Letter

Development of Ketone-Based Brominating Agents (KBA) for the Practical Asymmetric #-Bromination of Aldehydes Catalyzed by Tritylpyrrolidine

Aika Takeshima, Mio Shimogaki, Taichi Kano, and Keiji Maruoka

ACS Catal., **Just Accepted Manuscript** • Publication Date (Web): 01 May 2020

Development of Ketone-Based Brominating Agents (KBA) for the Practical Asymmetric α-Bromination of Aldehydes Catalyzed by Tritylpyrrolidine

Aika Takeshima,[#,†] Mio Shimogaki,[#,†] Taichi Kano,*[,†] and Keiji Maruoka*[,†,‡,§]

[†] Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

[‡] Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo, Kyoto 606-8501, Japan

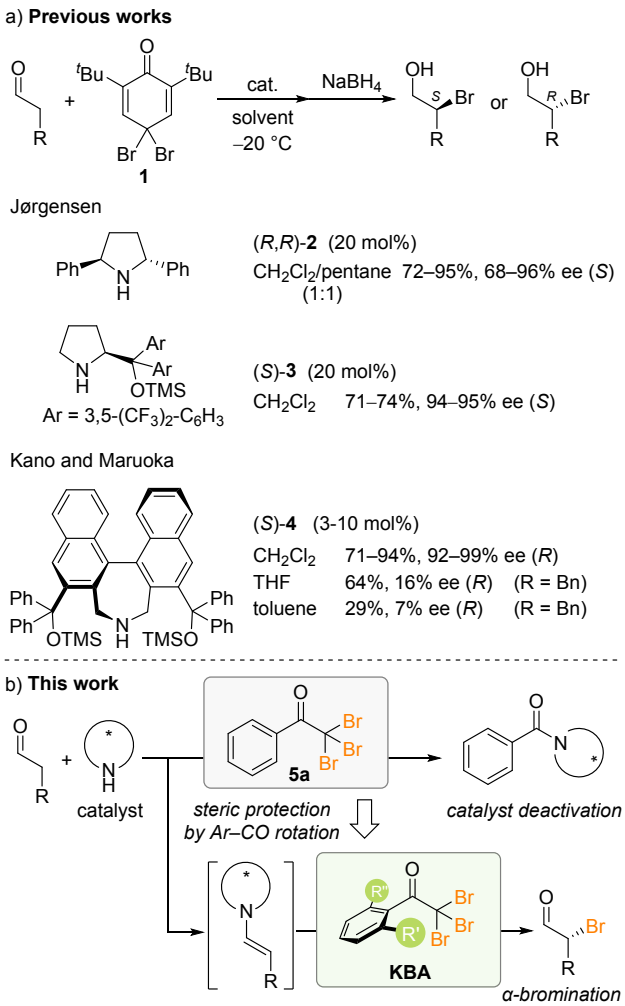
[§] School of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, China

ABSTRACT: Ketone-based brominating agents (KBA), *ortho*-substituted 2,2,2-tribromoacetophenones have been developed, and the highly enantioselective and practical α-bromination of aldehydes with KBA was achieved. The reaction could be performed in the presence of only 0.1–1 mol% of catalyst without using a halogenated solvent at 0 °C and was found to be scalable. *KEYWORDS, amine catalyst*, *asymmetric synthesis*, *brominating agent*, *enamine catalysis*, *organocatalysis*

