and ^{13}C NMR, and IR-analysis. In most cases GC-MS analyses of reactions indicate only single amination products. However, a small amount (up to 5%) of azoxybenzene, a common side product in amination reactions, was also detected in a few cases.[15] The structure of the amination product (**1d**) from the

DOI: 10.1021/acs.orglett.5b00710
Org. Lett. 2015, 17, 2122−2125

α-acetyl butyrolactone (**d**) was confirmed by X-ray crystallographic analysis for the first time (Figure 1).[16]

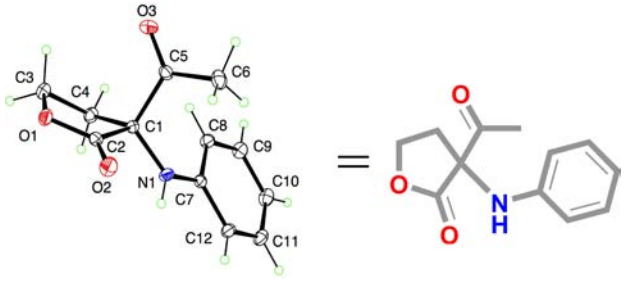
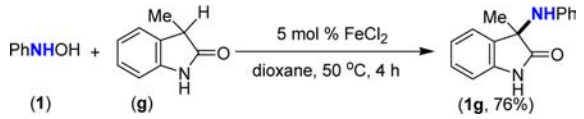


Figure 1. An ORTEP view with atomic numbering scheme of amination product **1d**.

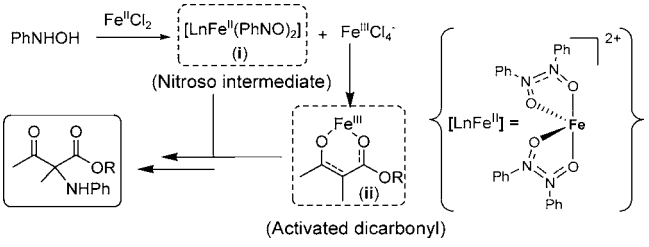
Encouraged by these results, and considering the biological significance of oxindoles containing a 3,3-disubstituted quaternary carbon, we intended to perform an α-amination on 3-methyl-2-oxindole (**g**). In fact, 3,3-disubstituted oxindoles are widely present in natural products and bioactive molecules such as the vasopressin VIb receptor antagonist SSR-14945, the gastrin/CCK-B receptor antagonist AG-041R, and the anti-inflammatory agent BMS-561392.[17] In particular, 3-substituted oxindoles bearing a heteroatom on a quaternary carbon are extremely important in medicinal chemistry, and thus their synthesis has been a topic of interest in recent years.[18] Gratifyingly, α-amination of 3-methyl-2-oxindole afforded the desired amination product in 76% yield (Scheme 5).

Scheme 5. Fe-Catalyzed α-Amination of 3-Methyl-2-oxindole



As discussed earlier, we hypothesize that the Fe-catalyst plays a dual role in generating the activated nitroso intermediate (**i**)[10b,c] as well as in activating the dicarbonyl compound (**ii**), ultimately resulting in both intermediates reacting together to produce the desired amination product (Scheme 6). This type

Scheme 6. Catalytic Pathway for Direct α-Amination of 1,3-Dicarbonyl Compounds



of dual activation catalysis has made significant progress in recent years as a powerful tool for organic synthesis with improved kinetics and higher selectivities.[19] On treatment of 2-methyl ethylacetoacetate with $FeCl_3$, the observed absorbance and wavelength in UV–vis and IR-spectroscopic analysis of carbonyl groups changed, which supports our hypothesis on catalytic dicarbonyl activation[20] (Scheme 6). We are currently involved in studying the full scale kinetics of these amination reactions to deduce the reaction mechanism. Previously reported α-amination reactions utilize two different catalysts to serve different purposes,[5] whereas the current method utilizes only a single catalyst.

