DOI: 10.1002/adsc.200900869

Pentafluorophenylammonium Trifluoromethanesulfonimide: Mild, Powerful, and Robust Catalyst for Mukaiyama Aldol and Mannich Reactions between Ketene Silyl Acetals and Ketones or Oxime Ethers

Ryohei Nagase,[a] Jun Osada,[a] Hiroaki Tamagaki,[a] and Yoo Tanabe[a,*]

[a] Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2–1 Gakuen, Sanda, Hyogo 669-1337, Japan
Fax: (+81)-79-565-9077; phone: +81-79-565-8394; e-mail: tanabe@kwansei.ac.jp

Received: December 17, 2009; Published online: April 22, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900869.

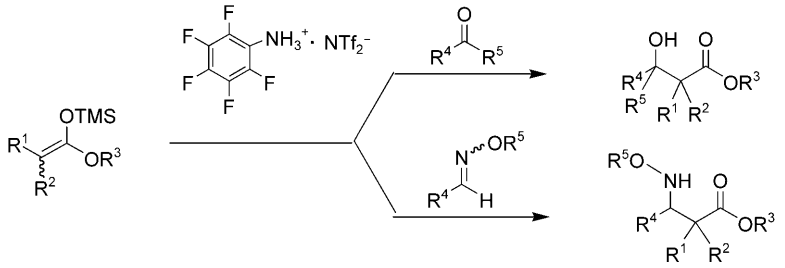
Abstract: Pentafluorophenylammonium trifluoromethanesulfonimide ($C_6F_5N^+H_3{\cdot}NTf_2^-$) promotes Mukaiyama aldol and Mannich reactions using ketene silyl acetals with ketones and oxime ethers, respectively. The present robust method is mild, but powerful enough to utilize less accessible electrophiles such as enolizable ketones and oxime ethers to produce a variety of β-hydroxy esters and β-alkoxyamino esters, respectively. Mechanistic investigation revealed *in situ* generation of trimethylsilyl bistriflimide [Tf_2N(TMS)], the truly active catalyst, which was supported by rational ^{1}H NMR measurements.

Keywords: ketene silyl acetals; ketones; Mannich addition; Mukaiyama aldol addition; oxime ethers; pentafluorophenylammonium trifluoromethanesulfonimide

Catalytic aldol and Mannich additions are well-recognized as fundamental and pivotal C–C bond forming reactions for the preparation of the ubiquitous β-hydroxy and β-amino carbonyl core building blocks found in natural products and pharmaceuticals.[1] Due to the intrinsic lower reactivity of ketones and reversible retro-aldol tendency, only a few reports have appeared with regard to cross-aldol reactions between different ketones or between ketones and carbonyl equivalents, such as enol silyl ethers and ketene silyl acetals (KSA).[2] Ishihara's group recently reported a notable Lewis base-catalyzed Mukaiyama aldol addition of KSAs with non-enolizable ketones to give the corresponding β,β-disubstituted β-hydroxy esters (tertiary aldols).[3] There are two related methods for direct cross-aldol reaction between different ketones using stoichiometric Lewis acids, $Sn(OTf)_2$[4] and $TiCl_4$,[5] wherein strong metal chelate formation drives the aldol addition between different ketones.

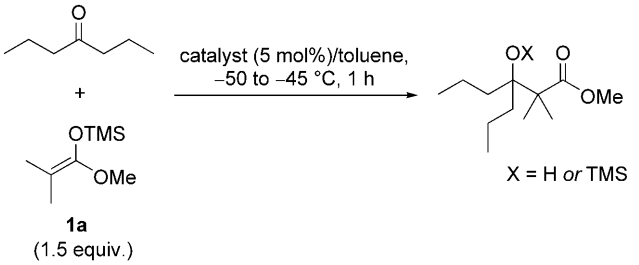
In connection with our long-standing interests in the development of Ti- (or Zr-) Claisen condensations,[6] relevant aldol[7] and Mannich reactions,[8] we report herein the pentafluorophenylammonium trifluoromethanesulfonimide (triflylimide) ($C_6F_5N^+H_3{\cdot}NTf_2^-$) [true catalyst is Tf_2N(TMS), generated *in situ*]-catalyzed Mukaiyama aldol reaction between KSAs and ketones, and Mannich reaction between KSAs and oxime ethers (Scheme 1).

The initial attempt was guided by the reaction between KSA **1a** and the significantly less reactive 4-heptanone using several acid catalysts (Table 1). As expected, the reaction did not proceeded in the absence of a catalyst (entry 1). Use of CSA (camphorsulfonic acid) and PPTS (pyridinium *p*-toluenesulfonate), as well as TMSOTf and pentafluorophenylammonium triflate (PFPAT; $C_6F_5N^+H_3{\cdot}OTf^-$),[9] resulted in almost no reaction (entry 2). Tf_2NH and Tf_2N(TMS) catalysts have attracted considerable attention for their use in aldol and Diels–Alder reactions due to their super acidity.[10] Indeed, the reaction using the Tf_2NH or Tf_2N(TMS) catalyst[10h] afforded the desired aldol adduct **2a**, but this result proved difficult to reproduce with constant results (entry 3). The difficulty is considered to be attributed to the hygroscopic and sublimation properties of these catalysts for the present case, which requires both high reactivity and robustness. To overcome this problem, stable and easily handled ammonium salts of Tf_2NH were screened. Although pyridinium and diphenylammonium salts were not effective, the highly acidic but significantly



Scheme 1. $C_6F_5N^+H_3{\cdot}NTf_2^-$-catalyzed Mukaiyama aldol and Mannich reactions.

