

CHEMISTRY

A **European** Journal



Accepted Article

Title: Triflimide: An Overlooked High-Performance Catalyst of the Mukaiyama Aldol Reaction of Silyl Ketene Acetals with Ketones

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201803142

Link to VoR: <http://dx.doi.org/10.1002/chem.201803142>

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Triflimide: An Overlooked High-Performance Catalyst of the Mukaiyama Aldol Reaction of Silyl Ketene Acetals with Ketones

Han Yong Bae and Benjamin List*

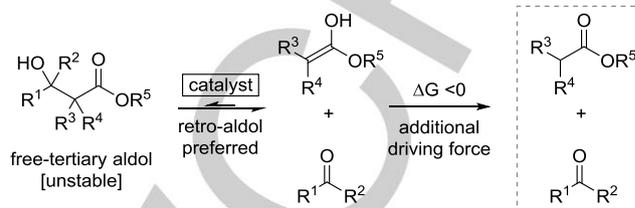
Abstract: The Mukaiyama aldol reaction is a widely applied carbon–carbon bond forming reaction. However, despite numerous well-established methods using aldehydes as acceptors, only few examples exist with ketones. Herein we report a highly practical catalytic approach to this transformation, namely, the triflimide catalyzed Mukaiyama aldol reaction of silyl ketene acetals with ketones. This method exhibits a broad substrate scope, is very rapid, tolerates functionalized substrates, and requires only parts-per-million catalyst loadings with preparative scale reactions up to hundreds of grams in excellent purity (>99%).

The catalytic aldol reaction of ester enolates is an important and versatile carbon–carbon bond forming reaction. While a number of useful versions of this reaction with aldehydes have previously been established.^[1] The utilization of ketones as electrophiles to afford tertiary β -hydroxy esters is rare. A key challenge in this disconnection is the propensity of tertiary aldols to undergo the thermodynamically favoured retro-aldolization (Scheme 1A).^[2] This is in sharp contrast to the Mukaiyama aldol reaction of ketones with silyl ketene acetals (SKAs) which is thermodynamically favoured, possibly due to the absence of the enol to ketone tautomerization (Scheme 1B).

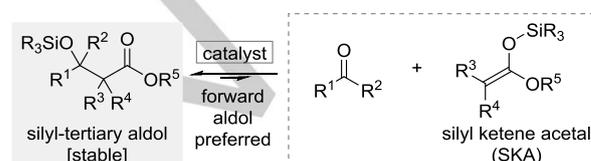
Since Mukaiyama's seminal studies,^[3a] an extension of this methodology to the reaction of SKAs with ketones has been highly sought-after.^[3b,c] After the first approach by Denmark and co-workers on an asymmetric variant using enantiopure bis-*N*-oxides as a Lewis base catalyst,^[4a] few studies on novel enantioselective, catalytic methods have followed.^[4b–e] Our group very recently disclosed an enantiopure imidodiphosphorimidate catalyzed variant, which gives high enantioselectivities (up to >99:1 e.r.) in the presence of parts-per-million (ppm) levels of catalyst loadings.^[5]

Regarding non-asymmetric Mukaiyama aldol reactions of SKAs with ketones, a metal-catalyzed method (CuF·3PPh₃·2EtOH with (EtO)₃SiF)^[6] and a Lewis base catalyzed method (sodium phenoxide–phosphine oxide)^[7] have been reported (Scheme 1C). Alternatively, organocatalytic systems such as C–H acids,^[8a,b] a hydrogen-bond-assisted disulfonamide catalyst^[8c] and Schreiner's thiourea catalyst in combination with nitro compounds^[8d] have previously been investigated with some success. Despite these advances, however, a catalytic method that is convenient, broadly applicable, practical, and scalable remains desirable.

A. Challenging: Direct aldol addition of esters to ketones

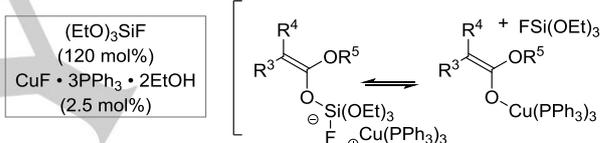


B. Mukaiyama aldol addition of SKAs to ketones

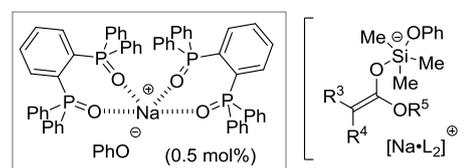


C. Previous studies

Shibasaki et al. (2003, Ref. 6)