α-Bromocarbonyl compounds can serve as versatile synthetic intermediates in the formation of carbon–carbon bonds as well as various carbon–heteroatom bonds because of the high leaving group ability of bromine atom.[1] Asymmetric enamine catalysis is one of the powerful organocatalytic strategies for the stereoselective α-halogenation of aldehydes and ketones.[2–7] In this area, a number of catalytic asymmetric α-fluorinations and α-chlorinations of carbonyl compounds have been developed to date.[3–5] On the other hand, only a few asymmetric α-brominations have been investigated despite high synthetic utility of the products.[6] In the previous attempts for α-bromination of aldehydes, a high catalyst loading of (*R*,*R*)-**2** or (*S*)-**3** (20 mol%) was required, probably due to undesired side reactions such as bromination of the amine catalyst (Scheme 1a).[3e,6a] We have also developed the asymmetric α-bromination of aldehydes catalyzed by the binaphthyl-based secondary amine (*S*)-**4**, in which the amount of catalyst could be reduced, since the introduction of steric bulkiness into the catalyst circumvents the catalyst deactivation by the brominating agent.[6b] However, both yield and enantioselectivity strongly depend on the solvent, and use of CH_2Cl_2 was necessary rather than industrially usable solvents such as THF and toluene.[8] The low enantioselectivities in non-halogenated solvents might be attributed to the racemic pathway with the reactive brominating agent **1**. We hypothesized that if a milder brominating agent suppresses the catalyst deactivation and the non-catalyzed racemic process, the highly enantioselective bromination would be promoted by a small amount of chiral amine catalyst even in a non-halogenated solvent.

In the course of our recent studies on enamine catalysis, debromination of an α,β-unsaturated tribromomethyl ketone was observed in the presence of pyrrolidine and an aldehyde. We realized that this result must be due to the bromination of the aldehyde and/or pyrrolidine. We first focused on 2,2,2-tribromoacetophenone (**5a**) which might show the potential as a brominating agent. However, rapid amidation of **5a** occurred in the presence of a secondary amine.[9] Based on this result,

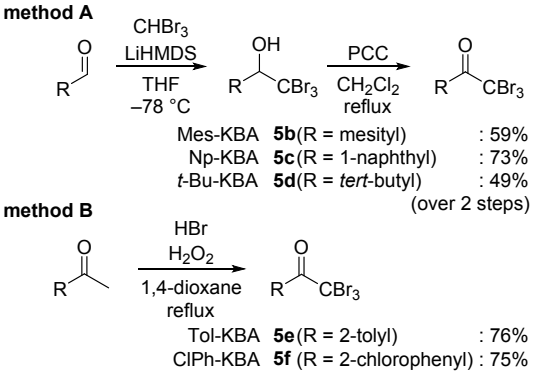
Scheme 1. Asymmetric α-Bromination of Aldehydes Catalyzed by Chiral Secondary Amines



ketone-based brominating agents (KBA), 2,2,2-tribromoacetophenones bearing *ortho*-substituents, which may suppress the catalyst deactivation through the amidation, were designed (Scheme 1b). It was postulated that the nucleophilic addition of the secondary amine catalysts to the carbonyl group along the Bürgi-Dunitz trajectory could be hampered by the *ortho*-substituent because the *ortho*-substituted aryl ring twists out of the plane of the carbonyl group. Herein, we report the development of novel brominating agents and their application to the amine-catalyzed asymmetric α-bromination of aldehydes. Our strategy could provide a practical solution to circumvent the high catalyst loading and the use of undesirable solvents.

Several KBAs were prepared via two routes. KBA **5b**–**5d** could be synthesized from the corresponding aldehydes through two steps. They were formed by nucleophilic addition of tribromomethyllithium to the aldehyde, followed by oxidation of the resulting alcohol (Scheme 2: method A). KBA **5e** and **5f** could be prepared in one step from the corresponding ketones by a simpler method using readily available reagents (Scheme 2: method B).[10] The obtained KBAs are relatively stable even at room temperature, while **5e** gradually decomposes into the corresponding dibromomethyl ketone. KBA **5d** could be stored at –20 °C. KBA **5b, 5c** and **5f** are bench-stable and have been maintained for several months without change.

