

# Gallium(III) Triflate Catalyzed Diastereoselective Mukaiyama Aldol Reaction by Using Low Catalyst Loadings

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A mild method for the diastereoselective Mukaiyama aldol reaction is reported. By using a low loading of the gallium(III) triflate catalyst (down to 0.01 mol-%), the transformation proceeds efficiently to afford the corresponding  $\beta$ -hydroxy

Introduction

The  $\beta$ -hydroxy carbonyl functionality is an extremely common feature in many natural products and biologically active molecules.<sup>[1]</sup> For the formation of this motif, the Mukaiyama aldol reaction is certainly one of the most notable C-C bond-forming reactions, by focusing on the addition of silvl enolates to aldehydes in the presence of Lewis acids.<sup>[1a,2]</sup> Initially mediated by stoichiometric amounts of TiCl<sub>4</sub>,<sup>[2a,2b]</sup> the first catalytic version of this reaction was reported by Bergman and Heathcock in 1989.<sup>[3]</sup> Subsequently, numerous Lewis acid catalysts conjointly used with chiral ligands have been reported for catalytic asymmetric Mukaiyama aldol reactions.<sup>[4]</sup> Since the initial studies by Mukaiyama on the TiCl<sub>4</sub>-mediated addition of silvl enolates to aldehydes, many Lewis acid catalysts have been reported to mediate this C-C bond-forming reaction. Some of the Lewis acids used include BF3. OEt2, SnCl4, Sn(OTf)<sub>2</sub>, Yb(OTf)<sub>3</sub>, and silyl triflates. Yet, moisture sensitivity of these catalysts and the high cost of some of them often restrain their use. In addition, most of the reported reactions involved the use of the Lewis acid in large amounts or even in stoichiometric amount.<sup>[2d]</sup>

The identification of new efficient and green catalysts is an essential concern nowadays. The pioneering work by Olah into Friedel–Crafts reactions identified gallium triflate as a strong Lewis acid.<sup>[5]</sup> Since then, Ga(OTf)<sub>3</sub> has been used for numerous organic transformations and is now considered a key catalyst for the development of sustainable synthetic processes.<sup>[6]</sup> Following our studies involving green Lewis acids derived from main group metals,<sup>[7]</sup> we want to disclose our results with the use of low loadings of ketones in yields up to 92 %. To the best of our knowledge, this is the first report of a metal triflate acting as a safe, bench-stable, and slow-releasing source of triflic acid for the Mukaiyama aldol reaction.

 $Ga(OTf)_3$  for an efficient and diastereoselective Mukaiyama aldol reaction. An asymmetric version of this reaction was already described by using a high catalyst loading of  $Ga(OTf)_3$  (20 mol-%).<sup>[8]</sup> Considering the importance of catalytic processes nowadays, there was clearly a need to develop new efficient methods with the use of a much lower amount of catalyst.

## **Results and Discussion**

Our initial studies began with the model coupling of benzaldehyde (2a) with propiophenone-derived silvl enol ether 1 by using a catalytic amount of  $Ga(OTf)_3$  (Table 1). First, we screened various solvents at room temperature with the use of 1 mol-% catalyst (Table 1, entries 1–6). The use of acetonitrile or dichloromethane as the solvent allowed the formation of desired  $\beta$ -hydroxy ketone 3a in excellent yields but with low diastereoselectivities after a short reaction time (Table 1, entries 1 and 2). Upon conducting the reaction in diethyl ether or 2-methyltetrahydrofuran, low yields of aldol product 3a were obtained as a result of partial hydrolysis of silvl enol ether 1 and the formation of byproducts such as ethers and acetals (Table 1, entries 3 and 4).<sup>[9]</sup> In a protic solvent or under aqueous conditions, silyl enol ether 1 was rapidly hydrolyzed into propiophenone, and only a trace amount of the product was observed (Table 1, entries 5 and 6; DME = 1,2-dimethoxyethane). Indeed, triflic acid is known to be easily generated from Ga(OTf)<sub>3</sub> in water, and the amount of HOTf released in the media causes rapid decomposition of the silvl enol ether.<sup>[8,10]</sup> The high reactivity observed at 22 °C in either acetonitrile or dichloromethane meant the reaction temperature could be lowered in these solvents (Table 1, entries 7 and 8), which led to an improvement in the diastereoselectivity (Table 1, entry 8).



