Accepted Manuscript

Octahedral Iridium Complex Catalyzed α-Chlorination of 2-Acyl Imidazoles with Tosyl Chloride

Tao Deng, Pranjal P. Bora, Shao-Xia Lin, Yi Li, Qiang Kang

Please cite this article as: Deng, T., Bora, P.P., Lin, S-X., Li, Y., Kang, Q., Octahedral Iridium Complex Catalyzed α-Chlorination of 2-Acyl Imidazoles with Tosyl Chloride, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.01.078

# Octahedral Iridium Complex Catalyzed α-Chlorination of 2-Acyl Imidazoles with Tosyl Chloride

Tao Deng,[a] Pranjal P. Bora,[b] Shao-Xia Lin,[b] Yi Li*[a] and Qiang Kang*[b]

[a]Department of Chemistry, Fuzhou University, 350116, P. R. China.

[b]Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, 155 Yangqiao Road West, Fuzhou, 350002, P. R. China.

*Corresponding author. Tel.: (+86) 591-63173548; fax: (+86) 591-63173548; e-mail address: liyi-chem@fzu.edu.cn; kangq@fjirsm.ac.cn

Abstract: An efficient and catalytic α-chlorination of 2-acyl imidazoles with readily available tosyl chloride catalyzed by an octahedral iridium complex under mild condition was reported. A range of 2-acyl imidazoles were converted to their corresponding α-chlorination products in good to excellent yields.
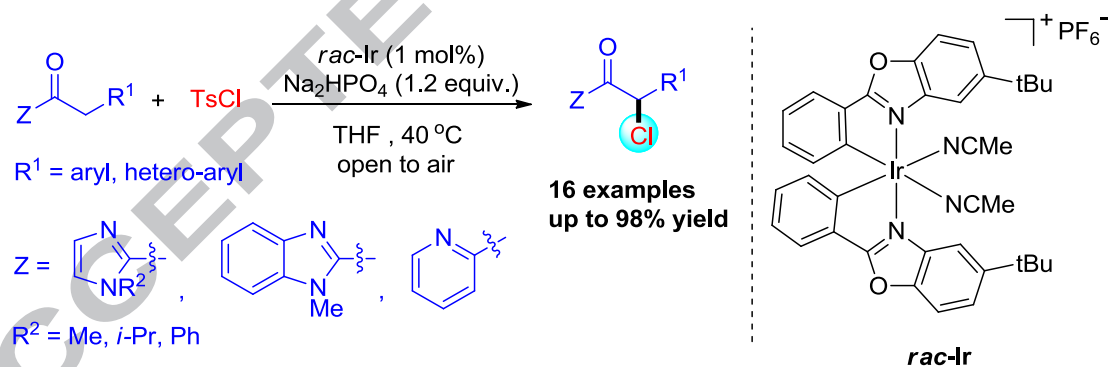
Keywords: α-chlorination, octahedral complex, Iridium, tosyl chloride, 2-acyl imidazoles

1. Introduction:

The carbon-halogen bond formations especially C-Cl bond forming reactions are of both synthetic and historic significance. Among the various C-Cl bond forming reactions, direct catalytic α-chlorination of carbonyl compounds is of great