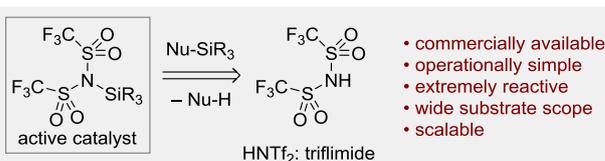


Ishihara et al. (2007, Ref. 7)



D. This work: PPM level catalyst enabled

Mukaiyama aldol reaction of SKA to ketone



Scheme 1. Catalytic methods toward the aldol reaction of esters with ketones; (A) The direct catalytic aldol reaction of esters with ketones is thermodynamically disfavored; (B) Catalytic Mukaiyama aldol reaction of SKA with ketones; (C) Previous examples of catalytic Mukaiyama aldol reaction of SKA to ketone; (D) This work: large-scale, PPM level catalyst enabled general Mukaiyama aldol reaction of SKA to Ketone

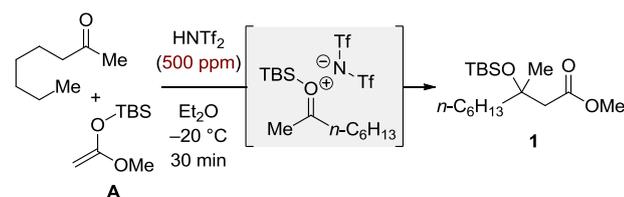
Triflimide (HNTf₂: bis(trifluoromethanesulfonyl)imide) is a useful strong acid catalyst ($pK_a = 0.3$ in MeCN)^[9] for various transformations, including aldol reactions, cycloadditions, allylations, Friedel–Crafts reactions, Nazarov cyclizations, Michael additions, Mannich reactions,^[10a,b] [3,3]-sigmatropic rearrangements^[10c] and others.^[10d] The Yamamoto group has investigated ketone-derived trialkyl-silyl enol ethers,^[11] or aldehyde-derived tris(trimethylsilyl)silyl “super silyl” enol ethers^[12]

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for the synthesis of β -siloxy aldehydes via Mukaiyama aldol reaction. Aldehydes were utilized as electrophiles and a general method using ketones as electrophiles remained elusive.^[13] Herein we report a general, in situ generated silyl-triflimide catalyzed Mukaiyama aldol reactions of silyl ketene acetals with ketones (Scheme 1D). The developed scalable methodology provides a wide variety of silicon protected tertiary aldols within short reaction times (30 min) using only ppm level catalyst loadings.

Table 1. Development of suitable reaction conditions.



Entry	Variation from the standard conditions	Conv. (%) ^[a]
1	None	>99 ^[b]
2	5 mol% HNTf ₂ , <10 s	>99 [impure] ^[b,c]
3	without HNTf ₂ , 24 h	0
4	<i>p</i> -TsOH instead of HNTf ₂ , 24 h	0
5	HOTf instead of HNTf ₂ , 24 h	16
6	BF ₃ ·Et ₂ O instead of HNTf ₂ , 24 h	<1
7	5 mol% BF ₃ ·Et ₂ O instead of HNTf ₂ , 24 h	99 ^[b]
8	PhMe instead of Et ₂ O	99 ^[b]
9	CH ₂ Cl ₂ instead of Et ₂ O	99 ^[b]
10	at 20 °C	>90 [decomposition] ^[b,c]

Standard conditions: reactions were performed with 2-octanone (0.5 mmol, 1.0 equiv., 64 mg), SKA **A** (0.6 mmol, 1.2 equiv., 113 mg), and HNTf₂ (500 ppm = 0.05 mol%, 0.07 mg) in Et₂O (1.0 mL, 0.5 M) at -20 °C. [a] Conversion was determined by ¹H NMR integration. [b] Isolated yield after chromatographic purification. *p*-Ts = 4-Me-C₆H₄SO₂. [c] Partial decomposition occurs.