Table 1. Screening of acid catalysts.



Entry	Catalyst	Yield [%][a]
1	none	trace
2	CSA, PPTS, TMSOTf, PFPAT[b]	trace
3	Tf_2NH, Tf_2N(TMS)	trace–*ca.* 30[c]
4	$PyH^+{\cdot}NTf_2^-$, $PhNH_3^+{\cdot}NTf_2^-$	trace
5	$C_6F_5N^+H_3{\cdot}NTf_2^-$	75–77

[a] Conversion determined by ^{1}H NMR.
[b] $C_6F_5NH_3^+{\cdot}OTf^-$.
[c] Not reproducible.

moisture-insensitive $C_6F_5N^+H_3{\cdot}NTf_2^-$ produced successful and reproducible results (entries 4 and 5).[11] Thus, we chose $C_6F_5N^+H_3{\cdot}NTf_2^-$ as a robust catalyst for the present study.

Table 2 lists the successful results of the present $C_6F_5N^+H_3{\cdot}NTf_2^-$-catalyzed Mukaiyama aldol reaction using a variety of KSAs **1a**–**1f** and ketones under optimized conditions. The salient features are as follows: (i) The reaction using not only simple KSAs **1a**–**1c**, but also stereocongested TBS-substituted KSAs **1d**, proceeded smoothly to give the desired β,β-disubstituted β-hydroxy esters (tertiary aldols) in good to excellent yield. (ii) A striking aspect is that enolizable ketone acceptors were applicable as the substrate with much better performance compared to Ishihara's base-catalyzed method.[3] In general, enolizable ketones are prone to be transformed to the corresponding enol silyl ethers by the reaction with KSAs.[12] (iii) Acid labile KSAs **1e** and **1f** underwent the reaction smoothly without loss of the *t*-Bu group (entries 5, 6, 11, and 12).[13] (iv) Benzophenone, methyl pyruvate, and phenacyl chloride were applicable as the acceptor (entries 22–24). Thus, a variety of inaccessible tertiary aldols were provided by the present method. (v) The *syn*/*anti* selectivity was poor or moderate due to the intrinsic difficulty of ketone-ketone cross-aldol additions based on the poorer differentiation between ketone substituents than that of aldehydes.

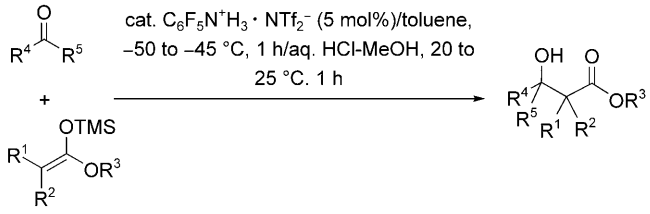
Next, we applied the present method for the reaction between KSA **1a** and four α,β-unsaturated ketones. In clear contrast to the case of using saturated ketones, Michael-type 1,4-addition predominated over the aldol addition to give 5-oxo esters **10**–**13** (Scheme 2).[14]

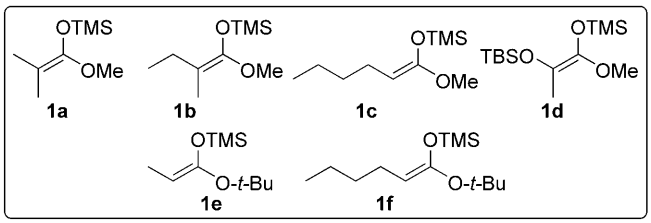
Scheme 3 illustrates a plausible mechanism for the present reaction. Initially, $C_6F_5N^+H_3{\cdot}NTf_2^-$ reacts with a KSA **1** to form the key Tf_2N(TMS) catalyst with release of an intact (much less reactive) methyl ester and $C_6F_5NH_2$. Tf_2N(TMS) activates a ketone to give intermediate **A**, which couples with **1** giving an aldol adduct intermediate **B**. Then **B** rearranges into a TMS aldol adduct **2** with reproduction of Tf_2N(TMS) possibly through path *b* rather than path *a*, according to the Yamamoto group's extensive studies,[10e,f,g,h,i] and the catalytic cycle is completed. It is worth noting that Tf_2N(TMS) is considered to be the true active catalyst, despite the use of the parent simple Brønsted catalyst, $C_6F_5N^+H_3{\cdot}NTf_2^-$.

