A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Catalytic Enantioselective Direct Aldol Addition of Aryl Ketones to α-Fluorinated Ketones

Authors: Connor Jack Thomson, David M Barber, and Darren James Dixon

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201916129
Angew. Chem. 10.1002/ange.201916129

Link to VoR: http://dx.doi.org/10.1002/anie.201916129
http://dx.doi.org/10.1002/ange.201916129

WILEY-VCH

10.1002/anie.201916129

WILEY-VCH

COMMUNICATION

Catalytic Enantioselective Direct Aldol Addition of Aryl Ketones to α-Fluorinated Ketones

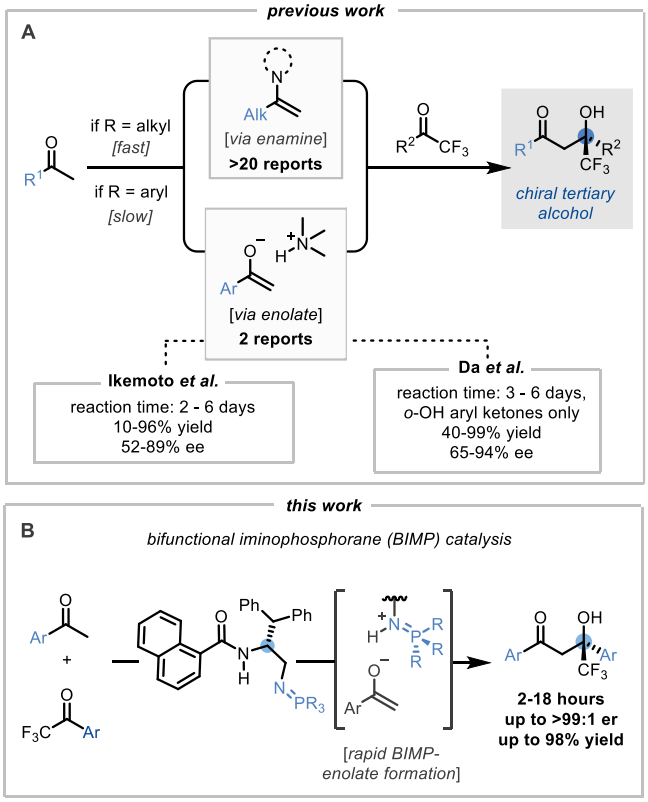
Connor J. Thomson[a], David M. Barber[b] and Darren J. Dixon[*][a]

Abstract: *The catalytic enantioselective synthesis of α-fluorinated chiral tertiary alcohols from (hetero)aryl methyl ketones is described. The use of a bifunctional iminophosphorane (BIMP) superbase was found to facilitate direct aldol addition by providing the strong Brønsted basicity required for rapid aryl enolate formation. The new synthetic protocol is easy to perform and tolerates a broad range of functionalities and heterocycles with high enantioselectivity (up to >99:1 er). Multi-gram scalability has been demonstrated along with catalyst recovery and recycling. NMR studies identified a 1400-fold rate enhancement under BIMP catalysis, compared to the prior state of the art catalytic system. The utility of the aldol products has been highlighted with the synthesis of various enantioenriched building blocks and heterocycles, including 1,3-aminoalcohol, 1,3-diol, oxetane and isoxazoline derivatives.*

The direct aldol reaction is amongst the most powerful synthetic tools in organic chemistry.[1] Such reactions offer access to fundamental synthetic intermediates with perfect atom economy and do not require pre-formation of a stoichiometric enolate, enol silane or enamine equivalent.[2] Pioneering work by Wiechert, Barbas and List has inspired numerous enantioselective modifications,[3] thereby allowing the application of aldol chemistry to the construction of optically active natural products, macromolecules and pharmaceutically active ingredients.[4] Further significant contributions from the groups of MacMillan,[5] Shibasaki,[6] Maruoka,[7] and others,[8] have continued to enhance the utility of this routine reaction.

The enantioselective aldol reaction is wide reaching with respect to the variety of electrophilic acceptors able to react efficiently with ketone donors under mild conditions.[9] However, it is still limited with respect to the range of compatible donor synthons. Aliphatic ketones have been used extensively in the aldol manifold, partly due to their ease of activation through primary or secondary amine catalysts operating *via* enamine intermediates.[10] Meanwhile, the use of aryl ketones as nucleophilic donors remains highly challenging; reluctant formation of aryl enamines precludes amine catalysis from being synthetically useful in this context.[9a,11] Furthermore, direct access to enolate intermediates is limited by the relatively high pK_a (~25 in DMSO) of aryl ketones, and is challenging in the absence of strong stoichiometric organometallic bases such as LDA.[12]

α-Fluorinated ketones are competent aldol acceptors and serve as a convenient fluorine source;[13, 14] there are over 20 reports of enantioselective direct aldol additions of aliphatic ketones to trifluoromethyl ketones in the primary literature.[15] However, to the best of our knowledge only two such reports exist for the corresponding reaction with aryl ketones. These reports from Ikemoto and Da both utilise Takemoto's tertiary amine



