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Highly Enantioselective Organocatalytic Trifluoromethyl Carbinol Synthesis—A Caveat on Reaction Times and Product Isolation

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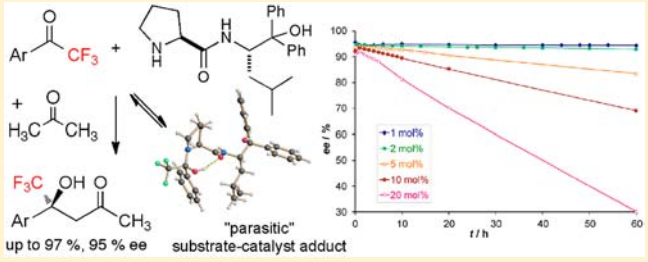
Supporting Information

ABSTRACT: Aldol reactions with trifluoroacetophenones as acceptors yield chiral α-aryl, α-trifluoromethyl tertiary alcohols, valuable intermediates in organic synthesis. Of the various organocatalysts examined, Singh's catalyst [(2*S*)-*N*-[(1*S*)-1-hydroxydiphenylmethyl-3-methylbutyl]-2-pyrrolidinecarboxamide] was found to efficiently promote this organocatalytic transformation in a highly enantioselective manner. Detailed reaction monitoring (^{19}F-NMR, HPLC) showed that, up to full conversion, the catalytic transformation proceeds under kinetic control and affords up to 95% ee in a time-independent manner. At longer reaction times, the catalyst effects racemization. For the product aldols, even weak acids (such as ammonium chloride) or protic solvents, can induce racemization, too. Thus, acid-free workup, at carefully chosen reaction time, is crucial for the isolation of the aldols in high (and stable) enantiomeric purity. As evidenced by ^{19}F-NMR, X-ray structural analysis, and independent synthesis of a stable intramolecular variant, Singh's catalyst reversibly forms a catalytically inactive ("parasitic") intermediate, namely a *N*,*O*-hemiacetal with trifluoroacetophenones. X-ray crystallography also allowed the determination of the product aldols' absolute configuration (*S*).



1. INTRODUCTION

Organofluorine compounds are of ever increasing importance as pharmaceuticals, agrochemicals, functional materials, or catalysts.[1] This development calls for a new synthetic methodology for the stereoselective introduction of fluorine or fluorine containing substructures. Over the past decade, organocatalysis has emerged as a highly efficient synthetic tool for enantioselective transformations.[2] Among those, the asymmetric organocatalytic aldol reaction still serves as one of the most powerful carbon−carbon bond forming methods, providing access to β-hydroxycarbonyl compounds in an enantioselective fashion.[3] We recently reported that the enantioselective organocatalytic aldol addition of acetone to aldehydes can be combined, in a one-pot procedure, with the diastereoselective enzymatic reduction of the aldols' keto-function. As a result, all four stereoisomeric 1,3-diols can be produced at will, with diasteriomeric ratio (dr) typically >20:1 and virtually perfect enantiomeric purity (ee >98%; Scheme 1, top).[4] We are currently aiming at the development of a related approach providing chiral 1,3-diols carrying a trifluoromethyl substituent at the quaternary chiral center. In general, the switch from aldehydes to ketones as aldol acceptors still represents a challenge in organic synthesis, and accordingly, only few examples are known in this field. The focus of the work described herein was on the use of trifluoromethyl ketones **1** as electrophiles, which allows the preparation of chiral β-trifluoromethyl-β-hydroxy ketones of type **3** (Scheme 1, bottom) by aldol addition of acetone (**2**).

In this paper, we describe the development of a practical and highly enantioselective aldol reaction providing β-trifluoromethyl-β-hydroxy ketones of type **3** with up to 95% ee (and known absolute configuration). The development of the method hinges on our careful reaction analysis (revealing surprising effects of "standard" sample preparation protocols) and a detailed mechanistic study which, *inter alia*, identified a "parasitic" adduct formation between the organocatalyst and the trifluoromethyl ketone substrate.

A literature search for trifluoromethyl ketones as acceptors in asymmetric organocatalytic aldol reactions yielded only a few results. In 2005, Zhang and co-workers reported the first example of a proline-catalyzed asymmetric aldol addition of methyl ketones to aryl trifluoromethyl ketones, affording β-trifluoromethyl-β-hydroxy ketones in satisfactory yields, but with only moderate enantioselectivity of up to 64% ee.[5] A few years later, the use of L-proline bearing a bulky tris-

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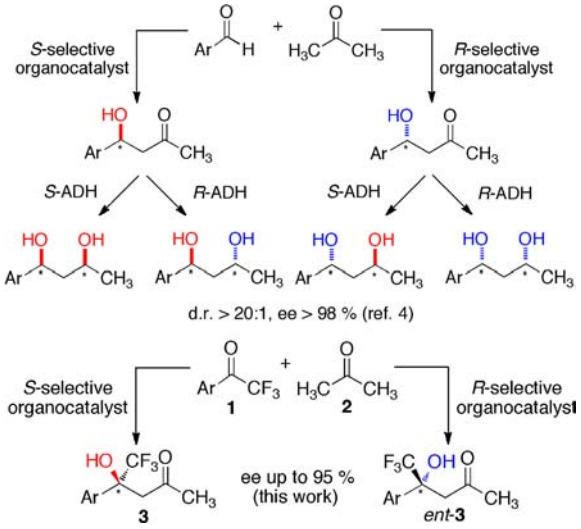
Scheme 1. (Top) Combined Organo- and Biocatalytic Reaction Sequence for the Synthesis of Chiral 1,3-Diols from Aldehydes (ref 4); (Bottom) Acetone (2) Addition to Trifluoroacetophenones 1 (This Paper), Affording *tert*-Aldols 3 with a CF_3-Group



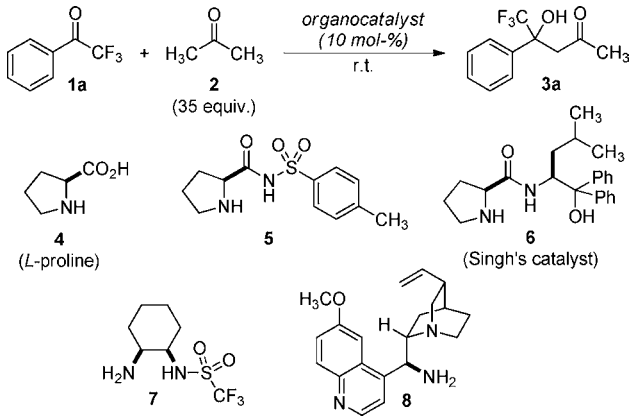
(trimethylsilyl)silyloxy group at position 4 of the pyrrolidine ring was described by Yuan and Zhang.[6] Here, α,β-unsaturated trifluoromethyl ketones acted as acceptor. With a catalyst loading of 5 mol % at −20 °C, the 1,2-addition of acetone proceeded to give the aldol adducts in good yield and up to 91% ee, albeit at long reaction times of 3−7 days. Very recently, in the course of our study, Nakamura et al. have developed an improved enantioselective aldol reaction of acetone with trihalomethyl ketones catalyzed by the TFA salt of *N*-(8-quinolinesulfonyl)prolinamide.[7] β-Trifluoromethyl-β-hydroxy ketones were obtained in good yields and with up to 90% enantiomeric excess, employing 10 mol % of the catalyst at −20 °C over 48 h. Absolute product configuration was not determined. For a practical process, a further increase in enantioselectivity, at low catalyst loading, short reaction time, and preferably at room temperature is desirable—in other words, improvement of *both* the catalyst activity and enantioselectivity. Herein, we describe the practical and highly enantioselective preparation of β-trifluoromethyl-β-hydroxy ketones **3** using readily accessible Singh's catalyst.[8,9] Detailed kinetic and spectroscopic analyses of this aldol reaction turned out to be the key to success and additionally identified reaction intermediates and a "parasitic" catalyst-substrate adduct.