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Table 1. Optimization of reaction conditions – solvent and temperature. $^{[a]}$ 

Table 3. Catalytic diastereoselective Mukaiyama aldol reaction – aldehyde  $scope^{[a]}$ 

Ph + Ph H		1) Ga(OTf) <sub>3</sub> (1.0 mol-%) solvent, temperature 2) 1 м аq. HCl/THF, 22 °C Рг			O OH Ph	
1	2a				3a	
Entry	Solvent	Temp. [°C]	Time [h]	syn/anti <sup>[b]</sup>	Yield [%]	
1	MeCN	22	1	56:44	90	
2	$CH_2Cl_2$	22	1	57:43	95	
3	Et <sub>2</sub> O	22	24	54:46	42	
4	2-MeTHF	22	24	40:60	30	
5	EtOH	22	0.5	_	_	
6	DME/H <sub>2</sub> O (4:1)	22	1	_	_	
7	MeCN	-40	1.5	55:45	90	
8	$CH_2Cl_2$	-78	3	70:30	92	

[a] Silyl enol ether (1.5 equiv.), benzaldehyde (1 equiv.). [b] Determined by analysis of the crude material by <sup>1</sup>H NMR spectroscopy.

The loading of  $Ga(OTf)_3$  was then examined under the best reaction conditions, that is, by using  $CH_2Cl_2$  at -78 °C (Table 2). Decreasing the loading to 0.2 or 0.1 mol-% did not greatly affect the reaction time, but good yields were maintained (Table 2, entries 2 and 3). Moreover, the diastereoselectivity was significantly improved up to 85:15 (Table 2, entry 2). Even with a very low catalyst loading of 0.01 mol-%, a very good yield could be obtained, albeit with an extended reaction time (Table 2, entry 4).

Table 2. Optimization of reaction conditions - catalyst loading.<sup>[a]</sup>

OSiMe <sub>3</sub>	+ Ph H	1) Ga(OTf) <sub>3</sub> (x m CH <sub>2</sub> Cl <sub>2</sub> , –78 ° 2) 1 м аq. HCl/Tl	nol-%) C HF, 22 °C Ph <sup>^</sup>	O OH
1	2a			3a
Entry	Ga(OTf) <sub>3</sub> load [mol-%]	ling Time [h]	syn/anti <sup>[b]</sup>	Yield [%]
1	1	3	70:30	92
2	0.2	4	85:15	80
3	0.1	4	83:17	79
4	0.01	30	70:30	90

[a] Silyl enol ether (1.5 equiv.), benzaldehyde (1 equiv.). [b] Determined by analysis of the crude material by <sup>1</sup>H NMR spectroscopy.

From a practical point of view-mainly in terms of shorter reaction times -0.2 mol-% Ga(OTf)<sub>3</sub> was kept as the optimal catalyst loading, and a wide range of aldehydes were tested in the Mukaiyama aldol reaction with propiophenone-derived silyl enol ether 1 (Table 3). In rare cases, if reactivity problems were encountered, the temperature and/or the catalyst loading were/was consequently adjusted.