importance. The α-chlorinated carbonyl compounds are versatile intermediates and building blocks in organic synthesis as they can be easily converted into a wide range of functionalized molecules including biologically active compounds and drugs.[1] As a result, a significant number of catalytic methods were developed towards the α-chlorination of carbonyl compounds by varying catalysts, chlorinating agents and carbonyl substrates. A range of catalysts including organocatalyts,[2] Lewis acids,[3] amberlyst[4] and transitional metal complexes[5] had been explored for α-chlorination of carbonyl compounds. Likewise, various chlorinating agents ranging from inorganic compounds to polychlorinated organic molecules were also explored. However, the choice of chlorinating agents plays crucial role, as it strongly influence the reaction mechanism, yield, selectivity and nature of by-products.[6] Historically, molecular chlorine had been used as a chlorinating agent, but the high reactivity and difficulty in handling of this gas make it impractical.[7] Commonly used chlorinating agents N-chlorosuccinimide (NCS)[2a-2e, 5] N-chlorophthalimide,[8] 2,2,6,6-tetrachlorocyclohexanone,[9] hexachlorocyclohexadienone,[10] and trichloroquinolinone[2i] required a relatively large cost. Sulfuryl chloride,[11] trichloromethylsulfonyl chloride[12] and trifluoromethylsulfonyl chloride[13] were also employed with limited success. *p*-Toluenesulfonyl chloride (TsCl) is a widely available chemical reagent, which have been industrially produced on ton scale. Given to its wide availability and low cost, it appears to be a very attractive chlorinating agent. In 1999, Brummond and co-workers employed TsCl as a source of "Cl$^+$" for the α-chlorination of ketones, in the presence of stoichiometric amount of strong base LDA.[14] Herein, we reported a catalytic protocol for the α-chlorination of 2-acyl imidazoles with TsCl catalyzed by an octahedral iridium complex.[15]

2. Results and discussion

To start with, the reaction of 2-acyl imidazole **1a** with TsCl was carried out in the presence of 5 mol% Sc(OTf)$_3$ as catalyst and Na$_2$HPO$_4$ (1.2 equiv.) as additive in THF at 40 ^{o}C under air atmosphere (entry 1, Table 1). To our dismay, trace amount of the α-chlorination product **3a** was observed from GC analysis. However, a promising result was achieved with Cu(OTf)$_2$ as catalyst, which resulted in 31% GC yield of **3a** (entry 3). Interestingly, the yield of **3a** was greatly improved to 85% when 1 mol% of racemic octahedral rhodium complex, *rac*-Rh was employed as catalyst (entry 4). The use of racemic octahedral iridium complex, *rac*-Ir (1 mol%) further improved the

yield to 97% (entry 5). Increase of catalyst loading to 2 mol% resulted in 98% yield (entry 6) while lowering the catalyst loading (0.5 mol%) decreased the yield to 77% (entry 7). As anticipated, the reaction could not deliver the desired product in the absence of catalyst (entry 8). Other bases such as $NaHCO_3$, KF and Et_3N were also screened, giving average to good yields of the desired product **3a** (entries 11-13). While, in the absence of base, only 7% GC yield of **3a** was observed, demonstrating the necessity of base additives in the reaction (entry 14). Interestingly, the reaction was found to be strongly influenced by the solvent used. No product formation was observed in MeCN, $CHCl_3$, 1,4-dioxane and toluene (entries 15-18), while trace amount of chlorination product **3a** was achieved in DMF (entry 19).

Table 1 Optimization of reaction conditions[a]
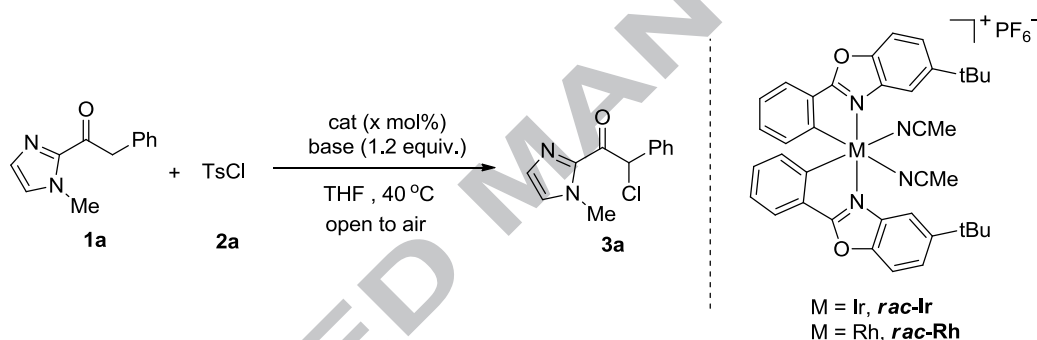
Entry	cat (x mol%)	Base(1.2 equiv)	Solvent	Yield (%)[b]
1	Sc(OTf)$_3$ (5)	Na$_2$HPO$_4$	THF	trace
2	Yb(OTf)$_3$ (5)	Na$_2$HPO$_4$	THF	trace
3	Cu(OTf)$_2$ (5)	Na$_2$HPO$_4$	THF	31
4	*rac*-Rh (1)	Na$_2$HPO$_4$	THF	85
5	*rac*-Ir (1)	Na$_2$HPO$_4$	THF	97
6	*rac*-Ir (2)	Na$_2$HPO$_4$	THF	98
7	*rac*-Ir (0.5)	Na$_2$HPO$_4$	THF	77
8	-	Na$_2$HPO$_4$	THF	trace
9[c]	*rac*-Ir (2)	Na$_2$HPO$_4$	THF	87
10[d]	*rac*-Ir (2)	Na$_2$HPO$_4$	THF	82
11	*rac*-Ir (2)	NaHCO$_3$	THF	59
12	*rac*-Ir (2)	KF	THF	54
13	*rac*-Ir (2)	Et$_3$N	THF	73