Scheme 2. Synthetic Routes for KBA 5b–5f



To evaluate the potential of the newly synthesized compounds **5** as brominating agent for the enamine catalysis, we monitored the transformation of **5** in the presence of one equivalent of pyrrolidine by ^{1}H NMR (Figure 1). Additionally, they were compared with other standard brominating agents. Use of 2,2,2-tribromoacetophenone (**5a**) promptly gave amide **6**, which suggests deactivation of the pyrrolidine-based secondary amine catalyst. In contrast, no or low conversion of **5b**–**5f** to **6** was observed after 16 h. In particular, **5b** and **5d** hardly changed in the presence of pyrrolidine. KBA **5c** and **5e** were gradually converted to dibromomethyl ketone **7**. In the case of **5f**, the corresponding carboxylic acid **8** was obtained.[11] Unidentified by-product was observed in some cases. On the other hand, relatively reactive brominating agents such as *N*-bromosuccinimide, *N*-bromoacetamide and 1,3-dibromo-5,5-dimethylhydantoin were rapidly decomposed by pyrrolidine. In the case of the brominating agent **1**, the decomposition rate was faster than that of **5f**. After 40 min, 20% of **1** decomposed and 50% remained after 2 h. Furthermore, to confirm whether the amine-catalyzed bromination proceeds via the enamine intermediate, the reaction between 3-phenylpropanal (**9a**) and **5f** in the presence of a secondary amine or tertiary amine was examined in $CDCl_3$ at room temperature. As expected, the α-bromination with pyrrolidine proceeded rapidly. In contrast, the reaction did not proceed with *N*-methylpyrrolidine (See SI for details). From these results, *ortho*-substituted tribromoacetophenones were confirmed to be promising brominating agents in enamine catalysis.

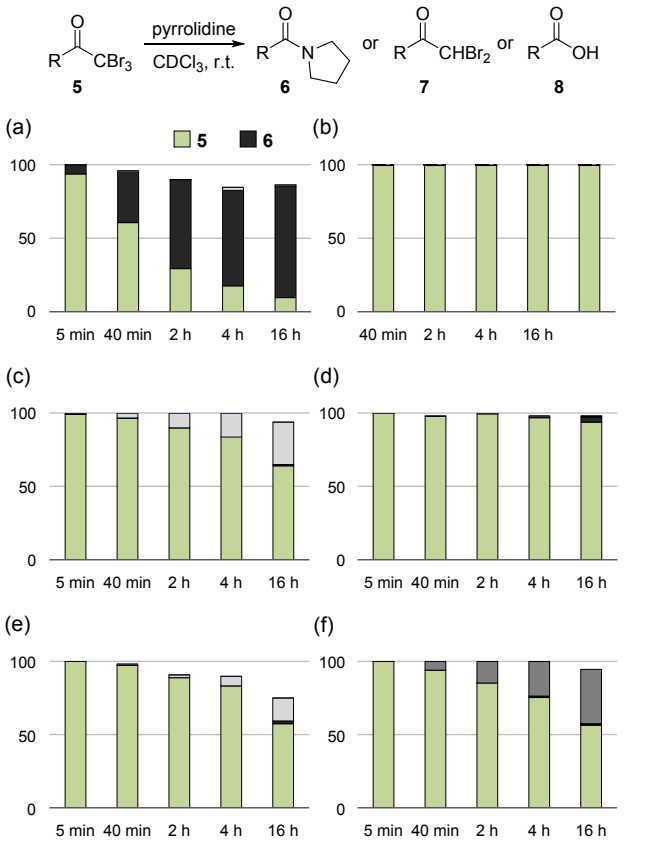


Figure 1. Decomposition of **5** monitored by ^{1}H NMR spectroscopy: (a) **5a** (R = Ph), (b) **5b** (R = Mesityl), (c) **5c** (R = 1-naphthyl), (d) **5d** (R = *tert*-butyl), (e) **5e** (R = 2-tolyl), and (f) **5f** (R = 2-chlorophenyl). The ratio of four compounds was determined with an internal standard.