Differently substituted benzaldehydes reacted smoothly and delivered the products in good yields with good selectivities (Table 3, entries 1–12). For *para*-substituted benzaldehydes, yields ranging from 76 to 83% were obtained at -78 °C, along with good diastereoselectivities (73:27 to 85:15; Table 3, entries 1–6). A very good yield of 87% was also obtained with less-reactive 4-nitrobenzaldehyde; the low diastereoselectivity was probably due to the increased

	OSiMe <sub>3</sub>	+	1) Ga(OTf) <sub>3</sub> (0.2 mol-%) CH <sub>2</sub> Cl <sub>2</sub> , –78 °C		o L	OH	
Ph	$\sim$	R <sup>h</sup>	2) 1 м aq. HCl/THF, 22 °C			Ph' Y	R
	1	2				3	
	Entry	Aldehyde	R	Product	syn/anti <sup>[b]</sup>	Yield [%]	
	1		Н	3a	85:15	80	
	2		4-Me	3b	80:20	76	
	3		4-MeO	3c	_[c]	_[c]	
	4		4-F	3d	77:23	83	
	5	Ŷ	4-Cl	3e	73:27	76	
	6		4-Br	3f	76:24	79	
	7 <sup>[d]</sup>		$4-NO_2$	3g	53:47	87	
	8	R	2-F	3h	48:52	82	
	9		2-Cl	3i	19:81	74	
	10		2-Br	3j	18:82	76	
	11		$2-NO_2$	3k	27:73	83	
	12		$2-CF_3$	31	17:83	92	
		Ŷ					
	13	Т		3m	70:30	89	
		~~~0					
	14			3n	82.18	66	
	14			511	02.10	00	
	15	Ŷ	Ph	30	58:42	62	
	16		$C_{5}H_{11}$	3p	55:45	90	
	17	R	SiMe <sub>3</sub>	3a	59:41	72	
		0 0					
	18	<u>о</u> Н		3r	87:13	56	
		Ŷ					
	19 <sup>[d]</sup>	,s, Ц		3s	76:24	38	
	a o[e]	P				~	
	2014	~~~н		3t	72:28	64	
		о О					
	21 <sup>[d]</sup>			311	75.25	28	
	21			Ju	15.25	20	
		$\sim$					
		, Υ		2	06.4	10	
	2201	У_н		3V	96:4	46	

[a] Silyl enol ether (1.5 equiv.), benzaldehyde (1 equiv.),  $CH_2Cl_2$ , -78 °C, 4–192 h. [b] Determined by analysis of the crude material by <sup>1</sup>H NMR spectroscopy. [c] Complex mixture of aldol products and byproducts. [d] Ga(OTf)<sub>3</sub> (1 mol-%), 0 °C. [e] Ga(OTf)<sub>3</sub> (0.2 mol-%), 0 °C.

catalyst loading and reaction temperature (Table 3, entry 7). However, upon using an aldehyde bearing a strong electrondonating group, such as 4-methoxybenzaldehyde, a complex mixture of aldol products and byproducts was obtained, which rendered purification very difficult (Table 3, entry 3). Notably, reverse selectivity was observed with *ortho*-substituted benzaldehydes (Table 3, entries 8–12). Although similar chemical yields were obtained (74 to 92%), the *anti* isomers were formed as the major products.

The reaction proceeded smoothly with 2-naphthylcarboxaldehyde, and the product was isolated in very good yield with good diastereoselectivity (Table 3, entry 13). Conjugated aldehydes such as cinnamaldehyde (Table 3, entry 14) and acetylenic aldehydes (Table 3, entries 15–17) provided the corresponding aldol products in moderate to good yields, though low diastereoselectivities were recorded in the series of acetylenic aldehydes. Our method was further extended to heteroaromatic aldehydes, which gave the aldol products with good diastereoselectivities but in poor chemical yields (Table 3, entries 18 and 19). For aliphatic aldehydes, the corresponding aldol products were obtained with good diastereoselectivities but in low yields owing to incomplete conversion to the products (Table 3, entries 20–22).