2. RESULTS AND DISCUSSION

2.1. Catalyst Screening. Ideally, the aldol addition of acetone (**2**) to trifluoromethyl ketones such as trifluoroacetophenone (**1a**) should proceed at room temperature and without additional solvents. In our catalyst screening, the reaction was monitored by TLC and ^{19}F NMR, using 0.2 mmol of trifluoroacetophenone (**1a**) in an excess of acetone-d_6 (35 equiv) and in the presence of 10 mol % of the catalyst (relative to **1a**). The results are summarized in Table 1.

Among the catalysts tested, we identified the proline amide **6** ("Singh's catalyst") as the most effective one: the desired aldol adduct **3a** was obtained in excellent yield and with high enantioselectivity of 93% ee, over a period of only 3 h (entry 3).[10] Both proline (**4**) and the *N*-tosylated proline amide **5**[11]

Table 1. Aldol Addition of Acetone (2, Reagent/Solvent) to 2,2,2-Trifluoroacetophenone (1a) to Afford 3a in the Presence of 10 mol % of Various Catalysts



entry	catalyst	additive (10 mol %)	time (h)	conversion (%)[a]	ee **3a** (%)[b]
1	**4**		3	quant	36
2[c]	**5**		6	quant	60
3[c]	**6**		3	quant	93
4	**7**		168	80	5
5	**8**		168	57	3
6	**8**	TFA	168	65	2
7	**8**	TfOH	168	70	2

[a]Conversion was determined by ^{19}F NMR of the reaction mixture. [b]The reaction mixture was quenched with sat. NH_4Cl before analysis, and the ee of product **3a** was determined by HPLC using a Daicel Chiralcel OD-H column. [c]The reaction was performed in a NMR tube and directly monitored by ^{19}F NMR.

were catalytically highly active, too, and gave **3a** quantitatively in a short reaction time, albeit with much lower asymmetric induction compared to the case of **6** (entries 1 and 2). Chiral primary amine catalysts were also examined. With the *cis*-DACH-derived organocatalyst **7**[12] and 9-amino-9-deoxyepiquinine (**8**),[13] low catalytic activity and poor enantiocontrol were observed (entries 4 and 5). The slow conversion may be due to the sluggish generation of the enamine intermediate. We found that the addition of acid in combination with **8** accelerated the reaction, but the product enantiomeric excess remained negligible (entries 6 and 7).

In summary, compound **6** proved to be the catalyst of choice for promoting the enantioselective addition of acetone to trifluoroacetophenone (**1a**) at room temperature. As Singh's catalyst **6** has been shown to perform well in combined asymmetric organo- and biocatalytic reaction sequences (Scheme 1),[4] our current results open a perspective for the chemoenzymatic synthesis of 1,3-diols harboring a trifluoromethyl carbinol. This extension of our current work shall be addressed in future studies. A further advantage of organocatalyst **6** is that it can readily be prepared on large laboratory scale in a one-pot procedure, starting from cheap proline and the corresponding leucine ester.[9]

2.2. Kinetic Investigations on the Direct Aldol Addition of Acetone to 1a in the Presence of Catalyst 6. We have recently reported the significant influence of kinetic versus thermodynamic control on the enantioselectivity of the organocatalytic aldol reaction of acetone with 3-chlorobenzaldehyde in the presence of catalyst **6**.[4b] In that study, we found that, at 5 mol % catalyst loading, the reaction rapidly reached

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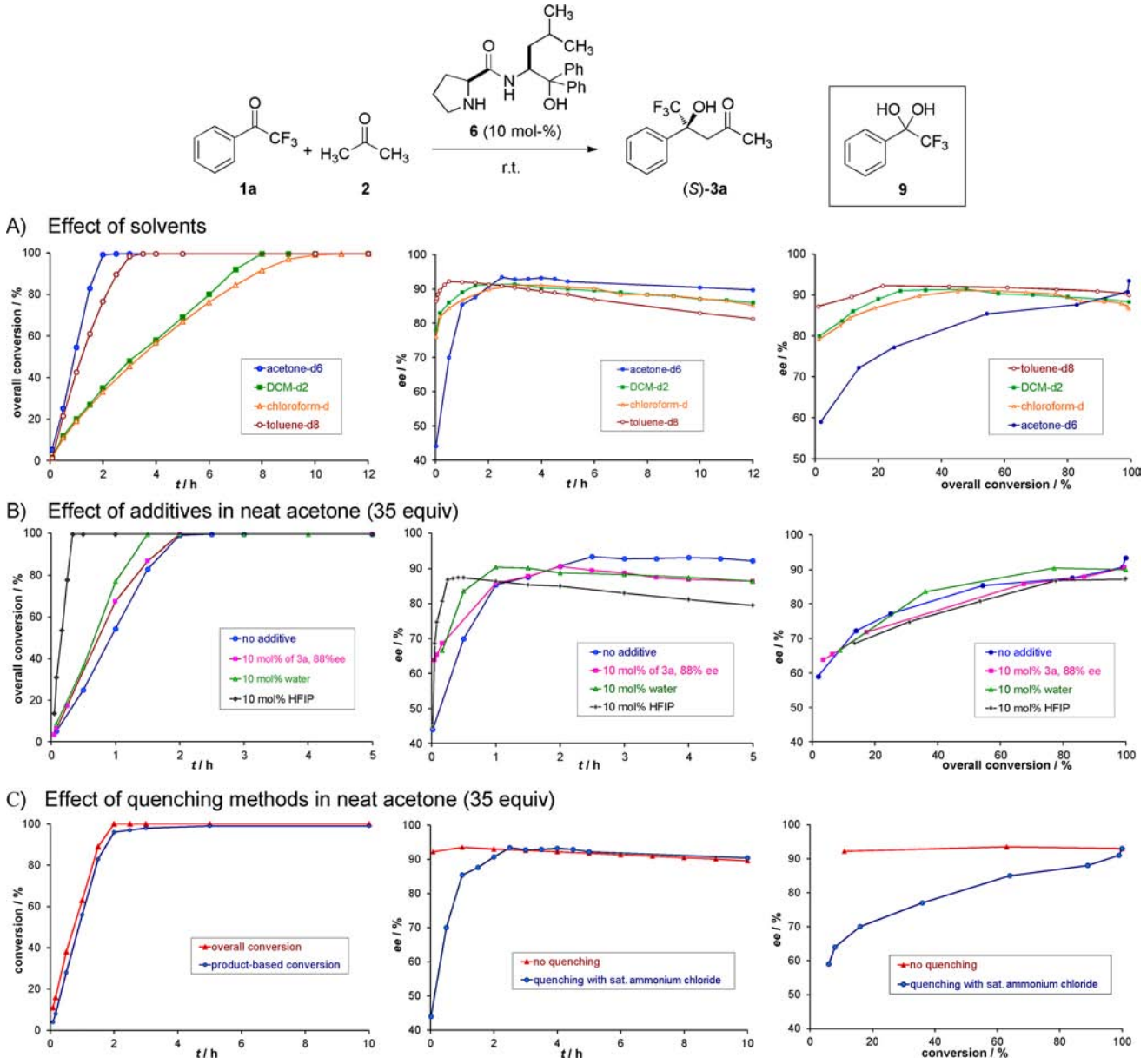

Figure 1. Kinetic investigations on the effect of solvents (A), of additives (B), and of quenching methods (C) on the aldol reaction of acetone to trifluoroacetophenone (**1a**) in the presence of 10 mol % of the catalyst **6**. For A and B, the reaction mixture was quenched with sat. NH_4Cl before HPLC analysis of the enantioselectivity.

equilibrium (<30 min), thus switching from kinetic to thermodynamic control, leading to a depletion in enantiomeric purity of the product. This earlier observation prompted us to investigate the formation of the aldol adduct **3a** and its enantiomeric excess as a function of time. For this purpose, the conversion of **1a** was monitored by in situ ^{19}F NMR. Additionally, the enantiomeric ratio of the product **3a**/*ent*-**3a** was determined by chiral HPLC, after a "mini workup" of aliquots of the reaction mixture. This mini workup consisted in quenching the sample with sat. NH_4Cl, and extraction of the product **3**/*ent*-**3** with Et_2O. Figure 1 summarizes the results: In the left column, the conversion of starting trifluoroacetophenone **1a** is plotted as a function of reaction time. In the middle column, the enantiomeric excess of the product aldol **3a** is given as a function of reaction time. The graphs in the right column depict the enantiomeric excess of the product **3a** as a function of conversion of the starting **1a**.