In conclusion, we have developed an Fe-catalyzed direct α-C–H amination of 1,3-dicarbonyl compounds using arylhydroxylamines. This approach is highly *N*-selective and produced important classes of α-amino carbonyl compounds in excellent yields. Various carbonyl compounds have been implicated for amination including β-ketoesters, 1,3-diketones, ethyl-2-oxocyclopentane carboxylate, and 3-methyl-2-oxindole. The amination product of α-acetyl butyrolactone was also confirmed by X-ray crystallographic analysis. Further investigations and studies are being directed toward understanding the reaction mechanism and developing the direct asymmetric amination of carbonyl compounds.

■ ASSOCIATED CONTENT

Supporting Information

Details of experimental procedure, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all isolated compounds, HR-MS spectra for **6a** and **1g**. This material available for free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: rss1805@louisiana.edu.
*E-mail: sxm2239@louisiana.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are thankful for the financial support of the Louisiana Board of Regents [LEQSF(2013-16)-RD-B-06].

■ REFERENCES

(1) (a) Meltzer, P. C.; Butler, D.; Deschamps, J. R.; Madras, B. K. *J. Med. Chem.* **2006**, *49*, 1420. (b) Carrol, F. I.; Blough, B. E.; Abraham, P.; Mills, A. C.; Holleman, J. A.; Wolchenhauer, S. A.; Decker, A. M.; Landavazo, A. K.; McElroy, T.; Navarro, H. A.; Gatch, M. B.; Forster, M. J. *J. Med. Chem.* **2009**, *52*, 6768. (c) Bouteiller, C.; Becerril-Ortega, J.; Marchand, P.; Nicole, O.; Barre, L.; Buisson, A.; Perrio, C. *Org. Biomol. Chem.* **2010**, *8*, 1111. (d) Meyers, M. C.; Wang, J.-L.; Iera, J. A.; Bang, J.-K.; Hara, T.; Saito, S.; Zambetti, G. P.; Appella, D. H. *J. Am. Chem. Soc.* **2005**, *127*, 6152. (e) Ando, R.; Sakaki, T.; Morinaka, Y.; Takahashi, C.; Tamao, Y. EP 603769 A1 19940629, 1994.

(2) (a) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292. (b) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917.

(3) (a) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790. (b) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (c) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028.

(4) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W. D.; MacMillan, W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074.

(5) (a) Baidya, M.; Griffin, K. A.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 18566. (b) Selig, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7080. (c) Sandoval, D.; Frazier, C. P.; Bugarin, A.; Read deAlaniz, J. *J. Am. Chem. Soc.* **2012**, *134*, 18948. (d) Xu, C.; Zhang, L.; Luo, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 4149.

(6) Kano, T.; Shirozu, F.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 18036.

(7) (a) Momiyama, N.; Yamamoto, H. *Org. Lett.* **2002**, *4*, 3579. (b) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360.

DOI: 10.1021/acs.orglett.5b00710
Org. Lett. 2015, 17, 2122–2125

(8) (a) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629. (b) Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746. (c) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686. (d) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335. (e) Bolm, C.; Legros, J.; Paih, J. L.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (f) Sherry, B. D.; Furstner, A. *Acc. Chem. Res.* **2008**, 1500.

(9) Jiang, H.; Yao, W.; Cao, H.; Huang, H.; Cao, D. *J. Org. Chem.* **2010**, *75*, 5347 and references cited therein.

(10) (a) Srivastava, R. S.; Nicholas, K. M. *J. Chem. Soc., Chem. Commun.* **1996**, 2335. (b) Srivastava, R. S.; Khan, M. A.; Nicholas, K. M. *J. Am. Chem. Soc.* **1996**, *118*, 3311. (c) Srivastava, R. S.; Nicholas, K. M. *J. Am. Chem. Soc.* **1997**, *119*, 3302. (d) Srivastava, R. S.; Nicholas, K. M. *Chem. Commun.* **1998**, 2705. (e) Srivastava, R. S.; Nicholas, K. M. *Organometallics* **2005**, *24*, 1563. (f) Srivastava, R. S.; Khan, M. A.; Nicholas, K. M. *J. Am. Chem. Soc.* **2005**, *127*, 7278. (g) Srivastava, R. S.; Tarver, N. R.; Nicholas, K. M. *J. Am. Chem. Soc.* **2007**, *129*, 15250. (h) Srivastava, R. S.; Bertrand, R., III; Nicholas, K. M. *Tetrahedron Lett.* **2011**, *52*, 3478. (i) Murru, S.; Gallo, A. A.; Srivastava, R. S. *J. Org. Chem.* **2012**, *77*, 7119. (j) Murru, S.; Srivastava, R. S. *Eur. J. Org. Chem.* **2014**, 2174. (k) Murru, S.; McGough, B.; Srivastava, R. S. *Org. Biomol. Chem.* **2014**, *12*, 9133.