Our reaction conditions were then applied to silyl enolates **4–9** (Table 4). Acetophenone-derived silyl enol ether reacted smoothly under the standard conditions to afford the corresponding aldol product in high yield (Table 4, entry 1). Low selectivities were obtained with cyclohexanone- and 3pentanone-derived silyl enol ethers, but the corresponding  $\beta$ -hydroxy ketones were nevertheless isolated in moderate to good yields (Table 4, entries 2 and 3). (*O,O*)- and (*O,S*)-Silyl ketene acetals were also suitable substrates for the reaction, which furnished the corresponding ester and thioester products in good yields (Table 4, entries 4 and 5). Finally, a vinylogous Mukaiyama aldol reaction<sup>[7c,11]</sup> was successfully carried out. It proceeded exclusively through  $\gamma$ -addition, and the corresponding vinylogous aldol was obtained in good yield (Table 4, entry 6).

Table 4. Catalytic diastereoselective Mukaiyama aldol reaction – silyl enolate scope.  $\ensuremath{^{[a]}}$ 



[a] Silyl enol ether (1.5 equiv.), benzaldehyde (1 equiv.). [b] Determined by analysis of the crude material by <sup>1</sup>H NMR spectroscopy. [c]  $Ga(OTf)_3$  (0.2 mol-%), -78 °C. [d]  $Ga(OTf)_3$  (1.0 mol-%), -78 °C. [e]  $Ga(OTf)_3$  (1.0 mol-%), 0 °C. [f]  $Ga(OTf)_3$  (0.2 mol-%), -45 °C.

Given that  $Ga(OTf)_3$  is known to be easily hydrolyzed, which leads to the release of triflic acid into the medium,

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we cannot rule out that HOTf is the actual catalytic species involved in the process. To discriminate between these two possible reaction pathways, the aldol reaction was carried out in the presence of 2,6-di(*tert*-butyl)pyridine (DTBP), which is known to inhibit any potential Brønsted acid catalysis.<sup>[12]</sup> Under our reaction conditions with the use of DTBP [silyl enol ether 1 (1.5 equiv.), benzaldehyde (2a, 1.0 equiv.),  $Ga(OTf)_3$  (0.2 mol-%), DTBP (0.6 mol-%), -78 °C, 4 h], the aldol reaction was completely inhibited (complete recovery of the starting materials). Additional control experiments were performed with triflic acid. Upon using 0.6 mol-% HOTf, only byproducts were formed and no trace amount of desired  $\beta$ -hydroxy ketone **3a** was observed. Lowering the catalyst loading of HOTf to 0.2, 0.1, and 0.01 mol-% resulted in the formation of small amounts of aldol product 3a (20-40% yield), along with the same byproducts. Upon using 0.001 mol-% HOTf, no reaction occurred. Furthermore, TMSOTf, which could be generated by the protodesilylation of the silyl enol ether,<sup>[13]</sup> provided the aldol adduct in the same low yield as that provided with HOTf. All these results suggest that a Brønsted acid is clearly involved in the process. However, the observation that the yield of the HOTf-catalyzed reaction is lower than that of the Ga(OTf)<sub>3</sub>-catalyzed process suggests that a gallium(III) salt is likely to be involved to some extent as a Lewis acid as well. Probably, Brønsted acid activation of the Lewis acid occurs.