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Preparation and application of 2-(arylmethoxy)isopinocampheols for the asymmetric aldol reaction of 3,3,3-trifluoropropionates

P. Veeraraghavan Ramachandran *, Gowrisankar Parthasarathy, Pravin D. Gagare

Herbert C. Brown Center for Borane Research, Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907-2084, USA

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ABSTRACT

The preparation of 2-(arylmethoxy)isopinocampheols from pinanediol via the DIABL-H reduction of the corresponding aryl aldehyde acetals has been described. A systematic examination of the asymmetric aldol reaction of 3,3,3-trifluoropropionates led to the double diastereoselective aldol reaction of 2-(arylmethoxy)isopinocampheyl 3,3,3-trifluoropropionates providing *anti*-α-trifluoromethyl-β-hydroxy esters in 63–85% yields, ⩾99% *anti*-selectivity and 80–96% de for the *anti*-isomer.

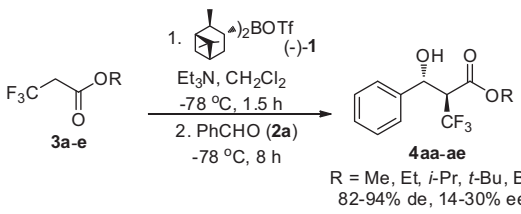
Enantioselective synthesis of partially-fluorinated molecules is often challenging[1] and contributes to the success of agrochemicals and pharmaceuticals.[2] Over the past two decades, as part of our program on fluoroorganic synthesis via boranes,[3] we have developed several protocols involving hydroboration,[4] allylboration,[5,6] reduction,[7] and homologation.[8] We recently reported a highly *anti*-selective enolboration–aldolization of 3,3,3-trifluoropropionates using dialkylboron triflates.[9] In continuation, both the reagent-[10] and substrate-controlled[11] asymmetric variants of the reaction failed, necessitating the development of a synergistic approach. Described herein are the details of the systematic investigation that led to the double asymmetric aldol reaction of diisopinocampheylboron enolates of 2-(arylmethoxy)isopinocampheyl-3,3,3-trifluoropropionates.[12]

Taking cue from the diisopinocampheylboron triflate [(−)-Ipc$_2$BOTf, (−)-**1**]-controlled aldol reaction of non-fluorinated propionates in excellent ee,[10] benzaldehyde (**2a**) was initially aldolized with diisopinocampheylboron enolates of methyl-(**3a**), ethyl-(**3b**), isopropyl-(**3c**), benzyl-(**3d**), and *tert*-butyl 3,3,3-trifluoropropionates (**3e**).[13] Contrary to the non-fluorinated derivatives, the enantioselectivities for the α-trifluoromethyl-β-hydroxy esters **4aa–ae**[14] were disappointingly poor (14–30%), although the diastereoselectivities were good, ranging from 82% to 94% (Scheme 1).

The substrate-controlled asymmetric ester aldol reaction[11] of (−)-norephedrine-derived 3,3,3-trifluoropropionates **3f** and **3g** was then pursued. Enolization with bis-*exo*-2-norbornylboron triflate (Nrb$_2$BOTf, **5**),[9] followed by aldolization of benzaldehyde provided reasonable *anti:syn* selectivity (73:27 and 94:6, respectively) and low diastereoselectivity (14% and 58%, respectively) for the *anti*-isomers **6af** and **6ag**, respectively (Table 1).

Aldol reaction of bis-*exo*-norbornylboron enolates of (−)-isopinocampheyl- (**3h**), (+)-menthyl- (**3i**), and (−)-8-phenylmenthyl (**3j**) trifluoropropionates with benzaldehyde provided the corresponding aldol products (**6ah–j**) in 96–98% *anti*-selectivity and 20–68% de (Table 1).