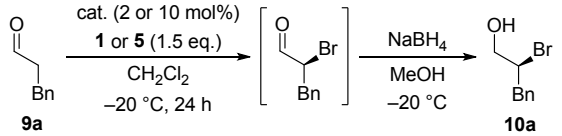
The novel brominating agents were applied to the asymmetric α-bromination of 3-phenylpropanal (**9a**) in CH_2Cl_2 in the presence of 10 mol% of a secondary amine catalyst at –20 °C, and the results are shown in Table 1. Readily available chiral pyrrolidines were selected as catalysts. Whereas the reaction with tribromoacetophenone (**5a**) in the presence of **11** hardly proceeded (entry 1), use of bulky Mes-KBA **5b** gave the bromination product **10a** in moderate yield due to suppression of catalyst deactivation (entry 2). We then examined other amine catalysts to improve the enantioselectivity (entries 3–9). The reaction using **3** afforded the product in low yield in spite of excellent enantioselectivity (entry 3). Use of catalyst **4** led to excellent yield and high enantioselectivity (entry 4). In the reactions with catalysts **12**–**14**, low to moderate enantioselectivities were observed (entries 5–7). In contrast, use of catalysts **15** and **16** with two substituents in *cis* configuration gave **10a** in good yield with excellent enantioselectivity due to the steric effect of the silyloxy group (entries 8 and 9).[12] The catalyst **15** was selected for further study in terms of accessibility. α-Bromination using the other KBAs was next investigated (entries 10–13). In most cases examined, **10a** was

obtained in moderate to excellent yields with high enantioselectivities. The reaction using *t*-Bu- KBA **5d** afforded the product in low yield with reduced enantioselectivity (entry 11). The acetophenone framework was found to be important for the present asymmetric bromination. Regarding brominating agent, readily available ClPh-KBA **5f** was determined to be the choice. The catalyst loading could be reduced to 2 mol% without significant loss of enantioselectivity (entry 14). Incidentally, the reaction using brominating agent **1** under identical conditions did not proceeded at all (entry 15).

The solvent and additive effects were then examined to optimize the reaction conditions (Table 2). Although CH_2Cl_2 was the optimal solvent in terms of both yield and enantioselectivity, **10a** was obtained in moderate to high yield with good enantioselectivity in all solvents tested (entries 1–7). To avoid halogenated solvents, toluene was selected for further study. Even when the catalyst loading was reduced to 2 mol%, the reaction proceeded to give **10a** in high yield (entry 8). We were pleased to find that addition of *p*-nitrobenzoic acid drastically accelerated the reaction (entry 9) and the enantioselectivity was maintained at 0 °C (entry 10). While the yield was decreased, the reaction proceeded even with 0.5 mol% catalyst loading (entry 11). Use of a reduced amount of **5f** (1.1 eq.) at higher concentration led to a good yield and excellent enantioselectivity (entry 12). The yield was improved by addition of water, and excellent yield and enantioselectivity were achieved with low catalyst loading (entry 13). Such a low catalyst loading is rare not only for organocatalytic brominations but organocatalysis with secondary amines in general.[13]

With low catalyst loading, the asymmetric α-bromination of several other aldehydes **9** with ClPh-KBA **5f** was examined in toluene at 0 °C, and the results are shown in Table 3. Increasing the amount of acid could further reduce the catalyst loading (entry 1). In most cases, the asymmetric α-bromination of aldehydes proceeded to give the corresponding bromohydrin **10** in good to excellent yields and enantioselectivities with 0.1–1 mol% of catalyst. However, moderate enantioselectivity was observed in the reaction of **9d** (entry 4). The yield was low when using sterically hindered aldehyde **9f** (entry 6). The reaction of phenylacetaldehyde **9i** did not proceed (entry 9). The use of ketones such as cyclohexanone and diethyl ketone under identical conditions also resulted in no reaction.

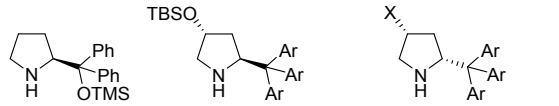
Table 1. Asymmetric α-bromination of 3-phenylpropanal using pyrrolidine-based amine catalysts[a]



9a **10a**

entry	**1** or **5**	cat. (mol %)	yield (%)[b]	ee (%)[c]
1	**5a**	**11** (10)	trace	-
2	**5b**	**11** (10)	61	36
3	**5b**	**3** (10)	9	94
4	**5b**	**4** (10)	99	–91
5	**5b**	**12** (10)	83	28
6	**5b**	**13** (10)	83	64
7	**5b**	**14** (10)	99	–48
8	**5b**	**15** (10)	87	–96
9	**5b**	**16** (10)	79	–98
10	**5c**	**15** (10)	67	–97
11	**5d**	**15** (10)	15	–90
12	**5e**	**15** (10)	99	–96
13	**5f**	**15** (10)	85	–96
14[d,e]	**5f**	**15** (2)	81	–94
15[d,e]	**1**	**15** (2)	nd[f]	-

[a]The reactions were performed on 0.1 mmol scale in 0.5 mL of CH_2Cl_2. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral column. [d]Use of 0.2 mL of CH_2Cl_2. [e]Performed for 83 h. [f]Not detected.