<sup>[14]</sup> Moreover, the concentration of HOTf in the reaction medium seems crucial. We assume that the slow release of HOTf from the hydrolysis of Ga(OTf)<sub>3</sub> is the sine qua non condition for the reaction to proceed in good yields. Even if CH<sub>2</sub>Cl<sub>2</sub> was systematically freshly distilled from CaH<sub>2</sub>, the residual water content<sup>[15]</sup> slowly hydrolyzed Ga(OTf)<sub>3</sub> into HOTf. Interestingly, if the model reaction was carried out in the presence of 4 Å molecular sieves,<sup>[16]</sup> the reaction was completely inhibited and the starting materials were quantitatively recovered. This result lends further support to the argument that slow hydrolysis of Ga(OTf)<sub>3</sub> is essential to the success of this aldol reaction.

#### Conclusions

In conclusion, we have developed an efficient process that allows formation of aldol products under mild conditions with a very low catalyst loading of  $Ga(OTf)_3$ . A wide range of substrates can be used in this diastereoselective Mukaiyama aldol reaction. To the best of our knowledge, this is the first example of a metal triflate acting as a safe and stable slow-releasing source of triflic acid to be reported for the Mukaiyama aldol reaction. HOTf is not bench stable, and special care is needed to handle this strong acid. In contrast,  $Ga(OTf)_3$  is a stable white solid that can be easily weighed. Although only moderate stereoselectivities were obtained,  $Ga(OTf)_3$  was demonstrated to be very efficient to get the Mukaiyama aldol reaction to proceed by using only very low catalyst loadings (down to 0.01 mol-%). Moreover, both  $Ga(OTf)_3$  and HOTf have

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never been extensively used as a catalyst for the Mukaiyama aldol reaction,<sup>[17]</sup> which renders our methodology innovative. Beyond the fact that Ga(OTf)<sub>3</sub> acts as a HOTf surrogate, it also surpasses it in terms of efficiency and cleanliness of the reaction,<sup>[18]</sup> presumably because of its involvement to some extent as a Lewis acid. Other applications in synthesis will be reported in due course.

## **Experimental Section**

General Information: All reactions were performed in flame-dried  $12 \times 75$  mm culture tubes under an atmosphere of nitrogen or argon. Dichloromethane (CH2Cl2) was distilled from CaH2. Solid aldehydes were used as received and liquid aldehydes were distilled prior to use. Gallium(III) triflate was purchased from Strem Chemical. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded with a 400 MHz spectrometer in CDCl<sub>3</sub>. For <sup>1</sup>H NMR (400 MHz), tetramethylsilane served as an internal standard ( $\delta = 0$  ppm) and data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad), coupling constant, and integration. For <sup>13</sup>C NMR (100 MHz),  $CDCl_3$  was used as internal standard ( $\delta = 77.23$  ppm) and spectra were obtained with complete proton decoupling. IR spectra were recorded with a FTIR spectrometer with ZnSe ATR accessory. High-resolution mass spectra (HRMS) were recorded with an ESI TOF mass spectrometer. Flash column chromatography was performed on silica gel (230-400 mesh), and analytical thin-layer chromatography was carried out by using 250 µm commercial silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance and/or aqueous potassium permanganate

