Tetrahedron Letters 57 (2016) 1220–1223

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Tertiary amino thiourea-catalyzed asymmetric cross aldol reaction of aryl methyl ketones with aryl trifluoromethyl ketones

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ARTICLE INFO

Article history:
Received 13 November 2015
Revised 27 January 2016
Accepted 1 February 2016
Available online 4 February 2016

Keywords:
Aldol reaction
Thiourea
Bifunctional catalyst
Organocatalysis
Trifluoromethyl ketones

ABSTRACT

An enantioselective aldol reaction of aryl methyl ketones with aryl trifluoromethyl ketones catalyzed by tertiary amino thiourea has been established. Under mild conditions, the corresponding β-trifluoromethyl-β-hydroxy ketone products were obtained with up to 89% ee.

Fluorinated compounds constitute an essential class of materials in organic chemistry due to their unique physical and biochemical properties. Of particular interest are α-trifluoromethylated alcohols, which are commonly found as subunits in chiral pharmaceutical and agrochemical products. Therefore, their synthesis has received much attention in recent years.[1]

The organocatalytic asymmetric aldol reaction[2] of ketones with trifluoromethyl ketones has proven to be a powerful tool for the preparation of α-trifluoromethylated tertiary alcohols under relatively mild conditions with high levels of stereoselectivity. In a pioneering endeavor, in 2005 Zhang and coworkers described the L-proline catalyzed reaction of acetone with 2,2,2-trifluoromethyl aryl ketones to give the corresponding tertiary alcohols with a moderate enantioselectivity.[3] Since then, several reports involving the reaction of aliphatic ketone donors with trifluoromethyl ketones catalyzed by secondary or primary amines have emerged.[4,5] Mechanistically, the efficiency of these catalytic systems relies on the ability of the amine to activate the ketone donor via the formation of an enamine intermediate.[6] Aryl ketones are poor substrates in the secondary or primary amine catalyzed reactions due to their low ability to form enamine intermediates. To our knowledge, there has been no report of an organocatalyzed enantioselective direct aldol reaction between aromatic ketones and trifluoromethyl ketones to give optically active β-trifluoromethyl-β-hydroxy aryl ketones. The only known catalytic method for the preparation of these valuable compounds is the decarboxylative aldol reaction of β-ketoacids with trifluoromethyl ketones in the presence of biscinchona alkaloids.[7] Alternatively, in 2010 Zhao and coworkers reported a successful enantioselective direct aldol reaction of aryl methyl ketones with isatin derivatives catalyzed by quinidine thiourea.[8] In their proposed mechanism, the tertiary amine moiety of the catalyst deprotonates the ketone donor at α-position of the carbonyl to generate an enolate, while the acidic thiourea moiety activates the acceptor through hydrogen bonding and directs its approach for the enolate attack. Inspired by this groundbreaking study, we anticipated that such a mechanism would render aryl methyl ketones effective nucleophiles in the aldol reaction with trifluoromethyl ketones. Herein, we describe the development of an enantioselective direct aldol reaction of aryl methyl ketones with aryl trifluoromethyl ketones catalyzed by a chiral tertiary amino thiourea (see Fig. 1).

In our preliminary investigation we screened various bifunctional catalysts bearing tertiary amino and hydrogen bond donor moieties. As shown in Table 1, all the catalysts under study promoted the reaction of acetophenone with an equivalent amount of 3′,5′-dichloro-2,2,2-trifluoroacetophenone in toluene to give the intended aldol product. However, the so-called Takemoto thiourea (**4c**)[9] gave the best outcome in terms of reaction rate and enantioselectivity (entry 4) and was used in the later stages of optimization.

With the optimum catalyst in hand, the reaction medium was examined (Table 2). While all commonly used organic solvents investigated proved effective, dibutyl ether stood out as it allowed

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http://dx.doi.org/10.1016/j.tetlet.2016.02.001
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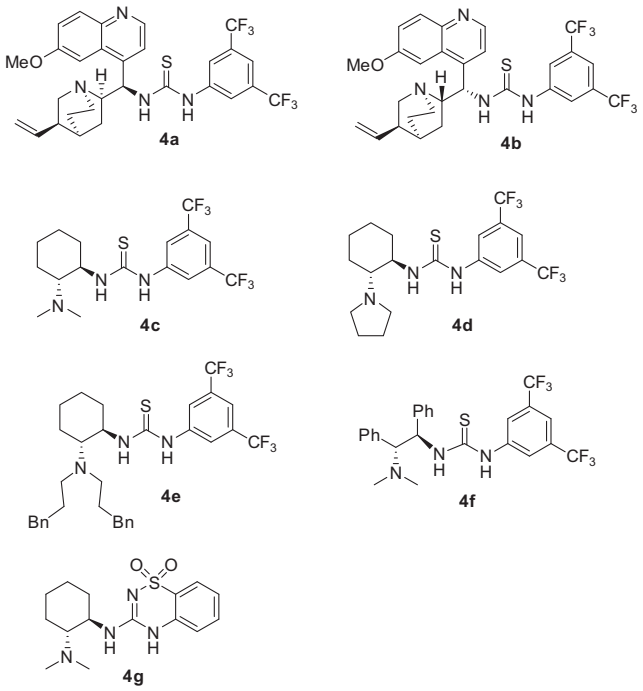


Figure 1. Bifunctional catalysts employed in this study.