Our studies commenced when we made a peculiar observation in the reaction of 2-octanone with 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (SKA **A**). While 5 mol% of HNTf₂ very rapidly (<10 seconds, entry 2 of Table 1) and exothermically promoted the desired Mukaiyama aldol reaction with full conversion, partial decomposition led to inseparable side products (see the Supporting Information for detail). In contrast, with only 0.05 mol% (= 500 ppm) of the catalyst, compound **1** was cleanly obtained as the sole product within 30 minutes and in quantitative yield (entry 1). In either the presence of no catalyst or a weaker Brønsted acid (*p*-TsOH, p*K*_a = 8.5 in MeCN),^[9a] the desired product was not obtained (entries 3 and 4). Triflic acid (HOTf, trifluoromethanesulfonic acid, p*K*_a = 0.7 in MeCN),^[9] which is known to in situ generate TBS-OTf as less

reactive silyl Lewis acid,^[14] provided only 16% conversion to the aldol adduct (entry 5). BF₃·OEt showed no activity under identical conditions (entry 6), however, increasing the acid loading to 5.0 mol% enabled full conversion (entry 7). Instead of diethyl ether, solvents such as toluene and dichloromethane were also successful media (entries 8 and 9). However, it is noteworthy that performing the reaction at elevated temperature (20 °C, entry 10) led total decomposition. Gratifyingly, lowering the catalyst loading to 50 ppm (= 0.005 mol%, 0.007 mg) still gave full conversion to the desired product. Notably, the purity of SKA **A** played an important role for the successful outcome of the reaction, i.e. no reaction occurred in the presence of impure SKA **A**. It is likely that trace amounts of an amine base from the preparation of the SKA inhibits the acid catalyst (for a general procedure for the preparation of SKA, see Ref. 15).^[5]

With optimized reaction conditions in hand, the scope of ketone electrophiles in the Mukaiyama aldol reaction was studied (Table 2). To our delight, a variety of alkyl-alkyl ketones (entries 1–12), an alkynyl-alkyl ketone (entry 13) and (hetero)aryl-alkyl ketones (entries 16–36) successfully provided the desired products with excellent yields (up to 99%).^[16] Cyclic ketones, from simple cyclopentanone to cyclododecanone, all afforded the desired products with excellent yields (entries 37–43). Interestingly, 5 α -cholestan-3-one was smoothly converted to product **45** (entry 44, 89%, d.r. = 84:16).

Next, different types of SKAs were investigated (Table 3). Propionate-derived SKA **B** (*E/Z* = 5:1) reacted with a variety of ketones to provide products **46–48** (entries 1 to 3, 99% yields, [*Erythro:Threo*] = 83:17 to 85:15). The corresponding *Z*-enriched SKA **B** (*Z/E* >20:1) gave the same major diastereomer of product **46** (d.r. = 89:11), albeit with relatively lower reactivity (entry 4, no reaction occurred at -20 °C; 99% yield at 0 °C). The established catalytic system also readily enabled vinylogous aldol reactions of ketones,^[17] not only with TBS (SiMe₂*t*-Bu: **C** and **D**, entries 5 and 6), but also with TMS (SiMe₃: **E**, entry 7) protecting groups. Other silyl group variants of SKA **A**, such as TMS (**F**), TES (SiEt₃, **G**) and TIPS (Si*i*-Pr₃, **H**) incorporated SKAs also afforded the desired tertiary aldol products (**52–54**).

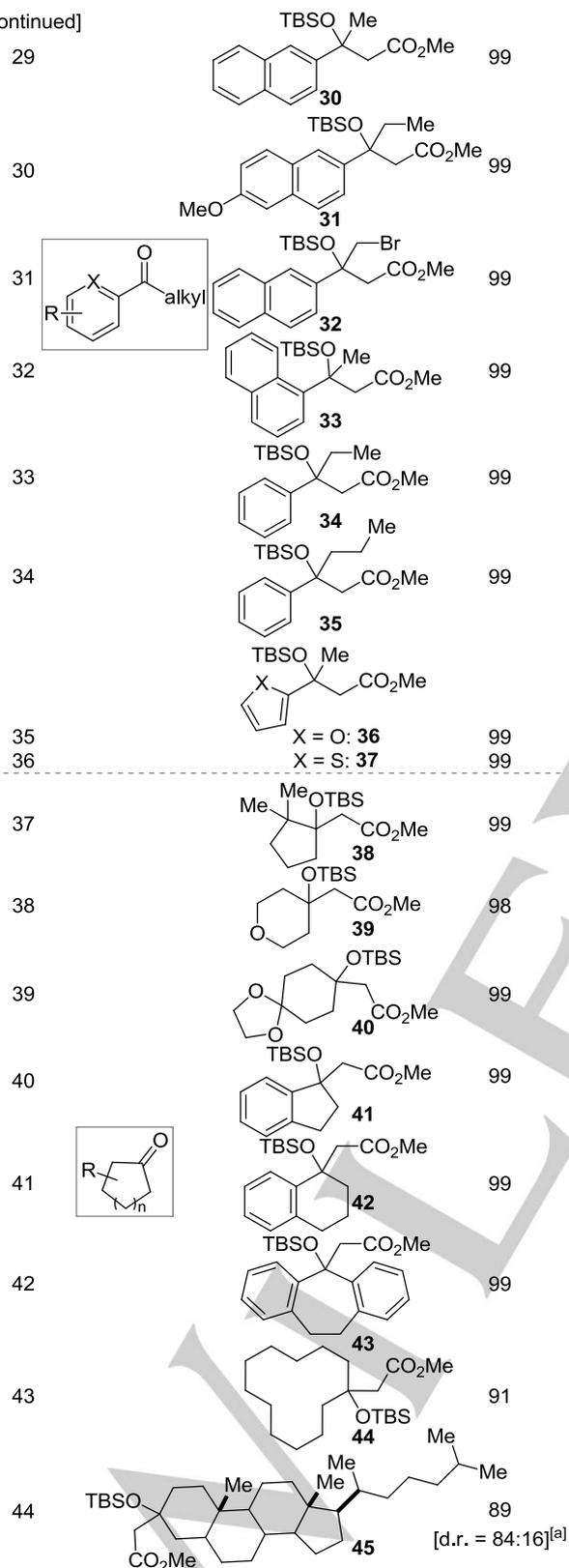
Table 2. Substrate scope of ketone electrophiles in Mukaiyama aldol reaction.