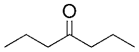
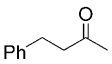
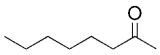
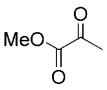
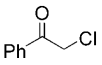
^{1}H NMR monitoring study of a mixture of KSA **1a** and catalytic $C_6F_5N^+H_3{\cdot}NTf_2^-$ (20 mol%) in toluene-d_8 at −20 °C, rationally supported the present hypothesis: the generation not of parent Tf_2NH but of NTf_2(TMS) with methyl isobutyrate was unambiguously observed (Figure 1).

With these results in hand, we next investigated the $C_6F_5N^+H_3{\cdot}NTf_2^-$-catalyzed Mannich reaction between KSAs **1** and oxime ethers. Oxime ethers are well-known superior isosters to imines due to easier preparation and inherently higher stability, especially for reliable aliphatic aldoximes derived from aldehydes bearing a hydrogen in the α-position. The Mannich reaction using oxime ethers, therefore, has a clear advantage over that of imines due to its wide variation. Nonetheless, to the best of our knowledge, there is a sole report on this topic:[15] the TMSOTf-catalyzed reaction between KSAs and only two oxime ethers. However, this method lacks substrate generality due to insufficient reactivity. Recently, we reported the

Table 2. $C_6F_5N^+H_3{\cdot}NTf_2^-$-promoted Mukaiyama aldol reaction between KSAs **1** and ketones.

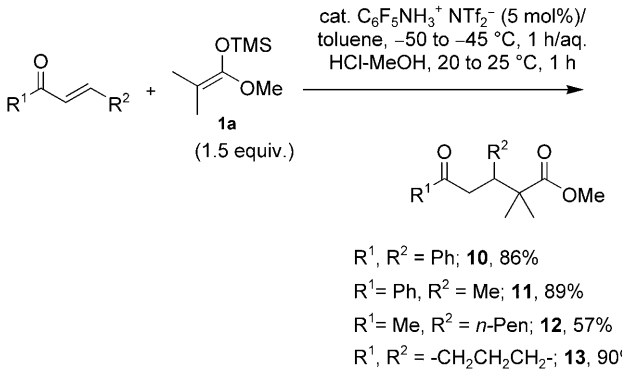




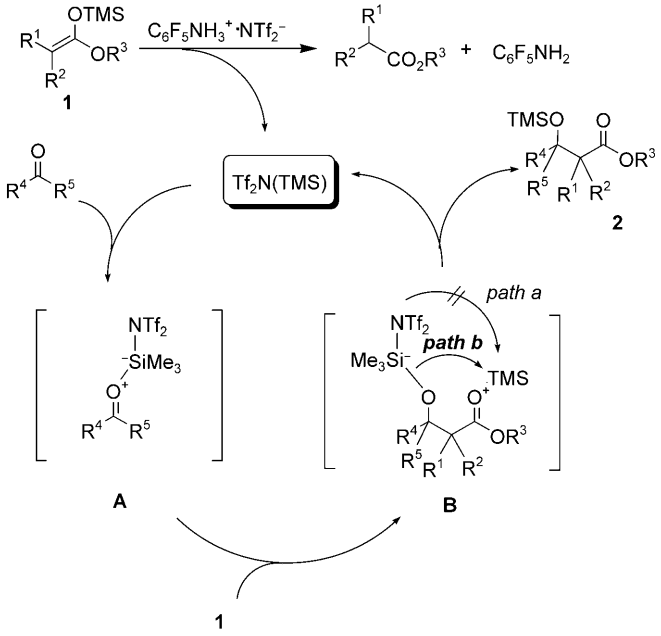
Entry	Ketone	KSA	Product	*de*[a]	Yield [%][b]
1		**1a**	**2a**	–	77
2		**1b**	**2b**	–	57
3		**1c**	**2c**	–	91
4		**1d**	**2d**	–	76[c]
5		**1e**	**2e**	–	75
6		**1f**	**2f**	–	59
7		**1a**	**3a**	–	86
8		**1b**	**3b**	1:1	92
9		**1c**	**3c**	2:1	91
10		**1d**	**3d**	1:1	90
11		**1e**	**3e**	1:1	77
12		**1f**	**3f**	4:1	59
13		**1a**	**4a**	–	71
14		**1c**	**4c**	2:1	89
15		**1d**	**4d**	1:1	84[c]
16		**1a**	**5a**	–	83
17		**1c**	**5c**	–	91
18		**1d**	**5d**	–	88[c]
19		**1a**	**6a**	–	84
20		**1c**	**6c**	1:1	78
21		**1d**	**6d**	1:1	94[c]
22		**1a**	**7a**		98
23		**1a**	**8a**		68
24		**1a**	**9a**		92

[a] Determined by ^{1}H NMR. The *syn*/*anti* ratio was not assigned.
[b] Isolated yield.
[c] Carried out at 0–5 °C for 3 h. Based on its TMS ether.

$TiCl_4$-(*s*-Bu)$_2$NH-mediated direct reaction between esters and oxime ethers,[8] but this method requires α-brominated ester substrates.