Scheme 1. A) Previous work on the direct aldol addition of aryl methyl ketones to α-fluorinated ketones. B) This work: BIMP superbase catalyzed formation of (hetero)aryl enolates facilitates rapid aldol addition.

catalyst as a weak base to promote enolate formation. Although demonstrating synthetic utility, these examples are limited by long reaction times of 6 days for unbiased substrates.[11, 16] Additionally, although Da's report affords products with high er, the method is restricted to aryl ketones bearing an *ortho*-hydroxy substituent. Highlighting the challenging nature of this reaction is the absence of metal-catalyzed or stoichiometric enantioselective methods in the literature. The low catalytic activity observed in existing reports is likely due to the weak Brønsted basicity of the tertiary amine catalyst, resulting in slow activation of the pro-nucleophile. Consequently, the identification of new catalyst systems able to efficiently activate aryl ketones towards aldol chemistry would significantly advance the field. In order to overcome the inherently low reactivity of aryl ketones as pro-nucleophiles, we envisaged the use of a bifunctional iminophosphorane (BIMP) superbase to rapidly generate a reactive enolate species from the donor aryl methyl ketone and simultaneously activate an acceptor ketone through hydrogen-bonding interactions.[17] Herein we report our findings.

Our studies began by assessing organocatalysts in the reaction of acetophenone (**1a**) with 2,2,2-trifluoroacetophenone (**2a**) (Table 1A). As expected, the weakly basic bifunctional cinchona alkaloid catalyst **A** was not proficient in the model reaction (Table 1A, entry 1). Pleasingly, however, promising

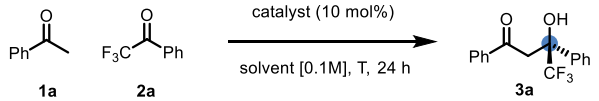
[a] C. J. Thomson, Prof. Dr. D. J. Dixon, Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, United Kingdom
[b] Dr. D. M Barber, Research & Development, Weed Control Chemistry, Bayer AG, Crop Science Division, Industriepark Höchst, Frankfurt am Main, 65926, Germany
[*] darren.dixon@chem.ox.ac.uk

10.1002/anie.201916129

WILEY-VCH

COMMUNICATION

A Optimization of reaction conditions



Entry	Cat.	Solvent	T	Conversion (%)[a]	er[b]
1	A	Et_2O	rt	trace	N.D.
2	B	Et_2O	rt	64	62:38
3	C	Et_2O	rt	52	61:39
4	D	Et_2O	rt	8	N.D.
5	E	Et_2O	rt	63	74.5:25.5
6	F	Et_2O	rt	>95	75:25
7	F	CPME	rt	>95	82:18
8	F	CPME	-15 °C	>95	90:10
9	G	CPME	-15 °C	>95	94:6
10[c]	**H**	**CPME**	**-15 °C**	**96[d]**	**97:3**

B Selected catalysts

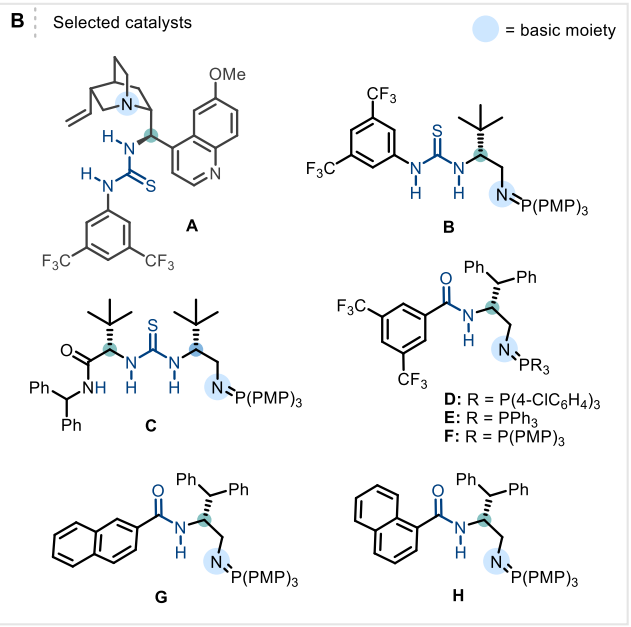


Table 1. A) Optimization of the direct aldol addition of acetophenone (**1a**) to 2,2,2-trifluoroacetophenone (**2a**). B) Selected catalysts investigated for the model reaction of **1a** with **2a.** [a] determined by ^{1}H NMR analysis of crude reaction mixture. [b] determined by HPLC analysis on chiral stationary phase. [c] 18 hour reaction time. [d] isolated yield. N.D. = not determined. CPME = cyclopentyl methyl ether. PMP = *para*-methoxy phenyl.

selectivity and reactivity was observed when treating equimolar amounts of **1a** and **2a** with 10 mol% BIMP catalyst **B** in Et_2O at room temperature; aldol adduct **3a** was obtained in 62:38 er and 64% conversion after 24 hours (Table 1A, entry 2). Having established proof of concept, focus turned to optimization of catalyst structure and reaction conditions (Table 1B). The modular nature of BIMP catalysts facilitates rapid optimization of catalyst structure: the chiral back-bone can be amino-acid derived; the variation of the H-bond donor requires only trivial coupling of the primary amine to a carboxylic acid or iso(thio)cyanate; and phosphine variation is conveniently performed as a final-step *in situ* Staudinger reaction. Fine-tuning of the catalyst revealed the strongly basic and sterically demanding 1-naphthyl amide catalyst **H** to be optimal, which, in combination with a solvent change to CPME and cooling to -15 °C, afforded **3a** in 97:3 er and 96% isolated yield (see ESI for details)[18].