Entry	Ketone	Product	Yield (%)
1			99
2			98
3			99
4			99
5			99
6			97
7			99
8			99
9			95
10			98
11			96
12			89 [d.r. = 83:17] ^[a]
13			91
14			43 [1,4-adducts = 57%] ^[a]
15			98 [1,4-adducts <1%] ^[a]

[continued]

16			99
17			99
18			99
19			99
20			99
21			99
22			99
23			99
24			99
25			99
26			99
27			99
28			99

[continued]



Reactions were performed with ketone (0.5 mmol, 1.0 equiv.), SKA **A** (0.6 mmol, 1.2 equiv., 113 mg), and HNTf₂ (500 ppm = 0.05 mol%, 0.07 mg) in Et₂O (1.0 mL, 0.5 M) at -20 °C. Yield was determined after chromatographic purification. TBDPS = SiPh₂t-Bu. [a] Determined by ¹H NMR analysis.

Table 3. Substrate scope of SKA nucleophiles in Mukaiyama aldol reaction.

Entry	SKA	Product	Yield (%)
1			99 [d.r. = 83:17] ^[a]
2			99 [d.r. = 85:15] ^[a]
3			99 [d.r. = 85:15] ^[a]
4 ^[b]			99 [d.r. = 89:11] ^[a]
5 ^[b]			84
6 ^[b]			88
7 ^[b]			87
8			99
9			99
10			99

Reactions were performed with ketone (0.5 mmol, 1.0 equiv.), SKA **B-H** (0.6 mmol, 1.2 equiv.), and HNTf₂ (500 ppm = 0.05 mol%, 0.07 mg) in Et₂O (1.0 mL, 0.5 M) at -20 °C. Yield was determined after chromatographic purification. TMS = SiMe₃; TES = SiEt₃; TIPS = Si*i*-Pr₃. [a] Ratio of the [Erythro:Threo],

which is determined by ^1H NMR analysis. See the Supporting Information for detail. [b] Reaction was performed at 0 °C.