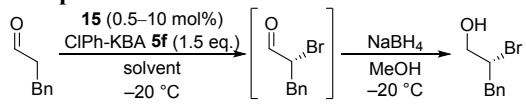


11

12: Ar = Ph
13: Ar = 3,5-Xy

14: X = H, Ar = Ph
15: X = OTBS, Ar = Ph
16: X = OTBS, Ar = 3,5-Xy

Table 2. Optimization of reaction conditions[a]

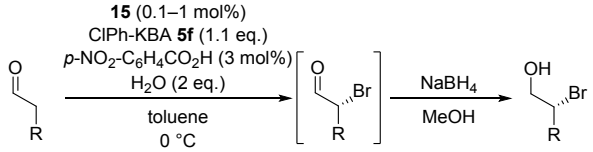


9a **10a**

entry	**15** (mol %)	solvent	*t* (h)	yield (%)[b]	ee (%)[c]
1	10	CH_2Cl_2	24	99	96
2	10	$CHCl_3$	24	46	84
3	10	$PhCF_3$	24	67	90
4	10	THF	24	52	82
5	10	CPME	24	79	90
6	10	hexane	24	88	83
7	10	toluene	24	89	93
8	2	toluene	65	99	86
9[d]	2	toluene	4	90	92
10[d,e]	2	toluene	1	99	94
11[d,e]	0.5	toluene	8	58	85
12[d,e,f]	0.5	toluene	4	76	97
13[d,e,f,g]	0.5	toluene	5	96	97

[a]The reactions were performed on 0.1 mmol scale in 0.2 mL of the solvent. [b]NMR yield. [c]Determined by HPLC analysis using a chiral column. [d]Using three times the amount of *p*-nitrobenzoic acid to the catalyst. [e]Performed at 0 °C. [f]Using **5f** (1.1 eq.) in 0.1 mL of toluene. [g]H_2O (2 eq.) was added.

Table 3. Scope of α-bromination of aldehydes[a]

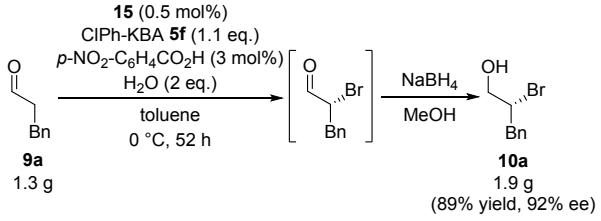


9 **10**

entry	R	**15** (mol %)	*t* (h)	yield (%)[b]		ee (%)[c]
1	Bn	0.1	74	**10a**	91	93
2	Bu	0.5	24	**10b**	87	94
3	CH_2Cy	1	3	**10c**	99	97
4[d]	Cy	1	23	**10d**	75	83
5[d]	*i*-Pr	1	27	**10e**	76	95
6[d]	*t*-Bu	1	24	**10f**	14	92
7	allyl	1	25	**10g**	87	93
8	CH_2OBn	1	8	**10h**	84	85
9	Ph	1	24	**10i**	nd[e]	-

[a]The reactions were performed on 0.1 mmol scale in 0.1 mL of toluene. [b]Isolated yield. [c]Determined by HPLC analysis using a chiral column. [d]Performed at 10 °C. [e]Not detected.

Scheme 3. Gram–scale Synthesis



We performed large scale asymmetric α-bromination using 1.3 g of 3-phenylpropanal (**9a**). As can be seen from the result in Scheme 3, the yield and the enantioselectivity were maintained at the same level, which indicates great possibilities for practical applications.