Having established an efficient protocol, a variety of (hetero)aryl methyl ketones and α–fluorinated ketones were evaluated (Scheme 2A). Minimal fluctuation of enantioselectivity was observed when substituents on the aryl ring of either ketone was varied, with the products generally obtained in good to excellent yield. Potentially incompatible functionalities were well-tolerated, with cyano, nitro and vinyl substituted ketones providing the aldol adducts **3f**-**3h** efficiently and selectively. Reaction of 1,4-diacetylbenzene (**1n**) furnished the bis-aldol product (**3n**) in 95:5 er and with high diastereoselectivity (20:1 dr). Pleasingly, the scope of this transformation was extended to provide a variety of heterocyclic products. Quinoline, pyrazine, pyridine, thiophene, thiazole and pyrazolyl substrates were all compatible with the iminophosphorane catalyst system, and competently furnished the medicinal chemistry-relevant products **3t**-**3z** with high enantioselectivity (92:8 to >99:1 er) and yield. Importantly, our method could be extended to other α-fluorinated ketones. Tertiary alcohol products bearing chlorodifluoromethyl, perfluoroethyl and perfluoroheptyl substituents at the newly formed stereocentre (**3aa**-**3ac**) were obtained with high er (96:4 to 97.5:2.5 er). These products are the first examples of an enantioselective aldol reaction of aryl ketones with α-fluorinated ketones other than α-CF_3. In general, the reaction profile was very clean, with only the product, catalyst and any unreacted substrate present in the crude reaction mixture. Enolisable aryl ketones other than methylketones, such as propiophenone, failed to afford any desired aldol product; most likely due to rapid reversibility by a retro-aldol reaction.[19]

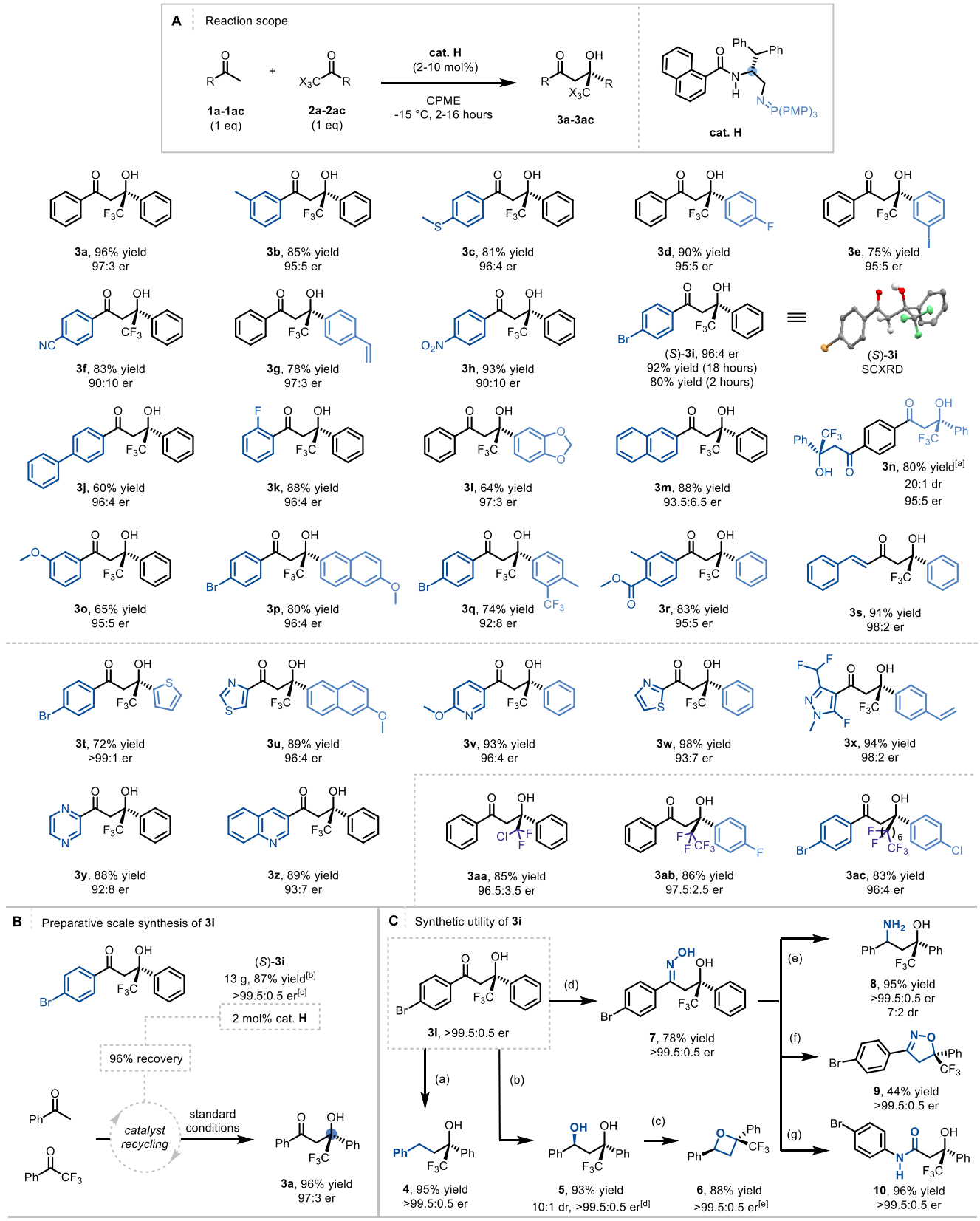
To substantiate the scalability of this methodology, the reaction of **1i** with **2a** was performed on an 8-gram scale using a reduced catalyst loading of 2 mol% to afford 13 grams of aldol-adduct **3i** as a single enantiomer after one recrystallization, and without the need for column chromatography (Scheme 2B). Notably, catalyst **H** was recovered in 96% yield simply by adding water to the crude reaction mixture to induce precipitation. No erosion of enantioselectivity or yield was observed when recycling the recovered catalyst in the synthesis of model substrate **3a**, thus demonstrating the possible commercial capability of this methodology and the wider BIMP family of catalysts.