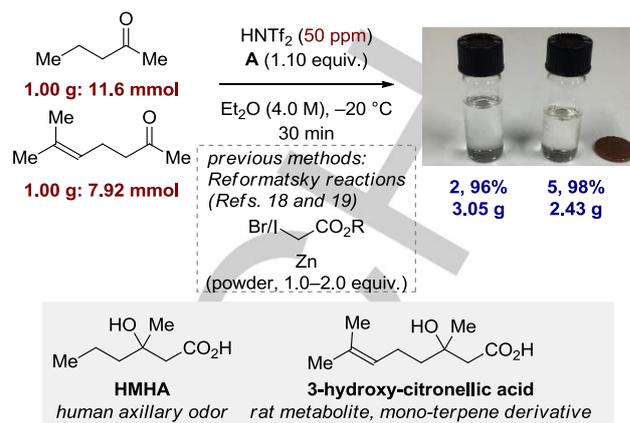
To demonstrate the synthetic practicability of the method, large scale syntheses of biologically relevant molecules were performed (Scheme 2). Initially, starting from each 1.00 g of 2-pentanone (11.6 mmol) and 6-methyl-5-hepten-2-one (7.92 mmol), 3-hydroxy-3-methylhexanoic acid^[18] (HMHA: induces human axillary odor) precursor **2** (96% yield, 3.05 g) and 3-hydroxy-citronellic acid^[19] (rat metabolite, mono-terpene derivative) precursor **5** (98% yield, 2.43 g) were obtained, respectively (Scheme 2A). Reformatsky reactions in the presence of stoichiometric to excess amount of Zn were previously used to obtain these tertiary aldols.^[18,19] Next, 20.0 g (129 mmol) of *p*-chloroacetophenone was converted to 44.2 g of product **19** (Scheme 2B, >99% yield, >99 % purity by GC analysis, see the Supporting Information for detail). Without further purification, 1,2-addition of methylmagnesium iodide (MeMgI) and subsequent TBS deprotection with tetra-*n*-butylammonium fluoride (*n*-Bu₄NF) lead to Fempentadiol **55** (81%, over two steps), which is used as tranquilizer and antidepressant.^[20] Finally, 100 g (795 mmol) of 6-methyl-5-hepten-2-one was successfully converted to 251 g of product **5** in excellent purity, using only 25 ppm of HNTf₂ (Scheme 2C, >99% yield, >99 % purity by GC analysis).^[21]

In summary, we have developed a powerful and general triflimide catalyzed Mukaiyama aldol reaction of silyl ketene acetal with a large variety of ketones. The discovery of this overlooked catalyst system was enabled by utilizing a very low catalyst loading at low temperature and with purified SKA. The developed method displays extreme reactivity with simple ketones and diverse SKAs. Its robustness presumably stems from the self-repair mechanism, compensating the very high water sensitivity of the silylated catalyst. Additionally, the method is very rapid and scalable, features that potentially enable its practical application in target-oriented synthesis.

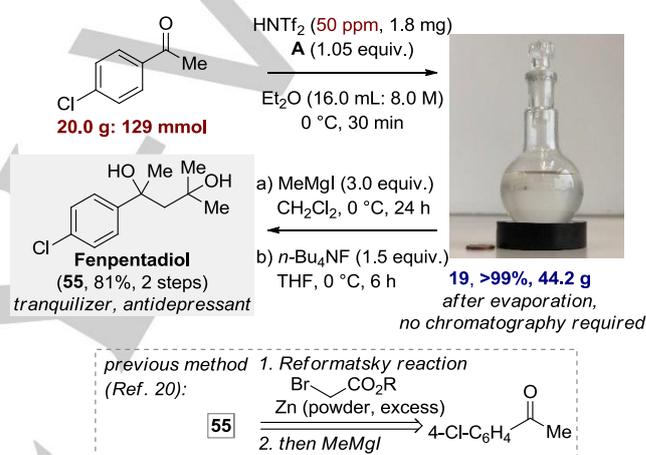
Experimental Section

A general procedure for hundred-gram scale Mukaiyama aldol reaction of silyl ketene acetal with ketone. To a flame dried J. Young Schlenk flask, HNTf₂ (5.6 mg, 0.020 mmol, 0.0025 mol% = 25 ppm) and 6-methyl-5-hepten-2-one (100 g, 795 mmol, 1.00 equiv.) was added under Ar atmosphere. Dried Et₂O (99.0 mL, 8.00 M) was added via syringe at 23 °C. The reaction mixture was cooled to -78 °C and SKA **A** (157 g, 835 mmol, 1.05 equiv.) was slowly added at this temperature, then warmed up to 23 °C and stirred for 72 h. The solvent and remaining SKA **A** (boiling point = 62 °C/12 mbar) was evaporated *in vacuo* to afford the desired tertiary aldol product **5** (251 g, >99%) in excellent purity (>99% by GC analysis), without further purification. ^1H NMR (500 MHz, CDCl₃) δ 5.27–4.90 (m, 1H), 3.64 (s, 3H), 2.49 (m, 2H), 2.09–1.99 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.60–1.54 (m, 2H), 1.36 (s, 3H), 0.85 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (126 MHz, CDCl₃) δ 171.66, 131.56, 124.45, 74.71, 51.40, 46.84, 42.94, 28.00, 25.89, 25.84, 23.11, 18.28, 17.71, -1.92, -1.95; HRMS (*m/z*): [M + Na]⁺ calcd. for C₁₇H₃₄O₃SiNa: 337.2169; found: 337.2172.