2.2.1. Effect of Solvents. Solvent effects on the addition of acetone to trifluoroacetophenone (**1a**) are summarized in the top row (A) of Figure 1. As indicated by the blue line, with 10 mol % of the catalyst **6** in neat acetone-d_6 (35 equiv), the reaction equilibrium was reached in ca. 2.5 h (quantitative conversion, 93% ee).[14] At extended reaction times, thermodynamic control results in a slow decrease of product enantiomeric excess. The most astonishing feature of the reaction course is, however, the *increasing* enantiomeric excess of the product **3a** in the initial phase of the reaction, i.e. over the course of the reaction under kinetic control (<2.5 h). Theoretically, one would have expected time-independent ee in this regime. This remarkable phenomenon was similarly observed when the reaction was run in other solvents, such as CD_2Cl_2, $CDCl_3$, or toluene-d_8 (10 equiv of acetone-d_6 were used in these cases). All reactions studied occurred in the homogeneous phase, except for the reaction in toluene-d_8, for

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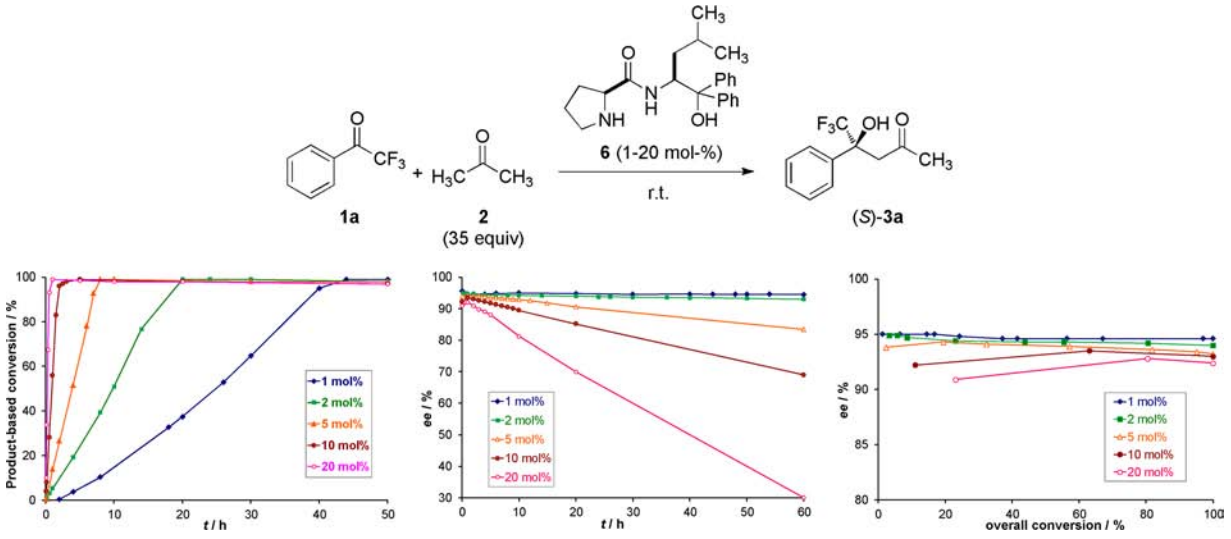

Figure 2. Effect of catalyst (**6**) loading on the aldol addition of acetone (**2**) to trifluoroacetophenone (**1a**), shown as relationships of product-based conversion vs time (left), the enantioselectivity vs time (middle), and the enantioselectivity vs conversion (right).

which we observed a slightly turbid solution. Consequently, enantioselective amplification based on phase behavior, such as solid-solute equilibria in certain amino acid mediated aldol reactions,[15] could be excluded.

In our search for an explanation for this unusual effect, we first considered and evaluated the possibility of a kinetically induced amplification,[16] via either an autocatalytic[17] or an autoinductive[18] process in which the reaction product itself acts as a catalyst or is involved in the formation of a more selective catalyst. By addition of the aldol product **3a** (90% ee) to the mixture of **1a** and acetone in the absence of the catalyst **6**, no (further) formation of the aldol adduct **3a** occurred. This indicates that the effect is not due to autocatalysis.

2.2.2. Effect of Additives [Middle Row (B) of Figure 1]. We next examined whether a catalyst-product adduct (**6**−**3a**) may form in the course of the reaction and may act as a "secondary" catalyst of higher enantioselectivity. When 10 mol % of **3a** (88% ee) was added, right at the beginning, to the reaction mixture containing 10 mol % of the catalyst **6**, the optical purity of the product **3a** still increased gradually [compare blue (no additive) and pink (with additive) lines in the middle row (B) of Figure 1]. This result excludes enantioselective autoinduction by the reaction product in this transformation.

In principle, a time course such as the blue line in Figure 1, middle row (B), could also be rationalized by a less selective catalyst (or racemization catalyst) being present at the onset of the reaction and being consumed/deactivated in the course of the reaction. We excluded this possibility by running our standard aldol reaction (in acetone-d_6) to completion and adding the substrate **1a** once again. No effect on the ee/time-course resulted (graph not shown).

It has been demonstrated that Singh's catalyst (**6**) is compatible with aqueous media;[4,8] in fact, water increases the rate and enantioselectivity of aldol reactions catalyzed by **6**.[8] We therefore investigated the effect of water as an additive in our reaction. Upon addition of water (10 mol %), the reaction became faster and reached completion within 1.5 h, at slightly decreased enantiopurity of the product [90% ee; Figure 1, row B; compare green and blue lines]. Note, however, that, in the presence of trifluoroacetophenone (**1a**), water in the reaction mixture is scavenged in the form of its hydrate, the *gem*-diol **9** (as evidenced by ^{19}F NMR analysis). As revealed by control experiments, this species accelerates the reaction but does not account for the observed increase in ee over time.[19] A similar effect was also observed when 10 mol % of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was added. In this case, conversion was complete within 20 min, while the enantiomeric excess decreased slightly to 87% *ee* [at complete conversion (Figure 1, row (B), black line]. It is evident from the graphs that HFIP, as a mildly acidic (pK_a 17.2 in DMSO)[20] additive, enhances the rate of the reaction in both the kinetic and thermodynamic regimes. For the latter, this corresponds to an increased rate of racemization. With this in mind, we turned to investigate the effect of the mildly acidic (NH_4Cl) aqueous workup.