Scheme 2. $C_6F_5N^+H_3{\cdot}NTf_2^-$-promoted Michael reaction between KSAs **1a** and α,β-unsaturated ketones.



Scheme 3. Plausible reaction mechanism for the aldol addition between KSAs **1** and ketones.

Table 3 lists the successful results of a mild and powerful Mannich reaction between KSAs **1a**–**1d** and various oxime ethers.

The salient features are as follows: (i) In all cases examined, the present reaction proceeded smoothly to give the desired β-alkoxyamino esters in good to excellent yield (NB: all new compounds). (ii) A comparable experiment on entry 1 using TMSOTf as catalyst resulted in almost no reaction under identical conditions. (iii) *O*-Benzyloximes as well as *O*-methyloximes were applicable (entries 14–21). (iv) Several functionalities in the oxime ethers, such as terminal Br, TBSO, and MeO_2C groups, were compatible (entries 16–21). (v) The *syn*/*anti* selectivity was poor or moderate similar to the aforementioned cross-aldol reaction.

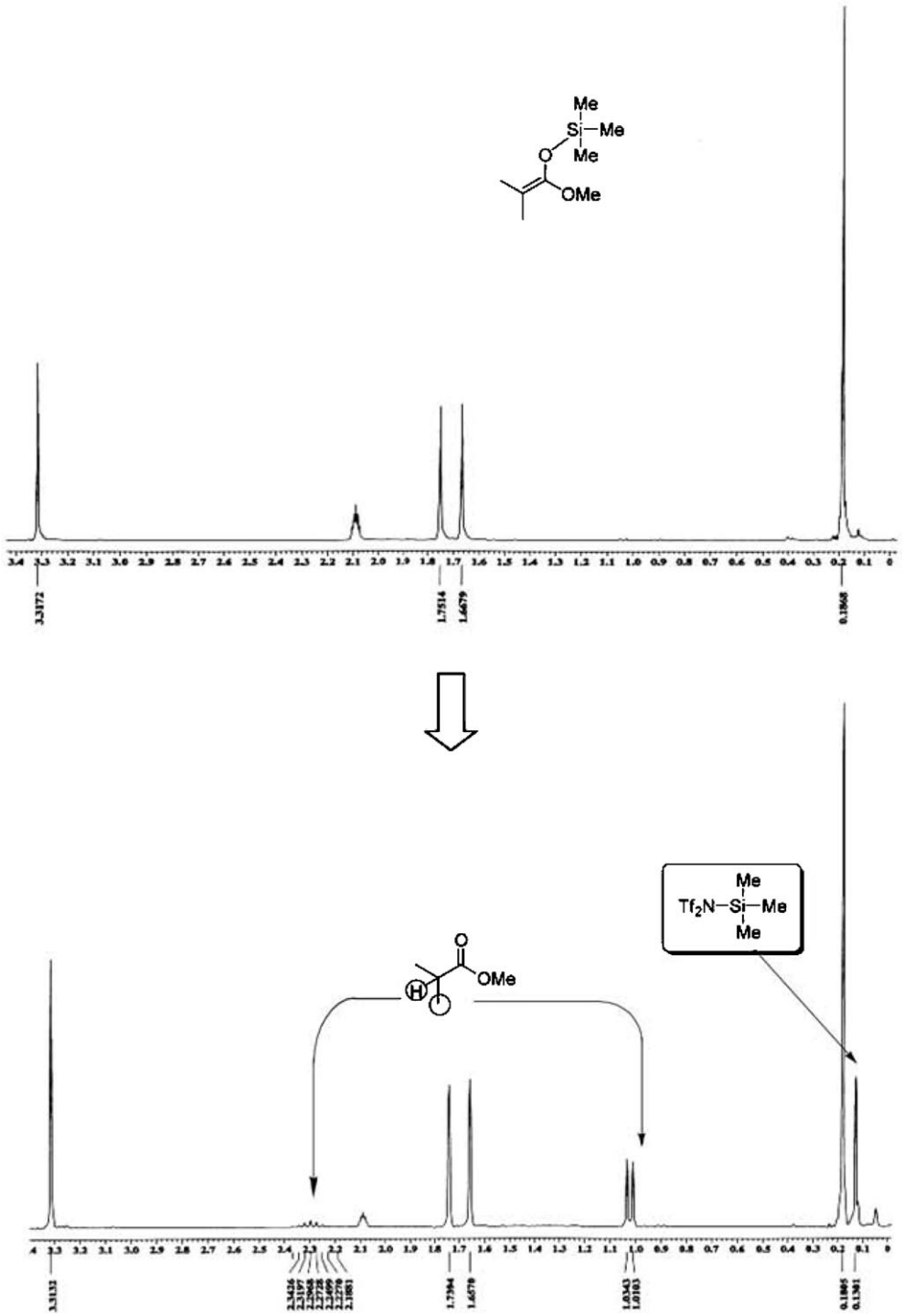
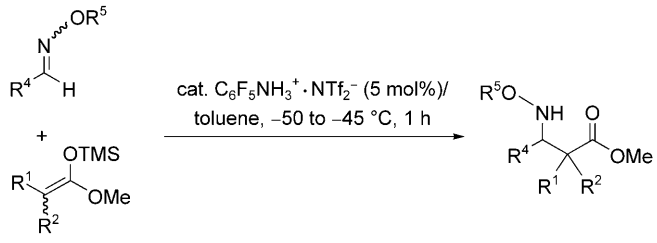


Figure 1. ^{1}H NMR monitoring study using a mixture of KSA **1a** and catalytic $C_6F_5N^+H_3{\cdot}NTf_2^-$ (20 mol%) in toluene-d_8.