In summary, we have developed useful ketone-based brominating agents (KBA) for asymmetric α-bromination of aldehydes. With ClPh-KBA, the reaction can be performed using a low catalyst loading in non-halogenated solvent at the moderate and practical temperature. This new type of brominating agents will be of value for other bromination reactions.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge via the Internet at http://pubs.acs.org.

General Information, Preparation of Brominating agents, NMR spectra, and HPLC spectral.

AUTHOR INFORMATION

Corresponding Author

* E-mail: kano@kuchem.kyoto-u.ac.jp
* E-mail: maruoka@kuchem.kyoto-u.ac.jp

ORCID

Taichi Kano: 0000-0001-5730-3801
Keiji Maruoka: 0000-0002-0044-6411

Author Contributions

#These authors contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI Grant Numbers JP26220803, JP18H01975, JP20H04815 (Hybrid Catalysis) and JP18J01780. M. S. is grateful for Fellowships for Young Scientists from the Japan Society for the Promotion of Science (JSPS).

REFERENCES

(1) (a) Jiang, H.; Elsner, P.; Jensen, K. L.; Falcicchio, A.; Marcos, V.; Jørgensen, K. A. Achieving Molecular Complexity by Organocatalytic One-Pot Strategies–A Fast Entry for Synthesis of Sphingoids, Amino Sugars, and Polyhydroxylated α-Amino Acids. *Angew. Chem., Int. Ed.* **2009**, *48*, 6844–6848. (b) Britton, R.; Kang, B. α-Haloaldehydes: Versatile Building Blocks for Natural Product Synthesis. *Nat. Prod. Rep*. **2013**, *30*, 227–236. (c) Zou, Y.-Q.; Guo, W.; Liu, F.-L.; Lu, L.-Q.; Chen, J.-R. Visible-light-induced Photocatalytic Formyloxylation Reactions of 3-Bromooxindoles with Water and DMF: The Scope and Mechanism. *Green Chem*. **2014**, *16*, 3787–3795.

(2) (a) Oestreich, M. Strategies for Catalytic Asymmetric Electrophilic α Halogenation of Carbonyl Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 2324–2327. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev*. **2007**, *107*, 5471–5569. (c) Ma, J.-A.; Cahard, D. Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions. *Chem. Rev*. **2008**, *108*, 1–43. (d) Ueda, M.; Kano, T.; Maruoka, K. Organocatalyzed Direct Asymmetric α-Halogenation of Carbonyl Compounds. *Org. Biomol. Chem*. **2009**, *7*, 2005–2012. (e) Lectard, S.; Hamashima, Y.; Sodeoka, M. Recent Advances in Catalytic Enantioselective Fluorination Reactions. *Adv. Synth. Catal*. **2010**, *352*, 2708–2732. (f) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. Mechanisms in Aminocatalysis. *Chem. Commun*. **2011**, *47*, 632–649. (g) Valero, G.; Companyó, X.; Rios, R. Enantioselective Organocatalytic Synthesis of Fluorinated Molecules. *Chem.–Eur. J.* **2011**, *17*, 2018–2037. (h) Kano, T. C–X Bond Formation: α-Halogenation of Carbonyl Compounds. *Comprehensive Chirality*, Volume 6; Elsevier Science: Amsterdam, **2012**, 488–505. (i) Shibatomi, K.; Narayama, A. Catalytic Enantioselective α-Chlorination of Carbonyl Compounds. *Asian J. Org. Chem*. **2013**, *2*, 812–823. (j) Chung, W.-J.; Vanderwal, C. D. Stereoselective Halogenation in Natural Product Synthesis. *Angew. Chem., Int. Ed.* **2016**, *55*, 4396–4434.