2.2.3. Effect of Workup/Product Isolation. Typically, aliquots withdrawn from the reaction mixture were quenched with aqueous NH_4Cl prior to HPLC analysis. Alternatively, they were either diluted (1% *i*PrOH in *n*-hexane) and injected directly or filtered through a short pad of silica gel (same solvent mixture) prior to analysis. Figure 1, row C, summarizes the results (compare red and blue lines). Upon omission of the aqueous NH_4Cl quenching, the measured enantiomeric excess of the product **3a** (93% ee) becomes time independent; that is, the initial increase in ee has vanished. This clearly indicates that even the mildly acidic workup procedure previously used effected racemization of the aldol product **3a**, in particular at low conversion. When the reaction reaches equilibrium, the acidic quenching has much less or no influence on the enantiopurity of the product, as shown by the superposition of the blue and red lines (Figure 1, row C). Clearly, at low conversion, the substrate (i.e., aldol **3a**) to catalyst ratio is highest.[21] The above results raise an important caveat for the handling of β-hydroxyketones of type **3a** (and other organic reaction products), which are prone to racemization in the presence of traces of remaining catalyst and/or acids.

2.3. Effect of Catalyst Loadings. We furthermore investigated the effect of catalyst loading (**6**, 1−20 mol %) on the aldol addition to trifluoroacetophenone (**1a**) in acetone-d_6 ("no-quench" ee-analysis). The results are illustrated in Figure 2. As expected, increasing catalyst loading results in increased reaction rate. The initial rates are roughly propor-

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tional to the catalyst concentration; the reaction thus shows first order kinetics in catalyst. Higher catalyst concentrations at the same time effect an earlier onset of the thermodynamic regime, i.e. racemization. From a practical point of view, a catalyst loading of 1−2 mol % proved optimal, as the kinetic regime extended to at least 60 h, during which the product enantiomeric excess remained virtually unchanged (Figure 2, blue and green lines). In contrast, with catalyst loadings of 5−20 mol %, equilibrium was reached quickly [0.5, 3, and 8 h for catalyst loadings of 20, 10, and 5 mol %, respectively], after which the ee value gradually eroded. In summary, the best results with respect to yield, product enantiopurity, and reaction time were achieved with just 2 mol % of the catalyst **6**: the reaction was complete in 18 h to give a quantitative yield of the aldol **3a** with 94% ee. By lowering the catalyst loading to 1 mol %, the reaction took longer time for completion (up to 45 h), while there was no significant increase in enantiomeric excess (95% ee).

2.4. Characterization of a Substrate−Catalyst Adduct Formed in the Reaction of Acetone with Trifluoroacetophenone (1a) in the Presence of the Catalyst 6. In the course of in situ ^{19}F NMR monitoring of the reaction between **1a** and acetone, in the presence of the catalyst **6**, we noted the transient appearance of small resonances of unknown species at $\delta = -76.3$ and -77.2 ppm (Figure 3, highlighted by the green box) and even smaller peaks in the region of $\delta = -81$ and -82 ppm.

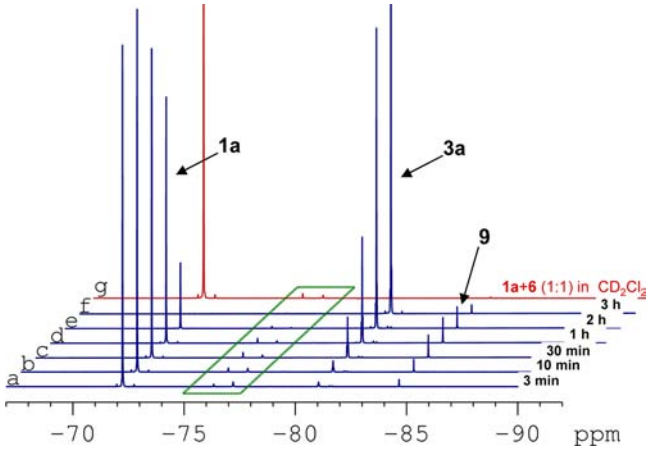
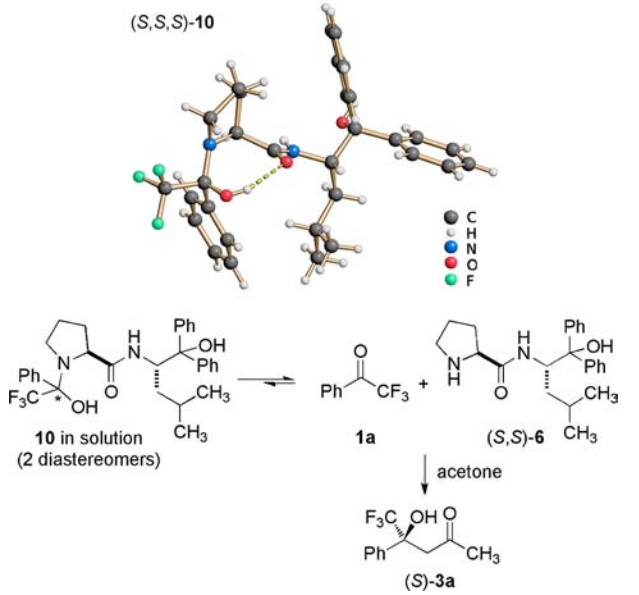


Figure 3. ^{19}F NMR spectra of the reaction mixture of **1a** and acetone-d_6 in the presence of 10 mol % of the catalyst **6** as a function of time (blue lines a−f) and of a 1:1 mixture of **1a** and **6** in CD_2Cl_2 (red line g).

These signals completely vanished when the reaction was complete (Figure 3, trace f). Clearly, the formation of these intermediates must originate from trifluoroacetophenone (**1a**), as it is the only source of ^{19}F. No signal in the above-mentioned regions was detected in the spectrum of **1a** alone in acetone-d_6. However, upon mixing **1a** and the catalyst **6** in a ratio of 1:1 in CD_2Cl_2, we could again observe two small peaks between $\delta = -76$ and -78 ppm (Figure 3, trace g). This suggests that the species giving rise to those resonances result from the interaction of trifluoroacetophenone (**1a**) with Singh's catalyst **6**.

To our delight, slow evaporation of a solution of **6** and **1a** (1:1) in DCM furnished crystals suitable for X-ray analysis. Thus, we were able to establish, for the first time, the molecular structure of the adduct (*S*,*S*,*S*)-**10** by X-ray diffraction analysis, as shown in Scheme 2. The carbinolamine **10** results from the

Scheme 2. X-ray Crystal Structure of (*S*,*S*,*S*)-10 (Top); in Solution, 10 Reverts to 1a and 6; Subsequent Reaction with Acetone Gives Rise to the Aldol Adduct 3a (Bottom)



nucleophilic addition of the pyrrolidine-NH of **6** to the carbonyl group of **1a**. In principle, two diastereomeric carbinolamines can result from the addition of **6** to **1a** [(*S*,*S*,*S*)-**10** and (*R*,*S*,*S*)-**10**]. The crystal structure of (*S*,*S*,*S*)-**10** indicates that there is an intramolecular hydrogen bond between the quaternary OH group and the carbonyl oxygen atom. This hydrogen bond may well account for the preferred crystallization of the (*S*,*S*,*S*)-diastereomer. Note that similar hydrogen bonding interactions have been invoked in the stabilization of tetrahedral carbinolamine intermediates formed in the early stages of the catalytic cycle of iminium−enamine catalysis, involving proline or derivatives thereof.[2c] To the best of our knowledge, **10** represents the first spectroscopically and X-ray crystallographically characterized catalyst−substrate adduct of this type.