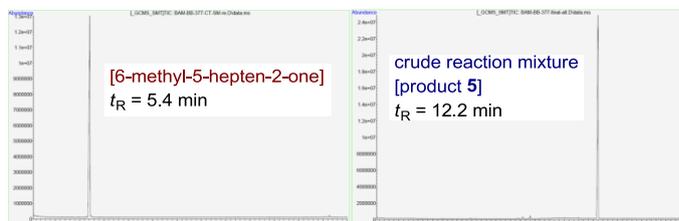
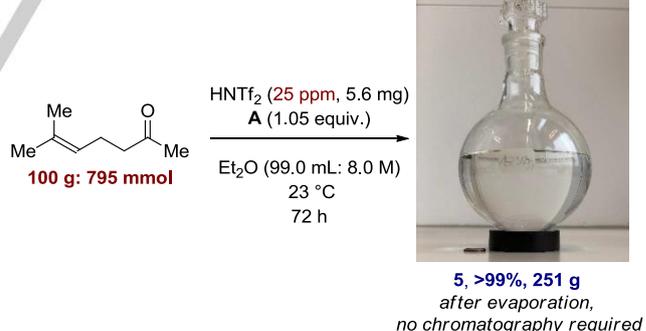
A. gram scale



B. deca-gram scale



C. hundred-gram scale



Scheme 2. Preparative scale syntheses of biologically relevant molecules; (A) Gram scale syntheses of HMHA precursor **2** and 3-hydroxy-citronellic acid precursor **5**; (B) Deca-gram scale synthesis of product **19** (in 50 mL RBF) and further short total synthesis of Fempentadiol (**55**); (C) Hundred-gram scale synthesis of product **5** (in 500 mL RBF, up scheme), GC-traces of 6-methyl-5-hepten-2-one (left) and the crude reaction mixture (right), respectively.

Acknowledgements

Generous support from the Max Planck Society, the Deutsche Forschungsgemeinschaft (Leibniz Award to B.L. and Cluster of Excellence RESOLV, EXC 1069), and the European Research Council (Advanced Grant "C–H Acids for Organic Synthesis, CHAOS") are gratefully acknowledged. We thank Jennifer L. Kennemur for her suggestions during the preparation of this manuscript, the technicians of our group, and the members of our NMR, MS and GC departments for their excellent service.

Conflict of interest

The authors declare no conflict of interest.

Keywords: Mukaiyama aldol reaction • aldol reaction of ketone • Lewis acid catalysis • parts-per-million catalyst loading • tertiary aldols • silyl ketene acetal