With the aim of demonstrating the utility of β-fluorinated-β-hydroxy ketone products, we explored enantiopure **3i** as a scaffold for downstream derivatization (Scheme 2C). Hydrogenation of ketone **3i** with palladium on carbon under acidic conditions afforded the γ-benzylic tertiary alcohol **4**. Meanwhile hydrogenation under neutral conditions gave diol **5**, which was efficiently cyclized to oxetane **6** by an intramolecular Mitsunobu reaction. Furthermore, oxime **7** was identified as a versatile intermediate for further derivatization of the β-hydroxyketone backbone; condensation with hydroxylamine cleanly afforded **7** as a 4:1 mix of *E*/*Z* isomers, which was purified to a single isomer for subsequent transformations. 1,3-Aminoalcohol **8** was thus obtained in 7:2 dr and high yield *via* classical hydrogenation. Cyclization of **7** afforded enantioenriched isoxazoline **9**; such heterocycles are prominent motifs in agrochemicals.[20] Lastly, acid catalyzed Beckmann rearrangement of the oxime smoothly furnished secondary amide **10**.

10.1002/anie.201916129

WILEY-VCH

COMMUNICATION



Scheme 2. A) Scope of the BIMP catalyzed direct aldol addition of (hetero)aryl methyl ketones to α-fluorinated ketones. B) Preparative scale synthesis of **3i**. C) Derivatization of **3i**: (a) H_2, Pd/C, HCl, EtOH, RT, 4 h; (b) H_2, Pd/C, EtOH, -10 °C, 4 h; (c) DIAD, PPh_3, benzene, RT, 30 min; (d) $NH_2OH.HCl$, pyr, 50 °C, 4 h; (e) H_2, Pd/C, EtOH, rt, 18 h; (f) DIAD, $P(PMP)_3$, THF, -15 °C, 24 h; (g) $POCl_3$, HCl, CH_2Cl_2, rt, 1 h. Stereochemical configuration was assigned by analogy with (*S*)-**3i** (determined by single crystal X-ray diffraction studies). [a] with 3.0 eq of **2n**, er of minor diastereomer is >99.5:0.5. [b] TBME [1.0 M], -15 °C, 36 h. [c] after single recrystallization (94.5:4.5 crude er). [d] tentative assignment of absolute stereochemistry based on ^{1}H-^{1}H NOE NMR data. [e] tentative assignment of relative configuration based on ^{1}H-^{19}F NOE NMR data.

10.1002/anie.201916129

Monitoring the reaction over time by NMR demonstrated the exceptionally enhanced reactivity of iminophosphorane catalyst **H** compared to Takemoto's thiourea catalyst **I**, and cinchona alkaloid **A** (Figure 1). Notably, this study shows a >1400-fold rate enhancement relative to the prior state of the art catalytic system (catalyst **I** used under the conditions reported by Ikemoto), [11] and that synthetically useful yields can be obtained in minutes; 83% conversion and 80% isolated yield after 120 minutes. The pK_{BH+} of catalyst **H** was found to be 25.5 (in MeCN), suggesting that the strong basicity of the iminophosphorane group is responsible for activation of high pK_a aryl ketone substrates. However, no reaction was observed when catalyst **H** was *N*-methylated. Hence, it is likely that the significant rate enhancement is due to synergistic effects between the amide and iminophosphorane groups of **H**; thus supporting the theory that BIMP catalysts operate with bifunctional activation of one or more substrates.