Chiral esters **3g** and **3j** were selected for a synergistic double diastereoselection study due to the high de achieved in the substrate-controlled reactions. The corresponding diisopinocampheylboron enolates were too slow to react (5% conversion) under the standard conditions. However, the enolization of **3f**, with either (+)- or (−)-**1**, followed by the reaction with benzaldehyde provided an *anti:syn* selectivity of 68:32 and 71:29, respectively, and a de of 12% and 14%, respectively, for the *anti*-isomer of the product **6af**. The esters



Scheme 1. Examination of the reagent-controlled aldol reaction of trifluoropropionates.

* Corresponding author.
E-mail address: chandran@purdue.edu (P.V. Ramachandran).

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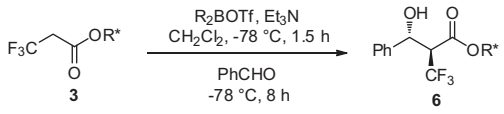
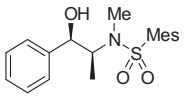
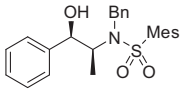
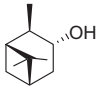
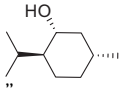
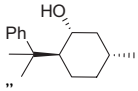
Table 1
Comparison of **1** and **5** for the enolboration–aldolization of chiral 3,3,3-trifluoropropionates

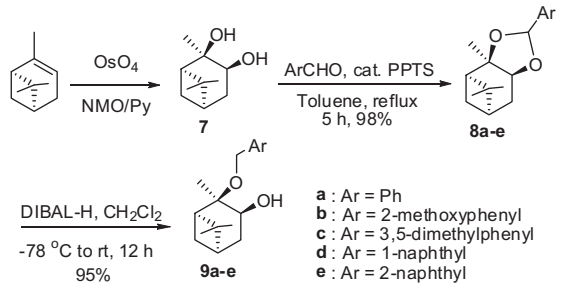


	3	R.OH	R_2BOTf	Aldol[b] 6[a]	*anti*:*syn*[c]	% de of *anti*[c]
1	**3f**		**5**	**6af**	73:27	14
2	**3f**	"	(−)-**1**	**6af**	71:29	14
3	**3f**	"	(+)-**1**	**6af**	68:32	12
4	**3g**		**5**	**6ag**	94:6	58
5	**3g**	"	(−)-**1**	**6ag**	d	d
6	**3h**		**5**	**6ah**	96:4	20
7	**3h**	"	(−)-**1**	**6ah**	90:10	50
8	**3i**		**5**	**6ai**	95:5	20
9	**3i**	"	(−)-**1**	**6ai**	97:3	50
10	**3j**		**5**	**6aj**	98:2	68
11	**3j**	"	(−)-**1**	**6aj**	d	d

[a] See footnote 14.
[b] The yields of the aldol products were 58–69%.
[c] *anti*:*syn* ratios and % de of *anti*-isomers were determined by ^{19}F NMR spectroscopy.
[d] Only ~5–6% conversion was observed by ^{19}F NMR spectroscopy.

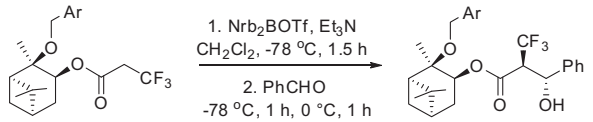
3h and **3i** disclosed an improved 50% de for the *anti*-isomers (*anti*-selectivity of 90% and 97% for **6ah** and **6ai**, respectively), when compared to the substrate-controlled reaction (Table 1). The synergistic effect of two pinane moieties prompted the preparation and examination of bulkier isopinocampheols.

The formation of an inseparable mixture of products during the attempted preparation of trifluoropropionate from (+)-3-*O*-benzylpinanediol[15] motivated the design of new chiral auxiliaries, (+)-2-arylmethoxyisopinocampheols (**9**). Accordingly, (−)-(1*R*, 2*R*, 3*S*, 5*R*)-pinane-2,3-diol (**7**), derived from (−)-α-pinene, was converted to the acetals **8a–e** with the corresponding aromatic aldehydes and reduced with DIBAL-H to provide (+)-2-(benzyloxy)- (**9a**), (+)-2-(2-methoxybenzyloxy)- (**9b**), (+)-2-(3,5-dimethylbenzyloxy)-



Scheme 2. Preparation of (+)-2-(arylmethoxy)isopinocampheols.