- [1] For comprehensive books, see: a) R. Mahrwald Ed., In *Modern aldol reactions*, Wiley-VCH Verlag GmbH & Co. 2004. b) R. Mahrwald Ed., In *Modern methods in stereoselective aldol reactions*, Wiley-VCH Verlag GmbH & Co. 2013. For reviews, see: c) S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, 9, 357–389. d) R. Mahrwald, R., *Chem. Rev.* **1999**, 99, 1095–1120.
- [2] a) M. L. Elliott, F. J. Urban, J. Bordner, *J. Org. Chem.* **1985**, 50, 1752–1755. b) R. Matovic, A. Ivkovic, M. Manojlovic, Z. Tokic-Vujosevic, R. N. Saicic, *J. Org. Chem.* **2006**, 71, 9411–9419.
- [3] a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, 2, 1011–1014. b) K. Saigo, M. Osaki, T. Mukaiyama, *Chem. Lett.* **1975**, 4, 989–990. c) J.-x. Chen, K. Sakamoto, A. Orita, J. Otera, *J. Org. Chem.* **1998**, 63, 9739–9745.
- [4] For the catalytic asymmetric Mukaiyama aldol reaction with ketone, see: a) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2002**, 124, 4233–4235. b) S. E. Denmark, Y. Fan, M. D. Eastgate, *J. Org. Chem.* **2005**, 70, 5235–5248. c) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, 128, 7164–7165. For reviews, see: d) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647–1675. e) S. Adachi, T. Harada, *Eur. J. Org. Chem.* **2009**, 3661–3671.
- [5] H. Y. Bae, D. Höfler, P. S. J. Kaib, P. Kasaplar, C. K. De, A. Döhring, S. Lee, K. Kaupmees, I. Leito, B. List, *Nat. Chem.*, **2018**, DOI = 10.1038/s41557-018-0065-0.
- [6] K. Oisaki, Y. Suto, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, 125, 5644–5645.
- [7] M. Hatano, E. Takagi, K. Ishihara, *Org. Lett.* **2007**, 9, 4527–4530.
- [8] a) H. Yanai, Y. Yoshino, A. Takahashi, T. Taguchi, *J. Org. Chem.* **2010**, 75, 5375–5378. b) D. Höfler, M. van Gemmeren, P. Wedemann, K. Kaupmees, I. Leito, M. Leutzsch, J. B. Lingnau, B. List, *Angew. Chem. Int. Ed.* **2017**, 56, 1411–1415. c) L. Ratjen, M. v. Gemmeren, F. Pescialoi, B. List, *Angew. Chem. Int. Ed.* **2014**, 53, 8765–8769. d) K. V. Bukhryakov, V. G. Desyatkin, V. O. Rodionov., *Chem. Commun.* **2016**, 52, 7576–7579.
- [9] a) The reported pK_a values of HOTf and HNTf₂ in MeCN are 0.7 and 0.3, respectively. See: A. Kütt, T. Rodima, J. Saame, E. Raamat, V. Mäemets, I. Kaljurand, I. A. Koppel, R. Y. Garlyuskayte, Y. L. Yagupolskii, L. M. Yagupolskii, E. Bernhardt, H. Willner, I. Leito, *J. Org. Chem.* **2011**, 76, 391–395. b) However, relative acidities between HOTf and HNTf₂ are the subject of debate, because those values are highly dependent on the solvation and concentration. See: C. Thomazeau, H. Olivier-Bourbigou, L. Magna, S. Luts, B. Gilbert, *J. Am. Chem. Soc.* **2003**, 125, 5264–5265.
- [10] a) For comprehensive information regarding triflimide catalyzed reactions, see: J. Sun, "Triflimide", In *e-EROS Encyclopedia of reagents for organic synthesis*, John Wiley & Sons, Ltd, 2010 and references therein. b) For a short review, see: V. L. Rendina, *Synlett* **2011**, 3055–3056 and references therein; Selected recent studies, see: c) O. Gutierrez, B. F. Strick, R. J. Thomson, D. J. Tantillo, *Chem. Sci.* **2013**, 4, 3997–4003. d) J. C. T. Reddel, W. Wang, K. Koukounas, R. J. Thomson, *Chem. Sci.* **2017**, 8, 2156–2160.
- [11] a) K. Ishihara, Y. Hiraiwa, H. Yamamoto, *Synlett* **2001**, 1851–1854. b) K. Ishihara, Y. Hiraiwa, H. Yamamoto, *Chem. Comm.* **2002**, 15, 1564–1565. c) Y. Hiraiwa, K. Ishihara, H. Yamamoto, *Eur. J. Org. Chem.* **2006**, 1837–1844.
- [12] For an account, see: a) W. Gati, H. Yamamoto, *Acc. Chem. Res.* **2016**, 49, 1757–1768. For examples, see: b) M. Boxer, H. Yamamoto, *J. Am. Chem. Soc.*, **2006**, 128, 48–49. c) M. Boxer, H. Yamamoto, *J. Am. Chem. Soc.*, **2007**, 129, 2762–2763. d) M. Boxer, H. Yamamoto, *J. Am. Chem. Soc.*, **2008**, 130, 1580–1582. e) B. J. Albert, H. Yamamoto, *Angew. Chem. Int. Ed.* **2010**, 49, 2747–2749. f) B. J. Albert, Y. Yamaoka, H. Yamamoto, *Angew. Chem. Int. Ed.* **2011**, 50, 2610–2612. g) J. Saadi, M. Akakura, H. Yamamoto, *J. Am. Chem. Soc.*, **2011**, 133, 14248–15251. h) P. B. Brady, H. Yamamoto, *Angew. Chem. Int. Ed.* **2012**, 51, 1942–1946. i) P. B. Brady, B. J. Albert, M. Akakura, H. Yamamoto, *Chem. Sci.* **2013**, 4, 3223–3231. j) A. Izumiseki, H. Yamamoto, *J. Am. Chem. Soc.*, **2014**, 136, 1308–1311. k) P. B. Brady, S. Oda, H. Yamamoto, H., *Org. Lett.*, **2014**, 16, 3864–3867. l) W. Gati, H. Yamamoto, *Chem. Sci.* **2016**, 7, 394–399.
- [13] Examples on the triflimide catalyzed Mukaiyama-type ketone cross-aldol reactions are known, see: Ref. 11a.
- [14] a) B. Mathieu, L. Ghosez, *Tetrahedron* **2002**, 58, 8219–8226. b) A. Hasegawa, K. Ishihara, H. Yamamoto, *Angew. Chem. Int. Ed.* **2003**, 42, 5731–5733.
- [15] a) For a general procedure of the preparation of SKA **A**. To a solution of *n*-butyllithium (2.5M in hexanes; 18.0 mL, 45.0 mmol, 1.10 equiv) in 60 mL of anhydrous THF, was dropwise freshly distilled diisopropylamine (5.0 mL, 36 mmol, 1.2 equiv.) at 0 °C and stirred for 20 min. The reaction mixture was cooled to –78 °C, 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU; 7.9 mL, 65.5 mmol, 1.6 equiv.) was added, and stirred for 30 min. *tert*-Butyldimethylsilyl chloride (7.4 g, 49 mmol, 1.2 equiv.; dissolved in 10 mL anhydrous THF) was slowly added at –78 °C and stirred for 12 h at room temperature. The volatile components were removed in vacuo, and the resulting residue was dissolved in pentane (100 mL), washed with water (1 × 100 mL), saturated aqueous copper sulfate (CuSO₄; 3 × 100 mL), saturated aqueous sodium bicarbonate solution (1 × 100 mL), and brine (1 × 100 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, and distilled in the presence of CaH₂ to give the SKA **A** in 4.5 g (58% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.53 (m, 2H), 7.52 (m, 1H), 7.41–7.36 (m, 3H), 6.70 (d, *J* = 16.3 Hz, 1H), 2.37 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 198.40, 143.46, 134.47, 130.56, 129.02, 128.30, 127.20, 27.57. b) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, 124, 12964–12965. c) For a discussion regarding the effect of the quality of SKA on the reaction outcome, see: T. Gatzemeier, P. S. J. Kaib, J. B. Lingnau, R. Goddard, B. List, *Angew. Chem. Int. Ed.* **2018**, 57, 2464–2468.
- [16] An α,β-unsaturated ketone such as benzylideneacetone-type benzylideneacetone gave a mixture of 1,2-adduct **15** (43%) and 1,4-adducts (57%). 3-Methyl-4-phenylbut-3-en-2-one gave exclusively 1,2-adduct **16** (98%). See Ref. 5.
- [17] X. Moreau, B. Bazán-Tejeda, J.-M. Campagne, *J. Am. Chem. Soc.* **2005**, 127, 7288–7289.
- [18] a) Y. Hasegawa, M. Yabuki, M. Matsukane, *Chem. Biodivers.* **2004**, 1, 2042–2050. b) M. Troccaz, G. Borchard, C. Vuilleumier, S. Raviot-Derrien, Y. Niclass, S. Beccucci, C. Starckenmann, *Chem. Senses* **2009**, 34, 203–210.