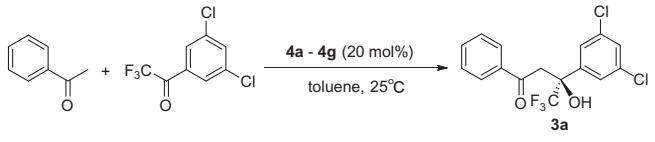
the highest levels of chemical yield and enantiomeric excess (entry 6).

The optimized conditions were then extended to other substrates.[10] First, acetophenone as the nucleophile was reacted with a variety of aromatic electrophiles (Table 3). Ketones having electron withdrawing groups on the aromatic rings afforded the aldol products in good to excellent yields with good enantiomeric excess (Table 3, entries 1–3). Low chemical yields were obtained when electrophiles with electron rich aromatic rings were used (entries 5 and 6). The somewhat lower enantiomeric excess of **3f** may be attributed to the relatively small size of the thienyl group. From these results it appears that electron deficient acceptors facilitate the reaction while this electronic effect has no significant impact on the enantioselectivity. Next, 3′,5′-dichloro-2,2,2-trifluoroacetophenone as the electrophile was treated with a variety of aromatic nucleophiles (Table 4). The reaction with ketones bearing $-NO_2$ and $-CF_3$ groups on the aromatic ring afforded excellent yields with moderate enantiomeric excess (entries 1 and 2). The observed shorter time, compared to that of the reaction with acetophenone (Table 3, entry 1), may be attributed to the higher reactivity due to the increased acidity of the α proton. On the other hand, when ketones bearing electron rich aromatic rings were used as nucleophiles the corresponding products were obtained in good to excellent yields with good enantioselectivity (entries 3–5). It is noteworthy that, while electron deficient ketones favored the reaction rate, the highest levels of enantiomeric excess were achieved when electron rich donors were used (entries 1 and 2 vs. 3–5). Similarly, **3l** was obtained in excellent yield albeit with a lower enantiomeric excess, perhaps due to the relatively small size of the furyl group (entry 6).

The S configuration of the products was determined by comparison of the optical rotation of **3d** with that reported in the literature.[7b]

Recent investigations on amino thiourea catalysis carried out by various research groups have shown that the dual activation of the nucleophile and the electrophile may take place via different pathways.[11] Based on the insights provided by these studies, three possible transition states are proposed to account for the reactivity and enantioselectivity observed in the present reaction (Fig. 2). In A, the generally accepted Takemoto model, acetophenone is activated by the tertiary amine in the catalyst skeleton via deprotonation and subsequent hydrogen bonding of the resulting enolate with the protonated amine. Besides, the thiourea moiety forms two hydrogen bonds with the carbonyl group of 2,2,2-trifluoroacetophenone.[12] These hydrogen bonds activate the electrophile and direct its position during the nucleophilic approach. The *re* attack is preferred since the interaction of the aromatic ring of 2,2,2-trifluoroacetophenone with the enolate is avoided and leads to the formation of the major S enantiomer. In B, the Papai model, an opposite coordination pattern is displayed in which the thiourea binds and activates the nucleophile while the protonated amine activates the electrophile and directs its position. Finally, in C, the Wang model, the deprotonated nucleophile is engaged in two hydrogen bond interactions involving the protonated amine and the proximal thiourea N–H while the distal thiourea N–H activates the electrophile.

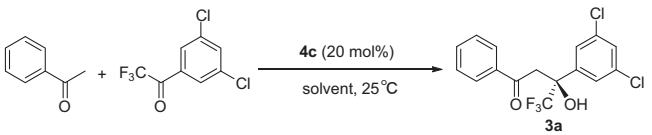
Table 1
Screening of catalysts for the asymmetric addition of acetophenone to 3′,5′-dichloro-2,2,2-trifluoroacetophenone[a]



Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	None	0	—
2	**4a**	29	62
3	**4b**	64	−70
4	**4c**	90	76
5	**4d**	55	68
6	**4e**	44	54
7	**4f**	38	63
8	**4g**	61	49

[a] Reaction conditions: acetophenone (1.0 mmol), 3′,5′-dichloro-2,2,2-trifluoroacetophenone (1.0 mmol), catalyst (0.2 mmol) and toluene (1.0 mL) at 25 °C for 48 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

Table 2
Screening of solvents for the reaction of acetophenone with 3′,5′-dichloro-2,2,2-trifluoroacetophenone[a]



Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	Toluene	90	76
2	Chlorobenzene	90	73
3	THF	71	66
4	CPME	85	74
5	Diisopropyl ether	83	74
6	*n*-Bu_2O	96	76
7	MTBE	84	73
8	DMSO	54	22
9	$CHCl_3$	78	73
10	*n*-BuCl	92	70

[a] Reaction conditions: acetophenone (1.0 mmol), 3′,5′-dichloro-2,2,2-trifluoroacetophenone (1.0 mmol), **4c** (0.2 mmol) and a solvent (1.0 mL) at 25 °C for 48 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.