(3) Fluorination of linear aldehydes: (a) Enders, D.; Hüttl, M. R. Direct Organocatalytic α-Fluorination of Aldehydes and Ketones. *Synlett* **2005**, 991–993. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjœrsgaard, A.; Jørgensen, K. A. Enantioselective Formation of Stereogenic Carbon–Fluorine Centers by a Simple Catalytic Method. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703–3706. (c) Steiner, D. D.; Mase, N.; Barbas III, C. F. Direct Asymmetric α-Fluorination of Aldehydes. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706–3710. (d) Beeson, T. D.; MacMillan, D. W. C. Enantioselective Organocatalytic α-Fluorination of Aldehydes. *J. Am. Chem. Soc*. **2005**, *127*, 8826–8828. (e) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjœrsgaard, A.; Jørgensen, K. A. A General Organocatalyst for Direct α-Fluorination of Aldehydes: Stereoselective C–C, C–N, C–F, C–Br, and C–S Bond-Forming Reactions. Scope and Mechanistic Insights. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.

(4) Fluorination of α-branched aldehydes: (a) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. Non-Biaryl Atropisomers in Organocatalysis. *Chem.–Eur. J*. **2006**, *12*, 6039–6052. (b) Shibatomi, K.; Yamamoto, H. Stereoselective Synthesis of α,α-Chlorofluoro Carbonyl Compounds Leading to the Construction of Fluorinated Chiral Quaternary Carbon Centers. *Angew. Chem., Int. Ed.* **2008**, *47*, 5796–5798. (c) Shibatomi, K.; Okimi, T.; Abe, Y.; Narayama, A.; Nakamura, N; Iwasa, S. Organocatalytic Asymmetric Fluorination of α-Chloroaldehydes involving Kinetic Resolution. *Beilstein J. Org. Chem*. **2014**, *10*, 323–331. (d) Witten, M. R.; Jacobsen, E. N. A Simple Primary Amine Catalyst for Enantioselective α-Hydroxylations and α-Fluorinations of Branched Aldehydes. *Org. Lett*. **2015**, *17*, 2772–2775. (e) Shibatomi, K.; Kitahara, K.; Okimi, T.; Abe, Y.; Iwasa, S. Enantioselective Fluorination of α-Branched Aldehydes and Subsequent Conversion to α-Hydroxyacetals *via* Stereospecific C–F Bond Cleavage. *Chem. Sci*. **2016**, *7*, 1388–1392. (f) Fjelbye, K.; Marigo, M.; Clausen, R. P.; Juhl, K. *Synlett* **2017**, *28*, 425–428. (g) Arimitsu, S.; Yonamine, T.; Higashi, M. Cinchona-Based Primary Amine Catalyzed a Proximal Functionalization of Dienamines: Asymmetric α-Fluorination of α-Branched Enals. *ACS Catal*. **2017**, *7*, 4736–4740. (h) Cui, L.; You, Y.; Mi, X., Luo, S. Asymmetric Fluorination of α-Branched Aldehydes by Chiral Primary Amine Catalysis: Reagent-Controlled Enantioselectivity Switch. *J. Org. Chem*. **2018**, *83*, 4250–4256.

(5) Chlorination of aldehydes: (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. Direct and Enantioselective Organocatalytic α-Chlorination of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109. (b) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. Highly Enantioselective Direct Organocatalytic α-Chlorination of Ketones. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507–5510. (c) Halland,

N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. Direct Organocatalytic Asymmetric α-Chlorination of Aldehydes. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791. (d) Kang, B.; Britton, R. A General Method for the Synthesis of Nonracemic *trans*-Epoxides: Concise Synthesis of *trans*-Epoxide-Containing Insect Sex Pheromones. *Org. Lett*. **2007**, *24*, 5083–5086. (e) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. Enantioselective Linchpin Catalysis by SOMO Catalysis: An Approach to the Asymmetric α-Chlorination of Aldehydes and Terminal Epoxide Formation. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121–5124. (f) Fadeyi, O. O.; Schulte, M. L.; Lindsley, C. W. General Access to Chiral *N*-Alkyl Terminal Aziridines via Organocatalysis. *Org. Lett*. **2010**, *14*, 3276–3278. (g) Wang, L.; Cai, C.; Curran, D. P.; Zhang, W. Enantioselective α-Chlorination of Aldehydes with Recyclable Fluorous (*S*)-Pyrrolidine-Thiourea Bifunctional Organocatalyst. *Synlett* **2010**, 433–436. (h) Jimeno, C.; Cao, L.; Renaud, P. Trichloromethanesulfonyl Chloride: A Chlorinating Reagent for Aldehydes. *J. Org. Chem*. **2016**, *81*, 1251–1255.