^{19}F NMR analysis of (*S*,*S*,*S*)-**10** in toluene-d_8 shows two small peaks at $\delta = -76.4$ and -77.5 ppm, together with a large peak of trifluoroacetophenone (**1a**) at -72.2 ppm (Figure 4, trace b). Apparently in solution, the equilibrium of the reversible **1a**−**6** addition lies far on the side of dissociation. We assign the two weak resonances at $\delta = -76.4$ and -77.5 ppm to the two diastereomers of **10**. When acetone was used as solvent, the formation of the aldol adduct **3a** was additionally observed (Figure 4, trace c). In fact, the NMR spectrum obtained from dissolution of **10** in acetone-d_6 closely resembles that of the reaction mixture containing **1a** and a catalytic amount of **6** (Figure 4, compare traces c and a). Consequently, both diastereomers of intermediate **10** are formed, in small amount, from the reversible addition of the chiral amine catalyst **6** to the trifluoroketone **1a**. In the presence of acetone, the released catalyst **6** promotes the aldol addition of the former to **1a**, resulting in a shift of equilibrium between **1a** and the carbinolamine **10** (Scheme 2). Once **1a** was completely consumed to give **3a**, the resonances of the intermediate **10** disappeared. As mentioned before, in an acetone solution of **10**

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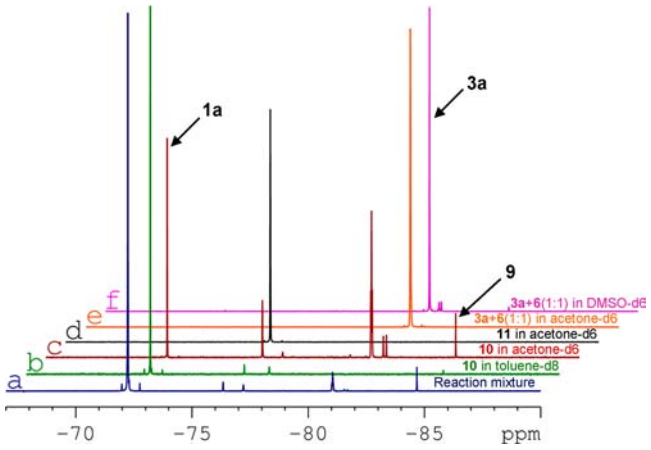
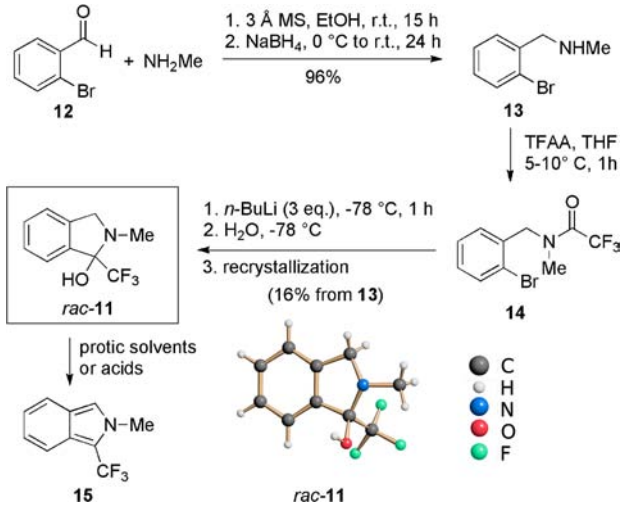


Figure 4. ^{19}F NMR spectra of (a) the reaction mixture of **1a** and 10 mol % of **6** in acetone-d_6 at t = 10 min; (b) **10** in toluene-d_8; (c) **10** in acetone-d_6; (d) *rac*-**11** in acetone-d_6; (e) a 1:1 mixture of **3a** and **6** in acetone-d_6; (f) a 1:1 mixture of **3a** and **6** in DMSO-d_6.

(and also in the course of the aldol reaction), we furthermore observed two weak ^{19}F-NMR resonances in the region δ = −81 and −82 ppm (Figure 4, traces a and c). These resonances could also be generated by mixing the catalyst **6** with the *aldol product* **3a**, in particular in DMSO-d_6 as solvent (Figure 4, traces e and f). In the absence of further data, we tentatively assign these resonances to catalyst−product adducts, presumably of the iminium or enamine type.[22]

To further support our assignment of the transient ^{19}F NMR resonances at δ = −76.4 and −77.5 ppm, we synthesized a cyclic, and thus more stable, carbinolamine mimic of **10**: namely the *iso*-indolinol *rac*-**11**. As depicted in Scheme 3, by

Scheme 3. Synthesis of *rac*-11 and Its X-ray Structure

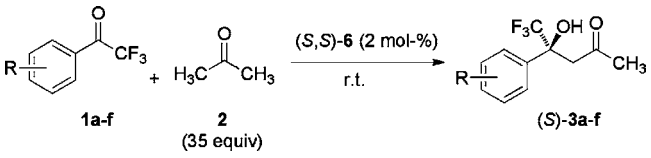


starting from 2-bromobenzaldehyde (**12**), *rac*-**11** could be synthesized in a three step sequence comprising reductive amination,[23] trifluoroacetylation of the resulting amine **13**, and final cyclization of **14** via lithium−halogen exchange. We noted that the carbinolamine *rac*-**11** is prone to dehydration, affording the *iso*-indole **15** (see SI for spectra of **15**). Nevertheless, pure *iso*-indolinol *rac*-**11** could be obtained by crystallization. The structure of *rac*-**11** was established by ^{1}H and ^{13}C NMR, and additionally confirmed by X-ray diffraction analysis (Scheme 3). Avoiding contact with acids and low temperatures is crucial for the long-time storage of *rac*-**11**.

As shown in Figure 4, trace d, the quaternary CF_3 group of **11** resonates at δ = −76.0 ppm, which is almost identical to the lower-field resonance of the carbinolamines **10**. The model compound *rac*-**11** furthermore enabled us to examine the catalytic activity of such carbinolamine adducts. To this end, we mixed *rac*-**11** (10 mol %) and trifluoroacetophenone (**1a**) in acetone-d_6. No aldol adduct **3a** was formed under these conditions, indicating the catalytic inactivity of *rac*-**11**. We extrapolate from this that the "real" carbinolamines **10** are catalytically inactive, too.

2.5. Substrate Scope of the Reaction. Besides the parent compound **1a**, five substituted trifluoroacetophenones **1b−f** were reacted with acetone (neat) in the presence of 2 mol % of catalyst **6**. In several cases, commercially available trifluoroacetophenones contained traces of trifluoroacetic acid, as evidenced by ^{19}F NMR. To achieve reproducible and comparable results in the aldol reactions, it was crucial to remove these impurities by storing the starting materials over $MgSO_4$/$NaHCO_3$ and filtering through neutral Al_2O_3 prior to use. The aldol reactions were conducted on 2−5 mmol scale, and they were monitored by TLC. Upon completion, the products **3a−f** were isolated from the reaction mixture, without aqueous workup, by short column chromatography. The results are summarized in Table 2.

Table 2. Enantioselective Addition of Acetone to Various Aryl Trifluoromethyl Ketones 1a−f in the Presence of 6 (2 mol %) to Afford the Aldols 3a−f



entry[a]	3	R	time (h)[b]	yield (%)[c]	ee (%)[d,e]	$[\alpha]_D^{20}$
1[f]	**3a**	H	20 (18)	91	92 (93)	+24
2	**3b**	*p*-Me	25 (24)	90	94 (94)	+24
3	**3c**	*p*-OMe	42 (40)	92	95 (95)	+24
4	**3d**	*o*-OMe	20 (19)	97	84 (84)	+29
5	**3e**	*p*-F	10 (9)	90	94 (94)	+23
6[f]	**3f**	*p*-Cl	24 (18)	92	92 (93)	+23

[a]Unless otherwise noted, the reaction was carried out on the 2 mmol scale (substrates **1a−f**) in dry acetone (35 equiv), in the presence of catalyst **6** (2 mol %), at room temperature. [b]In parentheses: reaction time for completion in acetone-d_6 (0.2 mmol scale); monitoring by ^{19}F NMR (see details in SI). [c]Isolated yields by column chromatography. [d]The ee value of the isolated products was determined by HPLC analysis using a Daicel Chiralcel OD-H column. [e]Values in parentheses refer to crude product, before column chromatography. [f]The reaction was performed on 5 mmol scale.