(11) (a) Kawthekar, R. B.; Kim, G.-J. *Synth. Commun.* **2008**, *38*, 1236. (b) Kawthekar, R. B.; Bi, W.; Kim, G.-J. *Appl. Organomet. Chem.* **2008**, *22*, 583. (c) Chen, S.-W.; Thakur, S. S.; Li, W.; Shin, C.-K.; Kawthekar, R. B.; Kim, G.-J. *J. Mol. Catal. A: Chem.* **2006**, *259*, 116.

(12) (a) Srivastava, A.; Ma, Y.; Pankayatselvan, R.; Dinges, W.; Nicholas, K. M. *J. Chem. Soc., Chem. Commun.* **1992**, 853. (b) Johannsen, M.; Jorgensen, K. A. *J. Org. Chem.* **1994**, *59*, 214; *J. Org. Chem.* **1995**, *60*, 5979. (c) Souto, J. A.; Zian, D.; Muniz, K. *J. Am. Chem. Soc.* **2012**, *134*, 7242.

(13) (a) Møller, E. R.; Jorgensen, K. A. *J. Org. Chem.* **1996**, *61*, 5770. (b) Cenini, S.; Ragaini, F.; Tollari, S.; Paone, D. *J. Am. Chem. Soc.* **1996**, *118*, 11964. (c) Kolel-Veetil, M.; Khan, M. A.; Nicholas, K. M. *Organometallics* **2000**, *19*, 3754. (d) Ho, C.-M.; Lau, T.-C. *New J. Chem.* **2000**, *24*, 859. (e) Wyle, M. J.; Fowler, F. W. *J. Org. Chem.* **1984**, *49*, 4025. (f) Birtwistle, D. H.; Brown, J. M.; Foxton, M. W. *Tetrahedron* **1988**, *44*, 7309. (g) Back, T. G.; Bethell, R. J.; Parvez, M.; Taylor, J. A. *J. Org. Chem.* **2001**, *66*, 8599.

(14) Check the general procedure in the Supporting Information.

(15) To minimize the side product formation, we have used a syringe pump for slow delivery of a phenylhydroxylamine solution.

(16) Monoclinic crystal system, space group $P21/c$ with a = 8.0212(4) Å, b = 19.5872(9) Å, c = 6.8796(3) Å, β = 99.680(2)°, V = 1065.48(9) Å^3, and Z = 4. Data were collected at 90 K using Mo Kα radiation on a Bruker Kappa APEX-II DUO diffractometer. A 2θ range from 2.0° to 33.1° gave 4055 independent reflections. The structure was solved using SHELXS97 and refined to R1 = 0.042, wR2 = 0.113, and GOF = 1.04 for 3679 $I > 2\sigma(I)$ data. This crystal structure is deposited at the Cambridge Crystallographic Data Centre (CCDC). The data have been assigned to deposition number CCDC 1045915. The data can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(17) (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

(18) (a) Deng, Q.-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356. (b) Ren, L.; Lian, X.-L.; Gong, L.-Z. *Chem.—Eur. J.* **2013**, *19*, 3315. (c) Hu, F.-L.; Wei, Y.; Shi, M.; Pindi, S.; Li, G. *Org. Biomol. Chem.* **2013**, *11*, 1921. (d) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003.

(19) (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (c) Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 2339. (d) Strater, N.; Lipscomb, W. N.; Klabunde, T.; Krebs, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2024. (e) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566. (f) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117.

(20) We observed the absorbance peak at 260 nm for the 2-methyl ethylacetoacetate which disappeared upon addition of $FeCl_3$. IR analysis indicates shifting of the carbonyl-ester peak from 1736 to 1743 cm^{-1} upon addition of $FeCl_3$.

DOI: 10.1021/acs.orglett.5b00710
Org. Lett. 2015, 17, 2122−2125