14	*rac*-Ir (2)	-	THF	7
15	*rac*-Ir (1)	Na$_2$HPO$_4$	MeCN	-
16	*rac*-Ir (1)	Na$_2$HPO$_4$	CHCl$_3$	-
17	*rac*-Ir (1)	Na$_2$HPO$_4$	1,4-dioxnae	-
18	*rac*-Ir (1)	Na$_2$HPO$_4$	toluene	-
19	*rac*-Ir (1)	Na$_2$HPO$_4$	DMF	trace

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), cat. (x mol %), base (0.12 mmol), solvent (2 mL) at 40 °C for 24 h under air atmosphere. [b]Determined by GC. [c]Carried out at room temperature. [d]Carried out at 60 °C.

A comparative study of the α-chlorination of 2-acyl imidazoles with different chlorinating agents such as NCS, trichloroisocyanuric acid, LiCl and trifluoromethylsulfonyl chloride, was also carried out (Table 2). The chlorination of 2-acyl imidazoles with trifluoromethylsulfonyl chloride under the optimized reaction conditions gave less than 10% GC yield of **3a** (entry 4, Table 2) while other chlorinating agents failed to produce the desired product (entries 1-3, Table 2). Based on these investigations, the optimal reaction conditions for the α-chlorination of 2-acyl imidazoles with tosyl chloride was identified as following: 2-acyl imidazole (1 equiv.) and tosylchloride (1.5 equiv.) in the presence of 1 mol% *rac*-Ir and 1.2 equivalent of Na$_2$HPO$_4$ in THF at 40 °C.
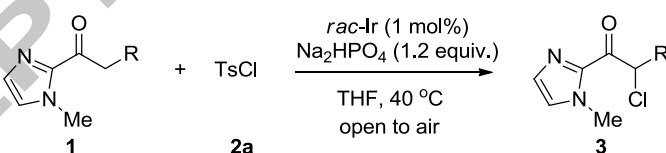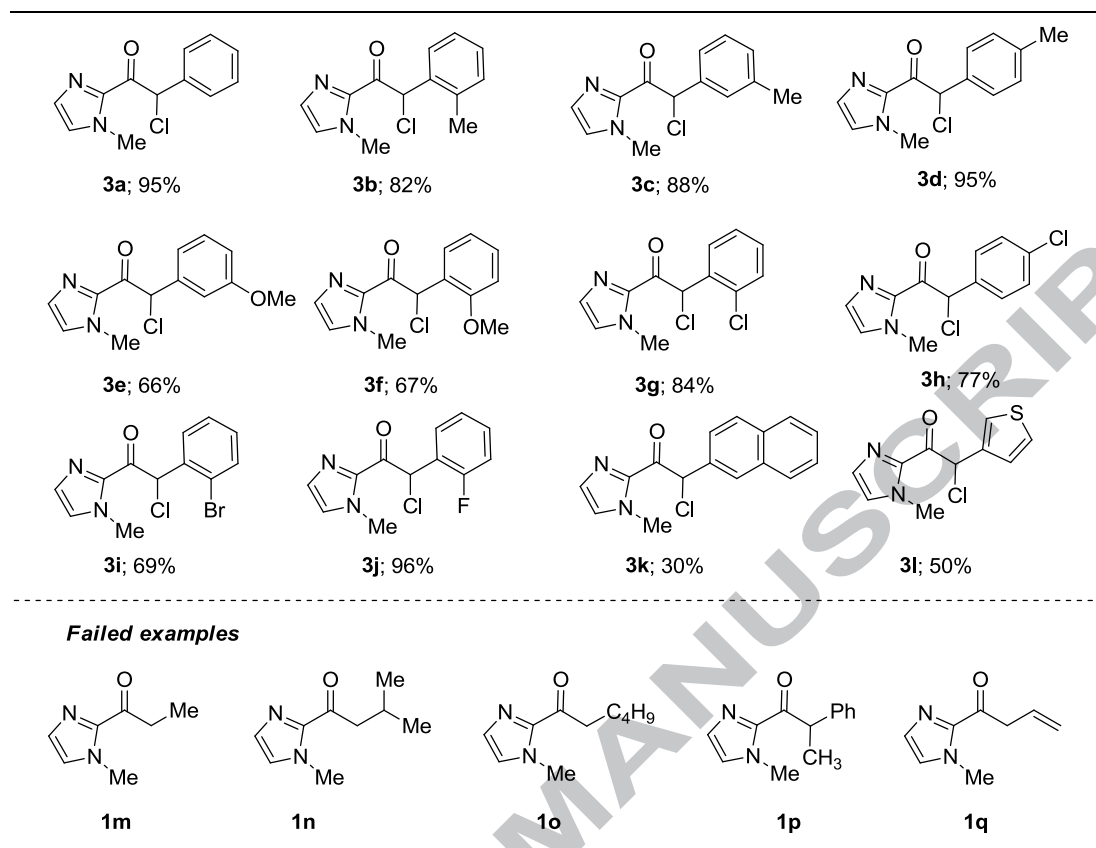
Table 2. Screening chlorinating agents[a]
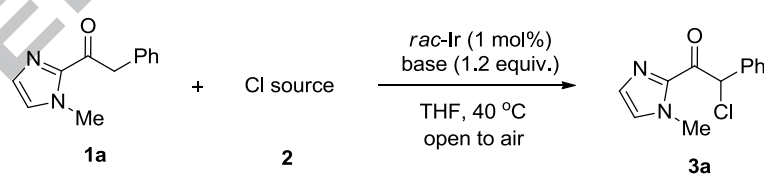
Entry	Cl source	Base (1.2 equiv)	Solvent	Yield (%)[c]
1	NCS	Na$_2$HPO$_4$	THF	trace
2	TCCA[b]	Na$_2$HPO$_4$	THF	trace
3	LiCl	Na$_2$HPO$_4$	THF	trace
4	CF$_3$SO$_2$Cl	Na$_2$HPO$_4$	THF	7

*a*Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), *rac*-Ir (1 mol %), base (0.12 mmol) in THF (2 mL) at 40 ^{o}C for 24 h under air atmosphere. *b*TCCA= Trichloroisocyanuric acid. *c*Determined by GC.