Figure 1 also revealed a significant rate decrease over the course of the reaction, suggesting product inhibition and/or catalyst decomposition. Indeed, binding of the aldol product **3w** to catalyst **H** was later suggested by product-doping experiments, in which lower reaction rates were observed with increasing doping of **3w** from the beginning of the reaction. Furthermore, evidence for a 1:1 complex of catalyst **H** and product **3a** (97:3 er) was found using Job's method, which showed a maximum at 0.5 mol fraction on a standard Job plot (see ESI). Lastly, background catalyst degradation was found to occur *via* an aza-Wittig reaction between the iminophosphorane moiety of catalyst **H** and the trifluoroketone.[21] This decomposition is significantly reduced by slow addition of the trifluoromethylketone to the reaction mixture, and this technique was found to be crucial during the large-scale synthesis of **3i** at low catalyst loading (2 mol%).

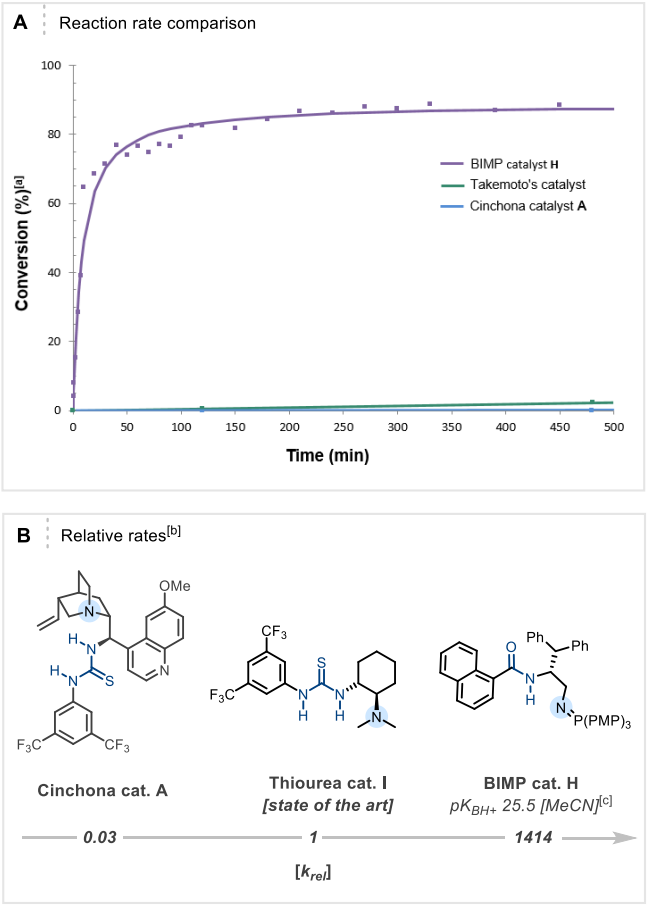


Figure 1. A) Graph of conversion over time for BIMP catalyst **H**, catalyst **I** and cinchona catalyst **A** in the direct aldol addition of **1a** to **2a**. B) Catalyst structures and relative rate values. [a] determined by quantitative ^{1}H NMR. [b] determined from the relative intial slope of conversion vs. time plots for each catalyst. [c] determined by NMR. Relative rates for catalyst **A** and **H** were measured under standard conditions; relative rate for cat. **I** was measured using the optimal conditions reported by Iketmoto (ref 11).

In summary, an efficient and general method for the direct aldol addition of (hetero)aryl methyl ketones to α–trifluoro and α-perfluoro aryl ketones has been developed. The new protocol affords enantioenriched α-fluorinated alcohols in high yield and er, and is tolerant of a diverse range of substituted aromatics, heterocycles, and α–fluorinated ketones. The design and use of a novel and recyclable catalyst with high Brønsted basicity is key to allowing rapid access to chiral scaffolds from readily available ketones. Importantly, ^{1}H NMR studies demonstrated a >1400-fold rate enhancement compared to existing catalytic systems. The reported method is amenable to multigram scale synthesis, and a range of late-stage derivatizations has highlighted the synthetic utility of a reaction product in downstream functionalization, with potential applications in agrochemical and pharmaceutical contexts.

Acknowledgements

DJD and CJT wish to thank Bayer AG for generous financial support. Dr Heyao Shi is also thanked for X-ray structure determination of compound **3i**, and Dr Amber L. Thompson and Dr Kirsten E. Christensen (Oxford Chemical Crystallography) for X-ray mentoring.

Keywords: enantioselective catalysis, superbase, aryl enolates, aldol, organocatalysis

[1] a) Y. Yamashita, T. Yasukawa, W. J. Yoo, T. Kitanosono, S. Kobayashi, *Chem. Soc. Rev*. **2018**, *47*, 4388; b) A. T. Nielsen and W. J. Houlihan, *Organic Reactions*, John Wiley & Sons, Inc., **2004**; c) T. Mukaiyama, *Organic Reactions*, John Wiley & Sons, Inc., **2004**.