We were delighted to find that, under these conditions, the desired products **3a−f** could be isolated in excellent yields of 90−97% and with high enantiopurity of typically 92−95% ee [with the exception of *o*-methoxy trifluoroacetophenone (**3d**), 84% ee; Table 2, entry 4],[24] which were only marginally lower than that measured from the reaction mixtures (for the reaction profiles of the substrates **3b−f**; see Supporting Information). With regard to reaction rates, the following trend was found: *p*-F (**3e**) ≫ unsubstituted (**3a**) ≈ *o*-OMe (**3d**) ≈ *p*-Cl (**3f**) ≈ *p*-

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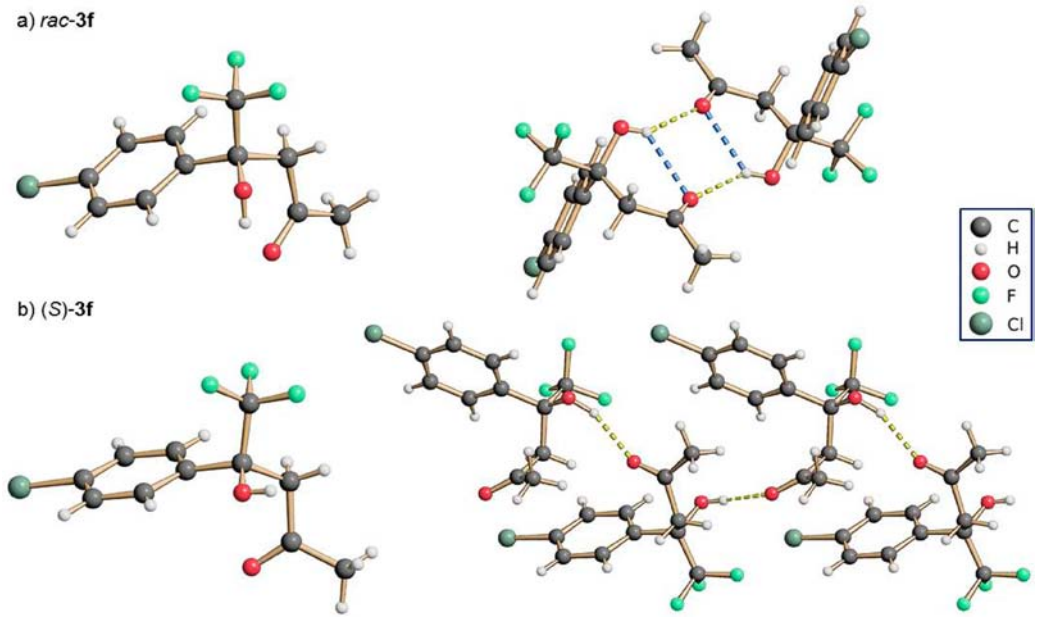

Figure 5. X-ray crystal structures of *rac*-**3f** (a) and (*S*)-**3f** (b).

Me (**3b**) ≫ *p*-OMe (**3c**). This trend roughly reflects the expected electrophilicity of the ketone substrates.

2.6. Absolute Configuration of the Aldol Adducts: To clarify the absolute configuration of the aldol adducts,[25] we attempted the crystallization of heavy-atom containing **3f** and the determination of its absolute configuration by anomalous X-ray scattering. In our first experiments, we employed optically active **3f** (92% ee) and attempted crystallization from protic solvents, such as EtOH. We were surprised to find that the crystals grown under these conditions were those of the racemate (*rac*-**3f**). X-ray crystallographic analysis furthermore revealed that *rac*-**3f** crystallizes in the form of cyclic hydrogen-bonded (*R*+*S*)-dimers, as shown in Figure 5a. We next attempted the crystallization of highly enantiomerically enriched **3f** directly after purification, by evaporation of the solvent under reduced pressure. To our delight, crystals of enantiomerically pure **3f**, suitable for X-ray structural analysis, could be grown at low temperature (0 °C). The absolute configuration was determined to be (*S*), as shown in Figure 5b. This material crystallized in a noncentrosymmetric space group (*P*1) with a Flack parameter[26] of 0.02(6), indicating that the crystals of (*S*)-**3f** are indeed enantiomerically pure. Importantly, X-ray diffraction (Figure 5) revealed that (*S*)-**3f** and *rac*-**3f** show distinct intermolecular hydrogen bonding interactions. Whereas enantiomerically pure (*S*)-**3f** forms an endless, zigzag-patterned ribbon, *rac*-**3f** exists in the crystal as a heterochiral dimer, with a cyclic hydrogen bonding network consisting of two bifurcated OH-hydrogen bonds. Interestingly, the specific hydrogen bonding patterns observed here are reminiscent of what we previously reported for the racemic and the enantiopure forms of 1-phenyl-2,2,2-trifluoroethanol (PhTFE). In the crystal structures of the latter, (*R*)-PhTFE crystallizes in endless zigzag chains, whereas the racemic PhTFE forms cyclic (2*R*+2*S*)-tetramers.[27] In addition, the crystal packing of (*S*)-**3f** reveals no *intra*molecular hydrogen bond between the carbonyl oxygen atom and the OH group, which is found in the case of *rac*-**3f**. Instead, there are significant *inter*molecular hydrogen-bonding interactions between three molecules of (*S*)-**3f** found in the asymmetric unit, in which the quaternary OH group of one molecule forms an intermolecular hydrogen bond with the carbonyl oxygen atom of another molecule. In line with the structural differences described above, the two materials *rac*-**3f** and (*S*)-**3f** exhibit significantly different melting points of 82 and 42 °C, respectively. The predominantly formed configuration of the other products **3a**−**e** is, in analogy, assumed to be (*S*) as well [when using (*S*,*S*)-configurated Singh-catalyst **6**].

3. CONCLUSIONS

On the basis of reaction analysis and the resulting mechanistic insight, we have developed a high-yielding and enantioselective aldol addition of acetone to aryl trifluoromethyl ketones, proceeding at room temperature. Employing Singh's catalyst **6** at low loading of 2 mol %, high yields (90−97%) of the resulting *β*-trifluoromethyl-*β*-hydroxy ketones **3a**−**f** were obtained under proper reaction conditions, with very high enantiomeric excesses (84−95%). To achieve these numbers, it was crucial to identify (and to avoid) conditions that induce racemization of the aldol adducts **3**: protic solvents, including aqueous solution, the presence of acid, and high catalyst loadings of ≥5 mol %. This study also demonstrated the importance of careful sample preparation for reaction analysis. Moreover, we characterized the structure of the "parasitic" (i.e., catalytically incompetent) intermediate **10**, which is formed reversibly from the amine catalyst **6** and the aldol acceptor component, i.e. ketone **1a**. Further studies in our laboratory aim at the combination of the organocatalytic aldol process described herein with subsequent biocatalytic reduction, to generate the corresponding chiral 1,3-diols in stereochemically defined form.

4. EXPERIMENTAL SECTION

4.1. General. ^{19}F NMR spectra were measured on a Bruker Avance 400 instrument; ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance 400, a Bruker DRX 500, or a Bruker Avance II 600 instrument at 25 °C and are referenced to the solvent used. IR spectra were recorded on a Shimadzu IR Affinity-1 FT-IR spectrometer. HPLC analyses were performed on a Merck Hitachi LaChrom HPLC

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instrument. Optical rotations were measured on a Perkin-Elmer 343 Plus polarimeter. Melting points were determined on a Büchi apparatus and are uncorrected.