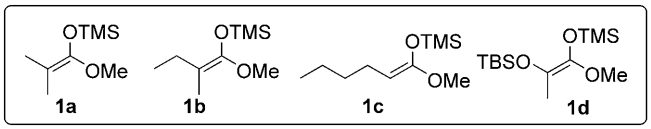
As was described in the previous report,[8] β-methoxyamino esters, obtained by the present Mannich reaction, can be converted to the corresponding β-amino esters using Zn-AcOH reagent. In addition, a mild catalytic hydrogenation of β-*O*-benzyloxime ester products **18a** and **21a** proceeded smoothly to give the corresponding β-amino esters **22** and **23** (Scheme 3).

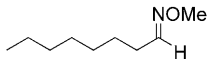
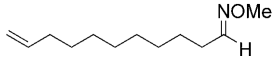
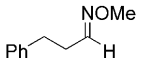
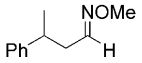
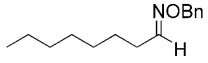
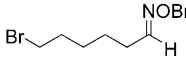
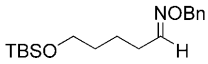
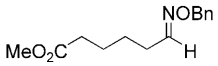
In conclusion, we have developed efficient Mukaiyama aldol and Mannich reactions between KSAs and ketones or oxime ethers, respectively, promoted by the $C_6F_5N^+H_3{\cdot}NTf_2^-$ catalyst (total 44 examples). The present method provides a new avenue for the

Table 3. $C_6F_5NH_3^+ \cdot NTf_2^-$-promoted Mannich reaction between KSAs **1** and oxime ethers.



1a – d (1.5 equiv)



Entry	Oxime ether	KSA	Product	*de*[a]	Yield [%][b]
1		**1a**	**14a**	–	97 (<10%)[c]
2		**1b**	**14b**	1:1	94
3		**1c**	**14c**	1:1	98
4		**1d**	**14d**	1.5:1	82[d]
5		**1a**	**15a**	–	83
6		**1b**	**15b**	1:1	81
7		**1c**	**15c**	1:1	84
8		**1d**	**15d**	1.5:1	65[d]
9		**1a**	**16a**	–	89
10		**1c**	**16c**	1:1	86
11		**1d**	**16d**	1.5:1	88[d]
12		**1a**	**17a**	4:1	96
13		**1c**	**17c**	2.3:1	99
14		**1a**	**18a**	–	99
15		**1c**	**18c**	1.5:1	92
16		**1a**	**19a**	–	86
17		**1c**	**19c**	1.5:1	86
18		**1a**	**20a**	–	83
19		**1c**	**20c**	1.5:1	87
20		**1a**	**21a**	–	87
21		**1c**	**21c**	1.5:1	82

[a] Determined by ^{1}H NMR. The *syn*/*anti* ratio was not assigned.
[b] Isolated yield.
[c] Use of TMSOTf.
[d] Carried out at 0–5 °C for 3 h.

synthesis of a variety of quite less accessible β-hydroxy esters and β-alkoxyamino esters of interest, especially, in the context of natural product synthesis and process chemistry.

Experimental Section

All reactions were carried out in oven-dried glassware under an argon atmosphere. TLC analysis was performed on 0.25 mm Silica gel Merck 60 F_{254} plates. Melting points were determined on a hot stage microscope apparatus (Asone) and are uncorrected. NMR spectra were recorded on a JEOL DELTA 300 spectrometer, operating at 300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR. Chemical shifts (δ ppm) in $CDCl_3$ are reported downfield from TMS (=0) or $CHCl_3$ (=7.26) for ^{1}H NMR. For ^{13}C NMR, chemical shifts are reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. Mass spectra were measured on a JEOL JMS-T100 LC spectrometer. For the measurement of HR-MS, the corresponding TMS ethers were used.

Typical Procedure for Aldol Reaction between KSAs 1a and 4-Heptanone (Table 2, entry 1)

1-Methoxy-1-trimethylsiloxy-2-methyl-1-propene (**1a**; 261 mg, 1.5 mmol) was added to a stirred solution of 4-heptanone (114 mg, 1.0 mmol) and $C_6F_5N^+H_3 \cdot NTf_2^-$ (23 mg, 0.05 mmol) in toluene (0.5 mL) at −50 to −45 °C under an argon atmosphere, followed by stirring at the same temperature for 1 h. The mixture was quenched with water, and then extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was added to a stirred solution of 6 M HCl aqueous solution (2.0 mL) in MeOH (2.0 mL) at 20–25 °C, followed by stirring at the same temperature for 1 h. The mixture was quenched with water and then extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane:Et_2O=30:1) to give the desired product **2a**;[16] yield: 167 mg (77%); colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.89 (6H, t, J=6.9 Hz), 1.22 (6H, s), 1.27–1.54 (8H, m), 3.70 (1H, s), 3.71 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.8, 17.4, 21.3, 38.6, 50.3, 51.8, 76.0, 179.4; IR (neat): ν=3505, 2961, 2874, 1734, 1701, 1273, 1150 cm^{-1}.