[2] a) C. Stewart, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 8696; b) A. Fernández-Mateos, S. E. Madrazo, P. H. Teijón, R. R. González, *J. Org. Chem.* **2009**, *74*, 3913; c) S. Guizzetti, M. Benaglia, L. Raimondi, G. Celentano, *Org. Lett.* **2007**, *97,* 1247; d) I. R. Correa, R. A. Pilli, *Angew. Chem. Int. Ed.* **2003**, *7*, 3017; e) J. Nebot, P. Romea, F. Urpí, *J. Org. Chem*. **2009**, *74*, 7518.

[3] a) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed*. **1971**, *10*, 496; b) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc*. **2000**, *122*, 2395; c) R. Mahrwald, *Modern Aldol Reactions*, Wiley-VCH, Weinheim, **2004**; d) B. List, *Acc. Chem. Res.* **2004**, *37*, 548; e) B. List, *Tetrahedron* **2002**, *58*, 5573; f) N. S. Chowdari, D. B. Ramachary, A. Cordova, C. F. Barbas, *Tetrahedron Lett*. **2002**, *43*, 9591; g) R. Thayumanavan, F. Tanaka, C. F. Barbas, *Org. Lett*. **2004**, *6*, 3541; h) N. Mase, F. Tanaka, C. F. Barbas, *Angew. Chem, Int. Ed*. **2004**, *43*, 2420; i) I. Ibrahem, W. Zou, Y. J. Wagner, R. A. Lerner, C. F. Barbas, *Science* **1995**, *270*, 1797; j) C. F. Barbas, A. Heine, G. Zhong, T. Hoffmann, S. Gramatikova, R. Bjornestedt, B. List, J. Anderson, E. A. Stura, I. A. Wilson, R. A. Lerner, *Science* **1997**, *278*, 2085; k) T. Hoffmann, G. Zhong, B. List, D. Shabat, J. Anderson, S. Gramatikova, R. A. Lerner, C. F. Barbas, *J. Am. Chem.*

Soc. **1998**, *120*, 2768; l) F. Tanaka, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc*. **2000**, *122*, 4835.

[4] a) A. Matsuzawa, C. R. Opie, N. Kumagai, M. Shibasaki, *Chem. Eur. J*. **2014**, *20*, 68; b) K. Alagiri, S. Lin, N. Kumagai, M. Shibasaki, *Org. Lett.* **2014**, *16*, 5301; c) D. Sureshkumar, Y. Kawato, M. Iwata, N. Kumagai, M. Shibasaki, *Org. Lett*. **2012**, *14*, 3108; d) D. A. Evans, D. M. Fitch, T. E. Smith, V. J. Cee, *J. Am. Chem. Soc*. **2000**, *122*, 10033; e) S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, M. J. Di Grandi, *J. Am. Chem. Soc*. **1996**, *118*, 2843.

[5] a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2002**, *124*, 6798; b) A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752; c) I. K. Mangion, A. B. Northrup, D. W. C. MacMillan, *Angew. Chem. Int. Ed*. **2004**, *43*, 6722; d) R. Ian Storer, David W. C. MacMillan, *Tetrahedron* **2004**, *60*, 7705.

[6] a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871; *Angew. Chem.* **1997**, *109*, 1942; b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168; c) M. Shibasaki, N. Yoshikawa, *Chem. Rev*. **2002**, *102*, 2187; d) H. Sasai, T. Suzuki, S. Arai, T. Aria, M. Yoshikawa, M. Shibasaki, *J. Am. Chem. Soc*. **1992**, *114*, 4418.

[7] a) T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem. Int. Ed*. **2005**, *44*, 3055; b) T. Kano, H. Sugimoto, K. Maruoka, *J. Am. Chem. Soc*. **2011**, *133*, 18130; c) T. Ooi, M. Kameda, M. Taniguchi, K. Maruoka, *J. Am. Chem. Soc*. **2004**, *126*, 9685; d) T. Ooi, M. Taniguchi, M. Kameda, K. Maruoka, *Angew. Chem. Int. Ed*. **2002**, *41*, 4542.

[8] a) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev*. **2010**, *39*, 1600; b) Corey, E. J.; Zhang, F.-Y. *Org. Lett*. **1999**, *1*, 1287; c) B. M. Trost, H. Ito, *J. Am. Chem. Soc*. **2000**, *122*, 12003; d) T. March, A. Murata, Y. Kobayashi, Y. Takemoto, *Synlett* **2017**, *28*, 1295; e) J. Saadi, H. Wennemers, *Nat. Chem*. **2016**, *8*, 276; f) Shota Sakamoto, Naoya Kazumi, Yusuke Kobayashi, Chihiro Tsukano, Yoshiji Takemoto, *Org. Lett.* **2014**, *16*, 4758; g) H. Torii, M. Nakadai, K. Ishihara, S. Saito and H. Yamamoto, *Angew. Chem. Int. Ed.* **2004**, *43*, 1983; h) Nobuko Ozasaa, Manabu Wadamotob, Kazuaki Ishiharaa, Hisashi Yamamoto, *Synlett* **2003**, *14*, 2219; i) K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843; j) B. M. Trost, V. S. C. Yeh, *Angew. Chem. Int. Ed.*, **2002**, 41, 861; k) C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem. Int. Ed.* **2005**, *44*, 3881; l) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. D. Downey, *J. Am. Chem. Soc.* **2003**, 125, 12692; m) H Li, B Wang, L Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732.