L-Proline (99%, BioChemica AppliChem), DL-proline (99%, Sigma Aldrich), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 99%, ABCR GmbH & Co. KG), deuterated acetone (99.8 %D, H_2O+D_2O < 0.02%, Euriso-Top), dry acetone (99.8%, extra dry, AcroSeal, Acros Organics) were purchased from the suppliers indicated and used as received. 2,2,2-Trifluoroacetophenone (**1a**, 99%, Sigma Aldrich), 4'-chloro-2,2,2-trifluoroacetophenone (**1f**, 99%, Sigma Aldrich), 4'-fluoro-2,2,2-trifluoroacetophenone (**1e**, Fluorochem), 4'-methoxy-2,2,2-trifluoroacetophenone (**1c**, Fluorochem), 2'-methoxy-2,2,2-trifluoroacetophenone (**1d**, Fluorochem) and 4'-methyl-2,2,2-trifluoroacetophenone (**1b**, Fluorochem) were stored over $MgSO_4/NaHCO_3$, and filtered through neutral Al_2O_3 prior to use.

4.2. General Procedure for Kinetic Investigations: Monitoring by ^{19}F NMR. To the aryl trifluoromethyl ketone **1** (0.2 mmol) was added a solution of catalyst **6** (7.3 mg, 0.02 mmol, 10 mol %) in deuterated acetone (0.5 mL, 35 equiv). When a different solvent was used for the reaction, acetone-d_6 (0.14 mL, 10 equiv) was mixed with that solvent to a total volume of 0.5 mL. The reaction mixture was transferred to a NMR tube and immediately monitored by ^{19}F NMR. The product-based conversion was determined from the ratio of the integral of the product signal in relation to the sum of integrals of all signals (substrate **1**, product, and side-products).

4.3. General Procedure for Kinetic Investigations: Monitoring by HPLC. The reaction mixture was prepared as described for ^{19}F NMR analysis. At intervals, aliquots were withdrawn and prepared for chiral HPLC analysis by one of the two following methods: (1) addition to saturated aqueous ammonium chloride and extraction with Et_2O prior to analysis; (2) filtration though a short pad of silica gel, eluting with 1% *i*-PrOH in *n*-hexane.

4.4. General Procedure for the Synthesis of 3a–f: Preparative Scale. A solution of the catalyst **6** (0.0367 g, 0.1 mmol) in dry acetone (12.5 mL) was added to the aryl trifluoromethyl ketone **1** (5 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. Upon completion, the reaction mixture was diluted with hexane (12.5 mL) and purified immediately by short column chromatography on silica gel (acetone/hexane) to give the aldol adducts (*S*)-**3**. See the Supporting Information for the spectra and HPL-chromatograms of the aldol products.

*5,5,5-Trifluoro-4-hydroxy-4-phenylpentan-2-one (**3a**).* This compound was prepared following the general procedure on a 5 mmol scale to afford **3a** as a colorless viscous liquid which solidified as a white solid upon standing at 0 °C (1.056 g, 91%, 92% ee); R_f = 0.60 (acetone/hexane 1:3); mp 39–41 °C (for *rac*-**3a**; mp 55–57 °C); $[\alpha]_D^{20}$ +24.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.44–7.38 (m, 3H, Ar–H), 5.50 (s, 1H, OH), 3.39 (d, *J* = 17.2 Hz, 1H, C*H*H), 3.23 (d, *J* = 17.2 Hz, 1H, CH*H*), 2.21 (s, 3H, CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 209.0 (C=O), 137.5, 128.8, 128.5, 127.4–121.7 (q, CF_3), 76.3–75.7 (q, $OCCF_3$), 45.1 (CH_2), 32.0 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.1 ppm. IR (ATR): $\tilde{\nu}$ = 3462, 3280, 2910, 1714, 1691 (s), 1456, 1411, 1365, 1344, 1199, 1159 (s), 1136, 1060, 991, 906, 761, 700, 675, 640 cm^{-1}.

*5,5,5-Trifluoro-4-hydroxy-4-p-tolylpentan-2-one (**3b**).* This compound was prepared following the general procedure on a 2 mmol scale to afford **3b** as a white solid (0.443 g, 90%, 94% ee); R_f = 0.50 (acetone/hexane 1:3); mp 56–58 °C; $[\alpha]_D^{20}$ +24.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.23 (d, *J* = 8.1 Hz, 2H, Ar–H), 5.42 (s, 1H, OH), 3.39 (d, *J* = 17.1 Hz, 1H, C*H*H), 3.21 (d, *J* = 17.1 Hz, 1H, CH*H*), 2.38 (s, 3H, CH_3), 2.21 (s, 3H, CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 209.1 (C=O), 138.7, 134.5, 129.2, 126.7, 127.4–121.7 (q, CF_3), 76.3–75.7 (q, $OCCF_3$), 45.1 (CH_2), 32.1 (CH_3), 21.0 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −80.5 ppm. IR (ATR): $\tilde{\nu}$ = 3444, 3394, 3035, 2927, 1714, 1701 (s), 1516, 1411, 1361, 1253, 1219, 1193, 1155 (s), 1138, 1109, 1047, 1022, 979, 920, 817, 806, 731, 715 cm^{-1}.

*5,5,5-Trifluoro-4-hydroxy-4-(4-methoxyphenyl)pentan-2-one (**3c**).* This was prepared following the general procedure on a 2 mmol scale to afford **3c** as a colorless viscous liquid (0.483 g, 92%, 95% ee); R_f = 0.37 (acetone/hexane 1:3); $[\alpha]_D^{20}$ +23.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 8.6 Hz, 2H, Ar–H), 6.93 (d, *J* = 8.8 Hz, 2H, Ar–H), 5.41 (br. s, 1H, OH), 3.83 (s, 3H, OCH_3), 3.36 (d, *J* = 17.1 Hz, 1H, C*H*H), 3.18 (d, *J* = 17.1 Hz, 1H, CH*H*), 2.22 (s, 3H, CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 209.1 (C=O), 159.9, 129.4, 127.5, 127.4–121.7 (q, CF_3), 113.8, 76.1–75.5 (q, $OCCF_3$), 55.2 (CH_3), 45.1 (CH_2), 32.1 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −80.7 ppm. IR (ATR): $\tilde{\nu}$ = 3417, 3007, 2962, 2916, 2841, 1705 (s), 1612, 1538, 1514, 1463, 1419, 1363, 1334, 1301, 1246, 1153 (s), 1152, 1058, 1029, 983, 912, 831, 800, 738, 713 cm^{-1}.

*5,5,5-Trifluoro-4-hydroxy-4-(2-methoxyphenyl)pentan-2-one (**3d**).* This was prepared following the general procedure on a 2 mmol scale to afford **3d** as a white solid (0.509 g, 97%, 84% ee); R_f = 0.36 (acetone/hexane 1:3); mp 64–74 °C; $[\alpha]_D^{20}$ +29.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.40–7.33 (m, 1H, Ar–H), 7.05 (t, *J* = 7.6 Hz, 1H, Ar–H), δ = 6.96 (d, *J* = 8.3 Hz, 1H, Ar–H), 5.66 (br s, 1H, OH), 3.90 (s, 3H, OCH_3), 3.84 (d, *J* = 16.7 Hz, 1H, C*H*H), 3.13 (d, *J* = 16.7 Hz, 1H, CH*H*), 2.19 (s, 3H, CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.8 (C=O), 157.1, 130.5, 130.2, 127.6–121.9 (q, CF_3), 124.0, 121.3, 112.1, 76.7–76.1 (q, $OCCF_3$), 55.8 (OCH_3), 46.3 (CH_2), 31.1 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −81.1 ppm; IR (ATR): $\tilde{\nu}$ = 3498, 3084, 3010, 2976, 2839, 1718 (s), 1600, 1587, 1490, 1465, 1435, 1402, 1361, 1342, 1246, 1228, 1170, 1155 (s), 1132, 1107, 1060, 1045, 1016, 987, 916, 754, 721, 702, 624 cm^{-1}; Anal. Calcd for $C_{12}H_{13}F_3O_3$: C, 54.96; H, 5.00. Found: C, 55.22; H, 5.43.