Typical Procedure for Aldol reaction between KSA 1d and Ketones (Table 2, entry 4)

4-Heptanone (114 mg, 1.0 mmol) and 2-*tert*-butyldimethylsiloxy-1-methoxy-1-trimethylsiloxy-1-propene (**1d**; 436 mg, 1.5 mmol) were successively added to a stirred solution of $C_6F_5N^+H_3 \cdot NTf_2^-$ (23 mg, 0.05 mmol) in toluene (0.5 mL) at 0–5 °C under an argon atmosphere, followed by stirring at the same temperature for 3 h. A similar work-up procedure as for preparing **2a** gave the desired product **2d**; yield: 306 mg (76%); colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.01 (3H, s), 0.076 (9H, s), 0.082 (3H, s), 0.82–0.93 (6H, m), 0.89 (9H, s), 1.15–1.49 (4H, m), 1.44 (3H, s), 1.50–1.79 (4H, m), 3.65 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ=−3.7, −2.9, 2.9, 15.0, 17.7, 17.8, 18.5, 22.4, 25.9, 37.4, 37.9, 51.3, 82.8, 83.9, 175.0; IR (neat): ν=2959, 1742, 1458, 1250, 1146, 1115, 1086, 1005, 839, 777 cm^{-1}; HR-MS (ESI): m/z=427.2677, calcd. for $C_{20}H_{44}O_4Si_2$ (M+Na$^+$): 427.2676.

Typical Procedure for Michael Reaction between KSA 1a and Benzalacetophenone (Scheme 2)

KSA **1a** (261 mg, 1.5 mmol) was added to a stirred solution of benzalacetophenone (208 mg, 1.0 mmol) and $C_6F_5N^+H_3{\cdot}NTf_2^-$ (23 mg, 0.05 mmol) in toluene (0.5 mL) at −50 to −45 °C under an argon atmosphere, followed by stirring at the same temperature for 1 h. A similar work-up procedure as for the aldol reaction gave the desired product **10**;[17] yield: 267 mg (86%).

Typical Procedure for Mannich Reaction between KSAs 1a and *O*-(Methyl)octanaldoxime (Table 3, entry 1)

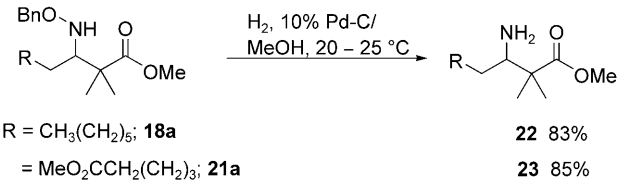
O-(Methyl)octanaldoxime (157 mg, 1.0 mmol) and KSA **1a** (261 mg, 1.5 mmol) were successively added to a stirred solution of $C_6F_5N^+H_3{\cdot}NTf_2^-$ (23 mg, 0.05 mmol) in toluene (0.5 mL) at −50 to −45 °C under an argon atmosphere, followed by stirring at the same temperature for 1 h. The mixture was quenched with water, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane:Et_2O = 15:1) to give the desired product **14a**; yield: 251 mg (97%); colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (3H, t, J = 6.5 Hz), 1.06–1.62 (12H, m), 1.155 (3H, s), 1.157 (3H, s), 3.11 (), 3.41 (3H, s), 3.65 (3H, s), 5.56 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.2, 22.6, 23.2, 27.6, 28.1, 29.2, 29.7, 31.8, 45.6, 51.6, 61.3, 66.2, 178.1; IR (neat): ν = 2928, 2857, 1736, 1466, 1435, 1263, 1192, 1142 cm^{-1}; HR-MS (ESI): m/z = 282.2040, calcd. for $C_{14}H_{29}NO_3$ (M + Na$^+$): 282.2045.