[9] For reactions with isatins, see: a) Q. Guo, M. Bhanushali, C.-G. Zhao, *Angew. Chem. Int. Ed*. **2010**, *49*, 9460; b) H. Gao, Z. L. Luo, P. J. Ge, J. Q. He, F. Zhou, P. P. Zheng, J. Jiang, *Org. Lett*. **2015**, *17*, 5962; c) G. Luppi, P. G. Cozzi, M. Monari, B. Kaptein, Q. B. Broxterman, C. Tomasini, *J. Org. Chem*. **2005**, *70*, 7418; for glyoxal derivatives, see: d) A. Matsuzawa, H. Noda, N. Kumagai, M. Shibasaki, *J. Org. Chem.* **2017,** *82*, 8304; e) Y. Hayashi M. Kojima, *ChemCatChem* **2013**, *5*, 2883; for keto-phosphonates, see: f) S. Samanta, C.-G. Zhao, *J. Am. Chem. Soc.* **2006**, *128*, 7442; g) J. Yu, X. Zhao, Z. Miao, R. Chen, *Org. Biomol. Chem*. **2011**, *9*, 6721; h) G. B. Vamisetti, R. Chowdhury, S. K. Ghosh, *Org. Biomol. Chem*. **2017**, *15*, 3869; for keto-esters, see: i) A.-J.Wei, J. Nie, Y. Zheng, J.-A. Ma, *J. Org. Chem.* **2015**, *80*, 3766; j) P. Li, J. Zhao, F. Li, A. S. C. Chan, F. Y. Kwong, *Org. Lett.* **2010**, *12*, 5616; for keto-acids, see: k) X.-Y. Xu, Z. Tang, Y.-Z. Wang, S.-W. Luo, L.-F. Cun, L.-Z. Gong, *J. Org. Chem.* **2007**, *72*, 9905; l) F. J. N. Moles, G. Guillena, C. Nájera, *RSC Adv.* **2014**, *4*, 9963.

[10] a) B. List, *Tetrahedron* **2002**, *58*, 5573; b) W. Notz, F. Tanaka, C. F. Barbas, *Acc. Chem. Res*. **2004**, *37*, 580; c) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed*. **2004**, *43*, 5138.

[11] L. M. Lutete, T. Miyamoto, T. Ikemoto, *Tetrahedron. Lett.* **2016**, *57*, 1220.

[12] a) W. S. Matthews, J. E. Bres, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, N. R. Vanier, *J. Am. Chem. Soc.* **1975**, *97*, 7006; b) B. D. Süveges, J. Podlech, *Eur. J. Org. Chem*. **2015**, 987.

[13] a) R. Pluta, N. Kumagai, M. Shibasaki, *Angew. Chem*. **2019**, *131*, 2481; b) X.-J. Li, H.-Y. Xiong, M.-Q. Hua, J. Nie, Y. Zheng, J.-A. Ma, *Tetrahedron* **2012**, *53*, 2117; c) J. Mo, R. Yang, X. Chen, B. Tiwari, Y. R. Chi, *Org. Lett*. **2013**, *15*, 50; d) J. Lin, T. Kang, Q. Liu, L. He, *Tetrahedron: Asymmetry* **2014**, *25*, 949; e) H. Zong, H. Huang, G. Bian, L. Song, *J. Org. Chem.* **2014**, *79*, 23; f) Y. Zheng, H.-Y. Xiong, J. Nie, M.-Q. Hua, J.-A. Ma, *Chem. Commun*. **2012**, *48*, 4308; g) S. Crotti, G. Belletti, N. DiIorio, E. Marotta, A. Mazzanti, P. Righi, G. Bencivenni, *RSC Adv*. **2018**, *8*, 33451

[14] For pertinent reviews on the importance of fluorine incorporation, see: a) D. O'Hagan, *Chem. Soc. Rev*. **2008**, *37*, 308l; b) V. Gouverneur, K. Müller, *Fluorine in Pharmaceutical and Medicinal Cemistry*, Imperial College Press, London (UK), **2012**; c) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37*, 320; e) R. Szpera, D. F. J. Moseley, L. B. Smith , A. J. Sterling, V. Gouverneur, *Angew. Chem. Int. Ed*. **2019**, *58*, 14824; f) D O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071; h) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho, F. D. Toste, *Chem. Rev*. **2018**, *118*, 3887; i) J.-P. Begue, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-VCH, Hoboken, **2008**; j) Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester (UK), **2009**.