Table 2
Examination of substrate-controlled aldol reaction



	Ester		Aldol		
	10	Ar	**11**[a]	*anti*:*syn*[b]	% de of *anti*[b]
1	**10a**	Ph	**11aa**	91:9	20
2	**10b**	2-MeO–C_6H_4	**11ab**	98:2	26
3	**10c**	3,5-Me_2–C_6H_3	**11ac**	96:4	24
4	**10d**	1-Naphthyl	**11ad**	98:2	22
5	**10e**	2-Naphthyl	**11ae**	97:3	22

[a] See footnote 14.
[b] *anti*:*syn* ratios and % de of *anti*-isomer were determined by ^{19}F NMR spectroscopy.

(**9c**), (+)-2-(1-naphthylmethoxy)- (**9d**), and (+)-2-(2-naphthylmethoxy)isopinocampheols (**9e**) in near quantitative yields (Scheme 2).[16]

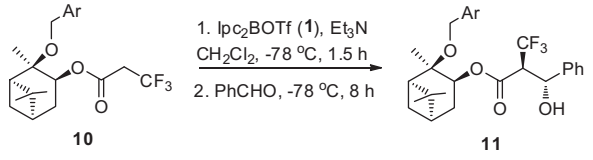
The substrate-controlled aldol reactions of 2-(arylmethoxy)isopinocampheyl 3,3,3-trifluoropropionates **10a–e** with **5** provided only ~20% de for the *anti*-isomers (Table 2).

The double diastereoselection approach was necessary for optimal results. Using the antipodes of **1**, (−)-Ipc_2BOTf was determined to be the matched reagent for the bulky (−)-isopinocampheol esters[17] derived from (−)-pinanediol. While esters **10a** and **10b** provided *anti*:*syn* selectivity of ~70:30 range, **10c–e** provided essentially pure *anti*-aldols (Table 3).

A series of aldehydes was then screened for the aldol reaction under the optimized conditions with the most favorable ester **10d**. The *anti*-α-trifluoromethyl-β-hydroxy esters, which were obtained in 63–85% yield, ⩾99% *anti*-selectivity and 80–90% de, display the generality of the reaction (Table 4).[18]

It was now incumbent upon us to determine the relative and absolute stereochemistry of the aldol products. We resorted to comparing the optical rotation of a known derivative since none of the derivatives could be crystallized for X-ray crystallographic structure determination. Thus, aldol **11ed** was reduced to diol, which was followed by TBS protection of the primary hydroxyl

Table 3
Examination of the double diastereoselection in aldol reaction



	Ester **10**	Ipc_2BOTf	Aldol			
			11[a]	Yield[b] (%)	*anti*:*syn*[c]	% de of *anti*[c]
1	**10a**	(−)-**1**	**11aa**	62	76:24	86
2	**10b**	(−)-**1**	**11ab**	64	70:30	54
3	**10c**	(−)-**1**	**11ac**	61	94:6	86
4	**10c**	(+)-**1**	**11ac**	60	⩾99:⩽1	75
5	**10d**	(−)-**1**	**11ad**	65	⩾99:⩽1	90
6	**10d**	(+)-**1**	**11ad**	60	⩾99:⩽1	60
7	**10e**	(−)-**1**	**11ae**	65	⩾99:⩽1	90
8	**10e**	(+)-**1**	**11ae**	63	⩾99:⩽1	62

[a] See footnote 14.
[b] % Isolated yield.
[c] *anti*:*syn* ratios and % de of *anti*-isomer were determined by ^{19}F NMR spectroscopy.