Typical Procedure for Mannich reaction between KSA 1d and *O*-(Methyl)octanaldoxime (Table 3, entry 4)

O-Methyloctanaldoxime (157 mg, 1.0 mmol) and KSA **1d** (436 mg, 1.5 mmol) were successively added to a stirred solution of $C_6F_5N^+H_3{\cdot}NTf_2^-$ (23 mg, 0.05 mmol) in toluene (0.5 mL) at 0–5 °C under an argon atmosphere, followed by stirring at the same temperature for 3 h. A similar work-up as for preparing **14a** [SiO_2 column chromatography (hexane:Et_2O = 80:1)] gave the desired product **14d**; yield: 309 mg (82%); colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.075 (3H × 3/5, s), 0.083 (3H × 2/5, s), 0.11 (3H × 3/5, s), 0.17 (3H × 2/5, s), 0.84–0.91 (12H, m), 1.16–1.56 (12H, m), 1.38 (3H × 2/5, s), 1.46 (3H × 3/5, s), 3.05 (1H × 3/5, dd, J = 2.1, 9.6 Hz), 3.14 (1H × 2/5, dd, J = 2.4, 9.3 Hz), 3.37 (3H × 2/5, s), 3.43 (3H × 3/5, s), 3.67 (3H × 2/5, s), 3.69 (3H × 3/5, s), 5.99 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −3.4, −3.1, −2.81, −2.77, 14.1, 18.4, 18.6, 22.6, 23.2, 24.2, 25.8, 25.9, 26.8, 27.2, 27.4, 28.0, 29.2, 29.6, 29.7, 31.8, 51.7, 60.7, 61.4, 66.6, 67.7, 77.8, 79.3, 175.2, 176.0; IR (neat): ν = 2930, 1754, 1464, 1254, 1192, 1130, 1005, 837, 779 cm^{-1}; HR-MS (ESI): m/z = 398.2707, calcd. for $C_{19}H_{41}NO_4Si$ (M + Na$^+$): 398.2703.

General Procedure of Catalytic Hydrogenation of β-(Benzyloxyamino) Esters (Scheme 4)

10% Pd-C (106 mg, 0.1 mmol) was added to a stirred solution of 3-(benzyloxyamino) ester **18a** or **21a** (1.0 mmol) in MeOH (3.0 mL), and the mixture was stirred equipped with an H_2 balloon for 16 h at 20–25 °C. The mixture was filtered thorough the Celite using a glass filter, and the filtrate was concentrated under reduced pressure. The obtained crude product was purified by SiO_2 column chromatography (hexane:AcOEt = 10:1) to give the desired product **22** or **23**.



Scheme 4. Deprotection of the benzyloxy group of Mannich-type adducts.

Supporting Information

Characterization data for all known products **3a**,[17] **3c**,[18] **3e**,[16] **5a**,[19] **5c**,[20] **7a**,[20] **8a**,[21] **10**,[17] **11**,[22] **12**,[23] **13**,[24] and all new products **2b–2f**, **3f**, **4a**, **4c**, **4d**, **5d**, **6a**, **6b**, **6d**, **9a**, **14a–14d**, **15a–15d**, **16a**, **16c**, **16d**, **17a**, **17c**, **18a**, **18c**, **19c**, **20a**, **20c**, **21a**, **21c** are available in the Supporting Information.

Acknowledgements

This research was partially supported by Grant-in-Aids for Scientific Research on Basic Areas (B) "18350056", Priority Areas (A) "17035087" and "18037068", and Exploratory Research "17655045" from the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

References

[1] a) C. H. Heathcock, in: *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, Vol. 2, p 181; b) J. Clayden, N. Greeves, S. Warren, P. Wothers, in: *Organic Chemistry*, Oxford, New York, **2001**, p 689.

[2] a) M. B. Smith, J. March, in: *March's Advanced Organic Chemistry*, 6th edn., Wiley, New York, **2006**, p 1351; for recent examples, see: b) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2002**, *124*, 4233; c) K. Oisaki, Y. Suto, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5644; d) S. E. Denmark, Y. Fan, M. D. Eastgate, *J. Org. Chem.* **2005**, *70*, 5235; e) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7164.

[3] M. Hatano, E. Takagi, K. Ishihara, *Org. Lett.* **2007**, *9*, 4527.

[4] T. Mukaiyama, N. Iwasawa, R. W. Stevens, T. Haga, *Tetrahedron* **1984**, *40*, 1381.

[5] Y. Tanabe, N. Matsumoto, T. Higashi, T. Misaki, T. Itoh, M. Yamamoto, K. Mitarai, Y. Nishii, *Tetrahedron (Symposium in Print)* **2002**, *58*, 8269.

[6] a) Y. Tanabe, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917; b) Y. Tanabe, R. Hamasaki, S. Funakoshi, *Chem. Commun.* **2001**, 1674; c) Y. Tanabe, A. Makita, S. Funa-

koshi, R. Hamasaki, T. Kawakusu, *Adv. Synth. Catal.* **2002**, *344*, 507; d) T. Misaki, R. Nagase, K. Matsumoto, Y. Tanabe, *J. Am. Chem. Soc.* **2005**, *127*, 2854; e) A. Iida, S. Nakazawa, T. Okabayashi, A. Horii, T. Misaki, Y. Tanabe, *Org. Lett.* **2006**, *8*, 5215.

[7] a) Ref.[5]; b) Y. Tanabe, K. Mitarai, T. Higashi, T. Misaki, Y. Nishii, *Chem. Commun.* **2002**, 2542; c) R. Nagase, N. Matsumoto, K. Hosomi, T. Higashi, S. Funakoshi, T. Misaki, Y. Tanabe, *Org. Biomol. Chem.* **2007**, *5*, 151; d) R. Nagase, M. Katayama, H. Mura, N. Matsuo, Y. Tanabe, *Tetrahedron Lett.* **2008**, *49*, 4509.