[15] a) W. Yang, Y.-M. Cui, W. Zhou, L. Li, K.-F. Yang, Z.-J. Zheng, Y. Lu, L.-W. Xu, *Synlett* **2014**, *25*, 1461; b) Q. Guo, M. Bhanushali, C.-G. Zhao, *Angew. Chem. Int. Ed*. **2010**, *49*, 9460; c) I. Vlasserou, M. Sfetsa, D.-T. Gerokonstantis, C. G. Kokotos, P. Moutevelis-Minakakis, *Tetrahedron*, **2018**, *74*, 2338; d) N. Duangdee, W. Harnying, G. Rulli, J.-M. Neudorfl, H. Groger, A. Berkessel, *J. Am. Chem. Soc*. **2012**, *134*, 11196; e) N. Hara, R. Tamura, Y. Funahashi, S. Nakamura, *Org. Lett*. **2011**, *13*, 1662; f) C. G. Kokotos, *J. Org. Chem*. **2012**, *77*, 1131; g) L.-H. Qui, Z.-X. Shen, C.-Q. Shi, Y.-H. Liu, Y.-W. Zhang, *Chin. J. Chem.* **2005**, *23*, 584; h) W. Yang, Y.-M. Cui, W. Zhou, L. Li, K.-Fang Yang, Z.-J. Zheng, Y. Lu, L.-W. Xu, *Synlett* **2014**, *25*, 1461.

[16] For previous reports see ref 11 and: a) P. Wang, H.-F. Li, J.-Z. Zhao, Z.-H. Du, C.-S. Da, *Org. Lett.* **2017**, *19*, 2634; for Takemoto's catalyst, see: b) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[17] a) M. G. Nunez, A. J. M. Farley, D. J. Dixon, *J. Am. Chem. Soc*. **2013**, *135*, 16348; b) A. M. Goldys, M. G. Nunez, D. J. Dixon, *Org. Lett*. **2014**, *16*, 6294; c) A. J. M. Farley, C. Sandford, D. J. Dixon, *J. Am. Chem. Soc*. **2015**, *137*, 15992; d) G. P. Robertson, A. J. M. Farley, D. J. Dixon, *Synlett*, **2016**, *27*, 21; e) M. A. Horwitz, B. P. Zavesky, J. I. Martinez-Alvarado, J. S. Johnson, *Org. Lett*. **2016**, *18*, 36; f) M. A. Horwitz, J. L. Fulton, J. S. Johnson, *Org. Lett*. **2017**, *19*, 5783; g) H. Shi, I. M. Michaelides, B. Darses, P. Jakubec, Q. N. N. Nguyen, R. S. Paton, D. J. Dixon, *J. Am. Chem. Soc.* **2017**, *139*, 17755; h) M. Formica, G. Sorin, A. J. M. Farley, J. Diaz, R. S. Paton, D. J. Dixon, *Chem. Sci*. **2018**, *9*, 6969.

[18] Subjecting enantioenriched product **3a** to the optimized reaction conditions showed no erosion of er after 7 days, suggesting the aldol products are resistant to the retro-aldol reaction under BIMP catalysis conditions.

[19] The synthesis of aldol products of this type (bearing an additional stereocentre at the alpha-keto position) is known to be extremely challenging due to rapid reversibility. For example, see: S. Sasaki, K. Kikuchi, T. Yamauchi, K. Higashiyama, *Synlett* **2011**, *10*, 1431.

[20] N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Ed.* **2010**, *87*, 1348.

[21] Synthesis and testing of the degradation product (the corresponding primary amine) confirmed it is catalytically inactive in the aldol reaction of **1a** with **2a**.

10.1002/anie.201916129

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

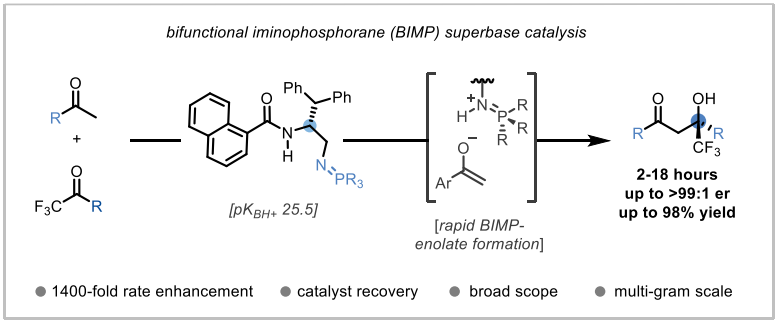
Layout 2:

COMMUNICATION

*Connor J. Thomson, David M. Barber and Darren J. Dixon**

1 – 5

Catalytic Enantioselective Direct Aldol Addition of Aryl Ketones to α-Fluorinated Ketones



The catalytic enantioselective synthesis of α-fluorinated chiral tertiary alcohols from (hetero)aryl methyl ketones is described. A novel BIMP superbase catalyst facilitates direct aldol addition up to >1400 times faster than the previous state of the art.