(6) Bromination of aldehydes: (a) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. Organocatalytic Asymmetric α-Bromination of Aldehydes and Ketones. *Chem. Commun*. **2005**, 4821–4823. (b) Kano, T.; Shirozu, F.; Maruoka, K. Direct Asymmetric Bromination of Aldehydes Catalyzed by a Binaphthyl-based Secondary Amine: Highly Enantio- and Diastereoselective One-pot Synthesis of Bromohydrins. *Chem. Commun*. **2010**, *46*, 7590-7592. See also ref 3e.

(7) Iodination of aldehydes: Kano, T.; Ueda, M.; Maruoka, K. Direct Asymmetric Iodination of Aldehydes Using an Axially Chiral Bifunctional Amino Alcohol Catalyst. *J. Am. Chem. Soc.* **2008**, *130*, 3728–3729. See also ref 6a.

(8) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; McElroy, C. R.; Sherwood, J. Tools and Techniques for Solvent Selection: Green Solvent Selection Guides. *Sustain. Chem. Process* **2016**, *4*, 1034–1058.

(9) (a) Turnbull, K.; Beladakere, R. N.; McCall, N. D. Activated Carbonyl Species for the Preparation of *ortho*-Acylarylsydnones. *J. Heterocyclic Chem*. **2000**, *37*, 383–388. (b) Jayaraman, A.; Cho, E.; Kim, J.; Lee, S. Decarboxylative Tribromination for the Selective Synthesis of Tribromomethyl Ketone and Tribromovinyl Derivatives. *Adv. Synth. Catal*. **2018**, *360*, 3978–3989.

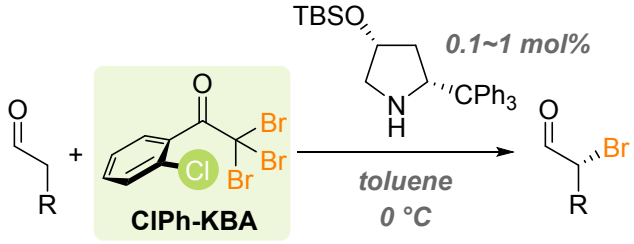
(10) Terent'ev, A. O.; Khodykin, S. V.; Krylov, I. B.; Ogibin, Y. N.; Nikishin, G. I. A Convenient Synthesis of 2,2-Dibromo-1-arylenthanones by Bromination of 1-Arylethanones with the H_2O_2–HBr System. *Synthesis* **2006**, *7*, 1087–1092.

(11) Interestingly, in the presence of catalyst **15**, decomposition of KBA **5f** to the carboxylic acid **8** was not observed under identical conditions.

(12) (a) Kano, T.; Mii, H.; Maruoka, K. Direct Asymmetric Benzoyloxylation of Aldehydes Catalyzed by 2-Tritylpyrrolidine. *J. Am. Chem. Soc*. **2009**, *131*, 3450–3451. (b) Shimogaki, M.; Maruyama, H.; Tsuji, S.; Homma, C.; Kano, T.; Maruoka, K. Synthesis of Chiral Tritylpyrrolidine Derivatives and Their Application to Asymmetric Benzoyloxylation. *J. Org. Chem*. **2017**, *82*, 12928–12932. (c) Kano, T.; Maruyama, H.; Homma, C.; Maruoka, K. Chiral Amine-Catalyzed Asymmetric Conjugate Addition of Aldehydes to α-Phenylselenoenones as Formal *Z*-Allylating Agents. *Chem. Commun*. **2018**, *54*, 176–179.

(13) An excellent example of enamine catalysis with low catalyst loading: Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. Enamine Catalysis with Low Catalyst Loading – High Efficiency via Kinetic Studies. *J. Am. Chem. Soc*. **2010**, *132*, 6–7.

Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal's Instructions for Authors for TOC graphic specifications.



✓ low catalyst loading ✓ non-halogenated solvent
✓ moderate and practical temperature