[8] T. Funatomi, S. Nakazawa, K. Matsumoto, R. Nagase, Y. Tanabe, *Chem. Commun.* **2008**, 771.

[9] Commercially available; TCI-P1626: a) T. Funatomi, K. Wakasugi, T. Misaki, Y. Tanabe, *Green Chem.* **2006**, *8*, 1022; b) A. Iida, J. Osada, R. Nagase, T. Misaki, Y. Tanabe, *Org. Lett.* **2007**, *9*, 1859.

[10] a) B. Mathieu, L. Ghosez, *Tetrahedron Lett.* **1997**, *38*, 5497; b) A. Ishii, T. Kotera, T. Saeki, K. Mikami, *Synlett* **1997**, 1145; c) K. Ishihara, Y. Hiraiwa, H. Yamamoto, *Synlett* **2001**, 1851; d) J. Cossy, F. Lutz, V. Alauze, C. Meyer, *Synlett* **2002**, 45; e) K. Ishihara, Y. Hiraiwa, H. Yamamoto, *Chem. Commun.* **2002**, 1564; f) D. Nakashima, H. Yamamoto, *Org. Lett.* **2005**, *7*, 1251; g) K. Inanaga, K. Takasu, M. Ihara, *J. Am. Chem. Soc.* **2005**, *127*, 3668; h) M. B. Boxer, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 48; i) Y. Hiraiwa, K. Ishihara, H. Yamamoto, *Eur. J. Org. Chem.* **2006**, 1837; j) K. Takasu, N. Shindoh, H. Tokuyama, M. Ihara, *Tetrahedron* **2006**, *62*, 11900; k) M. E. Jung, D. G. Ho, *Org. Lett.* **2007**, *9*, 375.

[11] pK_b values of counter amines: *ca.* 9.4 ($PhNH_2$), 13.8 (pyridine), 14.2 ($C_6F_5NH_2$), calculated by SciFinder Scholar®. Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris © 1994–2006 ACD/Labs. **Preparation of $C_6F_5N^+H_3{\cdot}NTf_2^-$**: A solution of 2,3,4,5,6-pentafluoroaniline (549 mg, 3.0 mmol) in toluene (3.0 mL) was added to a stirred solution of $(CF_3SO_2)_2NH$ (843 mg, 3.0 mmol) in toluene (6.0 mL) at 0–5 °C, and the mixture was stirred at the same temperature for 0.5 h. Evaporation of the solvent gave a crude solids which was washed with hexane (10 mL × 5) to give the desired pure product as colourless moisture-insensitive, and easily handled crystals; yield: 1.34 g (96%); mp 105–107 °C; ^{1}H NMR (acetone-d_6, 300 MHz): $\delta = 9.14$ (3H, br s); ^{13}C NMR (75 MHz): $\delta =$ 111.0, 120.9 [$^1J(^{13}C,^{19}F) = 321$ Hz], 137.8, 141.6, 142.6, 145.0, 146.0; IR (KBr): $\nu = 3403$, 1352, 1333, 1197, 1144 cm^{-1}.

[12] a) E. Nakamura, T. Murofushi, M. Shimizu, I. Kuwajima, *J. Am. Chem. Soc.* **1976**, *98*, 2346; b) J. J. Song, Z. Tan, J. T. Reeves, D. R. Fandrick, N. K. Yee, C. H. Senanayake, *Org. Lett.* **2008**, *10*, 877.

[13] Practical and robust method for the preparation of **1e** and **1f** and related KSAs: T. Okabayashi, A. Iida, K. Takai, Y. Nawate, T. Misaki, Y. Tanabe, *J. Org. Chem.* **2007**, *72*, 8142.

[14] It is a usual behaviour that Michael addition predominates over 1,2-type aldol addition; for an example, see Ref.[2a], p. 1110.

[15] K. Ikeda, K. Achiwa, M. Sekiya, *Tetrahedron Lett.* **1983**, *24*, 4707.

[16] G. Wenke, E. N. Jacobsen, G. E. Totten, A. C. Karydas, Y. E. Rhodes, *Synth. Commun.* **1983**, *13*, 449.

[17] S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1998**, *120*, 2985.

[18] K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7164.

[19] G. Bartoli, L. Lunazzi, M. Massaccesi, A. Mazzanti, *J. Org. Chem.* **2004**, *69*, 821.

[20] K. Takai, T. Ueda, N. Ikeda, T. Ishiyama, H. Matsushita, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 347.

[21] H. Doucet, J.-L. Parrain, M. Santelli, *Synlett* **2000**, 871.

[22] T. Mukaiyama, S. Kobayashi, M. Tamura, Y. Sagawa, *Chem. Lett.* **1987**, 491.

[23] T. Nakagawa, H. Fujisawa, Y. Nagata, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 236.

[24] K. Ishihara, N. Hanaki, M. Funahashi, M. Miyata, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1721.