       With the optimal reaction conditions in hand, a range of *N*-methyl-2-acyl imidazoles **1** were subjected to α-chlorination (Table 3). The 2-acyl imidazoles with electron rich phenyl ring (**1b-1f**) led to formation of corresponding α-chlorination products **3b-3f** in good to excellent yields. The position of the electron-donating group in the phenyl ring didn't have significant influence on the reaction yields as evident from the chlorination of 2-acyl imidazoles with methyl or methoxy substituent at different positions of the phenyl ring (**3b-3d** and **3e-3f**). Likewise, 2-acyl imidazoles with electron deficient phenyl rings having chloro-, bromo- and fluoro substitution also afforded the α-chlorinated products **3g-3j** in good yields. The 2-acyl imidazole with *o*-fluoro-phenyl group **1j** furnished the desired α-chlorinated product **3j** in 96% yield. However, 2-acyl imidazoles incorporating naphthyl (**1k**) or 3-thienyl groups (**1l**) resulted the chlorinated products **3k** and **3l** in relatively lower yields, 30% and 50% yields respectively, along with di-ketone compounds as by-products. However, alkyl substituted (**1m-1o**) and vinyl substituted (**1q**) acyl imidazoles failed to furnish the desired α-chlorinated products under our optimized reaction conditions.

**Table 3** Substrates scope of chlorination*a*

3a; 95%　　**3b**; 82%　　**3c**; 88%　　**3d**; 95%

3e; 66%　　**3f**; 67%　　**3g**; 84%　　**3h**; 77%

3i; 69%　　**3j**; 96%　　**3k**; 30%　　**3l**; 50%

Failed examples

1m　　**1n**　　**1o**　　**1p**　　**1q**

[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), *rac*-Ir (1 mol%), Na_2HPO_4 (0.12 mmol) in THF (2 mL) at 40 ^{o}C for 24 h under air atmosphere. Isolated yields were reported.

Next, we explored the substrate scope with 2-acyl imidazole with different N-substitutions (Table 4). Like the *N*-methyl 2-acyl imidazoles, *N*-isopropyl 2-acyl imidazole **4a** also afforded the desired α-chlorinated product **5a** in excellent yield (98%). However, the α-chlorinated product **5b** was achieved in comparatively lower yield (48%) from the *N*-phenyl 2-acyl imidazole **4b**. Then, we wondered if we could replace the imidazole moiety with other heterocyclic rings (Table 4). The chlorination of 2-acyl benzimidazole **4c** preceded smoothly under our optimized reaction conditions to furnish the α-chlorinated product **5c** in 88% yield. Likewise, 2-acyl pyridine **4d** also found to be compatible in our reaction conditions to afford desired product **5d** in 50% yield. However, no α-chlorinated product formation was observed in the case of 2-acyl thiazole **4e** and 2-acyl pyrazole **4f**.

**Table 4** Substrates scope of chlorination[a]
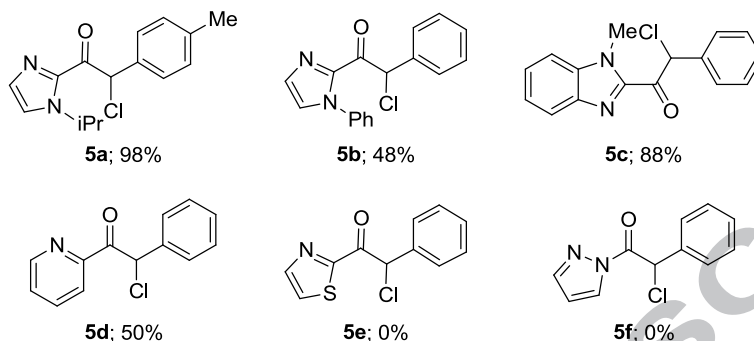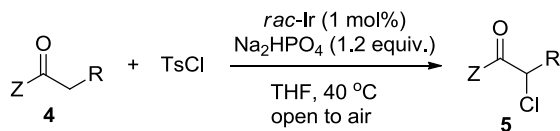
*a*Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), *rac*-Ir (1 mol%), Na$_2$HPO$_4$ (0.12 mmol) in THF (2 mL) at 40 $^{\circ}$C for 24 h under air atmosphere. Isolated yields were reported.