*4-(4-Fluorophenyl)-5,5,5-trifluoro-4-hydroxypentan-2-one (**3e**).* This was prepared following the general procedure on a 2 mmol scale to afford **3e** as a colorless viscous liquid (0.450 g, 90%, 94% ee); R_f = 0.57 (acetone/hexane 1:3); $[\alpha]_D^{20}$ +22.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 8.5, 5.3 Hz, 2H, Ar–H), 7.10 (t, *J* = 8.6 Hz, 2H, Ar–H), 5.53 (br s, 1H, OH), 3.33 (d, *J* = 17.2 Hz, 1H, C*H*H), 3.23 (d, *J* = 17.2 Hz, 1H, CH*H*), 2.24 (s, 3H, CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 208.9 (C=O), 163.7–162.1 (d, Ar–CF), 133.3, 128.1, 128.1, 127.2–121.5 (q, CF_3), 115.5, 115.4, 76.0–75.4 (q, $OCCF_3$), 45.0 (CH_2), 32.0 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −80.5 (CF_3), −113.1 (−113.2) (Ar–F) ppm. IR (ATR): $\tilde{\nu}$ = 3417, 3078, 3010, 2922, 1707 (s), 1604, 1510, 1419, 1363, 1334, 1234, 1157 (s), 1132, 1095, 1055, 993, 835, 736 cm^{-1}.

*4-(4-Chlorophenyl)-5,5,5-trifluoro-4-hydroxypentan-2-one (**3f**).* This was prepared following the general procedure on a 5 mmol scale to afford **3f** as a white semisolid (1.227 g, 92%, 92% ee); R_f = 0.52 (acetone/hexane 1:3); mp 42–44 °C (for *rac*-**3f**; mp 82–85 °C); $[\alpha]_D^{20}$ +22.8 (*c* 1.0, $CDCl_3$); ^{1}H NMR (600 MHz, $CHCl_3$): δ = 7.53 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.40 (d, *J* = 8.6 Hz, 2H, Ar–H), 5.52 (s, 1H, OH), 3.33 (d, *J* = 17.3 Hz, 1H, C*H*H), 3.23 (d, *J* = 17.3 Hz, 1H, CH*H*), 2.24 (s, 3H, CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 208.8 (C=O), 136.1, 135.0, 128.7, 127.6, 127.1–121.4 (q, CF_3), 76.0–75.5 (q, $OCCF_3$), 44.9 (CH_2), 32.0 (CH_3) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = −80.4 ppm. IR (ATR): $\tilde{\nu}$ = 3398, 3095, 3008, 2918, 1705 (s), 1598, 1492, 1417, 1363, 1332, 1244, 1159 (s), 1136, 1093, 1055, 1014, 991, 914, 827, 758, 732 cm^{-1}.

4.5. Synthesis of *rac*-11. *N-Methyl-2-bromobenzylamine (**13**).* To a mixture of 2-bromobenzaldehyde (1.850 g, 10 mmol) and 3 Å molecular sieves (2 g) in dry ethanol (4 mL) was added CH_3NH_2 (4 mL, 33% solution in ethanol, 32 mmol) under argon. The reaction mixture was stirred for 15 h at room temperature. The resulting mixture was cooled down to 0 °C, and $NaBH_4$ (0.567 g, 15 mmol) was added. The reaction mixture was then stirred at room temperature for 24 h. Water (10 mL) was added, and the molecular sieves were filtered off. The filtrate was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. After removal of the solvent, the crude product was obtained as a clear pale yellow liquid. Purification by flash column chromatography on SiO_2 (ethyl acetate/*n*-hexane) afforded the desired product **13** as a clear colorless liquid (1.911 g, 96% yield); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H, Ar–H), 7.39 (dd, *J* = 7.6 Hz, 1.4 Hz, 1H, Ar–H), 7.32–7.27 (m, 1H, Ar–H), 7.14 (td, *J* = 7.8 Hz, 1.6 Hz, 1H, Ar–H), 3.85 (s, 2H, NCH_2), 2.47 (s, 3H,

NCH_3), 1.51 (bs, 1H, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.1, 132.8, 130.3, 128.6, 127.4, 124.0, 55.8 (CH_2), 35.9 (CH_3) ppm; IR (ATR): $\tilde{\nu}$ = 3319 (br), 3059, 2931, 2843, 2791, 1591, 1566, 1487, 1438, 1352, 1199, 1130, 1103, 1024, 823, 744 (s), 655 cm^{-1}.

N-Methyl-1-(trifluoromethyl)isoindolin-1-ol (rac-11). To a solution of **13** (0.600 g, 3 mmol) in dry THF (0.6 mL) was added TFAA (0.6 mL, 4.2 mmol), in a dropwise manner, with ice cooling (5−10 °C). The mixture was stirred in the ice bath for an additional 1 h. After removal of THF and TFAA under vacuum, compound **14** was obtained, and it was used in the next step without further purification. To a solution of **14** in dry THF (12 mL) was added *n*-Buli (3.5 mL, 2.5 M in hexane, 8.7 mmol) in a dropwise manner at −78 °C under Ar. The reaction mixture was stirred at the same temperature for 1 h and quenched with water (5 mL) at −78 °C. The mixture was immediately extracted with diethyl ether (3 × 15 mL), and the combined extracts were dried over $MgSO_4$. After removal of the solvent, and upon storage at 0 °C, the desired product *rac*-**11** separated from the yellow oily crude material as a pale yellow solid (0.101 g, 16% yield); mp 82−84 °C; ^1H NMR (600 MHz, acetone-d_6): δ = 7.51 (d, J = 7.7 Hz, 1H, Ar−H), 7.41 (d, J = 7.4 Hz, 1H, Ar−H), 7.35 (t, J = 7.4 Hz, 2H, Ar−H), 5.62 (s, 1H, OH), 4.24 (d, J = 13.4 Hz, 1H, C*H*H), 4.02 (d, J = 13.4 Hz, 1H, CH*H*), 2.71 (s, 3H, NCH_3) ppm; ^{13}C NMR (150 MHz, acetone-d_6): δ = 140.2, 138.6, 129.3, 127.8−122.1 (q, CF_3), 127.2, 123.7, 122.3, 92.7−92.1 (q, $OCCF_3$), 57.8 (CH_2), 32.5 (CH_3) ppm; ^{19}F NMR (376 MHz, acetone-d_6): δ = −75.9 ppm; IR (ATR): $\tilde{\nu}$ = 3062 (br), 3045, 2962, 2848, 1614, 1595, 1471, 1458, 1354, 1280, 1259, 1157 (s), 1147 (s), 1132 (s), 1085, 1006, 916, 765, 742, 673, 638 cm^{-1}.

CCDC 869533−CCDC 869536 contain the supplementary crystallographic data for this paper [compounds (*S*,*S*,*S*)-**10**, *rac*-**11**, *rac*-**3f**, and (*S*)-**3f**]. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HPLC, NMR (^1H, ^{13}C, ^{19}F) and IR data of the aldols **3a−f**, of the catalyst−substrate adduct **10**, and of the model compound *rac*-**11** (including synthetic intermediate **13** and *iso*-indole **15**); additional kinetic data and reaction monitoring by ^{19}F-NMR; X-ray data of **3f**, *rac*-**3f**, **10**, and *rac*-**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) Lowering the reaction temperature did not significantly affect product enantiopurity: when the reaction was carried out at −20 °C and at 0 °C, the product **3a** was obtained in 94% *ee* after 50 h and in 94% *ee* after 10 h, respectively.

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