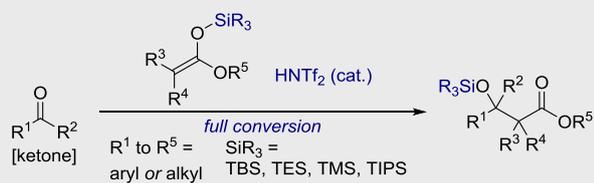
- [19] a) A. Fkyerat, N. Burki, R. Tabacchi, *Tetrahedron: Asymm.* **1996**, *7*, 2023–2028. b) A. Chadha, K. M. Madyastha, *Xenobiotica* **1984**, *14*, 365–374.
- [20] a) J. Elks Ed., In *The Dictionary of Drugs: Chemical Data, Structures and Bibliographies*; Springer. 2014. b) Noël, J. P. Noël, A. Benakis, R. Valette, M. Herbert, L. Pichat, *J. Labelled. Comp.* **1972**, *8*, 157–174. c) US Patent 3,660,560 patented 2 May 1972.
- [21] Compared with previous experiments, extended time (72 h) and higher temperature (23 °C) were applied in this hundred-gram scale reaction, due to the lower catalyst loading (25 ppm). We speculate that higher catalyst loading may accelerate the reaction rate.

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Han Yong Bae and Benjamin List*

Page No. – Page No.**Triflimide: An Overlooked High-Performance Catalyst of the Mukaiyama Aldol Reaction of Silyl Ketene Acetals with Ketones**

- ppm-level catalyst loading: down to 25 ppm
 - broad substrate scope: 54 examples
 - scalable to 251 gram with excellent purity
- 5 mol%: <10 s, partial decomposition
0.05 mol% (=500 ppm): >99% yield