In order to understand this transformation, controlled experiments were carried out as showed in Scheme 1. When the reaction was carried on in a sealed tube, the reaction failed to afford desired product, which indicated that oxygen is necessary for titled transformation. When 1 equivalent of TEMPO was introduced to the reaction, the reaction also failed to give any product with starting material **1a** completely recovered, which implied that radical process might be involved in this transformation (eq 1, Scheme 1).[16] α-Carbonyl carbon radicals derived from imidazole substrate might not be generated since no product was obtained in this reaction conditions with TEMPO.[17] Based on the literature report[18] that *rac*-Ir complex is known as photocatalyst, further experiment was carried on under visible light irradiation (eq 2, Scheme 1). The reaction could occur under these conditions, however, resulting in desired product **3a** in 20% yield along with di-ketone product **6** in 72% yield.[19]
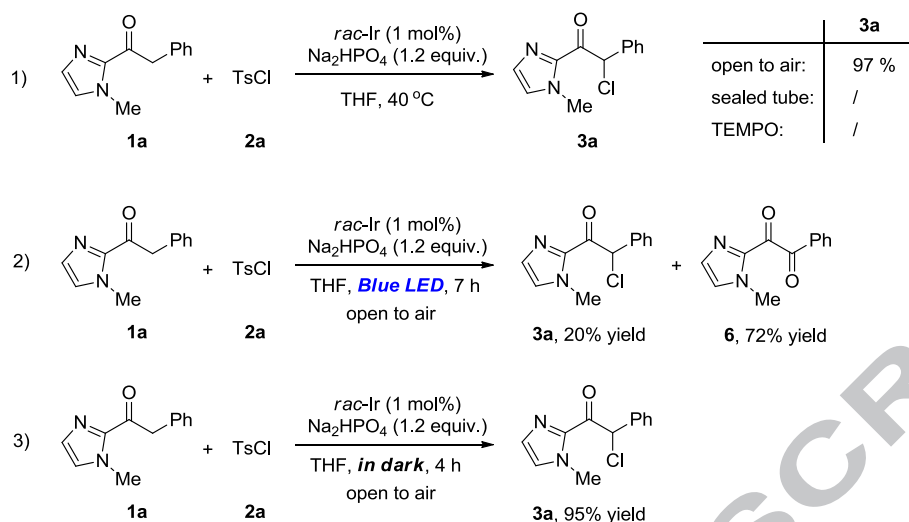
Scheme 1. Controlled experiments.

In addition, we attempted to investigate the asymmetric version of this protocol. For this purpose, Δ-Ir complex (1 mol%) was employed as catalyst for the title reaction. The reaction worked smoothly to afford corresponding product **3a** in 95% yield, however, without enantioselectivity (Scheme 2).
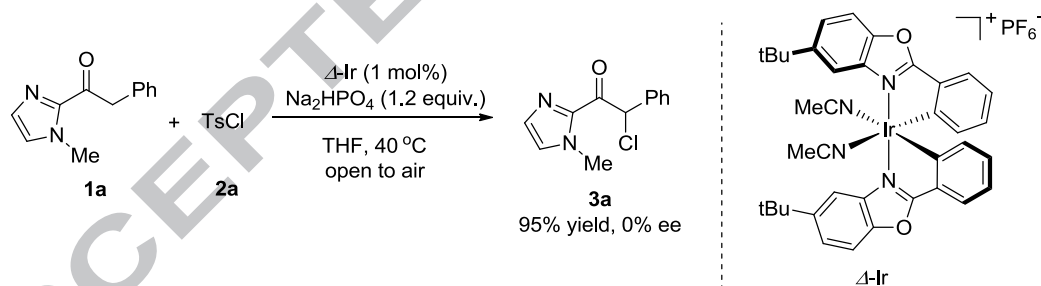
Scheme 2. Attempt towards asymmetric synthesis of **3a**.