Typical Procedure for the Gallium Triflate Catalyzed Mukaiyama Aldol Reaction: A mixture of Ga(OTf)<sub>3</sub> (0.2–1.0 mol-%) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was cooled to -78 °C. Aldehyde (1 mmol) and silvl enol ether (1.5 mmol) were subsequently added to the mixture. The reaction mixture was stirred at the same temperature until the aldehyde was completely consumed (monitored by TLC). The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (5 mL). The resulting mixture was extracted with diethyl ether  $(3 \times 10 \text{ mL})$ , and the combined organic layer was dried with MgSO<sub>4</sub>. The solvents were evaporated under reduced pressure (rotary evaporator). The crude product was dissolved in THF (1.5 mL) and 1 M HCl (0.75 mL) was added. The mixture was stirred for 15-30 min and then quenched and extracted as mentioned above. The product was purified by chromatography on silica gel (hexane/ethyl acetate). The syn/anti ratio was determined by <sup>1</sup>H NMR spectroscopy. The diastereoisomers of products 3h-l, 11, and 15 were separated by silica gel flash column chromatography.

**3-(2-Fluorophenyl)-3-hydroxy-2-methyl-1-phenylpropan-1-one** (3h): Colorless oil, yield 211.8 mg (82%). Reaction time = 8 h.  $R_f$  (hexane/AcOEt = 4:1) = 0.51 (*syn*), 0.41 (*anti*). IR (neat):  $\tilde{v}$  = 3488, 3446, 2972, 1917, 1674, 1595, 1455, 1219, 1001, 969, 828, 659 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *syn*-**3h**):  $\delta$  = 1.15 (d, J = 7.3 Hz, 3 H), 3.84 (dq, J = 7.3, 2.0 Hz, 1 H), 3.89 (br. s, 1 H), 5.54 (d, J = 2.0 Hz, 1 H), 7.00–7.08 (m, 1 H), 7.14–7.22 (m, 1 H), 7.22–7.31 (m, 1 H), 7.44–7.54 (m, 2 H), 7.56–7.68 (m, 2 H), 7.95–8.04 (m, 2 H) ppm. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *anti*-**3h**):  $\delta$  = 1.16 (d, J = 7.2 Hz, 3 H), 3.62 (d, J = 6.2 Hz, 1 H), 3.95 (dq, J = 7.2, 7.2 Hz, 1 H), 5.34 (dd, J = 7.2, 6.2 Hz, 1 H), 6.97–7.06 (m, 1 H), 7.09–7.17 (m, 1 H), 7.19–7.28 (m, 1 H), 7.39–7.47 (m, 2 H), 7.47–7.58 (m, 2 H), 7.90–7.98 (m, 2 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, *syn* + *anti*):  $\delta = 10.9$ , 15.7, 44.9, 47.0, 67.8 (d, J = 1.7 Hz), 70.8 (d, J = 1.8 Hz), 115.2 (d, J = 21.4 Hz), 115.5 (d, J = 22.0 Hz), 124.4 (d, J = 3.5 Hz), 124.6 (d, J = 3.4 Hz), 128.5 (d, J = 4.4 Hz), 128.6 (d, J = 4.3 Hz), 128.7, 128.8, 128.9, 129.0 (d, J = 8.3 Hz), 129.0 (d, J = 12.9 Hz), 129.1, 129.4 (d, J = 8.3 Hz), 129.6 (d, J = 13.5 Hz), 133.7, 133.9, 135.8, 136.7, 159.4 (d, J = 244.5 Hz), 160.2 (d, J = 245.4 Hz), 205.2, 206.0 ppm. HRMS (ESI-TOF): calcd. for  $C_{16}H_{15}FNaO_2^+$  [M + Na]<sup>+</sup> 281.0948; found 281.0948.