In conclusion, we had developed an efficient and catalytic approach for α-chlorination of 2-acyl imidazoles with readily available and cheap tosyl chloride, catalyzed by an octahedral iridium complex with as low as 1 mol% catalyst loading. The α-chlorinated 2-acyl imidazoles were achieved in good to excellent yields under mild condition. Likewise, 2-acyl benzimidazole and 2-acyl pyridine also afford the

corresponding α-chlorinated products. The reaction might proceed via a free-radical process based on the controlled experiments performed.

Acknowledgements

References and notes

1. House, H. *Modern Synthetic Reactions*, *2nd edn.*, W. A. Benjamin, New York, **1972**, 459; b) De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*, John Wiley & Sons, New York, **1988**; c) Larock, R. C. *Comprehensive Organic Transformations*, 2nd edn., Wiley-VCH, New York, **1999**; d) Thomas, G. *Medicinal Chemistry: An Introduction*, Wiley, New York, **2000**.

2. Selected examples of organocatalytic α-chlorination, see: (a) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790; (b) Halland, N.; Lie, M. A.; Kjarsgaard, A.; Marigo, M.; Schiot, B.; Jorgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 7083; (c) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507; (d) Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083; (e) Bergeron-Brlek, M.; Teoh, T.; Britton, R. *Org. Lett.* **2013**, *15*, 3554; (f) Marigo, M.; Kumaragurubaran, N.; Jorgensen, K. A. *Chem. Eur. J.* **2004**, *10*, 2133; (g) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; T. Lectka *J. Am. Chem. Soc.* **2001**, *123*, 1531; (h) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108; (i) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219.

3. (a) Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429; (b) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 15038.

4. Meshram, H. M.; Reddy, P. N.; Sadashiv, K.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 623.

5. Selected examples of transition metal complex catalyzed α-chlorination, see: (a) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709; (b) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425; (c) Zheng, W.; Zhang, Z.; Kaplan, M. J.; Antilla, J. C. *J. Am. Chem. Soc.* **2011**, *133*, 3339; (d) Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324; (e) Frings, M.; Bolm, C. *Eur. J. Org. Chem.* **2009**, 4085.

6. Bures, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741.

7. (a) Dick, C. R. *J. Org. Chem.* **1962**, *27*, 272. (b) Bongini, A.; Cainelli, G.; Contento, M.; Manescalchi, F. *J. Chem. Soc., Chem. Commun.* **1980**, 1278.

8. Shirakawa, S.; Tokuda, T.; Kasai, A.; Maruoka, K. *Org. Lett.* **2013**, *15*, 3350.

9. Lee, E. C.; McCauley, K. M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 977.

10. Douglas, J.; Ling, K. B.; Concellon, C.; Churchill, G.; Slawin, A. M. Z.; Smith, A. D. *Eur. J. Org. Chem.* **2010**, 5863; (b) France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245.

11. Masschelein, K. G. R.; Stevens, C. V. *Tetrahedron Lett.* **2008**, *49*, 4336.

12. Jimeno, C.; Cao, L.; Renaud, P. *J. Org. Chem.* **2016**, *81*, 1251.

13. (a) Wender, P. A.; Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107,* 7771; (b) G. H. Hakimelahi, G. Just, *Tetrahedron Lett.* **1979**, *38*, 3643.

14. Brummond, K. M.; Gesenberg, K. D. *Tetrahedron Lett.* **1999**, *40*, 2231.

15. Huo, H.; Fu, C.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2014**, *136*, 2990.

16. Su, Y.; Zhang, L.; Jiao, N. *Org. Lett.* **2011**, *13*, 2168.

17. Huang, X.; Webster, R. D.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2016**, *138*, 12636.

18. Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Rose, P.; Chen, L. A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100.

19. α-Halogen ketones could be transferred to di-ketone compounds catalyzed by photocatalyst under visible light irradiation, see ref. 16.

Highlight

- ◆ Well-defined octahedral iridium complex is employed in catalytic α-chlorination.
- ◆ TsCl is employed as a Cl source.
- ◆ As low as 1 mol% of catalyst is employed.
- ◆ The reactions are conducted under air condition.