3-(2-Bromophenyl)-3-hydroxy-2-methyl-1-phenylpropan-1-one (3i): Colorless oil, white solid (m.p. 90-95 °C), yield 242.5 mg (76%). Reaction time = 5 h.  $R_f$  (hexane/AcOEt = 4:1) = 0.64 (syn), 0.47 (anti). IR (neat):  $\tilde{v} = 3506, 3485, 2982, 1960, 1819, 1662, 1592,$ 1468, 1370, 1214, 917, 681 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, syn-**3j**):  $\delta$  = 1.11 (d, J = 7.3 Hz, 3 H), 3.98 (dq, J = 7.3, 1.4 Hz, 1 H), 4.10 (d, J = 1.4 Hz, 1 H), 5.51 (dd, J = 1.4, 1.4 Hz, 1 H), 7.13–7.21 (m, 1 H), 7.35-7.42 (m, 1 H), 7.47-7.58 (m, 3 H), 7.59-7.65 (m, 1 H), 7.67–7.72 (m, 1 H), 8.00–8.07 (m, 2 H) ppm. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *anti-***3j**):  $\delta$  = 1.31 (d, *J* = 7.2 Hz, 3 H), 3.96 (br. s, 1 H), 4.06 (dq, J = 7.2, 6.0 Hz, 1 H), 5.38 (d, J = 6.0 Hz, 1 H), 7.04-7.11 (m, 1 H), 7.23-7.30 (m, 1 H), 7.37-7.44 (m, 2 H), 7.46-7.56 (m, 3 H), 7.81–7.87 (m, 2 H) ppm. <sup>13</sup>C NMR (100 MHz,  $CDCl_3$ , syn + anti):  $\delta = 10.6$ , 16.1, 43.1, 45.8, 72.0, 75.5, 121.5, 122.6, 127.6, 128.0, 128.5, 128.6, 128.9, 128.9, 129.1, 129.1, 129.3, 129.3, 132.9, 132.9, 133.7, 134.1, 135.7, 136.7, 140.3, 141.8, 205.7, 206.9 ppm. HRMS (ESI-TOF): calcd. for  $C_{16}H_{15}BrNaO_2^+$  [M + Na]<sup>+</sup> 341.0148; found 341.0151.

3-Hydroxy-2-methyl-3-(2-nitrophenyl)-1-phenylpropan-1-one (3k): Orange oil and yellow crystals (m.p. 94-99 °C), yield 237.2 mg (83%). Reaction time = 120 h.  $R_{\rm f}$  (hexane/AcOEt = 4:1) = 0.32 (syn), 0.21 (anti). IR (neat):  $\tilde{v} = 3477, 3380, 2978, 2855, 2359, 1682,$ 1519, 1160, 1000, 883, 703, 681 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *syn*-3k):  $\delta$  = 1.17 (d, J = 7.3 Hz, 3 H), 4.01 (dq, J = 7.3, 1.8 Hz, 1 H), 4.24 (br. s, 1 H), 5.80 (d, J = 1.8 Hz, 1 H), 7.42–7.53 (m, 3 H), 7.57-7.64 (m, 1 H), 7.65-7.72 (m, 1 H), 7.94-8.07 (m, 4 H) ppm. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *anti*-**3**k):  $\delta$  = 1.34 (d, J = 7.2 Hz, 3 H), 4.09 (dq, J = 7.2, 5.3 Hz, 1 H), 4.43 (br. s, 1 H), 5.55 (d, J = 5.3 Hz, 1 H), 7.32–7.43 (m, 3 H), 7.50–7.57 (m, 2 H), 7.67–7.71 (m, 1 H), 7.79-7.89 (m, 3 H) ppm. 13C NMR (100 MHz, CDCl<sub>3</sub>, syn + anti):  $\delta = 11.2, 16.6, 44.3, 45.6, 68.9, 72.5, 124.7, 125.0, 128.5,$ 128.6, 128.6, 128.9, 129.0, 129.1, 129.2, 129.9, 133.5, 133.6, 134.0, 134.1, 135.6, 136.5, 137.3, 138.2, 147.5, 148.4, 205.7, 206.6 ppm. HRMS (ESI-TOF): calcd. for  $C_{16}H_{16}NO_4^+$  [M + H]<sup>+</sup> 286.1074; found 286.1075.

3-Hydroxy-2-methyl-1-phenyl-3-[2-(trifluoromethyl)phenyl|propan-1-one (31): White solids [m.p. 30-35 (syn), 90-95 °C (anti)], yield 286.0 mg (92%). Reaction time = 48.5 h.  $R_{\rm f}$  (hexane/AcOEt = 4:1) = 0.53 (syn), 0.39 (anti). IR (neat):  $\tilde{v}$  = 3463, 3420, 2987, 2976, 1975, 1849, 1667, 1597, 992, 867, 772, 684 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, syn-3l):  $\delta = 1.20$  (d, J = 7.3 Hz, 3 H), 3.74 (dq, J = 7.3, 1.2 Hz, 1 H), 4.13 (d, J = 1.2 Hz, 1 H), 5.67 (dd, J = 1.2, 1.2 Hz, 1 H), 7.39–7.45 (m, 1 H), 7.46–7.53 (m, 2 H), 7.58–7.65 (m, 2 H), 7.65–7.71 (m, 1 H), 7.89–7.98 (m, 3 H) ppm. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *anti-3*I):  $\delta$  = 1.08 (d, J = 7.3 Hz, 3 H), 3.60 (d, *J* = 5.6 Hz, 1 H), 3.97 (dq, *J* = 7.3, 6.0 Hz, 1 H), 5.53 (dd, *J* = 6.0, 5.6 Hz, 1 H), 7.34–7.41 (m, 1 H), 7.41–7.48 (m, 2 H), 7.52–7.59 (m, 2 H), 7.63-7.68 (m, 1 H), 7.73-7.79 (m, 1 H), 7.90-7.97 (m, 2 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, *syn* + *anti*):  $\delta$  = 10.6, 15.9, 45.0, 47.8, 68.6 (q, J = 1.8 Hz), 71.6 (q, J = 2.2 Hz), 124.6 (q, J = 273.5 Hz), 124.8 (q, J = 274.0 Hz), 125.9 (q, J = 5.9 Hz), 126.2 (q, J = 5.9 Hz), 126.7 (q, J = 30.0 Hz), 127.8, 128.1 (q, J = 29.9 Hz), 128.1, 128.5, 128.6, 128.8, 128.9, 129.1, 129.3, 132.0, 132.6, 133.7, 134.1, 135.5, 136.8, 140.1 (q, J = 1.2 Hz), 141.4 (q, J = 1.2 Hz),

204.9, 206.8 ppm. HRMS (ESI-TOF): calcd. for  $C_{17}H_{16}F_3O_2{}^+$  [M + H]^+ 309.1097; found 309.1095.

**3-Hydroxy-2-methyl-1-phenyl-5-(trimethylsilyl)pent-4-yn-1-one (3q):** Colorless oil, yield 188.0 mg (72%). Reaction time = 192 h.  $R_{\rm f}$  (hexane/AcOEt = 4:1) = 0.45 (*syn*), 0.40 (*anti*). IR (neat):  $\tilde{v}$  = 3445, 2960, 2174, 1678, 1596, 1448, 1372, 1249, 967, 838, 706, 686 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *syn*-**3q**):  $\delta$  = 0.12 (s, 9 H), 1.41 (d, J = 7.2 Hz, 3 H), 3.21 (br. s, 1 H), 3.68 (dq, J = 7.2, 4.2 Hz, 1 H), 4.82 (d, J = 4.2 Hz, 1 H), 7.43–7.52 (m, 2 H), 7.55–7.62 (m, 1 H), 7.91–8.01 (m, 2 H) ppm. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *anti*-**3q**):  $\delta$  = 0.13 (s, 9 H), 1.31 (d, J = 7.2 Hz, 3 H), 3.12 (br. s, 1 H), 3.77 (dq, J = 7.5, 7.2 Hz, 1 H), 4.70 (d, J = 7.5 Hz, 1 H), 7.43–7.52 (m, 2 H), 7.55–7.62 (m, 1 H), 7.91–8.01 (m, 2 H) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, *syn* + *anti*):  $\delta$  = 0.0, 0.0, 12.8, 15.7, 46.5, 47.1, 63.9, 65.3, 90.5, 91.1, 104.5, 105.1, 128.7, 128.8, 128.9, 129.0, 133.7, 133.8, 136.0, 136.6, 203.9, 204.2 ppm. HRMS (ESI-TOF): calcd. for C<sub>15</sub>H<sub>21</sub>O<sub>2</sub>Si<sup>+</sup> [M + H]<sup>+</sup> 261.1305; found 261.1303.

**Supporting Information** (see footnote on the first page of this article): Copies of the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra and characterization data for all compounds.

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- [16] Freshly distilled CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred over activated 4 Å molecular sieves (50 mg) for 1 h. The resulting mixture was then transferred under an atmosphere of nitrogen into the reaction test tube containing Ga(OTf)<sub>3</sub>. After cooling down to -78 °C, the reagents were successively added.
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- [18] If 0.01 mol-% of Ga(OTf)<sub>3</sub> was used, an excellent yield of **3a** was obtained (t = 30 h, *synlanti* = 70:30, yield 90%), whereas HOTf only afforded low yields of the aldol product.

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